Postdischarge Mortality Prediction in Sub-Saharan Africa

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abstract

BACKGROUND: Although the burden of postdischarge mortality (PDM) in low-income settings appears to be significant, no clear recommendations have been proposed in relation to follow-up care after hospitalization. We aimed to determine the burden of pediatric PDM and develop predictive models to identify children who are at risk for dying after 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 on admission.

RESULTS: Overall PDM was high (3.6%), with half of the deaths occurring in the first 30 days. One primary predictive model for all ages included young age, moderate or severe malnutrition, a history of diarrhea, clinical pneumonia symptoms, prostration, bacteremia, having a positive HIV status, the rainy season, and transfer or absconding, with an area under the curve 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 old was used to identify as predictors being a neonate, having a low weight-for-age *z* score, having breathing difficulties, having hypothermia or fever, having oral candidiasis, and having a history of absconding or transfer to another hospital, with an area under the curve of 0.76 (0.72–0.91) at day 90 of follow-up.

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

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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 Cousens conceptualized and designed the study, interpreted data set results, and critically reviewed the manuscript for its content; Drs Alonso, Menéndez, Macete, Sacoor, Varo, Sitoe, Acácio, Nhampossa, and Sigaúque coordinated and supervised data collection and critically reviewed the manuscript for its scientific content; Mr Massora and Dr Mandomando were responsible for laboratory procedures, the quality of the Centro de Investigação em Saúde de Manhiça laboratories facilities, and the interpretation of results; Mr Quintó and Ms Casellas led

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

WHAT THIS STUDY ADDS: The predictive models presented in this study could be applied at hospital discharge, and children who are at risk for dying could be identified through their use. This could allow for the design of a better postdischarge plan, health education to the families, and follow-up care.

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The last 25 years have witnessed a significant (49%) reduction in under-5 child mortality globally,[1] but this is insufficient to meet the two-thirds reduction objective set by the fourth Millennium Development Goal, particularly among many low-income countries (LICs).[2]

In the last decades, algorithms for the diagnosis and treatment of children who are sick have been implemented to address the management of disease during the acute phase and have contributed to improve child survival.[3] The authors of such guidelines and recommendations, however, have historically failed to address the days immediately after hospitalization, which is a critical period for child survival.[4]

Contrary to what occurs in industrialized countries (where postdischarge mortality [PDM] is limited to certain small, high-risk groups),[5,6] children in LICs appear to be at an increased risk of mortality after hospitalization for any illness.[4,7–13] Researchers in previous studies among admitted children, albeit scarce, have estimated the risk of PDM to range between 3.3% and 13%.[9,14,15] For specific diseases, PDM risks have ranged between 2.0% and 2.6% for malaria,[16,17] 2.9% and 7% for diarrhea,[18,19] 2.7% and 11.6% for anemia,[20] and 1% and 15% for pneumonia[15,21] and remained at 2.8% for invasive bacterial infections.[7] Most of these deaths have been described as clustering 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 children who are discharged from the hospital would be unfeasible and unaffordable in resource-constrained settings.[13] Thus, early identification of children who are vulnerable appears to be essential to designing more targeted interventions to prevent PDM.[13] Improving the discharge process and postdischarge care will be a critical step to further reducing child mortality.[4] We therefore aimed to determine the burden of pediatric PDM in a semirural area in Southern Mozambique, identify predictors of mortality after discharge, and derive models that could be used to efficiently stratify children according to PDM risk.

METHODS

Study Site and Population

This study was conducted in Manhiça in Southern Mozambique, a semirural setting with a predominantly young population (45% are <15 years of age). In 2015, the national under-5 mortality rate was 78.5 in 1000 live births.[22] The Manhiça Health Research Centre (Centro de Investigação em Saúde de Manhiça [CISM]) runs a demographic surveillance system (DSS) in the area, and a pediatric morbidity surveillance system (MSS) has been implemented for nearly 2 decades at the neighboring Manhiça District Hospital (MDH) and 5 additional peripheral health posts, accurately capturing standardized morbidity data for ∼3000 admissions and >75 000 annual outpatient visits annually. The 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 ∼9%[25] and contributes 10% to the under-5 mortality nationally.[26] A detailed description of the CISM and study area can be found elsewhere.[27,28]

Study Design and Definitions

A retrospective cohort study of children <15 years old who were discharged from MDH for a 17-year-long period was conducted by using the DSS and MSS databases. We analyzed the burden of PDM over 3 different time periods: 1 (1–30 days), 2 (31–60 days), and 3 (61–90 days) months postdischarge. PDM among infants <3 months old was analyzed 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 readmissions within the following 90 days to avoid restarting the period at risk every time. Postdischarge death was defined as a death occurring >24 hours after and within 90 days of discharge from MDH; a community death was a death occurring outside a health facility within 90 days after discharge; and a facility death was a death occurring at any health facility within 90 days after discharge from MDH. Children dying during a readmission within the follow-up period were considered as dying a hospital death within the follow-up period (Supplemental Fig 5). In Supplemental Table 4, we summarize other relevant definitions.

MSS

Morbidity surveillance data that were routinely collected for all children <15 years old during the study period were analyzed, including clinical data, basic laboratory investigations (malaria microscopy, hematocrit, and glycaemia), and diagnoses based on the *International Classification of Diseases, 10th Revision* since 2003. All diagnoses before July 2003 were coded according to a list of codes created by the CISM since 1996. Outcomes and medications prescribed were also analyzed. For children who were admitted, blood culture results (which are systematically performed for all children <2 years old and in older children with severe diseases) were available. HIV status information, although not routinely collected, was available for those patients with suspected immunosuppression.

DSS

The CISM's DSS, which was started in 1996, now covers the entire Manhiça district (2380 km^2; total population of ~183 000 inhabitants). The DSS is used to capture sociodemographic data and other major events, such as migration, marital status, pregnancy, outcome results, births, and deaths and is updated twice annually. During periods in which the entire district was not covered, in our analysis, we only included inpatients as part of the DSS. Through a unique identifier number, the 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 plus 1 day was used as the date of entry to the study, whereas postdischarge death, loss to follow-up, or the end of the follow-up period (90 days after discharge) was considered the exit time. For each variable with a high proportion of missing values (<15%) but that was suspected to be a strong confounder, a "missing or unknown" category was created. To achieve the study objectives, data analysis was split in 2 parts: (1) determining burden and identifying associations, in which descriptive statistics were calculated for all explanatory variables, Kaplan-Meier curves were produced for all categorical predictors to look for differences in survival with different values of the predictor, and associations between potential predictors and risk of death after discharge were explored in univariable Cox regression models; and (2) selecting and validating predictive models, in which the data set was randomly split into 2 subsets (training set containing 80% of data and the validation set with the remaining 20%) that were then compared to confirm that there were no important differences between the 2 subsets. Those predictors that revealed evidence of an association ($P \leq .05$) 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 on the basis of their suitability for different contexts: model 2, in which the primary model is used as reference but that includes only variables with minimal costs; model 3, which is based exclusively on clinical variables collected on admission; and model 4, which includes predictors of PDM restricted to infants <3 months old. The area under the curve (AUC) was plotted for each model over time by using the following training set: formula $H(t) = H_0(t) \times \exp(b_1X_1 + b_2X_2 + b_3X_3 + ... + b_kX_k)$. Confidence intervals (CIs) of AUC were estimated with 1000 bootstrap replicates by using the bias-corrected percentile method.[29] Because there could be >1 admission for some children, the models described above were estimated by taking into account within-child clustering. In analyses, we used Stata Statistical Software Release 15 (Stata Corp, College Station, TX). A graphical representation of AUCs was done in R (R Core Team, Vienna, Austria) by using the survivalROC package.

Ethical Considerations

In this study, we examined data collected in the context of routine clinical practice. The DSS and MSS that were ongoing in the study area have been approved by the National Ethics Committee of Mozambique.

RESULTS

Overall Characteristics of the Study Population

From January 1, 2000, to December 31, 2016, 58 990 inpatient records were checked, of which 29 574 (50%) were initially excluded (Fig 1). There were 3097 observations of children living in the study area who were readmitted within the follow-up period (Supplemental Fig 5); hospital deaths (2.5%; 662 of 26 319 remaining children) and 25 deaths in the first 24 hours (<0.1%) were also excluded (Fig 1). Thus, 25 632 inpatient records of 18 023 children <15 years old who were admitted to MDH were included in the analysis (Table 1). There were 2055 observations of 2049 infants <3 months old that were also analyzed separately (Supplemental Table 5).

Incidence of Postdischarge Deaths and Potential Predictors of PDM

During the 90-day follow-up period, 935 (3.6%) deaths after discharge occurred among the 25 632 admissions, with 783 (83.7%) of those occurring at the community level and 488 (52.2%) of those occurring within the first 30 days of discharge. The median time to death was 28 days (interquartile range 11–53 days). The risk of postdischarge deaths varied over time (Fig 2A, Supplemental Fig 6) and by age (Fig 2B) similarly to the risk of inpatient mortality (Fig 2C).

Forty-five variables were tested for their univariable association with PDM (Table 1). Infants <3 months old were more likely to die than older children (Fig 3A, Supplemental Table 5). Similarly, poorer nutritional levels were clearly linked to PDM (Fig 3B).

Predictive Models and Validation

Supplemental Table 6 includes a comparison of the training and validation sets. Nineteen variables were associated with a higher risk of PDM in the multivariate analysis (primary model, Table 2). Infants <3 months old had the highest rate of PDM, and this decreased with increasing age ($P < .001$; Supplemental Table 7). The rate of PDM varied between the rainy and dry seasons (hazard ratio [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 another 13 clinical variables were associated with PDM. Children with a positive

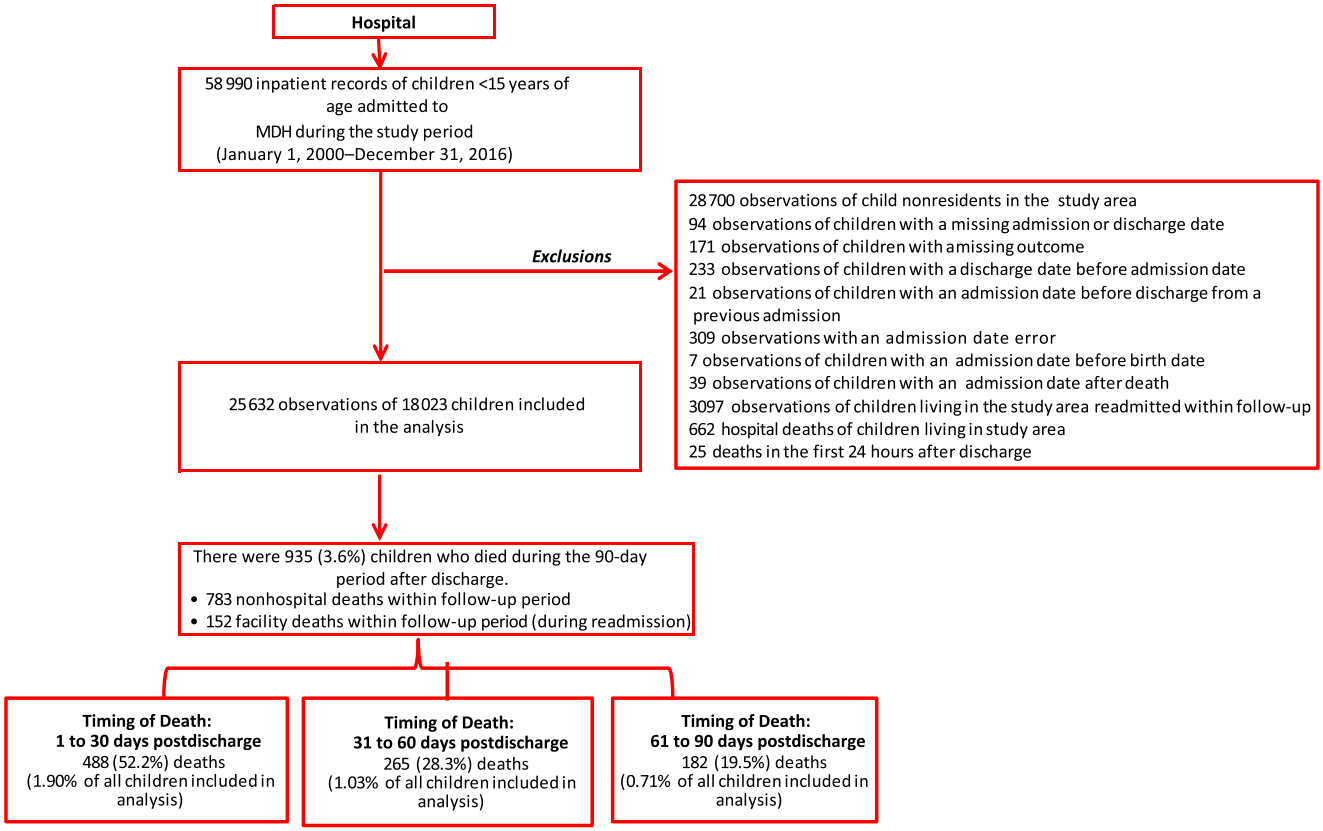

FIGURE 1
Study profile.

blood culture result (HR 1.68; 95% CI 1.33–2.12) and a positive HIV test result (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 ~0.80 during the 90-day follow-up period, being 0.79 (95% CI 0.75–0.82) at day 90. At an HR cutoff point of 1.08, it had a sensitivity of 80%, specificity of 60%, and positive predictive value (PPV) of 6.9% (Fig 4, Table 3). According to this model, 1.9% of all children who are discharged will die in the first 90 days after discharge.

The time-varying AUC of the 2 additional simplified models (Table 2) is compared in Supplemental Fig 7A. Model 2, in which we excluded blood culture but maintained minimal cost tests, performed similarly to the primary model, with an AUC of ~0.80% until 60 days after discharge. Model 3, in which we included only clinical variables, performed slightly worse, with an AUC of ~0.75 during the whole period. Model 4, which we limited to infants <3 months old, included variables such as breastfeeding and weight-for-age *z* score (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 (Supplemental Table 7). 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 an HR cutoff point of 0.5, it had a sensitivity of 79%, specificity of 53%, and PPV of 12.8% (Table 3, Supplemental Fig 7B). The AUC and model characteristics at probability cutoffs used to ensure a sensitivity of >80% are shown in Supplemental Table 5. The CI of the AUC between the training and validation sets and between the primary model and other models overlapped, meaning no significant differences between them were found.

DISCUSSION

This analysis, which is based on >20 000 hospital discharges and 935 postdischarge deaths, is the largest study to date in which researchers evaluate PDM in the first 3 months after hospital discharge from a rural district hospital in an LIC and represents a systematic approach to ascertaining predictors of PDM in a resource-constrained environment.

The cumulative 3-month PDM found in this study (3.6%) is lower than that reported in the 1990s from other African settings, where the incidence

TABLE 1 Sociodemographic and Clinical Characteristics and Univariate Analysis of Predictors of Admission Associated With PDM in Southern Mozambique Based on 25 632 Observations and 935 Postdischarge Deaths

Characteristics on Admission	Total Observations Included (N = 25 632), n (%)	Children Dying Within 90 d After Discharge[a] (N = 935), n (%)[b]	Univariate HR[c]	95% CI	P[d]
Demographic characteristics					
Age					<.001
<3 mo	2055 (8.0)	126 (6.1)	1.00	—	—
4–<1 y	5203 (20.3)	276 (5.3)	0.86	0.70–1.06	.164
1–5 y	14 558 (56.8)	450 (3.1)	0.50	0.41–0.60	<.001
>5 y	3816 (14.9)	83 (2.2)	0.35	0.26–0.46	<.001
Female sex	11 571 (45.3)	425 (3.7)	1.01	0.89–1.15	.838
Rainy season	15 624 (61.0)	602 (3.9)	1.16	1.02–1.33	.029
Anthropometric characteristics					
Wt for height z score (mean ± SD)	−0.93 (0.01)	−1.99 (0.13)	0.63	0.57–0.69	<.001
Nutritional status by WHZ[e] z score, SD					<.001
>−1	5994 (23.4)	57 (0.9)	1.00	—	—
>−2 to <−1	2749 (10.7)	35 (1.3)	1.34	0.88–2.04	.172
>−3 to <−2	1486 (5.8)	34 (2.3)	2.42	1.58–3.71	<.001
<−3	1030 (4.0)	57 (5.5)	5.94	4.12–8.57	<.001
Unknown	14 373 (56.1)	752 (5.2)	5.62	4.30–7.36	<.001
History of current disease[f]					
Fever	23 424 (91.4)	797 (3.4)	0.54	0.45–0.64	<.001
Cough	16 324 (63.7)	705 (4.3)	1.78	1.53–2.06	<.001
Diarrhea	5015 (19.6)	336 (6.7)	2.36	2.06–2.69	<.001
Vomiting	6004 (23.4)	268 (4.5)	1.32	1.15–1.52	<.001
Breathing difficulties	5303 (20.8)	298 (5.6)	1.81	1.58–2.08	<.001
Anorexia	1648 (6.5)	101 (6.1)	1.79	1.46–2.20	<.001
Blood in urine	97 (0.4)	5 (5.2)	1.43	0.59–3.44	.429
History of seizures	2658 (10.4)	39 (1.5)	0.37	0.27–0.51	<.001
Symptoms and signs on admission					
Axillary temperature, °C					<.001
Normothermia (35.5–37.4)	9840 (37.0)	427 (4.3)	1.00	—	—
Hypothermia (<35.5)	513 (2.0)	30 (5.8)	1.31	0.90–1.89	.158
Fever (≥37.5)	15 598 (61.0)	476 (3.1)	0.67	0.59–0.77	<.001
Heart rate					.647
Normal	16 697 (65.5)	600 (3.6)	1.00	—	—
Bradycardia	1902 (7.5)	75 (3.9)	1.10	0.87–1.40	.436
Tachycardia	6876 (27.0)	259 (3.8)	1.05	0.90–1.21	.518
Increased respiratory rate	11 560 (45.3)	351 (3.0)	1.37	1.20–1.57	<.001
Skin pinch goes back slowly	2007 (8.1)	186 (9.3)	3.03	2.58–3.56	<.001
Dehydration	3907 (15.3)	248 (6.3)	2.04	1.77–2.37	<.001
Pallor	4228 (16.5)	141 (3.3)	0.90	0.75–1.07	.227
Jaundice	328 (1.1)	8 (2.4)	0.66	0.33–1.32	.243
Edema (any location)	1371 (5.4)	130 (9.5)	2.96	2.46–3.57	<.001
Skin flaking off	464 (1.8)	46 (9.9)	2.90	2.15–3.90	<.001
Depigmented or reddish hair	1460 (5.7)	216 (14.8)	5.30	4.55–6.18	<.001
Oral candidiasis	493 (1.9)	108 (21.9)	7.44	6.08–9.09	<.001
Swollen lymph nodes	827 (3.2)	113 (13.7)	4.33	3.56–5.25	<.001
Conjunctivitis	416 (1.6)	24 (5.8)	1.62	1.08–2.43	.020
Ear discharge	641 (2.5)	57 (8.9)	2.59	1.98–3.38	<.001
Lower chest wall indrawing	5488 (21.4)	298 (5.4)	1.73	1.51–1.99	<.001
Nasal flaring	4123 (16.1)	206 (5.0)	1.48	1.27–1.73	<.001
Pathologic breathing pattern	1018 (3.7)	54 (5.3)	1.50	1.14–1.97	.004
Auscultatory crackles	5314 (20.8)	320 (6.0)	2.02	1.77–2.31	<.001
Wheeze and/or roncus	3090 (12.1)	127 (4.1)	1.15	0.96–1.39	.138
Heart gallop	882 (3.4)	32 (3.6)	0.99	0.70–1.41	.972
Palpable liver	677 (2.6)	38 (5.6)	1.57	1.14–2.18	.006
Palpable spleen	5378 (21.0)	145 (2.7)	0.69	0.58–0.82	<.001
Neck stiffness	203 (0.8)	11 (5.4)	1.51	0.83–2.74	.175
Abnormal fontanel (among applicable)	922 (8.7)	70 (7.6)	1.55	1.21–1.99	<.001
Prostration	3261 (13.0)	146 (4.5)	1.29	1.08–1.54	.005
BCS score on admission					.047
Normal (5)	24 320 (95.0)	870 (3.6)	1.00	—	—

TABLE 1 Continued

Characteristics on Admission	Total Observations Included ($N = 25\,632$), n (%)	Children Dying Within 90 d After Discharge[a] ($N = 935$), n (%)[b]	Univariate HR[c]	95% CI	P[d]
Abnormal (3–4)	873 (3.4)	39 (4.5)	1.26	0.91–1.73	.164
Deep coma (≤2)	396 (1.6)	22 (5.6)	1.57	1.03–2.41	.037
Investigations					
Malaria diagnosis result					<.001
Negative	9431 (36.8)	581 (6.2)	1.00	—	—
Positive	12 232 (47.7)	202 (1.7)	0.26	0.22–0.31	<.001
Test not done	3969 (15.5)	152 (3.8)	0.61	0.51–0.74	<.001
Glycaemia, mmol/L					.189
Normoglycemia (2.5–11.0)	21 384 (83.4)	798 (3.7)	1.00	—	—
Hypoglycemia (<2.5)	2413 (9.4)	83 (3.4)	0.92	0.73–1.15	.471
Hyperglycemia (>11.0)	1835 (7.2)	54 (2.9)	0.78	0.60–1.03	.084
Blood culture result					
Negative	24 316 (94.9)	798 (3.3)	1.00	—	—
Positive	1296 (5.1)	136 (10.5)	3.32	2.77–3.98	<.001
Anemia					.902
None	8806 (34.4)	319 (3.6)	1.00	—	—
Mild to moderate	13 624 (53.1)	495 (3.6)	1.00	0.87–1.15	.997
Severe	3202 (12.5)	121 (3.8)	1.04	0.84–1.28	.709
HIV status					<.001
Test not done	24 128 (94.1)	867 (3.6)	1.00	—	—
Negative	1246 (4.9)	25 (2.0)	0.55	0.37–0.82	.004
Positive	258 (1.0)	43 (16.7)	4.97	3.59–6.88	<.001
Outcome of the admission[g]					<.001
Discharged alive	24 145 (94.2)	666 (2.8)	1.00	—	—
Absconded	805 (3.1)	161 (20.0)	8.18	6.87–9.74	<.001
Transferred	682 (2.7)	108 (15.8)	6.30	5.12–7.75	<.001

BCS, Blantyre coma scale; WHZ, wt for height; —, not applicable.
[a] Refers both to community deaths and deaths in readmission during the follow-up period.
[b] Percentage represents risk among children with the same characteristics.
[c] HRs and CIs were derived from a Cox regression model.
[d] Derived from a Wald test.
[e] See definitions in Supplemental Table 4.
[f] Reported by the child carer.
[g] Hospital deaths and deaths in the first 24 h were omitted.

risk was estimated at between 6.1% and 13%,[14,15] but similar to that in other more recent PDM studies.[7,9,10,18] Importantly, the inpatient mortality found in our cohort (2.5%) aligned closely with that reported in other settings.[13,14]

With these findings, we highlight that the risk of dying is greatest in the first 30 days immediately after discharge,[7,10] which is the most critical period for survival.[10,15,18] Overall, trends of PDM for all ages changed over time. PDM rates increased over the period from 2000 to 2010 and subsequently declined. This trend cannot be explained by an increase in inpatient mortality because this has been progressively decreasing since 2001 (Fig 2C). One could speculate that variations in the epidemiology of a single disease may have played a significant role in PDM variations (Supplemental Fig 8). 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 onward, trends that are inversely proportional to those of the PDM curve. Children who are admitted with malaria, are readily treatable, and have a rapid recovery are probably less likely to be associated with postdischarge 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 that is also reported in Kenya.[9] Similarly, although the HIV incidence is now much higher in the area than it was 1 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 who are admitted with other diseases with a greater incidence of postdischarge deaths, such as SAM, revealed an overall tendency that is 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 *Haemophilus influenzae* type b (2009), *pneumococcus* (2013), and

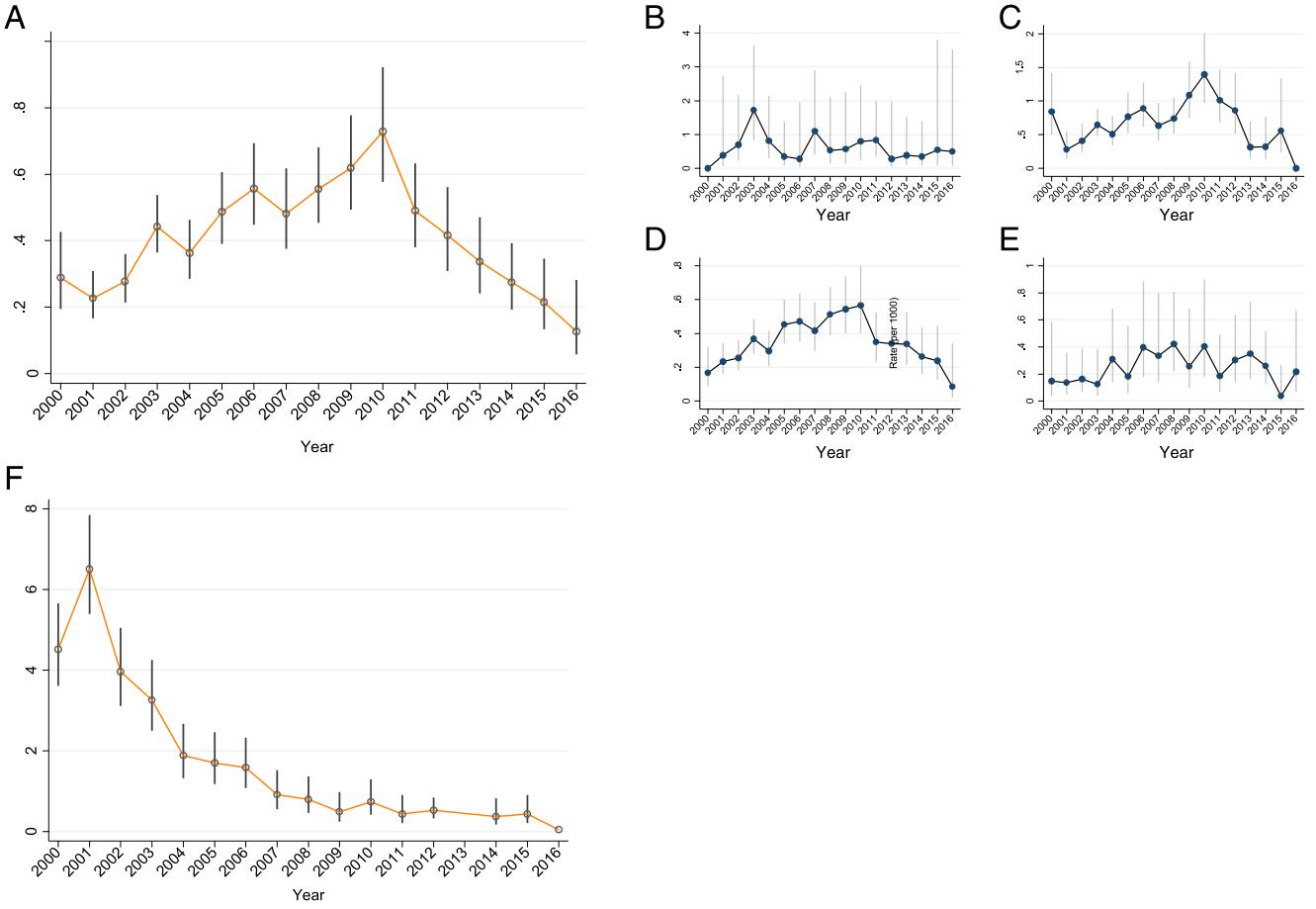

FIGURE 2

Mortality trends over time during the 17-year-long study period. A, Yearly incidence of PDM for all ages. B, Yearly incidence of PDM by age group: 0–3 months. C, Yearly incidence of PDM by age group: 4–11 months. D, Yearly incidence of PDM by age group: 1–5 years. E, Yearly incidence of PDM by age group: 5–15 years. F, Yearly incidence of inpatient mortality for all ages.

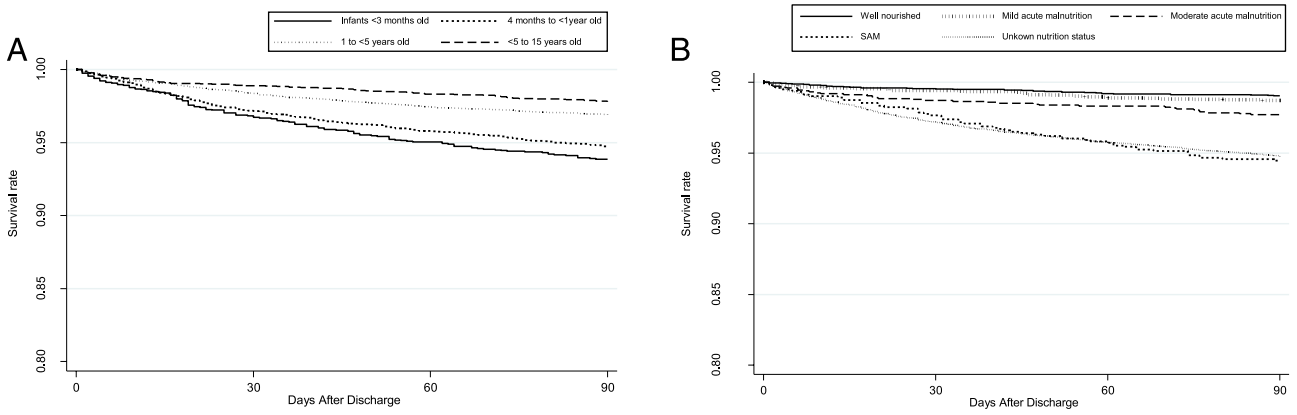

FIGURE 3

Kaplan-Meier failure estimates for 935 deaths during the 90-day follow-up period after discharge from MDH. A, By age group. B, By category of nutritional status.

rotavirus (2015), have reduced hospital admissions and may also have contributed to these decreasing trends. PDM trends over time among infants <3 months old differed slightly from other age groups, with a peak in 2003 and stable rates thereafter. In this highly vulnerable age group, effective interventions that are specifically designed to reduce mortality have not been fully implemented in the study area.

TABLE 2 Estimation of Predictive Models Derived From the Primary Model, Including Predictors Associated With Postdischarge Death Among 20 506 Observations of Children <15 Years Old and 750 Deaths in the First 90 Days After Discharge

Characteristics on Admission	Primary Model			Model 2			Model 3		
	Adjusted HR[a]	95% CI	*P*[b]	Adjusted HR[a]	95% CI	*P*[b]	Adjusted HR[a]	95% CI	*P*[b]
Age			<.001			<.001			.002
<3 mo	1.00	—		1.00	—		1.00	—	
4–<1 y	0.92	0.71–1.20		0.93	0.72–1.20	.041	0.79	0.62–1.03	
1–5 y	0.69	0.53–0.91		0.71	0.54–0.92	<.001	0.66	0.51–0.86	
>5 y	0.54	0.38–0.76		0.54	0.38–0.76	<.001	0.55	0.39–0.77	
Rainy season	1.22	1.03–1.43	.018	1.22	1.04–1.44	.017	1.25	1.07–1.46	.005
Anthropometric characteristics									
Nutrition status by WHZ *z* score, SD[c]			<.001			<.001			<.001
>−1	1.00	—		1.00	—		1.00	—	
>−2 to <−1	1.23	0.75–2.01		1.27	0.77–2.07		1.32	0.81–2.14	
>−3 to <−2	2.40	1.49–3.87		2.44	1.51–3.93		2.30	1.41–3.75	
<−3	3.26	2.08–5.12		3.28	2.08–5.16		4.16	2.71–6.40	
Unknown	2.99	2.12–4.21		3.09	2.19–4.35		3.72	2.64–5.23	
History of current disease[d]									
Diarrhea	1.72	1.45–2.03	<.001	1.70	1.44–2.01	<.001	1.58	1.32–1.89	<.001
Cough	1.32	1.07–1.62	.009	1.31	1.07–1.61	.010	1.25	1.02–1.53	.030
Breathing difficulties	—	—	—	—	—	—	1.36	1.09–1.70	.007
Symptoms and signs on admission									
Increased respiratory rate	1.41	1.18–1.68	<.001	1.42	1.19–1.69	<.001	1.27	1.07–1.52	.007
Skin pinch goes back slowly	—	—	—	—	—	—	1.51	1.20–1.90	<.001
Nasal flaring	0.69	0.55–0.86	<.001	0.69	0.56–0.87	.001	0.79	0.65–0.97	.022
Auscultatory crackles	1.37	1.12–1.67	.002	1.41	1.16–1.71	<.001	1.44	1.19–1.75	<.001
Oral candidiasis	2.64	1.98–3.52	<.001	2.72	2.03–3.64	<.001	3.51	2.70–4.58	<.001
Edema (any location)	1.86	1.39–2.48	<.001	1.83	1.67–2.44	<.001	2.48	1.88–3.27	<.001
Depigmented or reddish hair	2.03	1.60–2.57	<.001	2.08	1.64–2.64	<.001	2.42	1.90–3.07	<.001
Swollen lymph nodes	1.89	1.42–2.51	<.001	1.87	1.41–2.49	<.001	2.23	1.70–2.93	<.001
Ear discharge	1.76	1.20–2.58	.004	1.74	1.16–0.59	.007	1.76	1.24–2.49	.001
Prostration	1.42	1.15–1.75	.001	1.44	1.17–1.77	<.001	1.41	1.15–1.73	.001
Investigations							Excluded	Excluded	Excluded
Malaria diagnosis result			<.001			<.001	Excluded	Excluded	Excluded
Negative	1.00	—		1.00	—		Excluded	Excluded	Excluded
Positive	0.44	0.36–0.54		0.43	0.35–0.52		Excluded	Excluded	Excluded
Test not done	0.86	0.46–0.73		0.84	0.68–1.04		Excluded	Excluded	Excluded
Blood culture result				Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Negative	1.00	—	—	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Positive	1.68	1.33–2.12	<.001	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
HIV status			<.001			<.001	Excluded	Excluded	Excluded
Test not done	1.00	—		1.00	—		Excluded	Excluded	Excluded
Negative	0.53	0.35–0.80		0.53	0.35–0.80		Excluded	Excluded	Excluded
Positive	1.77	1.07–2.91		1.80	1.07–3.01		Excluded	Excluded	Excluded

TABLE 2 Continued

Characteristics on Admission	Primary Model			Model 2			Model 3		
	Adjusted HR[a]	95% CI	*P*[b]	Adjusted HR[a]	95% CI	*P*[b]	Adjusted HR[a]	95% CI	*P*[b]
Outcome of the admission[e]			<.001			<.001	Excluded	Excluded	Excluded
Alive	1.00	—		1.00	—		Excluded	Excluded	Excluded
Absconded	5.23	4.22–6.50		5.50	4.45–6.79		Excluded	Excluded	Excluded
Transferred	4.48	3.31–6.05		4.57	3.36–6.21		Excluded	Excluded	Excluded

WHZ, wt for height; —, not applicable.
[a] HRs and CIs were derived from a Cox regression model.
[b] Derived from a Wald test.
[c] See definitions in Supplemental Table 4.
[d] Reported by the child carer.
[e] Hospital deaths and deaths in the first 24 h were omitted.

The primary model including all available useful variables performed remarkably well, particularly when predicting the risk of dying in the first month after discharge. This model predicts that 1.9% of children who are discharged from the hospital will die in the first 90 days after discharge. When applying a score based on this model to a population that is similar to ours and using an HR cutoff of 1.08, roughly 80% of children who are likely to die after discharge would be identified, and the referral population would have a mortality risk of ∼7%. This model, however, includes blood culture results, which is an expensive determination that requires laboratory infrastructures that are seldom available in poor settings. The 2 alternative simplified models including more easy-to-collect laboratory results (model 2) or only clinical variables (model 3) seem more applicable and still revealed a good predictive capacity for PDM. Importantly, model 4, which was developed for infants <3 months old, includes only few variables, all of which are easily and readily obtainable in most resource-constrained contexts and can be used to identify 85% of infants <3 months old who are at risk for dying in the first days after discharge and nearly 80% during the remaining follow-up period.

SAM is a recognized predictor of PDM,[8–10,13,18] as we confirm with our models. The chronicity of malnutrition, the fact that it can predispose people to an array of coinfections and complications, and its association with HIV infection in Manhiça[30] may all be used to explain its associated prolonged mortality risk. On the other hand, children with unknown nutritional status had a higher risk of dying compared with children who were well nourished. This may be partly explained in cases of severe disease, in which the severity of the children on admission did not allow for the collection of anthropometric measurements. HIV positivity, which is a clear predictor of PDM,[13,20] remained a strong independent predictor in our model even after adjusting for malnutrition. The rainy season was also associated with a higher risk of PDM because more children are admitted during this season, likely because of the greater number of admissions and severe diseases occurring in this season.

In this series, the type of outcome at discharge, and particularly being transferred or absconding from the hospital, were the greatest predictors of PDM. In this setting, children are usually transferred to a higher-level health facility whenever they are sick or require a more specialized evaluation or supportive care, justifying their greatest PDM risk. Children who abscond against medical recommendations (3.1% of the study sample) had an extremely high risk of PDM and represent 1 of every 5 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. Sociobehavioral studies in which researchers address this phenomenon and the perceptions of health professionals of its serious consequences are needed.

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

TABLE 3 Model Characteristics at Probability Cutoffs, Ensuring a Sensitivity of >80%

Model	AUC (95% CI)			Score Cut Point			Sensitivity, %			Specificity, %			PPV, %		
	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
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

—, not applicable.

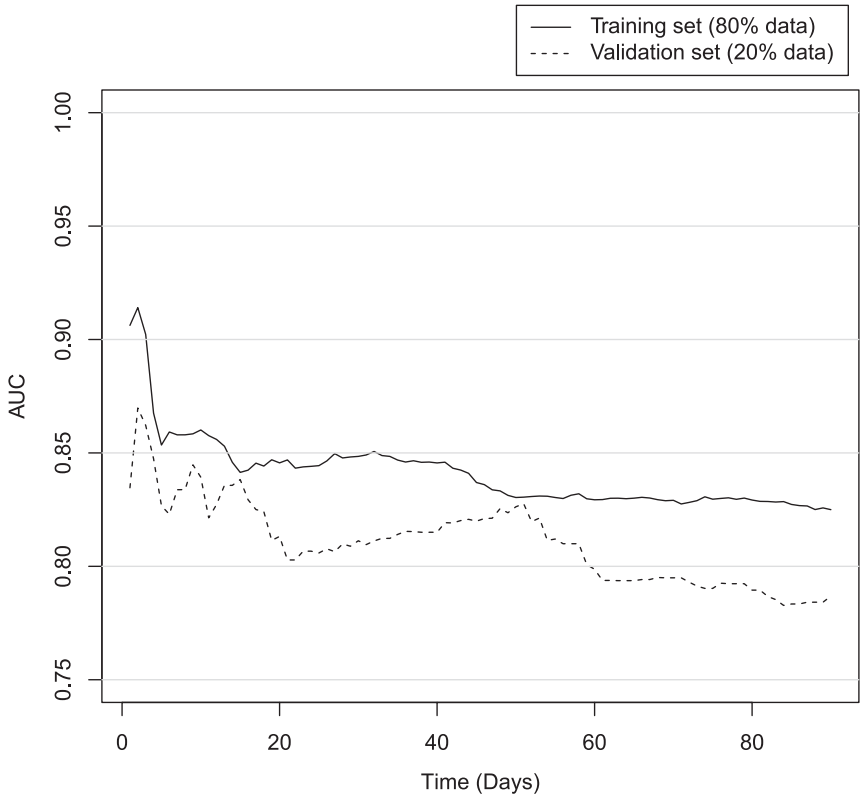

FIGURE 4
The time-varying AUC of the primary model in which we compare the training and validation sets.

Researchers using effective models for identifying children who are at risk for 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 the Integrated Management of Childhood Illness, based in predictive models and applied at discharge, could be used to pinpoint children who require a more rigorous follow-up after hospitalization. However, the identification of high risk does not imply that risk can be reduced. Future researchers should consider validating these models in different contexts and prospectively assessing their accuracy to identify children who are at risk for dying after discharge in resource-constrained settings. Once identified, these children at higher risk of PDM could benefit from strategies to prevent postdischarge death, and these strategies should be especially focused on the first 30 days after discharge because it is the period with the highest risk of PDM. Community-based interventions driven by community health workers, consisting of pre- and postnatal home visits, in which they support low birth weight infants and sepsis case management and facilitate 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 on reducing PDM could be similar. Alternative strategies, including the prophylactic use of antimicrobial agents in those children who are at high risk, should also be explored. However, a recent clinical trial conducted in Kenya in which researchers explored the efficacy of daily postdischarge cotrimoxazole prophylaxis in children who were admitted with complicated SAM without HIV revealed no reduction in

mortality during the first year after admission.[32]

Continued investment in child mortality data collection and understanding circumstances of pediatric death after a hospital discharge is needed 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 because of the fact that approximately half of the 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 the clinical predictors were collected at the time of admission, and some of 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 who were readmitted 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 because they were considered to be hospital deaths. However, they merely represented <0.1%. The inclusion of children who were transferred or absconded from the hospital may be an overestimation of the incidence of PDM because they were not officially discharged, but this is an extremely frequent occurrence in African settings and needs to be taken into consideration, particularly in light of the strength and magnitude of the statistical associations found. Importantly, we could not assess the role of low birth weight in infants as a likely risk factor for PDM because this information was not available. On the other hand, the low specificity and PPV found could compromise the feasibility of interventions to prevent PDM because a high number of children would be classified as being at a high risk of dying after discharge. However, these models would allow for the identification of the majority of children who are at risk of PDM. Finally, our predictive models lack external validation.

CONCLUSIONS

In this study, we highlight the importance and oversight of PDM 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 in which children who are identified as being at a higher risk are targeted and guaranteed adequate follow-up at the hospital or even at the household level could possibly increase their survival possibilities. The implementation of such strategies could prevent avoidable deaths, especially among neonates and infants who suffer the highest burden of PDM.

ABBREVIATIONS

AUC: area under the curve
CI: confidence interval
CISM: Centro de Investigação em Saúde de Manhiça
DSS: demographic surveillance system
HR: hazard ratio
LIC: low-income country
MDH: Manhiça District Hospital
MSS: morbidity surveillance system
PDM: postdischarge mortality
PPV: positive predictive value
SAM: severe acute malnutrition
WAZ: weight-for-age *z* score

the data analysis, interpreted data set results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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