Peer Review File

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Reviewer A

Comment: It is mentioned that ADAMTS13 activity and inhibitor were tested in 56.7% and 46.7%, respectively. What were the true diagnosis of those who did not get ADAMTS13 testing? How about their plasmic or French score?

Response: We appreciate your insightful question and would like to provide additional information regarding patients who did not undergo ADAMTS13 testing in our study.

The study is retrospective in nature, and our data collection process relied on existing patient records from the included countries. We specifically included patients with a diagnosis of iTTP within the past 36 months. Unfortunately, the available data did not include information on PLASMIC and French Scores for those patients. While we understand the importance of comprehensive diagnostic information, especially regarding PLASMIC and French Scores, our study is limited to the data that was available from the patient records within the specified timeframe.

The decision to perform ADAMTS13 testing, as well as the availability of diagnostic tools and laboratory practices, can vary widely among different healthcare settings. In our discussion section, we highlighted that a significant portion of ADAMTS13 tests were conducted in laboratories located outside of the country. This can influence both the diagnostic process and the financial aspects of patient care.

Comment: In Table 6, some of the plasmic or French score are quite low, suggesting that those patients may not have iTTP at all. This may obscure the rate of mortality and the time of response to treatment. Please expand it or discuss this as the limitation of the study.

Response: Thank you for pointing this out to us. The variability in PLASMIC and French TMA scores highlights a limitation of our study. The reliance on these scoring systems can introduce subjectivity in the diagnosis, and the potential for misclassification of patients with lower scores cannot be dismissed. This limitation may lead to an underestimation of the mortality rate and a skewed perception of the time it takes for patients to respond to treatment. We have added this limitation in the discussion section (*highlighted on pages 20-21*)

Comment: In Table 5, is the rate of clinical remission between various groups of treatment statistically significant?

Response: Added and highlighted in Table 5 and 3.5 subsection of the results section (*highlighted on page 15*).

Comment: Table 1 lists all the clinical presentations, which may be moved to suppl. table. The information is important but it should be quite familiar to the readers these days and some of them are quite non-specific, so it may not be really helpful for the readers.

Response: Addressed; moved as supplementary Table 1.

Reviewer B

Comment: Based on this statement “Page 8 line 163; Therefore, this retrospective study designed in order to better understand the nature of this disease and the local burden on the patients and healthcare systems in Arabian Gulf countries…” this study is designed to understand the challenges of diagnosis and treatment of TTP and the effects of these challenges on local healthcare systems. However, there is no data in the result section or discussion on this topic.

It is not clear, why the local healthcare system and patients have financial burdens. I believe, the authors should briefly explain some factors listed below that are important for patient care these countries. - The healthcare system (private, governmental hospitals, etc.) - Insurance system (private, national, etc.) - Cost of ADAMTS13 activity test and who pays the cost (insurance, patient, etc.)

Response: Thank you for pointing this out to us. Discussed and highlighted on pages 19-20.

Comment: In this study, in almost half of the patients (43.3%); ADAMTS13 activity was not measured. I wonder if the authors observed any differences in patients' care who had measured ADAMTS13 activity and not.

Response: Addressed; Further analysis was performed, as appropriate, based on the available data (highlighted on page 14).

Comment: If the authors could present the data for comparison of financial costs and burden of the healthcare system in these groups (activity measured or not) would be helpful to emphasize the study aim.

Response: This study evaluated the local burden by examining parameters such as the number/volume of plasma exchange sessions, duration of hospitalization days, and ICU stay; however, cost assessment was not feasible due to unavailable data, given the retrospective nature of the study, and a significant portion of patients underwent ADAMTS13 testing outside the country.

Comment: PLT normalization was shorter in patients treated with caplacizumab. I wonder if caplacizumab has any effect on the length of stay in the hospital in your study

Response: Further analysis was performed, as appropriate, based on the available data (highlighted on page 15 and Supp. T5.

Comment: If there is an observation for rates of exacerbation or readmission to the hospital of patients who received caplacizumab or not. If you have the data, please present it.

Response: Not feasible due to unavailable data on rates of exacerbation or readmission for those patients, given the retrospective nature of the study

Comment: Page 14 line 297: PLASMIC and French TMA scores were used the asses the disease severity." These scoring systems are used for diagnosis. Unfortunately, there are no severity scoring systems on iTTP yet. Please correct the sentence

Response: Thank you for pointing this out to us. Addressed and highlighted

Comment: Could you please explain the ATHENA abbreviation?

Response: Acquired Thrombotic ThrombocytopEnic Purpura LaNdscAping In Gulf Countries (ATHENA study)

Comment: Page 17 line 357-359: ADAMTS13 enzyme level" should be ADAMTS 13 activity level.

Response: Thank you for pointing this out to us. Addressed and highlighted

Reviewer C

Comment: To minimize the risk of selection bias in the study, data on how many patients with a diagnosis of iTTP during the study period were identified, and which were the reasons for excluding them from the study are needed.

Response: Our study is retrospective in nature, and as such, it included all patients who met the eligibility criteria during the specified study period. Given the retrospective design, there was no active selection or exclusion of patients; rather, we aimed to capture and analyze data from all eligible patients diagnosed with iTTP within the defined timeframe.

Comment: In Table 1, some additional laboratory data at diagnosis (LDH, serum creatinine, cardiac troponin, Hb level…) will be of help to better identify the severity of the disease.

Response: Further analysis was performed, as appropriate, based on the available data: We have incorporated additional laboratory data at diagnosis into Table 1 and highlighted on Page 13, as requested. However, hemoglobin levels were not included due to unavailable data for those specific patients.

Comment: Which criteria were used to define response, exacerbation, and relapse?

Response: Addressed and highlighted in the methods section on page 10

Comment: Did every patient receive front-line therapy with PEx and steroids; If not, indicate the reasons for not administering this treatment.

Response: The study is retrospective in nature, and the available data do not provide information on whether every patient received front-line therapy with PEx and steroids. Unfortunately, we do not have access to the specific reasons for not administering this treatment in individual cases as such data were not available for analysis.

Comment: What were the criteria for administering caplacizumab to some patients? How were these patients selected and for how long did they receive this drug?

Response: As mentioned, this study is retrospective in nature, not prospective, and the available data do not provide detailed information on the criteria for administering caplacizumab to some patients, and how these patients were selected.

Comment: How many patients receive rituximab. Did Rtx treatment impact the time of response or the relapse rate?

Response: Highlighted and addressed in Table 5. Further analysis was performed; data on the time of response or the relapse rate are unavailable. We have investigated whether the rate of clinical remission between various treatment groups is statistically significant, as requested by #R1 [highlighted on page 15 and Table 5].

Comment: Please define the dose and schedule of caplacizumab treatment.

Response: We have incorporated additional data on caplacizumab doses into Table 1; however, no clear data regarding the treatment schedule was obtained from the patients' records.

Comment: Which was the cause of death in the two patients who died due to no iTTP-related causes?

Response: We appreciate this important inquiry. However, we were limited to the data present in the patient records, and unfortunately, the causes of death for these individuals were not documented.

Comment: The introduction section is too long and some paragraphs (e.g., lines 125-131) must be deleted

Response: Thank you for pointing this out to us; addressed.