

## Burden of Pediatric Cancer Treatment: Results of Online Pediatric Cancer Registry Prototype 1 at A Third Referral Hospital in Indonesia

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### Abstract

**Background:** Despite the impressive progress of high-income countries, childhood cancer survival remains low in low and middle-income countries. Cancer is yet to be considered as a significant public health issue which has implicate only few pediatric cancer registry has been well established. The study aimed to describe the burden of pediatric cancer treatment in a third referral hospital in Indonesia through pediatric cancer registry.

**Methods:** A-three-year retrospective analysis of 15 pediatric cancer diagnosed in children aged under 14 years was conducted at Dr Hasan Sadikin General Hospital, Bandung. Data were extracted from Online Bandung Pediatric Cancer Registry Prototype 1 and analyzed for age, gender, type of cancer. The outcomes were classified as treatment abandonment, treatment refusal, interrupted treatment, death during treatment, and completed treatment.

**Results:** Seven-hundred and seventy-three children, 452 males and 321 females, were diagnosed with 15 types of malignancies. Peak incidence for each malignancy was different: at a young age was found in retinoblastoma and hepatoblastoma (mean; 3yo) while at adolescence in bone tumor and chronic myelocytic leukemia (9.1; 10 yo respectively). Distribution of the foremost malignancies recorded was: acute lymphoblastic leukemia (44.5%), retinoblastoma (15.2%), and non-Hodgkin lymphoma (8.9%). The cancer cure rate was very low (9.5%), treatment abandonment was still high (41.7%) and most patients died (27.8%) in the course of therapy either from advanced disease, infection, or late presentation. Meanwhile, 167 patients still continued the interrupted treatment.

**Conclusions:** Cancer management is the burden for hospital, however the general outcome is very poor.

**Keywords:** Cancer management, developing countries, health care burden, pediatric cancer registry

### Introduction

The incidence of pediatric cancer is increasing, data from the International Agency for Research on Cancer (IARC) showed approximately 175,000 new cases of childhood cancer (0-14 years) per year. Most new cases (84%) or 147,000 new cases occur in developing countries that are associated with lower life expectancy.<sup>1</sup> Currently, in developing countries the priority of health development is prevention of infectious diseases and nutritional improvements in accordance with the global commitments of the Sustainable Developmental Goals (SDG), however with improved nutrition and decreased infectious diseases cannot protect children from cancer.<sup>2</sup> In addition, the increase in industrialization

and urbanization life also contributes to the increase in incidence of cancer. Indonesia as a developing country currently, faces the burden of multiple diseases, namely the increase of non-infectious diseases, one of which is childhood cancer.<sup>2,3</sup>

The prevalence of cancer patients in Indonesia regardless of age is 1.4 per mil' which may not describe the real number because there are still many unreported cases. Moreover, Indonesia did not have the real number of pediatric cancer.<sup>4</sup> Compared to high-income countries (HICs), the annual incidence of childhood cancer is approximately 140 per 1 million children younger than age 15 years. Incidence rates from low and middle income country (LMIC) registries are generally

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significantly lower, as annual rates per 1 million children of 45.6 in Namibia and 64.4 in India, respectively. Some of this variation may relate to differences in environmental exposures or to biologic susceptibility.

Furthermore, cancer management strategies in LMICs started from understanding the burden and the importance of managing childhood cancer such as in Indonesia. The burden of cancer in Indonesia was unknown mainly because of lack of statistics or under-reporting like the other LMICs. From a survey of health care workers in 10 LMICs, including Bangladesh, Philippines, Tanzania, and Vietnam, only 15–37 percent of the expected patients were seen.<sup>5</sup> However, deficiencies in diagnosis and registration likely contributed significantly to differences in the reported incidence of cancer, both overall and of particular sub types. Moreover, expansion of current cancer registries, improvement in diagnosis and registration, and novel methodologies are needed to establish the true pediatric cancer burden. High quality pediatric cancer registry is still a luxury in LMICs that still needs to be established and developed in LMICs such as Indonesia.<sup>2,6</sup>

The Bandung Pediatric Cancer Registry as a hospital-based cancer registration is the first step in establishing regional and national cancer registries. Hospital cancer registration is an important data supplier in some hospital cancer registries in some developing countries. In addition, registration of quality cancer hospitals with good data quality and ongoing implementation is a solid framework for regional and national cancer registration planning.<sup>7</sup>

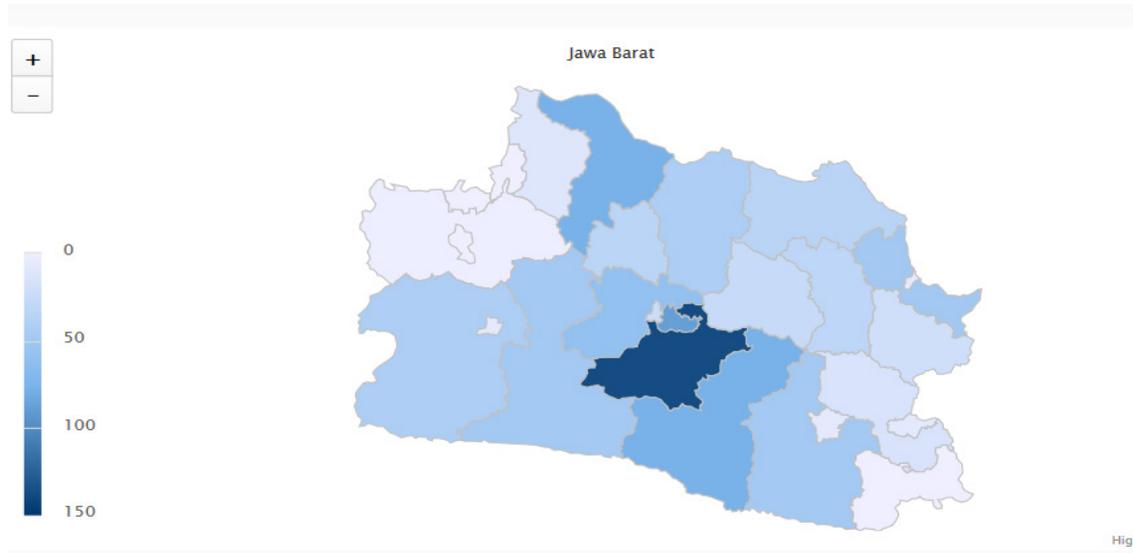
The outcomes are the other side of the problems of childhood cancer in LMICs which show that the cure rate is very low and the treatment abandonment is high.<sup>8</sup> The study was aimed to describe the burden of pediatric cancer treatment in one of the third referral hospital in Indonesia through online Bandung Pediatric Cancer Registry Prototype 1.

## Methods

The study setting was at Dr. Hasan Sadikin Hospital (RSHS), the third referral hospital in West Java with almost 1000-bed capacity. Dr Hasan Sadikin General Hospital is the core in pediatric oncology services in West Java. The Hematology Oncology Unit of the Department of Child Health has 32-bed capacity and offers chemotherapy. Moreover, radiation therapy and radio nuclear treatment are also available.

However, there is still inadequate human resource especially the typical nurse who has the capacity in providing chemotherapy care. Meanwhile, most medical expenses are charged to the national insurance (*Badan Penyelenggara Jaminan Sosial*, BPJS). Basic diagnostic investigations such as complete blood count, liver and kidney function tests are readily available. Diagnostic tests such as histopathology are also available however; the diagnosis was mostly based on fine needle aspiration biopsy. Though, this Unite serves immunohistochemistry, cytology, and molecular diagnostics were not available as well as imaging modalities were limited with one magnetic resonance imaging (MRI) and two computerized tomography (CT) imagers. Multiple treatments with chemotherapy, radiation and surgery are offered at the hospital. Chemotherapy protocols are derived from evidence-based protocols. However, regardless of the protocol, inconsistent availability of cytotoxic drugs often dictated the regimen delivered to the patients.

A pre-existing database of Online Bandung Pediatric Cancer Registry had been established at Dr. Hasan Sadikin Bandung in 2016. The data based collected medical information such as laboratory, pathology and radiology results as well as demographic data. There were two registrars focused for inputting data from medical records, and one validator. Moreover, Online Bandung Cancer Registry was a customized cancer registry which followed the principle of hospital based cancer registry and accommodated the function of electronic medical record. This registry could be accessed by a special code by an authorized person. All children aged 0–14 years who were admitted to the Paediatric Oncology Ward, Department of Child Health between January 2014 and December 2016 with confirmed cancer were enrolled in Online Bandung Pediatric Cancer Registry. The initial inclusion criteria for the study was limited to patients registered in the database. Clinical diagnoses were typically established based on history, physical exam, chest x-ray, ultrasound and occasionally CT scan. Based on medical record reviews, one outcome assignment was determined for each patient with Treatment Abandonment/Treatment default: as absence from cure-directed therapy for four or more weeks and the patient was not a candidate for palliative care. Upfront treatment abandonment also known as treatment refusal occurred if the patient fails to start treatment to accomplish cure or definitive control. Interrupted treatment: the



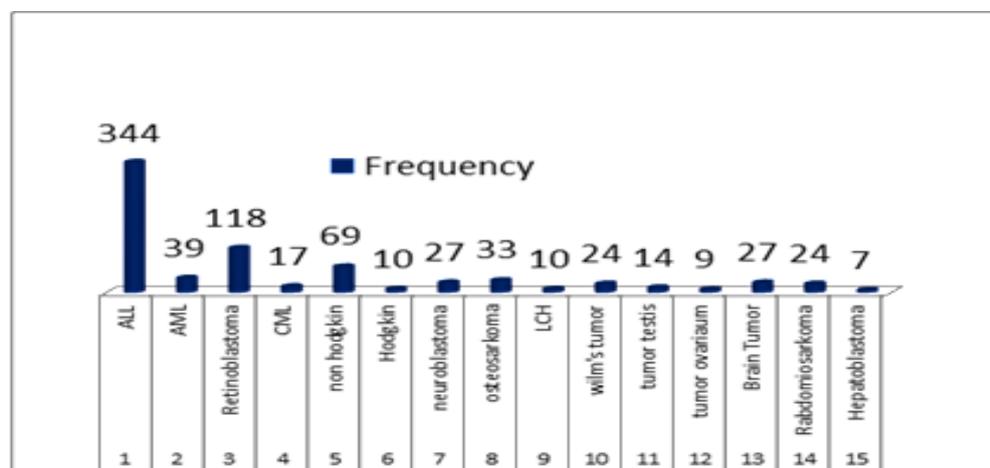
**Figure 1** Distribution of Pediatric Cancer Patients in West Java Province

category of interrupted treatment includes the terminology describing missed treatment: if the patient misses some therapy but not to extent impacting disease control, lost to follow up (LTFU) for a short duration while on treatment (less than the time period that would define abandonment for patients with that diagnosis), refusal of specific treatment components for a specified time, and discontinued treatment with a specified intent. Complete treatment: completion or treatment to accomplish cure or definitive control. Death during treatment: if the patient died during the cure of directed treatment due to advance

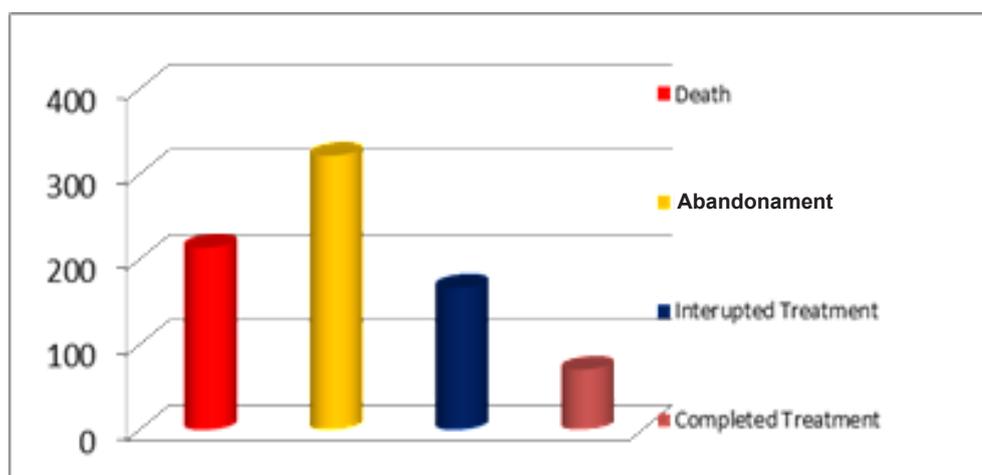
disease, infection, toxicity of chemotherapy.<sup>8,9</sup> Online Bandung Pediatric Cancer Registry prototype 1 is a new online web-based cancer registry which inputs all data from the pediatric hematology oncology division. The obtained data were later imported into a password-protected Microsoft Excel 2010 and underwent descriptive analysis.

**Results**

The online database included 773 children admitted to the Pediatric Oncology ward,



**Figure 2** Distribution of Pediatric Cancer Patients Based on Type of Malignancies



**Figure 3 The Outcome of Pediatric Cancer Treatment**

Department of Child Health, Dr. Hasan Sadikin Hospital with a confirmed malignancy during the enrollment period (2014–2016). The Online Bandung Pediatric Cancer Registry was a new registry which input all the data from medical records of pediatric cancer during the

period 2014–2016 including the new cases and follow up of the patients as online medical records. The distribution of pediatric cancer patients at Dr. Hasan Sadikin Hospital during study period showed patients mostly came from all regions around West Java Province,

**Table 1 Respondent's General Characteristics**

Diagnosis of Malignancy	Treatment Abandonment n (%)	Interrupted Treatment n (%)	Completed Treatment n (%)	Death during Treatment n%
Acute lymphoblastic Leukemia (ALL)	103 (30.5%)	115(33.4%)	18 (5.2%)	108(31.3%)
Acute Myeloblastic Leukemia (AML)	20(51%)	4(10.2%)	0 (0%)	15(38.4%)
Retinoblastoma	45(38.1%)	16(13.6%)	43(36.4%)	14(11.9%)
Chronic Myelocytic Leukemia (CML)	16(94.1%)	0(0%)	0(0)	1(5.9%)
Non Hodgkin Lymphoma	35(50.7%)	7(10.1%)	3(4.3%)	24(34.7%)
Hodgkin Lymphoma	7(70%)	1(10%)	2 (20%)	0(0%)
Neuroblastoma	8(29.6%)	5(18.5%)	2(7.4%)	12(44.4%)
Osteosarcoma	21(63.6%)	2(6.1%)	1(3%)	9(27%)
LCH (Langerhans histiocytosis)	6(60%)	2(20%)	1(10%)	1(10%)
Wilms Tumor	8(33.3%)	5(20.8%)	4(16.7%)	7(29.1%)
Testicular Cancer	11(78.6%)	1(7.1%)	0(0%)	2(14.3%)
Ovarian Cancer	5(55.5%)	1(11.1%)	0(0%)	3(27.4%)
Brain Tumor	21(77.8%)	3(11.1%)	0(0%)	3(11,1%)
Rhabdomyosarcoma	11(45.8%)	3(12.5%)	0(0%)	10(41.6%)
Hepatoblastoma	2(28.5%)	0(0%)	0(0%)	5(71.4%)
Total	321 (41.5%)	165 (21.33%)	74 (9.5%)	214(27.7%)

except from Bogor, Depok, and Tangerang who preferred going to Jakarta region (Figure 1).

Regions located close to Dr. Hasan Sadikin Hospital had the highest number of patients coming to Dr. Hasan Sadikin Hospital, respectively *Kabupaten Bandung*, *Kota Bandung*, and *Garut*. They were diagnosed with 15 types of malignancies during the study period (Figure 2). The distribution of the foremost malignancies recorded were as follows: acute lymphoblastic leukemia (ALL) (44.5%), retinoblastoma (15.2%), and non-Hodgkin lymphoma (8.9%).

The number of patients consisted of 452 male and 321 female, presenting male to female ratio of 1.4:1. The peak incidence for each malignancy was different, at younger age was found in retinoblastoma and hepatoblastoma (mean; 3yo) while at adolescence in bone tumor and chronic myelocytic leukemia (CML) (9.1; 10 y.o respectively). The treatment outcome of pediatric cancer at Dr. Hasan Sadikin General Hospital was still unsatisfactory. The cancer cure rate was very low (9.5%), treatment abandonment was still high (41.7%) and most of the patients died (27.8%) in the course of therapy either from advanced disease, infection, or late presentation addressing palliative care management which started at early presentation. In addition, 167 patients still continued their interrupted treatment (Figure 3).

Furthermore, CML, testicular cancer, brain tumor, and osteosarcoma were the four diagnoses which have the highest number of treatment abandonment among 15 type of childhood cancer diagnosis (Table 1).

## Discussion

Cancer registration is an indispensable instrument in cancer control programs.<sup>2</sup> The history of cancer registry in Indonesia began at the Department of Pathology, Diponegoro University in Semarang in 1970, and the semi population based cancer incidence data have been available since 1985, allowing comparisons across the country focused on gastrointestinal malignancies. There is currently a new major effort started by the Dharmas National Cancer Center Jakarta to set up a partial population-based registry in 2007. Until now there is no specific cancer registry for pediatric population.<sup>10,11</sup> The Online Bandung Pediatric Cancer Registry prototype 1 was the first attempt to help measuring the burden of pediatric cancer patients in West Java Province. The Online

Pediatric Cancer Registry is intended to widen utilization among hospitals in Indonesia which serve pediatric oncology treatment, starting from creating a hospital based cancer registry. The Online Bandung Pediatric Cancer Registry Prototype 1 was established in 2016 which complied with the principle of cancer registration including data collection, verification, validation, management and analysis, and data publication. This new application also accommodates the use of SRIKANDI and CANreg5 IARC.<sup>12</sup>

Based on this registry we found that mostly patients came from *Kabupaten Bandung* (17.8%), which is an industrial district, however we could not find any relationship between socio environmental factors except the distance of Dr. Hasan Sadikin General Hospital from the patient's residence was close enough for parents to travel with their children to seek for medical services at Dr. Hasan Sadikin General Hospital. A study in Africa<sup>13</sup> found that demography was one of the factors of treatment abandonment for childhood cancer lower risk if patients were residing in the same location with the cancer center (Odds Ratio [OR]=0.41 (95% confidence interval [CI]: 0.21–0.81; p=0.01).<sup>13</sup> Perez et al.<sup>14</sup>, furnished some evidence that living in the proximity of industrial (<2.5 km) and urban sites may be a risk factor for childhood leukemia. Further investigations should be conducted to explore this factor in our population. The industrial site referred to in Peres' study was particularly the site of glass and mineral fibers (OR2.42;95% CI1.49–3.92), surface treatment using organic solvents (OR1.87;95% CI1.24–2.83), galvanization (OR1.86;95% CI1.07–3.21), production and processing of metals (OR1.69;95 CI1.22–2.34), and surface treatment of metals (OR1.62;95% CI1.22–2.15), and urban areas (OR 1.36;95% CI1.02–1.80).

The most frequent cancer type among children between 0–14 years old in LMICs in Asia<sup>15</sup> were as follows: leukemia (35.8%), brain tumor (12.4%), nonHodgkin lymphoma (7.4%), Hodgkin lymphoma(4.3%), kidney tumor 3.9%, liver 2.1 %, ovary tumor 1.3%. This was in line with the new data from distribution of the most common cancers in children less than 15 years of age in selected populations around the world which showed that leukemia was the most common among the pediatric malignancies (51%), followed by brain tumor (17%), non-Hodgkin lymphoma (11%), Hodgkin lymphoma (5%), kidney tumor (6%), and other (10%).<sup>16</sup> Comparing those data with

data in Dr. Hasan Sadikin General Hospital, the differentiation was on the second rank which was retinoblastoma in our population and brain tumor in the other populations. Furthermore, some factors contributing to these were the difficulty of diagnosis of brain tumor, late presentation of brain tumor, and unregistered cases of brain tumor. In addition, retinoblastoma in our registry was the second common pediatric malignancy. There were some factors contributing to this, which might be due to the National Eye Cancer Hospital location in Bandung, thus most of the case across Indonesia referred to Dr. Hasan Sadikin Hospital, or the detection of retinoblastoma in West Java was well established so more patients could undergo treatment. The number of new cancer cases in children at Dharmais Cancer Hospital between 2010–2013 showed different results, lymphoma is the second most common cause after leukemia.<sup>4</sup> Due to sporadic data around hospitals in Indonesia, it was common if we found variation in pediatric cancer. Thus, it is essential that a National pediatric cancer registry should be immediately established.

The abandonment of treatment is a major cause of therapeutic failure in these resource-poor countries, affecting up to 50–60% of cases. Abandonment constitutes failure to start or complete curative treatment.<sup>9</sup> This study found that the number of treatment was 41.5%. These numbers should be considered and not to be ignored. In 2010, Pediatric Oncology in Development Countries (PODC) has developed a special working group for these problems and made some recommendations which are (1) abandonment of treatment should be documented as an adverse event in childhood cancer studies in resource poor countries. Patients who do not begin or complete treatment should not be excluded from survival analyses. Event-free survival should be analyzed in two ways: by treating abandonment as an adverse event and by censoring cases at the time of abandonment for some children may be cured if they abandoned treatment after completing most of their planned therapy, these two estimates may reflect the upper and lower bounds of the true event-free survival estimate; (2) abandonment of treatment may be defined as a failure either to begin (conventionally termed refusal) or to continue the planned course (abandonment), because both are likely to have related underlying causes and could benefit from similar interventions. However, the timing of abandonment should be

documented to help to identify related factors. Third, treatment in resource poor settings may be interrupted for various reasons, including financial and transportation difficulties. When such interruptions herald full abandonment and what the effect on outcomes will be are difficult to predict. Treatment abandonment is a complex and multifactorial phenomenon. With increased recognition of the role of treatment abandonment on global pediatric cancer outcomes, factors beyond social/economic status and beliefs have emerged. Our results provided insights regarding the role of established determinants of treatment abandonment in different geographical and economic contexts, allow probing of key determinants by deliberating their mechanisms, and allow building an expanded conceptual model of established and emerging determinants treatment abandonment.<sup>17</sup> Our study did not explore the factor that might contribute to the determinant of treatment abandonment or interrupted treatment, such as diagnosis, treatment, prognosis, social economic factor. The limitation of our medical records is the unavailability of data in medical records whether the intended treatment is curative or palliative.

This study can describe the burden of pediatric cancer management in tertiary hospitals in Indonesia, hence we should have a strategy to improve pediatric oncology services including endeavors to make RSHS as a dedicated hospital for pediatric oncology treatments, and to make collaborations in HIC through twinning programs.

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