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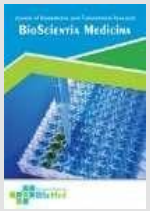

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Re-evaluating WHO Warning Signs in Pediatric Dengue: Abdominal Pain, Not Vomiting, is Associated with Plasma Leakage

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A B S T R A C T

Background: Dengue virus infection represents a significant cause of morbidity and mortality in pediatric populations across endemic regions. The progression to severe disease is characterized by a critical phase of plasma leakage. The World Health Organization (WHO) has established warning signs to aid in clinical triage, yet the independent clinical significance of these signs, particularly abdominal pain and vomiting, requires more precise clarification to optimize patient management. **Methods:** This study was a retrospective, cross-sectional analysis conducted at Wangaya General Hospital in Denpasar, Indonesia. Electronic medical records of 172 pediatric patients hospitalized with a diagnosis of dengue between January and May 2024 were reviewed. The primary outcome was significant plasma leakage, defined as a hematocrit increase of 20% or more from the admission baseline. Bivariate and multivariate logistic regression analyses were performed to determine the association of abdominal pain and vomiting with plasma leakage, controlling for the confounding effects of age, gender, and the day of fever at assessment. **Results:** In the multivariate logistic regression model, the presence of abdominal pain was independently and significantly associated with an increased likelihood of plasma leakage (Adjusted Odds Ratio [aOR]: 2.15, 95% Confidence Interval [CI]: 1.05–4.41; p=0.036). Conversely, the association for vomiting was not statistically significant after adjustment for confounders (aOR: 1.25, 95% CI: 0.65–2.42; p=0.508). The co-occurrence of both symptoms was also identified as a significant indicator of plasma leakage in the adjusted model (aOR: 2.09, 95% CI: 1.01–4.34; p=0.047). **Conclusion:** In this retrospective analysis of a hospitalized pediatric study, abdominal pain emerged as a robust independent correlate of significant plasma leakage, whereas vomiting did not. This differential association suggests that abdominal pain should be weighted more heavily in the clinical assessment of children with dengue as a key indicator of ongoing or impending hemoconcentration. These findings, while limited by their retrospective nature, can help refine clinical risk assessment in resource-constrained settings.

1. Introduction

Dengue virus infection, a mosquito-borne flaviviral illness, has emerged as a paramount global health threat in the 21st century. Transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, its geographic reach has expanded dramatically, placing nearly half of the world's population at risk.[1] The clinical manifestations of dengue are notoriously diverse, spanning a wide spectrum from asymptomatic infection and a mild, self-limiting febrile illness to a severe, life-threatening syndrome.[2] This severe form, historically termed dengue hemorrhagic fever (DHF), is distinguished by its cardinal pathophysiological feature: a transient but profound increase in vascular permeability. This vascular dysfunction precipitates the leakage of plasma from the intravascular to the extravascular space, leading to hemoconcentration, third-space fluid accumulation, and, in the most severe cases, circulatory collapse, known as dengue shock syndrome (DSS).[3]

The global burden of dengue is disproportionately borne by the nations of the Asia-Pacific region. Indonesia, a vast archipelago with a large population, exists in a state of hyperendemicity, where the co-circulation of all four dengue virus serotypes fuels frequent outbreaks and complex clinical challenges.[4] The national health statistics paint a sobering picture of this reality; in the initial five months of 2024, Indonesia reported 88,593 cases of DHF, with 621 resulting fatalities. This highlights the persistent and formidable threat the virus poses. Within this context, the pediatric population, especially school-aged children, demonstrates a particular vulnerability to the severe manifestations of the disease.[5] This heightened risk makes the early detection of clinical deterioration and the judicious management of complications in children a public health and clinical imperative of the highest order.

The cornerstone of effective dengue management is the anticipation and identification of the critical phase of plasma leakage, which typically occurs between the third and seventh day of illness.[6] Timely and appropriate intravenous fluid therapy during this narrow window is crucial for preventing the progression to shock. To aid clinicians in this critical task, the World Health Organization (WHO) has promulgated a set of clinical "warning signs." These signs, which include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, and liver enlargement, are designed to function as a clinical alert system, identifying patients who are at an elevated risk of progressing to severe dengue and who therefore require intensified monitoring, often within a hospital setting.[7]

While the collective utility of this constellation of signs is well-established, a persistent question in clinical practice is whether all warning signs possess equal clinical weight and significance. Abdominal pain and vomiting are among the most frequently observed warning signs in pediatric dengue. Persistent vomiting is a significant clinical issue in its own right, capable of causing dehydration and electrolyte imbalances that complicate patient management. Intense abdominal pain, however, may be a more direct harbinger of the underlying pathophysiology of severe disease, potentially signaling processes such as acute hepatomegaly, the development of ascites, or inflammation of the gallbladder and pancreas.[8] The existing scientific literature presents a somewhat inconsistent and fragmented picture regarding the independent association of these symptoms with severe outcomes. Some studies have demonstrated strong links between both symptoms and plasma leakage, while others have reported weaker or non-significant correlations, particularly for vomiting.[9] This ambiguity can translate into clinical uncertainty, especially in resource-constrained environments where decisions regarding hospitalization, resource allocation, and the intensity of monitoring are critical.

The novelty of this research lies in its focused and rigorous effort to disentangle and quantify the independent clinical associations of two of the most common warning signs—abdominal pain and vomiting—with objectively measured plasma leakage in a contemporary pediatric study from a hyperendemic Indonesian region. While many studies have assessed warning signs as part of a composite group, this investigation sought to provide a more granular, comparative analysis by employing multivariate statistical methods to control for key confounding variables.[10] Therefore, the primary aim of this study was to determine the independent statistical association between the presence of abdominal pain and persistent vomiting with the occurrence of significant plasma leakage in hospitalized pediatric patients with dengue infection. A secondary aim was to investigate the association of their co-occurrence with the same outcome measure, thereby providing a more nuanced understanding to help refine clinical risk stratification and guide more informed clinical decision-making at the bedside.

2. Methods

A retrospective, cross-sectional analytical study was conducted. This design was selected to efficiently

investigate the associations between predefined clinical variables and outcomes using existing clinical data from a specific period, providing a snapshot of real-world clinical practice and patient presentations at a single tertiary care center. The research was performed within the Pediatric Inpatient Ward of Wangaya Regional General Hospital, a major government healthcare facility located in Denpasar, the capital of Bali, Indonesia. This hospital serves a large and diverse urban and suburban population in a province characterized by one of Indonesia's highest dengue incidence rates. The study protocol received formal ethical approval from the Institutional Review Board of Wangaya General Hospital. Given the retrospective nature of the study and the use of fully anonymized data, the ethics committee waived the requirement for individual patient or guardian consent. All patient data were de-identified prior to analysis to ensure strict confidentiality and privacy. The target population for this study included all pediatric patients, defined as individuals aged 0 to 18 years, who were diagnosed with dengue infection and admitted to the study hospital. A consecutive sampling methodology was utilized, wherein every patient meeting the eligibility criteria during the study period, from January 1st, 2024, to May 31st, 2024, was included in the initial study.

The inclusion criterion for the study was any pediatric patient (aged 0–18 years) admitted to Wangaya General Hospital with a clinical diagnosis of probable dengue who presented with one or both of the warning signs of interest: vomiting or abdominal pain. Exclusion criteria were carefully defined to minimize the risk of confounding. Patients were excluded if their electronic medical record contained a documented concomitant diagnosis that could independently account for the symptoms of vomiting or abdominal pain, such as confirmed bacterial gastroenteritis, acute appendicitis, or dyspepsia. Patients who received a blood transfusion during their hospitalization were excluded, as this intervention directly alters hematocrit levels and would make it impossible to accurately assess hemoconcentration resulting from plasma leakage. Lastly, patients receiving medications known to cause significant bone marrow suppression were excluded to avoid confounding effects on hematological parameters.

Data were abstracted from the hospital's electronic medical record (EMR) system by two trained researchers who used a standardized data extraction form created in Microsoft Excel. To ensure the quality and consistency of the data abstraction process, a random sample of 10% of the included records was independently re-abstracted by both researchers. The inter-rater reliability was then calculated using Cohen’s Kappa, which yielded a coefficient greater than 0.90, indicating excellent agreement between the abstractors. The following variables were collected: Demographic Data: Age (in years), gender; Clinical Data: Day of fever at the time of hospital admission, documented presence of vomiting, documented presence of abdominal pain; Laboratory Data: Serial complete blood count results, with specific attention to the hematocrit value recorded at the time of admission (baseline) and the highest hematocrit value recorded during the critical phase of the illness. Operational Definitions: Probable Dengue: A clinical diagnosis based on WHO criteria, defined as a patient residing in or having traveled to a dengue-endemic area presenting with fever accompanied by two or more of the following clinical findings: nausea, vomiting, rash, headache, retro-orbital pain, myalgia, or arthralgia; Vomiting (as a Warning Sign): Documented presence of three or more distinct episodes of vomiting within a 12-hour period, or any vomiting explicitly described in the EMR as "persistent," "profuse," or associated with a documented inability to tolerate oral fluids; Abdominal Pain (as a Warning Sign): Documented presence of abdominal pain that was described in the EMR as "persistent," "severe," "progressively intensifying," or noted by the attending clinician as causing significant distress to the child or interfering with their normal activities; Plasma Leakage (Primary Outcome): The primary outcome variable for this study was the presence of significant plasma leakage, defined as

evidence of hemoconcentration. This was calculated as an increase in the peak hematocrit level of 20% or more from the baseline hematocrit value recorded upon the patient's admission to the hospital. This standardized definition was applied consistently across all patients included in the final analysis.

All collected data were compiled, cleaned, and analyzed using the SPSS Statistics software package, version 23. Descriptive statistics, including frequencies and percentages for categorical variables and means and standard deviations for continuous variables, were used to summarize the demographic and clinical characteristics of the study study. The inferential statistical analysis was conducted in two primary stages. First, bivariate analyses were performed to examine the unadjusted association between each independent variable of interest (abdominal pain, vomiting, and their co-occurrence) and the binary outcome of plasma leakage. The Chi-square (x^2) test was used for this purpose, and Crude Odds Ratios (CORs) with their corresponding 95% Confidence Intervals (CIs) were calculated. Second, to address the potential for confounding and to estimate the independent association of each warning sign with the outcome, a multivariate logistic regression analysis was conducted. A regression model was constructed with the presence or absence of plasma leakage as the dependent variable. The primary independent variables entered into the model were the presence of abdominal pain and the presence of vomiting. To control for their potential confounding effects, the following covariates were also included in the model: patient age (as a continuous variable), gender, and the day of fever at the time of clinical assessment. The results of this multivariate analysis were presented as Adjusted Odds Ratios (aORs) with their corresponding 95% CIs. For all statistical tests, a two-tailed p-value of less than 0.05 was considered to indicate statistical significance.

3. Results

Figure 1 showed a clear and systematic process of patient selection for this retrospective cohort study, meticulously detailing the journey from the initial pool of potential subjects to the final analytical cohort. The selection process began with a total of 270 pediatric patients who were admitted to Wangaya General Hospital between January and May 2024 with a clinical diagnosis of dengue infection and were subsequently assessed for eligibility. This initial number represents the entire population of dengue admissions during the study period from which the sample was drawn. From this initial population, a total of 98 patients were systematically excluded based on predefined criteria designed to ensure the integrity and validity of the study's findings. This exclusion phase was critical for minimizing bias and eliminating potential confounding factors that could have influenced the results. The reasons for exclusion were categorized into two distinct groups. The primary reason for exclusion was the presence of a confounding comorbidity, which accounted for the removal of 68 patients. These were concurrent clinical conditions, such as documented acute gastroenteritis or dyspepsia, that could independently produce symptoms of vomiting or abdominal pain. The exclusion of these patients was essential to ensure that the symptoms being analyzed were attributable to the dengue infection itself and not to another underlying pathology. A further 30 patients were excluded from the study due to incomplete serial hematocrit data in their medical records. As the primary outcome of the study was significant plasma leakage, defined by a specific rise in hematocrit, the absence of these crucial laboratory values made it impossible to accurately assess the outcome, thus necessitating their removal from the final analysis. Following this rigorous and transparent screening process, a final cohort of 172 patients was established. This group, having met all inclusion criteria and having no exclusion criteria, represented the definitive sample population whose data were carried forward for the comprehensive bivariate and multivariate statistical analyses presented in this manuscript.

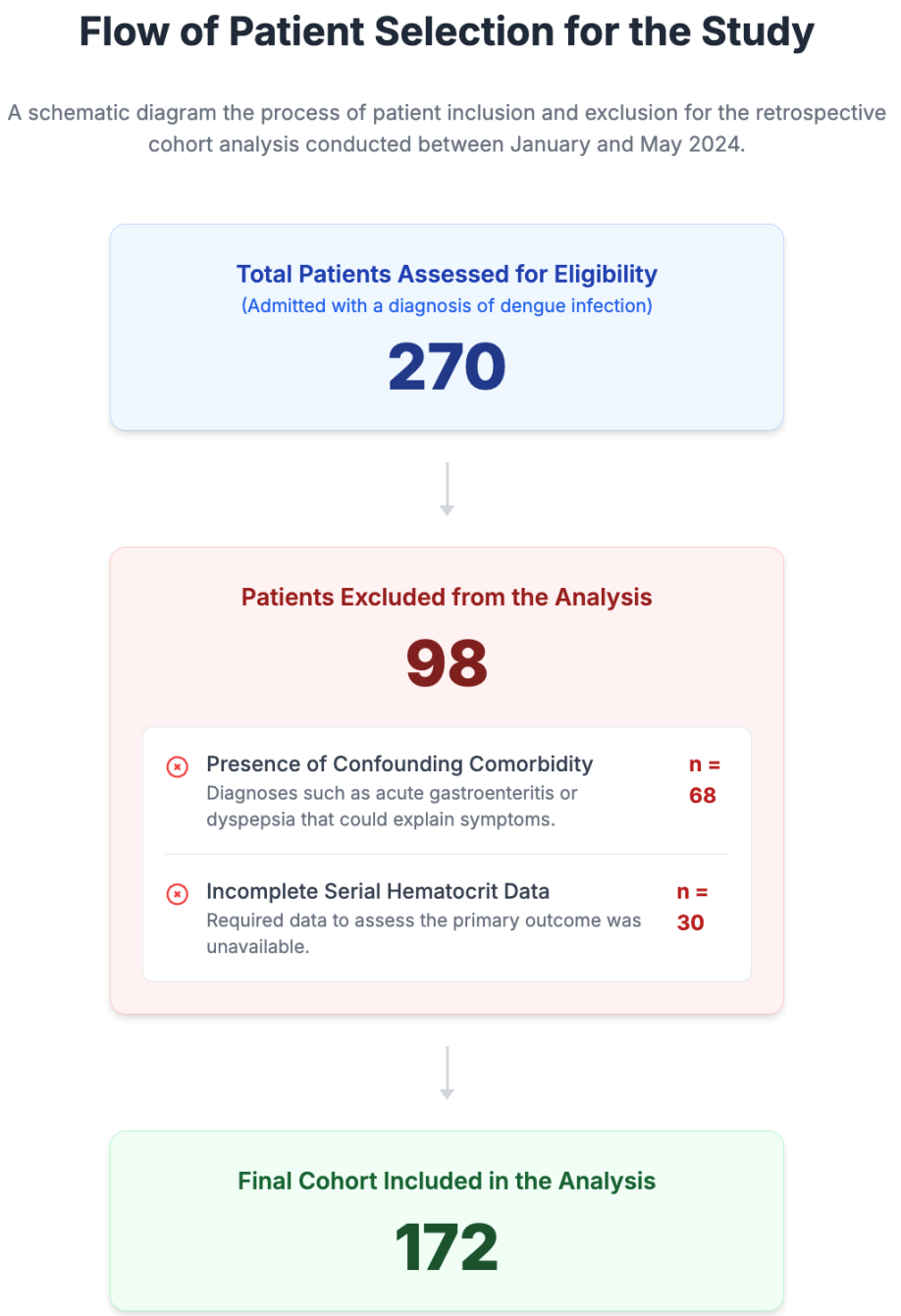

Figure 1. Flow of patient selection for the study.

Figure 2 showed a comprehensive graphical summary of the demographic and clinical characteristics of the final study cohort, which comprised 172 pediatric patients. This visual dashboard provides an immediate and clear understanding of the patient population whose data formed the basis of this investigation. The analysis of the study demographics reveals key insights into the patient profile. The mean age of the children included in the study was 10.8 years, with a standard deviation of 4.1 years, indicating that the patient group was predominantly composed of older children and adolescents. The gender distribution was nearly balanced, with a slight male predominance; 51.2% (n=88) of the patients were male, while 48.8% (n=84) were female. This near-equal distribution suggests

that, within this hospitalized cohort, gender, was not a major differentiating factor in the presentation of dengue with warning signs. A more detailed breakdown of the age group distribution underscores the finding that older children were most affected. The largest single group consisted of adolescents aged 12 to 18 years, who made up more than half of the cohort at 54.1% (n=93). School-aged children between 6 and 12 years constituted the next largest segment, at 31.4% (n=54). Younger children were represented in smaller numbers, with those aged 1 to 6 years accounting for 14.0% (n=24) of the cohort, and infants under one year being the smallest group at just 0.6% (n=1). This distribution highlights that in this particular endemic setting, severe dengue requiring hospitalization and presenting with these specific warning signs is predominantly a condition affecting school-aged children and adolescents. Figure 2 also provides a clear overview of the clinical presentation in terms of the primary warning signs under investigation. Abdominal pain was the most frequently documented warning sign, present in a substantial majority of the patients, at 73.2% (n=126). Vomiting was also a common feature, though less prevalent than abdominal pain, recorded in 59.8% (n=103) of the children. Furthermore, a significant portion of the cohort, 40.1% (n=69), presented with both abdominal pain and vomiting concurrently. This indicates a considerable overlap in the clinical presentation and underscores the importance of assessing the independent and combined significance of these highly prevalent symptoms.

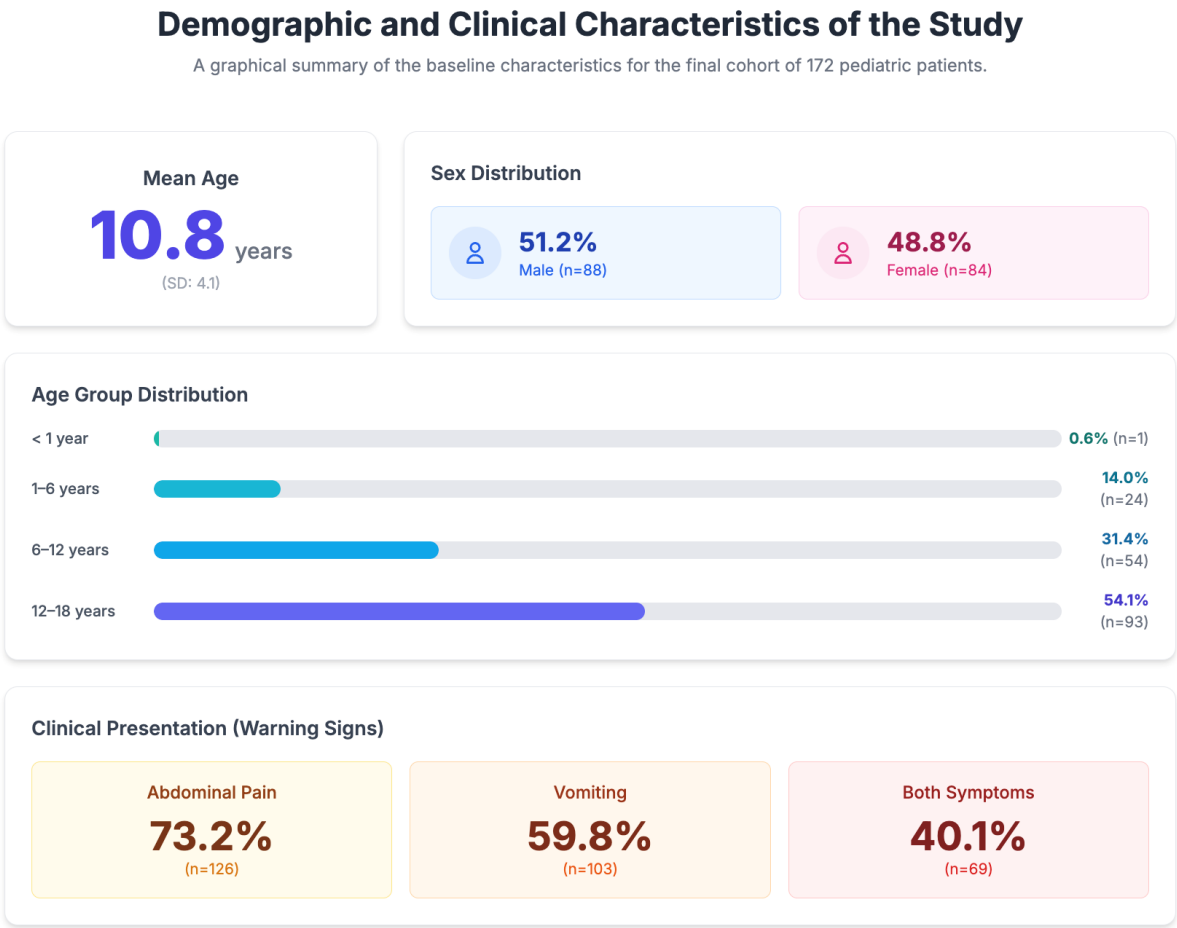

Figure 2. Demographic and clinical characteristics of the study.

Figure 3 showed a detailed comparative analysis of the baseline demographic and clinical characteristics of the 132 patients for whom the primary outcome could be determined, stratified into two distinct groups: those who developed significant plasma leakage (n=84) and those who did not (n=48). This side-by-side visualization provides a powerful and immediate insight into the factors that differentiate these two clinical pathways. The most striking and statistically significant finding presented in the figure is the difference in the prevalence of abdominal pain between the two groups. A substantial majority, 81.0%, of the children who experienced plasma leakage reported abdominal pain as a warning sign. This is in stark contrast to the group without plasma leakage, where only 58.3% of patients had the same symptom. The statistical analysis confirms the importance of this observation, yielding a p-value of 0.007, which indicates a highly significant association. This finding strongly suggests that, within this cohort, the presence of abdominal pain was a key clinical feature distinguishing patients who would go on to develop significant hemoconcentration. In contrast, the data for vomiting tells a different story. While the prevalence of vomiting was slightly higher in the group with plasma leakage (65.5%) compared to the group without (56.3%), this difference was not statistically significant, with a p-value of 0.288. This lack of a significant association highlights a critical divergence from abdominal pain, suggesting that vomiting, while a common symptom, was not a primary differentiating factor between the two outcome groups in this unadjusted analysis. Figure 3 further reveals that the demographic characteristics of the two groups were remarkably similar. The mean age of the patients with plasma leakage was 11.1 years, which was not significantly different from the 10.4 years in the group without leakage (p=0.381). Likewise, the gender distribution was nearly identical in both groups, with males constituting 52.4% of the leakage group and 54.2% of the non-leakage group (p=0.855). The timing of the illness, as measured by the mean day of fever at assessment, was also comparable, at 4.8 days for the leakage group versus 4.5 days for the non-leakage group (p=0.198). In essence, the narrative told by this figure is one of distinction amidst similarity. While the two groups were largely indistinguishable based on their age, gender, or the day of illness, they were clearly and significantly separated by the presence of abdominal pain. This singles out abdominal pain as the most important clinical correlate of plasma leakage in this initial bivariate comparison, laying a strong foundation for the subsequent multivariate analysis designed to confirm its independent significance.

Figure 4 showed a detailed graphical and statistical summary of the bivariate analysis, presenting the initial, unadjusted associations between the key clinical warning signs and the primary outcome of plasma leakage. This visual representation effectively breaks down the crude odds ratios, offering a first look at the strength of the relationship between each symptom and the development of significant hemoconcentration. The most compelling and statistically robust finding presented in the figure 4 pertains to the presence of abdominal pain. The analysis revealed a Crude Odds Ratio (COR) of 2.93, a powerful indicator suggesting that, in this initial assessment, children presenting with abdominal pain had nearly three times the odds of having significant plasma leakage compared to those without the symptom. The strength of this association is further substantiated by the 95% Confidence Interval (CI), which ranged from 1.35 to 6.35. Critically, this entire interval lies well above the value of 1.0, indicating that the possibility of there being no effect is statistically excluded. The highly significant p-value of 0.007 provides definitive statistical support for this strong positive association. The accompanying forest plot visualization makes this finding intuitive; the point estimate for the odds ratio is positioned far to the right of the "no effect" line, and the entire confidence interval bar is also clearly situated in the territory of increased risk. In stark contrast, the analysis for vomiting painted a much different and less conclusive clinical picture. The Crude Odds Ratio for vomiting

was 1.47, suggesting a potential 47% increase in the odds of plasma leakage. However, this finding lacked statistical certainty. The 95% Confidence Interval for this odds ratio was wide, ranging from 0.74 to 2.93. The crucial aspect of this interval is that it crosses the value of 1.0, meaning that the data is consistent with both a potential increase in risk and a potential decrease in risk, and therefore, no definitive conclusion of an association can be drawn. The p-value of 0.288 confirms this lack of statistical significance. The forest plot for vomiting visually captures this ambiguity perfectly, showing the confidence interval bar straddling the vertical "no effect" line, a classic representation of a non-significant result. Finally, the figure 4 examined the clinical utility of identifying patients who presented with both symptoms concurrently. This analysis yielded a Crude Odds Ratio of 2.25, indicating that children with both abdominal pain and vomiting had more than double the odds of having plasma leakage compared to those with only one or neither symptom. The 95% Confidence Interval for this combined presentation was 1.09 to 4.63. As this interval is entirely above 1.0, and supported by a statistically significant p-value of 0.027, this finding suggests that the co-occurrence of these two signs is a significant indicator of increased risk. This figure 4 provides a clear narrative from the initial unadjusted analysis. It effectively differentiates between the warning signs, highlighting abdominal pain as a potent and highly significant clinical correlate of plasma leakage. At the same time, it casts considerable doubt on the independent associative strength of vomiting. This initial analysis powerfully establishes the rationale for the subsequent, more sophisticated multivariate analysis, which is necessary to confirm if these associations hold true after accounting for other potentially confounding factors.

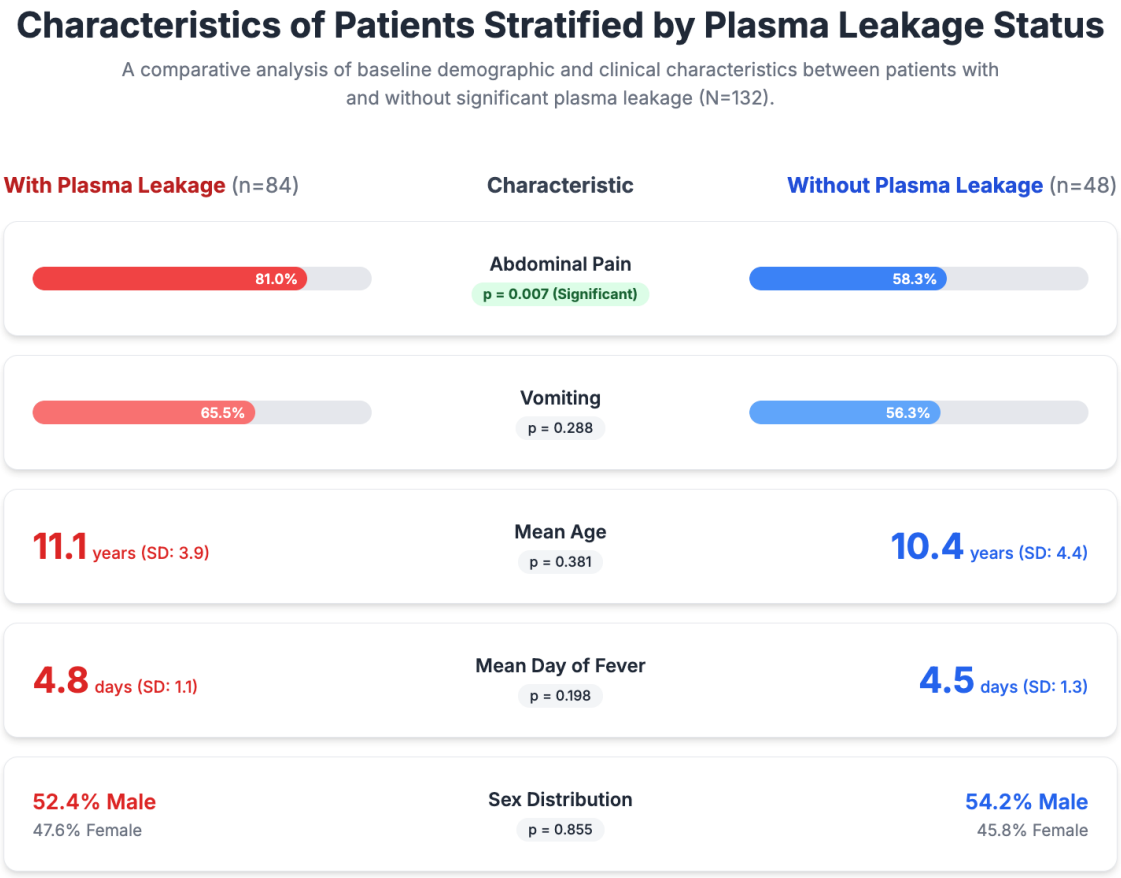

Figure 3. Characteristics of patients stratified by plasma leakage status.

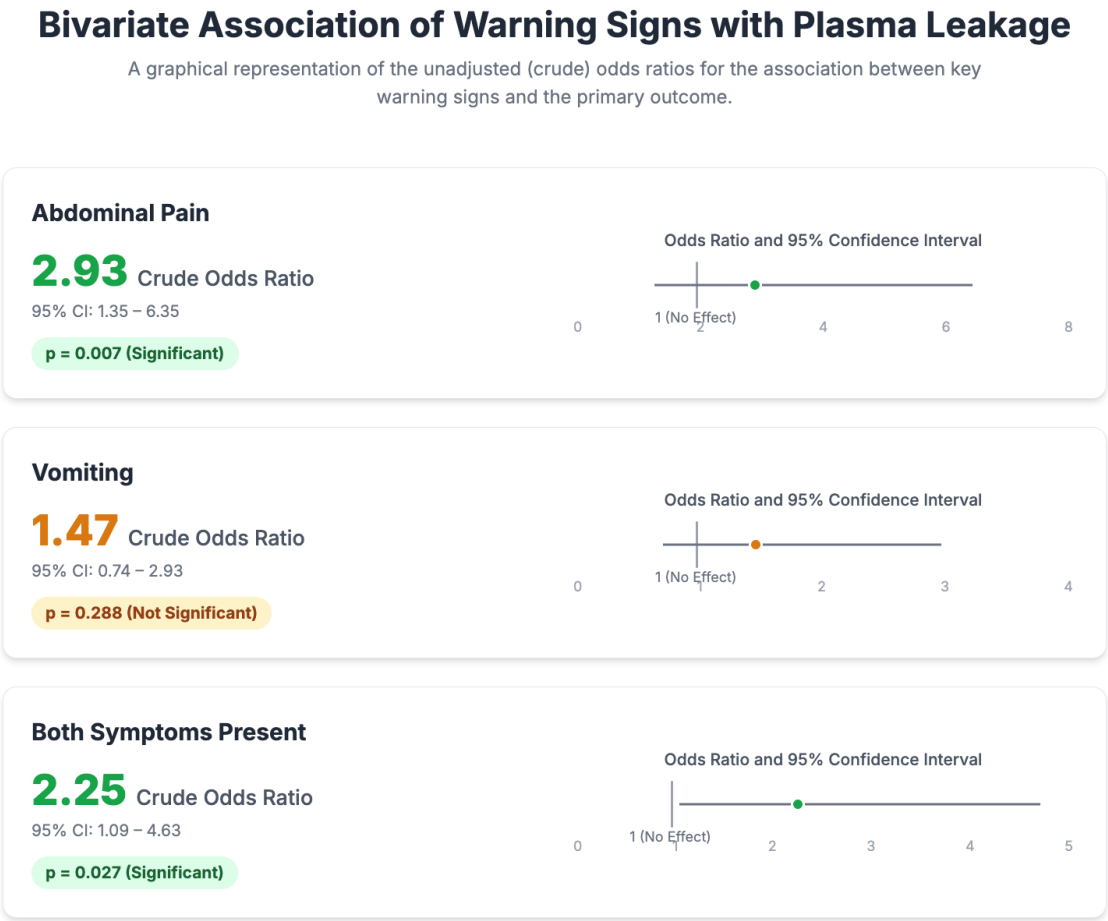

Figure 4. Bivariate association of warning signs with plasma leakage.

Figure 5 showed the definitive results of the multivariate logistic regression analysis, representing the analytical core of this investigation. This figure provides a graphical and statistical depiction of the final, adjusted odds ratios (aORs) for the association between the primary warning signs and the presence of significant plasma leakage. By statistically controlling for the potential confounding effects of patient age, gender, and the day of fever at assessment, this analysis offers a more accurate and nuanced estimate of the true, independent relationship of each clinical sign with the study's primary outcome. The most clinically and statistically compelling finding presented in the figure is the independent association of abdominal pain with plasma leakage. After accounting for all other variables in the model, the analysis yielded an Adjusted Odds Ratio of 2.15. In narrative terms, this means that even when comparing children of the same age, gender, and at the same stage of their febrile illness, those who presented with abdominal pain had more than double the odds of having significant plasma leakage compared to those who did not. The statistical robustness of this finding is confirmed by the 95% Confidence Interval, which ranged from 1.05 to 4.41. The fact that the entire interval lies above the null value of 1.0 demonstrates that the association is not due to chance. The p-value of 0.036 falls comfortably below the conventional threshold for statistical significance, providing strong evidence to

reject the null hypothesis. The forest plot visualization provides an immediate and intuitive confirmation of this result; the point estimate and the entire confidence interval bar are positioned clearly to the right of the vertical "no effect" line, signifying a clear and significant increase in risk. This powerful result establishes abdominal pain as a robust and independent clinical correlate of plasma leakage in this patient cohort. In striking contrast, the analysis for vomiting tells a completely different clinical story. After adjusting for the same confounding variables, the Adjusted Odds Ratio for vomiting was 1.25. While this suggests a potential 25% increase in the odds of leakage, the finding lacked any statistical significance, with a p-value of 0.508. The reason for this non-significance is clearly illustrated by the 95% Confidence Interval, which spanned from 0.65 to 2.42. Because this interval contains values both below 1.0 (suggesting a potential protective effect) and above 1.0 (suggesting a potential risk), the data cannot distinguish the true effect from chance. The forest plot for vomiting visually captures this statistical uncertainty, with the confidence interval bar clearly intersecting the vertical "no effect" line. This demonstrates that, after controlling for other factors, vomiting, as an isolated symptom, was not independently associated with the presence of plasma leakage in this study. The figure 5 also presents the analysis for patients who presented with both symptoms concurrently. This analysis yielded an Adjusted Odds Ratio of 2.09, which was also statistically significant with a p-value of 0.047. This indicates that the presence of both abdominal pain and vomiting together more than doubled the odds of a child having plasma leakage, even after adjusting for age, gender, and day of illness. The 95% Confidence Interval for this combined presentation was 1.01 to 4.34. The fact that the lower bound of this interval is just barely above 1.0 suggests that while the association is statistically significant, it is a borderline finding. This implies that the combination of symptoms is indeed a significant indicator of risk, likely driven by the powerful effect of abdominal pain, but its additional contribution beyond abdominal pain alone may be modest. In synthesizing these results, the multivariate analysis provides a clear and compelling clinical narrative. It refines the initial findings from the bivariate analysis by isolating the independent contribution of each warning sign. The strong association of abdominal pain with plasma leakage was not explained away by other factors; it remained a potent and significant indicator. Conversely, the weak and non-significant association initially seen with vomiting was confirmed in the adjusted model, suggesting it is not a primary, independent correlate of the specific outcome of hemoconcentration. This rigorous analysis elevates the study's conclusions, providing stronger evidence that in the clinical assessment of a child with dengue, the development of abdominal pain should be considered a more ominous and significant sign than the presence of vomiting alone.

4. Discussion

This retrospective investigation was designed to critically dissect the clinical associations of two cardinal WHO warning signs—abdominal pain and vomiting—with the pivotal event of plasma leakage in a hospitalized study of Indonesian children with dengue.[11] The principal and most compelling finding of this study, substantiated by a rigorous multivariate analysis, is the significant and independent association between the presence of abdominal pain and the occurrence of significant plasma leakage. In contrast, vomiting, while a common and clinically important symptom, did not emerge as a statistically significant independent correlate of hemoconcentration in this specific patient population.[12] This differential finding provides a more refined, evidence-based perspective on the clinical utility of these signs, suggesting they should not be weighted equally in the critical process of risk assessment. The robust association between abdominal pain and plasma leakage, which persisted after adjusting for key confounders (Adjusted Odds Ratio: 2.15), is a finding of profound clinical relevance.

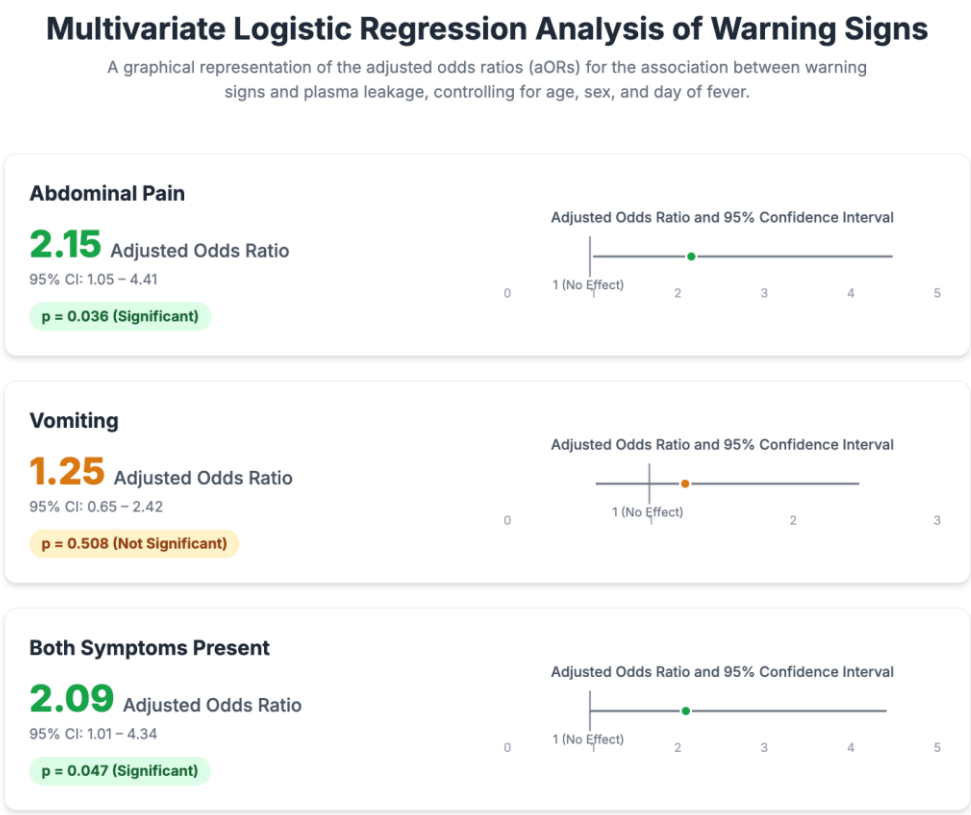

Figure 5. Multivariate logistic regression analysis of warning signs.

It strongly supports the hypothesis that abdominal pain in dengue is far from being a non-specific, generalized complaint. Instead, it should be viewed as a direct or indirect manifestation of the core pathophysiological processes that define severe dengue. The genesis of abdominal pain in these patients is multifactorial, arising from a cascade of events initiated by the systemic increase in vascular permeability. One of the primary mechanisms is the development of acute hepatomegaly. The dengue virus can cause direct hepatocellular injury and inflammation, leading to liver swelling.[13] This rapid enlargement stretches the liver's fibrous outer layer, Glisson's capsule, which is densely innervated with pain receptors, resulting in a constant, dull, or aching pain in the right upper quadrant.

Furthermore, the hallmark of severe dengue is the leakage of plasma into extravascular spaces. When this occurs within the abdomen, it leads to the accumulation of free fluid, or ascites. This fluid accumulation increases intra-abdominal pressure and can cause peritoneal irritation, contributing to generalized abdominal pain and tenderness. The vascular leakage process is not confined to the peritoneum; it also affects the viscera.[14] Dengue-associated acalculous cholecystitis, an inflammation of the gallbladder in the absence of gallstones, is a well-documented phenomenon. It is thought to result from direct viral infection of the gallbladder epithelium and edema of the gallbladder wall secondary to localized plasma leakage, causing significant pain. Similarly, pancreatitis, though less common, can also occur and contribute to severe epigastric pain. Therefore, the clinical sign of abdominal pain serves as a powerful integrated signal of these underlying events—hepatitis, ascites, and visceral inflammation—all of which are direct consequences of the vascular leakage that this study aimed to measure via hemoconcentration. The significant statistical link found in our analysis provides a strong rationale for

elevating abdominal pain to a high-priority warning sign that should trigger immediate and thorough assessment for other signs of impending shock.[15]

Perhaps the most striking and thought-provoking finding of this study is the lack of a statistically significant independent association between vomiting and plasma leakage. This outcome is particularly noteworthy because "persistent vomiting" is explicitly enshrined as a key warning sign in both national and international dengue management guidelines.[16] This finding necessitates a careful and nuanced interpretation. It does not imply that vomiting is a benign or unimportant symptom in dengue; its role in causing dehydration, electrolyte disturbances, and poor oral intake is undisputed and requires diligent clinical management.[16] However, our data suggest that as an isolated sign, it may be a less specific indicator of the specific pathophysiological event of significant plasma leakage compared to abdominal pain.

Several factors may explain this observation. First, the etiology of vomiting in dengue is remarkably diverse. It can be a direct result of viral gastritis, a response to developing metabolic acidosis, a centrally mediated effect on the chemoreceptor trigger zone in the brainstem, or simply a consequence of the high fever and general malaise. Because not all of these pathways are directly and temporally linked to the peak increase in vascular permeability, the symptom of vomiting may be a less specific marker for the critical event of hemoconcentration. Second, as our data indicate, the onset of vomiting often occurs earlier in the course of the illness than the peak of plasma leakage.[17] This temporal disconnect could dilute its statistical association when measured in a cross-sectional manner. A symptom that occurs on day three of fever may be less strongly correlated with a peak hematocrit rise that occurs on day five. Finally, it is crucial to acknowledge that this non-significant finding could be influenced by the inherent limitations of a retrospective study. The potential for inconsistent documentation and misclassification of "persistent vomiting" based on chart review is substantial and could have biased the result towards the null, masking a true but potentially weaker association.

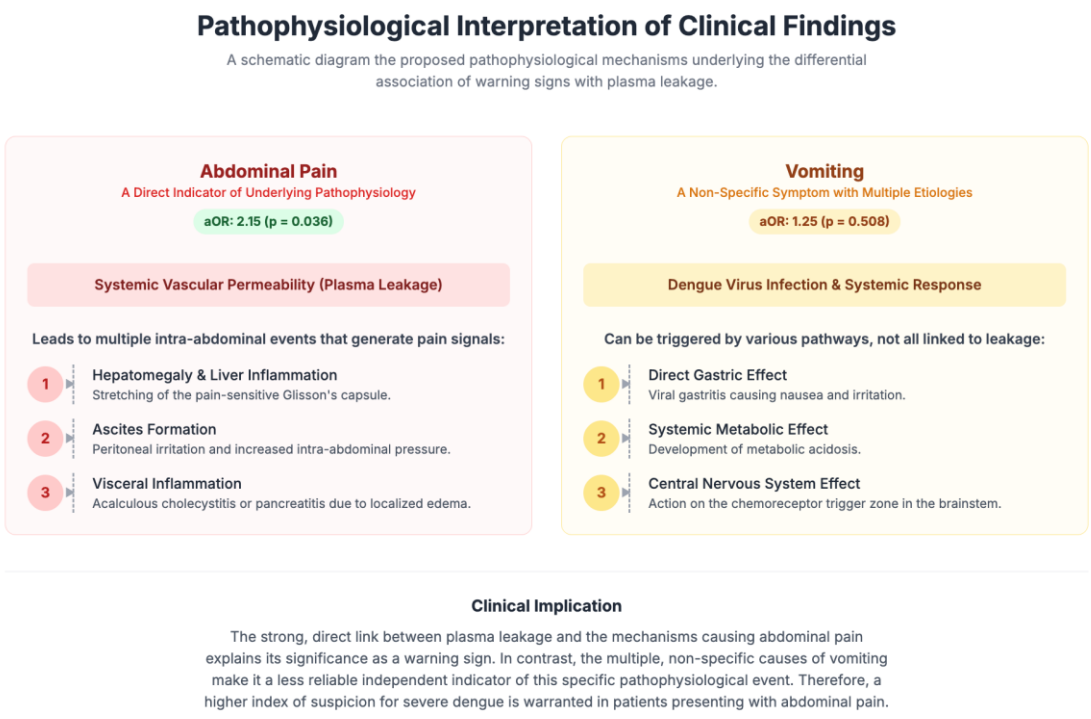

Figure 6. Pathophysiology interpretation of clinical findings.

Figure 6 showed a compelling schematic diagram that provides a clear and insightful pathophysiological interpretation of the study's central findings. The figure elegantly contrasts the clinical warning signs of abdominal pain and vomiting, visually explaining why one serves as a potent, direct indicator of severe disease while the other is a more generalized, non-specific symptom. It effectively bridges the statistical results of the study with the underlying biological mechanisms of dengue virus infection. On the left side of the figure 6, dedicated to Abdominal Pain, the diagram immediately establishes it as "A Direct Indicator of Underlying Pathophysiology," reinforcing this with the statistically significant adjusted odds ratio of 2.15. The core premise illustrated is that the symptom of abdominal pain is not an arbitrary event but is directly and mechanistically linked to the cardinal feature of severe dengue: Systemic Vascular Permeability, or plasma leakage. The figure then delineates three distinct but concurrent pathways through which this single pathophysiological event generates pain signals within the abdomen. The first pathway identified is Hepatomegaly and Liver Inflammation. The diagram explains that systemic plasma leakage, combined with direct viral injury to liver cells, causes the liver to swell. This enlargement stretches the fibrous outer layer of the liver, known as Glisson's capsule, which is rich in pain-sensitive nerve endings. The stretching of this capsule is a well-established cause of the persistent, dull, aching pain in the right upper quadrant frequently reported by patients with severe dengue. The second pathway is Ascites Formation. As vascular permeability increases, plasma fluid escapes from the blood vessels and accumulates in the peritoneal cavity. This accumulation of fluid, known as ascites, leads to increased intra-abdominal pressure and causes irritation of the peritoneum, the sensitive lining of the abdominal cavity. This process results in a more generalized and diffuse abdominal pain and tenderness. The third pathway highlighted is Visceral Inflammation. The localized edema resulting from plasma leakage can affect other intra-abdominal organs. The figure specifically mentions acalculous cholecystitis (inflammation of the gallbladder wall) and pancreatitis (inflammation of the pancreas). Both of these conditions are known complications of severe dengue and are potent sources of intense abdominal pain. In essence, the left panel of the figure masterfully illustrates that abdominal pain acts as a powerful and integrated clinical signal. It is not just a symptom but a direct report from the body that the critical, underlying processes of plasma leakage—liver swelling, fluid accumulation, and visceral edema—are actively occurring. This direct mechanistic link provides a clear and logical explanation for its strong and statistically significant association with hemoconcentration. Conversely, the right side of the figure, dedicated to Vomiting, presents a starkly different narrative. It is appropriately labeled as "A Non-Specific Symptom with Multiple Etiologies," a conclusion supported by its non-significant adjusted odds ratio of 1.25. The diagram proposes that vomiting originates from the more general state of "Dengue Virus Infection & Systemic Response," rather than being a specific consequence of plasma leakage. It then outlines three separate and divergent etiological pathways that can trigger vomiting, not all of which are linked to the severity of vascular leakage. The first pathway is a Direct Gastric Effect, suggesting that the dengue virus itself can cause a form of viral gastritis. This direct irritation of the stomach lining can induce nausea and vomiting, often early in the course of the illness, independent of whether significant plasma leakage will eventually occur. The second pathway is a systemic metabolic effect. The profound systemic inflammatory response characteristic of dengue can lead to the development of metabolic acidosis. Acidosis is a powerful stimulus for the body's chemoreceptors and is a well-known cause of nausea and vomiting. This pathway is related to the overall severity of the systemic illness but not necessarily to the specific degree of plasma leakage at any given moment. The third pathway described is a Central Nervous System Effect. The virus or the inflammatory cytokines it triggers can act directly on the chemoreceptor trigger

zone in the brainstem, a region that controls the vomiting reflex. This central stimulation can induce vomiting without any direct involvement of the gastrointestinal tract or significant plasma leakage. The clinical implication, as summarized at the bottom of Figure 6, is clear and logically derived from this comparison. The strong, direct, and multi-faceted mechanistic link between the event of plasma leakage and the various causes of abdominal pain provides a robust explanation for its significance as a warning sign. In contrast, the multiple, diverse, and non-specific pathways that can lead to vomiting make it a much less reliable independent indicator of the specific pathophysiological event of plasma leakage. Therefore, the figure 6 compellingly concludes that a higher index of suspicion for severe dengue is warranted in patients presenting with abdominal pain, as this symptom is more likely to be a true signal of the underlying vascular catastrophe that defines severe disease.

The analysis of the co-occurrence of both symptoms revealed that the combination of abdominal pain and vomiting was a significant indicator of plasma leakage, even after adjusting for confounders.[18] This suggests a potential additive or synergistic effect. From a pathophysiological standpoint, a child presenting with both symptoms may be experiencing a more intense and widespread systemic inflammatory response. The presence of abdominal pain signals significant localized vascular leakage and organ involvement, while concurrent persistent vomiting may reflect a greater degree of systemic metabolic derangement or inflammatory cytokine storm.[19] Therefore, the clinician encountering a child with this dual presentation should recognize it as a signal of a more advanced disease state, conferring a very high probability of significant vascular permeability and warranting the most intensive level of monitoring and care. While this study's primary focus is on the clinical associations, the discussion of the study's methodological strengths and limitations is pertinent for context. The use of multivariate analysis adds a layer of rigor, and the focus on a well-defined pediatric population in a hyperendemic area provides valuable regional data. However, the retrospective design inherently limits the ability to establish causality and is subject to information and selection biases that have been considered in the interpretation of these results.[20]

5. Conclusion

This investigation into the clinical significance of key WHO warning signs in pediatric dengue provides compelling, statistically-adjusted evidence that not all signs carry equal weight in their association with plasma leakage. The central conclusion of this study is that abdominal pain is a strong and independent correlate of significant hemoconcentration in hospitalized children with dengue. In contrast, vomiting, while a frequent and clinically relevant symptom for patient hydration and comfort, did not demonstrate a significant independent association with this critical marker of disease severity in our study. This differential finding is of direct clinical importance. It suggests that the presence of new or worsening abdominal pain should be interpreted as a more specific and urgent alarm bell for ongoing or impending plasma leakage than vomiting alone. This symptom likely reflects direct pathophysiological consequences of vascular leakage, such as hepatomegaly and ascites, making it a more reliable indicator for the clinician at the bedside. Therefore, its documentation should trigger a heightened level of vigilance, including more frequent monitoring of vital signs and serial hematocrit levels, to preempt the development of hypovolemic shock. While all WHO warning signs are valuable, this research supports a more nuanced, risk-stratified approach, empowering clinicians in resource-limited settings to better allocate their attention and resources to the children at highest risk. Prospective, multi-center studies are warranted to validate these findings and formally integrate this weighted approach into future clinical management guidelines.

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