JTAM (Jurnal Teori dan Aplikasi Matematika)
http://journal.ummat.ac.id/index.php/jtam
p-ISSN 2597-7512 | e-ISSN 2614-1175
Vol. 10, No. 1, January 2026, pp. 1601-1614

Analysis of DHF Patients Based on Laboratory Examination Results with Nonparametric Approach

Tiani Wahyu Utami[1*], M. Al Haris[1], Nadia Khoirunnafisa Salma[1]
[1]Statatistic Program Study, University Muhammadiyah Semarang, Indonesia
tianiutami@unimus.ac.id

Article History:
Received : 31-07-2025
Revised : 29-08-2025
Accepted : 29-08-2025
Online : 17-01-2026

Keywords:
Dengue Hemorrhagic Fever;
Nonparametric Regression;
GCV;
Spline Estimator.

ABSTRACT

The dengue virus, which is spread by the Aedes aegypti mosquito, is the cause of Dengue Hemorrhagic Fever (DHF). In the city of Semarang, there was a threefold increase in cases of DHF compared to previous years. This type of research is quantitative research because it produces function that describes the relationship to what extent changes in predictor variable are related to changes in response variable to understand the level of association. Modelling the link between response and predictor factors is the aim of this study. Platelet as the response variable and hemoglobin and leukocyte as the predictor variables, so that the obtained model can be used as a prediction, especially regarding the dynamics of platelet changes influenced by hemoglobin and leukocytes. The pattern of the relationship between platelets and the suspected influencing factors does not form specific pattern, so the Nonparametric Spline method is used in this study. The Spline method is chosen for its flexibility; this model tends to independently seek data estimates, the completion of this study using R software. In the Spline method, there are knot points indicating data changes. The selection of optimum knot points is done by choosing the minimum GCV value The secondary data used came from Roemani Muhammadiyah Hospital's 2023 medical records. The data include platelet count, hemoglobin, and leukocyte. Based on the modeling conducted using truncated spline, the optimum knot points on the linier spline are determined to be 3 knot points with a coefficient determination of 83.58%. The coefficient of determination of 83.58% indicating that 83.58% of the variation in response variable can be explained by predictor variables studied in the regression model. This value indicates that predictor variables have a strong ability to explain changes in response variable.

Crossref
https://doi.org/10.31764/jtam.v10i1.33609

A. INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is a disease caused by dengue virus infection. Clinical symptoms that occur in DHF are bleeding that can cause shock and potentially lead to death. Four serotypes of viruses from the genus Flavivirus, family Flaviviridae are the cause of dengue hemorrhagic fever (Hidayah et al., 2017). Based on data from the Semarang City Office of DHF cases from 2019 to 2023, in 2022 the increase in DHF cases in Semarang City increased rapidly. This was due to several factors, including in 2022 there were many incidents of increased water volume due to high rainfall intensity which caused many nests of aedes aegypti mosquitoes (Faridah et al., 2022). WHO has issued a decision to confirm the diagnosis of DHF using one of the non-specific laboratory indicators, namely Thrombocytopenia or a platelet count of less than 100,000/ml (Ojha et al., 2017).

Expert in tropical infectious diseases, in his research explained that when infected with DHF, there is a decrease in the number of platelets or thrombocytopenia (platelet count <100,000/mm3). This is caused by plasma leakage in the capillary blood vessels, and the body tries to close the gap with the help of platelets (Jayashree et al., 2011). Alzeredo et al. (2015) revealed that one of the problems often faced by all DHF patients is Dengue Shock Syndrome (DSS), which is caused by plasma leakage. The World Health Organization or WHO good or bad prognosis in DHF patients can be determined when the disease is recognized when the patient is in the hospital (Ajlan et al., 2019).

Bhatt et al. (2021) revealed that the main pathophysiology of DHF is the manifestation of bleeding and circulatory failure. Platelet, hemoglobin, and hematocrit examinations play an important role in diagnosing DHF, especially if there is already a plasma leak that can cause shock (Ratulangi et al., 2025). Platelet examinations need to be done because bleeding is usually caused by thrombocytopenia. (Utami et al., 2024). The diagnosis of DHF is largely determined by hemoglobin, especially in cases of plasma leakage that can lead to shock. In the early stages, hemoglobin levels are usually normal or slightly decreased in the first few days, then increase as blood concentration increases, which is the first hematologic change found in DHF (Schechter et al., 2018).

Increased hematocrit and hemoglobin indicate the level of hemoconcentration, which plays an important role in evaluating plasma leaks to prevent shock (Utami et al., 2025). The average DHF patient experiences a period of illness of eleven days, with an average fever period of six days. Observations on the number of platelets in DHF patients were carried out in different time spans and subjects. Therefore, the use of longitudinal data is needed to fully explain the dynamics of changes in conditions (Prawanti et al., 2019). Nonparametric regression can be used to analyze data that is not normally distributed. Nonparametric regression does not depend on a particular form of functional relationship between the response variable and the predictor variable (Budiantara et al., 2015). In conditions like this, parametric regression analysis cannot produce accurate results, so nonparametric regression is more appropriate to use. This study used longitudinal data. Longitudinal data require small (sufficient) sample size to detect significant changes over time and to achieve sufficient statistical power in the analysis.

The nonparametric regression approach basically has a high level of flexibility because the regression function is assumed to be smooth and there is no specification of a particular form, so that in its estimation it can apply a certain smoothing method by looking at the data pattern (Fitriyani et al., 2021). There are several smoothing techniques that can be applied to the nonparametric regression approach, one of which is using the spline estimator (Iriany and Fernandes, 2023). The Spline segmented polynomial model is more flexible than ordinary polynomials. The ability to segment allows the regression model to adapt to the local characteristics of the data (Ramli et al., 2020). The Spline method is chosen and used when the scatter plot between the response and predictor variables does not show a clear pattern or is randomly distributed. By using the Spline method, it is expected to obtain the best regression model for the data, as explained by (Maharani & Saputro, 2021).

Research on DHF disease using Semiparametric regression has been studied by (Utami, et al, 2024). Research on the Effect of Maternal Age, Hemoglobin Levels, Platelets, and Blood Leukocytes in Pregnant Women on the Incidence of Low Birth Weight has been studied by

(Nurrahma et al., 2023). Then research on Nonparametric Spline Truncated Regression Modeling on Longitudinal Data (Case Study: Percentage of Poor Population in Papua Province 2016-2019) was studied by (Dani et al., 2021) and research on Modelling Scholastic Aptitude Test of State Islamic Colleges was studied by (Setyawati et al., 2021). Previous research on platelets in DHF patients was conducted by Sifriyani et al. (2023) using bi-response nonparametric spline regression, however, this study used cross-sectional data and the variables used were hematocrit and hemoglobin.

The Spline method is chosen and used when the scatterplot between the response and predictor variables does not show a clear pattern or is randomly distributed. By using the Spline method, it is expected to obtain the best regression model for the data. The scatterplot between platelets as a response variable with various predictor variables, namely leukocytes, hemoglobin and observation time is suspected to have no data pattern or is called a random pattern, then the appropriate method is Nonparametric Spline Regression. Based on the previous explanation and currently there is no research that examines the relationship between platelet counts in DHF patients using longitudinal data regarding nonparametric Spline regression which is influenced by leukocytes, hemoglobin and observation time during hospitalization, then a study was conducted in modeling nonparametric spline regression using data on platelet counts, hemoglobin, leukocytes, and observation time in DHF patients at Roemani Hospital Semarang.

B. METHODS

The secondary data used in this study came from the medical records of 5 DHF patients with six examination times, obtained from Roemani Hospital Semarang in 2023. This study used longitudinal data. Longitudinal data require small (sufficient) sample size to detect significant changes over time and to achieve sufficient statistical power in the analysis. The patients in this study, all Grade III DHF patients, exhibited significant plasma leakage, characterized by symptoms such as cold, clammy skin and restlessness. They also experienced a weak and rapid pulse, low blood pressure, or a narrow pulse pressure.

The data includes information on the number of platelets, hemoglobin levels, leukocyte levels, and observation time. The variables used are the number of platelets (Y) as the response variable and hemoglobin levels (X) and leukocyte levels (Z) as predictor variables. The method used to select knot points on the Spline is the Generalized Cross Validation method, with variations in the use of 1 knot, 2 knots and 3 knots in the Spline nonparametric and measuring the goodness of the model using the coefficient of determination. The following is a Table 1 showing the variables used in this study.

Tabel 1. Variabel Penelitian

Variable	Name Variable	Operational Definition
y_{ij}	Platelet Level in Subject-i, Observation-j	Platelet count in patients observed on a particular day.
t_{ij}	Examination Time (per day) in Subject-i, Observation-j	Daily Time of inpatients in the Hospital.
x_{ij}	Hemoglobin Level in Subject-i, Observation-j	Hemoglobin count in patients observed on a particular day.

Variable	Name Variable	Operational Definition
z_{ij}	Leukocyte Level in Subject-i, Observation-j	Leukocyte count in patients observed on a particular day.

1. Platelets

Platelets are blood cell fragments that do not have a nucleus and are formed in the bone marrow. Mature platelets are about 2-1 μm in size and are shaped like biconvex discs with a volume of about 5-8 fl. As many as 20-30% of platelets undergo sequestration in the spleen, which is the process by which platelets are taken by the spleen. This process occurs after platelets leave the bone marrow. Platelets are an important component in the structure of blood, because they play a role in the hemostasis process (Shakya & Singh, 2024).

2. Hemoglobin

Hemoglobin (Hb) in red blood cells can reach about 34 g/dL, but does not exceed the maximum limit that can be produced by the metabolic process in the formation of cell Hb. Hb levels in healthy individuals are usually around this value. Hb production in the bone marrow affects the amount of Hb in cells; if Hb production decreases, the percentage of Hb in cells will also decrease. In addition, the hematocrit (Ht) level, which normally ranges from 40-50%, also affects the Hb level in cells. If the Ht value is within the normal range, it also indicates that the Hb level in the cells is most likely normal (Devi et al., 2024).

3. Leukocytes

Leukocytes, also known as white blood cells, are produced by hemopoietic tissue in the form of granulocyte types, by lymphatic tissue in the form of non-granular types. Leukocytes play an important role in the immune system to fight infection. The number of leukocytes in the body is estimated to be between 4,000 and 11,000/mm3. The number of leukocytes varies from time to time depending on the foreign objects encountered and their function to protect the body from infection. This occurs within limits that can still be tolerated by the body without causing any disruption of function (Devi et al., 2024). The following are the research steps taken to answer the problem formulation:

a. Create descriptive statistics to determine the characteristics of the data.
b. Identify data patterns based on scatterplots to find patterns in the data between each predictor variable and the responder variables.
c. Modeling the Platelets with Nonparametric Spline regression approach of 1 knot, 2 knots, 3 knots on longitudinal data. Nonparametric Spline regression by knots in general is any function that can be written in the form:

$$f(t)=\sum_{i=1}^{p-1}\alpha_i t^i+\sum_{j=1}^{k}\delta_j\left(t-\xi_j\right)_+^{p-1} \quad (1)$$

with $(t-\xi_j)_+^{p-1} = \begin{cases} (t-\xi_j)^{p-1}, t \geq \xi_j \\ 0, t < \xi_j \end{cases}$; α and δ are real, $\xi_1, \xi_2, ..., \xi_k$ are knot points that show behavior pattern of the function at different sub-intervals

d. Select the optimal knot point using the Generalized Cross Validation (GCV) method by looking at the smallest GCV value.

$$GCV(k) = \frac{n^{-1}\sum_{i-1}^{n}(y_i - \hat{y}_i)^2}{\left[n^{-1}trace\left(I - X(k)\left(X(k)^t X(k)\right)^{-1} X(k)^t\right)\right]^2} \tag{2}$$

e. Model the number of platelets with the optimal knot point. Next, calculate the coefficient of determination value based on the estimation results.
f. Analysis of the results obtained from the model. Analysis of DHF patients based on laboratory examination results, namely platelet variables influenced by hemoglobin, leukocyte and observation time variables while being treated in hospital using the Nonparametric Spline Regression approach.

The following is a flowchart for completing this research in Figure 1.

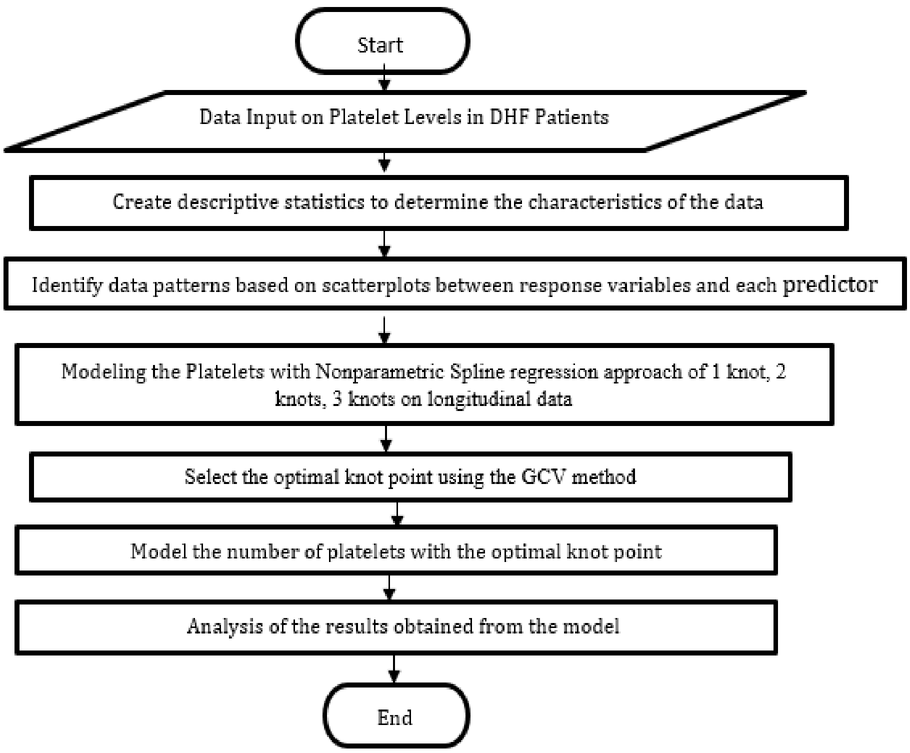

Figure 1. Research steps flowchart

C. RESULT AND DISCUSSION

1. Descriptive analysis

Descriptive statistics are used to see the general picture of the data used. The following are the results of the analysis as shown in Table 2.

Table 2. Descriptive Variables

	Minimum	Maximum	Average	Variance
Platelets (/mm3)	17.000	211.000	69.900	2189.57
Hemoglobin (gram/dL)	10.9	16.2	13.8	3.02
Leukocyte (μL)	1.2	11.3	5.1	9.50

The number of platelets in human blood varies but usually ranges from 150,000 to 450,000 cells/μL. It can be seen in the descriptive analysis above that the average number of platelets in 5 DHF patients with 6 examination times is 69,900 cells/μL which means that the average DHF patient experiences thrombocytopenia. Then the normal range of hemoglobin levels in adult men is 13.8 g/dL - 17.2 g/dL while for adult women it is 12.1 g/L - 15.1 g/dL, the average in the 5 DHF patients above is 13.8 meaning that almost all patients have normal hemoglobin levels although there are some patients who have low hemoglobin levels which can indicate anemia. Then the normal range of leukocyte levels in adults is 4,500 - 11,000 cells/μL if seen in the descriptive analysis table above the minimum value of 1,200 and the maximum of 11,300 leukocyte levels indicate that there are patients with leukocyte levels below the normal range (leukopenia) there are also patients who have leukocyte levels exceeding the normal limit or often referred to as leukocytosis. After gaining a general understanding of DHF and the factors that influence it, the next step is to explore the correlation between the response variable, namely the number of platelets, with each predictor variable, namely Hemoglobin (X) and Leukocyte (Z). An illustration of the relationship can be found in the Figure 2 below.

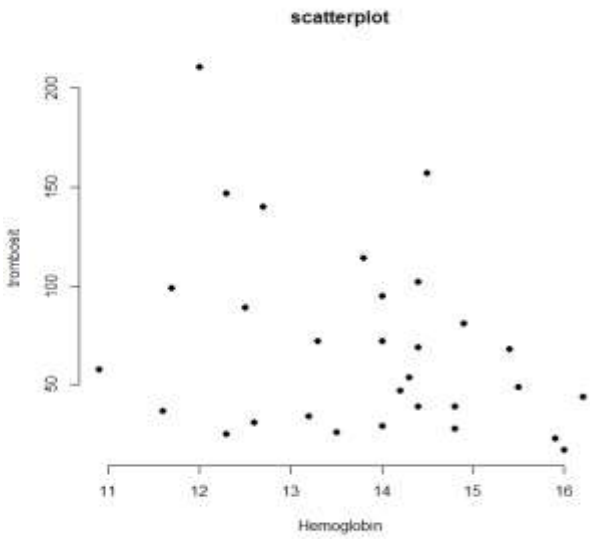

Figure 2. Scatterplot of platelet count and hemoglobin

It is evident from the scatter plot of hemoglobin and platelet count in Figure 2 that there is no clear pattern or linear relationship between the two variables. Consequently, it is believed that the connection is nonparametric regression. The following is a graph showing the distribution of platelet and leukocyte counts, as shown in Figure 3.

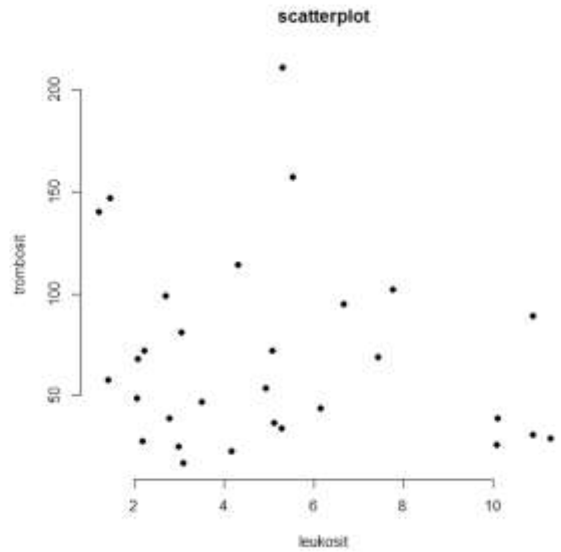

Figure 3. Scatterplot of platelet count and leukocyte

It is evident from the scatterplot of leukocyte and platelet count in Figure 3 that there is no clear pattern or linear relationship between the two variables. Consequently, it is believed that the connection is nonparametric regression.

2. Modeling the Platelets with a Nonparametric Spline linear regression

The point where the data pattern changes in an interval is called a knot point. The location of the knot point plays a crucial role in forming an optimal nonparametric regression model by Spline estimator. The GCV method uses the minimum GCV value to determine the best knot point location. The following is the process of selecting the optimal knot point. According to (Maharani & Saputro, 2021), in the GCV method, the GCV value is calculated by summing the squares of the residuals that have been corrected by the squares of the factors. A smaller GCV value indicates that the resulting model is better (Islamiyati et al., 2022).

a. Optimal Knot Point Selection with One Knot Point

The process of selecting the optimal knot point begins by using one knot point. Using a linear order (m=1), one knot point (r=1), and three predictor variables (p=2), the estimation of the nonparametric regression model by Spline estimator with one knot point on the platelet count of dengue fever patients is as follows (Wu and Zhang, 2006):

$$\hat{y} = \hat{\beta}_0 + \hat{\beta}_1 X + \hat{\beta}_2 (X - K_1)_+^1 + \hat{\beta}_3 Z + \hat{\beta}_4 (Z - K_2)_+^1 \quad (3)$$

Next, equation (1) will be applied to the DBD data to determine the optimal knot point with one knot point on each predictor variable. Table 3 presents ten GCV values that are between the minimum GCV values using one knot point.

Table 3. GCV Value of One Knot Point

One Knot Point		GCV
X	Z	
11.333	2.031	**2274.895**
11.441	2.237	2279.785
11.224	1.826	2284.687
11.873	3.058	2295.873
11.982	3.263	2297.993
11.765	2.852	2301.979
11.116	1.621	2314.554
11.657	2.647	2325.780
11.549	2.442	2326.273
14.469	7.985	2331.449

Based on the table above, the minimum GCV value of the nonparametric regression Spline with one knot point is 2274.895. The hemoglobin level variable (X) has an optimal knot point at point 11.333, which means that the change in hemoglobin level behavior is at that point. The leukocyte level variable (Z) has an optimal knot point at point 2.031, which indicates that there is a change in leukocyte level behavior at that point.

b. Optimal Knot Point Selection with Two Knot Points

After calculating the minimum GCV value with one knot point. Next, we also tried selecting the optimal knot point with two points on each predictor variable. The goal is to find the minimum GCV value. By choosing a linear order (m = 1), two knot points (r = 2), and two predictor variables (p = 2), the results estimation of the nonparametric regression model by Spline estimator with two knot points for the number of platelets in dengue fever patients are as follows:

$$\hat{y} = \hat{\beta}_0 + \hat{\beta}_1 X + \hat{\beta}_2 (X - K_1)_+^1 + \hat{\beta}_3 (X - K_2)_+^1 + \hat{\beta}_4 Z + \hat{\beta}_5 (Z - K_3)_+^1 + \hat{\beta}_6 (Z - K_4)_+^1 \quad (4)$$

Table 4 presents ten GCV values that are between the minimum GCV values using two knot points.

Table 4. GCV Value of Two Knot Points

Two Knot Points		GCV
X	Z	
11.982	3.263	**1836.109**
13.171	5.521	
12.090	3.468	1846.515
12.198	3.674	
11.982	3.263	1856.352
12.306	3.879	
11.982	3.263	1859.872
13.280	5.727	
12.090	3.468	1863.27
12.306	3.879	
11.982	3.263	1870.874

Two Knot Points		GCV
X	Z	
12.198	3.674	
11.873	3.058	1888.646
13.171	5.521	

Based on the table above, the minimum GCV value of the nonparametric regression by Spline estimator with two knot points is 1836.109. This minimum GCV value is obtained from the calculation results for each predictor variable. The hemoglobin level variable (X) has an optimal point of 11.982 and 13.171. While the leukocyte level variable (Z) is at knot points 3.263 and 5.521.

c. Selecting the Optimal Knot Point with Three Knot Points

The next step after obtaining the minimum GCV value for two knot points is to determine the optimal knot point using 3 knot points. In this context, the linear order (m = 1) is selected with three knot points (r = 3) as an option and using two predictor variables (p = 2). The following is an estimation of nonparametric regression model by Spline estimator with three knot points for platelet counts in dengue fever patients.

$$\hat{y} = \hat{\beta}_0 + \hat{\beta}_1 X + \hat{\beta}_2 (X - K_1)_+^1 + \hat{\beta}_3 (X - K_2)_+^1 + \hat{\beta}_4 (X - K_3)_+^1 + \hat{\beta}_5 Z + \hat{\beta}_6 (Z - K_4)_+^1 + \hat{\beta}_7 (Z - K_5)_+^1 + \hat{\beta}_8 (Z - K_6)_+^1 \quad (5)$$

Table 5 presents ten GCV values that are between the minimum GCV values using three knot points.

Table 5. Three-Knot GCV Values

Three Knot Points		GCV
X	Z	
12.955	5.111	
13.063	5.316	**1270.95**
13.280	5.727	
12.955	5.111	
13.063	5.316	1298.805
13.388	5.932	
12.955	5.111	
13.063	5.316	1402.911
13.604	6.343	
12.955	5.111	
13.063	5.316	1434
13.496	6.137	
12.955	5.111	
13.063	5.316	1438.161
13.712	6.548	
12.955	5.111	
13.063	5.316	1504.658
13.820	6.753	

Based on the table above, the minimum GCV value of the nonparametric Spline truncated regression with three knot points is 1270.95. This minimum GCV value is obtained from the calculation results for each predictor variable. The hemoglobin level variable (X) has optimal points of 12.955, 13.063, and 13.280. While the leukocyte level variable (Z) is located at knot points 5.111, 5.316, and 5.727.

3. Comparison of the GCV Value

The determination of the optimal Spline regression model depends on the location and number of knot points. Differences in the location of knot points can produce different Spline regression models. Therefore, the selection of the right knot points needs to be done carefully. The Table 6 below shows the location of the best knot points and the minimum GCV value for each variable.

Table 6. Comparison of GCV Values

Number of Knot Points	GCV	R^2
1	2274.895	25.36
2	1836.109	49.01
3	**1156.35**	**83.58**

The optimal knot point in Spline regression is determined based on achieving the minimum GCV value. Table 6 presents a comparison of the minimum GCV values for one, two, and three knot points. The results show that GCV reaches a minimum value at three knot points, which is 1156.35, with a level of fit (R^2) reaching 83.58%. This means that 83.58% of the variation in the platelet count variable (dependent variable) is explained by the hemoglobin level (X) and leukocyte level (Z) variables.

4. Best Model Selection

Estimation is a method that utilizes statistical sample data to estimate or determine the relationship of parameters in a population. The Ordinary Least Square (OLS) method is applied to estimate parameters in the nonparametric regression Spline model by minimizing the total residual squares. The estimated parameter values for the Truncated Spline with three nodal points are as shown in Table 7.

Table 7. Best Model Parameter Estimates

Parameter	Value
β_0	-334.73
β_1	37.01
β_2	-4445.15
β_3	6493.52
β_4	-2107.38
β_5	-9.80
β_6	783.73
β_7	-1015.45
β_8	225.77

The regression model produced by achieving the minimum GCV value is a Truncated Spline model with three knot points. Here are the details.

$$\hat{y} = \hat{\beta}_0 + \hat{\beta}_1 X + \hat{\beta}_1 (X - K_1)_+^1 + \hat{\beta}_2 (X - K_2)_+^1 + \hat{\beta}_3 (X - K_3)_+^1 + \hat{\beta}_2 Z + \hat{\beta}_4 (Z - K_4)_+^1 + \hat{\beta}_5 (Z - K_5)_+^1 + \hat{\beta}_6 (Z - K_6)_+^1$$

$$\hat{y} = -334{,}73 + 37{,}01X - 4445{,}15(X - 12{,}955)^1 + 6493{,}52(X - 13{,}063)_+^1 - 2107{,}38(X - 13{,}280)_+^1 - 9{,}80Z + 783{,}73(Z - 5{,}111)_+^1 - 1015{,}45(Z - 5{,}316)_+^1 + 225{,}77(Z - 5{,}727)_+^1$$

Based on the model obtained, it can be explained as follows.

a. The relationship between hemoglobin levels and the number of patient platelets is as follows.

$$\hat{y} = -334{,}73 + 37{,}01X - 4445{,}15(X - 12{,}955)^1 + 6493{,}52(X - 13{,}063)_+^1 - 2107{,}38(X - 13{,}280)_+^1$$
$$= \begin{cases} -334.73 + 37{,}01x & , \quad x < 12{,}955 \\ 57252{,}19 - 4408{,}14x & , \quad 12{,}955 \le x < 13{,}063 \\ -27572{,}66 + 2085{,}38x & , \quad 13{,}063 \le x < 13{,}280 \\ 413{,}34 - 22x & , \quad x \ge 13{,}280 \end{cases}$$

Based on the model above, it can be interpreted that if the hemoglobin level is less than 12.955 and if the hemoglobin level increases by one percent, then the platelet count will increase by 37.01. Then if the hemoglobin level is between or equal to 12.955 to 13.063 then if the hemoglobin level increases by one percent, the platelet count will decrease by 4408.14. If the hemoglobin level is between or equal to 13.063 to 13.280 then if the hemoglobin level increases by one percent, the platelet count will increase by 2085.38. If the hemoglobin level is more than 13.280 then if the hemoglobin level increases by one percent, the platelet count will decrease by 22. Hemoglobin levels in DHF patients can vary. In the early stages of DHF, Hb levels may be normal, but later they can increase. Normal hemoglobin levels in adults are generally 12-16 g/dL. Based on the model, it can be analyzed that if hemoglobin levels exceed 13.280 or are above normal, platelet counts will decrease. This is consistent with research conducted by (Faridah et al., 2022), so that DHF sufferers immediately receive treatment so that the platelets do not decrease too much.

b. The relationship between leukocyte levels and the patient's platelet count as follows.

$$\hat{y} = -334{,}73 - 9{,}80Z + 783{,}73(Z - 5{,}111)_+^1 - 1015{,}45(Z - 5{,}316)_+^1 + 225{,}77(Z - 5{,}727)_+^1$$
$$= \begin{cases} -334{,}73 - 9{,}80z & , \quad z < 5{,}111 \\ -4340{,}37 + 773{,}93z & , \quad 5{,}111 \le z < 5{,}316 \\ 1057{,}76 - 241{,}52z & , \quad 5{,}316 \le z < 5{,}727 \\ -235{,}23 - 15{,}75z & , \quad z \ge 5{,}727 \end{cases}$$

Based on the model above, it can be interpreted that if the platelet count is less than 5.111 and if the leukocyte level increases by one percent, then the platelet count will decrease by 9.8. Then if the leukocyte level is between or equal to 5.111 to 5.316 then if the leukocyte level increases by one percent, the platelet count will tend to increase by 783.73. If the leukocyte level is between or equal to 5.316 to 5.727 then if the leukocyte level increases by one percent, the platelet count will decrease by 241.52. If the leukocyte level is more than 5.727 then if the leukocyte level increases by one percent, the platelet count will decrease by 15.75. In DHF patients, leukocytes increase, indicating the presence of parasites in the body. Based on the obtained model, it can be analyzed that leukocytes above 5.727 or above normal will gradually decrease the platelet count in DHF patients. This is consistent with research conducted by Suhartati et al. (2025) so treatment for DHF patients is necessary to prevent a decrease in platelets that could be dangerous for the patient.

D. CONCLUSION

The following conclusions can be drawn from the results of the research and discussions that have taken place: (1) The following is the best Spline regression model for predicting platelet counts in DHF patients at Roemani Hospital Semarang in 2022 using the nonparametric Spline regression approach, namely:

$$\hat{y} = -334{,}73 + 37{,}01X - 4445{,}15(X - 12{,}955)^1 + 6493{,}52(X - 13{,}063)_+^1 - 2107{,}38(X - 13{,}280)_+^1 - 9{,}80Z + 783{,}73(Z - 5{,}111)_+^1 - 1015{,}45(Z - 5{,}316)_+^1 + 225{,}77(Z - 5{,}727)_+^1$$

The best model was obtained using three knot points with the smallest GCV value of 1156.35 and the R^2 value obtained was 83.58%. %. The coefficient of determination of 83.58% indicating that 83.58% of the variation in response variable can be explained by predictor variables studied in the regression model. This value indicates that predictor variables have a strong ability to explain changes in response variable; (2) The relationship between hemoglobin levels and the number of platelets in a patient is that if the hemoglobin level exceeds 13.280 or above normal, the number of platelets will decrease gradually so that DHF sufferers immediately receive treatment so that the platelets do not decrease too much. The relationship between leukocyte levels and the patient's platelet count are that if the leukocytes are above 5.727 or above normal, it will slowly cause the platelet count in DHF patients to decrease, so treatment is needed for DHF patients to prevent a decrease in platelets which can be dangerous for the patient; and (3) For future researchers, to obtain a more suitable model for predicting platelet counts in dengue fever patients at Roemani Hospital in Semarang, it is recommended to increase the number of variables with significant influences. Furthermore, a nonparametric truncated spline regression model can be developed using 4 and 5 knot points to obtain the minimum GCV results. Other approaches such as wavelets and Fourier series can also be used to obtain better results.

ACKNOWLEDGEMENT

Thank you to the RISETMU Research Grant Batch VIII of the Muhammadiyah PP DIKTILITBANG Council (2120/I.3/D/2024) in collaboration with the Institute for Research and Community Service (LPPM) of Muhammadiyah University of Semarang for financial support for this.

REFERENCES

Ajlan, B. A., Alafif, M. M., Alawi, M. M., Akbar, N. A., Aldigs, E. K., & Madani, T. A. (2019). Assessment of the new World Health Organization's dengue classification for predicting severity of illness and level of healthcare required. *PLoS neglected tropical diseases*, 13(8), e0007144. https://doi.org/10.1371/journal.pntd.0007144

Alzeredo, E. L., Monteiro, R. Q., Pinto, L. M. O. (2015). Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammatory Mediators, *Mediators of Inflammation*, vol. 2015, Article ID 313842, 16 pages. https://doi.org/10.1155/2015/313842

Bhatt P, Sabeena SP, Varma M, Arunkumar G. (2021) Current understanding of the pathogenesis of dengue virus infection. *Current microbiology*;78(1), 17-32. https://doi.org/10.1007/s00284-020-02284-w

Budiantara, I.N., Ratnasari, V., Ratna, M. and Zain, I. (2015). The combination of spline and kernel estimator for nonparametric regression and its properties. *Applied Mathematical Sciences*. 9(122) pp. 6083-6094. DOI:10.12988/ams.2015.58517.

Dani, A. T. R., Ni'matuzzahroh, L., Ratnasari, V., & Budiantara, I. N. (2021). Pemodelan Regresi Nonparametrik Spline Truncated pada Data Longitudinal. *Inferensi.* 4(1), 47–55. http://dx.doi.org/10.12962/j27213862.v4i1.8737

Devi, A. R. R., Rohmah, A. N., & Astuti, T. D. (2024). The relationship of leukocyte number and plattle number in patients with dengue fever (DHF) at Puskesmas Piyungan. *Journal of Indonesian Medical Laboratory and Science*, 5(1), 46–54. https://doi.org/10.53699/joimedlabs.v5i1.212

Faridah, I.N.; Dania, H.; Chen, Y.-H.; Supadmi, W.; Purwanto, B.D.; Heriyanto, M.J.; Aufa, M.A.; Chang, W.-C.; Perwitasari, D.A. (2022). Dynamic Changes of Platelet and Factors Related Dengue Haemorrhagic Fever: A Retrospective Study in Indonesian. *Diagnostics*. 12(4), 950. DOI: https://doi.org/10.3390/diagnostics12040950.

Fitriyani, N., Hadijati, M., Harsyiah, L., Sauri, M.S. (2021). Mixed Truncated Spline and Kernel Nonparametric Regression Model on Population Growth Rate in West Nusa Tenggara Province, *IOP Conference Series: Materials Science and Engineering*, 1115 012054. https://doi.org/10.1088/1757-899X/1115/1/012054.

Hidayah, N., Iskandar, Abidin, Z. (2017). Prevention of Dengue Hemorrhagic Fever (DHF) Associated with the Aedes aegypti Larvae Presence based on the Type of Water Source, *The Journal of Tropical Life Science*, Vol. 7, No. 2, pp. 115 -120. DOI: https://doi.org/10.11594/jtls.07.02.05.

Iriany A and Fernandes AAR (2023) Hybrid Fourier series and smoothing spline path non-parametrics estimation model. Front. *Appl. Math. Stat.* 8:1045098. doi: 10.3389/fams.2022.1045098

Islamiyati, A., Kalondeng, A., Sunusi, N., Zakir, M., Amir, A. K. (2022) Biresponse nonparametric regression model in principal component analysis with truncated spline estimator, *Journal of King Saud University - Science*, Volume 34, Issue 3, 101892, ISSN 1018-3647, https://doi.org/10.1016/j.jksus.2022.101892.

Jayashree, K., Manasa, G.C., Pallavi, P. et al. (2011). Evaluation of Platelets as Predictive Parameters in Dengue Fever. *Indian Journal of Hematology and Blood Transfusion*, vol. 27, pp 127–130. https://doi.org/10.1007/s12288-011-0075-1.

M. Maharani and D. R. S. Saputro, (2021). Generalized Cross Validation (GCV) in Smoothing Spline Nonparametric Regression Models, *in IOP Conference Series: Earth and Environmental Science*, IOP Publishing Ltd, doi: 10.1088/1742-6596/1808/1/012053.

Nurrahma, H. A., Yulice, S. N, Andreanyta, M., and Paramita N. (2023). The Effect of Maternal Age, Hemoglobin, Platelet, and Blood Leukocyte Levels in Pregnant Women on the Incidence of Low Birth Weight (LBW) (Analytical Observational Study at Sultan Agung Islamic Hospital). *MPPKI Journal*, 6 (4), 632-39. https://doi.org/10.56338/mppki.v6i4.3009.

Ojha, A., Nandi, D., Batra, H., Singhal, R., Annarapu, G. K., Bhattacharyya, S., ... & Guchhait, P. (2017). Platelet activation determines the severity of thrombocytopenia in dengue infection. *Scientific reports*, *7*(1), 41697. https://doi.org/10.1038/srep41697

Prawanti, D. D., Budiantara, I. N., & Purnomo, J. D. (2019, June). Parameter interval estimation of semiparametric spline truncated regression model for longitudinal data. In *IOP Conference Series: Materials Science and Engineering* (Vol. 546, No. 5, p. 052053). IOP Publishing. https://doi.org/10.1088/1757-899X/546/5/052053.

Ratulangi, A. D., Djohan, H., & Kamilla, L. (2025). The Relationship Between NS1 Examination and the Examination of Hemoglobin, Hematocrit, Leukocytes, Platelets, and Erythrocytes in Dengue Fever Patients in The Pediatric Ward. *MEDICA (International Medical Scientific Journal)*, *7*(1), 32-39. https://doi.org/10.53770/medica.v7i1.486

Ramli, M., Ratnasari, V., & Budiantara, I. N. (2020, June). Estimation of matrix variance-covariance on nonparametric regression spline truncated for longitudinal data. In *Journal of Physics: Conference Series* (Vol. 1562, No. 1, p. 012014). IOP Publishing. https://doi.org/10.1088/1742-6596/1562/1/012014

Setyawati, M., Chamidah, N., & Kurniawan, A. (2021, February). Modelling scholastic aptitude test of state islamic colleges in Indonesia using least square spline estimator in longitudinal semiparametric regression. In *Journal of Physics: Conference Series* (Vol. 1764, No. 1, p. 012077). IOP Publishing. https://doi.org/10.1088/1742-6596/1764/1/012077

Schechter, L. M., Creely, D. P., Garner, C. D., Shortridge, D., Nguyen, H., Chen, L., Hanson, B. M., Sodergren, E., Weinstock, G. M., Dunne, W. M., Jr, van Belkum, A., & Leopold, S. R. (2018). Extensive Gene Amplification as a Mechanism for Piperacillin-Tazobactam Resistance in Escherichia coli. *mBio*, *9*(2), e00583-18. https://doi.org/10.1128/mBio.00583-18

Shakya, Jagrati and Singh, Ajit. (2024). Platelets A Tiny Cell Fragments. Research & Reviews Journal of Oncology and Hematology. Vol 13. https://www.researchgate.net/publication/383414344_Platelets_A_Tiny_Cell_Fragments

Diu, M. Y., Mar'ah, Z., Anggraini, D., & Jalaluddin, S. (2023). Modeling of dengue hemorrhagic fever cases in AWS Hospital Samarinda using bi-responses nonparametric regression with estimator spline truncated. *Commun. Math. Biol. Neurosci.*, *2023*. https://doi.org/10.28919/cmbn/7888

Suhartati, Ariyadi, T., Setiawan, E.K., (2025). Correlation Between Leukocyte and Platelet in Patients with Degree 1 and 2 Dengue Fever Ajibarang Hospital. Medicina Moderna, 32(1). https://doi.org/10.31689/rmm.2025.32.1.47

Utami, T. W., Chamidah, N., & Saifudin, T. (2024). Platelet modeling in DHF patients using local polynomial semiparametric regression on longitudinal data. *JTAM (Jurnal Teori dan Aplikasi Matematika)*, *8*(1), 231-243. https://doi.org/10.31764/jtam.v8i1.17427

Utami, T. W., Chamidah, N., Saifudin, T., Lestari, B., & Aydin, D. (2025). Estimation of Biresponse Semiparametric Regression Model for Longitudinal Data Using Local Polynomial Kernel Estimator. Symmetry, 17(3), 392. https://doi.org/10.3390/sym17030392

Wu, H., and Zhang, J.T. (2006) *Nonparametric Regression Methods for Longitudinal Data Analysis*. John Wiley & Sons, Inc., Canada.