Original Article

Factors Predicting Severe Dengue in Children within 72 Hours of Illness Onset

Tram Van Ta [1]*, Thanh Cong Huynh [1], Hai Thanh Tran [2], Hien The Pham [3], Cameron Simmons [4], Tuan Minh Nguyen [4], Dung Van Do [5]

[1] Tien Giang General Hospital, Tien Giang province, Vietnam. [2] Tien Giang Medical College, Tien Giang province, Vietnam. [3] Le Loi Hospital, Ba Ria - Vung Tau province, Vietnam. [4] Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam [5] University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam.

Abstract

Background: Dengue fever (DF) is the most rapidly spreading mosquito-borne viral disease in the world. In the epidemic zones, dengue is a leading cause of hospitalization and death in children. The World Health Organization (WHO) has identified warning signs for cases likely to deteriorate, but these signs and symptoms often appear after 72 hours. Thus, this study was conducted to identify a group of patients at risk of severe dengue disease in the early 72-hour period, helping doctors give indications for hospital admission and closely monitor for early detection of severe complications for timely treatment. **Objective:** To determine factors predicting severe dengue in children within 72 hours of illness onset in an outpatient setting. **Methods:** Prospective cohort studies were conducted from June 2012 to December 2014 at Tien Giang Central General Hospital. **Results:** Of 1,039 cases of children with clinically suspected dengue who qualified for inclusion in the analysis, 283 patients were laboratory-confirmed dengue by one of the composite gold standards, including RT-PCR, NS1 ELISA or IgM seroconversion in the convalescent blood samples. There were 13 severe dengue cases with shock syndrome, severe bleeding, and respiratory distress. Early factors predicting severe dengue within 72 hours of illness onset were as follows: high hematocrit, platelet count ≤100.000/mm^3, albumin level ≤40 g/l, AST≥80 U/L, ALT≥40 U/L at enrolment and DENV-2 infection. **Conclusions:** Severe dengue can lead to death in dengue children patients. If, within 72 hours of illness onset, children with dengue have high hematocrit, platelet count ≤100.000/mm^3, albumin level ≤40 g/l, AST≥80 U/L, ALT≥40 U/L at enrolment and DENV-2 infection, clinical doctors, especially doctors in primary settings, should ensure timely diagnosis and treatment, as well as closely monitor this patient group who are at risk to develop severe dengue within the next days.

Keywords: dengue, children, early prognosis

Introduction

Dengue fever (DF) is the most rapidly spreading mosquito-borne viral disease in the world. [1,2] In the epidemic zones, dengue is a leading cause of hospitalization and death in children. Around the world, an estimated 2.5 billion people live in dengue-epidemic countries. 70 to 500 million dengue cases occur annually in over 100 countries, causing approximately 40 million cases of infection with clinical symptoms and leading to 20,000 deaths.[3,4] In Vietnam, there have been many studies conducted to evaluate the economic impact of DF on health systems; for example, DF resulted in the economic burden of US$ 37,686 in 2015[5] and a mean cost per case of US$ 139.3±61.7 in 2016.[6] For these reasons, dengue remains one of the most dangerous illnesses, as well as a burden on affected societies.

In community-oriented research, many authors have explored the practical competency required to treat and prevent dengue.[7-9] However, dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. The World Health Organization (WHO) has identified warning signs of cases likely to deteriorate, but these signs and symptoms often appear after 72 hours.[3] Therefore, we conducted this study to identify a group of patients at risk of developing severe dengue disease within the early 72-hour period, helping doctors to provide indications for hospital admission and to closely monitor for early detection of severe complications to ensure timely treatment. In addition, the study suggests clinical trials of therapeutic interventions to prevent possible serious complications in the future.

Materials and Methods

Study design and study site

Prospective cohort studies were conducted from June 2012 to December 2014 at Tien Giang Central General Hospital (TCGP). Tien Giang province, which is in the southwestern region of Vietnam, is 70 km from Ho Chi Minh City to the southwest. TCGP, located along National Highway 1, Phuoc Thanh Commune, My Tho City, is the largest hospital in Tien Giang province.

Data collection

Patients visiting the paediatric clinic of Tien Giang Central General Hospital were selected for this study if they met the following criteria: (i) medical history of fever or fever at

Address for correspondence: Tram Van Ta (PhD., MD.), 02 Hung Vuong Street, Ward 1, My Tho City, Tien Giang province, Vietnam.
E-mail: tavantram @ gmail.com

How to cite this article: Van Ta, T., Cong Huynh, T., Thanh Tran, H., The Pham, H., Simmons, C., Minh Nguyen, T., Van Do, D. Factors Predicting Severe Dengue in Children within 72 Hours of Illness Onset. Arch Pharma Pract 2019;10(3):87-91.

presentation and fever within the first 72 hours of illness; (ii) clinical manifestations of DF; (iii) between the ages of 1–15 years; (iv) consent to participate in the research was provided in writing.

Exclusion criteria were as follows: (i) reevaluated by the study team to achieve a more appropriate diagnosis; (ii) preexisting conditions such as hepatitis, liver failure, kidney failure, sequelae of brain or cerebral palsy and/or musculoskeletal injury.

Sub-clinical laboratory tests

All patients meeting all criteria mentioned above were selected for the study and concurrent RT-PCR. If the RT-PCR result was negative, the patient received an additional NS1 Ag ELISA (BioRad) test. All patients who were hospitalized during follow-up and 10% of the patients enrolled in the original study were randomly selected to be reexamined and to undergo double diagnostic serologic tests for the detection of IgM antibodies. The gold standard for diagnosing dengue is met when one of the RT-PCR NS1 or Ag ELISA tests is positive or if there is the positive transfer of IgM antibodies. Severe cases are defined according to the WHO's 2009 standards as meeting one of the following three criteria: (1) severe plasma loss associated with shock or respiratory failure, (2) severe hemorrhage, and (3) severe organ failure, such as liver failure, impaired acute kidney disease, encephalopathy or myocarditis.[3]

When entering the study, patients' clinical data were collected and blood was taken for hematological tests, biochemistry, and diagnosis of DF. At the same time, patients were monitored every day by phone and visited every one or two days. If the patient was hospitalized, further clinical and paraclinical signs were recorded during hospitalization.

Data analysis

The analysis results were processed using SPSS 12.0 software. Statistical significance was considered when the p-value was less than 0.05.

Ethical approval

The study protocol was granted by the Council of Medical Ethics at TCGP. The purpose of the research was clearly explained to the patients participating in the study, and all interviews were voluntary.

Results

Characteristics of the studied population

A total of 1,039 patients with fever lasting less than 72 hours and who were clinically suspected as having DF participated in the study, including 1,037 cases with sufficient data to be introduced into the analysis. The characteristics of patients are presented in Table 1. There were 283 cases (27.2%) of a definitive diagnosis of DF, of which 13 were severe DF, accounting for 4.6% of the DF cases.

Table 1. Characteristics of studied patients

Variable (n)	Median/ Percentage %(n)
Demographic characteristics	
Age (years) (N=1039)	6 (4-9)
Gender	
Male	56.8% (590)
Female	43.2% (449)
History and clinical characteristics*	
Date of illness on the study (N=1039)	
Day 1	5.8% (60)
Day 2	52.3% (543)
Day 3	42.0% (436)
Body temperature (°C)	
Vomiting (%, n)	42.2% (438)
Abdominal pain (%, n)	27.9% (290)
Skin hemorrhage (%, n)	0.7% (7)
Mucosal hemorrhage (%, n)	1.2% (12)
Blushing face (%, n)	0.8% (8)
Hepatomegaly (%, n)	0.0% (0)
Rash (%, n)	0.2% (2)
Conjunctival hyperemia (%, n)	0.3% (3)
Subclinical*	
WBC[1] (10^3/mm^3)	7.1 (4.7-10.5)
PLT[2] (10^3/mm^3)	231 (185-285)
Hct (%)	37.4 (34.9-39.8)
ALB[3] (g/L)	44.2 (42.3-46.2)
AST[4] (U/L)	43 (36-53)
ALT[5] (U/L)	17 (13-24)
CK[6] (U/L)	94 (71-125)
NS1 Strip[7] (+) (%, n)	19.0% (197)
RT-PCR (+) (%, n)	25.2% (262)
Definitive diagnosis of DF (N = 1039)	27.2% (283)
Hospitalization (%, n)	21.8% (226)
Severe DF (%, n)	1.3% (13)
Serum reaction (N = 299)	
Primary infection	60.5% (181)
Reinfection	39.5% (118)
Serum type (N=262)	
1	29.4% (77)
2	23.3% (61)
3	3.1% (8)
4	44.3% (116)

* All tests were performed when the patients had participated in the study. [1]WBC: white blood cell, [2]PLT: platelet, [3]ALB: albumin, [4]AST: aspartate aminotransferase, [5]ALT: alanine aminotransferase, [6]CK: creatine kinase, [7]NS1 Strip: quick test to detect NS1 DENV.

The results presented include the median and interquartile range for continuous variables, frequency, and percentage for classification variables. In 283 cases of the definitive diagnosis of DF, there were 13 cases of severe DF accounting for 4.6%. The serious complications in our study included the following: shock, severe hemorrhage, and respiratory failure, accounting for 69.2%; 38.5%, and 46.2%, respectively, including some cases of shock accompanied by severe bleeding, respiratory failure or both. Complications of liver failure, central nervous system damage, as well as other organ failures, were not found in our study.

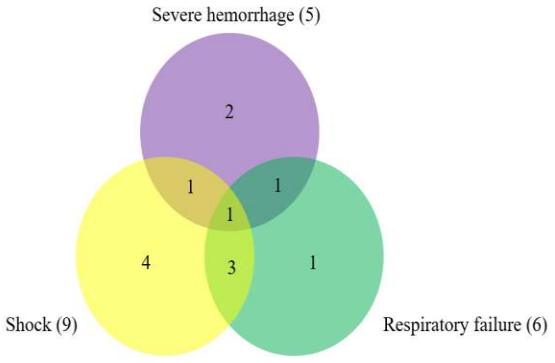

Figure 1. Venn diagram of severe complications of DF

The relationship between epidemiological, clinical, hematological, and biochemical features and serotype type with severe DF

Table 2. The relationship between epidemiological, clinical, hematological, and biochemical features and serotype types with severe DF

Factors	Severe DF (N=13) n (%)	Non-severe DF (N=270) n (%)	OR (95% CI)	P
Age (year)	8 ± 2.6	8.2 ± 3.2		0.859
Male	9 (69.2%)	153 (56.7%)	1.72 (0.52-5.72)	0.376
Day of illness				0.624*
Day 1	1 (7.7%)	17 (6.3%)		
Day 2	4 (30.8%)	120 (44.4%)		
Day 3	8 (61.5%)	133 (49.3%)		
Vomiting	5 (38.5%)	116 (43.0%)	0.83 (0.265-2.602)	0.749*
Abdominal pain	4 (30.8%)	73 (27.0%)	1.2 (0.36-4.01)	0.768*
Mucosal hemorrhage	0 (0%)	5 (1.9%)	1.05 (1.02-1.07)	0.621*
Skin hemorrhage	0 (0%)	6 (2.2%)	1.05 (1.02-1.07)	0.587*
Hepatomegaly	0 (0%)	0 (0%)	-	-
WBC (10^3/mm^3)	4.7 (3-5.4)	4.3 (3.4-5.98)		0.775
PLT ≤ 10^5/mm^3	3 (23.1%)	15 (5.6%)	5.1(1.27-20.50)	0.011*
Hct (%)	40.5 ± 2.7	38.5 ± 3.8		0.059
ALB ≤ 40 g/L	4 (30.8%)	25 (9.3%)	4.36 (1.25-15.17)	0.012*
AST ≥ 80 U/L	8 (61.5%)	45 (16.7%)	8 (2.5-25.58)	<0.001
ALT ≥ 40 U/L	8 (61.5%)	50 (18.5%)	7.04 (2.21-22.43)	<0.001
CK (U/L)	107 (66-165)	107.5 (80-152)		0.861
NS1 Strip (+)	9 (69.2%)	183 (67.8%)	1.07 (0.32-3.57)	0.913
DENV-2 infection	8 (61.5%)	53 (19.6%)	6.55 (2.06-20.84)	<0.001*
Immune response				
Primary infection	2 (15.4%)	43 (30.7%)	0.41 (0.087-1.93)	0.246*
Reinfection	11 (84.6%)	97 (69.3%)	1	

* Using the correct Fisher test

Upon univariate analysis, we obtained results that are shown in **Table 3.**

Table 3. Univariate analysis of variables predicting severe DF

	Univariate analysis		
	OR	95% CI	p
PLT ≤ 10^5/mm^3	5.10	1.27-20.50	**0.011**
ALB ≤ 40 (g/l)	4.36	1.25-15.17	**0.012**
AST ≥ 80 (U/L)	8.00	2.50-25.58	**<0.0001**
ALT ≥ 40 (U/L)	7.04	2.21-22.43	**<0.0001**
DENV-2 (+)	6.55	2.06-20.84	**<0.0001**

In a univariate analysis of the population with laboratory-confirmed dengue, we noted the factors associated with severe dengue during the first 72 hours of fever as follows: platelet count less than or equal to 100,000/mm^3 (OR=5.1, 95% CI: 1.27–20.50, p=0.011), blood albumin level ≤40 g/l (OR=4.36, 95% CI: 1.25–15.17, p=0.012), AST enzyme ≥80 U/L (OR=8.00, 95% CI: 2.50–25.58, p <0.0001), ALT enzyme ≥40 U/L (OR=7.04, 95% CI: 2.21–22.43, p<0.0001) at the time of study entry and DENV-2 infection (OR= 6.55, 95% CI: 2.06-20.84, p<0.0001). These data objectively identified early tests related to cases that will develop into severe DF.

Discussion

Despite improvements in treatment and resuscitation, DF with severe complications is still a cause of many deaths in many Asian and Latin American countries. The mortality rate of DF has decreased over the past two decades and is now less than 1% with appropriate treatment[3] but can be as high as 26% in severe DF if the virus is incorrectly treated. One of the costs of achieving a low mortality rate is the burden placed on the health system for hospitalization and the close monitoring of a large number of cases of DF, rather than outpatient care. The early prognosis of severe DF within the first 72 hours at a clinic is challenging for doctors, even paediatric or infectious-disease specialists. Typical symptoms and signs of complications generally only appear during the dangerous stage from the fourth to the sixth day of the disease.[1] Therefore, in many places, doctors working in clinics or emergency departments often have cautious access to suspected cases of DF, and patients are admitted to the hospital for follow-up. This results in the limited sharing of medical resources, the incorrect classification of patients, unnecessary hospitalization and increased costs for patients.

The mean age of the patients in the study with severe DF was 8.0±2.6 years, and there were no statistically significant differences in the mean age between the two groups of patients with severe and non-severe DF. Nguyen Tien Huy performed a meta-analysis of 26 studies on children with dengue and showed that age is negatively associated with dengue shock syndrome (OR:0.67, 95% CI: 0.54-0.84).[10] Research by K.L. Anders on children admitted to 3 hospitals, including Tropical Hospital in Ho Chi Minh City, Children's Hospital 1 and Children's Hospital 2, from 1996 to 2009, showed that children from 6–10 years of age were at the highest risk of shock; however, the mortality was highest in younger age groups.[11]

The percentage of males with severe DF was 69.2% compared to the non-severe group at 56.7%; however, the difference was not statistically significant. Medical literature has noted a strong relationship between being female and developing DF shock syndrome in many previous studies.[10,11] The most common symptoms aside from fever during the first 72 hours of severe DF are abdominal pain and vomiting, but we found no association between these two symptoms during the first 72 hours and severe DF. Similarly, symptoms that are uncommon in the first 72 hours, such as skin and mucosal haemorrhage and hepatomegaly, have not yet proven to be early prognostic factors for severe DF. This shows that during the first 72 hours of the disease, clinical signs and symptoms of severe DF are very difficult to identify. The distinction (if any) between severe and non-severe groups was based mainly on testing.

In severe cases of DF, our study still showed leukopenia, a median white blood cell count of 4.7 (3–5.4) x 10^3/mm^3, but there was no statistically significant difference between median WBC count in the first 72 hours between the 2 groups of severe and non-severe DF. The average Hct during the first 72 hours in children with severe DF was 40.5±2.7%, higher than those with non-severe DF (38.5±3.8%); however, the difference does not have statistical significance (p=0.059). Ampaiwan Chuansumrit's study showed that an increase in Hct above 25% could be a predictive factor of DF shock during fever, with a correlation risk of 4.8 (95% CI: 1.1–21.3) [12].

In DF, platelet counts tend to decrease during the fever period, then decrease to the lowest during the danger period. Previous

studies often used platelet counts <50,000/mm^3 during the critical period as a marker of severe DF. This level of thrombocytopenia has been shown to be associated with the development of haemorrhagic complications and shock in adults. Our study helps to identify early, within 72 hours, the group of patients with platelet counts less than or equal to 100,000/mm^3 who are at risk of progressing to severe DF (OR=5.10 [1.27-20.50], p= 0.011). In Potts's study, the lowest number of decreased platelets was associated with severe DF in the multivariate analysis model.[13] Ampaiwan Chuansumrit's study showed that a platelet count decrease of less than 40,000/mm^3 could be a predictor of DF shock during fever, with a correlation risk of 7.7 (95% CI, 2.2–26.5).[12]

Along with Hct, blood albumin is considered to be a marker of plasma loss. The decrease in blood albumin and the presence of proteinuria are well recognized in dengue infection. Proteins that are albumin or less in size and including albumin are lost first. This phenomenon is always accompanied by a small but decisive change in the filtering characteristics of glycocalyx (the glucid crust of the cell). Both DENV and NS1 are known to be associated with heparan sulphate, the main structural component of glycocalyx, and increased urine heparin sulphate excretion has been detected in children with severe dengue. All signs of plasma loss (blood concentration, pleural effusion, peritoneal fluid, decreased albumin and decreased blood protein) are strongly associated with DF shock.[10] However, the phenomenon of plasma loss occurred strongly during the dangerous stage of the disease. We investigated whether blood albumin in the early 72-hour period could help predict a severe prognosis of DF. The study results showed that blood albumin ≤40 g/l can be used as a prognostic factor for early severe DF (OR=4.36; 95% CI, 1.25–15.17; p=0.012). This result reinforces that the stage of acute fever, in severe cases of DF, plasma loss still occurs and does so more so than in non-severe DF patients. Our results were consistent with the research of Luis Ángel Villar-Centeno, the author who showed that the concentration of albumin <4g/dl (OR = 3.46; 95% CI, 1.96–6.12; p< 0.001) is associated with the severity of the disease.[14] A study in Vietnam by Nguyen Thi Hanh Tien on children with fever showed that the urine albumin-to-creatinine ratio is higher in DF patients than in other patients, but the difference between the two diagnostic groups in the early stage of fever is poor.[15] Low-grade albuminuria is common, even in relatively mild cases of DF, but is also present in other fevers. Simple testing of urine albumin-to-creatinine ratio is unlikely to be useful in the early diagnosis or prognosis of risk in epidemic zones of DF.

Hepatitis in DF, characterized by the increase of AST and ALT, has a specific pattern. Many documents reported that AST had increased at a higher rate[16] and at a higher ratio than ALT. There was also an increase and decrease in AST before ALT.[16] Although AST is higher than ALT, its origin from the musculoskeletal system or liver has not been proven.[16] In this study, we tried to assess the possibility of increased AST and ALT in the early identification of severe DF. Results showed that AST ≥80 U/L could be a prognostic factor for severe DF in the first 72 hours with OR=8.00 (95% CI, 2.50–25.58), p<0.001. At the same time, ALT ≥40 U/L can also be a prognosis factor for severe early DF in the first 72 hours with OR=7.04 (95% CI 2.21–22.43), p<0.001. In Potts's study, the highest AST concentration, >100 U/L, was found to be associated with severe DF in the multivariate analysis model.[13] The literature noted the association between elevated liver enzymes and heterogeneity. A research group in Thailand showed that AST was associated with DF, while ALT was not; another group showed that both AST and ALT were significantly associated with severe cases (AST p<0.001, ALT p=0.003). Both have been reported to be significantly associated with clinical plasma losses; however, the magnitude of the association was not reported. A study in Vietnam by D.T. Trung found that both AST and ALT were associated with shock.[13] They found that the levels of AST and ALT during the critical period in patients with shock were significantly higher than in the non-shock group (p<0.01). The study also found that liver enzyme elevations were weakly associated with the lowest platelet values. A study in Singapore showed no association between elevated liver enzymes and mortality (AST p=0.14, ALT p=0.11), and another study showed that elevated liver enzymes have not been able to differentiate the classification of severe DF.

Known biomarkers, such as increased AST, ALT, hematocrit and decreased serum albumin and platelets, are associated with severe DF, but the evidence is inconsistent.[10,17] Recently, the concern about creatine kinase as a biomarker for DF has increased. Each of these biomarkers represents a specific basic pathophysiological process. Hct and serum albumin have long been believed to represent plasma loss. The number of platelets and leukocytes also shows a good reflection of the condition. CK reflects muscle injuries, and ALT is related to liver damage.[18] Therefore, we also evaluated whether or not CK enzyme concentration in the first 72 hours can help predict severe DF. The research results have not yet proven this; CK levels in the first 72 hours between two groups of patients with severe and non-severe DF did not differ statistically. Md Sani et al. studied 365 adult DF patients hospitalized in Kuala Lumpur to evaluate CK enzyme in the prognosis of severe DF. The results showed that CK has not been proved to be a valuable marker of serious illness.[18] The research of Leis Angel Villar-Centeno et al. showed that cases of DF have had higher levels of lactate dehydrogenase (LDH), CK and AST and blood albumin, total cholesterol and triglycerides lower than dengue fever, and any increase in CK that occurred 48–96 hours after onset are associated with more severe disease.[17]

In the serotype, Watts et al. found that reinfection of DENV-2 among patients with Asian genes was related to DF and DF shock syndrome in Southeast Asia and the Americas.[19] Furthermore, many previous documents have reported that DENV-2 has been associated with severe DF. Our results were also suitable to show that although DENV-4 have the highest circulation ratio, accounting for 44.3%, in severe DF cases, DENV-2 accounted for the highest rate (61.5%; 8/13 cases), and DENV-2 infection increased the risk of severe DF, OR=6.55 (95% CI, 2.06–20.84), p<0.001. Biswas's results in Nicaragua were similar, with 60% of severe DF cases caused by DENV-2, followed by DENV-3 (25%) and DENV-1 (10%).[20]

A variety of mechanisms has been accepted to explain the increased risk of severe DF in reinfection cases, including the increase of antibody-dependent infections, complement activation by virus-antibody complexes and pathology of T-cell–mediated immunity. Patients with severe DF showed an increase in the concentration of cytokine, interferon-ɤ, and interleukin-2, as well as soluble forms of CD8, CD4, and interleukin-2 receptor α chain. Several studies have shown that patients with severe DF

had decreased levels of C3, C4, and C5 and increased levels of C3a. Biswas's research showed that the rate of primary infection and reinfection had been nearly similar to each other in the cases of DF, while the majority (70%) of severe DF is reinfection.[20] In our study, the classification of the immune response (primary infection, reinfection) was only possible for hospitalizations and 10% of the cases randomized because only these patients had double serum samples for serological tests provided. The results have not yet shown the association between severe DF and reinfection, p=0.246.

Conclusion

Severe DF, including dangerous forms, has contributed to the increase in the mortality rate for children with DF. In the first 72 hours of fever, the Hct of the patient group with severe DF was higher than that of the non-severe group. At the same time, in the first 72 hours, if paediatric patients with low platelet count less than or equal to 100,000/mm^3, blood albumin decreasing ≤40 (g/l), AST increasing ≥80 (U/L) and ALT increasing ≥40 (U/L), they were diagnosed with dengue virus type 2 infection. Clinicians, especially those at the clinic or at the primary health facility, should be instructed to guide diagnosis and management in order to closely monitor this group of patients likely to have a severe progression in the next few days; the intervention can be timely and properly administered to reduce the mortality rate of the disease.

Acknowledgments

We acknowledge our colleagues at Tien Giang Central General Hospital, who have always supported us, and patients in this research with their whole heart. Furthermore, we truly appreciate the patients and their family members who participated in this clinical study.

Conflict of interests

The authors have no conflicts of interest to declare in this work.

Funding

None.

References

1. Ojewumi ME, Adeyemi AO, Ojewumi EO. Oil extract from local leaves-an alternative to synthetic mosquito repellants. Pharmacophore. 2018;9(2):1-6.
2. Ortega AB, Duque P, Liria J, Arrivillaga-Henríquez J, Salazar J, Burgaleta EB, Navarro JC. Mosquito Diversity and Public Services as Risk factors for Emerging Diseases in a Small Village, Ecuador Amazon. Entomology and Applied Science Letters. 2018 Oct 25;5(3):91-105.
3. World Health Organization, Special Programme for Research and Training in Tropical Diseases. Dengue: guidelines for diagnosis, treatment, prevention and control. 2009.
4. Supadmi W, Perwitasari DA, Abdulah R, Suwantika AA. Correlation of rainfall and socio-economic with incidence dengue in Jakarta, Indonesia. Journal of Advanced Pharmacy Education & Research| Jan-Mar. 2019;9(1):134-42
5. Vo NT, Phan TN, Vo TQ. Direct medical costs of dengue fever in Vietnam: A retrospective study in a tertiary hospital. The Malaysian journal of medical sciences: MJMS. 2017 May;24(3):66-72.
6. Pham LD, Phung NH, Le NT, Vo TQ. Economic report on the cost of dengue fever in Vietnam: case of a provincial hospital. ClinicoEconomics and outcomes research: CEOR. 2017;9:1-8.
7. Le NQ, Van Tran T, Tran TT, Dang NT, Truong QK, Vo TQ. The economic impact of asthma treatment on patients, 2014-2017: The Vietnamese experience from a public hospital. JPMA. The Journal of the Pakistan Medical Association. 2019 Jun 1;69(6):S2-9.
8. Nguyen PV, Vo TQ, Nguyen TD, Chung TP, Ho NP. Dengue fever in Southern of Vietnam: A survey of reported knowledge, attitudes, and practices. JPMA. The Journal of the Pakistan Medical Association. 2019 Jun;69(6):S118-30.
9. Vo TQ, Phuong TP. Revisiting dengue-related knowledge, attitudes and practices: A cross-sectional study in Ho Chi Minh City, Vietnam, 2018. JPMA. The Journal of the Pakistan Medical Association. 2019 Jun;69(6):S108-17.
10. Huy NT, Van Giang T, Thuy DH, Kikuchi M, Hien TT, Zamora J, Hirayama K. Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS neglected tropical diseases. 2013 Sep;7(9): e2412.
11. Anders KL, Nguyet NM, Chau NV, Hung NT, Thuy TT, Farrar J, Wills B, Hien TT, Simmons CP. Epidemiological factors associated with dengue shock syndrome and mortality in hospitalized dengue patients in Ho Chi Minh City, Vietnam. The American journal of tropical medicine and hygiene. 2011 Jan 5;84(1):127-34.
12. Chuansumrit A, Puripokai C, Butthep P, Wongtiraporn W, Sasanakul W, Tangnararatchakit K, Chunhakan S, Yoksan S. Laboratory predictors of dengue shock syndrome during the febrile stage. Southeast Asian J Trop Med Public Health. 2010 Mar 1;41(2):326-.
13. Potts JA, Thomas SJ, Srikiatkhachorn A, Supradish PO, Li W, Nisalak A, Nimmannitya S, Endy TP, Libraty DH, Gibbons RV, Green S. Classification of dengue illness based on readily available laboratory data. The American journal of tropical medicine and hygiene. 2010 Oct 5;83(4):781-8.
14. Villar-Centeno LÁ, Lozano-Parra A, Salgado-García D, Herrán ÓF. Biochemical alterations as prediction markers for the severity of illness in dengue fever patients. Biomedica. 2013 Sep;33:63-9.
15. Nguyen TH, Phung KL, Huynh TL, Tran VN, Phan TT, Nguyen TT, Simmons C, Wolbers M, Wills B. Assessment of Microalbuminuria for Early Diagnosis and Risk Prediction in Dengue Infections. PLoS One. 2013. 8(1): e54538.
16. Hien TT, Vinh NN, Hien PT, Chinh NT, Simmons C, Wills B. Liver involvement associated with dengue infection in adults in Vietnam. The American journal of tropical medicine and hygiene. 2010 Oct 5;83(4):774-80.
17. Villar-Centeno LA, Díaz-Quijano FA, Martínez-Vega RA. Biochemical alterations as markers of dengue hemorrhagic fever. The American journal of tropical medicine and hygiene. 2008 Mar 1;78(3):370-4.
18. Sani SS, Han WH, Bujang MA, Ding HJ, Ng KL, Shariffuddin MA. Evaluation of creatine kinase and liver enzymes in identification of severe dengue. BMC infectious diseases. 2017 Dec;17(1):505.
19. Watts DM, Porter KR, Putvatana P, Vasquez B, Calampa C, Hayes CG, Halstead SB. Failure of secondary infection with American genotype dengue 2 to cause dengue haemorrhagic fever. The Lancet. 1999 Oct 23;354(9188):1431-4.
20. Biswas HH, Ortega O, Gordon A, Standish K, Balmaseda A, Kuan G, Harris E. Early clinical features of dengue virus infection in nicaraguan children: a longitudinal analysis. PLoS neglected tropical diseases. 2012 Mar;6(3): e.1562.