

SURVIVAL ANALYSIS OF UNDER-FIVE CHILDREN WITH SEVERE ACUTE MALNUTRITION IN WOLDIA HOSPITAL: RETROSPECTIVE COHORT STUDY

Aragaw Asfaw Hasen

*Department of statistics, College of Natural and Computational Sciences,
Samara University, Afar, Ethiopia*

Corresponding Author: aragawasfaw5@gmail.com

Abstract: Globally, 52 million children of age under five years were affected by acute malnutrition from which 17 million were severely wasted. In Ethiopia every month over 25,000 children with severe acute malnutrition are admitted to hospitals, if not identified early and treated properly, these children could die. Therefore, this study aimed to assess the survival status and its determinants of under-five children with severe acute malnutrition admitted to inpatient therapeutic feeding center in Woldia Hospital. A retrospective cohort study was conducted. The study population was children with severe acute malnutrition in hospital from September 2017 to August 2019. The accounted proportion of death of under-five children was 10%. And mean survival time of the patient was 4.48 weeks. Both estimates were almost on the recommended Sphere standard which should < 10% and <4 weeks respectively. From model, HR for age groups (24-35) is 0.000 with 95% CI [0.000-4.591], wasting is 0.010 with 95% CI [0.000-0.065], referred from is 0.000 with 95% CI [0.000-0.061], cough 133.04 with 95% CI [3.596-4922.83], HIV is 1209.61 with 95% CI [1.137-1286998.42], IV antibiotic is 0.000 with 95% CI [0.000-0.037] and amoxicillin is 0.001 with 95% CI [0.000-0.736] were significant predictors for time to death of under-five children with SAM. From the fitted model, age of the children, admission criteria, children referred from, cough, HIV, IV antibiotic treatment and Amoxicillin are the covariates that have significant effect on time to death of under five children by SAM at 5% level of significance. Early identifying cases and giving special attention for children with co morbidities such as HIV and cough is vital for decrease child mortality Ethiopia.

Keywords: Severe acute malnutrition; inpatient; semi parametric; non-parametric; death

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1. INTRODUCTION

Nutrition is a key determinant of good health and is critical for survival, good quality of life and well-being. Adequate nutrition is essential in early childhood to ensure healthy growth, proper organ formation and function, a strong immune system, and neurological and cognitive development. Malnutrition is a pathological state resulting from a relative or absolute deficiency

or excess of one or more essential nutrients. Malnutrition refers to deficiencies in a person's intake of energy and/or nutrients (Musa et al., 2014). Globally, 52 million children of age under five years were affected by acute malnutrition from which 17 million were severely wasted. Data shows that more than half of all wasted children in the world live in Southern Asia and Sub-Saharan African countries. In Africa, 14.0 million children under 5 are wasted, of which 4.1 million are severely wasted (UNICEF, WHO, & WB, 2012). Children with severe acute malnutrition are nine times more likely to die than well-nourished children as a direct result of malnutrition itself. There are also indirect deaths as a result of childhood illnesses like diarrhea and pneumonia among malnourished children (UNICEF, 2015).

According to the global nutrition report of 2018 the burden of malnutrition across the world remains unacceptably high, and progress unacceptably slow. Children under five years of age face multiple burdens: 150.8 million are stunted, 50.5 million are wasted and 38.3 million are overweight. Meanwhile 20 million babies are born of low birth weight each year (GNR, 2018). According to the EDHS 2016 report about 38%, 10% and 24% of under five years of age children in Ethiopia were stunted, wasted and underweight respectively (CSA, 2016). According to the report of the new standards for the management of acute malnutrition in Ethiopia, Every month over 25,000 children with severe acute malnutrition are admitted to hospitals, if not identified early and treated properly, these children could die (WHO, 2019). A study of systematic review and meta-analysis in Ethiopia shows that the pooled estimates of treatment outcomes in terms of death, recovery, defaulter and transfer out and non-response rates were 10.3%, 70.5%, 13.8% and 5.1% respectively. Diarrhea, dehydration and anemia were statistically significant predictors of mortality among these children (Wagnew et al., 2019).

A Community based unmatched case-control study conducted at East Gojjam Zone, North West Ethiopia, Severe acute malnutrition was significantly associated with age groups birth-24 months (AOR = 2.64, 95% CI 1.17–5.95 (Awoke, Ayana & Gualu, 2018)). A retrospective facility-based cross-sectional study was conducted Wolaita Zone, Southern Ethiopia, Children provided with amoxicillin were 1.52 times more likely to recover compared to their counterparts (AOR = 1.52 at 95% CI (1.77, 3.89)). The likely recovery of children provided with amoxicillin were explained by supportive effect of antibiotics mainly amoxicillin in treatment progress of SAM at OTP (Kabalo and Seifu, 2017). A facility-based retrospective record review study results in South Wollo Zone shows that of the total under five children recorded, 75.4% of children were recovered and discharged, 10.3% were defaulters, 3.4% died, 7.4% were non responders, and 3.4% were unknown (Hassen et al., 2019).

The retrospective cohort study results in Haramaya Dilchora Referral Hospital, Eastern Ethiopia revealed that 7.6% study participants had died, most of whom had died within the first week of admission to hospital, 69.9% had been cured, and the rest were defaulted and transferred out. The mean survival of the children with HIV/AIDS, pneumonia, diarrhea, dehydration, and those who took intravenous antibiotics and fluid were significantly lower than that of their counterparts. The significant predictors of the mortality of the SAM children were loss of appetite, malaria, and HIV sero-positivity (Oumer, Mesfin & Demena, 2016).

1.1. Minimum Standards of SAM management Sphere project

They provide benchmarks against which to interpret the functioning of individual therapeutic feeding program (FMOH, 2007).

Table 1 Reference values for the main indicators ©Sphere project

	Acceptable	Alarming
Recovery rate	> 75%	< 50%
Death rate	< 10%	> 15%
Defaulter rate	< 15%	> 25%
Length of stay	< 4 weeks	> 6 weeks

As review of different literature as depicted in the above section, Despite the existence of SAM management at hospital or health center level in every corner of the country, deaths due to SAM is indicated to be still high. Therefore this study aimed to answer the research questions:

- a. What looks like the survivalship function of underfive children with SAM?
- b. What are determinant factors of time to death of under-five children with SAM?

2. METHODS

2.1. Source of Data

The study used secondary data source that consider the recorded data of two years (September 2017 to August 2019) under five children admitted to the therapeutic feeding unit of Woldia General Hospital that fulfills the inclusion criteria. From the recorded 2 year data of 200 under five children with SAM 150 patients fulfils the inclusion criteria are included in this study. STATA 14.2 and SPSS for window version 20 was used for the analysis and graphics.

2.2. Study Variables

2.2.1. *Dependent Variable*

The response variable is time-to-death by SAM is obtained by calculating the difference (in weeks) from the start of admission to the child was died or censored. The length of stay (Time) in admission to hospital until the death or censored can be coded as (1= death, 0=censored).

2.2.2. *Independent Variables*

The independent variables (covariates) in this study include Socio-demographic and related variables (sex, age, residence, appetite, breast feeding status at admission), anthropometric measurements and history of the patient (MUAC, weight, height, admission criteria, admission type, referred from, cough, oedema, fever, anemia, pneumonia, vomiting, diarrhea, HIV, TB) and routine medications (IV antibiotics, amoxicilline, penicilline, folic acid, vitamin A).

2.3. Survival data analysis

The response variable time-to-death by SAM was obtained by calculating the difference (in weeks) from the admission of the child in hospital until the child was died or censored. Children were considered to be died and discharged, which is our event of interest. The statistical method

called survival analysis is appropriate to assess the stated objectives of this study. Survival analysis is used for data in the form of times from a well-defined time origin until the occurrence of some particular event or end point. A survival time is censored if all is known that is began or ended within some particular interval of time, and thus the total time length is not known exactly (Gardiner, 2010).

2.3.1. Non Parametric Methods

Non parametric methods are known as distribution free methods. The aim of non-parametric estimation of the survival function is to come up with graphical summaries of the survival times for a given group of individuals considered in the study. These graphical summaries are for the hazard and the survival function. After estimating the survival function, the median and other percentiles can be obtained which help to give a more detailed analysis. Among the various non-parametric tests one can find in the statistical literature, the Mantel- Haenzel test, currently called the “log-rank” test is used.

2.3.2. Semi-parametric method

A Cox model is a statistical technique for exploring the relationship between the survival time and several explanatory variables. The most commonly used regression model is the Cox-proportional hazard model. With this model the distribution for the baseline hazard function is not specified implies vary with time and that is why it is called a semi-parametric model. The Cox-proportional hazard model is a more general model in modeling the hazard and survival function because it does not place distributional assumptions on the baseline hazard (Prentice, 1992) . The Cox model was introduced by Cox (1972). It has the from:

$$h_i(t | x) = h_0(t) \exp(X_i^t \beta) \quad (1)$$

Where $h_0(t)$ is the baselinehazard function; X_i is a vector of covariates and β a vector of parameters for fixed effects. The corresponding survival function for Cox-PH model is given by:

$$S(t, X) = [S_0(t)]^{\exp\{\sum_{i=1}^p \beta_i X_i\}} \quad (2)$$

Where $S_0(t)$ the baseline survival function. The measure of the effect of the given covariates onsurvival time is given by the hazard ratio. Consider a categorical variable with two levels say $X = 1$ and $X = 0$, then the hazard ratio for the two groups is defined as:

$$HR = \frac{h(t | x = 1)}{h(t | x = 0)} = \exp(\beta) \quad (3)$$

When $HR = 1$, it implies that the individuals in the two categories are at the same risk of getting the event, when $HR > 1$, it implies that the individuals in the first category ($X = 1$) are at a high risk of getting the event and if $HR < 1$, the individuals in the second category ($X = 0$) are at a high risk of getting the event. The regression coefficients in the proportional hazards Cox model, which are the unknown parameters in the model, can be estimated using the method of maximum

likelihood. In Cox proportional hazards model the vector of parameters β can be estimated without having any assumptions about the baseline hazard $h_0(t)$, partial likelihood estimation.

3. RESULTS AND DISCUSSION

3.1. Results

3.1.1. Descriptive and non-parametric survival analysis results

Descriptive analysis is the beginning of any statistical analysis before proceeding to more complicated models. It is mainly concerned with describing the data in terms of graphs tables and percentages to understand the nature of the data. This research has taken 150 under five children with SAM who were followed up during the time from September 2017 to August 2019 at Woldia General Hospital therapeutic feeding center.

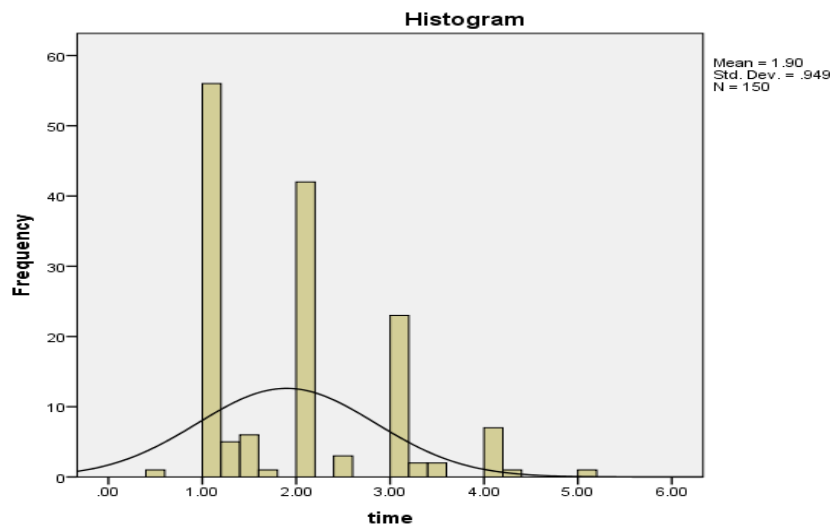


Figure 1 Histogram for time to death of underfive children in the hospital

From the above histogram of the data we can see that observations follow right censoring mechanism, random type in particular. Right censored in this case patients might die beyond the study period, lost to follow up (defaulters) and might cure. Hence we apply the survival analysis statistical method for this research to handle censoring. The following KM Curves shows that the cumulative survival and hazards function of underfive children with severe acute malnutrition in woldia general hospital. Cummulative survival function decreases while cummulative hazard function increases through study time.

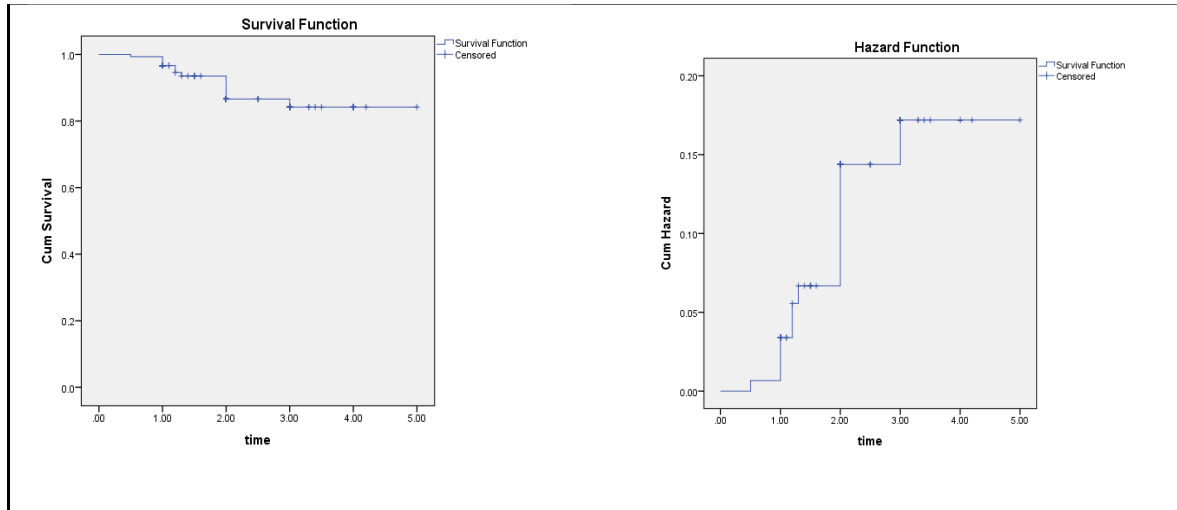


Figure 2 Cumulative survival and hazards function of underfive children

Table 1 Summary statistics for the estimated survival time of underfive children

Deaths	Censored	Total	Mean survival time	95% confidence interval	
				LCL	UCL
15 (10%)	135 (90%)	150	4.48weeks	4.425	4.733

The accounted death and censored of patients in the study period was 15 (10%) and 135 (90%), respectively. The proportion of death in this study was on the recommended Sphere standard which should < 10% (FMOH, 2007). The estimated mean survival time of the patient was 4.489 weeks with 95% confidence interval 4.425 to 4.733 weeks. The variable included in this study is categorized in to three parts for better description. These are socio-demographic related variables, anthropometric measurements, co- morbidity and routine medication given in the therapeutic feeding center. The summary result for each category is discussed as follows.

3.1.2. Socio-demographic and related variables

From the above table, 75 (50%) were female and 75 (50%) were male. Under five children with SAM that are female patients were followed up for a mean survival time 4.43 also male patients followed up for a mean survival time 3.66 weeks. Of the 150 patients included, 125 (83.33%) were from rural and 25(16.7%) were from urban. This suggests that most of SAM patients of under-five children at therapeutic feeding center come from rural areas of the zone. The age distribution of patients of SAM is 56 (37.33%) were 0-11 months, 46 (30.7%) were between 12- 23 months 37(24.67%). From this SAM is more experienced in under age one.

3.1.3. Anthropometric measurements

Majority of 97 (64.67%) were 3-6.9 kg, Majority of 138 (92%) were with MUAC less than 11.5 cm. This implies that the majority of the patients have the MUAC less than the cutoff point of the WHO SAM case identification. When we see the admission criteria 43(28.7%) was only oedema (kuashorkor) 40(26.7%) were only wasting (marasmus) 14(9.3%) were both oedema and wasting 53(35.33%) were by MUAC. About 137(91.33%) under five childrens were referred from health centers.

3.1.4. Patients Co-morbidities

The common co-morbidities of under five children with SAM in the area, of 150 patients of SAM 90 (60%) were with cough, 15(10%) were with HIV, 90 (60%) cough 111(74%) were with vomiting, 11(7.33%) have TB, 15(10%) have HIV when they are admitted to the therapeutic feeding center.

3.1.5. Routine medications

As shown in the above table, of different routine medications given in the feeding center of 150 admitted under five children in the hospital 135(90%) were taken the vitamin A nutrient as medication and 132(88%) take IV-antibiotics, 134(89.33%) takes folic acid, 119(79.33%) takes amoxicillin, 107(71.33%) takes Penicilline, 135(90%) take vitamin A.

3.1.6. K-M estimated curves and log rank test of covariates

The figure below shows that height and penicillin observed that there is difference between curves of covariates. And also logrank test result of height of children and penicillin treatment have p value less than alpha value 0.05 suggests that there is difference between the probabilities of death occurring at any time point of the study time. But most of the covariates are insignificant. It is better to use semi parametric method (Cox PH model) to identify determinant factors of time to death of under five children by SAM.

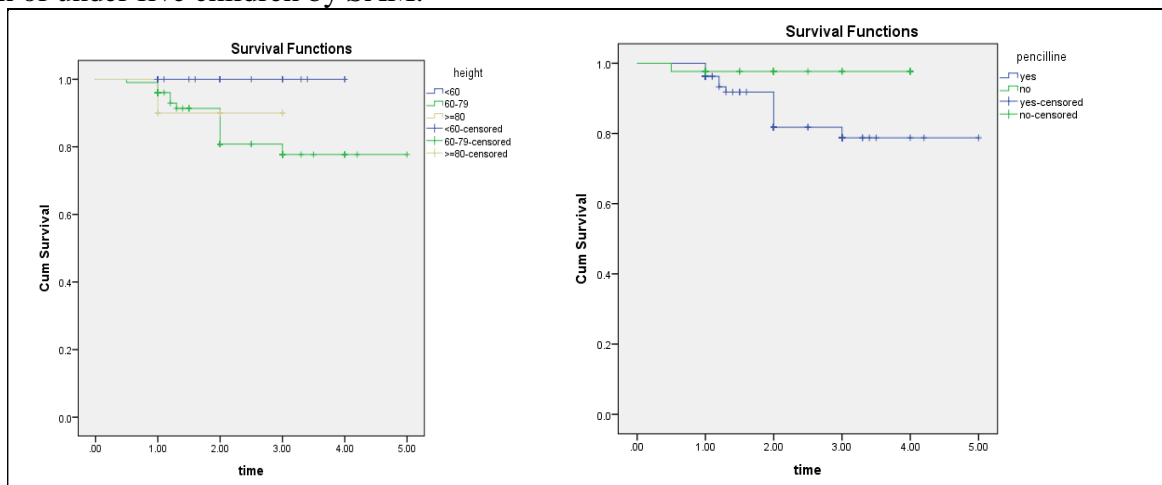


Figure 3 KM estimates of height and penicillin

3.1.7. Semi parametric methods results

Univariate analysis is the preliminary step of model development. It is recommended that use 25% level of significance to select candidate variables for the final model. After applying this method we observe we may lose significant predictors (clinically significant variables or significant on other literatures) on the survival status and mortality of under five children by SAM. It is known that variables, that were not important on their own, may become important in the presence of others. So we use all predictors to fit the COX PH model at 5% alpha level of significance and we try to assess the predictors of time to death of under five children by SAM admitted in the therapeutic feeding center of Woldia General Hospital.

Table 2: Estimated COX PH model for time to death by SAM of under five children at alpha 0.05

N	Covariates	Category	β	SE(β)	Wald	Df	Sig	HR	95% CI for HR	
									LCL	UCL
1	Age in month	0-11 months (ref)								
		12-23	-4.090	2.865	2.038	1	.153	.017	0.000	4.591
		24-35	-10.244	4.566	5.033	1	.025	.000	0.000	0.274
		36-47	-3.900	2.321	2.824	1	.093	.020	0.000	1.913
		48-59	-25.167	193.631	.017	1	.897	.000	0.000	7.741E+153
2	Admission criteria	Only oedema (ref)								
		Wasting	-11.672	4.561	6.549	1	.010	.000	0.000	0.065
		Oedema &wasting	-4.704	4.105	1.313	1	.252	.009	0.000	28.273
		MUAC	-9.827	4.550	4.664	1	.031	.000	0.000	0.403
3	Referred	Health centers (ref)								
		Self	-11.241	4.308	6.809	1	.009	.000	0.000	0.061
4	Cough	No (ref)								
		Yes	4.891	1.842	7.047	1	.008	133.04	3.596	4922.83
5	HIV	No (ref)								
		Yes	7.098	3.556	3.984	1	.046	1209.61	1.137	1286998.427
6	IV Antibiotic	No (ref)								
		Yes	-16.614	6.801	5.967	1	.015	.000	0.000	0.037
7	Amoxicillin	No (ref)								
		Yes	-7.189	3.512	4.190	1	.041	.001	0.000	0.736

β =Estimated parameters, WALD = Test Statistics, SE(β)= standard error of β , Df= degree of freedom, HR= Exp(B), Ref=Reference, Sig=p- value LCL= lower class limit, UCL= upper class limit.

3.1.8. Model diagnosis (Assessing Proportionality assumption)

Before making inference it is better to assess the basic assumption of Cox PH model assumes that the hazards of the groups is proportional over time. To do so, we apply the formal test and graphical method i.e. Plot of $\ln(-\ln(s(t)))$ vs $\ln(\text{time})$ if the PH assumption is satisfied this plot looks like parallel through study time. Let we see the plot of some covariates that have significant effect on the survival time of the multivariable Cox PH model and try to assess the PH assumption as follows. From the $\ln(-\ln(s(t)))$ vs $\ln(\text{time})$ plots above (Figure 4) of different covariates categories of these covariates is parallel. This implies that the proportionality assumption is satisfied.

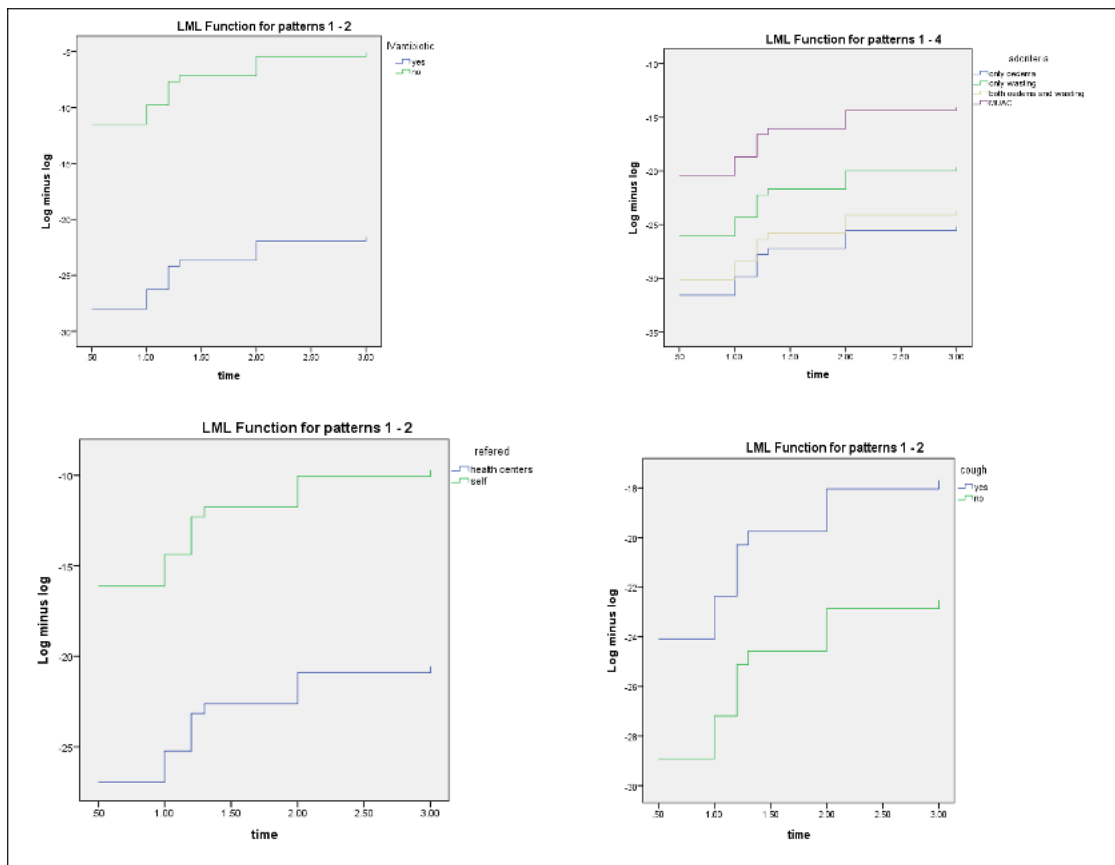


Figure 4 Plot of $\ln(-\ln(s(t)))$ Vs $\ln(\text{time})$ to assess the PH assumption of COX PH model.

3.1.9. Goodness of fit

After fitting the model we should check the goodness of fit of the model whether it fits the data well or not. We used the formal (Global test of $BETA = 0$) likelihood ratio test. As we see the table below, the likelihood ratio test, we have likelihood ratio at 36 degree of freedom is 75.15 and the p- value is 0.005, which is less than alpha 0.05. This implies that the estimated Cox PH model fits the data well.

Table 3 Formal test of goodness of fit of the estimated model (Likelihood ratio test)

-2 Log Likelihood	Chi-square	Df	Sig (p- value)
75.158	61.925	36	0.005

3.1.20. Interpretation of the model

From the estimated COX PH model age of the children, admission criteria, children referred from, cough, HIV, antibiotic treatment and amoxicillin are the covariates that have significant effect on time to death from SAM of under five children at 5% level of significance. The detail interpretation of these covariates based on the estimated Hazard ratio. The estimated HR for age groups (24-35 months) is 0.000 with 95% CI [0.000-4.591] and p- value 0.025, implies that children who are age group 24-35 months have less probability of dying by SAM than that of the children with age (0-11 months). This may be due to the age group 0-11 month's, If not identified early; they may have high risk of death.

The estimated HR for admission criteria of the children with only wasting is 0.010 with 95% CI [0.000-0.065] and p-value 0.000 similarly children registered with MUAC hazard ratio is 0.000 with 95% CI [0.000-0.403] and p value 0.025 which indicates that children admission criteria of the children with only wasting and MUAC have less probability of dying than that of with only oedema. The estimated HR of the child referred from is 0.000 with 95% CI [0.000-0.061] and p-value 0.009, which indicates that children referred by their own (self) to the feeding centre have low probability of dying than that of referred by the health centres. This might be due to that the habit of the people checking their children health status by their own is very important aspect for decreasing the child mortality.

When we see the co-morbidities HR of the children having cough is 133.04 with 95% CI [3.596- 4922.83] and p-value 0.008 which indicates that children with cough when admitted have high risk of death than that of without cough. Similarly The estimated HR with HIV is 1209.61 with 95% CI [1.137-1286998.42] and p-value 0.040 , implies that admitted children having HIV have high probability of death than that of without HIV. This might be the fact that HIV decreases the ability of the body protection of the disease by decreasing the number of white blood cells.

The estimated HR for taking Iv antibiotic treatment is 0.000 with 95% CI [0.000-0.037] and p- value 0.015 indicates that children who take the antibiotic treatment have low probability of dying than that of not taking it. Similarly the estimated HR for taking amoxicillin is 0.001 with 95% CI [0.000-0.736] and p- value 0.041 indicates that children who take amoxicillin treatment have low probability of dying than that of not taking it. This implies that if the treatments are given properly for the patients they have the capacity of decreasing child mortality by SAM.

3.2. DISCUSSION

This study investigated survival analysis of underfive children with severe acute malnutrition who were admitted at inpatient therapeutic feeding center Woldia General Hospital from September 2017 to August 2019. The finding of the study showed that among children treated for severe acute malnutrition the accounted death of patients in the study period was 10%. The proportion of death in this study was on the recommended Sphere standard which should < 10%.

However this finding is in line with previous study done debremakos (10.3%) (Wagnew et al. 2019), higher than the previous study done in Dilchora hospital (7.6 %) (Oumer et al., 2016), South wollo (3.4%) died (Hassen et al., 2019). This difference may be due to the differences in health seeking behavior, availability as well as accessibility of therapeutic foods and medications and also use of updated SAM treatment guideline. The mean length of time to death for children in the feeding center of 4.48 (weeks). It was almost in the international standard Sphere project set for the management of SAM which should be less than less than 4 weeks (FMOH, 2007).

The study finding showed majority 125 (83.33%) of the children admitted to therapeutic feeding center were from rural area which is consistent with a multicentre retrospective follow-up study in Amhara region, north-west Ethiopia (Awoke et al., 2018). The similarity of the study finding may be due to similar pattern of SAM distribution in Ethiopia mainly at rural areas. In this study the age of the children at admission with (0-11) months is 37.33 % indicates that majority of the children are below 1 year. The reason for the high proportion of cases of SAM to be among the age group less than 12 months might be due to sub optimal breast feeding and poor complementary feeding practices of the community. In this study the estimated HR for age groups (24-35 months) is 0.000 with 95% CI [0.000-4.591] and p-value 0.025, implies that children who are age group 24-35 months have less probability of dying by SAM than that of the children with age (0-11 months). This may be due to the age group (0-11) month's, If not treated early they may have high risk of death. The estimated HR for admission criteria of the children with only wasting is 0.010 with 95% CI [0.000-0.065] and p-value 0.000 similarly children registered with MUAC hazard ratio is 0.000 with 95% CI [0.000-0.403] and p value 0.025 which indicates that children admission criteria of the children with only wasting and MUAC have less probability of dying than that of with only oedema. When we see the co-morbidities HR of the children having cough is 133.04 with 95% CI [3.596-4922.83] and p-value 0.008 which indicates that children with cough when admitted have high risk of death than that of without cough. Similarly The estimated HR with HIV is 1209.61 with 95% CI [1.137-1286998.42] and p-value 0.040, implies that admitted children having HIV have high probability of death than that of without HIV. This might be the fact that HIV decreases the ability of the body protection of the disease by decreasing the number of white blood cells. This is in line with the study done in Dilchora Referral Hospital, Eastern Ethiopia (Oumer et al., 2016).

The estimated HR for taking antibiotic treatment is 0.000 with 95% CI [0.000-0.037] and p-value 0.015 indicates that children who take the antibiotic treatment have low probability of dying than that of not taking it. Similarly the estimated HR for taking amoxicillin is 0.001 with 95% CI [0.000-0.736] and p-value 0.041 indicates that children who take amoxicillin treatment have low probability of dying than that of not taking it. This implies that the treatments are given properly for the patients they have the capacity of decreasing child mortality by SAM. This result is in line with a study done Wolaita Zone, Southern Ethiopia (Kabalo & Seifu, 2017).

4. CONCLUSION

This study tried to investigate the survival analysis of under-five children with SAM admitted to therapeutic feeding unit in Woldia General Hospital, North Ethiopia. Accordingly proportion of death from SAM is 10% in the acceptable range of global Sphere standards which is to be <10%. The mean length of stay until death of children in the ITFU was 4.48 weeks. It is in the international standard (sphere) set for the management of SAM which should less than 4 weeks.

From the fitted Cox PH model, age of the children, admission criteria, children referred from, cough, HIV, IV antibiotic treatment and Amoxicillin are the covariates that have significant effect on time to death of under five children with SAM at 5% level of significance. Early Identifying cases and giving special attention for children with co morbidities such as HIV and cough is vital for decrease child mortality Ethiopia.

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