ORIGINAL RESEARCH ARTICLE

OPEN ACCESS

SURVIVAL OF MEDICALLY TREATED BETA THALASSAEMIA PATIENTS IN SRI LANKA (2000 – 2017)

*Anulawathie Menike, H.R. and Wijesinghe, P.C.

Department of Economics, University of Kelaniya, Sri Lanka

ABSTRACT

Beta thalassaemia is what is called an inherited disease due to abnormal hemoglobin production. It's not an infectious disease. Near to 3,500 patients with beta thalassaemia lives in Sri Lanka. The survival measures and factors that affect to survival thalassaemia patients in Sri Lanka is unclear. Therefore, this study was mainly performed to determine the statistical analyze on survival of the beta thalassaemia patients in Sri Lanka. Relevant data were collected from Hemals thalassaemia care unit in Ragama hospital during the time period between 2000 and 2017. To succeed the objectives new births, death rates, survival rates were measured. Analyzed data showed new affected births were decreasing after starting national prevention program in 2007. No significant difference occurred in survival time by gender. When considering the diagnosis types beta thalassaemia major patients had the least survival time compared to others. By considering these results it could be concluding that the survival of beta thalassaemia patients in Sri Lanka is still need of great attention.

INTRODUCTION

The research is basically focusing on the statistical analysis of survival of beta thalassaemia patients in Sri Lanka. When concentrating on thalassaemia, it was identified as the most common monogenetic disorder worldwide (Li, 2016). Thalassemia refers to an inherited disease due to abnormal hemoglobin production and not an infectious disease. As this disease is spread eagled around the world a large number of patients born and treating exclusively in prevalence areas. It believes that there is a protective effect against malaria in patients with thalassaemia (Weatherall and Clegg, 2001). Therefore more patients could be seen scattered to the regions that carry (or carried) malaria infection. Two major sub types of thalassaemia can identify as alpha thalassaemia and beta thalassaemia. This study is focus on beta thalassaemia patients in Sri Lanka. Sri Lanka is identified as an intermediate prevalence of beta thalassaemia. When considering about the survival of beta thalassaemia patients, the most important and influence factors are births, deaths and life time.

*Corresponding author: **Anulawathie Menike, H.R.**
Department of Economics, University of Kelaniya, Sri Lanka.

Without considering these facts it could not interpret an efficient analyze for survival. New affected births on beta thalassaemia play a major role by giving directions to reduce the future burdens on economic and social by thalassaemia. The impact on survival by deaths helps to identify the richness of health for beta thalassaemic patients in specific regions. By weighting the death rates it is easy to understand the complications arise with patients and for early identifying threats. Generally it takes large expense to manage those patients under standard treatments (Samarkoon and Wijesuriya, 2011). Life time of the patients realize whether these expenses are effective. There is no doubt that the survival of the patients has increased than the past. But it should prove statistically. As mention above, Sri Lanka is identified as an intermediate prevalence of thalassaemia. Though distribution of thalassaemia within country was unequal, some provinces specially North Western and Western province have identified as most prevalence areas (Samarakoon and Wijesuriya, 2011). The national prevention program was started in 2007 and apart for that concept of safe marriage has been introduced in recent past. These prevention strategies are helping to make changes in new births of beta thalassaemia. Although the medical specialists do their best to

protect the life of beta thalassaemia patients, sometimes unavoidable causes may happen. Arising complications due to medications or careless affection of patients will cause to decrease the life expectancy of beta thalassaemic patients. To avoid these failures, it's important to identify these complications before destruct patients' life. Therefore, it is essential to be aware and estimate these survival factors up to date. This research is basically focusing on analyzing and studying the factors which will be effects on survival of medically treated beta thalassaemia patients in Sri Lanka. By analyzing these factors it is able to pay special attention to the areas which has to adjust or further develop in order to enhance the survival rates of the beta thalassaemia patients. There are much statistical identification that have to explore in the field of beta thalassaemia. As a genesis to it, the current study tries to trot out some statistical measurements for above discussed survival factors.

MATERIALS AND METHODS

This cohort study was based only on secondary data. Patients with beta thalassaemia who had been treated from Hemals adolescent and adult thalassaemia care center in Ragama hospital were inclusion in the study group. As this hospital is adolescent and adult care unit, no patients under age 12 are treating. As a result of that new born affected babies were not registering to this unit. Therefore in order to identify the birth trends of beta thalassaemia patients' data could not be gained from the hospital. Because of that, gathering data on new births done by using a publication of Sri Lanka medical association in 2017 and it represented birth data on island wide. Deaths and survival analysis done by collecting patients' medical records in the hospital. For birth analysis only beta thalassaemia major patients were used. Deaths and survival analysis done to every diagnosis type of beta thalassaemia patients. The time period for the study was from 2000 to November 2017. As this thalassaemia caring unit was established in 2006, data on deaths and survival starts from 2006. All statistical analysis were carried out in IBM SPSS Statistics version 22 and Microsoft Excel. Prevalence of birth rate and cause specific death rate was calculated by using the demographical equations. The survival function was calculated by using the Kaplan-Meier method. The graphical representation of the life tables were obtained by Log Rank Method and they were compared.

Research objectives

- The main objective of the study is to determine the statistical analyze on survival of the beta thalassaemia patients in Sri Lanka. To succeed the objective new births, death rates, survival rates will be measure.
- To identify the difference of new births between pre and post preventing programs

Literature Review

New births in beta thalassaemia will critically affect to the survival of thalassaemia patients as it has social and economic problems to manage those patients. The best way to avoid new affected births is prevention. The prevalence areas should identify the need of prevention strategies to avoid new affected births. Majeed *et al.* (2013) for instance found that to reduce thalassaemia births, screening for thalassaemia traits in

relatives of thalassaemia affected patients was essential. From their view this will help to reduce the burden of transfusion and burden of treatment on economy. A study done in Iran by Miri, *et al.* (2013) have proved that thalassaemia prevention programs have played an effective role for reducing thalassaemia births in their country. Screening carrier couples and prenatal diagnosis were the main elements of their prevention program. A common reason to vary the survival rate of thalassaemia patients is death rate. Many researches done in different countries explored survival rate by calculating death records of beta thalassaemia patients. For instance, a cohort study done in Hamadan province located in west of Iran by Zamani, Khazaei, Rezaeian (2015) explored the survival rates and associated factors using death records. They found that no significant difference occurred in survival years between genders, blood groups, ferritin levels and haemoglobin level. Blood transfusions can mention as the most important medication for beta thalassaemia patients. The efficiency of this medication directly affects on patients survival time. For instance the survival rate can depend on the kinds of transfusion i.e. washed blood or filtrated blood (Roudbari, *et al.* 2008). It's clear that complications have become threat to the patients' survival time. Therefore, patients should take necessary curatives against these threats. For this, iron chelation therapy and bone marrow transplantation is the most common method used by the patients. According to these reviews measuring survival of beta thalassaemia patients are varying among countries. Though Sri Lanka is identified as an intermediate prevalence of thalassaemia there was no any researches found on the survival measures. Therefore this research tries to fill this gap by considering birth and death trends and life time of beta thalassaemia patients in Sri Lanka from 2006 to 2017.

RESULTS

Births of beta thalassaemia patients

Prevalence of birth rate (PBR) is an essential calculation for survival measurement. It expresses the number of existing cases of disease at a point in time divided by the total number of live births. Formula for calculating PBR is as follows.

$$\text{Prevalence of birth Rate} = \frac{\text{Annual affected births}}{\text{Annual live births}} \times 10{,}000$$

By using above formula the calculated prevalence of birth rates could be presented as follows. Referring the below calculated data, it demonstrated that fluctuated prevalence of birth rates occurred between 2000 and 2011. By studying the graph below this could be identified clearly. This graph is a representation of prevalence of birth rates with annual live births. In the year 2000 the birth prevalence of per 10,000 live births was 1.15. It has been gradually increased till 2003, but the rate of increasing has decreased. A great fall could be seen in year 2004. In the years of 2003 and 2005, the number of live births does not vary much. By comparing these two years it founds that there occurs a 0.297 decline of PBR in 2005. Though increased the PBR in 2006, this increase rate was less than the rate decreased in 2007. 2007 was the year when the national prevention program introduced to Sri Lankans. After introducing the prevention program, PBR has increased in 2008.

Table 1. Prevalence of birth rates of beta thalassaemia major patients (2000- 2016)

Year	PBR
2000	1.150
2001	1.255
2002	1.523
2003	1.619
2004	1.097
2005	1.322
2006	1.579
2007	1.216
2008	1.472
2009	1.032
2010	1.481
2011	1.816
2012	1.377
2013	1.285
2014	1.115
2015	0.478
2016	0.117

Source: Premawardhana et al. (2017)
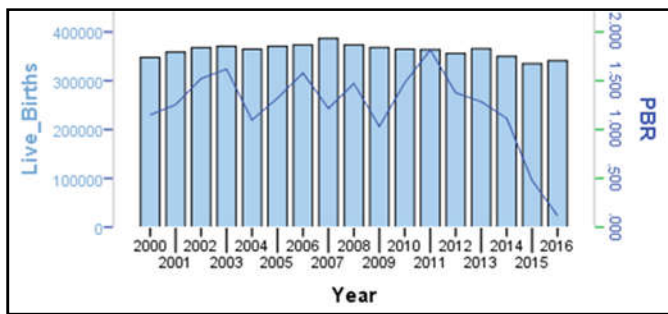
Source: Premawardhana et al. (2017)

Graph 1. Annual birth and prevalence of births of beta thalassaemia major patients (2000- 2016)

But when considering the years 2006 and 2008, even the annual live births were somewhat similar PBR value for 2008 (1.472) was less than the value in 2006 (1.579). Again in 2009 to 2010 it showed an increase of PBR, but the increasing rate was decreasing. Even there wasn't any significant difference of live births in 2011, PBR has reached to the peak level. This signs to think that there were more marriages between beta thalassaemia carrier couples. Luckily there was a gradual decline after 2011 to 2014. The rate of declining has been increased in the years of 2015 and 2016. By referring to these calculations it can get an idea about the effectiveness of prevention program.

Deaths of beta thalassaemia patients

As the table depicts more deaths were occured among female patients and it represent 65% from the total deaths. Similarly, patients who are suffering from beta thalassaemia major represent 60% of the births. Generally these patients received regular transfusions in every 3-4 weeks and advised to maintain haemoglobin level with an average number of 9.0 g/dl. Percentages for E beta thalassaemia and beta thalassaemia intermedia were 19% and 8% respectively. Though these patients do not need regular transfusions, other clinical managements were carried properly. In "other" category it includes some rare and uncommon diseases diagnosed in beta thalassaemia. It represented 13% from the total deaths. Mean ages of the patients were calculated compared as follows. As these deaths were occurred due to a special cause, measuring crude death rate will inadequately. A measurement called, "cause specific death rate" (CSDR) has

been decided for these situations. CSDR is the mortality rate from a specified cause for a population. It can calculate by using below equation.

$$CSDR = \frac{Deaths\ from\ a\ disease}{Mid\text{-}year\ population} \times 100,000$$

Calculated cause specific death rates can be present as follows. By representing these values in a line chart it's easy to interpret how the rates were changed by time.

**Table 2. Death patients by gender and diagnosis type (2008- 2017)**

Gender	Diagnosis type				Total
	Major	E beta	Intermedia	Other	
Male	9	2	1	1	13
Female	13	5	2	4	24
Total	22	7	3	5	37

Source: Hemals thalassaemia care center (2017)

Table 3. CSDR on beta thalassaemia patients (2008- 2017)

Year	CSDR
2008	0.015
2009	0.020
2010	0.053
2011	0.010
2012	0.015
2013	0.010
2014	0.000
2015	0.019
2016	0.014
2017	0.023

Source: Hemals thalassaemia care center (2017)
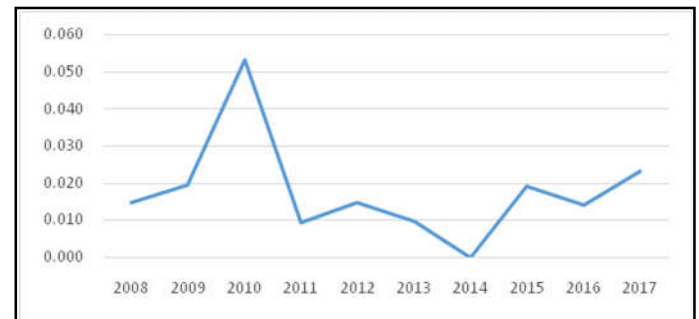
Source: Hemals thalassaemia care center (2017)

Graph 2. CSDR on beta thalassaemia patients (2008- 2017)

As the above table and graph depict the CSDR for beta thalassaemia patients has been varied very much through the period of time. No deaths were recorded from the beginning of the unit in 2006 to 2007. 3 deaths were happened in 2008 and therefore first calculated CSDR per 100,000 populations was 0.015. This rate was slowly increased (by o.oo5) in 2009. A rapid increase could see in 2010 and it was rapidly decreased in 2011. It is worth to find out the reason for this great accretion as such a variation had never happened again. As the medical officers said this caring unit is treating for adult and adolescent patients who are above 15 years old. As they newly registered in the unit their iron levels seems very high. It's a great risk to maintain the patients in a good condition. Therefore they may be easily affected by various infections such as spreading germs. As the immensely support and supervision given by the medical officers and nursing staff deaths could be reduced in 2011. From the year 2012 this

caring unit was moved to Kiribathgoda city with higher facilities and improved medication system for the patients. This was resulted to reduce mortality rate from 0.015 in 2012 to 0 in 2014. Again from the year 2015 few fluctuations have occurred. Iron overloads were the main cause for that. However, the increasing rate has been decreased in 2017 compared to the previous periods.

Survival of patients by gender

To identify the difference of survival time (age) between males and females, log rank test was used. Age was taken as the survival time variable. The developed hypothesis was represented below

- H_0: There is no significant difference between the survival times of females and males
- H_1: There is a significant difference between the survival times of females and males

The first and the best place to identify whether there is a difference in survival time, is the plot of the cumulative survival function. These survival curves are a visual representation of the life tables. It has presented as follows.
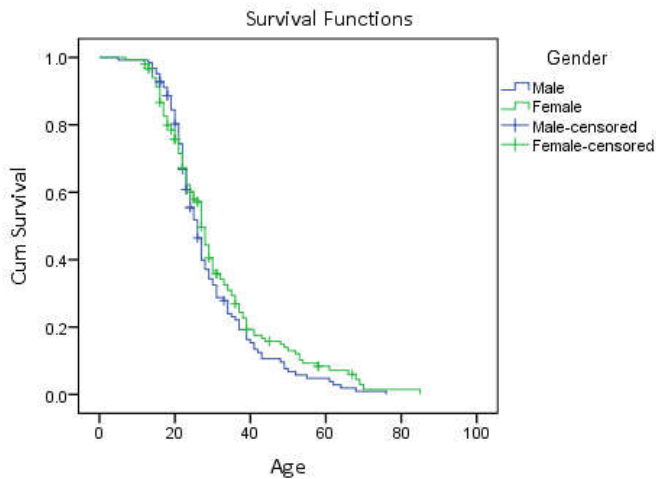
Source: Hemals thalassaemia care center (2017)

Graph 3. Survival function by gender

This plot help to understand the survival distribution compares between males and females. As the two curves are similarly shaped, it is saying that there is no significant difference in survival time by gender. When the age between 0-20 there is a quite high probability of survival in males than females. When growing older this probability becomes higher for females than males. Following table represent the estimated survival time for patients.

Table 4. Summary statistic for survival by gender

Gender	Mean			Median
	Estimate	Lower Bound	Upper Bound	
Male	29.3	26.96	31.56	26
Female	31.3	28.64	34.05	27
Overall	30.4	28.75	32.15	27

Source: Hemals thalassaemia care center (2017)

As the table depicts estimated mean time until death for all the beta thalassaemia patients in the unit was 30.4 years. Under the 95% confidential level, it could vary between 28.75 years and 32.15. Mean survival time for females is higher than males.

Also, the median time is 27 years for females compared to 26 years for males.

Table 5. The log rank test

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.574	1	.210

Test of equality of survival distributions for the different levels of Gender.

By using this test it has tested the above null hypothesis against to the alternative hypothesis. Calculated chi- square was 1.574 and p value was 0.210. In order to determine a significant difference occurred in survival times by gender the p value should be less than 0.05 (p<0.05). According to the above calculations it demonstrates the p value is higher than 0.05. Therefore, we could accept the null hypothesis.

Survival of patients by diagnosis type

The above survival time has been calculated by gender. Similarly, a difference could appear in the diagnosis type. Therefore another log rank test has run to test the null hypothesis that there is no difference in the overall survival distribution between diagnosis types.

- H_0: There is no significant difference between the survival times of diagnosis types
- H_1: There is a significant difference between the survival times of diagnosis types

Following graph depicts the survival functions for each diagnosis type.
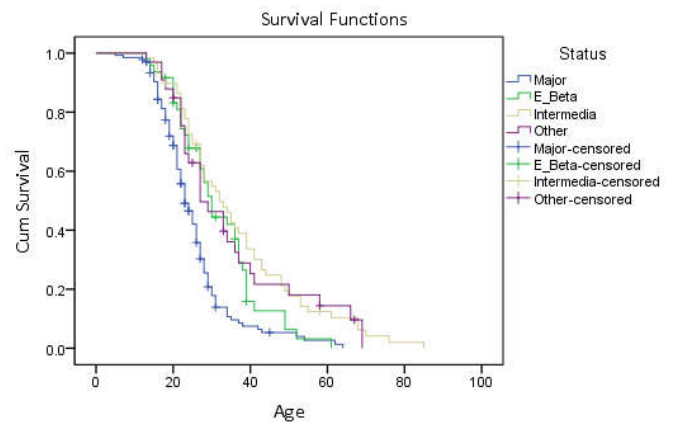
Source: Hemals thalassaemia care center (2017)

Graph 4. Survival functions by diagnosis type

Table 6. Summary statistic for patients by diagnosis type

Diagnosis Type	Mean			Median
	Estimate	Lower Bound	Upper Bound	
Major	25.3	23.5	27.2	23
E beta	31.7	28.4	35.1	30
Intermedia	36.7	32.3	41.1	32
Other	34.8	28.7	40.8	27
Overall	30.4	28.6	32.1	27

Source: Hemals thalassaemia care center (2017)

As the above graph shows it's clear that beta thalassaemia major patients have lower survival time than the other patients. At the beginning of the life, there is no difference among beta

thalassaemia patients. As they grow up survival time for beta thalassaemia major patients starts to fall. Beta thalassaemia intermedia patients have the highest survival age. By referring to the below table this difference can identify clearly. As this table represent estimated mean time is low for beta thalassaemia major patients.

Table 7. The log rank test

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	35.188	3	.000

Test of equality of survival distributions for the different levels of Status.
Source: Hemals thalassaemia care center (2017)

The highest survival time has gained by beta thalassaemia intermedia patients. When consider about the estimated overall mean survival time all the diagnosis types except beta thalassaemia major has exceeded the value. To confirm that there is a difference in survival time by diagnosis types calculated chi square value has given below. As the calculated p value is 0.000, it is less than 0.05 value. This rejected the null hypothesis which indicates an equal survival distribution occurs among every type of beta thalassaemia patients.

Conclusion

The number of annual births of beta thalassaemia major during the time period ranging from 2000 to 2007 when the national prevention program was established to run, shows a declining trend. But this falling the trend was quite slow. The overall prevalence of birth rate for beta thalassaemia major patients after introducing the national prevention program in 2007 was 1.13. This rate was lower than the average beta thalassaemia gene prevalence (1.5%) in the world. Therefore, it can conclude that the new births of beta thalassaemia patients are reducing slowly with the help of national prevention program. But it cannot say the prevention program was 100% successful as there were increases of births in some years. According to the death analysis some age related complications now occur less frequently with younger patients of beta thalassaemia. Compared to beta thalassaemia intermedia and E beta thalassaemia, beta thalassaemia major patients are liable to be death in their early adulthood.

When compared to beta thalassaemia major female patients, males are more protective. Survival measurements have proved that both female and male beta thalassaemia major patients have similar survival time. But there is a difference in survival time by the beta thalassaemia diagnosis type. For beta thalassaemia major patients survival ages are lower than others.

REFERENCE

Majeed, T., Akhter, M. A., Nayyar, U., Riaz, M. S. and Mannan, J. 2013. Frequency of beta-thalassaemia trait in families of thalassaemia major patients, Lahore. *J Ayub Med* Coll *Abbottabad*, *25*(3–4), 58–60.

Miri, M. M., Tabrizi, N. M., Hadipour, D. F., Sadeghian, V. F., Ahmadvand, A., Yousefi, D. S. and Manshadi, M. 2013. Thalassaemia in Iran in Last Twenty Years : the Carrier Rates and the Births Trend. *Iranian Journal of Blood and Cancer*, *6*(1), 11–18.

Premawardhana, A., Mudiyanse, R., Jifri, M., Nelumdeniya, U., Silva, D., Nizri, A., et al. (2017). An island wide hospital based epidemiological survey of haemoglobinopathies and an assessment of standards of care in 23 centres. Retrieved from http://repository.kln.ac.lk/handle/123456789/17845

Roudbari, M., Soltani, R. M. and Roudbari, S. 2008. The survival analysis of beta thalassaemia major patients in South East of Iran. *Saudi Medical Journal*, *29*(7), 1031–1035.

Samarakoon, P. S. and Wijesuriya, A. P. 2011. A clinical audit of thalassaemia management at the Lady Ridgeway Hospital for Children, Colombo. *SriLanka Journalof Child Health*, *40*(2), 48–53. http://doi.org/10.4038/sljch.v40i2.3090

Weatherall, D. and Clegg, J. 2001. *The thalassaemia syndroms.* Blackwell science Ltd.

Zamani, R., Khazaei, S. and Rezaeian, S. 2015. Survival analysis and its associated factors of beta thalassaemia major in Hamadan province. *Iranian Journal of Medical Sciences*, *40*(3), 233–239.

****