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# Analysis of APTT Values, Factor VIII Activity, Factor IX Activity, and Clinical Manifestations in Pediatric Hemophilia Patients at RSUD Dr. Soetomo Surabaya

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## ABSTRACT

***Background:*** Hemophilia is a blood clotting disorder caused by a deficiency of blood clotting factors, namely FVIII deficiency (Hemophilia A) and FIX deficiency (Hemophilia B). World epidemiological data shows that the prevalence rate of Hemophilia A is 85-90% and Hemophilia B is 10-15%. ***Objective:*** To analyze the correlations between Hemophilia factor activity with APTT values and clinical manifestations of pediatric Hemophilia patients at RSUD Dr Soetomo Surabaya. ***Methods:*** This study used a retrospective observational design. Subjects were pediatric hemophilia patients who met the inclusion criteria from total sampling data for the period January 2018-December 2022 from patient medical records. ***Results:*** It is known that the majority of pediatric Hemophilia patients in the age range of 2-10 years, as many as 50%. Descriptive statistical values were expressed in (mean ± SD), including APTT value (69 ± 25), FVIII activity (4.6 ± 5.9), and FIX activity (12 ± 15). The most clinical manifestation of bleeding was joint bleeding (hemarthrosis). There were 23 patients with Hemophilia A and 3 patients with Hemophilia B. There was no significant relationship between Hemophilia factor activity and APTT values using the Chi-Square Test statistical test. There was also no significant relationship between hemophilia factor activity and manifestations of hemophilia using the Kruskal-Wallis correlation test. ***Conclusion:*** The results of this study indicate that there are no correlations between Factor VIII activity and Factor IX activity with APTT values or with clinical manifestations that occur in patients.

***Keywords:*** Hemophilia; APTT value; FVIII activity; FIX activity; hemarthrosis.

## INTRODUCTION

Hemostasis is a process of the physiological function of the body that has the aim of maintaining blood dilution so that blood can still flow normally in blood vessels and block damage to blood vessel walls so as to reduce blood loss in the event of blood vessel damage [1]. This process is very complex as it involves various blood elements. If this system is disrupted, the physiological function of the coagulation system will be disrupted. This can be found in people with hemophilia. This hereditary disease cannot be cured, but it can be treated properly so that sufferers can live a normal life [2].

Hemophilia is the most common X-linked recessive blood clotting disorder in the world today. Hemophilia classification is divided into 2 types, namely hemophilia A and hemophilia B. Hemophilia A is a condition that occurs due to mutations in the factor VIII gene, which causes factor VIII deficiency. Meanwhile, hemophilia B occurs due to a deficiency in factor IX, which is needed in the process of forming fibrin threads [3]. There is also hemophilia C which occurs due to factor XI deficiency, but it is rare [4].

Based on survey results, there are approximately 400,000 cases of hemophilia worldwide. The prevalence rate of hemophilia A is around 1 in 10,000 births of male babies and includes 85-90% of all hemophilia cases. Meanwhile, hemophilia B is estimated to be around 1 in 30,000 births of male babies and includes 10-15% of all hemophilia cases [3]. In Indonesia alone, according to a survey by the World Federation of Hemophilia (WFH) in 2016, there were approximately 1465 people with hemophilia A cases, 194 people with hemophilia B cases, and 295 cases of hemophilia of unknown type [5]. According to the results of the latest survey conducted in 2018, there were around 25,000 cases of hemophilia out of 250 million people in Indonesia. Data obtained from the Indonesian Hemophilia Society Association (HMHI) in December 2018 showed that 10% of the total cases or around 2,098 Indonesians suffered from hemophilia, so there are likely to be many people with hemophilia who have not been diagnosed and registered [6]. Data also reported by the head of the East Java Hemophilia Society Association (HMHI) at the commemoration of World Hemophilia Day in Surabaya recorded around 333 people with hemophilia as of February 2016. This has increased compared to the previous year's data [7].

Hemophilia is a hereditary disease that has long been recognized worldwide. In confirming the diagnosis, it is necessary to measure the value of hemostasis faeces and coagulation factor activity. Until now, the analysis of APTT values, Factor VIII and IX activity, and clinical manifestations in pediatric Hemophilia patients at RSUD Dr Soetomo Surabaya has not been widely studied so it is necessary to conduct research to determine the distribution of pediatric Hemophilia patients in the mild, moderate, severe categories and analyze the relationship between Hemophilia factor activity with APTT values and clinical manifestations at RSUD Dr Soetomo Surabaya.

## METHOD

This study is a retrospective observational study using secondary data from medical records of pediatric hemophilia patients at the outpatient installation of Pediatric Hematology Oncology Department / SMF Pediatrics RSUD Dr. Soetomo Surabaya in January 2018-December 2022 who met the inclusion criteria, namely patients aged <18 years and the patient's family willing to give consent that patient data will be included as research samples. This study used descriptive statistical analysis to measure the frequency distribution of minimum and maximum ranges, mean, median, and standard deviation of APTT values, FVIII activity, FIX activity, and clinical manifestations. Chi-Square Test statistical test to test the correlation between Factor VIII activity and Factor IX activity with APTT values and the Kruskal-Wallis Test to test the relationship between Factor VIII activity and Factor IX activity with clinical manifestations of patients. Patients who had used drug therapy, such as Factor VIII or Factor IX therapeutic concentrates, and patients with bleeding complaints due to other causes, such as Thrombopholia and Deep Vein Thrombosis (DVT) were excluded from this study.

## RESULT AND DISCUSSION

The basic characteristics of the patients are shown in Table 1. The data amounted to 26 samples that met the inclusion criteria from a total of 298 data. Of the 26 samples, 96.15% were male and 3.85% were female. The majority of patients were children, aged between 2-10 years. Descriptive results of APTT values, Factor VIII activity, and Factor IX activity are attached in Table 1. The most common clinical manifestation was joint bleeding (hemarthrosis). The most common hemophilia was Hemophilia A, which was 23 patients with a percentage of mild Hemophilia A patients of 21.7%, moderate category of 43.5%, and severe category of 34.8%, followed by Hemophilia B as many as 3 patients with a percentage of mild Hemophilia B patients of 66.7% and severe category of 33.3%.

**TABLE 1:** Basic Characteristics.

| Characteristic | Overall, *N = 26* |
|---|---|
| ***Gender (N=26) (n, %)*** | |
| Male | 25 (96,15%) |
| Female | 1 (3,85%) |
| ***Age (N = 26) (n, %)*** | |
| Neonatal | 0 (0%) |
| Infant | 3 (11,54%) |
| Toddler | 3 (11,54%) |
| Child | 13 (50%) |
| Adolescent | 7 (26,92%) |
| ***APTT Value (N=56) (n seconds)*** | |
| Minimum | 28,20 |
| Maximum | 120 |
| Mean | 69,11 |
| Median | 74,65 |
| Standard Deviation | 25,43 |
| ***Factor VIII Activity (N=23) (n%)*** | |
| Minimum | 0,8 |
| Maximum | 26 |
| Mean | 4,65 |
| Median | 3 |
| Standard Deviation | 5,9 |
| ***Factor IX Activity (N = 3) (n%)*** | |
| Minimum | 1 |
| Maximum | 30 |
| Mean | 12,33 |
| Median | 6 |
| Standard Deviation | 15,5 |
| ***Clinical Manifestations (N = 26) (n, %)*** | |
| Purpura | 3 (11,5%) |
| Epistaxis | 1 (3,8%) |
| Hemarthrosis | 12 (46,2%) |
| Hematome | 2 (7,7%) |
| Gum bleeding | 8 (30,8%) |

| | |
|---|---|
| ***Types of Hemophilia (N = 26) (n, %)*** | |
| Hemophilia A | 23 (88,5%) |
| Hemophilia B | 3 (11,5%) |
| ***Classification of Hemophilia A (N = 23) (n, %)*** | |
| Mild | 5 (21,7%) |
| Moderate | 10 (43,5%) |
| Severe | 8 (34,8%) |
| ***Classification of Hemophilia B (N = 23) (n,%)*** | |
| Mild | 2 (66,7%) |
| Moderate | 0 (0%) |
| Severe | 1 (33,3%) |

Table 2 shows the percentage and results of the analysis of the correlation between Factor VIII activity and APTT values. It is known that the percentage of Hemophilia A with APTT values <70 seconds was 47.8% or 11 patients and the percentage of Hemophilia A with APTT values ≥70 seconds was 52.2% or 12 patients.

The Chi-Square Test statistical test was used to test the correlation between Factor VIII activity and the APTT value category. Based on the results of the statistical test, the p-value = 0.278 was obtained, so the relationship between Factor VIII activity and APTT value was not statistically significant.

**TABLE 2:** Correlation between Factor VIII Activity with APTT Values.

| APTT Value Category | Factor VIII Activity | | | Total | Percentage | P-Value |
|---|---|---|---|---|---|---|
| | >5-40% (Mild) | >1-5% (Moderate) | ≤1% (Severe) | | | |
| <70 sec | 3 | 6 | 2 | 11 | 47,8% | |
| ≥70 sec | 2 | 4 | 6 | 12 | 52,5% | 0,278 |
| **Total** | **5** | **10** | **8** | **23** | **100%** | |

Table 3 shows the percentage and result of the analysis of the correlation between Factor IX activity and APTT values. There was a percentage of Hemophilia B with an APTT value <70 seconds of 33.3% or 1 patient and a percentage of Hemophilia B with an APTT value ≥70 seconds of 67.7% or 2 patients.

This statistical test was also used to test the correlation between Factor IX activity and the APTT value category. Based on the results of statistical tests, the value of p=0.386 was obtained, so the relationship between Factor IX activity and APTT values was not significant.

**TABLE 3:** Correlation between Factor IX Activity with APTT Values.

| APTT Value Category | Factor VIII Activity | | | Total | Percentage | P-Value |
|---|---|---|---|---|---|---|
| | >5-40% (Mild) | >1-5% (Moderate) | ≤1% (Severe) | | | |
| <70 sec | 1 | 0 | 0 | 1 | 33,3% | |
| ≥70 sec | 1 | 0 | 1 | 2 | 66,7% | 0,386 |
| **Total** | 2 | 0 | 1 | 3 | 100% | |

According to Hammami in his research, an elongated APTT result indicates various things related to blood clotting, one of which is the presence of congenital deficiency of intrinsic system clotting factors, such as Factor VIII (Hemophilia A) and Factor IX (Hemophilia B). Meanwhile, a shortened APTT result may indicate cancer, acute bleeding, or the early stages of DIC. There are factors that can affect APTT test results, such as drugs that can prolong test values, improper blood and citrate ratios, and blood samples taken from heparin catheters.

In this study, there is a category of APTT values that are critical values for spontaneous bleeding in patients with hemophilia. Variations in APTT values can bias the results of the study due to the possibility that patients have received therapy or have not received therapy. However, statistical tests showed that there was no significant correlation between FVIII or FIX activity and APTT values.

In Table 4, it is shown the percentage and result of the analysis of the correlation between Hemophilia factor activity and clinical manifestations of the patient. The results showed that the incidence of joint bleeding and muscle bleeding was found in the severe category of Factor VIII activity (with FVIII activity ≤1% of normal values). Whereas, in the moderate category of Factor VIII activity (with FVIII activity >1-5% of normal values) and mild category of Factor VIII activity (with FVIII activity >5-40% of normal values) there were more cases of joint bleeding and gum bleeding.

The Kruskal-Wallis non-parametric correlation test was used to test the correlation hypothesis between Factor VIII activity and clinical manifestations that occur in patients with Hemophilia A. The results of the Kruskal-Wallis correlation test between clinical manifestations and Factor VIII activity obtained a value of p=0.487. Because the p-value> 0.05, the relationship between clinical manifestations and Factor VIII activity is not statistically significant.

**TABLE 4:** Correlation between Factor VIII Activity with Clinical Manifestation of Patients

| Clinical Manifestation of Patients | Factor VIII Activity | | | Total | Percentage |
|---|---|---|---|---|---|
| | >5-40% (Mild) | >1-5% (Moderate) | ≤1% (Severe) | | |
| Purpura | 0 | 1 | 1 | 2 | 8,7% |
| Epistaxis | 0 | 1 | 0 | 1 | 4,4% |
| Hemarthrosis | 2 | 4 | 5 | 11 | 47,8% |
| Hematome | 0 | 1 | 1 | 2 | 8,7% |
| Gum Bleeding | 3 | 3 | 1 | 7 | 30,4% |
| **Total** | **5** | **10** | **8** | **23** | **100%** |

In Table 5, it is shown the percentage and result of the analysis of the correlation between Hemophilia factor activity and clinical manifestations of the patient. The results of this study also showed that the incidence of skin bleeding (purpura) occurred in the severe category of Factor IX activity (with FIX activity ≤1% of normal values). Meanwhile, cases of joint bleeding (hemarthrosis) and gum bleeding occurred in the mild category of Factor IX activity (with activity >5-40% of normal values).

In this study, the Kruskal-Wallis non-parametric correlation test requires data in each category to compare medians between groups, the absence of data in one of the categories causes the statistics cannot be calculated in that category, so the Kruskal-Wallis correlation test related to the relationship between Factor IX activity and clinical manifestations of Hemophilia B patients cannot be performed.

**TABLE 5:** Correlation between Factor IX Activity with Clinical Manifestation of Patients.

| Clinical Manifestation of Patients | Factor VIII Activity | | | Total | Percentage |
|---|---|---|---|---|---|
| | >5-40% (Mild) | >1-5% (Moderate) | ≤1% (Severe) | | |
| Purpura | 0 | 0 | 1 | 1 | 33,3% |
| Epistaxis | 0 | 0 | 0 | 0 | 0% |
| Hemarthrosis | 1 | 0 | 0 | 1 | 33,3% |
| Hematome | 0 | 0 | 0 | 0 | 0% |
| Gum Bleeding | 1 | 0 | 0 | 1 | 33,3% |
| **Total** | **2** | **0** | **1** | **3** | **100%** |

## CONCLUSION

The largest age group in this study was the age group of 2-10 years. Descriptive statistical values were obtained expressed in (mean ± SD), including APTT values (69 ± 25), FVIII levels (11 ± 26), and FIX levels (39 ± 35). The most common clinical manifestation of bleeding was joint bleeding (hemarthrosis). The most common hemophilia at RSUD Dr. Soetomo is Hemophilia A. There is no significant relationship between the activity of the Hemophilia Factor and the APTT value of pediatric Hemophilia patients at Dr. Soetomo Hospital. There is no significant relationship between the activity of the Hemophilia Factor and the clinical manifestations of pediatric Hemophilia patients at RSUD Dr. Soetomo.

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## REFERENCES

[1] Puspita, D. A., Santosa, B., & Anggraini, H. (2017). PERBEDAAN HASIL PEMERIKSAAN PROTHROMBIN TIME PADA PLASMA SEGAR DAN PLASMA SIMPAN SUHU 2-8 °C SELAMA 2-8 JAM. Semarang: Repository Universitas Muhammadiyah Semarang.

[2] Sidiartha, I. (2018). KEADAAN HEMOSTASIS PADA PENDERITA. Denpasar: Repository Universitas Udayana.

[3] Darman, A., & Bahraen, R. (2023). HEMOFILIA: SUATU KELAINAN PADA FAKTOR PEMBEKUAN DARAH. Jurnal Medika Hutama, 04(02), 3299-3305.

[4] Mehta, P., & Reddivari, A. (2022). National Library of Medicine. Retrieved June 11, 2023, from https://www.ncbi.nlm.nih.gov/books/NBK551607/

[5] CDC. (2018). Centers for Disease Control and Prevention. Retrieved June 11, 2023, from https://www.cdc.gov/ncbddd/hemophilia/fac ts.html

[6] Sadikin, B. (2021, February 05). KEPUTUSAN MENTERI KESEHATAN REPUBLIK INDONESIA NOMOR HK.01.07/MENKES/243/2021 TENTANG PEDOMAN NASIONAL PELAYANAN KEDOKTERAN TATA LAKSANA HEMOFILIA. Jakarta: Menteri Kesehatan Republik Indonesia. Retrieved June 07, 2023, from https://peraturan.bpk.go.id/Home/Download/164799/Kepmenkes%20HK.01.07-Menkes-243-2021

[7] Arfani, F. (2016). ANTARA JATIM. Retrieved June 7, 2023, from https://jatim.antaranews.com/berita/178808/hmhi-333-orang-terdiagnosa-hemofilia-di-jatim