

Risicofactor analyse voor ongunstige uitkomst geïmporteerde malaria

Jaap van Hellemond

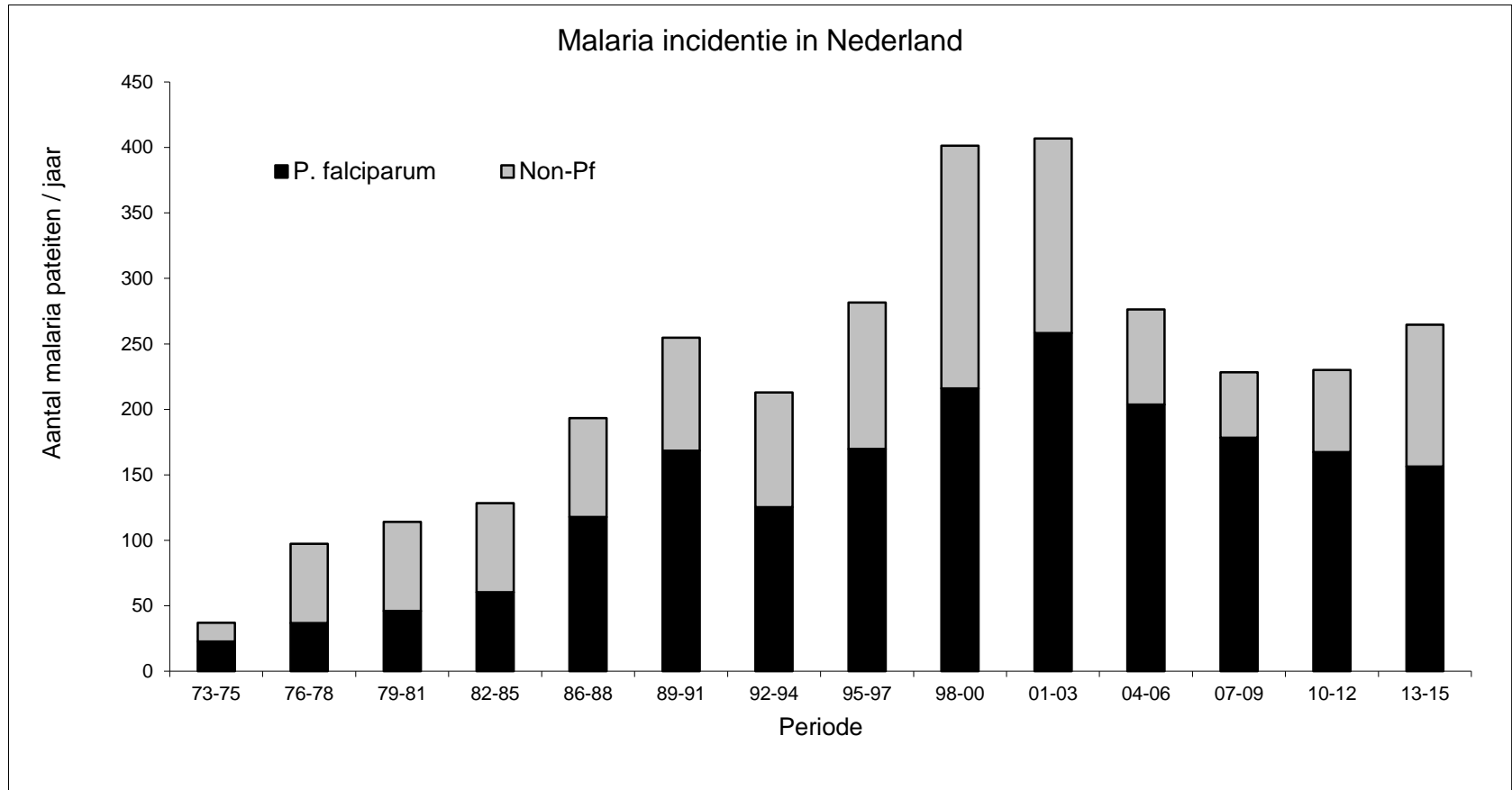
Risk factor analysis for unfavourable outcome in adult patients with imported *Plasmodium falciparum* malaria

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Malaria in non-endemic countries



Very low incidence → a clinical challenge

Malaria in non-endemic countries

Clinical challenge:

Very low incidence

Rapid disease progression in naïve adults:

Malaria in non-endemic countries

Clinical challenge:

Very low incidence

Rapid disease progression in naïve adults:

- Uncomplicated disease
- Severe disease
 - Organ failure
 - Life threatening
 - Intensive care treatment in specialized centres

What is severe malaria disease?

WHO criteria for severe malaria

WHO criteria severe malaria

Manifestation

Initial World Health Organization criteria from 1990 [\[11\]](#)

Cerebral malaria

Severe anemia

Renal failure

Pulmonary edema and acute respiratory distress syndrome

Hypoglycemia

Circulatory collapse (algid malaria)

Abnormal bleeding and/or disseminated intravascular coagulation

Repeated generalized convulsions

Acidemia/acidosis

Macroscopic hemoglobinuria

Features

Unrousable coma not attributable to any other cause, with a Glasgow Coma Scale score ≤ 9 . Coma should persist for at least 30 min after a generalized convulsion

Hematocrit $<15\%$ or hemoglobin $< 50 \text{ g/l}$ in the presence of parasite count $>10\,000/\mu\text{l}$

Urine output $<400 \text{ ml/24 hours}$ in adults ($<12 \text{ ml/kg/24 hours}$ in children) and a serum creatinine $>265 \mu\text{mol/l}$ ($> 3.0 \text{ mg/dl}$) despite adequate volume repletion

The acute lung injury score is calculated on the basis of radiographic densities, severity of hypoxemia, and positive end-expiratory pressure [\[26\]](#)

Whole blood glucose concentration $<2.2 \text{ mmol/l}$ ($<40 \text{ mg/dl}$)

Systolic blood pressure $<70 \text{ mmHg}$ in patients > 5 years of age ($< 50 \text{ mmHg}$ in children aged 1–5 years), with cold clammy skin or a core-skin temperature difference $>10^\circ\text{C}$

Spontaneous bleeding from gums, nose, gastrointestinal tract, or laboratory evidence of disseminated intravascular coagulation

≥ 3 convulsions observed within 24 hours

Arterial pH <7.25 or acidosis (plasma bicarbonate $<15 \text{ mmol/l}$)

Hemolysis not secondary to glucose-6-phosphate dehydrogenase deficiency

What is severe malaria disease?

WHO criteria for severe malaria

- defined to harmonize studies on severe malaria
 - Mixture of useful symptoms
 - Low care setting (only physical examination)
 - High care setting (laboratory parameters)
- risk factor analyses
- treatment optimisation

What is severe malaria disease?

WHO criteria for severe malaria

- defined to harmonize studies on severe malaria
 - risk factors
 - treatment optimisation

Endemic countries:

Inclusion: WHO criteria severe malaria

Outcome: mortality

.

WHO criteria severe malaria

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Added World Health Organization criteria from 2000 [\[12\]](#)

Impaired consciousness

Prostration or weakness

Hyperparasitemia

Hyperpyrexia

Hyperbilirubinemia

Features

Unrousable coma not attributable to any other cause, with a Glasgow Coma Scale score ≤ 9 . Coma should persist for at least 30 min after a generalized convulsion

Hematocrit $<15\%$ or hemoglobin < 50 g/l in the presence of parasite count $>10\,000/\mu\text{l}$

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Hemolysis not secondary to glucose-6-phosphate dehydrogenase deficiency

Rousable mental condition

$> 5\%$ parasitized erythrocytes or $> 250\,000$ parasites/ μl (in nonimmune individuals)

Core body temperature $>40^\circ\text{C}$

Total bilirubin >43 $\mu\text{mol/l}$ (> 2.5 mg/dl)

Malaria in non-endemic countries

Distinct from endemic countries in:

Naïve	vs	immune
Adults	vs	infants & pregnant women
High care	vs	low care
Rapid	vs	slow progression
Kidney	vs	cerebral malaria

Severe malaria disease in naive adults

≠

children endemic countries

Risk factor severe malaria in travellers

Inclusion: WHO criteria severe malaria

Outcome: mortality

Non-endemic countries: mortality is very low

Most studies used WHO definition as outcome!!!

WHO criteria severe malaria

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WHO criteria describe condition (disease status),
that does not necessarily predict outcome.

Risk factors for 'unfavourable outcome'

Alternative endpoint : 'unfavourable outcome',
defined as 1 or more of

- the occurrence of death
- prolonged duration of hospital stay (>120 hours)
- admission to an intensive care unit (ICU)
- referral for dialysis

Modified from Phillips *et al Clin Infect Dis. 2009;48:871–8*

Large array of parameters can be analysed for
association with 'unfavourable outcome' in
Rotterdam Malaria cohort (442 patients)

Univariate analysis

	Unfavourable n = 140 (31.7%)	Favourable n = 302 (68.3%)	OR (CI 95%)	P-value
Age (years)	44 (17-70)	39 (16-78)	1.39 (1.16-1.66) ^a	<0.001
Gender				0.001
Male	87 (62.1%)	235 (77.8%)	1.00 (reference)	
Female	53 (37.9%)	67 (22.2%)	2.14 (1.38-3.31)	
Ethnicity				0.001
African	51 (36.4%)	166 (55.0%)	1.00 (reference)	
Caucasian	73 (52.1%)	115 (38.1%)	2.07 (1.35-3.18)	0.001
Asian	10 (7.1%)	7 (2.3%)	4.65 (1.68-12.84)	0.003
Other	6 (4.3%)	14 (4.6%)	1.40 (0.51-3.82)	0.517
Immunity ^b				<0.001
Non-immune	89 (65.0%)	133 (45.7%)	1.00 (reference)	
Partially/semi-immune	48 (35.0%)	158 (54.3%)	0.45 (0.30-0.69)	
Use of chemoprophylaxis ^c				0.947
None	106 (76.8%)	217 (75.3%)	1.09 (0.48-2.47)	0.845
Inadequate	23 (16.7%)	51 (17.7%)	1.00 (0.40-2.54)	0.996
Adequate	9 (6.5%)	20 (6.9%)	1.00 (reference)	
Time between onset and admission ^d				0.625
< 8 days	91 (68.4%)	211 (72.5%)	1.00 (reference)	
8-14 days	26 (19.5%)	55 (18.9%)	1.07 (0.65-1.86)	0.733
15-28 days	14 (10.5%)	20 (6.9%)	1.62 (0.79-3.35)	0.191
> 28 days	2 (1.5%)	5 (1.7%)	0.93 (0.18-4.87)	0.929
Temperature (°C) ^e	38.9 (35.7-41.0)	38.3 (35.5-40.8)	1.44 (1.21-1.70)	<0.001
Blood pressure (mmHg) ^f				
Systolic	120 (64-181)	120 (80-197)	0.87 (0.77-0.98) ^a	0.025
Diastolic	70 (43-104)	71 (30-120)	0.778 (0.65-0.94) ^a	0.007
Pulse rate (beats/minute) ^g	100 (50-142)	90 (45-150)	1.31 (1.16-1.49) ^a	<0.001
Haemoglobin (mmol/L) ^h	8.3 (3.8-10.9)	8.5 (3.0-11.3)	0.78 (0.67-0.91)	0.001
Leukocyte count (x 10 ⁹ /L) ⁱ	5.5 (1.9-18.5)	4.8 (1.3-13.2)	1.23 (1.12-1.36)	<0.001
Thrombocyte count (x 10 ⁹ /L) ^j	54 (2-252)	102 (15-395)	0.54 (0.43-0.67) ^k	<0.001
C-reactive protein (mg/L) ^l	139 (5-476)	86 (1-363)	1.51 (1.31-1.74) ^k	<0.001
Sodium (mmol/L) ^j	132 (115-146)	135 (121-145)	0.17 (0.09-0.29) ^a	<0.001
Glucose (mmol/L) ^m	6.9 (4.1-33.8)	6.5 (4.4-26.0)	1.88 (0.76-4.65) ^a	0.173
Creatinine (μmol/L) ⁱ	97 (39-1081)	94 (48-228)	3.44 (1.76-6.74) ⁿ	<0.001
Urea (mmol/L) ^o	5.8 (2.2-55.8)	5.0 (2.1-19.9)	2.94 (1.99-4.36) ^p	<0.001
ASAT (U/L) ^q	56 (10-394)	32 (6-326)	2.37 (1.79-3.15) ^k	<0.001
ALAT (U/L) ^j	50 (11-655)	38 (11-242)	1.56 (1.23-2.00) ^k	<0.001
LDH (U/L) ^r	365 (120-2297)	262 (118-947)	1.61 (1.330-1.87) ⁿ	<0.001
Bilirubin total (μmol/L) ^s	31 (3-416)	21 (3-262)	2.73 (1.75-4.26) ^k	<0.001
Lactate (mmol/L) ^t	2.0 (0.6-6.2)	1.3 (0.5-4.6)	3.10 (2.22-4.33)	<0.001
Parasitaemia (trophozoites/μL) ^u	83,600 (49-(1,380,600))	4,245 (22-580,000)	2.91 (2.14-3.97) ^v	<0.001

Multi-variate analysis

	OR (95% CI)	P-value
Gender		0.001
Male	1.00 (reference)	
Female	3.41 (1.61-7.19)	
Temperature (°C)	1.69 (1.28-2.22)	<0.001
Leukocyte count (x 10⁹/L)	1.19 (1.02-1.39)	0.026
Thrombocyte count		0.022
≥ 50 x 10 ⁹ /L	1.00 (reference)	
< 50 x 10 ⁹ /L	2.34 (1.13-4.83)	
Urea (mmol/L)	3.34 (1.59-7.20) ^a	0.002
Lactate (mmol/L)	1.88 (1.26-2.81)	0.002
Parasitaemia		0.001
≤ 100,000 trophozoites/μL	1.00 (reference)	
> 100,000 trophozoites/μL	3.82 (1.78-8.21)	

OR, odds ratio; 95% CI, 95% confidence interval

The final regression model was based on 318 cases with available data (of a total of 442 cases).

Hosmer-Lemeshow test: $p = 0.887$

^aOR is given for a 5-unit change in the explanatory variable

Diagnostic performance of continuous variables

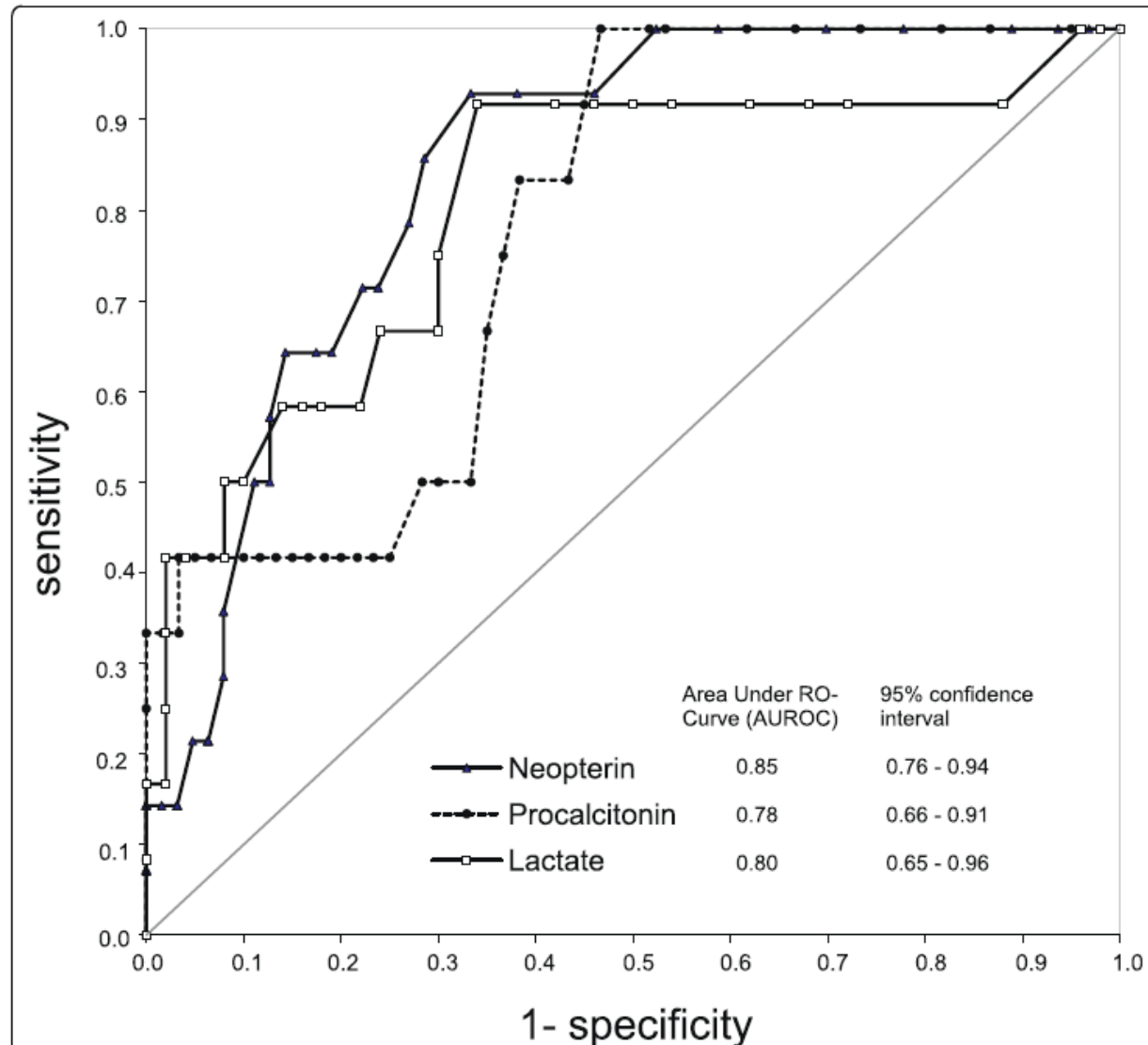


Figure 2 Receiver Operating Curves (ROC) characteristics of the diagnostic performance of neopterin, procalcitonin and lactate for severe *P. falciparum* malaria. The ROC curve is a graph of sensitivity (true positive fraction) plotted against 1-specificity (false positive fraction). The performance of a diagnostic variable can be quantified by calculating the area under the ROC curve (AUROC). The ideal test would have an AUROC of 1, whereas a random guess would have an AUROC of 0.5.

Diagnostic performance of continuous variables

	Temperature	Leukocyte count	Urea	Lactate	Parasite load
Cut-off^a	> 37.8 °C	> 5.9 x 10 ⁹ /L	> 7.3 mmol/L	> 1.5 mmol/L	> 34,300 trophozoites/μL
Sensitivity	0.78 (0.71-0.86)	0.85 (0.80-0.90)	0.35 (0.27-0.43)	0.77 (0.69-0.85)	0.68 (0.60-0.75)
Specificity	0.44 (0.38-0.50)	0.53 (0.45-0.62)	0.91 (0.87-0.94)	0.66 (0.60-0.72)	0.76 (0.71-0.81)
PPV	0.39 (0.33-0.45)	0.71 (0.65-0.77)	0.64 (0.54-0.75)	0.52 (0.45-0.60)	0.57 (0.49-0.64)
NPV	0.81 (0.75-0.88)	0.73 (0.64-0.81)	0.74 (0.70-0.79)	0.85 (0.80-0.91)	0.83 (0.79-0.88)
AUROC	0.63 (0.57-0.69)	0.62 (0.57-0.68)	0.64 (0.58-0.70)	0.76(0.70-0.81)	0.76 (0.72-0.80)
P-value^b	0.002	< 0.001	0.001	0.648	Reference

PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating characteristics (ROC) curve

^a Optimal cut-off point is determined using Youden's index

^bP value concerns pairwise comparison according to the DeLong method (28).

Plasma lactate > 1.5 mM predicts unfavourable outcome as good as parasite load !

Diagnostic performance of dichotomous variables

	Gender (female)	Thrombocyte count ($< 50 \times 10^9/L$)	Parasite load ($> 100,000$ trophozoites/ μL)
Sensitivity	0.38 (0.30-0.46)	0.44 (0.36-0.52)	0.47 (0.39-0.56)
Specificity	0.79 (0.73-0.83)	0.84 (0.80-0.88)	0.93 (0.90-0.96)
PPV	0.44 (0.35-0.53)	0.56 (0.47-0.65)	0.77 (0.68-0.86)
NPV	0.73 (0.68-0.78)	0.76 (0.72-0.81)	0.79 (0.75-0.83)

PPV, positive predictive value; NPV, negative predictive value

Thrombocyte count ($< 50 \times 10^9 /L$) predicts unfavourable outcome almost as good as parasite load !

Does WHO defined severe malaria predict unfavourable outcome?

	Adapted criteria Phillips et al.			
	Unfavourable (n = 140)	Favourable (n = 302)	OR (95% CI)	P-value
WHO criteria				<0.001
Severe (n = 59)	53 (37.9%)	6 (2.0%)	30.05 (12.50-72.27)	
Non-severe (n = 383)	87 (62.1%)	296 (98.0%)	1.00 (reference)	

WHO, World Health Organization

Sensitivity: 0.38 (0.30-0.46); specificity: 0.98 (0.96-1.00); positive predictive value: 0.90 (0.82-0.98); negative predictive value: 0.77 (0.73-0.81).

Yes, WHO defined severe malaria is

- High specificity
- Low sensitivity!!! (too stringent criteria)

Same analysis, but now for WHO defined severe malaria

	OR (95% CI)	P-value
Haemoglobin (mmol/L)	0.66 (0.44-0.97)	0.034
Creatinine (mmol/L)	12.72 (2.33-69.55) ^a	0.003
LDH (U/L)	1.67 (1.26-2.22) ^a	< 0.001
Bilirubin total (μmol/L)	5.67 (2.61-12.30) ^b	< 0.001
Parasitaemia		< 0.001
≤ 100,000 trophozoites/μL	1.00 (reference)	
> 100,000 trophozoites/μL	207.26 (33.24-1292.43)	

OR, odds ratio; 95% CI, 95% confidence interval; LDH, lactate dehydrogenase

The final regression model was based on 412 cases with available data (of a total of 442 cases).

Hosmer-Lemeshow test: $p = 0.995$

^a OR is given for a 100-unit change in the explanatory variable

^b OR is given for a 50-unit change in the explanatory variable

List of other parameters! (apart from parasite load)

Hb, Creat, LDH

Discussion: gender

Our study:

3-fold higher risk for unfavourable outcome

Males have higher risk for acquisition;
not much known about disease progression in travellers

Female patients presented with significantly higher

- parasite load on admission than male patients
(median of 19,600 trophozoites/ μ L vs 6,372 trophozoites/ μ L, $p = 0.019$)
- complication rate as compared to male malaria patients
(25.0% versus 10.5%, $p < 0.001$)

May be females presented at a later phase??

Discussion: markers for poor outcome

Our study:

Parasite load (> 2%) 4-fold increased risk
 (>10%) 200-fold increased risk

- Good parameter
- Long determination time en complex

Discussion: markers for poor outcome

Our study:

Thrombocyte count ($< 50 \times 10^9 /L$)

- Well known factor in severe malaria
- Easy and quick parameter

Discussion: markers for poor outcome

Our study:

Plasma lactate (> 1.5 mM); 2-fold increase

- Each unit increase; 2-fold increase of risk
- Easy and quick parameter !!!

Problem of malaria treatment in non-endemic countries

Determination of severity of disease

Results in delay in treatment / referral

Need for easy markers that identify and/or predict severe disease

Conclusions markers for poor outcome

Rotterdam malaria cohort study

Increased risk:

Parasite load (> 2 %)

Thrombocytopenia (<50 x 10⁹/L)

Plasma lactate (> 1.5 mM)

Indication for start parental treatment (artesunate) ?