LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Munirul Islam, M; Arafat, Y; Connell, N; Mothabbir, G; McGrath, M; Berkley, JA; Ahmed, T; Kerac, M (2018) Severe malnutrition in infants aged ¡6 months-Outcomes and risk factors in Bangladesh: A prospective cohort study. Maternal & child nutrition. e12642. ISSN 1740-8695 DOI: https://doi.org/10.1111/mcn.12642

DOI: 10.1111/mcn.12642

Received: 20 December 2017 | Revised: 29 May 2018 | Accepted: 6 June 2018
DOI: 10.1111/mcn.12642

ORIGINAL ARTICLE

WILEY Maternal & Child Nutrition

Severe malnutrition in infants aged <6 months—Outcomes and risk factors in Bangladesh: A prospective cohort study

M. Munirul Islam[1] | Yasir Arafat[2] | Nichola Connell[3] | Golam Mothabbir[2] | Marie McGrath[4] | James A. Berkley[5,6] | Tahmeed Ahmed[1] | Marko Kerac[7]

[1] Nutrition and Clinical Services Division, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b), Dhaka, Bangladesh

[2] Department of Health and Nutrition, Save the Children Bangladesh, Dhaka, Bangladesh

[3] Department of Global Health, Save the Children USA, Washington, District of Columbia, USA

[4] Emergency Nutrition Network, Oxford, UK

[5] KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya

[6] The Childhood Acute Illness & Nutrition Network (CHAIN), Nairobi, Kenya

[7] Department for Population Health & MARCH Centre, London School of Hygiene & Tropical Medicine, London, UK

Correspondence
Nichola Connell, Department of Global Health, Save the Children USA, 899 North Capitol Street NE, Suite 900, Washington, DC 20002.
Email: nicki@eleanorcrookfoundation.org

Abstract

Severe acute malnutrition (SAM) affects ~4 million infants under 6 months (u6m) worldwide, but evidence underpinning their care is "very low" quality. To inform future research and policy, the objectives of our study were to identify risk factors for infant u6m SAM and describe the clinical and anthropometric outcomes of treatment with current management strategies. We conducted a prospective cohort study in infants u6m in Barisal district, Bangladesh. One group of 77 infants had SAM (weight-for-length Z-score [WLZ] <−3 and/or bipedal oedema); 77 others were "non-SAM" (WLZ ≥−2 to <+2, no oedema, mid-upper-arm circumference ≥125 mm). All were enrolled at 4–8 weeks of age and followed up at 6 months. Maternal education and satisfaction with breastfeeding were among factors associated with SAM. Duration of exclusive breastfeeding was shorter at enrolment (3·9 ± 2.1 vs. 5.7 ± 2.2 weeks, P < 0.0001) and at age 6 months (13.2 ± 8.9 vs. 17.4 ± 7.9 weeks; P = 0.003) among SAM infants. Despite referral, only 13 (17%) reported for inpatient care, and at 6 months, 18 (23%) infants with SAM still had SAM, and 3 (3.9%) died. In the non-SAM group, one child developed SAM, and none died. We conclude that current treatment strategies have limited practical effectiveness: poor uptake of inpatient referral being the main reason. World Health Organization recommendations and other intervention strategies of outpatient-focused care for malnourished but clinically stable infants u6m need to be tested. Breastfeeding support is likely central to future treatment strategies but may be insufficient alone. Better case definitions of nutritionally at-risk infants are also needed.

KEYWORDS

breastfeeding, infants under 6 months, moderate acute malnutrition, mortality, risk factors, severe acute malnutrition

1 | INTRODUCTION

Undernutrition is responsible for 45% of all under-5 child deaths (Black et al., 2013) and affects progress towards numerous Sustainable Development Goals (Greenslade, 2015). Target 2.2 of Sustainable Development Goals 2 (Zero Hunger) aims to "By 2030, end all forms of malnutrition, including stunting and wasting in children under 5 years of age" (Sustainable Development Goals, 2015).

Over the last decade, the treatment of malnourished children aged 6–59 months has been revolutionized by a public-health focused model of care, "Community Management of Acute Malnutrition" (CMAM; Bhutta et al., 2017; Trehan & Manary, 2015). Yet, despite some 4 million infants worldwide being severely wasted (Kerac et al., 2011) with a higher risk of death than older children (Grijalva-Eternod et al., 2017), malnourished infants aged under 6 months (u6m) have long been neglected (Kerac, Mwangome, McGrath, Haider, & Berkley, 2015). This problem was most recently highlighted in the updated World Health Organization (WHO, 2013) guidelines on "The Management of Severe Acute Malnutrition (SAM) in Infants and Children." Although this document includes a chapter on infants u6m (for the first time), "very low quality" underlying evidence is acknowledged (WHO, 2013). Others, including 64 national and international experts who contributed to a 2015 Child Health and Nutrition Research Initiative research prioritization exercise, have also highlighted major evidence gaps around this vulnerable patient group (Kerac et al., 2015). Especially lacking is evidence for the potential safety and effectiveness of home-based treatment of clinically stable infants u6m with SAM (Kerac et al., 2015).

Bangladesh guidelines are typical of almost all current national SAM guidelines (Kerac et al., 2017) in that they only describe inpatient care (IPHN/DGHS/MoHFW/PRB, 2008). As in the early days of CMAM for older children, a shift to outpatient/community care is a significant paradigm change that is politically and programmatically sensitive (Kerac et al., 2015).

To move forward, data on potentially modifiable risk factors and outcomes using current inpatient-only treatments are needed. This is vital need for researchers, policymakers, and programme managers to design and test better future interventions. Our goal was to address these research gaps. Our first aim was to identify risk factors associated with infant u6m SAM and, second, to describe the clinical and anthropometric outcomes of treatment using current management strategies.

Key messages

- Infants with severe acute malnutrition (SAM) referred to inpatient care often do not access that care: This emphasizes the need for accessible and effective (not just efficacious) treatment strategies.
- Many infants identified as having SAM at 4–8 weeks age have recovered to normal weight-for-length by 6 months age, but other deficits persist compared with non-SAM infants (e.g., low weight-for-age and low length-for-age), and the role of intrauterine growth retardation is unclear. Future treatment strategies should include outpatient-based care options.
- Multiple risk factors associated with infant under 6 months malnutrition suggest that although breastfeeding support is a key part of future treatments, this alone may be insufficient. "Packages of care" addressing wider factors like social support and maternal well-being may be more successful than single, stand-alone, "magic bullet" interventions.

2 | PARTICIPANTS AND METHODS

2.1 | Study design and participants

We conducted a prospective cohort study. This involved two groups, each consisting of 77 infants aged 4–8 weeks (the age when future interventions to treat infant u6m SAM will be anticipated to begin; Mwangome, Fegan, Fulford, Prentice, & Berkley, 2012). One group comprised infants with SAM as defined by current WHO guidelines: weight-for-length Z-score (WLZ) <−3 and/or bilateral nutritional oedema (WHO, 2013); the other comprised age- and sex-matched infants who were not severely malnourished (non-SAM) defined as WLZ ≥−2 to <2 and mid-upper-arm circumference (MUAC) ≥125 mm. Exclusions were infants from twin/multiple pregnancies and those with obvious congenital anomalies that could affect feeding (e.g., cleft lip or palate).

Ethical approval was obtained from the Institutional Review Board of International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b; PR14112). Written informed consent was obtained from the infants' parents or legal guardians. The study is registered with the ISRCTN trial registry: http://www.isrctn.com/ISRCTN12494235.

2.2 | Variables

The primary outcome was the proportion of infants who died or who had SAM (defined as per WHO criteria as WLZ <−3 and/or MUAC <115 mm[1] and/or oedema) at age 6 months (180 completed days). Key secondary outcomes were changes in and absolute values of weight-for-length z-score (WLZ), weight-for-age z-score (WAZ), and length-for-age z-score (LAZ).

Maternal mental health status was assessed using the WHO Self Reporting Questionnaire 20 (SRQ 20; WHO, 1994). Mothers who had a high total score (≥13) or who answered "Yes" to question no. 17 ("Has the thought of ending your life been on your mind?") were referred to the outpatient psychiatry department at the nearby Sher-e-Bangla Medical College Hospital, Barisal, for appropriate management.

At cohort end line (age ≥ 6 months), infants' vital status, anthropometry, and dietary history were repeated.

2.3 | Data collection procedures

2.3.1 | Anthropometry

Anthropometric assessments were performed following the standard procedures (SMART, 2017). Length was measured using a portable length measuring board to 0.1 cm (Shorrboard, Weigh and Measure, LLC, Maryland, USA). Weight was measured using a digital scale accurate to 5 g (Digital Kinlee, Taiwan). MUAC was measured with UNICEF measuring tapes to 1 mm. Infants' reported birth date was verified against a birth certificate or immunization card whenever possible. Oedema was assessed by pressing the upper side of both feet by

[1]Note that for infants aged >6 months, WHO SAM criteria include MUAC <115 mm whereas for those aged <6 months, the case definition is based on WLZ and/or oedema alone.

pressing for 3 s. Maternal anthropometry was measured only for the prospective cohort study at enrolment: Weight was measured with a scale accurate to 100 g and height by a height board graduated to the nearest 0.1 cm. Regular checks of weighing scale and length/height board calibration were carried out with a known weight and length, respectively.

2.3.2 | Data collection procedures

SAM "case" infants were identified by household visits. Age- and sex-matched controls were also selected by household visits in Barisal district of Bangladesh. Study participants were identified by the set criteria as mentioned above.

For both parts of the study, data were collected electronically: This enabled immediate validation of key variables. Supervisors also checked incoming data daily for completeness and consistency.

2.4 | Sample size estimation and statistical analysis

Sample size for the prospective cohort study was estimated for comparing outcomes in the exposed group (SAM) and unexposed group (non-SAM) assuming that 25% of the participants in the SAM group would have SAM at 6 months of age and 6.3% of the participants in the non-SAM group would have SAM at the same time point (the prevalence of SAM in infants u6m in Bangladesh during designing the survey; NIPORT, Mitra, & ICF, 2013). With 5% level of significance and 80% power, 77 infants were required per group, assuming approximately 25% loss to follow-up at the end of 6 months. The following formula was used for sample size estimation: $\left[(p_A\ (1{-}p_A)/\kappa + p_B\ (1{-}p_B)\right]\left[(z_{1-\alpha/2} + z_{1-\beta})/(p_A{-}p_B)\right]^2$ [available at http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Equality].

Anthropometric z-scores (standard deviation scores) were calculated from raw age, sex, length, and weight data using WHO, 2006 growth standards and WHO Anthro software (WHO, 2006). LAZs and WLZs were calculated for infants who were ≥45 cm long (WHO 2005). WAZs were calculated for all infants. Those with extreme values were excluded from analysis following standard WHO "cleaning rules," WAZ <−6.0 or WAZ >+5.0, LAZ <−6.0 or LAZ >+6.0, and WLZ <−5.0 or WLZ >+5.0 *SD* (Crowe, Seal, Grijalva-Eternod, & Kerac, 2014).

Potential explanatory variables were grouped under household characteristics, maternal characteristics, and infant characteristics. Differences between groups were tested using chi-squared tests for proportions, Student's *t* test for normally distributed continuous variables, and Mann–Whitney *U* test for skewed continuous variables. Multivariable logistic regression was performed for adjustments of different variables and potential risk factors for SAM. Multiple linear regression analysis was also used to adjust the potentially confounding variables when different variables were compared for test of significance. The potential confounders were considered to be the age of the infants at the time of enrolment, monthly income, and maternal education. All the tests were considered as significant at $P < 0.05$. Statistical analysis was done with the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

3 | RESULTS

3.1 | Sociodemographic characteristics

Infants in the SAM group were over a week younger at enrolment than those in the non-SAM group (5.1 ± 1.2 weeks vs. 6.5 ± 1.2 weeks, $P = 0.001$). Median household monthly income was significantly lower ($P = 0.007$) in SAM group, and mothers were less educated ($P = 0.005$) also. Fewer households in the SAM group had electricity ($P = 0.013$). Other reported sociodemographic characteristics were comparable between groups (Table 1).

3.2 | Anthropometry

Table 2 shows full details of anthropometry of the SAM versus non-SAM infants. Because the infants were allocated to the two groups on the basis of their anthropometry, no statistical tests of differences at enrolment were performed. By 6-month end line, however, statistically significant differences were apparent between SAM and non-SAM infants: Daily weight gain (g·kg·day) was better among the SAM group, 8.6 versus 4.3 g·kg·day, $P < 0.0001$; MUAC increase was greater, 35.7 versus 13.2 mm, $P < 0.0001$; WLZ change was greater, 2.0 versus −0.24, $P < 0.0001$; and WAZ change was greater, 0.9 versus −0.4, $P < 0.0001$. However, there was a similar decline in LAZ of 0.6 Z-scores in both groups.

Mothers of the SAM infants were significantly lighter, shorter, and had lower MUAC than non-SAM mothers. Despite statistically significant differences, absolute values of maternal weight and height were close in the two groups, with only MUAC showing a clinically marked as well as statistically significant difference between the two groups (mean 1.3 cm lesser MUAC among mothers whose infants had SAM).

3.3 | Primary outcome

Table 3 shows the primary outcome, SAM status of the study participants at age 6 months. Eighteen (23%) infants were suffering from SAM at that time point. In this group, three (3.9%) infants had died, and five (6%) were lost to follow-up. Despite all 77 being referred for inpatient treatment of SAM, only 13 (17%) parents had reported for care and most who did left the hospital before attaining the discharge criteria. In the non-SAM group, only one (1%) infant developed SAM, none died, and five (6%) were lost to follow-up. In the SAM group, 43 (62%) were stunted at this time, and 27 (39%) severely stunted, compared with 11 (15%) stunted and none severely stunted in the non-SAM group ($P < 0.0001$).

3.4 | Dietary practices and sleep habits

Table 4 and Supporting Information Table 1 show dietary practices and sleeping habits of the study participants. Duration of exclusive breastfeeding both at enrolment and at study conclusion was significantly greater in non-SAM infants ($P < 0.0001$ and $P = 0.003$, respectively). More infants were reported to be still breastfeeding at age 6 months in the non-SAM group ($n = 72$, 100%) compared with the SAM group ($n = 60$, 87%; $P = 0.001$). At enrolment, 26 (34%) infants in the SAM group were not exclusively breastfed compared with a

TABLE 1 Sociodemographic characteristics of the study participants

Variables	SAM (*n* = 77)	Non-SAM (*n* = 77)	*P*
Age in weeks[a]	5.1 ± 1.2	6.5 ± 1.2	0.001[c]
Female sex, *n* (%)	33 (43)	33 (43)	1.00
Mother's age (year)[a]	24.7 ± 5.9	23.4 ± 4.7	0.13[c]
Maternal education (years)	6.4 ± 3.6	8.1 ± 3.8	0.005[c]
Family income (US$), median (interquartile range)[b]	90 (71, 128)	115 (83, 192)	0.007[d]
Has electricity, *n* (%)	47 (61)	62 (80)	0.013
Source of drinking water, *n* (%)			0.50
Stand pipe	2 (3)	0 (0)	
Tube well	75 (97)	77 (100)	
Source of water other household purposes, *n* (%)			0.45
Piped into dwelling	3 (4)	8 (10)	
Stand pipe	3 (4)	1 (1)	
Tube well	16 (21)	16 (21)	
Surface water	55 (71)	52 (68)	
Floor material, *n* (%)			0.11
Earth/sand/clay/mud/dung	65 (84)	56 (73)	
Cement/concrete	12 (16)	21 (27)	
Exterior wall of the house, *n* (%)			0.51
Cement/concrete	10 (8)	16 (12)	
Bricks	4 (3)	6 (5)	
Metal/asbestos sheets	76 (58)	74 (57)	
Other (cane/palm/trunks/bamboo/wood planks/shingles)	10 (8)	4 (3)	
Source of fuel, *n* (%)			0.26
Wood	54 (70)	63 (82)	
Straw/shrubs/grass	18 (23)	9 (11)	
Other (LPG/gas/kerosense/charcoal/animal dung)	5 (7)	5 (7)	
Types of toilet facility for household members, *n* (%)			0.68
Flush to septic tank/flush to pit latrine/ventilated improved pit latrine	10 (13)	15 (20)	
Pit latrine with slab	65 (84)	58 (75)	
Pit latrine without slab/open pit	2 (3)	4 (5)	
Practice of hand washing with soap while helping the child after defecation, *n* (%)			0.58
Always	24 (31)	26 (34)	
Sometimes	21 (27)	16 (21)	
Rarely	18 (23)	24 (31)	
Never	14 (18)	11 (14)	
Practice of hand washing with soap before preparing food, *n* (%)			0.50
Always	13 (27)	15 (20)	
Sometimes	17 (22)	10 (13)	
Rarely	17 (22)	21 (27)	
Never	30 (39)	31 (40)	
Practice of hand washing with soap after using toilet, *n* (%)			0.59
Always	50 (65)	55 (71)	
Sometimes	16 (21)	16 (21)	
Rarely	8 (10)	5 (7)	
Never	3 (4)	1 (1)	

Note. All tests of significance are Pearson chi-square test, unless mentioned. Level of significance <0.05. SAM: severe acute malnutrition.

[a]Mean ± *SD*.

[b]Median Interquartile Range.

[c]Student's *t* test.

[d]Mann–Whitney *U* test.

TABLE 2 Anthropometry of the study participants

Variables	SAM	Non-SAM	Unadjusted Difference (95% CI)	Unadjusted P	Adjusted (age, monthly income, maternal education) Difference (95% CI)	Adjusted P
Infant						
Body weight (kg)						
At enrolment, *n* = 154	2.67 ± 0.6	4.75 ± 0.5	—	—	—	—
At end line, *n* = 146	6.01 ± 1.06	7.56 ± 0.9	−1.58 (−1.9, −1.3)	0.001	−0.65 (−2.0, −1.26)	<0.0001
Change (end line—baseline)	3.29 ± 1.09	2.80 ± 0.74	0.45 (0.14, 0.76)	0.004	0.11 (−0.12, 0.52)	0.22
Daily weight gain (g·kg·day)	8.6 ± 3.8	4.3 ± 1.1	4.3 (3.4, 5.2)	<0.0001	0.55 (2.8, 4.8)	<0.0001
Length (cm)						
At enrolment, *n* = 154	50.7 ± 3.3	55.0 ± 1.9	—	—	—	—
At end line, *n* = 146	62.8 ± 3.1	65.9 ± 2.0	−3.26 (−4.09, −2.42)	0.001	−0.58 (−4.39, −2.47)	<0.0001
Change (end line—baseline)	11.9 ± 3.0	10.8 ± 1.8	0.88 (0.07, 1.70)	0.034	−0.04 (−1.05, 0.62)	0.61
MUAC (mm)						
At enrolment, *n* = 154	88.6 ± 10.4	128.0 ± 2.7	—	—	—	—
At end line, *n* = 146	125.4 ± 14.3	141.3 ± 10.0	−16.4 (−20.5, −12.3)	<0.0001	−0.56 (−20.89, −11.58)	<0.0001
Change (end line—baseline)	35.7 ± 16.6	13.2 ± 8.8	21.9 (17.5, 26.3)	<0.0001	0.60 (15.51, 25.38)	<0.0001
Oedema present			—			
At enrolment (*n* = 154), *n* (%)	2 (3)	0 (0)		0.16[a]	−0.21 (−0.02, 0.01)	0.80
At end line (*n* = 141), *n* (%)	3 (4)	1 (1)		0.30[a]	0.10 (−0.01, 0.03)	0.24
Weight-for-length *z*-score						
At enrolment, *n* = 154	−3.42 ± 0.6	0.41 ± 0.8	—	—	—	—
At end line, *n* = 146	−1.28 ± 1.3	0.16 ± 1.0	−1.46 (−1.86, −1.06)	0.001	−0.54 (−1.98, −1.05)	<0.0001
Change (end line—baseline)[b]	2.0 (1.1, 2.8)	−0.24 (−0.8, 0.4)	−8.29 (0, 0)	<0.0001[c]	0.68 (1.8, 2.8)	<0.0001
Weight-for-age *z*-score						
At enrolment, *n* = 154	−3.66 ± 1.3	−0.23 ± 0.8	—	—	—	—
At end line, *n* = 146	−2.62 ± 1.4	−0.59 ± 1.0	−2.07 (−2.48, −1.68)	0.001	−0.68 (−2.61, −1.70)	<0.0001
Change (end line—baseline)[b]	0.9 (−0.3, 2.0)	−0.4 (−0.8, 0.1)	−5.4 (0, 0)	<0.0001[c]	0·51 (0.89, 1.8)	<0.0001
Length-for-age *z*-score						
At enrolment, *n* = 154	−2.13 ± 1.6	−0.53 ± 0.9	—	—	—	—
At end line, *n* = 146	−2.57 ± 1.4	−1.14 ± 0.8	−1.50 (−1.87, −1.13)	0.001	−0.58 (−1.98, −1.13)	<0.0001
Change (end line—baseline)[b]	−0.6 (−1.4, 0.4)	−0.6 (−1.1, −0.2)	−0.7 (0.94, 0.95)	0.94[c]	0.03 (−0.34, 0.44	0.79
Mother						
Body weight (kg)	47.6 ± 8.5	52.3 ± 9.6	−4.74 (−7.64, −1.84)	0.002	0.19 (−6.30, −0.89)	0.009
Height (cm)	149.2 ± 5.6	151.7 ± 5.3	−2.54 (−4.28, −0.80)	0.004	−0.17 (−3.66, −0.15	0.034
Body mass index	21.3 ± 3.4	22.6 ± 3.4	−1.30 (−2.39, −0.21)	0.032	−0.14 (−2.01, 0.04)	0.06
MUAC (mm)	233.2 ± 26.3	245.5 ± 27.1	−12.4 (−20.89, −3.84)	0.012	−0.19 (−18.31, −1.97)	0.015

Note. All values are mean ± *SD*, unless mentioned. All tests of significance are Student's *t* test, unless mentioned. Level of significance <0.05. SAM: severe acute malnutrition; MUAC: mid-upper-arm circumference.

[a]Pearson chi-square test.

[b]Median Interquartile Range.

[c]Mann–Whitney *U* test.

significantly lower proportion of non-SAM infants (*n* = 10, 13%; *P* = 0.004). At study conclusion, 27 infants in SAM group were provided family food with a median age of introduction (13 weeks), a significantly lower age of introduction compared with the non-SAM group (21 weeks, *P* = 0.004).

3.5 | Factors associated with SAM

Table 5 highlights factors associated with an infant having SAM or not. Statistically significant associations were seen with exclusive breastfeeding status, age at time of enrolment into the study, years of maternal schooling, access to household electricity, and mother's satisfaction about breastfeeding at the time of enrolment.

3.6 | Maternal mental status

Maternal mental health was worse among mothers of SAM infants with a higher mean SRQ score at baseline: 8.4 ± 3.6 versus 6.8 ± 3.8, *P* = 0.003; seven (9%) versus one (1%) having a total score of ≥13 (*P* = 0.03). Four (5.2%) mothers responded “yes” to question no. 17 (suicidal intent) of SRQ 20 in the SAM group, whereas two (2.6%) mothers responded the same in non-SAM group (*P* = 0.68).

TABLE 3 Outcome status of the study participants at the end of 6 months (180 days), *n* (%)

Outcome status	SAM (*n* = 77)	Non SAM (n = 77)	P
Primary outcomes			<0.0001
SAM (WLZ <−3 or oedema)	18 (23.4)	1 (1.3)	
Not SAM	51 (66.2)	71 (92.2)	
Death (with malnutrition)	3 (3.9)	0 (0)	
Left the community or could not be contacted	5 (6.5)	5 (6.5)	
SAM vs. all other	18 (23.4)	1 (1.3)	<0.0001
Not SAM vs. all other	26 (66.2)	71 (92.2)	<0.0001
Death vs. not death	3 (3.9)	0 (0)	0.25
Left the community	5 (6.5)	5 (6.5)	1.0
Other nutritional outcomes			
Moderate acute malnutrition (WLZ ≥−3 to <−2)	13 (18.8)	1 (1.4)	<0.0001
Stunting (HAZ <−2)	43 (62.3)	11 (15.3)	<0.0001
Severe stunting (HAZ <−3)	27 (39.1)	0 (0)	<0.0001
Underweight (WAZ <−2)	47 (68.1)	5 (6.9)	<0.0001
Severe underweight (WAZ <−3)	27 (39.1)	0 (0)	<0.0001

Note. All test of significance are Pearson chi-square test unless mentioned. Level of significance <0.05. SAM: severe acute malnutrition; WLZ: weight-for-length z-score; HAZ: height-for-age z-score; WAZ: weight-for-age z-score.

4 | DISCUSSION

Malnutrition in infants u6m is an important public health problem in Bangladesh, whose significance and nature is highlighted by our results. Key findings in our prospective cohort study included that most infants identified as having SAM at 4–8 weeks of age did not access inpatient treatment when referred as per national protocol. Deaths in this group were higher than in the control group but not as high as reported in inpatient studies (Grijalva-Eternod et al., 2017). Although only a quarter of those with SAM at enrolment still had SAM at 6 months (end of study), other anthropometric deficits were marked. They had significantly more stunting (62% vs. 15%), more severe stunting (40% vs. 0%), and more underweight (68% vs. 7%). Risk factors associated with infant SAM included non-exclusive breastfeeding at enrolment, lack of maternal education, and mother not satisfied with breastfeeding at enrolment.

We followed SAM and non-SAM groups of infants from enrolment at 4–8 weeks old to 6 months of age. The fact that few of the SAM infants who were referred to inpatient care actually accessed that care is reminiscent of past experiences with older SAM-affected children. Before CMAM, when only inpatient-based care was available, coverage for such programmes was poor due to the high direct and opportunity cost of treatment (Collins, 2001). However efficacious such inpatient-only treatments might be, their overall effectiveness and public health impact is severely limited by this fact of low numbers of eligible patients accessing care that they need (Collins et al., 2006). Also reminiscent of the shift from inpatient-only care to CMAM outpatient-focused models, some professionals now are concerned about the safety of outpatient care for SAM infants u6m (Kerac et al., 2015). Addressing this concern, it is reassuring that despite the minimal (or no direct) treatment, over three-quarters of those with SAM at 4- to 8-week baseline no longer had SAM at age 6 months. This may represent catch-up growth, as suggested by greater rates of weight gain in the SAM group, and emphasizes infancy as a dynamic and important period of life (Jain & Singhal, 2012). The observation does not however mean that no interventions are needed: Ex-SAM infants had considerably more other anthropometric deficits than those who did not have SAM at baseline suggesting ongoing vulnerability. Of particular concern are those with concurrent deficits, such as those with both wasting and stunting together who are at greatly increased risk of mortality compared with those with one condition alone (Briend, Khara, & Dolan, 2015). There is potential for even better catch-up, and attempts to support this would fit well within the international focus on the critical “First 1,000 days” window of opportunity (Nabarro, 2013). Anthropometric deficits even in those who do not have SAM also raise important questions about whether the current criteria for identifying nutritionally vulnerable infants, based on WLZ (and oedema) alone, are in fact the best ones. Recent studies have suggested that MUAC and WAZ are in fact better in identifying high-risk infants u6m (Mwangome et al., 2012; Mwangome et al., 2017).

Our results also highlight the need to consider maternal factors when evaluating potentially at-risk infants. For instance, our observed association between SAM infants and maternal anthropometric deficit on univariate analysis is consistent with other evidence that maternal nutritional status has both short- and long-term associations with infant health (Liu et al., 2016; Wrottesley, Lamper, & Pisa, 2016). That supplementing undernourished mothers might have also benefits for their infants is biologically plausible but needs more evidence (Stevens et al., 2015).

Finally, the fact that we identified numerous risk factors associated with infant u6m SAM tallies well with another recent study, which found numerous risk factors in 20 national Demographic and Health Surveys (Kerac, Frison, Connell, Page, & McGrath, 2016). The exact risk factors do not however always agree—other studies in Bangladesh have identified other issues underlying malnutrition (Chowdhury et al., 2016). It may be that these factors are very population-specific.

TABLE 4 Dietary practices of the study participants

Variables	SAM	Non-SAM	*P*
Duration of exclusive breastfeeding (weeks)[a]			
At enrolment	3.9 ± 2.1 (*n* = 77)	5.7 ± 2.2 (*n* = 77)	<0.0001[c]
At end line	13.2 ± 8.9 (*n* = 69)	17.4 ± 7.9 (*n* = 72)	0.003[c]
Breastfeeding currently, *n* (%)			
At enrolment	74 (96; *n* = 77)	77 (100; *n* = 77)	0.25
At end line	60 (87; *n* = 69)	72 (100; *n* = 72)	0.001
Fed anything other than breast milk in last 24 hr, at enrolment, *n* (%)	(*n* = 77)	(*n* = 77)	0.004
Yes	26 (34)	10 (13)	
No	51 (66)	67 (87)	
Fed anything other than breast milk in last 24 hr, at end line, *n* (%)	(*n* = 65)	(*n* = 72)	0.18
Yes	57 (88)	56 (78)	
No	8 (12)	16 (22)	
Frequency of breastfeeding (times/day)[a]			
At enrolment	11.8 ± 3.5 (*n* = 74)	13.5 ± 2.6 (*n* = 77)	0.001[c]
At end line	9.3 ± 3.7 (*n* = 64)	10.2 ± 3.6 (*n* = 72)	0.13[c]
Duration of breastfeeding (min), at enrolment, *n* (%)	(*n* = 74)	(*n* = 77)	0.96
0–5 min	17 (23)	17 (22)	
>5–15 min	53 (72)	55 (71)	
>15–30 min	4 (5)	5 (7)	
Duration of breastfeeding (min), at end line, *n* (%)	(n = 60)	(n = 72)	0.13
0–5 min	19 (32)	14 (19)	
>5–15 min	39 (65)	51 (71)	
>15–30 min	2 (3)	7 (10)	
Mother's satisfaction with breastfeeding, at enrolment, *n* (%)	(*n* = 74)	(*n* = 77)	<0.0001
Very satisfied	6 (8)	36 (47)	
Satisfied	36 (48)	25 (33)	
Neither satisfied nor dissatisfied	16 (22)	8 (10)	
Dissatisfied	14 (19)	4 (5)	
Very dissatisfied	2 (3)	4 (5)	
Mother's satisfaction with breastfeeding, at end line, *n* (%)	(*n* = 63)	(n = 72)	0.001
Very satisfied	4 (6)	20 (28)	
Satisfied	23 (37)	28 (39)	
Neither satisfied nor dissatisfied	22 (35)	8 (11)	
Dissatisfied	11 (17)	8 (11)	
Very dissatisfied	3 (5)	8 (11)	
If the infant is getting family food, at enrolment, *n* (%)	(*n* = 75)	(*n* = 77)	0.49
Yes	1 (1)	0 (0)	
No	73 (95)	76 (99)	
Not known	3 (4)	1 (1)	
IF YES, at which age the family food was introduced (weeks)	(*n* = 1)	—	—
At enrolment, *n*	6		
If the infant is getting family food, at end line, *n* (%)	(*n* = 69)	(*n* = 72)	0.49
Yes	27 (39)	33 (46)	
No	41 (59)	38 (53)	
Not known	1 (2)	1 (1)	
If YES, at which age the family food was introduced (weeks)	13 (8, 21)	21 (20·3, 24)	0.004[d]
At end line[b]	(*n* = 27)	(*n* = 33)	

Note. All tests of significance are Pearson chi-square test, unless mentioned. Level of significance <0.05. SAM: severe acute malnutrition.

[a]Mean ± *SD*.

[b]Median Interquartile Range.

[c]Student's *t* test.

[d]Mann–Whitney *U* test.

TABLE 5 Factors associated with severe acute malnutrition in under 6 months old

Factors	Odds ratio	P	95% CI
Age of the infant	0.27	<0.0001	0.16, 0.44
Exclusive breastfeeding at enrolment	0.04	0.005	0.004, 0.36
Schooling years of mother	0.83	0.02	0.71, 0.97
Access to household electricity	0.27	0.02	0.09, 0.81
Satisfaction of mother about breastfeeding at enrolment	1.03	0.001	0.12, 8.9
Maternal anthropometry			
Body mass index	0.88	0.13	0.75, 1.04

Note. Level of significance <0.05.

We acknowledge the limitations of our work. First, our prospective cohort study only followed infants until 6 months of age, yet evidence is emerging that there are important longer term as well as short-term outcomes post-SAM (Lelijveld et al., 2016). Even for those apparently recovered from SAM, mortality and morbidity risks may be high (Berkley et al., 2016). Second, we acknowledge limitations inherent to current WHO case definitions in the 2013 Guidelines on Management of SAM (WHO, 2013). Infant SAM is there defined by a one-off measurement of anthropometry without considering underling aetiology and growth trend. The very label "SAM" is potentially misleading because not all infants with low weight-for-length have an acute deficit. Particularly problematic is not distinguishing between those infants who are "born small" due to either prematurity or intrauterine growth retardation and those infants who "become small" due to postnatal growth failure. We hope that future research, especially that based on birth cohorts with reliable antenatal and birth data, will improve epidemiological understanding in this area. Although there are calls for alternate case definitions better to identify and classify nutritionally at-risk infants (Lelijveld, Kerac, McGrath, Mwangome, & Berkley, 2017), low weight-for-length is also currently dominant in all national guidelines on SAM (Kerac et al., 2017). Important to note in this respect are two issues: whatever the aetiology, the great majority of such very small infants are at increased risk of morbidity and mortality (Carducci & Bhutta, 2018; NGA, 2017) as in our population, birth weights and gestational age is frequently unknown in many resource-poor settings. Hence, our conclusions regarding the need for packages of care still apply to all. These should take into account the fact that birth details will often not be known.

Finally, we acknowledge that great care should be taken when trying to ascribe causality in an observational study such as ours. Despite biological plausibility of cause–effect, it could, for example, be reverse causality, which explains some of our associations between suboptimal breastfeeding and SAM (i.e., a vulnerable infant becomes unwell and reduces/stops breastfeeding as a result—rather than an otherwise well infant stops breastfeeding and then becomes vulnerable). Intervention studies are needed to test hypotheses raised in our study, for example, to what extent can outpatient-based breastfeeding support reverse SAM and other anthropometric deficits observed in our population.

Balancing these limitations is the fact that ours is a novel and called-for paper (Mayberry et al., 2017), which we hope will stimulate and underpin larger scale future work exploring infant u6m malnutrition in both Bangladesh and elsewhere. Given paucity of evidence in this area, our data are important for such studies to plan key issues like sample size and consequent study logistics.

We conclude that current inpatient-focused treatment approaches to infant u6m SAM are suboptimal. The key problem highlighted in our results was that few carers access inpatient treatment when referred. Some form of treatment is needed—as suggested by infants in the SAM group being more underweight and more stunted than non-SAM controls. However, that many showed weight catch-up and no longer had SAM by 6 months suggests that it is reasonable to classify infants in the same way as older children with SAM, recognizing that some are clinically stable enough ("uncomplicated SAM") to be safely managed in community-based programmes as recommended by WHO (2013) SAM guidelines. In terms of risk factors, suboptimal breastfeeding is key but is not alone. Future interventions should evaluate the effectiveness of a package of interventions also addressing wider issues like home environment and maternal support/maternal mental health. Finally, we call for better ways of identifying at-risk infants are needed: Current case definitions of SAM are widely used but do not fully capture the many possible reasons why an infant may be small (Kerac & McGrath, 2017; Lelijveld et al., 2017). Improved classification and understanding of underlying aetiology in individual cases may allow more tailored treatments with greater probability of success.

ACKNOWLEDGMENTS

We would like to acknowledge many individuals and organizations who made this study possible including all the children and their families who took part in the study and the field study staff for their relentless contribution. We further acknowledge the support of the Technical Advisory Group members (Dr Nawshad Ahmed, Prof Mohammod Shahidullah, Dr Mohammad Sharif, Dr Altaf Hossain, Ms Rachel Fuli, Mr Andrew Musyoki, Dr Iftekhar Rashid, Dr Rukhsana Haider, and Dr Zeba Mahmud) for their valuable advice. Besides, our sincere gratitude to other colleagues who have provided feedback on the preliminary results when presented at technical meetings in Bangladesh.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

The authors' contributions were as follows: MK, MMI, MM, and NC conceived and designed the experiments. MMI, YA, GM, and TA performed the experiments. All authors contributed to specific areas of methods, data analysis, statistics, and write-up. MMI analysed the data and wrote the first draft of the manuscript. MK, YA, NC, MM, GM, JB, and TA contributed to the writing of the manuscript and agree with the manuscript's results and conclusions. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

ORCID

M. Munirul Islam http://orcid.org/0000-0002-8780-8760
Marko Kerac http://orcid.org/0000-0002-3745-7317

REFERENCES

Berkley, J. A., Ngari, M., Thitiri, J., Mwalekwa, L., Timbwa, M., Hamid, F., … Fegan, G. (2016). Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: A multicentre, double-blind, randomised placebo-controlled trial. *The Lancet Global Health*, *4*(7), e464–e473. https://doi.org/10.1016/S2214-109X(16)30096-1

Bhutta, Z. A., Berkley, J. A., Bandsma, R. H. J., Kerac, M., Trehan, I., & Briend, A. (2017). Severe childhood malnutrition. *Nature Reviews Disease Primers*, *3*, 17067. https://doi.org/10.1038/nrdp.2017.67

Black, R. E., Victora, C. G., Walker, S. P., Bhutta, Z. A., Christian, P., de Onis, M., … Maternal and Child Nutrition Study Group (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*, *382*(9890), 427–451. https://doi.org/10.1016/S0140-6736(13)60937-X

Briend, A., Khara, T., & Dolan, C. (2015). Wasting and stunting-similarities and differences: Policy and programmatic implications. *Food and Nutrition Bulletin*, *36*(1 Suppl), S15–S23.

Carducci, B.,& Bhutta Z. A. (2018). Care of the growth-restricted newborn. *Best Practice & Research. Clinical Obstetrics & Gynaecology*. pii: S1521–6934 (18)30044–0. https://doi.org/10.1016/j.bpobgyn.2018.02.003.

Chowdhury, M. R., Rahman, M. S., Khan, M. M., Mondal, M. N., Rahman, M. M., & Billah, B. (2016). Risk factors for child malnutrition in Bangladesh: A multilevel analysis of a nationwide population-based survey. *Journal of Pediatrics*, *172*, 194–201.e1.

Collins, S. (2001). Changing the way we address severe malnutrition during famine. *Lancet*, *358*(9280), 498–501.

Collins, S., Sadler, K., Dent, N., Khara, T., Guerrero, S., Myatt, M., … Walsh, A. (2006). Key issues in the success of community-based management of severe malnutrition. *Food and Nutrition Bulletin*, *27*, S49–S82.

Crowe, S., Seal, A., Grijalva-Eternod, C., & Kerac, M. (2014). Effect of nutrition survey 'cleaning criteria' on estimates of malnutrition prevalence and disease burden: Secondary data analysis. *PeerJ*, *2*, e380.

Greenslade, L. (2015). Architecture for impact: Nutrition and the Sustainable Development Goals. Available from: http://globalnutritionreport.org/2015/06/17/architecture-for-impact-nutrition-and-the-sustainable-development-goals/ (Accessed on September 23, 2017).

Grijalva-Eternod, C. S., Kerac, M., McGrath, M., Wilkinson, C., Hirsch, J. C., Delchevalerie, P., & Seal, A. J. (2017). Admission profile and discharge outcomes for infants aged less than 6 months admitted to inpatient therapeutic care in 10 countries. A secondary data analysis. *Maternal and Child Nutrition*, *13*(3). https://doi.org/10.1111/mcn.12345

Institute of Public Health Nutrition (IPHN), Director General of Health Services (DGHS), Ministry of Health and Family Welfare (MoHFW), Peoples Republic of Bangladesh (PRB). (2008). National guidelines for the management of severely malnourished children in Bangladesh. 2008. Available from: http://www.unicef.org/bangladesh/SAM_Guideline.pdf (Accessed on September 23, 2017).

Jain, V., & Singhal, A. (2012). Catch up growth in low birth weight infants: Striking a healthy balance. *Reviews in Endocrine and Metabolic Disorders*, *3*(2), 141–147.

Kerac, M., Angood, C., McGrath, M., Lelijveld, N., Trehan, I., & Manary, M. (2017). *Towards rollout of new WHO guidelines for improved management of severe acute malnutrition in infants aged <6 months: An AGREE appraisal of national guidelines*. Amsterdam, The Netherlands: Nutrition & Growth Conference.

Kerac, M., Blencowe, H., Grijalva-Eternod, C., McGrath, M., Shoham, J., Cole, T. J., & Seal, A. (2011). Prevalence of wasting among under 6-month-old infants in developing countries and implications of new case definitions using WHO growth standards: A secondary data analysis. *Archives of Disease in Childhood*, *96*(11), 1008–1013. https://doi.org/10.1136/adc.2010.191882

Kerac, M., Frison, S., Connell, N., Page, B., & McGrath, M. (2016). Improving the management of acute malnutrition in infants aged under 6 months: Malnutrition risk factors identified from secondary analysis of twenty demographic and health surveys 3nd International Conference on Nutrition and Growth. Vienna, Austria.

Kerac, M., & McGrath, M. (2017). Management of acute malnutrition in infants under 6 months of age. In *The biology of the first 1,000 days* (pp. 207–220). Routledge.

Kerac, M., Mwangome, M., McGrath, M., Haider, R., & Berkley, J. A. (2015). Management of acute malnutrition in infants aged under 6 months (MAMI): Current issues and future directions in policy and research. *Food and Nutrition Bulletin*, *36*(1 Suppl), S30–S34.

Lelijveld, N., Kerac, M, McGrath, M., Mwangome, M., & Berkley, J. A. (2017). A review of methods to detect cases of severely malnourished infants less than 6 months for their admission into therapeutic care. Available at http://www.ennonline.net/mamicasedetectionreview (Accessed on September 22, 2017).

Lelijveld, N., Seal, A., Wells, J. C., Kirkby, J., Opondo, C., Chimwezi, E., … Kerac, M. (2016). Chronic disease outcomes after severe acute malnutrition in Malawian children (ChroSAM): A cohort study. *The Lancet Global Health*, *4*(9), e654–e662. https://doi.org/10.1016/S2214-109X(16)30133-4

Liu, P., Xu, L., Wang, Y., Zhang, Y., Du, Y., Sun, Y., & Wang, Z. (2016). Association between perinatal outcomes and maternal pre-pregnancy body mass index. *Obesity Reviews*, *17*, 1091–1102. https://doi.org/10.1111/obr.12455

Mayberry, A., & CORTASAM members. (2017). Prioritising acute malnutrition research: Preliminary results of a CHNRI survey. Field Exchange 55, July 2017. p. 68. www.ennonline.net/fex/55/acutemalnutchnrisurveyprelim (Accessed on September 23, 2017).

Mwangome, M., Ngari, M., Fegan, G., Mturi, N., Shebe, M., Bauni, E., & Berkley, J. A. (2017). Diagnostic criteria for severe acute malnutrition among infants aged under 6 mo. *The American Journal of Clinical Nutrition*, *105*(6), 1415–1423. https://doi.org/10.3945/ajcn.116.149815

Mwangome, M. K., Fegan, G., Fulford, T., Prentice, A. M., & Berkley, J. A. (2012). Mid-upper arm circumference at age of routine infant vaccination to identify infants at elevated risk of death: A retrospective cohort study in the Gambia. *Bulletin of the World Health Organization*, *90*(12), 887–894.

Nabarro, D. (2013). Global child and maternal nutrition—The SUN rises. *Lancet*, *382*(9893), 666–667.

National Guideline Alliance (NGA) (UK) (2017). *Faltering growth—Recognition and management*. London: National Institute for Health and Care Excellence (UK).

National Institute of Population Research and Training (NIPORT), Mitra and Associates, and ICF International. (2013). Bangladesh Demographic and Health Survey 2011. Dhaka, Bangladesh and Calverton, Maryland, USA: NIPORT, Mitra and Associates, and ICF International. Available from: https://dhsprogram.com/pubs/pdf/fr265/fr265.pdf (Accessed on September 24, 2017).

SMART. (2017) SMART (standardized monitoring and assessment of relief and transitions). Available from: http://www.smartmethodology.org/ (Accessed on September 24, 2017).

Stevens, B., Buettner, P., Watt, K., Clough, A., Brimblecombe, J., & Judd, J. (2015). The effect of balanced protein energy supplementation in undernourished pregnant women and child physical growth in low- and middle-income countries: A systematic review and meta-analysis. *Maternal & Child Nutrition*, *11*(4), 415–432. https://doi.org/10.1111/mcn.12183

Sustainable Development Goals (SDG). (2015). Available from: https://sustainabledevelopment.un.org/ (Accessed on September 24, 2017).

Trehan, I., & Manary, M. J. (2015). Management of severe acute malnutrition in low-income and middle-income countries. *Archives of Disease in Childhood*, *100*(3), 283–287.

World Health Organization (WHO) (2006). *Anthro 2005 for personal computers manual: Software for assessing growth and development of the world's children*. Geneva: World Health Organization. Available from: http://www.who.int/childgrowth/software/WHOAnthro2005_PC_Manual.pdf 2006 (Accessed on September 24, 2017).

World Health Organization (WHO). (1994). A user's guide to the Self Reporting Questionnaire. WHO/MNH/PSF/94.8. Available from: http://apps.who.int/iris/bitstream/10665/61113/1/WHO_MNH_PSF_94.8.pdf (Accessed on September 24, 2017).

World Health Organization (WHO). (2013). Updates on the management of severe acute malnutrition in infants and children (Guideline). Available from: http://www.who.int/nutrition/publications/guidelines/updates_management_SAM_infantandchildren/en/index.html (Accessed on September 24, 2017).

Wrottesley, S. V., Lamper, C., & Pisa, P. T. (2016). Review of the importance of nutrition during the first 1000 days: Maternal nutritional status and its associations with fetal growth and birth, neonatal and infant outcomes among African women. *Journal of Developmental Origins of Health and Disease*, *7*, 144–162. https://doi.org/10.1017/s2040174415001439

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Munirul Islam M, Arafat Y, Connell N, et al. Severe malnutrition in infants aged <6 months—Outcomes and risk factors in Bangladesh: A prospective cohort study. *Matern Child Nutr*. 2018;e12642. https://doi.org/10.1111/mcn.12642