Author’s response to reviews

Title: A systematic review and meta-analysis of the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms

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Dear Editor and Reviewers,

Manuscript number: BCAN-D-18-02581

Thank you for your letter and insightful comments concerning our manuscript titled “A systematic review and meta-analysis of the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms: BCAN-D-18-02581”. We have studied your comments/suggestions carefully and have revised our manuscript accordingly (detailed below). All changes are highlighted in yellow in the revised manuscript.
Response to editor:

Thank you for submitting the interesting study. The review and meta-analysis tried to focus on the prevalence and characteristics of hemorrhage and thrombotic events occurred in patients BCR-ABL1 negative MPNs. It has better include the data regarding managements and clinical outcomes of these patients to make it become more welcome by clinicians who take care of the group of patients. Revision is recommended before acceptance for publication.

Reply: We would like to thank the editor for your time and effort to review our work. We hope that we have adequately addressed all the concerns raised by the reviewers in this revised manuscript.

In regard to the comment made by the editor, we agree that the data on managements and clinical outcomes of these patients would be of interest for clinicians. However, unfortunately, none of the included studies has provided specific data on the treatment and outcome of bleeding/thrombotic complications. Only information on overall managements and outcomes were available, which are now included in the revised manuscript as Additional file 3: TableS1. (result section, lines 129-130, page 6; and Additional file 3)
Response to reviewer 1 (Eugenia Allegra):

The review is interesting and focuses on the importance of thrombotic manifestations and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms. However, among the common sites, epistaxis is not reported despite being fairly common symptoms. I wanted to ask the authors if, from the selected works, they found some data about it.

Comment 1: I recommend additional statistical review

Reply: All of the statistical analyses were conducted by one of our co-authors, Patompong Ungprasert, MD, MS, who is a Statistician-Physician. Dr. Ungprasert has published over 100 meta-analyses in the past 6 years. Dr. Ungprasert has reviewed all the analyses again and we would like to confirm their accuracy.

Comment 2: However, among the common sites, epistaxis is not reported despite being fairly common symptoms. I wanted to ask the authors if, from the selected works, they found some data about it

Reply: Thank you for your suggestion. We have reviewed the included studies, extracted the data, and performed the analysis on the pooled prevalence of epistaxis in MPN patients. The result of this analysis as well as the forest plot has been added into the revised manuscript (result section, lines 166-167, page 7; and Additional file 5).

Response to reviewer 2 (Juan Manuel Mejía Arangure):

BCAND1802581 A systematic review and meta-analysis of the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms. The manuscript is very interesting and useful. However there are some points that the authors need to clarify.

Comment 1: In the introduction they need to mention why is important to know the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms. It is interesting, but why is it point important?

Reply: Thank you for your suggestion. We believe that baseline prevalence of thrombosis and bleeding are of clinical importance for clinicians who need to balance the risk between these two opposite complications as one of the aims of the treatments of MPN is to decrease the risk of thrombosis and some prescribed medications, such as aspirin, can increase the risk of bleeding. We have added this statement in the revised manuscript (introduction section, lines 67-71, page 3)
Comment 2: The authors decided that before of a conclusion on the prevalence or thrombosis and bleeding they must do a systematic review, this is an interesting point. But they did not discuss why the prevalence in the different populations is not equal. They mention some points in the discussion, but they do not analyze each point. If during the time the criteria for defining Philadelphia-negative myeloproliferative neoplasms have changed they must mention which are these changes. This aspect would be sufficient to explain the differences in the prevalence. The other point that they mention is the population from the studies were done. However they do not discuss this point how affected the results. For example they mention that the prevalence would vary for the different populations. But why is it? The prevalence of thrombosis and bleeding at diagnosis would be different by race or demographic characteristics of the populations? I believe that not. But, it is most probable that the differences in the technology for identifying thrombosis or bleeding in these patients would be affecting the prevalence.

Reply: We would like to thank the reviewer for this thoughtful comment. We agree with the reviewer that it is unlikely that demographic characteristics and ethnicity would significantly affect the prevalence of thrombosis and bleeding at diagnosis. We agree that 1) the differences in the technology used to identify thrombosis and bleeding in these patients and 2) evolution of the criteria used to define Philadelphia-negative myeloproliferative neoplasms over time are the more probable causes of the heterogeneity of the prevalence. We have revised our discussion accordingly. Moreover, we have provided more details on how the criteria have changed (discussion section, lines 209-222, page 9)

Comment 3: They used the Prisma criteria but they did not mention why they did not make a stratification by the quality of the studies.

Reply: We used PRISMA as the guidance on how to report the methods and outcomes of our meta-analysis. We were able to follow most of the guidance. However, we were not able to follow the guidance on quality assessment because the primary studies included in the meta-analysis were descriptive in nature (i.e., we investigated the prevalence of bleeding/thrombosis in only one cohort of patients with MPN in each study - no comparative analysis between cohort of MPN and cohort of healthy individuals was made) but the tools we have for quality assessment (such as Newcastle-Ottawa score and Jadad scale) are designed for analytical, comparative study.

Comment 4: Minor comment: For me it is not clear the definition of cohort that they used in theirs study.

Reply: The term “cohort” used in this meta-analysis simply refers to a group of patients. Therefore, any studies with at least one group of patients with Ph-negative MPN and reported their prevalence of thrombosis/bleeding are eligible for inclusion. We did not use the term cohort
to refer to classic analytical cohort study that consists of two groups of participants and compares the outcome of interest between the groups. Our apology that the definition was unclear. In the revised manuscript, we have modified our statement on the inclusion criteria to be more specific about our definition (method section, lines 85-88, page 4).