



Prognostic Factors of Severe Dengue Based on Individual Characteristics And Laboratory Examination: A Scoping Review

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Abstract

Introduction: Dengue fever is a major health problem in 48 countries worldwide. Complications and death can occur in patients who experience shock or prolonged infection. Dengue severity can be predicted based on individual characteristics and laboratory test results. However, previous studies have reported different prognostic factors. This review aimed to identify the characteristics and laboratory findings associated with severe dengue.

Methods: The inclusion criteria were observational studies published between January 2016 and May 2025 in the Scopus, PubMed, and Google Scholar databases, written in Indonesian or English, and available in full texts. Articles other than observational studies and those that did not provide PR/OR/RR were excluded from the study. Thirteen studies were eligible for assessment. This study followed the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) guidelines.

Results: Patient characteristics that served as prognostic factors for severe dengue included male sex, abnormal nutritional status, age 15–49 years, presence of comorbidities, and receiving health care for more than 1–2 days of hospitalization. Laboratory findings that act as prognostic factors include hemoconcentration, thrombocytopenia, leukopenia, and low hemoglobin levels. Based on patient characteristics, the dominant prognostic factors were comorbidities, nutritional status, and duration of healthcare. According to the laboratory findings, the dominant factors were hemoconcentration and thrombocytopenia.

Conclusion: The dominant prognostic factors for severe dengue are comorbidities such as hypertension, cardiovascular disease, and hemoconcentration. Further studies using a robust and comprehensive methodological approach are needed to validate the relationship between these prognostic factors.

Keywords: Severity, Dengue Infection, Prognostic Factors, Dengue Shock Syndrome

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Introduction

Dengue fever remains a major global public health concern.¹ Since the beginning

of 2025, at least 640,349 cases of dengue fever have been reported in 48 countries.² Dengue fever (DHF) cases in Indonesia in 2023 reached 114,720 cases and caused 894 deaths.^{3,4} The number of dengue infections increased in 2024, reaching 210,644 cases as of October, followed by 1,239 deaths.⁵

The World Health Organization (WHO) classifies dengue infection into several categories based on its clinical symptoms: dengue fever, dengue hemorrhagic fever, and severe dengue, which includes stages III and IV of dengue hemorrhagic fever, also known as Dengue Shock Syndrome (SSD).⁶ Symptoms experienced by dengue fever sufferers include fever, followed by headache, myalgia, arthralgia, the appearance of rash (purpura), leukopenia, and thrombocytopenia, although some do not show symptoms (asymptomatic). One of the distinguishing features between dengue hemorrhagic fever (DHF) and severe dengue is plasma leakage into the pleural and abdominal cavities.^{6,7} Bleeding can occur through nosebleeds, bloody stools, nausea and bloody vomiting, until the sufferer shows symptoms of shock.⁷

Complications can occur in patients with dengue if they experience severe shock or prolonged infections. Complications include organ failure, liver and kidney dysfunction, acute pulmonary edema and heart failure. Starting from being infected until the appearance of symptoms, the patient will go through a viremia or fever phase, a critical phase, and a recovery period.⁶ It is not uncommon to find cases where initial clinical symptoms are mild and then develop into severe cases, causing shock and death.⁷

The severity of dengue can be recognized through symptoms, laboratory test results, and patient characteristics. Patients who experience severe dengue generally experience dengue shock syndrome (SSD) or severe dengue.⁶⁻⁹ Various factors have been suggested to be associated with the severity of dengue infection, including individual characteristics such as abnormal nutritional status, childhood age, and male sex. In addition, the degree of severity can be identified through laboratory findings

such as leukopenia, thrombocytopenia, hemoconcentration, and decreased hemoglobin levels.⁹⁻¹² These factors can be used to predict severe dengue. Prognostic factors refer to various factors related to the development of the disease or clinical condition in the future clinical outcomes.¹³⁻¹⁵

Based on previous studies, there is considerable variation in the findings regarding the prognostic factors of severe dengue disease. Johanus's research at a hospital in Jakarta showed that male gender was a prognostic factor for severe dengue.¹⁶ In addition, study at a hospital in Denpasar found that patients who received health services for ≥ 4 days, experienced hemoconcentration up to 20%, and developed thrombocytopenia were more likely to progress to severe dengue, although gender and leukopenia were not identified as prognostic factors.¹⁷ Similarly, research by Xingyu Leng reported that the presence of comorbidities was a prognostic factor for severe dengue, consistent with studies by Cynthia Bernal, Wei Yao Ng, and Mathys Carras, which also demonstrated a significant association between comorbidities and an increased risk of severe dengue.¹⁸⁻²⁰ However, this is different from Anak Agung's findings in 2021 that hemoglobin levels, hemoconcentration, and leukocyte levels are not prognostic factors.²¹ Likewise, research by Hindra Irawan S revealed that male gender and leukopenia were not associated with severe dengue, whereas abnormal nutritional status and hemoconcentration were identified as significant prognostic factors.²²

Among these studies, there appears to be a gap in the findings that need to be addressed to determine the most relevant and consistent prognostic factors. The identification of prognostic indicators based on patient characteristics and laboratory factors is essential for the assessment of dengue cases, allowing early recognition and timely management to prevent progression to the critical phase of the disease. Therefore, conducting a systematic literature review on the prognostic factors of severe dengue is crucial to categorize and synthesize existing evidence related to the

characteristics and laboratory factors that influence disease prognosis and severity. Research published between 2016 and April 2025 will be included in the analysis. The results of this review are expected to contribute to the early detection, prevention, and control of dengue severity (SSD).

Methods

Study Design and Search Strategy

This study was a scoping review of the literature available in the electronic databases of PubMed, Scopus, and Google Scholar. The article search process is presented in a PRISMA diagram.²³ The literature search refers to the formulation of the population (severe dengue infection (SSD)), intervention (characteristics and laboratory results), comparison (non-severe dengue infection (non-SSD)), outcomes (prognostic factors for dengue severity (SSD]), and study design (cross-sectional, case-control, and cohort) (PICOS). Reference screening was first performed based on the title and abstract, which were then stored in Mendeley library. The second stage of screening was carried out by reviewing duplicate articles or papers that were not relevant to the context of the study. Additional references were obtained by screening the reference lists of previously identified articles. The keywords used are listed in the following table:

Inclusion Criteria

Eligible articles were full-text original observational studies published in English or Indonesian between January 2016 and May 2025 that presented PR, odds ratio (OR), or RR data.

Quality Assessment

A total of 34,539 articles were identified in the database search. The criteria were then applied based on the time span of January 2016–May 2025, resulting in 15,532 articles. There are 19,007 literatures that will be applied based on the use of English or Indonesian, and were able to issue 326 articles that did not comply, and 17,840 articles that did not meet the provisions of the type of observational study article and the availability of full text. Next, 841 articles were filtered based on their titles and abstracts, and 803 were excluded. The screening results yielded 38 articles, and exclusion criteria were applied to 24 articles. Eight articles used independent or dependent variables that did not discuss the prognostic factors of dengue severity or SSD, five articles were studies conducted in 2015, and 13 articles did not display PR/OR/RR. Thirteen articles were identified for further analysis.

Data Extraction

Articles were selected based on the inclusion criteria screened by two people and two reviewers. The captured information was then extracted using a table containing specific information such as the year, location, source, study design, population, and research results. After assessment, the eligible articles were included in this review.

Table 1. Keywords used

Keywords	Electronic Database
Factor OR prognostic AND factor AND dengue OR dengue fever OR dengue hemorrhagic fever AND severe OR severity OR degree AND of AND severity OR degree AND of AND severe	Scopus
((((Prognostic factor) AND (severity) OR (severe)) OR (degree of severity)) OR (degree of severe)) AND (dengue)) OR (dengue fever)) OR (dengue hemorrhagic fever)	Pubmed
Prognostic factor AND degree of dengue severity	Google Scholar

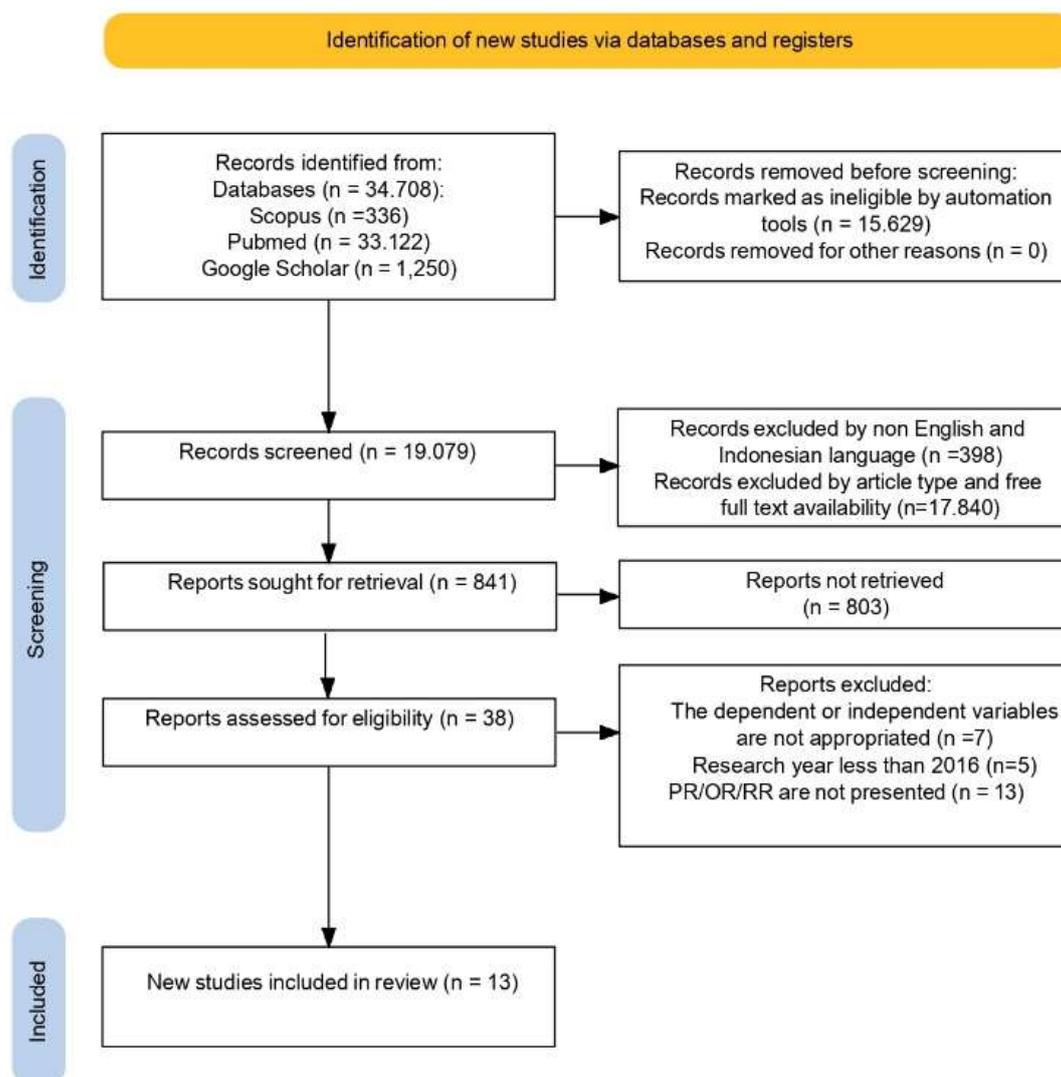


Figure 1. PRISMA Flowchart.

Results

Study Characteristics

Figure 1. shows the stages of data synthesis. Based on the inclusion and exclusion criteria, 13 articles were obtained that met the study of dengue severity and prognostic factors. Among the 13 articles reviewed, eight were cross-sectional, three were case-control, and two were cohort studies. Table 2 shows the characteristics of the studies that discussed the prognostic factors of dengue severity.

Prognostic Factors of Dengue Severity Based on Patient Characteristics

Five prognostic factors based on patient characteristics were identified in relation to severe dengue (SSD) in 11 studies. Sex was evaluated in four studies,

of which only one reported a significant association with disease severity. Nutritional status was assessed in five studies, two of which identified it as a prognostic factor of survival. Age was examined in four studies, with one reporting a significant association. Comorbidities were analyzed in four studies, three of which consistently demonstrated their prognostic value, while one reported no significant association with specific diseases. The duration of health care, reviewed in two studies, was consistently associated with increased severity when it exceeded two days.

Prognostic Factors for Dengue Severity Based on Laboratory Test Results

Four laboratory results were identified as prognostic factors for severe dengue infection. Hematocrit levels were assessed in seven studies, of which two reported a significant association with SSD, while the remaining studies found no such relationship. Thrombocytopenia was examined in seven studies, five of which consistently demonstrated its prognostic significance in HCC patients. Abnormal leukocyte levels were evaluated in six studies, three of which supported their prognostic relevance, while the other three reported no significant association. Hemoglobin levels were analyzed in three studies, all of which indicated that elevated

levels (>14 g/dL) may serve as a prognostic marker for severe dengue.

Summary of Consistent Prognostic Factor

The most consistently identified patient characteristics as prognostic factors across the reviewed articles were abnormal nutritional status (including both undernutrition and overnutrition) and cardiovascular comorbidities, including hypertension, which are associated with increased dengue disease severity. Based on laboratory findings, the most consistent prognostic indicators were hematocrit levels, particularly elevated or high hematocrit values.

Tabel 2. The synthesis of results from the included studies

No	Author (year)	Country	Study Design	Sample	Result
1	Johanus, Michelle, dan Klemens (2019)	Indonesia	Case-control	All child patients (0-17 years) were diagnosed with dengue infection (sample of 129 consisting of 43 cases and 86 controls)	Gender, hemoconcentration, and thrombocytopenia are prognostic factors for severe dengue (SSD).
2	Stephanie, I Wayan, dan I Kadek (2023)	Indonesia	Cross-sectional	All child patients (0-18 years) were diagnosed with dengue infection (sample of 75 people)	Nutritional status is not a prognostic factor for dengue severity.
3	Kadek, et al. (2018)	Indonesia	Cross-sectional	All patients were diagnosed with DHF and SSD (sample of 78 people)	Duration of illness until receiving health care, hemoconcentration, and thrombocytopenia are prognostic factors for dengue severity.
4	Hindra, Rossy, dan Hartono (2018)	Indonesia	Cohort Retrospective	All child patients (0-18 years) were diagnosed with dengue infection (sample of 145 people)	Hemoconcentration and nutritional status are prognostic factors for dengue severity.
5	Anak, dan Romy (2023)	Indonesia	Cross-sectional	All child patients (0-18 years) were diagnosed with dengue infection (sample of 58 people)	Nutritional status and thrombocytopenia are prognostic factors for dengue severity.
6	Erica, I Wayan, dan Made (2021)	Indonesia	Cross-sectional	All child patients (1-10 years) were diagnosed with dengue infection (sample of 58 people)	Leukopenia is a prognostic factor for dengue severity.
7	Irawan, et al. (2017)	Indonesia	Cross-sectional	All patients were diagnosed with dengue infection (sample of 70 people)	Hb levels, thrombocytopenia, and hemoconcentration are prognostic factors for severe dengue.
8	Xing Yu, et al. (2024)	Cina	Case-control Retrospective	All patients were diagnosed with dengue infection (sample of 1,027 people)	Comorbidity is a prognostic factor for dengue severity.
9	Cynthia, et al. (2023)	Paraguay	Cross-sectional	Sample of 145 people	Age, comorbidity, and leukopenia are prognostic factors for dengue severity.

No	Author (year)	Country	Study Design	Sample	Result
10	Mathys, et al. (2023)	Prancis	Prospective Cohort	All patients suspected of dengue infection (sample of 163 people)	Length of time receiving health services and comorbidities are prognostic factors for severe dengue.
11	Jingli, et al. (2023)	Bangladesh	Cross-sectional	All patients were diagnosed with dengue infection (sample of 1,090 people)	Age and leukocyte levels are not prognostic factors for severe dengue.
12	Sarunya, et al. (2020)	Thailand	Cross-sectional Retrospective	All child patients (1-15 years) were diagnosed with dengue infection (sample of 572 people)	Hb levels, hemoconcentration, thrombocytopenia, and leukocyte levels are prognostic factors for severe dengue.
13	Wei Yao, et al. (2022)	Malaysia	Case-control Retrospective	All patients diagnosed with dengue infection (aged 18 years and above) sample of 472 people (118 cases and 354 controls)	Comorbidities, especially hypertension and leukocyte levels, are prognostic factors for severe dengue.

Tabel 3. Summary checklist of prognostic factors reported in previous studies

Number of Article	Patient Characteristics Factors				Length of time to receive health service	Laboratory Test Results			
	Gender	Nutritional status	Age	Comorbidity		Hemato-crit level	Thrombo-cytopenia	Leuko-penia	Hemo-globin level
1	✓	✗	✗	-	-	✓	✓	-	-
2	-	✗	-	-	-	-	-	-	-
3	✗	-	-	-	✓	✓	✓	✗	-
4	✗	✓	✗	-	-	✓	-	✗	-
5	✗	✓	✗	-	-	✓	✓	✗	✗
6	-	-	-	-	-	-	-	✓	-
7	-	-	-	-	-	✓	✓	-	✓
8	-	-	-	✗	-	-	✓	-	-
9	-	-	✓	✓	-	✗	✗	-	-
10	-	-	-	✓	✓	-	-	-	-
11	-	-	✗	-	-	-	-	✗	-
12	-	-	-	-	-	✓	✓	✓	✓
13	-	-	-	✓	-	-	✗	✓	✗

Discussion

Prognostic Factors of Dengue Severity Based on Patient Characteristics

Gender

Although there are more than four studies in the literature that examine sex as a prognostic factor for SSD, this review identified four articles that met our criteria. One study identified sex as a prognostic factor for survival. Based on the studies analyzed, seven articles reported that male patients with dengue infection were more likely to experience severe dengue.¹⁶ in line

with the research findings at the Bunda Aliyah Mother and Child Hospital in Jakarta that men are at risk of experiencing SSD 2.7 times greater than women.¹⁶ The findings are consistent with research in Ponorogo which proves that the male gender statistically significantly increases the risk of SSD by 2.968 times greater.²⁴ Women have more estrogen hormone than men, which can influence the increase in the synthesis of Immunoglobulin G and Immunoglobulin A which are produced through B cell activity and plasma cell

differentiation.²⁵ So women have a stronger ability to bind antibodies to viral antigens.^{26–29} This makes the production of anti-dengue IgG in women faster and more effective.²⁴ In addition, men's habit of being active in public places more often than women increases the risk of greater infection.³⁰ However, research found at Sanglah General Hospital, Denpasar, Cipto Mangunkusumo Hospital, and in Asuncion, Paraguay did not find any significant differences in dengue severity between male and female patients.^{19,20,22} Variations in research findings may result from interactions between gender and other variables, so it is necessary to identify interactions between these variables.

Nutritional Status

Five research articles were identified regarding nutritional status as a prognostic factor for dengue severity (SSD). Two of them mentioned over- or under-nutritional status, which is commonly found in patients with SSD.²² Research at Cipto Mangunkusumo Hospital (RSCM) found that patients with over-nutrition to obesity have a 2.5 times greater risk and those with malnutrition have a 2.3 times greater risk of experiencing severe dengue compared to those with normal nutrition.²² This finding is supported by research by Anak Agung in 2021, which showed that obese dengue patients had a 1.89 times greater risk of developing SSD than those who were not obese.²¹ Patients with overnutrition generally experience increased production of white adipose tissue, which causes increased production of mediators (IL-6, IL-8, and TNF- α), which can increase capillary permeability, triggering severe plasma leakage.³² In addition, good and excess nutritional status has a well-developed immune system, which allows the virus to develop more.³³ Although research in Vietnam concluded that there was no difference in interferon and TNF- α levels between dengue infection and severe dengue (SSD) patients.³⁴ While malnourished people are generally more able to survive dengue virus infection because there is a lack of nutrients such as amino acids that are needed by the virus to reproduce. There will be obstacles in the maturation of T cells and interferon

production also decreases, which causes protection against dengue infection.³³ Different findings in the study by Stephanie et al. in Denpasar and Sultanah Aminah Hospital Malaysia, that the nutritional status of dengue infection sufferers was not significantly related to the occurrence of dengue severity (SSD).^{16,19,35} Some of these things are possible due to the relatively small number of samples compared to other studies. Moreover, the number of severe dengue cases is less than that of general dengue infections; therefore, the distribution between the groups is not proportional.

Age

Four articles discussed age as a prognostic factor for severe dengue (SSD). A study conducted in Asuncion, Paraguay, in 2023 concluded that older age increases the risk of severe dengue (SSD) by 1.07. The 15–49 years age group was identified as having a higher number of deaths and severe dengue cases than children.¹⁸ Adults are more likely to have bleeding that is more difficult to treat than plasma leakage in children. Furthermore, adults tend to have comorbidities that may increase the severity of infection. Plasma leakage in children through fluid replacement is considered more effective in preventing SSD.^{6,18,36} Severe dengue infection (SSD) can occur at any age, but it is generally more common in children.¹⁶ This finding is different from the research at RS Ibu Anak Bunda Aliyah Jakarta, where the severity of dengue tends to affect children aged <9 years, and the risk increases when aged 4–12 years and decreases with age. Although the statistical results do not show a significant relationship.¹⁶ Children have greater permeability and microvascular networks, making the body more susceptible to plasma leakage.³³ Endothelial cells are the target of viral infection because they are responsible for regulating permeability. The more cells that are infected, the more IL-6 and IL-8 production increases, worsening capillary leakage and triggering SSD. Research at RSCM in 2016 and at a hospital in Bangladesh in 2023 showed no significant relationship between age and the occurrence of SSD.^{22,37} The varying

research findings may be due to other factors that contribute to the severity of dengue infection, such as comorbidity status.³⁷

Comorbidity

Four articles discussed comorbidity as a prognostic factor for dengue severity (SSD). The four articles concluded that comorbidities in patients with dengue infection increased the risk of developing SSD. Comorbidities associated with dengue infection include Chronic Obstructive Pulmonary Disease (COPD), metabolic syndrome such as diabetes, cardiovascular disease such as heart and kidney disease, and other conditions such as cancer and autoimmune disease.^{18–20,38} Research conducted in Guangdong, China, found that people with COPD have a 7.29 times greater risk of experiencing SSD than those without COPD comorbidities.³⁸ In line with research at the Reunion University Hospital, France, in 2019, people with comorbid cardiovascular disease had a 2.75 times greater risk of dengue severity compared to people without comorbid cardiovascular disease.²⁰ Similarly, research findings in Malaysia on comorbidities and severity of dengue showed that people with comorbid hypertension had a 2.46 times greater risk of experiencing SSD.¹⁹ People with comorbidities tend to have higher average chymase levels.¹⁸ The release of chymase is regulated by anti-DENV antibodies, including anti-DENV IgG and anti-NS1, which function to enhance or inhibit mast cell degranulation.¹⁸ In patients with SSD who experience hypertension, their body experiences an increase in inflammatory markers (IL-6 and C-reactive protein), where the proinflammatory condition is related to the occurrence of blood vessel wall dysfunction that can trigger SSD manifestations. Bleeding in patients with dengue who experience hypertension and diabetes mellitus is also related to the endothelial glycocalyx layer, namely, through mast cell degranulation of chymase and tryptase, which increases and triggers damage to the blood vessel walls and plasma leakage. This makes chymase generally evaluated as a marker for SSD events.^{18,39–41} Different findings

were found in a study in Malaysia, that comorbidities, especially diabetes mellitus and hyperlipidemia, were not significant as prognostic factors for the occurrence of SSD.¹⁹

Length of time to receive health services

The duration of dengue patients receiving health services was identified in two studies. The length of time patients received health services after the onset of symptoms was influenced by several factors, including the distance between patients' residences and healthcare facilities, limited quality and quantity of healthcare resources that necessitate time-consuming referral systems, and a tendency among the community to delay treatment-seeking. These conditions lead many individuals to attempt self-medication before eventually seeking medical care when their health deteriorates. Patients with dengue infection are at greater risk of developing severe disease if they do not receive medical attention within 1–2 days after the initial onset of symptoms.^{17,20} Research conducted at Sanglah General Hospital, Denpasar, stated that dengue patients who received health services for ≥ 4 days would be at risk of experiencing SSD 7.12 times greater than patients who received treatment for < 4 days.¹⁷ In line with research at the Reunion University Hospital, France, dengue infection sufferers who do not receive health services for > 2 days after the onset of symptoms had a 2.46 times higher risk of SSD compared to those who receive health services for < 2 days.²⁰ This is because on the 3rd–7th day the body of the dengue patient experiences a decrease in fever and plasma leakage for 1–2 days. There is also an increase in capillary permeability, followed by an increase in the hematocrit levels. Therefore, in this condition, the patient is experiencing a critical phase and is susceptible to hypovolemic shock.⁴² Research on the relationship between length of service and SSD is limited. Further research is needed to examine factors such as length of service and dengue severity.

Prognostic Factors for Dengue Severity Based on Laboratory Test Results

Hemoconcentration

Seven articles were identified that examined hemoconcentration as a prognostic factor in patients with CRC. Five studies concluded that hemoconcentration was a prognostic factor, whereas two stated that it was not a prognosis for severe dengue (SSD). Research on hematocrit as a prognostic factor was conducted by Johanus et al. in 2019, who concluded that dengue patients who experienced an increase in hematocrit $\geq 46\%$ were at 3.36 times greater risk of experiencing SSD than patients who did not experience an increase in hematocrit $\geq 46\%$.¹⁶ This finding is in line with Kadek's research in Denpasar, where dengue infection patients who experience hemoconcentration $\geq 20\%$ have a 4.34 times greater risk of experiencing SSD.¹⁷ This is consistent with the research conducted by Hindra et al. at RSCM, Jakarta, which found that 98.1% of SSD patients experienced hemoconcentration $\geq 20\%$.²² This is also consistent with the research conducted at a hospital in Jambi, which showed significant hemoconcentration as a factor in severe dengue.⁴³ This finding is also supported by research results in Thailand, which showed that hemoconcentration $\geq 20\%$ can increase the risk of SSD 13.67 times greater.⁴⁴ An increase in hematocrit $> 10-15\%$ is early evidence of a critical phase. This is because an increase in hematocrit level is a sign of SSD. This can occur due to the patient experiencing dehydration or plasma leakage, which triggers an increase in hematocrit. This condition usually occurs for 1-2 days in the critical phase and when warning signs arise on the 3rd-7th day of illness.⁶ This is different from the results of a study conducted in Paraguay in 2018, which found that hemoconcentration was not a significant prognostic factor.¹⁸ Likewise, in a study conducted at RSUD Sanjiwani Gianyar, hematocrit levels could not be used as a reference because most patients had normal hematocrit levels. This occurs when the handling of fluid replacement for dengue infection patients is good, especially when entering the critical phase,

so that it can prevent the occurrence of severity.⁴⁵

Thrombocytopenia

Seven articles reviewed the relationship between thrombocytopenia and dengue severity (SSD). Five studies concluded that thrombocytopenia was a prognostic factor for SSD, whereas the other two found that thrombocytopenia was not a significant prognostic factor. A study in Thailand on platelet levels as a prognostic factor for SSD concluded that dengue patients with platelet levels $\leq 50,000$ had a 4.48 times greater risk of experiencing dengue severity.⁴⁴ This is in line with research at RSUD Sanjiwani Gianyar, which concluded that platelet levels in patients with severe dengue were low due to platelets that were easily damaged due to reactions to anti-dengue antibodies to form immunity. This finding is supported by research at RS Ibu Anak Aliyah Jakarta, which showed that thrombocytopenia can increase the risk of severe dengue by 13 times greater.¹⁶ This is also supported by findings at a hospital in Jambi that thrombocytopenia contributes to the severity of dengue.⁴³ Platelet levels are a marker of changes in the level of dengue infection. Platelet counts can decrease because the immunity that has been formed is damaged by macrophages. Moreover, the interaction between platelets and neutrophils triggers cell death and activates the platelets. This causes platelets to be destroyed in the spleen and liver so that their levels decrease.^{21,46} This finding is still consistent with research at Sanglah General Hospital, which found thrombocytopenia to be a prognostic factor with the greatest chance, namely 5.01 times greater risk of experiencing SSD.¹⁷ This is not in line with research in Guangdong, China and Asuncion Paraguay, that thrombocytopenia is not significant as a prognostic factor.^{18,38} This is possible because platelet levels are a marker of the course of dengue infection and not a factor in determining severity.⁴⁷

Leukopenia

Six studies discussed the relationship between leukocyte levels and severe dengue fever (SSD). Three studies found that abnormal leukocyte levels were

associated with SSD. However, the other three studies could not prove that leukocyte levels were a prognostic factor in HCC. Leukocyte levels are generally normal in the early stages of infection. A decrease in leukocyte levels ≤ 5000 cells/mm³ (leukopenia) predicts the occurrence of a critical period and plasma leakage.⁶ Research at Wangaya Regional Hospital, Denpasar, concluded that dengue infection patients with leukocyte levels $< 5,000$ cells/mm³ had a 4.29 times greater risk of experiencing SSD.⁴⁸ This finding is in line with research in Asuncion, Paraguay and Thailand. The average leukocyte level of patients with SSD was 2,155/mm³, which increased the incidence of SSD 1.43 times greater in Auncion, Paraguay.¹⁸ Meanwhile, 77.47% of patients with SSD in Thailand also experienced leukopenia with an average leukocyte level of 4,711/mm³.⁴⁴ Leukocyte levels are related to the body's immune response to viral infections. Viral infections promote the production of proinflammatory cytokines that suppress the bone marrow, coupled with the effects of viral infections that inhibit the production and proliferation of leukocytes in the bone marrow. In patients who experience leukopenia, the number of lymphocytes decreases and returns to normal but contains more neutrophils.^{17,49,50} The body's immune response increases neutrophil activation as an initial response to infection and fights the pathogens. While lymphocytes related to the adaptive immune response decrease because they move to the infected area to respond, and apoptosis (damage) can occur.⁵⁰ The peak of leukopenia occurs before the patient's fever decreases and 2-3 days later, it will return to normal.²²

These findings are not in accordance with research conducted at Sanglah General Hospital, Denpasar, which states that abnormal leukocyte levels of ≥ 5000 or < 5000 cells/mm³ are not significantly related to the occurrence of SSD.¹⁷ This is supported by Hindra's research at RSCM Jakarta and RSUD Sanjiwani Gianyar which concluded that leukocyte levels < 5000 cells/mm³ were not significant as a prognostic factor for SSD.^{21,22} This is possible due to the small sample size due to the application of inclusion criteria, so it

is possible that SSD patients with abnormal leukocyte levels were excluded.^{17,21,22}

Elevated Hemoglobin Level

Three articles examined the relationship between hemoglobin levels and severe dengue fever (SSD). One study concluded that hemoglobin levels above the normal limit were a prognostic factor of SSD. In comparison with another study, high hemoglobin levels were not significant prognostic factors. A study in Thailand concluded that dengue patients with hemoglobin levels > 14 g/dL had a 3.58 times greater risk than patients with Hb levels ≤ 14 .⁴⁴ In line with the fact that Hb levels are a prognostic factor, but with different findings, namely that patients with Hb levels < 14 g/dL have a 2.25 times greater risk of experiencing shock.⁴³ The findings differ from research at RSUP Sanjiwani that hemoglobin levels are not included in the prognosis factors for SSD. Although most patients who experience SSD have hemoglobin levels of 12-16 g/dL.²¹ Generally, an increase in hemoglobin occurs after several days of dengue infection and approaching shock. This increase is in line with the increase in hematocrit levels.⁵¹ High hemoglobin levels during shock are associated with increased vascular permeability and the release of liquid plasma from the vessels. Therefore, the volume of liquid blood plasma decreases, and there is an increase in red blood cells. Therefore, an increase in hemoglobin levels is a sign of SSD. However, low Hb levels can occur when bleeding results in loss of red blood cells.^{51,52} The existence of variations in research findings regarding hemoglobin levels as a prognostic factor indicates that increasing hemoglobin levels alone cannot be used as a reference for the occurrence of SSD and requires other laboratory examinations.

Although many studies have identified prognostic factors for severe dengue, inconsistencies remain in the findings related to patient characteristics and the laboratory results. Most of the reviewed studies were limited by small sample sizes, variations in patient characteristics, and differences in the laboratory parameters applied, thereby

restricting the ability to draw strong causal inferences regarding the prognostic factors. In addition, only a few studies have comprehensively examined both patient characteristics and laboratory findings in a single analysis. This highlights the importance of conducting more comprehensive research using multivariate analyses and prospective study designs to validate these associations.

Public Health Implications

The identification of patient characteristics and laboratory findings, particularly abnormal nutritional status, comorbidities such as hypertension and cardiovascular diseases commonly found in adults, as well as the distance and availability of health resources that affect the timeliness of treatment, and hemoglobin levels detected during screening, provide early indications of the potential for severe dengue. Therefore, these factors should be considered early warning signals in efforts to prevent and control dengue cases. Strengthening community-based surveillance and promoting early anticipation among high-risk groups, especially when early symptoms of dengue appear, are crucial public health measures for reducing disease severity and mortality caused by dengue infection.

Conclusion

Prognostic factors for severe dengue (SSD) include male sex, abnormal nutritional status, age (both younger children and older adults), presence of comorbidities, use of health services for more than 1–2 days, hemoconcentration, thrombocytopenia, leukopenia, and elevated hemoglobin levels. Based on patient characteristics, comorbidities, abnormal nutritional status, and receiving health services for more than 1–2 days were the most frequently identified prognostic factors in previous studies. Based on laboratory test results, hemoconcentration and thrombocytopenia were the most prominent prognostic factors in patients with SSD. Therefore, the identification of these factors is essential for the early detection and management of patients with dengue at high risk of SSD.

However, not all studies included in this systematic literature review comprehensively examined the relationship between these variables; therefore, there is still the possibility of influence from other variables that have not been analyzed. Therefore, further studies are needed with a stronger and more comprehensive methodological approach to validate the relationship between these factors as consistent determinants of prognosis in SSD cases.

Ethics Approval

Not Applicable

Availability of data and materials

Not Applicable

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Author Contribution

Dwi Susanti and Arlyn Manggar Sari contributed to the search and selection of the articles. Arlyn Manggar Sari was the main author. Dr. Muh Fauzi and Dr. Yudhy Darmawan provided advice and edited the manuscript. All authors have read and approved this study.

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