

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Time to recovery from severe acute malnutrition and its predictors: a multicenter retrospective follow up study in Amhara region, northwest Ethiopia
AUTHORS	Baraki, Adhanom; Akalu, Temesgen; Wolde, Haileab; Takele, Wubet; Mamo, Worku; Derseh, Behailu; Desyibelew, Hanna; Dadi, A.F.

VERSION 1 - REVIEW

REVIEWER	Stanley Zlotkin Hospital for Sick Children Centre for Global Child Health Toronto, Canada
REVIEW RETURNED	13-Nov-2019

GENERAL COMMENTS	<p>Children with edematous severe acute malnutrition needs longer treatment time to recover: a multicenter retrospective follow up study in Amhara region, northwest Ethiopia Review:</p> <p>Title: Only about one third of the children had edema,. And there were other factors significantly associated with time to recovery. Why did the authors focus on edema in the title.</p> <p>Line 100 You wrote: The minimum proportion of SAM children that must recover after therapy is 75% [6]. It should be The minimum proportion of SAM children expected to recover after therapy is 75% [6]</p> <p>Line 107-108: You wrote: The average recovery time and its important predictors are not well established in the region in a comprehensive way. I am not sure what you mean by this sentence. Which region are you referring to? Please re-write this sentence.</p> <p>Line 112 Spelling mistake. unites should be units.</p> <p>Line 110 add the word “of children with SAM”time to recovery of children with SAM....</p> <p>Line 116 - 118. Please provide more information on these health institutions. Are some community health posts? small hospitals?, referral hospitals? Is SAM treated in the same way at each institution?</p>
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	<p>Line 122-123. Did all children with SAM receive inpatient treatment - were any treated in the community? Usually inpatient treatment is for the sickest children with SAM (oedema, unable to eat, comatose, significant co-morbidity, etc).</p> <p>Line 124 - define cured.</p> <p>Line 128 - Were all children with SAM included in the study.</p> <p>Line 129 - how many records in total were reviewed.</p> <p>Line 132 - I do not understand your use of the lottery method. How were children with SAM identified?</p> <p>Line 135 - What data was collected on each subject with SAM?</p> <p>Table 1. What does frequency refer to? Is it the number of children with SAM? Could you add a variable to the table - the number with kwashiorkor vs marasmus?</p> <p>Line 158 Spelling mistake: children's should be children.</p> <p>Line 163. The caption reads 'time to recovery' but you are referring mainly to rate of recovery in the paragraph. Are these the same?</p> <p>Line 164 - please define recovery - what were the criteria used to define recovery?</p> <p>Line 167 - Figure 1. Please provide an explanation of what is in this figure. What is survival estimates referring to? What is analysis time? The caption needs to be expanded.</p> <p>Line 176 - does this mean that there were no difference in time to recovery among the various treatment centres?</p> <p>Line 182 -Are you referring to time to recovery or recovery rate? Do you mean that the recovery rate among female was 19% lower compared to males?</p> <p>Line 182 - paragraph I wonder whether a table would be a better way to express the results?</p> <p>Line 183 - What was the recovery rate for children with edematous malnutrition - it was omitted.</p> <p>Table 2. I am not sure that I understand the table. Does a CHR or AHRI less than 1 mean that the time to recovery was shorter whereas a CHR greater than 1 mean a longer time to recovery? Please explain and include the explanation on the table.</p> <p>Should table 2 be recovery rate rather than time to recovery?</p> <p>Table 2 Define the two types of hazard ratios you used (CHR vs AHR).</p> <p>Line 193 - what do you mean by type ion malnutrition. I thought all subjects had SAM?</p> <p>Line 198 - can a recovery rate be faster. Should be a higher or lower rate.</p>
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	<p>Line 199 - provide the recovery rates for these other Ethiopian studies.</p> <p>Line 100 You wrote: The minimum proportion of SAM children that must recover after therapy is 75% [6]. It should be The minimum proportion of SAM children expected to recover after therapy is 75% [6]</p> <p>Line 107-108: You wrote: The average recovery time and its important predictors are not well established in the region in a comprehensive way. I am not sure what you mean by this sentence. Which region are you referring to? Please re-write this sentence.</p> <p>Line 112 Spelling mistake. unites should be units.</p> <p>Line 110 add the word “of children with SAM”time to recovery of children with SAM....</p> <p>Line 116 - 118. Please provide more information on these health institutions. Are some community health posts? small hospitals?, referral hospitals? Is SAM treated in the same way at each institution?</p> <p>Line 122-123. Did all children with SAM receive inpatient treatment - were any treated in the community? Usually inpatient treatment is for the sickest children with SAM (edema, unable to eat, comatose, significant co-morbidity, etc).</p> <p>Line 124 - define cured.</p> <p>Line 128 - Were all children with SAM included in the study.</p> <p>Line 129 - how many records in total were reviewed.</p> <p>Line 132 - I do not understand your use of the lottery method. How were children with SAM identified?</p> <p>Line 135 - What data was collected on each subject with SAM?</p> <p>Table 1. What does frequency refer to? Is it the number of children with SAM? Could you add a variable to the table - the number with kwashiorkor vs marasmus?</p> <p>Line 158 Spelling mistake: children’s should be children.</p> <p>Line 163. The caption reads ‘time to recovery’ but you are referring mainly to rate of recovery in the paragraph. Are these the same?</p> <p>Line 164 - please define recovery - what were the criteria used to define recovery?</p> <p>Line 167 - Figure 1. Please provide an explanation of what is in this figure. What is survival estimates referring to? What is analysis time? The caption needs to be expanded.</p> <p>Line 176 - does this mean that there were no difference in time to recovery among the various treatment centres?</p>
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	<p>Line 182 -Are you referring to time to recovery or recovery rate? Do you mean that the recovery rate among female was 19% lower compared to males?</p> <p>Line 182 - paragraph I wonder whether a table would be a better way to express the results?</p> <p>Line 183 - What was the recovery rate for children with edematous malnutrition - it was omitted.</p> <p>Table 2. I am not sure that I understand the table. Does a CHR or AHR less than 1 mean that the time to recovery was shorter whereas a CHR greater than 1 mean a longer time to recovery? Please explain and include the explanation on the table.</p> <p>Should table 2 be recovery rate rather than time to recovery?</p> <p>Table 2 Define the two types of hazard ratios you used (CHR vs AHR).</p> <p>Line 193 - what do you mean by type of malnutrition. I thought all subjects had SAM?</p> <p>Line 199 - provide the recovery rates for these other Ethiopian studies.</p> <p>Conclusion: What specifically does this study add to the literature on recovery from SAM? How does it differ from similar studies on this topic from Ethiopia and elsewhere?</p>
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REVIEWER	Dr Raja Sriswan Mamidi ICMR-National Institute of Nutrition India
REVIEW RETURNED	23-Nov-2019

GENERAL COMMENTS	<p>General comments</p> <p>The article describes about the causes of recovery rates in these population. However, it is unclear from the paper, what was the treatment given to these children, whether they were treated according to the standard WHO guidelines, as, not all children are given Vitamin A and not all were given antibiotics (about 50% were not given).</p> <p>What were the morbidities during the recovery such as fever and diarrhea? Have they been recorded and analyzed as that will influence weight gain in these children.</p> <p>It is unclear about the recovery rates defined and what were the actual weight gains in these children i.e. how many had rapid catch up growth (>10g/kg/day) , moderate and poor catch up growth (<5 g/kg/day).</p> <p>Since it is a multi-centric study, it is unclear from the statistical section, whether any adjustment was made for the center the child was treated and if so how was it done. Whether there were any differences in recovery rates based on the center, the child was treated.</p> <p>The paper will benefit, if the authors can incorporate the suggestions.</p> <p>Specific comments</p>
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	<p>Line 1: Reference 1 is inappropriate and SAM is unlikely to be the most common form of under nutrition as stunting is more common than wasting.</p> <p>Line 92: Reference 2 is inappropriate and SAM does not contribute to 35% of deaths among children under five years, it is the overall under nutrition that contributes to these deaths.</p> <p>Line 121: For children less than six months, MUAC cut off values are not applicable.</p> <p>Line 123: Severe is mentioned as Sever</p> <p>Line 124: How the cure rates are defined are not clear, whether they have used as the diagnostic criteria are both MUAC and WHZ and the recovery rates are dependent on the initial criteria used.</p> <p>Line 132: Lottery method should be elaborated in statistical terms such as type of random sampling used.</p> <p>Line 203: The possible reason for lower recovery rates is not correct as the analysis have adjusted for these parameters.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments

Reviewer: 1

Reviewer Name: Stanley Zlotkin

Institution and Country: Hospital for Sick Children

Centre for Global Child Health

Toronto, Canada

Review:

#1: Title: Only about one-third of the children had edema, And there were other factors significantly associated with time to recovery. Why did the authors focus on edema in the title?

Authors' response#1: Dear Dr. Stanley Zlotkin, Thank you for your constructive comments and suggestions. We have also received this comment from the editors and we have modified the title as "Time to recovery from severe acute malnutrition and its predictors: a multicenter retrospective follow up study in Amhara region, northwest Ethiopia".

#2: Line 100 You wrote: The minimum proportion of SAM children that must recover after therapy is 75% [6]. It should be the minimum proportion of SAM children expected to recover after therapy is 75% [6]

Authors' response#2: Thank you, we have corrected as "The minimum proportion of SAM children expected to recover after therapy is 75%" (Introduction section line 98)

#3: Line 107-108: You wrote: The average recovery time and its important predictors are not well established in the region in a comprehensive way. I am not sure what you mean by this sentence. Which region are you referring to? Please re-write this sentence.

Authors' response#3: Dear sir, by saying the region we wanted to refer to the Amhara region which is the study area. We have corrected it as "The average recovery time and its important predictors are not well established in the Amhara region in a comprehensive way." (Introduction section lines 105 to 106)

#4: Line 112 Spelling mistake. units should be units.

Authors' response#4: Thank you. We have changed it. We have also improved overall English throughout the manuscript.

#5: Line 110 add the word "of children with SAM"time to recovery of children with SAM....

Authors' response#5: We have corrected the statement as "Therefore, this study was conducted to determine the median time to recovery among children with SAM. . ." (Introduction section lines 108 to 109)

#6: Line 116 - 118. Please provide more information on these health institutions. Are some community health posts? small hospitals?, referral hospitals? Is SAM treated in the same way at each institution?

Authors' response#6: Dear sir, we have mentioned the types of health institutions from which the data is collected. The treatment protocol of SAM is the same in all the institutions. We have made this clear in the as "A retrospective follow-up study was conducted from September 2012 to November 2016 in selected governmental health institutions in Amhara region, northwest Ethiopia. These institutions are: Felege Hiwot referral hospital, Debrebirhan referral hospital, University of Gondar comprehensive specialized hospital, selected health centers and health posts in rural North Gondar, Amhara Regional State, Ethiopia. The Pediatric department in these health institutions is among the main inpatient departments where complicated malnutrition children are treated, whereas the uncomplicated SAM children were treated as an outpatient. All institutions use the same severe acute malnutrition treatment protocol." (Method section Page 5 lines 114-121)

#7: Line 122-123. Did all children with SAM receive inpatient treatment - were any treated in the community? Usually inpatient treatment is for the sickest children with SAM (oedema, unable to eat, comatose, significant co-morbidity, etc).

Authors' response#7: Dear sir as you mentioned only children with complicated malnutrition get inpatient treatment, others were treated as an outpatient. This is mentioned in the method section page 5 lines 118 to 121.

#8: Line 124 - define cured.

Authors' response#8: Thank you for this fundamental comment. "A child above 6 months old is declared cured based on the SAM treatment protocol as Weight for Length $\geq 85\%$ or Weight for Height $\geq 85\%$ on more than one occasion (Two days for in-patients, two weeks for out-patients), and no edema for 10 days (In-patient) or 14 days (out-patient). Cure is declared for infants under 6 months old when it is clear that he/she is gaining weight on breast milk alone after the Supplemented Suckling technique has been used, there is no medical problem, and the mother has been adequately supplemented with vitamins and minerals, so that she has accumulated body stores of nutrients." This is mentioned in the method section from line 128 to 135.

#9: Line 128 - Were all children with SAM included in the study.

#9: Line 129 - how many records in total were reviewed.

#9: Line 132 - I do not understand your use of the lottery method. How were children with SAM identified?

Authors' response#9: Dear sir thank you for this vital question. All children who were treated for SAM from September 2012 to November 2016, were the study population. The included ones are (Sample) were those selected using simple random sampling (lottery method) from therapeutic feeding unit

registration logbooks, then their charts were reviewed (It's a secondary data). A total of 1690 records were reviewed. We have tried to make it clearer in the method section pages 5 – 6 (Lines 123 – 148)

#10: Line 135 - What data was collected on each subject with SAM?

Authors' response#10: Thank you, Doctor, we have mentioned the data collected in the "study population and variables" section of the method part from line 138-140 as "Data on independent variables: age, sex, residence, breastfeeding status, vaccination status, treatment duration, type of malnutrition, routine medications provided, and presence of co-morbidities were also collected."

#11: Table 1. What does frequency refer to? Is it the number of children with SAM? Could you add a variable to the table - the number with kwashiorkor vs marasmus?

Authors' response#11: Dear Doctor as you mentioned frequency in table 1 refers to the number of SAM children in each variable category. The number of children with kwashiorkor and Marasmus is also presented as SAM with edema and without edema (Edema: present/Absent) in the same table.

#12: Line 158 Spelling mistake: children's should be children.

Authors' response#12: Thank you, the correction is made.

#13: Line 163. The caption reads 'time to recovery' but you are referring mainly to rate of recovery in the paragraph. Are these the same?

Authors' response#13: Thank you, Doctor, for this crucial comment. The recovery rate mainly tells the proportion of individuals who recovered within the treatment time, whereas the time to recovery refers to the days taken for the children to recover; which means the two are different. We have also rephrased it as "There was a significant difference in the time of recovery between HIV free and positive children, where HIV negative children recovered faster" (Lines 186-188)

#14: Line 164 - please define recovery - what were the criteria used to define recovery?

Authors' response#14: Thank you, Doctor, we have defined recovery in the method section from lines 128 to 135.

#15: Line 167 - Figure 1. Please provide an explanation of what is in this figure. What is survival estimates referring to? What is analysis time? The caption needs to be expanded.

Authors' response#15: Dear Doctor, in survival estimate we show how fast an event (recovery in our case) occurs. The faster the line (curve) runs to zero the faster the occurrence of the event (recovery). We have mentioned this from line 186 to 188.

#16: Line 176 - does this mean that there were no difference in time to recovery among the various treatment centres?

Authors' response#16: Yes sir. We have tried to make it clearer by restating it as "The presence of a significant difference in the recovery time among treatment centers was considered by fitting a shared frailty model but the shared frailty term (Θ) was not significant showing no significant difference among the treatment centers." (Lines 198-201)

#17: Line 182 -Are you referring to time to recovery or recovery rate? Do you mean that the recovery rate among female was 19% lower compared to males?

Authors' response#17: Dear sir, in this sense the recovery rate is the speed of recovery since we are referring to the time to recovery. So what is reduced is the speed of recovery which is also commonly

reported as rate. But to avoid such ambiguity we have written it as “The recovery time was delayed by 19% among female children as compared to the male.” (Lines 208-209). Such amendments are made for all significant variable interpretations.

#18: Line 182 - paragraph I wonder whether a table would be a better way to express the results?

Authors' response#18: Thank you for your concern; we have included all the variables both significant and non-significant in table-2. This paragraph has only reported the significant ones for ease of understanding.

#19: Line 183 - What was the recovery rate for children with edematous malnutrition – it was omitted.

Authors' response#19: Thank you, sir, the recovery rate for edematous malnutrition in our study was 57.6% (95% CI: 52.9, 62.2) whereas the recovery rate for non-edematous malnutrition was 63.8 (95% CI: 61.1, 66.5). We have incorporated this from lines 182-183.

#20: Table 2. I am not sure that I understand the table. Does a CHR or AHR I less than 1 mean that the time to recovery was shorter whereas a CHR greater than 1 mean a longer time to recovery? Please explain and include the explanation on the table. Should table 2 be recovery rate rather than time to recovery?

Authors' response#20: Dear sir thank you for this nice question. CHR means the Crude hazard ratio (Bivariable analysis) whereas the multivariable output is termed as Adjusted hazard ratio (AHR). When the hazard ratio is less than one it means the speed of recovery is reduced by $(1-ARH)*100\%$, and if it is above 1 the speed of recovery is increased by the AHR factor. The heading is also appropriate.

#21: Table 2 Define the two types of hazard ratios you used (CHR vs AHR).

Authors' response#21: Dear sir, now we have put the full form in the table. We have also added where these hazard ratios come from line 204 to 205

#22: Line 193 - what do you mean by type ion malnutrition. I thought all subjects had SAM?

Authors' response#22: Dear Doctor, the type of malnutrition here refers to either edematous or non-edematous malnutrition.

#23: Line 198 - can a recovery rate be faster. Should be a higher or lower rate.

Authors' response#23: Thank you once again as mentioned above in this study the time to recovery is to refer to the speed of recovery, therefore with all due respect “faster” is an appropriate term.

#24: Line 199 - provide the recovery rates for these other Ethiopian studies.

Authors' response#24: Thank you, we have included the recovery rates of Ethiopian studies

#25: Conclusion: What specifically does this study add to the literature on recovery from SAM? How does it differ from similar studies on this topic from Ethiopia and elsewhere?

Authors' response#25: This study is different from other studies in that it used a relatively large sample size and has put a precise estimate of recovery time predictors. The study is not also only from a single institution which helps to consider possible confounding factors related to institutions. We have also revised the conclusion accordingly.

Reviewer: 2

Reviewer Name: Dr Raja Sriswan Mamidi

Institution and Country: ICMR-National Institute of Nutrition

India

General comments

#1: The article describes about the causes of recovery rates in these population. However, it is unclear from the paper, what was the treatment given to these children, whether they were treated according to the standard WHO guidelines, as, not all children are given Vitamin A and not all were given antibiotics (about 50% were not given).

Authors' response#1: Thank you Dr. Raja Sriswan Mamidi, for reviewing and giving constructive comments, questions, and suggestions. Children with severe acute malnutrition are treated using a treatment protocol (Chamois, S., Golden, M. & Grellety, Y. 2007. Ethiopia Protocol for the management of Severe Acute Malnutrition (2007)). But due to several reasons that include resource constraints, and poor adherence to the protocol the children may not get the recommended drugs. Since we have used secondary data, lack of appropriate registration after the children took medications can also be the possible reason for the discrepancy.

#2: What were the morbidities during the recovery such as fever and diarrhea? Have they been recorded and analyzed as that will influence weight gain in these children.

Authors' response#2: Dear sir, the co-morbidities including diarrhea, pneumonia, tuberculosis, and HIV/AIDS are summarized and reported in table-1. The magnitude of diarrhea is also reported from lines 177-178 as "Regarding co-morbidities, 575 (34.02%) of the children had diarrhea." There was no specific data regarding fever as it may overlap with the symptoms of other diseases like pneumonia and diarrhea.

#3: It is unclear about the recovery rates defined and what were the actual weight gains in these children i.e. how many had rapid catch up growth (>10g/kg/day) , moderate and poor catch up growth (<5 g/kg/day).

Authors' response#3: Thank you, Doctor, for this important question. We have included the requested information in the result section (lines 184 to 186) as the following: "A total of 578 (34.2%) had rapid catch up growth (>10g/kg/day) whereas 688(40.71%), and 424(25.09%) had medium (5g/kg/day-10g/kg/day) and poor (<5g/kg/day) catch up growth in the treatment time respectively."

#4: Since it is a multi-centric study, it is unclear from the statistical section, whether any adjustment was made for the center the child was treated and if so how was it done. Whether there were any differences in recovery rates based on the center, the child was treated.

The paper will benefit, if the authors can incorporate the suggestions.

Authors' response#4: Dear Doctor, we have assessed if there is a significant difference in the recovery rate statistically. We have mentioned from lines 198 to 201 as "The presence of a significant difference in the recovery time among treatment centers was considered by fitting a shared frailty model but the shared frailty term (Θ) was not significant showing no significant difference among the treatment centers."

Specific comments

#5: Line 1: Reference 1 is inappropriate and SAM is unlikely to be the most common form of under nutrition as stunting is more common than wasting.

Authors' response#5: Thank you so much, we have noticed this and rechecked the reference. The statement is also corrected as "Severe Acute Malnutrition (SAM) is the most extreme and visible form of under-nutrition" (Introduction section line 85)

#6: Line 92: Reference 2 is inappropriate and SAM does not contribute to 35% of deaths among children under five years, it is the overall under nutrition that contributes to these deaths.

Authors' response#5: Dear Doctor, we accept the comment and changed the SAM to Malnutrition (Introduction line 90).

#6: Line 121: For children less than six months, MUAC cut off values are not applicable.

Authors' response#6: Thanks sir, we have included the diagnostic criteria for infants from line 126 to 128 as follows ". . . whereas for infants diagnostic criteria used was, the infant is too weak or feeble to suckle effectively, or Weight-for-Length less than 70% and/or presence of bilateral edema."

#7: Line 123: Severe is mentioned as Sever

Authors' response#7: Thank you we have corrected this and also have improved the English throughout the manuscript.

#8: Line 124: How the cure rates are defined are not clear, whether they have used as the diagnostic criteria are both MUAC and WHZ and the recovery rates are dependent on the initial criteria used.

Authors' response#8: Dear sir we have briefly described the diagnostic criteria and definition of cure in the "study population and variables" section. For example cure is defined as follows: "A child above 6 months old is declared cured based on the SAM treatment protocol as Weight for Length $\geq 85\%$ or Weight for Height $\geq 85\%$ on more than one occasion (Two days for in-patients, two weeks for out-patients), and no edema for 10 days (In-patient) or 14 days (out-patient). Cure is declared for infants under 6 months old when it is clear that he/she is gaining weight on breast milk alone after the Supplemented Suckling technique has been used, there is no medical problem, and the mother has been adequately supplemented with vitamins and minerals, so that she has accumulated body stores of nutrients" (Lines 128 to 135)

#9: Line 132: Lottery method should be elaborated in statistical terms such as type of random sampling used.

Authors' response#9: Thank you, we have corrected it as simple random sampling (Line 145)

#10: Line 203: The possible reason for lower recovery rates is not correct as the analysis has adjusted for these parameters.

Authors' response#10: Dear Doctor thank you once again. We used diarrhea and vaccination status to explain the possible reason as you mentioned, for these variables are not included in the multivariable analysis. Diarrhea and vaccination status were excluded just by the bivariable analysis. Thus this association is not adjusted to these variables.

VERSION 2 – REVIEW

REVIEWER	Dr Raja Sriswan Mamidi ICMR-National Institute of Nutrition
REVIEW RETURNED	31-Dec-2019

GENERAL COMMENTS	Table 2: Indicate the co variate parameters below that were used for adjusted hazards ratio.
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VERSION 2 – AUTHOR RESPONSE

Reviewer 2: Dr Raja Sriswan Mamidi

Table 2: Indicate the co variate parameters below that were used for adjusted hazards ratio.

Authors' response: Thank you Dr Raja Sriswan Mamidi, The co-variates used to estimate the adjusted hazard ratio are all the variables considered in the multivariable analysis (Which had P-value less than 0.2). This is well mentioned in the result section (lines 202 - 204). We have also presented all significant and non significant variables used to calculate the adjusted hazard ratios in table-2.