

Burden and risk factors for relapse following successful treatment of uncomplicated severe acute malnutrition in young children: Secondary analysis from a randomised trial in Niger

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Abstract

This study aimed to quantify the burden of relapse following successful treatment for uncomplicated severe acute malnutrition (SAM) and to identify associated risk factors in rural Niger. We used data from 1490 children aged 6–59 months discharged as recovered from an outpatient nutritional programme for SAM and followed for up to 12 weeks after admission. Postdischarge SAM relapse was defined as weight-for-height Z-score <−3, mid-upper arm circumference (MUAC) <115 mm or bipedal oedema after having been discharged as recovered. Postdischarge hospitalisation was defined as admission to inpatient SAM treatment or hospitalisation for any cause after having been discharged as recovered. We used multivariate log-binomial models to identify independent risk factors. After programmatic discharge, 114 (8%) children relapsed to SAM and 89 (6%) were hospitalised. Factors associated with SAM relapse were discharge during the lean season (relative risk [RR] = 1.80 [95% confidence interval [CI] = 1.22–2.67]) and larger household size (RR = 1.56 [95% CI = 1.01–2.41]), whereas older child age (RR = 0.94 [95% CI = 0.88–1.00]), higher child MUAC at discharge (RR = 0.93 [95% CI = 0.87–1.00]) and maternal literacy (RR = 0.54 [95% CI = 0.29–0.98]) were protective factors. Discharge during the lean season (RR = 2.27 [95% CI = 1.46–3.51]) was independently associated with postdischarge hospitalisation. Future nutritional programmes in the context of Niger may consider modification of anthropometric discharge criteria or the provision of additional home support or follow-up during the lean season as potential interventions to prevent relapse. More research including postdischarge follow-up is needed to better understand the sustainability of treatment outcomes after discharge and the type of intervention

Clinical Trial Registration: ClinicalTrials.gov number, NCT01613547.

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that may best sustain recovery over time. Clinical Trial Registration: ClinicalTrials.gov number, NCT01613547.

KEYWORDS

community-based management of acute malnutrition, discharge, hospitalisation, Niger, relapse, severe acute malnutrition, wasting

1 | INTRODUCTION

Severe acute malnutrition (SAM) is a deadly condition contributing to 8% of mortality in children under 5 years of age (Black et al., 2013). Current community-based approaches for the treatment of SAM involve providing children with therapeutic foods and specialised clinical care on a weekly or biweekly basis until recovery (WHO, 2013; World Health Organisation et al., 2007). Recovery usually occurs between 4 and 8 weeks from admission after stabilisation of weight and clinical complications (WHO, 2013; World Health Organisation et al., 2007).

International guidelines typically evaluate the success of therapeutic feeding programmes by monitoring routine programme indicators, including recovery, death and default during treatment (Sphere Project, 2018). This practice has placed focus on measures of short-term weight gain and case fatality during treatment; however, it is becoming increasingly clear that the risk of relapse, illness and mortality after programmatic recovery from SAM treatment may remain elevated (Stobaugh et al., 2019). A recent systematic review showed that the proportion of children relapsing to SAM after successful discharge from nutritional programmes may be up to 37% (Stobaugh et al., 2019). Studies have also consistently documented elevated prevalence of postdischarge morbidities, suggesting that children's immunological recovery may lag behind anthropometric recovery and that children may remain at an increased risk of illness despite weight gain sufficient for successful programmatic discharge (Aprameya et al., 2015; Ashraf et al., 2012; Bahwere et al., 2017; Khanum et al., 1998).

A broad range of individual, case, and household factors are associated with relapse (Schaefer et al., 2020). Studies have consistently shown that lower anthropometric measures at admission to and discharge from nutritional programmes can be the primary risk factors for relapse (Stobaugh et al., 2019). Some studies have also identified measures of household socioeconomic status, sanitation practices, seasonality and child age, vaccination status and diet as factors associated with relapse (Abitew et al., 2020; Adegoke et al., 2020; Burza et al., 2016; Magnin et al., 2017; Schaefer et al., 2020; Somassè et al., 2016). Identifying risk factors for adverse outcomes following discharge, including relapse and hospitalisation, could help improve identification of children at greater risk for relapse for additional support or surveillance postdischarge and inform guidelines for programmatic discharge criteria and targeted interventions to improve the sustainability of recovery. The aim of this analysis was to evaluate the postdischarge outcomes of children recovered from

Key messages

- Following successful discharge from a community-based nutritional programme for severe acute malnutrition (SAM) treatment in rural Niger, the prevalence of SAM relapse was 8% and the prevalence of postdischarge hospitalisation was 6% within 12 weeks from admission.
- Factors associated with SAM relapse were child age at programme admission, child mid-upper arm circumference (MUAC) at discharge, discharge from the nutritional programme during the lean season, and maternal literacy.
- Anthropometry at discharge was a primary risk factor for relapse. MUAC at discharge performed better than weight-for-height Z-score (WHZ) in classifying SAM relapse cases. 'Optimal' cut-offs, defined using the Liu method which maximises the product of the sensitivity and specificity, were MUAC of 121 mm with 66% sensitivity and 67% specificity and WHZ of -1.38 with 54% sensitivity and 57% specificity.
- Future programmes may consider additional support or follow-up of children at high risk of postdischarge relapse or hospitalisation, including those discharged during the lean season. Modification of current anthropometric discharge criteria may also be explored as an actionable target to further reduce the risk of relapse.

SAM treatment up to 12 weeks following admission to outpatient SAM treatment in rural Niger and to identify individual and household factors associated with relapse and postdischarge hospitalisation.

2 | METHODS

2.1 | Study setting

This study was conducted in the rural Madarounfa Health District in the Maradi Region of Niger. Households are primarily subsistence farmers with food production linked to rain-fed agriculture resulting in annual harvests of staple crops. In the months preceding this harvest, food quantity and quality decrease while infectious illnesses, such as diarrhoea, pneumonia and malaria, increase. These changes

are associated with a seasonal peak in acute malnutrition among children under 5 years of age. The Maradi Region has some of the highest rates of acute malnutrition in Niger with a wasting prevalence among children under 5 years of age of 11% (Institut National de la Statistique, 2019), within the WHO 'high' prevalence category of 10%–15% (de Onis et al., 2019).

Médecins Sans Frontières (MSF), in collaboration with the Ministry of Health of Niger, has supported paediatric care in the Madarounfa Health District since 2001. Project activities were transferred to local control and implemented through a Nigerien nongovernmental organisation, Forum Santé Niger (FORSANI) in collaboration with the Ministry of Health from 2009 to March 2014. FORSANI provided care and treatment to over 30,000 children in the Madarounfa Health District each year with MSF support.

2.2 | Study population and procedures

From October 2012 to November 2013, children aged 6–59 months with uncomplicated SAM (defined as weight-for-height Z-score [WHZ] < -3 SD or mid-upper arm circumference (MUAC) < 115 mm) were enrolled in a randomised controlled trial to examine the effect of routine antibiotic use on nutritional recovery from uncomplicated SAM. Study procedures have been described elsewhere (Isanaka et al., 2016, 2020). In brief, children were randomised to receive amoxicillin (80 mg/kg/day) or placebo for 7 days. Children were seen weekly at the health centre for a minimum of 3 and a maximum of 8 weeks until they reached nutritional recovery. Nutritional recovery was defined as WHZ ≥ -2 SD and MUAC ≥ 115 mm and the absence of acute complications or bipedal oedema for at least 7 days, per the national protocol for integrated SAM management at the time of the study. Per the trial protocol, children had scheduled follow-up visits at 4, 8 and 12 weeks post-admission regardless of their treatment/recovery status. Caregivers were also invited to return to the health centres at any time in the event of a clinical deterioration. During each follow-up visit, anthropometry (weight to the nearest 100 g; length in children < 24 months of age or standing height in children ≥ 24 months of age to the nearest 0.1 cm; and MUAC to the nearest 0.1 cm) was assessed and a study physician performed a physical exam and took a medical history. All children received standard medical care for outpatient treatment of uncomplicated SAM as specified by the national guidelines of the Ministry of Health of Niger. At the time the parent trial was conducted, the standard of care involved the provision of a ready-to-use therapeutic food (170 kcal/kg/day), a single dose of vitamin A (100,000 UI for children < 4 kg, 200,000 UI for children 4–8 kg and 400,000 UI for children ≥ 8 kg), a single dose of folic acid (5 mg tablet), deworming (200 mg of albendazole for children < 8 and 400 mg for children ≥ 8 kg) and a measles vaccine if necessary (for children without a vaccination card at admission or at 9 months of age for children 6–8 months of age at admission). Malaria and/or anaemia treatment were also provided, if necessary. Further details on standard care in the parent trial have been previously published (Isanaka et al., 2016). At the time the

parent trial was conducted, children received a protection ration at the time of discharge from SAM treatment consisting of seven sachets of a ready-to-use therapeutic food. There was no moderate acute malnutrition (MAM) treatment programme in the study area at the time of the parent trial.

2.3 | Outcome measures

The primary outcomes of interest for this analysis were postdischarge SAM relapse (defined as WHZ < -3 SD, MUAC < 115 mm or bipedal oedema after recovery and up to 12 weeks from admission) and postdischarge hospitalisation (defined as admission to inpatient SAM treatment or hospitalisation for any cause, based on maternal report after recovery and up to 12 weeks from admission). Secondary outcomes of interest included the incidence of the following morbidities at any time during postdischarge follow-up: diarrhoea (≥ 3 loose stools in the previous 24 h), vomiting, cough, tachypnoea (respiratory rate ≥ 50 breaths per minute in children 6–11 months of age and ≥ 40 breaths per minute in children 12–59 months of age), fever (axillary temperature $> 38.5^\circ\text{C}$) and malaria with fever (positive rapid diagnostic test and axillary temperature $> 38.5^\circ\text{C}$).

2.4 | Statistical analysis

The analytic sample included 1490 children with WHZ ≥ -2 SD and MUAC ≥ 115 mm discharged from the outpatient SAM treatment programme as recovered. The present analysis excluded 41 children who were discharged as 'recovered' but did not achieve both anthropometric criteria for discharge. First, to describe the burden of postdischarge relapse and hospitalisation, we reported the number and proportion of children with postdischarge events. Second, to explore whether children were immunologically recovered at the time of discharge, we compared the incidence of individual morbidities before and after discharge, assuming similar or increased morbidity postdischarge would suggest insufficient immunological recovery. The incidence of morbidity during and after discharge from treatment was examined using generalised estimating equations with an unstructured correlation matrix, a log-Poisson link to derive incidence rate ratios and person-time since admission as an offset. Third, to identify risk factors for postdischarge SAM relapse and hospitalisation, we considered individual and household characteristics at admission into the nutritional programme and case characteristics at admission and discharge. Child characteristics included child age, sex and breastfeeding status at admission. Household characteristics included household food insecurity score based on the Household Food Insecurity Access Scale (Coates et al., 2007), number of children in the household, whether the child slept under a bednet the previous night, household wealth (calculated using principal components analysis using nine items for household asset and livestock ownership, and housing quality), maternal age and literacy. Case characteristics included child anthropometry at admission and discharge: WHZ,

TABLE 1 Descriptive characteristics of 1490 children recovered from outpatient treatment of severe acute malnutrition

Variables	N (%) or mean \pm SD
Individual characteristics	
Age at admission (in months)	17.2 \pm 8.5
Female sex	775 (52.0)
Case characteristics	
At admission	
Weight-for-height Z score (WHZ)	-3.0 \pm 0.6
Severe wasting (WHZ <-3 SD)	840 (56.4)
Mid upper arm circumference (MUAC, in cm)	11.3 \pm 0.4
MUAC <115 mm	1156 (77.6)
Height-for-age Z score (HAZ)	-3.0 \pm 1.2
Stunting (HAZ <-2 SD)	1174 (78.8)
Weight-for-age Z score (WAZ)	-3.7 \pm 0.7
Severe underweight (WAZ <-3 SD)	1270 (85.2)
Positive rapid diagnostic test for malaria	872 (58.5)
Axillary temperature >38.5° C	71 (4.8)
Diarrhoea in the past 24 h	477 (32.0)
Vomiting in the past 24 h	89 (6.0)
Cough in the past 24 h	257 (17.2)
Currently breastfed	898 (60.3)
At discharge	
WHZ	-1.2 \pm 0.5
Severe wasting (WHZ <-3 SD)	0 (0)
WHZ \geq -2 and <-1 SD	1089 (73.1%)
WHZ \geq -1 SD	401 (26.9%)
MUAC (in cm)	12.3 \pm 0.5
MUAC <115 mm	0 (0)
MUAC 115-125mm	896 (60.1%)
MUAC \geq 125 mm	594 (39.9%)
HAZ	-3.2 \pm 1.2
Stunting (HAZ <-2 SD)	1257 (84.4)
WAZ	-2.7 \pm 0.7
Severe underweight (WAZ <-3 SD)	479 (32.3%)
Length of stay in nutritional programme (in weeks)	4.2 \pm 1.4
Weight gain during nutritional programme (g/kg/day)	1.1 \pm 0.4
Discharged during the lean season	440 (29.5)
Household characteristics	
Number of children in the household	1.9 \pm 1.3

TABLE 1 (Continued)

Variables	N (%) or mean \pm SD
Food insecurity score (range 0-27)	8.2 \pm 8.3
Child slept under a bednet the previous night	1257 (84.4)
Wealth index	0.0 \pm 1.4
Maternal age (in years)	27.1 \pm 6.7
Mother is literate	273 (18.3)
Randomisation group	
Amoxicillin	760 (51.0%)
Placebo	730 (49.0%)

height-for-age Z-score (HAZ), stunting (HAZ <-2 SD), severe stunting (HAZ <-3 SD), weight-for-age Z-score (WAZ), severe underweight (WAZ <-3 SD) and MUAC, calculated using the 2006 WHO child growth standards (World Health Organisation, 2006), and length of stay in the programme, weight gain during the programme (g/kg/day) and season at discharge (lean season: July to September vs. harvest season: October to June). We used log-binomial models to identify independent risk factors for SAM relapse and hospitalisation. Crude models adjusted for the parent trial regimen (amoxicillin vs. placebo). Multivariable models adjusted for the trial regimen and for risk factors with a significant crude association at $p < 0.20$.

Finally, to further explore the predictive value and optimal cut-offs of WHZ and MUAC at discharge for SAM relapse and postdischarge hospitalisation at 12-weeks since admission, we constructed receiver operating characteristic curves and calculated the area under the curve (AUC). AUCs were compared using a bootstrap test with 10,000 replications, which we considered significant at $p < 0.05$. While there are several ways to define 'optimal' cut-offs for MUAC and WHZ at discharge to predict SAM relapse and hospitalisation, we defined the optimal cut-off in this analysis using the Liu method which maximises the product of the sensitivity and specificity (Liu, 2012). Statistical analysis was conducted in R version 4.1.2. (R Development Core Team, 2017).

3 | RESULTS

Recovered children included in this analysis were 17 months of age on average and 52% were female (Table 1). At admission, 79% were stunted. Children spent a mean of 4.2 weeks (SD 1.4 weeks) in the programme until recovery, resulting in a mean of 7.8 weeks of post-recovery follow-up in the present analysis. By the end of study follow-up at 12 weeks after admission, 114 (8%) of children relapsed to SAM and 89 (6%) were hospitalised. Supporting Information: Figure 1 shows the number of relapse and hospitalisation cases by week. SAM relapse occurred at 8.3 weeks (SD 3.0) postdischarge and hospitalisation at 7.7 weeks (SD 3.0) postdischarge, on average.

TABLE 2 Rate of morbidities (number of events per person-years) among recovered children, before and after nutritional programme discharge

	During programme ^a	Postdischarge	Incidence rate ratio (95% CI) ^b	p value
Any morbidity	19.93	21.41	1.08 (0.98–1.19)	0.14
Diarrhoea	6.30	5.31	0.84 (0.74–0.97)	0.01
Vomiting	1.64	1.44	0.88 (0.68–1.14)	0.34
Cough	6.10	5.53	0.91 (0.79–1.05)	0.20
Tachypnoea	0.47	0.55	1.16 (0.75–1.81)	0.50
Fever	3.42	5.07	1.49 (1.28–1.73)	<0.01
Malaria with fever	1.02	2.62	2.56 (2.04–3.22)	<0.01

Abbreviation: CI, confidence interval.

^aNumber of events per person-year from scheduled and unscheduled visits, with person-time for each morbidity including 7 days per scheduled visit +1 day per unscheduled visit.

^bIncidence rate ratio (95% CI) derived using generalised estimating equations with a log-Poisson link. All models adjusted for trial regimen (amoxicillin vs. placebo).

We found that the incidence of any morbidity, vomiting, cough and tachypnoea was similar during and after treatment, whereas the incidence of fever and malaria with fever was significantly higher postdischarge (Table 2). Only the incidence of diarrhoea was significantly lower postdischarge versus during treatment.

In multivariable analysis, independent risk factors for SAM relapse included younger child age, discharge during the lean season, and living in a household with two children compared to living in a household with one child (Table 3). Higher MUAC at discharge and maternal literacy were independent protective factors against SAM relapse. Discharge during the lean season was similarly independently associated with postdischarge hospitalisation (Table 4).

Lastly, to better understand anthropometry at discharge as a predictor of adverse events postdischarge, we examined the predictive value of MUAC and WHZ at discharge for SAM relapse and postdischarge hospitalisation at 12 weeks since admission. At 12 weeks since admission (end of study follow-up), the AUC for MUAC in predicting SAM relapse was significantly larger than the AUC for WHZ ($p < 0.01$): 0.71 (95% confidence interval [CI]: 0.65–0.77) vs. 0.56 (95% CI: 0.49–0.63) (Figure 1). Our analysis of the optimal cut-offs showed the optimal MUAC to be 121 mm with 66% sensitivity, 67% specificity and 0.71 AUC, and the optimal WHZ to be -1.38 with 54% sensitivity, 57% specificity and 0.56 AUC (Supporting Information: Table 1). With respect to postdischarge hospitalisation within 12 weeks since admission, the AUC for MUAC and WHZ did not significantly differ ($p = 0.53$): 0.52 (95% CI: 0.43–0.65) versus 0.56 (95% CI: 0.47–0.64) (Figure 1). Optimal cut-off for MUAC was 123 mm with 52% sensitivity, 56% specificity and 0.52 AUC, and optimal cut-off for WHZ was -1.39 with 54% sensitivity, 56% specificity and 0.56 AUC (Supporting Information: Table 2).

4 | DISCUSSION

In this study, we examined the burden and risk factors of SAM relapse and hospitalisation after discharge from an outpatient nutritional treatment programme in rural Niger. We found that 8% of children relapsed to SAM and 6% were hospitalised postdischarge up to 12 weeks from admission. Discharge during the lean season was a risk factor for both SAM relapse and hospitalisation, whereas older child age, smaller household size, higher child MUAC at discharge, and maternal literacy were protective factors for SAM relapse.

Available evidence suggests SAM relapse rates following outpatient treatment can range from 2% to 37% (Stobaugh et al., 2019). Our study adds to the limited literature by providing new estimates of SAM relapse and hospitalisation following outpatient treatment from rural Niger. Our estimate of 8% of SAM relapse is generally in line with other studies from West Africa indicating similar SAM relapse rates following outpatient treatment in Burkina Faso (10.5%) and the Gambia (6%) (Burrell et al., 2017; Somassè et al., 2016). Differences in SAM relapse rates can likely be explained by varying definitions of relapse, as well as duration and frequency of follow-up.

We found that several individual, case and household factors were associated with postdischarge SAM relapse and hospitalisation. Older children were at lower risk of relapse in line with recent evidence from Ethiopia (Lambebo et al., 2021). Older children may be protected from relapse due to fewer nutritional and health problems often associated with improper introduction of complementary foods in younger children (Lambebo et al., 2021). In terms of case characteristics, our results showed that season of discharge predicted SAM relapse and postdischarge hospitalisation. These findings are consistent with prior reports. In Bihar, India, Burza et al. (2016) found that children discharged into a season of low food security were more likely to relapse than children discharged during a season of high food security. A study in Malawi which followed children discharged from

TABLE 3 Risk factors for relapse to severe acute malnutrition (SAM) among 1490 children recovered from outpatient SAM treatment

	SAM relapse (n = 114) N (%) or mean ± SD	No SAM relapse (n = 1376) N (%) or mean ± SD	Crude ^a relative risk (95% CI)	p value	Multivariable relative risk ^a (95% CI)	p value
Individual characteristics						
Age (months)	13.6 ± 6.5	17.5 ± 8.5	0.94 (0.91–0.96)	<0.01	0.94 (0.88–1.00)	0.06
Female sex	66 (58)	709 (52)	1.26 (0.88–1.81)	0.20	---	
Breastfed at admission	83 (73)	815 (59)	1.76 (1.18–2.63)	<0.01	0.70 (0.32–1.56)	0.39
Case characteristics						
WHZ at admission	-2.74 ± 0.67	-3.01 ± 0.60	1.77 (1.39–2.26)	<0.01	1.05 (0.44–2.49)	0.92
MUAC at admission (in mm)	112 ± 4	113 ± 4	0.94 (0.90–0.98)	<0.01	0.97 (0.90–1.04)	0.36
HAZ at admission	-2.84 ± 1.14	-3.00 ± 1.22	1.11 (0.95–1.28)	0.18	1.00 (0.44–2.27)	0.99
Stunting at admission	86 (75)	1088 (79)	0.83 (0.55–1.25)	0.37	---	
Severe stunting at admission	45 (39)	681 (49)	0.69 (0.48–0.99)	0.04	-- ^b	
WAZ at admission	-3.54 ± 0.69	-3.72 ± 0.69	1.42 (1.11–1.84)	<0.01	1.03 (0.23–4.62)	0.97
Severe underweight at admission	93 (82%)	1177 (86%)	0.77 (0.49–1.21)	0.26	--	
WHZ at discharge	-1.30 ± 0.50	-1.24 ± 0.49	0.78 (0.53–1.15)	0.22	--	
MUAC at discharge (in mm)	121 ± 5	124 ± 5	0.88 (0.84–0.92)	<0.01	0.93 (0.87–1.00)	0.03
HAZ at discharge	-3.05 ± 1.10	-3.19 ± 1.16	1.10 (0.94–1.28)	0.23	---	
Stunting at discharge	96 (84)	1161 (84)	0.99 (0.61–1.61)	0.97	--	
Severe stunting at discharge	55 (48)	759 (55)	0.78 (0.54–1.10)	0.16		
Length of stay in nutritional programme (weeks)	4.0 ± 1.2	4.2 ± 1.5	0.90 (0.79–1.03)	0.13	0.84 (0.68–1.05)	0.12
Weight gain during nutritional programme (g/kg/day)	5.38 ± 2.68	6.20 ± 2.57	0.88 (0.81–0.95)	<0.01	0.93 (0.82–1.06)	0.27
Discharged during the lean season	50 (44)	390 (28)	1.87 (1.31–2.66)	<0.01	1.80 (1.22–2.67)	<0.01
Household characteristics						
Number of children in the household						
1	40 (35)	647 (47)	Ref.	0.04	Ref.	0.04
2	47 (41)	433 (31)	1.67 (1.12–2.51)		1.56 (1.01–2.41)	
≥3	27 (24)	296 (22)	1.43 (0.89–2.29)		1.33 (0.79–2.23)	0.28
Food insecurity score	8.1 ± 8.3	8.2 ± 8.3	1.00 (0.98–1.02)	0.89	---	
Child slept under a bednet the previous night	91 (80)	1166 (85)	0.73 (0.47–1.13)	0.16	0.76 (0.47–1.22)	0.25
Wealth quintile						
Poorest	20 (19)	266 (19)	Ref.			
Poorer	17 (15)	248 (18)	0.82 (0.44–1.51)	0.27	---	
Middle	27 (24)	272 (20)	1.16 (0.68–1.99)		---	
Richer	12 (11)	257 (19)	0.57 (0.29–1.14)		---	
Richest	20 (18)	253 (18)	0.94 (0.52–1.68)		---	

TABLE 3 (Continued)

	SAM relapse (n = 114) N (%) or mean ± SD	No SAM relapse (n = 1376) N (%) or mean ± SD	Crude ^a relative risk (95% CI)	p value	Multivariable relative risk ^a (95% CI)	p value
Maternal age (years)	27.4 ± 9.6	27.1 ± 6.5	1.01 (0.97–1.04)	0.72	---	
Mother is literate	134 (11)	260 (19)	0.58 (0.33–1.01)	0.06	0.54 (0.29–0.98)	0.04

Abbreviation: CI, confidence interval; HAZ, height-for-age Z-score; MUAC, mid-upper arm circumference; SAM, severe acute malnutrition; WHZ, weight-for-height Z-score.

^aAll models adjusted for trial regimen (amoxicillin vs. placebo).

^bExcluded due to collinearity with HAZ.

MAM treatment over the course of a year also found that 60% of the poor outcomes were observed in children discharged during the lean season (Chang et al., 2013). However, a third study from Burkina Faso found no differences in relapse risk between children who faced a food scarcity period and those who did not (Somassè et al., 2016). We extend prior studies by also showing that lean season discharge increased the risk of postdischarge hospitalisation in addition to increasing the risk of SAM relapse. Children discharged during the lean season may be at higher risk of adverse events postdischarge due to more limited food availability and accessibility relative to the harvest season, a seasonal pattern recognised in Niger. While future interventions to improve the sustainability of children's recovery in Niger could be targeted to seasons of low food security, more work is needed to better understand the type of postdischarge interventions that may help sustain recovery. Evidence from Malawi suggests that a comprehensive package of health and nutrition services delivered postdischarge from MAM treatment, including lipid-based nutrient supplement, deworming medication, zinc supplementation and malaria treatment and prevention, did not improve sustained recovery during 1 year of follow-up (Stobaugh et al., 2017). More work is needed to understand whether this type of comprehensive package could also be effective in sustaining long-term recovery and reducing relapse following SAM treatment. The feasibility, acceptability and cost-effectiveness of integrating these services in the Niger context should also be assessed.

In addition to the season of discharge, we found that anthropometry at discharge predicted SAM relapse, consistent with prior studies (Binns et al., 2016; Burrell et al., 2017; Burza et al., 2016; Magnin et al., 2017; Somassè et al., 2016). In our analysis, higher MUAC at discharge was protective against relapse, and MUAC of 121 mm at discharge (somewhat lower than international guidance recommending discharge at MUAC of 125 mm) was found to be optimal in predicting no SAM relapse at 12 weeks of admission. It is worth noting that the optimal WHZ cut-off of -1.38 identified in the present analysis was higher than the internationally used cut-off of -2 SD. The 'optimal' cut-offs presented in the current analysis, however, reflect one statistical optimisation maximising the product of the sensitivity and specificity. Other approaches could be used to determine optimal cut-offs that may better serve other programme objectives. For programmes seeking to otherwise maximise

sensitivity and/or specificity, our estimates of sensitivity and specificity provided for each level of MUAC and WHZ (Supporting Information: Tables 1 and 2) may serve as a resource in selecting alternative discharge criteria. We further note that as the AUCs for both MUAC and WHZ in predicting postdischarge relapse and hospitalisation were generally poor. Future research may be able to identify additional risk factors beyond anthropometry at discharge that can further improve identification of children at risk and targeting of postdischarge intervention.

In addition to identifying risk factors for postdischarge SAM relapse and hospitalisation, this analysis also suggests that children remain at elevated risk of certain morbidities after discharge. Prior studies have examined postdischarge morbidity among children discharged from inpatient treatment or day care nutritional rehabilitation centres and consistently documented elevated prevalence of respiratory illness, diarrhoea, cough and fever in the postdischarge period (Aprameya et al., 2015; Ashraf et al., 2012; Bahwere et al., 2017; Khanum et al., 1998). Evidence of increased morbidity postdischarge may suggest that children remain immunologically vulnerable even after they have reached anthropometric recovery and that additional support during the postdischarge period may be helpful to reduce vulnerability to infection. Our study builds on existing evidence by demonstrating elevated incidence of fever and malaria with fever after discharge from outpatient treatment, although the incidence of diarrhoea was lower in the postdischarge period than during nutritional treatment. We do, however, note the possibility for higher incidence of fever and malaria with fever may have resulted from increased presentation of fever after recovery compared to during treatment when the immune system may be compromised, resulting in increased malaria testing in the post-discharge period. The lower incidence of diarrhoea in the post-discharge period is likely unrelated to the trial amoxicillin regimen, which had only a transient effect on diarrhoea within the first week of admission to the programme (Isanaka et al., 2016). More research is needed to better understand immunological recovery as it relates to anthropometry during treatment and at the time of discharge, as well as to determine additional interventions that may specifically improve immune recovery and reduce postdischarge morbidity.

Our study is subject to limitations. We did not have a community control group and were unable to calculate excess risk of SAM and

TABLE 4 Risk factors for hospitalisation among 1490 children recovered from outpatient severe acute malnutrition (SAM) treatment

	Hospitalisation (n = 89) N (%) or mean (SD)	No hospitalisation (n = 1401) N (%) or mean (SD)	Crude ^a relative risk (95% CI)	p value	Multivariable relative risk ^a (95% CI)	p value
Individual characteristics						
Age (months)	16.2 ± 7.6	17.3 ± 8.6	0.98 (0.96–1.01)	0.24	---	---
Female sex	47 (53)	728 (52)	1.03 (0.69–1.55)	0.88	---	---
Breastfed at admission	52 (58)	846 (60)	0.93 (0.62–1.39)	0.71	---	---
Case characteristics						
WHZ at admission	-2.81 ± 0.66	-3.00 ± 0.60	1.56 (1.16–2.10)	<0.01	1.89 (0.70–5.07)	0.21
MUAC at admission (in mm)	113 ± 4	113 ± 4	1.00 (0.95–1.05)	0.92	---	---
HAZ at admission	-2.94 ± 1.15	-2.99 ± 1.21	1.03 (0.88–1.22)	0.69	---	---
Stunting at admission	68 (76)	1106 (79)	0.87 (0.54–1.40)	0.57	---	---
Severe stunting at admission	39 (44)	687 (49)	0.82 (0.55–1.23)	0.34	--	--
WAZ at admission	-3.59 ± 0.71	-3.71 ± 0.68	1.27 (0.94–1.70)	0.12	1.00 (0.70–1.43)	1.00
Severe underweight at admission	74 (83)	1196 (85)	0.86 (0.50–1.46)	0.57	--	--
WHZ at discharge	-1.32 ± 0.44	-1.24 ± 0.49	0.73 (0.46–1.14)	0.17	0.53 (0.17–1.62)	0.26
MUAC at discharge (in mm)	122 ± 5	123 ± 5	0.97 (0.93–1.01)	0.10	1.00 (0.95–1.05)	0.95
HAZ at discharge	-3.13 ± 1.10	-3.18 ± 1.16	1.04 (0.88–1.24)	0.67	---	---
Stunting at discharge	76 (85)	1181 (84)	1.08 (0.61–1.92)	0.78	---	---
Severe stunting at discharge	46 (52)	795 (55)	0.89 (0.59–1.33)	0.57	--	--
Length of stay in nutritional programme (weeks)	3.88 ± 1.3	4.2 ± 1.5	0.85 (0.73–1.00)	0.06	0.89 (0.66–1.20)	0.44
Weight gain during nutritional programme (g/kg/day)	5.6 ± 2.7	6.2 ± 2.6	0.91 (0.84–0.99)	0.03	1.02 (0.79–1.31)	0.90
Discharged during the lean season	43 (48)	397 (28)	2.23 (1.50–3.33)	<0.01	2.27 (1.46–3.51)	<0.01
Household characteristics						
Number of children in the household						
1	44 (49)	643 (46)	Ref.	0.39	---	---
2	23 (26)	457 (33)	0.75 (0.46–1.22)		---	---
≥3	22 (25)	301 (21)	1.06 (0.65–1.74)		---	---
Food insecurity score	7.2 ± 7.5	8.3 ± 8.3	0.98 (0.96–1.01)	0.25	---	---
Child slept under a bednet the previous night	73 (82)	1184 (85)	0.84 (0.50–1.42)	0.53	---	---
Wealth quintile						
Poorest	12 (13)	276 (20)	Ref.	0.61	---	---
Poorer	17 (19)	248 (18)	1.51 (0.73–3.10)		---	---
Middle	20 (22)	279 (20)	1.58 (0.79–3.18)		---	---
Richer	12 (13)	257 (18)	1.06 (0.48–2.31)		---	---
Richest	15 (17)	258 (18)	1.29 (0.61–2.71)		---	---

TABLE 4 (Continued)

	Hospitalisation (<i>n</i> = 89) N (%) or mean (SD)	No hospitalisation (<i>n</i> = 1401) N (%) or mean (SD)	Crude ^a relative risk (95% CI)	<i>p</i> value	Multivariable relative risk ^a (95% CI)	<i>p</i> value
Maternal age (years)	26.8 ± 10.1	27.1 ± 6.4	0.99 (0.96–1.03)	0.67	---	
Mother is literate	12 (13)	261 (19)	0.70 (0.38–1.26)	0.23	--	

Abbreviations: CI, confidence interval; HAZ, height-for-age Z-score; MUAC, mid-upper arm circumference; WHZ, weight-for-height Z-score.

^aAll models adjusted for trial regimen (amoxicillin vs. placebo).

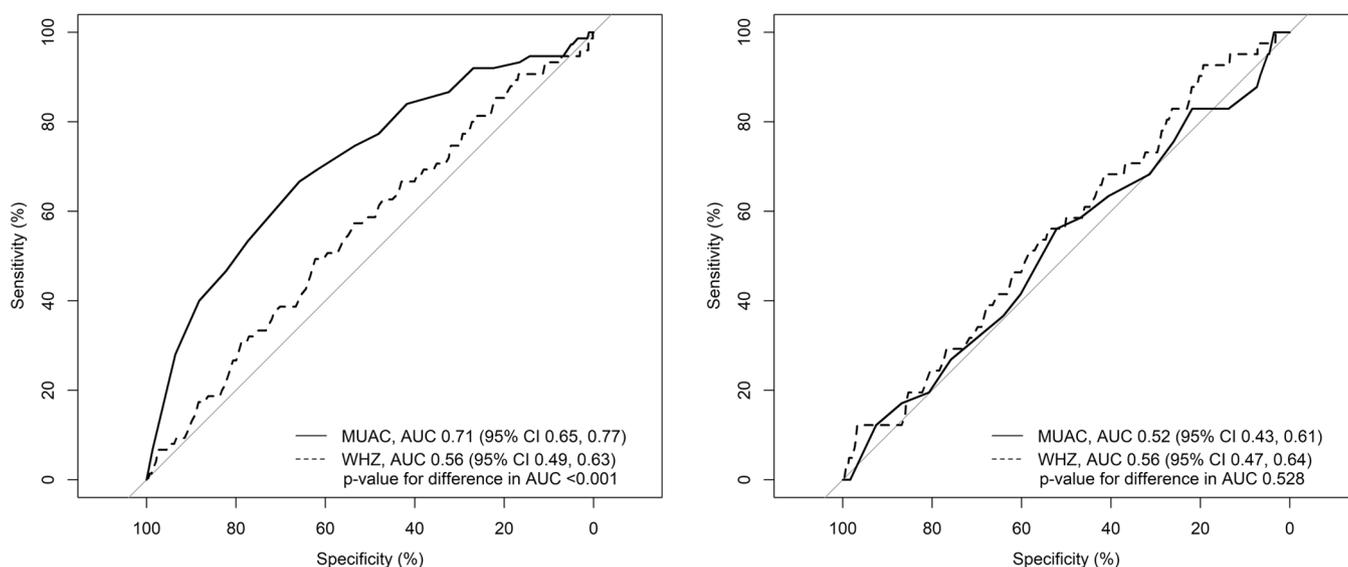


FIGURE 1 Receiver operating characteristic curves showing predictive value of mid-upper arm circumference (MUAC) and weight-for-height Z-score (WHZ) at discharge for postdischarge relapse to severe acute malnutrition (left) and postdischarge hospitalisation (right) at 12 weeks after admission

hospitalisation after discharge, as has been done elsewhere (Adegoke et al., 2020). Any excess risk might be attributed to the fact that children with SAM come from subgroups of the general population with a higher risk or vulnerability. In addition, we had a shorter period of follow-up relative to other studies (i.e., up to 12 weeks after admission and mean 7.8 weeks after programmatic recovery) and were unable to capture long-term risk of relapse and hospitalisation. Prior studies have shown that the risk of relapse and death is highest during the period immediately after discharge, with most events occurring within the first 12 weeks after initial recovery (Burza et al., 2016; Guesdon et al., 2021).

Despite these limitations, our study has important implications for nutritional programmes in Niger and other low-resource settings. Continued focus on short-term outcomes alone may not adequately reflect risk for children postdischarge and underestimate the adverse consequences associated with SAM. Future programmes may consider following children after discharge to monitor their nutritional and immunological recovery at home or in an integrated MAM treatment programme. In Niger, targeting follow-up interventions to children presenting with identified risk factors, for example, younger children and children discharged during the lean season, may help

increase intervention effectiveness and efficiency by focusing on subgroups that may benefit the most from postdischarge interventions. National and global guidance is needed to inform the frequency and duration of postdischarge follow-up, as well as the composition of specific interventions suitable for postdischarge follow-up, if implemented.

5 | CONCLUSION

In conclusion, we found that 8% of children discharged as nutritionally recovered from outpatient treatment of uncomplicated SAM in rural Niger relapsed to SAM and 6% were hospitalised within 12 weeks of admission. We found elevated morbidity in the postdischarge period, suggesting children may remain immunologically vulnerable even after programmatic recovery. Discharge during the lean season was a risk factor for postdischarge SAM relapse and hospitalisation, while younger child age and larger household size were also risk factors for SAM relapse. Higher child MUAC at discharge and maternal literacy were protective factors for relapse. MUAC at discharge performed better than WHZ in identifying cases

of SAM relapse, with statistically optimal cut-offs of 121 mm MUAC and -1.38 WHZ in this setting. With approximately 110,000 severely wasted children in Niger in 2019 (UNICEF et al., 2021), our findings of 8% relapse imply that nearly 9000 children require repeat nutritional treatment. Research and programmatic efforts should broaden focus from short-term programmatic outcomes towards consideration of sustained nutritional and immunological recovery to improve the long-term health of children treated for SAM. More consideration to alternative anthropometric discharge may be warranted, as one of the few modifiable factors to reduce SAM relapse in this context. In Niger, the national treatment protocol was revised in 2016 to increase the MUAC admission and discharge cut-off for SAM to 125 mm (Ministere de la Sante Publique et de la Lutte contre les Endemies, 2016). More data is needed on whether this increased cut-off has helped improve children's postdischarge outcomes in the Niger context.

AUTHOR CONTRIBUTIONS

Sheila Isanaka and Rebecca F. Grais designed the research. Fatou Berthé and Souna Garba conducted the research. Lilia Bliznashka, Kyra H. Grantz and Jérémie Botton conducted the statistical analyses. Lilia Bliznashka wrote the first draft of the manuscript. All authors provided important intellectual contributions, edited the manuscript and ensured its final contents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was reviewed and approved by the Comité Consultatif National d'Éthique in Niger and the Comité de Protection des Personnes in France. An independent data and safety monitoring board regularly reviewed progress and safety of the clinical trial. Trained research nurses explained the study aims and procedures to the caregivers of eligible children and written informed consent was obtained for the child's participation in the trial.

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