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Clinical and Laboratory Characteristics and Risk Factors for Fatality in Elderly Patients with Dengue Hemorrhagic Fever

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Abstract. To better understand the clinical and laboratory characteristics and to identify risk factor(s) for fatality in elderly patients with dengue hemorrhagic fever (DHF), 66 elderly (age ≥ 65 years) and 241 non-elderly adults (age, 19–64 years) with DHF were retrospectively analyzed. Compared with non-elderly adults, elderly individuals had significantly lower incidences of fever ($P = 0.002$), abdominal pain ($P = 0.003$), bone pain ($P < 0.001$), and skin rashes ($P = 0.002$); higher frequencies of concurrent bacteremia ($P = 0.049$), gastrointestinal bleeding ($P = 0.044$), acute renal failure ($P = 0.001$), and pleural effusion ($P = 0.010$); higher incidence of prolonged prothrombin time ($P = 0.025$); lower mean hemoglobin level ($P < 0.001$); longer hospitalization ($P = 0.049$); and a higher fatality rate ($P = 0.006$). Five elderly patients with DHF died. When compared with non-fatal elderly patients with DHF, a significant higher frequency in men ($P = 0.019$), those with chronic obstructive pulmonary disease ($P = 0.008$), those with dengue shock syndrome (DSS; $P < 0.001$), and those with acute renal failure ($P < 0.001$) was found in the elderly counterparts that died. Multivariate analysis showed that only DSS (odd ratio = 77.33, $P = 0.001$) was an independent risk factor for fatality in elderly patients.

INTRODUCTION

Dengue fever (DF) has been re-emerging over the last several decades, with an estimate of 50–100 million people infected annually and > 2.5 billion people living in geographic areas where the disease is endemic.[1,2] Clinical manifestations in dengue illness caused by dengue virus (DEN) range from sub-clinical or self-limited DF, to mild form dengue hemorrhagic fever (DHF) to the severe form DHF, dengue shock syndrome (DSS).[3,4] In Taiwan, a large dengue epidemic caused by DEN-2 virus occurred in the southern end of this island between June and December 2002.[5] In this epidemic, a large number of patients were adults in general and elderly individuals in particular,[5,6] which was in sharp contrast to the predominant pediatric patients seen in the dengue epidemics in southeast Asia.[7,8] Of note, advanced age *per se* has been previously reported to be a high risk factor for mortality in dengue virus infection.[9,10] Garcia-Rivera and Rigau-Perez[10] reported that the elderly seemed to be more likely than younger adults to develop severe illness when they were infected with DEN. Although dengue illness involving pediatric patients has been well studied,[3,7,8] little is known about dengue infection in adults and in elderly patients in particular. In view of the rapid expanding population of dengue infection around the globe,[1,2] it is essential to have a more comprehensive understanding of the clinical characteristics of dengue illness in adults, especially those in the elderly.[11] The aim of this study is to better understand the clinical characteristics of DHF in elderly and non-elderly adults, emphasizing the distinction of clinical manifestations of DHF between them, and to identify risk factor(s) for fatality in the elderly population.

MATERIALS AND METHODS

We conducted a retrospective study of adult patients with acute DHF admitted between June 1 and December 31, 2002 at Chang Gung Memorial Hospital-Kaohsiung, a 2,500-bed medical facility serving as a primary care and tertiary referral center in southern Taiwan. The medical charts of the included DHF patients were reviewed for collection of demographic, clinical, laboratory, and imaging information.

The diagnosis of dengue infection in a DEN-infected patient was based on one of the following criteria: 1) a positive reverse transcriptase-polymerase chain reaction result, 2) a positive enzyme-linked immunosorbent assay result for specific immunoglobulin M antibody for DEN in acute phase serum, or 3) at least 4-fold increase in dengue-specific hemagglutination inhibition titers in convalescent serum compared with that in acute-phase serum.[12,13] In the serologically confirmed DEN-infected patients, diagnosis of DHF was made based on the presence of hemorrhagia, thrombocytopenia ($< 100 \times 10^9$ cells/L), and clinical evidence of plasma leakage resulting from increased vascular permeability.[4] The severity of DHF was categorized into grades I–IV according to the World Health Organization (WHO) criteria.[4] DHF grade III was defined as circulatory failure manifested by a rapid and weak pulse, with narrowing pulse pressure (≤ 20 mm Hg), and DHF grade IV as profound shock, with undetectable pulse or blood pressures; DHF grades III and IV were collectively grouped as DSS.[4]

An elderly patient referred to one whose age was ≥ 65 years.[14] Gallbladder edema was defined as a thickened gallbladder wall > 3.5 mm.[15] Concurrent bacteremia was defined as a positive bacterial growth from blood that was sampled for culture within 72 hours after the patient was hospitalized for DHF. Acute renal failure (ARF) in adults with DHF was defined as a rapid increase in serum creatinine up to > 2 mg/dL in a patient with original normal kidney function or doubling of the baseline serum creatinine value within 3 days if he or she has an underlying chronic renal disease.[16] The diagnosis of rhabdomyolysis was made in a patient with abnormally high serum creatine kinase (normal, < 120 U/L) coupled with the presence of myoglobin in blood and/or urine.[17] Fatality referred to all-cause death within 1 week in patients with DHF.

The included patients were divided into two groups: the

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TABLE 1
Demographic, clinical, and imaging characteristics of 307 adult patients with dengue hemorrhagic fever*

Variable	Elderly (≥ 65 years) (N = 66)	Non-elderly (19–64 years) (N = 241)	P
Age (years; mean ± SD)	70.2 ± 4.7	48.8 ± 11.9	< 0.001
Male/female (%)	31 (47)/35 (53)	108 (44.8)/133 (55.2)	0.781
Underlying disease/condition† (%)			
Diabetes mellitus	19 (28.8)	43 (17.8)	0.058
Hypertension	35 (53)	57 (23.7)	< 0.001
Previous stroke	16 (24.2)	8 (3.3)	< 0.001
COPD	15 (22.7)	6 (2.5)	< 0.001
Chronic renal disease	10 (15.2)	4 (1.7)	< 0.001
Corticosteroid use	17 (25.8)	4 (1.7)	< 0.001
Malignancy	4 (6)	4 (1.7)	0.068
Heart disease	2‡ (3)	3§ (1.2)	0.293
DSS (%)	7 (10.6)	11 (4.6)	0.077
Length of fever (day; mean ± SD)	4.4 ± 2.5	4.5 ± 1.9	0.454
Acute renal failure (%)	8 (12.1)	4 (1.7)	0.001
Rhabdomyolysis, n/N (%)	3/7 (42.9)	0/4 (0)	0.236
Concurrent bacteremia,¶ n/N (%)	4/23 (17.4)	2/59 (3.4)	0.049
Receiving antibiotic therapy (%)	19 (28.8)	42 (17.4)	0.054
Pleural effusion (bilateral or unilateral), n/N (%)	26/46 (56.5)	60/173 (34.7)	0.010
Gallbladder edema, n/N (%)	16/31 (51.6)	73/131 (42.2)	0.693
Ascites, n/N (%)	10/31 (32.3)	54/131 (41.2)	0.418
Length of hospital stay (day; mean ± SD)	7.9 ± 4.9	6.3 ± 2.9	0.049
Fatality (%)	5 (7.6)	2 (0.8)	0.006

* Figures in the table refer to the number of patients (%), unless stated otherwise.
† An individual patient might have more than one underlying disease/condition.
‡ Both patients had coronary heart disease.
§ Two patients had coronary heart disease and one had aortic valve regurgitation.
¶ Of the four bacteremic patients in the elderly group, *Klebsiella pneumoniae* was isolated in two, *Moraxella lacunata* in one, and *Enterococcus faecalis* in another one; in the non-elderly group, *Klebsiella pneumoniae* was isolated in one patient, whereas *Rosemonas* species was isolated in another one.
COPD = chronic obstructive pulmonary disease; DSS = dengue shock syndrome; n/N = no. of patients/no. of patients with data available.

elderly (≥ 65 years of age) and non-elderly (19–64 years of age). Patients in the elderly group were further divided into fatal and non-fatal subgroups. We used univariate analysis to compare the demographic, clinical, laboratory, and imaging characteristics of patients between the elderly and non-elderly groups and variables between the fatal and non-fatal elderly subgroups. In univariate analysis, Student t test or Mann-Whitney U test was used for comparison between continuous variables, whereas the χ^2 test or Fisher exact test was used to assess differences between dichotomous variables. Significant variables in univariate analyses between the fatal and non-fatal subgroups were entered into a multivariate logistic regression model to identify the risk factor(s) for fatality in the elderly patients with DHF. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Sixty-six (31 men and 35 women; mean age, 70.2 ± 4.7 years) elderly and 241 (108 men and 133 women; mean age, 48.8 ± 11.9 years) non-elderly adults with DHF were included in this study; fever (ear temperature > 38°C) was found in 90.9% of the former and 99.2% of the latter ($P = 0.002$). The two leading symptoms other than fever and hemorrhagia among the 66 elderly were headache (45.4%) and cough (37.8%), whereas among the 241 non-elderly adults were bone pain (61%) and abdominal pain (53.9%). Demographic, clinical, and imaging information (Table 1), symptoms/signs (Table 2), and laboratory data (Table 3) of the included patients are summarized.

Between the elderly and non-elderly adults with DHF in this series, we found that the elderly group had significantly higher prevalences of hypertension, previous stroke, chronic obstructive pulmonary disease, chronic renal disease, and corticosteroid use (Table 1); higher incidences of concurrent bacteremia, gastrointestinal bleeding, acute renal failure, and pleural effusion (Table 1); lower frequencies of fever, abdominal pain, bone pain, and skin rashes (Table 2); higher incidence of prolongation of prothrombin time (PT) and

TABLE 2
Symptoms and signs of 307 adult patients with dengue hemorrhagic fever*

Symptom/sign	Elderly (≥ 65 years) [N = 66 (%)]	Non-elderly (19–64 years) [N = 241 (%)]	P
Fever	60 (90.9)	239 (99.2)	0.002
Abdominal pain	22 (33.3)	130 (53.9)	0.003
Bone pain	24 (36.4)	147 (61)	< 0.001
Retro-orbital pain	8 (12.1)	28 (11.6)	1.0
Headache	30 (45.4)	111 (46.1)	1.0
Arthragia	7 (10.6)	35 (14.5)	0.545
Cough	25 (37.8)	84 (34.9)	0.665
Myalgia	12 (18.2)	35 (14.5)	0.446
Rashes†	10 (15.2)	83 (34.4)	0.002
Dizziness	16 (24.2)	42 (17.4)	0.217
Nausea/vomiting	11 (16.7)	37 (15.4)	0.848
Diarrhea	7 (10.6)	39 (16.2)	0.332
Any hemorrhagic 5sign‡	56 (84.8)	216 (89.6)	0.279
Petechiae	35 (53)	158 (65.6)	0.084
Gastrointestinal bleeding	21 (32)	47 (19.5)	0.044
Gum bleeding	11 (17)	52 (21.6)	0.492
Hematuria	7 (10.6)	21 (8.7)	0.632
Hemaptysis	9 (13.6)	21 (8.7)	0.245
Subconjunctival hemorrhage	3 (4.5)	3 (1.2)	0.116
Epistaxis	1 (1.5)	6 (2.5)	1.0
Menorrhage	0	8 (3.3)	

* An individual patient might have more than one symptom and/or sign.
† Skin rash referred to the erythematous maculopapular lesions that developed on the trunk and/or limbs.
‡ One patient might have more than one hemorrhagic manifestation.

TABLE 3
Laboratory data of 307 adult patients with dengue hemorrhagic fever*

Variable	Elderly (≥ 65 years) (N = 66)	Non-elderly (19–64 years) (N = 241)	P
Peripheral WBC			
Leukopenia (< 4.0×10^9 cells/L) (%)	33 (50)	132 (54.8)	0.578
Leukocytosis (> 10.0×10^9 cells/L) (%)	6 (9.1)	12 (5)	0.236
Atypical lymphocytosis (> 5% of WBC), n/N (%)	37/61 (61)	116/221 (52.5)	0.310
Thrombocytopenia (< 100×10^9 cells/L) (%)	66 (100)	241 (100)	1.0
Hemoglobin (g/dL; mean ± SD)	12.9 ± 2.0	13.9 ± 2.1	< 0.001
Prolongation of APTT†, n/N (%)	36/37 (97.3)	126/135 (93.3)	0.692
Prolongation of PT‡, n/N (%)	3§/33 (9)	1§/134 (0.7)	0.025
AST (reference value < 40 U/L; mean ± SD)¶	352.9 ± 739.0	237.2 ± 600.4	0.653
ALT (reference value < 40 U/L; mean ± SD)**	175.5 ± 293.8	148.4 ± 399.9	0.596
Albumin (reference range, 3.5–4.5 g/dL; mean ± SD)††	3.1 ± 0.4	3.21 ± 0.5	0.155

* Data are number of patients (%), unless otherwise indicated.
† Prolongation of APTT was defined as one > 20% than that of control.
‡ Prolongation of PT was defined as one > 3 seconds than that of control.
§ All of the four patients had concurrent prolongation of APTT; none of them developed bacteremia.
¶ Data were available in 52 patients in the elderly group and in 201 patients in the non-elderly group.
** Data were available in 48 patients in the elderly group and in 157 patients in the non-elderly group.
†† Data were available in 29 patients in the elderly group and in 117 patients in the non-elderly group.
n/N = no. of patients/no. of patients with data available; WBC = white cell count; APTT = activated partial thromboplastin time; PT = prothrombin time; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

lower mean hemoglobin level (Table 3); longer hospital stay; and a higher fatality rate (Table 1). The incidence of DSS between the elderly and non-elderly groups was not statistically significantly different, although there was a trend suggesting a predilection for development of DSS in elderly patients with DHF (10.6% versus 4.6%; $P = 0.077$; Table 1). Concurrent prolongation of activated partial thromboplastin time (APTT) and PT was found in four patients (three of them were elderly) in this series, and active gastrointestinal bleeding developed in two of them (Table 3). Of note, the overall hemorrhagic events were not significantly different between the elderly and non-elderly patient groups ($P = 0.279$; Table 2).

Between the fatal ($N = 5$) and non-fatal ($N = 61$) subgroups in the elderly DHF patients, univariate analyses showed significant differences in male sex, chronic obstructive pulmonary disease, DSS, and acute renal failure (Table 4). Despite the higher prevalence of diabetes mellitus in the elderly group (Table 1), no significant difference in proportion of the underlying diabetes mellitus was found between the fatal and non-fatal subgroups (Table 4). Multivariate analysis showed that DSS (odd ratio = 77.33, with 95% confidence interval = 6.479–923.112; $P = 0.001$) was an independent risk factor for fatality in elderly patients with DHF.

DISCUSSION

To our knowledge, this is one of the few studies on DHF involving elderly patients.[9,10] Considering the trend of popu-

TABLE 4
Characteristics of the fatal ($N = 5$) and non-fatal ($N = 61$) subgroups in elderly patients (≥ 65 years) with dengue hemorrhagic fever*

Variable	Fatal ($N = 5$)	Non-fatal ($N = 61$)	P
Male:female ratio	5:0	26:35	0.019
Underlying condition† (%)			
Diabetes mellitus	1 (20)	18 (29.5)	1.0
Hypertension	3 (60)	32 (52.5)	1.0
Previous stroke	2 (40)	14 (23)	0.588
COPD	4 (80)	11 (18)	0.008
Chronic renal insufficiency	2 (40)	8 (13.1)	0.162
Corticosteroid used	1 (20)	16 (26.2)	1.0
Heart disease	0 (0)	2 (3.3)	1.0
DSS (%)	4 (80)	3 (4.9)	< 0.001
Rhabdomyolysis, n/N (%)	1/1‡ (100)	2/6§ (33.3)	0.429
Acute renal failure (%)	4 (80)	4 (6.6)	< 0.001
Gastrointestinal bleeding (%)	3 (60)	18 (29.5)	0.316
Concurrent bacteremia,¶ n/N (%)	2/5 (40)	2/18 (11.1)	0.194
No. patients with inappropriate antibiotic(s) therapy for concurrent bacteremia**/total patients (%)	1/2 (50)	1/2 (50)	1.0
Leukopenia (< 4.0×10^9 cells/L) (%)	2 (40)	31 (51)	1.0
Leukocytosis (> 10.0×10^9 cells/L) (%)	2 (40)	4 (6.6)	0.061
Hemoglobin (g/dL), median (range)	10.3 (9.7–18.7)	12.8 (7.3–18.3)	0.494
Pleural effusion (unilateral or bilateral), n/N (%)	4/5 (80)	22/41 (53.7)	0.369

* Data are number of patients (%), unless otherwise indicated.
† An individual patient might have more than one underlying condition.
‡ Acute renal failure developed in this patient.
§ Acute renal failure developed in one of these patients.
¶ Two *Klebsiella pneumoniae*, one *Moraxella lacunata,* and one *Enterococcus faecalis* isolates each were found in one individual patient.
** Inappropriate antibiotic therapy referred to the *in vitro* nonsusceptibility of the subsequently isolated bacterium from blood of the patient to the empirically administered antibiotic(s).
n/N = no. of patients/no. of patients with data available; COPD = chronic obstructive pulmonary disease; DSS = dengue shock syndrome.

lation aging in developed countries,[18] better understanding the characteristics in elderly patients with DHF is very important. Physiologic functions decline in aging people, making the elderly hosts subjected to higher risk of infection-related mortality and morbidity.[19–21] Biologic changes with aging (in hosts with coexisting underlying diseases in particular) often alter the otherwise typical clinical manifestations of an infectious disease in the affected patient.[19–21] Our data showed that, in the elderly population with DHF, fever was found in ~90%, and other clinical presentations such as abdominal pain, bone pain, and skin rashes were also found to be less frequently presented compared with their younger counterparts (Table 1); these findings highlight the importance of a diligent search for other clinical, laboratory and imaging manifestations (see Tables 1–3) of DHF in suspicious afebrile elderly patients in a dengue-endemic setting. Alertness to potential DHF and careful assessment of the increased capillary permeability may help avoid complications resulting from delayed identification of DHF in elderly patients.

In DHF, the intrinsic pathway of the coagulation cascade is triggered by thrombin (initially formed by tissue pathway and then rapidly inhibited) activating coagulation factor XI through positive feedback.[22,23] Factor XI generates additional thrombin by activation of factors IX and X.[22,23] Patients with DHF had a relatively lower level of thrombin-activatable fibrinolysis inhibitor.[22,23] Hemostasis defect in patients with DHF mainly results from an inadequate factor XI/thrombin/thrombin-activatable fibrinolysis inhibitor feedback loop, which leads to an imbalance between coagulation and fibrinolysis.[22,23] The trigger of the intrinsic pathway of the coagulation cascade is the major explanation of why prolonged APTT and normal PT were observed in a substantial number of patients with DHF.[22,23] Of note, in this series, prolonged PT was exclusively found in the elderly patients in whom no overt coexisting factors were seen (e.g., concurrent bacteremia), leading to disseminated intravascular coagulopathy (Table 3).[24] The pathophysiology of prolonged PT in these elderly patients with DHF is unclear. Because of the small number of cases, there was a lack of power to determine whether the concurrent APTT and PT prolongation aggravated hemorrhagia in the affected patients in this series.

Rhabdomyolysis was previously reported to be observed mainly in younger adults (< 35 years of age) with dengue virus infection.[25–27] As for the pathogenesis of rhabdomyolysis in dengue illness, direct invasion of muscle by dengue virus has not been unequivocally shown, and it was hypothesized that rhabdomyolysis results from the effects of overproduced myotoxic cytokines (tumor necrosis factors in particular) in dengue-affected patients.[25–27] Although the incidence of rhabdomyolysis was not statistically significant between the elderly and younger DHF patients, our series showed that rhabdomyolysis (42.9%) was not an uncommon complication in the elderly population (Table 1), implicating that clinicians should be alert to the possible rhabdomyolysis when caring for an elderly DHF patient, because this complication potentially leads to ARF if it is not recognized early enough and treated accordingly.[25–27]

A 0.3% ARF rate was previously reported in one series including 6,154 Thai patients with DHF.[28] In our series, the ARF rate was found to be 12.1% in the overall elderly patients with DHF (Table 1) and 80% in the fatal subgroup of elderly patients with DHF (Table 4). ARF is not an uncommonly encountered complication in elderly patients in general.[29] Aging-adherent structural and functional changes in the kidney render this organ susceptible to insults in elderly persons.[29] Multifactorial cause may lead to renal failure in elderly DHF patients.[29,30] Shock with kidney hypoperfusion resulting from plasma leakage in DHF/DSS may provoke ARF in elderly hosts.[30] A higher frequency of bacteremia in the elderly patients with DHF was found in this series (Table 1). ARF and prolonged fever (> 5 days) each were found in a previous study to be an independent risk factor for superimposing bacteremia in DHF adults in the same dengue epidemic as this one,[6] and some patients included in that study[6] might be involved in this series.

Secondary dengue infection[31,32] and virulence of the circulating DEN strain were previously reported to be risk factors for development of DHF/DSS.[33] Of note, in an dengue outbreak in Cuba in 1981,[34–36] race was identified as a risk factor for development of DHF/DSS (i.e., white persons outnumbered black ones in development of DHF/DSS)[35,36]; in children and adults alike, an antecedent bronchial asthma was found to be a predisposing factor for development of DHF/DSS and fatality,[36] whereas sickle cell anemia seemed to be a predisposing factor for death,[36] and a trend suggesting higher prevalence of diabetes mellitus was observed in adults who developed DHF/DSS and died.[36] Our data indicated that diabetes mellitus was not a risk factor for fatality in elderly patients with DHF.

When compared with their younger counterparts, patients with DHF ≥ 65 years of age[10] and > 50 years[9] in two separate series were reported to be at higher risk for hospitalization and death. In addition to the higher mortality rate in elderly with DHF, which was consistent with those reported previously,[9,10] increased hospitalization length was found in elderly patients with DHF in our series.

Our series showed that DSS is an independent risk factor for fatality in elderly patients with DHF. The general principle of treatment of patients with DSS is early recognition with prompt and vigorous fluid resuscitation[37,38]; however, to our knowledge, there has been no consensus thus far on how to implement intravenous fluid replacement specifically for DSS elderly patients with physiologically declining cardiopulmonary function. Our data highlights the urgent need to study how to optimize fluid replacement therapy to reduce the fatality rate in the elderly with DSS.

Being a retrospective study, some limitations must be addressed. First, because the study was conducted at a single medical center, the severity of DHF patients may be biased by referral pattern. Second, DHF patients being subjected to laboratory testing and imaging study may be biased by clinicians' selection based on his or her personal recognition of the clinical severity, leading to non-availability of such information in some of included patients whose manifestations were considered clinically less severe. Third, clinical outcomes of the included patients may be biased by the lack of a standardized protocol for management of DHF. In addition, the small number of fatal cases in elderly subgroup may make the statistical power quite small for multivariate analysis in identifying predictive factor for mortality in elderly patients with DHF. A prospective study with much larger sample size is needed to confirm the our observations. Nevertheless, our study improves awareness of DHF in the elderly by providing an deeper insight into DHF in aging people and highlights the

need for study on how to tailor treatment specifically for DHF in the elderly population.

In summary, our data showed the differences in clinical manifestations and laboratory characteristics between the elderly and younger adults with DHF. Among adults with DHF, the elderly have a higher mortality rate compared with the younger ones. DSS is an independent risk factor for fatality in elderly patients with DHF.

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