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Literature Review: Comparing Traditional and New Ways to Diagnose Hemophilia in Indonesia

Studi Literatur: Perbandingan Metode Konvensional Dan Modern Dalam Diagnosis Hemofilia Di Indonesia

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Abstract

Introduction: Hemophilia is a congenital bleeding disorder that necessitates laboratory diagnosis for treatment and monitoring of the treatment process due to a deficiency of factor VIII or IX. Objective: This study is a literature review comparing conventional and modern diagnostic methods for hemophilia in Indonesia. Methods: The research method used data from 2020-2025, identified through PubMed, Sciencedirect, and Google Scholar, focusing on hemophilia patients assessed with Activated Partial Thromboplastin Time (aPTT), factor VIII activity test, Bethesda test, Clot Waveform Analysis (CWA), and genetic analysis. Results: The results show that conventional methods such as the aPTT test and factor VIII, can be used for initial screening and disease classification, while the Bethesda test is considered effective for detecting inhibitors with highcost coverage and laboratory standards. Modern diagnostic techniques provide diagnostic advantages, such as the ability to differentiate mild, moderate, and severe hemophilia at a lower cost than chromogenic factor VIII testing. This is achieved by utilizing optical aPTT data to evaluate coagulation dynamics in real time and demonstrate a correlation with factor VIII activity. Genetic analysis using PCR, Sanger sequencing, and Next Generation Sequencing (NGS) can be techniques for identifying F8/F9 gene mutations but require supporting costs. Conclusions: Combining conventional and modern approaches is recommended to improve diagnostic accuracy and therapeutic effectiveness, and is expected to reduce the incidence of disease and mortality in individuals with hemophilia.

Keywords: Bethesda Assay, Clot Waveform Analysis, Genetic Analysis, Hemophilia

Abstrak

Pendahuluan: Hemofilia adalah kelainan perdarahan bawaan akibat defisiensi faktor VIII atau IX yang memerlukan diagnosis laboratorium untuk terapi dan memantau proses terapi. Tujuan: Penelitian ini merupakan studi literatur yang membandingkan metode diagnostik hemofilia konvensional dan modern di Indonesia. Metode penelitian menggunakan data dari tahun 2020–2025 yang diidentifikasi melalui PubMed, Sciencedirect, dan Google Scholar, dengan fokus pada pasien hemofilia yang dinilai dengan *Activated Partial Thromboplastin Time* (aPTT), uji aktivitas faktor VIII, Uji Bethesda, *Clot Waveform Analysis* (CWA), dan analisis genetik. Hasil: Hasil menunjukkan metode konvensional seperti uji aPTT dan faktor VIII dapat digunakan untuk skrining awal dan klasifikasi penyakit, sedangkan Uji Bethesda dinilai efektif untuk mendeteksi inhibitor dengan cakupan biaya dan standar laboratorium yang tinggi. Teknik modern memberikan keuntungan diagnostik seperti CWA menggunakan data aPTT optik untuk mengevaluasi dinamika koagulasi secara real-time dan menunjukkan korelasi aktivitas faktor VIII yang memungkinkan diferensiasi hemofilia ringan, sedang, dan berat dengan biaya lebih rendah dibandingkan dengan pengujian faktor VIII kromogenik. Analisis genetik menggunakan PCR, Sanger sequencing, dan Next Generation Sequencing (NGS) dapat menjadi teknik dalam mengidentifikasi mutasi gen F8/F9, namun memerlukan biaya yang mendukung. Kesimpulan: Menggabungkan pendekatan konvensional dan modern direkomendasikan untuk meningkatkan akurasi diagnostik dan efektivitas terapeutik, dan diharapkan dapat mengurangi angka kejadian penyakit dan kematian individu dengan hemofilia.

Kata kunci: Analisis Genetik, Bethesda Assay, Clot Waveform Analysis, Hemofilia

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1. Introduction

The global frequency of hemophilia is estimated at 1 in 5,000 to 10,000 male births for hemophilia A and 1 in 30,000 male births for hemophilia B (Darman & Bahraen, 2023). According to the Indonesian Hemophilia Association (HMHI), in 2018, there were2,098 cases of hemophilia, or only 10% of the

total hemophilia cases, with a total of 20,000–25,000 cases hroughoutIndonesia (Kementerian RI, 2021). The majority of cases, between 85 and 90 percent, are hemophilia A, while only 10 to 15 percent are hemophilia B (Timan et al., 2024).

Cases of hemophilia in children in Indonesia who have severe hemophilia A only receives fresh frozen plasma therapy without prior inhibitor testing, resulting in recurrent bleeding that is unresponsive to standard therapy (Chozie et al., 2022). Hemophilia diagnosis requires a fast and accurate procedure because inhibitors reduce the effectiveness of clotting factor therapy, so accurate results are key to management in determining the type of therapy, monitoring effectiveness, and preventing long-term complications (Angchaisuksiri et al., 2024). Patients are at risk of receiving inappropriate therapy without a proper diagnosis, which can lead to an increase in morbidity and mortality (Srivastava et al., 2020).

The development of hemophilia diagnostic methods began with conventional methods, such as the *Activated Partial Thromboplastin Time* (aPTT). The aPTT test is mainly used first because it is better at detecting deficiencies in factors VIII and IX compared to the prothrombin time (Wada et al., 2023). The development of hemophilia examination methods has progressed from conventional tests to modern methods such as *Clot Waveform Analysis* (CWA) and the *Rapid Bethesda Assay*. The rapid Bethesda test is as effective as conventional methods for detecting factor IX inhibitors in hemophilia B, with a faster analysis time (Sahud et al., 2020). One advantage of CWA analysis is its ability to display coagulation dynamics in real time. According to research conducted in Indonesia, CWA can differentiate hemophilia A from other conditions by observing changes in the coagulation curve pattern and a decrease in the Min1, Min2, and Max2 parameters related to factor VIII levels (Timan et al., 2024). Individual variation and weak clinical associations remain a problem in biomarker research, so a combination of the latest techniques, conventional genomic analysis, *Bethesda Assay*, and CWA is needed to provide a more accurate and relevant diagnosis in clinical practice (Bergen et al., 2021). The aim of this study is a literature study on the comparative analysis of conventional and modern hemophilia diagnostic methods, emphasizing their advantages, limitations, and relevance in clinical practice.

2. Method

This research is a literature study by reviewing relevant sources regarding hemophilia diagnosis in Indonesia through the PubMed, ScienceDirect, and Google Scholar databases. The selection process was carried out by using appropriate keywords, filtering articles based on titles and abstracts, and then thoroughly evaluating those that met the inclusion criteria, namely studies on hemophilia patients in Indonesia, and excluding animal studies and reviews without patient data. Data analysis was conducted narratively and quantitatively to compare the effectiveness of conventional and modern methods, such as the Bethesda Assay, CWA, and genetic analysis. This study focuses on the advantages, limitations, and clinical applications of each method in the context of healthcare services in Indonesia. Based on the search keywords, several journals met the inclusion criteria.

3. Result and Discussion

Based on 340 selected articles, 5 journals were found that met the criteria based on keywords and were compiled based on the comparative method. Diagnosis of hemophilia is very important to determine the most appropriate therapeutic management and long-term monitoring plan. Laboratory examinations for hemophilia can be classified into conventional and modern methods, each of which has different advantages, disadvantages, and effectiveness depending on the situation (Tiede et al., 2014). Examples of conventional methods that are often used include the Bethesda test, factor VIII activity examination, and APTT evaluation (Werwitzke et al., 2016). Although hemophilia patients generally show prolonged APTT time, this result is not specific because it can be influenced by other disorders, such as the presence of inhibitors or deficiencies of other coagulation factors (Sahud et al., 2020). Meanwhile, doctors can check for inhibitors that attack factor VIII with a test called the Bethesda test, which is often difficult to handle in patient care (Hermans et al., 2021). Although conventional examinations have significant diagnostic value, these methods still have limitations, such as high costs, variations between laboratories, and limited facilities in various regions in Indonesia.

Modern methods offer more accurate and efficient alternatives. One such method is CWA, which utilizes optical data from APTT measurements to assess detailed blood coagulation dynamics (Awane et al., 2023). CWA produces additional parameters such as Min1, Min2, Max2, and slope 2, which correlate with factor VIII activity (Siegemund et al., 2014). Research in Indonesia found that CWA can tell the difference between mild, moderate, and severe cases of hemophilia and is closely linked to FVIII activity levels. (Timan et al., 2024; Yolanda et al., 2022). Another benefit of this method is that it is less

expensive than the chromogenic FVIII test, and it can be carried out in facilities that have limited resources.

Table 1. Data on the use of conventional and modern methods in detecting hemophilia in Indonesia

Author & Year	Title	Sample	Method	Results
Kirana et al., (2024)	F8 Gene Splice Donor Mutation (c.1271+1G>A) in Individual with Mild Hemophilia A in Indonesia: A Case Study	11 hemophilia A patients	long-read NGS (Oxford Nanopore)	Intron 8 splice donor mutation(c.1271+1G>A) in one patient, effective NGS
			PCR & Sanger sequencing	Intron 8 splice donor mutation(c.1271+1G>A) in one patient, PCR-Sanger validation
Timan et al., (2024)	Clot waveform analysis to differentiate mild, moderate, and severe hemophilia A	139 hemophilia A patients	Clot Waveform Analysis (CWA)	CWA differentiates normal
			APTT & FVIII assay	Hemophilia for a longer pre-coagulation phase, lower Min1/Min2/Max2 values, and correlation with FVIII.
Yolanda et al., (2022)	Correlation between Slope 2 in Clot Waveform Analysis of APTT with Factor VIII Activity in Hemophilia A	43 hemophilia A patients	CWA (APTT slope 2)	Strong positive correlation ($r=0.854$; $p<0.001$) of the slope of 2 CWA with FVIII activity. CWA has the potential to replace expensive FVIII testing
Hermans et al., (2021)	Recombinant factor VIII Fc for the treatment of haemophilia A	over 500 hemophilia A patients.	rFVIIIFc	rFVIIIFc reduces ABR by up to 92%, offers dose flexibility & less frequent intervals, improves quality of life, and is safe without increasing inhibitors
Chozie et al., (2022)	FVIII inhibitor surveillance in children with hemophilia A in Indonesia	388 children with hemophilia Aged ≤18 years	Bethesda assay	Out of 388 patients, 9.6% had FVIII inhibitors, mostly in people with severe hemophilia. The average inhibitor level was 9.44 BU. There was a big difference in how often joints bled each year between those with low and high inhibitor levels. People without inhibitors didn't show this difference.

In addition, PCR, Sanger sequencing, and Next-Generation Sequencing (NGS) methods also play an important role in the ever-growing field of genetic analysis. The advantage of this method is that it can detect certain mutations in the F8 or F9 gene and provide a definite diagnosis (Selvatici et al., 2025). Genetic profiling also helps in predicting the risk of developing inhibitors, family ounselling, and detecting inherited diseases. Based on research in Indonesia, the Sanger sequencing method can be a technique to identify donor splice mutations in intron 8 (c.1271+1G>A) in hemophilia A patients (Kirana et al., 2024). Although this technology is very effective, its implementation still faces challenges in the form of high costs and the need for sophisticated facilities.

When compared based on its level of effectiveness, the Bethesda test is still used to detect inhibitors, although its use is limited. CWA excels in cost efficiency and ease of application, with high sensitivity and specificity in differentiating the severity of hemophilia. Genetic analysis is the most accurate method for establishing a diagnosis and providing family ounselling, but the relatively high cost and the need for facilities are still major obstacles. Several related research results have been described by Timan et al., (2024) and Yolanda et al., (2022) emphasizing

the effectiveness of CWA, while Kirana et al., (2024) show the advantages of NGS.

In addition to the diagnostic aspect, the development of therapy also reflects the progress of modern methods. According to Hermans et al., (2021), recombinant factor VIII Fc (rFVIIIFc), which has a longer duration in the body compared to standard factor VIII, can lower the annual rate of bleeding episodes by as much as 92%. This occurs because rFVIIIFc has a longer half-life, so that factor VIII levels in the blood can last longer. These findings demonstrate that modern innovations are not only relevant for diagnosis but also in the clinical management of hemophilia.

Overall, the results of the literature study show that conventional methods such as PCR-Sanger, FVIII activity examination, and APTT are still used as the basis for diagnosis. However, modern methods such as NGS and CWA offer higher effectiveness, both in terms of accuracy and cost and time efficiency (Hermans et al., 2021; Timan et al., 2024; Yolanda et al., 2022). A combination of modern and conventional approaches is an ideal strategy in Indonesia, especially to address limited laboratory resources and variations in facilities at various levels of health services.

4. Conclusion

Conventional and modern examination methods in the diagnosis of hemophilia: it can be concluded that conventional examinations, such as aPTT, factor VIII test, and *Bethesda assay* remain relevant as initial screening and for inhibitor detection but have limitations and variations between laboratories, as well as access and cost barriers in various regions of Indonesia. Meanwhile, modern screening techniques provide more accurate, sensitive, and efficient results. Techniques such as CWA and genetic analysis (PCR, *Sanger sequencing*, and NGS) can provide more specific, sensitive, and efficient results and can identify inhibitory issues.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Authors' contributions

ST performed the experiments and wrote the manuscript. ES performed the revision and the editing of the manuscript. VG, D and SW analyzed. CMT, ST supervised the overall project.

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