

# Predictive score for Dengue infection with complete blood count parameters, including the new monocyte distribution width

## a retrospective single center derivation and validation study



Naiyana Phuttasen<sup>1</sup>, Surapong Pornprasitsaeng<sup>1</sup>, Yupapin Onthong<sup>1</sup>, Thursdak Sinthana<sup>1</sup>, **Wasitthep Limvorapitak<sup>2</sup>**

<sup>1</sup>Div. of Hematology, Dept. of Medical Technology Laboratory, Thammasat University Hospital, <sup>2</sup>Div. of Hematology, Dept. of Internal Medicine, Fac. of Medicine, Thammasat University, Pathumthani, Thailand

**ABSTRACTS**

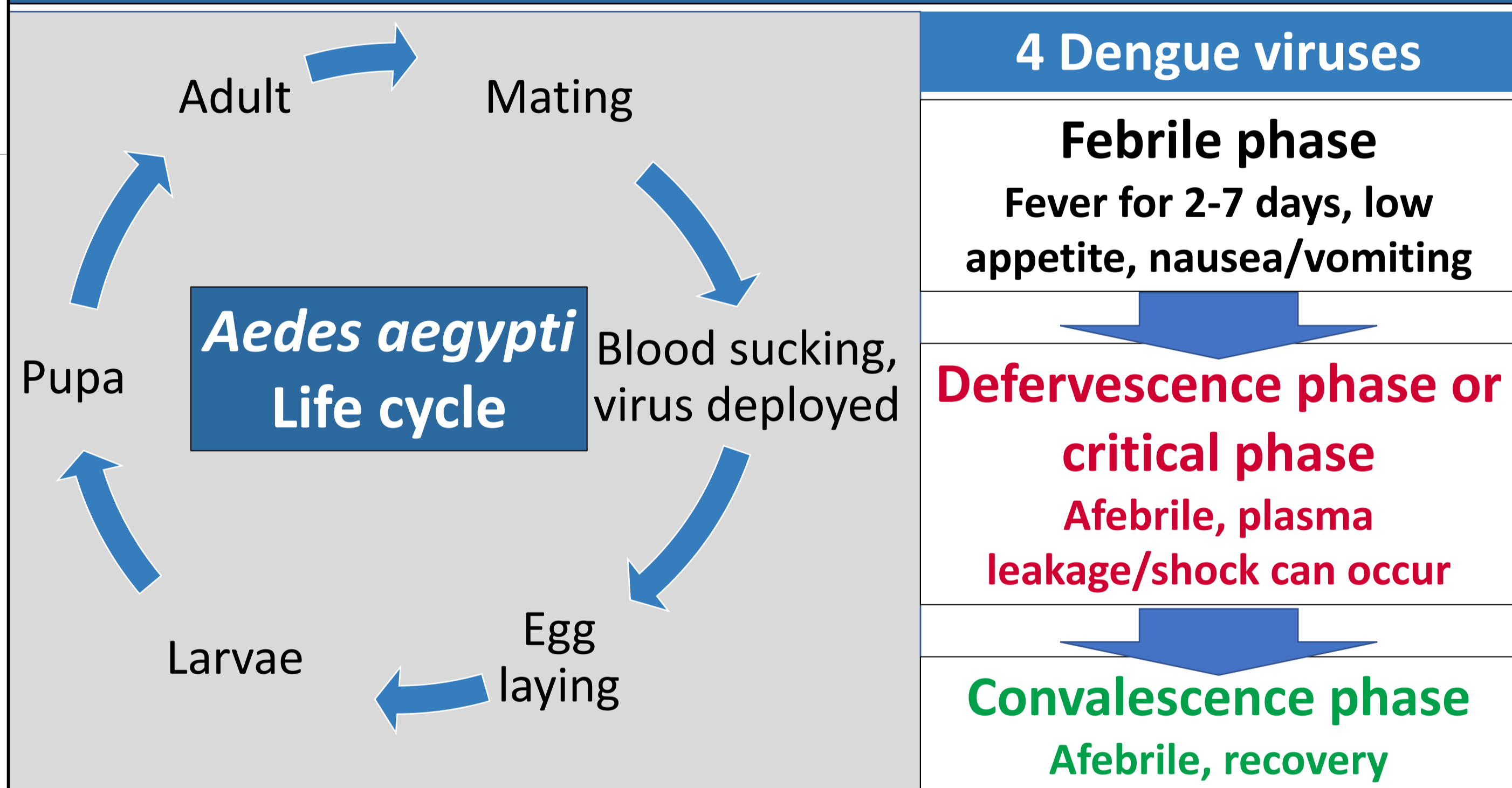
**Introduction:** Dengue infection is a differential diagnosis in patients with acute undifferentiated fever. Early detection and management may reduce mortality. Monocyte distribution width (MDW) is a new parameter in complete blood count (CBC). It is recently approved for early detection of sepsis. We have noticed high MDW in Dengue patients. This study aimed to describe MDW changes in Dengue infection and to develop predictive score for early detection of Dengue patients.

**Methods:** We retrospectively retrieved data of adult patients with acute fever who had CBC and Dengue serology (NS1 antigen, IgM and IgG) performed during September 2019 to May 2020 at Thammasat University Hospital. Medical records were reviewed. MDW was compared between groups. Patients were randomly divided into training and validation set. Predictive score was developed from the training set and validated in the validation set with multivariable analysis.

**Results:** A total of 431 patients, with Dengue infection in 127 patients (29.5%), were included in the analyses. The median (interquartile range) of MDW in Dengue patients were higher than non-Dengue patients [29.7% (26.5 – 34.7) vs. 24.2% (21.1 – 27.8),  $P < 0.001$ ]. In patients with confirmed Dengue infection, MDW increased with increasing severity. Training & validation set included 216 and 215 patients with 64 and 63 Dengue infection, respectively. Independent predictive factors of Dengue infection were white blood cell  $< 4 \times 10^9/L$  (score 1), platelet  $< 100 \times 10^9/L$  (score 1) and MDW  $> 24\%$  (score 1). No clinical features were independently predictive of Dengue infection. The area under receiver-operating-characteristic curve (95% confidence interval) of the prognostic score in the training and validation set were 0.839 (0.779 – 0.899) and 0.742 (0.674 – 0.811), respectively. With the cut-off score  $\geq 1$ , the sensitivity and specificity of the score were 92.2% and 40.8% in the training set and 88.9% and 44.1% in the validation set.

**Conclusion:** MDW increase in patients with Dengue infection and also increase with Dengue severity. We have developed and internally validated a simple predictive score for Dengue infection based on only results from CBC and MDW. Further large-scale external validation study is required to confirm the utility of our predictive score.

**INTRODUCTION**



- Monocytes play a crucial role in viral infection as part of innate immune response, hence frequent monocytosis in various viral diseases.
- Monocyte distribution width (MDW) has recently been approved for early detection of sepsis.
- This study aim to investigate the use of MDW in Dengue viral infection.

**MATERIALS & METHODS**

- **Study design:** Retrospective observational study
- **Venue:** Thammasat university hospital, a tertiary & referral center with 800 beds in Pathumthani province, Thailand
- **Duration:** September 2019 to May 2020
- **Inclusion:** Adults  $\geq 18$  years with acute febrile illness who had a complete blood count and Dengue test performed
- **Exclusion:** Patients without clinical note or no MDW parameter
- **Instrument:** Beckman-Coulter DxH 900 hematology analyzer

**RESULTS**

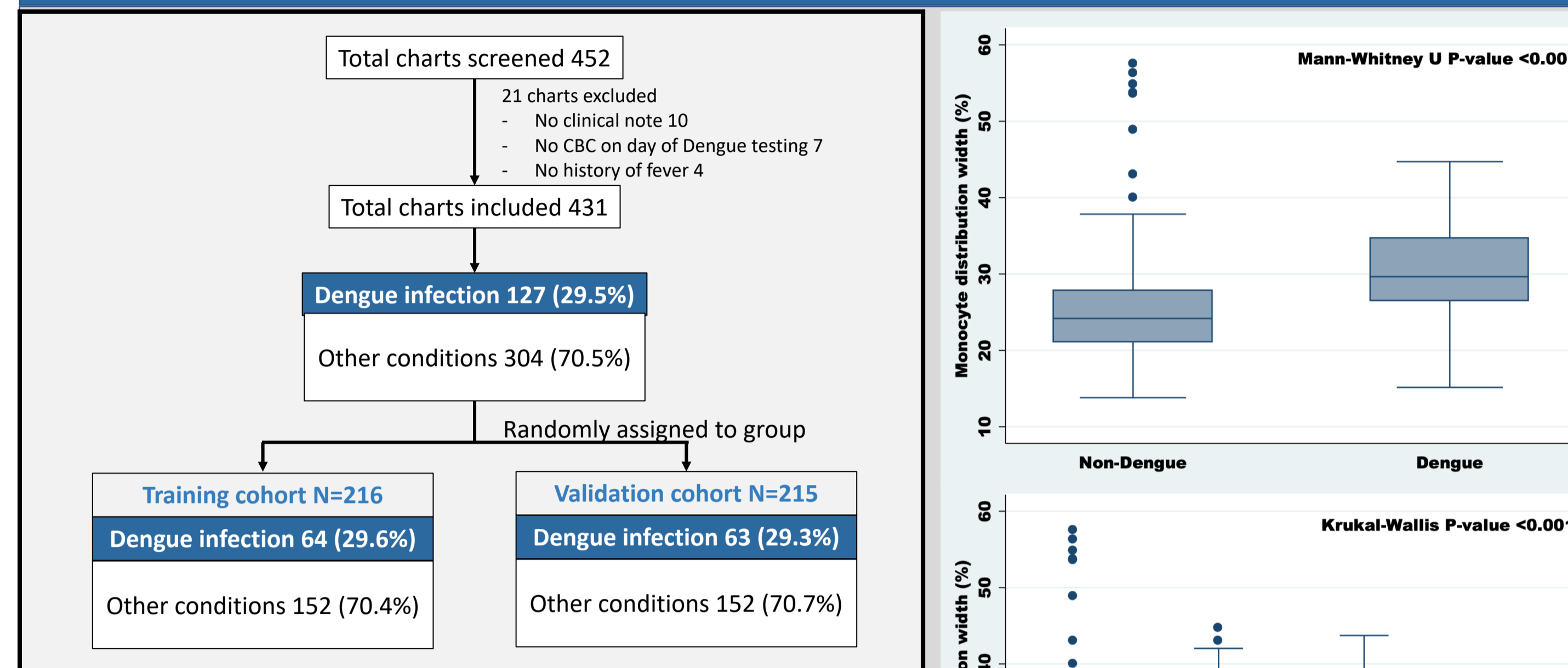


Figure 1 Study flow diagram

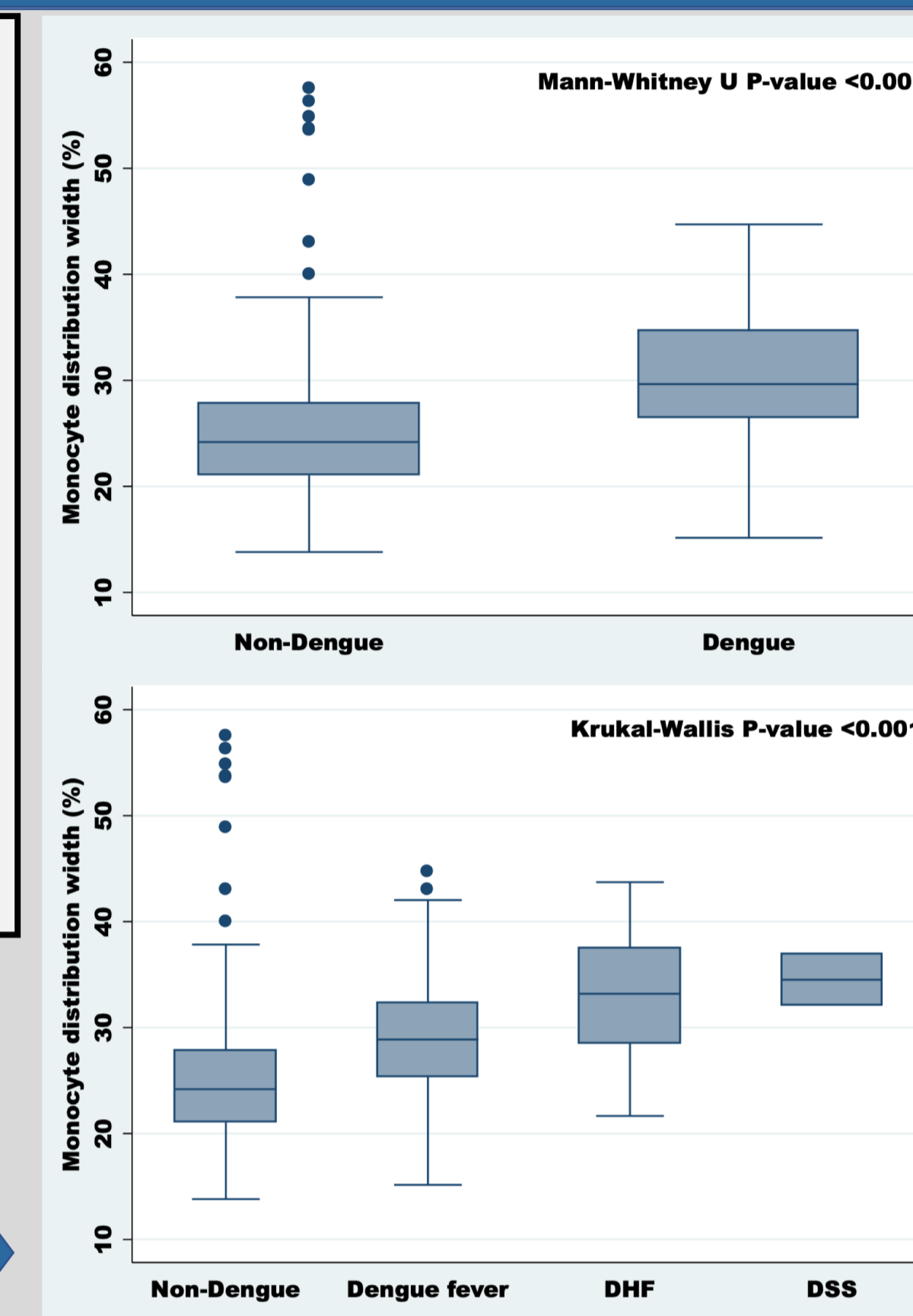


Figure 2 Monocyte distribution width by Dengue vs. non-Dengue and by severity (N = 431)

Table 1 Patients' characteristics

Characteristics	Training set		P-value	Validation set		P-value
	Non-Dengue (N=152)	Dengue (N=64)		Non-Dengue (N=152)	Dengue (N=63)	
Female sex	87 (57.2)	36 (56.3)	0.894	81 (53.3)	29 (46.0)	0.333
Median age (years) - IQR	40 (26-59)	34 (21-48)	0.003	37 (26-57)	28 (20-42)	<0.001
Median day of fever - IQR	4 (3-5)	4 (4-5)	0.343	4 (3-5)	4 (3-5)	0.733
qSOFA score of 2 or more	4 (2.6)	3 (4.7)	0.425	4 (2.6)	0	0.324
Organ specific symptoms			0.001			0.010
None	74 (48.7)	36 (56.3)		68 (44.7)	39 (61.9)	
Respiratory symptoms	60 (39.5)	12 (18.8)		63 (41.4)	14 (22.2)	
Gastrointestinal symptoms	16 (10.5)	16 (25.0)		17 (11.2)	9 (14.3)	
Genitourinary symptoms	6 (3.9)	1 (1.6)		10 (6.6)	1 (1.6)	
Median hemoglobin level (g/dL) - IQR	13.1 (11.9-14.1)	13.6 (12.1-15.2)	0.029	13.1 (12.1-14.2)	13.3 (12.5-14.5)	0.198
Median white blood cell (x10 <sup>9</sup> /L) - IQR	6.4 (4.8-9.5)	3.6 (3.1-4.9)	<0.001	7.2 (4.6-9.6)	3.7 (2.8-5.6)	<0.001
Median neutrophil count (x10 <sup>9</sup> /L) - IQR	4.6 (3.0-7.2)	2.1 (1.6-2.8)	<0.001	4.7 (2.7-6.9)	2.3 (1.6-3.7)	<0.001
Median lymphocyte count (x10 <sup>9</sup> /L) - IQR	1.1 (0.7-1.6)	1.0 (0.6-1.6)	0.349	1.2 (0.7-1.7)	0.8 (0.5-1.0)	<0.001
Median atypical lymphocyte (%) - IQR	3 (2-6)	13 (5-18)	0.082	4 (2-4)	11 (6-18)	0.086
Median monocyte count (x10 <sup>9</sup> /L) - IQR	0.6 (0.4-0.8)	0.3 (0.2-0.5)	<0.001	0.6 (0.4-0.8)	0.4 (0.2-0.7)	<0.001
Median monocyte distribution width (%) - IQR	24.7 (21.1-28.5)	30.9 (27.8-36.0)	<0.001	24 (20.6-27.5)	28 (24.5-32.3)	<0.001
Median platelet (x10 <sup>9</sup> /L) - IQR	193 (161-253)	121 (84-153)	<0.001	200 (144-251)	134 (93-167)	<0.001
Platelet less than 100 x 10 <sup>9</sup> /L	10 (6.6)	26 (40.6)	<0.001	16 (10.5)	19 (30.2)	<0.001
Platelet less than 150 x 10 <sup>9</sup> /L	28 (18.4)	44 (68.8)	<0.001	40 (26.3)	41 (65.1)	<0.001
Positive Dengue NS1Ag	1 (0.7)	41 (68.3)	<0.001	0	36 (62.1)	<0.001
Positive Dengue IgM	0	19 (29.7)	<0.001	0	23 (37.1)	<0.001
Positive Dengue IgG	26 (17.1)	33 (51.6)	<0.001	29 (19.1)	27 (43.6)	<0.001
Influenza Ag tested	94	26	1.000	96	37	1.000
Influenza A	7 (7.5)	1 (3.9)		10 (10.4)	0	
Influenza B	0	0		2 (2.1)	0	
Sepsis in the discharge summary	7 (4.6)	3 (4.7)	1.000	9 (5.9)	0	0.061
No hospital admission	130 (85.5)	38 (59.4)	<0.001	126 (82.9)	44 (69.8)	0.032
Requiring hospital admission	22 (14.5)	26 (40.6)		26 (17.1)	19 (30.2)	
Median length of stay (days) - IQR	7 (5-11)	5 (4-5)	0.004	6 (3-9)	4 (3-6)	0.320
In-hospital mortality	1 (0.7)	1 (1.6)	0.506	4 (2.6)	0	0.324
Status at 30 days			0.185			0.301
Alive	108 (71.1)	38 (59.4)		103 (67.7)	49 (77.8)	
Loss to follow-up	42 (27.6)	25 (39.0)		46 (30.3)	14 (22.2)	
Dead	2 (1.3)	1 (1.6)		3 (2.0)	0	

Abb.: IQR – interquartile range, qSOFA – quick sequential organ failure assessment. Data are presented as n (%) unless indicated otherwise.

Correspondences to: Wasitthep Limvorapitak, M.D.

E-mail: wasitthep@tu.ac.th

Table 2 Regression analyses for prediction of Dengue infection (stepwise backward)

Training model	Univariable analyses			Multivariable analyses			Regression coefficient
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value	
Female sex	0.96	0.53 – 1.73	0.894				
Age (for every decade increase)	0.78	0.66 – 0.93	<b>0.005</b>	Not significant			
qSOFA $\geq 2$	1.82	0.40 – 8.37	0.442	Not significant			
No organ specific symptoms	1.36	0.75 – 2.44	0.310	Not significant			
Hemoglobin (for every 1g/dL increase)	1.39	0.79 – 2.44	0.256	Not significant			
Leukopenia $< 4 \times 10^9/L$	7.42	3.85 – 14.33	<0.001	4.75	2.26 – 10.00	<0.001	1.56
Neutropenia $< 1 \times 10^9/L$	3.31	0.72 – 15.24	<b>0.124</b>	Not significant			
Lymphopenia $< 0.5 \times 10^9/L$	1.22	0.52 – 2.88	0.653	Not significant			
Monocytopenia $< 0.2 \times 10^9/L$	4.05	1.63 – 10.04	<b>0.003</b>	Not significant			
MDW $> 24\%$	8.93	3.64 – 21.94	<0.001	5.95	2.16 – 16.37	0.001	1.78
Platelet $< 100 \times 10^9/L$	9.72	4.31 – 21.89	<0.001	8.85	3.48 – 22.50	<0.001	2.18

**Dengue prediction score**

- Comprising 3 variables, 1 score each
1. Leukopenia less than  $4 \times 10^9/L$
  2. Monocyte distribution width  $> 24\%$
  3. Platelet less than  $100 \times 10^9/L$

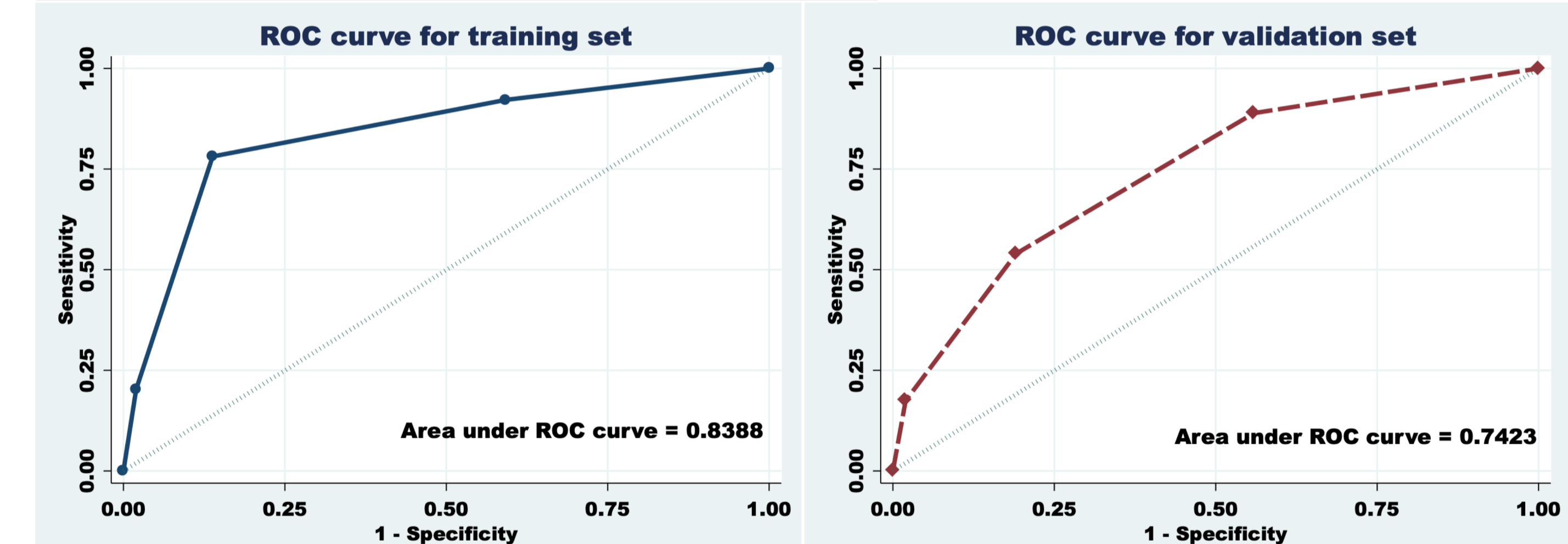


Figure 3 Receiver-operating characteristic curve showing performance of the prediction model in both training and validation set

Table 4 Number of patients classified by Dengue severity and Dengue score

Dengue score	Not Dengue	DF	DHF	DSS
0	129	11	1	0
1	125	27	4	0
2	44	42	17	1
3	6	13	10	1

False negative 16/127 (12.6%):  
 - DHF 5 pts, 3/5 had MDW  $> 24\%$   
 - DF 11 pts, no patient with MDW  $> 24\%$

False positive 6/304 (2.0%):  
 - Viral exanthem 3, virus not identified  
 - Acute pyelonephritis 1  
 - Sepsis 1

**CONCLUSIONS**

- MDW increase in Dengue infection correlate with Dengue severity.
- We have developed and internally validated a simple predictive score for Dengue infection based on only results from CBC and MDW.
- Further external validation study is required to confirm our findings.