Validation of Decision Groups in Patients with Dengue Fever: A Study during 2015 Outbreak in Taiwan

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Abstract. The management of dengue fever (DF) has been suggested to be categorized into decision groups A, B, and C; however, its usefulness in predicting mortality is still unclear, and hence we conducted this study to clarify this issue. We conducted a study by recruiting 2,358 patients with DF from the 2015 outbreak in the Chi-Mei Medical Center. Demographic data, vital signs, clinical symptoms and signs, coexisting morbidities, laboratory data, decision groups categorized according to World Health Organization for clinical management of dengue in 2012, and 30-day mortality rates were included for analysis. The overall 30-day mortality rate was 1.4%. The 30-day mortality rates in decision groups A, B, and C were 0%, 0.5%, and 46.2%, respectively. Compared with Group A, there was a higher mortality risk in Group C (odds ratio [OR]: 1.480, 95% confidence interval [CI]: 1.95–11.200). The area under the curve of the variable of Group C was excellent (OR: 0.92, 95% CI: 0.85–0.99). The sensitivity, specificity, positive predictive value, and negative predictive value for predicting 30-day mortality in Group C were 88.2%, 98.5%, 46.2%, and 99.8%, respectively. This study showed that decision Group C has a good predictive value for 30-day mortality. Further studies including validation in other nations are warranted.

INTRODUCTION

Dengue fever (DF) is a type of mosquito-borne viral infection that causes a heavy global burden on public health because of its dramatically growing incidence in recent decades.^{1,2} Dengue fever is usually found in tropical and subtropical climates worldwide, mostly in urban and semi-urban areas.^{1,2} It has been estimated that 390 million people are infected with DF each year, of whom 96 million show clinical manifestations^{1,2} and 3.9 billion people are at risk of infection with DF.³ Although the mortality is not high when adequate treatment is provided (~1%), the related final burden and loss of productivity are significant.^{1,2} An earlier study reported that the estimated annual expenditure spent on DF is 4.2 million US dollars in Malaysia, including the economic loss caused by forbidden travelers.⁴

Most people infected by dengue virus are asymptomatic or show minor systemic symptoms/signs such as high fever, headache, vomiting, muscle and joint pains, and a characteristic skin rash.^{1,5} Most of them recover completely; however, a small proportion of patients develop severe complications, including bleeding, plasma leakage, organ impairment, shock, and even death.^{1,5} Although the severe cases comprise only a minority of the infected people, identifying those with a high risk of mortality is very difficult.^{6,7} In 2012, the World Health Organization (WHO) suggested a classification into the decision groups by the warning signs, which consist of the following: 1) abdominal pain or tenderness, 2) persistent vomiting, 3) clinical fluid accumulation, 4) mucosal bleeding, 5) lethargy and restlessness, 6) liver enlargement > 2 cm, and 7) laboratory findings such as increase in hematocrit level

concurrent with a rapid decrease in platelet count.⁸ Patients without any of the warning signs are classified into Group A and they may be sent home.⁸ If the patients had negative warning signs but had coexisting conditions (such as pregnancy, infancy, old age, obesity, diabetes mellitus, hypertension, heart failure, renal failure, chronic hemolytic diseases such as sickle-cell disease, and autoimmune diseases) and social circumstances (such as living alone or living far from a health facility without reliable means of transport), then they are classified into Group B and referred for in-hospital care.⁸ Patients in Group C comprise those with positive warning signs and any of the following: 1) plasma leakage with shock and/or fluid accumulation with respiratory distress, 2) severe bleeding, or 3) severe organ impairment.⁸ If patients with positive warning signs do not fit the criteria of Group C, they are also classified into Group B.⁸ Emergency treatments are suggested for patients in Group C, including admission to the hospital and blood transfusion and fluid resuscitation as needed.⁸ However, the clinical usefulness of the decision groups for predicting mortality has not been validated, and hence we conducted this study to delineate this issue.

METHODS

Study design, setting, and participants. We conducted this retrospective case-control study in the Chi-Mei Medical Center (CMMC), a 1,276-bed tertiary medical center in southern Taiwan, which provides emergency care to nearly 145,000 patients, outpatient service to 1,600,000 patients, and admission service to 370,000 patients annually.⁹ We retrospectively collected the medical records of all the patients who visited CMMC and were diagnosed with DF from September 1, 2015 to December 31, 2015 (Figure 1). Dengue fever was defined based on the diagnosis by the treating physician according to the criteria, including 1) laboratory-confirmed

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FIGURE 1. Flowchart of this study. CMMC = Chi-Mei Medical Center; DF = dengue fever.

DF (i.e., nonstructural protein 1 [NS1], immunoglobulin M [IgM], and immunoglobulin G [IgG]), 2) residents in or had been to dengue-endemic areas, and 3) fever and two of the following symptoms: rash, nausea or vomiting, aches and pains, positive tourniquet test, leukopenia, and any warning sign.⁸ The test for NS1, IgM, and IgG in the study hospital is by SD BIOLINE Dengue Duo kit (Standard Diagnostics, Inc). According to the WHO guideline, the laboratory data are not necessary for the clinical diagnosis except in atypical cases or when carrying out differential diagnosis with other infectious diseases.⁸

Patients who had no data for 30-day mortality or had been treated in other hospitals were excluded.

Variables and collection of data. We collected all patients' demographic characteristics, vital signs, symptoms/signs, underlying comorbidities, laboratory data, decision groups, and 30-day mortality. Three trained registered nurses who were blinded to the hospital course and outcome of the recruited patients reviewed the data collection retrospectively. The decision groups A, B, and C were defined according to the criteria of the WHO.⁸ Outpatient clinic appointments were made with the patients in Group A who were sent home. A variable was defined negative if it was absent in the medical record.

Primary outcome. We defined the 30-day mortality as the primary outcome.^{10–12}

Ethics statement. This study was approved by the institutional review board at CMMC and strictly conducted according to the Declaration of Helsinki. All data were anonymized. The informed consent of the participants was waived because of the retrospective design of the study.

Statistical methods. One-way analysis of variance for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables were used for the univariate analysis among the three decision groups. Logistic regression was used for comparing the risk for 30-day mortality in the three decision groups. Because the mortality in Group A (reference group) was 0, we added "0.5" to it to calculate the odds ratio (OR) by logistic regression analyses. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were analyzed for predicting the 30-day mortality

TABLE 1
Comparison of demographic characteristics, vital signs, and symptoms/signs of dengue fever patients among the three decision groups

Variable	All N = 2,358 (100%)	Group A N = 1,469 (62.3%)	Group B N = 824 (34.9%)	Group C N = 65 (2.8%)	P value*
Age (years)	47.8 ± 21.9	38.4 ± 18.3	62.7 ± 18.5	70.5 ± 15.0	< 0.001
Gender					0.583
Male	1,161 (100)	735 (63.3)	396 (34.1)	30 (2.6)	–
Female	1,197 (100)	734 (61.3)	428 (35.8)	35 (2.9)	–
BMI (kg/m ²)	24.0 ± 4.7	23.7 ± 5.0	24.2 ± 4.5	24.5 ± 3.6	0.250
GCS ≤ 8	11 (100)	1 (9.1)	5 (45.5)	5 (45.5)	< 0.001
SBP (mm of Hg)	136.5 ± 27.5	133.6 ± 22.9	141.5 ± 27.8	135.0 ± 42.2	< 0.001
HR (beat/minutes)	98.2 ± 21.1	101.6 ± 20.5	92.8 ± 20.7	91.9 ± 20.0	< 0.001
BT (°C)	37.6 ± 1.2	37.7 ± 1.1	37.5 ± 1.2	37.8 ± 1.4	< 0.001
Symptoms/signs					
Fever/chills	1,996 (100)	1,295 (64.9)	651 (32.6)	50 (2.5)	< 0.001
Muscle soreness	849 (100)	595 (70.1)	245 (28.9)	9 (1.1)	< 0.001
Joint pain	113 (100)	70 (61.9)	42 (37.2)	1 (0.9)	0.432
Headache	461 (100)	321 (69.9)	132 (28.6)	8 (1.7)	0.001
Nausea/vomiting	442 (100)	228 (51.6)	198 (44.8)	16 (3.6)	< 0.001
Abdominal pain	304 (100)	143 (47.0)	152 (50.0)	9 (3.0)	< 0.001
Skin rash	287 (100)	214 (74.6)	66 (23.0)	7 (2.4)	< 0.001
Back pain	43 (100)	29 (67.4)	14 (32.6)	0 (0)	0.481
Diarrhea	253 (100)	136 (53.8)	112 (44.3)	5 (2.0)	0.004
Poor appetite	318 (100)	157 (49.4)	151 (47.5)	10 (3.1)	< 0.001
General malaise	576 (100)	294 (51.0)	259 (45.0)	23 (4.0)	< 0.001
Retro-orbital pain	44 (100)	34 (77.3)	9 (20.5)	1 (2.3)	0.114
Cough	200 (100)	117 (58.5)	75 (37.5)	8 (4.0)	0.343
Dizziness	292 (100)	114 (49.3)	139 (47.6)	9 (3.1)	< 0.001
Altered mental status	25 (100)	3 (12.0)	16 (64.0)	6 (24.0)	< 0.001
Dyspnea	90 (100)	30 (33.3)	49 (54.4)	11 (12.2)	< 0.001
Chest tightness	52 (100)	26 (50.0)	26 (50.0)	0 (0)	0.045
Ecchymosis/petechiae	21 (100)	5 (23.8)	15 (71.4)	1 (4.8)	0.001
Bleeding†	229 (100)	70 (30.6)	150 (65.5)	9 (3.9)	< 0.001

BMI = body mass index; BT = body temperature; GCS = Glasgow Coma Scale; HR = heart rate; SBP = systolic blood pressure. Data are expressed as n (%) or mean ± standard deviation.

* Comparison among the three decision groups.

† Included gum bleeding, epistaxis, vaginal bleeding, hematuria, gastrointestinal bleeding, and hemoptysis.

in the decision Group C. The area under the curve of Group C was also reported.

RESULTS

In total, 2,358 patients with DF comprising 1,161 males and 1,197 females were recruited in this study (Figure 1). Based on the WHO criteria, 1,469 patients were classified into decision Group A (62.3%), 824 patients were classified into Group B (34.9%), and 65 patients were classified into Group C (2.8%) (Table 1). Laboratory data showed that 85.8% of patients had positive NS1, 15.8% of patients had positive IgM, and 10.3% of patients had positive IgG.

The mean age ($\pm$ standard deviation) of all the patients was 47.8 ($\pm$ 21.9) years. Patients in Group C were older (70.5 ± 15.0 years) than those in Group B (62.7 ± 18.5 years) and Group A (38.4 ± 18.3 years) ($P < 0.001$). The parameters Glasgow Coma Scale ≤ 8 , nausea/vomiting, abdominal pain, poor appetite, general malaise, dizziness, altered mental status, dyspnea, ecchymosis/petechiae, bleeding, and underlying comorbidities, except liver cirrhosis, were significantly more common in groups B and C than in Group A (Table 2). Patients in Group C had higher levels of white blood cell count, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, high-sensitivity C-reactive protein, glucose, blood urea nitrogen, serum creatinine, and higher percentage of bacteremia and respiratory failure with intubation but lower levels of hemoglobin, platelet, and albumin than those in Group B and Group A (Table 2). Analyses of the Group C showed that 96.9% of patients received emergency treatment in the emergency department, 100% of patients received fluid resuscitation, 84.6% of patients received treatment with antibiotics, 81.5% of patients received blood transfusion, 10.8%

of patients received intubation, 10.8% of patients received treatment with vasopressor, and 96.6% of patients were admitted to the intensive care unit. All the patients in Group C were treated according to the WHO guidelines.⁸ The overall 30-day mortality rate was 1.4% (34/2,358). Septic shock was the major cause of death (88.2%, 30/34). The 30-day mortality rates of each decision group were 0% (0/1,469), 0.5% (4/824), and 46.2% (30/65) in groups A, B, and C, respectively (Table 2).

Compared with Group A, Group C had a significantly higher risk of mortality (OR: 1,475.0, 95% confidence interval [CI]: 194.3–11,197.9) (Table 3). Group B also had a higher 30-day mortality risk than Group A; however, the difference was not significant (OR: 7.2, 95% CI: 0.8–64.5) (Table 3). The sensitivity, specificity, PPV, and NPV for predicting the 30-day mortality in Group C were 88.2%, 98.5%, 46.2%, and 99.8%, respectively (Table 4). The area under the receiver operating characteristic curve of decision Group C for predicting 30-day mortality was excellent (OR: 0.92, 95% CI: 0.85–0.99) (Figure 2).

DISCUSSION

This study showed that the majority of patients with DF were classified into groups A and B. Patients in Group C were of older age and had more severe clinical symptoms/signs and poorer laboratory data and outcomes than those in Group B and Group A. The mortality risk was 0% in Group A and only 0.5% in Group B; however, it increased up to 46.2% in Group C. Patients in Group C had 1,475 times of mortality risk than those in Group A. Group C had an excellent discrimination, with 98.5% specificity and 99.8% NPV for predicting 30-day mortality, which suggested that using decision groups is a

TABLE 2

Comparison of underlying comorbidities, laboratory data, and 30-day mortality of dengue fever patients among the three decision groups

Variable	All N = 2,358 (100%)	Group A N = 1,469 (62.3%)	Group B N = 824 (34.9%)	Group C N = 65 (2.8%)	P value*
Underlying comorbidity					
Diabetes mellitus	327 (100)	61 (18.7)	235 (71.9)	31 (9.5)	< 0.001
Hypertension	603 (100)	104 (17.2)	453 (75.1)	46 (7.6)	< 0.001
Cancer	108 (100)	18 (16.7)	84 (77.8)	6 (5.6)	< 0.001
Chronic kidney disease	73 (100)	7 (9.6)	51 (69.9)	15 (20.5)	< 0.001
End-stage renal disease	29 (100)	5 (17.2)	17 (58.6)	7 (24.1)	< 0.001
Coronary artery disease	123 (100)	15 (12.2)	95 (77.2)	13 (10.6)	< 0.001
Congestive heart failure	43 (100)	3 (7.0)	38 (88.4)	2 (4.7)	< 0.001
Chronic obstructive pulmonary disease	33 (100)	3 (9.1)	27 (81.8)	3 (9.1)	< 0.001
Stroke	87 (100)	17 (19.5)	66 (75.9)	4 (4.6)	< 0.001
Liver cirrhosis	7 (100)	2 (28.6)	5 (71.4)	0 (0)	0.126
Chronic bedridden	13 (100)	2 (15.4)	7 (53.8)	4 (30.8)	< 0.001
Laboratory data					
White blood cell count (cells/mm ³)	5,101.5 $\pm$ 2,928.6	5,049.7 $\pm$ 2,595.3	5,070.9 $\pm$ 3,256.0	6,643.1 $\pm$ 4,703.0	< 0.001
Hemoglobin (g/dL)	13.8 $\pm$ 4.8	14.1 $\pm$ 5.6	13.5 $\pm$ 3.0	12.2 $\pm$ 2.9	< 0.001
Hematocrit (%)	41.1 $\pm$ 22.3	41.8 $\pm$ 22.1	39.8 $\pm$ 19.8	40.9 $\pm$ 45.7	0.124
Platelet (10 ³ /mm ³)	153.5 $\pm$ 79.2	174.4 $\pm$ 71.5	119.8 $\pm$ 78.9	114.7 $\pm$ 87.3	< 0.001
GOT (U/L)	83.4 $\pm$ 273.6	47.4 $\pm$ 53.8	97.6 $\pm$ 154.7	592.3 $\pm$ 1,293.9	< 0.001
GPT (U/L)	50.2 $\pm$ 121.3	39.5 $\pm$ 51.7	57.2 $\pm$ 72.3	190.9 $\pm$ 609.5	< 0.001
Hs-CRP (mg/L)	19.4 $\pm$ 35.0	12.2 $\pm$ 21.3	23.2 $\pm$ 40.0	54.2 $\pm$ 58.5	< 0.001
Glucose (mg/dL)	140.4 $\pm$ 65.8	123.8 $\pm$ 43.5	154.2 $\pm$ 74.7	186.8 $\pm$ 112.4	< 0.001
BUN (mg/dL)	20.5 $\pm$ 19.8	13.6 $\pm$ 14.1	21.5 $\pm$ 18.8	38.4 $\pm$ 29.4	< 0.001
Serum creatinine (mg/dL)	1.1 $\pm$ 1.3	0.9 $\pm$ 1.2	1.2 $\pm$ 1.0	2.7 $\pm$ 3.1	< 0.001
Albumin (g/dL)	3.3 $\pm$ 0.6	3.8 $\pm$ 0.5	3.3 $\pm$ 0.5	3.0 $\pm$ 0.6	< 0.001
Bacteremia	58 (100)	4 (6.9)	36 (62.1)	18 (31.0)	< 0.001
Respiratory failure with intubation	10 (100)	0 (0)	3 (30.0)	7 (70.0)	< 0.001
30-day mortality	34 (100)	0 (0)	4 (11.8)	30 (88.2)	< 0.001

BUN = blood urea nitrogen; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; Hs-CRP = high-sensitivity C-reactive protein. Data are expressed as n (%) or mean $\pm$ standard deviation.

* Comparison among the three decision groups.

TABLE 3

Comparison of the risk for 30-day mortality among the three decision groups by logistic regression analysis

Variable	OR	95% CI	P value
Group A	1 (reference)	—	—
Group B	7.2	0.8–64.5	0.078
Group C	1,475.0	194.3–11,197.9	< 0.001

CI = confidence interval; OR = odds ratio.

good method to select patients with DF with a high risk of mortality and provide them more intensive care.

Plasma leakage is the result of increased capillary permeability during the transition from the febrile to afebrile phase.⁸ Before plasma leakage, progressive leukopenia always develops first and is then followed by a rapid decrease in platelet count.¹³ An increasing hematocrit above the baseline usually precedes the changes in blood pressure and pulse volume.^{14,15} Pleural effusion and ascites are the two common manifestations of plasma leakage that can be detected by X-ray or ultrasound.⁸ In addition to plasma leakage, hemorrhagic manifestations such as easy bruising and bleeding at venipuncture sites are also commonly found.⁸ If a critical volume of plasma is lost through leakage, shock may develop and further cause metabolic acidosis and progressive organ impairments, such as hepatitis, renal failure, encephalitis, and myocarditis, and bleeding and disseminated intravascular coagulation.⁸

The patients classified as Group C are suggested to be admitted to a hospital with access to blood transfusion facilities.⁸ Intravenous fluid resuscitation with isotonic crystalloid solution or colloid solution to maintain an effective circulation during the period of plasma leakage is the essential treatment.⁸ Before starting intravenous fluid therapy, obtaining a reference hematocrit is suggested.⁸ Blood transfusion is only indicated in severe bleeding or unexplained hypotension.⁸ The goals of fluid resuscitation are improving central, peripheral, and end-organ perfusions.⁸ The patients classified as Group B are suggested to be admitted to the hospital because they approach the critical phase.⁸ The treatments are volume replacement and close monitoring.⁸ The patients in Group A may be sent home with outpatient management, including a clear and definitive advice of the care at home (i.e., bed rest and frequent oral fluid),⁸ paracetamol for high fever, and return back to the hospital if the condition deteriorates.⁸ All the patients in the present study were treated according to the WHO guidelines.⁸

Using the decision groups has the disadvantage that several warning signs need laboratory tests, which makes it difficult to practice in a DF outbreak with overwhelming suspected patients. For example, “liver enlargement > 2 cm” may need ultrasonography to examine the liver size, “clinical fluid accumulation” may need chest X-ray to verify the existence of pleural effusion and ultrasonography to verify ascites,

TABLE 4

Sensitivity, specificity, PPV, and NPV for predicting 30-day mortality in decision Group C

Variable	Sensitivity	Specificity	PPV	NPV
Group C	88.2%	98.5%	46.2%	99.8%

NPV = negative predictive value; PPV = positive predictive value. Relative to Group C, Group A and Group B are combined together for the analysis.

FIGURE 2. Area under the curve of Group C for predicting 30-day mortality. ROC = receiver operating characteristic. This figure appears in color at www.ajtmh.org.

and blood test is needed to assess hematocrit and platelet count. Another disadvantage in using the decision groups is the unclear border of the criteria of warning signs. For example, what is the degree to which “abdominal pain or tenderness,” “persistent vomiting,” “clinical fluid accumulation,” “mucosal bleeding,” “lethargy,” “hematocrit increase,” and “platelet decrease” fit the criteria? Several other decision methods have been proposed in addition to the decision groups proposed by the WHO. A study in Singapore proposed a “decision tree algorithm” to help predict the diagnosis and outcome in DF.¹⁶ The decision tree uses body temperature and simple blood tests, including white cell count, neutrophil count, lymphocyte count, hematocrit, and platelet, as the “node” for predicting the possibility of DF, and platelet, hematocrit, and IgG for predicting severe dengue in patients with DF.¹⁶ Another study in Singapore used bleeding, urea level, and total protein level to help select patients at high risk for dengue hemorrhagic fever among adult patients with DF.^{17,18} In 2013, a study in Vietnam developed a clinical decision rule to predict recurrent shock in DF.¹⁹ This study proposed the following five independent predictors for recurrent shock: admission day, purpura/ecchymosis, ascites/pleural effusion, blood platelet count, and pulse pressure.¹⁹ All the above-mentioned three methods have the advantage of more clear-cut decision points and provided another choice for clinical practice; however, further validation with more patients and other nations is warranted.

The strength of this study is that it is the first study to validate the 30-day mortality risk in DF stratified by decision groups; however, there are still some limitations. First, some variables may not have been collected completely because of the retrospective nature of the study. Second, this study was conducted in a tertiary medical center, indicating that the severity of patients might be higher than that of general DF patients, and therefore it might not reflect the real picture of

patients with DF. Third, despite the relatively large sample size of this study, the results may not be generalized to other nations because of the differences in race, medical treatment, types of dengue infection, and culture.

CONCLUSION

This study showed that although patients in decision Group C comprised only 2.8% of the total patients, the 30-day mortality rate was 46.2%, which was 1,475 times that in Group A. Using warning signs as the fundamental basis for classification, decision Group C showed an excellent discrimination, with 98.5% specificity and 99.8% NPV for predicting the 30-day mortality. Despite the abovementioned advantage, the decision groups have the disadvantages of requiring laboratory tests and unclear border of the criteria of warning signs. Further studies including validation in other nations and difficulties of the classification of decision groups are warranted.

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