Review Form 3

Journal Name:	Asian Hematology Research Journal
Manuscript Number:	**Ms_AHRJ_128531**
Title of the Manuscript:	**Prediction of the timely decaying efficiency of Factor VIII replacement therapy using Activated Partial Thromboplastin Time (aPTT) test in Hemophilia A patients undergoing treatment at The National Hospital of Sri Lanka (NHSL)**
Type of the Article	**Original Research Article**

PART 1: Comments

	Reviewer's comment	**Author's Feedback** *(Please correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Please write a few sentences regarding the importance of this manuscript for the scientific community. A minimum of 3-4 sentences may be required for this part.	I believe, this manuscript is significant to the scientific community as it explores a novel approach to predicting the decline in efficacy of Factor VIII replacement therapy in Hemophilia A patients. By utilizing the Activated Partial Thromboplastin Time (aPTT) test as a predictive tool, this study offers a potential non-invasive method for clinicians to monitor therapy effectiveness in real-time. Such an approach could enhance personalized treatment strategies, allowing for timely adjustments in therapy and potentially improving patient outcomes. Furthermore, the findings may contribute to optimizing therapeutic protocols, reducing treatment costs, and improving the overall management of Hemophilia A, especially in resource-limited settings.	
Is the title of the article suitable? **(If not please suggest an alternative title)**	**Alternative title** **"Prediction of the Timely Decline in Factor VIII Replacement Therapy Efficacy Using aPTT in Hemophilia A Patients at The National Hospital of Sri Lanka"**	

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Is the abstract of the article comprehensive? Do you suggest the addition (or deletion) of some points in this section? Please write your suggestions here.	**Introduction**: Hemophilia A is a genetic disorder caused by Factor VIII deficiency, and prophylactic Factor VIII replacement therapy is used to maintain baseline levels and prevent bleeding. This study aimed to investigate the relationship between Activated Partial Thromboplastin Time (aPTT) and the time since the latest Factor VIII treatment (T) to predict the duration of therapy efficiency. Additionally, it sought to establish a cut-off value for aPTT as an indicator of Elevated Factor VIII Levels (EFL) resulting from therapy. The study involved patients attending the Hemophilia Clinic at the National Hospital of Sri Lanka (NHSL) (n=61). **Materials and Methods**: The time from the latest Factor VIII treatment to blood collection (T) was recorded, along with patient data including age, weight, and Factor VIII dose. aPTT was measured using the COATRON-M4 coagulation analyzer, and EFL was calculated based on the administered dose. Bivariate correlation analysis was performed to explore associations between aPTT & T and aPTT & EFL. Kaplan-Meier survival analysis was used to estimate the duration of therapy efficacy following the latest Factor VIII dose. Finally, Receiver Operating Characteristic (ROC) curve analysis was conducted to determine the aPTT cut-off value indicative of EFL in the body. **Results**: aPTT showed a significant, strong positive correlation with the time since the latest treatment (T). Kaplan-Meier survival analysis estimated a median survival time of approximately 5 days, with the initial recurrence occurring at around 2 days and complete recurrence at approximately 8 days. ROC analysis identified aPTT cut-off value of 38.8 seconds, with a sensitivity of 95.2% and specificity of 37.2%. **Conclusion**: The results indicate that aPTT can predict the maximum duration of Factor VIII therapy efficiency in Hemophilia A patients. Cut-off values for aPTT as an indicator of EFL, determined through ROC analysis, were also established. However, further validation with a larger patient sample is required to confirm these findings. Keywords: Hemophilia A; Activated Partial Thromboplastin Time (aPTT); Prophylactic Factor VIII Replacement Therapy.	
Is the manuscript scientifically, correct? Please write here.	Yes, the manuscript appears to be scientifically correct based on the provided content. It employs appropriate statistical methods (e.g., Kaplan-Meier survival analysis, ROC curve analysis, and correlation analyses) to investigate the relationship between aPTT and the effectiveness of Factor VIII replacement therapy in Hemophilia A patients. The study design, including the use of relevant biomarkers and clinical data, aligns with standard approaches in clinical research. However, the manuscript could benefit from additional validation with a larger sample size and further exploration of potential confounding factors.	
Are the references sufficient and recent? If you have suggestions of additional references, please mention them in the review form.	Yes	

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Is the language/English quality of the article suitable for scholarly communications?	Yes	
Optional/General comments	- **Title revised** - **Abstract reorganised** - **Subtitles were rearranged as Introduction, Methods, Results, Discussion and Conclusion (including future perspective or recommendations** **Discussion Rewritten "Discussion** This study aimed to explore the relationship between Activated Partial Thromboplastin Time (aPTT) and the duration of efficacy of Factor VIII replacement therapy in Hemophilia A patients. The data analysis incorporated both descriptive and inferential statistics to determine the predictive value of aPTT for therapy efficiency. The findings indicate that aPTT is a useful marker for predicting the time until Factor VIII therapy loses its efficacy, which is essential for optimizing treatment regimens and patient care. The initial part of the analysis focused on testing the normality of the data, which showed that only the variable for weight followed a normal distribution, while other variables, including aPTT, age, time since last dose (T), and the amount of Factor VIII administered, did not. Consequently, both parametric and non-parametric statistical methods were applied to ensure robustness in the analysis. Bivariate correlation analysis revealed a significant positive correlation between aPTT and T, with a strong correlation coefficient ($r = 0.820$, $p < 0.0001$), indicating that higher aPTT values were associated with longer times since the last Factor VIII dose. However, aPTT showed a weak negative correlation with Elevated Factor VIII Levels (EFL), suggesting that as EFL increases, aPTT decreases. Kaplan-Meier survival analysis provided further insights into the temporal aspects of Factor VIII replacement therapy efficacy. The analysis demonstrated that the median survival time for therapy efficacy was approximately 5 days, with a recurrence of therapeutic inefficacy beginning around 2 days post-treatment and reaching complete recurrence at about 8 days. This suggests that the time period during which Factor VIII remains effective after administration is relatively short, which is crucial information for patients and clinicians in planning subsequent treatments. The ability to predict the duration of therapy efficacy can significantly reduce uncertainty in treatment schedules, allowing patients to manage their condition with greater confidence and less risk of bleeding. These findings are consistent with previous studies that used Kaplan-Meier survival analysis to assess the efficacy of other therapeutic options, such as immune-suppressive therapies and targeted treatments for acquired hemophilia A (AHA) [17, 18]. The ROC curve analysis further validated the use of aPTT as a predictor of EFL, with a cut-off value for aPTT determined to be approximately 38.8 seconds. This cut-off yielded a high sensitivity (95.2%) but a relatively low specificity (37.2%), indicating that aPTT is a highly sensitive marker for detecting low EFL, but it may not be as effective at distinguishing between patients with high and low Factor VIII levels. Despite the weak negative correlation with EFL, the cut-off value of 38.8 seconds can still serve as a practical clinical tool. If aPTT exceeds 39 seconds, EFL is likely below 25%, suggesting that the patient may need a dose adjustment or additional monitoring. These findings are consistent with previous research that used ROC curve analysis to establish cut-off values for aPTT in predicting Factor VIII inhibitor development [19, 20]. Although the results show promising potential for using aPTT as an indicator of Factor VIII therapy efficiency, it is important to recognize the limitations of this study. The sample size of 61 patients is relatively small, and a broader patient cohort would be necessary to confirm the findings and increase the generalizability of the results. Moreover, the low specificity of the aPTT cut-off value suggests that additional markers or tests may be required to enhance diagnostic accuracy. Future studies should consider incorporating other laboratory tests, such as Factor VIII activity assays or von Willebrand factor levels, to refine the prediction model and increase its clinical utility. In conclusion, this study demonstrates that aPTT is a valuable tool for predicting the duration of Factor VIII therapy efficacy in Hemophilia A patients. The findings highlight the potential of using aPTT to guide treatment decisions and improve patient outcomes by providing a more accurate timeline for the effectiveness of therapy. However, further research with a larger patient sample and additional markers is needed to validate these results and refine the clinical application of aPTT in managing Hemophilia A. **Future Perspectives and Recommendations:** Future research should expand the prediction of Factor VIII replacement therapy efficacy by	

	incorporating a combination of diagnostic tests, including aPTT, Factor VIII activity assays, Factor VIII concentration, and von Willebrand factor levels. Regular clinical monitoring, including bleeding assessment and inhibitor testing, is essential for evaluating patient response. A multi-laboratory approach could provide a more comprehensive understanding of coagulation status, improving treatment outcomes. Future studies should focus on refining these methods and developing personalized treatment strategies to enhance patient management and clinical outcomes. -	

PART 2:

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details)*	

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