

Development and validation of risk score to predict in-hospital mortality among severely malnourished children under the inpatient treatment center: A follow up study

Eskedar Getie Mekonnen

University of Gondar

Fasil Wagnew

Debre Markos University

Abel Fekadu Dadi

Flinders University

Hamid Yimam Hassen

University of Antwerp

Belayneh Ayanaw Kassie

University of Gondar

Ambaye Dejene Tilahun

University of Gondar

Almaz Tefera Gonete

University of Gondar

Gebrekidan Ewnetu Tarekegn

university of Gondar

Degefaye Zelalem Anlay

University of Gondar

Rahel Mulatie

Debretabor University

Wubet Worku Takele (✉ wubetakele380@gmail.com)

University of Gondar

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Abstract

Introduction: The prognosis of severely malnourished children is determined by various factors. The care provided to the child throughout the management is one of the most influencing factors for the child's status after treatment. There is no evidence-based model that shows the risk of mortality among severely malnourished children. Thus, this study aimed to develop and validate a model to predict mortality among children with severe acute malnutrition.

Method: We developed a prediction model using a retrospective cohort of 677 children with severe acute malnutrition admitted to the Amhara region referral hospitals. A stepwise multivariable analysis was done to develop the model. The accuracy of the model was evaluated using the area under the receiver operating characteristic curve (AUC) and calibration plot. All accuracy measures were internally validated using the bootstrapping technique. To improve the clinical applicability, a simplified risk score was developed to classify children with severe acute malnutrition at high or low risk of mortality. The clinical impact of the model was evaluated using a decision curve analysis across various threshold probabilities.

Result: Child's Age, the form of malnutrition, HIV/AIDS, heart failure, provision of antibiotics, and folic acid and vitamin A supplementation remained in the prediction model. The AUC of the model was 0.81 (95%CI: 0.76-0.85). The decision curve analysis indicated that the model provides higher net benefit across ranges of threshold probabilities.

Conclusion: The model can guide clinicians in identifying severely malnourished children with a high risk of mortality. As the model showed easily obtainable predictors of mortality, it provides a considerable opportunity for care providers to avert hundreds of mortalities among those children. The model needs to be externally validated in another context before utilizing it for clinical decision-making.

Introduction

Severe acute malnutrition (SAM) is defined as very low weight-for-height and/or visible severe wasting and/or the presence of nutritional edema and/or MUAC < 11.5 cm for age 6–59 months (1). The presentation of SAM among children can be wasting (marasmus), edema (kwashiorkor), or both (marasmic-kwashiorkor). SAM can also be complicated and uncomplicated based on the presence or absence of clinical features of infection or metabolic disturbance, severe edema, and/or poor appetite (1, 2).

Globally, about 25–35 million under-five children are severely malnourished, of which 13 million reside in sub-Saharan Africa, causing one million deaths every year (3). Malnutrition is the underlying cause for over 50% of the 10–11 million under-five children mortality from preventable causes, including diarrhea, pneumonia, measles, and malaria (2). SAM affects 13 million under-five children, and it is associated with 1 to 2 million preventable child deaths with a case fatality rate of 20–30% every year (4). The case fatality rate of SAM in Ethiopia accounts for 11.3% (5). The mortality rate among SAM children in many

countries of the world, including Ethiopia, is higher than the expected death rate according to the international sphere standard's reference (6).

Children with SAM face a nine to eleven times greater risk of morbidity and mortality than their healthy counterparts (4, 7). The rate of mortality is also disproportionately observed among SAM children (4). Form of SAM (being marasmic, kwashiorkor, and marasmic-kwashiorkor), type of SAM (complicated and uncomplicated), and vaccination status highly determine the prognosis of children with SAM (7). Likewise, different biochemical markers like low leptin level, a marker of adipose tissue reserve, and clinical modulator of immune function were significant predictors of mortality among SAM children (8). Moreover, factors such as age < 24 months, altered pulse rate and temperature, nasogastric tube feeding, hypoglycemia, and HIV co-infection have also elevated the risk of mortality among malnourished children (9, 10).

Ending childhood mortality and zero hunger are a global priority agenda that every nation strives to achieve (11). Ethiopia is also working on those priority agendas by providing SAM management in the community and stabilization centers (SC) and employing standard treatment protocols. Despite such efforts applied by the Ethiopian government, the rate of mortality among children receiving the treatment remains to be higher than expected (12). Admitting SAM children in SCs solely would not be a guarantee for positive treatment outcomes; instead, prioritizing children at higher risk of mortality by the clinicians is a foundation to improve the care, prognosis of the treatment, and reduce the risk of mortality. Identifying SAM children with a higher risk of mortality to provide the appropriate care is crucial, particularly in developing countries where resource constraint is the major barrier of health service delivery. This study aimed to develop and validate a risk score that predicts mortality among SAM children that help clinicians to screen high-risk children and manage them accordingly. We believe that this study would reduce the case fatality rate of SAM children by indicating children who actually need an intensive care and management.

Methods

Study design, period, and setting

A retrospective cohort study was conducted among infants and children hospitalized between October 2012 and September 2016 to the in-patient SAM treatment centers of two referral hospitals, in the Amhara region of Ethiopia. The two hospitals were randomly chosen from the five referral hospitals in the region that follow the national treatment protocol in admitting and treating infants and children with SAM. These hospitals have also separated in-patient treatment centers whereby severely malnourished children are admitted and receive appropriate nutritional and medical care.

Study population and sample

The study considered all severely malnourished infants and children aged 59 months or younger admitted to the SAM in-patient treatment centers of the selected hospitals. Admission criteria for SAM

were: the presence of severe wasting (weight-for-height/length 70%/<-3SD) and/or bilateral pitting edema of both feet and/or Mid-Upper Arm Circumference (MUAC) below 11.5cm (13, 14).

Inclusion and exclusion criteria

Only children whose hemoglobin level was measured at admission or before starting the transition phase of management were recruited. Since children at the transition phase of management will receive Ready-to-Use Therapeutic Feeding (RUTF) that has trace minerals and affect the hemoglobin estimation, they were excluded from the study. Similarly, children whose treatment outcome was declared, HIV status was confirmed, tested for tuberculosis, pneumonia, heart failure, malaria, and other medical complications were included. A total of 677 participants (259 from Felegehiwot and 418 from Debre Markos referral hospital) were selected employing a systematic random sampling technique in every three unit interval.

Variables of the study

Outcome variable

The outcome variable was mortality (died, alive). The death of children was ascertained using the attached death report note, which refers to the death of the children during the course of treatment (15).

Predictors

Socio-demographic characteristics: Age, sex, and residence; Comorbid medical conditions: HIV/AIDS, heart failure, diarrhea, pneumonia, anemia, and malaria; Medical care: antibiotics, folic acid, and vitamin A provision; Nutritional characteristics: the form of malnutrition (marasmic, kwashiorkor, and marasmic-kwashiorkor), and complicated or un-complicated SAM, and Maternal characteristics: Age at pregnancy, illness during pregnancy, nutritional status during pregnancy were considered as a predictor of mortality among SAM children.

Measurement

Type of SAM

was described using the clinical presentations of children as marasmus, kwashiorkor, and mixed form (marasmic-kwash); SAM infants and children who had no edema, but the presence of fat wastage were explained as marasmic. Infants and children with SAM who had edema and muscle wastage were declared as having Kwashiorkor form of malnutrition. Lastly, infants and children who had mixed forms of clinical presentations of SAM were diagnosed as having 'marasmic-kwash'.

Anemia

children with a hemoglobin concentration of less than 11g/dl were considered to be anemic (16).

HIV status

was determined using the confirmatory tests as per the national test algorithm. For children under 18 months, their HIV status was ascertained by Polymerization Chain Reaction (PCR) test, and they were considered 'positive' if their result was 'positive' (17). While the HIV status of children older than eighteen months was diagnosed using any confirmatory test and recorded as either 'positive' or "negative" (18).

Tuberculosis

Tuberculosis (TB) cases confirmed with sputum culture were considered.

Other medical conditions

The medical records were reviewed to confirm whether antibiotics, folic acid, and vitamin A had been administered throughout SAM treatment. The presence of diarrhea, pneumonia, heart failure, and malaria was also extracted from the medical record. For malaria and pneumonia, those diagnoses made only by confirmatory tests were considered (19).

Data extraction and quality assurance

The data were extracted using a data abstraction form comprising of the outcome and all potential predictors. Before the commencement of the data collection, two days of training were given for two data collectors and one supervisor in each hospital briefing the study's objectives, the kind of data to be extracted, and how it should be extracted. A pretest was administered to understand and map the variables that are available in the medical chart. Only medical complications ascertained by the confirmatory diagnostic tests and clinical criteria were considered to ensure the quality of measurement. The completeness of the data was checked daily. Finally, the datasets from the two hospitals were merged.

Data processing and analysis

The collected data were entered into Epi-data version 4.4.3.1 and exported to R statistical programming language version 4.1.0 for processing and analyses. All continuous independent variables were categorized. The outcome variable was dichotomized and coded as "0" and "1", representing died and alive, respectively. For continuous variables, the normality test was done using the Shapiro-Wilk test. Categorical variables were summarized using absolute and relative frequency, whereas numerical variables were described using mean with standard deviation (SD) or median with Interquartile Range (IQR).

Model development and validation

Bivariate analysis was done using a logistic regression model to identify factors associated with mortality that will be further included to build the prediction model. Variables with a p-value less than 0.25 in the bivariate analysis were fitted to the multivariable analysis. A p-value of ≤ 0.05 in the multivariable analysis was considered to identify significant variables.

The model performance was evaluated for its discrimination and calibration statistically. The Hosmer-Lemeshow test statistics examined the reduced model fitness.

Discrimination was evaluated based on the Area Under the curve of Receiver Operating Characteristic (AUROC) with 95% CI. AUROC curve was used to assess the performance of a categorical classifier using "pROC" packages of R software with the plot of sensitivity (true positive rate) versus 1-specificity (false positive rate) (20). AUROC of < 0.5 was interpreted as having no information, between 0.5 and 0.7 poor, 0.7–0.9 good, and > 0.9 excellent discrimination ability (21). A bootstrapping technique was applied to assure the internal validity of the model using 1,000 samples with replacement from the dataset with complete predictors to see optimism and overfitting. The 'Youden index' was used to determine the optimal cutoff point for the predicted probability of mortality and risk stratification based on the developed clinical prediction model. Sensitivity, specificity, negative predictive value, and positive predictive value were calculated for evaluation of the clinical performance of the model.

The developed risk prediction model was used to predict the risk of mortality among SAM children. The occurrence relationship was established based on the identified predictor variables included.

Pr (mortality) = f (anemia, heart failure, folic acid, vitamin A, age, types of SAM, HIV status, antibiotics).

Pr (Y = 1) = f ($\beta_0 + \beta_1$ anemia + β_2 heart failure + β_3 folic acid + β_4 vitamin A + β_5 age + β_6 types of SAM + β_7 HIV status + β_8 antibiotics).

The risk prediction model was developed based on the original beta coefficients and simplified risk score. Risk scores were calculated for all variables included in the final model by dividing the coefficients of each predictor by the lowest coefficient, and scores were rounded to the nearest integer. Finally, total risk scores were determined by pooling up scores of each variable effect for individuals.

A decision curve analysis was performed based on a risk threshold preference to evaluate the public health impact and clinical utility of the developed model.

The result is presented based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statements (22).

Ethical Considerations

Ethical clearance was obtained from the ethical review board of the school of nursing on behalf of the institutional review board of the University of Gondar (V/P/RCS/04/231/2020). A permission letter was also obtained from the respective hospitals. As the study was conducted through a review of records, consent was not taken from the mothers or caregivers of the study participants. During data extraction, patients' identifiers, including names and identification numbers, were anonymized.

Results

Socio-demographic characteristics

Above half (53.3%) of the participants were females. The median age of the participants was 16 months (IQR: 15). Nearly half (49.9%) of children fall in the age category of 6–23 months, and one in every 10 participants was younger than six months. Moreover, about three-fourths (72.7%) of children were from rural areas.

Medical complications and related characteristics

The highest and least medical complications that SAM children admitted to the in-patient treatment centers experienced were diarrhea (38.5%) and malaria (2.4%), respectively (Fig. 1).

As shown in Table 1 below, more than one-fifth (64.8%) of SAM children have experienced marasmus form of malnutrition and 41.6% of them developed anemia.

Table 1
medications administered and nutritional characteristics of children admitted with SAM in the in-patient treatment centers of Amhara regional referral Hospital, 2021 (n = 677).

Variables		Number	Percentage
Anemia	Yes	282	41.6
	No	395	58.4
Antibiotics	Given	301	44.5
	Not given	376	55.5
Vitamin-A	Given	481	7.1
	Not given	196	28.9
Folic acid	Given	558	82.4
	Not given	119	17.6
Type of SAM	Marasmus	439	64.8
	Kwashiorkor	141	20.8
	Marasmus-Kwashiorkor	97	14.4

Prediction model for identifying predictors of mortality

Overall, the incidence of death among children with SAM throughout the course of treatment was 14.03% (11.6, 16.8). Socio-demographic characteristics (age, sex, and residence), medical complication (heart failure, diarrhea, tuberculosis, HIV, malaria, anemia, and pneumonia), Medical care (Antibiotics, folic acid, and vitamin A provision), and nutritional factors (type of SAM) were predictors tested for their association with mortality in the bi-variable analysis. Ten predictors (age, type of SAM, anemia, heart failure, diarrhea,

tuberculosis, HIV, folic acid, vitamin A, and antibiotics administration status) were significant at a p-value of 0.25 and entered in the multivariable model. Finally, eight factors remained to be the predictors of mortality. The predictor's risk score ranges between 1 and 15; while '1' belongs to the age category, '15' is for HIV status (Table 2).

Table 2

A prediction model for identifying predictors of mortality among children with SAM admitted to the in-patient treatment centers of Amhara region hospitals using a simplified score, 2021 (n = 677).

Predictors	Bi-variable analysis		Multivariable analysis	Simplified risk score
	β (95%CI)	p-value	β (95%CI)	
Anemia (yes)	0.66 (0.22, 1.10)	0.003	0.61 (0.12, 1.10)	5
HIV infection status (positive)	1.79 (1.01, 2.56)	0.000	2.02(1.11, 2.92)	15
Diarrhea(yes)	0.33 (-0.11,0.76)	0.148	NA	NA
Heart failure (yes)	1.03 (0.34, 1.72)	0.003	1.29(0.47, 2.07)	10
Folic acid (not given)	0.95(0.45, 1.42)	0.000	1.018(0.425, 1.60)	7
Type SAM (maramic-kwash)	0.56(0.29, 0.83)	0.005	0.42(0.205, 0.65)	3
Tuberculosis (+ ve)	0.54(-0.15, 1.25)	0.128	NA	NA
Age in month (< 6)	0.78(0.12, 1.43)	0.019	0.13(0.35, 0.629)	1
Routine Antibiotics (not given)	1.05(0.55, 1.54)	0.000	1.27(0.740, 1.85)	9
Vitamin A(not taken)	1.4(0.95, 1.85)	0.000	1.01(0.47, 1.55)	7

AUROC and calibration

The discriminating ability of the model using predictors retained in the final reduced model in terms of area under the ROC using eight predictors was 0.81% (95% CI: 0.76–0.85%) applying the original beta coefficients (Fig. 2). Linear predictor for mortality of children from SAM was estimated using beta coefficients.

$Pr(Y = 1) = 1 / (1 + \exp(-(-4.24 + 0.615 * anemia (yes) + 2.02 * HIV-Status + 1.29 * heart failure (yes) + 1.018 * folic (not given) + 0.429 * type SAM (marasmus-kwash) + 0.136 * age (category represented by 1) +$

$1.27 \times \text{antibiotics (not given)} + 1.01 \times \text{vitamin A (not given)}$.

The developed model was well-calibrated ($p = 0.49$), suggesting that the model well represented the data (Fig. 3).

Risk prediction for risk of having mortality using a simplified risk score

A simplified risk score was calculated by dividing the coefficients of variables retained in the final reduced model to the lowest coefficient and rounding to the nearest integer. The possible minimum and maximum risk of mortality SAM children could have are 1 and 15, respectively. In other words, the lowest score was contributed by age while the highest is by HIV infection.

Simplified risk score for mortality = $5 \times \text{anemia (yes)} + 15 \times \text{HIV status (positive)} + 10 \times \text{heart failure (yes)} + 7 \times \text{folic (not given)} + 3 \times \text{type SAM (marasmic_kwash)} + 1 \times \text{age in month (< 6)} + 3 \times \text{antibiotics (not given)} + 7 \times \text{vitamin A (not given)}$ (Fig. 4).

Internal validation

The bootstrap technique of validation has been chosen over other methods. A total of 1000 samples with replacement from the original dataset with the same predictors were resampled for checking optimism and bias introduced during model development. After optimism was corrected, the model performance was 0.798 (95%CI; 0.752, 0.845) (Fig. 5).

Risk classification using a simplified risk score

Even though risk scores have comparable performance with the original beta coefficients, for easily practical applicability, the score using simplified risk score was used for risk classification. The performance of the model using risk score is 0.81 (95% CI: 0.763, 0.855). The simplified risk score ranges from 0 to 51. The optimal cutoff point for risk of mortality in children with SAM was determined using the Youden index. The proportion of mortality in groups of children with predicted low risk (< 19) was 4.57%, whereas high-risk groups (score ≥ 19) were 71 (36.2%). At this cutoff, the sensitivity, specificity, positive predictive value, and negative predictive value were 74.7%, 71%, 26.5%, and 95%, respectively. The positive and negative likelihood ratio was 2.57 and 0.35, respectively. The model accuracy of the simplified risk score was 81.5%.

Decision Curve Analysis

The developed model has the highest net benefit ratio starting from threshold probability > 0.18 up to around 0.78 compared to not admitting all to the intensive care unit (ICU) and admitting all to the ICU regardless of their risk. The model has a net benefit to those admitting all to the ICU regardless of their risk across thresholds ranging from 0 to 0.1. Therefore, the model is expected to have clinical and public health importance and its application is possible after validation (Fig. 6).

Discussion

SAM is a significant public health problem in many developing countries, including Ethiopia. Various factors determine the treatment outcome of these children admitted to the stabilization centers. In this study, we developed and internally validated a model to predict mortality (the most devastating outcome of SAM) among children younger than 59 months who were admitted to the in-patient treatment centers. Predicting the risk of mortality among SAM children is essential to provide appropriate care/clinical decisions (admitting high-risk children in ICU) that can avert the risk of death among those children having the high predictive probability of mortality.

The incidence of mortality among these children throughout the course of treatment was 14.03% (11.6, 16.8), which is higher than the expected death rate from SAM according to the international sphere standard's reference (6). In our study, a combination of eight factors that related to the child demographic characteristics (age), medical complications (HIV/AIDS, heart failure, and anemia), type of SAM (children with mixed forms of SAM), and the medical care being provided (children who didn't receive antibiotics, folic acid, and vitamin A) predict mortality among SAM children with a classification accuracy (AUROC) of 0.81, which is a good accuracy according to diagnostic accuracy classification. Likewise, our model consists of easily obtainable information in routine clinical practice to be used by both mid and lower-level health professionals in the primary care settings. Almost all (8) of the characteristics can be found registered in the medical recording of SAM children and/or from history taking.

A study by Van den Brink and his colleagues predict mortality among SAM children by fecal volatile organic compound (VOC) analysis through grouping VOC profiles according to other important clinical characteristics such as degree of edema, medical complications, comorbidities, antibiotic prescription, HIV, very low anthropometry, and age with an AUC of 0.71 (23). The former study predicts mortality with fair accuracy, which is lower than the current study. This could be due to the addition of different clinical parameters in the current model that have an additive effect in impairing the normal physiology of SAM children, resulting in greater AUC in our study. Moreover, examining the existence of VOC in the fecal components of SAM children may not be easily obtainable information in routine clinical and public health practice, particularly in a low-resource setting, which makes the model less practical.

This study has different strengths. Firstly, we used an adequate number of participants with the outcome (mortality) that ease the process to construct the model using arguably enough predictor variables. Secondly, we internally validated our model using bootstrapping technique resulting in a small optimism coefficient, indicating our model is less sample dependent and not overfitted. Thirdly, our prediction model is constructed from easily obtainable demographic and clinical characteristics of the children that make it applicable in primary care settings. However, the following limitations of this study should be considered while interpreting the findings. External validation of the model would be required before using it for the clinical decision-making process in another context. Although we have an adequate number of participants with the outcome, having a relatively low number of overall participants did not enable us to validate the model in separate datasets. Lastly, since the data were extracted from the medical recording

of SAM patients, some deviation in data quality is expected. Nevertheless, the model will provide its maximum benefit provided that all the required predictor information is collected.

Implication

The study implies that providing special care/clinical decisions (admitting high-risk children in ICU) using the model has a higher net benefit than not providing special care (not admitting all SAM children in the ICU) regardless of their risk threshold.

Conclusion

The model can guide clinicians in identifying SAM children with a high risk of mortality. As the model showed easily obtainable predictors of mortality, it provides an opportunity for care providers to avert hundreds of mortalities among those children. Thus, all the clinicians should consider improving the overall care provided in the in-patient treatment centers and delivering special care opportunities like ICU admission for children with a high-risk of mortality. Nevertheless, the model needs to be externally validated in the same and different context before using it for clinical decision-making.

Declarations

Acknowledgments

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Data availability statement

All necessary data are available in the manuscript if electronics data are requested to submit, corresponding author is ready to provide.

Consent for publication

Not applicable

Funding

The authors have not received any fund to carry out the study.

Ethical approval

Ethical clearance was secured from the ethical review committee of the three referral hospitals. Additionally, permission letter was obtained from the respective Hospitals. As the study was conducted through a review of records, consent was not applicable.

Competing interests

All authors have declared that there is no conflict of interest.

All necessary data are supplied and available in the manuscript, however, the corresponding author will provide the dataset on request.

Authors' Contributions

- Conceptualization: EGM and WWT
- Formal analysis: WWT, ADT, and EGM
- Investigation: AFD, EGM, AFD, and WWT
- Methodology: WWT, ADT, BAK, GWT, and EGM
- Project administration: EGM, AFD, ATG, and WWT
- Supervision: ATG, BAK, GWT, and FW
- Validation: WWT, DZA, FW, and EGM
- Writing-original draft: EGM, ADT, GWT, and WWT
- Writing-review and editing: WWT, EGM, ATG, AFD, DZA, GWT, and FW

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Figures

Figure 1

Medical complications observed among children with SAM.

Figure 2: AUC depicting the model calibration.

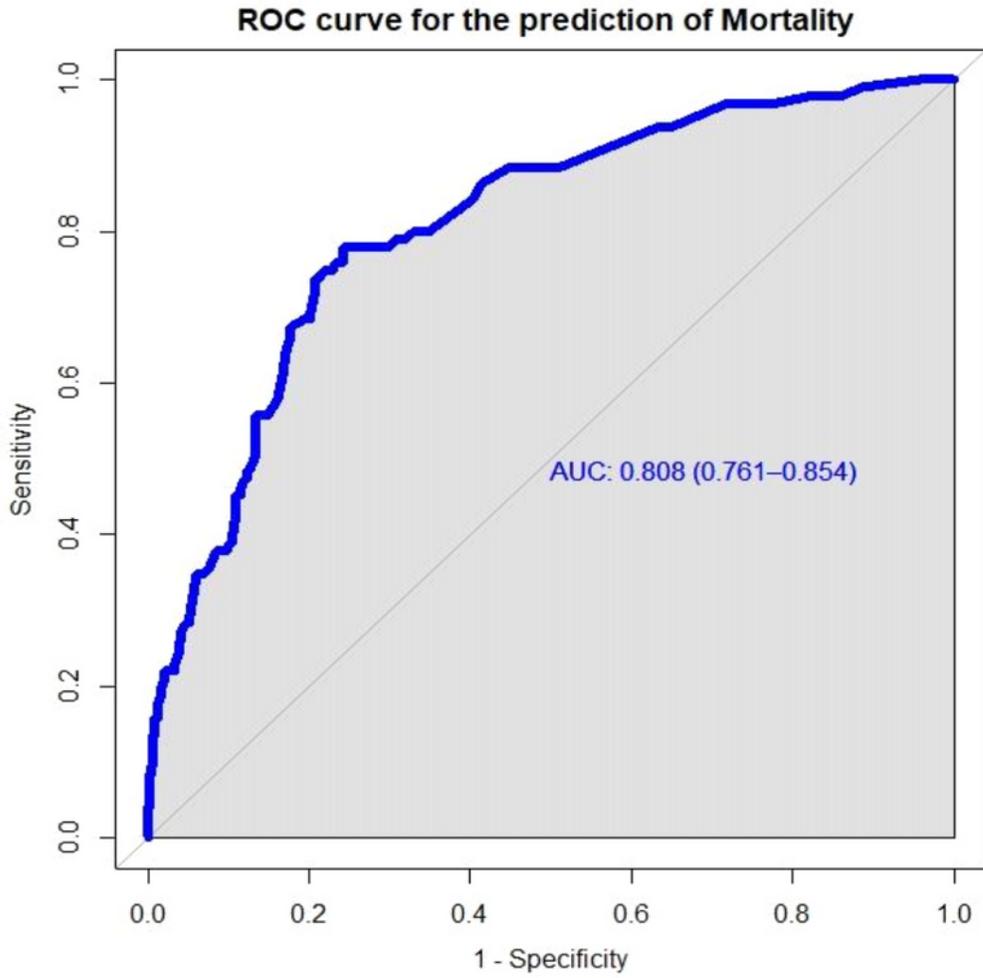


Figure 2

AUC depicting the model calibration.

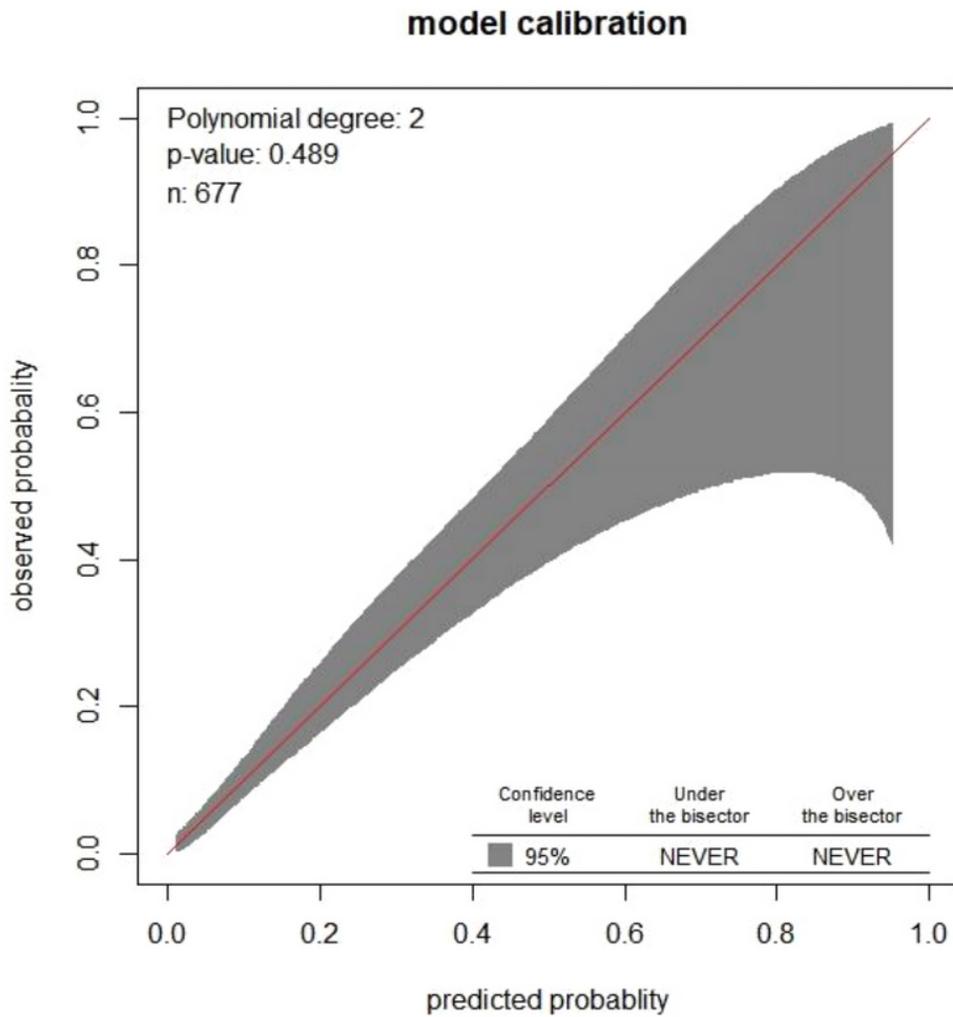


Figure 3

Figure reflecting predicted versus observed probability of mortality in the sample.

Figure 4

the ROC curve for mortality prediction model using the simplified risk score

ROC curve of mortality prediction model from SAM pt. after bootstrapp

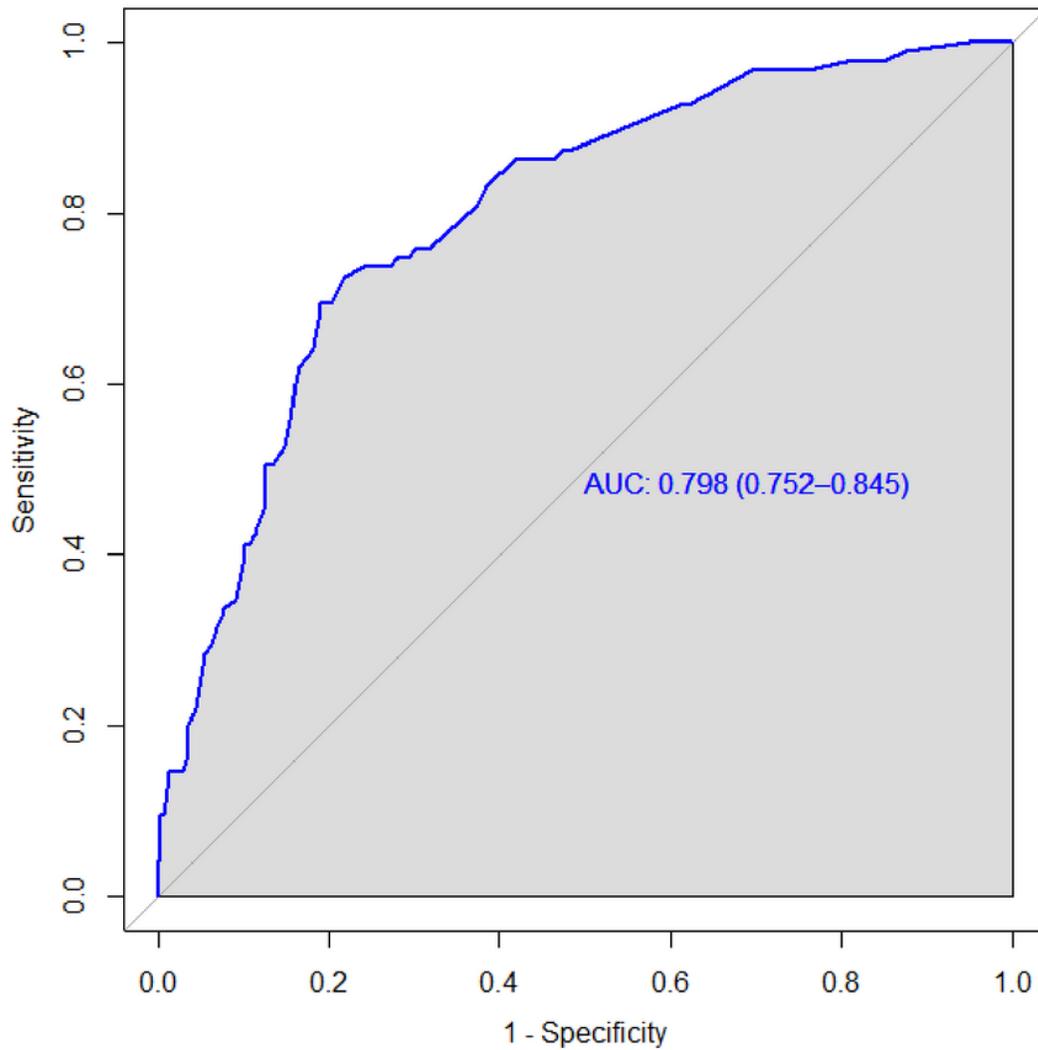


Figure 5

ROC curve of a mortality prediction model using the bootstrap technique

Figure 6

decision curve analysis of the model predicting mortality among SAM children

Supplementary Files

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