Supplementary Material

A Novel Random Forest Algorithm-Based Prediction Model for in-Hospital Mortality Risk in Congolese Children with Severe Malaria

Ken Bisabu Kelu, MD, M.Sc, PhD[1,2*], Vicky Mayifuila Niangi, MD[1,2], Gerrye Mubungu Lumbono, MD, PhD[2,3], Joseph Bodi Mabiala, MD, PhD[1,2], Celestin Nsibu Ndosimao, MD, PhD[1,2*#]

[1] Pediatric Emergency and Intensive Care Unit, Department of Pediatrics, University Hospital of Kinshasa, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

[2] Biomedical Sciences Department, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

[3] Reference Center for Rare and Undiagnosed Diseases, Genetics Center, Faculty of Medicine, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

Contents

Contents

I. Clinical definitions

1) **Severe malaria** (SM) was defined as a composite of any Plasmodium parasitemia (falciparum or other species), detected by asexual stages on a peripheral blood slide or a positive rapid diagnostic test in combination with one or more of the following clinical and/or laboratory features, including:

- (**1**) Impaired consciousness defined by a Blantyre coma score of <3,
- (**2**) Multiple convulsions defined by ≥2 seizures within a period of 24 hours,
- (**3**) Prostration defined by the inability to sit, stand, or walk without assistance,
- (**4**) Clinically significant bleeding documented by the presence of recurrent or prolonged bleeding from the nose, gums, or venipuncture sites, hematemesis or melena,
- (**5**) Acidosis defined by a standard base deficit of >8 meq/l, a plasma bicarbonate level of <15 mmol/l, or a venous plasma lactate level of ≥5 mmol/l,
- (**6**) Anemia defined by a hemoglobin level of ≤5 g/dl or a hematocrit of ≤15%, combined with a parasite density of >10,000/µl,
- (**7**) Hypoglycemia defined by a plasma or serum glucose level of <40 mg/dl (<2.2 mmol/l),
- (**8**) Parasitemia density of 10%,
- (**9**) Jaundice defined by a plasma or serum bilirubin level of >50 µmol/l (3 mg/dl) combined with a parasite density of >100,000/µl,
- (**10**) Renal impairment defined by a plasma or serum creatinine level of >3 mg/dl or a blood urea level of >20 mmol/l,
- (**11**) Pulmonary edema or Respiratory insufficiency defined by a confirmed edema on radiologic examination or an oxygen saturation of <92% while breathing ambient air with a respiratory rate of >30 breaths/min,
- (**12**) Shock or circulatory collapse documented by a systolic blood pressure (SBP) of <70 mm Hg, combined with evidence of impaired perfusion (cool extremities or prolonged capillary refill)[1,2].

2) **Cerebral malaria** (CM) was defined as the neurological component or complication of SM described as an otherwise unexplained coma combined with malaria parasitemia after other causes of encephalopathy have been ruled out[1-3].

3) **Severe Respiratory malaria** (SRM) was defined as the respiratory component or complication of SM diagnosed in presence of Pulmonary edema or Respiratory insufficiency, as defined above[1,2].

4) **Severe malarial anemia** was defined as the hematological component or complication of SM diagnosed in presence of hemoglobin level of ≤5 g/dl or a hematocrit of ≤15%, combined with a parasite density of >10,000/µl[1,2].

II. Estimation of unmeasured acid loads

To estimate the serum level of unmeasured acids, we calculated the standard base deficit, the anion gap and the strong ion gap.

1) **Standard Base Deficit** was calculated using the modified Van Slyke equation and corrected for differences in plasma albumin and phosphate using correction factors developed by Wooten[4,5]. Albumin is expressed in g/dL and phosphate in mg/dL.

SBDCAP = ($[HCO_3^-]$-24.4) + (8.3 *[Albumin]*0.15 + 0.29 * [Phosphate]*0.32) * (pH-7.4)

2) **Anion gap** was estimated and corrected for the negative charge of albumin and phosphate. Albumin is expressed in g/dL and phosphate in mg/dL.

AG =([Na] + [K]) – ([Cl] + $[HCO_3]$)

AGCAP = ($[Na^+]$ + $[K^+]$) - ($[Cl^-]$ + $[HCO_3^-]$) - (2 * [Albumin] + 0.5 * [Phosphate])

AGCAPL = ([Na] + [K]) – ([Cl] + $[HCO_3]$) -(2 x albumin g/dL + 0.5 x phosphate mg/dL) - [lactate mmol/L]]

AGCAPL = calculated AG - (2 x albumin g/dL + 0.5 x phosphate mg/dL) - [lactate mmol/L]]

AGCAPL = AGCAP - Lactate(mmol/L)

Phosphate (mEq/L) = Phosphore (mEq/L) x (0,309 x (pH - 0,469))

Phosphate (mmol/L) = Phosphore (mmol/L) x (0,309 x (pH - 0,469))

Phosphate (mg/dL) = (Phosphate (mmol/L) x 31) x 0,1

From mmol en mg: Value in mmol x atomic (or molecular) weight = value in mg

Atomic (or molecular) weight for Phosphore = 31

1L = 10 dL

Albuminate (g/L) = albumine (g/L) x (0,123 x (pH-0,632))

3) To calculate the **strong ion gap**, we used Stewart's Approach modified by Figge et al[6,7]. and determined the apparent strong ion difference (SIDa) and the effective strong ion difference (SIDe), as follows:

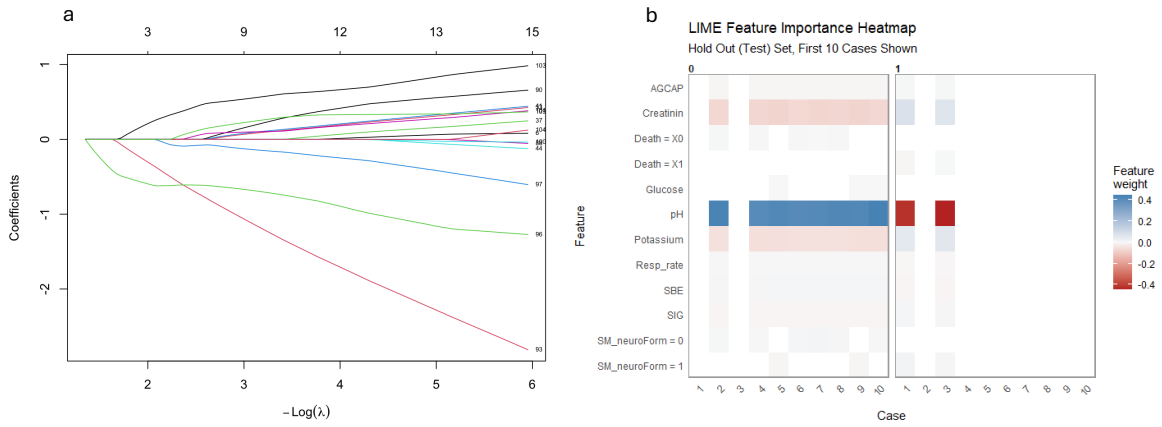
SIDa = ($[Na^+] + [K^+] + [Mg^{2+}] + [Ca^{2+}]$) - ($[Cl^-] + [Lactate^-]$)

SIDe = (2.46 * 10^$^{-8}$ * pCO_2 / 10^$^{-pH}$) + ([Albumin] * (0.123 * pH – 0.631)) + ($[PO^{4-}]$ * (0.309 * pH – 0.469)))

Finally, the strong ion gap (SIG) was calculated by subtracting the apparent and effective strong ion differences:

SIG = SIDa – SIDe

III. Supplementary Figures



Supplementary Figure (SF). (a) LASSO Coefficient Profiles of Selected Predictors, (b) LIME Feature Importance Heatmap.

IV. Supplementary Tables

Supplementary Table 1 (ST1): Selected variables using Univariable logistic regression (at *P*<0.1 threshold)

Variables	Beta (β)	Standard Error (SE)	z value	*p*-value
(Intercept)	-5.8397	1.3575	-4.302	1.69e-05
Febrile episode	1.0673	0.3094	3.449	0.000562
(Intercept)	-2.3979	0.4671	-5.134	2.84e-07
Coma1	1.5506	0.5807	2.670	0.00758
(Intercept)	-2.8904	0.5932	-4.873	1.1e-06
BCS1	1.8788	0.7227	2.600	0.009331
BCS2	2.7362	0.8132	3.365	0.000767
(Intercept)	-2.6912	0.5167	-5.209	1.9e-07
Cerebral Malaria1	2.0781	0.6209	3.347	0.000817
(Intercept)	-1.0460	0.3224	-3.244	0.00118
Severe Malaria Anaemia1	-1.3964	0.6129	-2.278	0.02272
(Intercept)	-2.2130	0.3981	-5.559	2.71e-08
Severe Respiratory Malaria	1.5711	0.5577	2.817	0.00485
(Intercept)	-2.6912	0.5167	-5.209	1.9e-07
Convulsions1	2.0781	0.6209	3.347	0.000817
(Intercept)	-1.9169	0.3387	-5.660	1.51e-08
Jaundice1	1.1548	0.5694	2.028	0.0426
(Intercept)	5.61837	1.67803	3.348	0.000813
Respiratory rate	-0.23992	0.05921	-4.052	5.08e-05
(Intercept)	-2.7881	0.5151	-5.412	6.22e-08
Ketoacidosis Respiration1	2.4627	0.6308	3.904	9.45e-05
(Intercept)	3.01488	1.22246	2.466	0.013654
PaO2	-0.06446	0.01834	-3.514	0.000441
(Intercept)	7.0021	1.9563	3.579	0.000345
PaCO2	-0.3479	0.0847	-4.107	4,00E-05
(Intercept)	330.27	90.70	3.641	0.000271
pH	-45.60	12.48	-3.654	0.000258
(Intercept)	-6.7378	1.4213	-4.740	2.13e-06
SBE	-0.3993	0.0895	-4.462	8.12e-06
(Intercept)	6.7750	1.9554	3.465	0.000531
Bicarbonate	-0.7462	0.1989	-3.751	0.000176
(Intercept)	-8.3601	1.9137	-4.369	1.25e-05
Lactate	1.0488	0.2639	3.974	7.06e-05
(Intercept)	5.03441	1.50001	3.356	0.00079
Glucose	-0.10574	0.02648	-3.994	6.51e-05

SupplementaryTable 1 (Continued)

(Intercept)	-14.1938	3.3014	-4.299	1.71e-05
Potassium	2.8392	0.7122	3.987	6.70e-05
(Intercept)	-5.08606	1.11555	-4.559	5.13e-06
Urea	0.05852	0.01677	3.490	0.000482
(Intercept)	-5.721	1.099	-5.206	1.93e-07
Creatinine	4.451	1.009	4.412	1.03e-05
(Intercept)	-3.5383	0.7095	-4.987	6.12e-07
Total Bilirubin	0.5616	0.1692	3.318	0.000905
(Intercept)	-0.7472	0.4047	-1.847	0.0648
DRT1	-1.3322	0.5517	-2.415	0.0157
(Intercept)	-16.5245	4.0313	-4.099	4.15e-05
AG	0.6162	0.1554	3.965	7.35e-05
(Intercept)	-7.5792	1.6526	-4.586	4.51e-06
AGCAP	0.5110	0.1207	4.233	2.31e-05
(Intercept)	-4.0514	0.8326	-4.866	1.14e-06
AGCAPL	0.4704	0.1213	3.877	0.000106
(Intercept)	7.7683	3.7942	2.047	0.0406
SIDa	-0.2588	0.1063	-2.435	0.0149
(Intercept)	16.8238	4.6273	3.636	0.000277
SIDe	-0.8478	0.2261	-3.749	0.000178
(Intercept)	-17.8290	4.6367	-3.845	0.000120
SIG	1.1322	0.2997	3.778	0.000158
(Intercept)	-11.7731	3.0833	-3.818	0.000134
SBDCAP	-0.7272	0.1963	-3.705	0.000211

SupplementaryTable 2 (ST2): Selected variables using Boruta algorithm

Variables	Mean Imp	Median Imp	Min Imp	Max Imp	normHits	decision
Sex	-0.34104595	-0.6195283	-1.41570767	1.41650192	0.00000000	Rejected
Age	-0.01783296	-0.3254476	-1.33665805	1.72473292	0.00000000	Rejected
Febrile episode	1.64935189	1.6989233	-0.05674481	3.60496675	0.21212121	Rejected
Coma	0.39431177	0.5303890	-1.08781557	2.27862327	0.00000000	Rejected
Convulsions	-0.04416196	-0.0921304	-1.24446734	1.05494733	0.00000000	Rejected
Jaundice	0.53917386	0.5484233	-1.00100150	2.17560709	0.01010101	Rejected
Respiratory rate	5.67633415	5.7115631	4.06147925	7.06531845	1.00000000	Confirmed
Ketoacidosis Resp	0.89112386	1.2115662	-1.39885192	2.52209598	0.01010101	Rejected
Cerebral malaria	1.21196391	1.3793734	-0.52205636	2.84395940	0.05050505	Rejected
SM anaemia	-0.63741080	-0.6633308	-1.40784953	0.03720332	0.00000000	Rejected
SRM	0.46770128	1.1284501	-1.86708755	1.62273242	0.00000000	Rejected
Stay_PICU	12.81344437	12.8425462	10.80130879	14.33448667	1.00000000	Confirmed
PaCO2	3.29389785	3.2518057	1.54243840	5.27964916	0.78787879	Confirmed
PaO2	2.87871086	2.9232370	0.87821458	4.82103846	0.67676768	Confirmed
pH	10.79578625	10.7880888	8.86891063	12.20488621	1.00000000	Confirmed
SBE	6.36325865	6.3589296	4.96788056	7.69649035	1.00000000	Confirmed
Bicarbonate	6.28324457	6.2690470	4.96415366	7.54111208	1.00000000	Confirmed
Lactate	2.72175775	2.7142984	0.29820431	4.48778237	0.63636364	Confirmed
Glucose	4.30055179	4.4270899	2.23854745	5.65367451	0.93939394	Confirmed
Potassium	5.58648739	5.6132067	3.96056221	7.05452164	0.97979798	Confirmed
Urea	1.89563239	1.9115318	-0.59294676	3.71779600	0.38383838	Rejected
Creatinine	4.22183119	4.2031433	2.52873867	6.50096447	0.93939394	Confirmed
Total Bilirubin	0.87082829	1.1249089	-0.55650019	1.85623335	0.01010101	Rejected
DRT	0.14746652	0.2467064	-1.72656062	1.63488066	0.00000000	Rejected
AG	4.95856201	4.9609096	3.50833241	6.40365420	0.98989899	Confirmed
AGCAP	5.80193668	5.8003642	3.73710395	7.79120291	1.00000000	Confirmed
AGCAPL	3.30781954	3.2956822	1.72827867	4.92477116	0.79797980	Confirmed
SIG	8.36546622	8.3596027	6.65309073	9.78125439	1.00000000	Confirmed
SBDCAP	7.57807765	7.5182092	6.31717389	8.83409452	1.00000000	Confirmed

Supplementary Table 3 (ST3): Variables with Non-zero importance score using LASSO feature selection

Variables	Coefficients	Step	Estimate	Lambda	Dev.ratio
(Intercept)	-2.58681601	1	-2.59	0.0487	0.679
Respiratory rate	-0.17131450	1	-0.172	0.0487	0.679
pH	-1.03491920	1	-1.03	0.0487	0.679
Glucose	-0.17485594	1	-0.175	0.0487	0.679
Potassium	0.21371373	1	0.213	0.0487	0.679
SBE	-0.11425534	1	-0.04	0.0487	0.679
Creatinine	0.65681653	1	0.656	0.0487	0.679
AGCAP	0.08313464	1	0.0844	0.0487	0.679
SIG	0.19303338	1	0.192	0.0487	0.679
Cerebral malaria	0.43301270	1	0.433	0.0211	0.801

Supplementary Table 4 (ST4): Variable importance from RF Model

Predictors	Importance
pH	100
Respiratory rate	85.64
SBE	85.22
SIG	76.2
AGCAP	66.53
Glucose	66.16
Potassium	65.05
Creatinine	55.04
Cerebral malaria	0

References

1. Daily JP, Parikh S. Malaria. *N Engl J Med*. 2025;392:1320-1333. doi: 10.1056/NEJMra2405313
2. WHO guidelines for malaria. In: *Geneva: World Health Organization*. 2024.
3. Postels DG, Katangwe-Chirwa T. Cerebral malaria. *Semin Pediatr Neurol*. 2025;54:101206. doi: 10.1016/j.spen.2025.101206
4. Siggaard-Andersen O. Acid-Base Balance In: *ENCYCLOPEDIA OF RESPIRATORY MEDICINE/Acid-Base Balance*. 2005:173-208.
5. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. *J Appl Physiol (1985)*. 2003;95:2333-2344. doi: 10.1152/japplphysiol.00560.2003
6. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol*. 1983;61:1444-1461. doi: 10.1139/y83-207
7. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Med*. 1992;120:713-719.