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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Samuels THA, Molloy SF, Lawrence DS, et al. Personalised risk-prediction tools for cryptococcal meningitis mortality to guide treatment stratification in sub-Saharan Africa: a prognostic modelling study based on pooled analysis of two randomised controlled trials. *Lancet Glob Health* 2025; **13:** e920–30.

Personalised risk prediction tools for cryptococcal meningitis mortality to guide treatment stratification: a pooled analysis of two randomised-controlled trials

Supplementary Appendix

Supplementary Methods

Sample size estimation

A total of 243/1488 participants (16.3%) reached the primary outcome (2-week mortality). There are no current widely used tools to predict mortality in HIV-associated cryptococcal meningitis. In other infectious diseases, the 4C mortality score is a widely used prediction tool to predict in-hospital mortality in COVID-19[1] and achieved a C-statistic of 0.8 in a recent individual participant data meta-analysis.[2] Based on this target C-statistic of 0.8, we estimated that 28 parameters could be considered for inclusion in the final model.[3]

Multiple Imputation

Multiple imputation was performed assuming missingness at random (i.e. missingness can be explained by the observed data), using the aRegImpute function in R[4,5]. All predictors, including transformations, considered for the final model were included in the imputation model to ensure compatibility. All primary analyses were performed in each multiply imputed dataset; parameters were pooled using Rubin's rules[6].

XGBoost modelling

XGBoost is an ensemble, gradient boosted decision tree method where a series of decision trees is constructed, with each tree seeking to sequentially minimise errors from preceding trees.

A range of XGBoost hyper-parameters were evaluated in the development dataset using a grid search, where default parameters were varied (Supplementary Table 2). We identified the best combination of hyper-parameters using 10-fold cross-validation in the development set, defined as the highest C-statistic.

A common critique of machine learning methods such as XGBoost is that they represent "black box" methods, where the plausibility of predictor-outcome associations cannot readily be evaluated.[7] To mitigate this criticism, we explored predictor-outcome associations in the final XGBoost model by using the model object to make predictions across a range of values for each predictor in turn, while fixing all other variables to the median (for continuous variables) or modal (for factor variables) values. We then plotted these associations visually for each variable. Furthermore, since machine learning models such as decision trees can include any number of interactions without prior specification, we also examined the presence of two-way interactions by varying 2 variables at a time. The first of these predictors was included as the x-axis, while the second was coloured as a factor (using the midpoint of quartiles from the observed data for continuous predictors). This enabled construction of a matrix of plots visualising XGBoost predictor-outcome associations, while examining for all possible two-way interactions.

The XGBoost model was trained and validated using stacked development and validation datasets including the 10 multiply imputed sets, respectively. Variable importance in the resulting model is shown in Supplementary Table 10.

Code Sharing

All analytical code used to generate the results in this manuscript will be made publicly available in a GitHub repository, including all R packages used with versions.

References

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required for developing a clinical prediction model. BMJ. 2020 Mar 18;368.

4. Gupta RK, Harrison EM, Ho A, et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. *The Lancet Respiratory Medicine* 2021; **9**(4): 349-59.

5. Harrell Jr FE et al. Harrell Miscellaneous. R Package “Hmisc”. Version 5.1-0. CRAN: Contributed Packages. Comprehensive R Archive Network (CRAN); 2023. p. 1–487..

6. Rubin DB. Multiple Imputation for Nonresponse in Surveys. Hoboken: John Wiley & Sons; 2004.

7. Murdoch WJ, Singh C, Kumbier K, Abbasi-Asl R, Yu B. Definitions, methods, and applications in interpretable machine learning. Proc Natl Acad Sci U S A. 2019 Oct 29;116(44):22071–80.

Supplementary Results

Supplementary Table 1: Candidate predictors for multivariable models

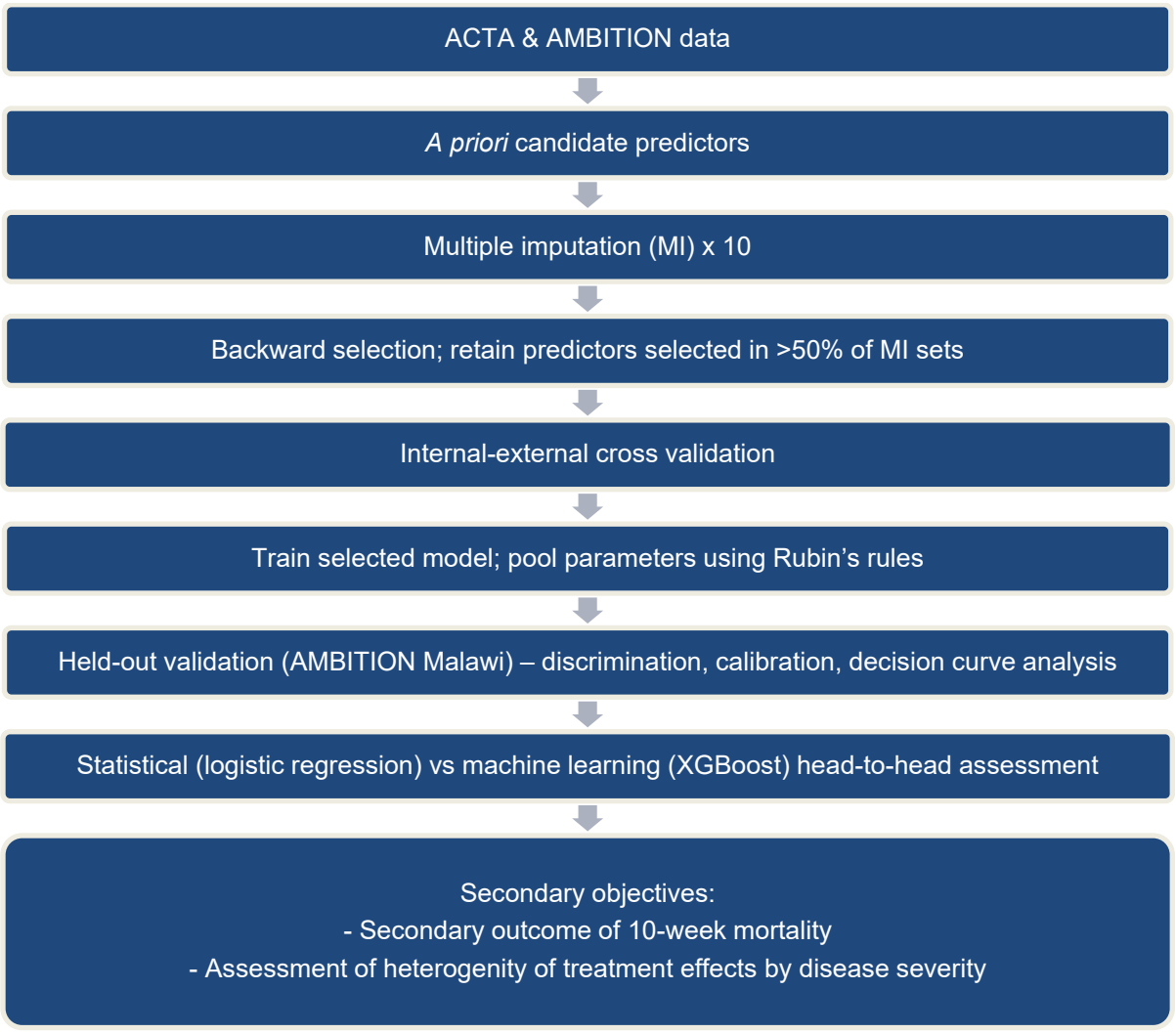
Predictors were rationalized *a priori* in accordance with the number of parameters considered for inclusion in the sample size calculation.

Predictor	**Model Inclusion**	**Variable type**	**Parameters included (including spline transformations)**
Age	Basic and Research	Continuous	2
Sex	Basic and Research	Binary	1
Weight	Basic and Research	Continuous	2
Seizures	Basic and Research	Binary	1
Glasgow Coma Score (GCS)	Basic and Research	Factor (15, 10-14, <10)	2
Eastern Cooperative Group (ECOG) performance status	Basic and Research	Factor (0, 1, 2, 3, 4)	4
Neutrophil cell count	Basic and Research	Continuous	2
Haemoglobin	Basic and Research	Continuous	2
CD4 count	Research only	Continuous	2
Cerebrospinal fluid (CSF) opening pressure	Research only	Continuous	2
CSF white cell count (WCC)	Research only	Continuous	2
Fungal burden in CSF	Research only	Continuous (log base 10 transformed)	2
Treatment arm	Basic and Research	Factor (Liposomal-Amphotericin-B Ambition regimen and the 1-week Amphotericin-B + Flucytosine arms from both ACTA and Ambition-cm trials, 1 week Amphotericin-B + Fluconazole, 2 weeks Amphotericin-B + Flucytosine, 2 weeks Amphotericin-B + Fluconazole, Flucytosine + Fluconazole oral regimen)	4

Supplementary Table 2: Hyper-parameters for XGBoost

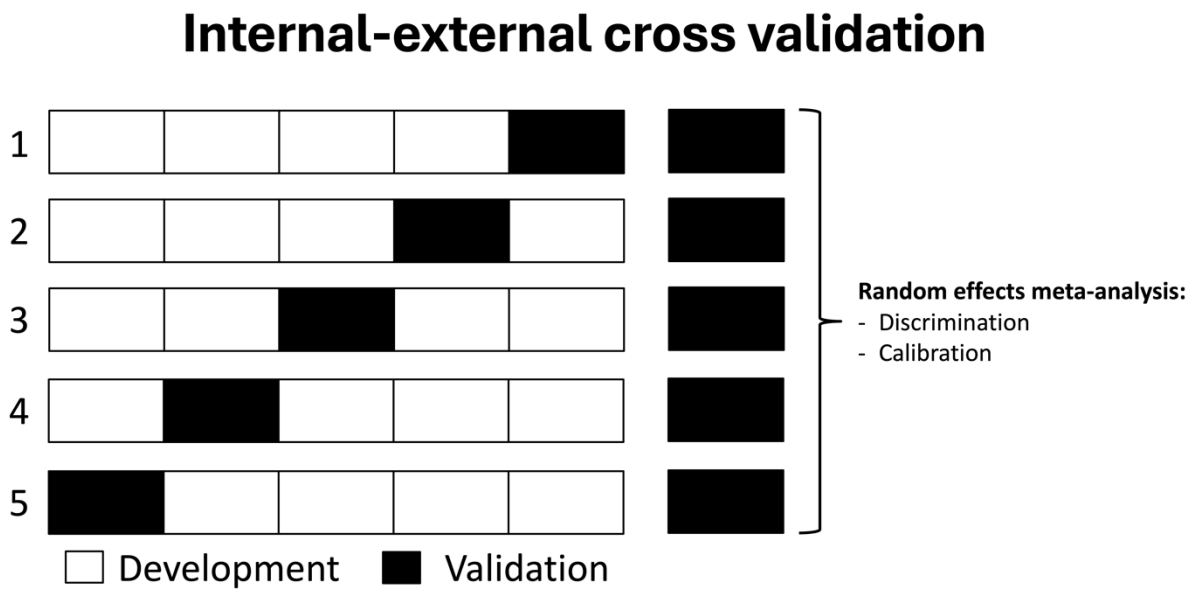
Parameter	Default values	Grid search values	Final selected value
nrounds	100	50, 100, 150	50
eta	6	4, 6, 8	0.1
max_depth	0.3	0.1, 0.3, 0.5	4
gamma	0	0, 1	0
colsample_bytree	1	0.8, 1	0.8
min_child_weight	1	1, 2, 3	2
subsample	1	0.8, 1	0.8

Supplementary Figure 1: Schematic showing analysis pipeline.

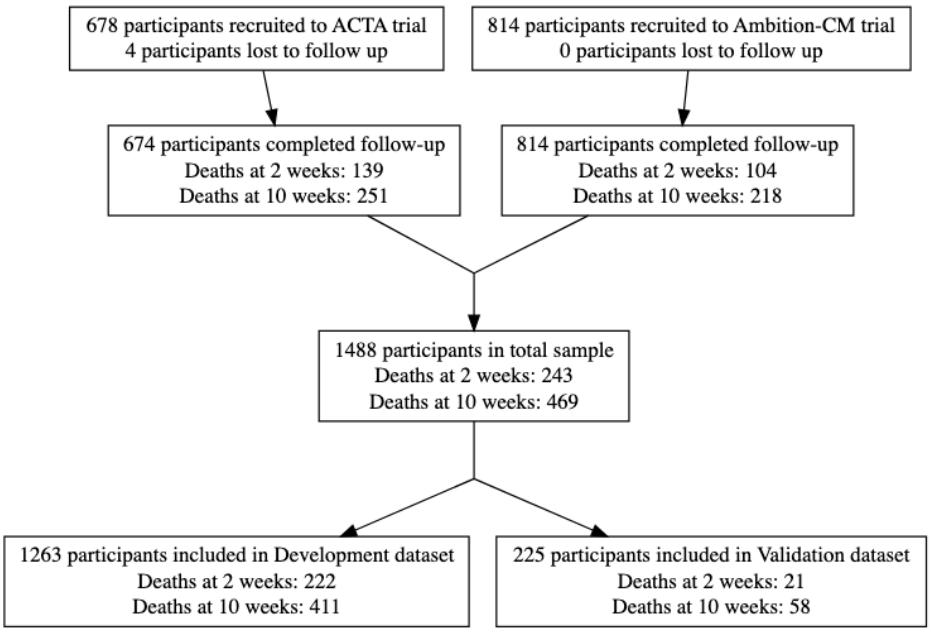


Supplementary Figure 2: Internal-External Cross-Validation

Schematic demonstrating the approach, including five example datasets for illustration.



Supplementary Figure 3: Participant Flow Diagram



Supplementary Table 3: Participant characteristics split by development and validation datasets

ECOG = Eastern Cooperative Oncology Group performance status; GCS = Glasgow Coma Scale; CSF = cerebrospinal fluid.

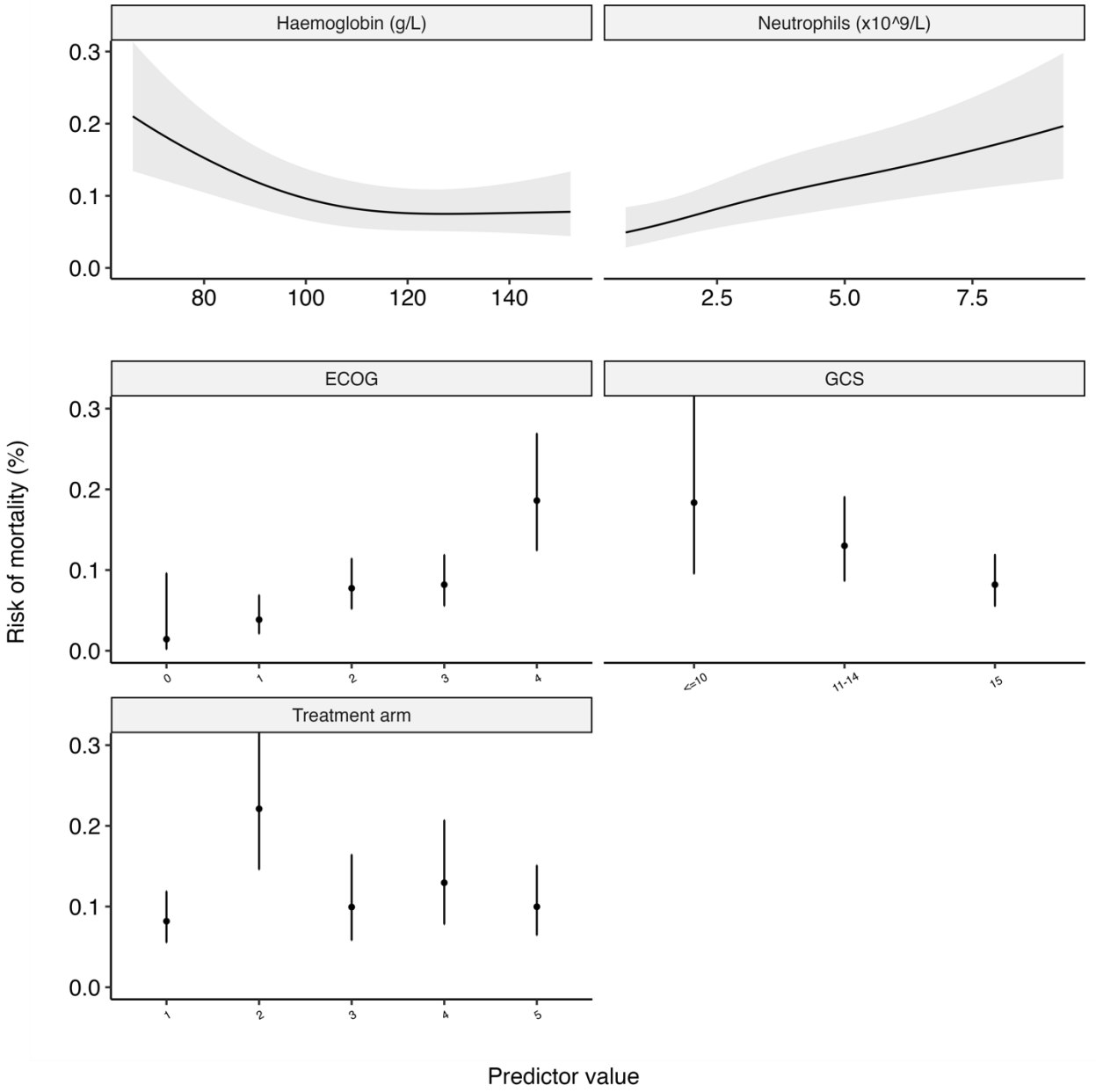
Characteristic	**Overall**, N = 1,488[1]	**Development**, N = 1,263[1]	**Validation**, N = 225[1]
Mortality at 2 weeks			
Alive	1,245 (84%)	1,041 (82%)	204 (91%)
Died	243 (16%)	222 (18%)	21 (9%)
Age; years	37 (32 to 43)	37 (32 to 43)	38 (32 to 44)
Sex			
Female	612 (41%)	526 (42%)	86 (38%)
Male	876 (59%)	737 (58%)	139 (62%)
Weight; kg	52 (47 to 60)	52 (47 to 60)	53 (46 to 60)
Missing	15	15	0
Seizures	204 (14%)	176 (14%)	28 (12%)
Missing	4	4	0
Treatment arm			
Ambition regimen	407 (27%)	294 (23%)	113 (50%)
1wk AmBd+5FC	518 (35%)	406 (32%)	112 (50%)
1wk AmBd+FLU	111 (7%)	111 (9%)	0 (0%)
2wks AmBd+5FC	115 (8%)	115 (9%)	0 (0%)
2wks AmBd+FLU	112 (8%)	112 (9%)	0 (0%)
FLU+5FC	225 (15%)	225 (18%)	0 (0%)
GCS score			
15	1,095 (74%)	929 (74%)	166 (74%)
11-14	327 (22%)	282 (22%)	45 (20%)
<=10	66 (4%)	52 (4%)	14 (6%)
ECOG performance status			
Normal	64 (4%)	57 (5%)	7 (3%)
Restricted activity	256 (17%)	217 (17%)	39 (17%)
Ambulatory	339 (23%)	299 (24%)	40 (18%)
Limited self-care	512 (34%)	425 (34%)	87 (39%)
Bedbound	316 (21%)	264 (21%)	52 (23%)

Characteristic	**Overall**, N = 1,488[1]	**Development**, N = 1,263[1]	**Validation**, N = 225[1]
Missing	1	1	0
White cell count; x10^9/L	4.20 (3.10 to 5.60)	4.20 (3.10 to 5.69)	4.30 (3.10 to 5.50)
Missing	12	12	0
Neutrophil count; x10^9/L	2.50 (1.66 to 3.80)	2.50 (1.69 to 3.86)	2.29 (1.64 to 3.33)
Missing	31	30	1
Haemoglobin; g/L	110 (96 to 126)	110 (96 to 126)	112 (97 to 125)
Missing	10	10	0
CD4 count; x10^6/L	27 (10 to 62)	26 (10 to 60)	35 (12 to 67)
Missing	88	73	15
CSF opening pressure; cmH20	22 (13 to 33)	22 (14 to 35)	20 (12 to 30)
Missing	54	54	0
CSF cell count; WBC per mm3	4 (1 to 37)	4 (1 to 32)	17 (3 to 68)
Missing	59	46	13
log(CSF quantitative culture)	4.79 (3.08 to 5.66)	4.81 (3.19 to 5.67)	4.61 (2.73 to 5.57)
Missing	40	40	0

[1]n (%); Median (25% to 75%)

Supplementary Figure 4: Multivariable associations between selected predictors and outcome in basic primary model

Continuous variables were modeled using restricted cubic splines. The final model parameters are pooled across multiply imputed datasets (total sample size for model development = 1,263 participants). For continuous variables, black lines represent point estimates and grey shaded regions represent 95% confidence intervals. For categorical variables, black dots represent point estimates and black lines represent 95% confidence intervals. Treatment arm 1 through 5 represent 1) the liposomal-amphotericin-B Ambition regimen and the 1-week amphotericin-B + flucytosine (1wk AmBd + 5FC) arms from both ACTA and Ambition-cm trials, 2) 1 week amphotericin-B + fluconazole, 3) 2 weeks amphotericin-B + flucytosine, 4) 2 weeks amphotericin-B + fluconazole and 5) flucytosine + fluconazole oral combination regimen, respectively. ECOG = Eastern Cooperative Oncology Group performance status; GCS = Glasgow Coma Scale.



Supplementary Table 4 and 5: Pooled model parameters for basic and research models

Relationships between independent predictors and outcome are reported as model coefficients. ECOG = Eastern Cooperative Oncology Group performance status; CSF = cerebrospinal fluid; QCC = quantitative cryptococcal culture; AmBd = Amphotericin B deoxycholate; 5FC = Flucytosine; FLU = Fluconazole.

Supplementary Table 4: Basic Model

Variable	Estimate	95% Confidence Int.
Intercept	-2.07	-4.51 to 0.37
Glasgow Coma Score: 11-14	0.52	0.12 to 0.91
Glasgow Coma Score: ≤10	0.92	0.24 to 1.61
ECOG: Restricted activity	1.02	-1.05 to 3.08
ECOG: Ambulatory	1.76	-0.26 to 3.77
ECOG: Limited self-care	1.82	-0.2 to 3.83
ECOG: Bedbound	2.76	0.73 to 4.78
Treatment: 1wk AmBd+FLU	1.16	0.65 to 1.66
Treatment: 2wk AmBd+5FC	0.21	-0.33 to 0.76
Treatment: 2wk AmBd+FLU	0.51	-0.03 to 1.05
Treatment: 5FC+FLU	0.22	-0.22 to 0.66
Neutrophils	0.32	0.05 to 0.59
Neutrophils (spline 1)	-0.21	-0.56 to 0.14
Haemoglobin	-0.03	-0.04 to -0.01
Haemoglobin (spline 1)	0.02	0 to 0.04

Restricted cubic spline knot positions are:

- Neutrophils = 1.1, 2.5, 5.6;
- Haemoglobin = 83, 110, 137.

Supplementary Table 5: Research Model

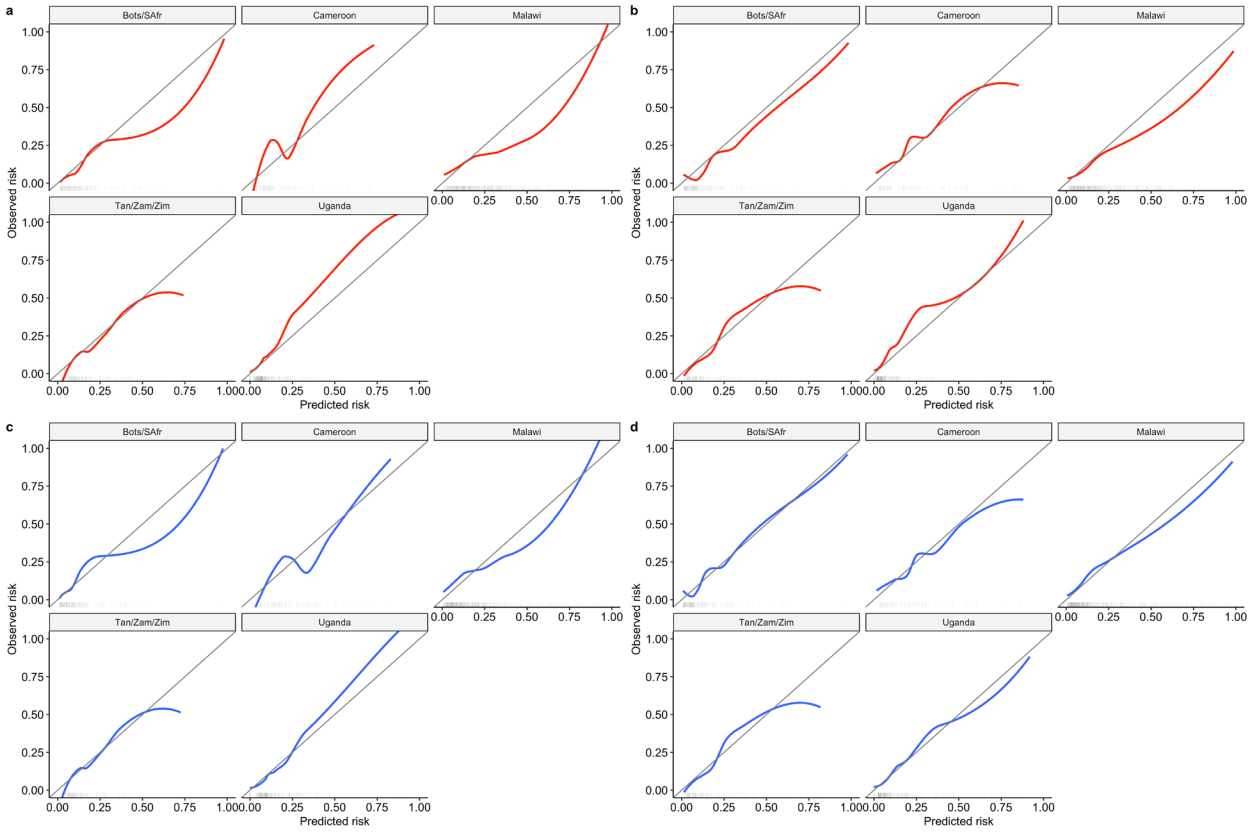
Variable	Estimate	95% Confidence Int.
Intercept	-1.70	-4.23 to 0.83
Glasgow Coma Score: 11-14	0.55	0.13 to 0.96
Glasgow Coma Score: ≤10	1.17	0.45 to 1.89
ECOG: Restricted activity	0.93	-1.15 to 3
ECOG: Ambulatory	1.69	-0.34 to 3.71
ECOG: Limited self-care	1.67	-0.35 to 3.7
ECOG: Bedbound	2.60	0.56 to 4.64
Treatment: 1wk AmBd+FLU	1.05	0.52 to 1.58
Treatment: 2wk AmBd+5FC	0.18	-0.39 to 0.74
Treatment: 2wk AmBd+FLU	0.42	-0.15 to 1
Treatment: 5FC+FLU	0.18	-0.28 to 0.64
Neutrophils	0.26	-0.01 to 0.54
Neutrophils (spline 1)	-0.11	-0.48 to 0.25
Haemoglobin	-0.03	-0.05 to -0.02
Haemoglobin (spline 1)	0.02	0 to 0.04
CSF Opening Pressure	0.00	-0.03 to 0.03
CSF Opening Pressure (spline 1)	0.02	-0.02 to 0.05
CSF QCC (log)	-0.26	-0.47 to -0.04
CSF QCC (log) (spline 1)	0.50	0.31 to 0.7

Restricted cubic spline knot positions are:

- Neutrophils = 1.1, 2.5, 5.6;
- Haemoglobin = 83, 110, 137;
- CSF Opening Pressure = 8, 22, 45;
- CSF QCC (log) = 0.7, 5, 6.3.

Supplementary Figure 5: Pooled calibration plots across multiply imputed development datasets, both before and after recalibration of intercepts to country of origin.

a) basic model; b) research model; c) basic model post-recalibration; d) research model post-recalibration. Plots in red are before recalibration and plots in blue are post-recalibration. Calibration is shown using a loess smoother. Rug plots, shown on the x-axis, plot the distribution of predicted risk.



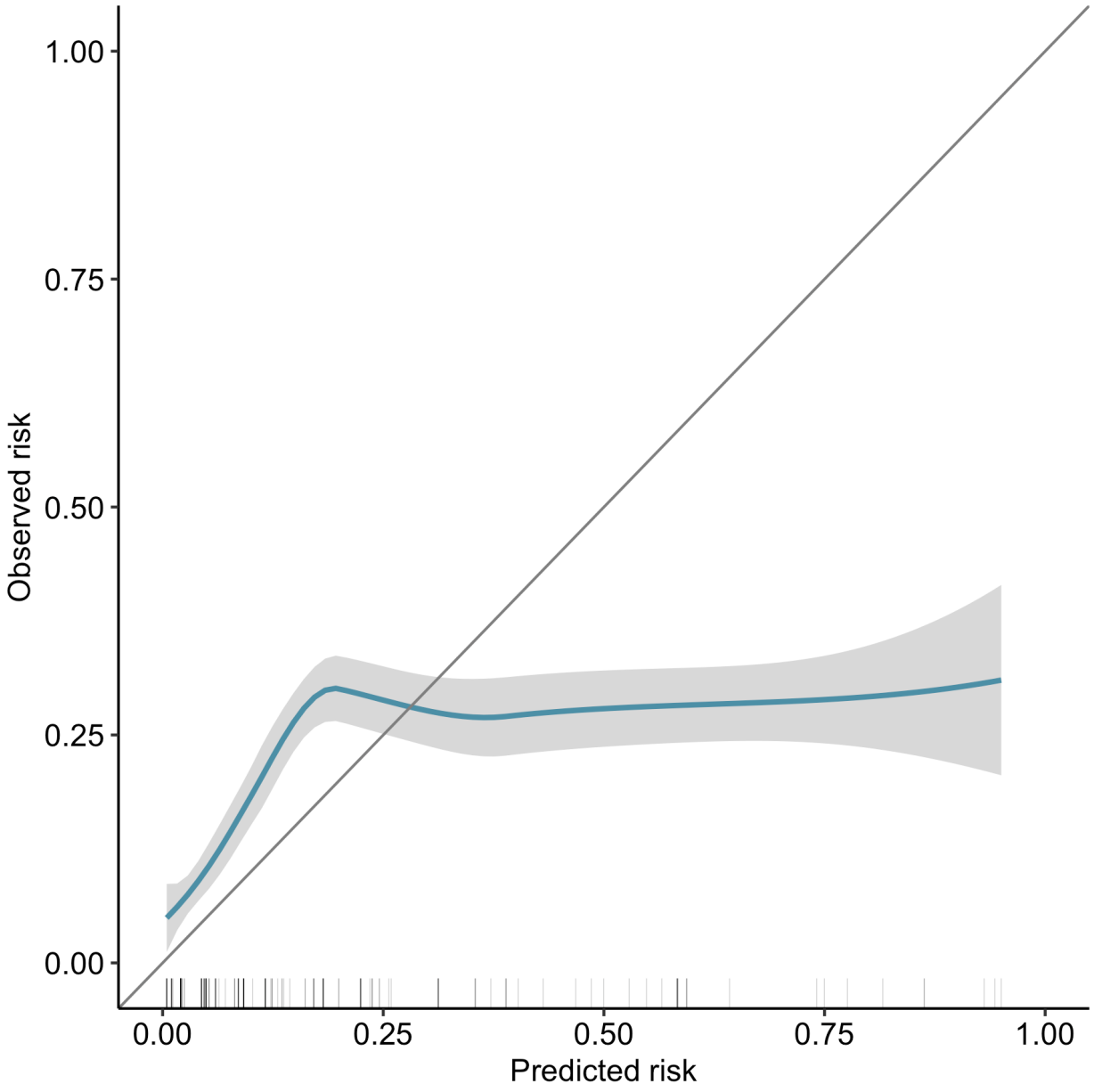
Supplementary Table 6: Discriminatory performance of Basic and Research models in held-out validation data, by age and sex

Basic and Research model discrimination, measured by c-statistic, in the held-out validation data is reported stratified by sex and age. Overall model discrimination is reported for comparison. Dichotomous age categorisation was defined by median age in the validation cohort. 95% confidence intervals are shown in brackets.

Variable	n	Basic	Research
Overall			
-	225	0.78 (0.70 - 0.87)	0.85 (0.79 - 0.92)
Sex			
Female	86	0.75 (0.60 - 0.90)	0.86 (0.73 - 0.99)
Male	139	0.81 (0.70 - 0.91)	0.85 (0.78 - 0.93)
Age			
38+	117	0.72 (0.60 - 0.84)	0.80 (0.68 - 0.92)
<38	108	0.83 (0.71 - 0.94)	0.89 (0.81 - 0.97)

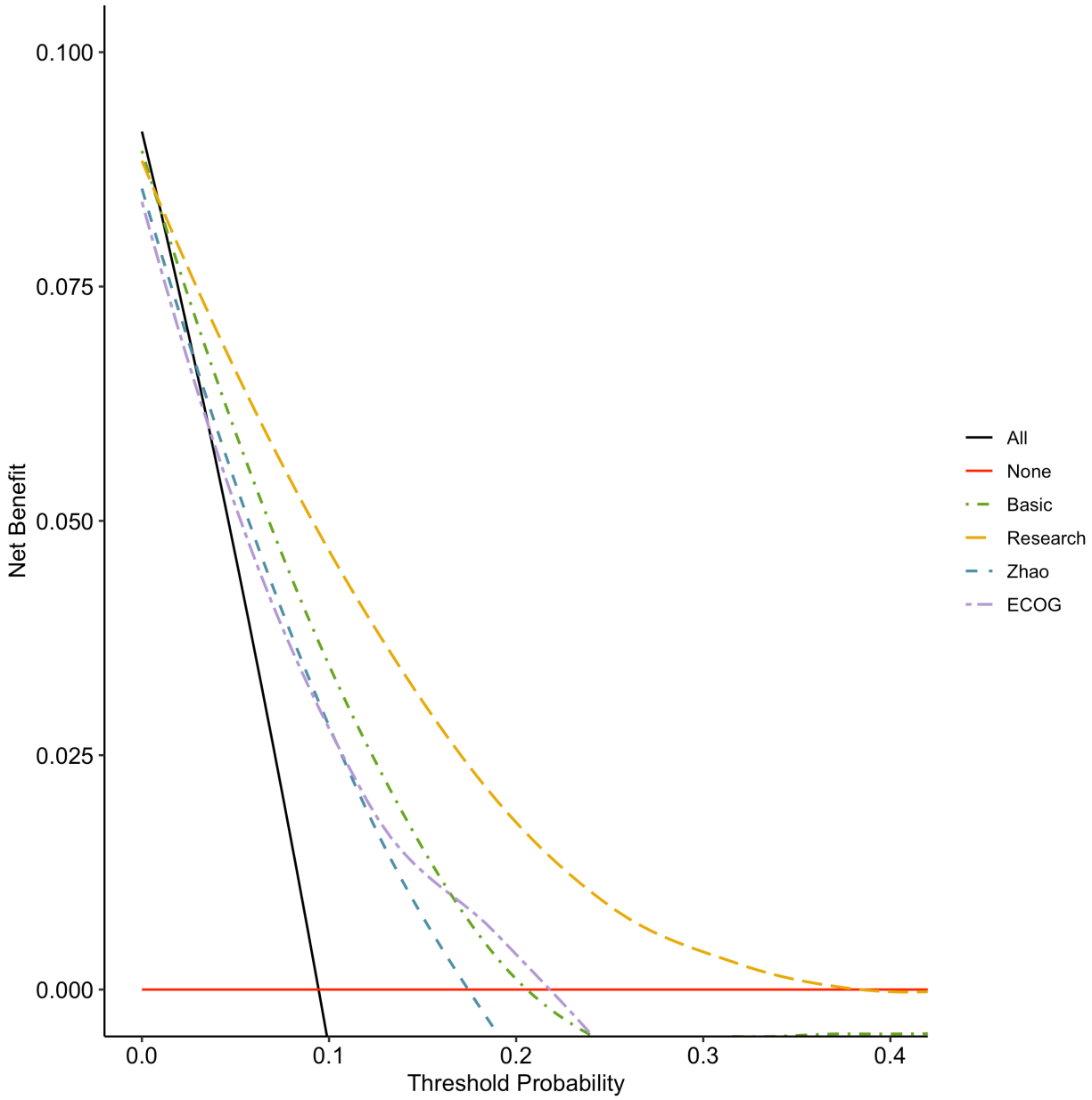
Supplementary Figure 6: Calibration of Zhao et al. model

Calibration is shown using a loess-smoother across multiply imputed datasets. The original variable coefficients were extracted from Zhao et al's model, a model intercept was derived from our validation data, and a regression model constructed to allow the calculation of predicted risk. The rug plot indicates the distribution of predicted risk.



Supplementary Figure 7: Decision Curve Analysis in held-out validation data

Net benefit is shown for each candidate model with loess smoothing, compared to the single best predictor (ECOG), Zhao et al's model, 'treat all' and 'treat none' approaches. As for supplementary figure 6, predictions from a regression model derived from Zhao model coefficients were used to avoid over-optimistic estimates of net benefit.



Supplementary Table 7: Performance of single predictors included in main models in held-out validation data

Individual factors making up both models were assessed for discriminatory ability against held-out validation data from Ambition trial in Malawi. Results sorted by C-statistic. Treatment arm was not included as all participants in the validation cohort received the same treatment factor level (1 week Amphotericin B + flucytosine or high-dose liposomal Amphotericin B). ECOG = Eastern Cooperative Oncology Group performance status; CSF = cerebrospinal fluid.

Predictor	C-statistic[1]
ECOG Performance Status	0.78 (0.71 - 0.85)
CSF Quantitative Culture (log cfu/ml)	0.72 (0.59 - 0.85)
Glasgow Coma Score	0.68 (0.56 - 0.79)
CSF Opening Pressure (cmH20)	0.67 (0.54 - 0.79)
Neutrophils (x10^9/L)	0.66 (0.53 - 0.79)
Haemoglobin (g/L)	0.55 (0.40 - 0.69)

[1]Brackets show 95% confidence intervals

Supplementary Table 8: Discrimination performance of the Basic and Research models compared to best single predictor (ECOG)

C-statistic of the basic and research models are each compared to ECOG alone. C-statistic difference and associated standard errors were calculated using paired DeLong tests on each individual multiply imputed dataset, before being pooled using Rubin's rules.

Model	C-statistic	C-statistic difference	p value
ECOG	0.78 (0.71 - 0.85)	-	-
Basic	0.78 (0.70 - 0.87)	0.01 (-0.04 to 0.05)	0.8
Research	0.85 (0.79 - 0.92)	0.07 (0.00 to 0.15)	0.048

Supplementary Table 9: Performance of single predictors included in main models by country in development data

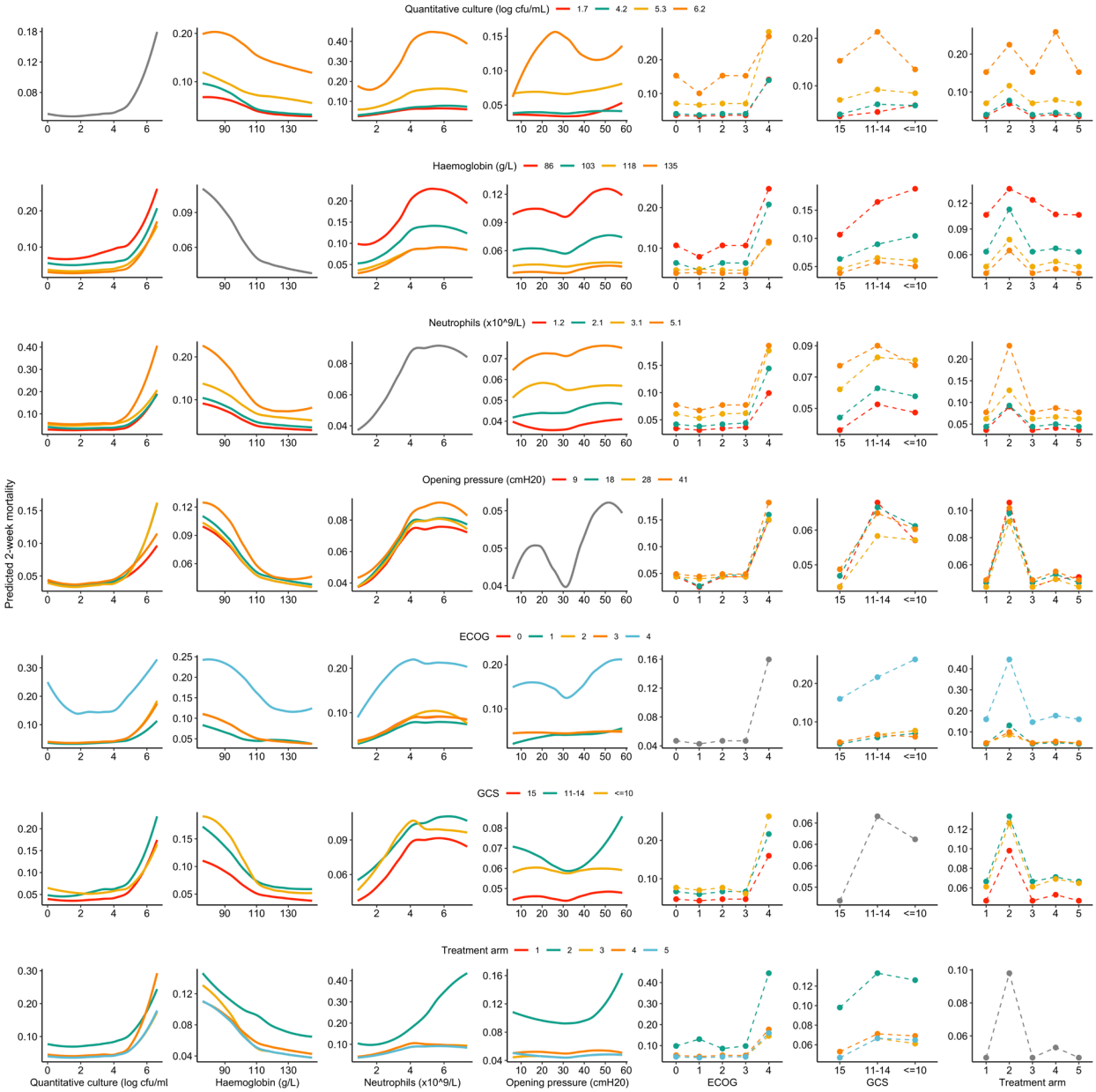
Individual predictors making up both models were assessed for discriminatory ability in an internal-external cross validation approach in the development dataset. GCS = Glasgow Coma Scale; ECOG = Eastern Cooperative Oncology Group performance status; CSF = cerebrospinal fluid; Tan = Tanzania; Zam = Zambia; Zim = Zimbabwe; Bots = Botswana; SAfr = South Africa.

	C-statistic[1]						
Location	ECOG	CSF Quantitative Culture	Neutrophils	GCS	CSF Opening Pressure	Haemoglobin	Treatment
Uganda	0.77	0.59	0.72	0.73	0.60	0.59	0.50
Tan/Zam/Zim	0.67	0.64	0.60	0.58	0.59	0.69	0.65
Malawi	0.66	0.68	0.60	0.62	0.53	0.54	0.55
Cameroon	0.64	0.61	0.63	0.57	0.63	0.54	0.62
Bots/SAfr	0.78	0.67	0.65	0.64	0.59	0.51	0.50

[1]C-statistic results coloured from a lighter to darker blue as C-statistic increases

Supplementary Figure 8: Associations between component variables in machine learning model

Matrix plot in which each column represents associations with that component variable of the model. Plots shown in grey on the diagonal represent the multivariable relationship between that variable and the mortality outcome. Other plots in the column represent the interaction between the column variable and the labelled row variables. Where the row variable is categorical, these interactions are plotted as separate lines representing the relationship between different levels of the row variable. Where the row variable is continuous, these lines represent quartiles of this variable. Treatment arm 1 through 5 represent 1) the liposomal-Amphotericin-B Ambition regimen and the 1-week Amphotericin-B + Flucytosine arms from both ACTA and Ambition-cm trials, 2) 1 week Amphotericin-B + Fluconazole, 3) 2 weeks Amphotericin-B + Flucytosine, 4) 2 weeks Amphotericin-B + Fluconazole and 5) Flucytosine + Fluconazole oral regimen, respectively.



Supplementary Table 10: XGBoost Machine Learning model Variable Importance

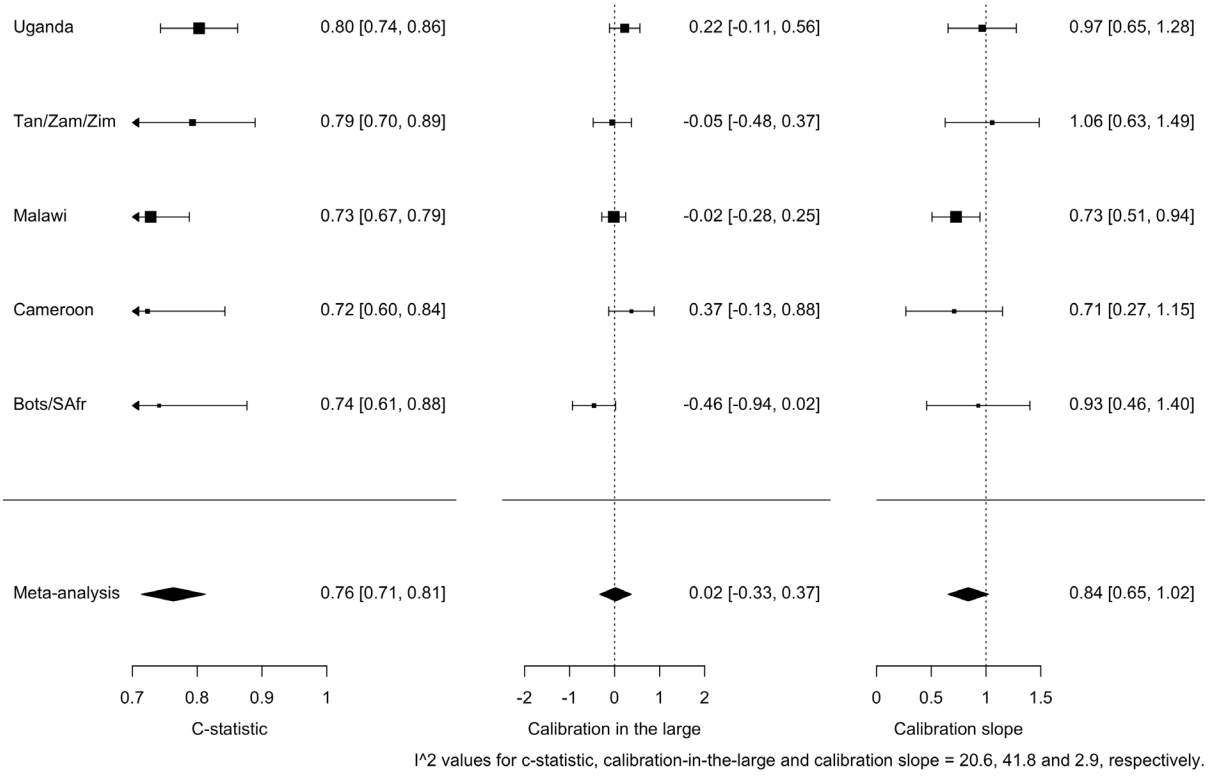
Variable importance is a measure of the contribution of individual variables to the model's predictive accuracy. Relative importance is reported here, where variable importance is scaled relative to the most important variable, which takes a value of 100. A variable of importance 50 contributes 50% as much to the model predictive accuracy as the most important variable. A relative importance of 0 indicates no contribution to predictive accuracy. For continuous variables, relative importance takes a single value. For categorical variables, relative importance takes a value for each of the possible values of that variable, excluding the 'baseline' value; relative importance is reported as a hyphen for the latter. Categorical variable levels are ordered by relative importance.

Variable[1]	**Level**	**Relative Importance**
CSF Opening Pressure		53.7
CSF QCC (log)		100
ECOG performance status	Bedbound	53.3
ECOG performance status	Restricted activity	3.2
ECOG performance status	Limited self-care	0.6
ECOG performance status	Ambulatory	0
ECOG performance status	Normal	-
GCS score	<=10	9.5
GCS score	11-14	6
GCS score	15	-
Haemoglobin		53.2
Neutrophils		65.5
Treatment	1wk AmBd+FLU	10.2
Treatment	2wks AmBd+FLU	3.5
Treatment	FLU+5FC	1.9
Treatment	2wks AmBd+5FC	0.3
Treatment	1wk AmBd+5FC/Ambition regimen	-

[1]QCC = Quantitative cryptococcal culture; AmBd = Amphotericin B deoxycholate; FLU = Fluconazole; 5FC = Flucytosine

Supplementary Figure 9: Internal-external cross validation results for the XGBoost Machine Learning model

Pooled estimates are calculated through random-effects meta-analysis (total sample size = 1,263 participants). Countries with n < 100 participants or x < 20 deaths were amalgamated and grouped by similarity of healthcare environment. Dashed lines indicate lines of perfect calibration in the large (0) and slope (1), respectively. Black squares indicate point estimates; bars indicate 95% confidence intervals; diamonds indicate pooled random-effects meta-analysis estimates. I^2 values for c-statistic, calibration-in-the-large and calibration slope are shown in the figure footer. Bots = Botswana; SAfr = South Africa; Tan = Tanzania; Zam = Zambia; Zim = Zimbabwe.



Supplementary Table 11: Variables selected into retrained 10-week mortality model

Variable selection was done in each imputed dataset using backward elimination using AIC. Variables retained in >50% of multiply imputed datasets were selected into the model. ECOG = Eastern Cooperative Oncology Group performance status; CSF = cerebrospinal fluid; MI = multiple imputation.

	Baseline Model	**Research Model**
Variable	Number of MI datasets selected (total n=10)[1]	Number of MI datasets selected (total n=10)[1]
Age	10 (100%)	10 (100%)
Sex	0 (0%)	0 (0%)
Weight	10 (100%)	3 (30%)
Seizure	10 (100%)	0 (0%)
GCS	0 (0%)	9 (90%)
ECOG	10 (100%)	10 (100%)
Treatment regimen	10 (100%)	10 (100%)
Neutrophil count	10 (100%)	10 (100%)
Haemoglobin	10 (100%)	10 (100%)
CD4 count		0 (0%)
CSF opening pressure		0 (0%)
CSF cell count		7 (70%)
CSF Quantitative Culture (log)		10 (100%)

[1]n (%)

Supplementary Figure 10: Multivariable model associations in predictors selected in retrained 10-week model

Supplementary Figure 10a shows the associations in the retrained basic model and is shown first, with 10b showing the associations in the retrained research model. Continuous variables were modeled using restricted cubic splines. The final model parameters are pooled across multiply imputed datasets (total sample size for model development = 1,263 participants). For continuous variables, black lines represent point estimates and grey shaded regions represent 95% confidence intervals. For categorical variables, black dots represent point estimates and black lines represent 95% confidence intervals. Treatment arm 1 through 5 represent 1) the liposomal-amphotericin-B Ambition regimen and the 1-week amphotericin-B + flucytosine (1wk AmBd + 5FC) arms from both ACTA and Ambition-cm trials, 2) 1 week amphotericin-B + fluconazole, 3) 2 weeks amphotericin-B + flucytosine, 4) 2 weeks amphotericin-B + fluconazole and 5) flucytosine + fluconazole oral combination regimen, respectively. ECOG = Eastern Cooperative Oncology Group performance status; GCS = Glasgow Coma Scale; CSF = cerebrospinal fluid.

A

B

Supplementary Tables 12 and 13: Pooled model parameters for (a) basic and (b) research 10-week model

Relationships between independent predictors and outcome are reported as coefficients. ECOG = Eastern Cooperative Oncology Group performance status; CSF = cerebrospinal fluid; QCC = quantitative cryptococcal culture; AmBd = Amphotericin B deoxycholate; 5FC = Flucytosine; FLU = Fluconazole.

(a)

Variable	Estimate	95% Confidence Int.
Intercept	0.81	-1.38 to 3
Age	0.02	-0.01 to 0.06
Age (spline 1)	0.02	-0.02 to 0.06
Weight	-0.03	-0.06 to 0
Weight (spline 1)	0.02	-0.02 to 0.06
Seizure: Yes	0.43	0.07 to 0.8
ECOG: Restricted activity	0.29	-0.59 to 1.17
ECOG: Ambulatory	0.54	-0.31 to 1.4
ECOG: Limited self-care	0.78	-0.06 to 1.63
ECOG: Bedbound	1.68	0.82 to 2.54
Treatment: 1wk AmBd+FLU	0.89	0.44 to 1.34
Treatment: 2wk AmBd+5FC	0.24	-0.2 to 0.69
Treatment: 2wk AmBd+FLU	0.59	0.14 to 1.04
Treatment: 5FC+FLU	0.23	-0.13 to 0.58
Neutrophils	0.18	-0.03 to 0.39
Neutrophils (spline 1)	-0.01	-0.3 to 0.28
Haemoglobin	-0.03	-0.04 to -0.01
Haemoglobin (spline 1)	0.02	0.01 to 0.04

Restricted cubic spline knot positions are:

- Age = 27, 37, 50;
- Weight = 42, 52, 69;
- Neutrophils = 1.1, 2.5, 5.6;
- Haemoglobin = 83, 110, 137.

(b)

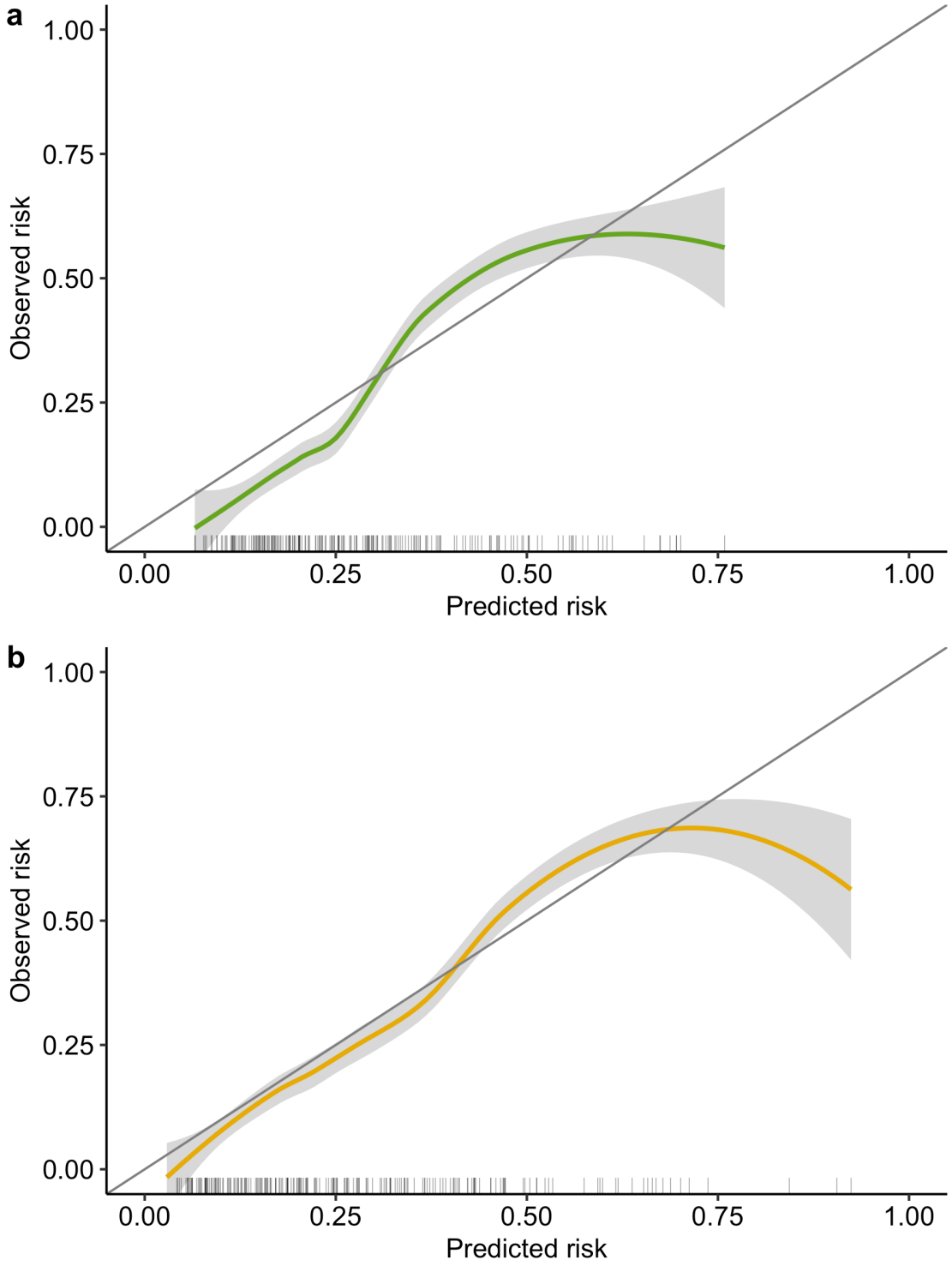
Variable	Estimate	95% Confidence Int.
Intercept	-0.15	-2.03 to 1.72
Age	0.01	-0.02 to 0.05
Age (spline 1)	0.03	-0.01 to 0.07
Glasgow Coma Score: 11-14	0.39	0.04 to 0.73
Glasgow Coma Score: ≤10	0.80	0.1 to 1.5
ECOG: Restricted activity	0.22	-0.67 to 1.11
ECOG: Ambulatory	0.50	-0.37 to 1.37
ECOG: Limited self-care	0.68	-0.17 to 1.54
ECOG: Bedbound	1.42	0.53 to 2.32
Treatment: 1wk AmBd+FLU	0.88	0.43 to 1.34
Treatment: 2wk AmBd+5FC	0.19	-0.27 to 0.66
Treatment: 2wk AmBd+FLU	0.57	0.11 to 1.03
Treatment: 5FC+FLU	0.23	-0.13 to 0.59
Neutrophils	0.13	-0.09 to 0.34
Neutrophils (spline 1)	0.05	-0.24 to 0.35
Haemoglobin	-0.03	-0.04 to -0.02
Haemoglobin (spline 1)	0.02	0 to 0.04
CSF White Cell Count	-0.01	-0.02 to 0
CSF White Cell Count (spline 1)	0.11	-0.01 to 0.23
CSF QCulture (log)	-0.07	-0.24 to 0.1
CSF QCulture (log) (spline 1)	0.28	0.13 to 0.44

Restricted cubic spline knot positions are:

- Age = 27, 37, 50;
- Neutrophils = 1.1, 2.5, 5.6;
- Haemoglobin = 83, 110, 137.
- CSF WCC = 0, 4, 135;
- log CSF QCC = 0.7, 5, 6.3;

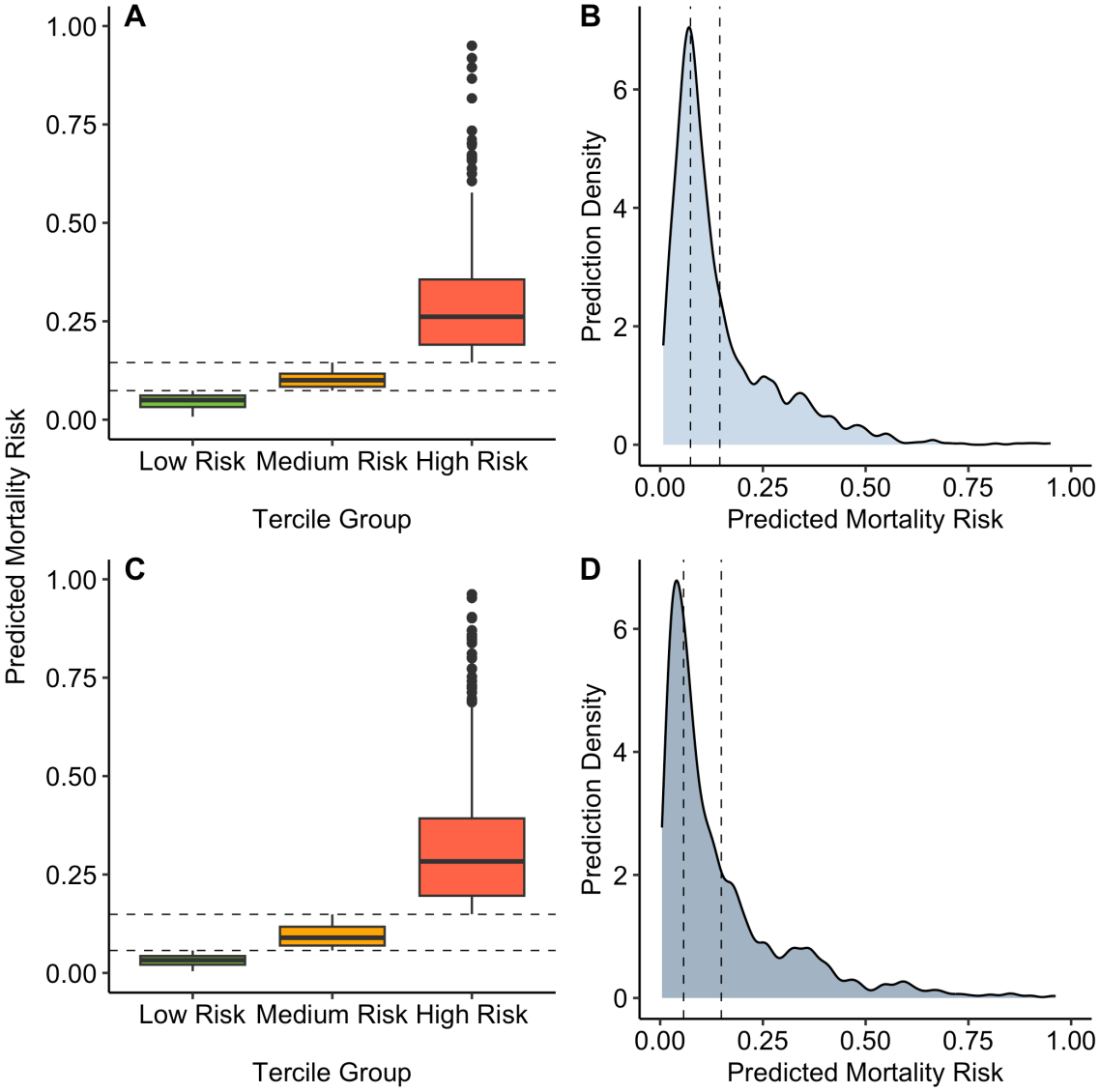
Supplementary Figure 11: Calibration plots of retrained 10-week mortality model in held-out validation data

(a) Basic Treatment Model; (b) Research Treatment Model



Supplementary Figure 12: Distribution of predicted mortality risk by risk tercile.

Boxplots and density plots showing the distribution of predicted 2-week mortality across the total MI cohort. Boxplots A and C show the distribution of risk by tercile, as derived from the Basic Model (A) and Research Model (C). Horizontal dashed lines represent the threshold of predicted mortality delineating each tercile. Tercile thresholds in the basic model predictions were 0.07 and 0.15 for Low/Medium Risk and Medium/High Risk respectively. Tercile thresholds in the research model were 0.06 and 0.15 respectively. Density plots B and D show the distribution of predicted risk across the total MI cohort, derived from the Basic Model (B) and Research Model (D). Vertical dashed lines delineate the tercile-derived thresholds of risk from (A) and (C), respectively. For the Basic Model, the median (IQR) mortality risk prediction was 0.10 (0.06 to 0.19) and the modal prediction was 0.08. For the Research Model, the median (IQR) mortality risk prediction was 0.09 (0.04 to 0.20) and the modal prediction was 0.04.



Supplementary Table 14: Ten-week mortality by Treatment Arm and Risk Tercile

Table showing 10-week mortality, stratified by risk tercile as defined by the Basic and Research Models. Deaths are reported for the Fluconazole + Flucytosine arm of the ACTA trial (Oral regimen), the single dose liposomal Amphotericin B arm (Ambition regimen) of the Ambition trial, and the 1-week Amphotericin B + Flucytosine arm of each of their respective trials. The Oral regimen in the ACTA trial and the Ambition regimen arm of the Ambition trial are labelled Intervention, and the 1-week Amphotericin B + Flucytosine arm is labelled standard of care (SOC). Deaths, mortality differences and hazard ratios are compared between the intervention (Oral regimen or Ambition regimen) and the standard of care for that trial and reported stratified by model and risk tercile. Deaths are described directly from the data and exclude patients for whom a risk category could not be attributed due to missing data. Mortality Difference and Hazard Ratios were calculated using multiply imputed data to account for missingness of predictor variables.

	Deaths		Mortality Difference		Hazard Ratio	
	SOC[1,2]	Intervention[2]	Intervention v SOC[1,3]	p value	Intervention v SOC[1,3]	p value
ACTA - Oral Regimen - Basic[4]						
Low Risk	6/44 (13.6%)	8/54 (14.8%)	1.5% (-16.2-19.2)	0.90	1.12 (0.4-3.15)	0.80
Medium Risk	10/41 (24.4%)	21/76 (27.6%)	3.8% (-13-20.5)	0.70	1.14 (0.55-2.36)	0.70
High Risk	10/24 (41.7%)	42/79 (53.2%)	11.7% (-8.5-31.8)	0.30	1.44 (0.73-2.85)	0.30
ACTA - Oral Regimen - Research[4]						
Low Risk	5/34 (14.7%)	10/44 (22.7%)	7.6% (-10.7-26)	0.40	1.65 (0.57-4.77)	0.40
Medium Risk	6/32 (18.8%)	12/70 (17.1%)	1.9% (-15.1-18.9)	0.80	1.08 (0.45-2.58)	0.90
High Risk	13/31 (41.9%)	43/70 (61.4%)	16.9% (-0.5-34.3)	0.06	1.67 (0.92-3.01)	0.09
Ambition – Ambition Regimen - Basic[4]						
Low Risk	26/157 (16.6%)	13/153 (8.5%)	-8.1% (-17.5-1.3)	0.09	0.5 (0.26-0.97)	0.04
Medium Risk	29/119 (24.4%)	30/123 (24.4%)	-0.4% (-11-10.1)	0.90	0.97 (0.58-1.62)	0.90
High Risk	60/126 (47.6%)	58/128 (45.3%)	-2.1% (-12.4-8.1)	0.70	0.96 (0.67-1.37)	0.80
Ambition – Ambition Regimen - Research[4]						
Low Risk	23/159 (14.5%)	14/155 (9%)	-5.5% (-14.6-3.7)	0.20	0.61 (0.31-1.18)	0.10
Medium Risk	34/126 (27%)	28/132 (21.2%)	-5.9% (-16-4.2)	0.20	0.77 (0.47-1.27)	0.30
High Risk	58/117 (49.6%)	59/117 (50.4%)	0.8% (-9.8-11.3)	0.90	1.03 (0.72-1.47)	0.90

[1]SOC = Standard of Care

[2]Brackets indicate proportions

[3]Brackets indicate 95% confidence intervals

[4]Risk groups were defined by terciles of predicted risk in the pooled dataset. Thresholds of 7.4% and 14.5% delineated Low-Medium and Medium-High risk respectively in the basic treatment model. Thresholds of 5.7% and 14.9% delineated Low-Medium and Medium-High risk respectively in the research treatment model.