Author’s response to reviews

Title: Factors associated with Developing a Fear of Falling in Subjects with Primary Open-angle Glaucoma

Authors:

Sayaka Adachi (syk2112@hotmail.co.jp)
Kenya Yuki (yukikenya114@gmail.com)
Sachiko Awano-Tanabe (s.awa@icloud.com)
Takeshi Ono (nmsccm2005@yahoo.co.jp)
Daisuke Shiba (shiba@personal.email.ne.jp)
Hiroshi Murata (hmurata-tky@umin.net)
Ryo Asaoka (ryoasa0120@mac.com)
Kazuo Tsubota (tsubota@z3.keio.jp)

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Reviewer reports:

Ivano Riva, MD (Reviewer 1): This is an interesting study in which Authors evaluated, at baseline and during a three-year follow-up, the influence of clinical parameters on the fear of falling in patients affected by primary open angle glaucoma. Age, female gender, inferior visual field defects and number of previous falls were clinical parameters included in the best model predicting fear of falling at baseline. The same clinical parameters predicted the development of fear of falling during the follow-up. Some points need to be addressed before publication:

1. Avoid to insert complex math formulae into the abstract, especially if they include abbreviations not previously explained. Abstract should be an argumentative section, summarizing study results and stimulating reader's interest on the topic.

Thank you very much indeed. We have revised the abstract to not include abbreviations. Our response to the comment regarding inclusion of the regression formula is given in the response to comment #7.
2. Intraocular pressure was not a criteria for patient enrollment. Does this mean normal tension glaucoma patients were included as well? If this is the case, it should be specified.

Thank you for this comment. We did not use IOP as an inclusion or exclusion criterion. Therefore, both primary open-angle glaucoma and normal tension glaucoma patients were included, as now added in the Method section. (page 8, line 126-127)

3. Taking into account visual acuity and computed total visual field deviation, population of the study is prevalently constituted by early/mid glaucoma patients. It would be interesting to have visual field MD for both the right and the left eye in Table 1. How can this datum influence the results?

We performed the model selection procedure again including MDs in right and left eyes. As a result, MDs in the right and left eyes were not selected. We did not add this result to the manuscript, but would be happy to do so, if the Reviewer suggests this.

4. Groups should be better defined in the Methods section. While it is reasonable to think that the "future fear of falling (+)" group consisted only of patients who developed fear of falling during the follow-up (i.e. had no fear of falling at baseline), this should be specified.

This has now been clarified in the Method section, thank you. (page 9, line 147-154, page 10, line 155-157)

5. Which is the meaning of "0.58xfemale" and "0.77xfemale" in the model equation? Did you numerically codify male and female gender? Please explain.

Gender information was used as a categorical variable. The coefficient associated with female suggests that fear of falling was increased by a value of 0.58 or 0.77, if a subject was female.

6. Statistics: In the methods section Authors stated a Wilcoxon test was used to compare numerical data between groups. Authors should better disclose the nature of the test they used. The Mann-Whitney test, also called Wilcoxon rank-sum test, is a non-parametric test used to compare two independent populations without normal distribution. The Wilcoxon signed-rank test is a non-parametric test used to evaluate the same hypothesis but with paired/matched samples (equivalent of paired t-test). Please specify.

Thank you very much. As now added in the manuscript, we used the Wilcoxon rank-sum test.

7. Statistics: Authors used a multiple logistic regression model to elaborate the best equation predicting the dependent variable (i.e.: fear of falling). Model selection was performed by means of the Corrected Akaike Information Criteria (AICc). AICc is a useful instrument to compare
predictive models, however it doesn't give any information on the model itself (for example, on the goodness of the model). If the aim of the Authors was to find the best subset of predictors for "fear of falling", I'd suggest to look at methods for variable selection in multiple regression analyses. Besides this, it would be interesting to have more information about the final model, and to know the significance of the association between each predictor and the dependent variable. Logistic regression equation are not of immediate interpretation, and equation coefficients (which are in log-odds units) are generally converted In odds ratio.

We thank the Reviewer for this insightful comment. AICc values may increase or decrease depending on the penalty of adding variables and the likelihood of the data conditioned by a given model. Moreover, the model minimizing AICc is the best model in terms of Kullback-Librer divergence between the true distribution and that conditioned by a given model. In this sense, AICc gives some information about the goodness of fit of the model. In contrast, the R2 value (now added in the manuscript) is increased by adding variables that are not selected in the optimal model. This is because, in general, the greater the number of independent variables, the higher the R2 value is. However, a high R2 value does not guarantee the usefulness of the model, because of the overfitting problem. AICc was developed to overcome this problem by considering a penalty when increasing the number of variables for the loglikelihood value. Thus, all variables selected in the optimal model can be considered significant, because they have been selected. Further, p values and odds ratios are is somewhat redundant (Spanos A. Ecology, 95(3), 2014 etc). Thus, we did not include estimates of significance and log converted coefficients, to avoid confusion. Model selection with AICc is an established method to assess the goodness of fit of models and the importance of variables, when the number of investigated variables is large. We chose AICc model selection method, because the degrees of freedom in a multivariate logistic regression model decreases with a large number of (i.e., redundant) variables. In evaluating the effect of each variable, it is therefore recommended to use model selection methods to improve the model fit by removing redundant variables, rather than using multiple logistic regression with all variables (Tibshirani RJ, Taylor J. Degrees of freedom in lasso problems. Ann Stat. 2012;40:1198–232. Mallows C. Some comments on Cp. Technometrics. 1973;15: 661–675.).

There are other methods to select variables, however, each of these is associated with possible bias. For instance, LASSO (and Ridge) regression is biased by the internal cross validation, Random Forests can consider only the order of the variables, and the magnitude of variables cannot be interpreted. We favor model selection with AICc for identifying the optimal model as it is a popular and well-understood method.

8. Some minor notes:

- Page 8, line 123, "insignificant senile cataract": Did you mean "significant senile cataract"?

Thank you for your comment. We deleted "clinically insignificant" in this sentence.

- Page 8, line 127 and followings: Reasons for patients exclusion should be in the Results section, and not In the Methods section.
We added explanations for patients' exclusion in the results section.

- Page 16, line 253: Correct [OR equal to 2.95 with a 95% CI of 1.52 to 5.70…] with [OR=2.95 with a 95% CI of 1.52 to 5.70…]

This statement is now corrected.

- Page 16, line 256-258: Sentence is not clear. Please reformulate sentence.

Thank you very much. This sentence has been revised.

Joanne Wood (Reviewer 2): The aim of this study was to examine the relationship between visual risk factors for prospective fear of falling in patients with POAG.

While this is an important topic, the method used to assess the primary outcome measure - fear of falling - consists of one question "Are you afraid of falling?" with non-standardized response options of: "Not at all", "Not much", "Afraid" or "Very Afraid". There are many well-validated measures that are standard methods adopted to measure fear of falling. The use of the most severe response for fear of falling at the subsequent visits which was then dichotomised into (-) and (+) needs better justification.

Thank you for your insightful comments.

A single question to define prevalence of fear of falling has been used in several papers. Rebecca et al. used a single question to evaluate fear of falling by asking subjects that "On a scale of 1 to 5, how would you rate your fear of falling? One is not at all afraid and 5 is extremely afraid’. Responses were dichotomised into ‘not or slightly afraid’ (1 or 2) and ‘moderately or very afraid’ (3, 4 or 5) categories." (Falls and fear of falling: burden, beliefs and behaviours, Age and aging 2009, 38;423-428). Lach et al. also used a single question "At the present time are you very fearful, somewhat fearful, or not fearful that you might fall (fall again)?", and the fear of falling variable was collapsed into a dichotomous variable of fear/no fear. We dichotomized the response into two categories following these studies. Nonetheless we agree that validated questionnaires may be more appropriate and we have expanded our limitations to discuss this. (page 17, line 270-271)

Other issues are outlined below:

Abstract: Inclusion of regression models, eg. "The optimal regression model for patients' baseline fear of falling (+) = -7.0 + 0.062 x age + 0.58 x female - 0.088 x mTDIP + 0.87 x number of previous fall" in the abstract results are hard to interpret - the results should be expressed in a way that has meaning even to a reader who has not read the whole paper.

Thank you very much indeed. The abstract has been corrected.
Methods: The fear of falling measure is quite simplistic as outlined above - there are much more appropriate measures available.

Thank you for this comment. We do agree and have expanded the limitations section to emphasize this concern. (page 16, line 265-266, page 17, line 267-271)

Similarly, the measure of falls asks "How many times did you fall in the last year?" and "Have you experienced any injurious falls in the last year?" There is no definition of what constitutes a fall and the use of a single question to determine the number of falls is not considered the standard (as outlined by Hauer et al (2006) in their systematic review of definitions of falls)

We now discuss this in the limitation section, thank you. (page 17, line 268-271)

Why weren't falls rates and visual function measures also collected at the subsequent visits along with the fear of falling question - it seems unlikely that visual fields would not have been tested at the follow-up visits.

We tested visual fields at the follow-up visits.

Results: Why did 50 patients drop out from the study over the 3 year follow-up?

These patients did not appear in the outpatient clinic. We could not obtain any information about these drop-outs. This is a limitation that we now discuss in the manuscript. (page 17, line 274-275)

It would be good to get ranges as well as mean values for the various parameters described at baseline.

Thank you very much. We added these to Table 1 and 2.

The falls rates at baseline seems very low - general population studies of older adults are around 30%, whereas for this group it is only 6%.

The age range of our study subject was 40 to 85 years; the average age was much younger than previous papers. Another possible reason is that falling risk among older adults varies by racial/ethnic groups. We now discuss the low rate and possible reasons in the manuscript. (page 17, line 275-282, page 18, line 283-284)

The statistical analysis is unclear - there is a lot of complex modelling for predicting the outcome of fear of falling which is based on one simple question.

Model selection with AICc is an established method to assess the importance of variables, when the number of investigated variables is large. We chose AICc model selection method, because the degrees of freedom in a multivariate logistic regression model decreases with a large number of (i.e., redundant) variables. In evaluating the effect of each variable, it is therefore

How was the optimal model determined from the 2 raised to the power 13 combinations?

Thank you very much for this comment. We chose the optimal model from all possible combinations of included variables using the AICc statistics. In this case, there were 13 variables, so a model with the smallest AICc was identified from all 213 candidate models, as described in Method (Page 11 Line 185).