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The Issues Related to Children with Leukemia in Indonesia: An Integrative Review

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Abstract : *This integrative review, based on twenty-four studies from data resources, including Scopus, CINAHL, MEDLINE, PsycINFO, and Indonesia science and technology index (SINTA), was published from 2009 to 2019. The eligible studies were conducted in Indonesia, published in the English or Indonesian language, and reported the incident, survival rate, and physical or psychological effects of disease or chemotherapy. There were 23 quantitative studies and two qualitative studies. The theoretical or conceptual framework was not identified to guide and develop the studies. Most studies used retrospective and cross-sectional studies; the target population was acute lymphoblastic leukemia (ALL) and used small sample sizes for a cross-sectional study. The variables that were explored in the quantitative studies consisted of the incidence of leukemia, survival rate, abandonment of treatment, effects of disease or chemotherapy, quality of life (QOL), and others. The qualitative findings focused on the experience of being diagnosed with leukemia and its meaning in the adolescent context. The evidence from the studies showed that the incidence rate of all types of leukemia increases each year. The survival rate was lower than in other countries, with differences in numbers among hospitals. The effects of the disease and chemotherapy dominated the problem of children the low level of QOL. More research is necessary to explore the factors related to treatments' outcomes, particularly the aspects related to survival rate and QOL are using comprehensive data analysis, an appropriate theoretical framework to guide the study, more sample size, and involving multiple hospital settings.*

Keywords: cancer, children, Indonesia, leukemia, quality of life

INTRODUCTION

Leukemia is still dominate of childhood cancer prevalence In Indonesia. It led to the incidence of childhood cancer in Jakarta with an incident around 1.61 per 100,000 children during 2005-2007 (Wahidin et al., 2012). Moreover, the average annual incidence rate (AAIR) of childhood acute leukemia in Dr. Sardjito Hospital, Yogyakarta, the annual incidence rate (AIR) of childhood acute leukemia significantly increased from 35 in 1999 to 70 in 2009 (Supriyadi, Widjajanto, Veerman, et al., 2011). Leukemia consists of several types, in which acute lymphoblastic leukemia (ALL) is the most common type in children (77% cases) on a study of four hospitals between 2006 and 2010 (Supriyadi, Widjajanto, Purwanto, et al., 2011).

Even though leukemia incidence increases each year gradually, literature found the survival rate of leukemia in developed countries was high, 90.5% in the US and 91·6% in Germany, for example. However, different results occurred in developing and poor countries, where the survival rate was low, such as 52.4% in Cali, Colombia (Bonaventure et al., 2017; Siegel et al., 2022). Unfortunately, the increase in survival rates was not accompanied by an improvement in the treatment's negative effects, particularly chemotherapy, which causes toxicity and organ dysfunction (Eche & Aronowitz, 2018). Literature indicated that chemotherapy as the main treatment of leukemia causes a variety of physical and psychological changes in children such as nausea and vomiting, mucositis, fatigue, bleeding, infection, and behavioral or emotional problems (Mwirigi et al., 2017).

Studies from other countries explored various problems faced by children with leukemia with high-quality methods, appropriate sample size, and guided by a theoretical framework to guide the studies. Furthermore, some studies have moved from descriptive studies to data-based intervention studies, in which theory-informed intervention studies developed to improve family members' adjustment to cancer). However, there is little information about the state of knowledge of the issues related to children with leukemia in Indonesia. It will be less effective in planning care if health care providers do not understand children's problems with leukemia in the Indonesian context. Hence the purpose of this integrative review was to describe findings from studies of Indonesian children diagnosed with leukemia as a basis for facilitating new directions in research and clinical practice in nursing and medical areas. And so the research question that guided this review was, "What is the state of knowledge about children with leukemia in Indonesia?"

METHOD

This study's literature review includes a search of the electronic databases: Scopus, CINAHL, MEDLINE, PsycINFO, and Indonesia science and technology index (SINTA). Articles were reviewed for the years of publication from 2009 to 2019 in the English or Indonesian language. The keywords including "leukemia", "cancer", "children", "acute lymphoblastic leukemia", "pediatric oncology", "leukemia in Indonesia". Publications were included if they fulfilled all of the following criteria: (i) children with leukemia, (ii) Indonesian parents or children, (iii) the paper was published in English or Indonesian. We excluded publications if they did not report problems experienced by parents or children, including only genomic studies or drug effectiveness.

The eligible studies were those conducted in Indonesia, focused on children, reported the incident, survival rate, physical or psychological effects of disease or chemotherapy, and the problems during treatment and diagnosis. Duplicate records and irrelevant titles were removed before reviewing the abstracts and relevant full-text papers.

The researcher developed an electronic form to record detailed information about the research. The data extracted from the primary study and presented in this article included study characteristics, conceptual or theoretical frameworks, research variables, sampling techniques, caregivers' characteristics, and research findings.

RESULTS

Study Characteristics

This search removed 22 articles for duplication (Fig.1). Twenty-five studies met the inclusion criteria. The publications were from 7 international databases and 18 from the Indonesian data base. In the 25 studies in this review, 23 studies were quantitative design, and two studies were qualitative design. The quantitative studies comprised 7 cross sectional study (Agnes et al., 2019; Devi & Allenidekania, 2019; Fadhilah & Allenidekania, 2019; Mostert et al., 2008; Novrianda & Khairina, 2015; Rata et al., 2017; Sitaresmi et al., 2010), 10 descriptive retrospective cohort study (Alfina et al., 2011; Hapsari et al., 2013; Mostert et al., 2013; Permatasari et al., 2009; Simanjorang et al., 2013; Supriyadi, Widjajanto, Veerman, et al., 2011; Tehuteru, 2011; Widiaskara et al., 2016; Wijayanti & Supriyadi, 2017), 2 retrospective Case Control Study (Agnes et al., 2019; Hapsari et al., 2013), 3 quasi-experimental study (Anggraini, 2018; Kulsum et al., 2017; Novrianda & Khairina, 2015), and one randomized clinical trial (Sitaresmi et al., 2013) (table. 1). The qualitative studies comprised two phenomenological studies (Suryani & Syafiq, 2016; Widianita et al., 2009) (table. 2).
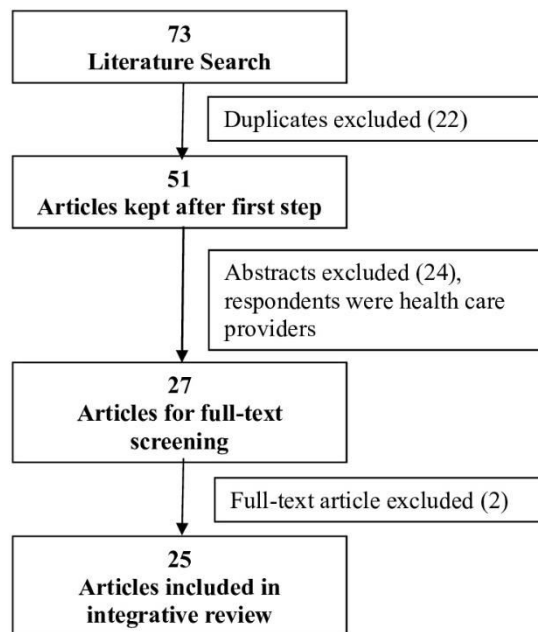
Figure 1 Flow diagram of study selection and review

Conceptual Frameworks

A conceptual framework is important issue to guide a study, without a conceptual framework, a study can be lack of meaning, and not acceptable to the theoretical constructs in the research field (Adom et al., 2018). All quantitative studies (22 studies) did not mention or describe the conceptual or theoretical frameworks that were used to guide the research.

Research Variables

The variables were explored in the quantitative studies, including outcomes of treatment (9 studies), three related to febrile neutropenia and child's quality of life, side effects of chemotherapy (two studies, 8.7%), refusal rate and abandonment, the incidence of leukemia, emotional support, pain, and mucositis (one study per variable, 4.33%). The qualitative studies explored the experience and the meaning of life during diagnosis with leukemia of adolescents.

Sampling Techniques and Child's Characteristics

Most of the sampling techniques were consecutive sampling (11 studies, 47.8%), snowballing sampling (2 studies, 8.7%), exhaustive sampling (1 study, 4.3%), stratified random sampling (1 study, 4.3%), and eight studies (34.8%) did not clearly mention the sampling technique. The data for the studies were gathered from several sources, including home setting (3 studies, 12.0%) and cancer centers or hospitals (twenty studies, 88.0%), consist of Dr. Sardjito Hospital (9 studies, 45%), Dharmais Cancer Hospital (3 studies, 15%), Dr. Cipto Mangun Kusumo (2 studies, 10%), Dr. M. Jamil (2 studies, 10%), Ulin Hospital (2, studies, 10%), Dr. Kariadi (1 study, 5%) Dr. Soetomo (1 study, 5%).

The number of study participants ranged from 25 to 720 parents or children in quantitative studies and 2 to 5 adolescents in qualitative studies. Most of the total sample for cross-sectional studies between 25 and 59; only 1 study recruited 159 participants. The sample size was from 26 to

720, 25-34 respondents for the quasi-experiment study, and 108 participants for randomized control trials for the retrospective studies.

The children's characteristics varied among the studies. The age of children ranged from 0 to 18 years, with most cases aged 1-10 years. Related to the types of leukemia, 19 studies (82.6%) explored only acute lymphoblastic leukemia, one study (4.3%) about AML, and 3 (13.1%) studies included all types of leukemia. Regarding the phase of treatment, 12 studies did not explicitly mention the phase of therapy, eight studies focused on chemotherapy, and three studies specifically were performed during the induction phase.

Research Findings

The quantitative studies reported various findings. For example, some studies reported that the survival rate as the outcome of treatment was low in all hospitals setting (Alfina et al., 2011; Mostert et al., 2010; Permatasari et al., 2009; Simanjorang et al., 2013; Sitaresmi et al., 2013; Sjakti et al., 2016; Tehuteru, 2011; Wijayanti & Supriyadi, 2017; Yakin et al., 2017). The most common adverse effects of chemotherapy and experienced by more than 50% of children, including fever, infection, bleeding alopecia, loss of appetite, fatigue, pain, fatigue, and mucositis (Agnes et al., 2019; Anggraini, 2018; Devi & Allenidekania, 2019; Fadhilah & Allenidekania, 2019; Sitaresmi et al., 2010; Widiaskara et al., 2016). Based on the side effects of chemotherapy experienced by children, infection is the most common cause of child deaths (Sjakti & Windiastuti, 2016).

Other pivotal findings were the quality of life of children was moderate (Kulsum et al., 2017; Novrianda & Khairina, 2015) and low nutritional status of children (Agnes et al., 2019). Furthermore, abandonment, lost follow-up, or treatment drop out of therapy are still being found despite a decrease in numbers (Alfina et al., 2011; Mostert et al., 2010; Sitaresmi et al., 2010; Tehuteru, 2011). Moreover, correlational studies indicated an association between several factors and leukemia symptoms in children. Malnutrition was associated with the febrile neutropenia (Agnes et al., 2019), emotional support had been related to the pain level (Rata et al., 2017), oral care was correlated with mucositis (Devi & Allenidekania, 2019), and physical activity influenced fatigue (Fadhilah & Allenidekania, 2019), for instance. Additionally, several intervention studies found that the medication diary book program affected lowering survival rate (Sitaresmi et al., 2013), Swedish massage affected QoL (Kulsum et al., 2017), and hypno-parenting affected children's fatigue (Anggraini, 2018). Finally, based on the qualitative studies, the experiences of Indonesian adolescent revealed several themes such as the following: (a) disappointed and hopeless during diagnosis, (b) psychological distress, (c) be closer to God, (d) perceived life is meaningful, (e) more spirit to make other happy (Suryani & Syafiq, 2016; Widianita et al., 2009).

Table 1. The Summary of Quantitative Studies

Author & year	Frame-work	Study Design	Sample & Setting	Instrument	Findings
1. Fadhilah & Allenidekani a (2019)	NA	Cross-sectional correlationnal study	45 children with ALL (3–16 years), in Jakarta	Physical Activity Questionnaire for Older Children (PAQ-C) Fatigue Onkologi Anak – Allen (FO-A)	• 51% of children having fatigue in a category less active, 49 % is active • There is statistically relationship between physical activity and fatigue in the children (p < .001, r = .558).
2. Devi & Allenidekania, (2019).	NA	Cross-sectional analytical study	34 children with ALL (3 - 12 years) in Jakarta, Indonesia	self-report questionnaire by the author Oral Assessment Guide(OAG)	• 51.5% of children having mucositis during chemotherapy • There was a statistical relationship between oral care practice at home and mucositis incidence (p = .039)
3. Agnes, Widjajanto, & Damayanti (2019).	N/A	Cross-sectional study	246 children with ALL during the induction phase, in Dr. Sardjito, Yogyakarta. 2013- 2015	Peripheral neutrophil counts	• 84% of children experienced once on FN, 16% was 2-3 times got FN • 15.3% of children with febrile passed away during the induction phase
4. Anggraini (2018).	NA	Quasi-experiment: a before-after study.	30 children with ALL (5-12 years) during chemotherapy, in Ulin Hospital, Banjarmasin, Kalimantan	Multidimensional Fatigue Scale (Varni, 2014)	• There was a significant difference in fatigue level among the patients before and after hypnoparenting (p = .001)
5. Alfina, Widjajanto, & Patria, (2018).	NA	A retrospective cohort study.	111 children with ALL (<18 years) with hyperleukocyte, in Dr.Sardjito Hospital,	Medical records Kaplan-Meier method.	• Two-year event-free survival (EFS) of WBC 50-200x10^9 group is 68%, EFS of WBC >200 x 10^9 group is 45% • Overall survival of WBC 50-200x10^9 group is 77%, OS of WBC >200 x 10^9 group is 68%, P= 0.16)

			Yogyakarta. 2010-2016		• The abandonment rate was 4.5%
6. Wijayanti, L. P., & Supriyadi, E. (2018).	NA	Retrospective study	309 children with ALL (< 18 years) in Dr. Sardjito Hopital, Yogyakarta. 2010 - 2015	Kaplan- Meier	• The overall survival of ALL patients was 56,1±3,9%. Grouping the risk based on the National Cancer Institute (NCI) was a prognostic factor for the survival rate of ALL patients.
7. Agnes, M., Widjajanto, P. H., & Damayanti, W. (2018).	NA	case-control study	100 children with ALL received induction phase chemotherapy (aged 1 month-18 years) from January 2013 to December 2015 (50 cases & 50 control)	Medical records from Sardjito General Hospital WHO child growth Z-score	• The percentage of nutritional status: severe malnutrition 6%, Malnutrition, 42%, good nutrition 48%, over-nutrition 4%. • Malnutrition was significantly correlated with febrile neutropenia (OR= 2.62; 95%CI 1.07- 6.45; p = .03).
8. Yakin, R., Syarif, S., & Tehuteru, E. S. (2017).	NA	Retrospective cohort study	68 children with ALL (1–15 years) in Dharmais Hospital, Jakarta. 2008–2016	Medical Record	• The probability of 3 years survival rate after remission were 30% (protocol 2006) and 27% (protocol 2013). • The difference score of 3 years survival rate between protocol 2006 & 2013 was HR 1,57 (CI 90% 0,577– 4,299). • There was no significant difference between protocol 2006 and protocol 2013 (p = .456).
9. Kulsum, D. U., Mediani, H. S., & Bangun, A. V. (2017).	NA	Quasi experiment-nonequivalent pretest-posttest control group	34 school-age children with leukemias in Rumah Cinta, Bandung	PedsQL general score dan cancer Module	• PedsQL general score before swedish massage therapy is 57,544 SD = 16,744 • PedsQL general score after swedish massage therapy is 85,933 SD =

					5,4682
					• There is a difference in QOL scores before and after Swedish massage therapy (p = 0,000).
10. Anggraini, S., & Trifianingsih, D. (2017).	NA	Cross-sectional	30 children with ALL who get pain during chemotherapy in Ulin Hospital, Banjarmasin	The scale of descriptive pain Faces pain rating scale	• 60.0% and 33.3% of children received emotional support from their families frequently • 63.3% of children having moderate pain, and 36.7% suffering mild pain • The emotional support is correlated with pain (p = 0.038).
11. Novrianda, D., Yetti, K., & Agustini, N. (2016).	NA	Cross-sectional study	25 children with ALL during chemotherapy in Dr. M.Djamil Hospital, Padang. 2013	Nurses role questionnaire PedsQLTM 4.0 Generic Core Scale	• The mean score of the PedsQLTM 4.0 Generic Scale is 69,2 SD 16,2 • There is correlation between nurses roles and child's QOL (r = .465, p = .019)
12. Sjakti, H. A., Gatot, D., & Windiastuti, E. (2016).	NA	Retrospective study	93 medical records of children with AML in Dr. Cipto Mangunkusumo Hospital, Jakarta. 2007-2010	Kaplan-Meier	• Overall survival (OS) was 46,2% • Event-free survival (EFS) was 6,5% • 53.8% (50) of children passed away • 62% of death caused by sepsis/infection.
13. Novrianda, D., & Khairina, I. (2015).	N/A	a quasi-experimental design Pretest-Posttest design	25 parents and children with ALL toddler-school aged in Dr. M. Djamil Hospital Padang February to November 2014 consecutive	PedsQLTM 4.0 Generic Core Scale PedsQLTM 3.0 Cancer Module	• PedsQLTM 4.0 Generic Core before & after : 64.28 SD 15. 88 vs. 69.65 SD 14.49 • PedsQLTM 3.0 Cancer Module before & after: 65.95 SD 14. 87 69.72 SD 13.85 • Before the intervention, the quality of life was significantly different from QOL after the educational

				sampling		intervention (p = 0.012 for generic; p = 0.000 for cancer).
14. Sitaresmi, M. N., Mostert, S., Gundy, C. M., Ismail, D., & Veerman, A. J. (2013).	NA	randomized stratified control group clinical trial	108 Parents of children with ALL (0–16 years), in Dr.Sardjito Hospital, Yogyakarta.	information-booklet Information-audiocassette Information DVD Kaplan Mayer		• The EFS-estimate at 3 years of highly educated mothers in the intervention group (62%) is higher than the control group (29) with *p* = 0.04. • There was no difference between EFS-estimates at 3 years of low-educated mothers between the intervention and control groups (26% vs. 18%, P=0.86).
15. Hapsari, M. M. D., Tamam, M., & Satrio, P. (2013).	NA	Retrospective Case-Control Study	26 medical records of children with ALL (1-14 years) suffered neutropenia in Dr. Kariadi Hospital, Semarang. 2010 - 2011.	Structured interview Medical record		• Poor/low economic social was a risk factor of neutropenia fever with OR value 4,591 times compared by non-poor patient (p=0,032; 95%CI=1,078-15,086). • High-Risk Chemotherapy, Nutritional status, the mean of intravenous therapy duration & hypoalbuminemia were not factors of neutropenia fever. • There were not significant factors influenced neutropenia fever occurrence.
16. Simanjorang, C., Kodim, N., & Tehuteru, E. (2013).	NA	Cohort Retrospective study	95 medical records of children with leukemia in Dharmais Hospital, Jakarta. 1997-2008.	Medical record Kaplan-Meier.		• The overall 5 years survival rate is 22.6% • Five years survival rate of AML is 4.6% • Five years survival rate of ALL is 28.9%. • The hazard ratio of AML is 1.643 times more than ALL.
17. Supriyadi, E.,	NA	Retrospective study	720 medical	Medical records		• The number of ALL = 496 (68.95%),

Widjajanto, P. H., Purwanto, I., Cloos, J., Veerman, A. J., & Sutaryo, S. (2011).			records of children with leukemia (0–14 years) in Dr. Sardjito Hospital, Yogyakarta. 1998 - 2009		AML = 170 (23.6%), CML = 30 (4.2%), and ALL-L3 = 24 (3.3%) • The estimated annual incidence rate (AAIR) of acute childhood leukemia was 46.2 per million per year. • The annual incidence rate (AIR) significantly increased from 35 in 1999 to 70 in 2009 (p = .003).
18. Tehuteru, E. S. (2011).	NA	Descriptive Retrospective	69 children with ALL in Dharmais Hospital, Jakarta. 2000 –2008	Medical record	• Symptoms at the first time admitted to hospital: 56.52% is fever, 69.57% is hepatomegaly, 14.49% is skeletal pain, and 39.13% is bleeding • At the and of the research, 44.93% of children passed away, 27.54% still alive, and 27.54% lost of follow up • EFS of ALL was 38,1%.
19. Mostert, S., Sitaresmi, M. N., Gundy, C. M., Janes, V., & Veerman, A. J. P. (2010).	NA	Retrospective study	283 medical records of children with ALL (0–16 years), in Dr.Sardjito Hospital, Yogyakarta. 1997–2002 =164 & 2004-2006 =119	The medical records Kaplan-Meier	After the education Programme: • Treatment refusal decreased from 14% to 2% • Event-free survival increased from 13% to 29% among poor patients. • Treatment dropout increased from 0% to 13% significantly among prosperous patients. • Toxic death increased significantly from 23% to 36%
20. Widiaskara, I. M., Permono, B., Ugrasena, I. D. G., & Ratwita, M. (2010).	NA	Descriptive retrospective study	82 medical records of children with ALL (4 months – 15 years), in Dr. Soetomo Hospital, Surabaya. 2006	Medical records	• The Symptoms of ALL: fever (70,7%), pale (50%), bleeding (62,1%), hepatomegaly (60,9%), splenomegaly (52,4%). • 36,8% of children passed away at the end of the induction phase • Most death caused by infection

21. Sitaresmi, M. N., Mostert, S., Schook, R. M., & Veerman, A. J. (2010).	NA	An exploratory, descriptive study.	159 children diagnosed with ALL in Dr. Sardjito Hospital, Yogyakarta. 2004 & 2007	Questionnaire Structured interview	(76%). • 25% of children refused or abandoned therapy. • For patients who refused or abandoned treatment,70% of children died, 30% of children were still alive • The Reasons for abandonment are financial problems (77%), transportation and distance to the hospital problems (60%), belief about incurability of ALL (22, 60%), and side effects of chemotherapy (35%)
22. Permatasari, E., Windiastuti, E., & lrawan Satari, H. (2009).	NA	Retrospective study	252 medical records of children with ALL in Dr. Cipto Mangunkusumo Hospital, Jakarta. 1998 - 2003	Medical record Kaplan-Meier	• Overall survival of children of 1-2 year old was 57%, aged 2-10 years was 47%, and 10-18 year old was 35%. • Five-year–event-free survival (EFS) of 1-2 year old was 40%, aged 2-10 years was 40%, 10-18 year old was 16% ($p < .05$)
23. Sitaresmi, M. N., Mostert, S., Purwanto, I., Gundy, C. M., Sutaryo, & Veerman, A. J. (2009).	NA	Longitudinal study .	51 parents of children with ALL, in Dr. Sardjito Hospital, Yogyakarta. 2004 and 2006.	Questionnaire Assessing 13 common symptoms	Side Effects of chemotherapy: • *Behavior alteration/irritable (92%)* • *The increased appetite (88%)* • *Infection (83%)* • Weight gain (80%) • Alopecia (80%) • Loss of appetite (79%) • Nausea and or vomiting (69%) • Stomatitis (63%) • Fatigue (57%) • Abdominal pain (57%) • Bleeding (29%).

- Impact of side effects on daily activities: 78% difficulties in walking, playing, or attending school)

Table 2. Summary of Qualitative Studies

Author & year	Framework	Study Design	Sample & Setting	Research focus	Findings
Suryani, A. E., & Syafiq, M. (2016).	N/A	*Interpretative phenomenology study*	5 *teenagers with leukemia*	The adolescent's e*xperience having leukemia*	Themes identified: • First experience during diagnosis including disappointment, denial, hopelessness, and puzzled • The psychological effects of a disease, including afraid to die, decreasing self-esteem, and shyness. • The positive effects of the disease: be closer to God, increased patience, and be optimistic. • The strategies to cope with the problem: seek support from the family members and friends
Widianita, P. L., Mikarsa, H. L., & Hartiani, F. (2009).	N/A	Qualitative study	2 adolescents aged 11-15 years with leukemia.	The meaning of life during diagnosed leukemia	• Life is meaningful. • Try to make other people happy and motivating them to be healthy.

DISCUSSION

This article is the first integrative review of children with leukemia in Indonesia. It is acknowledged that there may be several studies that might have been missed because the current database in Indonesia falls short of inclusivity; most of the studies were published in not reputable journals nor published in any journals. Even though this review included quantitative and qualitative studies, it is difficult to synthesize information and draw conclusions about the state of knowledge of children with leukemia in Indonesian culture. Hence, characteristics of children, some problems related to the treatment, and methodological issues will be discussed in this section.

Characteristics and Some Problems of Children with Leukemia

Leukemia had been suffered by the majority of children aged 1-10 years, it reached 77.6%, in which the highest incidence occurred on children 1-5 years old approximately 34% in Dharmais hospital and 45 % in Dr. Soetomo Hospital (Simanjorang et al., 2013; Supriyadi, Widjajanto, Purwanto, et al., 2011; Tehuteru, 2011; Widiaskara et al., 2016). This is in line with the theory that leukemia's peak incidence between 2 and 5 years, with mean of age, was 6.3 ± 0.5 years (Lustosa de Sousa et al., 2015; Vora, 2016).

The survival rate is a crucial indicator of children with leukemia. There was a different duration and result among hospitals in Dharmais Hospital. It appeared that the overall five-year survival rate of children with ALL was better than children with AML (22.6% vs. 4.6%). Moreover, this hospital's event-free survival was 30%-38.1% (Simanjorang et al., 2013; Tehuteru, 2011; Yakin et al., 2017). A more recent study found better results in survival rate for AAL patients of Dr. Sardjito Yogyakarta, approximately 56,1±3,9% (Wijayanti & Supriyadi, 2017). This result was almost the same as the finding from other countries in the ASEAN region, such as Thailand, where the five-year survival of children with cancer was 47.2% in 2001-2011 (Bidwell et al., 2019). Even though there was an improvement in survival rate every year, this figure is still much lower than the rate in developed countries, such as Netherland, which reached 91% (Reedijk et al., 2021). Also, this mortality rate was higher than in Western Asia countries which the mortality occurred between 1.1 and 2.9 patients per 100000 people (Khazaei et al., 2019). The survival rate differed between high-risk and standard-risk children, in which the two-year event-free survival (EFS) of children who had white blood cells (WBC) $50\text{-}200\text{x}10^9$ was 68% while children with WBC more than 200×10^9 was 45% (Alfina et al., 2011).

Chemotherapy is the main treatment of leukemia, has taken a long time, and provided adverse side effects (Hunger & Mullighan, 2015; Mwirigi et al., 2017). Most children experienced fatigue (51%), mucositis (51%), infection (84%), and pain (63%) (Agnes et al., 2019; Anggraini, 2018; Devi & Allenidekania, 2019; Fadhilah & Allenidekania, 2019; Sitaresmi et al., 2010; Widiaskara et al., 2016). Anticancer drugs resulted in high toxicity to the cells and organ dysfunction (Arora et al., 2010; Eche & Aronowitz, 2018). Fatigue was a direct effect of anemia, in which a study in Brazil found that 85% of children with leukemia suffered anemia, and 35% of them experienced severe anemia. This situation is closely related to the response to the therapy, such as infection, which was the main cause of child death (Lustosa de Sousa et al., 2015; Sjakti & Windiastuti, 2016).

Chemotherapy side effects ultimately affected the quality of life (Hunger & Mullighan, 2015). Quality of life was one indicator of leukemia treatment, which is of leukemia was quality of life which is an actual outcome of treatment to evaluate the interventions and care programs (Eiser et al., 1999; Eiser & Morse, 2001). This study found the two most widely used instruments in evaluating the quality of life of children with ALL was PedsQL TM 4.0 generic core and PedsQL TM 3.0 cancer Module. Based on a study on children under 18-year-old, stated that the most frequent tools to evaluate the QoL of children with cancer were PedsQL (Pediatric Quality of Life Inventory) 4.0 generic score scales and PedsQL 3.0 cancer module (Momani et al., 2016). The generic scale module score ranges from 57.5 – 6.65, while the PedsQL cancer module was 69.7. It has indicated a moderate level of quality of life (Kulsum et al., 2017; Novrianda et al., 2016; Novrianda & Khairina, 2015). A

low level of quality of life is common for children with ALL; a study found that 78.1% of children with ALL had a poor quality of life (Desouky et al., 2017). Additionally, a systematic review concluded that children's quality of life with ALL was low during active treatment until treatment completion (Fardell et al., 2017).

Last, even though the abandonment therapy, treatment dropped out and lost follow up rate continued to decline every year approximately from 13-27.5% in 2011 to 4.5% in 2018, this remains high compared to other countries (Alfina et al., 2011; Mostert et al., 2010; Sitaresmi et al., 2010; Tehuteru, 2011). Although this number was lower than abandonment treatment in China, which was only 3.1%, it was better than abandonment therapy in India reached 27.1% (Cai et al., 2019; Hazarika et al., 2019). Furthermore, a systematic review and meta-analysis study stated 30% of 10. 754 children with cancer abandoned treatment (Palagyi et al., 2021).

Methodological Issues and Theoretical Framework

This section discussed methodological issues, including the study's theoretical framework, study design, samples, and instrument issues. According to a massive literature review from 2009 to 2019, the theoretical framework was crucial issues in which there were restricted study guided by a theory-based conceptual framework as well as other countries. The theoretical framework is a pivotal tool to conduct a study to identify and clarify relationships of variables and provide directions for research investigation. Additionally, it is also crucial to base research on a conceptual framework; therefore, the findings contribute to the development and additional evidence supporting or refusing the theory (McGaghie et al., 2001; Mock et al., 2007).

Study Design and Samples Issues

Most studies were descriptive with a retrospective study design that describes some phenomena experienced by children during active treatment. Moreover, several studies evaluated the association among a single variable between an independent variable and a dependent variable. Thus, the studies resulted in very few hypotheses; the data analysis was only a t-test; therefore, no one study applied multivariate analysis or causal model. Although some findings were statistically significant, the association could not predict the outcome, not contribute to developing the theory and the evidence-based field.

The study sample mostly has taken small sample size was a weakness of those studies (ranged 44-98 participants). No one study reported the sample size calculation and power as well as international studies. The small sample size risky to reduce the entire population's representation provides bias of cases (Faber & Fonseca, 2014). Moreover, inappropriate sample size causes worthless results study, risky to increase type 1 error, fail to detect essential effects and have low power to detect the effects (Baguley, 2004). Nowadays, the sample size calculation is strongly recommended in research protocols and review boards for analyzing effectiveness data and the value of the results (Bader et al., 2018; Schoemann et al., 2017).

Instrument Issues

The issues related to instruments consist of the translation process, validity and reliability, and permission for using the instrument. Although there was one study that asked permission in using the HRQoL tool (Sitaresmi et al., 2008), other studies did not report the consent in using the tool. Moreover, the translation process was not reported in the studies, so that it could not identify the appropriateness of the translation process and its validity. Additionally, the reliability test had been performed using the same data from research participants. Consequently, the strength of the study and the validity of the result could be lower.

CONCLUSIONS

The number of childhood leukemia increases continuously in the future in the near future. Evidence from studies reviewed described that the survival rate was evaluated based on data from a single hospital. In the future, it is necessary to conduct research involving a broader setting involving several hospitals in the provincial and national. Moreover, the quality of life as an indicator of treatment outcome evaluated quite frequently using small size samples (< 100). Next, studies related to the quality of life need to evaluate children's quality of life using big sample sizes. It is also necessary to assess the factors or predictors associated with the quality of life using multivariate analysis to identify the main factor to support the intervention program. Therefore, a comprehensive study is crucial to identify the QoL of children with leukemia.

Based on research methodology, some studies correlated two variables, and the findings were statistically significant. Unfortunately, the single independent variable could not predict the outcome exactly as well as the small size of the sample. Furthermore, the absence of sample size calculation reports of all studies caused the study results did not represent the entire population, increasing the risk of type 1 error and failing or having low power to detect essential effects. In order to maximize the worth of the results study and prevent this issue, the next study needs to calculate the sample size and statistical power properly. Also, a conceptual framework is a crucial issue; it needs to be applied for the next study to result in high-quality research finding to support a theory. Finally, the instruments' issues were pivotal to improve the subsequent studies, using instruments will be selected carefully with high validity and reliability, and using an appropriate back-translation process.

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