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Original Article

The association of obesity and dengue severity in hospitalized adult patients

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KEYWORDS
Dengue;
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Abstract *Background:* Obesity is associated with unfavorable outcomes for infectious diseases. Most researches exploring the association between nutritional status and dengue severity have focused on pediatric populations, with only few studies assessing adult patients.
Methods: Adult patients with laboratory-confirmed dengue admitted to a tertiary hospital in southern Taiwan between 2014 and 2015 were enrolled retrospectively. Demographics, comorbidities, clinical presentation, laboratory findings, and outcomes were obtained from case-record forms. Patients were categorized into obese group and nonobese group. The obese group comprised patients with a body mass index of $\geq$27.5 kg/m^2.
Results: A total of 1417 hospitalized patients with dengue were evaluated. The mean age was 57.9 years (range: 18–92 years). The obese and nonobese groups comprised 333 (23.5%) and 1084 (76.5%) patients, respectively. The obese group included more patients with hypertension (85%, $p < 0.001$), diabetes mellitus (33%, $p < 0.001$), and congestive heart failure (6.3%, $p = 0.049$). Multivariate analysis revealed that the obese group had more petechiae (AOR: 1.353, 95% CI: 1.025–1.786, $p = 0.033$), more dyspnea (AOR: 1.380, 95% CI: 1.015–1.876,

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$p = 0.040$), and more severe hepatitis (AOR: 2.061, 95% CI: 1.050—4.048, $p = 0.036$). The obese group also had higher peak hematocrit values (44.1%, $p < 0.001$) and lower nadir platelet count (45.3 $\times$ $10^3/\mu L$, $p = 0.049$) than the nonobese group.
Conclusion: In adult patients with dengue, obese group had more petechiae, dyspnea, severe hepatitis, lower nadir of platelet count, and higher peak hematocrit level. We observed no difference in severe dengue or mortality between obese and nonobese group.

Introduction

Dengue, one of the most prevalent mosquito-borne diseases worldwide, is transmitted by mosquitos of the genus *Aedes*, especially *Aedes aegypt*[1] The dengue virus (DENV) is a small single-stranded ribonucleic acid virus belonging to the genus *Flavivirus*, family *Flaviviridae*.[1] Of the four DENV serotypes (DENV-1 to DENV-4), DENV-2 and DENV-3 are frequently associated with severe secondary dengue infections.[1] One model estimated that 390 million (95% credible interval: 284—528 million) dengue infections occur every year, of which 96 million (67—136 million) manifest apparently (any level of clinical or subclinical severity), and 70% of the actual burden is in Asia.[2] Another study estimated that 3.97 billion people across 128 countries are at risk of dengue infection.[3] According to the 2009 World Health Organization (WHO) dengue guidelines, dengue cases are classified into dengue without warning signs, dengue with warning signs, and severe dengue. Several risk factors thought to contribute to severe dengue have been investigated, including virological factors, prior exposure to DENV, older age, immunocompromised status, and coexisting conditions such as hypertension, diabetes mellitus, and chronic renal failure.[4—13]

Although previous studies have investigated the association between nutritional status and dengue disease severity, most have focused on pediatric populations, with controversial outcomes obtained.[14—20] According to WHO estimates, more than 1.9 billion adults are overweight, among whom more than 650 million are obese. Obesity is commonly associated with numerous comorbidities and is a major health burden. According to WHO guidelines, the dengue patients who have underlying diseases (diabetes mellitus, renal failure, and chronic haemolytic diseases), certain social circumstances (living alone, or living far from a health facility without reliable means of transport), warming signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement >2 cm, increase in hematocrit level concurrent with rapid decrease in platelet count) and risk factors (such as obesity, pregnancy, infancy, and old age) are worthwhile referring to the hospital for further observation and management[1] In recent decades, the population of obese adults has increased in Southeast Asia, where dengue is endemic; thus, how obesity affects dengue severity should be determined. In this study, we used a retrospective design to investigate the association between obesity and dengue severity.

Materials and methods

This retrospective study was conducted at Kaohsiung Medical University Hospital, a referral center in southern Taiwan. Between 2014 and 2015, 3862 adult patients (aged >18 years) with laboratory-confirmed dengue visited this hospital. Among them, 1417 hospitalized patients with recorded weight and height were enrolled for analysis (Fig. 1). In Taiwan, the laboratory diagnosis of dengue is made if one of the following criteria is met: (1) virus isolation; (2) positive result of real-time polymerase chain reaction; (3) positive result of higher titers of dengue-specific IgM and IgG antibodies in a single serum specimen in which cross-reaction to Japanese encephalitis virus has been excluded; (4) positive seroconversion or ≥4-fold increase in dengue-specific IgM or IgG antibodies from the acute phase compared with the convalescent phase; or (5) a positive test for dengue nonstructural protein 1 antigen test (Bio-Rad Laboratories, Marnes-la-Coquette, France). Clinical information was collected retrospectively from medical records.

Adult obesity was defined as body mass index (BMI) of ≥27.5 kg/m^2 on the basis of WHO recommendations for Asian populations.[21] According to the 2009 WHO dengue guidelines,[1] severe dengue was defined as dengue with one or more of the following conditions: (1) plasma leakage leading to shock and/or fluid accumulation with respiratory distress; (2) severe bleeding; and (3) severe organ

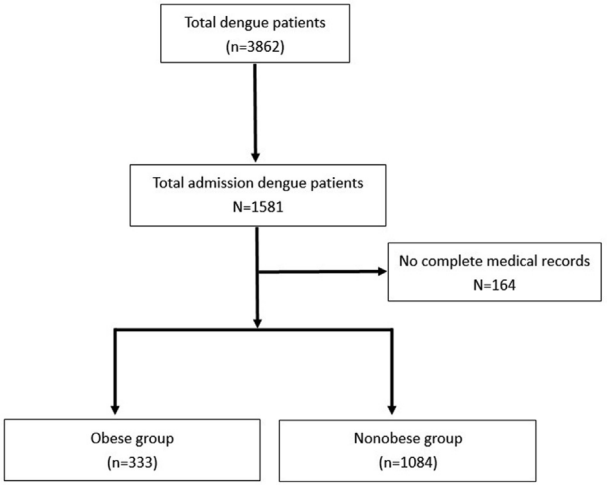

Figure 1. Flow chart of dengue infection to analysis.

impairment. Warning signs included abdominal pain, persistent vomiting, fluid overload, mucosal bleeding, lethargy or restlessness, liver enlargement of more than 2 cm, and increased hematocrit concurrent with a rapid decrease in platelet count.[1] Severe hepatitis was defined as aspartate aminotransferase or alanine aminotransferase level of >1000 IU/L. Significant increase in hematocrit was defined as a more than 20% increase in the hematocrit level.

We divided the enrolled patients into the obese group and nonobese group, and we compared the differences in categorical and continuous variables between the two groups. Data were analyzed using IBM® SPSS® Statistics 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using chi-squared test and are expressed as numbers and proportions. Continuous variables were analyzed using Student *t* test and are expressed as means and ranges. Significant variables in the univariate analysis between the obese and nonobese groups were further analyzed using logistic regression to confirm whether obesity was an independent risk factor. Two-tailed $p < 0.05$ was considered statistically significant.

This study was approved by the Institutional Ethics Committee of Kaohsiung Medical University Hospital (approval no. KMUHIRB-E(II)-20150222). Because this was a retrospective study, informed consent was not obtained from patients, and all data were analyzed with well de-identification.

Results

Out of 3862 patients with dengue who visited our hospital, we excluded 2281 nonhospitalized patients and 164 patients without complete medical records. Finally, 1417 hospitalized patients with complete medical records were enrolled for analysis (Fig. 1). Among the enrolled patients, 689 (48.6%) were male, and 728 (51.4%) were female, with a mean age of 57.9 years (range: 18–92 years). The mean BMI was 24.8 kg/m^2 (range: 14.7 kg/m^2–43.6 kg/m^2). The obese and nonobese groups comprised 333 (23.5%) and 1084 (76.5%) patients, respectively.

We compared demographics and comorbidities between the obese group and nonobese group (Table 1). No statistically significant difference in gender and age distribution was observed between the two groups. The obese group had more comorbidities than the nonobese group, namely hypertension (85% vs. 61.8%, $p < 0.001$), diabetes mellitus (33% vs. 21.1%, $p < 0.001$), and congestive heart failure (6.3% vs. 3.8%, $p = 0.049$).

The obese group had more petechiae (31.5% vs. 24.7%, $p = 0.014$), cough (39.0% vs. 31.5%, $p = 0.010$), and dyspnea (25.5% vs. 17.9%, $p = 0.002$) than the nonobese group (Table 2). Multivariate analysis also revealed that obesity was significantly associated with petechiae (AOR: 1.353, 95% CI: 1.025–1.786, $p = 0.033$) and dyspnea (AOR: 1.380, 95% CI: 1.015–1.876, $p = 0.040$), but not with cough (AOR: 1.275, 95% CI: 0.982–1.657, $p = 0.068$).

We observed that most warning signs were not significantly different between the two groups (Table 3), except epistaxis (9.3% vs. 5.6%, $p = 0.017$). We did not observe significant differences in dengue severity, mortality, and intensive care unit stay between the two groups, although severe hepatitis was more frequent in the obese group (4.8% vs. 2.0%, $p = 0.006$) (Table 3). Multivariate analysis revealed that severe hepatitis was more prevalent in the obese group (AOR: 2.061, 95% CI: 1.050–4.048, $p = 0.036$) (Table 3).

We also analyzed the peak and nadir values of laboratory findings in the obese and nonobese groups during the disease course. We observed that the mean peak hematocrit

Table 1 Comparison of demographics and comorbidities between the obese and nonobese groups.

	Obese group (n = 333)	Nonobese group (n = 1084)	OR	95% CI	*P*
Demography					
Age (mean ± standard deviation), years	59.0 ± 15.4	57.6 ± 18.0			0.171
Female	170 (51.0%)	558 (51.4%)			0.892
Comorbidities					
Peptic ulcer	41 (12.3%)	116 (10.7)	1.172	0.802–1.712	0.413
Alcoholism	6 (1.8%)	32 (3.0%)	0.603	0.250–1.455	0.256
Hepatitis B	35 (10.5%)	103 (9.5%)	1.119	0.746–1.677	0.587
Hepatitis C	15 (4.5%)	39 (3.6%)	1.264	0.688–2.323	0.450
Liver cirrhosis	2 (0.6%)	17 (1.6%)	0.379	0.087–1.650	0.179
Hypertension	283 (85.0%)	670 (61.8%)	3.497	2.528–4.839	<0.001
Diabetes mellitus	111 (33.3%)	229 (21.1%)	1.867	1.424–2.447	<0.001
Congestive heart failure	21 (6.3%)	41 (3.8%)	1.712	0.997–2.941	0.049
COPD	10 (3.0%)	34 (3.1%)	0.956	0.467–1.956	0.902
CVA	25 (7.5%)	65 (6.0%)	1.272	0.789–2.053	0.323
ESRD	6 (1.8%)	25 (2.3%)	0.777	0.316–1.911	0.582
CKD	16 (4.8%)	63 (5.8%)	0.818	0.466–1.436	0.484
Malignancy	31 (9.3%)	121 (11.2%)	0.817	0.539–1.237	0.339
Autoimmune disease	3 (0.9%)	6 (0.6%)	1.633	0.406–6.567	0.485

OR: Odds ratio, CI: Confidence interval, GERD: Gastroesophageal reflux disease, Old TB: Old tuberculosis, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, ESRD: End stage renal disease, CKD: Chronic kidney disease.

Table 2 Comparison of clinical presentation between the obese and nonobese groups.

	Clinical presentation							
	Obese group (n = 333)	Nonobese group (n = 1084)	OR	95% CI	*P*	AOR[a]	95% CI	*P*
Chills	117 (35.1%)	376 (34.7%)	1.02	0.788–1.319	0.880			
Headache	170 (51.1%)	528 (48.7%)	1.089	0.859–1.404	0.445			
Retro-orbital pain	29 (8.7%)	120 (11.1%)	0.766	0.501–1.173	0.219			
Back pain	40 (12.0%)	123 (11.3%)	1.067	0.729–1.560	0.739			
Bone pain	102 (30.6%)	298 (27.5%)	1.165	0.890–1.523	0.266			
Arthralgia	44 (13.2%)	147 (13.6%)	0.970	0.676–1.393	0.871			
Myalgia	231 (69.4%)	725 (66.9%)	1.121	0.860–1.462	0.397			
Rash	157 (47.1%)	490 (45.2%)	1.081	0.845–1.383	0.533			
Petechiae	105 (31.5%)	268 (24.7%)	1.402	1.071–1.835	0.014[b]	1.353	1.025–1.786	0.033
Diarrhea	159 (47.7%)	480 (44.3%)	1.150	0.899–1.471	0.266			
Sore throat	56 (16.8%)	202 (18.6%)	0.883	0.638–1.222	0.452			
Cough	130 (39.0%)	341 (31.5%)	1.395	1.082–1.800	0.010	1.275	0.982–1.657	0.068
Malaise	226 (67.9%)	772 (71.2%)	0.854	0.655–1.113	0.241			
Dizziness	136 (43.8%)	447 (41.2%)	1.113	0.868–1.426	0.399			
Dyspnea	85 (25.5%)	194 (17.9%)	1.572	1.175–2.104	0.002	1.380	1.015–1.876	0.040

[a] Multivariate logistic regression was performed. Adjust with hypertension, diabetes mellitus, and congestive heart failure.
[b] Significant at $p<0.05$.

value and nadir platelet count were higher (44.1% vs. 42.5%, $p < 0.0001$) and lower ($45.3 \times 10^3/\mu L$ vs. $50.2 \times 10^3/\mu L$, $p = 0.049$), respectively, in the obese group (Table 4). We also observed that severe thrombocytopenia (nadir platelet count $<20 \times 10^3/\mu L$) was more prevalent in the obese group (46.8% vs. 34.3%, $p < 0.001$) than in the nonobese group (Table 3).

Discussion

Obesity has been listed by WHO as a coexisting condition that may exacerbate dengue infection.[1] However, limited studies have been conducted on the association of obesity with dengue severity in adults. To date, only two studies, with small case numbers, have been reported.[16,22] Our retrospective study, on this issue, included the highest number of adult cases ever reported in the literature. To date, most studies discussing the relationship between obesity and dengue severity have focused on pediatric populations, with controversial results. Some studies have concluded that obesity was a risk factor for severe dengue and dengue hemorrhagic fever in pediatric patients, and that obese children were more likely to develop dengue shock syndrome and dengue hemorrhagic fever.[14,15,18,19] Obese children had a more unusual dengue presentation, more fluid overload, higher mean aminotransferase levels, and higher complication rates. Case fatality rates were also higher in obese children than in normal-weight children.[19] Other studies, however, have reported no association between obesity and dengue hemorrhagic fever, dengue shock syndrome, or dengue severity among children.[17,20] Among adult population, a retrospective study in Malaysia enrolled 335 hospitalized patients, including those older than 12 years and an unspecified proportion of adult patients. Although the study reported no association between obesity and severe dengue, obese patients more frequently had increased hematocrit level with decreased platelets and lower nadir platelet count.[22] However, adolescent patients are different from adults in terms of pathophysiology and host response to infection; hence, this study derived from a mixed adolescent and adult population may not be generalizable to all adult patients with dengue. In another study in Malaysia, which enrolled 173 nonhospitalized adult patients with a high mean BMI (37.4 ± 13.75 kg/m^2) and defined obesity according to the WHO criteria for Western countries, it observed that higher BMI was associated with higher odds of dengue with warning signs or severe dengue in the early phase of infection.[16] Our study enrolled only adult patients and defined obesity according to the WHO criteria for Asian countries; thus, our study provides a more appropriate investigation of the association between obesity and dengue severity. Although our study revealed no statistically significant association between obesity and severe dengue, obesity may still indirectly affect dengue severity. Obesity was confirmed to be associated with several comorbidities, such as hypertension, diabetes mellitus, and cardiovascular diseases, which are all recognized as risk factors for severe dengue.[7,9,23] We also observed that the obese group had more frequent petechiae and severe hepatitis, which are also risk factors for severe dengue.[7,10,23] These findings indicate that obesity may indirectly predispose adult patients with dengue to severe dengue, thus emphasizing the critical role of obesity in dengue infection.

Obesity is related to the incidence and severity of several infections such as nosocomial infections and surgical site infections, as well as more severe complications.[24] According to previous studies, obesity is characterized by a chronic low-grade inflammation status. Hyperplastic or hypertrophied adipose tissue produces several proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-10, which can lead to a state of oxidative stress, metabolic syndrome,

Table 3 Comparison of warning signs, severe dengue, disease severity, and mortality between the obese and nonobese groups.

	Obese group (n = 333)	Nonobese group (n = 1084)	OR	95% CI	*P*	AOR[a]	95% CI	*P*
Abdominal pain	174 (52.3%)	569 (52.5%)	0.990	0.775–1.267	0.939			
Lethargy	23 (6.9%)	73 (6.7%)	1.028	0.632–1.670	0.913			
Nausea	154 (46.2%)	515 (47.5%)	0.951	0.743–1.216	0.686			
Vomiting	115 (34.5%)	379 (35.0%)	0.981	0.758–1.270	0.886			
Consciousness change	31 (9.3%)	99 (9.1%)	1.021	0.669–1.560	0.922			
GI bleeding	98 (29.4%)	286 (26.4%)	1.164	0.887–1.527	0.274			
Hematuria	90 (27.0%)	289 (26.7%)	1.019	0.772–1.344	0.895			
Gum bleeding	53 (15.9%)	169 (15.6%)	1.025	0.732–1.435	0.886			
Epistaxis	31 (9.3%)	61 (5.6%)	1.721	1.097–2.702	0.017[b]	1.891	1.184–3.020	0.008[c] (Omnibus 0.061)
Severe hepatitis[d]	16 (4.8%)	22 (2.0%)	2.436	1.264–4.696	0.006	2.061	1.050–4.048	0.036
Fluid accumulation	40 (12.0%)	121 (11.2%)	1.087	0.743–1.590	0.669			
Hct change ≥20%	129 (38.7%)	384 (35.4%)	1.153	0.895–1.485	0.271			
Platelet $<20 \times 10^3/\mu L$	138 (46.8%)	330 (34.3%)	1.681	1.290–2.190	<0.001			
Severe dengue	42 (12.6%)	115 (10.6%)	1.126	0.834–1.773	0.308			
DHF	107 (32.1%)	306 (28.2%)	1.204	0.923–1.569	0.170			
Death	9 (2.7%)	26 (2.4%)	1.130	0.524–2.437	0.754			
ICU stay	27 (8.1%)	59 (5.4%)	1.531	0.954–2.458	0.075			

GI bleeding: gastrointestinal bleeding, Hct: hematocrit, DHF: dengue hemorrhagic fever, ICU: Intensive Care Unit.
[a] Multivariate logistic regression was performed. Adjust with hypertension, diabetes mellitus, and congestive heart failure.
[b] Significant at $p<0.05$.
[c] Multivariate logistic regression shows significant difference, however Omnibus test show no significant difference ($p=0.061$).
[d] Aspartate aminotransferase or alanine aminotransferase level more than 1000 IU/L.

Table 4 Comparison of laboratory findings and peak/nadir values between the obese and nonobese groups.

	Obese group (n = 333)	Nonobese group (n = 1084)	*P*
Hematocrit (%)	44.1 (25.4–92.4)	42.5 (25–58)	<0.0001[a]
Leukocyte ($X10^3/\mu L$)	2.9 (0.88–10.09)	2.7 (0.17–21.69)	0.078
Platelet ($X10^3/\mu L$)	45.3 (3–188)	50.2 (3–214)	0.049
	Obese group[b] (n = 330)	Nonobese group[b] (n = 1067)	
GOT (IU/L)	585 (20–36,981)	259 (18–23,960)	0.053
GPT (IU/L)	202 (11–6259)	140 (11–4388)	0.050

GOT: aspartate aminotransferase, GPT: alanine aminotransferase.
[a] Significant at $p<0.05$.
[b] There were only 1397 patients who had both GOT and GPT level for analysis.

atherosclerosis, and even cancer.[25] In addition, this type of adipose tissue produces several adipokines, such as leptin, resistin, and adiponectin. Among these adipokines, leptin aids in B cell maturation and development, along with alterations of lymphocytes. Leptin resistance, which has been reported in obese people, leads to the lack of memory B cell development, inhibition of the $CD8^+$ T cell response, and impaired memory T cell response, which are all crucial in the antiviral immune response.[25]

Our univariate analysis revealed that the obese group had more epistaxis and petechiae as well as higher peak hematocrit level than the nonobese group, indicating that obesity might exacerbate bleeding tendency and plasma leakage in dengue fever. Dengue fever causes plasma leakage through several mechanisms, including direct initiation of endothelial dysfunction, disruption of the glycocalyx layer of the endothelium, and reduction of nitric oxide levels.[26] Obesity downregulates adenosine monophosphate (AMP)–activated protein kinase (AMPK) under conditions of overnutrition and chronic inflammation.[27] According to a previous study, DENV also downregulates AMPK to increase the amount of lipids available for viral envelope formation during infection.[26] Taken together, these findings suggest that obesity may facilitate DENV replication, leading to more severe plasma leakage. During DENV infection, a cytokine storm occurs when dengue viremia begins to decline; the circulating proinflammatory cytokines cause increased endothelial permeability, which results in plasma leakage. Obesity may induce the production of proinflammatory adipokines, which increase the secretion of cytokines, including TNF-α and IL-6, causing more severe inflammation. In addition, increased inflammation causes higher levels of serum C-reactive protein, which leads to decreased nitric oxide production and the

loss of vasomotor function.[26] These mechanisms predispose obese people to vessel endothelial dysfunction and exacerbate the severity of dengue fever.

Our study also revealed a lower nadir platelet count in the obese group than in the nonobese group during the course of infection. This finding is consistent with that of Chuong et al. In their mouse model study, they demonstrated that obese mice infected with DENV serotype 2 had more severe morbidities and thrombocytopenia than healthy-weight mice.[28] Similarly, in a Malaysian study, Tan et al. reported a lower nadir platelet count in hospitalized obese patients with dengue.[22] The mechanisms underlying thrombocytopenia in DENV infection are not fully understood, and several hypotheses have been postulated. According to these hypotheses, dengue virus can directly or indirectly affect bone marrow progenitor cells, reduce the proliferative capacity of hematopoietic cells, or induce platelet consumption through disseminated intravascular coagulation (DIC), increased apoptosis, and antiplatelet antibodies.[29] In DENV infection, the adhesion of platelets to endothelial cells plays a crucial role in platelet consumption. The processes of platelet activation, aggregation, and adhesion to endothelial cells are stimulated by several proinflammatory cytokines and adipokines, such as TNF-α and leptin.[30] Obesity also creates a chronic low-grade inflammatory environment, which may contribute to persistent platelet activation[30,31] and predispose obese patients to more severe thrombocytopenia in DENV infection.

Regarding clinical presentation, our study showed a higher proportion of dyspnea in the obese group during the disease course, but no clear statistically significant difference was found in fluid accumulation, such as pleural effusion and ascites. Several studies have demonstrated that obesity causes hypoxemia through hypoventilation and impairment of lung function, and that obesity is associated with comorbidities such as congestive heart failure.[32] All these causes may lead to higher proportion of dyspnea in the obese group.

Liver injury is a common manifestation in dengue infection and is typically mild and self-limiting. Dengue-induced severe hepatitis occurs in approximately 4%—15% of patients,[33] but acute liver failure is rare.[34] The mechanism of liver injury in dengue infection involves several pathways, including direct viral infection of hepatocytes, dysregulation of immune responses to DENV infection, and ischemic change due to plasma leakage.[34] In our study, we observed that severe hepatitis was more frequent in the obese group than in the nonobese group. The obese group also had higher mean peak alanine aminotransferase levels. Previous postmortem studies have reported centrilobular necrosis, fatty alterations, hyperplasia of Kupffer cells, and congestion of hepatic sinusoids in fatal dengue cases.[35,36] Obesity causes nonalcoholic fatty liver disease and lipid accumulation in the liver, which leads to inflammation and increases oxidative stress.[37] Similar to the findings of our study, previous studies have reported higher aminotransferase levels in obese patients than in nonobese patients and a positive correlation between aminotransferase levels and BMI.[37] These histopathological and clinical findings may explain why obese patients with dengue have more frequent severe hepatitis than nonobese patients.

Our study has a few limitations. First, we enrolled hospitalized patients, who had more complete information and laboratory data than outpatients. However, this group might not be adequately representative of the entire patient population, indicating the possibility of selection bias. Second, our study had a retrospective design, which made it prone to record error and less evidence-based than a prospective study. Third, the DENV serotypes of the 2014 and 2015 outbreaks were different, which might have led to differences in severity. Because the exact serotype data for each hospitalized patient were not available, no subgroup analysis was performed.

Conclusion

Obese people typically have several comorbidities that predispose them to more severe complications of infection. Our study focused on dengue in adult patients, and we observed that obese patients had more petechiae and dyspnea and severe hepatitis, lower nadir platelet count, and higher peak hematocrit level. We observed no difference in severe dengue or mortality. Further prospective studies focusing on adult patients with dengue are required to investigate the role of obesity in dengue severity.

Declaration of competing interest

The authors declare no conflicts of interest in this work.

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