

Survival Rate and Determinants in Treatment of Children with Severe Acute Malnutrition using Outpatient Therapeutic Feeding Program in Sidama Zone, South Ethiopia

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Abstract: *The aim of this paper is to assess the recovery rate of outpatient therapeutic feeding program in treatment of severe acute malnutrition and its determinants at Sidama Zone, South Ethiopia. The data for this study are obtained from children who were discharged from the OTP between September 2013 and September 2015 G.C under the Health facility in Sidama Zone. The analytical methodologies used were the Kaplan-Meier to estimate the survival time and Cox regression model was employed to identify the covariates that have a statistical significant effect on the survival longevity of OTP patients. The estimation of the model parameters was done by partial maximum likelihood procedures. From the Cox regression model Health facility, Age, Medical complication history, intake of routine medication and interaction of Age by health facility were the factors for the recovery rate of OTP patients. Furthermore it was found that the survival probabilities of OTP patients with older age, without medical complication history and intake of routine medication.*

Keywords: *Sever acute malnutrition (SAM), Outpatient therapeutic feeding program (OTP), Cox regression models, and Partial likelihood ratio.*

I. Introduction

Malnutrition is abnormal physiological condition caused by deficiencies, excesses or imbalances in energy, protein and/or other nutrients. Malnutrition is also defined as a state in which the physical function of an individual is impaired to the point where he/she can no longer maintain adequate bodily performance processes such as growth, pregnancy, lactation, physical work, and resisting and recovering from disease. Malnutrition is categorized as acute (recent) or chronic (long term). It can be either under-nutrition or over-nutrition (obesity). There are four forms of under-nutrition: acute malnutrition, stunting, under-weight micronutrient deficiencies. The four forms can be categorized as either moderate or severe malnutrition and can appear isolated or in combination, but most often overlap in one client or population [7, 16, 18].

Severe acute malnutrition (SAM), is defined as a weight-for-height measurement of 70% or more below the median, or three SD or more below the mean National Center for Health Statistics reference values, which is called wasted; the presence of bilateral pitting edema of nutritional origin, which is called edematous malnutrition; or a mid-upper-arm circumference of less than 110 mm in children age 15 years [7]. Globally, it is estimated that there are nearly 60 million children with moderate acute malnutrition and 20 million who are severely acutely malnourished. About 9% of sub-Saharan African and 15% of south Asian children have moderate acute malnutrition and about 2% of children in developing countries have SAM. The majority of those affected are found in South Asia and Sub Saharan Africa. Approximately one million children die every year from severe acute malnutrition. It is reported that SAM is the commonest reason for pediatric hospital admission in many poor countries. Twenty five to 30% of children with severe malnutrition die during hospital admissions [24].

Ethiopia is one of the countries with highest under five child mortality rate, with malnutrition underlying to 57% of all children deaths [5, 22, 13]. According to 2011 EDHS report the percentage of children who are stunted (below-2 SD) is 44 percent; of which 21 percent are severely stunted. In rural areas, 46 percent of children are stunted, versus 32 percent of children in urban areas. Thirty percent or more of children are stunted in all regions except Addis Ababa (22%) and Gambela (27%). The percentage of stunting, wasting and underweight at SNNPR is 44.1, 7.6 and 28.3 respectively [11].

Problems with the treatment of SAM in OTP are:- Poor environment for malnourished children, Failure to treat the children in a separate area, Failure to complete the multi-chart correctly, Insufficient staff (particularly at night), poorly trained staff, Inaccurate weighing machines and Food prepared or given incorrectly [12]. Until recently, the management of SAM has been limited to hospital cares with limited coverage. Outpatient Therapeutic feeding Program (OTP) brings the service of management of SAM closer to the community by making services available at decentralized health facilities (primary health care units) in different resource limited countries such as Niger, North and South Sudan, Malawi, Chad and Ethiopia [25].

Therefore, as it was seen from different articles little is known about the treatment outcome and determinants of treatment success of OTP. Since the introduction of the OTP, there no any comprehensive study to evaluate the effectiveness of the program and identify any determinant factors in treating severely malnourished children in our country at health facility level except the study done in Tigray [25]. A qualitative study done in three regions of Ethiopia didn't even identify any determinant factors. The rationale for this study is that the outpatient therapeutic feeding program outcomes and determinant factors of success has been understood and necessary adjustment was made to improve effectiveness in the program. The study was generating further critical knowledge to fill up knowledge gap of the health care staff on the success of treatment and factors determining the treatment outcome. The generated knowledge was used to improve management of SAM thereby reducing the associated burden of disease. The Information that was derived from the study was also be used for policy implementation and in program planning.

II. Data and Methodology

2.1 Data Source

A retrospective longitudinal study was conducted among children aged 6-59 months who had been treated for SAM under the OTP from September 01, 2013- September 8, 2015. The research was carried out in Sidama Zone, South Ethiopia. Sidama Zone is located in SNNPR regional State and situated at about 274kms away from Addis Ababa, the capital city of Ethiopia. In this study, we considered 7 out of 131 governmental health centers (HCs) and 21 out of 525 governmental Health posts (HPs) which are participating in the program. The data used in this study are collected from 602 patients. All patients registered for treatment within the indicated fourteen weeks (except cases with missing values) in 7 health centers and 21 health posts on socio-demographic, baseline characteristics, outcome status and follow-up status at initiation of treatment from OTP register maintained by health center and health post OTP unit were considered. A structured and pretested data abstraction form are prepared and used for data collection. Data was abstracted within 30 days from OTP cards for socio-demographic, baseline characteristics, outcome status and follow-up status by using data collectors, principal investigators, Public health professionals (Health Officers).

2.2 Sampling design

Sampling frame and Procedure

In the study zone, there are twenty one districts. Populations living around these districts were assumed more or less homogenous. As the result, seven districts were selected at random using lottery method presuming that there was no information lost with the unselected districts. All OTP running institutions in the sampled districts were stratified into health centers and health posts. The under five population managed in each sampled health institutions was assessed and it outnumbered in health centers than health posts. By the fact that health centers within a district have similar settings, we selected health center from each district using simple random sampling. Out of the satellite health posts under the catchment area of the health center, we included health posts selected randomly using lottery method. In total, we prepared a sampling frame of children managed for SAM from health centers and satellite health posts in the districts. Samples were allocated to each health institution using the probability proportional to sampling. Finally, the children were selected by systematic random sampling from each institution based on their unique identification number. In this study systematic random sampling method is adopted as an appropriate sampling design for selecting a representative sample of the patients based on their OTP unique identification number.

Sample Size determination

The sample size for treatment recovery rate of OTP was determined using the sample size determination formula for single population proportion. Three different studies showed the treatment recovery rate of SAM under OTP. A study done in Tigray [25] showed recovery rate of 61.78% and two different studies [2, 23] in SNNPR showed recovery rate of 87% 64.4%. For this calculation, the proportion that gives the highest sample size i.e. 61.78% was taken from the above study. To draw a minimum sample size from the source population, the following standard method was used:

$$n_0 = \frac{z_{1-\alpha/2}^2 P(1-P)}{d^2} \quad (1)$$

Where, n_0 = sample size derived from estimation formula

$z_{1-\alpha/2}^2$ = confidence interval, i.e 1.96 to be 95% confident to be 95% confident

P = recovery rates of children who had been managed for SAM under OTP

d = margin of error

Further discussions on sampling methods are available in detail in (Cochran, 1977) [6, 8]. So by considering 10% none response rate and designing effect 1.5 the final sample size for determining the treatment recovery rate of OTP was 602.

2.3 Study variables

The response (dependent) variable is continuous and describes time to recovery from severe acute malnutrition (SAM) in weeks. The explanatory (independent) variables of interest in this analysis include socio-demographic, baseline characteristics, outcome status and follow up status of disease and treatment profiles.

Predictor Variables:

Socio-demographic and admission characteristics

Variable	Category
Health facility	1=Health post, 2= Health center
Age	0= \leq 24 months 1= \geq 24 months
Sex	1=Male 2=Female
Residence	1=Urban 2=Rural
Distance (time of travel)	0= \leq 1 hour 1 = 1 hour
Referred by	1 = Community volunteers 2 = Self-referred 3 = From EOS or CHD
Admission status	1=New 2 = Return after default 3=Readmission

Clinical characteristics of children on admission

Variable	Category
Diagnosis at admission	1=Marasmus, 2= Kwashakor 3=Marasmic-kwash
Appetite test on admission	1=Pass 2=fail
Routine medication at admission	1=Yes 2=No
Medical complication on admission	1=Yes 2=No
Weight gain for the first three consecutive weeks	1=Yes 2=No

2.4 Survival Data Analysis

The term survival analysis applies to techniques in which the data being analyzed represent the time it takes for a certain event to occur. The use of survival analysis, as opposed to the use of different statistical methods, is most important when there is no time-to-event record.

Descriptive Methods for Survival data

This method is important if individuals are homogeneous at least within groups. In such situation it is appropriate to use the Kaplan-Meier survival estimator. It is an estimator of the survivorship function (or survival probability) $S(t) = P(T \geq t)$ is defined as:

$$\hat{S}(t) = \sum_{t_{(i)} \leq t} \left[1 - \frac{d_j}{n_j} \right] \quad (2)$$

With the convention that $\hat{S}(t) = 1$ if $t \leq t_{(i)}$

Where, $n_j =$ number at risk of dying $t_{(i)}$

$d_j =$ observed number of deaths

$t_{(i)} =$ rank – ordered survival times

In this study, time to recovery from OTP will be estimated for intake of routine medication, presence of co-infections, age and sex of the child, intake of PlumpyNut, and appetite test result of the child using Kaplan-Meier procedure.

Comparison of Survivorship Functions

When comparing groups of subjects, it is always a good idea to begin with a graphical display of the data in each group. The figure in general shows if the pattern of one survivorship function lying above another which means the group defined by the upper curve lived longer, or had a more favorable survival experience, than the group defined by the lower curve. Now the statistical question is whether the observed difference seen in the figure is significant. The general form of this test statistic is given by

$$Q = \frac{[\sum_{i=1}^m w_i (d_{1i} - \hat{e}_{1i})]^2}{\sum_{i=1}^m W_i^2 \hat{v}_{1i}} \quad (3)$$

In this expression, $\hat{e}_{1i} = \frac{n_{1i}d_i}{n_i}$ and $\hat{v}_{1i} = \frac{n_{1i}n_{0i}d_i(n_i-d_i)}{n^2(n_i-1)}$

$n_{0i} =$ the number at risk at observed survival time $t_{(i)}$ in group 0

$n_{1i} =$ the number at risk at observed survival time $t_{(i)}$ in group 1

d_{0i} = the number of observed deaths in group 0
 d_{1i} = the number of observed deaths in group 1
 n_i = total number of individuals or risk before time $t_{(i)}$
 d_i = total number of deaths at $t_{(i)}$

2.5 Regression Models for Survival Data

One of the most popular types of regression models used in survival analysis is the Cox proportional hazard model.

The Cox Proportional Hazards Regression Model

The Cox Proportional Hazard Model is a multiple regression method used to evaluate the effect of multiple covariates on the survival. Cox (1972) proposed a semi-parametric model for the hazard function that allows the addition of covariates, while keeping the baseline hazards unspecified and can take only positive values. With this parameterization the Cox hazard function is

$$\lambda(t, X, \beta) = \lambda_0(t)e^{\beta'X} \quad (4)$$

Where

$\lambda_0(t)$ is the baseline hazard function that characterizes how the hazard function changes as a function of survival time,

$\lambda(t, X, \beta)$ represents the hazard function at time t with covariates $X = (X_1, \dots, X_p)$,

$\beta(\beta_1, \dots, \beta_p)$ is a column vector of p regression parameters,

$e^{\beta'X}$ characterizes how the hazard function changes as a function of subject covariates.

t is the failure time.

The survival time of each member of the sample is assumed to follow its own hazard function. In such a case, the above model can equivalently be written as

$$\lambda_i(t, x_i, \beta) = \lambda_0 \exp(\beta_1 x_{i1} + \dots + \beta_p x_{ip}), \quad i = 1, \dots, n \quad (5)$$

Where n is total number of observations in the study. $x_i = x_{i1} \dots x_{ip}$ is a column vector of measured covariates for the i^{th} individual (patient) which are expected to affect the survival probability.

The proportional hazards estimation method computes a coefficient for each predictor variable that indicates the direction and degree of flexing that the predictor has on survival. The proportional hazard model is the most popular regression method for analysis of censored survival data. The Cox proportional hazard model is formulated as the hazard function which measures the risk to death or rate of failure at time t .

Assumptions of Cox proportional hazard model

- (1) The baseline hazard $\lambda_0(t)$ depends on t , but not on covariates $x_1 \dots x_p$
- (2) The hazard ratio, i.e., $e^{\beta'X}$ depends on the covariates $X = (x_1 \dots x_p)'$ but not on time.
- (3) The covariates x_i do not depend on time t .

2.6 Parameter Estimation (Partial Likelihood)

Instead of constructing a full likelihood, we consider the probability that an individual experiences an event at time t_i given that an event occurred at that time. Let R_i denote the set of individuals at risk at time just prior to $t_{(i)}$. Assume that for the present case there is only one failure at time t_i , i.e., no ties. The probability that individual i with covariates x_i is the one who experience the event at time $t_{(i)}$.

P(individual i has experiences an event at time $t_{(i)}$ | one event at time $t_{(i)}$)

$$\frac{\lambda(t, x_i)}{\sum_{j \in R_t(i)} \lambda(t, x_j)} \quad (6)$$

Under the proportional hazards assumption on using equation (6), the ratio

$$\frac{\lambda_0(t) \exp(\beta'x_i)}{\sum_{j \in R_t(i)} \lambda_0(t) \exp(\beta'x_j)} \quad (7)$$

Shows the contribution to the partial likelihood at each death time $t_{(i)}$ by the individuals with covariate $x_{(i)}$ in the risk set $R_{(i)}$. Where $R_{(i)}$ is the overall subjects in the risk set at time $t_{(i)}$. By estimating the baseline hazards function, in the numerator and denominator, equation (7) becomes:

$$\frac{\exp(\beta'x_i)}{\sum_{j \in R_t(i)} \exp(\beta'x_j)} \quad (8)$$

Thus the partial likelihood is the product over all failure time $t_{(i)}$ for $i = 1, 2, \dots, m$ of the conditional probability (8) to give the partial likelihood

$$L_p(\beta) = \prod_{i=1}^m \frac{\exp(\beta' x_i)}{\sum_{j \in R_t(i)} \exp(\beta' x_j)} \quad (9)$$

The product is over the m distinct ordered survival times and $x_{(i)}$ denotes the value of the covariate for the subject with ordered survival time $t_{(i)}$. The log partial likelihood function is

$$l_p(\beta) = \sum_{i=1}^m \left[\beta' x_i - \ln \left(\sum_{j \in R_t(i)} \exp(\beta' x_j) \right) \right] \quad (10)$$

We obtain the maximum partial likelihood estimator by differentiating the right hand side of (10) with respect to the component of β , setting the derivative equal to zero and solving for the unknown parameters. The partial likelihood derived above is valid when there are no ties in the data set. But in most real situations tied survival times are more likely to occur. In addition to the possibility of more than one cure at a time, there might also be more than one censored observations at a time of cure. To handle this real world fact, partial likelihood algorithms have been adopted to handle ties. There are three approaches in common to estimate regression parameters when there are ties. The most popular and easy approach is Breslow's approximation.

The Breslow approximation

This approximation is proposed by Breslow and Peto by modifying the partial likelihood takes the following form

$$L_B(B) = \prod_{i=1}^m \frac{\exp(\beta' s_i)}{[\sum_{l \in R_t(i)} \exp(\beta' x_l)]^{d_i}} \quad (11)$$

Where s_i = the sum of covariates over d_i subjects at time $t_{(i)}$.

d_i = the number of deaths occurred at time $t_{(i)}$.

Now the partial log likelihood of (11) is given as

$$l_B(\beta) = \sum_{i=1}^m \left[\beta' s_i - d_i \ln \left(\sum_{l \in R_t(i)} \exp(\beta' x_l) \right) \right] \quad (12)$$

We obtain the Breslow maximum partial likelihood estimator, adjusted for tied observation, by differentiating equation (12) with respect to the component of β and setting the derivative equal to zero and solving for the unknown parameters.

2.7 Assessment of Model Adequacy

The methods for assessment of a fitted proportional hazards model are essentially the same as for other regression models. In general requirements for model assessment are

1. Methods for testing the assumption of proportional hazards
2. Subject-specific diagnostic statistics that extend the notations of leverage and influence to the Proportional hazards model, and

3. over all summary measures of goodness of fit.

In order to use the Cox model, we must check the assumption of whether the effects of covariates on hazard ratio remain constant over time. This is a critical assumption of proportional hazards model and must be checked for each covariate. Different studies [1] suggest that several tests and graphical techniques can be used to assess proportionality assumptions in fitting the Cox model. Another important aspect of model evaluation is a thorough examination of regression diagnostic statistics to identify which, if any, observations:

1. have an unusual configuration of covariates,
2. exert an undue influence on the estimate of the parameters, and
3. have an undue influence on the fit of the model.

Statistics similar to those used in linear and logistic regression are available to perform these tasks with a fitted proportional hazards model. There are some differences in the types of statistics used in linear and logistic regression and proportional hazards regression, but the essential ideas are the same in all the three settings. Leverage is a diagnostic statistic that measures how unusual the values of the covariates are for an individual. In linear and logistic regression leverage is the distance of the value of the covariates for a subject to the overall mean of the covariates. Leverage is not easily defined nor does it have the same nice properties in proportional hazards regression. This is due to the fact that subjects may appear in multiple risk sets and thus may be present in multiple terms in the partial likelihood. And finally, as in regression analysis, some measures analogous to R^2 may be of interest as a measure of model performance. There is not a single, simple, easy to calculate, useful, easy to interpret measure for a proportional hazards regression model. In particular, all measures depend on the proportion of values that are censored. A perfectly adequate model may have what, at

face value, seems like a terribly low R^2 due to a high percent of censored data. We use R^2 as it is the easiest and best one to use, and it is defined as

$$R_p^2 = 1 - \exp\left(\frac{2}{N}(LL_0 - LL_{\hat{\beta}})\right) \quad (13)$$

Where, N is the total number of observations in the model.

LL_0 is the Log partial likelihood for model zero.

$LL_{\hat{\beta}}$ is the Log partial likelihood for the fitted model with p covariates.

III. Results and Discussion

The results of the study are discussed in this section. The response variable, Time to recovery from SAM, is continuous. The censoring indicator (status) is 0 for censored observations and 1 for event, in our case cured. In this study Cox survival regression model is used to see the relationship between the proposed independent variables and the response variable. We start our data analysis by giving the summary statistics for the categorical variables considered in the study; we then proceed to the bivariate analysis, checking assumptions and complete the final model in multivariate analysis.

3.1 Summary Statistics

Socio demographic and admission characteristics of children

The medical cards of 602 patients have been reviewed of which 68.8% (total 414) are cure cases. A cured proportion seems lower for males (64.41%) than for females (68.91%). The Community volunteers group showed the highest percentage (71.05%) with respect to cure proportions than the other two groups and Health post groups revealed the highest proportion of cure (74.42%). A patient who took the treatment for the first time, which is a new case, seems to have lower cure proportion (69.76%) than the other two groups and Rural OTP patients cure proportion (70.41%) seems larger than Urban OTP patient. More than 24 months of OTP patients cure proportion (74.53%) seems larger than less than or equal to 24 months of OTP patient and Less than or equal to one hour of OTP patients cure proportion (97.01%) seems larger than more than one hour of OTP patient All the results have been summarized in Table1 below.

Table3.1 Socio Demographic and Admission Characteristics of Children by OTP Patient

Summary of the Number of Event and Censored values						
Characteristics	Category	Value	Total	Event /Cured	Censored	Percent Cured
Health facility	1	Health post	477	355	122	74.42
	2	Health center	125	59	66	47.2
Age of the child at admission	0	or = 24 months	268	243	25	62.94
	1	24 months	334	171	163	74.53
Sex of the child	1	Male	306	210	96	64.41
	2	Female	296	204	92	68.91
Place of residence	1	Urban	51	26	25	50.98
	2	Rural	551	388	163	70.41
Distance (time of travel) in hour	0	or = 1 hour	535	349	186	65.23
	1	1 hour	67	65	2	97.01
Referred by	1	Community volunteers	114	81	33	71.05
	2	Self-referred	353	242	111	68.55
	3	From EOS or CHD	135	91	44	67.4
Admission status	1	New	507	351	156	69.76
	2	Return after default	52	33	19	63.46
	3	Readmission	43	30	13	69.23

Clinical characteristics of children

Out of the total 602 children MUAC was taken for 504 (83.72%) children and It was observed 94 (15.61%) had edema. Overall median weight at admission was 7.5 kg (Inter quartile range: 6to10 kg). Median weight of marasmic patients was 6.8 kg (IQR 5.5 -8.8 kg), marasmic kwashiorkor patients 8 kg (IQR 6.8-9.5 kg), and patients with edema 9.95 kg (IQR 8.05-11.40 kg). Height was taken only for 84 (10.9%) children. Of the total 602 records of children examined, 60(10%) children had diarrhea, 60(60%) had vomiting, 51(8.5%) had cough, 46(7.6%) had blood in stool, 7(1.2%) had anemia and 3(0.5%) had skin infections. No children with severe symptoms were admitted to care centers. Children and mothers or care takers of the malnourished children were not totally tested for HIV. Of the total 602 children admitted to OTP 504 (83.7%) children were diagnosed as having marasmus (MUAC 11 cm), 94 (15.6%) children had kwashakor (bilateral pitting edema) and 4(0.7%) children had both MUAC 11 cm and bilateral pitting edema (Marasmic-kwash) (Table 3.2).

Table 3.2 Clinical Characteristics of Children on Admission under OTP from SAM

Characteristics	Category	Frequency number	Percent
Amoxicillin	yes	538	89.4
	no	62	10.3
Measles immunization	yes	519	86.2
	no	77	12.8
Vitamin A	yes	505	83.9
	no	91	15.1
Anti-malarial(co-artem)	yes	79	13.1
	no	428	71.1
Folic acid	yes	62	10.3
	no	437	72.6
General danger sign	yes	0	0
	no	602	100
Diarrhea	yes	60	10
	no	542	90
Vomiting	yes	60	60
	no	542	90
Cough	yes	51	8.5
	no	551	91.5
Blood in stool	yes	46	7.6
	no	556	92.4
Anaemia	yes	7	1.2
	no	595	98.2
skin infections	yes	3	0.5
	no	599	99.5
Breathing per minute	30	187	31.1
	30-39	307	51
	40-49	106	17.6
	50	2	0.3
Body temperature	Normal	578	96
	Fever	19	3.2
	Cold or hypothermic	5	0.8
Breast feeding	yes	256	44.2
	no	336	55.8
Diagnosis at admission	Marasmus	504	83.7
	Kwashakor	94	15.6
	Marasmickwash	4	0.7
Appetite test	pass	578	96
	fail	24	4

Recovery rate from SAM

Of the total 602 children admitted to OTP; the recovery rate from SAM was 414 (68.8%). Whereas 8(1.3%), 145(24.1%), 19 (3.2%), 14(2.3%), 2(0.3%) children died, defaulted, transferred, unknown (quit the program with unknown outcome status) and non responders (who did not reach any of the discharge criteria) respectively.

3.2 Descriptive analysis

Before proceeding to more complicated models, we make a descriptive analysis that will use as initiation to our subsequent findings. Here we start with the test of whether the observed differences in data summary among different factors are statistically significant or not with the help of log-rank test and Kaplan-Meier survival estimates. The log rank test is performed to test if there are statistically significant differences among the survival experience of the different groups of the covariates at 5% level of significance. The null hypothesis to be tested is that there is no difference between the probabilities of an event.

Table 3.3 Log Rank Test for Equality of Survival Experience among the Different Groups of Covariates

Test of Equality over Strata			
Variable	Chi-Square	DF	Pr Chi-Square
Health facility	17.215	1	0.000
Age of the child	8.896	1	0.003
Distance (time of travel) in hour	10.306	1	0.001
Sex	4.735	1	0.030
Place of residence	2.598	1	.107
Referred by	4.381	2	0.112
Admission status	2.270	2	0.321

Diagnosis	0.369	2	0.832
Medical Complication	16.007	1	0.000
Routine Medication	15.138	1	0.000
Weight gain	0.025	1	0.875
Appetite test	0.020	1	0.886

Table 3.3 shows that the different groups of Health facility, Distance (time of travel) in hour, Age of the child, Sex, Medical complication and Routine medication are statistically not equal in experiencing the cure event, whereas levels of Admission status, Diagnosis status, weight gain, Appetite test, Referred by and Place of residence are statistically the same in experiencing the event cure. The Log-rank test results suggests that Health facility, Distance (time of travel) in hour, Age of the child, Sex, Medical complication and Routine medication are significant covariates whose different levels have an impact in the survival longevity of OTP patients; while Admission status, Referred by, Diagnosis status, and Place of residence does not have an impact. Plots of different groups of Health facility, Distance (time of travel) in hour, Medical complication, Routine medication, Age of the child and sex of the child to compare the survival probability of OTP patients are given below.

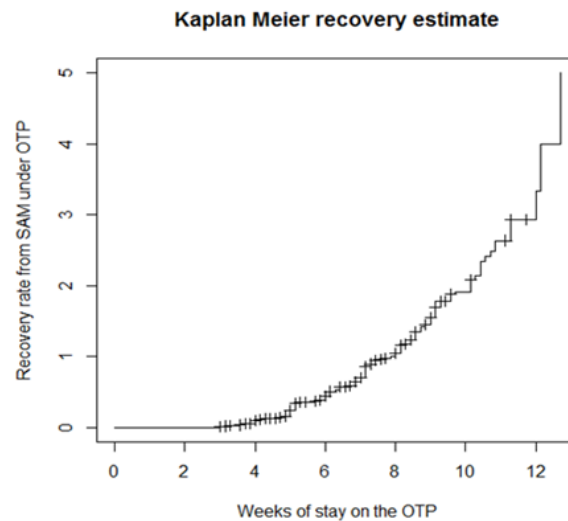


Fig. 3.1 Overall Kaplan Meier Recovery Estimate of Children Treated under OTP in Sidama Zone

The Kaplan-Meier estimator survival curve gives the estimate of survivor function among different strata or groups of covariates to make comparisons. Separate graphs of the estimates of the Kaplan-Meier survivor functions are constructed for different categorical covariates. In fig.1, the pattern that one survivorship function lying above another means the group defined by the upper curve has a better survival than the group defined by the lower curve. From the graph there are clear differences among the various groups of level of Health facility, Distance (time of travel) in hour, Age of the child, Sex, Medical complication and Routine medication. However, the difference is not clear among Admission status, Referred by, Weight gain, Appetite test and Place of residence.

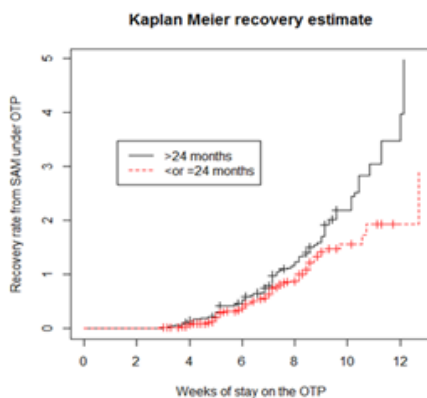


Fig. 3.2 Survival curves of OTP patients by age of child

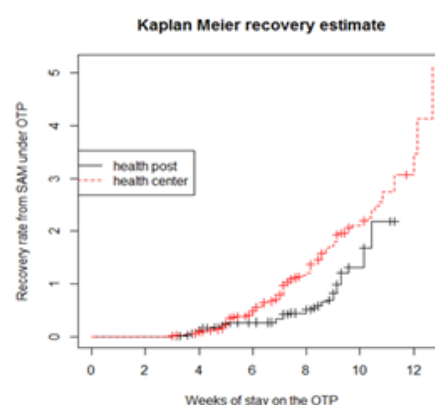


Fig. 3.3 Survival curves of OTP patients by health facility

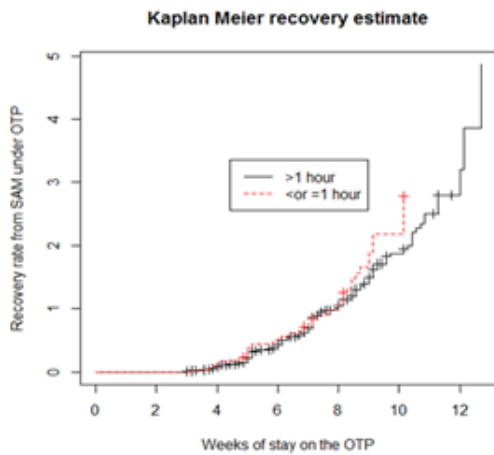


Fig. 3.4 Survival curves of OTP patients by distance (time of travel) in hour

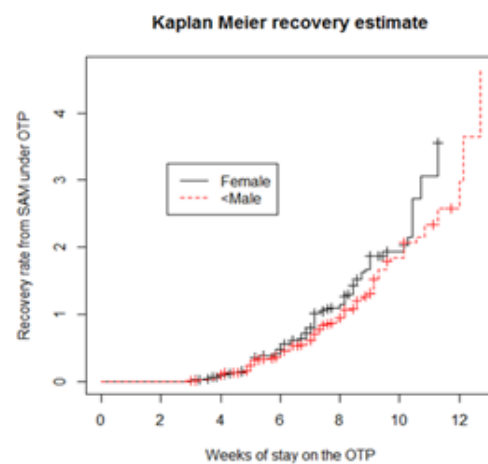


Fig. 3.5 Survival curves of OTP patients by sex of child

Fig 3.2 also supports that there is a difference in survival function between age in categories and further identifies that, in general greater than 24 months patients better than less than 24 month patients special after the patient treated about fourteen weeks.

Fig 3.3 also supports that Overall the median recovery time was 7.14 weeks. Likewise, to reach the minimum sphere standard recovery rate, set at 75%, the children were to stay for 8 weeks more under treatment. The median recovery time for children treated at health centers was 6.57 weeks and at health posts was 7.43 weeks. There were significantly different recovery rates among children who were treated in health centers and health posts.

Fig 3.4 also supports that there is a difference in survival function between time in categories and further identifies that, in general less than equal to one hour patients survive longer than greater than one hour patients the lowest chance to survive.

Fig 3.5 also supports that there is a difference in survival function between sex of the child and further identifies that, in general female patients survive better than male patients the lowest chance to survive.

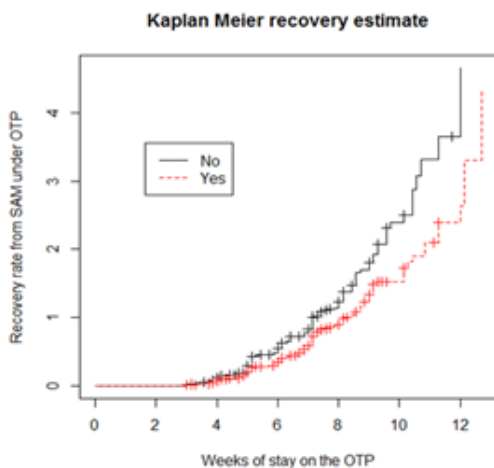


Fig. 3.6 Survival curves of OTP patients by medical complication history on admission

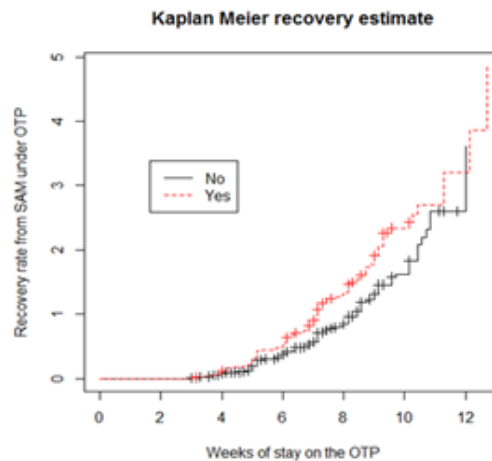


Fig. 3.7 Survival curves of OTP patients by routine medication at admission

Fig 3.6 also supports that there is a difference in survival function between medical complication history and further identifies that, in general without medical complication patients survive longer than with medical complication patients the lowest chance to survive.

Fig 3.7 also supports that there is a difference in survival function between routine medication and further identifies that, in general children who took drugs survive better than those who did not take the drugs.

3.3 Results of Cox-proportional hazard model

To assess the relationship between the outcome and explanatory variables, model development is necessary.

Bivariate Analysis

For each covariate we will use a bivariate Cox proportional hazards model analysis that contains a single independent variable in order to have an idea about each covariate. Likelihood ratio chi-square test is used to test the significance of bivariate relationship. In bivariate analysis, using likelihood ratio chi-square test, the variables that are found to be significant (p-value 0.2 is used as a criterion for significance) are Health facility (hfacility), Age of the child at admission (age), Sex, Routine medication (Rmedication), Referred by (Rferdby), Medical complication history (Mhistory) and Distance (time of travel) in hour (Dtimehr). Age of the child at admission, Routine medication at admission, Health facility and Medical complication on admission, with p-value less than 0.05 (standard level of significance), have relatively strong associations to the cure of OTP patients. The findings of Bivariate analysis.

Analysis of Maximum Likelihood Estimates						
Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr ChiSq	Hazard Ratio
Hfacility health center	1	0.4512	0.1489	8.473	0.004	1.753
Age > 24 months	1	-0.2786	0.1136	12.43	0.01416 *	0.7102
Sex female	1	-0.1732	0.1023	2.690	0.09051	0.811
Resdence urban	1	0.07588	0.20372	0.14	0.7095	1.079
Distimhr < or = 1hour	1	0.2369	0.1411	2.21	0.1373	1.224
Refeby rb2	1	0.03397	0.13026	0.261	0.794	1.03455
rb3	1	-0.21898	0.80334	1.407	0.159	0.8033
Adstats as2	1	-0.26546	0.18347	1.447	0.258	0.7669
as3	1	-0.04203	0.19073	0.220	0.826	0.9588
Diagoadmi di2	1	0.02925	0.1236	0.237	0.813	1.030
di3	1	0.2767	0.5037	0.549	0.583	1.319
Appetit At2	1	-0.06239	0.45034	0.02	0.8898	0.9395
Weightch WCH2	1	0.0299	0.1965	0.02	0.8791	1.03
Rmedication yes	1	0.36996	0.09887	14	0.0001	1.448
Mhistory no	1	-0.3821	0.0993	14.81	0.0001	0.6824

Table 3.4 Bivariate Analysis Result for Each Covariate

The bivariate analysis finding showed that; type of health facility, age of the child at admission, distance (time of travel) from home to health facility, Routine medication at admission, Medical complication history on admission, Referred by and Sex had significant association with survival time among children who recovered from OTP at 0.25 P-value.

Partial likelihood ratio test for the contribution of the interaction effect

From theoretical point of view the following possible interactions are expected. Moreover, we need to assess some realistic situations to see if two interaction effects can increase or decrease the survival time of OTP patients. The partial likelihood ratio test is used to identify the significance of some reasonable and possible interactions. The hypothesis to be tested is

H_0 : The model with only main effect fits the model equally well as the model having the main effect and their interaction as predictors.

H_1 : H_0 is not true

Decision: Reject H_0 at $\alpha = 0:05$ level of significance if $-2\text{LOG}L_2 - (-2\text{LOG}L_1) \geq X_1(\alpha = 0.05) = 3.84$, otherwise do not reject H_0 . This means we need to include the corresponding interaction in the multivariate analysis.

Table 4.5: Partial Likelihood Ratio Test for Checking Interaction Terms

Model Fit Statistics				
Variable	-2 LOG L2With main effects	-2 LOG L1 With main effects and	-2 LOG L2 - (-2 LOG L1)	Sig.

	only	interaction		
hfacility,age	4478.811	4468.482	10.328	Reject
hfacility,Mhistory	4474.43	4473.097	1.3323	Do not reject
hfacility,Rmedication	4482.173	4481.765	0.4085	Do not reject
age,Mhistory	4494.807	4494.439	0.367	Do not reject
age, Rmedication	4489.119	4485.977	3.142046	Do not reject
Mhistory, Rmedication	4489.736	4489.659	0.077	Do not reject

The table shows that only the interaction between health facility and age of patient (healthage) is significant. And this is an indication that the interaction of health facility (health center) and the age of the patient affects the survival time of the patient.

Multivariate Analysis

One problem with any bivariate analysis is that it ignores the possibility that a collection of covariates, each of which is weakly associated with the outcome, may have a significant effect when used together with other covariates in the model. If this is thought to be a possibility, then we should choose a significance level large enough to allow the suspected variables to become candidates for inclusion in the multivariate model. It is for this reason that we use p-value of 0.2 for selection of variables that are potentially candidates for the multivariate analysis from bivariate findings and those significant interactions on partial likelihood ratio test. To facilitate computation and interpretation, the coding scheme used in SPSS and R is given below in Table 3.8. The following table 3.6 shows multivariate analysis done using the significant variables in the bivariate analysis and significant interaction terms based on the likelihood ratio test.

Table 3.6 Partial Likelihood Estimates for Fitted Proportional Hazards Model

Analysis of Maximum Likelihood Estimates							
Variable	DF	Parameter Estimate	Standard Error	wald	Pr	ChiSq	Hazard Ratio
Hfacility health center	1	0.4512	0.1489	8.473	0.004		1.5702
Age							
24 monhs	1	-0.2786	0.1136	12.43	0.000422		0.7568
Sex female	1	-0.1732	0.1023	2.690	0.09051		0.8410
Rmedication							
yes	1	0.6375	0.1333	25.423	0.000		1.8918
Dtimehr							
≤ 1hr	1	0.2369	0.1411	2.33	0.09309		1.2673
Refeby							
refeby(2)	1	-0.2155	0.1519	1.142	0.1519		0.8061
refeby(3)	1	-0.2166	0.1814	0.002	0.23247		0.8053
Mhistory							
no	1	-0.8618	0.1328	41.825	0.000		0.4224
healthage	1	1.0184	0.3325	28.84	0.000		2.7268

The variables that are found to be insignificant at 10% level of significance in multivariate analysis are Sex of the child, distance (time of travel) in hour and referred by. We drop these variables for the next step and perform a multivariate analysis for the remaining five covariates. The following table shows the fitted Cox-proportional hazards model for covariates health facility, routine medication, age, medical complication history and the interaction of health facility and age of the child.

Table 3.7 Partial Likelihood Estimates for Significant covariates

Analysis of Maximum Likelihood Estimates								
Variable	DF	Parameter Estimate	Standard Error	wald	Pr	Hazard Ratio	95% CI for lower	95% CI for upper
hfacility health center	1	0.4923	0.1436	11.338	0.001	1.6360	1.2346	2.1680
age > 24 month	1	-0.2347	0.1052	12.407	0.001	0.7908	0.6435	0.9720
Rmedication RouM2	1	0.6411	0.1236	30.360	0.000	1.8985	1.4902	2.4188
Mhistory MedH2	1	-0.7390	0.1206	41.208	0.000	0.4776	0.3770	0.6050
healthage	1	0.8510	0.3336	24.048	0.01	2.3419	1.2178	4.5034

Table 3.7 presents computer output of the result of the fitted hazard model. Based on the result we look for predictors having statistical significant relationship with the hazards. All the covariates namely health facility, intake routine medication at admission, medical complication on admission, age of the child and interaction of health facility and age are significant at 5% level of significance. Since there is no continuous covariates, we cannot check the linearity of covariates in the model so, we consider the model that contains

these covariates as a preliminary final model and it could be the final model after we check proportionality assumptions.

3.4 Assessment of Model Adequacy

Having identified the final preliminary model the next step and most important in statistical analysis is to diagnose the fit of the model. After a model has been fitted to an observed set of survival data the adequacy of the fitted model needs to be assessed. The use of diagnostic procedures for model checking is an essential part of the model in process. In our survival regression analysis assessment of model adequacy we must

- i) test the assumption of proportional hazards
- ii) check influence and poorly fit subjects and
- iii) Overall summary measures of goodness of fit.

Assessment of the proportional hazards assumption

A proportional hazard is one of the very important assumptions in the Cox model. The proportional hazards assumption, which asserts that the hazard ratios are constant overtime, is vital to the interpretation and use of a fitted proportional hazards model. That means, the risk of failure must be the same no matter how long subjects have been followed. In order to test this assumption, graphical diagnoses of scaled Schoenfeld residuals and likelihood based tests, like Wald test can be employed to assess the proportional hazard assumption to covariates that are significant in the multivariate analysis. Under the assumption of proportionality of the proportional hazards model, the distribution of residuals over time is random and LOWESS smoothing line should be a straight line around zero.

One of the statistical tests for proportional hazards assumption is to generate time varying covariates by creating interactions of the predictors and a function of survival times, usually covariate time's log of time, and including these in the model. If any of the time dependent covariates are significant then those predictors do not show a proportional effect over the study period. That is the proportional hazard assumption fails to hold.

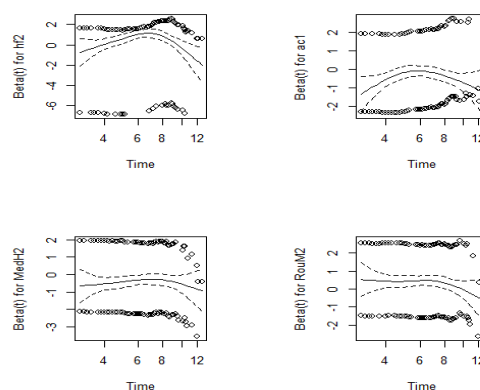
Table 3.8: R Result of the Assumption of Proportionality Test

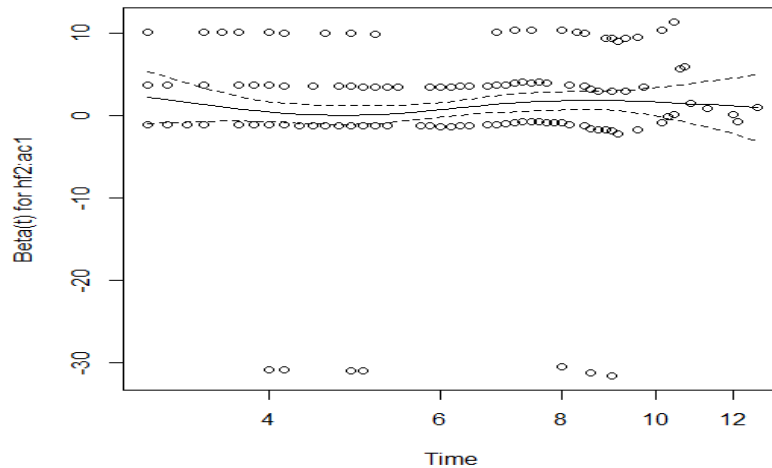
Analysis of Maximum Likelihood Estimates						
Covariate	DF	Parameter Estimate	Standard Error	wald	Pr ChiSq	Hazard Ratio
Hfacility	1	0.0279	0.1417	0.323	0.57	1.782
age	1	0.00926	0.1009	0.0352	0.851	1.427
Mhistory	1	0.0173	0.09933	0.124	0.725	1.488
Rmedication	1	-0.0586	0.09889	1.43	0.231	1.459
healthage	1	0.05843	0.3325	2.181	0.536	2.6781
Hfacilityt	1	-0.0104	0.07082	0.1440	0.986	1.105
aget	1	-0.1026	0.06517	4.286	0.2322	1.063
Mhistoryt	1	-0.0287	0.05899	0.4169	0.937	1.003
Rmedicationt	1	-0.0152	0.05959	0.2294	0.973	1.147
healthaget	1	0.01523	0.1784	0.85852	0.997	1.065

Table 3.8 shows the Wald chi-square value and corresponding p-values for each covariate. The result shows that, the p-value of the Wald test is greater than 0.05 for all covariates, implying that the proportionality assumption is satisfied. On the other hand, there are no covariates which show a trend/pattern with the time, which indicates the hazard ratios, will be constant over the study time.

Furthermore, plotting the scaled Schoenfeld residuals of each covariate against log time will be used to check whether the assumption of proportional hazards is violated or not.

Fig. 3.8 Graphical Assessment of the Proportional Hazard Assumptions





The graphical display shows plots of the scaled Schoenfeld residuals against the survival time for each covariate namely types of Health facility, Age, Medical complication history on admission, Intake of routine medication and the interaction of health facility and age of OTP patients show randomness. Moreover, the smoothed curve is an approximate horizontal line; so this also suggests that the above five covariates satisfied the assumption of proportional hazards.

Checking influential and poorly fit observation

The next step we follow in evaluation of regression diagnostic is to determine whether any particular observation, if any, has an undue impact (leverage) on inferences made on the basis of model fitted to an observed set of survival data. It is therefore of particular interest to examine the influence of each particular observation on these estimates. This is done by examining the extent to which the estimated parameters and the maximized likelihood in the fitted model are affected by omitting in turn the data record for each individual in the study. Thus, the DFBETA statistics is used to examine the untoward effect of each observation on the j^{th} parameter estimate and the maximized log partial likelihood, respectively in the fitted Cox regression model.

The largest difference for medical complication history on admission occurs for observation 504. The change in the parameter estimate on omitting the data for this observation is 0.01477070. Therefore, omission of this observation increases the hazard of recovery rate relative to the baseline hazard. The standard error of the parameter estimate for medical complication history on admission in the full data set is 0.1206, and so the maximum amount by which this estimate changed when one observation is deleted is about 12.2% of the standard error (less than one standard error). Thus, the change in medical complication history on admission effect by deleting this observation can be considered as insignificant. The largest difference for health facility and age of child occurs for observations both are 88. The change in the parameter estimate on omitting the data for each observations are 0.009972643 (5.9% of the standard error) and 0.02266566 (7.1% of the standard error) respectively. Both of them are within one standard error of the estimates. The effect of deleting these observations is increasing the relative hazard of recovery rate relative to the baseline hazard.

Omitting the data from observation 22 from the data set brought the largest changes in the parameter estimates for the variable routine medication at admission. The maximum change in the parameter estimates when this observation is omitted in turn is 0.01880559 (1.5% of the standard error) within one standard error of the estimates. The effect of deleting these observations is decreasing the relative hazard of recovery rates, but again these decreases are not great i.e., the change can be considered as insignificant. The differences in the parameter estimates for the levels of the categorical variables were assessed. Thus, at this point we can conclude that neither the estimates for each of the parameters nor the set of parameter estimates are affected by any of the observations in the data set.

Overall Goodness of Fit

We use R^2 as a measure of overall goodness of model fit. As it is defined in equation (13), it will be

$$R_p^2 = 1 - \exp\left(\frac{2}{602}(-2254.097 - (-2212.741))\right) = 0.12837$$

The model displayed in table 3.7 has passed all the tests for a good fitted model.

3.5 Interpretation and discussion of the results

The interpretation of the result from the fitted final model is based on the hazard ratios. The coefficient of the categorical covariates is interpreted as the logarithm of the ratio of the hazard of recovery rate to the

baseline (reference group) hazard. That is, they are interpreted by comparing the reference group with others. Thus, the interpretation of those variables that were significant in the final proportional hazards model of OTP patients is as follows.

The estimated hazard ratio of age of child which determined recovery rate of OTP children older than two years had 0.3739 times higher probability of getting recovered from SAM as compared children aged less than or equal two years (HR = 0.7908, 95% CI = 0.6435, 0.9720). The estimated hazard ratio of children admitted at health centers had 1.6360 times higher probability of getting recovered from SAM as compared to children admitted at health centers (HR = 1.6360, 95% CI = 1.2346, 2.1680). Likewise, recovery rate for OTP patients who's Multivariate Cox-regression pointed out that having medical complications at admission or during intervention and not taking the routine drugs had negative effect to the recovery rate.

Types of health facility and age of child are present in the model, with both main effects and their interaction. Since type of health facility is at two levels, we present hazard ratios for age of child at each type of health facility rather than for age of child at each age. The estimated log hazard as a function of the variables age of child, types of health facility and healthage (interaction effect of types of health facility and age) holding the other variables fixed is given as:

$$\text{Log } \hat{H}(\text{age, types of health facility, } z) = (\hat{\beta}_1 \text{ types of health facility} + \hat{\beta}_2 \text{ age} + \hat{\beta}_3 \text{ types of health facility} \times \text{age} + \hat{\beta}_4 z)$$

$$\hat{H}_R(\text{age, types of health facility} = 0) = \exp(0.4923 - 0.2347) = 1.778$$

$$\hat{H}_R(\text{age, types of health facility} = 1) = \exp(0.4823.234 + 0.8510) = 2.097$$

The interpretation is that age of child at health center increases the rate of recovery by 77.8% where as age of child at health post increases the rate of recovery by 9.7% this shows that recovery rate due to types of health facility is highly dependent on age of child.

In this retrospective follow up study the overall time to recovery from SAM using OTP and survival experience between different groups was assessed. The association between recovery rate from the OTP and independent predictors was also presented.

Overall the median recovery time was 7.14 weeks (50 days). It was outside of the acceptable minimum international standard [25] but it is well within the standard of the Ethiopian protocol for management of SAM which allows children to stay under treatment up to 8 weeks [25, 19]. This length of stay is slightly lower than other similar studies of OTP outcomes evaluation conducted in Bedawacho [8], Tigray [4], and Jimma [3]. However, it was also significantly higher than the study done in Southern Ethiopia where the length of stay was 21-25 days [21]. The possible explanation for this high estimated length of stay could be 174 (33.3%) children were allowed to stay 8-19 weeks more, under the intervention for better recovery. According to the Ethiopian OTP treatment guideline [6] these children should have been in-patients. That is, these children should have been referred to hospitals or other health facility which have SC service for inpatient treatment under TFU at their 8th week of stay under the OTP when they failed to reach any of the discharge criteria [14, 15]. But these 174 children stayed in the programs to recover from SAM.

The recovery rate was 68.8% which was lower than the international standard in which the minimum recovery rate was set at 75% [25] and it was slightly lower than the 2007 EFY annual OTP performance report of Sidama zone which was 69.4% [20]. This finding was also lower than findings from studies in Southern Ethiopia which shows 87% recovery rate [21], Bedawacho-Ethiopia which shows 85% recovery rate [8] and Southern Malawi which shows 89% recovery rate [15]; and, in all the three studies the defaulter rate was less than 10%. But it was higher than the study done in Tigray 61.78% recovery rate and Kenya 53.3% recovery rate [25, 10]; the defaulter rate in both of these studies was 13.85 and 40.6 respectively. This low recovery rate may be explained by high defaulter (22.7%) and unknown cases rate (6.2%).

In this study, it was found that children treated at health centers had 49% better recovery rate than children treated at health posts. This finding was different from studies done in Ethiopia [25] and Malawi [17]. According to the study done in Tigray [25] the recovery rates were similar for health centers and health posts. Also, according to the study from Malawi [17], there were no differences in recovery rate whether a severely malnourished child cared by medical professionals or a community health aid. Presence of better qualified health professionals at health centers than health posts might be the possible explanation for these findings.

Age of the child was the other important variable which determined recovery rate of OTP. Children older than two years had 0.733 times higher probability of getting recovered from SAM as compared to children aged less than or equal to two years. This finding was consistent with the study done in southern region of Ethiopia [21] which states that with increasing age, the death rate decreased and cure rate increased. But this finding has ill explained difference from the study done in Tigray [25].

IV. Conclusions and Recommendations

This study shows 68.8% of the patients were still alive at the end of fourteen weeks of OTP treatment. The Cox Proportional Hazards regression analysis was done to identify the effects of Health facility, Sex, Age,

Distance (time of travel) in hour, Referred by, Place of residence, Routine medication, Medical complication, Appetite test, Weight gain, Admission status and Diagnosis at admission of OTP patients on survival/cured probability of OTP patients.

This paper suggests that Health facility, Age of child, Medical complication, Routine medication and interaction of health facility and age of child have statistically significant effects on the survival longevity of OTP patients. On the other hand Sex, Referred by, Place of residence and Admission status have no impact on the survival experience of OTP patients. The result of this study also indicated that survival/cured status of OTP patients does not show differences based on Referred by, Place of residence, Weight gain, Appetite test, Diagnosis at admission and Admission status levels. However, it depends on different groups of Sex, Distance (time of travel) and Referred by. Similarly, patients with health center, older age, with routine medication and without medical problems are more likely to survive. The study also showed that the highest recovery rate was associated with age of child in greater than two years patients.

Based on the results of the study different factors are identified for the recovery rate of OTP Patients. Therefore, one can recommend recovery rate of OTP program should be monitored regularly, Decentralization of OTP program service from health centers to health posts should be carried out with great caution, and Special focus should be given to young children during outpatient therapeutic feeding program and Health care providers strongly advised to comply with OTP treatment protocols.

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