# COMPARISON OF THE 1997 AND 2009 WHO CLASSIFICATIONS FOR DETERMINING DENGUE SEVERITY IN THAI PATIENTS

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**Abstract.** The World Health Organization (WHO) proposed a revised dengue classification in 2009 to facilitate a more effective identification of severe dengue cases. We compared the two systems of dengue severity classification, 1997 and 2009 WHO guidelines, at a Thai tertiary-care teaching hospital. A total of 765 patients with dengue infection were studied: 510 (66.7%) were adults, and 496 (64.8%) were from the outpatient department. According to the WHO 2009 guidelines, 61.7%, 33.5%, and 4.8% were classified as having dengue without warning signs, dengue with warning signs, and severe dengue, respectively. When the WHO 1997 classification was applied, 87.2%, 11.4%, and 1.4% were classified as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), respectively. Seven cases (1%) of DF patients were categorized as severe dengue by severe bleeding. Of DHF patients, 10.3% had severe bleeding, and 10.3% had severe organ impairment. Overall, we observed that the 2009 WHO classification stratifies a much larger proportion of patients into a category requiring a higher level of medical and nursing care (dengue with warning signs or severe dengue) than the 1997 classification (DHF or DSS). However, DHF patients had a significantly higher frequency of in-patient treatment than dengue with warning signs patients (92% *vs* 53.1%; *p*<0.001). The 1997 classification appeared to identify truly severe cases while the 2009 guidelines were more useful in detecting a broad range of severe clinical manifestations such as severe bleeding. Further studies are needed to assess the utility of the WHO dengue severity classification guidelines and to identify areas that require modification.

**Keywords:** dengue, severity, severe dengue, WHO classification

## INTRODUCTION

Dengue remains the most prolific mosquito-borne infection worldwide. Data from the World Health Organization (WHO) noted a significant increase in the number of cases from 0.4 million cases in 1996 to 3.2 million cases in 2015 (WHO, 2012, 2016). Dengue infection is a systemic and dynamic disease with a wide clinical spectrum that includes both severe and non-severe clinical manifestations. While most patients recover following a self-limiting and non-severe clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without hemorrhage (Thisyakorn and Thisyakorn, 2015). The reasons for some patients progressing from non-severe to severe disease are yet to be determined. However, identifying such patients early is critical to provide appropriate treatment and to prevent the development of severe clinical conditions.

In the 1997 WHO guidelines, patients are classified in three separate categories: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) (WHO, 1997). The

diagnosis of DHF was restricted to those patients with the collective presence of fever, hemorrhagic tendency, thrombocytopenia, and signs of plasma leakage. DHF with signs of shock was classified as DSS. In 2009, a new classification of dengue proposed by WHO Tropical Disease Research was published. The new guidelines classify dengue into dengue without warning signs, dengue with warning signs and severe dengue (WHO, 2009).

Abdominal pain or tenderness, persistent vomiting, clinically manifesting fluid accumulation, mucosal bleeding, lethargy and restlessness, hepato-megaly, and an increase in hematocrit with a drop in platelet count are all listed as warning signs. Severe dengue is defined by the occurrence of plasma leak-age and/or fluid accumulation leading to shock or respiratory distress; and/or severe bleeding; and/or severe organ impairment (Table 1).

Although the revised scheme is more sensitive to the diagnosis of severe dengue and beneficial to triage and case management, there remain issues with its applicability. It is considered by many to be too broad, requiring more specific definition of warning signs. Quantitative research into the predictive value of these warning signs on patient outcomes and the cost effectiveness of the new classification system is required to ascertain whether the new classification system requires further modification, or whether elements of both classification systems can be combined (Hadinegoro, 2012).

This study aimed to compare the two systems of dengue severity classification, 1997 and 2009 WHO guidelines at a tertiary-care teaching hospital in Thailand.

## MATERIALS AND METHODS

### Study designs and setting

A retrospective cross-sectional study was conducted among 840 patients who were diagnosed with dengue infection at a tertiary care hospital in Thailand during 2014 to 2015. Patient records were reviewed. The diagnosis of dengue patients adhered to the criteria established by the WHO 2009 (WHO, 2009). After medical record review, 31 cases

were excluded due to misdiagnosis of dengue, 44 cases were excluded due to incomplete data; they were referred to another hospital in compliance with their health insurance. Finally there were 765 dengue patients; each patient was classified/graded according to both the 1997 (DF, DHF, and DSS) and the 2009 WHO guidelines (dengue without warning signs, dengue with warning signs and severe dengue) (Table 1). This study was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University.

### Statistical analysis

Descriptive statistics including frequency, percentage, range, mean, and standard deviation were calculated for the demographic and clinical data as appropriate. Treatment and outcomes of dengue using the 1997 and 2009 WHO classifications were analyzed. Categorical variables were compared using chi-square or Fisher's exact test as appropriate. Continuous variables were compared using the Student's $t$-test. Significance level was set at a $p$-value $< 0.05$.

## RESULTS

Of the 765 patients with dengue infection during the study period, 510 (66.7%) were adults and 394 (51.5%) were males. The mean age was 23.5 years (range 0-77 years). There were 496 (64.8%) patients treated in the outpatient depart-ment (OPD), and 269 (35.2%) were treated in the inpatient department (IPD).

According to the 2009 WHO classification, 472 patients (61.7%) were dengue without warning signs, 256 patients (33.5%) were dengue with warning signs, and the remaining 37 patients (4.8%) were severe dengue (Fig 1). Of the 37 patients with severe dengue, 14 (37.8%) had severe plasma leakage, 19 (51.4 %) had severe clinical bleeding, and 14 (37.8%) had severe organ involvement. Of the 14 patients with severe organ involvement, 11 patients had AST >1000 IU/l and/or ALT >1000 IU/l, 8 patients had alteration of consciousness, 4 patients had serum creatinine ≥3 times above baseline, and 3 patients had respiratory failure.

Table 1.  The WHO 1997 and 2009 classifications for dengue severity.

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### WHO 1997 classification for dengue severity

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**Dengue Fever**
Acute febrile illness with two or more of the following:
    Headache
    Retro-orbital pain
    Myalgia
    Leukopenia
    Arthralgia
    Rash
    Hemorrhagic manifestations
    Supportive serology or occurrence at the same location and time as other confirmed cases of dengue fever

**Dengue Hemorrhagic Fever**
All of the following must be present:
    Fever or history of acute fever, lasting 2–7 days, occasionally biphasic.
    Hemorrhagic manifestations: Positive tourniquet test;
        Petechiae, equimosis, purpura or bleeding from mucosa, gastrointestinal tract, injection sites or other locations;
        or hematemesis/melena.
    Thrombocytopenia (<100,000 platelets per mm$^3$)
    Evidence of plasma leakage due to increased vascular permeability

**Dengue Shock Syndrome**
DHF with hypotension for age or narrow pulse pressure (>20 mmHg), plus one of the following:
    Rapid and weak pulse
    Cold, clammy skin, restlessness

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### WHO 2009 classification for dengue severity

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**Dengue without Warning Signs**
Fever and two of the following:
    Nausea, vomiting
    Rash
    Aches and pains
    Leukopenia
    Positive tourniquet test

**Dengue with Warning Signs**
Dengue as defined above with any of the following:
    Abdominal pain or tenderness
    Persistent vomiting
    Clinical fluid accumulation
    Mucosal bleeding
    Lethargy, restlessness
    Liver enlargement >2 cm
    Laboratory: increase in HCT concurrent with rapid decrease in platelet count

**Severe Dengue**
Severe Dengue with at least one of the following criteria:
    Severe Plasma Leakage leading to:
        Shock
        Fluid accumulation with respiratory distress
    Severe bleeding as evaluated by clinician
    Severe organ involvement
        Liver: AST or ALT ≥1,000
        CNS: impaired consciousness
        Failure of heart and other organs

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According to the 1997 WHO classification, 667 patients (87.2%) were DF, 87 (11.4 %) were DHF, and 11 (1.4%) were DSS (Fig 1).

When comparing the 1997 classification to the 2009 classification, 70.8% of DF patient were categorized as dengue without warning signs, 28% as dengue with warning signs, and 1.0% as severe dengue. Of the DHF patients, 78.2% were categorized as dengue with warning signs and 21.8% as severe dengue. All of DSS were categorized as severe dengue. All dengue without warning signs were categorized as DF. Among dengue with warning signs patients, 73.4% were categorized as DHF and 26.6% as DSS. Of all severe dengue patients, 18.9% were categorized as DF, 51.4% as DHF, and 29.7% as DSS (Table 2).

Type of severe dengue by the 2009 WHO classification and disease severity by the 1997 WHO classification are shown in Fig 2. Seven cases (1%) of DF patients were categorized as severe dengue by severe bleeding. Of DHF patients, 10.3% had severe bleeding and 10.3% had severe organ impairment. Of DSS patients, 100% had severe plasma leakage, 27.3% had severe bleeding, and 27.3% had severe organ impairment.

Table 3 demonstrates types of treatment and outcomes among dengue patients classified by the two guidelines. Six cases required intensive care, and one died. In the 1997 classification, the majority of DF cases (73.3%) were treated as outpatients, and 26.7% were hospitalized, receiving some type of intravenous (IV) rehydration. Most DHF patients (92.0 %) were hospitalized, and 2.3% required intensive care unit (ICU). All DSS were hospitalized and 36.4% required ICU. In the revised 2009 classification, 20.8% of patients with dengue without warning signs and 53.1% of dengue with warning signs were hospitalized.
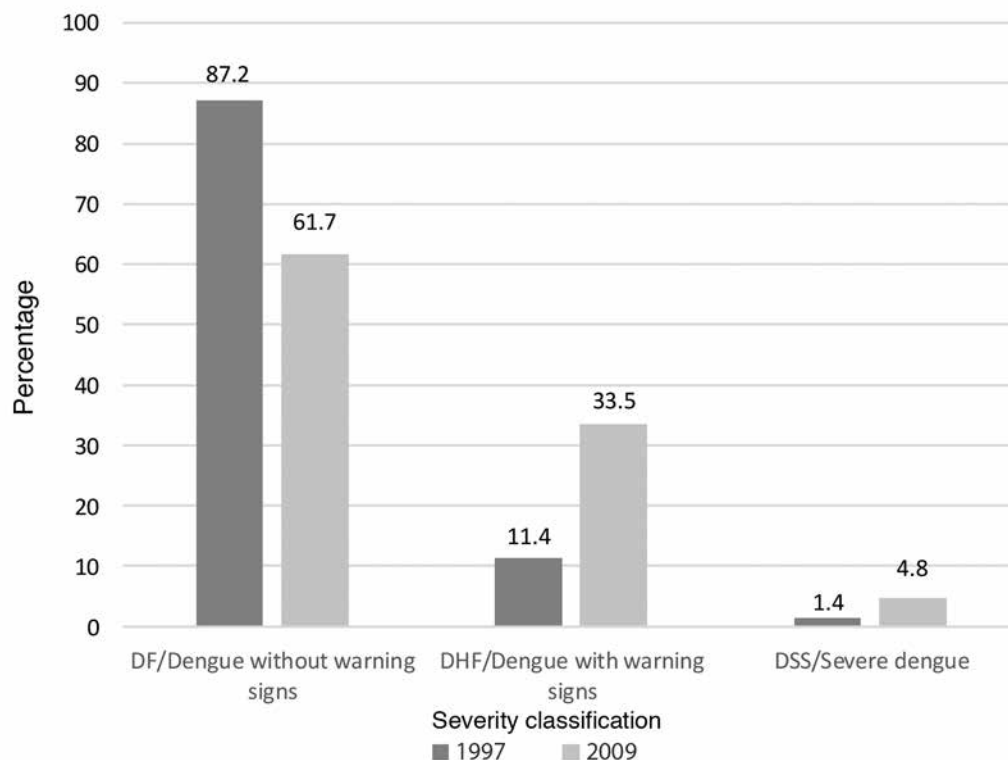


Fig 1–The 1997 and 2009 WHO classifications for dengue severity. DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.

Among patients with severe dengue, 94.6% were hospitalized, and 5.4% (2 patients) were treated as outpatients: these two patients had vaginal bleeding. Patients with DF had a significantly higher frequency of whole blood/pack red cell transfusion and hospitalization than patients with dengue without warning signs ($p$=0.023 and $p$=0.013, respectively). Patients with DHF had a significantly higher frequency of platelet transfusion and hospitalization than patients with dengue with warning signs ($p$=0.015 and

$p$=<0.001, respectively). Patients with DSS were significantly more likely to receive colloid for fluid resuscitation than severe dengue ($p$=0.017).

## DISCUSSION

There has been considerable debate on the application of both the 1997 and 2009 WHO dengue classification guidelines for diagnosis and management of dengue infection. Previous studies have shown that the 2009 guidelines, which focus

Table 2.  Distribution of dengue severity between the 1997 and 2009 WHO classifications.

| Disease severity by WHO 2009 | Disease severity by WHO 1997, $n$ (%) | | | Total $n$ (%) |
|---|---|---|---|---|
| | DF | DHF | DSS | |
| Dengue without warning signs | 472 (70.8) | 0 (0) | 0 (0) | 472 (61.7) |
| Dengue with warning signs | 188 (28.2) | 68 (78.2) | 0 (0) | 256 (33.5) |
| Severe dengue | 7 (1.0) | 19 (21.8) | 11 (100) | 37 (4.8) |
| Total $n$ (%) | 667 (87.2) | 87 (11.4) | 11 (1.4) | 765 (100) |

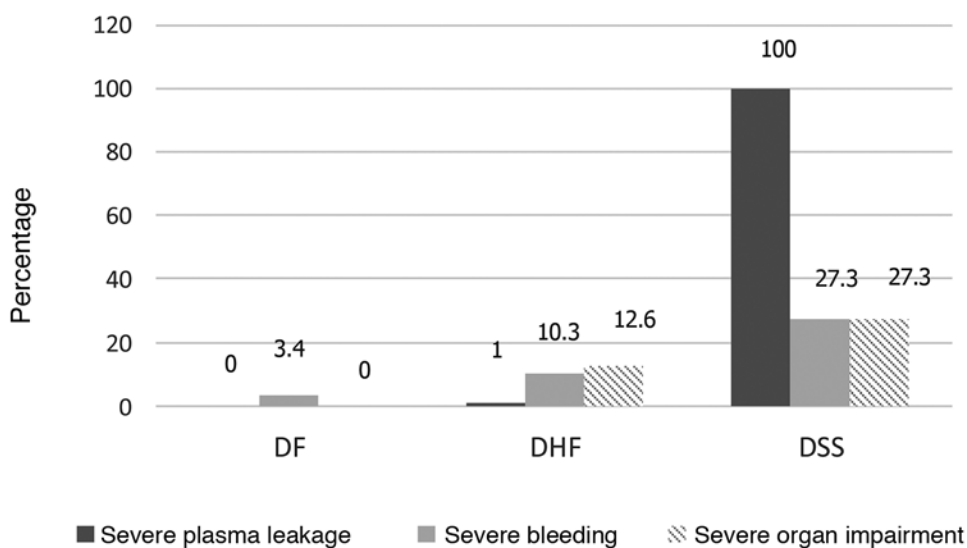DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.



Fig 2–Severe dengue classified by the 2009 WHO guidelines and disease severity classified by 1997 WHO guideline. DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome.

Table 3. Comparison of treatment and outcomes of dengue between the 1997 and 2009 WHO classifications.

| Treatment and outcomes | 1997 WHO classification, n (%) | | | 2009 WHO classification, n (%) | | | p-value | | |
|---|---|---|---|---|---|---|---|---|---|
| | DF | DHF | DSS | Dengue without warning signs | Dengue with warning signs | Severe dengue | DF vs Dengue without warning signs | DHF vs Dengue with warning signs | DSS vs Severe dengue |
| | (n=667) | (n=87) | (n=11) | (n=472) | (n=256) | (n=37) | | | |
| Colloid use | 0 (0) | 3 (3.4) | 7 (63.6) | 0 (0) | 2 (0.8) | 8 (21.6) | NA | 0.212 | 0.017* |
| Whole blood/Pack red cell transfusion | 7 (1.0) | 2 (2.3) | 2 (18.2) | 0 (0) | 6 (2.3) | 5 (13.5) | 0.023[a] | 1.341 | 1.626 |
| Platelet transfusion | 1 (0.1) | 7 (8.0) | 2 (18.2) | 0 (0) | 4 (1.6) | 6 (16.2) | 0.586 | 0.015[a] | 1.483 |
| Inotropic use | 0 (0) | 0 (0) | 1 (9.1) | 0 (0) | 0 (0) | 1 (2.7) | NA | NA | 0.819 |
| Ventilator/respiratory support | 0 (0) | 0 (0) | 3 (27.3) | 0 (0) | 0 (0) | 3 (8.1) | NA | NA | 0.248 |
| Chest drainage | 0 (0) | 0 (0) | 1 (9.1) | 0 (0) | 0 (0) | 1 (2.7) | NA | NA | 0.819 |
| Exchange transfusion | 0 (0) | 0 (0) | 1 (9.1) | 0 (0) | 0 (0) | 1 (2.7) | NA | NA | 0.819 |
| Hemodialysis | 0 (0) | 0 (0) | 1 (9.1) | 0 (0) | 0 (0) | 1 (2.7) | NA | NA | 0.819 |
| Hospitalization | 178 (26.7) | 80 (92.0) | 11 (100) | 98 (20.8) | 136 (53.1) | 35 (94.6) | 0.013[a] | <0.001[a] | 1.181 |
| ICU admission | 0 (0) | 2 (2.3) | 4 (36.4) | 0 (0) | 0 (0) | 6 (16.2) | NA | 0.128 | 1.928 |
| Death | 0 (0) | 0 (0) | 1 (9.1) | 0 (0) | 0 (0) | 1 (2.7) | NA | NA | 0.819 |

DF dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; NA, not analyzed. [a] $p<0.05$.

on the severity level, are considered to be more sensitive in capturing severe disease compared to the 1997 guidelines (Basuki *et al*, 2010; Narvaez *et al*, 2011; Horstick *et al*, 2014). However, problems with using the 2009 classification have also been noted. These include the requirements of additional training and dissemination of the guidelines for healthcare workers to remedy any confusion over the changes to the system (Barniol *et al*, 2011).

There was an increase in the diagnosis of the severe form of dengue infection using the 2009 guidelines compared to the 1997 guidelines. The proportion of patients with severe dengue was lower by the WHO 1997 guideline classification (12.8% with DHF or DSS) compared with the 2009 guidelines classification (38.3% with dengue with warning signs or severe dengue).

The 2009 classification captured a higher number of cases with severe dengue than those captured as DSS by the 1997 classification. Moreover, 7 (1.0 %) of DF cases (non-severe form) classified by the 1997 guidelines were classified as severe dengue (severe form) due to severe bleeding. Previous studies have demonstrated the overlap between case definitions of DF, DHF, and DSS (Phuong *et al*, 2004; Deen *et al*, 2006) while another study found that the 1997 classification did not detect severe dengue manifestations in some patients, particularly in adults (Balmaseda *et al*, 2005). Some manifestations of severe dengue, such as severe bleeding or organ failure were not included in the 1997 classification.

However, our study found that patients who had DHF by the 1997 classification were more likely to be hospitalized than patients who had dengue with warning signs by the 2009 classification (*p*<0.001). These results suggest that the 1997 WHO classification is more likely to identify clinically severe cases than the 2009 WHO classification.

The WHO 2009 guidelines recommend that all cases of severe dengue and dengue with warning signs should be hospitalized; this led to a 38.3% hospitalization rate among dengue patients in our

study. In comparison, based on the 1997 guidelines that recommend hospitalization among DHF and DSS cases, the rate would have been 12.8%. This raises a concern regarding the increasing workload for healthcare workers caring for hospitalized patients with dengue infection if the 2009 classification is used in Thailand (Kalayanarooj, 2011). This would have a significant impact on the utilization of hospital resources in the region.

We discovered a higher proportion of patients with dengue with warning signs compared with patients with DHF. This may have been due to the less stringent and non-specific classification of dengue with warning signs that allowed the capturing of more patients potentially at risk of developing severe manifestations. However, such a large number of patients classified as dengue with warning signs may lead to an increased burden on the healthcare system in resource-limited settings. Revision of the definitions of the warning signs is needed to accurately identify patients who actually require hospitalization.

To give a more complete overview, our study included both hospitalized patients and non-hospitalized patients with dengue infection. However, there are several limitations to note. First, the retrospective design of the study may be associated with incomplete data recording and misclassification bias. Forty-four cases were excluded due to incomplete data. Furthermore, 9 cases were originally diagnosed as DF but we reclassified them to DHF. In addition, 26 cases were also first diagnosed with DHF but reclassified as DF. This was in accordance with 1997 WHO classification. Second, there were few severe cases requiring intensive care and only one fatality, limiting our ability to assess the clinical relevance of both dengue classifications for detecting life-threatening situations.

In conclusion, we observed that the 2009 WHO classification stratifies a much larger proportion of patients into a category that requires a higher level of medical and nursing care (dengue with warning signs and severe dengue) than the 1997 classification (DHF or DSS). However, DHF

patients had a significantly higher frequency of hospitalization than dengue with warning signs patients. The 1997 WHO classification tended to identify truly severe cases versus the 2009 WHO classification; the use of the 2009 classification to determine dengue severity and guide management may result in increased unnecessary hospitalizations and an increased burden on resources in our setting where dengue infection is endemic. Nevertheless, the 2009 guidelines were more useful in detecting a broad range of severe clinical manifestations such as severe bleeding. Further studies are needed to assess the utility of the 2009 WHO classification guidelines and to identify areas that require modification.

## ACKNOWLEDGEMENTS

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