Observational Study

Predicting the mortality in geriatric patients with dengue fever

Hung-Sheng Huang, MD[a,b], Chien-Chin Hsu, MD, PhD[a,c], Je-Chiuan Ye, PhD[d], Shih-Bin Su, MD, PhD[b,e,f], Chien-Cheng Huang, MD, PhD[a,b,d,g,h,*], Hung-Jung Lin, MD, MBA[a,c,i]

Abstract

Geriatric patients have high mortality for dengue fever (DF); however, there is no adequate method to predict mortality in geriatric patients. Therefore, we conducted this study to develop a tool in an attempt to address this issue.

We conducted a retrospective case–control study in a tertiary medical center during the DF outbreak in Taiwan in 2015. All the geriatric patients (aged ≥65 years) who visited the study hospital between September 1, 2015, and December 31, 2015, were recruited into this study. Variables included demographic data, vital signs, symptoms and signs, comorbidities, living status, laboratory data, and 30-day mortality. We investigated independent mortality predictors by univariate analysis and multivariate logistic regression analysis and then combined these predictors to predict the mortality.

A total of 627 geriatric DF patients were recruited, with a mortality rate of 4.3% (27 deaths and 600 survivals). The following 4 independent mortality predictors were identified: severe coma [Glasgow Coma Scale: ≤8; adjusted odds ratio (AOR): 11.36; 95% confidence interval (CI): 1.89–68.19], bedridden (AOR: 10.46; 95% CI: 1.58–69.16), severe hepatitis (aspartate aminotransferase >1000 U/L; AOR: 96.08; 95% CI: 14.11–654.40), and renal failure (serum creatinine >2 mg/dL; AOR: 6.03; 95% CI: 1.50–24.24). When we combined the predictors, we found that the sensitivity, specificity, positive predictive value, and negative predictive value for patients with 1 or more predictors were 70.37%, 88.17%, 21.11%, and 98.51%, respectively. For patients with 2 or more predictors, the respective values were 33.33%, 99.44%, 57.14%, and 98.51%.

We developed a new method to help decision making. Among geriatric patients with none of the predictors, the survival rate was 98.51%, and among those with 2 or more predictors, the mortality rate was 57.14%. This method is simple and useful, especially in an outbreak.

Abbreviations: AOR = adjusted odds ratio, AST = aspartate aminotransferase, CDC = Centers for Disease Control, CI = confidence interval, CMMC = Chi-Mei Medical Center, DF = dengue fever, ECOG = Eastern Cooperative Oncology Group, GCS = Glasgow Coma Scale, hs-CRP = high-sensitivity C-reactive protein, IRB = Institutional Review Board, NPV = negative predictive value, PPV = positive predictive value, WBC = white blood cell, WHO = World Health Organization.

Keywords: dengue fever, elderly, geriatric, mortality, prediction

1. Introduction

Dengue fever (DF) is one of the prevalent arthropod-borne infections worldwide, especially in the tropics and subtropics, affecting 50 to 100 million people annually.[1–3] The prevalence of DF has increased 5-fold on average in the past 20 years, which resulted in an increased demand for and consumption of medical resources.[4] The majority of DF patients present subclinical or self-limiting symptoms; however, some patients, especially the

elderly, may develop serious complications such as coagulopathy, plasma leakage syndrome, and even death.[5] The reasons for the higher severity of DF in geriatric patients than in younger population include the high number of both comorbidities and hospital-acquired infections.[6]

The proportion of geriatric population (aged ≥65 years) is estimated to be rapidly increasing, from 6.2% of the world population in 1992 to 20% by 2050. Hence, DF in the geriatric patients becomes a very important issue, especially in an outbreak with limited medical resources and time. There is an expected age-related mortality in DF.[6] Although there are some studies reporting geriatric DF, the prediction of mortality in this population is still unclear. The World Health Organization (WHO) proposes 3 decision groups to help case management; however, the primary setting is not for the geriatric patients and the criteria for warning signs and severe dengue are not precise, which may limit the clinical use.[5] In 2015, there was a DF outbreak in Taiwan, which resulted in a significant number of geriatric patients infected with DF and related mortality. Therefore, we conducted this retrospective hospital-based case–control study to intend to develop a new, simple, and practical method for predicting mortality in geriatric DF patients.

2. Methods

2.1. Study design and setting

Chi-Mei Medical Center (CMMC) is a 1276-bed tertiary medical center that provides emergency care to approximately 145,000 patients, outpatient clinical service to 1,600,000 patients, and admission service to 370,000 patients annually in southern Taiwan.[7] In the DF outbreak in 2015, CMMC became the major care facility, especially for the severe cases in the endemic area. We retrospectively collected the medical records of all the geriatric patients (aged ≥65 years) with DF who visited CMMC between September 1, 2015, and December 31, 2015, for this study (Fig. 1). DF was defined in accordance with the criteria including laboratory-documented DF (i.e., nonstructural protein 1, immunoglobulin M, and immunoglobulin G), residents in dengue-epidemic areas or had been to the place, and fever and 2 of the following symptoms: rash, nausea or vomiting, aches and pains, positive tourniquet test, leukopenia, and any warning sign.[5]

Three trained registered nurses reviewed the medical records of the recruited patients. Consensus was made after consultation with the corresponding authors (CCH and HJL) in case of any question about the records. We included the following variables: age, sex, body mass index, vital signs, symptoms and signs, laboratory data, comorbidities, living status, decision group, and 30-day mortality. Patients with incomplete records about basic demographic data or outcome or treated in another hospital were excluded. The recruited patients were divided into the case (with mortality) and control (without mortality) groups for comparison.

2.2. Definitions of the variables and outcome measurement

We classified age into 3 subgroups as follows: young elderly (65–74 years), moderately elderly (75–84 years), and old elderly (≥85 years).[8,9] We defined categorical variables as follows: severe coma: Glasgow Coma Scale ≤8,[10] hypotension: systolic blood pressure <90 mm Hg,[11] tachycardia: heart rate >100/min,[12] bedridden: Eastern Cooperative Oncology Group
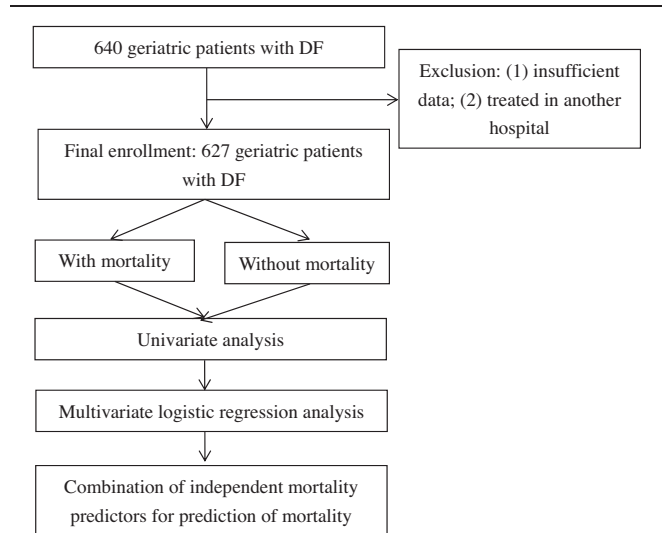

Figure 1. Flowchart of the study. DF = dengue fever.

(ECOG) score of 4 that included completely disabled, totally restrained in the bed or chair, and disabled to perform self-care activities,[13] anemia: hemoglobin <10 g/dL,[12] severe hepatitis: aspartate aminotransferase (AST) >1000 U/L,[14] and renal failure: serum creatinine >2 mg/dL.[11] Based on the WHO guideline for the severity of DF in 2012, we also divided the patients into decision groups A, B, and C.[5] We used 30-day mortality as the outcome measurement.[8,9,12]

2.3. Ethics statement

This study was approved by the Institutional Review Board at CMMC. Because this study was a retrospective observational study, informed consent from the patients was waived and the welfare of the patients was not affected.

2.4. Statistical analysis

We used data from Taiwan Centers for Disease Control (CDC) that reported 43,784 DF cases and 214 fatalities during the DF outbreak in 2015[15] to calculate the power for this study. The power was calculated as >0.999 using G*power 3.1.9.2 for analysis. Independent sample t test or Mann–Whitney–Wilcoxon test for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables were used to analyze the differences among the variables between the 2 groups. We included the variables with $P < .1$ by univariate analysis into multivariate logistic regression analysis to identify the independent mortality predictors, which were further combined together to predict the mortality. Bootstrapping method was used to evaluate the stability of the predictors.[9] We generated 1000 hypothetical study populations by using random sampling from actual study patients.[9] Coefficient point estimates with the reduced model for each hypothetical study population were estimated.[9] Hosmer–Lemeshow goodness of fit test was used to test the fit of the independent mortality predictors. We used a subset of patients (i.e., comorbidity of hypertension) to validate the independent mortality predictors. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for different combinations of independent mortality predictors are reported. We used SPSS version 20.0 to perform all the statistical analyses. The significance level was set at 0.05 (2 tails).

3. Results

In total, there were 627 patients recruited into this study, of which 27 patients (4.3%) had mortality (Table 1). Patients with mortality were of significantly older age than patients without mortality (mean ± standard deviation: 77 ± 7.45 vs 73.95 ± 6.19, $P = .046$). There was a trend of increased mortality rate among age subgroups [young elderly (65–74 years) vs moderately elderly (75–84 years) vs old elderly (≥85 years): 3.1% vs 4.9% vs 10.4%]. No significant difference was observed between the 2 sexes. Patients with mortality had a significantly higher percentage of severe coma, hypotension, dyspnea, anemia, decreased hematocrit, severe hepatitis, renal impairment, decreased albumin, prolongation of activated partial thromboplastin time, bacteremia, respiratory failure, comorbidity of diabetes mellitus, chronic kidney disease, coronary artery disease, and chronic bedridden, and higher white blood cell (WBC) counts and high-sensitivity C-reactive protein (hs-CRP) than patients without mortality (Tables 1–3, Tables 1, 2, and 3). The mortality rates in the 3 decision groups A, B, and C were 0%, 0.3%, and 48%, respectively.

We selected the variables with $P < .1$ and clinical significance in the univariate analysis for multivariate logistic regression analysis to investigate the independent mortality predictors. The selected variables were old elderly, severe coma, hypotension, diabetes mellitus, bedridden, WBC, anemia, severe hepatitis, hs-CRP, and renal failure. The multivariate logistic regression analysis revealed the following 4 independent mortality predictors: severe coma [adjusted odds ratio (AOR): 11.36; 95% confidence interval (CI): 1.89–68.19], bedridden (AOR: 10.46; 95% CI: 1.58–69.16), severe hepatitis (AOR: 96.08; 95% CI: 14.11–654.39), and renal failure (AOR: 6.03; 95% CI: 1.50–24.246) (Table 4). Bootstrapping methods also showed significant in the 4 independent mortality predictors (all $P < .05$). Hosmer–Lemeshow goodness of fit test showed a good fit in the 4 independent mortality predictors (all $P > .1$). The 4 independent mortality predictors remained significant in the geriatric DF patients with hypertension.

Furthermore, we combined the 4 independent mortality predictors to predict the mortality. The sensitivity, specificity, PPV, and NPV for patients with one of more predictors were 70.37%, 88.17%, 21.11%, and 98.51%, respectively (Table 5), and for patients with two or more predictors, the respective values were 33.33%, 99.44%, 57.14%, and 98.51%. Because there were no patients with 3 or more predictors, we could not evaluate their performance.

4. Discussion

The mortality rate of 4.3% observed among the geriatric DF patients in this study was higher than that in the general population (0.5%) reported by Taiwan CDC.[15] The mortality rate showed an increasing trend when we compared among the 3 age subgroups. Because of the differences in severity, distribution of patients, and definition of DF, a difference in the reported mortality among the studies about geriatric DF has been reported in the literature. A study in another tertiary medical center in Taiwan reported that geriatric DF patients had a 7.6% mortality rate, which was significantly higher than that in nongeriatric

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Table 1

Demographic characteristics, vital signs, and symptoms/signs of all the geriatric patients with DF[*].

Variable	All n = 627 (100%)	With mortality n = 27 (4.3%)	Without mortality n = 600 (95.7%)	P[‡]
Age, y	74.09 ± 6.28	77.0 ± 7.45	73.95 ± 6.19	.046
Age subgroup				
Young elderly (65−74 y)	353 (100)	11 (3.1)	342 (96.9)	.056
Moderately elderly (75−84 y)	226 (100)	11 (4.9)	215 (95.1)	
Old elderly (≥85 y)	48 (100)	5 (10.4)	43 (89.6)	
Sex				
Female	329 (100)	14 (4.3)	315 (95.7)	>.999
Male	298 (100)	13 (4.4)	285 (95.6)	
BMI, kg/m²	24.12 ± 4.00	24.99 ± 2.83	24.07 ± 4.05	.218
Severe coma (GCS ≤8)	10 (100)	3 (30)	7 (70)	.006
SBP, mm Hg	145.64 ± 29.85	140.93 ± 49.47	145.85 ± 28.7	.612
Hypotension (SBP < 90 mm Hg)	14 (100)	4 (28.6)	10 (71.4)	<.001
HR, beat/min	89.33 ± 19.05	88.67 ± 26.86	89.36 ± 18.66	.895
BT, °C	37.58 ± 1.18	38.06 ± 1.76	37.56 ± 1.15	.153
Symptoms/signs				
Fever/chills	495 (100)	22 (4.4)	473 (95.6)	.929
Muscle soreness	157 (100)	2 (1.3)	155 (98.7)	.053
Joint pain	34 (100)	1 (2.9)	33 (97.1)	>.999
Headache	93 (100)	3 (3.2)	90 (96.8)	.784
Nausea/vomiting	147 (100)	8 (5.4)	139 (94.6)	.587
Abdominal pain	94 (100)	3 (3.2)	91 (96.8)	.784
Skin rash	28 (100)	3 (10.7)	25 (89.3)	.114
Back pain	6 (100)	0 (0)	6 (100)	>.999
General malaise	219 (100)	12 (5.5)	207 (94.5)	.393
Retro-orbital pain	4 (100)	1 (25)	3 (75)	.162
Dyspnea	44 (100)	6 (13.6)	38 (86.4)	.008
Ecchymosis/petechiae	11 (100)	1 (9.1)	10 (90.9)	.386
Bleeding[‡]	27 (100)	1 (3.7)	26 (96.3)	>.999

Data are expressed as n (%) or mean ± standard deviation.

BMI = body mass index, BT = body temperature, DF = dengue fever, GCS = Glasgow Coma Scale, GI = gastrointestinal, HR = heart rate, SBP = systolic blood pressure, .

[*] Not every patient had all the data.

[†] Comparison between patients with and without mortality.

[‡] Bleeding included gum bleeding, epistaxis, vaginal bleeding, hematuria, GI bleeding, and hemoptysis.

Table 2

Comparison of comorbidities and living status in all the geriatric DF patients*.

Variable	All n = 627 (100%)	With mortality n = 27 (4.3%)	Without mortality n = 600 (95.7%)	P†
Comorbidity				
Diabetes mellitus	220 (100)	15 (6.8)	205 (93.2)	.038
Hypertension	395 (100)	19 (4.8)	376 (95.2)	.544
Cancer	69 (100)	3 (4.3)	66 (95.7)	>.999
Chronic kidney disease	58 (100)	11 (19)	47 (81)	<.001
Coronary artery disease	88 (100)	8 (9.1)	80 (90.9)	.040
Congestive heart failure	34 (100)	0 (0)	34 (100)	>.999
Chronic obstructive pulmonary disease	28 (100)	1 (3.6)	27 (96.4)	>.999
Stroke	64 (100)	1 (1.6)	63 (98.4)	.509
Liver cirrhosis	3 (100)	0 (0)	3 (100)	>.999
Pressure ulcer	65 (100)	1 (16.7)	5 (83.3)	.233
Bedridden	13 (100)	3 (23.1)	10 (76.9)	.015
Smoking	20 (100)	1 (5)	19 (95)	.591
Alcoholism	16 (100)	1 (6.2)	15 (93.8)	.510
Living status				>.999
With family	598 (100)	26 (4.3)	572 (95.7)	
Alone	22 (100)	1 (4.5)	21 (95.5)	
Long-term care	7 (100)	0 (0)	7 (100)	

Data are expressed as n (%) or mean ± SD.
DF = dengue fever.
* Not every patient had all the data.
† Comparison between patients with and without mortality.

patients (0.8%, P = .006).[16] Another study in Puerto Rico reported 0.9% mortality rate in geriatric patients (aged >65 years), which was significantly higher than 0.1% in the youth (aged 2–18 years).[17] Despite the difference, several studies have proved that older age is a risk factor for mortality after infection due to the decline of physiologic functions and increased comorbidities.[16,18–20]

Severe coma predicted mortality in geriatric DF patients. Altered mental status including lethargy and restlessness is one of the warning signs of DF, suggesting a more serious infection.[5]

Table 3

Comparison of laboratory data and decision groups in all the geriatric DF patients*.

Variable	All n = 627 (100%)	With mortality n = 27 (4.3%)	Without mortality n = 600 (95.7%)	P†
Laboratory data				
WBC, cells/mm³	5488.57 ± 3342.92	7500 ± 4911.13	5397.14 ± 3230.14	<.036
Band, %	1.2 ± 5.39	6.0 ± 15.88	0.98 ± 4.23	.113
Neutrophil, %	73.42 ± 14.79	77.15 ± 18.48	73.24 ± 14.58	.307
Lymphocyte, %	14.49 ± 10.01	8.74 ± 5.62	14.77 ± 10.1	<.001
Atypical lymphocyte, %	4.43 ± 4.08	3.34 ± 2.28	4.52 ± 4.18	.079
Anemia (hemoglobin < 10 g/dL)	46 (100)	5 (10.9)	41 (89.1)	.04
Hematocrit (%)	38.73 ± 18.99	34.95 ± 10.25	38.9 ± 19.28	.071
Platelet, 10³/μL	114.4 ± 34.948	94.85 ± 94.45	115.28 ± 78.88	.278
AST, U/L	142.96 ± 449.78	990.84 ± 1685.05	95.22 ± 130.52	.014
Severe hepatitis (AST > 1000 U/L)	10 (100)	6 (60)	4 (40)	<.001
ALT, U/L	67.54 ± 206.6	348.08 ± 912.7	54.86 ± 67.89	.114
hs-CRP, mg/L	29.03 ± 46.75	75.81 ± 75.45	25.84 ± 42.48	.008
Glucose, mg/dL	161.01 ± 81.75	196 ± 133.36	159.32 ± 78.19	.176
BUN, mg/dL	27.54 ± 24	46.9 ± 33.43	26.04 ± 22.52	.010
Renal impairment (serum creatinine > 2 mg/dL)	64 (100)	11 (17.2)	53 (82.8)	<.001
Albumin, g/dL	3.19 ± 0.55	2.85 ± 0.62	3.26 ± 0.51	.009
PT (s)	11.9 ± 9.37	12.94 ± 4.36	11.8 ± 9.69	.295
aPTT (s)	41.69 ± 21.66	68.59 ± 40.4	39.26 ± 17.28	.002
Bacteremia	49 (100)	10 (20.4)	39 (79.6)	<.001
Respiratory failure	6 (100)	5 (83.3)	1 (16.7)	<.001
Decision group				
Group A	73 (100)	0 (0)	73 (100)	.061
Group B	503 (100)	2 (0.3)	501 (99.7)	<.001
Group C	50 (100)	24 (48.0)	26 (52.0)	<.001

Data are expressed as n (%) or mean ± SD.
ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, DF = dengue fever, hs-CRP = high-sensitivity C-reactive protein, PT = prothrombin time, WBC = white blood cell count.
* Not every patient had all the data.
† Comparison between patients with and without mortality.

Table 4

Independent mortality predictors in geriatric DF patients by univariate and multivariate logistic regression analyses.

Variable	OR (95% CI)	AOR (95% CI)[*]	P
Severe coma (GCS ≤ 8)	10.59 (2.58–43.49)	11.36 (1.89–68.19)	.008
Bedridden	0.041 (1.91–28.54)	10.46 (1.58–69.16)	.015
Severe hepatitis (AST > 1000 U/L)	42.57 (11.17–162.241)	96.08 (14.11–654.39)	<.001
Renal impairment (serum creatinine >2 mg/dL)	7.10 (31.13–16.08)	6.03 (1.50–24.24)	.011

[*] Adjusted for old elderly, severe coma, hypotension, diabetes mellitus, bedridden, WBC, anemia, severe hepatitis, hs-CRP, and renal failure when appropriate.
AOR = adjusted odds ratio, AST = aspartate aminotransferase, CI = confidence interval, DF = dengue fever, GCS = Glasgow Coma Scale, hs-CRP = high-sensitivity C-reactive protein, OR = odds ratio, WBC = white blood cell.

However, altered mental status is difficult to define, and therefore severe coma that we used in the present study becomes a more practical variable in clinical practice, especially in an outbreak with limited time for healthcare providers. Severe coma has been recognized as a predictor for poor prognosis in geriatric medicine. For example, a study on geriatric fever in the emergency department reported that severe coma predicts mortality.[9] There was a 10-fold risk for mortality in geriatric patients with severe coma compared to geriatric patients without severe coma.[9] Another study reported that severe coma predicted mortality in patients with hyperglycemic crisis.[12] The odds ratio for mortality between patients with and without severe coma was 6.6 (95% CI: 1.8–24.0).[12]

Bedridden, defined as an ECOG score of 4,[13] was an independent mortality predictor in this study. Another common tool for evaluating performance status is the Karnofsky scale[21]; however, it is more complex and unpractical to perform for patients with suspected DF in the emergency department or outpatient clinic than the ECOG score. Bedridden are the most severe form of functional decline and a component of frailty.[22] Several studies have reported that frailty predicts morality in the elderly, including the surgical outcome,[23–26] and therefore identification and treatment of the frail elderly becomes a very important issue in the aging society.[26]

Severe hepatitis showed the highest risk for mortality, with an AOR of 96.08 in this study. Hepatic injury is not uncommon in patients with DF as a result of the virus directly attacking the liver cells or due to virus-related unregulated host immune change.[27] We defined severe hepatitis as AST >1000 U/L because the WHO 2009 dengue guidelines defined it as a criterion for severe dengue.[14] A study on DF reported that 95% of the inpatients had elevated AST (median of 174 IU/L; interquartile range: 87–371.5 IU/L) and 86% had elevated glutamic pyruvic transaminase (median of 88.50 IU/L; IQR: 43.25–188 IU/L).[28] In addition, AST > 300 IU/L in DF patients was associated with prolonged length of hospitalization and higher mortality rate.[28]

Chronic kidney disease is associated with all-cause mortality.[29] In this study, we defined "renal failure" as serum creatinine >2 mg/dL and found that it predicted mortality in geriatric DF patients. We did not classify renal failure into acute or chronic because most patients did not have previous data to be compared with. Although this limitation existed, the result in this study was compatible with previous studies that renal failure whether acute or chronic is associated with mortality in DF.[5,16,29] Hypotension, plasma leakage, aging-adherent renal alternation, and bacteremia were predicted to be the causes of acute renal failure in geriatric DF patients.[16,30] With increasing age, various glomerular and tubule-interstitial diseases could be commonly observed in the elderly, and aged arterial and arteriolar renal disease has been found susceptible to insults.[16]

Although this study has the strength of providing a new method to predict mortality and help decision making in geriatric DF, there are some limitations. First, the data were collected from 1 medical center and several cases were more severe than patients in other hospitals because CMMC is a tertiary medical center responsible for the critical cases in the endemic area, which might not reflect the general picture for all the geriatric patients. The interpretation in this study may not be suitable for the patients in the primary or secondary care facilities. Second, some data were not complete because of the retrospective design of this study. Third, this result may not be generalized to other hospitals or nations and further studies are warranted to validate it in the future.

5. Conclusions

This study showed that the mortality rate in geriatric DF patients was 4.3%. The following 4 independent predictors were identified that help us predict the mortality: severe coma, bedridden, severe hepatitis (AST >1000 U/L), and renal failure (serum creatinine >2 mg/dL). Among the geriatric DF patients with none of the predictors, the survival rate was 98.51%, whereas it was 57.14% among those with 2 or more predictors. This new method is simple and practical and may help healthcare providers to make decision, especially in an outbreak.

Table 5

Sensitivity, specificity, PPV, and NPV for mortality in geriatric DF patients.

Number of independent mortality predictors	≥1	≥2
Sensitivity, %	70.37	33.33
Specificity, %	88.17	99.44
PPV, %	21.11	57.14
NPV, %	98.51	98.51

DF = dengue fever, NPV = negative predictive value, PPV = positive predictive value.

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