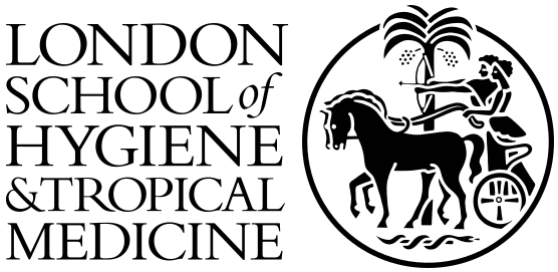

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Post-Discharge Mortality Prediction in Sub-Saharan Africa

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Post-Discharge Mortality Prediction in Sub-Saharan Africa

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ABBREVIATIONS.
Post-discharge mortality (PDM)
Area under the curve (AUC)
Low-income countries (LIC)
Manhiça Health Research Center (CISM)
Manhiça District Hospital (MDH)
Demographic surveillance system (DSS)
Morbidity surveillance system (MSS)
Human immunodeficiency virus (HIV)
International Statistical Classification of Diseases (ICD)
Kaplan-Meier (KM)
Severe acute malnutrition (SAM)
HR: hazard ratio
Weight-for-age Z-score (WAZ)
Weight-for-height Z-score (WHZ)
Low birth weight (LBW)
Management of Childhood Illness algorithm (IMCI)
Mass drug administration (MDA)

TABLE OF CONTENTS SUMMARY: This study shows the burden of post-discharge mortality in Southern Mozambique, identifying predictors which could efficiently stratify children with higher risk of dying following a hospital discharge.

WHAT'S KNOWN ON THIS SUBJECT: Post-discharge mortality is an important contributor to child mortality, ranging between 3.3% and 13%, although it is poorly recognized. No predictive models of post-discharge mortality among all cause-admissions in resource-constrained hospitals or among infants have been developed to date.

WHAT THIS STUDY ADDS: Predictive models presented in this study could be applied at hospital discharge and children at risk of dying could be identified through their use. This could allow designing a better post-discharge planning, health education to the families and follow-up care.

AUTHORS´CONTRIBUTIONS

Dr. Madrid conceptualized and designed the study, cleaned and analyzed data, interpreted data set results, drafted the initial manuscript, and reviewed and revised the manuscript. Drs. Bassat and Cousins conceptualized and designed the study, interpreted data set results, and critically reviewed the manuscript for its content.

Drs. Alonso, Menéndez, Macete, Sacoor, Varo, Sitoe, Acacio, Nhampossa and Sigaúque, coordinated and supervised data collection, and critically reviewed the manuscript for its scientific content.

Sergio Massora and Dr. Inacio Mandomando were responsible for laboratory procedures, quality of CISM laboratories facilities and interpretation of results. Mr. Quintó and Miss Casellas led the data analysis, interpreted data set results, and critically reviewed the manuscript.

All authors approved the initial manuscript (and subsequent versions) as submitted and agreed to be accountable for all aspects of the work.

ABSTRACT

Background: Although the burden of post-discharge mortality (PDM) in low-income settings appears significant, no clear recommendations have been proposed in relation to follow-up care after hospitalization. We aimed to determine the burden of paediatric PDM and develop predictive models to identify children at risk of dying following discharge.

Methods: Deaths after hospital discharge among children aged <15 years in the last 17 years were reviewed in an area under demographic and morbidity surveillance in Southern Mozambique. We determined PDM over time (up to 90 days) and derived predictive models of PDM using easily collected variables upon admission.

Results: Overall PDM was high (3.6%), with half of deaths occurring in the first 30 days. One primary predictive model for all ages included young age, moderate/severe malnutrition, history of diarrhoea, clinical pneumonia symptoms, prostration, bacteraemia, positive HIV status, rainy season and transfer or absconding, with an area under the curve (AUC) of 0.79 (0.75-0.82) at day 90 after discharge. Alternative models for all ages including simplified clinical predictors had a similar performance. A model specific to infants <3 months identified as predictors: being a neonate, low WAZ score, breathing difficulties, hypothermia or fever, oral candidiasis and history of absconding or transfer to another hospital, with an AUC of 0.76 (0.72-0.91) at day 90 of follow-up.

Conclusions: Death following discharge is an important although poorly recognized contributor to child mortality. A simple predictive algorithm based on easily recognizable variables could readily identify most infants and children at high risk of dying after discharge.

BACKGROUND

The last 25 years have witnessed a significant (49%) reduction in under-5 child mortality globally[1], but an insufficient one to meet the two thirds reduction objective set by the fourth millennium development goal, particularly among many low-income countries (LIC)[2].

In the last decades, algorithms for diagnosis and treatment of sick children have been implemented in order to address the management of disease during the acute phase and have contributed to improve child survival[3]. Such guidelines and recommendations, however, have historically failed to address the days immediately following hospitalization, a critical period for child survival[4].

Contrary to what occurs in industrialized countries, where post-discharge mortality (PDM) is limited to certain small, high-risk groups[5, 6], children in LIC appear to be at increased risk of mortality following hospitalisation for any illness[4, 7-13]. Previous studies among admitted children, albeit scarce, have estimated risk of PDM to range between 3.3% and 13%[9, 14, 15]. For specific diseases, PDM risks have ranged between 2.0-2.6% for malaria[16, 17], 2.9 to 7% for diarrhoea[18, 19], 2.7-11.6% for anaemia[20], 1-15% for pneumonia[15, 21] , and 2.8% for invasive bacterial infections[7]. Most of these deaths have been described to cluster in the first 30 days[13] and main predictors of PDM include a history of previous hospitalizations, young age, HIV infection and hospitalizations related to malnutrition or pneumonia[4].

A rigorous follow-up of all hospital discharged children would be unfeasible and unaffordable for resource-constrained settings[13]. Thus, early identification of vulnerable children appears essential to design more targeted interventions to prevent PDM[13]. Improving the discharge process and post-discharge care will be a critical step to further

continue reducing child mortality[4]. We therefore aimed to determine the burden of paediatric PDM in a semi-rural area from southern Mozambique, to identify predictors of mortality following discharge and to derive models that could efficiently stratify children according to PDM risk.

METHODS

Study site and population

This study was conducted in Manhiça, southern Mozambique, a semi-rural setting with a predominantly young population (45% <15 years of age). In 2015, the national under-5 mortality rate was 78·5/1000 live births[22]. Manhiça Health Research Centre (CISM), runs a demographic surveillance system (DSS) in the area, and a paediatric morbidity surveillance system (MSS) has been implemented for nearly two decades at the neighbouring Manhiça District Hospital (MDH) and five additional peripheral health posts, accurately capturing standardized morbidity data for ~3000 admissions and >75,000 annual outpatient visits, annually. Human immunodeficiency virus (HIV) prevalence in the area is among the highest in the world[23], with adult community prevalence peaking at 40%[24]. Vertical transmission of HIV has been estimated at around 9%[25] and contributing 10% to the under-5 mortality nationally[26]. A detailed description of CISM and study area can be found elsewhere[27, 28].

Study design and definitions

A retrospective cohort study of children <15 years discharged from MDH for a 17 year-long period was conducted, using the DSS and MSS databases. We analysed burden of PDM over three different time-periods: First (1-30 days), second (31-60 days) and third month (61-90 days) post-discharge. PDM among infants <3 months old was analysed

separately to check whether identified predictors differed from those of the older cohort. Only children living in the study area were included. We used a single-discharge approach, considering the first admission as reference admission, and not considering ulterior re-admissions within the following 90 days to avoid re-starting the period at risk every time. Post-discharge death was defined as a death occurring >24 hours after and within 90 days of discharge from MDH; community death as a death ocurring outside a health facility within 90 days after discharge; and facility death as a death ocurring at any health facility within 90 days following discharge from MDH. Chidren dying during a readmission within the follow-up period were considered as a hospital death within follow-up (supplementary figure S1). Supplementary table S1 summarizes other relevant definitions.

Morbidity surveillance system.

Morbidity surveillance data routinely collected for all children <15 years during the study period were analysed, including clinical data, basic laboratory investigations (malaria microscopy, haematocrit and glycaemia) and International Statistical Classification of Diseases-based diagnoses (ICD-10) since 2003. All diagnoses prior to July 2003 were coded according to a list of codes created by the CISM since 1996. Outcome and medications prescribed were also analysed. For admitted children, blood culture results, systematically performed for all children <2 years and, in older children, in those with severe disease, were available. HIV status information, although not routinely collected, was available for those patients with suspected immunosuppression.

Demographic Surveillance System

CISM's DSS, which started in 1996, now covers the entire Manhiça District (2380 km^2; total population of ~183000 inhabitants). DSS captures socio-demographic data and other major events like migration, marital status, pregnancy and outcome results, births and deaths and is updated twice annually. During periods in which the entire district was not covered, analysis only included inpatients being part of the DSS. Through a unique identifier number, DSS and MSS databases can be linked.

Data management and data analysis

A survival analysis was performed to model events within 90 days of discharge. The discharge date+1 day was used as date of entry to the study whilst post-discharge death, loss to follow-up or end of follow-up period (90 days after discharge), considered the exit time. For each variable with a high proportion of missing values (<15%) but suspected to be a strong confounder, a "missing or unknown" category was created. In order to achieve the study objectives, data analysis was split in two parts: a) *Determining burden and identifying associations*: Descriptive statistics were calculated for all explanatory variables. Kaplan-Meier (KM) curves were produced for all categorical predictors to look for differences in survival with different values of the predictor. Associations between potential predictors and risk of death after discharge were explored in univariable Cox regression models. *b) Selecting and validating predictive models:* The dataset was randomly split into two subsets (training set containing 80% of data and the validation set with the remaining 20%) which were then compared to confirm that there were no important differences between the two subsets. Those predictors showing evidence of an association (p-value ≤0.05) with the outcome in a univariable analysis were selected for potential inclusion in a multivariable Cox regression model (primary model). Three additional models were also examined based

on their suitability for different contexts: Model 2), which uses the primary model as reference, but includes only variables with minimal costs; Model 3) based exclusively on clinical variables collected on admission; and Model 4) predictors of PDM restricted to infants <3months. The area under the curve (AUC) was plotted for each model over time using the training set (formula: $H(t) = H_0(t) \times \exp(b_1X_1 + b_2X_2 + b_3X_3 + ... + b_kX_k)$). Confidence intervals of AUC were estimated by 1000 bootstrap replicates using the bias-corrected percentile method[29]. As there could be more than one admission for some children, the models described above were estimated taking into account within-child clustering. Analyses used Stata Statistical software (*Release 15*). Graphical representation of AUC curves was done in R (R Core Team; 2017) using the *survivalROC* package.

Ethical considerations

This study examined data collected in the context of routine clinical practice. DSS and MSS ongoing in the study area have been approved by the National Ethics Committee of Mozambique.

RESULTS

Overall characteristics of study population

From 1st January 2000 to 31st December 2016, 58990 inpatient records were checked of which 29574 (50%) were initially excluded (figure 1). 3097 observations of children living in study area readmitted within follow-up (supplementary figure S1), hospital deaths (2.5%, 662/26319 of remaining children) and 25 deaths in the first 24 hours (<0.1%) were also excluded (figure 1). Thus, 25632 inpatient records of 18023 children <15 years old admitted to MDH were included in the analysis (Table 1). 2055

observations of 2049 infants <3months were also analysed separately (supplementary table S2).

Incidence of post-discharge deaths and potential predictors of PDM

During the 90-day follow-up period, 935 (3.6%) deaths after discharge occurred among the 25632 admissions, with 783/935 (83.7%) occurring at the community level and 488/935 (52.2%) within the first 30 days of discharge. Median time to death was 28 days (IQR 11-53). The risk of post-discharge deaths varied over time (figure 2A and supplementary figure S2) and by age (figure 2B) similarly to the risk of inpatient mortality (figure 2C).

Forty-five variables were tested for their univariable association with PDM (table 1). Infants <3months were more likely to die than older children (figure 3A; supplementary table S2). Similarly, poorer nutritional levels were clearly linked to PDM (figure 3B).

Predictive models and validation

Supplementary table S3 presents the comparison of the training and validation sets. Nineteen variables were associated with higher risk of PDM in the multivariate analysis (primary model, table 2). Infants less than 3 months had the highest rate of PDM and this decreased with increasing age (p<0.001) (supplementary table S4). The rate of PDM varied between rainy and dry seasons (HR 1.22, 95% CI 1.03-1.43). Severe acute malnutrition (SAM) (HR 3.26, 95% CI (2.08-5.12) as well as other 13 clinical variables were associated with PDM. Children with a positive blood culture (HR 1.68, 95% CI 1.33-2.12) and a positive HIV test (HR 1.77, 95% CI 1.07-2.91) also had a higher rate of death during the follow-up period. Absconding (HR 5.23, 95% CI 4.22-6.50) or referral to a higher level of health care (HR 4.48, 95% CI 3.31-6.05) were clearly

associated with death. Children with a malaria diagnosis had a lower risk of PDM (HR 0.44, 95% CI 0.36-0.54). The AUC for this model was around 0.80 during the 90 days follow-up period, being, at day 90, 0.79 (95% CI 0.75 - 0.82). At a HR cut-off point of 1.08, it had a sensitivity of 80%, specificity of 60% and a positive predictive value (PPV) of 6.9% (figure 4 and table 3). According to this model, 1.9% of all discharges will die in the first 90 days after discharge.

Time-varying AUC of the two additional simplified models (table 2), is compared in supplementary figure S3A. *Model 2*, which excluded blood culture but maintained minimal cost tests, performed similarly to the primary model, with an AUC around 0.80% until 60 days after discharge. *Model 3*, which included only clinical variables, performed slightly worse, with an AUC ~0.75 during the whole period. *Model 4*, limited to infants <3months, included variables such as breastfeeding and weight-for-age (WAZ) to assess nutritional status, on account of the excess of missing height data. Neonates appeared to have the highest risk of PDM among this age group (supplementary table S4). This model had an AUC at day 30 of 0.84 (95% CI 0.72 - 0.91) and at day 90 of 0.76 (95% CI 0.72 - 0.91). At a HR cut-off point of 0.5, it had a sensitivity of 79%, specificity of 53% and a PPV of 12.8% (table 3 and supplementary figure S3B). AUC and model's characteristics at probability cut-offs ensuring sensitivity of >80% are shown in table 5. CI of AUC between training and validation set and between primary model and the other models overlapped, meaning no significant differences between them were found.

DISCUSSION

This analysis, based on more than 20000 hospital discharges and 935 post-discharge deaths, is the largest study to date evaluating PDM in the first three months following hospital discharge from a rural district hospital in a LIC, and represents a systematic approach to ascertain predictors of PDM in a resource-constrained environment.

The cumulative three-month post discharge mortality found in this study (3.6%) is lower than that reported in the 1990s from other African settings, where incidence risk was estimated between 6.1% and 13%[14, 15], but similar to other more recent PDM studies[7, 9, 10, 18]. Importantly, inpatient mortality found in our cohort (2.5%) aligned closely with that reported in other settings[13, 14].

These findings highlight that risk of dying is greatest in the first 30 days immediately following discharge[7, 10], the most critical period for survival[10, 15, 18]. Overall, trends of post-discharge mortality for all ages changed over time. PDM rates increased over the period from 2000-2010, subsequently declining. This trend cannot be explained by an increase in inpatient mortality, as this was progressively decreasing since 2001 (figure 2C). One could speculate that variations in the epidemiology of a single disease may have played a significant role in PDM variations (Supplementary figure S4). For instance, malaria used to be highly endemic in the area at the beginning of the study period, with a subsequent declining trend observed from the year 2005 onwards, trends inversely proportional to those of the PDM curve. Children admitted with malaria, readily treatable and with a rapid recovery, are probably less likely to be associated with post-discharge complications. This could partly explain why a diagnosis of clinical malaria has been shown to be an overall protective factor against PDM (HR 0.44, 95% CI 0.36-0.54) a finding also reported in Kenya[9]. Similarly, although HIV incidence is now much higher in the area than it was a decade ago, the increasing uptake of

antiretroviral drugs probably implies a better control of this infection on PDM in recent years when more admissions due to HIV have been registered. Trends in the proportion of children admitted with other diseases with greater incidence of post-discharge deaths, such as SAM, showed an overall tendency parallel to the PDM curve over time. However, the declining trend of PDM seen at the end of the study period cannot be exclusively explained by malaria, HIV or SAM trends. The progressive introduction of other life-saving interventions, such as vaccination against Hib (2009), pneumococcus (2013), and rotavirus (2015) have reduced hospital admissions and, may also have contributed to these decreasing trends. PDM trends over time among infants <3 months differed slightly from other age groups, with a peak in 2003, and stable rates thereafter. In this highly vulnerable age group, effective interventions specifically designed to reduce mortality, have not been fully implemented in the study area.

The primary model, including all available useful variables performed remarkably well, particularly to predict risk of dying in the first month following discharge. This model predicts that 1.9% of children discharging from the hospital will die in the first 90 days following discharge. Applying a score based on this model to a population similar to ours and using a HR cut-off of 1.08, roughly 80% of children likely to die following discharge would be identified and the referral population would have a mortality risk of approximately 7%. This model however includes blood culture results, an expensive determination that requires laboratory infrastructures seldom available in poor settings. The two alternative simplified models, including more easy-to-collect lab results (Model 2) or only clinical variables (Model 3) seem more applicable, and still showed a good predictive capacity for PDM. Importantly, model 4, developed for infants <3 months old, uses only few variables, all of them easily and readily obtainable in most

resource constrained contexts and could identify 0.85 of infants <3months at risk of dying in the first days after discharge and nearly 0.80 during the remaining follow-up period.

Severe acute malnutrition is a recognized predictor of PDM[8-10, 13, 18] as our models confirm. The chronicity of malnutrition, the fact that it can predispose to an array of co-infections and complications, and its association with HIV infection in Manhiça[30], may all contribute to explain its associated prolonged mortality risk. On the other hand, children with unknown nutritional status had higher risk of dying compared to well-nourished children. This may be partly explained in cases of severe disease, where the severity of the child upon admission did not allow collecting anthropometric measurements. HIV positivity, a clear predictor of PDM[13, 20], remained in our model a strong independent predictor, even after adjusting for malnutrition. Rainy season was also associated to higher risk of PDM as more children are admitted during this season, likely due to the greater number of admissions and severe disease occurring in this season.

In this series, type of outcome at discharge, and particularly being transferred or absconding from hospital, were the greatest predictors of PDM. In this setting, children are usually transferred to a higher-level health facility whenever they are very sick or when they require a more specialized evaluation or supportive care, justifying their greatest PDM risk. Children absconding against medical recommendations (3.1% of the study sample) had an extremely high risk of post-discharge mortality, and represent one out of every five deaths in our series. In Manhiça, absconding is a cultural and financial phenomenon, typically occurring when families anticipate a bad outcome and prefer their children to die at home, additionally sparing costs associated with the transport of

a corpse. Socio-behavioural studies addressing this phenomenon and the perceptions of health professionals of its serious consequences are needed.

The majority (83.7%) of deaths following hospital discharge occurred at the community, in the absence of any further contact with the health system. A study investigating cause of death in Manhiça using verbal autopsies documented that 53% of all paediatric deaths occurred at home[28]. These alarming figures reflect the generalized challenges in access to care, which become even more blatant following hospital discharge.

Effective models for identifying children at risk of PDM should take into consideration the existing resources but consider illness as a continuum transcending the information that the admission snapshot can provide. A score or similar algorithm to that proposed by IMCI, based in predictive models and applied at discharge, could pinpoint children requiring a more rigorous follow-up after hospitalization. However, the identification of high risk does not imply that risk can be reduced. Future research should consider validation of these models in different contexts and prospectively assessing their accuracy to identify children at risk of dying after discharge in resource-constrained settings. Once identified, these children at higher risk of PDM could benefit from strategies to prevent post-discharge death and these strategies should especially focus in the first 30 days after discharge as it is the period with the highest risk of PDM. Community-based interventions driven by community-health workers consisting in pre and post-natal home visits, supporting low birth-weight (LBW) infants and sepsis case management, facilitating referral in case of need have reduced neonatal and infant mortality in several countries[31]. Although these interventions have not been explored in children after a hospital admission, their impact reducing PDM could be similar.

Alternative strategies, utilizing the prophylactic use of antimicrobials in those children at high risk should also be explored. A recent clinical trial conducted in Kenya exploring the efficacy of daily post-discharge co-trimoxazole prophylaxis in children admitted with complicated SAM without HIV found however no reduction in mortality during the first year after admission[32].

Continued investment in child mortality data collection and understanding circumstances of paediatric death following a hospital discharge is needed in order to design innovative, effective and feasible strategies to reduce the risk of childhood preventable deaths after hospitalization.

This study has several limitations, including its retrospective nature. Selection bias may arise due to the fact that almost half of children admitted to MDH between 2000 and 2016 were excluded and this might affect the representativeness of the study sample. Another limitation includes the fact that all clinical predictors were collected at the time of admission, and some these clinical variables may have changed throughout the hospitalization. We decided to use a single-discharge approach within 90 days of follow-up to avoid double counting time at risk, excluding observations of children re-admitted during the follow-up period. This strategy may have resulted in a clearer picture of the true community PDM but also in an underestimation of the likely higher real-life true incidence. Another factor potentially underestimating PDM is the exclusion of deaths occurring in the first 24 hours after discharge, as they were considered as hospital deaths. However, they merely represented <0.1%. The inclusion of children who were transferred or absconded from the hospital may be overestimating the incidence of PDM since they were not officially discharged, but this is an extremely frequent occurrence in African settings, and needs to be taken into consideration,

particularly in the light of the strength and magnitude of the statistical associations found. Importantly, we could not assess the role of LBW in infants as a likely risk factor for PDM, since this information was not available. On the other hand, the low specificity and positive predictive value found could compromise feasibility of interventions to prevent PDM, as a high number of children would be classed as high risk of dying after discharge. However, these models would allow the identification of the majority of children with risk of PDM. Finally, our predictive models lack an external validation.

Conclusion

This study highlights the importance and oversight of post discharge mortality as a significant portion of the childhood mortality pie. Simple models including predictors easily collected with minimal cost, such as those presented in this article, need to be prospectively validated in different circumstances and settings. Specific interventions targeting children identified to be at higher risk and guaranteeing their adequate follow-up at the hospital or even at the household level could possibly increase their survival possibilities. Implementation of such strategies could prevent avoidable deaths, especially among neonates and infants who suffer the highest burden of PDM.

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Figure 1. Study profile

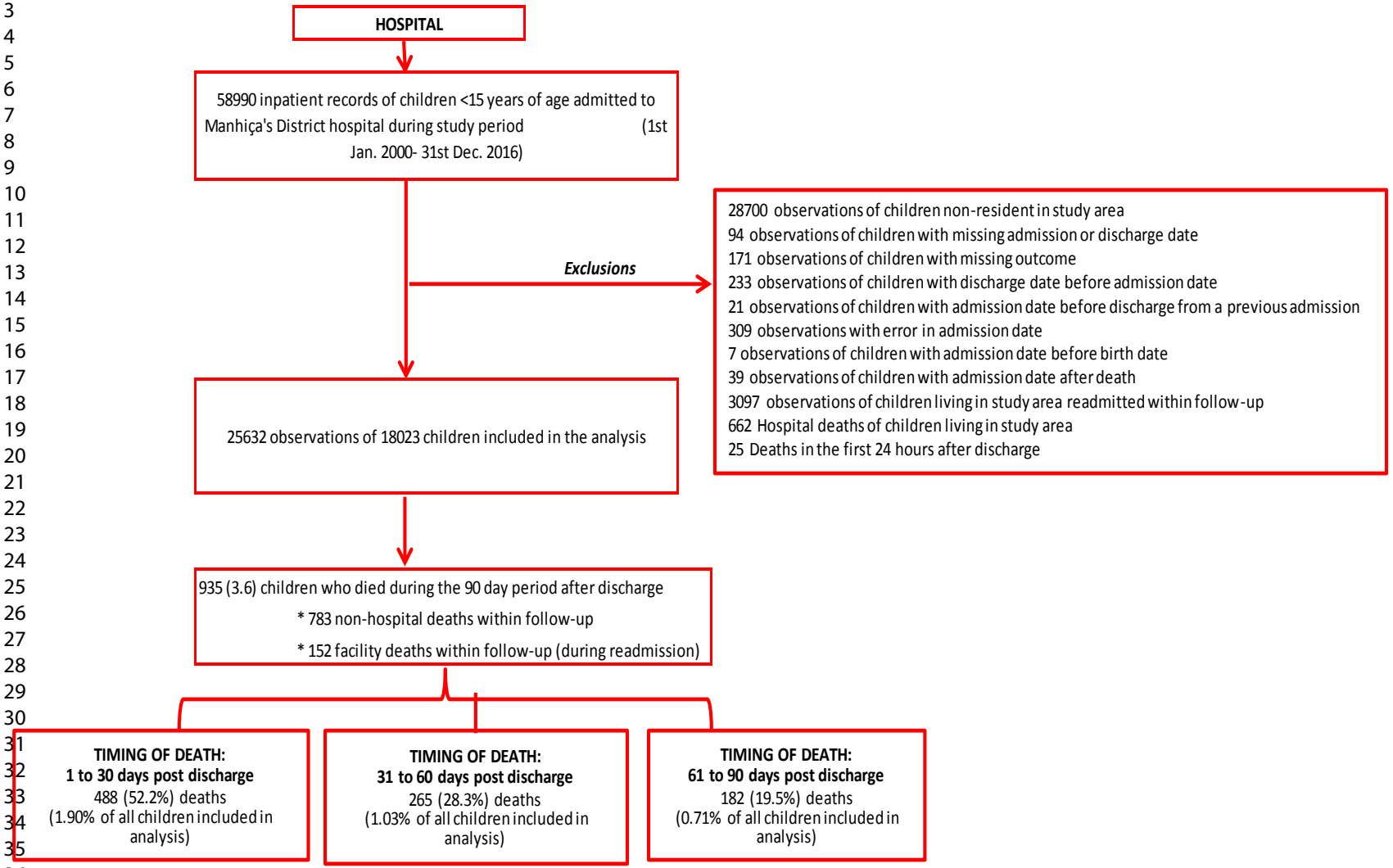
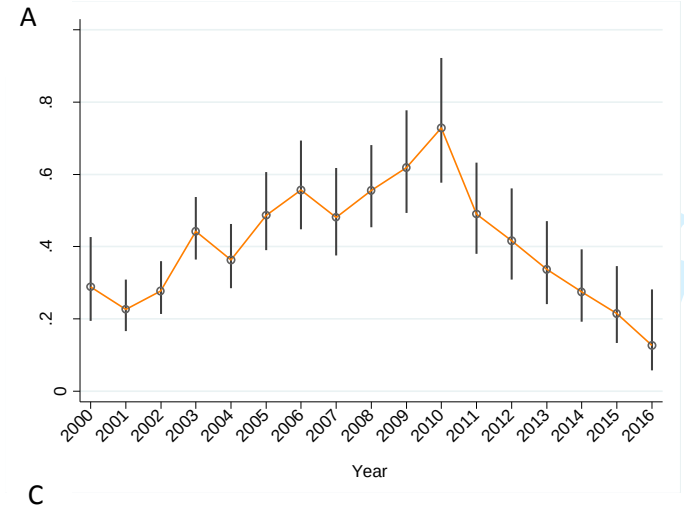
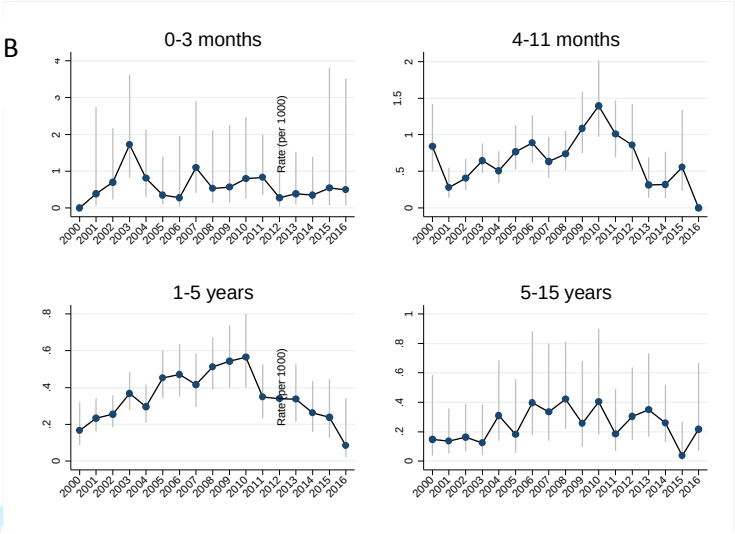
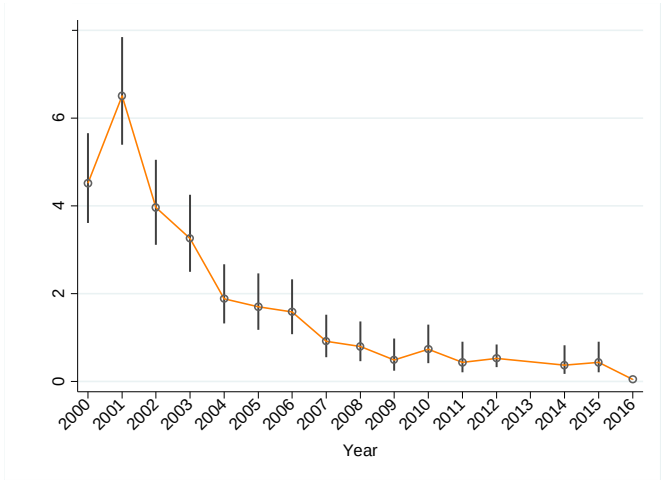


Figure 2: Mortality trends over time during the 17 year-long study period





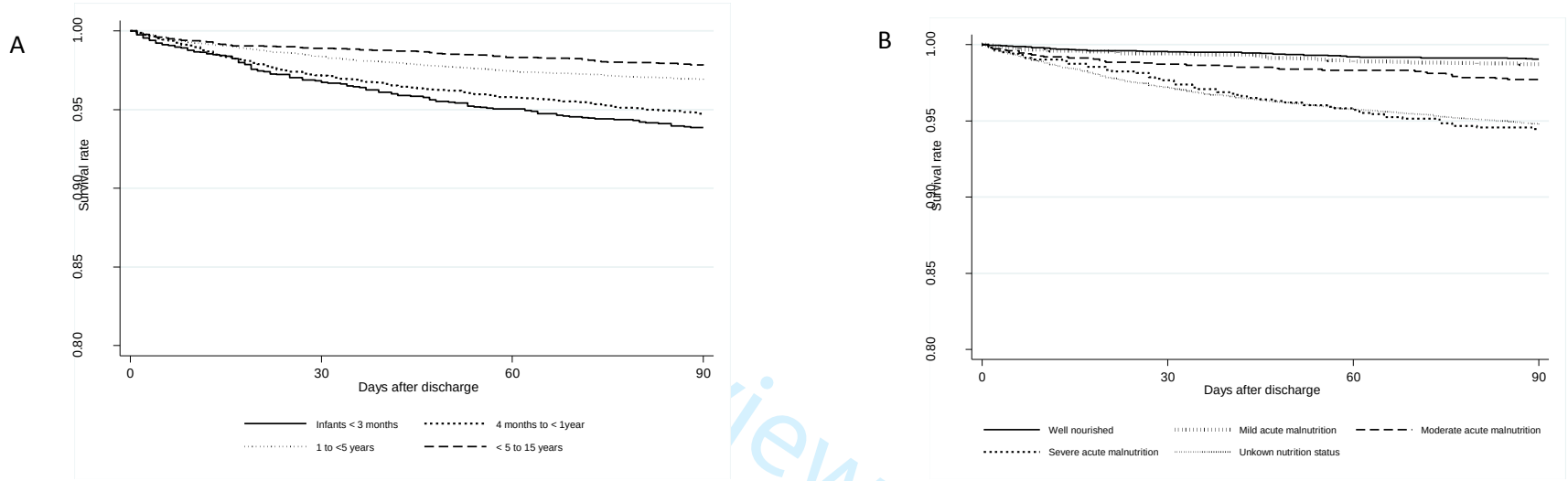


A) Yearly incidence of post-discharge mortality for all ages.

B) Yearly incidence of post-discharge mortality by age group.

C) Yearly incidence of inpatient mortality for all ages

Figure 3: Kaplan-Meier failure estimates for 935 deaths during 90 days follow-up after discharge from Manhiça District Hospital.



A) by age groups; B) by categories of nutritional status

The time−varying area under the curve of primary model comparing training and validation sets

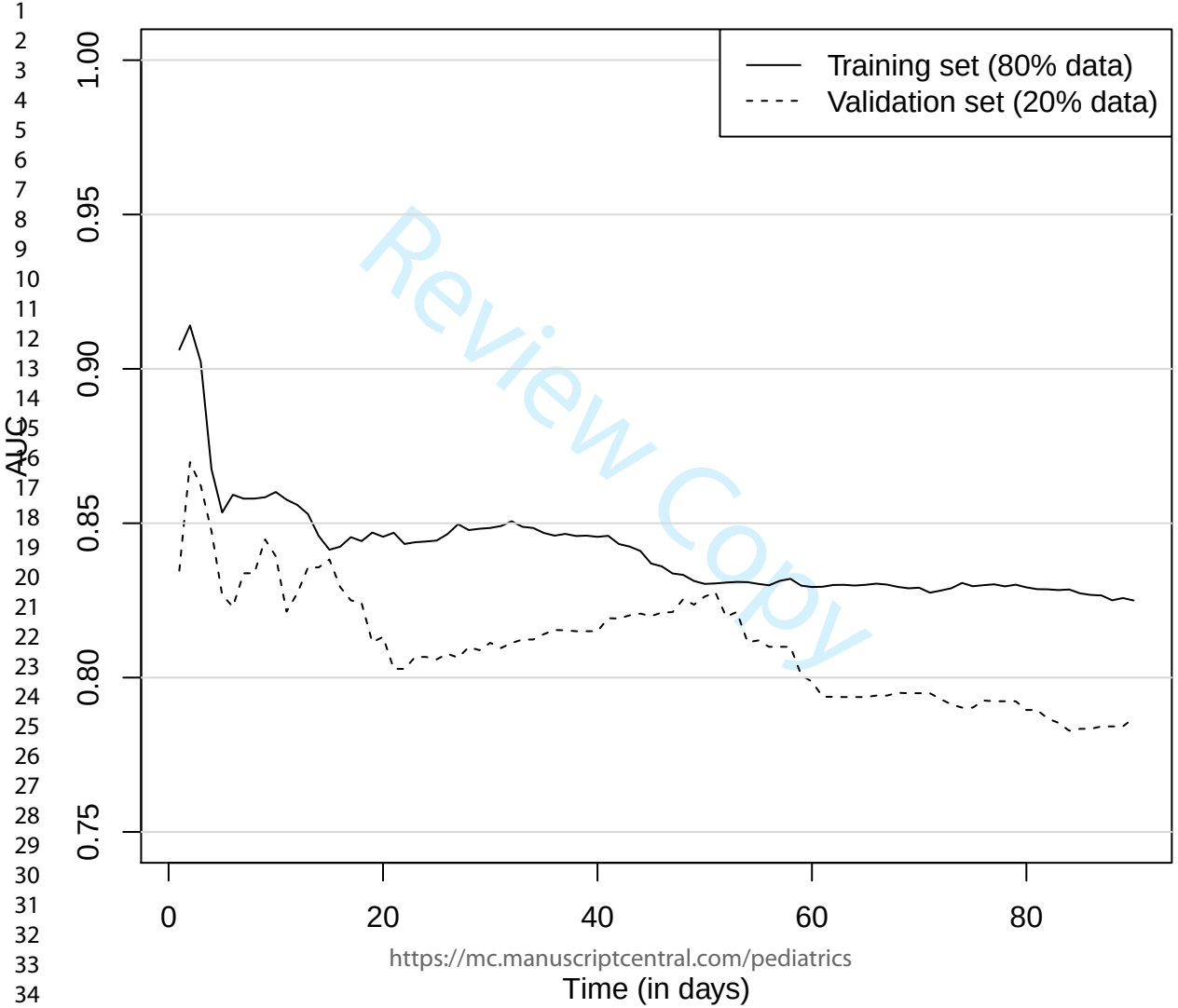


Table 1. Socio-demographic, clinical characteristics and univariate analysis of predictors on admission associated to post-discharge mortality in southern Mozambique, based on 25632 observations and 935 post-discharge deaths.

Characteristics on admission	Total observations included, N= 25632, n (%)	Children dying within 90 day after discharge[β] N= 935, n (%[h])	Univariate HR[Ψ]	95 % CI*	p value[θ]
Demographic characteristics					
Age					<0·001
< 3 months	2055 (8·0)	126 (6·1)	1·00		
4 to < 1year	5203 (20·3)	276 (5·3)	0·86	0·70 to 1·06	0·164
1 to 5 years	14558 (56·8)	450 (3·1)	0·50	0·41 to 0·60	<0·001
> 5 years	3816 (14·9)	83 (2·2)	0·35	0·26 to 0·46	<0·001
Female sex	11571 (45·3)	425 (3·7)	1·01	0·89 to 1·15	0·838
Rainy season	15624 (61·0)	602 (3·9)	1·16	1·02 to 1·33	0·029
Anthropometric characteristics					
Weight for height-z score (mean ±SD[ε])	-0·93 (0·01)	-1·99 (0·13)	0·63	0·57 to 0·69	<0·001
Nutritional status by WHZ[ɨ] z-score					<0·001
>-1 SD[ᵻ]	5994 (23·4)	57 (0·9)	1·00		
>-2 to <-1 SD[ᵻ]	2749 (10·7)	35 (1·3)	1·34	0·88 to 2·04	0·172
>-3 to <-2 SD[ᵻ]	1486 (5·8)	34 (2·3)	2·42	1·58 to 3·71	<0·001
< -3 SD[ᵻ]	1030 (4·0)	57 (5·5)	5·94	4·12 to 8·57	<0·001
Unknown	14373 (56·1)	752 (5·2)	5·62	4·30 to 7·36	<0·001
History of current disease*					
History of fever	23424 (91·4)	797 (3·4)	0·54	0·45 to 0·64	<0·001
History of cough	16324 (63·7)	705 (4·3)	1·78	1·53 to 2·06	<0·001
History of diarrhoea	5015 (19·6)	336 (6·7)	2·36	2·06 to 2·69	<0·001
History of vomiting	6004 (23·4)	268 (4·5)	1·32	1·15 to 1·52	<0·001
History of breathing difficulties	5303 (20·8)	298 (5·6)	1·81	1·58 to 2·08	<0·001
Anorexia	1648 (6·5)	101 (6·1)	1·79	1·46 to 2·20	<0·001
Blood in urine	97 (0·4)	5(5·2)	1·43	0·59 to 3·44	0·429
History of seizures	2658 (10·4)	39 (1·5)	0·37	0·27 to 0·51	<0·001

Symptoms and signs on admission					
Axillary temperature (ºC)					<0·001
Normothermia (35.5-37.4ºC)	9840 (37·0)	427 (4·3)	1·00		
Hypothermia (<35.5ºC)	513 (2·0)	30 (5·8)	1·31	0·90 to 1·89	0·158
Fever (≥37.5ºC)	15598 (61·0)	476 (3·1)	0·67	0·59 to 0·77	<0·001
Heart rate					0·647
Normal	16697 (65·5)	600 (3·6)	1·00		
Bradycardia	1902 (7·5)	75 (3·9)	1·10	0·87 to 1·40	0·436
Tachycardia	6876 (27·0)	259 (3·8)	1·05	0·90 to 1·21	0·518
Increased respiratory rate	11560 (45·3)	351 (3·0)	1·37	1·20 to 1·57	<0·001
Skin pinch goes back slowly	2007 (8·1)	186 (9·3)	3·03	2·58 to 3·56	<0·001
Dehydration	3907 (15·3)	248 (6·3)	2·04	1·77 to 2·37	<0·001
Pallor	4228 (16·5)	141 (3·3)	0·90	0·75 to 1·07	0·227
Jaundice	328 (1·1)	8 (2·4)	0·66	0·33 to 1·32	0·243
Oedema (any location)	1371 (5·4)	130 (9·5)	2·96	2·46 to 3·57	<0·001
Skin flaking off	464 (1·8)	46 (9·9)	2·90	2·15 to 3·90	<0·001
Depigmented or redish hair	1460(5·7)	216 (14·8)	5·30	4·55 to 6·18	<0·001
Oral candidiasis	493 (1·9)	108 (21·9)	7·44	6·08 to 9·09	<0·001
Swollen lymph nodes	827 (3·2)	113 (13·7)	4·33	3·56 to 5·25	<0·001
Conjunctivitis	416 (1·6)	24 (5·8)	1·62	1·08 to 2·43	0·020
Ear discharge	641 (2·5)	57 (8·9)	2·59	1·98 to 3·38	<0·001
Lower chest wall indrawing	5488 (21·4)	298 (5·4)	1·73	1·51 to 1·99	<0·001
Nasal flaring	4123 (16·1)	206 (5·0)	1·48	1·27 to 1·73	<0·001
Pathological breathing pattern	1018 (3·7)	54 (5·3)	1·50	1·14 to 1·97	0·004
Auscultatory crackles	5314 (20·8)	320 (6·0)	2·02	1·77 to 2·31	<0·001
Wheeze/roncus	3090 (12·1)	127 (4·1)	1·15	0·96 to 1·39	0·138
Heart gallop	882 (3·4)	32 (3·6)	0·99	0·70 to 1·41	0·972
Palpable liver	677 (2·6)	38 (5·6)	1·57	1·14 to 2·18	0·006
Palpable spleen	5378 (21·0)	145 (2·7)	0·69	0·58 to 0·82	<0·001
Neck stiffness	203 (0·8)	11 (5·4)	1·51	0·83 to 2·74	0·175
Abnormal fontanel (among applicable)	922 (8·7)	70 (7·6)	1·55	1·21 to 1·99	<0·001
Prostration	3261 (13·0)	146 (4·5)	1·29	1·08 to 1·54	0·005
BCS on admission					0.047
Normal (BCS=5)	24320 (95·0)	870 (3·6)	1·00		
Abnormal BSC (BCS=3-4)	873 (3·4)	39 (4·5)	1·26	0·91 to 1·73	0·164
Deep coma (BCS≤2)	396 (1·6)	22 (5·6)	1·57	1·03 to 2·41	0·037

Investigations					
Malaria diagnosis					<0·001
Negative	9431 (36·8)	581 (6·2)	1·00		
Positive	12232 (47·7)	202 (1·7)	0·26	0·22 to 0·31	<0.001
Test not done	3969 (15·5)	152 (3·8)	0·61	0·51 to 0·74	<0·001
Glycaemia					0.189
Normoglycaemia (2.5-11.0 mmol/l)	21384 (83·4)	798 (3·7)	1·00		
Hypoglycaemia (<2.5 mmol/l)	2413 (9·4)	83 (3·4)	0·92	0·73 to 1·15	0·471
Hyperglycaemia (>11.0 mmol/l)	1835 (7·2)	54 (2·9)	0·78	0·60 to 1·03	0·084
Blood culture					
Negative	24316 (94·9)	798 (3·3)	1·00		
Positive	1296 (5·1)	136 (10·5)	3·32	2·77 to 3·98	<0·001
Anaemia					0·902
No anaemia	8806 (34·4)	319 (3·6)	1·00		
Mild to moderate anaemia	13624 (53·1)	495 (3·6)	1·00	0·87 to 1·15	0·997
Severe anaemia	3202 (12·5)	121 (3·8)	1·04	0·84 to 1·28	0·709
HIV status					<0·001
Test not done	24128 (94·1)	867 (3·6)	1·00		
Negative	1246 (4·9)	25 (2·0)	0·55	0·37 to 0·82	0·004
Positive	258 (1·0)	43 (16·7)	4·97	3·59 to 6·88	<0·001
Outcome of the admission[η]					
					<0·001
Discharged alive	24145 (94·2)	666 (2·8)	1·00		
Absconded	805 (3·1)	161 (20·0)	8·18	6·87 to 9·74	<0·001
Transferred	682 (2·7)	108 (15·8)	6·30	5·12 to 7·75	<0·001

[†]SD: standard deviation. [ɨ]WHZ: Weigh-for-height. See definitions in Table S1. [β]It refers both to community deaths and deaths in a readmission during follow-up period. [ɳ]Percentage represents risk among children with same characteristics. [ψ] HR: Hazard ratios. HR and confidence intervals were derived from a Cox regression model.*Confidence intervals. [θ] P-value was derived from Wald test. BCS: Blantyre coma score. [ɤ]History of current disease reported by the child carer. [η]Hospital deaths and deaths in the first 24h omitted.

Table 2: Estimation of predictive models derived from the primary model including predictors associated to post-discharge death among 20506 observations of children less than 15 years old and 750 deaths in the first 90 days following discharge.

	PRIMARY MODEL			MODEL 2			MODEL 3		
Characteristics on admission	**Adjusted HR$^{\Psi}$**	**95 % CI***	**p value$^{\theta}$**	**Adjusted HR$^{\Psi}$**	**95 % CI***	**p value$^{\theta}$**	**Adjusted HR$^{\Psi}$**	**95 % CI***	**p value$^{\theta}$**
Demographic characteristics									
Age			<0·001			<0·001			0·002
< 3 months	1·00			1·00			1·00		
4 to < 1year	0·92	0·71 to 1·20		0·93	0·72 to 1·20	0·041	0·79	0·62 to 1·03	
1 to 5 years	0·69	0·53 to 0·91		0·71	0·54 to 0·92	<0·001	0·66	0·51 to 0·86	
> 5 years	0·54	0·38 to 0·76		0·54	0·38 to 0·76	<0·001	0·55	0·39 to 0·77	
Rainy Season	1.22	1.03 to 1.43	0·018	1.22	1.04 to 1.44	0·017	1.25	1·07 to 1·46	0·005
Anthropometric characteristics									
Nutrition status by WHZ‡ z-score			<0·001			<0·001			<0·001
>-1 SD†	1·00			1·00			1·00		
>-2 to <-1 SD†	1·23	0·75 to 2·01		1·27	0·77 to 2·07		1·32	0·81 to 2·14	
>-3 to <-2 SD†	2·40	1·49 to 3·87		2·44	1·51 to 3·93		2·30	1·41 to 3·75	
< -3 SD†	3·26	2·08 to 5·12		3·28	2·08 to 5·16		4·16	2·71 to 6·40	
Unknown	2·99	2·12 to 4·21		3·09	2·19 to 4·35		3·72	2·64 to 5·23	
History of current disease*									
History of diarrhoea	1·72	1·45 to 2·03	<0·001	1·70	1·44 to 2·01	<0·001	1·58	1·32 to 1·89	<0·001
History of cough	1·32	1·07 to 1·62	0·009	1·31	1·07 to 1·61	0·010	1·25	1·02 to 1·53	0·030
History of breathing difficulties	—	—	—	—	—	—	1·36	1·09 to 1·70	0·007
Symptoms and signs on admission									
Increased respiratory rate	1·41	1·18 to 1·68	<0·001	1·42	1·19 to 1·69	<0·001	1·27	1·07 to 1·52	0·007
Skin pinch goes back slowly	—	—	—	—	—	—	1·51	1·20 to 1·90	<0·001
Nasal flaring	0·69	0·55 to 0·86	<0·001	0·69	0·56 to 0·87	0·001	0·79	0·65 to 0·97	0·022
Auscultatory crackles	1·37	1·12 to 1·67	0·002	1·41	1·16 to 1·71	<0·001	1·44	1·19 to 1·75	<0·001
Oral candidiasis	2·64	1·98 to 3·52	<0·001	2·72	2·03 to 3·64	<0·001	3·51	2·70 to 4·58	<0·001
Oedema (any location)	1·86	1·39 to 2·48	<0·001	1·83	1·67 to 2·44	<0·001	2·48	1·88 to 3·27	<0·001
Depigmented or redish hair	2·03	1·60 to 2·57	<0·001	2·08	1·64 to 2·64	<0·001	2·42	1·90 to 3·07	<0·001

Swollen lymph nodes	1·89	1·42 to 2·51	<0·001	1·87	1·41 to 2·49	<0·001	2·23	1·70 to 2·93	<0·001
Ear discharge	1·76	1·20 to 2·58	0·004	1·74	1·16 to ·59	0·007	1·76	1·24 to 2·49	0·001
Prostration	1·42	1·15 to 1·75	0·001	1·44	1·17 to 1·77	<0·001	1·41	1·15 to 1·73	0·001
Investigations									
Malaria diagnosis			<0·001			<0·001	EXCLUDED		
Negative	1·00			1·00					
Positive	0·44	0·36 to 0·54		0·43	0·35 to 0·52				
Test not done	0·86	0·46 to 0·73		0·84	0·68 to 1·04				
Positive blood culture				EXCLUDED					
Negative	1·00								
Positive	1·68	1·33 to 2·12	<0·001						
HIV status			<0·001			<0·001			
Test not done	1·00			1·00					
Negative	0·53	0·35to 0·80		0·53	0·35 to 0·80				
Positive	1·77	1·07 to 2·91		1·80	1·07 to 3·01				
Outcome of the admission[η]									
			<0·001			<0·001			
Alive	1.00			1.00			EXCLUDED		
Absconded	5·23	4·22 to 6·50		5·50	4·45 to 6·79				
Transferred	4·48	3·31 to 6·05		4·57	3·36 to 6·21				

[ϯ] WHZ: weight for height. [ϯ]SD: standard deviation. See definitions in Table S1. [β]It refers both community deaths and deaths in a readmission during follow-up period. [Ψ]HR: Hazard ratios. HR and confidence intervals were derived from a Cox regression model .*Confidence intervals. [θ] P-value was derived from Wald test. [ϯ]History of current disease reported by the child carer. [η]Hospital deaths and deaths in the first 24h omitted. [δ]AUC: area under the curve.

Table 3: Model's characteristics at probability cut-offs ensuring sensitivity of >80%

Model	AUC[z] (95% CI)*			Score cut point			Sensitivity (%)			Specificity (%)			PPV[n] (%)		
	Day 30	Day 60	Day 90	Day 30	Day 60	Day 90	Day 30	Day 60	Day 90	Day 30	Day 60	Day 90	Day 30	Day 60	Day 90
Primary model (training)	0.81 (0.76 - 0.86)	0.80 (0.76 - 0.84)	0.79 (0.75 - 0.82)	1.09	1.08	1.08	84.3	83.0	80.3	60.0	60.0	60.0	4.2	6.0	6.9
Primary model (validation)	0.85 (0.83 - 0.87)	0.83 (0.81 - 0.85)	0.83 (0.81 - 0.84)												
Model 2	0.81 (0.76 - 0.86)	0.80 (0.76 - 0.84)	0.78 (0.75 - 0.82)	1.10	1.09	0.93	83.5	82.6	83.0	60.0	60.1	55.0	4.2	6.0	6.4
Model 3	0.78 (0.72 - 0.82)	0.75 (0.71 - 0.79)	0. 75 (0.71 - 0.78)	1.53	1.53	1.53	84.6	82.9	80.6	54.6	54.9	55.0	3.8	5.3	6.2
Model 4	0.84 (0.72 - 0.91)	0.76 (0.64 - 0.85)	0.76 (0.72 - 0.91)	0.9	0.5	0.5	87.0	78.8	78.7	64.1	52.6	52.9	11.4	11.6	12.8

[z]AUC: area under the curve; *CI: confidence intervals. [n]PPV: positive predictive value.

Supplementary information

Post-Discharge Mortality Prediction in Sub-Saharan Africa

Contents

Figure S1. Flow chart on how hospital readmissions of children were selected.

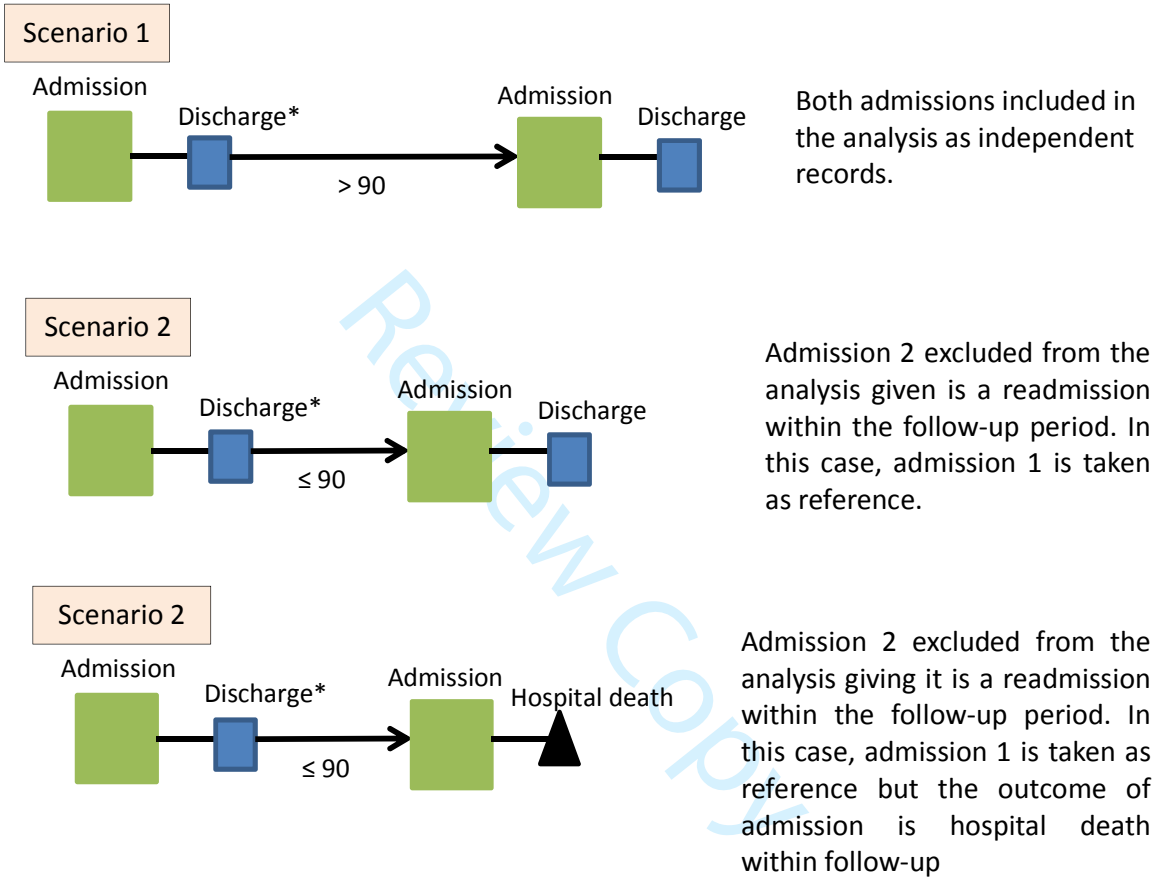


Figure S2: Number of admissions and post-discharge deaths in the first 90 days of follow-up by year.

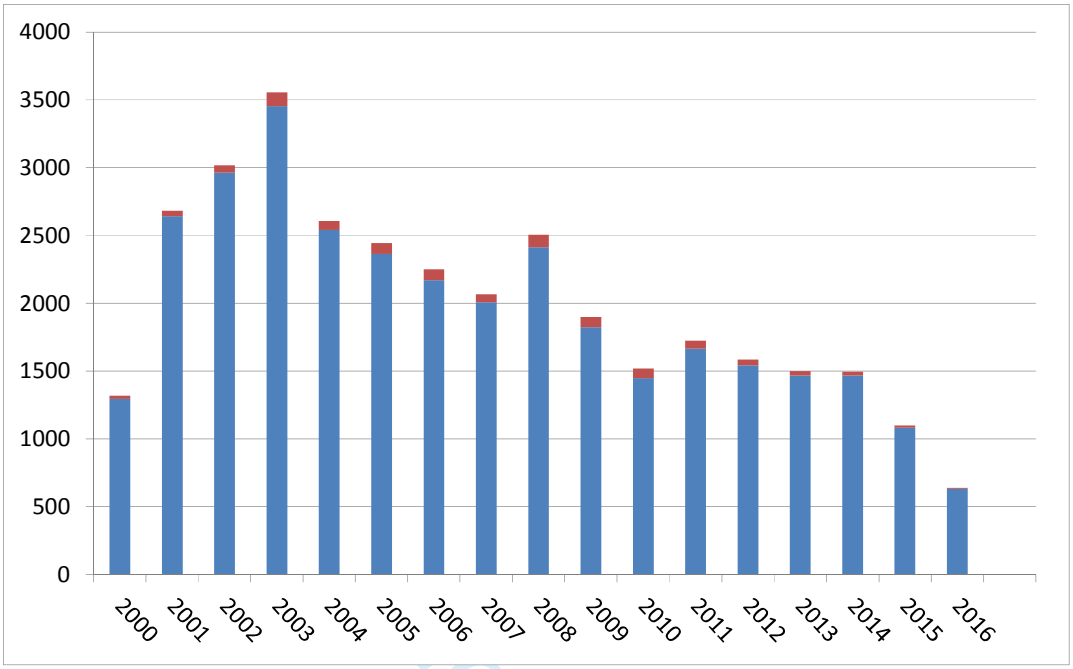
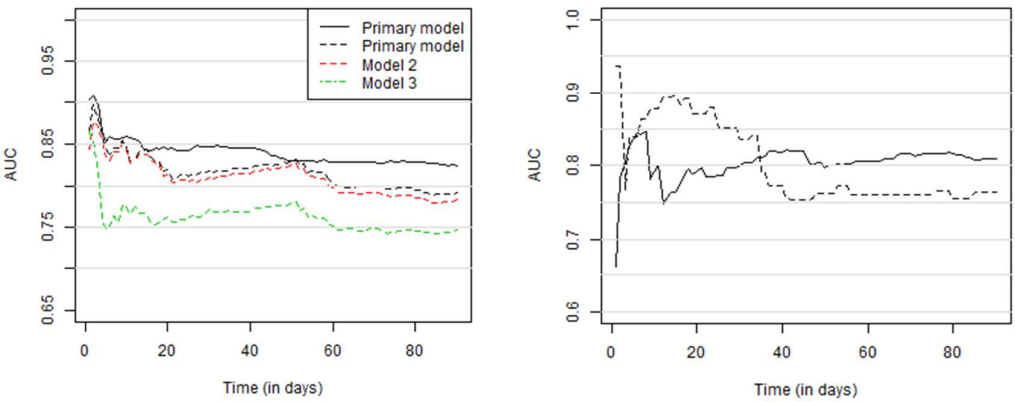
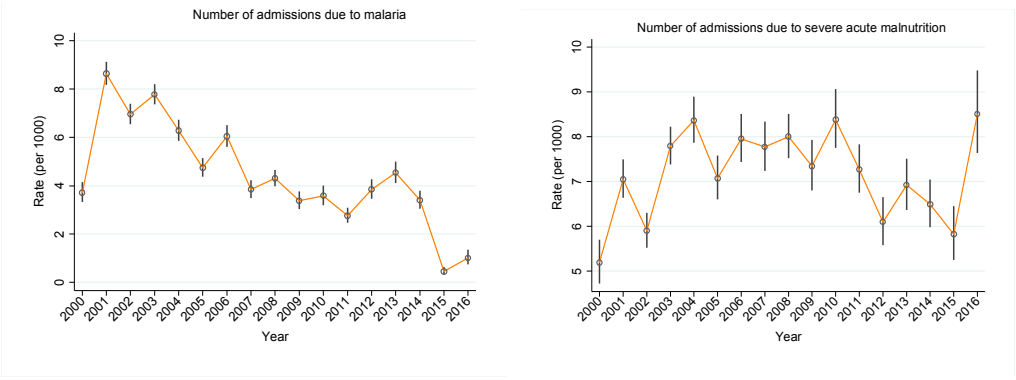


Figure S3: Time-varying area under the curve of predictive models estimated from primary model.



A) Comparison among primary model and estimated models 2 and 3. B) Comparison between training and validation set of estimated model 4 which includes exclusively infants <3 months.

Figure S4: Number of admissions due to specific diseases over time



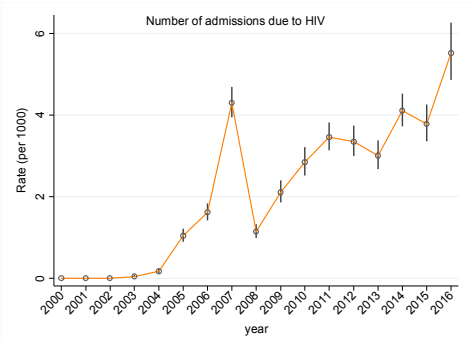


Table S1: Definitions

Rainy Season	November to April
Blantyre coma scale (BCS):	Based on pain response, cry or verbal response, eyes movement. Score 0 to 5 · Normal: 5 · Impaired consciousness: 3-4 · Coma: ≤ 2
WHZ	Weight-for-height z-score calculated using the WHO growth chart · >-1 DS: well nourished · >-2 to <-1DS: mild acute malnutrition · >-3 to <-2DS: moderate acute malnutrition · <-3DS: severe acute malnutrition
WAZ	Weight-for-age z-score calculated using the WHO growth chart · <-3DS: underweight
Malaria	A malaria case was defined as a child admitted with a clinical diagnosis of malaria with a positive P. falciparum asexual parasitaemia.
Increased Respiratory Rate **(IRR)**	• IRR in < 2 months old children = respiratory rate ≥ 60 • IRR in 2 - <12 months old children = respiratory rate ≥ 50 • IRR in 12 - <60 months old children = respiratory rate ≥ 40 • IRR in 60 - <120 months old children = respiratory rate ≥ 30 • IRR ≥ 120 months old children = respiratory rate ≥ 20
Heart rate normal ranges in beats per minute:	· 0 to 1 year: 110-160 · 1 -2 years: 100-150 · 2-5 years:95-140 · 5-12 years: 80-120 · >12 years: 60-100
Non-severe anaemia	· Children ≤ 28 days old with a packed cell volume (PCV) between 25- <42% · Children >28 days: PCV between 15- <33%
Severe anaemia	· Children ≤ 28 days old= PCV <25% · Children >28 days: PCV <15%
Hypoglycaemia	Blood glucose levels <3.0 mmol/L (categorized as severe if <2.5 mmol/L)
Hyperglycaemia	Blood glucose levels >11.0 mmol/L (categorized as severe if <2.5 mmol/L)
Hypothermia	Axillary temperature < 35°C
Verbal autopsy	Research method based on a structured interview conducted to family members of the deceased individual that helps to determine the probable causes of death in cases where there was no medical record or formal medical attention given, validated by World Health Organization

Table S2: Socio-demographic, clinical characteristics and univariate analysis of predictors on admission associated to post-discharge mortality among 2055 observations of infants less than 3 months of age and 126 post-discharge deaths in southern Mozambique.

Characteristics on admission	Total observations included N= 2055, n (%)	Infants < 3months dying within 90 day after discharge[β] N= 126, n (%[h])	Univariate[ż] HR[Ψ]	95 % CI*	p value[ɵ]
Demographic characteristics					
Age					
< 28 days	945 (46·0)	80 (8·5)	1·00		
≥ 28 days to < 3months	1110 (54·0)	46 (5·3)	0·48	0·33 to 0·69	<0·001
Female sex	934 (45·6)	61 (6·5)	1·12	0·79 to 1·60	0·502
Rainy season	1239 (60·3)	74 (6·0)	0·94	0·66 to 1·33	0·711
Anthropometric characteristics					
Weight for age-z score(mean ±SD[ŧ])	-0·22 (0·03)	-1·55 (0·12)	0·52	0·46 to 0·58	<0·001
Nutrition status by WAZ[ɨ] z-score					<0·001
>-1 SD[ŧ]	1458 (71·0)	38 (2·6)	1·00		
>-2 to <-1 SD[ŧ]	312 (15·2)	35 (11·2)	4·50	2·85 to 7·12	<0·001
>-3 to <-2 SD[ŧ]	155 (7·5)	29 (18·7)	7·90	4·87 to 12·83	<0·001
< -3 SD[ŧ]	61 (3·0)	17 (27·9)	12·14	6·90 to 21·35	<0·001
Unknown	69 (3·4)	7 (10·1)	4·05	1·81 to 9·07	<0·001
History of current disease[ż]					
Current breastfeeding	1489 (72·5)	91 (6·1)	0·43	0·25 to 0·75	0·003
History of fever	1660 (80·8)	101 (6·1)	0·96	0·62 to 1·49	0·853
History of cough	1326 (64·5)	95 (7·2)	1·71	1·14 to 2·56	0·010
History of diarrhoea	1706 (83·0)	28 (1·6)	1·44	0·94 to 2·19	0·094
History of vomiting	1713 (83·4)	35 (2·0)	1·98	1·34 to 2·93	0·001
History of breathing difficulties	748 (20·8)	64 (8·6)	1·81	1·28 to 2·58	0·001
Anorexia	168 (8·2)	19 (11·3)	2·07	1·27 to 3·39	0·004
History of seizures	42 (2·0)	3 (7·1)	1·16	0·37 to 3·61	0·795
Symptoms and signs on admission					
Axillary temperature (ºC)					0·0361
Normothermia (35.5-37.4ºC)	1081 (52·7)	54 (5·0)	1·00		
Hypothermia (<35.5ºC)	51 (2·5)	6 (11·8)	2·46	1·05 to 5·73	0·037

Fever (≥37.5ºC)	919 (44·8)	65 (7·1)	1·43	1·00 to 2·06	0·051
Heart rate					0·647
Normal	1352 (65·8)	86 (6·4)	1·00		
Bradycardia	169 (8·2)	9 (5·3)	0·84	0·42 to 1·67	0·616
Tachycardia	534 (25·9)	31 (5·8)	0·91	0·60 to 1·36	0·634
Increased respiratory rate	1101 (53·8)	86 (7·8)	1·93	1·32 to 2·82	0·001
Skin pinch goes back slowly	113 (5·5)	13 (11.5)	2·03	1·14 to 3·60	0·015
Dehydration	244 (11·9)	25 (10·2)	1·90	1·22 to 2·95	0·004
Pallor	126 (6·1)	6 (4·8)	0·76	0·33 to 1·72	0·510
Jaundice	42 (2·0)	3 (7·1)	1·14	0·37 to 3·49	0·813
Oedema (any location)	28 (1·4)	2 (7·1)	1·14	0·29 to 4·48	0·845
Skin flaking off	61 (3·0)	4 (6·6)	1·06	0·40 to 2·84	0·906
Depigmented or redish hair	17 (0·8)	3 (17·6)	3·19	0·99 to 10·27	0·052
Oral candidiasis	79 (3·9)	22 (27·8)	6·18	3·87 to 9·85	<0·001
Swollen lymph nodes	23 (1·1)	6 (26·1)	4·73	2·16 to 10·36	<0·001
Conjunctivitis	69 (3·4)	6 (8·7)	1·46	0·64 to 3·31	0·366
Ear discharge	46 (2·2)	4 (8·7)	1·46	0·54 to 3·98	0·457
Lower chest wall indrawing	795 (38·8)	61 (7·7)	1·50	1·06 to 2·13	0·022
Nasal flaring	582 (28·3)	38 (6·5)	1·10	0·75 to 1·60	0·631
Pathological breathing pattern	138 (6·7)	11 (8·0)	1·34	0·72 to 2·49	0·350
Auscultatory crackles	572 (27·9)	49 (8·6)	1·68	1·17 to 2·40	0·005
Wheeze/roncus	361 (17·6)	22 (6·1)	0·99	0·63 to 1·57	0·977
Heart gallop	37 (1·8)	2 (5·4)	0·86	0·22 to 3·38	0·828
Palpable liver	35 (1·7)	3 (8·6)	1·41	0·45 to 4·35	0·554
Palpable spleen	158 (21·0)	9 (7·1)	0·92	0·47 to 1·80	0·799
Abnormal fontanel	112 (5·6)	7 (6·3)	1·02	0·47 to 2·21	0·958
Prostration	398 (20·5)	25 (6·3)	1·06	0·68 to 1·66	0·782
BCS on admission					0.923
Normal (BCS=5)	1851 (90·3)	115 (6·2)	1·00		
Abnormal BSC (BCS=3-4)	164 (8·0)	9 (5·5)	0·88	0·44 to 1·72	0·701
Deep coma (BCS≤2)	35 (1·7)	2 (5·7)	0·91	0·23 to 3·67	0·898
Investigations					
Malaria diagnosis					<0·072
Negative	1257 (61·2)	88 (7·0)	1·00		
Positive	414 (20·2)	16 (3·9)	0·54	0·32 to 0·93	0.025
Test not done	384 (18·7)	22 (5·7)	0·81	0·51 to 1·29	0·389
Glycaemia					0.988

Normoglycaemia (2.5-11.0 mmol/l)	1799 (87·5)	110 (6·1)	1·00		
Hypoglycaemia (<2.5 mmol/l)	163 (7·9)	10 (6·1)	1·00	0·53 to 1·93	0·984
Hyperglycaemia (>11.0 mmol/l)	93 (4·5)	6 (6·5)	1·07	0·47 to 2·45	0·877
Blood culture					
Negative	1881 (91·7)	110 (5·8)	1·00		
Positive	171 (8·3)	16 (9·4)	1·62	0·96 to 2·72	0.071
Anaemia					0·008
No anaemia	951 (46·3)	41 (4·3)	1·00		
Mild to moderate anaemia	845 (41·1)	64 (7·6)	1·78	1·20 to 2·63	0·004
Severe anaemia	259 (12·6)	21 (8·1)	1·90	1·12 to 3·21	0·017
HIV status					0·001
Test not done	1850 (90·0)	115 (6·2)	1·00		
Negative	185 (9·0)	6 (3·2)	0·52	0·23 to 1·18	0·115
Positive	20 (1·0)	6 (25·0)	4·50	1·94 to 11·04	0·001
Outcome of the admission[n]					
					<0·001
Discharged alive	1906 (92·8)	91 (4·8)	1·00		
Absconded	85 (4·1)	19 (22·4)	5·23	3·19 to 8·59	<0·001
Transferred	64 (3·1)	16 (25·0)	6·31	3·61 to 11·02	<0·001

[t]SD: standard deviation. [i]WAZ: Weigh-for-age. [β]It refers both community deaths and deaths in a readmission during follow-up period. [h]Percentage represents risk among children with same characteristics. [z]Univariate model based on 2055 infants under 3 months and 126 deaths. [Ψ]HR: Hazard ratios. Hazard ratios and confidence intervals were derived from a Cox regression model.*Confidence intervals. [θ] P-value was derived from Wald test. [v]Validated predictive model base of 80% of data (1636 infants). BCS: Blantyre coma score. [ɤ]History of current disease reported by the child carer. [n]Hospital deaths omitted.

Table S3: Socio-demographic and clinical characteristics of children <15 years admitted at MDH comparing training (80% of data) and validation set (20% of data).

Characteristics at admission	Training set, N= 20506, n (%)	Validation set, N= 5126, n (%[h])	p value [θ]
Demographic characteristics			
Age			0·935
< 3 months	1655 (8·0)	400 (8·0)	
4 to < 1year	4162 (20·0)	1041 (20·0)	
1 to 5 years	11635 (57·0)	2923 (57·0)	
> 5 years	3054 (15·0)	762 (15·0)	
Sex			
Male	11234 (55·0)	2746 (54·0)	
Female	9206 (45·0)	2365 (46·0)	0·113
Rainy season	12464 (61·0)	3160 (62·0)	0·257
Anthropometric characteristics			
Nutrition status by WHZ[i] z-score			0·540
>-1 SD[†]	4822 (24·0)	1172 (23·0)	
>-2 to <-1 SD[†]	2210 (11·0)	539 (11·0)	
>-3 to <-2 SD[†]	1178 (6·0)	308 (6·0)	
< -3 SD[†]	808 (4·0)	222 (4·0)	
Unknown	11488 (56·0)	2885 (56·0)	
Nutrition status by WAZ[ż] z-score			0·538
>-1 SD[†]	8326 (41·0)	2078 (41·0)	
>-2 to <-1 SD[†]	5379 (26·0)	1376 (27·0)	
>-3 to <-2 SD[†]	3375 (16·0)	815 (16·0)	
< -3 SD[†]	2314 (11·0)	599 (12·0)	
Unknown	1112 (5·0)	258 (5·0)	
History of current disease[ż]			
Current breastfeeding	5976 (29·0)	1545 (30·0)	0·224
History of fever	18766 (92·0)	4658 (91·0)	0·147
History of cough	13061 (64·0)	3262 (64·0)	0·957
History of diarrhoea	4032 (20·0)	983 (19·0)	0·431
History of vomit	4827 (24·0)	1177 (23·0)	0·372
History of difficulty breathing	4258 (21·0)	1045 (20·0)	0·503

Anorexia	1317 (6·0)	331 (6·0)	0·926
Blood in urine	77 (0·0)	20 (0·0)	0·878
History of seizures	2105 (10·0)	553 (11·0)	0·278
Symptoms and signs on admission			
Axillary temperature (ºC)			0·366
Normothermia (35.5-37.4ºC)	7532 (37·0)	1948 (38·0)	
Hypothermia (<35.5ºC)	395 (2·0)	118 (2·0)	
Hyperthermia (≥37.5ºC)	12548 (61·0)	3050 (60·0)	
Heart rate (mean±SD)			0·414
Normal	13331 (65·0)	3366 (66·0)	
Bradycardia	1543 (8·0)	359 (7·0)	
Tachycardia	1375 (27·0)	5501 (27·0)	
Increased respiratory rate	9256 (45·0)	2304 (45·0)	0·791
Skin pinch goes back slowly	1591 (8·0)	416 (8·0)	0·397
Dehydration	3128 (15·0)	779 (15·0)	0·921
Pallor	3376 (16·0)	852 (17·0)	0·792
Jaundice	253 (1·0)	75 (1·0)	0·191
Oedema (any location)	1082 (5·0)	289 (6·0)	0·304
Skin flaking off	358 (2·0)	106 (2·0)	0·121
Depigmented or redish hair	1158 (6·0)	302 (6·0)	0·499
Oral candidiasis	379 (2·0)	114 (2·0)	0·080
Swollen lymph nodes	665 (3·0)	162 (3·0)	0·766
Conjuntivitis	333 (2·0)	83 (2·0)	0·981
Ear discharge	518 (3·0)	123 (2·0)	0·603
Lower chest wall indrawing	4406 (22·0)	1082 (21·0)	0·557
Nasal flaring	3297 (16·0)	826 (16·0)	0·957
Pathological breathing pattern	793 (4·0)	225 (4·0)	0·087
Auscultatory crackles	4253 (21·0)	1061 (21·0)	0·951
Wheeze/roncus	2480 (12·0)	610 (12·0)	0·709
Heart gallop	720 (4·0)	162 (3·0)	0·218
Palpable liver	523 (3·0)	154 (3·0)	0·007
Palpable spleen	4296 (21·0)	1082 (21·0)	0·804
Neck stiffness	167 (1·0)	36 (1·0)	0·417
Abnormal fontanella (among applicable)	760 (4·0)	162 (3·0)	0·158
Prostration	2606 (13·0)	655 (13·0)	0·987

BCS at admission			0·221
Normal (BCS=5)	19476 (95·0)	4844 (95·0)	
Abnormal BSC (BCS=3-4)	683 (3·0)	190 (4·0)	
Deep coma (BCS≤2)	308 (2·0)	88 (2·0)	
Investigations			
Malaria diagnosis			0·750
Negative	7529 (37·0)	1902 (37·0)	
Positive	9810 (48·0)	2422 (47·0)	
Test not done	3167 (15·0)	802 (16·0)	
Glycaemia			0.478
Normoglycaemia (2.5-11.0 mmol/l)	17124 (84·0)	4260 (83·0)	
Hypoglycaemia (<2.5 mmol/l)	1934 (9·0)	479 (9·0)	
Hyperglycaemia (>11.0 mmol/l)	1448 (7·0)	387 (8·0)	
Blood culture			0·473
Negative	19436 (95·0)	4880 (95·0)	
Positive	1054 (5·0)	242 (5·0)	
Test not done	16 (0·0)	4 (0·0)	
Anemia			0·420
Non anemia	7019 (34·0)	1787 (35·0)	
Non-severe anaemia	10900 (53·0)	2724 (53·0)	
Severe anaemia	2587 (13·0)	615 (12·0)	
HIV status			0·638
Test not done	19298 (94·0)	4830 (94·0)	
Negative	1006 (5·0)	240 (5·0)	
Positive	202 (1·0)	56 (1·0)	
Outcome of the admission[n]			
			0·217
Alive	19340 (94·0)	4805 (94·0)	
Absconded	637 (3·0)	168 (3·0)	
Transferred	529 (3·0)	153 (3·0)	

[ɬ]SD: standard deviation. [ɨ]WHZ: Weigh-for-height.See definitions in Table S1.[ƶ]WAZ: Weight-for-age. [β]It refers both communitary deaths and deaths in a readmission during follow-up period. [ɳ]Percentage represents risk among children with same chacarteristics. [Ψ]Hazard ratios and confidence intervals were derived from a Cox regression model.*Confidence intervals. [ɵ] P-value was derived from Wald test. BCS: Blantyre coma score. [ʭ]History of current disease reported by the child carer. [ɳ]Hospital deaths ommited.

Table S4: Estimation of a predictive model including predictors associated to post-discharge death among 1655 observations of infants less than 3 months old and 94 deaths in the first 90 days following discharge.

Characteristics on admission	Adjusted HR[Ψ]	95 % CI*	p value[θ]
Demographic characteristics			
Age			
< 28 days	1·00		
≥ 28 days to < 3months	0·43	0·33 to 0·68	<0·001
Anthropometric characteristics			
Nutrition status by WAZ[ɨ] z-score			<0·001
>-1 SD[†]	1·00		
>-2 to <-1 SD[†]	4·53	2·51 to 8·19	
>-3 to <-2 SD[†]	7·03	3·87 to 12·77	
< -3 SD[†]	13·49	7·43 to 24·51	
Unknown	5·11	1·77 to 14·72	
History of current disease[ж]			
History of breathing difficulties	1·68	1·13 to 2·52	0·011
Symptoms and signs on admission			
Axillary temperature (ºC)			0·020
Normothermia (35.5-37.4ºC)	1·00		
Hypothermia (<35.5ºC)	2·30	1·04 to 5·11	
Fever (≥37.5ºC)	1·67	1·10 to 2·53	
Oral candidiasis	4·32	2·51 to 7·43	<0·001
Outcome of the admission[ɳ]			
			<0·001
Discharged alive	1·00		
Absconded	5·23	2·97 to 9·20	
Transferred	5·92	2·78 to 12·64	

[†]SD: standard deviation. [ɨ]WAZ: Weigh-for-age. [β]It refers both community deaths and deaths in a readmission during follow-up period. [Ψ]HR: Hazard ratios. HR and confidence intervals were derived from a Cox regression model.*Confidence intervals. [θ] P-value was derived from Wald test. BCS: Blantyre coma score. [ж]History of current disease reported by the child carer. [ɳ]Hospital deaths omitted.

List word counts below (do not paste the text here). Please see the Decision Letter Attachment for allowances as they pertain to your manuscript type.

# of words in Abstract: **250** (250 words allowed)
# of words in Manuscript Body: **3534** (3000 allowed for Regular Articles/Quality Reports; 4000 Reviews/Special Articles; 800 Commentaries; 1200 Perspectives)
# of characters in Main Title: **52** characters (97 characters allowed, including spaces)
# of characters in Short Title: **33** (55 characters allowed, including spaces)
# of words in "Table of Contents Summary": **25** (25 words allowed; this section appears in all articles with abstracts)
# of words in "What's Known on this Subject": **39** (40 words allowed; this section appears in Regular Articles only)
# of words in "What this Study Adds": **40** (40 words allowed; this section appears in Regular Articles only)

2018-0606-R2– Post-Discharge Mortality Prediction in Sub-Saharan Africa -- by Madrid et al.

EDITOR/REVIEWER COMMENTS *Paste each of the editor and reviewer queries here.*	**AUTHOR'S RESPONSE** *Paste your answer to the editor and reviewer queries here. If you alter your manuscript to address this query, you MUST paste the relevant altered text here – verbatim as it appears in the manuscript.*	**REFERENCE PAGE** *State where* the change now appears in your newly revised manuscript.*	**CHANGE APPROVED? FOR EDITORIAL USE ONLY**
EXAMPLE: Reviewer 1's comment	EXAMPLE: A brief response to this reviewer's comment. The text now states: "insert relevant changed text here"	EXAMPLE 1: Page 7, lines 10-22 EXAMPLE 2: No change	
Editor comment 1: Change the main title (both in your paper and in online Step 1) to: Post-Discharge Mortality Prediction in Sub-Saharan Africa	Change applied	**Page 1 and online step 1**	
Editor comment 2: Change the short title (both in your paper and in online Step 1) to: Post-Discharge Mortality Prediction	Change applied	**Page 2 and online step 1**	
Reviewer 1´s comments:			
Concise, well written to frame the problem. I have one clarification re: page 6, lines 44-46: in terms of risk factors for reference 4 on PDM, it seems as though there is some collinearity between those 4 risk factors. Were all 4 significant on	These risk factors are coming up from a systematic review performed by Wiens et al (see reference 4 in the main text). They didn't perform a meta-analysis. Some of studies included in this systematic review found some of these variables significant in multivariate analysis (ref 7, 8 and 9)	**NA**	

multivariate analyses?			
To clarify, were you able to track mortality even if children presented to 1 hospital, were admitted/discharged, and then presented to another hospital at the time of the second visit? Do most children present to the same facilities over time?	There are two hospital which admit children in Manhiça district, Manhiça district Hospital (MDH), which is the main hospital in the study area, where the study was conducted and where most of admissions of study area occur & Chinavane Hospital, a small hospital about 60 minutes away from Manhiça town and who was created to support the staff and villagers working at a nearby Sugar Cane factory. This second hospital only admits a few paediatric patients per week. We have only captured admissions to MDH where morbidity surveillance is going on.	**NA**	
Page 8, line 38: the study period predates the advent of ICD-10; were patients in the earlier years reclassified into ICD-10? I am curious, as ICD-10 has a greater level of detail required for coding than earlier systems, and some of us find it challenging to assign ICD-10 codes prospectively, hence the challenge of applying this retrospectively.	All diagnoses prior to July 2003 were coded according to a list of codes created by the CISM since 1996. We started using ICD10 in 2003 and we also produced a conversion table for the previous codes. That table was developed by a group of experts including resident physicians, researchers of studies running in the area and statisticians. Certainly, the level of detail of the ICD10 is much higher than the other system and, therefore, the correspondence between both encodings was only possible at the level of ICD10 category (3 characters length). A brief explanation on this has been added in methods→ Morbity surveillance system: *"and International Statistical Classification of Diseases-based diagnoses (ICD-10) since 2003. All diagnoses prior to July 2003 were coded according to a list of codes created by the CISM since 1996".*	**Page 7, lines 16-18**	
How many children had none of the risk factors identified in the model?	In the training set, there is no case that does not have any risk factor of the primary model. The variable "age" is responsible for this. That is, all children under 3 months have some risk factor. However, if we do not take into account the variable "age", we found 58 individuals who do not have any risk factor. Authors believe this information is not necessarily relevant for the manuscript, and therefore, we have opted for not including any further comment related to this.	**NA**	
Verbal autopsies were mentioned in the methods, but I did not see the results in either the main or the supplementary tables. If the results are not presented, please remove reference to the verbal autopsies from the methods (and then please ignore my last comments on the methods section).	Verbal autopsies in methods are described as part of HDSS. However, following reviewer recommendations, we have removed them.	**Pag 8, lines 1-6**	
Page 24: please provide figure header and legend for this graphic	The title & legend of this graphic was entered through the submission website and updated in the corresponding figure. It is "The time-varying area under the curve of primary model comparing training and validation sets." Legend: "___ Training set (80% data) ----- Validation set (20% data)".	**Figure 4**	

Table 1: o I assume that not all variables were documented for all patients; these would be a comprehensive list of variables to collect uniformly even with prospective data collection. Were variables assumed to be negative unless documented as positive? Given the challenges to documentation, this is probably not an accurate assumption. Would it be possible to provide the denominator for the # of children in whom a given symptom was documented (as positive or negative)?	We did not include missing values for all variables as given the number of variables studied, the table would be endless. We followed the following methodology: For those variables with high proportion of missing values (>15%), we generated a new category for each variable called unknown or test not done to assess the effect of missing values and allow inclusion of more observations in the final model. This was already explained in methods "Data management & analysis", but we have added a further explanation: *"For each variable with a high proportion of missing values (<15%) but suspected to be a strong confounder, a "missing or unknown" category was created"*	**Page 8, lines 12-13**	
The model created has a very high AUC. However, the model would also apply to a large percentage of children admitted to inpatient units. As such, how would you apply the findings prospectively to reduce post-discharge mortality? I think a particular challenge would be how to avoid PDM beyond 30 days, as this may be due to a different illness and may be less amenable to intervention strategies than the < 30d PDM.	More than half of deaths occurred in the first 30 days. Then strategies would focus in avoiding death in this period. As explained in figure 1 and discussion, and seen in AUC (figure 3 in supplementary information) the model is better to predict deaths in these first 30 days. We have added some comments on top of what was stated in the previous version: "Once identified, these children at higher risk of PDM could benefit from strategies to prevent post-discharge death *and these strategies should especially focus in the first 30 days after discharge as it is the period with the highest risk of PDM*. *Community-based interventions driven by community-health workers consisting in pre and post-natal home visits, supporting low birth-weight (LBW) infants and sepsis case management, facilitating referral in case of need have reduced neonatal and infant mortality in several countries[31]. Although these interventions have not been explored in children after a hospital admission, their impact reducing PDM could be similar. Alternative strategies, utilizing the prophylactic use of antimicrobials in those children at high risk should also be explored.*"	**Page 15, lines 18-25**	
Why do you think there is higher mortality during the rainy season if it is not (page 11, line 50) associated with malaria?	This is because >60% of total admissions were in the rainy season and not only because of malaria but also due other causes including severe malnutrition (>60%) or HIV associated admissions (54%). Additionally, more children absconded (>60%) or were transferred to referral hospital (<60%) during the rainy season, and both are stronger predictors of PDM. We have added a comment in discussion: *"Rainy season was also associated to higher risk of PDM as more children are admitted during this season, likely due to the greater number of admissions and severe disease occurring in this season"*	**Page 14, lines 12-15**	
• Why do you think children with unknown WHZ scores had the same hazard ratio for mortality as children with severe malnutrition?	We explained this fact in draft versions, but due to limitation of words, we decided to remove it. We have added to discussion the following comment: "*On the other hand, children with unknown nutritional status had higher risk of dying compared to well-nourished children. This may be partly explained in cases of*	**Page 14, lines 7-11.**	

	severe disease, where the severity of the child upon admission did not allow collecting anthropometrics measurements."		
Reviewer 2´s comments:			
Given the lower specificity and PPV, the authors may need to recognize that many children will screen "positive" with their model. This does not mean it's still not a valuable output. It could, however, make interventions difficult. I think this warrants at least a line in the discussion. Given their AUC, spec / sens / PPV, I wouldn't be surprised if 50% of admitted children screened "positive". Doing an intervention in this case, would mean it needs to be really feasible. Might the model perhaps be most useful at identifying the kids who are unlikely to die rather than those most likely to die?	We agree with this comment and have added the following sentence in the discussion: *"On the other hand, the low specificity and positive predictive value found could compromise feasibility of interventions to prevent PDM, as a high number of children would be classed as high risk of dying after discharge. However, these models would allow the identification of the majority of children with risk of PDM."*	**Page 17, lines 3-8**	
If the authors can reduce acronyms (e.g., U5 for "under five" is probably not necessary), it would help readability. I recommend trying to limit to only established abbreviations and minimizing use in the abstract.	We have removed some acronyms such as U5 through the manuscript. We have used four acronyms in the abstract, three of them internationally accepted (HIV, WAZ & AUC). The only acronym introduced by authors is postdischarge mortality (PDM).	**Across the manuscript**	
The supplement definitions are important but pretty dense. This is in part because there are so many. An ideal world situation would be that the predictors are streamlined enough that these definitions could be included in the methods. Do they still feel each should remain?	Following the reviewer's suggestion, we have reduced the number of definitions, removing those clinical definitions which are internationally known.	**Supplementary information, table S1**	
Related to this - did the authors consider using any statistical corrections for multiple testing?	Correction for multiple comparisons was not performed because of the exploratory character of the research to make sure that all important associations were identified. Therefore, both the hypotheses emanating from previous studies and the robustness of the findings of this study were two key issues for the discussion of the results.	**NA**	
There are a lot of tables / figures - I think I count 9, many of which have multiple sub-figures. The tables also span multiple pages. I assume this will all have to be trimmed significantly. As a start, Table 2 / 4 might not be necessary in the primary analysis - consider moving to appendix or	Following reviewer's recommendations we have moved table 2 and 4 to the supplementary information section.	**Supplementary information, table S2 and S4**	

a subsequent paper.			
Can the authors please define what are verbal autopsies.	We have included this definition in Supplementary information, supplementary Table S1.	**Supplementary information, table S1**	
Can the authors please add what was the high proportion threshold above which a "missing" category was created?	As explained in a comment from reviewer #1, authors have added a further explanation: *"For each variable with a high proportion of missing values (<15%) but suspected to be a strong confounder, a "missing or unknown" category was created"*	**Page 8, lines 12-13**	

Instructions:

Please use this table format to answer the questions posed by the editors and reviewers of your paper. Copy and paste the editor/reviewer's question in the "Comments" column and your answer to that question in the corresponding "Response" column. Be sure to ALSO paste the corrected text along with your response. For minor copyediting changes such as spelling and grammar corrections, you may simply state that the error was corrected, without pasting the altered text.
* Use the page/line numbers from your revised .doc, .rtf, or .txt file; do *not* use the page/line numbers from the submission system's auto-generated PDF.

For clarity, use one row per question. Make sure to list the page and line reference where your change can be found. If no change was made, please make sure to note that in your response in addition to your reasoning. You may delete the sample row and insert rows to this table as needed.