SHORT-TERM OUTCOME OF HODGKIN LYMPHOMA PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA AND ITS PROGNOSTIC FACTORS

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LIST OF ABBREVIATIONS

ASCT	Autologous Stem Cell Transplantation
BV	Brentuximab Vedotin
CHL	Classical Hodgkin Lymphoma
CT	Computed Tomography
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ERβ	Estrogen-Receptors β
ESR	Erythrocyte Sedimentation Rate
GHSG	German Hodgkin Study Group
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
IFRT	Involved-Field Radiation Therapy
IPS	International Prognostic Score
LD	Lymphocyte-Depleted
LDH	Lactate Dehydrogenase
LR	Lymphocyte-Rich
MC	Mixed Cellularity

MMR	Mediastinal mass ratio
MNCR	Malaysia National Cancer Registry Report
MTR	Mediastinal thoracic ratio
NCCN	National Comprehensive Cancer Network
NLPHL	Nodular Lymphocyte-Predominant Hodgkin Lymphoma
NS	Nodular Sclerosis
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression-Free Survival
RT	Radiation Therapy

LIST OF SYMBOLS

/	Or
%	Percentage
≤	Less than or equal
<	Less than
≥	More than or equal
>	More than
U/L	Units per litre
β	Beta
α	Significant level
n	Number of subjects
1-b	Statistical power
A	Accrual time during which patient will be recruited
F	Additional follow up after end of recruitment
m_1	The median survival time on control treatment
m_2	The median survival time on experimental treatment
m	Ratio of control to experimental patients
p	Probability value

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ABSTRAK

HASIL JANGKA MASA PENDEK PESAKIT LIMFOMA HODGKIN DI HOSPITAL UNIVERSITI SAINS MALAYSIA DAN FAKTOR-FAKTOR PROGNOSTIK

Latar belakang: Secara umumnya, limfoma Hodgkin (HL) adalah sejenis kanser darah unik yang disifatkan oleh kehadiran sel Reed Sternberg dari biopsi kalenjar limfa. Ia adalah salah satu daripada kanser darah yang paling boleh dirawat dan mempunyai purata kelangsungan hidup keseluruhan (OS) yang lebih baik berbanding dengan jenis kanser- kanser darah yang lain. Kajian ini bertujuan untuk menentukan data sosio-demografi, ciri-ciri klinikal, ciri-ciri rawatan, kelangsungan hidup keseluruhan dan kelangsungan hidup bebas kemerosotan penyakit pesakit limfoma Hodgkin (HL) di hospital pengajar di Pantai Timur Semenanjung Malaysia.

Tatacara/kaedah: Kajian retrospektif telah dijalankan dari 1 Januari 2006 hingga 31 Disember 2018 dengan mengambil kira pesakit limfoma Hodgkin berumur 12 tahun dan ke atas. Data-data pesakit dari unit rekod Hematologi dan unit rekod perubatan telah dinilai. Data sosio-demografi, parameter penyakit dan ciri-ciri rawatan dikumpul dan dianalisis. Kaedah Kaplan-Meier digunakan untuk menganggarkan lengkung purata kelangsungan hidup keseluruhan (OS) dan kelangsungan hidup bebas kemerosotan penyakit (PFS).

Keputusan: Seramai 126 pesakit terlibat dalam kajian ini. Lebih daripada separuh bilangan pesakit adalah lelaki (55.6%) dan kebanyakan daripada pesakit , 123 (97.6%) adalah berbangsa Melayu (konsisten dengan populasi penduduk Melayu di Kelantan). Sklerosis nodular merupakan sub-jenis histologi yang paling banyak (52.4%) dan 77.8 % pesakit mengalami penyakit tahap akhir. Kira-kira separuh (49.2%) pesakit

telah menerima rawatan dalam tempoh 4 minggu selepas diagnosis. Seramai 97 pesakit HL telah menerima gabungan kemoterapi sahaja manakala 29 pesakit (23.1%) menerima gabungan rawatan sama ada dengan radioterapi atau imunoterapi. Seramai 43 pesakit bebas penuh dari penyakit selepas terapi rawatan pertama. Purata kelangsungan hidup keseluruhan (OS) dan kelangsungan hidup bebas kemerostan penyakit (PFS) untuk 3 tahun bagi keseluruhan kohort adalah 74.9% dan 59.5%. Ketumbuhan besar (bulky disease) dan paras ESR yang tinggi (elevated ESR) merupakan faktor prognostik yang mempengaruhi OS dan PFS dalam kajian ini.

Kesimpulan: Kajian ini memberikan pemahaman yang lebih mendalam tentang hasil jangka pendek limfoma Hodgkin dan faktor prognostiknya di Pantai Timur Semenanjung Malaysia. Kadar OS dan PFS adalah rendah di hospital ini. Oleh itu, tempoh kajian yang lebih lama diperlukan untuk mengenal pasti faktor risiko, keberkesanan protokol rawatan serta komplikasi berkaitan rawatan untuk mendapatkan OS dan PFS yang lebih baik pada masa hadapan.

Kata kunci : limfoma Hodgkin, purata kelangsungan hidup keseluruhan, kelangsungan hidup bebas kemerosotan penyakit, faktor prognostik, hasil rawatan.

ABSTRACT

SHORT-TERM OUTCOME OF HODGKIN LYMPHOMA PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA AND ITS PROGNOSTIC FACTORS

Background: In general, Hodgkin lymphoma is a unique hematopoietic malignancy characterized by the presence of Reed Sternberg cells from the lymph node biopsy. It is one of the most curable haematological malignancies with higher survival compared to other types of haematological malignancy. This study aimed to determine the socio-demographic, clinical characteristic, treatment characteristics, survival and relapse/ progression data of patients diagnosed with HL in a tertiary centre, East Coast of Peninsular Malaysia.

Methods: A retrospective study was conducted from 1st January 2006 to 31st December 2018 to include patients with HL aged 12 years and above. Patient's data from Haematological and medical records unit were assessed. We gathered and analysed information on socio-demographics, disease parameters, and treatment characteristics. The Kaplan-Meier method was used to estimate the OS and PFS curves.

Results: A total of 126 patients were recruited in this study. Slightly more than half of the patients were male (55.6%) and most of them, 123 patients (97.6%) were ethnic Malay (consistent with Malay population in Kelantan). Nodular sclerosis remains the most common histology subtypes (52.4%) and 77.8% patients presented with advanced stage of disease. About half (49.2%) of patients received treatment within 4 weeks after diagnosis. About 97 HL patients had received combined chemotherapy alone while 29 patients (23.1%) received combination modality therapy either with radiotherapy or immunotherapy. Following front-line treatment, only 43 patients

achieved complete response. The 3-year overall survival (OS) and progression-free survival (PFS) of the entire cohort were 74.9% and 59.5% respectively. Bulky disease and elevated ESR emerged as independent prognostic factors for both OS and PFS in this study.

Conclusion: This study dispenses a deeper understanding into the short-term outcome of Hodgkin lymphoma and its prognostic factors in the East Coast of Peninsular Malaysia. In our centre, both the OS and PFS rates were poor. To provide a better OS and PFS in the future, longer study duration is necessary to determine the risk factors, the effectiveness of treatment protocol, as well as treatment-related complication.

Keywords: Hodgkin lymphoma, Overall Survival, Progression-Free Survival, Prognostic Factors, Treatment outcome.

CHAPTER 1

1.1 INTRODUCTION

1.1.1 Epidemiology and incidence of Hodgkin lymphoma (HL)

Hodgkin lymphoma (HL) is a cancer of the lymphatic system characterized by the presence of cancerous Reed-Sternberg cells in an inflammatory background. It was first described in 1832 when Thomas Hodgkin, a British pathologist wrote a case series of lymphadenopathy and splenic enlargement (Singh et al., 2015).

Global cancer statistics estimated that there were 83,087 new cases (accounting for 0.5% of all new tumours) and 23,376 deaths of Hodgkin lymphoma worldwide in 2020 (Ferlay et al., 2021). According to the American Cancer Society registry, there will be about 8,540 new cases of Hodgkin lymphoma with 920 deaths in the United State (US) in 2022 (Siegel et al., 2022).

Hodgkin lymphoma has distinct epidemiologic characteristics and its occurrence varies with gender, age, and country (Nakatsuka and Aozasa, 2006). The incidence of HL showed a bimodal distribution which peaks during adolescents/ young adults and after the age of 55 years old (Bröckelmann et al., 2018). According to the Malaysia National Cancer Registry Report (MNCR) 2012-2016, both male and female patients with HL have the highest incidence peaks between the ages of 25-29 and 70-74 (Azizah et al., 2019).

The prognosis of Hodgkin lymphoma is basically based on the stage of the disease and many prognostic factors. The 5-year relative survival of HL patients from 2012 to 2018 was 89.1 percent, according to the National Cancer Institute's

Surveillance, Epidemiology and End Results Survey (SEER) study in the United States. Stage I HL had superior 5-year relative survival (92.4%) compared to stage IV HL, which has just 79.8% (2012-2018 SEER Data, National Cancer Institute,2021).

1.1.2 Classification of Hodgkin lymphoma

Based on morphology and immunohistochemistry, Hodgkin lymphoma is classified into classical (cHL) and nodular lymphocyte-predominant HL (NLPHL) (Maggioncalda et al., 2011; Shanbhag & Ambinder, 2018). cHL is further divided into four different histological subtypes including mixed cellularity (MC), nodular sclerosis (NS), lymphocyte-rich (LR), and lymphocyte-depleted (LD) (Maggioncalda et al., 2011). While NLPHL renders for only 5% of HL and typically has indolent biology, classical HL accounts for roughly 95% of HL and acts as an aggressive neoplasm.

The most common type of classical HL, accounting for around 70% of cases, is nodular sclerosis, which has a better prognosis generally than other subtypes of cHL. 20–25 % of those with cHL have mixed cellularity, which is frequently found in older men and is usually related to positive Ebstein–Barr virus (EBV) infection. Lymphocyte-rich classical Hodgkin lymphoma (LRcHL) contributes about 5% of all cHL. Patients with LRcHL typically present with early-stage disease and have peripheral adenopathy. It offers a better prognosis and outstanding treatment outcomes with combination chemotherapy regimens (Shimabukuro-Vornhagen et al., 2005). The least common subtype (1% of cases) is lymphocytes-depleted cHL. It is commonly connected to human immunodeficiency virus (HIV) infection and is more aggressive than other subtypes. Additionally, patients with mixed cellularity and

lymphocytes-depleted cHL have worse prognosis than those with nodular sclerosis cHL (Mani and Jaffe, 2009).

On the other hand, NLPHL is a rare entity of HL with an incidence of 0.1 to 0.2 / 100 000 per year. The disease-defining lymphocyte predominant cells consistently express CD20 however lack of CD30. Clinically, NLPHL mostly rather indolent course, and patients are usually diagnosed in the early stages. The important issue that has been highlighted in NLPHL is the recognition of the different growth patterns. Histologically, NLPHL cells show a nodular, nodular and diffuse, or predominantly diffuse pattern. There are six histologic patterns which have been identified : (A) classical B-cell-rich nodular, (B) serpiginous/interconnected nodular, (C) prominent extranodular LP cells, (D) T-cell-rich nodular, (E) diffuse (T-cell-/histiocyte rich large B-cell lymphoma [THRLBCL]-like), and (F) diffuse moth-eaten (B-cell-rich) (Alaggio et al., 2022). Atypical growth patterns (pattern C to F) are associated with more advanced disease at initial diagnosis, a worse progression-free survival (PFS) and earlier disease recurrence in comparison with typical growth patterns (pattern A and B) (Hartmann et al., 2019).

1.1.3 Staging and prognosis for Hodgkin lymphoma

Stage for Hodgkin lymphoma (HL) is identified using the Ann-Arbor staging classification as shown in Table 1.1.

Table 1. 1 : Ann-Arbor staging classification for Hodgkin lymphoma (Adapted from Bröckelmann et al., 2018).

Stage	**Characteristics**
Stage I	Involvement of a single lymphatic site or localized involvement of a single extra lymphatic organ or site
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of a single extra lymphatic organ or site in association with regional lymph node involvement on the same side of the diaphragm.
Stage III	Involvement of two or more lymph node regions or of extra lymphatic organs on both sides of the diaphragm
Stage IV	Non-localized, diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement
Addendum A	B symptoms are absent
Addendum B	B symptoms are present: fever (temperature >38^{O}C), drenching night sweats, and/or unexplained loss of >10% of body weight within the preceding 6 months.

However, the criteria in determining stage of HL (early, intermediate or advanced) not only depending on the clinical features of the disease as mentioned in Ann-Arbor classification, but also on the presence and absent of the various risk factors including extranodal involvement, mediastinal tumour ≥ 1/3 of the maximal

transverse diameter of the chest, involvement of ≥ 3 lymph node areas and an elevated erythrocyte sedimentation rate (ESR) of ≥ 50 or 30 mm/hr in patients with or without B symptoms (Bröckelmann et al., 2018).

HL patients usually can be classified into 3 groups: early-stage favourable (stage I-II); early-stage unfavourable (stage I-II with any unfavourable factors) and advanced- stage disease (stage III-IV). The NCCN and EORTC unfavourable factors for stage I–II disease include bulky mediastinal disease (MMR >0.33 and MTR >0.35, respectively) or bulky disease >10 cm, B symptoms, ESR ≥50, and >3 involved nodal regions. In contrast, the GHSG considers patients with >2 nodal regions as having unfavourable disease (Hoppe et al., 2020).

The most commonly used prognostic system is the International Prognostic System (IPS) which includes age 45 years or older; male gender; stage IV disease; albumin level below 4 g/dL; haemoglobin level below 10.5 g/dL; leucocytosis (white blood cell count >15,000/mm^3); and lymphocytopenia (lymphocyte count <8% of the white blood cell and/or lymphocyte count <600/mm^3) (Hasenclever D, 1998) . The IPS score helps to determine the clinical management and predict prognosis for patients with stage III-IV HL disease.

1.2 PREVALENCE OF HODGKIN LYMPHOMA IN MALAYSIA

In Malaysia, a retrospective study in a tertiary hospital in Johor found that most of the cHL patients were male (61.7%) and Malay (73.4%) (Boo et al., 2019). The most common histology subtypes were nodular sclerosis (77.6%), followed by mixed cellularity (6.4%) and lymphocyte-rich (1.1%). The most common presenting symptoms were palpable lymph node mass (81.4%), followed by lower limb weakness/ significant back pain (4.3%) and superior vena cava obstruction (3.2%). Majority of them had B symptoms upon diagnosis (73.4%). Among them, 59.6% had advanced-stage disease, while 40.4% had early-stage disease (Boo et al., 2019). All (100%) of them received chemotherapy and 13.8% of them received radiotherapy as consolidation post-chemotherapy. Among them, 76.1% achieved complete response, 16.3% patients had partial response, and 7.6% patients had progressive disease after front line treatment (Boo et al., 2019).

Another study conducted at Pantai Hospital KL reported a total of 210 cases of lymphoma from the year 2010-2015 with 12% of them being Hodgkin lymphoma cases, while the rest 88% were non-Hodgkin Lymphoma (NHL) cases (Salam et al., 2020). Among those HL cases, 88% of them were cHL and 12% of them were NLPHL cases. The highest incidence of HL was amongst those aged in the range from 20-29 years old (68.2%), and there are more female patients of HL compared to male (Salam et al., 2020). In terms of ethnicity, Indians had the highest incidence of HL, followed by Malays and Chinese (Salam et al., 2020).

In Malaysia, there is no specific written or published guideline that has been used in managing HL patients. Apparently, the decision is made based on expert consensus in this field. The common first-line treatment that has been used in Malaysia

is ABVD and BEACOPP regimen has been used in selected patients with high risk profile. Similarly, the ABVD and BEACOPP chemotherapy were the first-line treatment widely used to treat advanced-stage cHL (Vellemans & André, 2021).

In regards to treatment response evaluation, based on discussion with the clinical experts, most of patients underwent CT scan as initial and mid-cycle evaluation and followed by PET/CT scan at the end of therapy (Yassin et al., 2020). Patients who were treated in the centre where PET/CT scan are accessible more readily, they may have opportunity towards pre-treatment, interim and end of therapy with PET- CT. The use of immunotherapy agent as salvage or targeted therapy is very limited due to financial constraint and indicated individual will be enrolled into clinical trials for funding or financial support.

CHAPTER 2

LITERATURE REVIEW

2.1 Management of Hodgkin lymphoma

The goal of treatment in HL is to achieve a cure and HL is highly responsive to chemotherapy and radiation. The types of treatment are varied based on the clinical stage of HL. Duration of treatment and doses of radiation depends on the disease staging and presence of some adverse prognostic factors.

For the early-stage (stage I to stage II) cHL, patients are classified as having a favourable or unfavourable prognosis, based on the absence or presence of risk factors. The preferred treatment for early-stage disease is combined-modality therapy consisting of combination chemotherapy (typically ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine]) followed by involved-field radiation therapy (IFRT). For favourable disease, 2 cycles of ABVD followed by 20 Gy radiation is recommended with five-year survival of 95% (Bröckelmann et al., 2018). In the early unfavourable group, there is significantly higher rate of tumour control was achieved with two cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) followed by two cycles of ABVD than with four cycles of ABVD (5-year PFS 95.3% versus 89.3%; 5-year OS 97.2% versus 96.8%) (Bröckelmann et al., 2018).

In an advanced-stage HL, there has been much discussion on the optimal course of therapy. The standard of therapy in the United States continues to be 6 to 8 cycles of ABVD, which has a 60% 5-year failure-free survival rate and a 73% 5-year

OS. While in Europe, escalated BEACOPP regimen has been developed by the German Hodgkin Study Group which demonstrated better progression-free and overall survival rates. It is strongly recommended that patients with advanced HL who are younger than 60 years old have escalated BEACOPP chemotherapy followed by 30 Gy of radiation therapy for any remaining PET-positive lymphomas that measure greater than 1.5 cm following chemotherapy (Skoetz et al., 2013). Patients whose PET/CT revealed complete metabolic remission are recommended to be treated with a total of four cycles of escalated BEACOPP (5-year PFS, 92.2%; 5-year OS, 97.7%). Meanwhile, patients who have not yet achieved a metabolic remission on PET/CT, are strongly recommended to receive a total of six cycles of escalated BEACOPP (5-year PFS, 88.3%; 5-year OS, 95.5%) (Borchmann et al., 2017).

The escalated BEACOPP regimen should not be given to patients aged over 60 years, as they are more likely to develop severe toxicity and an increased rate of treatment-related mortality (Wongso et al., 2013). There is a high risk of severe toxicity including bleomycin-induced lung toxicity in older HL patients receiving more than 2 cycles of ABVD (Böll et al., 2016). Patients whose decreased exposure to bleomycin is preferred due to lung disease or other comorbidities can be considered for Stanford V chemotherapy (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone) (Evens et al., 2013).

Nonetheless, management of relapsed or refractory HL must be individualized. The recommended treatment will vary and depend on several factors including previous first-line treatment (radiation therapy alone, chemotherapy alone, or combined-modality therapy), patient age and medical comorbidities, duration of the first remission, and stage at relapse. For most patients with refractory or relapsed HL

who fail after chemotherapy or combined-modality therapy, the treatment of choice consists of high-dose chemotherapy (with radiation therapy for eligible patients), followed by autologous stem cell transplantation (ASCT) (Rancea et al., 2013). According to studies, individuals with complete response (CR) or with chemosensitive disease to second-line therapy have improved outcomes following high-dose therapy with autologous stem cell rescue (HDT/ASCT) compared with those with resistance to the treatment (Sirohi et al., 2008). Relapsed cHL patients who do not respond to salvage chemotherapy had significantly worse outcomes and should be candidates for novel approaches agents using antibody- drug conjugates or immunotherapy (Shanbhag and Ambinder, 2018).

Brentuximab vedotin (BV), is an anti- CD 30 antibody-drug conjugate that has been approved for relapsed and refractory Hodgkin lymphoma. BV can be used as maintenance treatment post-ASCT in patients at high risk for relapse such as those who were refractory to initial treatment, who relapsed within 12 months following initial treatment, or those with extranodal disease (Moskowitz CH et al., 2015). Alternatively, BV can be used following treatment failure with ASCT or failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidate for HDT/ASCT (Hoppe et al., 2020). In a pivotal phase II trial , BV induced overall response rate (75%) and complete response rate (34%) of patients with relapsed or refractory cHL after failed HDT/ASCT (Younes et al., 2012). In general, BV often caused peripheral sensory neuropathy. Nevertheless, many patients experienced improvement or resolution of symptoms several months after discontinuing therapy (Chen et al., 2016).

Patients with relapsed/refractory PD-1-positive lymphomas have also demonstrated activity in response to PD-1-blocking monoclonal antibodies (Hoppe et al., 2020). A phase I study has shown that 23 patients who had relapsed after ASCT and brentuximab vedotin, treatment with novel PD-1 antibody Nivolumab induced overall rate response (ORR) of 87% with PFS rate of 86% at 24 weeks (Ansell et al., 2015). Similarly to another study of 31 patients with relapsed or refractory HL and pre-treated with BV, the use of Pembrolizumab induced ORR of 65% (90% CI,48%-79%) with complete remission rate and partial remission rate of 16% and 48%, respectively (Armand et al., 2016).

Management of NLPHL is similar to cHL except for those with stage IA disease presenting without clinical risk factors. The prognosis of early-stage NLPHL is excellent, with progression-free survival and overall survival rates exceeding 90% after involved-field radiotherapy (IF-RT) alone or combined modality treatment (Eichenauer and Engert, 2017). As the lymphocyte-predominant cells of NLPHL expressed CD20, the localised NLPHL relapses can be effectively treated with antiCD20 antibodies such as rituximab or ofatumumab given as single agent (Eichenauer et al, 2016a). Additionally, a biopsy should be obtained in all patients suspected relapsed to exclude transformation into aggressive non-Hodgkin lymphoma before initiation of salvage therapy in NLPHL (Eichenauer et al, 2016b).

The interim response evaluation should be carried out by contrast -enhanced CT scan before radiotherapy in early and intermediate stages, and after four cycles of chemotherapy in advanced stages. The concept of response-adapted therapy based on interim positron emission tomography -computed tomography (PET-CT) has proven to be of prognostic importance. It seems to improve outcomes by identifying patients who are most likely to benefit from more potent treatment regimens. PET-adapted

approaches for early-stage HL have aimed to use interim PET results to identify patients who can safely avoid radiation. In one study, patients with non-bulky stage IA or IIA disease and negative PET findings after three cycles of ABVD had a very good prognosis either with or without consolidation radiotherapy (Radford et al., 2015).

Contrast -enhanced CT is mandatory for final staging at the end of initial therapy and it should be replaced by PET-CT if available according to the guideline and for staging and response assessment in lymphoma (Barrington et al., 2014; Cheson et al., 2014). PET is superior to classical CT in the assessment of remission after completed treatment due to its functional character. PET-CT can detect both anatomical information as well as metabolic information providing more data and thus giving more accurate results than CECT (Yassin et al., 2020).

2.2 Overall survival (OS) and progression-free survival (PFS) of Hodgkin lymphoma

The survival of Hodgkin lymphoma patients had improved significantly over the past decades due to the advancement in the treatment of HL. The findings from the SEER study showed that the 5-year survival of HL patients aged 20-49 years old was 89%, which had improved significantly from 1990 to 2014 (Mukhtar et al., 2018). Meanwhile, the 5-year survival for HL patients aged 75-85 years old was 37%, which showed significant improvement from the year 2005 onward (Mukhtar et al., 2018). A study in the Netherlands amongst HL patients aged 15-17 years old and 18-24 years old that were treated with combined modality therapy showed improvement in 5-years overall survival from 84% and 90% in 1990-1994 to 96% and 97% in 2010-2015, respectively (Reedijk et al., 2020). The study also found that the 5-years overall

survival for NLPHL was excellent (100%) while the survival for CHL exceeded 95% for children (aged <15 years), adolescents (aged 15-17 years), and young adults (aged 18-24 years) (Reedijk et al., 2020). A study among patients with HL in the United States showed 5-years OS between those who received CMT and chemotherapy alone was 97.3% and 94.5%, respectively (Jhawar et al., 2019).

A study on NLPHL patients in France and Belgium found that 10-year progression-free survival (PFS) was 44.2% while 10-year overall survival (OS) was 94.9% (Lazarovici et al., 2015). Meanwhile, the 4-year PFS estimates based on the types of treatment were 78.8% after chemotherapy or immune-chemotherapy, 79.6% after radiotherapy, 77.0% after rituximab alone, and 93.9% after combined modality treatment (Lazarovici et al., 2015). Radiotherapy is often used to treat patients with early stage of NLPHL, while chemotherapy is often used to treat NLPHL patients with advanced-stage. The 4-year PFS of 77.0% for rituximab alone indicated that it had lowest impact on controlling the disease progression than other treatments (Lazarovici et al., 2015).

Meanwhile, in Malaysia, the 2-year OS and 2-year PFS for cHL patients aged more than 13 years old were 96.5% and 71.1%, respectively (Boo et al., 2019), The 2-year OS for early-stage cHL was 100% and advanced-stage cHL was 93.9%. Meanwhile, the 2-year PFS for early-stage was 82.7% and advanced-stage was 62.8%. However, no association was found between stages of the disease with the overall survival and progression-free survival ($p>0.05$). The presence of extranodal disease was found to be significantly associated with poor 5-year PFS ($p=0.002$), but not with 5-year OS ($p>0.05$) (Boo et al., 2019).

2.3 Risk factors for Hodgkin lymphoma

Ethnicity is a significant predictor for HL. A study in Canada found a significant association between ethnicity and incidence of HL (Pahwa et al., 2009). They found that the risk of HL was greater among Eastern European and Western European descendants compared to North Americans. They also found that the risk of HL was lower in Asian descendants than North Americans (Pahwa et al., 2009).

Besides, family history of HL in a sibling or parent was strongly associated with the increased risk of HL in childhood through young adulthood (0-37 years old) (Crump et al., 2012). Family history of cancer was associated with paediatric/ adolescent HL, particularly among those family members that were diagnosed at <50 years of age and those occurring in the paternal line (Linabery et al., 2015). In regards to HL subtypes, mixed-cellular HL was significantly associated with family history of cancer, cancer in paternal lineage, early onset of familial cancer, as well as colorectal cancer. Meanwhile, lymphocyte-predominant HL was associated with later onset of familial cancer, cancer in paternal relatives, and family history of colorectal and gynaecological cancer (Linabery et al., 2015).

Previous studies had shown that cigarette smoking is one of the risk factors for HL (Kamper-Jørgensen et al., 2013; Shepherd et al., 2018). A multicentre study which involved European, United States, and Australian population found that current cigarette smokers had significantly higher rates of HL (1.97 fold) compared to never smokers, indicating that current cigarette smokers are risk factors for HL (Shepherd et al., 2018). Similarly, another study had shown that current cigarette smokers increased the risk of HL compared to never smokers whereas former cigarette smokers were not associated with increased risk of HL compared to never smokers (Kamper-Jørgensen

et al., 2013). Current cigarette smokers are significantly associated with an increased risk of mixed-cellularity as well as EBV-positive cHL across all age groups (Kamper-Jørgensen et al., 2013). They concluded that cigarette smoking is a modifiable risk factor to decrease the risk and incidence of HL (Kamper-Jørgensen et al., 2013).

2.4 Prognostic factors that influence survival of Hodgkin lymphoma

Socio-demographic is one of many prognostic factors that influenced the survival of HL patients. In general, women had greater survival than men (83% vs. 80%) (Mukhtar et al., 2018). A previous study reported that women patients with advanced-stage HL in the age groups of 20-39 years old and 40-59 years old had higher long-term survival rates than male patients (Li et al., 2018). The presence of estrogen in women might play an important role in their survival as estrogen-receptors β (ERβ) inhibit HL cancer cell proliferation and significantly impair HL growth (Pierdominici et al., 2017).

Younger age groups also had higher survival rates compared to older groups, across all stages of HL (Mukhtar et al., 2018). This might be due to older people who are more likely to have poor organ functions and are more vulnerable to the toxicities of radiation therapy compared to the younger people (Chang et al., 2017). The other reason is, the presence of co-morbidities in the elderly as well as their poor tolerance to the treatment (Mukhtar et al., 2017). Besides, older people usually have different diseases biology compared to younger people and were often diagnosed with advanced stage of HL (Evens et al., 2019). The previous study had proven that the presence of co-morbidities among HL patients increased the risk of death by two-fold (Keegan et al., 2018).

Ethnicity/ race also influenced the survival of the HL patients (Mukhtar et al., 2018). A study found that White Americans with HL had significant improvement in survival while Asian Americans with HL had the lowest rise in survival throughout the study period from 1990-2014, with no statistically significant increase in the survival rates among Asian American (Mukhtar et al., 2018). Another study found differences in survival between white and black children and adolescents (Kahn et al., 2016). Similarly, a study conducted in California among newly diagnosed classic HL patients found that Black (regardless of stages of the disease) and Hispanic (late-stage disease) had higher risks in mortality than White patients (Keegan et al., 2016). The same finding was also obtained from an American study as they reported that Black patients were 63% more likely to die than White patients (Jhawar et al., 2019).

Besides, there is an association between marital status and the survival of HL patients as widowed patients had a significantly higher risk of mortality (Wang et al., 2017). They also reported that widowed patients had poorer cause-specific survival than married patients. The survival of widowed patients with stage III/ IV Hodgkin Lymphoma decreased sharply in the first 2 years, and they had the worse 5-years cause-specific survival compared to married, never married, and divorced patients (Wang et al., 2017). The possible explanation for the association between marital status and survival of HL is the psychological factors as married patients have shown to be less stress and anxious than unmarried patients after diagnosis of the disease. A previous study had reported an increase in psychotic drug prescriptions due to depression and anxiety after HL diagnosis and first years into survivorship (Øvlisen et al., 2020). Poor mental health (unrecognized depression and anxiety) could substantially reduce quality of life in patients surviving cancer and even increase mortality (Pinquart and Duberstein, 2010).

The previous study has shown disparities in primary lymph node sites with HL survival and mortalities. HL patients with the primary disease of intra-abdominal lymph node sites had the worst overall survival compared to the head, face, and neck (HFN) primary lymph node sites which had a better overall HL survival (Ebied et al., 2018). The intra-abdominal lymph node sites had worse survival because of its association with older age and advanced stage of HL as it usually occurs in patients with older age and with advanced stage. Moreover, the primary occurrence of HL in the pelvic lymph node sites was significantly associated with 2 times the probability of 1-year overall mortality (Ebied et al., 2018). On the contrary, a population-based study in the Netherlands found no significant association between sites of treatment with the 5-years overall survival, after adjusting for gender, treatment modalities, and follow-up time (Reedijk et al., 2020).

Another factor that influences the survival of HL patients is the differences in treatment (Keegan et al., 2016). The previous study amongst patients with early-stage NLPHL (stage I/ II) had reported that radiation therapy (RT) was associated with the improvement of overall survival, while the use of chemotherapy did not (Parikh et al., 2016). The 5-year overall survival for patients receiving chemotherapy was 88.1% which was significantly lower than those patients receiving radiation therapy with 5-year overall survival of 94.1% ($p=0.003$) (Parikh et al., 2016). Treatment of HL stage I-II with chemotherapy (CT) alone has been associated with higher HL mortality compared to radiotherapy (RT) alone and a combination of RT and CT (de Vries et al., 2021).

Meanwhile, another study reported that early treatment of NLPHL with chemotherapy or radiotherapy significantly reduced the risk of progression compared

to watchful waiting (period of observation of at least 3 months without any treatment), indicating that undergoing treatment after diagnosis improved the progression-free survival (PFS) compared to not receiving any treatment (Lazarovici et al., 2015). However, the early treatment only seems to improve the progression of the disease but has no impact on the overall survival of the patients. Moreover, the study also found that treatment with rituximab alone and complete surgical resection of primary lymph nodes did not significantly improve the PFS compared to watchful waiting (Lazarovici et al., 2015).

A study among HL patients aged less than 21 years old reported that the use of combined-modality treatment (CMT) was significantly associated with the improvement in their overall survival (Jhawar et al., 2019). The 5-year overall survival for those patients who received CMT was significantly higher than those receiving chemotherapy alone (97.3% vs. 94.5%; $p<0.001$) (Jhawar et al., 2019). The use of CMT as treatment has been associated with better overall survival (OS) and relative survival (RS) of HL patients than chemotherapy alone (Olszewski et al., 2015). Besides, age, presence of B symptoms, and use of transplant procedure were significantly associated with the overall survival of HL patients (Jhawar et al., 2019). In contrast, a retrospective study in Canada found that the presence of B symptoms is the prognostic factor for PFS alone instead of OS, while stage IV HL and bulk were the prognostic factors for both OS and PFS (Marr et al., 2017). Relapse-free survival at four years for bulky patients was 80.5% (CI: 73%, 88.9%) compared to 94.4% (CI: 89.1%, 100%) for non-bulky; Cox HR 4.21 (CI: 1.43, 12.38) (Kumar et al., 2016). However, contradicting those studies, a study in Malaysia found no significant association between B symptoms, bulk, stage of HL, LDH levels, and age of the patients with their OS and PFS (Boo et al., 2019).

The association between time of diagnosis to treatment initiation (TDT) in HL has not been clearly studied. TDT was defined as the duration of time elapsed from the date of definitive pathologic diagnosis of HL to the date of the first dose of chemotherapy. In a study among 810 patients with classical HL treated with ABVD, the 5-year overall survival (OS) was 92% TDT ≤ 4 weeks, 92% TDT 5–8 weeks, and 83% TDT > 8 weeks (p=0.007) (Brooks et al., 2016). A study by Phipps et al., 2018, showed that patients with Diffuse large B-cell lymphoma (DLBCL) treated within a 4-week TDT period had a significantly better OS (p = 0.025, HR 1.575; 95% CI 1.058–2.345) and PFS (p =0.006, HR 1.658; 95% CI 1.156–2.379) as compared to patients with TDT >4 weeks. Meanwhile, in a retrospective study in DLBCL patients receiving curative chemotherapy with rituximab, those who initiated curative chemotherapy > 8 weeks after diagnosis experiences worse outcomes (Hay et al., 2015). The reasons for the late initiation of treatment were identified which included delay in process of referral, staging, or scheduling of treatment, patient refusal of offered treatment at an initial presentation, and lastly due to revised pathological diagnosis (Brooks et al., 2016).

2.5 Problem statement and rationale of the study

Previous study in Malaysia has shown that 2-yr OS an PFS rates were 96.5% and 71.1%, respectively (Boo et al., 2019). Similarly, studies in Brazil and Saudi Arabia reported the 3-year OS and 5-year OS were 90% and 91% respectively (Gaiolla, 2017; Shafi et al., 2017). Despite the excellent results of OS rate and PFS rates of HL showed by many published literature, but in some population, the reported OS and PFS is still lower than those observed in developed countries especially in advanced stage disease. In one study in India demonstrated the 5-year OS of adult HL patients was only 60% (Hasmukh Jain et al., 2015). Unfortunately, there is still a paucity of local published data about the outcome of Hodgkin lymphoma and the associated prognostic factors.

Therefore, we aimed to determine the impact of selected prognostic factors on the short-term outcome of Hodgkin lymphoma patients that were treated in Hospital USM. In the end, we hope that this study will be more valuable to us in the future when dealing with Hodgkin lymphoma patients.

CHAPTER 3

3.1 OBJECTIVES

3.1.1 General objective

The general objective of this study is to study the short-term outcome, 1-year and 3-year of overall survival (OS) and progression-free survival (PFS) and the prognostic factors among Hodgkin lymphoma patients treated in Hospital Universiti Sains Malaysia (USM).

3.1.2 Specific Objectives

1) To determine the 1 year and 3-year overall survival (OS) and progression free survival (PFS) among Hodgkin lymphoma patients receiving treatment in Hospital USM.
2) To determine the influence of selected prognostic factors i.e. socio-demographic factors (age, gender, ethnicity), disease parameter (e.g. stage of disease, LDH, ESR, presence of B symptom, extranodal involvement, bulky disease) and treatment characteristics (timing from diagnosis to initial treatment, treatment modality) with the overall survival (OS) and progression -free survival (PFS) in patients with Hodgkin lymphoma in Hospital USM.

3.2 RESEARCH QUESTIONS

1) What is the 1-year and 3-year overall survival and progression- free survival among Hodgkin lymphoma patients treated in Hospital USM?
2) What are the prognostic factors that influence the overall survival and progression-free survival among Hodgkin lymphoma patients treated in Hospital USM?

3.3 RESEARCH HYPOTHESIS

1) The socio- demographic factors (age, gender, ethnicity), disease parameter (e.g. stage of disease, LDH, ESR, presence of B symptom, extranodal involvement, bulky disease) and treatment characteristics (timing from diagnosis to initial treatment, treatment modality) are significant prognostic factors that contribute to overall survival (OS) of Hodgkin lymphoma patients in Hospital USM.

2) The socio- demographic factors (age, gender, ethnicity), disease parameter (e.g. stage of disease, LDH, ESR, presence of B symptom, extranodal involvement, bulky disease) and treatment characteristics (timing from diagnosis to initial treatment, treatment modality) are significant prognostic factors that contribute to progression-free survival (PFS) of Hodgkin lymphoma patients in Hospital USM.

CHAPTER 4

METHODOLOGY

4.1 Study design

This study is a retrospective cohort study involving a review of medical records of HL patients undergoing follow -up in the clinic or admission into the wards in Hospital USM.

4.2 Period of data recruitment and study duration

Data will be collected on Hodgkin lymphoma patients based on medical records in the database registry between 1st January 2006 and 31st December 2018 with an additional follow up period of three years between 1st January 2019 and 31st December 2021 . The study will be conducted within 4 months starting from March until June 2022.

4.3 Study area

This study was conducted at Day Care Haematology and Haematological ward Hospital USM, which is a tertiary centre of referral for most haematological patients from East Coast states of Peninsular Malaysia.

4.4 Conceptual framework

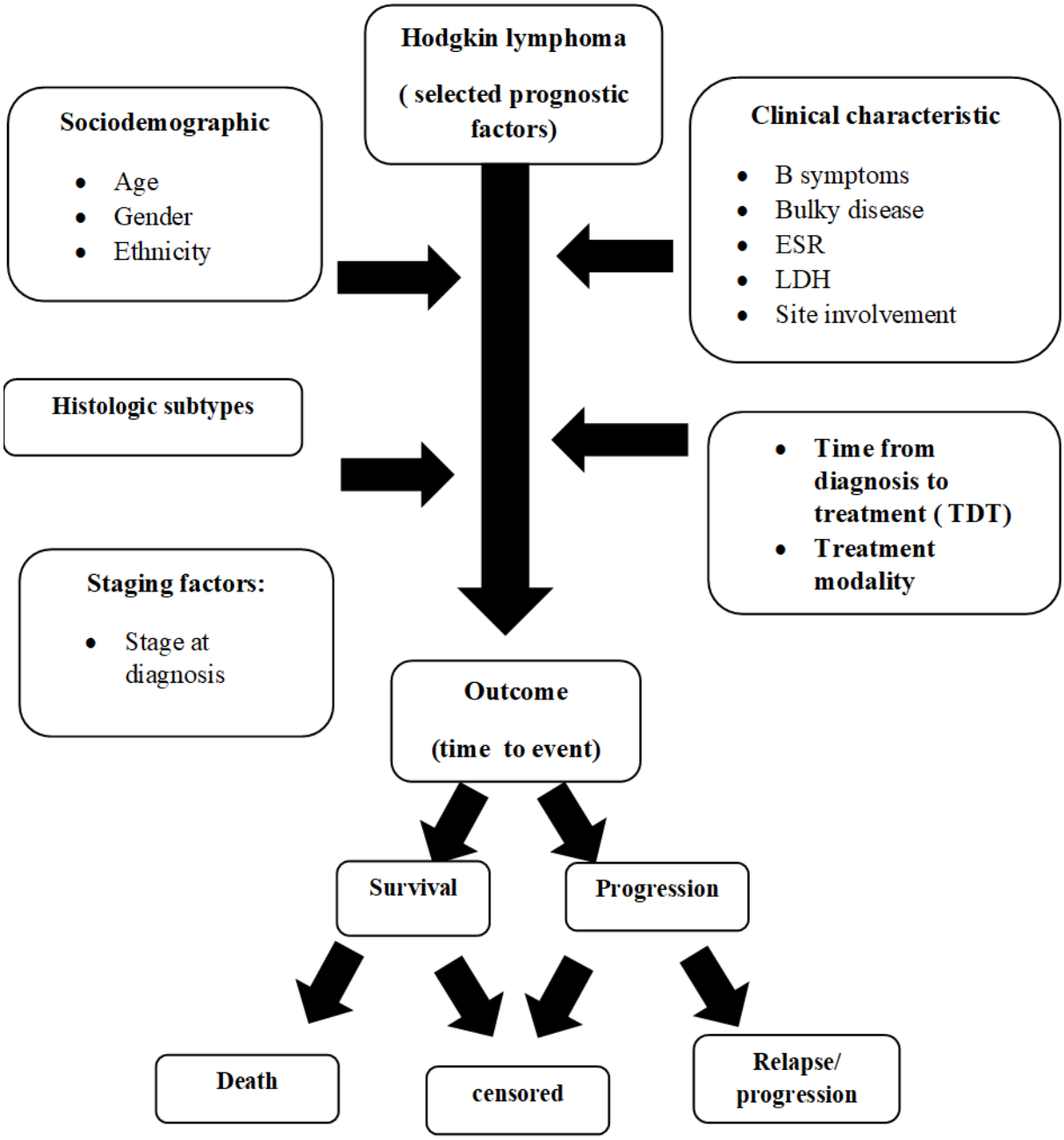

Figure 4. 1: Conceptual framework