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# SURVIVAL ANALYSIS OF PEDIATRIC CANCER PATIENTS IN SRI LANKA: GRAPHICAL APPROACH

**H.A.H.C Munasinghe**

Lecturer, School of Computing, NSBM Green University, Sri Lanka

## ABSTRACT

Globally several studies have assessed the survival of cancer patients including cancers in pediatric age group. However there are limited publications on survival of cancer patients in developing countries. So far, no study was conducted in Sri Lanka to assess the survival status of cancers in pediatric age group. The objective of this study was to estimate the survival time for a group of cancer patients and to compare survival time between two or more groups. Another objective of this study was to assess the relationship between explanatory variables and survival time of cancer patients.

In this research a descriptive study on cancer patients of pediatric age group was conducted to determine some of the prognostic factors. A survival analysis was conducted to determine how do particular circumstances or characteristics influence on the survival of cancer patients in pediatric age group in Sri Lanka. In the analysis socio demographic factors and other relevant details of the cancer patients were extracted from the records of the statistical unit of National Cancer Institute Maharagama. All the nonmalignant patients were removed from the sample. This resulted a sub sample of 424 patients. The data were analyzed by routine statistical methods and appropriate survival analysis techniques. First to estimate time to death for pediatric cancer patients, survival curve was fitted using Kaplan Meier method for the whole sample. Then to compare time to death between two or more groups, Kaplan Meier survival curves were fitted for treatment setting, ethnicity, gender, cancer types, female age groups and male age groups.

It is found that Lymphoid Leukemia is the most common cancer type among males as well as females. According to the sample more than 50% of the patients have at least survived for 5 years while 21.46% of patients have died before five years. The estimated probability that a patient will survive for 1074 days or more is 0.785. In general survival probability of the

patients who are in wards are lower than for the patients who are coming for clinics. This may be because the patients who are in wards present with more severe disease and more comorbidities. Survival probabilities of the patients who have other Leukemia's of specified cell types, Leukemia's of unspecified cell types and Lymphoid Leukemia are lower than other cancer types. Patients who have cancers in other connective soft tissue subcutaneous have the longest survival time.

Survival time of cancer patients is associated with different factors such as gender, ethnicity, age, cancer type and treatment setting. Lymphoid Leukemia, brain cancers, unknown cancers and Myeloid Leukemia are the common cancer types in the pediatric age group in Sri Lanka. Among them dominating cancer type is Lymphoid Leukemia with a percentage of 35.14%. There is a male predominance in the sample comprising of 58.01%. Survival analysis suggests that there is a good probability for a cancer patient to survive more than 1074 days rather than dying with cancer.

**Key words:** Cancer, Pediatric age group, Survival

## 1. INTRODUCTION

Although cancer in children is rare, it is the leading cause of death by disease past infancy among children. In United States, it is estimated that 15,780 children and adolescents ages 0 to 19 years will be diagnosed with cancer and 1,960 will die of the disease in the year 2014 [1].

Leukemia, brain and central nervous system tumors, lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms tumor, bone cancer, and gonadal (testicular and ovarian) germ cell tumors are the most common types of cancer diagnosed in children and adolescents . As of January 1, 2010, there were approximately 380,000 survivors of childhood and adolescent cancer (diagnosed at ages 0 to 19 years) alive in the United States [13]. The number of survivors will continue to increase, given that the incidence of childhood cancer has been rising slightly in recent decades and that survival rates overall are improving.

When considering the Sri Lankan context, in the last decade, childhood mortality from infections and congenital diseases has been so greatly reduced that cancers, albeit rare, are the second principal cause of death. Only accidents cause more deaths in children less than 12 years of age in Sri Lanka. Childhood cancers make up 2% of all cancers in Sri Lanka [8].

According to the cancer register published in 2005 by the Ministry Of Health the number of children affected were as follows: males between the age group of 1-14 was 187, Females - 179 patients. Out of those 50 percent of them were leukemic patients. Other patients had cancers in brain, bone, ovary, testis, thyroid and muscle. The number of cases are rising due to several reasons. The availability of modern medical diagnostic facilities in most of the major hospitals and the easy access to the medical facilities, plus availability of specialist doctors in this field in rural hospitals. Hence the number of cases reported are more. Another important reason is that parents are more aware about the diseases compared to a few decades ago.

And also there are some other factors that have contributed to this rise in pediatric cancer. Familial cancers due to genetic mutations, over exposure to environment factors like heavy metal containing chemicals and inadvertent use of pesticide and other toxic chemicals for agriculture could also have led to cancers of brain and leukemia.

The overall outlook for children with cancer has improved greatly over the last half-century. In 1975, just over 50 percent of children diagnosed with cancer before age 20 years survived at least 5 years [3]. In 2004-2010, more than 80 percent of children diagnosed with cancer before age 20 years survived at least 5 years [6].

All kinds of cancer, including childhood cancer, have a common disease process — cells grow out of control, develop abnormal sizes and shapes, ignore their typical boundaries inside the body, destroy their neighbor cells, and ultimately can spread ( metastasize) to other organs and tissues. As cancer cells grow, they demand more and more of the body's nutrition. Cancer takes a child's strength, destroys organs and bones, and weakens the body's defenses against other illnesses. The sites of cancer are different for each type, as are treatment and cure rates.

The main objective of this study was to conduct a survival analysis of cancers in pediatric group in Sri Lanka. The other objectives were to estimate time to event for a group of individuals and to assess the relationship between explanatory variables and time to event. Assessment of the survival of cancer patients in pediatric age groups is very important to provide a quality care for survival cancer patients. Further, having knowledge on some prognostic factors is very important in future planning for improving the survival of these

patients. So far, no study was conducted in Sri Lanka in this regard. This study is planned to fulfill this emerging need.

## 2.MATERIALS AND METHODS

A descriptive study of cancer patients in pediatric age group was conducted to determine some of the prognostic factors. A survival analysis was conducted to determine how do particular circumstances or characteristics increase or decrease the probability of survival of cancer patients in pediatric age group in Sri Lanka. Information of the cancer patients in pediatric age group diagnosed in 2009 was obtained from the National Cancer Institute Maharagama (NCIM), with the permission of the director NCIM.

### 2.1 Study setting

National Cancer Institute Maharagama (NCIM)

The National Cancer Institute is a teaching hospital, managed under supervision of the Ministry of Health Sri Lanka. It is the premium hospital where cancer patients from all over the island are admitted. It is dedicated to diagnose, treat and follow up cancer patients in Sri Lanka. The wards in the institute are allocated according to gender, age and cancer type of the patients. As a result, the information for the study was obtained from a study population, which covers a majority of the whole island.

In general, there are about 125000 outdoor patients and 43000 indoor patients per year receiving treatment. Among them nearly 5% of the patients have been diagnosed as in pediatric age group. There are 21 wards consist of 750 beds. Under the guidance of director, twenty-six consultants and more than thousand health workers provide their service.

### 2.2 Study Population

All cancer patients of pediatric group in Sri Lanka will consider as the study population.

### 2.3 Sample

A sample of data of the cancer patients of pediatric age group was obtained from the National Cancer Institute Maharagama, with the permission of the director NCIM. Information of all the pediatric patients who diagnosed in 2009 was collected from the medical statistic unit of National Cancer Institute Maharagama (NCIM). Initially details from 455 records at the medical statistic unit was obtained to an Excel sheet. Then the sample was obtained with regard to exclusion criteria.

### 2.4 Inclusion criteria

Malignant patients who received treatment in 2009

### 2.5 Exclusion criteria

Non-malignant patients who came for treatment in 2009

### 2.6 Sample size

431 Malignant patients in pediatric age group, who diagnosed in 2009 was considered as the sample.

### 2.7 Description of the data

Data of the following variables were collected in order to conduct the descriptive and the survival analysis.

**Table 01: Variables and operationalization of variable**

| VARIABLE | OPERATIONALIZED VARIABLE (INDICATOR) | MEASUREMENT |
|---|---|---|
| Sex | Sex of the patient as mentioned in the records of NCIM | "Male" or "Female" |
| Ethnicity | Ethnicity of the patient as mentioned in the records of NCIM | "Sinhala", "Tamil", "Moor" or "Other" |
| District | District which the patient is currently living as mentioned in the records of NCIM | "Colombo", "Gampaha", "Kurunagala", "Rathnapura", "Kalutara", "Kandy", "Ampara", "Ampara", "Anuradapura", "Matara", "Galle","Puttalama", "Badulla", "Batticaloa", "Kegalle", "Vauniya", "NuwaraEliya", "Polonnaruwa", "Hambantota", "Jaffna", "Monaragala" |
| Survival time | Patient's date of admission to the hospital and the date of death was extracted from the records of NCIM. Difference of the date of admission and the date of death was considered as the survival time of the patient after knowing the disease. | Survival time was measured by days. Patients who was alive at the end of the study period was considered as censored.<br><br>Survival time* = Date of admission – Date of death |
| Status | At the end of the study it was recorded whether the patient is alive or dead using the | "Survived", "Died" |

| | | |
|---|---|---|
| | records of NCIM | |
| Treatment setting | Whether the patients are coming for clinics or wards was recorded as mentioned in the records of NCIM | "Ward (Wd)", "Clinical (Cl)" |
| Age | Sex of the patient as mentioned in the records of NCIM | Age was measured by years. |
| Cancer type | Cancer type of the patient according to the diagnosis, was mentioned using the International Classification of Diseases (ICD)**. | "C-07-Parotid Gland", "C-09-Tonsil",<br>"C-11-Nasopharynx",<br>"C-22-Liver and intrahepatic Bile ducts",<br>"C-38-Heart Mediastinum and Pleura",<br>"C-40-Bone and Articular Cartilage of Limbs",<br>"C-41-Bone and Articular Cartilage of Other and Unspecified; sites",<br>"C-43-Melanoma of Skin", "C-44-Skin Other",<br>"C-47-Peripheral Nerves and Autonomic Nervous System",<br>"C-48-Retroperitoneum and Peritoneum",<br>"C-49-OtherConnective soft tissue Subcutaneous",<br>"C-56-Ovary",<br>"C-57-Other and Unspecified female genital Organs",<br>"C-58-Placenta", "C-62-Testis",<br>"C-64-Kidney,except Renal Pelvis",<br>"C-69-Eye and Adnexa", "C-71-Brain",<br>"C-72-Spinal Cord,Cranial Nerves,& Other parts of Nervous System",<br>"C-73-Thyroid Gland", "C-74-Adrenal Gland" ,<br>"C-75-Other Endocrine Glands & Related Structures",<br>"C-80-Without Specification of Sites",<br>"C-81-Hodgkin's Disease",<br>"C-82-Follicular Non-Hodgkin's Lymphoma",<br>"C-83-Diffuse Non-Hodgkin's Lymphoma",<br>"C-84-Peripheral & Cutaneous T-cell Lymphoma",<br>"C-85-Other & Unspecified; type of Non-Hodgkin's Lymphoma",<br>"C-91-Lymphoid Leukemia",<br>"C-92-Myeloid Leukemia",<br>"C-94-Other Leukemia's of Specified Cell Types",<br>"C-95-Leukemia of Unspecified Cell Type",<br>"C-96-Other & Unspecified: Lymphoid, Haematopoietic& Related Tissue",<br>"Unknown" |

Age was taken down and after discussing with doctors, later categorized under the following headings for descriptive analysis and survival analysis.

- Female_Newborn-2years = Female patients; $0 < age \leq 2$
- Female_2years-4years = Female patients; $2 < age \leq 4$
- Female_4years-6years = Female patients; $4 < age \leq 6$
- Female_6years-8years = Female patients; $6 < age \leq 8$
- Female_8years-10years = Female patients; $8 < age \leq 10$
- Female_10years-12years = Female patients; $10 < age \leq 12$
- Female_12years-14years = Female patients; $12 < age \leq 14$
- Female_14years-16years = Female patients; $14 < age \leq 16$
- Male_Newborn-2years = Male patients; $0 < age \leq 2$
- Male_2years-4years = Male patients; $2 < age \leq 4$
- Male_4years-6years = Male patients; $4 < age \leq 6$
- Male_6years-8years = Male patients; $6 < age \leq 8$
- Male_8years-10years = Male patients; $8 < age \leq 10$
- Male_10years-12years = Male patients; $10 < age \leq 12$
- Male_12years-14years = Male patients; $12 < age \leq 14$
- Male_14years-16years = Male patients; $14 < age \leq 16$

Later districts were also categorized according to their provinces.

- Central Province = Kandy, Matale, Nuwara Eliya
- Eastern Province = Ampara, Batticaloa, Trincomalee
- Northern Province = Jaffna, Killinochchi,Mannar, Mullaitivu, Vavuniya
- North Central Province = Anuradhapura, Polonnaruwa
- North Western Province = Kurunegala, Puttalam
- SabaragamuwaProvince = Kegalle, Ratnapura
- Southern Province = Galle, Hambantota, Matara
- Uva Province = Badulla, Monaragala
- Western Province = Colombo, Gampaha, Kalutara

Cancer type were also taken down and with the guidance of the doctors, later categorized under the following headings for survival analysis.

| | |
|---|---|
| Cancer type 01 | "C-40-Bone and Articular Cartilage of Limbs",<br>"C-41-Bone and Articular Cartilage of Other and Unspecified; sites" |
| Cancer type 02 | "C-07-Parotid Gland", |

| | |
|---|---|
| | "C-09-Tonsil",<br>"C-11-Nasopharynx",<br>"C-22-Liver and intrahepatic Bile ducts",<br>"C-38-Heart Mediastinum and Pleura",<br>"C-43-Melanoma of Skin",<br>"C-44-Skin Other",<br>"C-48-Retroperitoneum and Peritoneum",<br>"C-58-Placenta",<br>"C-62-Testis",<br>"C-64-Kidney,except Renal Pelvis" |
| Cancer type 03 | "C-47-Peripheral Nerves and Autonomic Nervous System",<br>"C-72-Spinal Cord,Cranial Nerves,& Other parts of Nervous System" |
| Cancer type 04 | "C-49-OtherConnective soft tissue Subcutaneous" |
| Cancer type 05 | "C-56-Ovary",<br>"C-57-Other and Unspecified female genital Organs" |
| Cancer type 06 | "C-69-Eye and Adnexa", |
| Cancer type 07 | "C-71-Brain" |
| Cancer type 08 | "C-73-Thyroid Gland",<br>"C-74-Adrenal Gland" ,<br>"C-75-Other Endocrine Glands & Related |

| | |
|---|---|
| | Structures” |
| Cancer type 09 | “C-81-Hodgkin's Disease”,<br>“C-83-Diffuse Non-Hodgkin's Lymphoma” |
| Cancer type 10 | “C-82-Follicular Non-Hodgkin's Lymphoma”,<br>“C-84-Peripheral & Cutaneous T-cell Lymphoma”,<br>“C-85-Other & Unspecified; type of Non-Hodgkin's Lymphoma” |
| Cancer type 11 | “C-91-Lymphoid Leukemia” |
| Cancer type 12 | “C-92-Myeloid Leukemia” |
| Cancer type 13 | “C-94-Other Leukemia’s of Specified Cell Types”,<br>“C-95-Leukemia of Unspecified Cell Type” |
| Cancer type 14 | “C-96-Other &Unspecified:Lymphoid, Haematopoietic& Related Tissue” |
| Cancer type 15 | “Unknown” |

Data were entered to Excel and MINITAB and analyzed using MINITAB and R.

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**2.8 Survival analysis**

Survival analysis is known as the analysis of data in the form of times from a well-defined time origin until the occurrence of a subsequent event. Most often in medical research the

recruitment of an individual into an experimental study is considered as the time origin. If the subsequent event is the death of a patient, the resulting data are literally survival times. But in some studies end point is not always fatal. It can be the relief of pain or the recurrence of symptoms. Such cases are known as time to event data. This research is focused on the survival time of pediatric cancer patients from entry to a diagnosis until death.

**2.9 Survival function**

Let T be the time of occurrence for some event (survival time). since T can take any non-negative value, it can be considered as a random variable. Let t be the actual survival time of an individual. Then t can be considered as a value of the variable T. Since T can take different values it has a probability distribution. Furthermore, suppose that T has a probability distribution with underlying probability density function $f(t)$.Then the cumulative density function of T is defined as,

$$F(t) = P(T < t) = \int_0^t f(u)du$$

This represents the probability that survival time is less than some value t. Then the survival function is defined as ,

$$S(t) = P(T \geq t) = 1 - F(t)$$

This represents the probability that survival time is greater than or equal to some value t. Hence the survival function represents the probability that an individual survives from the time origin to sometime beyond t.

**2.10 Kaplan-Meir method for estimating the survivor function**

Kaplan-Meir method is one of the widely used methods to estimate the survivor function. When the data set contains no censored observations KM estimator is very simple. The sample proportion of observations with event time is greater than $t$, is considered as the KM estimator when there is no censoring. Suppose that all the observed event times are less than c when all the censored observations are censored at the same time c. $(t \leq c)$

In such situations the sample proportion of observations with event times greater than $t$ is still considered as the estimator of the survivor function. But the procedure for evaluating the KM estimator is different when some censoring times are smaller than some event times$(t > c)$.In such cases KM estimator is computed as follows. Suppose $t_1 < t_2 < \cdots < t_k$ , are k distinct event times. There are $n_j$ individuals who are said to be at risk at each time $t_j$. People who have not experienced an event and people who have been censored prior to time $t_j$. are

considered as at risk. And the cases which censored at exactly time $t_j$ are also considered as at risk at $t_j$. And let the number of individuals who die at $t_j$ be equal to $d_j$ Then the KM estimator is defined as

$$\hat{S}(t) = \prod_{j:t_j \leq t} \left[1 - \frac{d_j}{n_j}\right]$$

When $t$ is less than $t_1, \hat{S}(t)$ is equal to 1.

When $t$ is greater than $t_k$ with no censoring $\hat{S}(t)$ is equal to 0

When $t$ is greater than $t_k$ with censoring $\hat{S}(t)$ is undefined.

**2.11 Comparison of survival curves with the Log rank test**

Log rank test compares the entire survival experience between two or more groups. So it can be considered as a way of testing whether the survival curves are identical or not. Log rank test can be used to compare the survival curves which derived from Kaplan-Meier method.

Hypothesis of interest

H0: The two (or all) survival cures are identical

H1: The two (or all) survival cures are not identical

**2.12 Log rank statistic**

Suppose there are k number of groups. Then the log rank statistic is defined as,

$$\mathrm{X}^2 = \sum_{j=1}^{k} \left\{ \frac{(\sum O_{jt} - \sum E_{jt})^2}{\sum E_{jt}} \right\}$$

$\sum O_{jt}$ is the observed number of events in the jth group over time

$\sum E_{jt}$ is the sum of the expected number of events in the jth group over time

Log rank statistic has a chi square distribution with k-1 degrees of freedom.

**3.RESULTS AND DISCUSSION**

This section describes the results of this research. All the data outputs and statistical tests are included in this section.

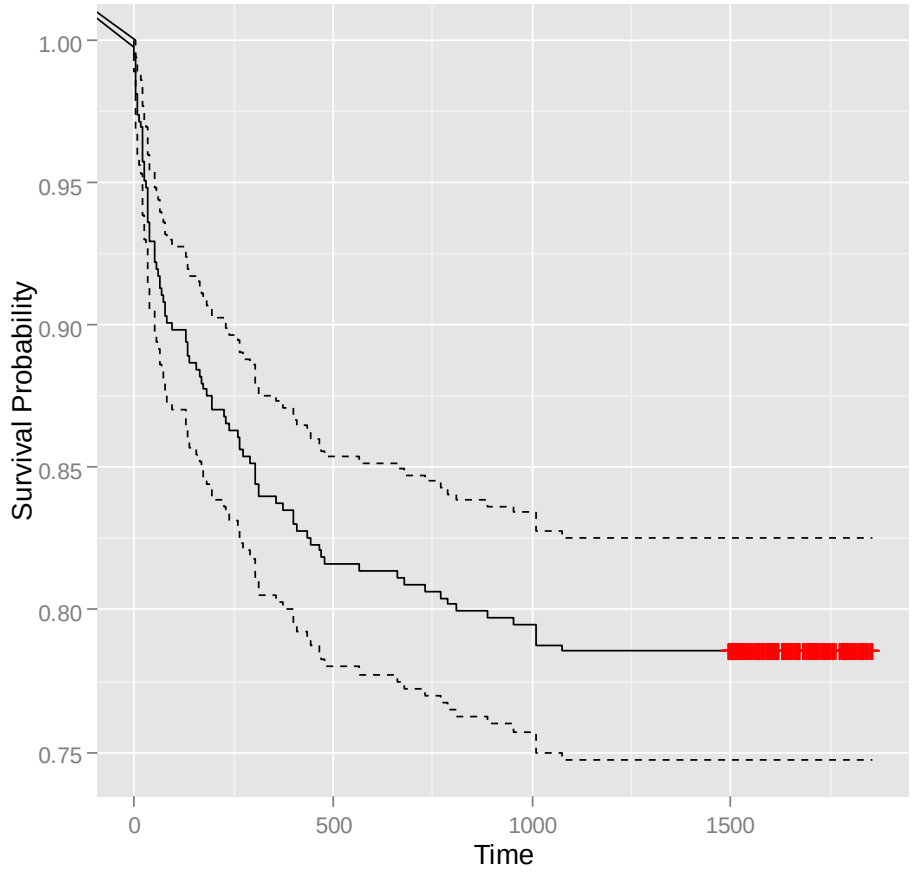



**Figure 01: Survivor function for pediatric cancer patients**

As it can be seen in figure 01, the curve slopes down to a lower value. It stops at the highest censoring time (1074 days). It is clear that at 1074 days KM (Kaplan Meier) estimate is 0.758. Hence the estimated probability that a patient will survive for 1074 days or more is 0.785. It suggests that there is a good probability for a cancer patient to survive for more than 1074 days.

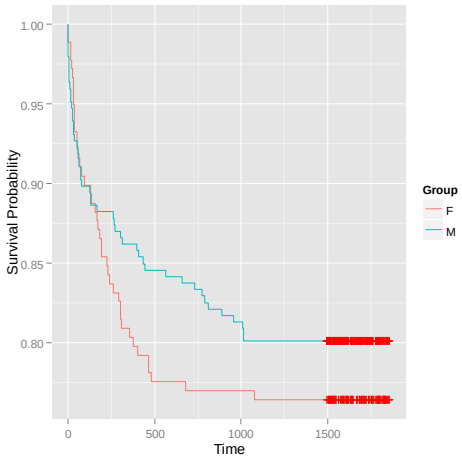



**Figure 02: Survival curves for Gender**

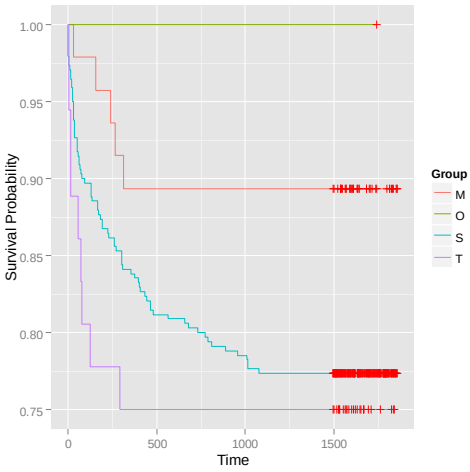



**Figure 03: Survival curves for Races**

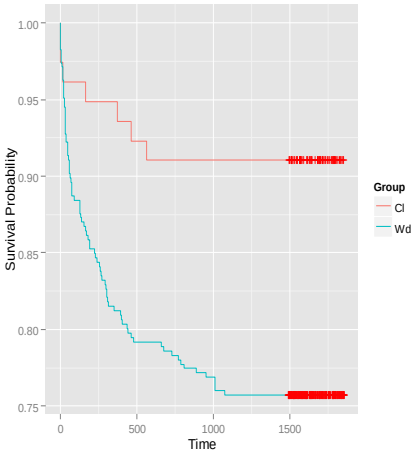
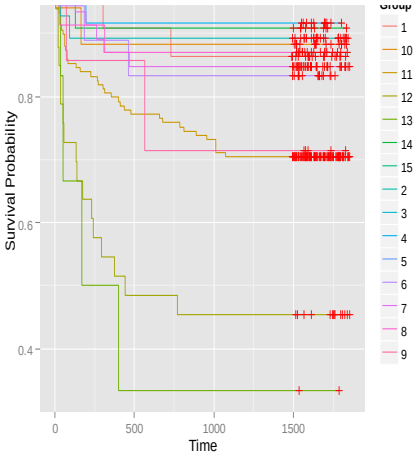



**Figure 04: Survival curves for Treatment setting**

**Figure 05: Survival curves for cancer type**



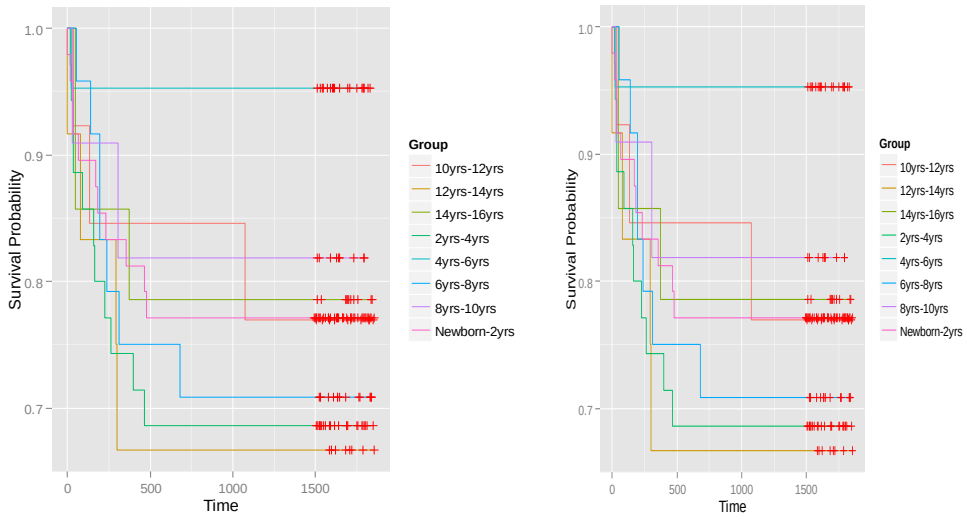



**Figure 06: Survival curves for Female age groups** **Figure 07: Survival curves for male age groups**

| Group | Chi square statistic | P value of the log rank test |
|---|---|---|
| Gender | 0.8 | 0.369 |
| Race | 0.255 | 0.255 |
| Treatment setting | 8.3 | 0.00401 |
| Cancer Type | 64.6 | 1.79e-08 |
| Female age groups | 6.1 | 0.529 |
| Male age groups | 18.3 | 0.0105 |

**Table 02: Log rank test results for the groups**

As for the results of the log rank test we can see that there is a significant different between the survival curves of the treatment setting, cancer types and male age groups. Figure 4, clearly shows that survival probability of the patients who are in wards are lower than for the patients who are coming for clinics. This may be because patients who are in wards present with more severe disease and more comorbidities.

According to figure 5, survival probabilities of cancer type 13 and 11 are lower than other cancer types. Patients of cancer type 4 have the largest survival time. According to figure 7, male patients of age group 4 – 6 years have the highest survival probability while the patients of age group 12 – 14 have the lowest survival probability.

## 4.Conclusions and Discussion

As for the descriptive analysis, Lymphoid Leukemia, brain cancers, Unknown cancers and Myeloid Leukemiaare the common cancer types in the pediatric age group in Sri Lanka. Among them the dominating cancer type is Lymphoid Leukemia with a percentage of 35.14%. There is a male predominance in the study sample comprising of 58.01%

According to the sample majority of the patients have at least survived for 5 years while 21.46% of patients have died before five years.

The estimated probability that a patient will survive for 1074 days or more is 0.785. It suggests that there is a good probability for a cancer patient to survive for more than 1074 days rather than dying with the cancer. In general survival probability of the patients who are in wards are lower than for the patients who are coming for the clinics. Survival probabilities of cancer type 13 and cancer type 11 are lower than other cancer types. And patients of cancer type 4 has the longest survival time. Among males, patients of age group 4years-6years has the highest survival probability and the patients of age group 12years-14years has the lowest survival probability.

Patterns in survival can provide information regarding the impact and severity of cancer. Recognizing the differences in survival rate among different groups could assist uncovering failures in systemic policy and inappropriate program delivery, and furthermore support the planning of systems for enhanced cancer control.

In this study, expansive analysis of data on associated factors for survival of pediatric cancer patients was not possible within ethnic minorities due to low presentation frequencies in the sample. Very few patients were recorded from Northern Province, this may be due to transport difficulties. And there were large number of patients from urban areas. Therefore, the findings could not be generalized.

This analysis does not include the effect of treatment methods on survival of cancer patients. Therefore, we cannot compare the difference between treatment methods.

This is the initial stage as descriptive cross-sectional study and survival analysis with regard to main factors associated with pediatric cancer patients. It would be importance to further investigate the association of survival with other factors as food habits, stage of the cancer and histology.

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