# 论文回修常见问题与回复策略

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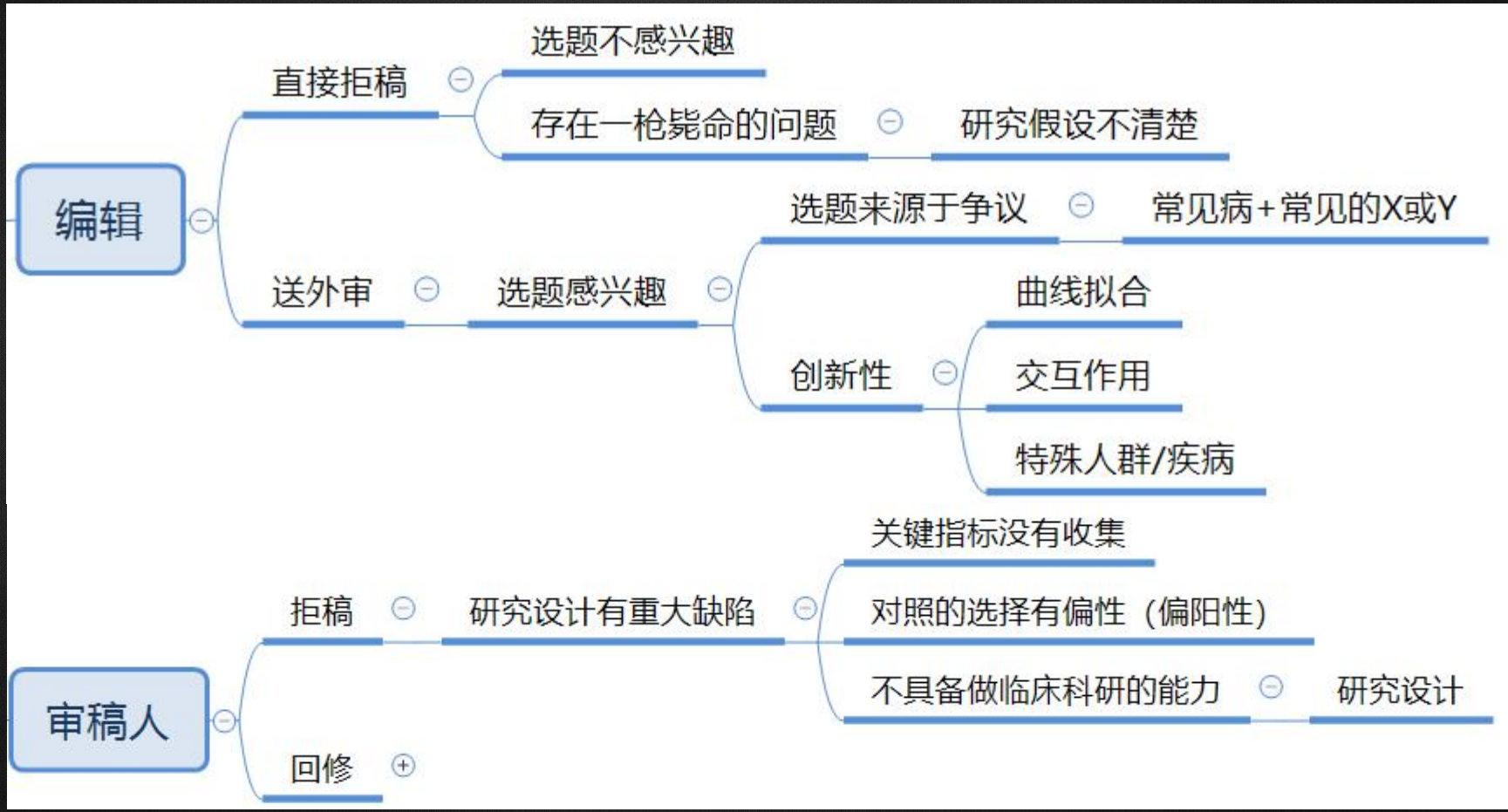
# 拒稿常见原因和解决方案



# 论文回修常见问题：临床研究设计要点

- 明确的研究假设
- 清晰的研究设计
- 结果及临床意义
- 证据力度的思辨

# 1.研究假设：不明确

Reviewer 1
1. Major comments
The aim of the study is obscure.
The primary outcome should be definite clearly.
2. Minor comments
The aim of the study should be consistent in the abstract section and the introduction section

论文手稿：

- 本研究临床数据资料很好（病种、样本量、随访）
- 题目：研究X1和X2与Y1的关系
- 摘要方法：
  - X1和X2与Y1的关系（β）
  - X1和X2与Y2和Y3的关系（OR、HR）
  - X1和X2对Y1的预测价值（其他方法）

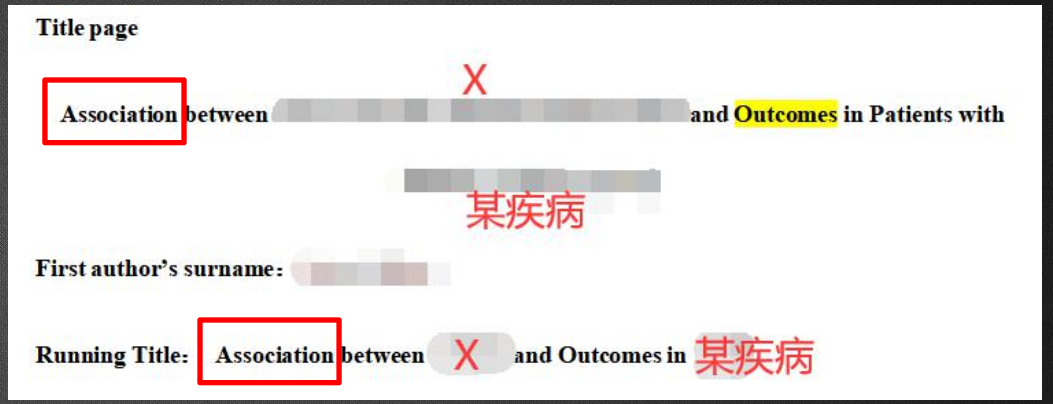
# 1.研究假设：关联分析和预测模型混淆

Reviewer 1

2. in the univariate cox analysis, X has a HR *, while P value was not less than 0.05. Does this X was not a significant predictor in this cohort? Base on previous study, X was consistently shown to have significant prediction value in ……. Please clarify this finding in the present study.

审稿人让补充：预测模型的统计分析结果

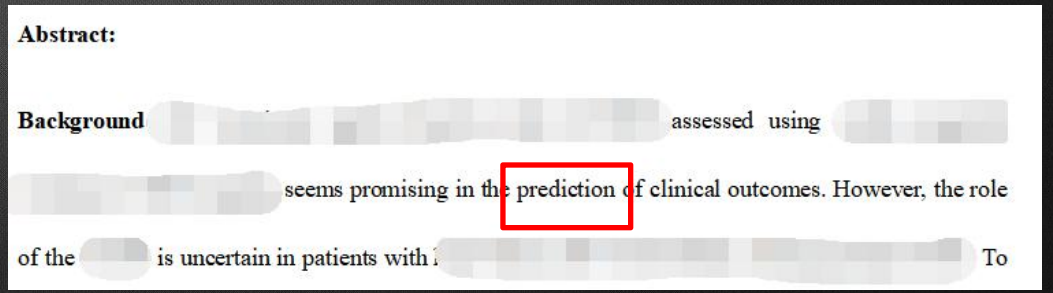
论文手稿：摘要中出现prediction，结果中有ROC曲线


Title page

Association between X and Outcomes in Patients with 某疾病

First author's surname:

Running Title: Association between X and Outcomes in 某疾病


Abstract:

Background assessed using seems promising in the prediction of clinical outcomes. However, the role of the is uncertain in patients with To

# 2.研究设计：不明确

Reviewer 1

1. Major comments

Question 1. Please provide more detailed description of the study setting in the Introduction. How many subjects were excluded because of exclusion criteria?

论文回修：

增加Flow chart

Response: Thank you for your serious and rigorous review. We are sorry that the original manuscript did not clearly explain the subject exclusion process. We have added the flow chart of subject selection to the revised manuscript (Page , Figure ) a

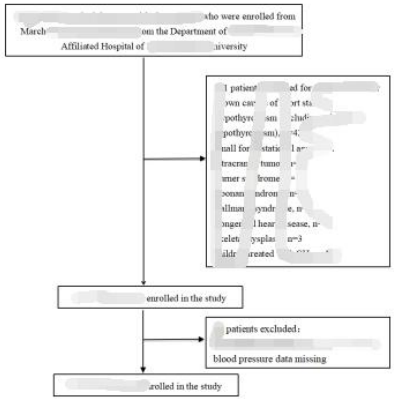



**Figure 1.** Flow chart of the study population

# 结果：其他因素的影响

X是严重程度分了三个组（无、中、重），Y是疾病进展（二分类变量，是否进展）。

0.435表示严重程度中和无的人相比，疾病进展风险降低56.5%。3.279表明严重程度中和无的人相比，疾病进展风险增加2.279倍。可以看出两个模型结果是反的：一个得出保护因素，一个得出危险因素。

审稿人的问题：为什么两个模型得出结果不同？

Multivariable COX model in total patient

| | Hazard Ratio of progress(95%CI) P | | | | | |
|---|---|---|---|---|---|---|
| | Adjust I | | Adjust II | | Adjust III | |
| Severity | | | | | | |
| Non | 1.0 | | 1.0 | | 1.0 | |
| Mild | 0.398(0.267-0.592) | <0.001 | 0.435(0.287-0.660) | <0.001 | 3.279(0.802-13.407) | 0.098 |
| Severe | 0.313(0.189-0.519) | <0.001 | 0.313(0.185-0.528) | <0.001 | 2.043(0.539-7.744) | 0.293 |

Adjust I model adjust for: Pathology; Liver metastasis; Cycle;

Adjust II model adjust for: Age, Hight; Weight; KPS; Pathology; Liver metastasis; Cycle;

Adjust III model adjust for: Age, Hight; Weight; KPS; Pathology; Liver metastasis; Cycle; Timing of C

# 结果：其他因素的影响

两模型的差别是调整变量不同，模型3多调整了一个变量（发生C的时间），即多调整了Timing of C的作用，严重程度的保护作用消失（从0.435变为3.27）。表明在考虑到Timing of C的作用后，严重程度对Y的保护作用就消失了。

根据这个回归分析结果，审稿人建议把研究的X换成时间（Timing of C），因为这个因素的作用很强，并且也有临床意义。

Multivariable COX model in total patient

| | Hazard Ratio of progress(95%CI) P | | | | | |
|---|---|---|---|---|---|---|
| | Adjust I | | Adjust II | | Adjust III | |
| Severity | | | | | | |
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[1].Chen, Y., et al., **Timing of chemotherapy-induced neutropenia** predicts prognosis in metastatic colon cancer patients: a retrospective study in mFOLFOX6 -treated patients. BMC Cancer, 2017. 17(1).

[2].Chen, Y., et al., **Timing of chemotherapy-induced neutropenia**: the prognostic factor in advanced pancreatic cancer patients treated with gemcitabine / gemcitabine-based chemotherapy. Oncotarget, 2017. 8(39): p. 66593-66600.

# 结果：其他因素的影响

## 其他因素Z对X和Y关系的影响如何？

常见二次回修拒稿原因

- 用文献回复：Z指标对结果影响不大/没影响
- 用临床经验回复：根据我的临床经验，Z的影响不用考虑

用数据回复：

（1）按Z分层，看X和Y的关系在不同层是否稳定存在。

- 各层结果一致：用图表回复审稿人。一致是指回归分析效应值的方向和大小，不看p值。因为分层后样本量小，p值不显著很正常。
- 不一致：重新做纳排标准

（2）调整Z与不调整Z，看X和Y的关系（回归分析效应值）变化

- 变化不大：用表回复审稿人，展示调整Z和不调整Z的结果
- 变化大：完善正文的调整策略，结合文献背景解读结果

# 实例

X：睡眠时间（连续变量）Y：SBP和DBP（连续变量）研究人群：青少年
结论：男性中睡眠时间增加与SBP升高有关联；女性中睡眠时间增加与SBP升高有关联。

**Table 2:** Linear regression coefficients (β) of the association between sleep duration (by 1 hour increment) and blood pressure in adolescents aged 12 to 17, 2013-2014.

| | Systolic blood pressure | | Diastolic blood pressure | |
|---|---|---|---|---|
| | β (95% CI) | *P* value | β (95% CI) | *P* value |
| **Boys** | | | | |
| Unadjusted | - 1.20 (-1.4; -0.9) | < 0.0001 | | |
| Adjusted | | | | |
| Model 1 | - 0.90 (-1.1; -0.6) | < 0.0001 | | |
| Model 2 | - 0.15 (-0.3; 0.09) | 0.2 | | |
| Model 3 | - 0.40 (-0.6; -0.12) | 0.004 | | |
| Model 4 | 0.18 (-0.0; 0.4) | 0.1 | | |
| **Girls** | | | | |
| Unadjusted | - 0.251 (-0.4; -0.0) | 0.009 | | |
| Adjusted | | | | |
| Model 1 | - 0.183 (-0.3; 0.0) | 0.052 | | |
| Model 2 | 0.004 (-0.1; 0.1) | 0.96 | | |
| Model 3 | 0.127 (-0.0; 0.3) | 0.1 | | |
| Model 4 | 0.241 (0.0; 0.4) | 0.009 | | |

Model 1: Adjusted for stage of sexual maturity. Model 2: Adjusted for age. Model 3: Adjusted for stage of sexual maturity, BMI, physical activity, smoking, screen time and skin color. Model 4: Adjusted age, BMI, physical activity, smoking, screen time and skin color.

从审稿人的角度看科研态度和技术细节

原创 胡丽华博士 EmpowerStats 2019-05-21

1. In model 4, although there was no significant statistical difference, the results showed that sleep duration was positively associated with BP after adjusting the age, suggesting age was the mediator of this association. I am interested in the relationship between sleep duration and BP stratified by age groups.

*We understand and describe age acts as a confounding variable (common understanding to reviewer #1). Therefore, it was used in the adjustment of the model and not in the stratification.*

*In addition, the age range of the sample is very narrow, ranging from 12 to 17 years.*

未发表论文手稿
重要信息模糊处理

# 证据力度

## 审稿人让补充一个资料（作者可以做到的事情）

回修策略：照着做

# 实例

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**Epidemiology/Population**

## Noninvasive Central Systolic Blood Pressure Is More Strongly Related to Kidney Function Decline Than Peripheral Systolic Blood Pressure in a Chinese Community–Based Population

Fangfang Fan, Litong Qi, Jia Jia, Xin Xu, Yan Liu, Yang Yang, Xianhui Qin, Jianping Li, Haixia Li, Yan Zhang, Yong Huo

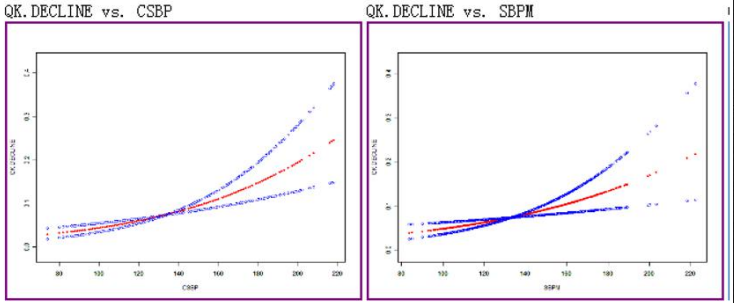
***Abstract***—This study aimed to investigate the association of noninvasive central aortic blood pressure with kidney function decline in a Chinese community–based population with normal kidney function at baseline. A total of 3153 Chinese participants from an atherosclerosis cohort were included in our analysis. The primary outcome was renal function decline defined as a drop in estimated glomerular filtration rate (eGFR) category accompanied by a ≥25% drop in eGFR from baseline; or a sustained decline in eGFR of >5 mL/min per 1.73 $m^2$/y. The secondary outcomes were rapid eGFR decline (a decline in eGFR of >3 mL/min per 1.73 $m^2$/y) and new incidence of chronic kidney disease. Participants were 56.6±8.5 years old, 36.0% were males, and 48.8% had hypertension. Mean (SD) baseline eGFR was 101.2±10.6 mL/min per 1.73 $m^2$. After a mean 2.35-year follow-up, the incidence of renal function decline, rapid eGFR decline and chronic kidney disease were 7.3%, 19.7%, and 0.7%, respectively. In multivariate logistic-regression analyses, central and peripheral systolic blood pressure (SBP) were both independently associated with all outcomes after adjustment for various confounders. When peripheral SBP was forced into the model with central SBP simultaneously, its significant association with the 3 outcomes all disappeared; however, central SBP was still significantly related with all outcomes even after further adjusting peripheral SBP. In conclusion, central SBP is a stronger predictor compared with peripheral SBP for early kidney function decline in a Chinese community–based population with normal kidney function at baseline. (***Hypertension***. 2016;67:1166–1172. DOI: 10.1161/HYPERTENSIONAHA.115.07019.) • Online Data Supplement

**Key Words:** atherosclerosis ■ blood pressure ■ glomerular filtration rate ■ hypertension ■ incidence

pSBP和cSBP与肾功能进展的关系

回修时遇到的问题：不同实验室/方法检测的肌酐，测量的差异对结果有何影响？

主要终点-Renal function decline



# 实例

Serum creatinine (μmol/L) at baseline was measured using an enzymatic method in the laboratory of Chinese PLA General Hospital, whereas Jaffe kinetic method was used for the measurement of serum creatinine on a Hitachi 7180 Automatic Analyzer at revisit in the laboratory of Peking University First Hospital. To ensure the comparability, 10 patients in each decile interval of the creatinine level at revisit (100 totally) and 23 participants with extreme values (8 with creatinine <40 μmol/L and 15 with creatinine >120 μmol/L) were selected for calibration. Plasma creatinine at baseline and revisit and serum creatinine at revisit of these 123 participants (369 samples totally) were measured in the State Key Laboratory for Organ Failure Research in Nanfang Hospital of Southern Medical University. Three linear regression models were developed using creatinine of these 123 participants as follows (Scr: serum creatinine, μmol/L and Pcr: plasma creatinine, μmol/L):

1. $Revisit\_Scr_{enzyme}=0.98\times Revisit\_Scr_{jaffe}-26.19$ ($R^2=0.94$);
2. $Revisit\_Scr_{enzyme}=1.01\times Revisit\_Pcr_{enzyme}+1.40$ ($R^2=0.99$);
3. $Baseline\_Scr_{enzyme}=0.93\times$ $Baseline\_Scr_{enzyme}$ (calculated from model 2)$+2.66$ ($R^2=0.98$).

Serum creatinine measured by Jaffe kinetic method at revisit was transformed into values by enzymatic method according to model 1. Model 2 was used for the transformation from plasma creatinines to serum ones. Baseline serum creatinine measure by enzymatic method was calibrated to new values according to model 2 and model 3. Thus, both serum creatinines at baseline and revisit were transformed into values measured by enzymatic method and calibrated by the values measured in the State Key Laboratory Organ Failure Research in Nanfang Hospital of Southern Medical University.

面对数据存在的问题，思考相应解决的方法，并在文中认真呈现出来。

问题：

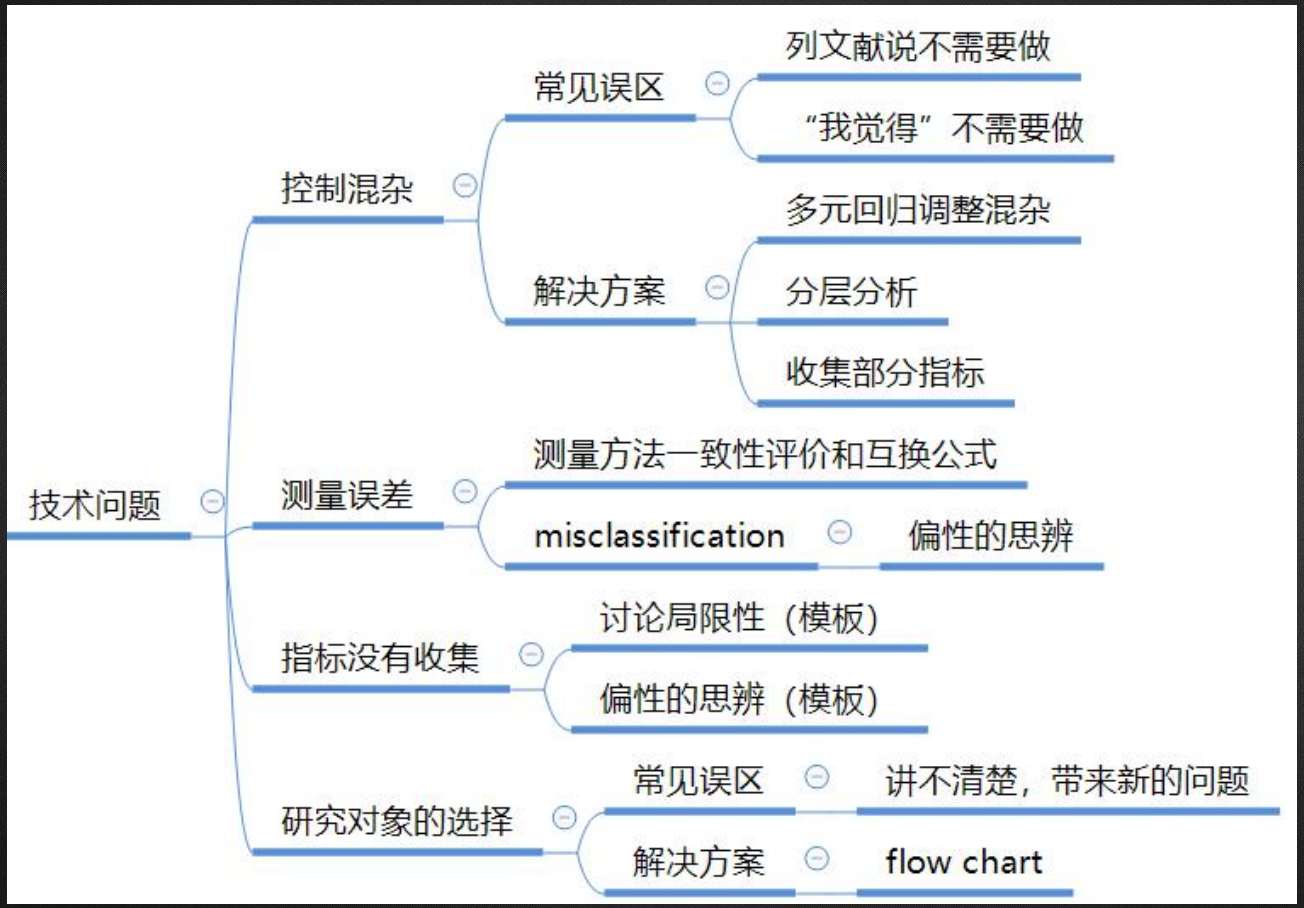
- 基线和出组的血肌酐分别是在301应用血清酶法和北大医院应用血清苦味酸法检测，而我们基线只保留了血浆，出组保留了血清和血浆；

- 需要将两者统一到同一中心实验室的结果。

解决方法：

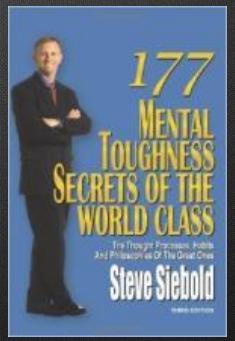
- 挑选123例患者的样本再次在南方医检测；
- 建立回归模型，将基线和出组的结果进行转换；
- 针对审稿人意见，详细回答。

# 小结


技术问题
控制混杂
常见误区
列文献说不需要做
“我觉得”不需要做
解决方案
多元回归调整混杂
分层分析
收集部分指标
测量误差
测量方法一致性评价和互换公式
misclassification
偏性的思辨
指标没有收集
讨论局限性（模板）
偏性的思辨（模板）
研究对象的选择
常见误区
讲不清楚，带来新的问题
解决方案
flow chart

# T.F.A.R

Thinking → Feeling → Action → Results

# Thank you for your time!