Supplementary Material

Evaluation of host biomarkers to support the development of a point-of-care diagnostic test to guide antibiotic use in bacterial/non-bacterial acute febrile illness cases

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Biomarker selection

Biomarkers evaluated were selected based on reported performances for distinguishing bacterial versus non-bacterial infections in prior publications, which were systematically reviewed in 2016 by Kapasi et al.[1] and other key publications (Supplementary Table 1). Biomarker performances reported in the 2016 systematic review were compared with reported performances in a later systematic review conducted in 2020.[2]

Supplementary Table 1. Biomarkers included based on Kapasi et al.'s (2016) systematic review and other key publications.

Biomarker	**Performance, 2016 systematic review**
C-reactive protein (CRP)	1
FebriDx (MxA+CRP)	2
Galectin-9	*2*
Gamma-induced protein 10 (IP-10)	2*
Haptoglobin	2[#]
Heparin-binding protein (HBP)	3
Human neutrophil lipocalin (HNL)	2
Interferon gamma (IFN-gamma)	3
Interleukin-4 (IL-4)	2
Interleukin-6 (IL-6)	3
Lipopolysaccharide binding protein (LBP)	3[$]
Procalcitonin (PCT)	1
Secretory phospholipase 2 (sPLA2)	2
Soluble triggering receptor expressed on myeloid cells 1 (sTREM-1)	3[§]
TNF-related apoptosis-inducing ligand (TRAIL)	2*
Included based on key publications in the field	
Biomarker	**Publication**
A-1-acid glycoprotein	Struck et al.[3]
Chitinase-3-like protein 1 (CHI3L1)	Erdman et al.[4]
Complement 2	Struck et al.[3]
Complement C4b	Struck et al.[3]
Neutrophil gelatinase-associated lipocalin (NGAL)	Huang et al.[5]

Performances were scored as: 1, high-performing biomarker (meets the current TPP minimum diagnostic performance criteria, i.e. ≥0.90 and 0.80 sensitivity/specificity); 2, moderately performing biomarker (≥0.65 and 0.65 and <0.90 and 0.80 sensitivity/specificity); 3, AUROC >0.8; 4, low-performing biomarker; 5, not evaluated. *As part of the signature CRP+IP-10+TRAIL; # as part of the signature Haptoglobin+IL-10+TIMP1; $ in respiratory tract infections as part of the signature CRP+LBP; § as part of the signature sTREM+CRP; 1 only in the context of meningitis, otherwise low performance.

Reference laboratory methodology

Materials, equipment, and software

All assay reagents used were delivered with the commercial kits and were used as described in the corresponding kit manuals. Supplementary Table 2 shows the commercial human multi-analyte kits and ELISA kits used.

Supplementary Table 2: Commercial human multi-analyte kits and ELISA kits used.

Analytes	**Assay type**	**Provider**	**Reference laboratory that performed the analysis**
CHI3L1, Gal-9, IL-4, IL-6, IP-10, IFN-gamma, sPLA2, sTREM-1, TRAIL	Luminex, 9-plex	Biotechne/ R&D Systems	NMI
NGAL, LBP	Luminex, 2-plex	Biotechne/ R&D Systems	NMI
C2, C4b	Luminex, 2-plex	Merck	NMI
HP, AGP	Luminex, 2-plex	Merck	NMI
PCT	Luminex, 1-plex	Biotechne/ R&D Systems	NMI
	Immunoassay	Elecsys BRAHMS, Roche	MVZ Limbach

HNL	ELISA	Diagnostics Development	NMI
CRP	ELISA	Biotechne/ R&D Systems	NMI
	Immunoassay	Elecsys BRAHMS, Roche	MVZ Limbach
HBP	ELISA	Axis-Shield	on-site

NMI, The Natural and Medical Sciences Institute (NMI) at the University of Tübingen, Reutlingen, Germany; MVZ Labor, Dr. Limbach & Kollegen, Heidelberg, Germany

For data generation, the Luminex FLEXMAP 3D instrument, operated with xPONENT Software V4.2, was used for the bead-based Luminex assays. The data evaluation was performed using Bio-Rad Bio-Plex Manager Software 6.1.1. To generate the data for the ELISAs at NMI a BioTek ELx 808 absorption reader was used. The embedded software Gen5 (BioTek) was used for data evaluation. At MVZ Limbach, a Cobas 8000 immunoanalyzer (Roche Diagnostics) was used for data generation.

Methods

All assays were processed according to the manufacturer's protocol. Standard curves, quality control (QC) samples, and blanks were analysed in duplicate; samples were assayed singly. Two or three QC samples were measured on each assay plate. QC samples were taken to cover the range of the standard curve (low, mid, and high level). All QC samples were prepared and aliquoted in larger quantities at the beginning of sample screening so that a fresh aliquot could be used for each measurement, and all QC samples underwent the same freeze–thaw cycle. The performance of the standard curves was controlled over the entire measurement period based on %CVs of the standard point duplicates (<20% and <25% for the last standard point) and percentage recovery on the basis of the nominal concentrations. If permitted by the dilution factor, samples out of the dynamic range were re-analysed with a lower or higher dilution factor.

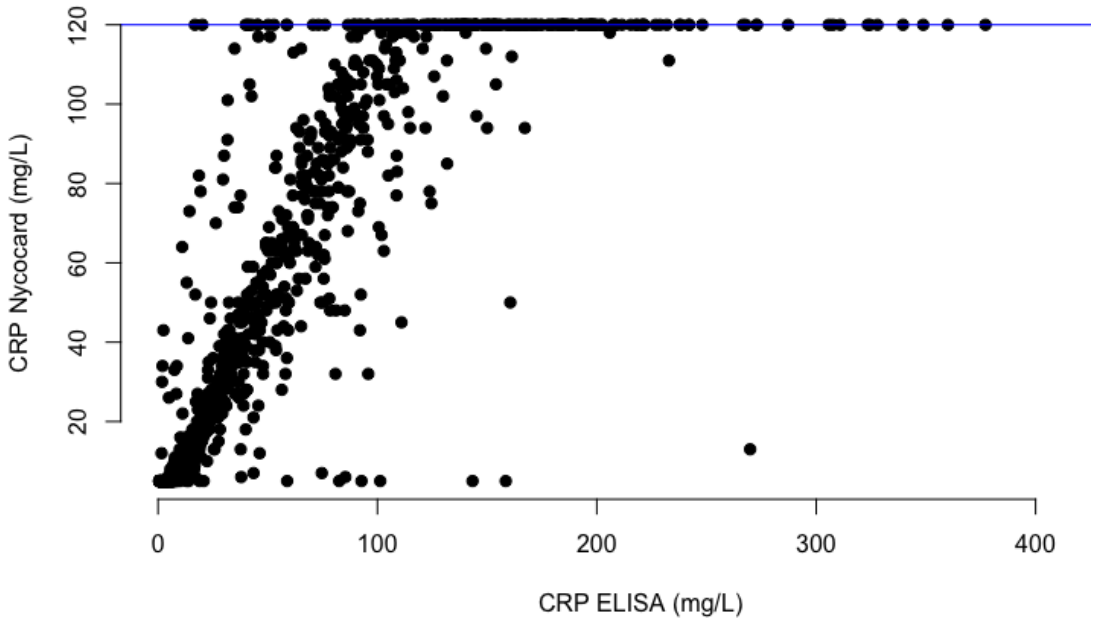
Heparin-binding protein (HBP) assay

The commercially available Axis-Shield heparin-binding protein ELISA for citrated plasma was validated for human EDTA plasma. Calibration curve, limit of detection (LOD), assay range, precision, parallelism, and spike-in recovery experiments were performed.

The ELISA was processed according to the assay protocol provided with the kit. Validation was performed using a fit-for-purpose approach and under consideration of the recommendations for assay validation given in guidelines from health authorities (European Medicine Agency (2011); Food and Drug Administration (2018)). This was a short validation with a limited number of samples.

Except for the percentage recovery, all analysed parameters met the criteria during the validation of the HBP ELISA using human EDTA plasma instead of the recommended citrated plasma matrix. The assay performance seemed to be stable for the sample evaluation using the kit.

Supplementary Figure 1: Analytical assessment of CRP Nycocard vs CRP ELISA



Statistical analysis

This section contains additional figures and tables related to the statistical analysis.

Supplementary Table 3: Number and percentage of missing values for the biomarkers included in the statistical analysis

	Electronic group[¶] [n (%)]	Strict group[§] [n (%)]	Loose group[#] [n (%)]
White blood cells	6 (0.8%)	11 (0.8%)	15 (0.8%)
HAEMATO COUNT	6 (0.8%)	11 (0.8%)	15 (0.8%)
Lymphocytes	6 (0.8%)	12 (0.9%)	17 (1%)
Neutrophils	22 (3%)	64 (5%)	90 (5%)
CRP NYCOCARD	5 (0.7%)	10 (0.7%)	14 (0.8%)
IL-6	10 (1.5%)	20 (1%)	24 (1%)
Gal-9	10 (1.5%)	20 (1%)	24 (1%)
CHI3L1	10 (1.5%)	20 (1%)	25 (1%)
IP-10	10 (1.5%)	20 (1%)	24 (1%)
TRAIL	10 (1.5%)	20 (1%)	24 (1%)
IL-4	13 (2%)	24 (2%)	29 (2%)
sPLA2	10 (1.5%)	20 (1%)	24 (1%)
NGAL	29 (4%)	138 (10%)	197 (11%)
LBP	30 (4%)	139 (10%)	198 (11%)
C2	10 (1.5%)	21 (1.5%)	25 (1%)
AGP	10 (1.5%)	21(1.5%)	25 (1%)
HP	11(1.6%)	24 (2%)	29 (2%)

¶ Total number of subjects in the Electronic group: 677
§ Total number of subjects in the Strict group: 1376
# Total number of subjects in the Loose group: 1777

Kruskal-Wallis tables

Supplementary Table 4: Kruskal-Wallis table results for the electronic classification

	Age	Sex	Malaria	Country	Comorbidities	Malnutrition*	Prior antibiotics	Temperature ≥38°C	Chikungunya
White blood cells	1.2145E-13	1.9808E-01	1.0985E-02	3.4408E-01	8.4018E-01	2.7154E-01	4.3535E-01	3.4408E-01	5.4183E-09
HAEMATO COUNT	2.8040E-45	1.0446E-09	4.3461E-28	1.3185E-36	6.8045E-02	9.1321E-01	6.9000E-01	9.9455E-01	3.6951E-08
Lymphocytes	1.3850E-45	8.0680E-03	3.1562E-29	4.5414E-32	1.0022E-05	4.4874E-01	4.5900E-01	5.4198E-08	1.9910E-11
Neutrophils	5.6495E-03	3.9147E-01	1.1337E-04	1.8674E-17	1.5980E-02	4.2719E-01	4.3608E-01	3.0003E-08	6.5439E-04
CRP NYCOCARD	1.4485E-03	4.2297E-01	1.3861E-15	3.0332E-07	2.1171E-01	4.6667E-01	8.4615E-01	3.0231E-03	2.1171E-01
IL-6	9.2626E-06	2.5277E-01	4.6686E-34	4.2810E-21	6.1106E-03	7.1615E-01	5.8674E-02	2.0177E-10	9.2626E-06
Gal-9	7.8084E-11	3.3296E-01	1.2731E-07	2.2471E-07	4.3173E-01	5.3845E-01	9.9020E-02	3.6659E-01	8.5282E-04
CHI3L1	3.6874E-01	1.5427E-01	2.2593E-04	3.5942E-05	9.0961E-01	8.0977E-01	7.9973E-01	2.5264E-02	2.5264E-02
IP-10	7.0235E-01	7.0235E-01	4.0429E-09	7.0486E-10	4.9729E-01	7.0235E-01	4.0169E-01	3.6086E-08	3.3476E-01
TRAIL	1.4108E-03	1.5429E-02	6.7710E-19	6.9473E-56	9.2177E-01	2.2485E-02	9.5591E-01	9.7926E-04	1.8702E-06
IL-4	1.4190E-03	8.9566E-02	1.7896E-25	1.1179E-73	4.2256E-01	8.9341E-03	8.9692E-01	3.0403E-03	2.2958E-09
sPLA2	9.5993E-05	9.2127E-01	2.8477E-20	5.6810E-03	1.5011E-01	9.2127E-01	6.1633E-01	7.4323E-03	7.4323E-03
NGAL	2.6841E-02	7.1924E-01	1.2498E-05	6.4604E-21	7.1924E-01	2.6841E-02	5.1387E-01	1.2498E-05	9.6273E-03
LBP	2.2658E-11	5.1481E-02	1.8527E-54	2.1544E-101	8.2974E-02	5.3837E-03	1.1745E-01	3.5938E-09	6.0583E-19
C2	1.7219E-02	3.0063E-01	6.8628E-13	6.8628E-13	6.2951E-02	8.5874E-01	5.6324E-01	4.4637E-01	6.2045E-03
AGP	5.1888E-03	2.0274E-01	3.6747E-16	1.3445E-16	1.5176E-01	9.8963E-01	6.3154E-01	2.3325E-01	3.1922E-05
HP	2.9420E-07	2.7390E-01	1.8393E-25	2.4997E-25	2.7390E-01	2.7390E-01	4.0178E-01	7.2077E-01	2.9140E-03
C4b	5.6159E-19	6.7010E-02	4.5041E-81	1.9491E-84	6.7179E-03	6.7179E-03	3.3168E-01	1.8052E-01	8.0363E-18

Different colours based on significance: green ($p < 0.05$, slight significance); orange ($p < 0.01$, high significance); red ($p < 0.001$, strong significance). * Malnutrition status calculated based on WHO body mass index criteria.

Kruskal-Wallis tables

Supplementary Table 5: Kruskal-Wallis table results for the strict classification

	Age	Sex	Malaria	Country	Comorbidities	Malnutrition*	Prior antibiotics	Temperature ≥38°C	Chikungunya
White blood cells	3.1149E-20	2.4091E-01	3.6749E-09	9.3997E-03	3.1632E-01	6.3502E-02	6.3502E-02	9.1443E-01	1.7973E-08
HAEMATO COUNT	6.1835E-100	1.9994E-04	5.6304E-55	3.7852E-68	1.6199E-04	8.0189E-01	7.1282E-01	2.9137E-01	1.7149E-10
Lymphocytes	8.4778E-84	1.5291E-01	2.6779E-44	2.7404E-58	6.3047E-07	6.1980E-03	4.5554E-01	7.1024E-22	8.6226E-15
Neutrophils	8.9513E-04	1.7152E-01	7.9838E-14	1.9134E-37	4.5549E-02	5.2789E-01	4.5549E-02	3.0001E-19	4.1217E-02
CRP NYCOCARD	1.6547E-02	5.7656E-02	2.4570E-38	6.2991E-11	7.4370E-01	3.0220E-01	7.4370E-01	9.7289E-15	3.0220E-01
IL-6	2.5704E-02	1.2888E-01	2.5131E-68	3.4758E-27	1.4641E-01	8.1220E-01	6.6933E-02	4.3924E-26	2.5371E-04
Gal-9	7.4424E-19	3.5455E-03	1.3432E-11	1.3757E-08	1.1615E-01	3.9116E-01	1.3397E-01	2.2573E-01	2.4249E-03
CHI3L1	2.8335E-01	1.5433E-01	3.6787E-11	7.4319E-16	2.8335E-01	2.8335E-01	2.8335E-01	8.7744E-06	1.5017E-03
IP-10	2.4521E-01	6.8716E-01	8.5656E-31	1.5503E-36	2.1157E-01	3.0336E-01	3.2906E-01	4.1236E-22	3.2906E-01
TRAIL	6.4358E-04	2.4206E-01	3.7467E-46	4.5806E-127	7.7652E-01	8.3869E-04	7.7652E-01	2.8337E-17	1.7642E-08
IL-4	4.2108E-04	5.9858E-01	2.5949E-55	2.7083E-159	3.3368E-01	8.0705E-05	6.5563E-01	2.2888E-11	2.2888E-11
sPLA2	3.0005E-14	1.1264E-01	4.1355E-60	4.7055E-09	6.7473E-04	2.2676E-01	3.6531E-01	1.0844E-09	4.7059E-05
NGAL	7.7462E-02	1.1300E-01	6.0927E-16	1.3720E-35	5.9955E-01	4.9221E-02	4.4419E-01	1.4382E-19	8.8808E-03
LBP	1.3509E-14	3.4123E-01	6.0660E-94	1.9360E-197	2.1248E-02	3.6673E-05	3.0644E-01	2.3473E-28	7.4289E-21
C2	7.2674E-07	4.3157E-01	2.3145E-26	4.5324E-25	6.8236E-03	4.3157E-01	4.3157E-01	8.8206E-03	2.1062E-03
AGP	4.8513E-04	1.7379E-01	5.0587E-21	7.1496E-23	1.5900E-01	7.9521E-01	9.7767E-01	1.1305E-01	1.4880E-05
HP	1.2127E-13	6.3311E-01	1.6366E-46	3.0053E-46	2.9299E-03	5.6523E-01	5.6523E-01	9.0316E-01	4.8596E-04
C4b	6.3193E-21	1.9231E-02	1.6664E-139	3.1999E-147	1.9749E-04	2.6638E-04	9.3349E-01	8.0678E-03	3.0903E-25

Different colours based on significance: green ($p < 0.05$, slight significance); orange ($p < 0.01$, high significance); red ($p < 0.001$, strong significance). * Malnutrition status calculated based on WHO body mass index criteria.

Kruskal-Wallis tables

Supplementary Table 6: Kruskal-Wallis table results for the loose classification

	Age	Sex	Malaria	Country	Comorbidities	Malnutrition*	Prior antibiotics	Temperature ≥38°C	Chikungunya
White blood cells	2.0574E-28	9.8759E-01	1.8484E-08	4.5260E-03	9.0171E-02	4.8259E-02	1.0890E-01	7.4007E-01	1.8484E-08
HAEMATO COUNT	1.3083E-126	1.8619E-04	6.2835E-56	7.7962E-76	1.1102E-06	7.8862E-01	7.9391E-01	2.9434E-01	1.2853E-10
Lymphocytes	4.9651E-101	2.9461E-01	4.6796E-45	1.6372E-67	4.8743E-07	6.6823E-04	2.9461E-01	2.4236E-29	4.3110E-15
Neutrophils	1.1310E-04	7.2677E-01	7.2742E-15	1.6127E-46	2.0313E-01	4.6743E-01	2.0038E-01	1.2920E-24	2.9723E-02
CRP NYCOCARD	1.3614E-01	4.4123E-03	1.0347E-57	2.4703E-15	4.0226E-01	5.2068E-01	5.9738E-01	6.7648E-18	1.3614E-01
IL-6	9.5250E-02	4.8736E-02	8.6303E-95	1.9688E-31	1.5356E-01	8.2374E-01	9.3076E-02	6.1774E-34	2.1766E-05
Gal-9	2.0463E-27	1.4431E-03	1.9318E-13	6.8273E-10	2.3586E-01	2.3586E-01	3.6447E-02	2.3586E-01	3.0166E-03
CHI3L1	2.7483E-01	5.3541E-02	3.6128E-14	3.6128E-14	2.8535E-01	7.9359E-01	3.0946E-01	1.4718E-04	7.1655E-04
IP-10	4.1384E-01	7.8674E-01	6.5193E-43	4.2202E-47	7.9605E-02	3.6101E-01	4.1384E-01	1.4436E-34	4.1902E-01
TRAIL	2.4722E-02	1.3918E-01	6.2828E-56	2.9185E-156	8.2684E-01	6.2797E-05	8.2684E-01	2.4486E-17	1.1148E-09
IL-4	1.1448E-02	3.1911E-01	3.0844E-69	1.7484E-206	3.9276E-01	4.7672E-08	5.7785E-01	2.1611E-12	1.2664E-13
sPLA2	8.3753E-18	2.7317E-01	1.5890E-82	1.2702E-09	1.2356E-04	3.7225E-01	4.1002E-01	8.1232E-15	4.0213E-05
NGAL	1.5706E-01	2.0650E-02	3.7486E-27	2.2848E-43	3.7129E-01	1.4239E-01	3.9957E-01	1.3734E-24	5.3057E-03
LBP	1.6567E-10	4.3865E-01	2.1107E-116	2.4278E-254	8.2765E-03	5.4993E-07	6.1624E-01	1.4861E-39	1.4254E-24
C2	2.1035E-04	1.4593E-01	7.6005E-28	2.1865E-27	4.8543E-02	2.9326E-01	3.8932E-01	9.8425E-03	1.2901E-03
AGP	2.5076E-03	9.5273E-02	1.9870E-26	3.2726E-28	9.3140E-02	8.9492E-01	9.5756E-01	9.5273E-02	3.2225E-06
HP	5.7640E-15	7.2685E-01	2.8376E-51	7.9667E-51	7.2760E-03	6.9555E-01	6.9555E-01	9.7145E-01	1.7228E-04
C4b	3.9077E-15	9.3037E-03	9.3567E-160	3.4449E-171	6.9926E-04	2.2357E-03	8.6228E-01	2.2357E-03	1.0351E-29

Different colours based on significance: green ($p < 0.05$, slight significance); orange ($p < 0.01$, high significance); red ($p < 0.001$, strong significance). * Malnutrition status calculated based on WHO body mass index criteria.

Supplementary Table 7: Univariate analysis of 18 individual biomarkers[#] among malaria-negative patients with all referrence groups (electronic, strict, loose). Common biomarkers such as CRP and haematological biomarkers were included for reference. In this context we defined performance as follows: green (AUROC ≥0·7), yellow (AUROC > 0·65 and <0.7), orange (AUROC 0·6–0·65), and red (AUROC <0·6).

	Brazil AUROC** (CI), N			Gabon AUROC** (CI), N			Malawi AUROC** (CI), N		
	Electronic	Strict	Loose	Electronic	Strict	Loose	Electronic	Strict	Loose
Haematological biomarkers									
Lymphocyte count	0·67 (0·59-0·74), 257	0·66 (0·59-0·72), 408	0·66 (0·6-0·72), 442	0·58 (0·45-0·71), 81	0·52 (0·4-0·63), 167	0·55 (0·45-0·65), 222	0·56 (0·47-0·66), 154	0·51 (0·45-0·58), 303	0·52 (0·47-0·58), 461
Neutrophil count	0·77 (0·7-0·84), 257	0·8 (0·74-0·86), 408	0·79 (0·73-0·84), 442	0·78 (0·66-0·89), 80	0·72 (0·62-0·83), 165	0·67 (0·57-0·77), 219	0·67 (0·58-0·77), 143	0·73 (0·67-0·79), 273	0·7 (0·65-0·76), 414
RBC count	0·61 (0·52-0·69), 258	0·58 (0·51-0·65), 408	0·58 (0·51-0·64), 442	0·55 (0·41-0·68), 81	0·52 (0·41-0·63), 167	0·53 (0·43-0·63), 222	0·46 (0·36-0·56), 155	0·53 (0·46-0·59), 305	0·56 (0·5-0·61), 463
WBC count	0·81 (0·75-0·87), 257	0·83 (0·77-0·88), 408	0·82 (0·77-0·87), 442	0·67 (0·54-0·79), 81	0·6 (0·48-0·72), 167	0·61 (0·5-0·71), 222	0·69 (0·6-0·78), 155	0·72 (0·66-0·78), 304	0·68 (0·63-0·73), 461
Protein biomarkers									
AGP	0·59 (0·51-0·68), 252	0·54 (0·47-0·61), 402	0·52 (0·46-0·59), 434	0·77 (0·65-0·9), 80	0·7 (0·59-0·82), 163	0·65 (0·55-0·75), 220	0·56 (0·46-0·66), 158	0·54 (0·48-0·6), 309	0·54 (0·49-0·59), 466
Chitinase 3-like 1	0·58 (0·5-0·66), 246	0·54 (0·47-0·6), 394	0·55 (0·49-0·61), 424	0·6 (0·46-0·74), 79	0·6 (0·48-0·72), 162	0·62 (0·52-0·72), 217	0·49 (0·39-0·59), 155	0·5 (0·43-0·56), 304	0·5 (0·44-0·55), 462
CRP*	0·61 (0·52-0·69), 259	0·61 (0·54-0·68), 412	0·62 (0·55-0·68), 446	0·71 (0·59-0·82), 81	0·65 (0·55-0·75), 167	0·63 (0·53-0·72), 224	0·55 (0·45-0·65), 156	0·6 (0·54-0·67), 305	0·58 (0·53-0·63), 462
IP-10/IP-10/CRG-2	0·6 (0·52-0·68), 252	0·53 (0·46-0·59), 402	0·53 (0·47-0·59), 434	0·6 (0·48-0·73), 80	0·51 (0·4-0·62), 164	0·52 (0·43-0·62), 221	0·66 (0·56-0·75), 158	0·6 (0·53-0·66), 309	0·61 (0·56-0·66), 466
Galectin-9	0·63 (0·55-0·71), 252	0·56 (0·49-0·63), 401	0·57 (0·5-0·63), 433	0·7 (0·58-0·83), 80	0·6 (0·48-0·71), 163	0·54 (0·43-0·64), 219	0·71 (0·62-0·8), 158	0·61 (0·55-0·67), 309	0·63 (0·57-0·68), 466
hCC2	0·51 (0·43-0·6), 244	0·51 (0·44-0·58), 392	0·52 (0·46-0·59), 424	0·55 (0·41-0·69), 77	0·52 (0·4-0·64), 159	0·51 (0·41-0·61), 216	0·59 (0·49-0·69), 158	0·55 (0·49-0·62), 309	0·55 (0·5-0·6), 466
HBP***	0·67 (0·52-0·81), 113	0·68 (0·55-0·8), 144	0·64 (0·51-0·76), 151	..	..	..	0·53 (0·39-0·68), 63	0.55 (0.44-0·66), 106	0·52 (0·41-0·63), 124
HPTGN	0·48 (0·4-0·57), 248	0·51 (0·44-0·58), 398	0·51 (0·45-0·58), 430	0·64 (0·5-0·78), 77	0·62 (0·51-0·74), 159	0·55 (0·45-0·66), 214	0·54 (0·45-0·64), 157	0·51 (0·45-0·58), 307	0·51 (0·46-0·57), 464

IL-4	0·58 (0·5-0·65), 249	0·53 (0·47-0·59), 398	0·54 (0·48-0·59), 429	0·46 (0·4-0·52), 79	0·49 (0·45-0·53), 163	0·51 (0·47-0·55), 220	0·48 (0·4-0·57), 157	0·48 (0·42-0·53), 306	0·47 (0·42-0·51), 463
IL-6	0·49 (0·43-0·54), 247	0·49 (0·44-0·54), 395	0·48 (0·43-0·52), 426	0·51 (0·47-0·55), 80	0·51 (0·48-0·55), 164	0·51 (0·47-0·55), 221	0·56 (0·47-0·65), 158	0·61 (0·55-0·67), 307	0·59 (0·54-0·64), 465
LBP	0·58 (0·5-0·66), 248	0·54 (0·48-0·61), 397	0·52 (0·46-0·58), 429	0·69 (0·56-0·83), 78	0·67 (0·55-0·78), 160	0·6 (0·5-0·71), 217	0·52 (0·42-0·61), 157	0·54 (0·47-0·61), 267	0·53 (0·47-0·59), 394
Lipocalin-2/NGAL	0·49 (0·41-0·57), 249	0·51 (0·44-0·57), 396	0·51 (0·44-0·57), 428	0·67 (0·54-0·8), 79	0·6 (0·49-0·72), 163	0·58 (0·48-0·68), 219	0·56 (0·46-0·66), 156	0·65 (0·59-0·72), 265	0·61 (0·56-0·67), 392
sPLA/Lp-PLA2	0·54 (0·46-0.62), 252	0·53 (0·46-0·59), 402	0·52 (0·45-0·58), 434	0·58 (0·44-0·71), 80	0·54 (0·43-0·65), 164	0·58 (0·48-0·68), 221	0·58 (0·47-0·68), 158	0·55 (0·49-0·61), 308	0·56 (0·51-0·61), 466
TRAIL	0·56 (0·49-0·64), 252	0·53 (0·47-0·59), 402	0·53 (0·48-0·59), 434	0·5 (0·5-0·5), 74	0·5 (0·49-0·5), 156	0·49 (0·48-0·5), 212	0·61 (0·51-0·71), 157	0·62 (0·56-0·68), 306	0·62 (0·57-0·67), 463

Supplementary Table 8: Univariate analysis – Overall (malaria-positive and malaria-negative) population

	Overall - Malaria negatives AUROC (CI), N			Overall - Malaria positives AUROC (CI), N		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.74, (0.7-0.79), 493	0.75, (0.71-0.78), 880	0.72, (0.68-0.75), 1127	0.65, (0.57-0.73), 174	0.65, (0.58-0.71), 481	0.64, (0.59-0.7), 630
RBC count	0.58, (0.53-0.63), 494	0.52, (0.48-0.56), 880	0.51, (0.47-0.54), 1127	0.58, (0.5-0.67), 175	0.5, (0.44-0.56), 481	0.51, (0.46-0.57), 630
Lymphocyte count	0.66, (0.61-0.71), 491	0.57, (0.53-0.61), 877	0.55, (0.51-0.58), 1123	0.63, (0.54-0.71), 174	0.57, (0.5-0.63), 480	0.54, (0.49-0.6), 627
Neutrophil count	0.71, (0.66-0.75), 480	0.75, (0.71-0.79), 847	0.73, (0.69-0.76), 1079	0.67, (0.59-0.75), 172	0.65, (0.58-0.71), 461	0.65, (0.59-0.71), 603
IL-4	0.36, (0.31-0.42), 486	0.4, (0.35-0.44), 868	0.61, (0.57-0.64), 1113	0.66, (0.58-0.74), 175	0.59, (0.53-0.65), 478	0.58, (0.53-0.63), 624
TRAIL	0.36, (0.3-0.41), 489	0.63, (0.59-0.67), 871	0.63, (0.59-0.67), 1117	0.68, (0.6-0.76), 175	0.6, (0.54-0.66), 478	0.58, (0.53-0.64), 625
IL-6	0.61, (0.55-0.66), 489	0.49, (0.45-0.53), 873	0.49, (0.45-0.53), 1120	0.42, (0.33-0.5), 175	0.57, (0.5-0.63), 478	0.53, (0.48-0.59), 626
CRP NycoCard	0.52, (0.47-0.57), 496	0.57, (0.53-0.61), 884	0.57, (0.53-0.6), 1132	0.52, (0.43-0.6), 175	0.49, (0.43-0.56), 481	0.5, (0.44-0.55), 630
Gal-9	0.52, (0.47-0.57), 490	0.54, (0.5-0.58), 875	0.56, (0.52-0.59), 1122	0.57, (0.48-0.65), 176	0.54, (0.48-0.6), 480	0.53, (0.48-0.59), 629
CHI3L1	0.56, (0.51-0.62), 489	0.55, (0.51-0.59), 873	0.55, (0.51-0.59), 1119	0.5, (0.41-0.59), 176	0.52, (0.45-0.58), 480	0.5, (0.44-0.55), 627
IP-10	0.53, (0.48-0.58), 489	0.52, (0.48-0.56), 874	0.52, (0.49-0.56), 1120	0.56, (0.47-0.64), 176	0.53, (0.47-0.59), 478	0.51, (0.45-0.56), 627
sPLA2	0.52, (0.47-0.57), 490	0.52, (0.48-0.56), 874	0.52, (0.49-0.56), 1121	0.49, (0.4-0.58), 176	0.54, (0.48-0.61), 479	0.54, (0.49-0.6), 628
NGAL	0.61, (0.56-0.66), 489	0.62, (0.57-0.66), 833	0.6, (0.57-0.64), 1049	0.61, (0.52-0.7), 157	0.56, (0.49-0.62), 403	0.56, (0.51-0.62), 527
LBP	0.74, (0.69-0.78), 488	0.69, (0.65-0.73), 832	0.67, (0.64-0.71), 1048	0.67, (0.58-0.76), 158	0.58, (0.52-0.64), 404	0.57, (0.51-0.62), 529
C2	0.59, (0.54-0.64), 483	0.56, (0.52-0.6), 866	0.56, (0.52-0.59), 1113	0.63, (0.55-0.72), 176	0.59, (0.53-0.66), 480	0.56, (0.5-0.61), 629
AGP	0.67, (0.62-0.72), 490	0.6, (0.56-0.64), 874	0.58, (0.55-0.62), 1120	0.52, (0.43-0.6), 176	0.52, (0.45-0.59), 480	0.53, (0.47-0.59), 629
HBP	0.67, (0.57-0.76), 179	0.64, (0.56-0.72), 254	0.61, (0.53-0.68), 280	0.55, (0.37-0.72), 57	0.52, (0.42-0.63), 141	0.53, (0.43-0.64), 149
HP	0.55, (0.49-0.6), 489	0.5, (0.46-0.54), 871	0.52, (0.48-0.56), 1116	0.58, (0.49-0.66), 175	0.55, (0.48-0.61), 473	0.54, (0.48-0.59), 622

Supplementary Table 9: Univariate analysis – malaria-positive population

	Malawi - Malaria positives AUROC (CI), N			Gabon - Malaria positives AUROC (CI), N		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.67 (0.58-0.76), 132	0.68 (0.61 – 0.75), 369	0.67 (0.61-0.72), 491	0.67 (0.44-0.91), 42	0.61 (0.38-0.83), 112	0.61 (0.44-0.78), 139
RBC count	0.69 (0.6-0.79), 131	0.55 (0.48-0.61), 367	0.53 (0.47-0.59), 488	0.56 (0.31-0.81), 43	0.51 (0.3-0.71), 113	0.49 (0.33-0.65), 140
Lymphocyte count	0.7 (0.61-0.79), 131	0.59 (0.53-0.66), 368	0.57 (0.51-0.62), 488	0.72 (0.51-0.93), 42	0.66 (0.47-0.85), 112	0.67 (0.52-0,.82), 139
Neutrophil count	0.62 (0.52-0.72), 129	0.65 (0.57-0.72), 348	0.66 (0.6-0.72), 463	0.53 (0.31-0.76), 43	0.59 (0.39-0.79), 113	0.59 (0.43-0.75), 140
IL-4	0.46 (0.36-0.56), 132	0.47 (0.4-0.53), 369	0.48 (0.42-0.53), 488	0.44 (0.38-0.5), 40	0.46 (0.44-0.49), 103	0.5 (0.42-0.57), 127
TRAIL	0.6 (0.51-0.7),132	0.55 (0.49-0.62), 369	0.54 (0.48-0.59), 488	0.5 (0.5-0.5), 43	0.5 (0.5-0.5), 109	0.53 (0.47-0.6), 136
IL-6	0.6 (0.5-0.7), 131	0.58 (0.51-0.65), 367	0.54 (0.48-0.6), 485	0.45 (0.32 - 0.57), 42	0.47 (0.37-0.57), 103	0.45 (0.37-0.53), 127
CRP NycoCard	0.48 (0.38-0.58), 131	0.54 (0.47-0.61), 367	0.53 (0.47-0.59), 489	0.59 (0.32-0.86), 44	0.59 (0.36-0.82), 114	0.57 (0.4-0.75), 141
Gal-9	0.58 (0.48-0.69), 132	0.56 (0.49-0.62), 369	0.54 (0.47-0.6), 491	0.57 (0.34-0.8), 43	0.5 (0.32-0.68), 109	0.56 (0.42-0.71), 136
CHI3L1	0.56 (0.46-0.66), 132	0.55 (0.48-0.62), 367	0.55 (0.49-0.61), 487	0.52 (0.26-0.79), 43	0.53 (0.31-0.75), 106	0.63 (0.44-0.81), 131
IP-10	0.67 (0.58-0.76), 132	0.56 (0.49-0.63), 363	0.52 (0.46-0.59), 484	0.51 (0.33-0.69), 40	0.49 (0.35-0.63), 104	0.48 (0.35-0.61), 129
sPLA2	0.53 (0.43-0.64), 133	0.56 (0.48-0.63), 370	0.56 (0.5-0.62), 492	0.49 (0.24-0.74), 43	0.56 (0.34-0.77), 109	0.49 (0.32-0.67), 136
NGAL	0.5 (0.39-0.61), 114	0.5 (0.43-0.58), 291	0.49 (0.42-0.55)386	0.65 (0.44-0.91), 41	0.59 (0.41-0.77), 106	0.54 (0.38-0.7), 131
LBP	0.47 (0.35-0.59), 115	0.54 (0.46-0.61), 295	0.54 (0.48-0.6), 393	0.6 (0.34 - 0.85), 42	0.58 (0.37-0.8), 105	0.65 (0.48-0.81), 131
C2	0.62 (0.52-0.72), 133	0.57 (0.5-0.64), 369	0.54 (0.48-0.6), 491	0.72 (0.54-0.9), 43	0.72 (0.57-0.87), 105	0.64 (0.48-0.8), 131
AGP	0.54 (0.44 - 0.64), 133	0.52 (0.44-0.59), 371	0.48 (0.42-0.54), 493	0.51 (0.27-0.75), 43	0.53 (0.33-0.74), 109	0.58 (0.41-0.76), 136
HBP	0.55, (0.37-0.72), 57	0.53, (0.43-0.64), 143	0.54, (0.44-0.64), 151	..	..	..
HP	0.58 (0.48-0.68), 133	0.54 (0.47-0.61), 365	0.51 (0.45-0.57), 487	0.57 (0.33-0.8), 42	0.56 (0.36-0.76), 107	0.61 (0.46-0.77), 134

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65,) red (AUROC <0.6)

Univariate analysis – age subgroups

Supplementary Table 10: Univariate analysis - age less than 6 years (non-malaria)

	Malawi - Malaria negatives AUROC (CI), N			Brazil - Malaria negatives AUROC (CI), N			Gabon - Malaria negatives AUROC (CI), N		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.83, (0.73-0.94), 61	0.79, (0.71-0.87), 122	0.76, (0.69-0.84), 170	0.52, (0.25-0.78), 21	0.65, (0.46-0.85), 34	0.69, (0.51-0.86), 38	0.78, (0.62-0.94), 32	0.68, (0.52-0.83), 75	0.65, (0.52-0.79), 105
RBC count	0.65, (0.49-0.8), 62	0.58, (0.48-0.68), 123	0.58, (0.5-0.67), 172	0.6, (0.33-0.86), 21	0.56, (0.35-0.77), 33	0.59, (0.39-0.78), 37	0.6, (0.4-0.81), 32	0.56, (0.4-0.72), 75	0.53, (0.38-0.67), 105
Lymphocyte count	0.58, (0.43-0.72), 60	0.53, (0.42-0.64), 121	0.48, (0.38-0.57), 170	0.63, (0.36-0.89), 21	0.67, (0.44-0.91), 34	0.7, (0.5-0.9), 38	0.71, (0.53-0.89), 32	0.6, (0.44-0.76), 75	0.63, (0.49-0.76), 105
Neutrophil count	0.82, (0.7-0.93), 57	0.79, (0.7-0.88), 108	0.77, (0.69-0.86), 148	0.58, (0.32-0.85), 21	0.56, (0.36-0.77), 34	0.6, (0.41-0.79), 38	0.86, (0.72-0.99), 32	0.79, (0.67-0.92), 74	0.7, (0.58-0.83), 103
IL-4	0.54, (0.39-0.68), 63	0.5, (0.41-0.59), 125	0.48, (0.41-0.56), 174	0.63, (0.38-0.88), 20	0.66, (0.49-0.84), 31	0.62, (0.44-0.8), 33	0.43, (0.31-0.55), 30	0.49, (0.43-0.56), 72	0.51, (0.44-0.57), 103
TRAIL	0.57, (0.39-0.75), 63	0.6, (0.5-0.69), 125	0.59, (0.51-0.67), 174	0.5, (0.23-0.77), 20	0.63, (0.43-0.82), 31	0.59, (0.4-0.79), 33	0.5, (0.5-0.5), 28	0.5, (0.5-0.5), 69	0.49, (0.48-0.51), 99
IL-6	0.59, (0.44-0.73), 63	0.61, (0.52-0.7), 125	0.6, (0.52-0.68), 174	0.41, (0.29-0.53), 20	0.39, (0.29-0.49), 29	0.39, (0.3-0.49), 31	0.5, (0.5-0.5), 31	0.5, (0.5-0.5), 73	0.49, (0.47-0.5), 104
CRP NycoCard	0.56, (0.37-0.74), 61	0.61, (0.51-0.71), 121	0.59, (0.5-0.68), 169	0.49, (0.22-0.76), 21	0.59, (0.38-0.79), 34	0.6, (0.42-0.79), 38	0.76, (0.57-0.95), 32	0.62, (0.49-0.76), 75	0.57, (0.45-0.69), 106
Gal-9	0.79, (0.66-0.92), 63	0.59, (0.49-0.69), 125	0.57, (0.48-0.66), 173	0.47, (0.2-0.75), 20	0.5, (0.28-0.72), 31	0.52, (0.3-0.73), 33	0.66, (0.45-0.87), 31	0.6, (0.43-0.76), 72	0.54, (0.4-0.69), 102
CHI3L1	0.56, (0.4-0.72), 62	0.52, (0.42-0.63), 124	0.54, (0.45-0.63), 173	0.61, (0.35-0.87), 20	0.66, (0.47-0.86), 31	0.67, (0.49-0.86), 33	0.68, (0.49-0.88), 31	0.62, (0.45-0.79), 73	0.61, (0.47-0.75), 102
IP-10	0.67, (0.51-0.83), 63	0.62, (0.52-0.72), 125	0.6, (0.51-0.68), 174	0.65, (0.39-0.9), 20	0.7, (0.51-0.89), 31	0.64, (0.45-0.84), 33	0.71, (0.53-0.9), 31	0.52, (0.38-0.67), 73	0.51, (0.38-0.63), 104
sPLA2	0.66, (0.5-0.82), 63	0.55, (0.45-0.66), 125	0.56, (0.47-0.65), 174	0.65, (0.38-0.91), 20	0.69, (0.48-0.9), 31	0.68, (0.48-0.88), 33	0.58, (0.37-0.78), 31	0.57, (0.41-0.72), 73	0.59, (0.45-0.73), 104
NGAL	0.61, (0.44-0.77), 63	0.68, (0.58-0.78),	0.67, (0.59-0.76),	0.67, (0.41-0.93), 20	0.58, (0.38-0.79),	0.52, (0.31-0.72),	0.63, (0.43-0.83), 31	0.6, (0.44-0.77),	0.57, (0.43-0.71),

		109	144		31	33		73	103
LBP	0.47, (0.31-0.63), 63	0.5, (0.39-0.62), 109	0.53, (0.43-0.63), 144	0.47, (0.2-0.75), 20	0.46, (0.25-0.68), 30	0.48, (0.27-0.7), 32	0.73, (0.53-0.93), 30	0.7, (0.53-0.86), 70	0.59, (0.44-0.75), 101
C2	0.51, (0.34-0.69), 63	0.56, (0.45-0.66), 125	0.52, (0.44-0.61), 174	0.47, (0.18-0.76), 19	0.64, (0.41-0.87), 29	0.62, (0.4-0.83), 31	0.51, (0.29-0.73), 30	0.48, (0.32-0.64), 71	0.5, (0.36-0.64), 102
AGP	0.54, (0.38-0.7), 63	0.56, (0.45-0.66), 125	0.57, (0.48-0.66), 174	0.72, (0.48-0.96), 20	0.57, (0.34-0.81), 31	0.61, (0.39-0.82), 33	0.8, (0.63-0.98), 31	0.72, (0.56-0.88), 72	0.62, (0.48-0.76), 103
HBP	0.67, (0.45-0.89), 26	0.55, (0.37-0.73), 45	0.54, (0.37-0.71), 48	..	..	..	..	..	..
HP	0.64, (0.49-0.78), 62	0.57, (0.46-0.67), 124	0.57, (0.48-0.66), 173	0.68, (0.42-0.93), 20	0.61, (0.38-0.84), 31	0.62, (0.41-0.84), 33	0.78, (0.59-0.97), 28	0.72, (0.57-0.88), 69	0.63, (0.49-0.77), 100

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65), red (AUROC <0.6)

Supplementary Table 11: Univariate analysis - aged between 7 and 15 years (non-malaria)

	Malawi - Malaria negatives AUROC (CI), N			**Brazil - Malaria negatives AUROC (CI), N**			**Gabon - Malaria negatives AUROC (CI), N**		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.49, (0.26-0.73), 28	0.69, (0.54-0.84), 50	0.75, (0.64-0.86), 81	0.79, (0.61-0.96), 34	0.83, (0.71-0.95), 69	0.82, (0.71-0.94), 75	0.46, (0.27-0.65), 47	0.51, (0.34-0.67), 87	0.47, (0.31-0.62), 112
RBC count	0.62, (0.41-0.84), 28	0.54, (0.37-0.7), 51	0.57, (0.44-0.7), 82	0.7, (0.51-0.88), 34	0.61, (0.45-0.78), 69	0.6, (0.44-0.75), 75	0.56, (0.38-0.75), 47	0.55, (0.4-0.7), 87	0.48, (0.35-0.62), 112
Lymphocyte count	0.76, (0.58-0.94), 28	0.67, (0.51-0.83), 51	0.62, (0.49-0.74), 82	0.6, (0.37-0.83), 34	0.69, (0.54-0.85), 69	0.71, (0.56-0.86), 75	0.59, (0.42-0.76), 47	0.61, (0.48-0.74), 87	0.55, (0.43-0.68), 112
Neutrophil count	0.46, (0.23-0.7), 26	0.7, (0.54-0.86), 45	0.76, (0.64-0.87), 73	0.73, (0.53-0.93), 34	0.82, (0.69-0.95), 69	0.8, (0.68-0.93), 75	0.66, (0.46-0.86), 46	0.61, (0.43-0.8), 86	0.61, (0.44-0.78), 111
IL-4	0.56, (0.34-0.78), 28	0.46, (0.31-0.6), 50	0.48, (0.37-0.6), 80	0.73, (0.53-0.92), 33	0.62, (0.47-0.77), 69	0.59, (0.45-0.74), 75	0.46, (0.41-0.5), 47	0.48, (0.46-0.5), 86	0.51, (0.45-0.57), 112
TRAIL	0.48, (0.23-0.73), 28	0.6, (0.45-0.76), 50	0.57, (0.45-0.7), 80	0.55, (0.34-0.77), 33	0.53, (0.38-0.68), 69	0.52, (0.38-0.66), 75	0.5, (0.5-0.5), 45	0.49, (0.48-0.51), 83	0.49, (0.47-0.5), 109
IL-6	0.45, (0.21-0.69), 28	0.56, (0.4-0.71), 51	0.55, (0.44-0.67), 82	0.46, (0.34-0.58), 33	0.44, (0.33-0.56), 69	0.43, (0.33-0.53), 75	0.53, (0.44-0.62), 47	0.53, (0.46-0.6), 86	0.54, (0.46-0.62), 112

CRP NycoCard	0.56, (0.34-0.78), 28	0.61, (0.46-0.77), 51	0.62, (0.5-0.74), 82	0.57, (0.33-0.81), 34	0.52, (0.35-0.68), 71	0.51, (0.35-0.68), 77	0.75, (0.59-0.92), 47	0.71, (0.55-0.87), 87	0.69, (0.56-0.83), 113
Gal-9	0.67, (0.43-0.9), 28	0.68, (0.53-0.84), 51	0.66, (0.54-0.78), 82	0.71, (0.52-0.9), 33	0.57, (0.41-0.73), 69	0.54, (0.39-0.7), 75	0.79, (0.62-0.95), 47	0.61, (0.44-0.77), 86	0.55, (0.39-0.71), 112
CHI3L1	0.53, (0.28-0.78), 28	0.6, (0.44-0.76), 51	0.61, (0.49-0.73), 82	0.69, (0.5-0.87), 32	0.66, (0.52-0.79), 67	0.59, (0.44-0.73), 71	0.53, (0.32-0.73), 46	0.58, (0.41-0.74), 84	0.62, (0.47-0.77), 110
IP-10	0.64, (0.42-0.86), 28	0.56, (0.39-0.72), 51	0.59, (0.46-0.72), 82	0.73, (0.53-0.92), 33	0.62, (0.46-0.78), 69	0.58, (0.42-0.73), 75	0.6, (0.41-0.78), 47	0.48, (0.31-0.66), 86	0.52, (0.37-0.67), 112
sPLA2	0.47, (0.21-0.72), 28	0.55, (0.39-0.72), 51	0.56, (0.43-0.68), 82	0.54, (0.33-0.76), 33	0.49, (0.35-0.64), 69	0.56, (0.43-0.7), 75	0.46, (0.28-0.64), 47	0.52, (0.36-0.67), 86	0.44, (0.29-0.59), 112
NGAL	0.56, (0.32-0.8), 28	0.68, (0.52-0.85), 46	0.73, (0.61-0.85), 73	0.71, (0.52-0.9), 33	0.68, (0.54-0.82), 69	0.64, (0.5-0.78), 75	0.7, (0.52-0.89), 46	0.6, (0.44-0.77), 85	0.59, (0.44-0.74), 111
LBP	0.54, (0.3-0.77), 28	0.59, (0.42-0.75), 46	0.58, (0.45-0.72), 73	0.68, (0.5-0.87), 33	0.66, (0.52-0.8), 69	0.67, (0.54-0.8), 75	0.71, (0.52-0.9), 46	0.66, (0.48-0.84), 85	0.63, (0.46-0.79), 111
C2	0.62, (0.34-0.9), 28	0.53, (0.36-0.7), 51	0.53, (0.41-0.66), 82	0.54, (0.31-0.76), 32	0.57, (0.4-0.74), 67	0.61, (0.45-0.77), 73	0.62, (0.42-0.81), 45	0.46, (0.27-0.65), 83	0.52, (0.36-0.68), 109
AGP	0.57, (0.3-0.83), 28	0.55, (0.39-0.71), 51	0.52, (0.39-0.65), 81	0.53, (0.3-0.76), 33	0.6, (0.44-0.75), 69	0.61, (0.46-0.75), 75	0.75, (0.56-0.94), 47	0.68, (0.5-0.86), 86	0.67, (0.52-0.83), 112
HBP	0.76, (0.28-1), 10	0.58, (0.29-0.87), 19	0.65, (0.39-0.91), 23	## Unbalanced classes	0.92, (0.69-1), 8	0.72, (0.28-1), 9	..	..	..
HP	0.5, (0.25-0.76), 28	0.51, (0.35-0.67), 51	0.5, (0.37-0.63), 82	0.52, (0.3-0.75), 32	0.62, (0.46-0.78), 68	0.6, (0.45-0.76), 74	0.53, (0.33-0.73), 47	0.54, (0.37-0.7), 85	0.53, (0.38-0.67), 109

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65), red (AUROC <0.6)

Supplementary Table 12: Univariate analysis - aged more than 15 years (non-malaria)

	Malawi - Malaria negatives AUROC (CI), N			**Brazil - Malaria negatives AUROC (CI), N**			**Gabon - Malaria negatives AUROC (CI), N**		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.67, (0.53-0.82), 66	0.71, (0.62-0.8), 132	0.68, (0.6-0.75), 210	0.84, (0.77-0.91), 202	0.84, (0.77-0.9), 305	0.83, (0.77-0.89), 329	2 patients in total	5 patients in total	5 patients in total
RBC count	0.59,	0.53,	0.51,	0.56,	0.56,	0.55,	-	-	-

	(0.44-0.73), 65	(0.43-0.63), 131	(0.43-0.59), 209	(0.45-0.67), 203	(0.47-0.64), 306	(0.47-0.63), 330			
Lymphocyte count	0.5, (0.34-0.66), 66	0.53, (0.43-0.63), 131	0.49, (0.41-0.57), 209	0.67, (0.58-0.76), 202	0.65, (0.57-0.72), 305	0.64, (0.57-0.71), 329	-	-	-
Neutrophil count	0.65, (0.49-0.81), 60	0.7, (0.6-0.8), 120	0.66, (0.59-0.74), 193	0.82, (0.74-0.9), 202	0.82, (0.76-0.89), 305	0.82, (0.75-0.88), 329	-	-	-
IL-4	0.4, (0.28-0.52), 66	0.47, (0.39-0.54), 131	0.45, (0.39-0.52), 209	0.56, (0.47-0.65), 196	0.53, (0.46-0.6), 298	0.54, (0.47-0.6), 321	-	-	-
TRAIL	0.68, (0.54-0.82), 66	0.65, (0.56-0.73), 131	0.66, (0.59-0.73), 209	0.57, (0.48-0.65), 199	0.54, (0.47-0.61), 302	0.54, (0.48-0.61), 326	-	-	-
IL-6	0.59, (0.46-0.72), 67	0.63, (0.54-0.72), 131	0.59, (0.52-0.66), 209	0.51, (0.44-0.58), 194	0.51, (0.45-0.58), 297	0.5, (0.44-0.56), 320	-	-	-
CRP NycoCard	0.53, (0.38-0.68), 67	0.6, (0.5-0.7), 133	0.57, (0.49-0.64), 211	0.66, (0.57-0.76), 204	0.65, (0.57-0.73), 307	0.66, (0.58-0.73), 331	-	-	-
Gal-9	0.72, (0.59-0.86), 67	0.6, (0.5-0.7), 133	0.63, (0.56-0.71), 211	0.61, (0.52-0.71), 199	0.56, (0.48-0.65), 301	0.57, (0.5-0.65), 325	-	-	-
CHI3L1	0.52, (0.36-0.67), 65	0.51, (0.41-0.61), 129	0.53, (0.45-0.61), 207	0.66, (0.58-0.75), 194	0.62, (0.54-0.69), 296	0.62, (0.55-0.69), 320	-	-	-
IP-10	0.64, (0.48-0.79), 67	0.59, (0.49-0.69), 133	0.61, (0.53-0.68), 210	0.59, (0.5-0.68), 199	0.52, (0.44-0.6), 302	0.53, (0.45-0.6), 326	-	-	-
sPLA2	0.53, (0.37-0.69), 67	0.54, (0.44-0.64), 132	0.54, (0.46-0.62), 210	0.58, (0.48-0.67), 199	0.56, (0.48-0.64), 302	0.56, (0.48-0.63), 326	-	-	-
NGAL	0.49, (0.33-0.65), 65	0.62, (0.51-0.72), 110	0.53, (0.44-0.62), 175	0.55, (0.46-0.65), 196	0.54, (0.46-0.62), 296	0.53, (0.45-0.61), 320	-	-	-
LBP	0.56, (0.41-0.7), 66	0.56, (0.45-0.67), 112	0.53, (0.44-0.61), 177	0.65, (0.56-0.74), 195	0.6, (0.52-0.67), 298	0.56, (0.49-0.64), 322	-	-	-
C2	0.67, (0.53-0.81), 67	0.59, (0.49-0.69), 133	0.58, (0.51-0.66), 210	0.5, (0.4-0.6), 193	0.51, (0.43-0.58), 296	0.51, (0.44-0.59), 320	-	-	-
AGP	0.6, (0.45-0.75), 67	0.57, (0.47-0.67), 133	0.54, (0.46-0.62), 211	0.65, (0.55-0.74), 199	0.58, (0.5-0.66), 302	0.56, (0.49-0.64), 326	-	-	-
HBP	0.48, (0.25-0.71), 28	0.54, (0.36-	0.47, (0.31-	0.66, (0.51-0.81), 107	0.66, (0.53-	0.63, (0.5-	-	-	-

		0.72), 44	0.63), 55		0.79), 136	0.76), 142			
HP	0.53, (0.39-0.67), 67	0.58, (0.48-0.68), 132	0.5, (0.42-0.58), 209	0.56, (0.46-0.66), 196	0.47, (0.39-0.55), 299	0.48, (0.4-0.55), 323	-	-	-

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65) red (AUROC <0.6)

Supplementary Table 13: Univariate analysis - age less than 6 years (malaria)

	Malawi - Malaria positives AUROC (CI), N			**Gabon - Malaria positives AUROC (CI), N**		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.64, (0.47-0.81), 50	0.71, (0.59-0.82), 148	0.7, (0.6-0.8), 178	0.62, (0.23-1), 11	0.62, (0.36-0.88), 44	0.62, (0.41-0.83), 56
RBC count	0.51, (0.33-0.68), 49	0.55, (0.44-0.65), 147	0.55, (0.44-0.65), 177	0.7, (0.34-1), 11	0.63, (0.42-0.84), 44	0.62, (0.45-0.8), 56
Lymphocyte count	0.45, (0.26-0.64), 49	0.58, (0.47-0.7), 147	0.55, (0.44-0.66), 177	0.57, (0.17-0.96), 11	0.6, (0.34-0.86), 44	0.63, (0.42-0.85), 56
Neutrophil count	0.59, (0.41-0.77), 49	0.65, (0.53-0.76), 140	0.66, (0.56-0.76), 169	0.7, (0.3-1), 11	0.49, (0.24-0.75), 44	0.55, (0.35-0.75), 56
IL-4	0.68, (0.5-0.86), 50	0.62, (0.52-0.71), 148	0.58, (0.49-0.67), 178	0.5, (0.5-0.5), 11	0.47, (0.42-0.51), 39	0.48, (0.44-0.51), 51
TRAIL	0.73, (0.56-0.89), 50	0.59, (0.48-0.69), 148	0.56, (0.47-0.66), 178	0.5, (0.5-0.5), 11	0.5, (0.5-0.5), 41	0.5, (0.5-0.5), 53
IL-6	0.6, (0.4-0.79), 49	0.64, (0.53-0.74), 147	0.63, (0.53-0.72), 175	0.47, (0.2-0.73), 11	0.48, (0.33-0.62), 37	0.48, (0.36-0.59), 49
CRP NycoCard	0.52, (0.33-0.7), 48	0.58, (0.48-0.69), 145	0.56, (0.46-0.66), 175	0.78, (0.47-1), 11	0.66, (0.41-0.91), 44	0.63, (0.42-0.84), 56
Gal-9	0.58, (0.37-0.79), 49	0.54, (0.43-0.65), 148	0.53, (0.43-0.64), 178	0.5, (0.05-0.95), 11	0.63, (0.45-0.82), 41	0.6, (0.44-0.76), 53
CHI3L1	0.53, (0.36-0.7), 50	0.6, (0.49-0.71), 148	0.57, (0.47-0.67), 178	0.47, (0.07-0.86), 11	0.54, (0.28-0.79), 40	0.56, (0.33-0.8), 51
IP-10	0.73, (0.57-0.9), 50	0.58, (0.47-0.69), 143	0.57, (0.47-0.67), 172	0.77, (0.38-1), 11	0.45, (0.26-0.64), 39	0.48, (0.32-0.64), 51
sPLA2	0.49, (0.3-0.69), 50	0.63, (0.52-0.75), 148	0.62, (0.52-0.72), 178	0.73, (0.38-1), 11	0.52, (0.27-0.78), 41	0.52, (0.31-0.73), 53
NGAL	0.61, (0.43-0.79), 47	0.56, (0.44-0.68), 118	0.54, (0.43-0.65), 141	0.87, (0.6-1), 11	0.62, (0.4-0.85), 40	0.61, (0.41-0.8), 52
LBP	0.55, (0.3-0.79), 48	0.48, (0.37-0.59), 122	0.52, (0.41-0.62), 147	0.45, (0.03-0.87), 11	0.58, (0.33-0.83), 41	0.61, (0.4-0.81), 53
C2	0.57, (0.38-0.76), 50	0.57, (0.47-0.68), 148	0.56, (0.46-0.67), 178	0.58, (0.2-0.97), 11	0.78, (0.6-0.96), 38	0.77, (0.6-0.93), 50
AGP	0.68, (0.52-0.84), 50	0.6, (0.49-0.71), 149	0.57, (0.47-0.68), 179	0.63, (0.24-1), 11	0.52, (0.32-0.73), 41	0.46, (0.27-0.65), 53
HBP	0.55, (0.27-0.84), 33	0.62, (0.49-0.76), 78	0.63, (0.49-0.76), 82	..	..	..
HP	0.72, (0.58-0.87), 50	0.59, (0.48-0.7), 147	0.56, (0.46-0.67), 177	0.57, (0.18-0.95), 11	0.45, (0.21-0.69), 40	0.47, (0.26-0.68), 52

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65), red (AUROC <0.6)

Supplementary Table 14: Univariate analysis - aged between 7 and 15 years (malaria)

	Malawi - Malaria positives AUROC (CI), N			Gabon - Malaria positives AUROC (CI), N		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.67, (0.51-0.82), 51	0.7, (0.6-0.8), 134	0.66, (0.57-0.75), 185	**## unbalanced classes (24 non-bacterial, 1 bacterial) for 25 patients**	**## unbalanced classes (54 non-bacterial, 1 bacterial) for 55 patients**	0.47, (0.03-0.91), 72
RBC count	0.74, (0.6-0.87), 51	0.55, (0.43-0.68), 134	0.53, (0.43-0.63), 185	-	-	0.67, (0.28-1), 73
Lymphocyte count	0.64, (0.49-0.79), 51	0.59, (0.47-0.7), 134	0.55, (0.46-0.64), 184	-	-	0.44, (0.14-0.75), 72
Neutrophil count	0.63, (0.47-0.79), 50	0.67, (0.56-0.78), 127	0.67, (0.58-0.76), 174	-	-	0.51, (0.17-0.86), 73
IL-4	0.53, (0.36-0.7), 51	0.54, (0.44-0.64), 134	0.53, (0.45-0.61), 184	-	-	0.62, (0.27-0.96), 65
TRAIL	0.51, (0.35-0.68), 51	0.52, (0.41-0.63), 134	0.54, (0.45-0.63), 184	-	-	0.62, (0.38-0.87), 72
IL-6	0.62, (0.46-0.78), 50	0.57, (0.46-0.68), 132	0.51, (0.41-0.6), 181	-	-	0.41, (0.37-0.46), 67
CRP NycoCard	0.55, (0.39-0.71), 51	0.52, (0.4-0.64), 134	0.51, (0.41-0.61), 185	-	-	0.59, (0.21-0.97), 73
Gal-9	0.6, (0.44-0.76), 51	0.53, (0.42-0.65), 134	0.55, (0.45-0.65), 185	-	-	0.64, (0.23-1), 72
CHI3L1	0.53, (0.36-0.69), 51	0.49, (0.38-0.6), 133	0.54, (0.45-0.64), 183	-	-	0.61, (0.08-1), 69
IP-10	0.63, (0.47-0.79), 50	0.56, (0.45-0.68), 133	0.53, (0.43-0.63), 184	-	-	0.55, (0.11-0.99), 67
NGAL	0.55, (0.38-0.71), 51	0.52, (0.41-0.64), 134	0.53, (0.44-0.63), 185	-	-	0.56, (0.13-0.99), 72
HNL	0.67, (0.48-0.85), 42	0.47, (0.35-0.59), 108	0.57, (0.48-0.67), 150	-	-	0.66, (0.33-1), 69
LBP	0.61, (0.44-0.78), 42	0.59, (0.47-0.71), 108	0.56, (0.46-0.66), 151	-	-	0.9, (0.77-1), 67
C2	0.62, (0.46-0.78), 51	0.57, (0.46-0.68), 133	0.54, (0.45-0.64), 184	-	-	0.73, (0.47-0.98), 70
AGP	0.6, (0.44-0.76), 51	0.55, (0.43-0.67), 134	0.52, (0.42-0.62), 185	-	-	0.53, (0.07-0.99), 72
HBP	0.64, (0.39-0.9), 21	0.46, (0.28-0.65), 50	0.49, (0.31-0.67), 55	-	-	-

HP	0.54, (0.37-0.7), 51	0.49, (0.38-0.59), 132	0.49, (0.4-0.59), 183	-	-	0.79, (0.6-0.98), 71

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65) red (AUROC <0.6)

Supplementary Table 15: Univariate analysis - aged more than 15 years (malaria)

	Malawi - Malaria positives AUROC (CI), N			**Gabon - Malaria positives AUROC (CI), N**		
	Electronic	**Strict**	**Loose**	**Electronic**	**Strict**	**Loose**
WBC count	0.54, (0.32-0.76), 31	0.56, (0.37-0.75), 87	0.65, (0.51-0.78), 128	2 patients in total	11 patients in total	11 patients in total
RBC count	0.42, (0.2-0.63), 31	0.58, (0.42-0.73), 86	0.57, (0.44-0.7), 126	-	-	-
Lymphocyte count	0.77, (0.61-0.94), 31	0.64, (0.5-0.78), 87	0.66, (0.55-0.77), 127	-	-	-
Neutrophil count	0.5, (0.28-0.73), 30	0.55, (0.35-0.74), 81	0.62, (0.48-0.77), 120	-	-	-
IL-4	0.53, (0.33-0.73), 31	0.5, (0.34-0.66), 87	0.48, (0.37-0.59), 126	-	-	-
TRAIL	0.62, (0.42-0.82), 31	0.6, (0.44-0.76), 87	0.63, (0.51-0.75), 126	-	-	-
IL-6	0.67, (0.47-0.87), 32	0.52, (0.35-0.69), 88	0.54, (0.41-0.66), 129	-	-	-
CRP NycoCard	0.57, (0.36-0.78), 32	0.52, (0.37-0.68), 88	0.52, (0.4-0.64), 129	-	-	-
Gal-9	0.61, (0.4-0.82), 32	0.59, (0.44-0.73), 87	0.52, (0.39-0.65), 128	-	-	-
CHI3L1	0.64, (0.43-0.85), 31	0.53, (0.37-0.69), 86	0.52, (0.4-0.65), 126	-	-	-
IP-10	0.66, (0.45-0.87), 32	0.52, (0.35-0.69), 87	0.58, (0.44-0.71), 128	-	-	-
sPLA2	0.62, (0.42-0.82), 32	0.53, (0.37-0.69), 88	0.56, (0.44-0.69), 129	-	-	-
NGAL	0.7, (0.48-0.92), 25	0.55, (0.35-0.75), 65	0.56, (0.41-0.7), 95	-	-	-
LBP	0.37, (0.14-0.6), 25	0.47, (0.29-0.66), 65	0.59, (0.46-0.73), 95	-	-	-
C2	0.64, (0.43-0.85), 32	0.59, (0.42-0.76), 88	0.47, (0.33-0.6), 129	-	-	-
AGP	0.68, (0.49-0.87), 32	0.47, (0.31-0.63), 88	0.52, (0.39-0.64), 129	-	-	-
HBP	0.8, (0.34-1), 7	0.62, (0.29-0.95), 23	0.62, (0.29-0.95), 24	-	-	-
HP	0.52, (0.31-0.73), 32	0.51, (0.35-0.67), 86	0.53, (0.41-0.64), 127	-	-	-

Green (AUROC ≥ 0.7), yellow (AUROC ≥ 0.65 and <7), orange (AUROC 0.6-0.65) red (AUROC <0.6)

Supplementary Table 16: Multivariate analysis – non-malaria population; haematological biomarkers

Haematological biomarkers

Overall						
Multivariate models' variables			**Classification group**	**Best multivariate model/models: mean (SD) AUROC**	**Best host-biomarker: mean (SD) AUROC**	**Multivariate AUROC gain/loss (%)**
Rulefit	**Logistic - RFA**	**Logistic - SW**				
country , neutrophil count WBC count, lymphocyte count, fever duration, temperature, pulse rate, respiratory rate	country neutrophil count, fever duration	country neutrophil count fever duration respiratory rate	L	RF/SW/RFA: 0.75 (0.03)	WBC count : 0.7 (0.03)	+7%
			S	SW: 0.83 (0.04)	WBC count: 0.78 (0.03)	+6%
			E	SW/RFA: 0.83 (0.02)	WBC count: 0.77 (0.03)	+8%
Gabon*						
Gabon performance evaluation using the Overall model and Gabon data extracted from the Overall test sets			L	SW:0.7 (0.12)	WBC count : 0.7 (0.03)	
			S	SW: 0.77 (0.12)	WBC count: 0.73 (0.03)	+5%
			E	RFA: 0.77 (0.08)	WBC count: 0.75 (0.03)	+3%
Malawi						
diastolic blood pressure, HAEMATO_C lymphocyte count, neutrophil count, pulse rate, temperature, fever duration	fever duration neutrophil count	fever duration neutrophil count	L	RFA: 0.74(.05)	neutrophil count: 0.72(.06)	+3%
			S	SW: 0.73(.06)	neutrophil count: 0.72(.07)	+1%
			E	RFA: 0.66(.16)	WBC count: 0.7 (0.05)	-6%
Brazil						
diastolic blood pressure, haematocrit lymphocyte count, neutrophil count, pulse rate, temperature, fever duration, respiratory rate, WBC count	WBC count respiratory rate neutrophil count	WBC count respiratory rate	L	RFA: 0.82 (0.08)	WBC count: 0.81 (0.08)	+1%
			S	RFA: 0.82 (0.08)	WBC count: 0.81 (0.08)	+1%
			E	RFA: 0.84 (0.07)	WBC count: 0.83 (0.07)	+1%

E, electronic classification group; S, strict classification group; L, loose classification group; RF, Rulefit; RFA, logistic recursive feature addition; SW, stepwise logistic regression. Green (gain, i.e. multivariate models have better performances than univariate models); red (loss, i.e. univariate models have better performances than multivariate models).
*Multivariate performances for Gabon were computed using the Overall population-trained model as a predictor model and tested with Gabon data due to the limited data.

Supplementary Table 17: Multivariate analysis – non-malaria population; protein biomarkers

Protein biomarkers
Overall

Multivariate models' variables			Classification group	Best multivariate model/models: mean (SD) AUROC	Best host-biomarker: mean (SD) AUROC	Multivariate AUROC gain/loss (%)
Rulefit	**Logistic - RFA**	**Logistic - SW**				
CRP AGP LBP NGAL pulse rate respiratory rate diastolic blood pressure temperature country	CRP country LBP NGAL pulse rate	CRP country NGAL pulse rate respiratory rate temperature	L	RF/RFA/SW: 0.66 (0.05)	LBP: 0.62 (0.04)	+6%
			S	RF: 0.74 (0.04)	LBP: 0.66 (0.05)	+12%
			E	RFA: 0.76 (0.04)	LBP: 0.75 (0.04)	+1%
Gabon*						
Gabon performance evaluation using the Overall model and Gabon data extracted from the Overall test sets			L	SW: 0.64 (0.12)	LBP: 0.62 (0.04)	+3%
			S	RFA: 0.7 (0.11)	LBP: 0.66 (0.05)	+6%
			E	RFA: 0.7 (0.09)	LBP: 0.75 (0.04)	-7%
Malawi						
IP-10 Gal-9 NGAL temperature CRP respiratory rate fever duration pulse rate diastolic blood pressure	Gal-9 NGAL temperature	Gal-9 NGAL temperature pulse rate fever duration	L	SW: 0.7 (0.06)	Lipocalin. 2: 0.65 (0.06)	+8%
			S	RF/ SW: 0.67 (0.06)	Lipocalin. 2: 0.64 (0.06)	+5%
			E	RF: 0.71 (0.12)	IP-10: 0.69 (0.08)	+3%
Brazil						
CRP, Gal-9, AGP pulse rate, diastolic blood pressure respiratory rate, temperature	Gal-9, TRAIL, NGAL	Gal-9, pulse rate, fever duration, NGAL, temperature	L	RF: 0.67 (0.04)	CRP: 0.65 (0.06)	+3%
			S	SW/RFA: 0.66(.04)	CRP: 0.65 (0.05)	+1%
			E	SW/RFA: 0.65(.05)	CRP: 0.63 (0.08)	+3%

E, electronic classification group; S, strict classification group; L, loose classification group; RF, Rulefit; RFA, logistic recursive feature addition; SW, stepwise logistic regression. Green (gain, i.e. multivariate models have better performances than univariate models); red (loss, i.e. univariate models have better performances than multivariate models).

* Multivariate performances for Gabon were computed using the Overall population-trained model as a predictor model and tested with Gabon data.

Supplementary Table 18: Multivariate analysis – non-malaria population; haematological and protein biomarkers

Haematology + protein biomarkers						
Overall						
Multivariate models' variables			**Classification group**	**Best multivariate model/models: mean (SD) AUROC**	**Best host-biomarker: mean (SD) AUROC**	**Multivariate AUROC gain/loss (%) ** multivariate and single host-biomarkers ratio**
Rulefit	**Logistic - RFA**	**Logistic - SW**				

AGP LBP NGAL neutrophil count WBC count Country temperature fever duration pulse rate respiratory rate	Country neutrophil count fever duration LBP	Country neutrophil count fever duration respiratory rate	L	SW/RFA/RF:0.75(.03)	WBC count: 0.7 (.03)	+7%
			S	SW:0.83(.04)	WBC count: 0.78(.03)	+6%
			E	SW/RFA:0.83 (.03)	WBC count: 0.77 (0.04)	+8%
Brazil						
Gal-9, neutrophil count, WBC count, CRP, sPLA, respiratory rate, temperature, diastolic blood pressure, fever duration, pulse rate	neutrophil count, WBC count, respiratory rate, Gal-9	WBC count, Gal-9 respiratory rate	L	SW: 0.82 (0.06)	WBC count: 0.8 (0.06)	+2.5%
			S	RFA: 0.82 (0.06)	WBC count: 0.8 (0.06)	+2.5%
			E	SW: 0.85 (0.06)	WBC count: 0.83 (0.07)	+2%
Gabon*						
Gabon performance evaluation using the overall model and Gabon data extracted from the Overall test sets			L	SW/RFA: 0.7 (0.12)	WBC count: 0.7 (.03)	-
			S	SW/RFA: 0.76 (0.12)	WBC count: 0.78(.03)	-3%
			E	RFA: 0.77 (0.07)	WBC count: 0.77 (0.04)	-
Malawi						
IP-10 Gal-9 LBP neutrophil count WBC count NGAL pulse rate respiratory rate temperature diastolic blood pressure fever duration	neutrophil count, WBC count fever duration, IP-10	neutrophil count WBC count, fever duration, IP-10, temperature	L	SW/RFA: 0.74 (0.06)	neutrophil count: 0.72 (0.03)	+3%
			S	SW: 0.73 (0.06)	neutrophil count: 0.72 (0.07)	+1%
			E	RFA: 0.72 (0.6)	WBC count: 0.7 (0.)	+2%

E, electronic classification group; S, strict classification group; L, loose classification group; RF, Rulefit; RFA, logistic recursive feature addition; SW, stepwise logistic regression. Green (gain, i.e. multivariate models have better performances than univariate models); red (loss, i.e. univariate models have better performances than multivariate models).

* Multivariate performances for Gabon were computed using the Overall population-trained model as a predictor model and tested with Gabon data.

Supplementary Table 19: Multivariate analysis – malaria population; haematological biomarkers

Haematological biomarkers						
Overall						
Multivariate models' variables			**Classification group**	**Best multivariate model/models : mean (SD) AUROC**	**Best host-biomarker: mean (SD) AUROC**	**Multivariate AUROC gain/loss (%)**
Rulefit	**Logistic - RFA**	**Logistic - SW**				

haematocrit lymphocyte count neutrophil count diastolic blood pressure fever duration pulse rate respiratory rate country temperature	neutrophil count WBC count country	lymphocyte count neutrophil count country	L	RFA: 0.68 (0.04)	neutrophil count: 0.65 (0.05)	+5%
			S	SW: 0.66 (0.05)	neutrophil count: 0.6 (0.08)	+10%
			E	RF: 0.69 (0.07)	neutrophil count: 0.61 (0.08)	+13%
Gabon*						
Gabon performance evaluation using the Overall model and Gabon data extracted from the Overall test sets			L	SW: 0.67 (0.18)	neutrophil count: 0.65 (0.05)	+3%
			S	SW: 0.75 (0.2)	neutrophil count: 0.6 (0.08)	+25%
			E	Not sufficient data		
Malawi						
diastolic blood pressure lymphocyte count neutrophil count temperature WBC count haematocrit pulse rate respiratory rate fever duration	neutrophil count, WBC count, temperature	WBC count,	L	RFA: 0.7 (0.06)	WBC count: 0.69 (0.05)	+1%
			S	SW: 0.69 (0.07)	WBC count: 0.69 (0.07)	-
			E	RFA: 0.6 (0.14)	lymphocyte count: 0.67 (0.05)	-10%

E, electronic classification group; S, strict classification group; L, loose classification group; RF, Rulefit; RFA, logistic recursive feature addition; SW, stepwise logistic regression. Green (gain, i.e. multivariate models have better performances than univariate models); red (loss, i.e. univariate models have better performances than multivariate models).

* Multivariate performances for Gabon were computed using the Overall population-trained model as a predictor model and tested with Gabon data.

Supplementary Table 20: Multivariate analysis – malaria population; protein biomarkers

Protein biomarkers						
Overall						
Multivariate models' variables			**Classification group**	**Best multivariate model/models: mean (SD) AUROC**	**Best host-biomarker: mean (SD) AUROC**	**Multivariate AUROC gain/loss (%)**
Rulefit	**Logistic - RFA**	**Logistic - SW**				
AGP diastolic blood pressure Gal-9 C2 LBP pulse rate respiratory rate temperature fever duration	C2	country respiratory rate temperature AGP	L	SW: 0.62 (0.07)	CHI3L1: 0.57 (0.03)	+ 9%
			S	SW: 0.64 (0.04)	_NGAL: 0.6 (0.06)	+ 7%
			E	SW: 0.67 (0.08)	C2: 0.63 (01)	+ 6%

Gabon*						
Gabon performance evaluation using the Overall model and Gabon data extracted from the Overall test sets			L	SW: 0.67 (0.17)	CHI3L1: 0.57 (0.03)	+ 18%
			S	RFA: 0.81 (0.12)	NGAL: 0.6 (0.06)	+35%[$]
			E	Not sufficient data		
Malawi						
diastolic blood pressure CHI3L1 IP-10 fever duration Gal-9 C2 pulse rate respiratory rate temperature	respiratory rate, sPLA	respiratory rate, sPLA	L	RFA/SW: 0.57 (0.06)	IP-10: 0.57 (0.05)	-
			S	SW/RFA: 0.62 (0.09)	HCC2_PL: 0.62 (0.06)	-
			E	SW/RFA: 0.61 (0.06)	IP-10: 0.66 (0.09)	-7%

E, electronic classification group; S, strict classification group; L, loose classification group; RF, Rulefit; RFA, logistic recursive feature addition; SW, stepwise logistic regression. Green (gain, i.e. multivariate models have better performances than univariate models); red (loss, i.e. univariate models have better performances than multivariate models).
*Multivariate performances for Gabon are computed using the Overall population-trained model as a predictor model and tested with Gabon data. [$]This output has to be considered an outlier due to biomarker data imbalance between pipeline data and the available Gabon data set.

Supplementary Table 21: Multivariate analysis – malaria population; haematological and protein biomarkers

Protein + haematological biomarkers						
Overall						
Multivariate models' variables			**Classification group**	**Best multivariate model/models: mean (SD) AUROC**	**Best host-biomarker: mean (SD) AUROC**	**Multivariate AUROC gain/loss (%)**
Rulefit	**Logistic - RFA**	**Logistic - SW**				
AGP_Pl diastolic blood pressure Gal-9 C2 LBP. NGAL neutrophil count respiratory rate temperature pulse rate fever duration	country WBC count	country, Wbc_c,	L	SW/RFA: 0.68 (0.04)	neutrophil count: 0.65 (0.05)	+5%
			S	RFA/SW: 0.66 (0.05)	neutrophil count: 0.6 (0.08)	+10%
			E	RFA/SW: 0.66 (0.11)	HCC2_PL: 0.63 (0.1)	+5%
Gabon*						
Gabon performance evaluation using the Overall model and Gabon data extracted from the Overall test sets			**L**	**RFA/SW: 0.66 (0.18)**	neutrophil count: 0.65 (0.05)	+1%
			S	RFA/SW: 0.7 (0.2)	neutrophil count: 0.6 (0.08)	+17%
			E	Not sufficient data		
Malawi						
CHI3L1 IP-10 Gal-9 C2 neutrophil count respiratory rate temperature	C2 neutrophil count WBC count	WBC count	**L**	**SW: 0.69 (0.05)**	**WBC count: 0.69 (0.05)**	-
			S	RFA: 0.73 (0.07)	WBC count: 0.69 (0.07)	+6%
			E	RFA: 0.72. (0.1)	lymphocyte count: 0.67 (0.05)	+7%

diastolic blood pressure pulse rate fever duration						

E, electronic classification group; S, strict classification group; L, loose classification group; RF, Rulefit; RFA, logistic recursive feature addition; SW, stepwise logistic regression. Green (gain, i.e. multivariate models have better performances than univariate models); red (loss, i.e. univariate models have better performances than multivariate models).

*Multivariate performances for Gabon are computed using the Overall population-trained model as a predictor model and tested with Gabon data.

Supplementary Material References

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