Identification of dengue patients with high risk of severe disease, using early clinical and laboratory features, in a resource-limited setting

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Received: 26 November 2019 / Accepted: 26 May 2020

Abstract

Only a minority of dengue infections lead to plasma leakage (critical phase [CP]). Early identification of the risk for CP is helpful for triage of patients. This study aimed to identify early clinical predictors of CP that will aid in patient triage during early illness. A retrospective, case-record-based analysis was performed on all microbiologically confirmed (NS1-antigen- or dengue-IgM-antibody-positive), dengue patients (n = 697), admitted to our unit from 01.01.2017 to 30.06.2017. Bivariate analysis was performed to identify clinical and laboratory parameters that predicted CP. Stepwise multivariate logistic regression with backward elimination ($p < 0.05$) was used to identify independent risk factors for CP. CP developed in 226 (32.4%) patients. Mortality was 1.0%. Predictors for CP ($p < 0.05$) within the first three days included age category 41–50 years (OR = 1.96), females (OR = 2.09), diabetes (OR = 1.30), persistent vomiting (OR = 2.18), platelet count < 120,000/mm^{-3} (OR = 1.91) and AST > 60 IU/L (OR = 3.72). On multivariate analysis, other variables except diabetes remained significant. Elevated transaminase levels remained the strongest independent predictor of CP (OR 2.83). The absence of all five risk factors excluded CP (negative predictive value: 97.2%). Age 41–50 years, female gender, persistent vomiting, thrombocytopenia, and elevated transaminases were early predictors of CP in dengue fever. The absence of these can be used to identify patients who may not require hospital admission. Elevated transaminase was the strongest predictor of CP during early illness.

Introduction

Dengue fever (DF) is one of the most prevalent arbovirus infections throughout the world. It is reported in 128 countries with an estimated at-risk population of 3.97 billion [1]. The annual global incidence of DF is estimated to be 60 million, resulting in 10,000 deaths and 1.14 million disability-adjusted life years (DALYs) [2]. Its economic burden is estimated to be US $ 8.9 billion globally, with a higher impact on countries and individuals with a lower socioeconomic status [3, 4].

Dengue infection is asymptomatic in many individuals. Another large proportion will develop a simple febrile illness, identified as DF. Initial clinical presentation of symptomatic DF is indistinguishable from any other febrile infection, which presents with fever, myalgia, headache and vomiting [5]. Only a few patients develop complications, usually 3–4 days after the onset of fever [6]. The most serious complication is increased vascular permeability leading to plasma leakage (critical phase [CP]), haemorrhage, and haemodynamic collapse that may progress to multi-organ dysfunction and death. Mortality in DF is estimated to be 0.8–2.5% [5]. Extremes of age, obesity, diabetes, and haemolytic diseases have been identified to increase the risk of severe dengue and mortality [5, 6].

Based on the presence or absence of these complications, dengue infection was classified into DF, dengue haemorrhagic fever, and dengue shock syndrome in 1975. This was adopted by the World Health Organization (WHO) in 1997

Handling Editor: Tim Skern.

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[7]. Later, WHO updated this with a simpler classification, where dengue infections were classified as "dengue" and "severe dengue". This classification also identifies "warning signs" to help clinicians triage patients, with CP with progression to severe dengue to receive close monitoring and intensive therapy [5]. However, only a handful of these signs will be evident early in the course of the illness and be useful for early detection of severe disease.

Several attempts have been made to identify risk factors that predict severity and mortality in DF [3, 8–10] . A recent comprehensive literature review confirmed that routinely used parameters such as ALT are poor predictors of severe dengue or liver failure when used alone [11]. Experts agree that there is a relative paucity of validated clinical and laboratory early warning signs to predicting outcome in dengue that can be applied in resource-poor settings. This study aimed to identify the clinical and laboratory markers that are present during the early phase of infection (on or before day 3 of the illness) that predict development of plasma leakage (CP) in DF in a resource-limited setting.

Materials and methods

Study setting

This retrospective study included patients admitted with DF to the University Medical Unit, Colombo North Teaching Hospital (CNTH), Ragama, Sri Lanka. Records of all of the patients admitted with DF over a period of seven months (01.01.2017–30.06.2017) were reviewed.

Definitions

DF was confirmed either by the rapid detection of non-structural protein 1 (NS1) antigen (RapiGEN BIOCREDIT, Republic of Korea, sensitivity 98.5%, specificity 98.6%) or by the detection of dengue IgM antibodies by ELISA (enzyme-linked immunosorbent assay; CE-CTK biotech test kits, United States, sensitivity 96.6%, specificity 98.1%) or both. In accordance to the existing guidelines, onset of CP (plasma leakage leading to severe dengue) was defined as plasma leakage of any degree into serous body cavities (identified by clinical examination, detected and confirmed by serial ultrasound scans of the chest or lateral decubitus chest X-ray for the presence of pleural effusions and clinical examination, or detected and confirmed by ultrasound scan of abdomen for the presence of ascites) or a rise in haematocrit of > 20% from the baseline of a patient or population of same age and gender [5]. Development of the CP was used as the outcome variable, which is the dependent variable.

Data collection

A team of physicians who were not directly involved in the care of these patients carried out the patient record review, data extraction, and data entry. Data on demographic characteristics of the patient, disease characteristics, investigations, daily clinical status, interventions carried out, and outcome were recorded. During data entry, contradictions and abnormal values were rechecked individually with patient records, and further clarifications were made with senior members of the clinical and research teams. Data were entered in duplicate, the databases were compared, and discrepancies were re-corrected by reviewing physical records to improve accuracy.

Missing values ranged from 2 to 4% of the variables of interest. These were replaced with computed values corresponding to the sample mean of each continuous variable. If a dichotomous variable (e.g., headache or vomiting) was not mentioned in the patient record, it was assumed that the symptoms were absent and recorded as a negative. Data were analysed using Stata version 13 (StataCorp, College Station, Texas, USA).

Data analysis

For continuous variables, values are reported as median and interquartile ranges. Dichotomous variables are reported as numbers and percentages. Student's t-test and χ^2 test (or Fisher's exact test, where appropriate) were used to compare continuous and categorical variables, respectively. Bivariate logistic regression was carried out to identify individual risk associations for the development of CP. Risk factors that had a probability < 0.05, were included in stepwise multiple logistic regression analysis (step back) to identify the independent predictors for developing of CP. We also compared the predictive values for the presence of one to four of the identified risk factors compared to the absence of any of the risk factors.

Ethical clearance

Ethical clearance was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka, and permission to carry out the study was obtained from the hospital authorities of CNTH, Ragama, Sri Lanka.

Results

A total of 697 patients were included in the study. Patients with missing values for key haematological and laboratory characteristics for day one were excluded. The median age (IQR) was 32 (21–46), and 340 (48.8%) were females. There

were seven deaths during the study period (mortality: 1.0%). Critical phase (CP) developed in 226 (32.4%) patients.

Patient characteristics of those who developed CP (severe dengue) and those without CP (uncomplicated dengue) are compared in Table 1. Diabetes and hypertension were the common comorbidities seen in 8.6% and 6.9%, respectively. Disease characteristics (clinical features and laboratory values) of patients who developed CP (severe dengue) and patients without CP (uncomplicated dengue) are compared in Table 2. Patients commonly presented between the third and fourth days of the illness. Laboratory values on the day of presentation and those farthest outside the normal range are tabulated separately in Table 2. Patients developed typical haematological and biochemical markers of CP during the fifth and sixth day of the illness. These included lower total white cell counts, lower platelet counts, higher haematocrits, and higher transaminase levels ($p < 0.05$).

The results of the bivariate and multivariate analysis for the independent predictors for the development of CP are presented in Table 3. Independent risk predictors for CP ($p < 0.05$) in the first three days of the illness (at the time of presentation) were as follows: age category 41-50 years (OR = 1.96), female gender (OR = 2.09), diabetes (OR = 1.30), persistent vomiting (OR = 2.18), platelet count of $<120{,}000/mm^{-3}$ (OR = 1.91), and AST > 60 IU/L (OR = 3.72). On multivariate analysis, diabetes was non-significant and the other five factors remained statistically significant: age category 41–50 years (OR = 1.82, $p < 0.05$), female gender (OR = 1.83, $p < 0.01$), persistent vomiting (OR = 2.01, $p < 0.01$), platelet count of $<120{,}000/mm^{-3}$ (OR = 1.88, $p < 0.01$), and AST > 60 IU/L (OR = 2.83, $p < 0.01$) (Table 3). An elevated transaminase level (AST > 60 IU/L) was the strongest independent predictor of development of CP in early DF. Similarly age category 41-50 was the least significant.

We also compared the predictive values for the presence of one to four identified risk factors compared to the absence of any of the risk factors (Table 4). When none of the risk factors were present, CP could be excluded with a negative predictive value of 97.2%. The positive predictive value of having three or more risk factors was 58.2%.

Discussion

Approximately 5% of patients with DF develop severe dengue with CP characterized by plasma leakage [5]. Hospital admission and monitoring of all patients with DF is difficult, especially in the early course of the illness, during large epidemics. It is therefore important to identify predictors of severe dengue (to select patients at risk of CP) during the early stages of febrile illness to triage patients requiring hospital admission and escalation of care.

We report three clinical and two simple laboratory parameters, age category 41-50 years, female gender, persistent vomiting, low platelet count ($<120{,}000/mm^3$), and

Table 1 Patient characteristics

Characteristic	Severe dengue fever (developed CP)		Dengue fever (uncomplicated without CP)		Total		*p* value
	n = 226	n (%)	n = 471	n (%)			
Age category (years)							
< 20	47	(20.8)	106	(22.5)	153	(21.9)	0.61
21–30	53	(23.4)	135	(28.7)	188	(26.9)	0.14
31–40	46	(20.4)	96	(20.4)	142	(20.4)	0.99
41–50	37	(16.4)	42	(8.9)	79	(11.3)	0.04
51–60	26	(11.5)	48	(10.2)	74	(10.6)	0.60
> 61	17	(7.5)	44	(9.3)	61	(8.8)	0.42
Gender							
Male	88	(38.9)	269	(57.1)	357	(51.2)	<0.01
Female	138	(61.1)	202	(42.9)	340	(48.8)	<0.01
Comorbidities							
Diabetes mellitus	34	(15.0)	26	(5.5)	60	(8.6)	<0.01
Hypertension	22	(9.7)	26	(5.5)	48	(6.9)	0.07
Dyslipidemia	9	(3.9)	19	(4.0)	28	(4.0)	0.97
Ischaemic heart disease	4	(1.8)	10	(2.1)	14	(2.0)	0.75
Asthma	8	(3.5)	18	(3.8)	26	(3.7)	0.85
Chronic kidney disease	1	(0.4)	3	(0.6)	4	(0.6)	0.42
Hypothyroidism*	4	(1.8)	5	(1.1)	9	(1.3)	0.44

CP critical phase

Table 2 Disease characteristics

Characteristic	Severe dengue fever (developed CP)		Dengue fever (uncomplicated without CP)		p value[†]
	n = 224		n = 470		
Duration of fever at presentation, mean (standard deviation)	3.14 (1.38)		3.56 (1.52)		<0.01
Clinical symptoms, number (%)					
Nausea	53	(23.4)	126	26.8	0.62
Vomiting	127	(56.2)	160	33.9	<0.01
Diarrhoea	48	(21.2)	94	19.9	0.81
Right hypochondriac pain	76	(33.6)	74	15.7	0.88
Laboratory characteristics (on the day of admission)					
Haemoglobin (g/dl)	13.05	(2.4)	13.35	(2.4)	0.30
Haemotocrit (%)	38.89	(7.7)	39.52	(6.2)	0.11
White cell count (mm^{-3})	4.15	(2.3)	4.25	(2.2)	0.50
Platelet count (10^3 mm^{-3})	94.23	(57.0)	126.77	(49.5)	<0.01
ALT (U/L)	106.46	(88.8)	69.01	(58.9)	0.02
AST (U/L)	184.14	(86.0)	89.13	(65.0)	0.01
Laboratory characteristics (most extreme reading)					
Minimum haemoglobin (g/dl)	11.77	(2.6)	12.40	(2.30)	<0.01
Maximum haematocrit (%)	34.69	(7.1)	36.63	(6.80)	<0.01
Minimum white cell count (10^3 mm^{-3})	2.86	(1.4)	3.10	(1.54)	0.02
Minimum platelet count (10^3 mm^{-3})	27.35	(21.0)	62.16	(54.40)	<0.01
Maximum ALT (U/L)	151.05	(102.30)	109.64	(95.50)	<0.01
Maximum AST (U/L)	242.13	(133.00)	135.72	(121.00)	<0.01

CP critical phase, *ALT* alanine transaminase, *AST* aspartate transaminase

Continuous variables are reported as the mean and SD; dichotomous variables are reported as the number and the percentage

[†] p values were obtained by Wilcoxon rank test for continuous variables and Chi-square test for dichotomous variables

Table 3 Bivariate and multivariate analysis of early disease characteristics to identify patients with increased risk of CP

Early disease characteristic*	Bivariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age category 41–50 years	1.96 (1.22, 3.13)	0.005	1.82 (1.00, 2.73)	< 0.05
Female gender	2.09 (1.51, 2.89)	< 0.01	1.83 (1.12, 2.24)	< 0.01
Vomiting	2.18 (1.57, 3.01)	< 0.01	2.01 (1.43, 2.83)	< 0.01
Diabetes	1.30 (1.08, 2.26)	0.03	1.13 (0.92, 2.26)	0.34
Hypertension	1.73 (0.96, 3.14)	0.07	–	–
Right hypochondriac pain	0.97 (0.63, 1.49)	0.879	–	–
WBC	0.97 (0.90, 1.05)	0.414	–	–
AST (>60)	3.27 (2.23, 4.78)	< 0.01	2.83 (1.89, 4.21)	< 0.01
ALT (>60)	1.72 (1.25, 2.38)	< 0.01	–	–
Platelets < 120×10^3 mm^{-3}	1.91 (1.39, 2.64)	< 0.01	1.88 (1.34, 2.64)	< 0.01

CP critical phase, *CI* confidence interval, *ALT* alanine transaminase, *AST* aspartate transaminase

*Characteristics present during the first three days of the illness. When multiple readings were obtained, the most extreme value occurring on the first three days of the illness was considered

an elevated transaminase level (>60 IU/L) during the first three days of the illness, that predict CP in DF. These are all simple parameters, easily assessed at presentation within the first three days of the illness. The absence of all of these risk factors during the early febrile phase indicates that the development of CP in DF is unlikely. This can reduce unnecessary

Table 4 Odds ratios for development of CP as the number of risk factors increases

Number of risk factors for CP	Odds ratio	95% CI		*p* value
1	6.02	2.51	14.45	0.01
2	8.72	3.64	20.90	<0.001
3	22.14	9.06	54.12	<0.001
4	61.88	19.03	201.18	<0.001

When none of these risk factors are present, CP could be excluded with a negative predictive value of 97.2%. The positive predictive value of having three or more risk factors was 58.2%

CP critical phase, *CI* confidence interval

*Values reported in relation to having no risk factors

hospital admissions and also provide guidance to escalation of monitoring and treatment of already admitted patients.

Previous studies have attempted to identify risk factors that predict the severity in DF in adults. In a study from Malaysia that included 199 patients with severe dengue, mortality was predicted by lethargy, bleeding, low serum bicarbonate, and high lactate [9]. In another retrospective study from Singapore, mortality was predicted by the presence of bleeding, a unit decrease in total protein (g/L), a unit increase in blood urea (mmol/L), and a unit decrease in lymphocyte proportion [3]. A study of over 1100 paediatric patients with DF in Thailand identified patients at low risk for CP based on their total white cell count (>8500/mm^3), monocyte percentage>9%, platelet count (>160,000/mm^3) and haematocrit <40, using a stepwise risk stratification system [10]. In a retrospective analysis, Zhang et al. found that the AST/platelet count ratio index (APRI) best predicted mortality [12]. This was reproduced in another study by Yeh et al., which also found that these values on day 3 had the best predictive value [13]. Another cohort study from Colombo, Sri Lanka, found younger age and higher AST to be associated with severe dengue [14]. Tests for some of these identified risk factors for adults are not routinely preformed on admission and may not be available in resource-poor settings, whereas the risk factors for CP in DF identified in the present study are applicable and can be tested in such settings.

In a study of paediatric patients from Thailand in 2010, Potts et al. found that the white cell count, monocyte count, platelet count and haematocrit showed high sensitivity in predicting severe dengue [10].

Liver involvement in DF is multifactorial [15, 16]. Several studies from different geographical locations, including Thailand, India, Malaysia, Pakistan and Vietnam, have all reported an association between elevated transaminase levels and the severity of dengue infection [17–19]. We observed that the presence of early hepatitis (AST > 60/IU/L) early in the course of illness was the strongest independent predictor of development of CP in DF. A recent study from Sri Lanka found that only right hypochondriac tenderness (which may be the result of hepatic inflammation) was useful as an early clinical predictor for plasma leakage [8]. Another recent study from Sri Lanka demonstrated that, among confirmed dengue patients, younger age and a higher AST level in early infection were associated with subsequent plasma leakage [14]. Therefore, liver involvement in DF seems to be a key initial manifestation that precedes plasma leakage, and further studies are warranted to investigate its pathophysiology.

An early drop in platelet count and persistent vomiting were expected risk factors for severe DF. However, female gender was also identified as an independent risk factor for the development of CP in DF in this study. This may be due to females having a higher percentage of body fat, and it is known that a higher BMI is a risk factor for severe dengue in both adults and children [20, 21]. The age category 41-50 years was also an independent predictor for the development of CP. We could not explain this, but we presume that this group of previously fit individuals may have mounted a good immune response against dengue virus, resulting in a higher immune-mediated propagation of the illness.

There are many newer potential markers of severe dengue that are currently being evaluated [22]. With in-depth understanding of the pathophysiology of severe dengue, the potential to use markers of endothelial dysfunction as early predictors of severe dengue is increasingly recognized. Soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble thrombomodulin, and angiopoietin-2 are altered in dengue and dengue critical phase [13]. Tests of endothelial function such as venous plethysmography, assessment of flow-mediated dilatation of the brachial artery, and peripheral artery tonometry have been evaluated in many conditions with endothelial injury, including severe sepsis [23]. Some of these are being investigated in dengue [22]. However, most of these are still experimental, and even when available may be too expensive to be used in many countries where DF is prevalent.

The strengths of this study are the relatively large number of patients, all with serologically confirmed DF, and the use of only clinical and simple laboratory tests that are routinely carried out in patients with suspected DF at presentation and during the early course of the illness. There are, however, several limitations of this study. This was a retrospective case-record-based study. Therefore, detailed analysis of trends and clinical features of the patients such as pulse rate, blood pressure, vascular filling and treatment required or given to patients was not possible. In order to overcome this, we made every attempt to ensure the accuracy of the collected data, as described in Materials and methods. Another limitation is that this study was limited to hospitalized patients and did not include patients with milder

infections who may not have sought hospital care. Furthermore, although different subtypes of dengue virus are known to cause infections that differ in severity and clinical presentation, we have no data on virus subtypes and their influence on CP illness. The majority of the infections in this study are likely to have been secondary dengue infections. Previous seroprevalence studies from Sri Lanka have reported 68.2% seropositivity for dengue among healthy individuals [24]. We were not able to confirm this by performing a dengue virus IgG ELISA assay for the study population.

In conclusion, age category 41–50, female gender, persistent vomiting, thrombocytopenia, and the presence of elevated transaminases during the first three days of the illness independently predicted the development of severe dengue with CP. Elevated transaminase levels were the strongest predictor of CP, highlighting the importance of liver involvement in the development of severe dengue. In the absence of any of these risk factors during the early febrile phase of DF, the development CP seems unlikely, a finding that can help to triage patients early in the course of DF, especially in a resource-limited setting.

Acknowledgements We thank the many physicians involved in the management of the study population with DF for their assistance in collecting clinical information and preparing the analytical data.

Author contributions MAN, APDeS and HJdeS conceptualized and designed the study. AKMAU collected data. IKL analysed the data assisted by MAN and HJdeS. MAN, KVL, HJdeS and IKL prepared the manuscript. MAN, IKL, KVL, APDeS, and HJdeS were substantially involved in revision of the manuscript. All authors checked the final manuscript before submission.

Funding None.

Data availability statement The datasets generated during and/or analysed during the current study are not publicly available, as during ethical clearance we did not obtain permission to do so, but they are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest None declared.

Ethical approval Granted by the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.

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