OPEN PEER REVIEW

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Anesthesiology and Pain Medicine
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Peer Review Report for "Predicting Factors of Pain Duration in Patients with Chronic Pain: A Large Population-based Study"

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Review Timeline:

Submit Date:	28 Jun 2019
Revised Date:	26 Oct 2019
Accepted Date:	27 Jan 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) — 24 Aug 2019

Dear AE,
My opinion are as follows:
1- "Long pain duration " should be changed to " chronic pain ".
2- Keywords should be revised and edited again.
3- Exclusion and inclusion criteria should be revised and edited again.
4-"BS" and "MS" should be explained.
5- Causes of pain should be defined (What are the causes of pain in population study?).
6- The results are too imperfect and need to be explained clearly.
7- The discussion part is too imperfect.
8- Some of the references are too old and new references should be used.
9- Method is extremely imperfect.
10- The scale for pain assessment should be explained.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 25 Aug 2019

Dear AE,

Old age and abnormal BMI are accompanied by many internal diseases that not included in the exclusion criteria but affect the pain.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 27 Aug 2019

Dear EIC
Based on reviewers' comments this manuscript needs major revision before publishing at Anesth Pain Med.
Regards

REFEREE: EIC | **Revision** (0) 27 Aug 2019

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Professor Imani, Editor-in-Chief,
and dear associate editor,

On behalf of my co-authors, we are sincerely thankful for the opportunity we have to revise our manuscript. We aknowlege the editors and reviewers for their positive and constructive comments on our manuscript entitled:

“Predicting factors of pain duration in patients with chronic pain; A large population-based study”.

We have carefully studied reviewer’s comments and have made revisions which is highlighted in yellow in the manuscript. The valuable comments of the editors enabled us to improve our report.

We would like to express our great appreciation to you and reviewers for comments on our manuscript.

Corresponding Author.

Reviewers’ Comments:

Reviewer 1:
dear author
old age and abnormal BMI are accompanied by many internal diseases that not included in the exclusion criteria but affect the pain

Reply: Dear reviewer, we are sincerely thankful for your attention and comment. You are absolutely right. Age and, for example, obesity can be associated with many medical conditions that they themselves may affect other medical outcomes as well.

We re-evaluated the methodology of our study with a second epidemiologist to make sure that the primary design of the study was accurate. Our methodology was approved again by a second epidemiologist. I provide you the explanations with sincere respect:

This study is a risk-assessment investigation. We tried to introduce risk factors that may be correlated with chronicity (pain duration) of chronic pain. For example, in similar risk-assessment studies which evaluate the risk factors for myocardial infarction (MI): risk factors like age (old age), BMI (obesity), Diabetes, … may be introduced as risk factors for MI. Meanwhile, each one of the mentioned risk factors can be associated with many other medical conditions, and all of these medical conditions can affect many other medical conditions. For example, if we assume that age (old age) is a risk factor for MI, then we may argue that the age itself is associate with increased risk of DM, and therefore, age is not the real risk factor. The older age is associated with the higher incidence of diabetes; therefore, the real risk factor is not age, but is diabetes and so on; consequently, we will never reach to a final conclusion. There are only two methods to solve this dilemma. The first one is to match two groups of patients in terms of all possible and imaginable risk factors for a single outcome unless only one risk factor that would be the main risk factor which would be the subject of the study. Therefore, there should be only one risk factor which is different in the

two groups of the study. Subsequently, only one medical outcome should be evaluated in a cohort and prospective study as you properly mentioned. Whereas, this design of study is almost never possible in the real world.

The second solution to this dilemma is: using ‘logistic regression models’ through two steps of analysis. The first step is a uni-variable analysis and the second step is a multivariable logistic regression analysis of different possible models. By using these complex mathematical/statistical calculations, we will be able to evaluate the impact of many risk factors together in a single population of study. The logistic regression models enable us to omit the impact of each risk factor by mathematical calculation and /or to keep the influence of other risk factors on a specified medical outcome. In other words, the effect of each risk factor will be calculated with complex mathematical calculations and the confounding effect of other risk factors will be omitted by mathematical calculation in different models of risk factors. For example, in this study we defined our outcome as ‘pain chronicity’. We also listed all possible risk factors for our outcome, pain chronicity, from our data base. We evaluated the risk factors in two steps. In the first step, the risk factors who had a kind of correlation with the outcome, entered the multivariable logistic regression models. Those risk factors with low correlation with the outcome were entered in the multivariable analysis. Different models of risk factors were analyzed by multivariable logistic regression analysis. Finally, the best models with highest correlation remained in the results.

Moreover, we double-checked the methodology of the study with a second epidemiologist and statistician to make sure that we evaluated the risk factors in the right way.

Logistic regression analysis is the contemporary methodology to evaluate risk factors for the medical conditions in risk-assessment studies. By the way, it is always possible that we would not be able to consider all possible confounding/influencing factors to enter them in the univariable models; or it is always possible that we would not be able to design or analyze all possible models in the multivariable logistic regression analysis. Consequently, we added and highlighted the phrases that addressed this concern in the limitation section of the manuscript.

Again, we are thankful for your valuable comment.

Reviewer 2:
My opinion are as follows:

Reply: Dear reviewer, we are grateful for your attention and we appreciate the time you spent to review our manuscript.

1-"Long pain duration " should be changed to " chronic pain ".

Reply: Thank you for your comment. All patients recruited in this study had chronic pain, however, we were evaluating the ‘chronicity’. We were not investigating the risk factors for the development of chronic pain. The outcome we were working on was ‘chronicity’ which was expressed as ‘pain duration’. It is certainly different from chronic pain. The question of our study was: what are the risk factors that may be correlated with the longer pain duration in chronic pain patients? For example, please assume that there are two chronic pain patients with a certain chronic pain condition: fibromyalgia or post herpetic neuralgia (PHN). If the treatment condition would be the same in both patients, why some patients suffer from fibromyalgia/PHN for 10 years, while other patients get rid of fibromyalgia/PHN after 5 years? In other words, why the ‘chronic pain’ subsides after 5 years in some patients? Why

the same chronic pain condition (fibromyalgia/PHN) lasts forever in other patients? We emphasis that the treatment condition would be the same in both patients. As we mentioned in our method section, we recruited the patients who were referred to our tertiary care pain center. We evaluated our patients before we started our specialized pain treatments. In fact, our patients had not had any specialized pain treatment when we conducted our study on their pain condition. We re-emphasized and highlighted this point in the introduction and method section.

2- Keywords should be revised and edited again.

Reply: thank you for your remark. New keywords were added and highlighted in the text.

3-Exclusion and inclusion criteria should be revised and edited again.

Reply: Dear reviewer, we have explained more explicitly the exclusion and inclusion criteria section. However, if our explanation has not covered your points, we would be more than happy, if you could kindly explain more precisely the areas of your concern. We will certainly address those points. Thank you again for your attention.

4-"BS" and "MS" should be explained.

Reply: Thank you. We should have explained the abbreviations more clearly in the text. BS: Bachelor of Science; and MS: Master of Science. We clearly defined and highlighted them in the text and table 1.

5-Causes of pain should be defined (What are the causes of pain in population study?).

Reply: thank you for your comment. Our patients had diverse underlying chronic pain conditions including: CRPS (I,II), fibromyalgia, phantom/stump pain, chronic persistent post-surgical pain, post herpetic neuralgia, lumbar/cervical facetogenic pain, sacroiliac joint dysfunction, different kinds of poly/mono-neuropathies, all kinds of neuralgias including GON & LON neuralgias, migraine, atypical facial pain, trigeminal neuralgia, cluster-type headaches, piriformis syndrome, cervical/lumbosacral radicular pain, etc. We mentioned and highlighted this issue in the manuscript. We had already discussed the limitations that might be associated with this issue in the limitation section.

6-The results are too imperfect and need to be explained clearly.

Reply: thank you for your comment. We tried to more clearly explain and highlight the data provided in the result section. However, we tried to obey the rule: not to repeat the results were presented in the tables in the text of the manuscript again. We have explained the results in the discussion section as well. Meanwhile, we would appreciate it if you could precisely explain where the data are vague, we would certainly explain the referred results more clearly in the text. We are thankful for your comments.

7-Discussion part is too imperfect.

Dear reviewer, thank you for your attention. We are very motivated to improve the quality of our report. We would be more than happy if you could kindly address more precisely the

parts of the discussion that needs to be improved. We would certainly take care of that part to be able to meet your valuable points. We would appreciate your time and attention.

The discussion part covers the explanation for the results obtained in the study. It discusses the effects of the age, sex, BMI, different types of pain intensities, inadequate pain treatment, and different socioeconomic variables on the pain duration. Please let us know where we should explain more. Thank you very much.

8-Some of references are too old and new references should be used.

Reply: Thank you. New references are added and highlighted as ref. # 7, 8, 36, and 43. Their relevance with this study is also mentioned and highlighted in the text, as in introduction paragraph 2, discussion section, paragraph 5 and 8.

9-Method is extremely imperfect.

Reply: Thank you for your comment. Based on other valuable comments some parts of the method section have been fixed up and are highlighted in the text. However, we would be more than happy if you could kindly refer where we should address in order to improve our manuscript. We are very grateful for your attention.

10-The scale for pain assessment should be explained.

Reply: Dear reviewer, thank you for your points: PI was evaluated by the validated Persian version of the Brief Pain Inventory (BPI). BPI was developed by Pr. Cleeland. Then it got a great reputation in the pain literature. BPI was validated in 18 different languages. Recently, it has been validated in Persian language through an accredited methodology published in Journal of Pain and Symptom Management, the journal published the validation of the BPI in other languages. Pr. Cleeland also co-authored this paper (Validation of BPI in Persian). BPI measures both pain intensity and pain interference with different domains of the life. Its simplicity enables patients to complete it in a short time. The BPI is a multidimensional measurement tool. It contains a figure of the body on which patients can mark their painful sites. The BPI has four Numeric Rating Scales (NRS) to measure pain intensities at its least, worst, average, and current severity. The patients can also indicate their pain relief in a percentage scale. The BPI has seven NRS that show the pain interferes with function, mood, and enjoyment. The BPI was introduced more clearly in the text and it was highlighted as well.

We are sincerely thankful from the EIC, associate editor(s) and reviewers for the time they spent on our manuscript. We are very dedicated to improve our manuscript based on the valuable comments of the reviewers. Please let us know any area that needs more explanation or should be further worked on. Again, we are very thankful from the editors and reviewers.

Best regards,

Corresponding author.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 27 Jan 2020

Dear AE,
The revised manuscript ID#95776 was reviewed, and it is acceptable.
Sincerely

REFEREE: Associate Editor | **Revision** (1) — 27 Jan 2020

Dear EIC,
Based on reviewers' comments this manuscript can be consider for publishing at Anesth Pain Med.
Regards

REFEREE: EIC | **Revision** (1) — 27 Jan 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.