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Impact of Nutritional Status on the Severity of Dengue Infection Among Pediatric Patients in Southern Thailand

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Background: Given the lack of specific antiviral drugs and effective vaccine for dengue infection, factors such as host nutritional status that may alter disease progression require investigation. This study examined the relationship between baseline nutritional status and severity of dengue infection in pediatric patients.

Methods: Data from dengue patients 1–14 years of age treated at four hospitals in southern Thailand (2017–2018) were reviewed. Dengue infection was classified as dengue fever, dengue hemorrhagic fever and dengue shock syndrome. Children's nutritional status was assessed based on international and national growth charts. Binary logistic regression was used to identify factors associated with dengue severity and malnutrition.

Results: Overall, 248, 281 and 43 patients had dengue fever, dengue hemorrhagic fever and dengue shock syndrome, respectively. Overweight was associated with increased risk of dengue severity [odds ratio (OR) = 1.76, 95% confidence interval (CI): 1.13–2.75, P = 0.012; OR = 1.84, 95% CI: 1.09–3.09, P = 0.022, per international and national growth criteria, respectively). Stunting was associated with decreased risk of dengue severity (OR = 0.54, 95% CI: 0.33–0.88, P = 0.013; OR = 0.61, 95% CI: 0.39–0.95, P = 0.030, per international and national growth criteria, respectively). Being overweight was significantly and positively associated with levels of hemoglobin >14 g/dL, hematocrit >42%, hemoconcentration ≥20% and platelet count ≤50,000/mm^3, whereas being stunted was significantly and negatively associated with levels of hemoglobin >14 g/dL and hematocrit >42%.

Conclusions: These findings support a hypothesis that malnutrition might influence the severity of dengue infection through host immune response. Overweight children with dengue infections should be closely observed for early signs of severe dengue infection.

Key Words: nutritional status, dengue, severity, pediatric patients, overweight

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Dengue infection is a common mosquito-borne viral disease, with an estimated annual case count of 60 million and 10,000 associated deaths worldwide.[1] People who contract the infection usually experience a self-limiting febrile illness or dengue fever (DF), which rarely progresses to a severe form, such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).[2,3] However, the highest dengue incidence and associated mortality have been reported in Southeast Asia,[1] where a severe form of dengue infection is among the leading causes of death among children.[4] In Thailand, DHF and DSS are more common in patients 5–14 years of age than in those who were 15 years or older.[5,6] In fact, 70% of associated deaths have been reported in patients younger than 15 years.[5] Although a licensed vaccine against the dengue virus (DENV) is currently available in Thailand,[7] its safety and efficacy by age and dengue serostatus are variable. Therefore, the vaccine is not recommended for use in children under 9 years of age or dengue seronegative individuals not previously infected with dengue.[8] Additionally, no specific treatment exists for DENV infection.[9]

In patients with severe dengue infection, early diagnosis and proper supportive care can reduce the risk of mortality.[10] Identifying risk factors associated with severe forms of dengue infection is crucial to accurately select patients most likely to benefit from appropriate early interventions. Previous studies have explored the impact of malnutrition, defined as a disorder of nutritional status, including undernutrition (wasting, stunting and underweight) and overnutrition (overweight and obesity),[11] on dengue severity, but findings have been inconsistent.[12–19] Accumulating evidence suggests that excess body weight increases the risk of more severe form of dengue infection,[12–14] possibly through activation of an inflammation pathway. In addition, stunting[15] and being underweight[15,16] have been reported as protective factors, possibly due to the suppressed immune response present in undernourished children. Other studies have suggested that nutritional status was unlikely to significantly affect the severity of dengue infection.[17–19] Although this relationship remains unclear, height and weight data are collected as part of routine practice in general hospitals, to easily assess nutritional status of individuals. Thus, nutritional status derived from these anthropometric measures could be examined as a predictor of dengue severity.

The anthropometric measurements are commonly used for nutritional assessment in children to classify nutritional status into four categories: normal, wasting, stunting and overweight.[12–19] However, children can experience concurrent stunting and wasting.[20] Similarly, they can also experience stunting and overweight.[20] These conditions are associated with greater susceptibility to mortality and chronic diseases,[21,22] and they are now seen as a specific problem requiring special attention. To the best of our knowledge, this is the first study to investigate the effect of these conditions on the severity of dengue infection in children.

Thailand is considered a DENV hyperendemic region,[23] with cyclical epidemics occurring every 1 to 2 years.[6] Although DENV is present across 77 provinces of Thailand, in 2018, Nakhon Si Thammarat province in southern Thailand was reported to have the third-highest incidence rate out of all provinces, with 254.79 cases per 100,000 person-year.[6] In addition, childhood obesity is a major public health problem in Thailand,[24] with obesity prevalence

among Thai children 3–18 years of age estimated at 7.6%.[25] Given the suspected link between obesity and increased inflammatory response, compared with non-obese children, children with obesity might be at higher risk of developing a severe form of dengue infection. Thus, this study examined the influence of baseline nutritional status on the risk of developing a severe form of dengue infection in pediatric patients under the age of 15 years. The presented findings might improve our understanding of the effect of nutritional status on outcomes associated with dengue infection in pediatric populations, improving our ability to predict the likely severity of dengue disease.

MATERIALS AND METHODS

Study Design and Population

A retrospective, cross-sectional analytic study was conducted based on medical records acquired from four hospitals [a tertiary care hospital (Maharaj Nakhon Si Thammarat Hospital), and 3 secondary care hospitals (Thungsong Hospital, Sichon Hospital and Thasala Hospital in Nakhon Si Thammarat Province) in southern Thailand]. Medical records of children 1–14 years of age admitted with the diagnosis of DENV infection between January 2017 and December 2018 were retrieved from the hospital database, using the following International Classification of Disease 10th edition codes: A90 (DF), A91 (DHF) and A910 (DHF with shock).[26] The sample size was determined for a finite population using a previously described formula[27]:

$$n = \frac{Np(1-p)z^2_{1-\alpha/2}}{d^2(N-1) + p(1-p)z^2_{1-\alpha/2}}$$

Based on this calculation, the minimum required sample size (n) was 553 patients, given a population (N) of 943,[28] expected prevalence of pediatric dengue (p) of 3.6%,[29] acceptable margin of error (d) of 1%, and confidence level of 95%. After a 5% adjustment to account for expected incomplete medical records, a final sample size of 580 participants was obtained. In each hospital, pediatric dengue patients were randomly selected with probabilities proportional to size. Data on patient characteristics, signs and symptoms, physical examination results and routine laboratory profiles at admission and during hospitalization were recorded in the case record form. The case record form was approved by a pediatrician, an expert nurse in pediatrics, and a nursing lecturer. Data collection was conducted by three public health technical officers with at least 5 years of working experience, who were trained and acquainted with the procedure protocol. Subsequently, all dengue cases were reviewed and confirmed by the researchers. Inclusion criteria were children 1–14 years of age who met the clinical and hematologic criteria for dengue infection according to the criteria established by the World Health Organization (WHO) 1997 guidelines.[2] Patients with underlying hematologic diseases, congenital heart disease, bronchial asthma and other simultaneous infections or misdiagnosis of dengue disease were excluded.

Classification of Dengue Severity

The present study patients were diagnosed based on the criteria established by the WHO 1997 guidelines.[2] In short, these guidelines classified dengue cases as DF, DHF (Grade I and II) and DSS (DHF Grades III and IV).[2,30] DF was defined as acute febrile illness with 2 or more of the following symptoms: headache, retro-orbital pain, myalgia, leukopenia, arthralgia, rash and hemorrhagic manifestations. DF is distinct from DHF/DSS in that there is no evidence of plasma leakage.[30] DHF was classified into 4 grades of severity: Grade I (fever and plasma leakage without spontaneous bleeding), Grade II (Grade I manifestations with spontaneous bleeding), Grade III (Grade I and II manifestations with evidence of shock), and Grade IV (Grade I and II manifestations with evidence of profound shock and undetectable blood pressure or pulse).[30]

Classification of Nutritional Status

Admission data on height in centimeters (cm), weight in kilograms (kg), and birth date of the included patients were extracted from medical records. Weight and height measurements were converted to age- and sex-standardized Z scores for malnutrition indicators according to the WHO[31,32] and Thai[33] growth charts. Based on the 2006 WHO Growth Standards[31] and 2007 WHO Growth References,[32] height-for-age Z scores (HAZ), and body mass index-for-age Z scores (BAZ) were calculated using the WHO Anthro software program (WHO, Geneva, Switzerland) for children under the age of 5 years[34] and the WHO AnthroPlus software program (WHO, Geneva, Switzerland) for children 5–14 years of age.[35] In addition, using Thai Growth references for children 1–14 years of age,[33] HAZ and weight-for-height Z scores (WHZ) were calculated using the INMU-Thai Growth (Institute of Nutrition, Mahidol University, Thailand).[36] The children were categorized into 5 nutritional status groups: stunting, normal stature, wasting, having a healthy weight and being overweight. Additionally, a combination of 2 nutritional indicators (HAZ and BAZ for the WHO criteria and HAZ and WHZ for the Thai criteria) was applied as previously described.[20] Each of the categories corresponded to a particular nutritional status: normal stature with healthy weight, normal stature with wasting, normal stature with an overweight status, stunting with healthy weight, concurrent wasting and stunting and concurrent stunting and overweight status (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E77, which shows the Z score cutoff points used to categorize children into different nutritional status groups).

Ethics Statement

The study protocol followed the principles of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of Walailak University (WUEC-19-120-01). Permission to collect the data was obtained from the hospital directors of Maharaj Nakhon Si Thammarat Hospital, Thungsong Hospital, Sichon Hospital and Thasala Hospital.

Statistical Analysis

The proportion of patients with a characteristic of interest was compared among the dengue severity groups (DF, DHF and DSS) with the χ^2 test or Fisher exact test. Continuous variables were expressed as mean ± SD or median and interquartile range and compared among the severity groups by ANOVA or Kruskal-Wallis test. Percentage of hemoconcentration was calculated as the difference between the hematocrit level within 24 hours before defervescence and the baseline hematocrit level on admission, divided by the baseline hematocrit level on admission, and then multiplied by 100.[18] Hemoglobin level, percentage hematocrit, percentage hemoconcentration and platelet and white blood cell (WBC) counts were dichotomized at 14 g/dL, 42%, 20%, 50,000/mm^3 and 5000 cells/mm^3, respectively, as these levels were previously associated with a higher rate of complications.[30] Logistic regression analysis with adjustment for age and gender was used to identify factors associated with dengue severity or nutritional status. The results were expressed as odds ratios (OR) with 95% confidence intervals (CI) and Wald test P value. P values <0.05 were considered indicative of statistical significance. All statistical analyses were performed in R software, version 3.5.1, 2018 (R Core Team, Vienna, Austria).[37]

RESULTS

Among 572 children, 248 had DF, 281 had DHF (Grade I, 176 children; Grade II, 105 children) and 43 had DSS group (Grade III, 33 children; Grade IV, 10 children). The patients' average age was 9.44±3.65 years. Demographic and clinical characteristics of the sample are shown in Table 1. The majority of DENV cases (84.79%) were confirmed among children over the age of 5 years, without gender differences. There were no differences among the groups in the frequency of symptoms, such as headache, myalgia, retro-orbital pain, cough, vomiting, nausea, diarrhea, constipation, petechiae, purpura or ascites. Patients with DHF or DSS were more likely to have longer hospitalization (4–6 days), abdominal pain, dry lips, rash, hematemesis, melena, bleeding per gum, epistaxis, hepatomegaly, volume overload and pleural effusion, compared with patients with DF.

Among-groups comparisons of hematologic profiles obtained before the day of defervescence, defined as the approximate onset of plasma leakage in patients with DHF,[38] are shown in Table 2. Patients with DHF or DSS had significantly higher levels of hemoglobin, hematocrit, percentage of hemoconcentration, and WBC, neutrophil, and atypical lymphocyte counts, but significantly lower platelet and lymphocyte counts than had those with DF. There were no among-group differences in monocyte count. Factors associated with increased risk of severe dengue infection (DHF and DSS) were levels of hemoglobin >14 g/dL (OR = 3.58, 95% CI: 2.26–5.66, $P = 0.000$), hematocrit >42% (OR = 3.30, 95% CI: 2.09–5.19, $P = 0.000$), hemoconcentration ≥20% (OR = 13.67, 95% CI: 3.21–58.18, $P = 0.000$), platelet count ≤50,000/mm^3 (OR = 4.48, 95% CI: 2.57–7.80, $P = 0.000$) and WBC count >5000/mm^3 (OR = 2.21, 95% CI: 1.38–3.52, $P = 0.001$) (Table 3).

Nutritional status on the day of admission in 572 patients treated for dengue disease was assessed according to the WHO and Thai criteria (Table, Supplemental Digital Content 2, http://links.lww.com/INF/E78, which shows distribution of nutritional status in pediatric patients with DF, DHF and DSS). Overall, the Thai criteria were associated with a higher prevalence of stunting and wasting and a lower prevalence of being overweight compared with the WHO criteria (15.91% vs. 13.64%; 17.48% vs. 13.11% and 23.25% vs. 30.07%, respectively). Based on the WHO and Thai criteria, there were significant differences in the nutritional status assessed by HAZ and combined indicators among patients with DF compared with those with severe dengue infection (DHF and DSS) (Table 4). However, there was no significant difference between DF and severe dengue infection (DHF and DSS) groups in the distribution of nutritional status assessed with BAZ or WHZ indicators.

TABLE 1. Demographic and Clinical Characteristics of Pediatric Patients Treated for Dengue Infection at 4 Hospitals in Southern Thailand (2017–2018)

	Total	DF	DHF	DSS	
	n = 572	n = 248	n = 281	n = 43	
Variable	n (%)	n (%)	n (%)	n (%)	χ^2
Gender					
Male	303 (52.97)	129 (52.02)	157 (55.87)	17 (39.53)	4.156*,ns
Female	269 (47.03)	119 (47.98)	124 (44.13)	26 (60.47)	
Age in months					
12.0–60.9	87 (15.21)	45 (18.15)	38 (13.52)	4 (9.30)	14.573*,†
61.0–120.9	208 (36.36)	92 (37.10)	91 (32.38)	25 (58.14)	
121.0–179.9	277 (48.43)	111 (44.75)	152 (54.10)	14 (32.56)	
Length of hospital stay					
1–3 days	431 (75.35)	205 (82.66)	200 (71.17)	26 (60.47)	24.378*,‡
4–6 days	125 (21.85)	35 (14.11)	77 (27.40)	13 (30.23)	
>6 days	16 (2.80)	8 (3.23)	4 (1.42)	4 (9.30)	
Clinical presentation					
Headache	215 (37.59)	91 (36.69)	114 (40.57)	10 (23.26)	4.914*,ns
Myalgia	163 (28.50)	75 (30.24)	80 (28.74)	8 (18.60)	2.436*,ns
Retro-orbital pain	3 (0.52)	2 (0.81)	0 (0.00)	1 (2.33)	4.591§,ns
Cough	204 (35.66)	96 (38.71)	96 (34.16)	12 (27.91)	2.406*,ns
Vomiting	271 (47.38)	107 (43.15)	140 (49.82)	24 (55.81)	3.683*,ns
Nausea	129 (22.55)	65 (26.21)	59 (21.00)	5 (11.63)	5.227*,ns
Abdominal pain	123 (21.50)	41 (16.53)	74 (26.33)	8 (18.60)	7.730*,¶
Dry lips	141 (24.65)	56 (22.58)	67 (23.84)	18 (41.86)	7.527*,¶
Diarrhea	141 (24.65)	58 (23.39)	75 (26.69)	8 (18.60)	1.689*,ns
Constipation	5 (0.87)	1 (0.40)	4 (1.42)	0 (0.00)	1.404§,ns
Rash	51 (8.92)	7 (2.82)	37 (13.17)	7 (16.28)	20.463*,‡
Petechiae	98 (17.13)	39 (15.73)	47 (16.73)	12 (27.91)	3.894*,ns
Purpura	2 (0.35)	1 (0.40)	0 (0.00)	1 (2.33)	4.537§,ns
Hematemesis	10 (1.75)	0 (0.00)	5 (1.78)	5 (11.63)	18.213‡,§
Melena	17 (2.97)	0 (0.00)	10 (3.56)	7 (16.28)	34.337*,‡
Bleeding per gum	12 (2.10)	0 (0.00)	11 (3.91)	1 (2.33)	9.840*,†
Epistaxis	26 (4.55)	4 (1.61)	18 (6.41)	4 (9.30)	9.399*,†
Hepatomegaly	23 (4.02)	5 (2.02)	14 (4.98)	4 (9.30)	6.363*,¶
Volume overload	10 (1.75)	0 (0.00)	2 (0.71)	8 (18.60)	33.760‡,§
Pleural effusion	11 (1.92)	0 (0.00)	4 (1.42)	7 (16.28)	26.900‡,§
Ascites	2 (0.35)	0 (0.00)	1 (0.36)	1 (2.33)	4.287§,ns

The proportions of patients with a characteristic of interest among the groups were compared using the χ^2 test* or Fisher exact test.§

Asterisk indicates a significant difference among the groups: †$P < 0.01$, ‡$P < 0.001$ and ¶$P < 0.05$.

ns indicates a non-significant finding at $P \geq 0.05$.

TABLE 2. Patients' Hematologic Profiles Obtained Within 24 Hours Before Defervescence of Dengue Infection

	DF (n = 248)		DHF (n = 281)		DSS (n = 43)		Test of Significance
	n	Mean ± SD; Median, IQR	n	Mean ± SD; Median, IQR	n	Mean ± SD; Median, IQR	
Fever day	248	4.72 ± 1.33; 5.00, 1.00	281	4.93 ± 1.73; 5.00, 2.00	43	4.58 ± 1.14; 5.00, 1.00	1.327*,†
Hemoglobin, g/dL	244	12.71 ± 1.35; 12.70, 1.60	278	13.19 ± 1.80; 13.05, 2.30	42	14.01 ± 1.53; 14.25, 2.63	27.635*,†
Hematocrit, %	248	38.06 ± 3.56; 37.70, 5.35	281	39.82 ± 5.00; 39.20, 6.75	43	42.45 ± 4.78; 42.10, 7.40	36.710*,†
Hemoconcentration, %	248	4.81 ± 4.15; 3.71, 4.86	281	7.44 ± 6.10; 6.06, 6.96	43	13.71 ± 10.45; 11.33, 18.30	52.232*,†
Platelets, cells/mm^3	248	96,673.79 ± 32,846.34; 95,000.00, 30,500.00	281	80,502.06 ± 38,911.50; 82,000.00, 46,500.00	43	55,534.88 ± 37,268.23; 55,000.00, 53,000.00	66.040*,†
WBC, cells/mm^3	248	3,484.23 ± 1,777.68; 3,235.00, 1,722.50	281	3,971.03 ± 2,242.98; 3,490.00, 2,140.00	43	4,711.63 ± 2,186.29; 4,200.00, 3,300.00	15.463*,†
Neutrophils, %	246	37.97 ± 15.04; 37.15, 21.20	281	38.74 ± 16.18; 37.00, 24.00	42	47.94 ± 14.54; 47.50, 21.75	14.288*,†
Monocytes, %	234	8.58 ± 4.87; 8.00, 6.00	273	8.35 ± 4.59; 8.00, 6.00	42	9.47 ± 5.86; 8.00, 6.00	0.693*,ns
Lymphocytes, %	248	48.17 ± 13.87; 48.00, 18.15	281	45.90 ± 14.66; 46.00, 20.10	42	36.87 ± 12.26; 36.90, 21.25	11.578†,‡
Atypical lymphocytes, %	160	5.72 ± 5.39; 4.00, 6.00	176	7.89 ± 7.72; 6.00, 8.75	29	7.79 ± 7.78; 6.00, 12.00	6.873*,§

One-way analysis of variance (ANOVA)
‡or Kruskal-Wallis test
*was used to compare profiles of the dengue severity groups. Significant differences are indicated as follows:
†$P < 0.001$,
§$P < 0.05$ and
IQR indicates interquartile range.

TABLE 3. Hematologic Risk Factors for Developing DHF and DSS Among Pediatric Patients

	DF	DHF/DSS			
	n = 248	n = 324	Adjusted OR*	95% CI of Adjusted OR	*P* Value
	n (%)	n (%)			
Hemoglobin, g/dL					
≤14	213 (87.30)	210 (65.63)	1.00		
>14	31 (12.70)	110 (34.37)	3.58	2.26–5.66	0.000
Hematocrit, %					
≤42	216 (87.10)	217 (66.98)	1.00		
>42	32 (12.90)	107 (33.02)	3.30	2.09–5.19	0.000
Hemoconcentration,%					
<20	246 (99.19)	294 (90.74)	1.00		
≥20	2 (0.81)	30 (9.26)	13.67	3.21–58.18	0.000
Platelets, cells/mm^3					
>50,000	231 (93.15)	242 (74.69)	1.00		
≤50,000	17 (6.85)	82 (25.31)	4.48	2.57–7.80	0.000
WBC, cells/mm^3					
≤5000	217 (87.50)	251 (77.47)	1.00		
>5000	31 (12.50)	73 (22.53)	2.21	1.38–3.52	0.001

*Adjusted for age and gender; children with DF served as the reference in all analyses.

Stunting assessed by HAZ based on either the WHO or Thai criteria was associated with decreased risk of developing severe dengue infection (DHF and DSS) compared with those with a normal stature (OR = 0.54, 95% CI: 0.33–0.88, $P = 0.013$; OR = 0.61, 95% CI, 0.39–0.95, $P = 0.030$, respectively) (Table 4). Moreover, being overweight combined with having a normal stature was a risk factor for developing DHF and DSS based on either set of criteria (OR = 1.76, 95% CI: 1.13–2.75, $P = 0.012$; OR = 1.84, 95% CI: 1.09–3.09, $P = 0.022$, respectively) compared with having a healthy weight combined with a normal stature. Further analysis indicated associations between baseline malnutrition and hematologic characteristics of severe dengue infection (Table 5). Patients with hemoglobin level >14 g/dL, hematocrit >42%, hemoconcentration ≥20% and platelet count ≤50,000/mm^3 were significantly more likely to be overweight with a normal stature, while patients with hemoglobin level >14 g/dL and hematocrit >42% were significantly less likely to have stunted growth.

DISCUSSION

Early identification of hospitalized patients at higher risk of developing a severe form of dengue infection is a challenge for physicians. Several factors, including nutritional status, have been associated with dengue infection severity; however, the effect of nutritional status on dengue disease severity remains controversial.[12–19] This study reported on the association between nutritional status and hematologic profile and the risk of development of severe dengue infection among hospitalized pediatric patients in Nakhon Si Thammarat province in southern Thailand.

Nutrition is considered an important determinant of immune function. Previous studies have suggested that in either primary or secondary DENV infection, an exacerbated host immune response might play a pivotal role in pathogenesis of severe dengue disease.[39] In this study, stunting, which results from chronic undernutrition, emerged as a protective factor against development of DHF and DSS. This finding is consistent with previous studies, which reported that children with DHF were less likely to be undernourished than were healthy controls.[15,16] This effect of undernutrition might be associated with a dysfunction of the innate and adaptive immune systems[40]; for example, lower lean mass deposition has been related to persistent low-level inflammation among Gambian adolescents.[41] Specifically, undernutrition impairs immune priming by dendritic cells and monocytes and impairs effector memory T-cell function.[42]

Moreover, stunting that occurred concurrently with either wasting or being overweight was not found to be associated with the severity of dengue infection in this study. The factors resulting in this state of concurrence have not been completely clarified, but evidence indicates that considerable excess mortality is experienced by children who have concurrent stunting and wasting[21] and those with stunting who are overweight.[22] Because characteristics specific to each individual with each of these conditions contribute to the development of different nutritional states, health professionals need to assess each condition and prioritize the management of care accordingly.

In the present study, children who were overweight with normal stature were at risk for developing severe dengue infection. For overweight children with a normal stature, their status suggests that they did not experience substantial difficulties owing to limitations in food access, as their growth occurred within the expected range

TABLE 4. Associations Between Nutritional Status and Severity of Dengue Infection Among Pediatric Patients

Growth Charts	Nutritional Indicator	Nutritional Status	DF n = 248 n (%)	DHF/DSS n = 324 n (%)	χ^{2}*	Adjusted OR†	95% CI of Adjusted OR	*P* Value‡
WHO growth charts	HAZ	Normal stature	204 (82.26)	290 (89.51)	6.27§	1.00		
		Stunting	44 (17.74)	34 (10.49)		0.54	0.33–0.88	0.013
	BAZ	Healthy weight	150 (60.48)	175 (54.01)	2.79ns	1.00		
		Wasting	32 (12.90)	43 (13.27)		1.17	0.70–1.94	0.554
		Overweight	66 (26.61)	106 (32.72)		1.32	0.90–1.94	0.150
	Combination of HAZ and BAZ	Normal stature + healthy weight	135 (54.44)	162 (50.00)	14.87§	1.00		
		Normal stature + wasting	29 (11.69)	39 (12.04)		1.13	0.66–1.93	0.650
		Normal stature + overweight	40 (16.13)	89 (27.47)		1.76	1.13–2.75	0.012
		Stunting + healthy weight	15 (6.05)	13 (4.01)		0.70	0.32–1.53	0.368
		Stunting + wasting	3 (1.21)	4 (1.23)		1.10	0.24–5.03	0.899
		Stunting + overweight	26 (10.48)	17 (5.25)		0.54	0.28–1.05	0.069
Thai growth charts	HAZ	Normal stature	199 (80.24)	282 (87.04)	4.85§	1.00		
		Stunting	49 (19.76)	42 (12.96)		0.61	0.39–0.95	0.030
	WHZ	Healthy weight	150 (60.48)	189 (58.33)	2.79ns	1.00		
		Wasting	48 (19.36)	52 (16.05)		0.88	0.56–1.37	0.568
		Overweight	50 (20.16)	83 (25.62)		1.29	0.85–1.95	0.228
	Combination of HAZ and WHZ	Normal stature + healthy weight	130 (52.42)	173 (53.40)	15.46¶	1.00		
		Normal stature + wasting	44 (17.74)	45 (13.89)		0.77	0.48–1.25	0.291
		Normal stature + overweight	25 (10.08)	64 (19.75)		1.84	1.09–3.09	0.022
		Stunting + healthy weight	20 (8.07)	16 (4.94)		0.57	0.28–1.16	0.121
		Stunting + wasting	4 (1.61)	7 (2.16)		1.41	0.40–4.98	0.589
		Stunting + overweight	25 (10.08)	19 (5.86)		0.58	0.30–1.10	0.095

*Chi-squared test;
†adjusted for age and gender;
‡*P* value derived from Wald test;
§$P < 0.05$,
¶$P < 0.01$.

TABLE 5. Association Between Malnutrition and Hematologic Characteristics Indicative of Dengue Severity in Pediatric Patients

	Stunting*		Overweight and Normal Stature†	
	WHO Growth Charts	Thai Growth Charts	WHO Growth Charts	Thai Growth Charts
	Adjusted OR‡ (95% CI)	Adjusted OR‡ (95% CI)	Adjusted OR‡ (95% CI)	Adjusted OR‡ (95% CI)
Hemoglobin, g/dL				
≤14	1.00	1.00	1.00	1.00
>14	0.40 (0.20–0.80)§	0.26 (0.13–0.55)¶	3.02 (1.95–4.69)¶	3.17 (1.93–5.22)¶
Hematocrit, %				
≤42	1.00	1.00	1.00	1.00
>42	0.52 (0.27–1.01)ns	0.35 (0.17–0.69)§	2.38 (1.53–3.71)¶	2.51 (1.53–4.13)¶
Hemoconcentration, %				
<20	1.00	1.00	1.00	1.00
≥20	0.22 (0.29–1.63)ns	0.49 (0.22–1.08)ns	2.53 (1.16–5.50)‖	2.71 (1.17–6.28)‖
Platelets, cells/mm^3				
>50,000	1.00	1.00	1.00	1.00
≤50,000	0.51 (0.25–1.07)ns	0.55 (0.27–1.11)ns	2.25 (1.40–3.62)§	1.98 (1.16–3.37)‖
WBC, cells/mm^3				
≤5,000	1.00	1.00	1.00	1.00
>5,000	1.02 (0.54–1.91)ns	0.96 (0.53–1.74)ns	1.32 (0.78–2.21)ns	1.64 (0.93–2.90)ns

*The binomial outcome takes the value 1 if stunting is present and the value 0 if otherwise.
†The binomial outcome takes the value 1 if overweight and normal stature are present and the value 0 if otherwise.
‡Adjusted for age and gender; significant findings are indicated as
§$P < 0.01$,
¶$P < 0.001$ and
‖$P < 0.05$; ns indicates non-significant findings at $P \geq 0.05$.

and being overweight may be a result of a systemic positive energy balance.[20] This finding is similar to those in previous studies reporting that excess body weight was associated with the severity of dengue infection.[12–14] A growing body of evidence suggests that obesity-associated increase in chronic, low-grade inflammation with excess production of leptin, interleukin-1β, interleukin-6 and tumor necrosis factor-α and reduction in adiponectin (anti-inflammatory) levels[43] affects immune cell function during infection.

Some hematologic characteristics associated with a severe form of dengue infection were positively associated with being

overweight and negatively associated with stunting, supporting the hypothesis about the effect of baseline malnutrition on immunopathogenesis of DENV infection. Hematologic risk factors for developing a severe form of dengue infection in the present study were hemoglobin levels >14 g/dL, hematocrit >42%, hemoconcentration ≥20%, platelet count ≤50,000/mm^3 and WBC count >5000/mm^3. This finding is consistent with previous studies, supporting a hypothesis that a decrease in platelet count with a concomitant rise in levels of hemoglobin and hematocrit, and hemoconcentration is a marker of plasma leakage through the blood vessels characteristic of DHF.[18,44] In the course of DHF, platelets lead to increased vascular permeability that result from inflammation, increasing the concentration of hemoglobin and hematocrit due to fluid leakage.[3] In addition, leukopenia is usually observed over the course of both DF and DHF.[44] However, in our study, WBC count >5000/mm^3 was a risk factor for a severe form of dengue infection, which is a finding similar to that previously reported.[45] In fact, in children with DF, mild leukocytosis has been reported at the onset of the disease, with leukopenia occurring later in the process[46]; in addition, leukocytosis may be a warning sign of a severe dengue infection superimposing a bacterial infection.[47]

In contrast to the present study, several previous studies have reported no association between malnutrition and the severity of dengue infection.[17–19] Differences among the previous studies in host genetics, sample size and the operational definition of malnutrition might account for these inconsistent findings. In particular, the use of different approaches for classifying nutritional status makes between-study comparisons difficult. For instance, a study by Malavige et al[17] used a body mass index-for-age indicator based on the National Center for Health Statistics criteria, while Tantracheewathorn et al[18] used weight-for-age indicator based on the National Thai Growth References. There is considerable controversy regarding which growth classification system is the most suitable for use at a national level in context of a particular population.[25,48] In Thailand, the latest version of the Thai Growth References for weight, height and nutritional indicators was developed based on a cross-sectional study of children and adolescents that followed its cohort from birth until they turned 19 years old (since 1999).[33] However, there remain concerns about the appropriateness of national growth charts based on outdated population data. The present study, therefore, estimated children's nutritional status based on both national and international growth charts.

This study has some limitations. Data on the type of dengue infection (primary or secondary infection) and DENV serotype were not available due to participating hospitals' financial constraints. As a result, we were unable to determine whether the dengue infection type or the DENV serotype have any effect on the risk of dengue severity among malnourished children. Additionally, due to its cross-sectional design, this study precludes any conclusions regarding a causal relationship between baseline nutritional status and the risk of developing severe dengue infection. Future large-scale prospective cohort studies on the effects of nutritional status on dengue severity in regions with high dengue prevalence might help elucidate the role of malnutrition in dengue infection.

This study has several strengths. First, the quality of the data, including patient demographic, clinical and laboratory characteristics, was assured by using a validated case report form and a standardized protocol for data collection. In addition, the included dengue cases were recruited from 4 hospitals across the province, suggesting results applicability in a community healthcare setting. The eligibility criteria used in this study further strengthened the quality of the findings.

In summary, the present findings suggest that overweight children with dengue infection might be at a higher risk of developing a severe form of infection. Physicians should closely monitor such patients for early signs of severe dengue disease. Given the hypothesized link between baseline malnutrition and immunopathogenesis of DENV infection, future prospective cohort studies should examine the mechanisms of host immune response to DENV infection among different nutritional status groups. Being overweight and having a dengue infection are significant sources of morbidity; coordinated public health policies that involve nutrition and dengue prevention might reduce associated morbidity among children with these conditions.

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