Author's response to reviews

Title: Portal Vein Thrombosis; Risk factors, Clinical presentation and Treatment.

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Author's response to reviews: see over
1 Reviewer's report. **Reviewer:** Angelo Andriulli

**Major Compulsory Revisions**

The paper by Søgaard and coworkers addresses an infrequently explored issue, the clinical presentation, treatment and risk factors for portal vein thrombosis. However, the retrospective schedule of the study affects seriously, in my opinion, the relevance of reported findings and detracts considerably the clinical indication of their conclusion.

**Answer:** *Due to the rare condition, randomized trials are not feasible, and we believe that our results though retrospective, do contribute to the understanding of a less examined condition.*

Indeed, with such an approach one is left wondering about the soundness of some of their recommendations on the value of anticoagulation therapy, the use of prophylactic banding of large varices, and the screening for prothrombotic conditions in all affected patients. As a matter of fact, not all enrolled patients were subjected to screening for prothrombotic factors, of the 48 patients with esophageal varices the primary prophylaxis consisted in endoscopic treatment in 24% and in β-blockers administration in other 42%, and so on...

Without a pre-planned schedule of treatment and a systematic search for risk factors, the merit of the present report seems relies on the description of clinical presentation and complications of patients with portal vein thrombosis presenting at a tertiary university hospital in Denmark. Therefore, the Authors’ aim to describe risk factors and treatment remains unestablished. All suggestions pertinent to the two previous topics need to be tuned down throughout the Discussion.

**Answer:** *We agree that the most significant findings/observations in this retrospective study are the description of risk factors, clinical presentation and complications, and therefore in the revised version of the MS the treatment suggestions have been tuned down as kindly suggested. (Abstract conclusion, and parts of the discussion has been changed accordingly)*

**Minor suggestion:**

- In Table 1, among the several prothrombotic disorders appears mentioned “hormone replacement therapy”. According to recent investigations, hormone replacement therapy has been associated to thrombosis only in carriers of a genetic prothrombotic predisposition. Could you, please, discuss this point?

**Answer:** *We agree that HRT is associated with thrombosis primarily in the case of a prothrombotic conditions. Among the 4 patients being on HRT 2 also had prothrombotic predisposition, (antiphospholipid syndrome and hyperhomocysteinemia). In the revised table I only the 2 mentioned above are included.*

- in Table 1, I wonder whether hepatitis B virus should be enlisted among the abdominal infections which might predispose patients to portal vein thrombosis. While I agree that all other abdominal infection, reported in the Table, might be considered as risk factors, I would suggest to discuss further the point for hepatitis B virus.

**Answer:** *On further consideration, we have decided not to report incidence of hepatitis B as a risk factor. Thank you for drawing attention to this.*
Reviewer's report: lucio amitrano

General
The authors deal with a rare disorder whose prognosis and treatment are not yet well established. Thus, further studies are required and the study is timely. Nevertheless, it has many drawbacks:

Major Compulsory Revisions

The present study is retrospective and includes 67 patients. Yet, the authors describe a follow-up till death or December 2005. How did the authors follow-up the patients?

Answer: Follow up was established from the time of admission or until death or Dec 2005. The patients were followed during outpatient visits or during admissions at the department for complications of PVT or other conditions.

How were the events and death identified?

Answer: In the methods section (page 4) we describe how events and death were identified i.e from patient files or the patient administrative system. “The following data were extracted from the clinical records…. finally the cause of death.”

Did the authors loose any patients at follow-up?

Answer: Two patients were referred to their primary hospital; however living status was investigated from the patient administrative system.

- In the methods section, methods utilized for identification of inherited or acquired thrombophilic disorders (homocysteine, lupus anticoagulant…) have to be described.

Answer: In the revised manuscript we write “prothrombotic disposition was diagnosed by coagulation mapping at the Centre for Haemophilia and Thrombosis at Skejby University Hospital, Denmark. The following parameters were examined: hyperhomocysteinemia, antiphospholipid syndrome, Factor V Leiden gene mutation, increased Von Willebrandt Factor, antithrombin III deficiency, and Protein C and Protein S deficiency.

- Prevalence of clinical presentation of PVT (i.e. modality of onset) have to be described (gastrointestinal bleeding, abdominal inflammation, abdominal pain), and separated from events occurring during the follow-up.

Answer: The clinical presentations of the patients at admission are described in Clinical manifestation in the result section and are given in Table II.

- As imaging procedures are concerned, were the patients submitted only to Doppler ultrasound, TC or MRI or more than one procedures?

Answer: In all patients diagnosed by means of Doppler ultrasound, CT angiography was later performed. MRI-scanning was only performed in 5 of the patients with a positive Doppler ultrasound.
- How were cancer and cirrhosis diagnosed?

Answer: *Cancer was diagnosed by histological evaluation of primary tumour or metastasis or by imaging techniques. Liver cirrhosis was diagnosed either by liver biopsy or by relevant alcohol intake to induce liver cirrhosis or by US demonstrating the characteristic bulky surface of a cirrhotic liver. Often a combination of diagnostic measures was used.*

- Lastly, cancer or cirrhosis cannot be considered together with other etiologies in modern studies on PVT exploring natural history since they strongly influence prognosis and treatment. Moreover, since most of the patients are no cancer no cirrhosis patients, it makes no sense to analyze the whole group of patients compared to patients without cancer or cirrhosis. The differences, if any, could not be detected.

I strongly advice to separate non cirrhotic non cancer patients from the other and perform an analysis of comparison of the two groups rewriting all the results section.

Answer: *We agree in your suggestion of separating cancer patients and cirrhosis patients from other etiologies; therefore in the revised version we have performed new analysis and rewritten the results section.*

Minor Essential Revisions

- In the imaging section, the sentences are not clear the total numbers need to be checked.

Answer: *Thank you for pointing this out, we hav changed it accordingly.*

- How was sensitivity calculated?

Answer: *Sensitivity was calculated by dividing the number of patients with a positive examination by patients who had examination done. For instance, of 63 patients who where examined by UL, only 51 patients had a positive UL. (51/63= 81%).*

- Splenomegaly should be considered in clinical presentation not in complication section

Answer: *We agree in this consideration, and it has been changed as suggested.*

- Incidence and kind of events during the follow-up have to be described. Did the patients present any futher thrombotic complications?

Answer: *The incidence of different events of the patients during follow-up are described in Complications in the result section and are given in Table IV. Regarding other thrombotic complications; these have not been registered.*

- How was recanalization evaluated especially in chronic PVT where a cavernoma can be present?

Answer: *Evaluated by CT, when a patient had more than two CTs performed over time, and improved blood flow to the liver was demonstrated.*
3 Reviewer's report. Reviewer: Stephen Riordan

Reviewer's report:
General
This report concerning risk factors, clinical presentation and treatment of portal vein thrombosis based on a retrospective case series is timely in view of the increasing recognition of this disorder and current uncertainty as to its most appropriate management, particularly with regard to the role for anticoagulation. In keeping with other reports, the analysis points to several contributing factors in a substantial proportion of cases. Of major therapeutic relevance, the report adds support to the notion that anticoagulant therapy should be strongly considered, even in the setting of complicating varices.

Major Compulsory Revisions

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
The data concerning risk factors for portal vein thrombosis at the top of page 8 are confusing and should be clarified.

Answer: Due to the many risk factors it is difficult to clarify further without losing information.

Similarly, Tables 2, 3 and 4 should be re-labelled so as to clarify exactly what groups the sample sizes of 67 and 48 actually refer
Answer: We have clarified the new groups in the tables.

The authors refer to statistical analyses being performed but no statistical values are listed in the text – this should be clarified

Answer: We have added that “Significance was calculated with Pearson’s Chi-squared test. P < 0.05 was considered statistically significant in a two-sided test. Biochemical data were analysed by Kruskall-Wallis test followed by the Man-Whitney test.” in the methods section.