

Response to the Comments point by point

We feel great thanks for the Reviewer's professional review work on our article. We appreciate for these valuable comments which are really helpful for improving the quality of our article. We have carefully revised the manuscript point by point following the suggestions as follows.

Response to Reviewer #1

As it is an editorial, I made subtle changes towards language polishing. On Science, I would appreciate if the authors explain the role of Factor VIII and X and its role in anticoagulation. A figure would be a wonderful pathway explanation to readers.

Response: We sincerely appreciate the Reviewer for the constructive comments. We have revised the corresponding sections according to the suggestions.

- 1) We have added more explanation of the role of factors VIII and X and detailed introduction of pathophysiology of PC deficiency in the revised manuscript (**lines 48-53, page 4**): *"Thrombin with thrombomodulin cleaves PC, converting it into its activated form, the activated PC (APC). Along with its co-factor protein S, APC inhibits thrombin generation by inactivating activated factors V (Va) and VIII (VIIIa). Both Va and VIIIa are required for factor X activation, which then converts prothrombin to thrombin. Factors Va and VIIIa act as substrates for APC, which irreversibly inactivates them through proteolytic activity on cleavage sites, thereby inhibiting their procoagulatory effect."*
- 2) We have added a figure (**Figure 1**) to help explain the pathophysiology of PC deficiency according to the suggestion.

Response to Reviewer #2

Authors are advised to consider the following points:

- 1) The introduction part was left with no citation. Also, throughout manuscript, some sentences are missing citation.

Response: We thank the Reviewer very much for this valuable suggestion. We have added corresponding citations in the updated version.

- 2) Minor mistakes in spelling should be corrected, for example "synthesised".

Response: We really appreciate the Reviewer for the careful review and this comment. We have carefully checked the spelling throughout the manuscript and revised the corresponding sections according to the suggestions.

- 3) Authors are advised to elaborate more about the subject of editorial and present some new information to attract readers attention.

Response: We sincerely appreciate the reviewer for this constructive comment which helps improve our article a lot. We have added new information and more discussion from recently published studies in the revised manuscript as follows: **(page 6, lines 59-64)** *"It has been reported that more than 500 mutations identified throughout the PROC gene length may lead to inherited PC deficiency. The molecular basis of inherited protein C deficiency is complicated, results from a recent study has demonstrated that nucleotide variations in the signal peptide and propeptide of PC lead to PC deficiency by differently affecting the biological process of PC, including posttranscriptional pre-mRNA splicing, translation, and posttranslational modification and process"*, and **(page 5-6, lines 93-96)** *"In addition, according to a recent guideline, subcutaneous PC concentrate with or without VKA may be the most appropriate long-term management for severe congenital PC deficiency patients, whereas there is little data available on pharmacokinetics and the most appropriate dosing regimen"*.

Response to Editors' Comments

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

1) Advantages and disadvantages: The reviewers have given positive peer-review reports for the manuscript. Classification: Grade C and Grade B; Language Quality: Grade B and Grade B. Authors are advised to consider the following points: The introduction part was left with no citation. Also, throughout manuscript, some sentences are missing citation. Minor mistakes in spelling should be corrected, for example "synthesised". Authors are advised to elaborate more about the subject of editorial and present some new information to attract readers attention.

Response: We sincerely appreciate the Editors for the positive comments and thoughtful review of this article. We have revised the manuscript according to the Reviewers' and Editorial Office's comments.

2) References: A total 12 references are cited, but no published in the last 3 years. The reviewer didn't request the authors to cite improper references published by him/herself.

Response: We thank the Editors for this comment. We have conducted a comprehensive literature review and added related citations in the revised manuscript.

3) Language evaluation: The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Response: We thank the Editors for this comments. We have asked Prof. Gary Tse from Kent and Medway Medical School, Canterbury, Kent, UK to help check the manuscript. We have now revised the grammar, style and syntax in the updated version. Acknowledgment for their help has also been stated in the revised manuscript.

4) Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. If there is no PMID or DOI, please provide the website address.

Response: We thank the review for this comment. We have revised the form of references according to the comments in the updated version.

5) The article which this editorial discussed has not been listed in the references list. Please add the article which this editorial discussed into the main text and references list

Response: We thank the review for this comment. We have added the citation of the article this editorial discussed in the revised manuscript.