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Applicability of protocols from high-income countries in a resource limited setting; real world data of histopathology, clinical features and long-term outcome of Hodgkin Lymphoma in Sri Lanka

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ABSTRACT

Background:: There is a significant disparity in global cancer care and out-come between countries. We aimed to provide data on characteristics, average cost of treatment and survival estimates in patients with Hodgkin Lymphoma in Sri Lanka.
Methods: All patients diagnosed with Hodgkin Lymphoma between 01.05.2013 and 01.10.2020 were included in the analysis.
Findings: Classical Hodgkin Lymphoma(cHL) diagnosed in 85%; 68% presented with B symptoms and 61% had advanced stage of disease. Treatment was discontinued by 23% either before or just after starting treatment of whom 72% percent were females. The complete response (CR) rate of patients who continued treatment was 86% while the estimated five-year survival rate is 92%. Seventeen percent of these patients died but only two percent due to Hodgkin Lymphoma or associated treatment in the group which continued treatment compared to 45% in the group who defaulted treatment (p-value 0.0002). Five-year survival rate of patients who defaulted treatment was 50% while patients who continued treatment have an estimated five-year survival rate of 90%. Average cost of first line treatment was between US$ 2280 and US$ 7642. First treatment failure may incur substantially higher health care costs.
Interpretation: This is the only well characterized study on long-term survival of patients with Hodgkin Lymphoma in Sri Lanka. We have shown that it is possible to successfully apply western treatment and supportive care protocols to the local population. This published data will help to bench mark and improve the treatment and develop blood cancer care in the local setting.

1. Introduction

Hodgkin Lymphoma (HL), first described by the British pathologist Thomas Hodgkin [1] is a B cell malignancy and is the commonest lymphoma among young adults in the west, but there are no records

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Research in context

Evidence before this study

There is no published substantial research related to any type of blood cancer in Sri Lanka. We searched PubMed identify studies published between database inception up to December 31, 2020, with no language restrictions. Using the search terms "Hodgkin Lymphoma", "survival" and "Sri Lanka" there was only one published study, which was related to global burden on disease and not related to the aim of this study. There were few studies reported from low-income countries showing substantial variations in five-year overall survival of Hodgkin Lymphoma but none from Sri Lanka. In addition, many of these have limited value when adapting strategies to improve survival in Sri Lanka because they are outdated, heterogenous in nature, have large numbers lost to follow-up, and because of sparse clinical or therapeutic data.

Added value of this study

This is a part of larger hospital-based blood cancer cohort treated in the first dedicated blood cancer facility in Sri Lanka. This is the first such facility in the country used for training purposes in addition to treating patients. Western protocols were successfully implemented for treatment and detailed demographic and clinical data on this cohort is being collected, in which participants are followed up regularly. This is the first study which can be used as a proof of concept of successful use of dedicated blood cancer centre and protocols from high-income countries for treating Hodgkin Lymphoma in a country where patients believe in various other traditional treatment modalities.

Implications of all the available evidence

There is an excessive mortality and paucity of local data for a cancer that is potentially curable in the west. This study confirms outcome for local patients with Hodgkin Lymphoma to be comparable to high-income countries. This holds promise for blood cancer care in Sri Lanka and will give trust and belief to patients and medical staff alike about the achievable targets. Results of this study suggest mortality can be reduced and burden on health care system can be minimized if diagnosed and treated in the appropriate setting.

available of its incidence or long-term survival in Sri Lanka. With improvement in polychemotherapy and radiotherapy (RT) it has a cure rate of about 85 to 90% in high income-countries [2,3]. However relapsed / refractory disease has limited long-term survival and haemopoietic stem cell transplants and novel agents [4] are utilized in managing such patients. Data related to geographical differences, clinicopathological and global survival variability are not well documented and there is a correlation between poverty and lack of accessibility to health care and vice versa in low-income countries [5].

Health systems in low -income countries face the struggle of providing most basic health care and potentially lifesaving chemotherapy regimens. Limited resources in low -income countries are not considered in evidence-based guidelines from high-income countries. Sri Lanka is a developing country with a diverse healthcare structure, without a dedicated Haemato-Oncology / Clinical Haematology centres, transplant facilities or access to novel anti-cancer agents at the time this study was started. There are no published data on characteristics or survival of HL in Sri Lanka. Our first author has more than two decades of work experience in the United Kingdom (UK) in level 3 haemato-oncology care centres. We established the Lanka Hospital Blood Cancer Centre (LHBCC) in 2013 in a self-funded hospital in Colombo, Sri Lanka in collaboration with colleagues in government subsidised hospitals. In line with centres in the UK, LHBCC consists of designated in-patient and out-patient space, staff and a strategy to treat blood cancers using treatment protocols from the UK [6]. In addition, LHBCC was used for training purposes of first Haemato-Oncology trainees from government subsidised hospitals.

The aim of the study was to analyse patient and disease characteristics and evaluate survival parameters in patients diagnosed with HL. Treatment and supportive care protocols from the UK [6] were used with the experience of the first author at tertiary care centres in the UK. In the absence of published local data, we used studies from other Asian countries and from high-income countries for comparison.

2. Methods

2.1. Study site

All patients with a diagnosis of HL presented to the LHBCC between 01 May 2013 and 01 October 2020 were included in the analysis. LHBCC is a dedicated unit for treatment of haematological malignancies with trained staff. Modified standard operating procedures (SOPs) from high-income countries were used in treatment and in supportive care [6]. A link system was created with the Lanka Hospital Diagnostics (LHD) and blood bank for rapid access of blood test results and blood products. All nursing staff had yearly training on administration of chemotherapy and on supportive care methods. New posts of head of nursing in Oncology and clinical nurse specialists (CNS) in Haemato-Oncology were created. Relevant training was arranged locally and in centres in Singapore and India. Medical aspects of Haemato-Oncology services provided by full time British trained Clinical Haematologist and visiting General Oncologists and other supportive care specialists.

2.2. Treatment and data collection

The diagnosis was based on a WHO classification of haematological malignancies [7] and the clinical staging was done based on Ann-Arbor staging system [8,9]. All patients were histologically confirmed and radiologically staged. Details of all patients including demographic characteristics, clinical findings, laboratory parameters, treatment cost, response and survival parameters were recorded. All authors had access to data. Patients were treated with combination chemotherapy with Doxorubicin, Bleomycin, Vinblastine and Dacarbazine (ABVD); Chlorambucil, Vinblastine, Procarbazine, Prednisolone (ChlVPP); Cyclophosphamide, Vincristine, Doxorubicin, Prednisolone (CHOP) with or without Rituximab. Three patients received RT in addition to chemotherapy while four were diagnosed concurrently with tuberculosis (TB) and received anti TB treatment (ATT). Most patients were treated on an out-patient basis unless they developed febrile neutropenia or it was decided by the primary physician to admit patients for in-ward care.

Treatment outcome was evaluated by measuring complete response (CR) rate and five-year overall survival (OS) rates with subanalysis performed according to age, gender, stage, histological type and B symptoms at presentation. Response to treatment was evaluated at the end of second cycle of planned first line treatment. CR was defined as not having radiologically significant lymphadenopathy on computerized tomography (CT) or on positron emission tomography (PET) and OS was defined as the time from the diagnosis to death related to HL. Death directly related to HL or treatment was defined as a disease related death. Direct cost of treatment was obtained from hospital records.

2.3. Statistical analysis

Response to therapy and the disease status at last follow-up were recorded and analysis were performed utilizing various survival analysis techniques through RStudio (RStudio Team, 2020). When patients did not experience the event of interest by his/her last follow-up such patients were considered as censored. To estimate the survival curves and compute the related summary measures, Kaplan-Meier (KM) estimator was used. Statistical comparisons of survival curves among various interested groups were conducted using log-rank tests. The level of significance of all statistical tests were fixed at 0.05 level. The median follow-up which is the median observation time to the event of interest. The median length of follow-up was computed using reverse Kaplan-Meier (KM) estimator [10].

2.4. Ethical committee approval

Study was considered as a quality improvement activity and approval was obtained from the Lanka Hospitals medical research and the ethics committee for the collection and analysis of anonymized data. Informed consent was obtained from all patients.

2.5. Role of the funding source

No external funding used for the study.

3. Results

3.1. Age and gender of patients with HL presented to LHBCC

A total of 50 patients who presented to LHBCC were recruited for analysis. Three patients presented with relapsed / resistant disease, hence were excluded from the survival analysis. Median age at presentation was 32 (range 12 to 83 years; Q1 at 24.5 and Q3 at 48.5 resulting in an interquartile range of 24); male to female ratio was 1.13:1.

3.2. Histological subtypes and staging of HL presented to LHBCC

Eighty five percent had Classical Hodgkin Lymphoma (cHL) (14 NS, 19 MC, 7 cHL nos) and 15% had Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL); 68% presented with B symptoms; 61% in advanced stage (stage III & IV).

3.3. Treatment and follow up of patients with HL in LHBCC

Twenty three percent did not start or continue treatment. Seventy two percent of those who defaulted treatment were females. Seventy eight, seventeen and five percent received ABVD, R-CHOP and ChlVPP respectively. Three patients received RT while four patients received ATT. Ninety eight percent were followed up till 31.12.2020 or till death.

Baseline demographic characteristics and treatment received on newly diagnosed patients with HL is in Table 1 and Fig. 1.

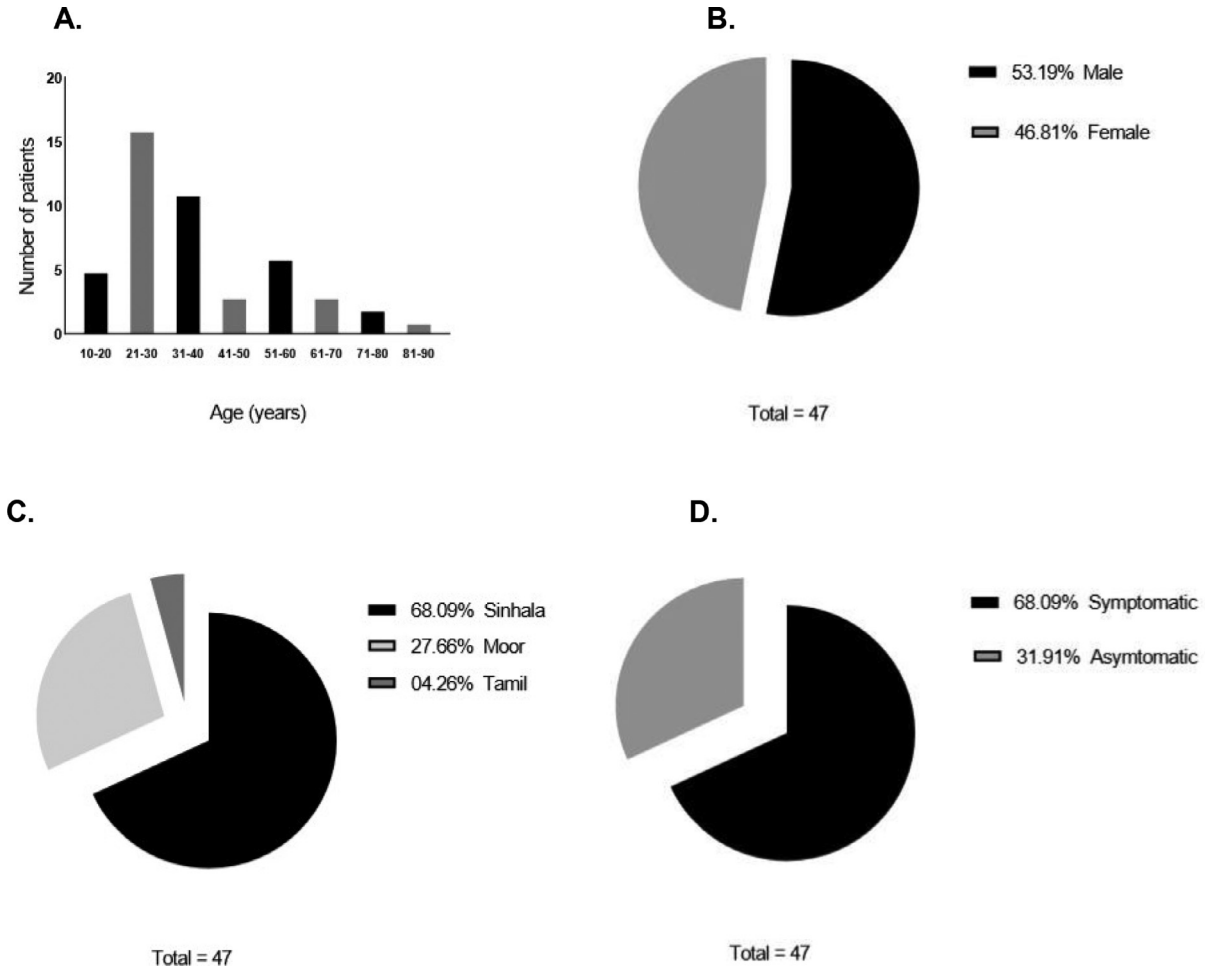


Fig. 1. (A) Age, (B) Gender, (C) Ethnicity, (D) Presence of B symptoms at presentation, (E) Histological type and (F) Stage at presentation of newly diagnosed HL presented to LHBCC. Proportion opted for treatment (G), proportion defaulted treatment (H) and type of treatment given (I) in LHBCC.

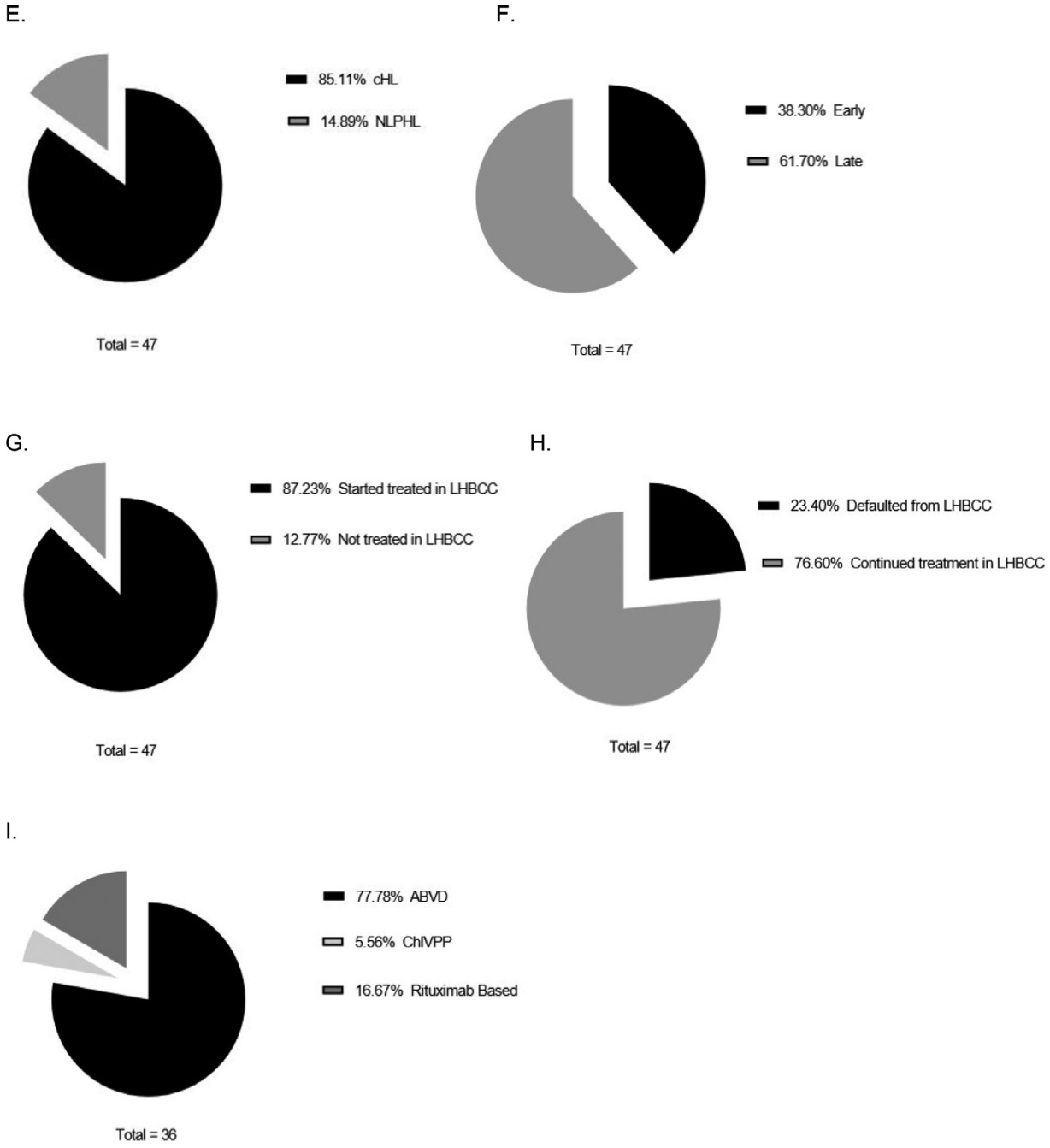


Fig. 1. Continued.

3.4. Response of patients with HL treated in LHBCC

Ninety seven percent showed good response which is defined as more than 50% volume reduction [11] while one patient had stable disease. Eighty six percent of patients who continued treatment achieved CR.

Five patients did not achieve CR at the end of treatment. Two received peripheral blood stem cell transplant (PBSCT) abroad after second line rescue treatment. Two received consolidation RT as they could not take the option of PBSCT due to financial reasons, while one patient died while receiving treatment due to chronic obstructive pulmonary disease, pulmonary fibrosis and chest infection.

3.5. Survival of patients with HL treated in LHBCC

Up to 01.12.2020, 17% have died but we observed only two percent died due to Hodgkin Lymphoma / associated treatment in the group who continued treatment compared to 45% from the group of patients who defaulted treatment (p-value 0.0002). Median follow-up of the cohort is 47 months. Median OS of patients who achieved CR is not reached. The estimated five-year OS of patients who achieved CR is 92%. As illustrated in Table 2B there was a significant difference (p-value of 0.00025) in five-year OS according to age (< 40 and ≥ 40) but not according to gender (p-value 0.9), stage (p-value 0.1), histological type (p-value 0.4) or patients presented with B symptoms (p-value 0.2). Discontinuation /not starting treatment was

the main factor in those with reduced survival. As shown in Fig. 2 patients who continued treatment had an estimated five-year survival rate of 90%, which is comparable with survival rates of high-income counttries [2].

3.5. Financial cost of treatment in HL in LHBCC

As detailed in Table 3, mean cost of first line treatment in LHBCC for ABVD; ABVD+IP; and R-Based was US$ 2280, US$ 4694 and US$ 7642 respectively.

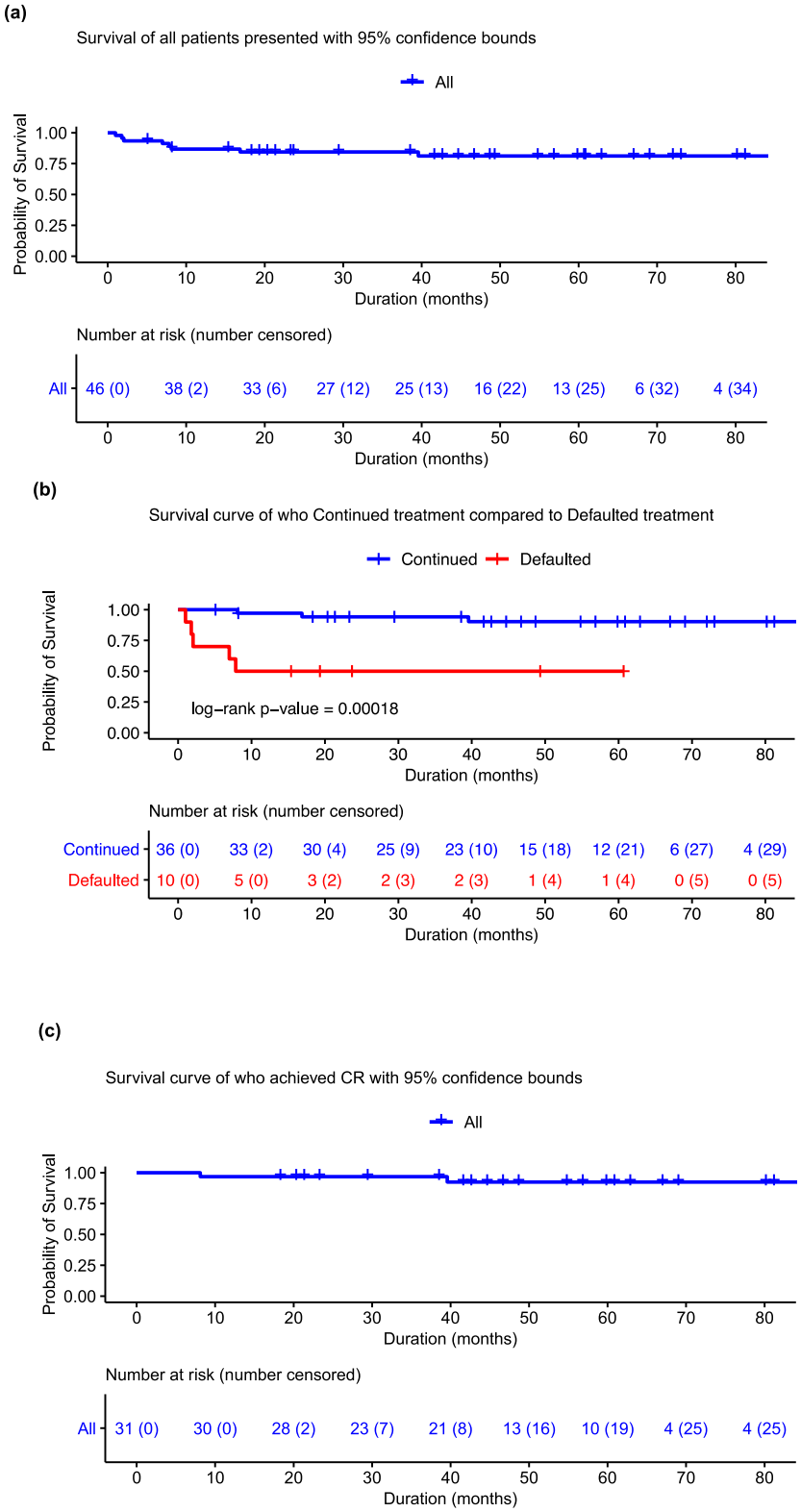


Fig. 2. Kaplan-Meier Survival Curves of HL Patients (a) survival curve of who started treatment (b) survival curve of who continued treatment compared to defaulted treatment (c) survival curve of who achieved CR (d) survival curves by age at diagnosis <40 versus ≥40 (e) survival curves by gender (f) survival curves by stage (stage I-II versus stage III-IV) (g) survival curves for CHL and NLP HL (h) survival curves by presence of B symptoms.

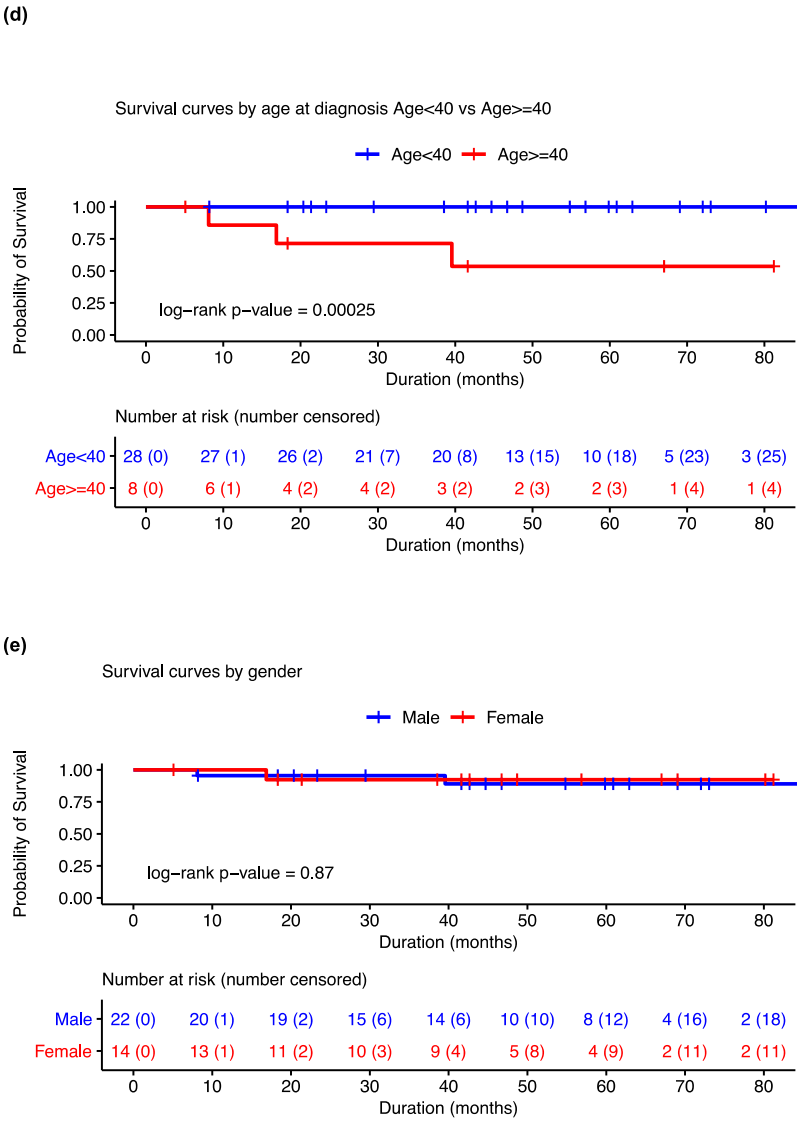


Fig. 2. Continued.

In a single example of relapsed disease, the cost of rescue treatment was US$ 108247.

We illustrate details of one patient to highlight the economic impact of relapsed disease in Sri Lanka. The subject is a 29-year-old female with stage IIIB NSHL treated with dose reduced ABVD and consolidation RT. She presented to LHBCC with relapsed disease within few months of RT. She received further two lines of therapy to achieve a CR and was followed by a PBSCT abroad. This was an uncommon example of a patient who could raise funds to receive above treatment but majority are likely to succumb to their disease due to financial constraints. The total cost including chemotherapy and hospital admissions of her care from the time she presented with relapse was US$ 108247 compared to the average cost of US$ 2280 to US$ 7642 first line treatment in LHBCC.

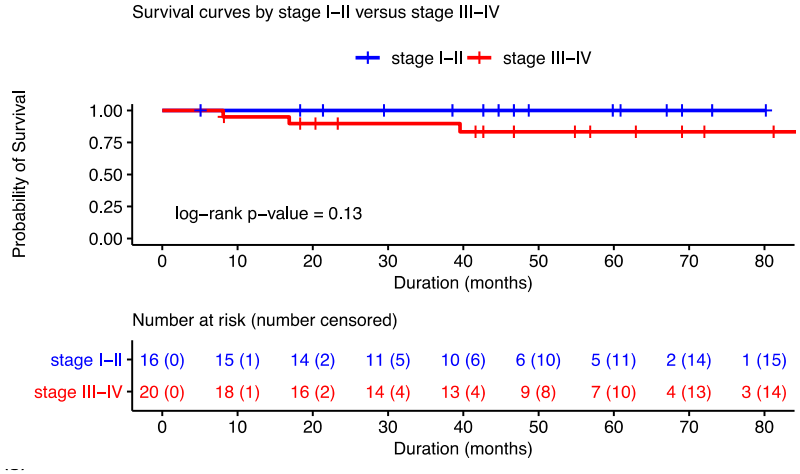
4. Discussion

Current trials in HL in the West aim to reduce treatment related late effects while maintaining the excellent survival rates [12,13]. However, curing most blood cancers is challenging in low-income countries, especially in a country without free and easy access to the specialty of blood cancer care centres, PET scans, transplant facilities or newer treatment options. Asian studies comparing clinicopathological features and survival parameters with data from the west have shown lower incidence of lymphomas but worse prognosis [14,15]. There is a paucity of trained hematopathologists, proper patient referral system, facilities for immunohistochemistry and centralized review process.

It is known that clinical characteristics and epidemiology of Hodgkin Lymphoma in Asia are different from Western countries [16]. Two main types are NLPHL and cHL. cHL is the commonest in the west accounting for up to 90% of cases [17]. In line with above we also had 85% cHL and 15% NLPHL. There is a discrepancy between the commonest cHL subtype among different studies from low-income countries. While Nodular Sclerosis HL (NSHL) is the main sub-type according to some, mixed cellular HL (MCHL) is reported to be the main subtype in others [16,18,19]. It is possible that different low-income countries have different histological sub types or there is no uniformity in presentation or reporting due to lack of robust cancer services.

According to studies in the high-income countries, the peak incidence of HL is among individuals of 15-35 years and a second peak in late life for subtypes other than NSHL [20]. However, second peak is not reported among Asian and black populations [21]. In line with prior published studies, median age at presentation in our cohort was 32 years (with Q1 at 24.5 and Q3 at 48.5 resulting in an

(f)



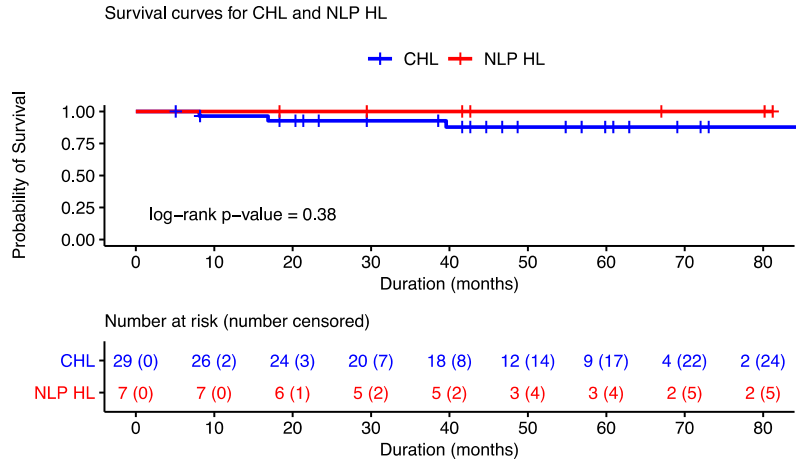


Fig. 2. Continued.

(h)

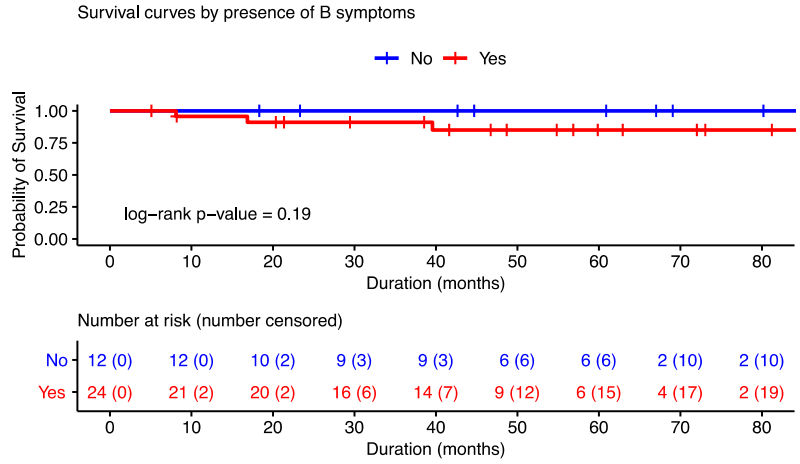


Fig. 2. Continued.

Table 1
Baseline demographic characteristics on newly diagnosed patients with HL treated in LHBCC

Variable	n (%) / Median (IQR)
Age (years)	32 (30)
Gender (male)	25 (53%)
Ethnicity	
Sinhala	35 (70%)
Moor	13 (26%)
Tamil	02 (04%)
B symptoms at presentation	32 (68%)
Histological type	
cHL	40 (85%
NLPHL	07 (15%)
Stage	
Early (I/II)	18 (39%)
Late (III/ IV)	29 (61%)
Proceeded to receive treatment	41 (87%)
Total Defaulted	11 (23%)
Treatment type	
ABVD	28 (78%)
ChlVPP	2 (05%)
Rituximab based	6 (17%)

cHL(Classical Hodgkin Lymphoma); NLPHL (Nodular Lymphocyte Predominant Hodgkin Lymphoma); ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine); ChlVPP (Chlorambucil, Vinblastine, Procarbazine, Prednisolone)

Table 2B
Survival analysis using Kaplan-Meier method of who continued treatment by (a) Age <40 Vs ≥ 40 (b) Gender (Male Vs Female) (c) Stage early Vs Late (d) Histology cHL sub-types Vs NLPHL (f) B symptoms at presentation Vs No B symptoms.

Group	Median OS	p-value
(a)Age <40 year Vs ≥ 40 years	Not reached	0.0002
(b)Gender Male Vs Female	Not reached	0.9
(c)Stage early Vs Late	Not reached	0.1
(d)Histology cHL sub-types Vs NLPHL	Not reached	0.4
(e)B symptoms at presentation Vs No B symptoms	Not reached	0.2

cHL(Classical Hodgkin Lymphoma); NLPHL (Nodular Lymphocyte Predominant Hodgkin Lymphoma)

interquartile range of 24) and the greatest number of patients are between 20 and 40 years (57%). It is difficult to assess the bi-modal distribution due to the small size of the series.

Our cohort has shown only a very slight male predominance (1.13:1) which is not in keeping with other published data [22,23]. Chinese and Indian reports show higher male to female ratio similar to studies from high-income countries [16,24]. It is possible that this may not be true representation of disease among males in Sri Lanka or male patients were not presenting for treatment to a self-financed treatment centres and depend on alternative treatment methods / centres.

Patients usually present with early stage disease in high-income countries, (I, II), and with advanced stage disease (III, IV) developing countries [19]. Initial staging in our study is mostly based on CT unlike in studies from high-income countries due to limited access to PET scans [13]. There was only one PET scanner for a population of nearly 22 million. The radio-active reagent is imported from neighboring India. In our cohort, 61% presented with advanced stage disease. This is similar to previously published results from other low-income countries and from Asians and Black population living in high-income countries [21,24]. According to data from high-income countries about 40% of cHL present with B symptoms but NLPHL rarely present with B symptoms [7]. However, in our study 68% of the total cohort presented with B symptoms while it was 72% among cHL and 42% in NLPHL. Sixty one percent in early stage (stage I/II) and 72% in late stage (stage III/IV) patients had B symptoms on presentation. Similar data are reported from other low-income countries with majority of patients presenting with B symptoms [24]. This is likely due to lack of knowledge related to early signs of cancer and additionally due to lack of proper infrastructure for early cancer detection as in the west.

Twenty three percent did not start or continue treatment in LHBCC. Compliance with trial protocols is more than 90% as reported by Johnson et al [13]. As reported by Maddi R N et al., 15-20% has refused treatment while 20-25% were lost to follow up [23]. This is the real-world scenario, which is different to data published in western trials[13]. One of the important findings in our cohort was higher number of females defaulting treatment which is of serious concern. It is likely that socio-economical and financial reasons play a part in patients decision to decline treatment.

Five-year survival rate in HL has improved significantly from being less than 10% in the 1960s [25]. Recent studies by Radford J et al., 2015 and Johnson P al., 2016 has shown three - year OS rate of 99% and 95.8% in early stage and late stage disease respectively [12,13]. However real-world data have shown survival figures which are significantly lower than reported in the high- income countries; five-year OS of 79.7% and 78.9% [23,26]. Our cohort shows five-year estimated survival rate of 81% with patients who continued treatment achieving five-year survival rate of 90%. This is the only available Sri Lankan study with long term follow up of 98% of patients up to a median follow up of nearly four years.

There were three deaths during the study period but none directly due to HL. Two patients died due to coronary artery disease while on complete remission and one died due to chronic obstructive pulmonary disease, pulmonary fibrosis and respiratory tract infection. Out of eleven patients who did not continue treatment in LHBCC, five had died due to HL, five are alive and survival status of one is not available. There is a significant heterogeneity between different hospitals with regards to diagnostic and treatment facilities and access to trained personnel and supportive care in Sri Lanka. Unlike in the high-income countries, different hospitals are likely to have different approaches to the same disease based on whether they are self-financed or government subsidised. Though this is a small study, it is apparent that higher mortality is associated with defaulting treatment in LHBCC.

Approximately 10% - 15% of early stage disease and 15% - 30% of advanced disease may not respond to treatment or show early relapse. Usual practice is to treat them with rescue chemotherapy followed by PBSCT. As reported previously there is disparity in cancer

Table 2A
Survival analysis using Kaplan-Meier method. Median follow-up (95% CI) (months), Median OS (months), Estimated 3-year OS, estimated 5-year OS and p value of (a)total cohort (46) (b) who continued treatment (c) who achieved CR (31) (d) who defaulted treatment (10) (e) comparison of who continued vs defaulted.

	Median follow-up (95% CI) (months)	Median OS (months)	Estimated 3-year OS	Estimated 5-year OS	Log-rank p-value
Total (46)	46 (41,60)	Not reached	85%	81%	
Continued (36)	46 (42,62)	Not reached	90%	90%	
Achieved CR (31)	46 (42,62)	Not reached	97%	92%	
Defaulted (10)		7	50%	50%	
Continued vs Defaulted		0.0002			

*One record removed as lost to follow up

Table 3
Cost of first line treatment for HL in LHBCC.

Variable	Mean	SD	Minimum	Q1	Median	Q3	Maximum	Range	IQR
ABVD	2280	286	1827	2005	2394	2499	2549	722	494
ABVD+IP	4694	2272	2679	3277	4083	4958	11503	8825	1681
R-Based	7642	1551	5657	6215	7497	9257	9683	4026	3042

†Excludes once received RT and who did not achieve CR
All in numbers in US$. Calculated cost includes all costs incurred over multiple admissions over the period of this study.
cHL(Classical Hodgkin Lymphoma); NLPHL (Nodular Lymphocyte Predominant Hodgkin Lymphoma); IP (in-patient care); R-Based (Rituximab based treatment).

care out-comes among high-, middle- and low-income countries due to unavailability of drugs and other treatment modalities [27]. Although consolidation with radiotherapy is the desired treatment in early stage HL, radiotherapy as consolidation in advanced HL with residual disease is not the standard of care in high-income countries. However, this may be an option when other modalities like PBSCT are not available [28].

Our data showed mid treatment desired response of 97% but 13% had residual disease at the end of planned therapy. All patients who had residual disease presented with B symptoms; three NS and two MC sub-types; three late stage and two early stage. However, numbers are too small to compare clinical characteristics with the ones who achieved CR. Tao et al., reported eight percent partial response and three percent progressive disease in a Chinese study [29]. Unfortunately, treatment options for this group are almost non-existent in Sri Lanka.

Patients are requested to pay all or part of the cost of the care in self-financed hospitals in Sri Lanka. There are few charitable organizations and government funds they can apply for help based on the individual or family income. Patients have to bear surgical expenses in addition to costs of chemotherapy, radiological, histopathological investigations. The average cost of first line treatment in LHBCC was US$ 2280 to US$ 7642. This has to be interpreted considering per capita nominal gross domestic product (GDP) in Sri Lanka is US$ 3,830 compared to US$ 68309 in the United States [30]. Publications on the cost analysis in treatment of HL in the resource constrained setting is sparse. Stefan et al., published data on the cost of treating HL in South Africa [31]. According to their data average cost of similar treatment is US$ 6647 while early diagnosis, use of less toxic protocols such as ABVD, close monitoring to prevent complications and elimination of unnecessary tests and investigations may reduce the overall cost.

Three patients with relapsed / refractory disease who had their first treatment elsewhere presented to LHBCC during the trial period. This may be a gross underrepresentation of the actual situation. Patients who fail first line treatment for HL are shown to utilize more health care resources and incur higher economic burden in high-income countries [32]. Patients with at least two lines of treatment were projected to incur US$ 535846 of health care costs in the US [32].

Full dose chemotherapy without dose reduction may give the maximum benefit [33]. We believe a substantial proportion of HL patients in Sri Lanka will progress/ relapse due to sub-optimal treatment due to various reasons. The most effective way to rectify is by training / educating health care professionals. Although first line treatment is beyond reach of most in low-income countries, cost of relapsed disease is prohibitive. Further studies are needed to determine affordable, optimal first line treatment options that could reduce the risk of progression / relapse of disease.

We acknowledge that a limitation of this study was the small sample size which may have been result of selection bias towards better outcome. In addition, it is not possible to compare with other general oncology centres or generalize these findings to the entire country. A larger study may be needed in the future with development of the specialty of 'blood cancer care' in Sri Lanka.

This is the only documented study related to outcome and applicability of western treatment and supportive care protocols to Sri Lankan patients with any type of blood cancer. In addition, here we have presented data to support the feasibility of establishing a successful dedicated Haemato-Oncology / Clinical Haematology unit where not only patients were treated according to western protocols but also participated in sub specialty training for Haemato-Oncology trainees from government subsidized hospitals. This real-world data identifies areas which need further attention and stress the importance of 'right' treatment on the first presentation to improve outcome. We believe this published data will help to bench mark and in the development of the specialty of blood cancer care in the local setting.

Authors' contributions

SH, JB contributed to the conception, design, acquisition and analysis of data, writing, review and editing, provided health care to patients. TS, SA, NP, GA, EP, MH, AW, GS, LK, VS, SS, PJ, RW, GG, CS, SM, BW: contributed to acquisition of data, writing, review and editing, provided health care to patients. CJ: contributed to the conception, design, acquisition and analysis of data, writing, review and editing, All co-authors reviewed manuscript and agreed about the contents.

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Data sharing statement

Data used in this study are available from the corresponding authors upon reasonable request.

Declaration of Competing Interest

The authors have no conflict of interest for the publication of this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100998.

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