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Bilirubin Cut-off Level to Predict Fatal Outcome of Severe Falciparum Malaria with Jaundice

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Abstract

Background: Although jaundice is WHO (2010) criteria for severe malaria. However total bilirubin level in the severe malaria patients with jaundice was not mentioned. The objective of this study was to find the cut-off point of total bilirubin level sensitive to detect fatal outcome in severe malaria patients with jaundice.

Methods: 174 severe falciparum malaria patients were included into the study. Clinical and laboratory data of the survived severe malaria patients and fatal severe malaria patients were compared. Receiver Operative Curve (ROC) was constructed to evaluate sensitivity of total bilirubin to detect fatal jaundiced patients.

Results: There were 29 fatal patients (17%). Out of 117 jaundiced patients, 27 patients were fatal (23%). ROC showed low bilirubin as 2 mg/dl was early observed in 97% fatal severe malaria patients with jaundice.

Conclusion: Cut-off of bilirubin level in jaundiced severe malaria patients should be ≥ 2 mg/dl which could detect fatal outcome with sensitivity of 97%.

Keywords: Hyperbilirubinemia; Jaundice; Fatal; Falciparum; Malaria

Introduction

Jaundice is the useful indicator of severe malaria [1]. World Health Organization (WHO) defined severe malaria if the patients had jaundice by clinically examination of the sclera and/or mucosal surfaces of the mouth [2]. However WHO did not mention the cut-point of total bilirunin level of jaundice [2-4]. There are no normal levels of total bilirubin as total bilirubin is an excretion product, and a level found in the body reflects the balance between production and excretion. Different sources provide reference ranges that are similar but not identical. However jaundice becomes visible when total bilirubin level is about 2-3 mg/dl [5,6]. The objective of this study was to find cut-off point of total bilirubin level which was high sensitive to detect fatal outcome in severe falciparum malaria patients with jaundice.

Methods

Patients: 174 adult patients aged ≥ 18 years old with severe falciparum patients, established by blood smear, admitted to Hospital for Tropical diseases, Mahidol University, Thailand were studied. The complications were defined as a malarial illness with at least one of the following complications: prostration, impaired consciousness, respiratory distress (acidotic breathing), multiple convulsion (more than 2 observed within 24 hours), pulmonary edema, abnormal bleeding (from gums, nose, gastrointestinal tract, and/or substantial laboratory evidence of disseminated intravascular coagulation), hemoglobinuria, severe anemia (with hemoglobin <5 g/dl), hypoglycemia (with plasma glucose <40 mg/dl), acidemia (arterial pH <7.35) or acidosis (with plasma bicarbonate concentration <15 mmol/l), renal impairment (urine output of <400 ml in 24 hours, failing to improve after rehydration, and serum creatinine of >3 mg/dl), hyperparasitemia (above 5% parasitemia), and jaundice (clinically defined as icteric sclera at initial presentation). Patients with mixed malarial infection other than falciparum mono-infection; history of underlying hepatobiliary tract diseases; taking alcohol, medicines, or herb one month prior admission were excluded from the study. Blood were drawn on the first day of admission prior antimalarial drugs were given.

Treatment: All severe malaria patients were treated with intravenous arteunate 2.4 mg/kg at time 0, 12, 24 hour of admission, then once daily until the patients could take oral medication, then treatment was switched to artesunate 4 mg/kg/day for 3 days combined with mefloquine 25 mg/kg in 2 divided doses 12 hourly apart. All patients were admitted in intensive care unit. The survived patients were continuously admitted to the hospital for 28 days for clinical and laboratory follow-up.

Measurement: On admission day, blood smears, biochemical tests including conventional liver function tests, plasma glucose, blood urea nitrogen, serum creatinine and electrolytes were performed.

Statistical analysis: Quantitative parameters were compared by Chi-squared test. Quantitative parameters were compared using Student's unpaired *t*-test and as appropriate between survived and fatal patients. Numerical valued were given in the test as means ± standard deviation of means (SD) and p values less than 0.05 were regarded as significant.

Results

Table 1 showed that fatal patients were older, had higher body mass index, pulse rate, respiratory rate, White Blood Cell (WBC) count,

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	SMS (N=145)	SMD (N=29)
Gender (%) (Male/Female)	114 (78.6) / 31 (21.4)	22 (75.9) / 7 (24.1)
Mean (SD) of Age (years) †	27.52 (10.66)	39.48 (16.32)
Mean (SD) of Body Mass Index (kg/m^2) †	20.42 (3.30)	25.27 (3.50)
Mean (SD) of Duration of fever before admission (days)	4.54 (1.92)	4.76 (1.53)
Geometric mean parasite count (/μL) (Min-Max)	81,844.88 (230-1,154,250)	92,707.02 (256-1,335,320)
Initial vital signs [Mean (SD)]		
Auxiliary temperature (˚C)	38.14 (1.03)	4.76 (1.53)
Pulse rate (bpm) †	100.36 (15.02)	113.31 (1.48)
Respiratory rate (bpm) †	25.85 (5.04)	31.66 (6.83)
Systolic blood (mmHg)	107.79 (15.11)	113.34 (28.49)
Diastolic blood (mmHg)	64.60 (11.81)	71.42 (19.98)
Hematology profiles [Mean (SD)]		
WBC (×10^9/L) †	7.45 (4.15)	15.71 (10.90)
Neutrophil (%)	69.63 (10.83)	65.33 (9.58)
Eosinophil (%)	1.80 (1.37)	2.00 (1.41)
Lymphocyte (%)†	17.44 (8.53)	22.89 (9.00)
Hb (g/dl)	15.02 (15.14)	14.21 (13.96)
Plt (×10^9/L)	49.14 (53.13)	36.89 (21.34)
Biochemistry profiles [Mean (SD)]		
Glucose (mg/dL)	131.49 (46.86)	130.68 (84.20)
BUN (mg/dl) †	40.59 (36.76)	61.80 (37.76)
Creatinine (mg/dL) †	1.77 (1.54)	2.91 (1.95)
Direct Bilirubin (mg/dL) †	3.65 (5.41)	8.42 (8.28)
Total Bilirubin (mg/dL)	7.41 (9.70)	11.14 (7.72)
Albumin (g/dL)	3.27 (0.70)	3.15 (0.49)
Globulin (g/dL)	3.03 (0.50)	2.80 (0.39)
ALP (U/L) ‡	119.87 (60.45)	93.58 (72.12)
AST (U/L) ‡	95.88 (100.19)	491.07 (1029.09)
ALT (U/L) ‡	64.09 (47.79)	223.93 (398.81)
Sodium (mmol/L)	132.17 (4. 72)	133.18 (8.39)
Potassium (mmol/L)	3.85 (0.63)	5.37 (6.37)
Chloride (mmol/L)	99.15 (4.55)	96.43 (11.27)
Bicarbonate (mmol/L) ‡	19.90 (3.90)	15.97 (8.28)

†: p-value < 0.01, ‡: p-value <0.05
SMS: Severe *P. falciparum* malaria patients with survival; SMD: Severe *P. falciparum* malaria patients with death

Table 1: Clinical characteristics and laboratory data of study patients on admission.

lymphocyte count, blood urea nitrogen (BUN), and creatinine (Cr), and lesser bicarbonate than the survived patients. Regarding to liver function tests, direct bilirubin and transaminses were higher in fatal patients than survived patients. Fatal patients had total bilirubin of 11.14 ± 9.36 (1.70-29.90) mg/dl [mean ± SD (range)]. However alkaline phosphatase was higher in survived patients than fatal patients.

In Table 2, out of 174 patients, there were 29 (17%) fatal patients. Impaired consciousness, metabolic acidosis, jaundice, spontaneous bleeding, respiratory distress, renal failure were significant risks of fatality. Jaundice was the third fatal risk after impaired consciousness and metabolic acidosis. Severe malaria patients with jaundice had 8 fold risk of death. However, past history of malaria in the last 1 year, myalgia, and anorexia were significant protective factors of fatal outcome. Jaundice was found in 117 (67%) severe malaria patients. Total bilirubin ≥ 2 mg/dl was found in 114 (97%) of jaundiced severe malaria whereas >bilirubin 3 mg/dl was found in 111 (94%) of jaundiced severe malaria patients.

Table 3 showed that bilirubin level ≥ 2, ≥ 3, and ≥ 4 mg/dl were significantly observed in 114 (97%), 111 (95%), and 97 (83%) jaundiced patients respectively. Only 3 patients with total bilirubin <2 mg/dl were identified to have clinically jaundice. Total bilirubin level ≥ 2, ≥ 3, and ≥ 4 mg/dl were significantly observed in 28 (97%), 28 (97%), and 24 (83%) of 29 of fatal malaria patients. Jaundiced patients with total bilirublin levels of ≥ 2 and ≥ 3 mg/dl gave similar sensitivity of 97% for fatal outcome. Receiver operative curve was constructed to evaluate the diagnostic performance of total bilirubin levels in identifying fatal outcome of severe malaria with jaundice (Figure 1). The results showed

	Number of diagnosis (N=174)	Number of Death (N=29)	Crude odds ratio (95% CI)	p-values*
Past history of malaria in last 1 yr	38	3	0.59 (0.10-2.24)	0.037
Overweight by BMI	14	3	6.09 (0.85-32.99)	0.082
Normal weight by BMI	96	3	0.28 (0.04-1.39)	0.705
Underweight by BMI	42	3	1.36 (0.21-6.73)	0.568
Chill-rigors	132	17	2.21 (0.48-10.31)	0.372
Headache	130	9	0.66 (0.07-31.97)	0.529
Myalgia	117	5	0.06 (0.02-0.18)	<0.001
Weakness	115	6	0.44 (0.10-1.88)	0.372
Abdominal pain	49	3	0.93 (0.22-3.91)	0.992
Anorexia	109	4	0.06 (0.02-0.18)	<0.001
Nausea	99	4	0.31 (0.07-1.22)	0.126
Vomiting	86	3	0.29 (0.07-1.23)	0.154
Diarrhea	27	4	3.79 (0.94-15.21)	0.068
Hepatomegaly	76	8	0.90 (0.33-2.42)	0.884
Splenomegaly	17	3	1.87 (0.48-7.26)	0.406
Anemia	17	5	2.30 (0.74-7.14)	0.138
Respiratory Distress	31	14	6.97 (2.87-16.92)	<0.001
Hypoglycemia	7	3	6.60 (1.35-32.20)	0.034
Circulatory collapse	8	3	3.23 (0.72-14.35)	0.130
Renal failure	46	17	5.66 (2.43-13.17)	<0.001
Spontaneous bleeding	15	8	7.51 (2.46-22.86)	<0.001
Multiple convulsion	7	2	3.29 (0.59-18.31)	0.188
Metabolic Acidosis	31	15	8.63 (3.53-21.13)	<0.001
Haemoglobinuria	86	11	1.28 (0.48-3.37)	0.613
Impaired conscious	9	5	12.58 (3.02-52.33)	<0.001
Hyperparasitemia	112	17	0.74 (0.33-1.68)	0.479
Jaundice	117	27	8.25 (1.88-36.06)	<0.001

*Chi-square or Fisher Exact tests were used for analysis of p-values

Table 2: Clinic-pathologic manifestations of study patients on admission and number of deaths.

Total bilirubin levels (mg/dL)	Validity results		
	Sensitivity (%)	Specificity (%)	Accuracy (%)
<1.99	100	18.62	15.51
2.00	96.55	25.51	37.35
2.50	96.55	35.17	45.40
3.00	96.55	44.82	53.44
3.50	93.10	52.41	59.19
4.00	86.20	59.31	63.79
5.00	79.31	66.20	68.39
6.00	72.41	73.10	72.98
7.00	65.51	80.00	77.58
8.00	58.62	83.44	79.31
9.00	51.76	86.20	80.45
10.00	41.32	88.27	80.45
>10.01	0	100	83.33

Table 3: Validity results in difference levels of serum bilirubin to detect fatal outcome of severe malaria with jaundice.

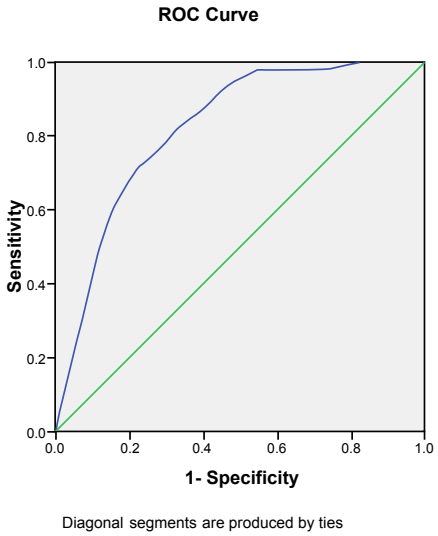

Figure 1: Receiver operative curve was constructed to evaluate the diagnostic performance of total bilirubin levels in identifying fatal outcome of severe malaria with jaundice.

the prognostic power of total bilirubin levels to be good, with area under the curve (95% CI) of 82.1 (76.2-87.9), p<0.001.

Discussion

Although complications and deaths were frequently observed in jaundice patients. Jaundiced severe patients had 8 fold higher risk of fatality than non-jaundiced patients. Nearly all jaundiced patients (97%) could be detected when the total bilirubin level was low as 2 mg/dl. Sensitivity to detect fatality was similar in patients with total bilirubin ≥ 2 and ≥ 3 mg/dl. Therefore total bilirubin ≥ 2 mg/dl was better than total bilirubin ≥ 3 mg/dl since it will be earlier and sensitive laboratory indicating fatal outcome in jaundiced severe malaria.

The causes of hyperbilirubinemia in malaria included intravascular hemolysis from parasitized and non-parasitized red blood cells and also hepatic dysfunction during acute malaria illness [1]. Although there are earlier literatures regarding jaundice in falciparum malaria, no report shows total bilirubin level of 2 mg/dl is higher sensitive than 3 mg/dl to predict fatal outcome in severe malaria [7-10].

In conclusion, cut-point of total bilirubin level in severe malaria with jaundice should be ≥ 2 mg/dl. Total bilirubin level of ≥ 2 mg/dl was also sensitive to detect fatal outcome in severe malaria with jaundice.

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