

# Peer Review File

**Article Information:** Available at <http://dx.doi.org/10.21037/tau-20-1056>

## **Reviewer A**

Overall, this study is a fairly straightforward retrospective evaluation of young men with ED. There are a number of other studies that look at risk factors for ED, and it is well known that dyslipidemia, diabetes, and renal insufficiency are associated with ED. So from a novelty standpoint, this paper does not significantly add to our knowledge base. However, the data do contribute to the existing body of literature on this subject, and it is important to continue to drive home the learning point that there is a clear relationship between metabolic risk factors and erectile dysfunction in younger men -- with a goal of making sure that young men are properly risk stratified in an era when young men may become complacent with easy access to PDE-5 inhibitors from the internet. Attached are suggestions on how to modify the article, which should be revised before publication.

The title is very declarative. Although the title statement does restate a finding of the study, perhaps softer wording should be used to describe the study in the title. The odds ratios are not compelling enough for me to buy in to the title chosen.

Response: Thanks for your great suggestion. This study is a retrospective study, so risk factors cannot be determined. For the odds ratios value close to 1, in this study, the control group patients were assigned a value of 0, and the ED group patients were assigned a value of 1. LDLC, BG, CR, and AST as numerical variables only change between 0 and 1, resulting in OR values of LDLC, BG, CR, and AST close to 1. But The odds ratios are statistically significant, so we think that Elevated low-density lipoprotein, blood glucose and creatinine are related factors in 20~40 years old men with erectile dysfunction are more appropriate. At the same time, we changed the risk factor that needs to be modified in the article to related factor. We have also revised the title of the article. The new title is: "Relationship between the risk factors of cardiovascular disease by testing biochemical markers and young men with erectile dysfunction: a case-control study" (see Page 1, Line 1).

Page 1, Line 21: Remove word "some"

Response: Thank you, we have corrected. See Page 1, Line 21.

Page 1, Line 22: Remove "s" from diseases

Response: Thank you, we have revised. See Page 1, Line 22.

Page 1, Line 22: Suggest – "but the presence of such risk factors in young men with ED age 20-40 years is unclear."

Response: Thank you, this is a great suggestion, we have followed, please see Page 1, Line 22.

Page 2, Methods

- Please specify the type of clinic from which patients were recruited

Response: We thank very much for this suggestion, We thank very much for this suggestion.

ED group

A total of 289 cases complaining with ED who presented at the Department of Andrology in China-Japan friendship hospital from October 2016 to October 2019 were recruited. We have modified the corresponding part as advised. See Page 5, line 3.

Control group

1155 male individuals aged between 20–40 years without ED for physical examinations in our Health Checkup Center of China-Japan Friendship Hospital were recruited as a control group. We have modified in our manuscript (see Page 6, line 7).

- Page 2, Line 11: Suggestion – “The ED group was then subdivided...”

Response: Thank you for your suggestion, we have revised the sentence (see Page 2, Line 12).

Page 2, Conclusion

The author should consider stating that the elevated markers were “predictors” for erectile dysfunction, rather than firm “risk factors.” The odds ratios are statistically significant but perhaps the authors can comment on the relative values of the odds ratios (they don't seem to be very dramatic).

Response: We thank very much for this suggestion. This study is a retrospective study, so risk factors cannot be determined. For the odds ratios value close to 1, in this study, the control group patients were assigned a value of 0, and the ED group patients were assigned a value of 1. LDLC, BG, CR, and AST as numerical variables only change between 0 and 1, resulting in OR values of LDLC, BG, CR, and AST close to 1. The odds ratios are statistically significant.

"Predictors" has two meanings: predictors and related factors. From the perspective of this test method, the description of results "predictors" is better than "risk factors". This study is a retrospective study, and the odds ratios are statistically significant, so we think it is more appropriate to use related factors. In the revised manuscript, the "risk factor" that needs to be replaced in the article is replaced with "related factor" (see Page 2, Line 1; Page 14, Line 17; Page 15, Line 20; Page 17, Line 11; Page 17, Line 18; Page 18, Line 8; Page 19, Line 9; Page 19, Line 16).

Page 3, line 6: Suggestion: “inability to attain and/or maintain”

Response: Thank you, we have revised the sentence as “Erectile Dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance”. (see Page 3, line 7).

Page 3, line 12: Suggestion: “The percentage of young men presenting to the clinic for ED has increased...”

Response: Thank you, really appreciate. We have modified the sentence as you suggest, “ The percentage of young men presenting to the clinic for ED has increased

from 5% to over 15% from 2010 to 2015". (see Page 3, line 13).

Page 4, line 13: Suggestion: "The pathogenesis of ED is often multifactorial and while risk factors based on the metabolic profile of older men with ED have been identified, those of young men with ED remain to be elucidated."

Response: Thank you, really helpful. See Page 4, line 13.

Page 4, line 16: Suggestion: "protective factors in young men with ED through comprehensive serological testing."

Response: Great. We followed your suggestion. The sentence is modified as "The objective of this study is to investigate the association of CVD risk and protective factors in young men with ED through comprehensive serological testing". (see Page 4, line 16).

Page 4, Methods

- Can the author clarify if ED was based on complaint of inability to "attain and maintain" an erection or "attain and/or maintain" an erection

Response: We are very sorry for this confusion. To be honest, we did not use the International Index of Erectile Function (IIEF) questionnaire for the diagnosis of ED in the outpatient clinic. Indeed, We asked the patients who complained with erectile dysfunction the following three questions:

Question 1: Is the libido normal (yes/no).

Question 2: Is the erection hard enough for penetration during sexual intercourse (yes/no).

Question 3: Whether the penis flaccidity occurs resulting in inability to maintain erection before ejaculation (yes/no).

Meanwhile, erectile function was assessed by the a erection hardness score (EHS) tactile tool (consisting of four columnar bodies, whose hardness represents erection hardness score grade 1-4, provided by Pfizer Inc). The patient judges his erection hardness by touching the hardness of the columns. If the answer of question 1 is normal, the answers of questions 2 and (or) 3 are yes, combined with an EHS 1 and 2 indicates the presence of ED.

In the revised manuscript, we have made a detailed description on how to diagnose ED cases. (see Page 5, line 7).

- For the patients who did not have erectile dysfunction, how exactly were they recruited? Unclear if they were from the same clinic and were randomly surveyed for ED or if they were from the hospital system seen for other chief complaints and were surveyed for ED.

Response: We are very sorry for this confusion. 1155 cases who did not have erectile dysfunction in control group were collected at Health Checkup Center in China-Japan Hospital. In our hospital, male external genitalia examination is part of the routine surgical physical examination. During the male external genital examination, the doctor will ask the participant the following questions.

Question 1: Have you had sexual intercourse in the past 3 months? (yes/no)

Question 2: Is the erection hard enough for insertion during sexual intercourse (yes/no).

Question 3: Whether the penis flaccidity occurs resulting in inability to maintain sexual intercourse before ejaculation (yes/no).

If participants are unable to determine whether the erection is normal, erection hardness score (EHS) tactile tool mentioned above can be used as a further assessment tool. If the answer of question 1 is yes, the answers of questions 2 and (or) 3 are no, combined with an EHS 3 and 4 indicates the normal erectile function. In the revised manuscript, we have made a detailed description on how to exclude ED cases in the control group (see Page 6, line 10).

- Did the patients in the control group also have the same exclusion criteria such as no Peyronie's, mental disorder, etc., as patients with ED did?

Response: We are very sorry for this confusion. The patients in the control group also have the same exclusion criteria such as mental disorder, penile malformation, spinal cord or pelvic trauma, and peyronie disease, as patients with ED group. Medical-history taking and physical examination were carried out to exclude the above diseases. In the revised manuscript, we have made it clear, and have made necessary changes (see Page 7, line 1).

Page 12, line 9: Suggestion: Replace “management” with “evaluation”

Response: Thank you, we have followed your suggestion. See Page 13, line 9.

Page 16, line 12: Suggestion: “In chronic renal failure (CRF) patients, the serum Cr value of those with ED was higher than those without ED.”

Response: Thank you for your great suggestion. We have done this. See Page 17, line 21.

Page 17, line 1: Suggestion: “Elevated UA and HCY have previously been considered risk factors of ED and CVD.”

Response: Thank you. We followed your suggestion. See Page 18, line 10.

### **Reviewer B**

In this prospective, single institutional study, the authors evaluate the serological data of outpatients diagnosed with erectile dysfunction over a 3-year period. The authors note that cardiovascular disease and erectile dysfunction share common risk factors, and such risk factors in young men aged 20-40 with erectile dysfunction are unclear.

Response: We thank very much for all suggestion. In the revised manuscript, we italicize the modified description text.

While care is taken to search through serological data of men presenting in predefined age groups, do you believe that a sufficient definition of erectile dysfunction is made? What objective data supports classifying the outpatients as having erectile

dysfunction?

Response: We are very sorry for this confusion. To be honest, we did not use the International Index of Erectile Function (IIEF) questionnaire for the diagnosis of ED in the outpatient clinic. Indeed, We asked the patients who complained with erectile dysfunction the following three questions:

Question 1: Is the libido normal (yes/no).

Question 2: Is the erection hard enough for penetration during sexual intercourse (yes/no). Question 3: Whether the penis flaccidity occurs resulting in inability to maintain erection before ejaculation (yes/no). Meanwhile, erectile function was assessed by the a erection hardness score (EHS) tactile tool (consisting of four columnar bodies, whose hardness represents erection hardness score grade 1-4, provided by Pfizer Inc). The patient judges his erection hardness by touching the hardness of the columns. If the answer of question 1 is normal, the answers of questions 2 and (or) 3 are yes, combined with an EHS 1 and 2 indicates the presence of ED. In the revised manuscript, we have made a detailed description on how to diagnose ED cases (see Page 5, line 7).

Would the degree of erectile dysfunction be more appropriately classified through employment of the IIEF or similar questionnaires, ultrasound, medication history, or sexual history, among other key history points?

Response: We thank very much for this valuable suggestion. As the reviewers pointed out, if the IIEF questionnaire is used for erectile function grading and the relationship between different grades of ED and biochemical markers is further analyzed, the conclusion will be more meaningful. Indeed, the erection hardness score (EHS) tactile tool (consisting of four columnar bodies, whose hardness represents grade 1-4, provided by Pfizer Inc) was used to assess the erection hardness in the study. The patient judges his erection hardness by touching the hardness of the columns. Through this evaluation method, we divide erectile function into ED and normal erectile function. EHS 1 and 2 indicates the presence of ED, EHS 3 and 4 indicates the normal erectile function.

Additionally, please address the etiology of the erectile dysfunction (aside from exclusion criteria (history of mental disorder, penile malformation spinal cord or pelvic trauma and Peyronie's disease).

Response: We thank very much for this valuable suggestion. Serum total testosterone (TT) and Prolactin (PRL) levels were also measured. Among the 289 patients in the ED group, only 1 patient had abnormal TT, and its TT=6.30nmol/L ( $\leq 8$ nmol/L). In our trial, we focused on cardiovascular risk factors, so the patient's TT and PRL were not described.

The importance of elucidating risk factors for erectile dysfunction is important in all age groups, as erectile dysfunction may herald the diagnosis of diabetes, peripheral vascular disease, cardiovascular disease, or similarly metabolic syndrome. The authors have performed a granular search for serological components of young men

with a complaint of questionable erectile function, although in light of inadequate evaluation of the subjects' erectile dysfunction, can sufficient conclusions be generally applied?

Response: We thank very much for this suggestion. In the revised manuscript, we have already explained about ED diagnostic criteria in detail. Erectile dysfunction shares the common risk factors with cardiovascular disease. The purpose of our manuscript is to further clarify whether the conclusion is appropriate for young ED patients.

In the past, young ED patients were believed to be primarily of psychogenic origin. In this era when PDE5 inhibitor is very convenient to buy online, young ED patients usually buy drugs by themselves instead of consulting with physician and seeking for etiology and corresponding therapy. This phenomenon has been also confirmed by a recently published article (see Reference) .

In the revised manuscript, we further analyzed the data of 289 ED patients and the results showed that the proportion of young ED patients with completely normal biochemical markers indicators is very low 51cases(17.65%). Therefore, early detection of the underlying comorbidities and corresponding intervention are very valuable to prevent the further decline of erectile function and the occurrence of cardiovascular diseases in young ED patients.

Reference

Lin H, Zhao L, Wu H, Cao M, Jiang H. Sexual life and medication taking behaviours in young men: An online survey of 92 620 respondents in China. *Int J Clin Pract.* 2020 Jan;74(1):e13417.