Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Seydel KB, Kampondeni SD, Valim C, et al. Brain swelling and death in children with cerebral malaria. N Engl J Med 2015;372:1126-37. DOI: 10.1056/NEJMoa1400116

Supplementary Appendix

Title: Brain Swelling Predicts Death in Pediatric Cerebral Malaria

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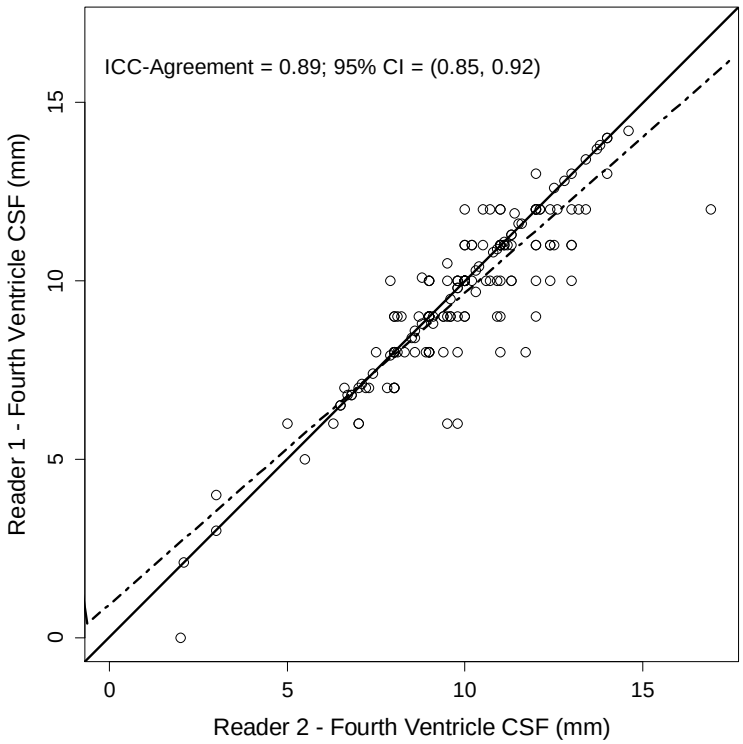
Figure S1 – Scatterplot of concordance between MRI readings of two independent radiologists. Concordance between the two readings in both post-pontine (fourth ventricle) CSF (A) and pre-pontine CSF (B) was good. Straight solid line represents the line of perfect agreement, dashed line represents the regression line of observed agreement. Also shown is the intraclass correlation coefficient (ICC) of agreement with 95% confidence interval (CI).

A)



B)

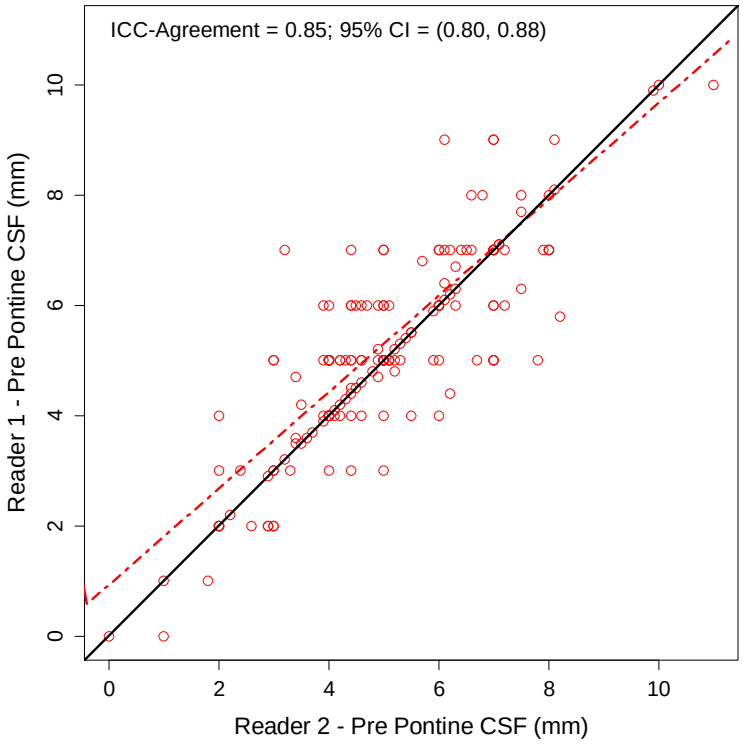


Table S1 — Association of clinical and laboratory findings at admission with the subsequent risk of death in patients with retinopathy-positive cerebral malaria who underwent an admission MRI scan.

	Survivors (N = 143)	Deaths (N = 25)	P *
Demographic			
Age (months), *mean ± SD*	**52 ± 27**	**50 ± 30**	**0.76**
Gender (male), *n (%)*	**74 (52%)**	**11 (44%)**	**0.52**
MUAC, *mean ± SD*	**15.1 ± 1.7**	**14.9 ± 1.6**	**0.57**
Weight (kg), *mean ± SD*	**14 ± 5**	**13 ± 4**	**0.39**
Height (cm), *mean ± SD*	**98 ± 16**	**95 ± 14**	**0.39**
History of Present Illness			
Duration of fever (hrs) prior to admission, *mean ± SD*	**64.2 ± 32.3**	**55.3 ± 31.6**	**0.21**
Duration of coma (hrs) prior to admission, *mean ± SD*	**15.6 ± 20.8**	**14.5 ± 15.4**	**0.76**
History of seizures prior to admission, *n (%)*	**123 (88%)**	**20 (80%)**	**0.32**
Clinical Examination on Admission			
Temperature (°C), *mean ± SD*	**38.8 ± 1.2**	**38.8 ± 1.3**	**0.94**
Pulse rate (beats/min), *mean ± SD*	**152 ± 24**	**156 ± 26**	**0.47**

Respiratory rate (/min), *mean ± SD*	**44 ± 11**	**47 ± 12**	**0.20**
Liver size (cm below costal margin), *mean ± SD*	**1.4 ± 1.6**	**1.7 ± 1.6**	**0.32**
Jaundice, *n (%)*	**12 (8%)**	**3 (12%)**	**0.47**
Spleen size (cm below costal margin), *mean ± SD*	**0.9 ± 1.4**	**0.7 ± 1.2**	**0.73**
Nasal flaring, *n (%)*	**20 (14%)**	**6 (24%)**	**0.23**
Deep breathing, *n (%)*	**29 (20%)**	**5 (20%)**	**1.00**
Blantyre Coma Score, *n (%)*			**0.09**
0	**13 (9%)**	**2 (8%)**	
1	**71 (49%)**	**15 (60%)**	
2	**59 (41%)**	**8 (32%)**	
Neck rigidity, *n (%)*	**5 (3%)**	**1 (4%)**	**1.00**
Seizures at time of admission, *n (%)*	**28 (20%)**	**4 (16%)**	**0.79†**
Papilledema[@], *n (%)*	**46 (33%)**	**10 (40%)**	**0.50**
CSF opening pressure (mm CSF), *median (IQR)*[&]	**140 (100, 180)**	**170 (119, 230)**	**0.33**
Laboratory Findings on Admission			
Hematocrit (%), *mean ± SD*	**20.8 ± 5.6**	**20.9 ± 4.6**	**0.89**
Severe anemia (hematocrit ≤ 15), *n (%)*	**20 (14%)**	**2 (8%)**	**0.59**

Platelets (x 10^9/dl blood), *median (IQR)*	**54 (34, 87)**	**46 (25, 71)**	**0.17**
Thrombocytopenia (platelets ≤ 150 x 10^9/dl), *n (%)*	**127 (93%)**	**22 (96%)**	**1.0**
Parasitemia (10^3/µl blood), *median (IQR)*	**55778 (12660, 220000)**	**71280 (31680, 528000)**	**0.23**
White blood cell (10^9/ µl blood), *median (IQR)*	**8.4 (6.6, 12.7)**	**11.7 (6.7, 19.4)**	**0.05**
Sodium[#] (mEq/L)	**136.3 ± 7.4**	**136.0 ± 4.7**	**0.89**
Chloride[#] (mEq/L)	**103.5 ± 6.8**	**103.6 ± 4.8**	**0.97**
Potassium[#] (mEq/L)	**4.0 ± 0.7**	**3.8 ± 0.6**	**0.40**
Calcium[#] (mmol/L)	**2.1 ± 0.4**	**2.1 ± 0.4**	**0.98**
Lactate (mmol/l), *mean ± SD*	**6.8 ± 4.2**	**9.8 ± 4.2**	**0.001**
Hyperlactatemia (lactate ≥ 5), *n (%)*	**82 (58%)**	**21 (84%)**	**0.31**
Blood Glucose (mmol/l), *mean ± SD*[%]	**6.3 ± 2.9**	**6.8 ± 3.5**	**0.52**
Hypoglycemia at or immediately prior to admission, *n (%)*	**31 (22%)**	**7 (28%)**	**0.48**
CSF white cell count ≥5, *n (%)* [&]	**13 (11%)**	**3 (20%)**	**0.42 †**
Median (IQR) of values ≥ 5	**7 (5, 10)**	**9 (6, 12)**	**0.70**
HIV positive ^	**2 (9.5%)**	**17 (13.1%)**	**0.75 †**

SD = standard deviation, MUAC = mid-upper arm circumference, IQR = interquartile range
* P-values were estimated through t-tests when reporting means, Wilcoxon rank sum tests when reporting medians, and Pearson X^2 when reporting proportions, except where marked with † when Fisher Exact tests were used.
[@] Calculated on 164 patients (25 deaths, 139 survivors)
[&] A total of 107 children who survived and 15 children who died had CSF analysis.
[#] Calculated on 148 patients (*12/25 deaths, 136/143 survivors)*

[%] Calculated on those patients who had not received dextrose prior to admission, n=115 for survivors and 19 for deaths.
^ Calculated on patients who underwent HIV testing, n=130 for survivors and 21 for deaths.
No CSF or blood cultures resulted in growth of a pathogen.

Table S2. MR Protocols. Shaded areas denote scan sequences that remained constant for all three years.

2009	**Sag T1 Flair ***	**Axial T1 ***	**Axial T2 ***	**Cor T2 ***	**DWI ***	**Axial T2 Flair**	**Axial GRE**	**Axial PD**
Parameters					b=200			
Acquisition mode	2D	2D	2D	2D	2D	2D	2D	2D
Acquisition sequence	T1 Flair	FSE-XL	FRFSE-XL	FRFSE-XL	EPI	T2 Flair	GRE	FREFSE-XL
TE (ms)	24	20	123	110	140	100	16.4	35
TR (ms)	2200	550	3300	3525	8000	7850	500	3150
TI (ms)	750					750		11
Echo Train Length		11	11	12				
Excitation Flip Angle(degrees)							35	
No. of excitations	1	3	3	3	1	3	3	3
FOV	25	18.75	18.75	18.75	18.75	25	18.75	18.75
Matrix Size	256x128	288x160	256x128	288x192	64x64	256x128	256x128	384x256
No. of slices	20	26	24	26	24	24	24	24
Slice Thickness (mm)	6.0	6.0	6.0	7.0	6.0	6.0	6.0	6.0
Slice Gap (mm)	1.5	0.3	0.3	1.0	1.0	0.3	0.3	0.3

2010	**Sag T1 Flair**	**Axial T1**	**Axial T2**	**Cor T2**	**DWI**	**DWI**	**Axial GRE**
Parameters					b=200	b=900	
Acquisition mode	2D	2D	2D	2D	2D	2D	2D
Acquisition sequence	T1 Flair	FSE-XL	FRFSE-XL	FRFSE-XL	EPI	EPI	GRE
TE (ms)	24	20	123	110	140	140	16.4
TR (ms)	2200	550	3300	3525	8000	8000	500
TI (ms)	750						
Echo Train Length		11	11	14			
Excitation Flip Angle(degrees)							35
No. of excitations	1	3	3	3	1	1	3
FOV	25	18.75	18.75	18.75	18.75	18.75	18.75
Matrix Size	256x128	288x160	256x128	288x192	64x64	64x64	256x12
No. of slices	20	26	24	26	24	24	24
Slice Thickness (mm)	6.0	6.0	6.0	7.0	6.0	6.0	6.0
Slice Gap (mm)	1.5	0.3	0.3	1.0	1.0	1.0	0.3

2011	**Sag T1 Flair**	**Axial T1**	**Axial T2**	**Cor T2**	**DWI**	**DWI**	**DWI**	**DWI**	**Axial T2**
Parameters			straight		b=200 straight	b=900 straight	sag	coronal	oblique
Acquisition mode	**2D**	**2D**	**2D**	**2D**	**2D**	**2D**	**2D**	**2D**	**2D**
Acquisition sequence	**T1 Flair**	**FSE-XL**	**FRFSE-XL**	**FRFSE-XL**	**EPI**	**EPI**	**EPI**	**EPI**	**FRFSE-XL**
TE (ms)	**24**	**20**	**123**	**110**	**140**	**140**	**140**	**140**	**123**

TR (ms)	2200	550	3300	3525	8000	8000	8000	8000	3300
TI (ms)	750								
Echo Train Length		11	11	14					11
No. of excitations	1	3	3	3	1	1	1	1	3
FOV	25	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Matrix Size	256x128	288x160	256x128	288x192	64x64	64x64	64x64	64x64	256x128
No. of slices	20	26	24	26	24	24	24	24	24
Slice Thickness (mm)	6.0	6.0	6.0	7.0	6.0	6.0	6.0	6.0	6.0
Slice Gap (mm)	1.5	0.3	0.3	1.0	1.0	1.0	1.0	1.0	0.3

Table S3 – Agreement between readings of two independent radiologists of MRI features

MRI Feature	Overall Agreement N (%)	Kappa (95% CI)*
Volume Indicators		
Severely Increased Brain Volume*	145 (87%)	0.73(0.61-0.83)
Fourth Ventricle CSF	see ICC	see Supplementary Figure 1a
Pre-pontine CSF	see ICC	see Supplementary Figure 1b
T2 Changes		
Subcortical white matter	136 (81%)	0.58 (0.45-0.71)
Periventricular white matter	130 (79%)	0.55 (0.42-0.68)
Thalamus	127 (76%)	0.53 (0.42-0.66)
Cortical gray matter	134 (81%)	0.38 (0.22-0.54)
Posterior fossa	129 (79%)	0.53 (0.39-0.67)
Corpus callosum	147 (89%)	0.78 (0.69-0.88)
Pons	128 (78%)	0.57 (0.45-0.69)
Brainstem	133 (80%)	0.60 (0.48-0.73)
Basal ganglia	148 (88%)	0.61 (0.46-0.77)
DWI changes	143 (89%)	0.78 (0.69-0.88)
Supratentorial gray matter	158 (96%)	0.82 (0.68-0.96)
Posterior fossa	159 (95%)	0.56 (0.29-0.82)
Corpus callosum	144 (89%)	0.77 (0.67-0.87)
Basal ganglia	138 (83%)	0.62 (0.49-0.75)
Anatomic Comparisons (T2 and/or DWI		
Posterior fossa	120 (71%)	0.49 (0.36-0.61)
T/P/O predominance	154 (91%)	0.65 (0.49-0.82)
Patchy lesions	125 (74%)	0.40 (0.26-0.54)

MRI = magnetic resonance imaging; CI = confidence interval; CSF = cerebrospinal fluid.
* When the feature had three categories, we estimated weighted Kappas using linear weights.

Table S4 – Comparison of clinical and laboratory findings of retinopathy-positive CM patients who did undergo MRI and those who died prior to undergoing MRI

	Underwent MRI (N = 168)	Died prior to MRI (n=15)	P *
Demographic			
Age (months), *mean ± SD*	**51 ± 28**	**50 ± 34**	**0.81**
Gender (male), *n (%)*	**85 (49%)**	**9 (60%)**	**0.48**
MUAC, *mean ± SD*	**15 ± 2**	**15 ± 2**	**0.96**
Weight (kg), *mean ± SD*	**14 ± 5**	**13 ± 5**	**0.72**
Height (cm), *mean ± SD*	**98 ± 16**	**96** ± 19	**0.64**
History of Present Illness			
Duration of fever prior to admission (hrs), *median, IQR*	**48 (48, 72)**	**48 (27, 48)**	**0.06**
Duration of coma prior to admission (hrs), *median, IQR*	**8 (5, 18)**	**6 (4,7)**	**0.04**
History of seizures prior to admission	**143 (85%)**	**13 (87%)**	**0.61**[#]
Clinical Examination			
Temperature (°C), *median (IQR)*	**38.9 (37.4, 39.6)**	**38.8 (37.9, 39.3)**	**0.53**
Pulse rate (beats/min), *median (IQR)*	**150 (137, 170)**	**154 (136, 181)**	**0.62**
Respiratory rate (/min) *mean ± SD*	**45 ± 11**	**46 ± 9**	**0.78**

Liver size (cm below costal margin), *mean ± SD*	**1.4 ± 1.6**	**1.3 ± 1.9**	**0.73**
Jaundice, *n (%)*	**15 (9%)**	**1 (7%)**	**0.61**
Spleen size (cm below costal margin) *mean ± SD*	**0.8 ± 1.3**	**0.9 ± 1.7**	**0.81**
Nasal flaring *n (%)*	**26 (15%)**	**4 (27%)**	**0.79[#]**
Deep breathing *n (%)*	**34 (20%)**	**7 (47%)**	**0.03**
BCS, *n (%)*			
0	**15 (9%)**	**3 (20%)**	**0.38**
1	**86 (51%)**	**7 (47%)**	
2	**67 (39%)**	**5 (33%)**	
Neck rigidity, *n (%)*	**6 (3%)**	**1 (7%)**	**1.0[#]**
CSF opening pressure (mm CSF), *median (IQR)[&]*	**150 (110, 200)**	**185 (110, 300)**	**0.43**
Laboratory Findings			
Hematocrit (%), *mean ± SD*	**20.8 ± 5.4**	**22.2 ± 7.2**	**0.38**
Severe anemia (hematocrit ≤ 15), *n (%)*	**22 (13%)**	**3 (20%)**	**0.70[#]**
Platelets (10^6/dl blood), *median (IQR)*	**54 (31, 84)**	**51 (18, 88)**	**0.68**
Thrombocytopenia (platelets ≤ 150,000/dl), *n (%)*	**153 (94%)**	**13 (87%)**	**0.64[#]**
Parasitemia (10^3/µl blood), *median (IQR)*	**57920 (15420, 249505)**	**56960 (14180, 166170)**	**0.99**
White blood cell (10^3/ml blood) , *median (IQR)*	**8.5 (6.6, 13.9)**	**10.9 (6.9, 11.7)**	**0.93**

Lactate (mmol/l), *mean ± SD*	**7.3 ± 4.3**	**10.1 ± 4.5**	**<0.05**
Hyperlactatemia (lactate ≥ 5), *n (%)*	**102 (61%)**	**12 (80%)**	**0.14[#]**
Hypoglycemia at or immediately prior to admission, *n (%)*	**14 (8%)**	**1 (7%)**	**1.0[#]**
CSF white cell count >5, *n (%)*	**18 (11%)**	**1 (11%)**	**1.0[#]**

* P-values were estimated through t-tests when reporting means, Wilcoxon rank sum tests when reporting medians, and Pearson X^2 or Fisher Exact test (marked by a [#]) when reporting proportions.