PROCALCITONIN AND CLINICAL FACTORS ASSOCIATED WITH SEVERE DENGUE INFECTION IN HOSPITALISED ADULTS IN MALAYSIA

Dr. Huzairi Bin Sani

■ Disclaimer : No conflict of interests

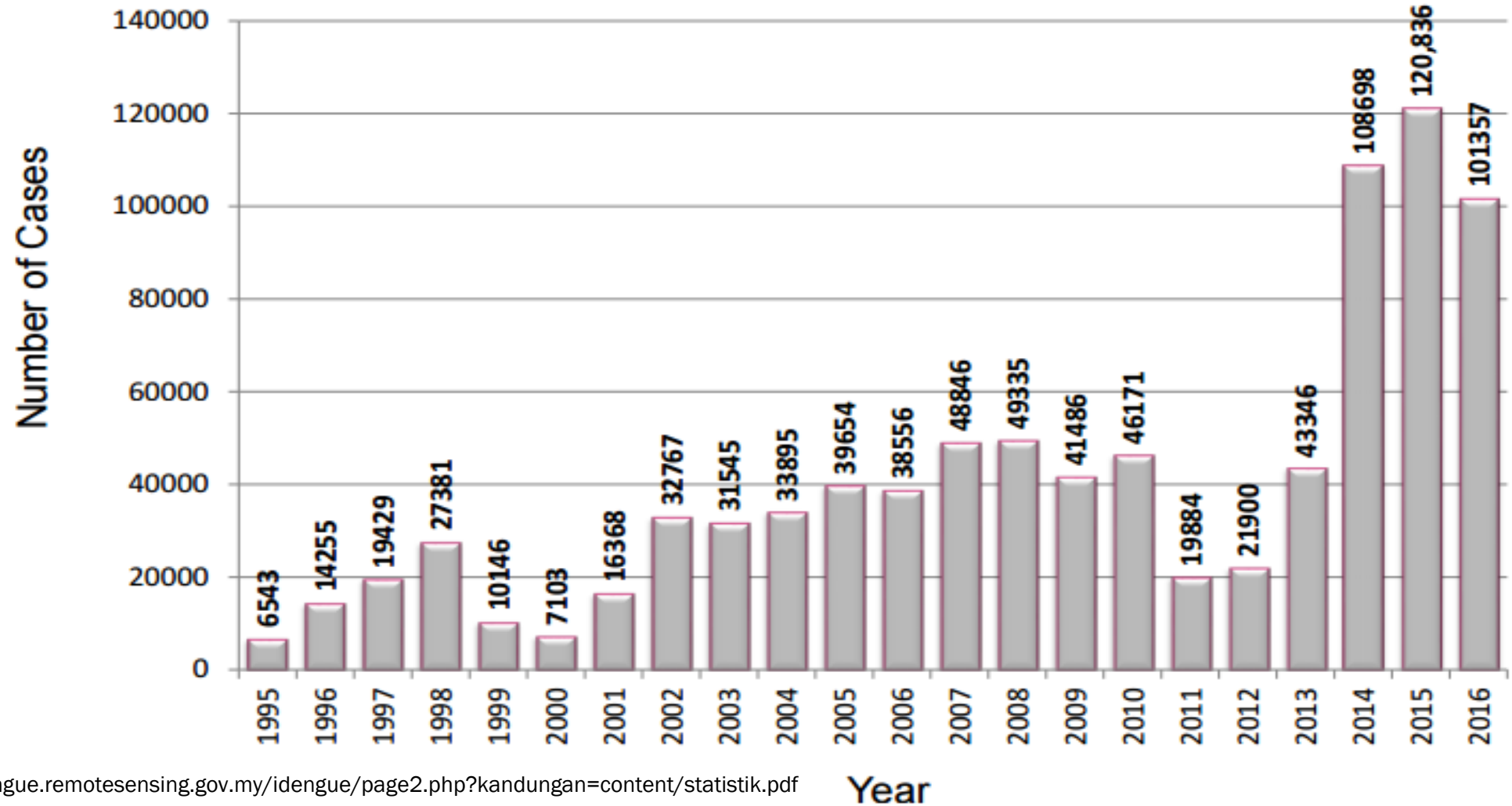# Dengue virus
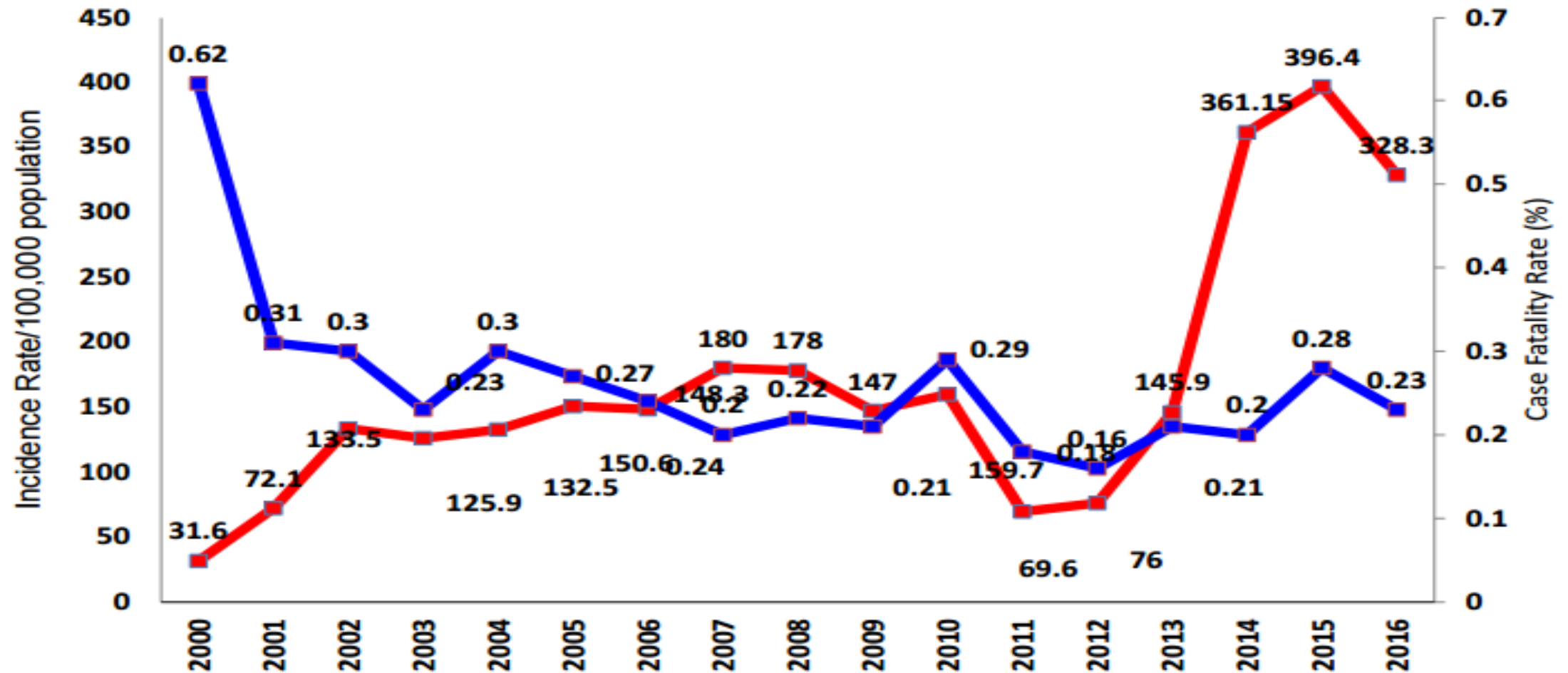# DEN 1 – DEN 4

- Vector - *Aedes aegypti & Aedes albopictus*

MALAYSIA
DENGUE CASES 1995 – 2016

http://idengue.remotesensing.gov.my/idengue/page2.php?kandungan=content/statistik.pdf

MALAYSIA
DENGUE INCIDENCE RATE & CASE FATALITY RATE
FOR YEAR 2000-2016

http://idengue.remotesensing.gov.my/idengue/page2.php?kandungan=content/statistik.pdf

Phases of dengue illness

- Febrile phase

- Critical phase (deferverscense phase)

- Recovery phase

Probable dengue	Dengue fever with warning signs	Severe Dengue
Live in / travel to endemic area.	Abdominal pain or tenderness	Severe plasma leakage leading to • Shock (DSS) • Fluid accumulation with respiratory distress
Fever and 2 of the following criteria:	Persistent vomiting	Severe bleeding As evaluated by clinician
Nausea, vomiting	Clinical fluid accumulation	Severe organ involvement • Liver : AST or ALT >= 1000 • CNS : Impaired consciousness • Heart • Other organs
Rash	Mucosal bleed	
Aches and pains	Lethargy, restlessness	
Tourniquet test positive	Liver enlargement > 2cm	
Leukopenia	Laboratory : increase in HCT concurrent with rapid decrease in platelet count	
Any warning sign		

Procalcitonin

■ Inflammatory marker

■ Several studies have also proven PCT to be superior to tumor necrosis factor alpha, IL-6 and CRP in prognosticating critically ill patients (de Werra et al., 1997; Oberhoffer M, 1999)

Objectives

- To determine the level of Procalcitonin in inpatient adults with dengue fever

- To determine association of warning signs, clinical assessment, and biochemical parameters with severe and non-severe dengue fever

Study design & site

Study	Description
Site	Selayang Hospital, Selangor, Malaysia
Design	Prospective observational study
Population	Dengue fever with warning signs admitted to Selayang Hospital

Eligibility criteria

Inclusion criteria

- Patients aged 18 years and above
- Confirmed Dengue Fever by NS-1 antigen or IgM Serology
- Fever less than 10 days
- Patient with warning signs admitted to Selayang Hospital

Exclusion criteria

- Patients who had burns injury
- Patient who had a recent trauma or fall
- Patients who had undergone a recent surgery
- Patients with acute or chronic pancreatitis
- Patients who were diagnosed with malignancy (NET, MTC, carcinoid tumor, small cell lung cancer)
- Patients with obvious source of other infections e.g. abscess, cellulitis, pneumonia, meningitis.

- Patients aged $\geq$ 18 years old
- Fever < 10days
- Confirmed dengue fever by NS-1 or serology

Exclusion criteria

- Burns
- Trauma

- Surgery
- Pancreatitis
- Neoplasm
- Possible co-infections

Day of admission

- Admitted
- Consented

- Demographics & clinical assessment
- Routine blood investigations

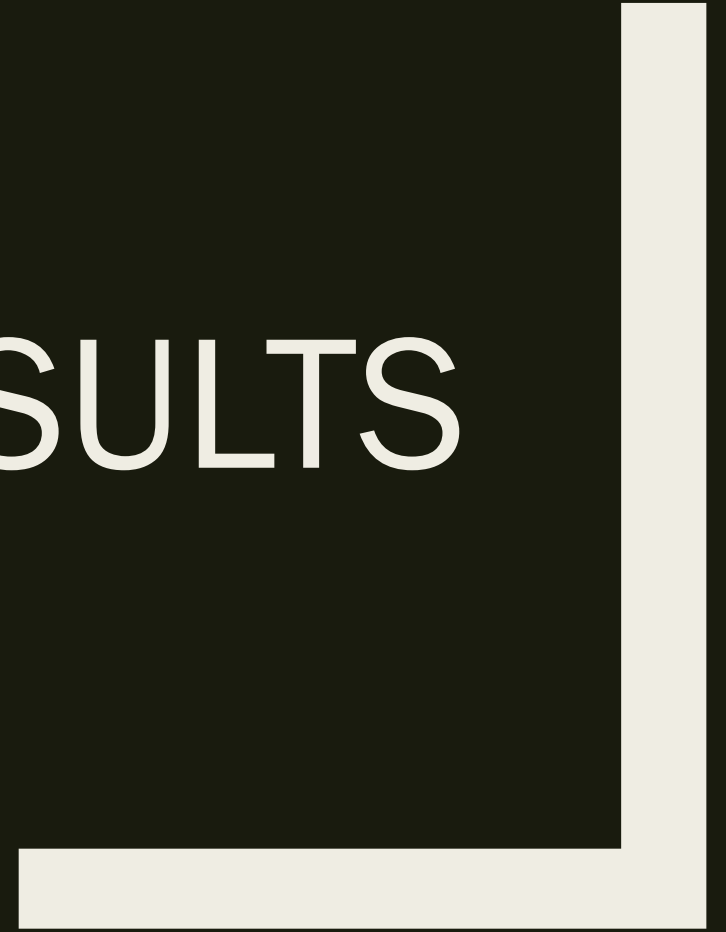2 mL plasma in EDTA bottle for procalcitonin

Clinical progress & laboratory investigations review

Follow up

Review final diagnosis on discharge summary

Statistical analysis

RESULTS

```
260 suspected dengue cases admitted under Internal
Medicine, Selayang Hospital

(September 2017 - February 2018)
```

```
127 excluded:
- 57 Negative dengue test on day of admission
- 54 other infections
- 16 below 18 years old
```

```
117 non severe dengue cases
```

```
16 severe dengue cases:
-    7 severe plasma leakage
-    9 severe organ impairment
```

```
2 deaths
```

Demographics and baseline characteristics on day of admission (n=133)

Baseline characteristics	Statistics
Age, median (IQR), years	30 (23-46)
Gender, n (%)	
Male	75 (56.4%)
Female	58 (43.6%)
Race, n (%)	
Malay	74 (56.1%)
Indian	26 (19.7%)
Chinese	23 (17.4%)
Orang Asli	8 (6.1%)
Pregnant, n (%)	4 (6.9%)
Day of illness, median (IQR), days	5 (3-6)
Days of admission, median (IQR), days	4 (3-5)
Warning signs, n (%)	
Vomiting	67 (50.4%)
Diarrhoea	66 (49.6%)
Raised haematocrit with low platelet	61 (45.9%)
Abdominal pain	32 (24.1%)
Lethargy	16 (12%)
Mucosal bleeding	12 (9%)
Tender hepatomegaly	2 (1.5%)
Clinical fluid accumulation	1 (0.8%)

Baseline characteristics on day of admission (n=133)

Variables	Statistics
Vital signs,	
Decompensated shock, n (%)	8 (6%)
Pulse rate >90 beats per minute, median (IQR)	100 (95-105)
Pulse rate <90 beats per minute, median (IQR)	76 (72-84)
Febrile phase, n (%)	88 (66%)
Defervescence phase, n (%)	45 (34%)
Respiratory rate per minute, median (IQR)	20 (18.5-20)
Blood parameters, median (IQR)	
Haemoglobin, g/dL	14.3 (13.1-16.0)
Platelet x 10^9 cells/L	80 (36-132)
Haematocrit, %	42 (39-46)
Urea, mmol/L	3.3 (2.6-4.6)
Sodium, mmol/L	133 (131-135)
Potassium, mmol/L	3.6 (3.2-3.9)
Creatinine, µmol/L	71 (56-90)

Median values of biomarkers

Baseline characteristics	Descriptive statistics Median (IQR)
Procalcitonin, ng/ml	0.28 (0.17-0.62)
Lactate, mmol/L	1.63 (1.21-2.22)
White blood cell x 10^9 cells/L	3.3 (2.3-5.2)
Albumin, g/L	38 (34-41)
AST, IU/L	93 (55-183)

Warning signs between non-severe and severe group

	Non severe (n=117) n (%)	Severe (n=16) n (%)	p value
Age	30 (23-46)	28 (18-59)	0.630
Gender			
Female	49 (42)	7 (44)	0.277
Defervescence phase	36 (30.8)	9 (56.3)	**0.043**
Warning signs			
Abdominal pain	28 (23.9)	4 (25)	0.925
Vomiting	59 (50.4)	8 (50)	0.974
Diarrhoea	62 (52.9)	4 (25)	0.060
Lethargy	9 (7.7)	7 (43.8)	**0.000**
Spontaneous bleeding	9 (7.7)	3 (18.8)	0.159
Tender hepatomegaly	2 (1.7)	0 (0)	1.000
Clinical fluid accumulation	0 (0)	1 (6.3)	0.120

Statistical analysis using chi-squared or Fisher's exact tests for categorical variables, significant p-value <0.05

Vitals signs between non-severe and severe group

Clinical parameters	Non-severe Median (IQR)	Severe Median (IQR)	p-value
Systolic blood pressure, mmHg	120 (107–129)	94 (84-106)	**0.000**
Diastolic blood pressure, mmHg	76 (67–82)	56 (49-65)	**0.000**
Pulse rate per minute	88 (76–98)	92 (88-101)	0.275
Temperature, °C	38.2 (37.6-38.8)	37.8 (37.1-38.3)	0.069
Respiratory rate per minute	20 (18-20)	20 (19-21)	0.093

Statistical analysis using Mann Whitney U test
Significant p-value <0.005

Biochemical analysis between non-severe and severe group

Parameter	Non-severe Median (IQR)	Severe Median (IQR)	p-value
Haemoglobin, g/dL	14.4 (13.2-16.2)	13.6 (11.7-14.9)	**0.028**
Neutrophils, absolute count	1.7 (1.1-2.7)	1.7 (1.5-3.3)	0.281
Lymphocytes, absolute count	0.9 (0.6-1.7)	1.2 (0.8-2.2)	0.191
Haematocrit, %	42.3 (39.0-46.9)	39.5 (33.5-41.8)	**0.022**
Urea, mmol/L	3.3 (2.6-4.6)	3.5 (2.7-5.1)	0.504
Sodium, mmol/L	133 (131-135)	135 (132-138)	0.262
Potassium, mmol/L	3.6 (3.2-3.9)	3.6 (3.4-3.9)	0.390
Creatinine, umol/L	72 (58-89)	59 (54-96)	0.487
Bilirubin, umol/L	10 (8-15)	10 (7-14)	0.478

Statistical analysis using Mann Whitney U test, significant p-value <0.05

Univariate analysis of blood parameters between non-severe and severe group

Categorical parameter	Non-severe (n=117) n (%)	Severe (n=16) n (%)	p-value
White cell count >3.0 x10^9/L	62 (53)	11 (69)	0.235
Albumin <35 g/L	31 (26)	9 (56)	**0.015**
AST > 120 u/L	54 (46)	6 (38)	0.514
Lactate > 2mmol/L	37 (32)	2 (13)	0.870
Procalcitonin > 0.3 ng/mL	54 (46)	9 (56)	0.448

Statistical analysis using chi-squared or Fisher's exact tests.

Significant p-value <0.05
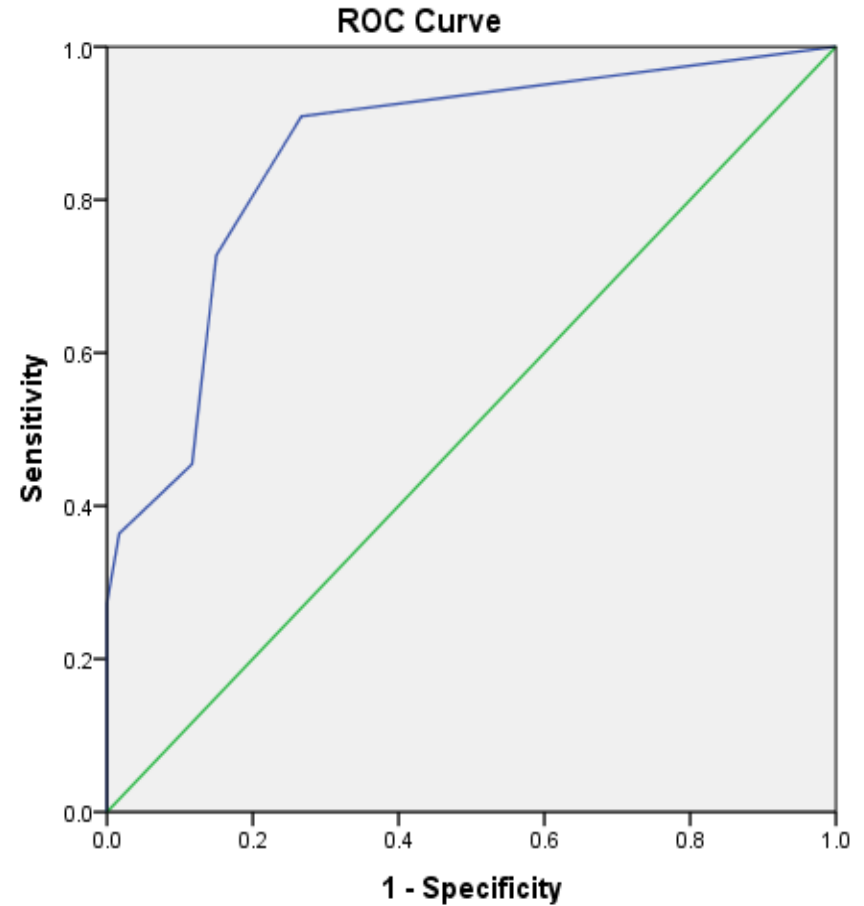
Multivariate analysis on significant parameters

Variable	Odds ratio	95% Confidence interval	p-value
Defervescence phase	2.6	0.73-9.21	0.138
Lethargy	10.95	2.71-44.22	**0.001**
Albumin < 35 g/L	5.72	1.55-21.05	**0.009**
Procalcitonin >0.3 ng/mL	1.36	0.39-4.7	0.629

Significant p-value <0.05

ROC curve between significant parameters & PCT
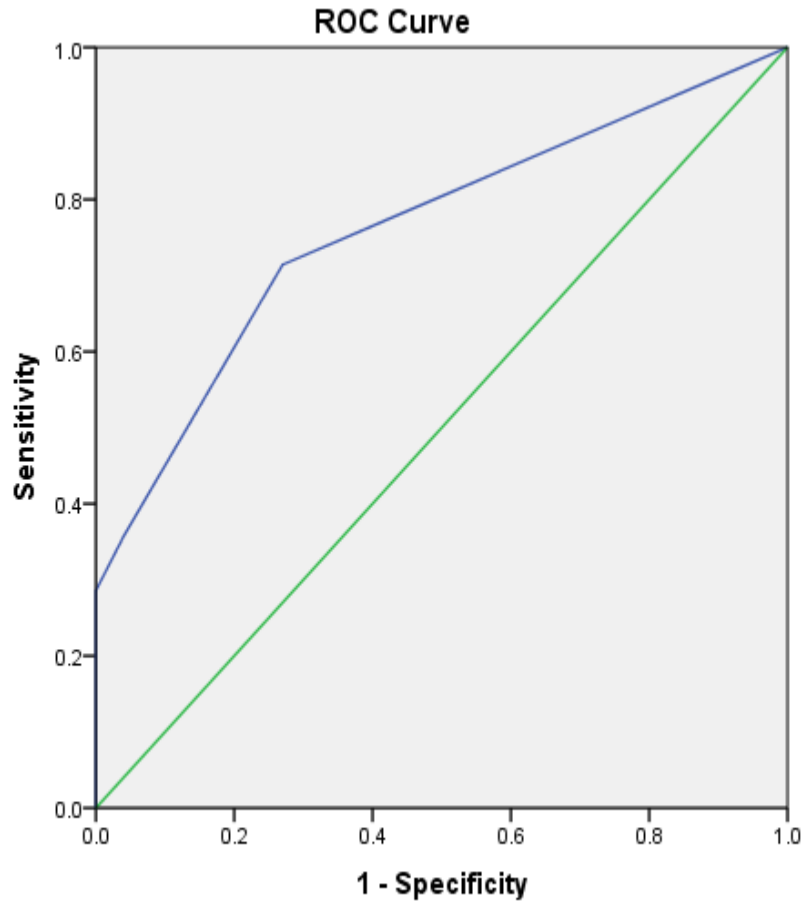
Plasma albumin, lactate and plasma procalcitonin in relation to survival outcome

Blood parameter	Survival (n=131)	Death (n=2)	Significance
Albumin, g/L	38 (34-41)	19 (17-21)	0.165
Plasma lactate, mmol/L	1.63 (1.21-2.22)	1.34 (1.26-1.42)	0.494
Plasma procalcitonin, ng/mL	0.28 (0.17-0.57)	3.6 (3.2-4.0)	**0.021**

Significant p-value <0.05

DISCUSSION

Warning signs

- Severe dengue were likely to present with lethargy on admission
- This complaint or symptom should be taken seriously by attending physician

Biomarker

- Plasma albumin of <35 g/L significantly associated with severe dengue

- Systemic inflammatory response causes reduced production, increased catabolism and third space loss (Benoît Ruot, 2000)

- Albumin is used as a parameter in calculating APACHE-III score to prognosticate critically ill patients → highlights it as a significant negative acute phase reactant (Knaus, 2002)

- New Delhi, India: low albumin has a significant value on dengue survival outcome (Saroch et al., 2017)

PCT as predictor of severe dengue

- PCT prediction improves when combined with lethargy and hypoalbuminemia of <35 g/L (AUROC 0.86)
- ROC analysis of these three parameters revealed a **sensitivity of 73%** and **specificity of 85%** in predicting severe dengue on the first day of admission to hospital

Limitations of study

- Single-centred

- Limited sample size especially in severe dengue group

- PCT was only done once on admission without subsequent repeats throughout course of illness

CONCLUSION
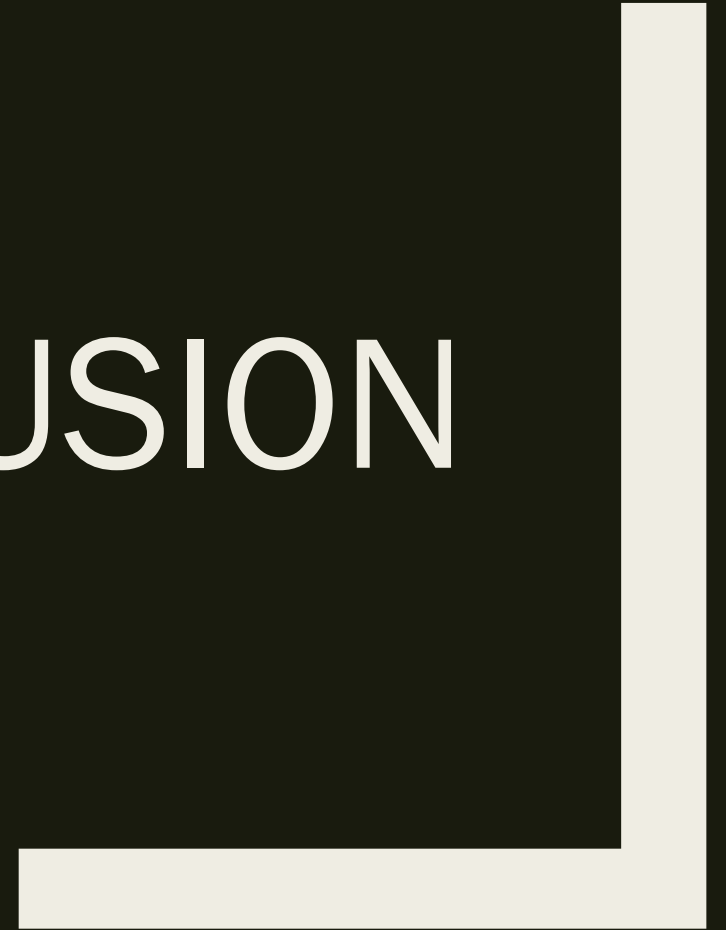
- 2 significant presenting features of severe dengue:
  - *Lethargy –often overlooked and dismissed*
  - *Plasma albumin of <35 g/L*

- PCT may be useful in the prognostication of dengue fever where:
  (1) At a cut-off of >0.3 ng/mL, it predicts severe dengue at a sensitivity level of 73% and specificity of 85% when combined with lethargy and albumin <35 g/L; and
  (2) It is significantly associated with death when raised to a median of 3.6 ng/mL

THANK YOU