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Assessment of proteinuria by urine dipstick as a predictive marker for dengue hemorrhagic fever in pediatric patients

Pornchanun Jarutunyaluk[1], Ekachai Pradermdussadeeporn[2], Weerapong Chaya[3], Kanchana Tangnararatchakit[1], Ampaiwan Chuansumrit[1], Nopporn Apiwattanakul[1]✉

[1]*Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Bangkok 10400, Thailand*

[2]*Division of Pediatrics, Queen Savang Vadhana Memorial Hospital, 290 Jermjormpol Road, Chon Buri 20110, Thailand*

[3]*Division of Pediatrics, Sawanpracharak Hospital, 43 Athakavi Road, Nakhon Sawan 60000, Thailand*

ABSTRACT

Objective: To investigate whether urinary dipstick proteinuria or urine protein creatinine ratio (UPCR) could predict leakage in children with dengue virus infection.

Methods: This was a prospective cross-sectional study. A total of 141 hospitalized patients with confirmed dengue virus infection were enrolled from three hospitals in Thailand. Once daily, complete blood count, serum albumin, and random morning urine dipstick protein were collected from the day of admission to the day after defervescence. Morning UPCR was only measured in patients from one hospital due to logistic reasons.

Results: There were 81 and 60 patients in the dengue fever (DF) and DHF groups, respectively. The proportion of patients with proteinuria detected using urine dipstick in the DHF group was higher than that in the DF group from Day-1 (one day before defervescence) to Day +1 (one day after defervescence). Urine dipstick for proteinuria of ≥1+ had sensitivity and specificity of 12.8% and 94.4% on Day-1, and 18.9% and 98.6% on Day 0 (the day of defervescence) to differentiate DHF from DF. For UPCR, cut-off values of approximately 0.2 g/g from Day-2 to Day+1 yielded a sensitivity of 71.6%-94.4% and a specificity of 55.6%-100% in differentiating between DF and DHF.

Conclusions: Dipstick proteinuria of ≥1+ on Day-1 to Day+1 after defervescence had poor sensitivity but good specificity in differentiating DHF from DF. UPCR performed better but was less convenient and more expensive than urine dipsticks.

KEYWORDS: Dengue; Pediatric, Proteinuria; Urine dipstick; Urine protein creatinine ratio

1. Introduction

Dengue infection has been an endemic disease in Thailand and other countries in the tropical region since the 1950s[1]. More than thousands of infected patients have been reported each year despite awareness and prevention policies. The disease is prevalent across all age groups; the highest is those 10-14 years old[2]. Dengue infection

Significance

Dengue hemorrhagic fever (DHF) is a severe form of dengue virus infection. However, not all dengue virus-infected patients develop DHF. There has been evidence that a significant proportion of dengue virus-infected patients develop proteinuria. This study explored whether proteinuria detected by urine dipstick could predict DHF in pediatric patients. Proteinuria (≥1+) on the defervescent day or one day before the defervescent day could predict DHF with a specificity of 75.0%-84.6%. However, the sensitivity was low. This indicated that if the urine protein is ≥1+, patients have a high probability of developing DHF, but DHF cannot be ruled out if the test is negative.

✉To whom correspondence may be addressed. E-mail: nopporn.api@mahidol.ac.th

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has protean clinical manifestations ranging from asymptomatic infection, mild symptoms such as undifferentiated fever, dengue fever (DF) to severe dengue infection such as dengue hemorrhagic fever (DHF), which involves plasma leakage into the interstitium and potential spaces such as pleural cavity and peritoneal cavity. Leakage is prominent when fever begins to defervesce and usually lasts 24-48 hours[3]. The clinical course of DHF can potentially result in dengue shock syndrome (DSS) if plasma leakage is massive, leading to various complications, including death, if not diagnosed and treated properly. Disease severity can be minimized by early diagnosis and appropriate intravenous fluid replacement for plasma leakage.

The World Health Organization (WHO) has set criteria for diagnosing DHF based on clinical symptoms and laboratory results, including thrombocytopenia and evidence of plasma leakage. Rising hematocrit, hypoalbuminemia, pleural effusion, or ascites are evidence of plasma leakage. These pieces of evidence may occur late and may be noticeable after the leakage has taken place for a time that may be too late for prompt intervention. There are still no early non-invasive predictors to detect plasma leakage[4]. Early prediction of plasma leakage is therefore important for identifying patients requiring closed monitoring.

Proteinuria can be found in dengue infection[5-7]. Patients with dengue infection have a higher urine albumin creatinine ratio than patients with other febrile illnesses[8]. Evidence suggests significant proteinuria is determined by the urine protein creatinine ratio (UPCR) in patients with DHF[9-12]. The relationship between proteinuria by urine dipstick results and the occurrence of DHF is still controversial in the existing literature[8,13]. In addition, the association between proteinuria and DHF has been well-studied in the adult population but not in the pediatric population[12]. Moreover, when detecting significant proteinuria in dengue-infected patients is still not established, as most studies did not correlate the occurrence of proteinuria with the phases of illness in the clinical course of DHF.

Since UPCR might not be accessible in all healthcare settings, using a urine dipstick could be an alternative method[14]. However, proteinuria by urine dipstick may be affected by various factors, including extreme values of urine specific gravity and pH value[15]. High urine specific gravity can lead to elevated values of protein on dipsticks[16,17]. Hence, interpreting proteinuria results from dipstick should take into account these potential interferences.

This study aimed to explore whether proteinuria tested using a urine dipstick could predict leakage in children with dengue infection and to determine an appropriate cut-off value for proteinuria using a urine dipstick to differentiate DHF from DF. A comparison of the urine dipstick with UPCR to differentiate DHF from DF was also performed.

2. Subjects and methods

2.1. Study design, site and population

We conducted a multicenter prospective cohort study at Ramathibodi Hospital, Queen Savang Vadhana Memorial Hospital, and Sawanpracharak Hospital. Children aged 0-18 years with serologically confirmed dengue infection according to the WHO SEARO 2011 criteria[4,18] in the febrile or critical stages were included. Patients with underlying kidney diseases, such as nephrotic syndrome, glomerulonephritis, chronic kidney disease, acute kidney injury, urinary tract infection, and renal tubular acidosis, were excluded. Patients in the recovery stage, those admitted after the defervescent day, and those whose defervescent day could not be clearly identified were excluded. In addition, patients who had urine dipstick pH>9, and concomitant use of drugs that can cause proteinuria were also excluded.

2.2. Ethical approval

Participants and legally authorized representatives signed informed consent forms. This study was approved by the ethical committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (approval No.: MURA2022/226; approval date: April 5, 2022) to enroll patients from April 22, 2022, to November 2023, the ethical committee of Queen Savang Vadhana Memorial Hospital to enroll patients from July 2022 to July 2023 (approval No.: 027/2022; approval date: July 21, 2022), and Sawanpracharak Hospital from June 2022 to June 2023 (approval No. 15/2565; approval date: June 10, 2022) . Informed consent was obtained from legally authorized representatives and assent was obtained from participants aged >7 years old. All patients received treatment according to the standard dengue management guidelines, including monitoring of vital signs, urine output, and signs of bleeding.

2.3. Data collection

Patient information, including sex, age, underlying diseases, current medications, and latest creatinine (Cr) levels were recorded. A positive serum NS1 or serum dengue IgM confirmed the diagnosis of dengue infection. The diagnosis of DHF was based on WHO SEARO 2011 criteria[18]. Random morning proteinuria was detected by urine dipstick using a Siemens Multistix 10SG reagent strip (Siemens Helathineers, Forchheim, Germany); complete blood count (CBC) and serum albumin were collected daily from the day of admission to one day after defervescence. Morning urine samples for urine protein creatinine ratio (UPCR) were collected from patients at Ramathibodi Hospital (UPCR could be accomplished only in Ramathibodi Hospital because of logistic reasons). Urine protein was measured by Pyrogallol Red Molybdate method (Abbott, Wiesbaden, Germany).

2.4. Primary outcomes

Daily proteinuria was determined by urine dipstick and daily proteinuria by UPCR.

Patients with dengue infection were confirmed by positive serum NS1 or Dengue IgM tests[4,18]. Dengue fever (DF) was diagnosed according to the criteria set by the World Health Organization (WHO) South-East Asia in 2011[18]. Clinical manifestations included a high-grade fever lasting 2-7 days, accompanied by two or more of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia/ bone pain, rash, hemorrhagic manifestations, leukopenia (white blood cell count <5 000/mm^3), thrombocytopenia (platelet count <150 000/mm^3), hematocrit rising (5%-10%), and there was no evidence of plasma leakage.

Dengue hemorrhagic fever (DHF) was diagnosed in patients who presented with clinical manifestations of DF with platelet count <100 000/mm^3 and objective evidence of plasma leakage shown by any of the following: hemoconcentration (hematocrit increase >20% from baseline), or pleural effusion/ascites, or hypoproteinemia/ hypoalbuminemia.

2.5. WHO classification of dengue infections and grading of severity of DHF

Grading severity of DHF based on WHO 1997 criteria was used[19]. Grade Ⅰ refers to patients with a positive tourniquet test and/or easy bruising. Grade Ⅱ refers to spontaneous bleeding. Grade Ⅲ refers to circulatory failure evidenced by rapid, weak pulse and narrowing of pulse pressure (<20 mmHg) or hypotension. Grade Ⅳ refers to profound shock and undetectable blood pressure and pulse.

2.6. Proteinuria by urine dipstick

In this study, urine dipstick read as trace, and 1+, 2+, 3+, and 4+ were categorized as positive proteinuria by urine dipstick.

2.7. Day of defervescent (Day 0)

Regarding the pathophysiology of plasma leakage in DHF, the maximal degree of leakage usually occurs around the day of defervescence, defined as Day 0, which was the day when body temperature reached 37.5 ℃ without a subsequent elevation. The days related to the day of defervescence, which were 1 or 2 days before the day of defervescence, were designated as Day-1, Day-2, etc, and the days that were 1 or 2 days after the day of defervescence were designated as Day+1 or Day+2, respectively.

2.8. Statistical analysis

Continuous data are presented as mean and standard deviation if the data were normally distributed or median and interquartile range when not normally distributed, respectively. Comparisons between groups were performed using the Student's *t*-test if the data were normally distributed or Mann-Whitney *U*-test if the data were not normally distributed. Categorical data were presented as percentages, and comparisons were performed using the *Chi*-square test. The cutoff values of proteinuria by urine dipstick or UPCR to differentiate DHF from DF were determined using the maximum area under the curve (AUC) in the Receiver Operating Characteristic Curve (ROC curve). Logistic regression analysis was performed to determine the association between proteinuria and DHF. Sample size calculation was based on the study conducted by Vasanwala *et al.*, which showed the incidences of significant proteinuria (defined as UPCR > 20 mg/mmol or a dipstick result > 2+) of 61% in DF and 85% in DHF[12]. This would need 50 patients per group. Statistical analyses were performed using STATA version 17 (STATA Corp, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

A total of 141 hospitalized patients aged 1-18 years who had serologically confirmed dengue infection were enrolled; 87 (62%) were male. There were 43 cases from Ramathibodi Hospital (RA), 49 from Sawanpracharak Hospital (SPR), and 49 from Queen Savang Vadhana Memorial Hospital (SV).

DF and DHF were diagnosed in 81 and 60 patients, respectively. The patients were followed up at the median of 4 days (IQR 3, 5). For the severity grading of DHF cases, there were 43, 10, 2, and 5 cases of grade Ⅰ, Ⅱ, Ⅲ, and Ⅳ, respectively (Supplementary Table 1). Patients with DHF had significantly lower serum albumin levels and platelet counts but higher absolute neutrophil counts on day 0 than those with DF (Table 1).

3.2. Laboratory results

3.2.1. Urine specific gravity

Since urine specific gravity may affect dipstick proteinuria values[16], we compared the urine specific gravity of patients with DF and those with DHF. The urine specific gravity between these two groups did not reach statistical significance differences from Day-3 to Day+1. (Supplementary Figure 1).

3.2.2. Urine dipstick protein analysis

In the DHF group, the proportion of patients with proteinuria on urine dipstick (from trace to 4+) was higher than that in the DF group from Day-3 to Day+1, and the differences reached statistical

Table 1. Baseline characteristics of patients with dengue fever and dengue hemorrhagic fever.

Clinical variables	Dengue fever		Dengue hemorrhagic fever		*U*-value	*P*-value
	n	median (IQR)	*n*	median (IQR)		
Age, years	81	10.0 (6.0,13.0)	60	12.0 (8.0, 13.5)	2934	0.035
Maximal hematocrit rising, %	81	8.8 (5.1, 12.2)	60	15.7 (9.9, 23.0)	2714	<0.001
WBC at day 0*, $\times10^3$ cells/mm^3						
Total WBC	74	3.5 (2.5, 4.8)	57	4.2 (2.7, 6.6)	2512	0.062
Absolute neutrophil count	73	1.0 (0.7, 1.5)	54	1.7 (0.9, 3.3)	2 470	0.001
Absolute lymphocyte count	73	1.8 (1.3, 2.5)	54	1.7 (1.1, 2.4)	1699	0.185
Absolute monocyte count	71	0.2 (0.2, 0.3)	53	0.3 (0.2, 0.6)	2181	0.131
Platelet count at day 0, $\times10^3$ cells/mm^3	75	105.0 (62.0,141.0)	57	53.0 (32.0, 87.0)	1059	<0.001
Serum albumin at day 0, g/dL	40	3.8 (3.6, 4.0)	50	3.3 (3.0, 3.5)	746	<0.001

*Not all patients had the information of day 0 available, WBC: white blood cell count.

significance on Day-1, Day 0, and Day+1 (Table 2). The degree of proteinuria according to the day of defervescence is shown in Figure 1. Logistic regression analysis showed that urine dipstick proteinuria was significantly associated with DHF on Day-1, Day 0 and Day+1. Since urine specific gravity could influence proteinuria by urine dipstick, the odds ratios (*OR*) were adjusted for urine specific gravity. Adjusted *OR* for association between DHF and positive proteinuria by urine dipstick reached statistical significance on Day-1 (adjusted *OR* 2.62, 95% *CI* 1.13-6.20, *P*=0.025), Day 0 (adjusted *OR* 3.18, 95% *CI* 1.44-7.03, *P*=0.004), and Day+1 (adjusted *OR* 8.07, 95% *CI* 2.22-29.30, *P*=0.002) (Table 3).

Table 2. Percentage of patients having positive proteinuria by urine dipstick in patients with dengue fever and dengue hemorrhagic fever [*n* (%)].

Days related to defervescence	Dengue fever	Dengue hemorrhagic fever	χ^2	*P*-value
Day-3	30 (26.7)	23 (52.2)	3.61	0.058
Day-2	48 (35.4)	37 (56.8)	3.85	0.050
Day-1	71 (39.4)	47 (66.0)	7.96	0.005
Day 0	74 (29.7)	53 (56.6)	10.24	0.001
Day+1	38 (15.8)	34 (50.0)	9.66	0.002

Table 3. Odds ratio (*OR*) and adjusted *OR* with urine specific gravity from logistic regression analysis of association between dengue hemorrhagic fever and positive proteinuria by urine dipstick.

Days related to defervescence	*OR* (95% *CI*)	*P*-value	Adjusted *OR* (95% *CI*)	*P*-value
Day-3	3.00 (0.95, 9.48)	0.061	3.19 (0.89, 11.44)	0.075
Day-2	2.39 (0.99, 5.77)	0.052	2.38 (0.92, 6.20)	0.075
Day-1	2.98 (1.38, 6.42)	0.005	2.62 (1.13, 6.20)	0.025
Day 0	3.29 (1.57, 6.91)	0.002	3.18 (1.44, 7.03)	0.004
Day+1	5.33 (1.77, 16.04)	0.003	8.07 (2.22, 29.30)	0.002

3.2.3. Urine protein creatinine ratio analysis

DHF patients consistently exhibited significantly higher UPCR values than DF patients, as evidenced by statistical significance on Day-2 [0.34 g/g; IQR (0.21, 1.01)] *vs.* 0.12 g/g; IQR (0, 0.18)], Day-1 [0.47 g/g; IQR (0.22, 2.67) *vs.* 0.19 g/g; IQR (0.00, 0.27)], Day 0 [0.45 g/g; IQR (0.25, 1.87) *vs.* 0.06 g/g; IQR (0.00, 0.25)] and Day+1 [0.36 g/g; IQR (0.18, 3.50)] *vs.* 0.17 g/g; IQR (0.09, 0.20)] (Table 4) However, no statistically significant difference was observed between the two groups on Day-3.

3.3. Cut-off values of urine dipstick protein to differentiate DF from DHF

Since significant proteinuria by urine dipstick was found on Day-1, Day 0, and Day+1, the appropriate cut-off proteinuria levels for urine dipstick protein to distinguish between DHF and DF analyzed by ROC curve were sought. On Day-1, the performance of using the cut-off level of ≥ trace had a sensitivity of 66.0% and a specificity of 60.6%, while using the cut-off level of ≥1+ had a sensitivity of 12.8%, a specificity of 94.4%, an ROC area of 0.64. On Day 0, the cut-off level of ≥ trace had a sensitivity of 56.6% and a specificity of 71.6%, while using the cut-off level of ≥1+, had a sensitivity of 18.9%, a specificity of 98.6%, and an ROC area of 0.67. The data are summarized in Supplementary Tables 2, 3, and 4 and Figure 2.

3.4. Cut-off values of UPCR to differentiate DF from DHF

Diagnostic performance was evaluated to determine the most appropriate cut-off values for UPCR in distinguishing DHF from DF. The optimal values were 0.221 g/g for Day-2 (sensitivity 75.0%, specificity 100.0%, ROC area 0.90), 0.198 g/g for Day-1 (sensitivity 84.6%, specificity 55.6%, ROC area 0.82), 0.258 g/g for Day 0 (sensitivity 72.2%, specificity 83.3%, ROC area 0.87), and 0.213 g/g for Day+1 (sensitivity 70.6%, specificity 80.0%, ROC area 0.77). The data are summarized in Supplementary Tables 5, 6, 7, and 8 and Figure 3.

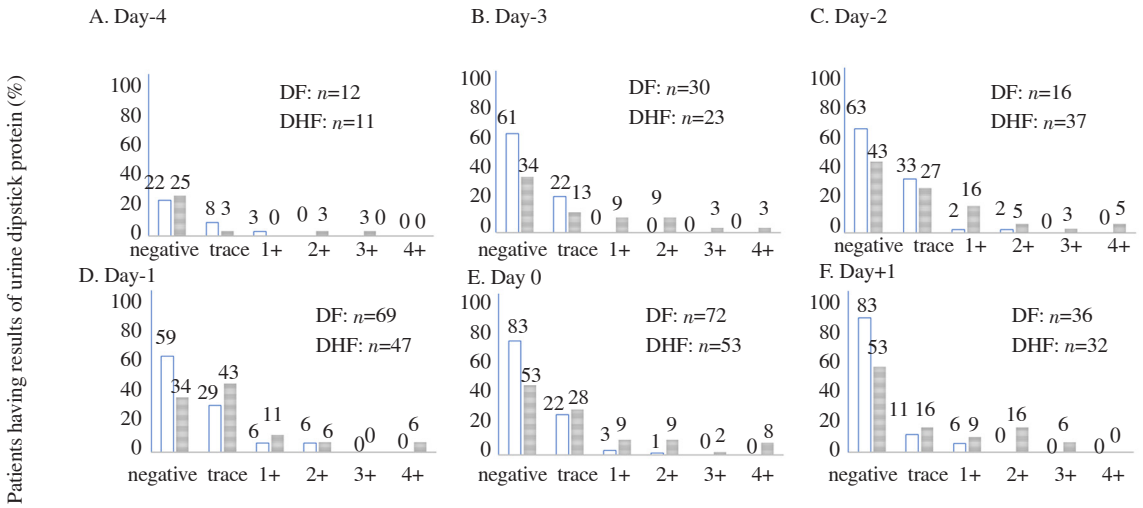

Figure 1. Urine dipstick protein values in dengue fever (DF) and dengue hemorrhagic fever (DHF) patients related to the day of defervescence. White bars represent DF group and dashed bars represent DHF group. Proportions of patients having positive urine dipstick protein on A) Day-4, B) Day-3, C) Day-2, D) Day-1, E) Day 0 and F) Day+1 are demonstrated. The proportions of patients having proteinuria from dipstick were higher in the DHF group than in DF group on Day-3 (P=0.011), Day-2 (P=0.022), Day-1 (P=0.019), Day 0 (P=0.001), and Day+1 (P=0.006) by the *Chi*-square test. No statistically significant difference on Day-4 was observed (P=0.626). Numbers (n) indicate numbers of patients in DF or DHF group according to the day of defervescence. Numbers on the top of each bar indicate the percentages of patients having the result of urine dipstick protein.

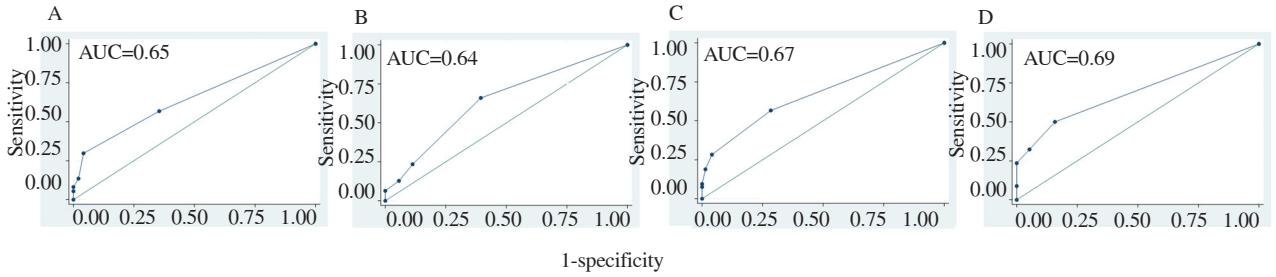

Figure 2. Receiver operating characteristic (ROC) curves of urine dipstick in differentiating between patients with DF and DHF related to the days of defervescence. Area under the curve (AUC) of each day of defervescence is shown; A) day-2, B) day-1, C) day 0, D) day+1.

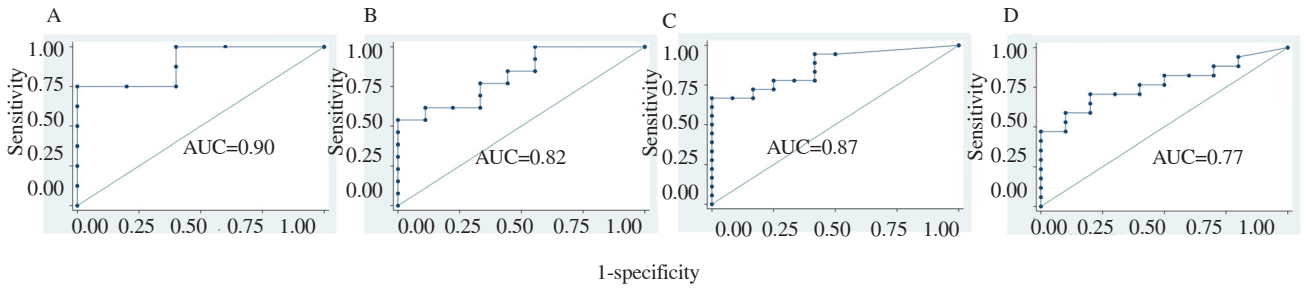

Figure 3. Receiver operating characteristic (ROC) curves of urine protein creatinine ratio (UPCR) in differentiating between patients with DF and DHF related to the days of defervescence. Area under the curve (AUC) of each day of defervescence is shown; A) day-2, B) day-1, C) day 0, D) day+1.

Table 4. Urine protein creatinine ratio values (g/g) in dengue fever and dengue hemorrhagic fever related to the day of defervescence.

Days related to defervescence	Dengue fever		Dengue hemorrhagic fever		*U*-value	*P*-value
	n	median (IQR)	*n*	median (IQR)		
Day-3	3	0.00 (0.00, 0.23)	5	0.18 (0.16, 0.27)	3	0.177
Day-2	5	0.12 (0.00, 0.18)	8	0.34 (0.21, 1.01)	4	0.019
Day-1	9	0.19 (0.00, 0.27)	13	0.47 (0.22,2.67)	21	0.012
Day 0	12	0.06 (0.00, 0.25)	18	0.45 (0.25, 1.87)	29	0.001
Day+1	10	0.17 (0.09, 0.20)	17	0.36 (0.18, 3.50)	39	0.021

4. Discussion

DHF involves plasma leakage and has the potential to progress to dengue shock syndrome (DSS), leading to various complications, including death. Patients with DHF may exhibit proteinuria[20], which is more common than those with DF[5-7]. This study supported the findings that pediatric patients with DHF had a higher tendency to have proteinuria tested by urine dipstick than those with DF. The UPCR values were also higher in patients with DHF. We propose that using a urine dipstick or UPCR along with other markers such as complete blood count may be valuable for identifying dengue patients who require hospitalization or close monitoring. In addition, urine dipsticks also provide information regarding patients' hydration or starvation status. This would guide clinicians in further managing dengue patients at the end of the febrile stage. Urine dipstick is easily accessible in resource-limited settings. Using a urine dipstick was also more convenient and much cheaper than using UPCR (0.32 USD *vs.* 3.46 USD per sample), making it potentially more suitable for resource-limited settings. However, UPCR showed better performance in differentiating DHF from DF, as evidenced by the higher value of the area under the ROC curve. In the clinical monitoring of patients with dengue infection, using urine dipstick will provide not only information regarding patients' hydration status and degree of starvation, but also the prediction of possible plasma leakage.

Constantiner *et al.* reported that proteinuria detected by urine dipstick could be affected by urine specific gravity and considering it along with results of proteinuria can be effectively used to identify patients having significant proteinuria instead of using UPCR. In cases of urine with higher specific gravity, interpretation of proteinuria by urine dipstick should be more cautious[16]. Nevertheless, our study found no statistically significant difference in urine specific gravity between DF and DHF, and the odds ratio of the association between DHF and proteinuria remained significant after adjusting for urine specific gravity. This indicated that specific gravity should not significantly impact the results of urine protein from dipsticks on the prediction of DHF in the current study. Patients with DHF tend to have more intravascular volume depletion due to leakage; hence, urine specific gravity was suspected to be higher. However, all patients in the current study were hospitalized, and intravenous fluid was administered with close monitoring to minimize this difference.

Patients with DHF exhibited significantly higher proteinuria, as demonstrated by urine dipstick and UPCR, compared with DF patients from Day-1 to Day+1 for dipstick and from Day-2 to Day+1 for UPCR. The diagnostic performance in determining the cut-off values of UPCR and urine dipstick protein to differentiate DHF from DF, as indicated by the area under the ROC curve, demonstrated that UPCR exhibited very good to excellent diagnostic performance, whereas urine dipstick showed satisfactory diagnostic performance. The current study demonstrated that proteinuria ≥1+ by urine dipstick had high specificity (>85%) but low sensitivity to predict DHF from the late febrile stage to the day of defervescence. If positive and negative predictive values were calculated, on the day of defervescence, positive proteinuria of ≥1+ would predict the probability of 83% of having DHF (positive predictive value = 83%). Therefore, patients with proteinuria ≥1+ may need hospitalization for closed monitoring. However, the negative predictive value was only 65%, meaning that 35% of dengue-infected patients with proteinuria <1+ may still have DHF. If the cut-off value of ≥ trace is to be used, this would compromise the specificity, decreasing to 60%-70% but increasing sensitivity to 55%-65%. This reflected 60% and 70% of positive and negative predictive values, respectively. Previous data on proteinuria by urine dipstick were quite limited, with no established cut-off value to distinguish DHF from DF in pediatric patients. In addition, previous studies did not precisely demonstrate the correlation of proteinuria from dipsticks with the days of defervescence. Some previous studies have even indicated no significant difference in peak urine dipstick protein values between patients with DF and those with DHF. Moreover, one study found that urine dipstick protein and UPCR cannot be used to predict the occurrence of severe dengue[13]. For UPCR, in the current study, the most appropriate UPCR values to differentiate DF from DHF from Day-2 to Day 0 were found to be around 0.19-0.25 g/g. This aligns with 0.2 g/g which is used to signify abnormal proteinuria[21]. Prior studies consistently demonstrated a statistically significant correlation between elevated UPCR levels and the occurrence of DHF[9-12]. The UPCR cut-off values obtained from the current study closely aligned with the previous finding which used the cut-off value of 0.256 g/g to differentiate between DF and DHF[12]. The current study added the information that UPCR could be a good marker used to differentiate DF from DHF in pediatric patients beginning from the late febrile stage to the day of defervescence with better sensitivity than urine dipstick.

The strength of the current study lies in its multicenter design, analyzing and presenting data based on days related to defervescence, aligning with the pathophysiology of the disease. Analysis based on the day of fever onset would lead to more heterogeneity of the results, as patients would have a febrile stage lasting from 2 to 7 days. The pathophysiology of each specific day after fever onset differs depending on when the leakage occurs. In DHF, leakage typically occurs on the day of defervescence. The current study explored the relationship between proteinuria and UPCR, providing accurate quantitative information, and urine dipstick protein, which is more practical in a clinical setting. Urine specific gravity, which potentially influences urine dipstick protein

values, was also considered, an aspect that has not been extensively studied before. We established cut-off values and diagnostic performance for urine dipstick protein in differentiating DHF from DF patients, serving as an early predictor during the early onset of minimal plasma leakage at the late febrile stage. Nevertheless, the current study had some limitations. First, most patients in this study had DF and grade Ⅰ or Ⅱ in the DHF group. These results may not be fully extrapolated to settings with a higher incidence of grade Ⅲ or Ⅳ DHF. Second, we enrolled only patients who were hospitalized. We did not enroll patients in the outpatient setting who might have less severe disease. In addition, dengue-infected patients with undifferentiated fever and those with asymptomatic dengue infection, which constituted the majority of dengue-infected patients (>75%)[22,23], were not enrolled. This might impact the results, as less severe dengue-infected patients might have different severity of proteinuria. Third, the dengue virus serotypes in the enrolled patients were not determined. However, available data showed that all serotypes co-circulated but certain serotypes might predominate at certain time periods[24]. A previous study showed that infection with dengue serotype 2 might increase the risk of severe disease[25]. Investigating whether different dengue virus serotypes would result in different degrees of proteinuria severity would be interesting. Fourth, as patients with DF and DHF in the current study had no significant difference in urine specific gravity, using a urine dipstick to indicate proteinuria has to be more cautious if patients have extreme values of urine specific gravity, such as less than 1.005 or more than 1.025. Lastly, further studies using other brands of commercial urine dipsticks are warranted.

Proteinuria may be used with other parameters for clinical monitoring of patients with dengue infection. Dipstick proteinuria greater than the trace starting from Day-1 to Day+1 demonstrated poor sensitivity but good specificity with a favorable positive predictive value. UPCR performed better in distinguishing between DF and DHF, although it is less convenient and more expensive than a urine dipstick.

Conflict of interest statment

We declare that we have no conflict of interest.

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Authors' contributions

PJ performed research conceptualization, data collection, data analysis and interpretation, drafting the manuscript, critical revision of the manuscript, approval of the manuscript, and funding management. EP performed research conceptualization, data collection, critical revision of the manuscript, and approval of the manuscript. WC performed research conceptualization, data collection, critical revision of the manuscript, and approval of the manuscript. KT performed research conceptualization, data collection, critical revision of the manuscript, and approval of the manuscript. AC performed research conceptualization, data collection, critical revision of the manuscript, and approval of the manuscript. NA performed research conceptualization, data analysis and interpretation, critical revision of the manuscript and approval of the manuscript.

Data availability statement

The data presented in this study are available upon request from the corresponding authors. The data are not publicly available unless permitted by the Faculty of Medicine Ramathibodi Hospital, Mahidol University.

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