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Contact With The General Practitioner Among Non-Hodgkin Lymphoma Survivors Diagnosed at Young Age (18-35): A Cohort Study in Norway.

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Abstract

Background: Cancer is the most common cause of disease-related death in children, adolescents, and young adults in high-income countries. In Norway, leukemia, non-Hodgkin lymphoma and cancer in the central nervous system are the most common cancers among children. These represent nearly 60% of all cancer cases in boys and girls. Hodgkin's lymphoma accounts for about 10% of all lymphomas and the remaining 90% are referred to as non-Hodgkin lymphoma (NHL).

Objective: The main objective of this study was to investigate late effects of cancer among survivors of NHL diagnosed at the age 18-35 years in Norway.

Methods: Nationwide longitudinal register-based study investigating General practitioners (GPs) consultations among
adolescents, and young adults (AYAs) diagnosed with NHL at the age of 18-35 years in Norway. All GP consultations were identified from the national GP claims register for 2006-2017. We compared diseases and complaints for which NHL cases and AYAs without cancer in the same age contacted their GP using logistic regression models. The follow-up period was divided into three periods according to GP consultations presented in the first year, 2-5 years, 6-10 years after the cancer diagnosis.

Results: A total of 2,224,484 AYA were included in the study whereas 275 were survivors of NHL. Compared with AYAs without cancer, NHL survivors had significantly more overall GP visits 6 years postdiagnosis for symptoms and complains related to blood and immune system OR=1.64 95% CI:1.59-1.69, digestive system OR=1.09 95% CI:1.04-1.14, neurological system OR=1.06 95% CI:1.02-1.11, respiratory system OR=1.09 95% CI:1.05-1.13), skin OR=1.10 95% CI1.06-1.14, urological system OR=3.86 95% CI:3.09-4.81, and general and unspecified symptoms OR=1.10 95% CI 1.06-1.13. These health problems were statistically significant in mature B cell lymphoma, mature T-cell and NK-cell lymphomas, and NHL NOS (not otherwise specified).

Conclusion: Compared with AYAs without cancer, NHL survivors have an increased contacts with the GP for health problems for up to 10 years postdiagnosis. Our results indicate the need of follow-up programs for possible late effects of cancer treatment.

***Categories*:** Non-Hodgkin Lymphoma, General Practice (GP), Hematology

Keywords: adolescents and young adults, urological, blood and immune system, skin, respiratory, neurological, musculoskeletal, digestive, general and unspecified late effects, follow up, clinical trials, multidepartment treatment, survivorship care plan

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Abbreviations

GPs- General practitioners

NHL- Non- Hodgkin lymphoma

ECOG- Eastern cooperative oncology groups

LDH- Lactate dehydrogenase”

OS- Overall survival data from blood

MRI- Magnetic resonance imaging

CT scan- Computed tomography scan

PET scan- Positron emission tomography

RHA- Regional health authorities

FHI- Public health institute of Norway

ICPC- International classification of the primary health care

KUHR- Control and Payment of Health Reimbursement

OR- Odd ratio

CI- confidence interval

REK- Regional Committees for Medical and Health Research Ethics (Regionale komiteer for medisinsk og helsefaglig forskningetikk)

NK-cells- Natural killer cells

MFMER- Mayo Foundation for Medical Education and Research

DLBCL- Diffuse large B cell lymphoma

CSF- Cerebro-spinal fluid

HIV-AIDS- Human Immunodeficiency Virus- Acquired Immunodeficiency Syndrome

DNA- Deoxyribose nucleic acid

CD cells- Clustre of differentiation cells

mAbs- Monoclonal antibodies

FCR- Fear of cancer reoccurrence

PTSS/D- Post traumatic stress or syndrome

SCP- Survivorship care plan

HCPs- Health care professionals

1. Introduction

Cancer is the most common cause of disease-related death in children, adolescents, and young adults in high-income countries.[1] In Norway about 1157 new cases of non-Hodgkin lymphoma (NHL) are diagnosed each year.[2] Around 3% are diagnosed among young adults at the age of 20-34 years.[3]

The age range for AYACs varies by organization and institution. A broader age range (15-39 years) was proposed by the Progress Review Group, convened in 2005 by a partnership between the National Cancer Institute and the Live Strong Foundation (Barr RD et al, 2016). In the present study we included adolescent and young adults with cancer at the age 18-35 years (hereafter referred as AYACs).

1.1 Why research on cancer in adolescent and young adults?

Scientists know little about how cancer among adolescents and young adults differs from that of other age groups, in part because young people rarely contribute tumor samples for research.[4] Adolescents and young adults diagnosed with NHL have been an understudied population and there is limited description of late effects after the diagnosis.[5,6] Several psychosocial issues have been identified among AYACs distinguishing them from pediatric and adult populations. AYACs are an important group because the age of setting a goal in their life, having relationship, completing fixed set education level, achieving that goal, living the life freely both economically, socially, and mentally as well.[7] Another study showed that this is the transitional age for human where person from childhood goes to adolescence or person from adolescence age goes to being young adult, meaning that man goes through many physical, psychological ups and downs. That's why this age is also called as the age of vulnerability in the person's life.[8]

In the Nordic countries adolescent and young adults' patients have a relative hight survival rate. A recent study shows a 5-year survival of 86 in the period 2000-2013.[9] AYACs survivors have less chances of having death than the older patients leading to the various late effects especially psychological and physical such as cardiotoxicity, nephrotoxicity, development of secondary cancers hence increased need of the care. In addition, this age group of survivors had also showed that they did not get the amount of psychological care and motivation or support which is generally need of the hour to them.[10]

1.2 Non-Hodgkin lymphoma

Non-Hodgkin's lymphoma is a type of cancer that begins in the lymphatic system, which is part of the body's germ-fighting immune system. In non-Hodgkin's lymphoma, white blood cells called lymphocytes grow abnormally and can form growths (tumors) throughout the body. The lymphatic system is one of the systems of our body, made up of thin tubes (lymphatic vessels or lymph vessels), which is a significant portion of our body's defense system. It acts to fight against pathogens and to destroy the abnormal and old cells like cancer cells.[11]

Non-Hodgkin lymphomas encompass a heterogeneous group of cancers, 85-90% of which arise from B lymphocytes; the remainder derive from T lymphocytes or NK lymphocytes. This diverse group of malignancies usually develops in the lymph nodes, but can occur in almost any tissue, and ranges from the more indolent follicular lymphoma to the more aggressive diff use large B-cell and Burkitt's lymphomas. Several different classification systems have been proposed that have grouped these malignancies according to their histological characteristics. The most recent system is the fourth edition of the WHO classification of tumors of haemopoietic and lymphoid tissues, published in 2008.[12]

B and T lymphocytes are important members of the immune system that above all serve to protect against infectious agents. In general, B cells produce antibodies with antigen-binding capacity, whereas T cells recognize antigen presented by other cells. As in cancer development in general, neoplastic transformation of T or B cells represents a multistep process with progressive accumulation of genetic lesions that result in clonal expansion and establishment of a solid or leukemic tumor. Mechanisms may involve dysregulation of cell growth, cell signaling pathways and programmed cell death (apoptosis). The intricate rearrangements in B-cell immunoglobulin or T-cell receptor genes during the normal differentiation and adaptation of these cells represent genetically vulnerable stages. During these processes, physiologically occurring DNA double strand breaks pave the way for aberrant chromosomal translocations, which are typical of NHL tumors. In fact, chromosomal translocations have been observed in up to 90% of NHL cases. These translocations, with or without additional genetic lesions, can precipitate the activation of oncogenes or inactivation of tumor suppressor genes.[13]

1.2.1 Types of Non-Hodgkin lymphoma among adolescent and young adults

Mature B-lymphocyte neoplasms account for the majority of NHL in AYACs, however the distribution of histological entities undergoes a distinct shift during the teenage years. While Burkitt lymphoma is the most common NHL of childhood, diffuse large B-cell lymphoma

predominates after the age of 15 years. In older adolescence and young adulthood, primary mediastinal B-cell lymphoma and follicular lymphoma become important diagnostic entities.[14]

Other less common mature B-NHL in AYACs include nodal marginal zone lymphoma and rare variants of diffuse large B-cell lymphoma. Other distinct subsets of B-NHL tend to occur in the setting of immunodeficiency and include primary central nervous system lymphoma, primary effusion lymphoma, plasmablastic lymphoma, and post-transplant lymphoproliferative disease (Hochberg J et al, 2016).

1.2.2 Risk Factors of Non-Hodgkin lymphoma

Research efforts have been made in the past two decades to understand factors that might account for the incidence patterns and trends. The next section describes some of the established and postulated risk factors for the development of NHL.

Immune Modulation. Congenital and acquired states of immunosuppression are the strongest factor known to increase NHL risk.[15] These conditions include ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable hypogammaglobulinemia, X-linked lymphoproliferative syndrome, and severe combined immunodeficiency. Epstein-Barr virus (EBV) appears to be an important cofactor, and host defects in immune regulation resulting in uncontrolled infection and proliferation of B-lymphocytes likely contribute to the development of NHL.

Viruses. Several viruses have been implicated in the pathogenesis of NHL, including Epstein-Barr Virus,[16] human T-cell lymphotrophic virus, Kaposi sarcoma-associated herpesvirus,[17] also known as human herpesvirus, and hepatitis C virus.[18]

Bacterial Infections. Chronic gastric infection with H. pylori has been linked to the development of low-grade, gastric mucosa-associated lymphoid tissue lymphoma.[19,20]

Infection with B. burgdorferi, the causative agent in Lyme disease, has been detected in about 35 % of patients with primary cutaneous B-cell lymphoma.[21] Herpes zoster has also been associated with Hodgkin lymphoma and NHL.[22] Findings on infectious agents are consistent with the idea of chronic antigenic stimulation or inflammation in the pathogenesis of NHL.

Family History. A history of NHL or other hematolymphoid cancer in close relatives has repeatedly been shown to increase the risk of NHL by 2- to 3-fold.[23] Familial aggregation has been associated with an inherited defect of immune function in some instances, but no such

abnormality can be discerned in most families. Lymphomas may also cluster within families, not because of an inherited susceptibility, but because of shared environmental determinants.[24]

Exposures to radiation and certain chemicals. Exposure to sunlight and other sources of UV radiation, with possible immunosuppressive effects, has been suggested as a risk factor for NHL.[25],[26] Several occupations have been associated with increased risk for the development of NHL, including farmers, pesticide applicators, benzene workers, rubber workers, petroleum refinery workers, dry cleaners, firefighters, and chemists.[27,28,29]

Gender, age race or ethnicity. risk of having NHL increase with the age. Studies show that the distribution of age and gender differed between NHL-subtypes.[30] There are also reported racial differences for patients diagnosed with NHL. For patients diagnosed with natural killer T-cell NHLs, Asian/Pacific Islanders along with Hispanic whites had the highest age-adjusted incidence rates.[31]

1.2.3 Signs and symptoms of non-Hodgkin lymphoma

There might be a different type of sign and symptoms related to NHL which depends on the subtype of NHL, origin of generation and stages of the lymphoma, but on the other hand, some people do not show any sign and symptoms until and unless it grows large. Similarly, if person have one or more similar sign and symptoms as of NHL does not mean that he has developed the NHL because of resemblance of NHL symptoms with other infections.[32]

Ansell SM (2015) shows that the most common types of symptoms of NHL is the swellings in the different parts of the body such as neck, throat, armpit, groin, where the swelling is an enlarged lymph node. Development of NHL may show the bigger lymph nodes which could be above the collar bone, around the neck, under the armpit, groin areas. But it is seen that lymph nodes are often swollen by the infections rather than lymphoma and these nodes are called reactive or hyperplastic nodes. Under the skin person will feel the lump of mass which could be non- painful. In addition, the abdominal symptoms such as swelling, painful abdomen, nausea, vomiting, blotting, water accumulation in the abdomen etc. could be caused by the abdominal lymphoma because of swollen nodes or organ. For example - we have spleen, liver. These types of enlargements may lead to loss of appetite even for the small meal. Enlarged lymph nodes of the abdomen may cause gut to slide further and will become stuck in next part of the gut which ultimately result in in symptoms such as blood vomiting, or blood in the stool,

severe pain in the stomach, and blockage of the urine. Similarly, if thymus or lymph nodes region develop the lymphoma then it may cause the constant coughing, difficulty in breathing, wheezing, chest pain or pressure due to the pressure in the trachea (windpipe). Due to the close passage of the superior vena cava (SVC- blood from the head and arms to back to the heart) along with the thymus and lymph nodes, may lead to the enlargement in the head, arms, and chest region and which ultimately leads to the uneasiness in the breathing and sometimes may cause the stroke as well (SVC syndrome) (Ansell SM, 2015).

Sapkota S et al (2021) found out that if man develops the lymphoma in any region of the brain, then it may lead to symptoms like headache, depression, anxiety, over thinking, weakness, different behaviour than the usual and sometimes epilepsy as well. The lymphoma that develops around the brain and spinal cord may lead to symptoms such as double vision, facial numbness and trouble speaking etc. Likewise, lymphoma in the skin is also called as Cutaneous T-cell lymphoma which causes the signs/symptoms like rashes causing redness in the skin, skin with patchy, lump, and dry scales, swollen lymph nodes, loss of hair, thickened skin on the hands and soles of the leg, tumours of skin etc. We have many types of cutaneous T-cell lymphoma but mycosis fungoides is known as the most common type one, whereas Sezary syndrome is the least common one which causes redness of the whole body´s skin (Ansell SM (2015). Miscellaneous sign and symptoms could be fever for at least 14 consecutive days, usually in the late afternoon and at the early evening having temperature of less than 102 degree Celsius that come and go, extremely tired feeling with itchiness throughout the body- they may feel exhausted even though they are in resting period and at the same time they might be very much itchy in the whole part of the body, heavy night sweats- they may even have to change the pyjamas and bed sheets overnight, heavy weight loss- they may lose weight up to 5-10 kg and headaches, seizures, bone pain, visual problem, mood swings, weakness etc. (Ansell SM, 2015).

1.2.4 Diagnosis

According to study of Sapkota S et al (2021), when suspects of the NHL go for the visit of the doctor with the symptoms of the NHL, then doctor may take some family medical history or the date, severity, types, frequency, progression of the symptoms and may recommend one or few of the following tests.

Physical exam: In this test, doctor checks the lymph nodes physically that how does it look or feel to the patient and himself when he touches it. And he may try this test anywhere in the suspect body. For example- armpit, underarm, groin region, neck and may look symptoms that resembles the swollen spleen or liver.

Blood and urine tests: These tests are done to wipeout the chances of having other diseases or infections. In the blood test- they may look for the WBC counts, platelets count, hemoglobin level, albumin level, and likewise in the urine test, they may look for the pus cells in the urine along with albumin count, acidity of the urine and color of the urine as well. And following diseases could be found with blood and serum tests which resembles the like symptoms of the NHL.

Complete blood count: It could find out anemia, thrombocytopenia, leukopenia, pancytopenia, lymphocytosis, and thrombocytosis. And these types of changes in the blood counts may be because of extensive bone marrow infiltration, hypersplenism from splenic involvement, or blood loss from gastrointestinal tract.

Serum chemistry tests: This test help to rule out tumor lysis syndrome, especially in aggressive type of lymphoma such as Burkitt or lymphoblastic lymphoma. Similarly, Lactate dehydrogenase level is increased in the lymphoma patients but at the same time it can be seen because of high tumor burden or extensive infiltration of the liver.

Imaging tests: We have various imaging tests such as CT-scan (Computed tomography-scan), MRI (magnetic resonance imaging), and Positron emission tomography (PET). These tests are done mainly to know if the sign of the lymphoma exists in the other parts as well or not. Mainly CT scan of neck, chest, abdomen, and pelvis, or PET scan. Dedicated imaging such as MRI of the brain and spinal cord or testicular ultrasound could be done (Mayo Foundation for medical education and research).

Lymph node/ tissue biopsy test: In this test, part or the whole lymph node tissues is taken out to have the laboratory test to find out the types and subtypes of the lymphoma. And the lymph node can be sent for the biopsy if the lymph nodes show the characteristics such as huge enlargement and increase in the size of the lymphoma consistently for the next four weeks or more. Generally, lymph nodes having the size of 2.25cm or more with bi-perpendicular

diameter or single diameter of 2cm or more, is the best outcome of the diagnosis. Hence, excisional biopsy of the lymph nodes is also called the best way of diagnosing since it gives the chance to find out the tissue's characteristics in many ways such as histologically, immunologically, molecular biologically and histopathologically, whereas Fine Needle Aspiration method of diagnosis is not performed as it has many cons than pros to proper diagnosis of NHL.

Bone marrow test: In this test, bone marrow fluid (bone marrow aspiration) or the solid (bone marrow biopsy) is taken out by puncturing the bone marrow of the larger bones such as hipbone with the help of the needle. We can this test only by performing bone marrow aspiration by removing the solid part of the bone marrow but generally examination of both solid and liquid part of the bone marrow is recommended to have the higher efficacy in the diagnosis. This test is done to find out the if the bone marrow is performing its function properly or not, to find out the iron levels of the blood, development speed of the disease and other diseases related to the bone marrow and blood, to find out the cancer types such as leukemia, lymphomas, multiple myeloma etc. and to find out the fever´s origin as well (Mayo Foundation for medical education and research).

Lumbar puncture test: This type of the test is carried out to figure out the involvement of lymphoma to the fluid around the neck. There are different types of NHL types such as Burkitt lymphoma, DLBCL, HIV-NHL, peripheral T cell lymphoma, Mantle cell lymphoma, Precursor Tor B cell lymphoblastic leukemia/lymphoma which have at least two extra nodal sites of the disease such as epidural, bone marrow, paranasal sinus sites. In this test, needle is used to take the fluid out of the spinal cord located at the back of our body, this type of fluid is called cerebrospinal fluid (CSF). Flow cytometry and cytology tests is done with the CSF.

Other tests or procedures: Depending on the progression in the diagnosis of the lymphoma, doctor may or may not ask for the other tests or the procedures. Further tests or procedures can also be performed by the doctor to find out the subtypes of the lymphoma as many types of isoforms do exist, and to find out the perfect match type of treatment to increase the affectivity of the treatment (Mayo Foundation for medical education and research).

On the other hand, we have the other types of diseases which shows the similar types of signs//symptoms like NHL and they are Hodgkin lymphoma, Epstein Barr virus infection,

Systemic lupus erythematosus, Intussusception, Appendicitis, Toxoplasmosis, primary tumor causing metastasis (e.g., nasopharyngeal carcinoma, soft tissue sarcoma), malignancies or lymphoproliferative disorders like granulocytic sarcoma, multicentric Castleman disease, lymph node infiltration and reactive follicular hyperplasia because of bacterial infections. But above-mentioned diseases lymphadenopathy which could be general one or localized one and generally they can be differentiated from the NHL. But under the confusing situation of the diagnosis, the medical technologist discusses with the other experts and generally perform the method called Flow cytometry and cytogenetics (Sapkota S et al ,2021)[33]

1.2.5 Staging system for non-Hodgkin lymphoma

Ansell SM et al (2015) explained the importance of staging of the lymphomas. According to them management of NHL is further determined by the stage of the disease and by the presence or absence of prognostic indicators of disease outcome. This system was developed in 1971 predominantly for Hodgkin lymphoma but has been adapted for use in staging patients with non-Hodgkin lymphoma. The staging system identifies the number of tumor sites, specifically nodal or extra nodal involvement, the location of the disease, and the presence or absence of constitutional symptoms. The predominant goal of staging is to identify patients with truly localized disease who may benefit from a combined modality approach of treatment for example chemotherapy and radiotherapy. There are mainly four types of NHL stages, where early stage is stage one and advanced stage is stage four and stages mainly depend on following parameters: where the lymphoma is, how many areas of lymph nodes are affected, if other organs in the body are also affected or not (Ansell SM 2015).

1.2.5.1 Staging-Ann Arbor staging system for Lymphoma.

Stage I: Involvement of lymph-node region (I) or extra nodal site (IE).

Stage II: Involvement of two or more lymph-node regions or lymphatic structures on the same side of the diaphragm alone or with involvement of limited, contiguous, extra lymphatic organ or tissue (IIE).

Stage III: Involvement of lymph-node regions on both sides of the diaphragm (III), which may include the spleen (IIS) limited contiguous, extra lymphatic organ or tissue or both (IIES).

Stage IV: Diffuse or disseminated foci of involvement of one or more extra lymphatic organs or tissues with or without associated lymphatic involvement.

The stages are subdivided according to the presence or absence of other symptoms such as fevers (>38.5^{o}C), weigh loss (>10%) in the period of the six months before diagnosis of the lymphoma and too much night sweats.

1.2.6 Treatment and side effects among adolescents and young adults

According to Sapkota S et al 2021 & Shankland KR et al 2012[34], we have the following treatment methods for the non-Hodgkin lymphoma:

Radiation oncology: This treatment is given to them who are in early stage of the development of lymphoma such as stage I and II, where this therapy is normally combined with the chemotherapy and given. In addition, if the lymphoma is of advance stage or aggressive type, then radiation therapy is given after the chemotherapy treatment. Side effects of this treatment is also normally manageable, but in some case may show some damaging effects as well. This therapy is also given if the lymphoma is found in one or two spots of our body and slow growing one. In this therapy, highly powerful energy rays such as X-rays and protons is given by laying down the patient into the table and rotating the beam giving machine around the table to direct to the specific point of the body.

Chemotherapy: It is a kind of therapy where different types of drugs is given in the different forms of the drugs such as injection, capsules, tablets etc. This therapy can be given alone or by combining with other therapies such as radiation therapy, immunotherapy, or stem cell therapy. It is a starting good treatment method and preferred method if the relapse of the lymphoma occurs. It is also used in the stem cell therapy or bone marrow transplant. This is a method of killing the rapidly growing cancerous cells with the strong drugs. It shows normally mild and manageable side effects such as fever, mouth sores, pain, bleeding, easy bruising, constipation etc. and in few cases, it shows serious complications such as kidney problems, infertility, risk of second cancers, peripheral neuropathy, as well. It is also used in treating the bone marrow diseases and immune system disorders.

Targeted drug therapy: In this treatment method, the specific abnormalities that is inside the cancer cells, is found and blocked and thereby causing the cancer cells to die. Generally, this method of treatment is combined with the chemotherapy or with stem cell transplantation to

increase the effectiveness of the treatment, but only this method also can be given. This method is given also in the relapse cases of the lymphoma to treat.

Engineering immune cells to fight lymphoma: It is a type of treatment method where specialized engineered immune cells i.e. Chimeric antigen receptor (CAR) - T cell is given to the patient´s body which fights with the cancerous cells and kill them. This method is normally used as the alternative treatment method if other methods of treatment do not work at all, or it can also be used specifically to some subtypes.

Bone marrow transplant: In this method, the recipient patient´s body´s immune system and bone marrow is suppressed with immunosuppressor or radiation therapy, or by chemotherapy and then health bone marrow from patient´s own body (autologous transplant) or from donor (allogeneic transplant), is transferred into the patients. This treatment is performed to make the bone marrow function the normal as before. This method is also called as stem cell transplant. This method is used as if other method of the treatment do not work or could be used as specialized method for some specific subtypes of lymphoma. This method is advanced and complicated method than the other. It may show the risks such as stem cell failure (grafting), organ damage, cataracts, infertility, secondary cancers, And Graft-versus-host disease etc.

Immunotherapy: Here the patient´s own immune system is used to fight the deadly cancer cells and kill them. In this method, the immune system disturbs the process of hiding the protein cells of the cancerous cells to the immune system and then ultimately killing the cancer cells. It is used as the alternative method of treatment and could be specialized method for some forms of subtypes.

Immune checkpoint inhibitors: Our immune system has the element that act as the checkpoint to prevent our body's healthy cells from being attacked by immune system, and sometimes these lymphoma cells use these checkpoints to grow. So, these checkpoints inhibitors can be used as the immune therapy. This method is under the last phase of the clinical trial.

Chimeric antigen receptor (CAR) T-cell therapy: In this treatment method where blood is withdrawn from the patient and T cell's proteins of the blood is changed than the original one, which then can attach into the lymphoma cells and kill the lymphoma cells. These types of the

T cells are normally multiplied for many times and given back to the patients. This study also is in last steps of clinical trial phase.

Monoclonal antibodies (mAbs): These are the artificial immune proteins where some of these proteins can kill the cancer cells on its own, or some are attached with the radioactive particles. These antibodies specifically target the cancer cells and kill it without producing much of the side effects than the other treatment methods. The example of (mAbs) are such as Rituximab, brentuximab.

1.2.6.1 Side effects of treatment

There could be two types of side effects i.e. short term and long term side effects, which depends on time of time of seen side effects and how long it lasts (duration).

Short term: short term side effects are those effects which will be repaired by the body's own repairing system once the treatment is over. This treatment which damages the abnormally rapidly dividing cells and stops its being spread to the other parts of the body. Where, Cancer cells are also rapidly dividing cells and few other cells which is normal but still rapidly divide which need continuous supply of new cells i.e hair, nail and skin cells, hence short-term side effects are caused and will be repaired on its own and recover (Shankland KR et al., 2012).
According to Shankland KR et al 2012, short term side effects of treatments include the following:

- A fall in white blood cells count leading to more vulnerability to infectious diseases like fever, common cold, pneumonia, TB, malaria, dysentery, cholera etc.
- Difficulty in breathing and patient looks like having a jaundice.
- A fall in platelet cells count which helps to clot the blood, leading to bruising and more bleeding from normal wound also.
- Inflammation and pain in the mouth and neck.
- Constipation or loose poo
- anxiety, depression
- osteoporosis
- Others: hypo or hyper-thyroid, speaking problem, swallowing issues, heart diseases, pneumonia, skin cancers and breast cancers, fatigue, cognitive changes, decrease in libido

Long term: Most chemotherapy side effects are temporary and disappear once treatment is over. As the different people body reacts differently to the same treatment, some people may have the long-term effects for many months or many years even after treatment gets over. Long term side effects for radiotherapy and chemotherapy include early menopause, fertility problems, hormonal changes, heart or lung problems, asthma, secondary malignancy. Anthracyclines showed secondary malignancies and infertility. Similarly, Hemopoietic stem cell transplantation also showed development of secondary malignancies, fatigue, infertility, and cardiac toxicities (Shankland KR et al, 2012).

1.2.7 Follow up

It is very important to follow the advice of the doctor or specialist who handled the case**.** Generally, patient meet with the cancer specialist nurse in the follow up to have the general health checkups and if needed she/he recommends to other health professional such as GP, specialist such as psychologist or psychotherapist etc. Survivors may be asked for then how well they are recovering like their developments, if they are having any problems such as in fertility, getting employment, second cancer etc. following treatment, cancer relapse (coming back of same cancer). It is important to come on the regular visits as suggested by the specialists or personal doctor, and if you feel like you are experiencing any unexpected or odd signs and symptoms than what doctors told you before, just rush to the doctor. Survivors do need to book for the appointments to have a visit with the personal doctor and the appointment time is often very short to discuss all the curiosities of the survivors. Hence, survivor need to be prepared by going through the internet, books, leaflets from the hospital or from friends who if have gone through the same medical condition, before visiting the doctors and should ask the queries which is very much confusing to him even after doing possible research of his disease (Sapkota S et al 2021 & Shankland et al 2012).

Study of Sapkota S et al 2021 enlightened that the survivors may need to do the preparation to the follow ups in the following ways:

Restrictions before appointment: There might be sorts of preparation that the survivors need to do such as dieting, doing some types of exercise or taking any specific medicine before visit, and required documents such as ID, insurance card etc**.**

Taking notes: It's very important to take a note on unexpected or expected the signs and symptoms, changes in the lifestyle, any other medicines, supplements, or vitamin intakes before the regular or unexpected emergency visit**.**

Being prepared for the kinds of question to ask for: The survivor with all the information he has regarding his disease, other diet, medicines, lifestyle changes or signs and symptoms, survivor should note the possible questions to ask which is making him confused. Making the list of questions is important because of often short appointment time duration and to make full use of it**.**

Taking a companion along with for the visit: it is always better to have someone with the survivor for the follow up because the survivor generally does go through some tension or anxiety or depression, and for which he may not remember all the information or suggestion that is said by the personal doctor or may interpret the actual information given to the survivor. Thus, having a companion or family member is useful during the visit**.**

And with the proper interaction with the personal doctor: If personal doctor feel that the signs and symptoms are unusual than the regular one, then he may refer to the laboratory for some blood, skin, sputum or all the tests along with imaging test such as x-ray, video x-ray, MRI or CT-scan. And according to the reports from the tests, personal doctor may suggest the survivor with the medications and suggestions or may refer further to the specialists.

Sapkota S et al, 2021 study presented that the following are the questions that could be asked to the personal doctors when visiting:

Are all the signs and symptoms under control?

What was the reason for unexpected signs and symptoms? (in case of emergency or sudden meet)

Is there is any need of further tests or visits to confirm the new disease or cancer?

Are signs and symptoms under control or not? Has my cancer got relapsed or any other secondary cancer developed? If yes- what type of cancer got developed now? Aggressive or slow one?

Do I need to visit the many specialists to confirm the type of cancer and treatment or not? - If not, what type of treatment is required for how long, what are the side effects and adverse effects of the drugs?

What is the best method of treatment secondary, relapsed cancer in my case? Do you have any recommendations if your loved one were in the same medical condition like me?

How costly is the treatment and till what time should I take the treatment? Is treatment too costly or does my insurance cover the treatment?

What is the lifestyle that needs to follow from now? How much can I work and how much should I rest?

Can I go into the visit of my friend and family or travel to any other places?

Do you have any brochures or website about the new disease that you suggest for?

Finally, the survivors should not have any sorts of hesitations to ask the few other questions if time permits.

1.3 Health related quality of life among of non-Hodgkin lymphoma survivors

Health-related quality of life assessment in clinical research is very much important which help to facilitate the communication between patients and HCPs, to improve satisfaction in the patients, reduce hospital admission and for better healing/ treatment of the disease. AYAs with the diagnosis of the cancer showed worse health-related quality of life when compared to the cancer free population because of the risk factors such as socio-economic status, poor sex life, unemployment, high levels of distress and physical signs and symptoms.[35]

1.3.1 Physical well-being

A review conducted by Leak et al, 2011[36] found that AYAs cancer survivor have poorer physical well-being than the cancer free population. Prolonged and late physical effects include:

- System specific, i.e., damage, such as damage, failure or premature aging of organs, immunosuppression or compromised immune systems, and endocrine damage.
- Second malignant neoplasms such as an increased risk of a certain cancer associated with the cytotoxic or radiological cancer therapies.
- Functional changes such as lymphedema, incontinence, pain syndromes, neuropathies, and fatigue); change of the body look which could be due to for example amputations, ostomies, skin appearance change, hair fall and other related health problems for example osteoporosis, arthritis, scleroderma, and hypertension.

In addition, a smaller number of participations in the activities such as sports, gym, social programs such as birthday parties, marriage parties etc. and sexual dysfunction. Similarly,

chances of reoccurrences of the same cancer also will be there. Meanwhile, long term physical effects are more determined by the types of cancer, age, and income level of the survivors. For example**,** secondary cancer especially when treated with the radiotherapy or chemotherapy including alkylating agents such as cyclophosphamide and anticancer plants drug called podophyllotoxins. For instance, leukemia after treatment using alkylating agent along with development of other cancers such as breast cancer, bone cancer and thyroid cancer after radiotherapy (Stein KD et al, 2008)[37]

Husson et al (2018 & 2021) stated that AYA survivors with reported infertility were having regret feeling for not discussing about the preventing reproduction options, some showed their sadness with the current partners, and some were feeling fear of not getting partner and whole life distress regarding it. In addition, because of the intensive treatment schemes of the NHL mostly, the survivors may have the problems such as erectile dysfunction, premature ejaculation, pain during sex for men and dryness of the vagina, early menopause, loss of elasticity of vagina may decrease the interest in sex and may decrease the confidence on performing the intimate sex with their partners.

1.3.2 Psychological well-being

Several studies report psychological problems among NHL survivors.[38,39,40] The psychological distress in the rest of the life of the survivors is significantly high among AYAs than older and younger patients as the younger survivors normally cannot figure out the consequences of the cancer diagnosis, whereas the older survivors have the previous experience of handling tough situations which makes both these age group less vulnerable to the psychological distress. But due to the many factors such as physical appearance change(loss of hair, body weight loss/gain), fear of body not returning to the original appearances, fear of not being recognized by others, fear of discrimination, fear of replace of cancer, lack of self-worthiness against opposite sex and in the whole society leading them to feeling of shame, isolated from society, anxiety, depression, fatigue, sleep problems, cognitive limitation, opioid/alcohol dependence post-traumatic stress and other behavior changes with full of frustration or sadness. Other studies showed that the cancer diagnosis has the detrimental mental effect which can bring to the condition of post-traumatic stress syndrome or symptom which could lead to more incidents of traffic accidents, sexual harassments etc. Also, after the diagnosis of the cancer, AYA patients showed thinking such as what kind of treatment they will give and will I be able to survive after the treatment, does society accept me after the treatment, which ultimately leading them to long

term depression. In addition, according to one study, the HCPs are not evaluating the psychological problems of theirs AYA patients when they come for the follow ups. Similarly, the AYAs themselves delaying the report related to psychological issues because of their self-coping confidence, fear of stigma. In addition, when AYAs are diagnosed with the advanced stage of cancer, then it could be more challenging for them to handle because they have not faced adverse experiences in their life to process the progression and degree of the challenges of the diseases, hence having less mental ability to cope with cancer. Other studies showed that they showed high fears of welfare of their children or family as well. Similarly, many AYAs reported that they were isolated, misunderstood from the society and they took the diagnosis of cancer as the shock thinking cancer as older people related disease. According to the study, patients who die in the hospital do use the palliative care very late hence they receive the intensive treatment until their death (Husson et al 2018, Stein KD et al 2008 & Naughton MJ et al 2014).

1.3.3 Social well-being

Meeneghan et al (2014) enlightened that this is the age of exploring sex and relationship goals. Indulging himself in the romantic relationship, having good sex life, having girlfriend and baby or family, but cancer diagnosis may lead to loss of social contacts and loss of self-esteem, self-worth and ultimately leading to lack of communication for the rest of their life. Diagnosis of cancer always leads to move home and dependent to the parents, or spouse or partner etc. The feeling of infantilized or being overprotected may lead to toxic feelings/thinking in their minds. Shielding the stigma of the cancer family by himself because of guilt feeling. They feel the driving energy of keep moving to take care the older parents, wife/co-habitants and children although having the feeling of sick. Similarly, children of the AYA cancer survivors may experience problems such as behavioral, cognitive, and physical functioning. Because of all these, the feelings such as isolation, alienation, lack of being socialized, social anxiety and loneliness. It's a difficult time to maintain the relationship and make the new relationships, hence feeling of insecurity, anxiety and loneliness may develop. Similarly, survivors reported problems on dare to share the health issues of their cancer among friends and family due to social stigma about cancer. Burden for the parents as well as they have given more focus to the AYAs care instead of job and refreshing activities, may lead to extra stress for the whole family. Furthermore, only few percentages of NHL survivors are married and most of them got divorce or separated after being diagnosed with cancer. Many reported that the partners were not willing

help them through this financial and emotional challenging time leading to marital distress and divorce or breakups. Furthermore, because of many factors such as feeling of insecure, lack of self-confidence, feeling of sick and infertility and other health related concerns halting them to initiate in the new cheerful relationship. Social support interventions are also need of hour to them for making new contacts and maintaining the old contacts. Similarly, because of chances of being destroyed reproductive cells at the time of treatment for example- chances of acute ovarian failure/premature menopause in women and chances of development of azoospermia permanently/temporarily, may lead to huge challenge in wish of the survivors of having baby. Even though there is availability fertility preservation options discussion before initiating the treatment, around 50% do not discuss regarding it with theirs HCPs because of sadness and lack of self-esteem on their reproductive ability and options. Which may result in issues with their social relationship, dating and further family planning.[41]

1.3.4 Functional well-being

Functional well-being denotes the functional limitation of physical participation and performance in the daily life activities, i.e., they do suffer in their own personal care, they do have hard time managing day to day regular life routine such as doing their assignment or going to the job or school. Whatever job, assignment, or project they do, they could not perform according to their full potential (Husson et al, 2021).

A study conducted by Aziz 2007[42] found that risk of deleterious effect in physical function, intelligence function, role function and social well-being function across all stages of the NHL treatment. Because of the diagnosis of the cancer, the person cannot complete the course load, assignments, ands exams at the right time as the absenteeism just increases, which may lead to the loss of social contacts, network where man can feel the worth of himself, but due to all consequences, individuals can feel left behind. According to one Dutch study, among individuals with NHL diagnosis, 55% cannot complete the higher degree. Hence to return to the school and to complete the study, must the hospital and school should have good co-operation. Because of the diagnosis of the cancer, 28% of cancer survivors could not return to the job for 15-35 months in AYA age group, 50% said that because of highly intensive treatment methods, they had problems of memory- and to focus on the job. And lack of the confidence. Similarly, many complained about the discrimination from the colleagues and employers, and that is why they had to adjust their job-related goals according to one of the American studies.

Survivors felt that they had less productivity and more healthcare expenses compared to their colleagues. They also presented that they had more household expenses and less income. Hence, they need to rely on their parents, which may lead to the feelings of dependency and confidence. Less burden in the Norway because of welfare system which gives the right to every individual to have the free treatment of NHL (Husson et al, 2021).

1.3.5 Spiritual and existential well-being

Spiritual well-being is not like spirituality, but it is a part of spirituality. It is basically meaning for not losing the hope in the life ahead and keeping oneself motivating. It is also said that it is well being in relation with the god or spiritual force. Here, we are studying only the value of spiritual well beings during and post treatment of the cancer survivors on the AYA age group. The multidimensional aspect of our life, where spiritual wellbeing is related to hope aligned with good known as vertical dimension, and existential wellbeing is horizontal dimension that tells about perception of life and experience of living during and after the treatment of the AYA patients. Researchers found out that the spiritual well-being is very important among AYA cancer survivors that helps to cope with psychosocial problems, physical symptoms, and functional disability, as it helps to readjust their life's goal and objectives, as it gives new hopes, new way, motivation and strength to lead their life around the tough environment post treatment in a positive way.[43] But the AYA patients who is diagnosed with the NHL showed loss of hope, loss of driving force in their life which could be related to theirs education, job, relationship, physical appearances or social wellbeing. They were found to be in hopeless condition citing for their lack of self-esteem and lack of feeling of being exist in the family or society or in the job or friend circle (Clay KS et al, 2010).

1.4 The Norwegian health care system and general practitioners' role.

The Norwegian health care system is founded on the principles of universal access, decentralization, and free choice of provider. Public health services are delivered at the local and national levels.[44]

Primary care is provided at the municipal level, mostly by self-employed physicians and as part of municipal public services (e.g., nursing homes and home-based services). General practitioners (GPs) act as gatekeepers, referring patients to more complex care. Inpatient

specialized care is mainly provided by hospital trusts owned by the RHAs, as well as some contracted private facilities.[45]

Hospitals also provide outpatient specialist care in their outpatient departments. A deliberate substitution policy has been pursued since the late 1980s with the aim of replacing relatively expensive inpatient care with less-costly outpatient and day care and bringing care closer to patients' homes.

GPs have a key role in the health system as gatekeepers for the patients about accessing specialist care. Their responsibilities include making primary diagnoses; treating simple everyday problems; issuing sickness certificates; prescribing drugs; issuing referrals to physiotherapists, chiropractors, and nursing homes; and referring patients to specialist care (i.e., hospitals and privately practicing specialists) when necessary. Only physicians or ambulance services can refer patients for emergency hospital consultation or for admission to hospital. GPs are also obliged, through their contracts with municipalities, to serve as on-call physicians in the local emergency centers. Moreover, they play an important role in health promotion and public health.

The patient's first contact with the health care system is usually through the regular GP or the on-call physician at one of the emergency centers that are in all municipalities. However, in case of medical emergencies, patients may attend the emergency department at the nearest hospital. For elective specialist care, the GP can either make an appropriate appointment on behalf of the patient or provide a referral so that the patient can arrange the appointment (Sperre Saunes et al, 2020).

Emergency care services are largely the responsibility of municipalities at the primary care level, and are provided by GPs or local emergency centers, which are a first point of contact in case of medical emergency. More than a quarter of spending on health in Norway is devoted to long-term care. It is provided in three types of setting: patients' homes, nursing homes or sheltered homes run by the municipalities. Except for home care, long-term care in municipal settings requires substantial co-payments by users.

1.5 Literature review

Cancer in AYACs represents a unique disease constellation with distinct epidemiological, clinical, and biological characteristics that resemble neither to childhood cancer nor cancer in older adults. The lower incidence of AYACs-onset cancer, along with the paucity of data from cancer clinical trials in this age group, limit substantially our knowledge on this group of patients with cancer.[46]

The next section presents a summary of published research about late effects of cancer among survivors of non-Hodgkin lymphoma.

1.5.1 Late effects of cancer among children, adolescents, and young adults

Vandrass F et al. (2021)[47] conducted a study in Norway among young adult cancer survivors (19-39 years) of different types of cancers including NHL where they study long-term late cancer effects. They found that the fear of cancer recurrence is frequent even decades beyond treatment completion in young adult cancer survivors.

Sender A. et al. (2019)[48] conducted a study to analyze the supportive care needs of young adult cancer patients, including NHL, how they change over time and the variables associated with those needs. They found a high number of cancer survivors reported having at least one unmet supportive care needs at both after 12 months of diagnosis and after 4 years of diagnosis. Moreover, they found that the more the supportive care better quality of life.

A recent study conducted by Ocier K et al 2021, showed that younger B-cell non-Hodgkin's lymphoma survivors had higher relative risks than older cancer survivors of chronic rheumatic disease of the heart, peri-, endo-, and myocarditis, diseases of the arteries, and hypotension. They conclude that elevated relative risks of heart disease overall and congestive heart failure is seen in both younger and older survivors of B-cell non-Hodgkin's lymphoma.

A study from Canada by McBride ML et al,[49] among survivors of cancer included survivors of non-Hodgkins lymphoma and diagnosed before age 20 years showed that approximately 97% of survivors saw at least 1 physician in the 3-year period, compared with 50% of the general population sample. The probability of a GP visit was 96% higher, and the likelihood of a specialist visit was 157% higher than for the general population. Survivors were more than twice as likely to see GPs at least 10 times and had 49% more visits than the general population.

Martens Ac et al. (2001[50]) conducted a cohort study in USA among cancer survivors who were diagnosed before the age of 21 and who had a long-term survivorship >5 years to find out the main causes of death. They found that the main cause of deaths was due to recurrence of cancer (67%), secondary cancer, pulmonary and cardiac diseases, along with treatment related secondary cancers from agents such as radiation, alkylating agents, and epipodophyllotoxins. They conclude at while recurrent disease remains a major contributor to late mortality in 5-year survivors of childhood cancer, significant excesses in mortality risk associated with treatment-related complications exist up to 25 years after the initial cancer diagnosis.

Several studies among children show that survivors of childhood cancer have increased risks for morbidity and mortality due to the late effects of cancer therapy, and recognition of these increased risks has resulted in modifications to treatment regimens with the goals of improving cure rates while reducing the risk and severity of late effects. However, more recently treated survivors of childhood cancer have experienced improvements in health outcomes, because efforts on better childhood cancer treatment regimens to maximize cure while reducing risk of late effects.[51] Norwegian long-term survivors of childhood malignant lymphomas are showing improved level of knowledge of their diagnosis and treatment modalities during the last decade. Still, independent of age at diagnosis and level of education, they are insufficiently aware of their risk of late effects.[52]

Several studies report late effects of cancer among adults' survivors of non-Hodgkin's lymphoma. A study conducted by Ehrhardt et al,[53] showed that adult survivors of childhood non-Hodgkin's lymphoma experience impaired neurocognitive function, which is associated with lower social attainment and poor health-related quality of life.

A summary from the 6th International Symposium on Childhood, Adolescent and Young Adult non-Hodgkin lymphoma held in Netherlands in 2018,[54] conclude that children and adolescent NHL survivors are at significant risk of late mortality from secondary neoplasms, recurrent/progressive disease and chronic health conditions, and late morbidity of multiple organ systems and poor health-related quality of life. A highlight the importance of to identify at-risk patients who are at significantly increased risk of these complications.

2. Research question, hypothesis and aims of the study

2.1 Research questions

Which health problems are more frequently presented in general practitioner consultations among survivors of non-Hodgkin lymphoma diagnosed at young age (18-35 years)?

Can we find the differences on the types of health problems presented in general practitioner consultations across non-Hodgkin lymphoma subtypes?

2.2 Hypothesis

We hypothesize that survivors of non-Hodgkin lymphoma diagnosed at young age (18-35 years) consult their family doctor more often than individuals in the same age without a cancer diagnosis.

2.3 Aims of the study

To analyse the frequency and distribution of health problems most encountered in general practitioner consultations among survivors of non-Hodgkin lymphoma diagnosed at young age (18-35 years) from the first until 10 years after the cancer diagnosis.

To compare the most common health problems among survivors of non-Hodgkin lymphoma diagnosed at young age (18-35 years) with adolescents and young adults without cancer at the same age.

3. Materials and methods

3.1 Overview of variables and registries used in the present study

In the present study, we used the data from following registries of Norway:

3.1.1 Study population

From *the Central Population Register from Statistics Norway* we identified the study population. *Cancer cases* were all individuals diagnosed at the age of 18-35 with a primary cancer of non-Hodgkin lymphoma between 2001 and 2017 and who were living in Norway in the study period. *Non-cancer cases* were all persons born in Norway between 1970 and 1997 without a cancer diagnosis.

3.1.2 Variables on cancer diagnosis and GP consultations

Data from the Central Population Register from Statistics Norway was linked to the following registries using patients' personal Norwegian ID number:

From *the Norwegian Cancer Registry,*[55] we included following variables: date and age of cancer diagnosis, type of cancer, histology, and date of death. Non-Hodgkin lymphomas cases were coded using the International Classification of Diseases for Oncology, third edition.[56] The following ICD-O-3 codes was used: 9591, 9670, 9671, 9673, 9675, 9678–9680, 9684, 9689–9691, 9695, 9698–9702, 9705, 9708, 9709, 9714, 9716–9719, 9727–9729, 9731–9734, 9760–9762, 9764–9769, 9970.

From *the Control and Payment of Health Reimbursement*,[57] we included information on all GP consultations in the period 2006-2017. From the registry we obtained information on date of the consultation, codes indicating contact type with the GP, main diagnosis and/or other bi-diagnoses based on the International Classification of Primary Care, 2nd edition (ICPC-2).[58]

3.1.3 Statistical Analysis

First, I present descriptive analyses of the number of GP consultations after the cancer diagnosis. The follow-up period was divided into three periods according to GP consultations presented in the first year, 2-5 years, 6-10 years after the cancer diagnosis. The independent

samples t-test (two-sided) was used to find out if there was difference between mean values of cases and non-cases population. P value of 0.05 or less was statistically significant in the study.

Logistic regression model was used to compare the risks of having different types of complaints/symptoms among cases and the non-cases based on the odds-ratio (OR) and 95% confidence interval (CI). Non-Hodgkin lymphoma (yes/no) was the dependent variable and types of complaints/symptoms independent variable. The model was adjusted for four age, sex, and year of consultation.

The analysis of health problems was across 17 types of ICPC-2 body chapters. In addition, the ICPC-codes chapters of pregnancy, family planning and female genital among female population and male genital symptoms was analysed among male population respectively. Cancer cases were analysed including all the NHL types combined and by four main types separately. We also conducted analyses including diagnosis/disease component in each body system chapter. For this, to reach enough statistical power we included all non-Hodgkin cases

The sub-analysis across NHL subtypes were also carried out with binary logistic regression models by using subtypes of non-Hodgkin lymphoma (Precursor cell lymphoma/ Mature B-cell lymphoma/ Mature B-cell lymphoma/NOS) as dependent variable and by adjusting the same three factors of the study as mentioned above.

All the analysis was carried out by the SPSS (version-28).

3.1.4 Ethical considerations

The present project was approved by the Regional Committee for Medical and Health Research Ethics, (REK Sør-Øst: 2016/1305). As this is a register-linked study, the approval also covers exemption from informed consent because that would not be feasible to acquire.

Only unidentified files were used in the project. Data is stored in Services for sensitive data (TSD) at the University of Oslo. Data storage and processing of the link file was processed according to established security routines. The University of Oslo and the City of Oslo have established systems for internal control and routines for information security.

4. Results

4.1 Descriptive analysis

Table 1 presents the Distribution of demographic and clinical characteristics of the study population. The mean age of diagnosis is found to be 29 years. Among the study population 156 (57%) were males and 119 (43%) were females.18-19 years age group accounted for 16 (6%) patients and the age group of 30-35 accounted for 149 (54%) patients which are found as the lowest and the highest numbers of patients of the age groups in the study. In the subtypes of NHL, the number of mature B cell lymphoma patients were found to be 199 (72%) as the highest while number of precursor cell lymphoma patients were found to be the lowest number as 10 (3.5%).

Table 1. Distribution of demographic and clinical characteristics of the study population

Variable	**Survivors**		**General population**	
	Number	**Percent**	**Number**	**Percent**
Diagnosis age				
18-19	16	5,8		
20-24	46	16,7		
25-29	64	23,3		
30-35	149	54,2		
Type cancer				
Precursor cell lymphomas	10	3,6		
Mature B cell lymphoma	199	72,4		
Mature T-cell and NK-cell lymphomas	56	20,4		
Non Hodgkin NOS	10	3,6		
Sex				
Men	156	56,7	1143295	51,4
Woman	119	43,3	1081189	48,6
Birth year				
1970-1974	22	8,0	420889	18,9
1975-1979	78	28,4	396971	17,8
1980-1989	83	30,2	405568	18,2
1985-1989	55	20,0	409250	18,4
1990-1997	37	13,5	591806	26,6

SD: Standard deviation

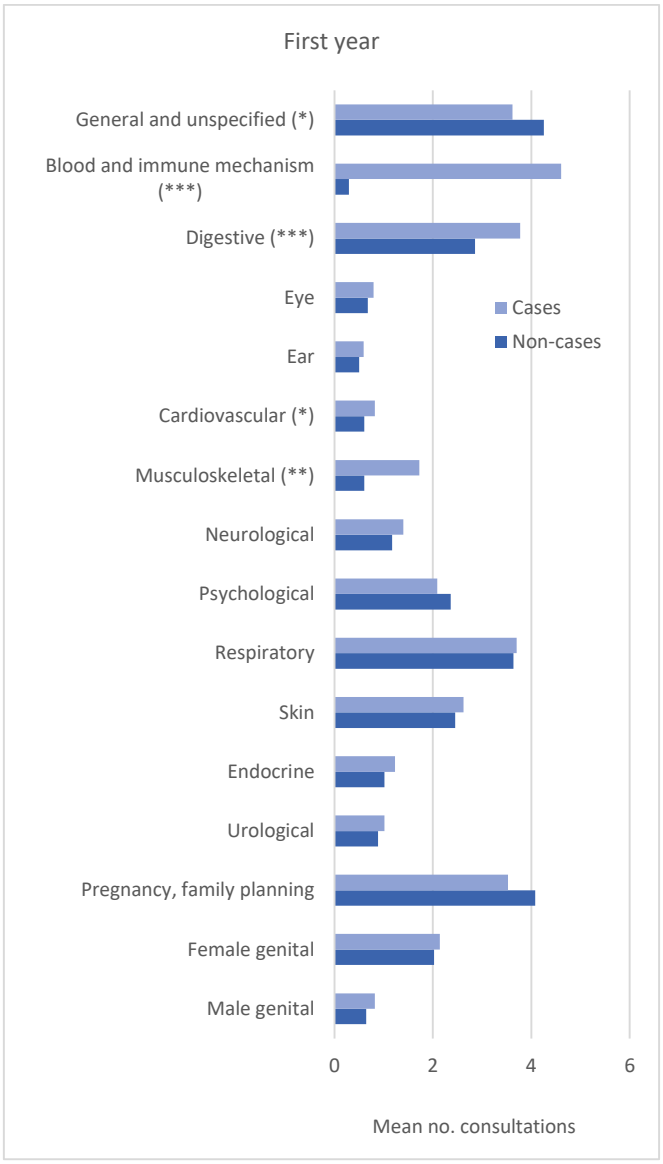

Figure 1. Average number of consultations in general practice (GP) across ICPC-2 diagnoses among adolescents and young adults' survivors of non-Hodgkin lymphoma the first year after the cancer diagnosis compared to the cancer free population.

*p < 0.05

**p<0.01

***p <0.001

Figure 1 shows the comparison of the mean consultations in the first year of follow up between cases and non-cases population. In the first year, the most frequent type of diagnosis/complaints is found out to be blood forming organ and immune mechanism, followed by digestive, musculoskeletal, and cardiovascular with mean consultations of 4.7, 3.8,1.7, 0.8, stands in the 1st, 2nd, 3rd & 4th most frequent and significant types respectively.

In addition, comparing mean consultations between cases and non-cases in the first year of the diagnosis NHL survivors consulted their GP more often than non-cases for symptoms in the blood and immune system ($p<0.001$), digestive ($p<0.001$), musculoskeletal ($p<0.01$), and cardiovascular system ($p<0.05$).

The most common reason for contact with the GP in in the first year of the cancer diagnosis were general and unspecified symptoms with numbers of NHL survivors of 246 and a mean consultation of 4,3 consultations per year (Table 2). Likewise, musculoskeletal complaints were the most frequent health problem in the period of 2-5 years of follow up with numbers of NHL survivors with these complaints of 275 and a mean consultation of 8,2 in the period.

Musculoskeletal with numbers of NHL survivors with these complaints of 275 and (mean- 8.2) and digestive symptoms numbers of NHL survivors with these complaints of 275 and with (mean value of 8,2) were the most frequents after 6 years of the cancer diagnosis.

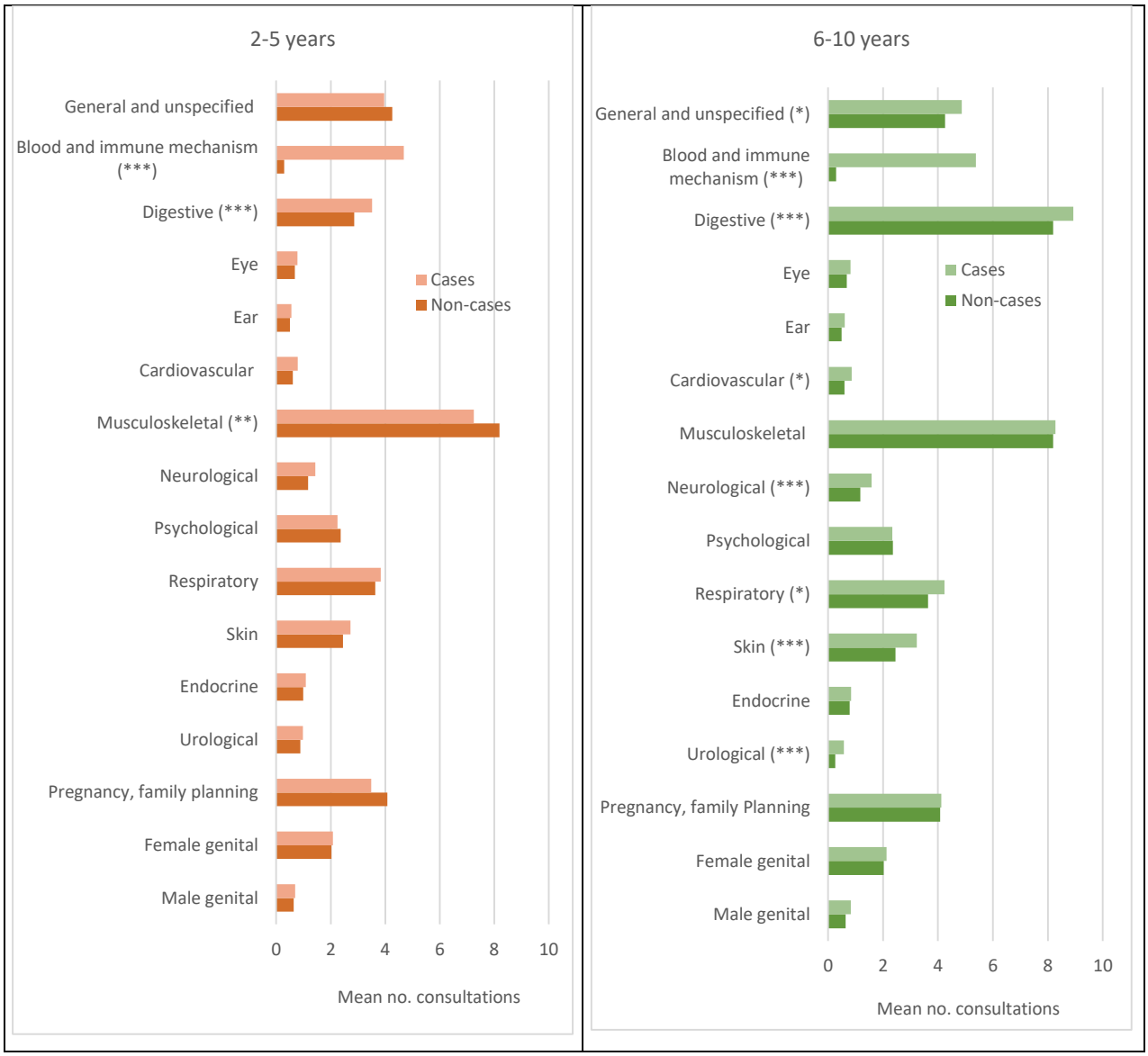

Figure 2. Average number of consultations in general practice (GP) across ICPC-2 diagnoses among adolescents and young adults' survivors of non-Hodgkin lymphoma 2-5 years and 6-10 years after the cancer diagnosis compared to the cancer free population.

*p < 0.05

**p<0.01

***p <0.001

Figure 2 shows the mean consultations of the cases and non-cases in the 2-5 years and 6-10 years of follow up. In the 2-5 years of follow up, the diagnosis/complaints related to blood forming organ and immune mechanism was statistically significant along with digestive system with the mean consultations of 4.8 and 3.5 respectively, At the same time, diagnosis/complaints related to musculoskeletal is more frequent than the others.

Similarly in the 6-10 years of follow up, it is observed that the diagnosis/complaints related to digestive system as the most frequent and significant one, followed by blood forming organ and immune mechanism, respiratory, skin, neurological, cardiovascular & urological with mean consultations values of 9, 5.5, 4.3, 3.2, 1.5, 0.9, 0.7 respectively.

In addition, when comparing the mean consultations between cases and non-cases: two to five years after the cancer diagnosis contacts with GP were more often compared with cancer free population for problems in the blood and immune system ($p<0.001$) and digestive system ($p<0.001$). Six years after the cancer diagnosis many diseases and complaints leading to consultations with the GP seen more often among NHL survivors compared with the free cancer population were reported in the following code groups: blood and immune system ($p<0.001$), digestive system ($p<0.001$), neurological system ($p<0.001$), skin ($p<0.001$), urological system ($p<0.001$), respiratory system ($p<0.05$), cardiovascular system ($p<0.05$), along with general and unspecified ($p<0.05$) were more often among cases compared to non-cases study population.

4.2 Results from the logistics regression models

The odds ratios for GP contacts regarding each ICPC-2 charter are shown Table 2. The risk of consulting with GP in the first year of follow up for having health problems related to non-Hodgkin disease and its treatment was 32% higher among NHL survivors compared with cancer free population (blood and immune system OR=1.32 95% CI:1.27-1.37). Risk of musculoskeletal complaints was also higher among NHL survivors compared with cancer free population (OR=1.19 95% CI: 1.14-1.23).

Similarly, health problems with higher risk of presentation in GP consultation: two to five years after the cancer diagnosis were health problems related to blood and immune mechanism having 50% more chances in NHL survivors than in cancer free patients (OR=1.50, 95% CI:1.45-1.55) along with diagnosis//complaints related to respiratory system (OR=1.03, 95% CI:1.00-1.07).

Furthermore, in the follow up of 6-10 years after diagnosis, the diagnosis/complaints related to urological system showed highly statistically significant with 86% more odds of complains among NHL survivors compared to cancer free population (OR=3.86, CI: 3.09-4.61) and diagnosis/complaints related to blood and immune mechanism showed 64 % more chances of development in the NHL survivor patients than in the cancer free population (OR=1.64, CI:

1.59-1.64). Likewise, diagnosis/complaints related to skin, digestive system, respiratory system, and neurological system also showed statistically significant numbers with value of OR=1.10, 95% CI: 1.06-1.14, OR=1.09, 95% CI: 1.04-1.14, OR=1.09, 95% CI: 1.05-1.13, OR=1.06, 95% CI: 1.02-1.11) respectively.

Table 2. Logistic regression model showing health problems in general practice (GP) among non-Hodgkin lymphoma survivors after the cancer diagnosis compared to the free cancer population.

	Follow-up period								
	First year			**2-5 years**			**6-10 years**		
	Cases*		**OR (95% CI)**	**Cases***		**OR (95% CI)**	**Cases***		**OR (95% CI)**
ICPC-2 category	**1**	**>1**		**1**	**>1**		**1**	**>1**	
General and unspecified	68	178	0.87 (0.83-0.90)	58	188	0.99 (0.96-1.03)	46	200	1.10 (1.06-1.13)
Blood and immune system	38	196	1.32 (1.27-1.37)	40	194	1.50 (1.45-1.55)	31	203	1.64 (1.59-1.69)
Digestive	11	175	0.99 (0.94-1.03)	15	171	1.02 (0.99-1.06)	5	270	1.09 (1.04-1.14)
Eye	63	41	0.96 (0.86-1.07)	64	40	1.02 (0.94-1.11)	61	43	1.05 (0.98-1.13)
Ear	39	34	0.98 (0.87-1.11)	46	27	1.02 (0.92-1.12)	40	33	1.03 (0.95-1.12)
Cardiovascular	47	43	0.90 (0.83-0.99)	46	44	0.99 (0.92-1.06)	45	45	1.03 (0.97-1.10)
Musculoskeletal	62	85	1.19 (1.14-1.23)	37	238	0.92 (0.89-0.95)	16	259	1.01 (0.98-1.05)
Neurological	46	66	0.98 (0.92-1.04)	46	66	1.02 (0.97-1.07)	41	71	1.06 (1.02-1.11)
Psychological	32	91	0.92 (0.88-0.97)	26	97	0.98 (0.94-1.01)	27	96	0.99 (0.96-1.02)
Respiratory	54	182	0.93 (0.89-0.96)	53	183	1.03 (1.00-1.07)	43	193	1.09 (1.05-1.13)
Skin	70	135	0.96 (0.91-1.01)	63	142	1.03 (0.99-1.07)	54	151	1.10 (1.06-1.14)
Endocrine/metabolic and nutritional	37	64	0.94 (0.88-1.00)	32	66	0.97 (0.92-1.03)	27	51	0.96 (0.90-1.03)
Urological	36	59	0.95 (0.88-1.03)	39	56	1.01 (0.95-1.08)	79	16	3.86 (3.09-4.81)
Pregnancy, childbearing, family planning	19	69	0.90 (0.84-0.96)	17	71	0.95 (0.91-1.00)	11	77	1.00 (0.96-1.05)
Female genital	26	52	0.94 (0.86-1.03)	26	52	0.99 (0.93-1.06)	23	55	1.01 (0.95-1.08)
Male genital	19	31	1.00 (0.88-1.14)	20	30	0.92 (0.81-1.05)	19	31	1.03 (0.94-1.14)

Cases represent number of NHL survivors with one or more than one GP consultation.

CI: confidence interval. OR, odds ratios.

The model was adjusted for birth year, sex, and year of consultation.

Figure 3 and appendix 1 show the results from the logistic regression models were codes into each ICPC-2 charter were analysed. ICPC-codes found to be statistically significant increased among NHL survivors compared with cancer-free population were general and unspecified symptoms, blood, blood forming organs and immune mechanism, digestive, musculoskeletal, neurological, respiratory, skin, urological, pregnancy, childbearing, family planning and female genital related diseases/complaints. Complaints/disease related to blood, blood forming organ and immune mechanism and symptoms in the respiratory system were found to be the most common type along with skin and general and unspecified complains.

Disease/complaints related to general and unspecified, swelling in the different parts of the body showed 15 % more chances of occurrences in the NHL survivors than the cancer free patients with OR=1.15, 95% CI: 1.06-1.24. Similarly, disease/complaints related to fever and infectious diseases showed to be 12% and 9% more chances of development in the NHL survivors than the cancer free patients with OR=1.12, 95% CI: 1.06-1.17 and OR=1.09, 95% CI:1.00-1.19 respectively. But complaints related to weakness/tiredness in general was most frequent type in 79 NHL survivors.

In the blood, blood forming organs and immune mechanism the ICPC codes found to be the most frequent and significant result among NHL survivors were complains related to Hodgkin's disease or cancer treatment. OR= 1.41, 95% CI:1.35-1.47.

Similarly, enlarged/painful lymph glands and malignant neoplasm blood other showed 24% and 16% higher chances of developments in the survivors than in the cancer free population with OR=1.16, 95% CI:1.16-1.32 and OR=1.16, 95% CI:1.11-1.21 respectively.
Complaints/disease related to respiratory system such as, acute tonsillitis was found as the most significant with OR=1.16, CI: 1.07-1.25 in 39/275 NHL survivors, whereas acute bronchitis/bronchiolitis and respiratory infection were having 11 and 10% chances of occurrences in the survivors with OR=1.07-1.05 & 1.07-1.14 respectively. On the other hand, cough and sinusitis were seen in 94/275 and 57/275 with OR=1.06, CI: 1.04-1.09, OR=1.05, CI: 1.02-1.08 respectively. The most frequent type of complaints/disease was acute upper respiratory infection. In addition, in complaints/diseases related to skin, localized lump/swelling and nevus/mole were found out to be the most significant three with OR=1.13, CI: 1.06-1.21, OR=1.10, CI: 1.03-1.18 & OR=1.10, CI: 1.02-1.17 respectively. Similarly,

complaints/disease related to skin symptoms/complaints, acne also significant with OR=1.09, CI: 1.01-1.09, OR=1.09, CI: 1.00-1.20 respectively.

Figure 3a. Cancer related symptoms and congenital anomalies

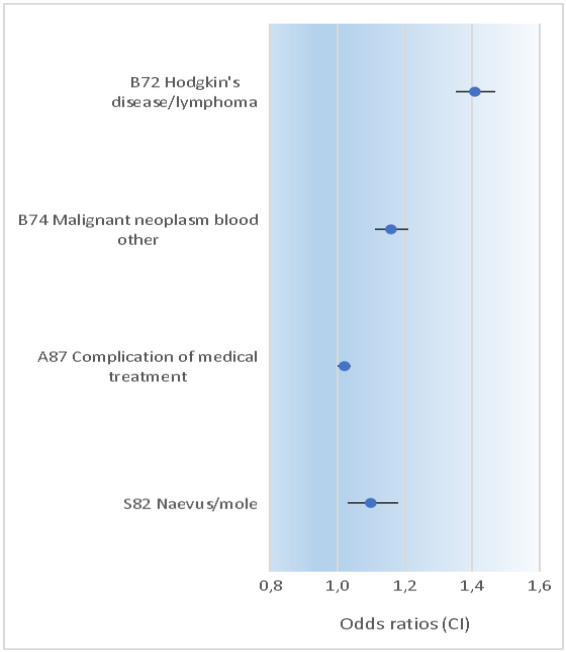

Figure 3c. symptoms/complaints

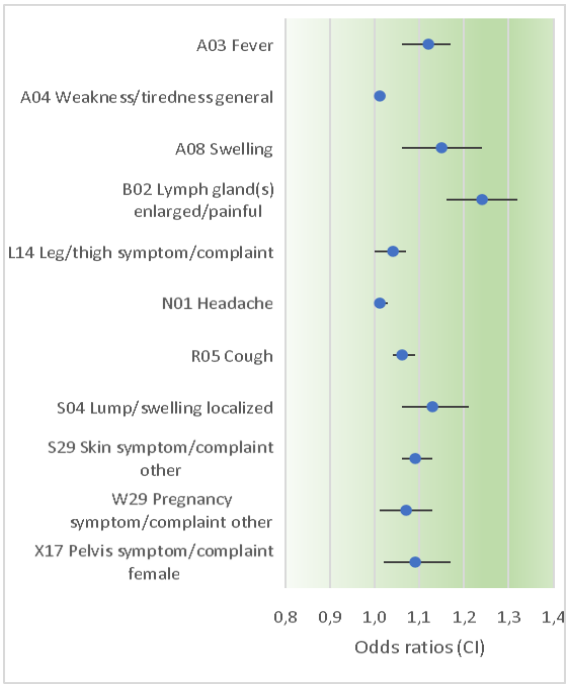

Figure 3b. Infections

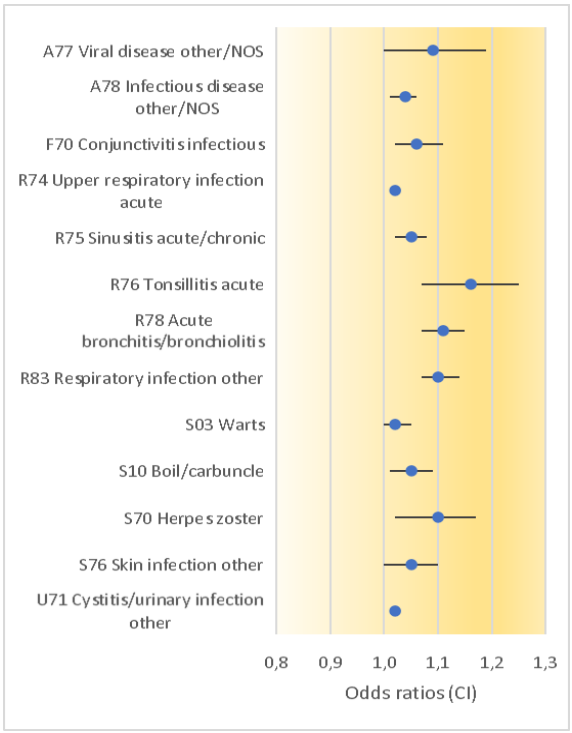

Figure 3d. Other diagnoses

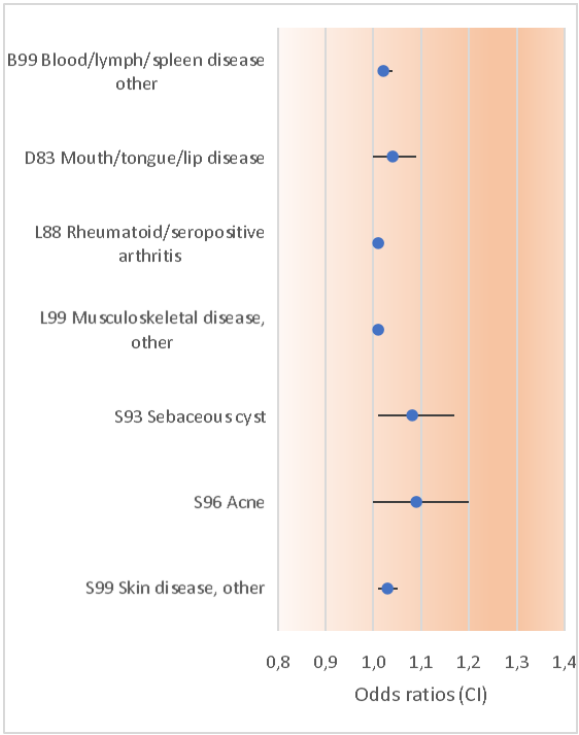

Figure 3. Logistic regression models showing groups of symptoms statistically significant among adolescents and young adults comparing non-Hodgkin survivors with cancer free population in a 10-year follow-up period.

In the digestive system related ICPC codes related to mouth/tongue/lip disease was found out to be the significant with OR=1.04, CI:1.00-1.09. Whereas disease/complaints related to the Eye and Neurological is found to be conjunctivitis infections and headache complained by the same numbers of NHL survivors of 51/275 with OR=1.06, CI: 1.02-1.11. and OR=1.01. CI: 1.00-1.03 respectively. Similarly, disease/complaints related to musculoskeletal system (L), leg/thigh symptoms/complaints were most significant with OR=1.04, CI: 1.00-1.07. Furthermore, complaints/disease related to urological, pregnancy, childbearing, family planning and female genital, found out to be cystitis/urinary infection, pregnancy symptoms/complaints other and pelvis symptoms/complaints as the significant complained by 64/275, 15/119 and 12/119 of NHL survivors with OR=1.02, CI:1.01-1.03, OR=1.07, CI:1.01-1.03, OR=1.09, CI:1.02-1.17 respectively.

Meanwhile, we could not see the significant and prevalent chronic disease in the study. We only found pneumonia and asthma as the chronic disease in this study.

4.3 Results showing analyses of non-Hodgkin lymphoma subtypes

Appendix 1 shows logistic regression model showing health problems in general practice (GP) statistically significant among non-Hodgkin lymphoma survivors across NHL subtypes after the cancer diagnosis compared to the free cancer population.

The chance of developing general and unspecified complaints/disease in the first years after the cancer diagnosis in the precursor cell lymphoma subtype was 1,29 higher in NHL survivors compared with the cancer-free population (OR=1.29, CI:1.07-1.56. In the period 2-5 years the odds were 1.69 (OR=1.69, CI:1.43-2.01), and in the period 6-10 year OR=1.83, CI:1.56-2.10. Similarly, non-Hodgkin NOS also showed the higher chances of showing general and unspecified complaints/disease in the 2-5 years and 6-10 years of follow up with OR=1.24, CI:1.03-1.50 & OR= 1.31, CI:1.07-1.61 respectively.

Moreover, the chance of developing blood and immune mechanism related complaints/diseases is seen in all the subtypes of lymphoma in all the years of follow up except in the precursor cell lymphoma. The highest risk was observed in the period 6-10 years after the cancer diagnosis and among NHL subtype non-Hodgkin NOS (OR=1.64, CI:1.40-1.91). Furthermore, chances of development of urological complaints/disease is seen significantly high in the period 6-10 years in the mature B cell lymphoma, mature T and NK cell lymphoma and Non-Hodgkin NOS subtypes of lymphoma with OR=4.41, CI:3.45-5.62, OR=2.59, CI (1.37-4.89), OR=3.87, CI:1.59-6.15 respectively.

Appendix 1. Logistic regression model showing health problems in general practice (GP) statistically significant among non-Hodgkin lymphoma survivors across NHL subtypes after the cancer diagnosis compared to the free cancer population.

Type cancer/period	**General and unspecified**	**Blood**	**Digestive**	**Musculoskeletal**	**Psychological**	**Respiratory**	**Skin**	**Urological**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Precursor cell lymphomas								
First year	1.29 (1.07-1.56)							
2-5 year	1.69 (1.43-2.01)							
6-10 year	1.83 (1.56-2.14)							
Mature B cell lymphoma								
First year		1.31 (1.26-1.36)		1.18 (1.13-1.24)				
2-5 year		1.50 (1.44-1.56)						
6-10 year	1.09 (1.05-1.14)	1.64 (1.58-1.70)	1.09 (1.04-1.15)	1.05 (1.00-1.11)		1.09 (1.05-1.13)	1.07 (1.02-1.11)	4.41 (3.45-5.62)
Mature T-cell and NK-cell lymphomas								
First year		1.32 (1.21-1.44)						
2-5 year		1.44					1.14	

		(1.33-1.55)					(1.06-1.24)	
6-10 year		1.61 (1.51-1.72)		1.18 (1.08-1.29)		1.08 (1.00-1.16)	1.22 (1.13-1.32)	2.59 (1.37-4.89)
Non-Hodgkin NOS								
First year		1.61 (1.27-2.06)		1,24 (1,04-1,49)				
2-5 year	1.24 (1.03-1.50)	1.61 (1.36-1.90)			1,24 (1,07-1,44)			
6-10 year	1.31 (1.07-1.61)	1.64 (1.40-1.92)			1,24 (1,08-1,44)		1,22 (1,01-1,46)	3,87 (2,43-6,15)

CI: confidence interval. OR odds ratios.

The model was adjusted for birth year, sex, and year of consultation.

5. Discussion

5.1 Main findings

Adolescents and young adults diagnosed with NHL have been an understudied population and there is limited description of late effects after the diagnosis.[59,60] To our knowledge, this is the first large-scale study of GP consultations among adolescents and young adults' survivors of NHL. The present study shows that demand for physician care among these cancer survivors is considerably greater than for the general population, and this need persists many years after the diagnosis. Health problems related to NHL disease and its treatment in almost all NHL subtypes is still important not only in the first years but also 6-10 years after the cancer diagnosis. We further found that NHL survivors also had significantly more overall GP visits for symptoms and complains related to musculoskeletal system, digestive system, neurological system, respiratory system, psychological, skin, urological system, and general and unspecified symptoms. These health problems were statistically significant in mature B cell lymphoma, mature T-cell and NK-cell lymphomas, and NHL NOS (not otherwise specified).

Excess of contacts with a doctor was greater for infection diseases in the respiratory system, urinary infection, skin, Herpes Zoster, and infections in the eyes. Headache, fever, weakness/tiredness general, cough, skin symptoms, and pregnancy and pelvis complain were higher among these survivors than expected in the general population. Musculoskeletal problems including rheumatoid/seropositive arthritis in addition to others musculoskeletal disease was also overrepresented in NHL survivors.

5.2 Comparison with previous research

Direct comparison with other large studies into health problems among adolescent and young adults in general practice is not possible because of the absence of similar studies. The only similar study the authors were able to identify was the population-based British Columbia study reported by Andrea C Lo et al, 2021.[61] The study is based on self-reported late effects and included 79 individuals aged 15-24 years NHL survivors and 226 survivors of Hodgkin lymphoma. They report among all lymphoma survivors, significant high risk of hypothyroidism, secondary malignancy, symptomatic pulmonary toxicity, esophageal

complications, xerostomia/dental decay, cardiac disease, and infertility among these survivors. Health problems in the mouth as well as pelvis complain are reported in our study.

A study conducted in USA among NHL survivors (average median age 49), showed that survivors had significant problems related to thyroid functions (hyperthyroidism or hypothyroidism), heart diseases, problems in normally speaking and swallowing foods, pulmonary fibrosis/pneumonia, and secondary breast cancer development is seen as primary findings till the 5th years of follow-ups care.[62,63] Our study also showed diseases/complaints such as pneumonia, thyroid dysfunctions, and swallowing.

Another study in USA suggested that the people do lose their neurocognitive ability (decrease in the memory and intelligence and interpreting things), neuropathy, and psychological complaints/symptoms such as they do tend to go in depression, anxiety, sleep disturbances, psychosocial complaints.[64] In the present study, neurological symptoms was higher among NHL survivors. Similarly, other studies done by Vandrass FK et al. (2021) & Saloustros E et al (2017) showed that the in survivors of cancer diagnosed at young age showed complaints such as loss of neurocognitive ability i.e. abnormal mindset and behaviour psychological complaints such as anxiety, depression, panic, secondary cancer development percentage was significantly high. The result of the present study also aligns in the same direction with this study.

Likewise, studies conducted by the Armstrong et al 2016 and Husson et al 2017 have reported the health issues in the NHL-AYA survivors such as fatigue, poor quality of physical health, psychological distress, problem in neurocognitive function such as memorizing the things, decrease in motor functioning, loss of motor skills which involves the activities such as walking, running, riding bike etc, where we know that to perform such activities by our body, our body´s nervous system, muscles and brain should work together at the same time. Our study also supports complaints of most of the health problems[65]

Another study by Mellblom et al 2021, including Norwegian children and AYA survivors of NHL report that 33% of NHL self-reported 5 or more late effects.[66]Among most common health problems were psychological, memory and concentration problems, fatigue, reduced fertility, numbness in hands/feet, muscle cramps, hormonal changes, and dental problems. Some of these health problems are found in our study.

Musculoskeletal complains were the most frequent health problem reported after the first year of the cancer diagnosis. Musculoskeletal symptoms such as leg/thigh symptom/complaint, rheumatoid/seropositive arthritis, and other musculoskeletal disease were higher in NHL survivors compared to the general population. In the past decades, a higher incidence of lymphomas particularly NHL has been reported in patients with a range of chronic autoimmune and inflammatory rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome (pSS), dermatomyositis, and celiac diseases.[67] Furthermore, Wang and colleagues, 2020 report that the association between NHL and chronic autoimmune and inflammatory diseases can be bidirectional.[68] Among 25,074 patients with NHL, they found that 49 developed pSS. Some possible explanations may be that pSS may develop before NHL, but it was late diagnosed, the two entities might have similar genetic factors, may be due effects of cancer treatment, or at lymphoma cells may influence the immune system.

Similarly, studies conducted by the Ansell SM 2015, Hocheburg et al 2018, have reported that the NHL-AYA survivors showed health issues such as development of secondary cancers, relapse of the cancer, cardiac toxicity, infertility, and same kinds of health problems were showed by our study as well.

Furthermore, according to Hocheberg et al 2018 & Howlader et al 2017, more cases of NHL in AYA age group were found in males than females. Our study also found the same finding.[69]

Other studies conducted in adults NHL survivors show also higher relative risks of chronic rheumatic disease. Ocier K et al 2021, show that B-cell non-Hodgkin's lymphoma adult survivors had higher relative risks of chronic rheumatic disease of the heart valves, cardiovascular disease, acute renal failure, pneumonia, and nutritional deficiencies 5 years after cancer diagnosis.[70,71] Our study supports those findings. In addition, rheumatoid/seropositive arthritis, cystitis/urinary infection other, acute bronchitis, and other respiratory infections are also higher in NHL survivors than expected in the general population.

5.3 Implications of the present study and recommendations

The clinical application of the present study is that the new results can be used to increase the awareness GPs and oncologist about long term effects of cancer among survivors of NHL who were diagnosed at young age. The present study also can contribute to knowledge to improve the primary health care services and more effective.

Need of increasing awareness: In the Nordic countries adolescent and young adults' patients have a relatively higher survival rate.[72] This implies that outcomes experienced by NHL survivors translates into increased use of health service resources. From the data presented in this paper, adolescent, and young adults' survivors of NHL face unique medical, psychosocial, and supportive care needs. It is important to understand health care utilization among cancer survivors for future health planning. Similarly, few studies conducted in Norway among NHL-AYA cancer patients have showed that the specialist (secondary care), GPs (Primary care) and even survivors of the NHL are lacking the knowledge of the late effects, lacking good communication between the GPs and specialists, deficiencies in the follow-up. Hence, it shows the high importance of the education and awareness program about importance of early use of palliative care, fertility preservation program before and after the treatment, genetic cancer and its syndrome and testing, psychological distress(patients), age specific changes of children to AYA, for both medical service provider and taker, which can be done by the social medias, cancer awareness campaign, by keeping the chapter about cancer in the high school, by organizing online meetings, by making easy meeting place for the cancer survivors in the referral centers so that they could share and learn from each-others experiences, and by organizing yearly conference by making sure the participation of AYA cancer patients.[73,74,75,76]

The need of more clinical trials: HCPs and other treating institute is needed to have the knowledge and experience specifically related to AYAs about NHL or other cancers to give them proper guidance regarding referrals to the expert centers when needed as the present HCPs training program do not have any program which is specifically related to AYAs patients' issues resulting in unmet physical, psychosocial needs. Lack of good referral patterns, as more than 75% is managed by community physicians but not by the specialist hospital or referrals centers. Hence delay in the diagnosis, treatment and less clinical trial participation, hence limited knowledge in this cancer population. That's why, AYA treatment and follow up care needs to be raised to improve the satisfaction in the patients, for better clinical outcomes (trial

participation), survival and health-related quality of life and should be discussed in the angle of worldwide than just focusing on the high-income countries. Similarly, there is high need of the more clinical trials specifically in this group as survival rate in this age group is less compared to older and younger age group because of-lack of participation in the clinical trials by this age group patients/survivors. In addition, full span study from 0-39 years groups also needs of an hour to understand the tumor biology, for risk stratification, and for finding out targeted cell therapy novel therapeutics which gives more effective treatment and less side or long-term effects (Rostgard K et al, 2019).[77]

The need of multidepartment treatment: Due to the lack of all the information needed to handle this unique age group leading to complexity in the providing the quality medical service just by the GPs, hence pronounced need of the multidisciplinary supportive care with multiple expertise of the same type of cancer with specialized nurses, fertility and sexual experts, dieticians, physical therapists, psychologists and social workers to give them education regarding importance of participation of them in the clinical trials and make them enroll to the trials, sexual and fertility, age specific information and other issues such as physical, psychological and economical related counselling. Furthermore, just one time treatment of the cancer is not enough as the chances of relapse and occurrence as secondary cancers is much higher, and side effects and long-term adverse effects is also much there. The subtype of NHL and the type of treatment given to the survivor, medical histories of the survivor, lifestyle of the survivor etc. determine the importance of the shared care among the health care practitioners. The present study show that NHL survivors have long term effects and health problems which need immense support and care. Specialist's care may be required for some survivors who shows more complicated side effects after the treatment. So, there should be multiple referral centers with experts of multidepartment. Survivors/patients who will need multidepartment care can have a rehabilitation program with the visit of multi- disciplined specialists is highly beneficial to manage the side effects and uplift the morale of the patients at the same time (Sapkota S et al, 2021, Husson et al, 2018).

The need of Survivorship care Plan (SCP): The need of the SCP for individual patient based on the specific age is important to have**,** as It is highly challenging to live with the NHL without knowing in basic knowledge about the life threatening signs/symptoms or late effects such as chances of development of secondary cancers, cardiac toxicity, neurocognitive dysfunction, psychological distress, reoccurrence/relapse of the cancers, treatments and lifestyle to follow

after the treatment such as quitting smoking or other dependencies, having balanced diet which is rich in vitamins, minerals and proteins and doing daily exercises with yoga. It's important to know about these points because there is high chances of reoccurrence of cancer and development of secondary, and patient may could have the life-threatening late effects such as cardiotoxicity, pulmonary disease etc. Hence, survivors and health care providers do need to have knowledge about the points, so that both the medical service giver and taker can be aware about any symptoms which is usual/unusual or any sign/symptom of the late effects which is life threatening (Sapkota S et al, 2021, Husson et al, 2018). New knowledge about these health problems can help to increase awareness on long-term treatment-related toxicities and their impact on the quality of life in survivors.

5.3 Strengths and limitations

The strengths of this study include a well-defined study population with a large sample size including an entire cohort of individual with minimal selection bias. Another major strength is that the consultation frequency used in this study reflects the true usual GP consultation pattern among cases and cancer-free population in Norway. The use of nationwide data registers has several well-known strengths and limitations: The claims register (KUHR) for Norwegian GP used is nearly complete for the studied years, as >99% of the population were included in the regular GP scheme and risk for bias is small.

Long follow-up duration of the study period which make possible to analyze health problems in different points after the cancer diagnosis and to identify long-term effects. In the present study was possible to have a control group which can help to ensure the internal validity and strength the findings of the study.

The most important limitation of this study is at in the KUHR registry is a potential variability and lack of specificity of the GPs' diagnoses, which were not formulated for research purposes. However, this problem was reduced by grouping by charter in the regression models. Another limitation was at predictor variables available in the dataset are limited and the study could have been improved with more information on cancer treatment and possible confounders, especially regarding the social context.

6. Conclusion

According to woodward et al (2011), adolescents and young adults' group is less researched group regarding cancers or NHL compared with old age groups.

The present study shows that demand for physician care among these cancer survivors is considerably greater than for the general population, and this need persists many years after the diagnosis. Health problems related to NHL disease and its treatment in almost all NHL subtypes is still important not only in the first years but also 6-10 years after the cancer diagnosis. We further found that NHL survivors also had significantly more overall GP visits for symptoms and complains related to musculoskeletal system, digestive system, neurological system, respiratory system, psychological, skin, urological system, and general and unspecified symptoms. These health problems were statistically significant in mature B cell lymphoma, mature T-cell and NK-cell lymphomas, and NHL NOS (not otherwise specified).

In addition, excess of contacts with a doctor was greater for infection diseases in the respiratory system, urinary infection, skin, Herpes Zoster, and infections in the eyes. Headache, fever, weakness/tiredness general, cough, skin symptoms, and pregnancy and pelvis complain were higher among these survivors than expected in the general population. Musculoskeletal problems including rheumatoid/seropositive arthritis in addition to others musculoskeletal disease was also overrepresented in NHL survivors.

Furthermore, our results highlight the importance of follow up by this group of survivors. According to previous studies, AYAs are in the age of passion, exploring the world, setting, and achieving goals related to family, relationship, education etc. Hence this age is highly transitional one, and once the person on this age diagnosed with the NHL cancer which acts like a shock for the individual which becomes highly challenging for the person to handle himself. This is vulnerable age to that individual, hence the most important thing to do at this moment is giving high level of psychological care and support such as proper handling of the patient with good behavior, proper patient counselling by the knowledgeable GPs etc. (Hauken et al 2019, Husson et al, 2018).

At the end, AYA population is known as unique or distinct when it comes to the cancer community because of the many challenges which they face when compared to the older and

pediatric patients because of many factors at the time of diagnosis such as morphology and biology of the tumor, psychological challenges and other problems about care and follow-up for many years after the treatment. It is also the known fact that the cancer in AYA age group is rare and that is why less participation of the AYA population in the clinical trials as they take it for granted (Rostgard K et al, 2019). Similarly, health care providers also have lack of information about this age group as less research have been done in this age group, hence most of the treatment methods and care plan is generally followed of pediatric patients which is much better because of so much research in pediatric age group (Vandrass Fk et al 2021, Sapkota S et al 2021, Hauken et al 2019, Husson et al, 2018).

Appendix 2. Logistic regression model showing diagnosis/disease component in each ICPC-2 body system chapter and comparing non-Hodgkin survivors with cancer free population during the follow up period (1-10 years)

ICPC-2 category	Cases	OR (95% CI)
General and unspecified		
A03 Fever	34	1.12 (1.06-1.17)
A04 Weakness/tiredness general	79	1.01 (1.00-1.01)
A08 Swelling	31	1.15 (1.06-1.24)
A77 Viral disease other/NOS	20	1.09 (1.00-1.19)
A78 Infectious disease other/NOS	24	1.04 (1.01-1.06)
A87 Complication of medical treatment	17	1.02 (1.00-1.04)
Blood, blood forming organs and immune Mechanism		
B02 Lymph gland(s) enlarged/painful	42	1.24 (1.16-1.32)
B72 Hodgkin's disease/lymphoma	205	1.41 (1.35-1.47)
B74 Malignant neoplasm blood other	28	1.16 (1.11-1.21)
B99 Blood/lymph/spleen disease other	21	1.02 (1.01-1.04)
Digestive		
D83 Mouth/tongue/lip disease	26	1.04 (1.00-1.09)
Eye		
F70 Conjunctivitis infectious	51	1.06 (1.02-1.11)
Musculoskeletal		
L14 Leg/thigh symptom/complaint	16	1.04 (1.00-1.07)
L88 Rheumatoid/seropositive arthritis	12	1.01 (1.00-1.02)
L99 Musculoskeletal disease, other	24	1.01 (1.01-1.02)
Neurological		
N01 Headache	51	1.01 (1.00-1.03)
Respiratory		
R05 Cough	94	1.06 (1.04-1.09)
R74 Upper respiratory infection acute	132	1.02 (1.01-1.03)
R75 Sinusitis acute/chronic	57	1.05 (1.02-1.08)
R76 Tonsillitis acute	39	1.16 (1.07-1.25)
R78 Acute bronchitis/bronchiolitis	54	1.11 (1.07-1.15)
R83 Respiratory infection other	40	1.10 (1.07-1.14)
Skin		
S03 Warts	20	1.02 (1.00-1.05)
S04 Lump/swelling localized	23	1.13 (1.06-1.21)
S10 Boil/carbuncle	20	1.05 (1.01-1.09)

S29 Skin symptom/complaint other	28	1.09 (1.06-1.13)
S70 Herpes zoster	24	1.10 (1.02-1.17)
S76 Skin infection other	16	1.05 (1.00-1.10)
S82 Naevus/mole	56	1.10 (1.03-1.18)
S93 Sebaceous cyst	12	1.08 (1.01-1.17)
S96 Acne	11	1.09 (1.00-1.20)
S99 Skin disease, other	34	1.03 (1.01-1.05)
Urological		
U71 Cystitis/urinary infection other	64	1.02 (1.01-1.03)
Pregnancy, childbearing, family planning		
W29 Pregnancy symptom/complaint other	15	1.07 (1.01-1.13)
Female genital		
X17 Pelvis symptom/complaint female	12	1.09 (1.02-1.17)

CI: confidence interval. OR odds ratios.

The model was adjusted for birth year, sex, and year of consultation.

Appendix 3. Article of the thesis which we want to publish in the international journal

Most Common Health Problems in General Practice (GP) Among Adolescents, and Young Adults' Survivors of Non-Hodgkin Lymphoma: A Register-Based Cohort Study in Norway.

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Abstract

Background: Studies on late effects among adolescents and young adults (AYAs) survivors of non-Hodgkin lymphoma (NHL) is scarce. The lower incidence, along the lack of data from clinical trials, limit substantially our knowledge on this group of survivors. The aim was to investigate distribution of health problems in general practice (GP) among NHL survivors and to compare with the cancer-free population.

Methods: Nationwide longitudinal register-based study investigating general practice (GP) consultations among
NHL survivors who were at the age of 18-35 years in Norway. All GP consultations were identified from the national GP claims register for 2006-2017. We compared diseases and complaints for which NHL cases and non-cases (AYAs of the same age without cancer) contacted their GP using logistic regression models. The follow-up period was divided into three periods according to GP consultations presented in the first year, 2-5 years, 6-10 years after the cancer diagnosis.

Results: A total of 2,224,484 AYA were included in the study whereas 275 were survivors of NHL. NHL survivors in the first year of the diagnosis consulted their GP more often than non-

cases for symptoms in the blood and immune system ($p<0.001$), digestive ($p<0.001$), musculoskeletal ($p<0.01$), and cardiovascular system ($p<0.05$). Moreover, 6 years postdiagnosis NHL survivors compared with non-cases, had still higher risk for symptoms in the blood and immune system and digestive system with 1.1 to 1.6-fold significantly increased; but also, other system such as, neurological system, respiratory system, skin, urological system, and general and unspecified symptoms from 1.1 to 3.8-fold significantly increased. These health problems were statistically significant in mature B cell lymphoma, mature T-cell and NK-cell lymphomas, and NHL NOS (not otherwise specified).

Conclusion: Compared with non-cases, NHL survivors have an increased contacts with the GP for health problems for up to 10 years postdiagnosis. Our results indicate the need of follow-up programs for possible late effects of cancer treatment.

Categories: Non-Hodgkin Lymphoma, General Practice (GP), Hematology
Keywords: adolescents and young adults, urological, blood and immune system, skin, respiratory, neurological, musculoskeletal, digestive, general and unspecified late effects, follow up, clinical trials, multidepartment service, survivorship care plan

1. Introduction

Cancer is the most common cause of disease-related death in adolescents, and young adults (AYAs) in high-income countries.[78] In Norway about 1157 new cases of non-Hodgkin lymphoma (NHL) are diagnosed each year.[79] Around 3% are diagnosed among young adults at the age of 20-34 years.[80] The age range for AYAs varies by organization and institution but is typically defined as 15-39 years.[81]

After many years of research focusing on cancer in children and in older adults, attention has turned to AYAs, in part because of only modest survival gains compared to other age groups.[82] There is still a significant increase in late mortality from all causes, recurrence/progression and health-related causes in these group. Significant cause of late mortality in children and adolescent NHL survivors include secondary malignancies, cardiomyopathy, and pneumonia. Significant late morbidity also includes defects in neurocognitive function, poor health quality

of life and lower social attainment.[83] Moreover, differences in epidemiology, disease characteristics, tumour biology and treatment response highlight AYA as a distinct group from younger children and older adults with NHL.

A summary from the 6th International Symposium on Childhood, Adolescent and Young Adult non-Hodgkin lymphoma held in Netherlands in 2018,[84] highlight the importance of to identify at-risk patients who are at significantly increased risk of complications. They report that children and adolescent survivors of non-Hodgkin lymphoma are at significant risk of chronic health conditions, late morbidity of multiple organ systems and poor health-related quality of life. As well, late mortality from secondary neoplasms and recurrent/progressive disease.

In the present study we use data from the Norwegian Control and Payment of Health Reimbursement (KUHR).[85] The registry contains information on bills from health services, which have been reimbursed to patients by the state. All GPs are required to use at least one code from the International Classification of Primary Care (ICPC)[86] to report clinical signs, symptoms, and diagnoses; diagnoses are entered into the KUHR database.

The aim of the study was to analyse the frequency and distribution of health problems most encountered in general practitioner consultations among survivors of non-Hodgkin lymphoma from the first until 10 years after the cancer diagnosis and compare with cancer-free population.

2. Materials and methods

2.1 Study population and data sources

The present study includes a cohort of individuals born in Norway between 1970 and 1997. We used the patients' personal Norwegian ID number to link to several registries.

Cancer cases were identified from the Norwegian Cancer Registry.[87] All individuals diagnosed with a primary NHL at the age of 18-35 years in the period 2001-2017 were include in the study. Non-cases were all individuals in the cohort without NHL or other type of cancer diagnosis. From the Norwegian Cancer Registry, we obtained information on the following variables: date and age of cancer diagnosis, histology, and date of death. Primary cases of NHL were coded using the International Classification of Diseases for Oncology, third edition (ICD-O-3).[88] De following ICD-O-3 codes was included: 9591, 9670, 9671, 9673, 9675, 9678–9680,

9684, 9689–9691, 9695, 9698–9702, 9705, 9708, 9709, 9714, 9716–9719, 9727–9729, 9731–9734, 9760–9762, 9764–9769, 9970. NHL subgroups were classified according to the ICD-O-3.

All GP consultations between 2006 and 2017 within the study population were identified from the national KUHR registry.[89] Diseases and complaints presented to the GP were based on ICPC-2 codes.[90] The follow up period was categorized as consultations presented during the first year, 2-5 years and 6-10 years after the cancer diagnosis.

2.2 Statistical analysis

Differences in frequency of GP consultations between cases and non-cases were tested using t-tests for independent samples (two-sided). Mean consultations in each follow-up period were based on the total number of consultations in each period. Consultation frequency for each symptom was treated as a continuous variable. Each symptom/complain was analysed separately in each follow-up periods.

We compared diseases and complaints for which cases and non-cases contacted their GP using logistic regression models, presented with odds ratio (OR) and 95% confidence intervals (CI). The model was adjusted for birth year, sex, and year of consultation. A P value of 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS (version 28). ICPC-2 chapters pregnancy, family planning and female genital were analysed among females and male genital symptoms among males respectively. Cancer cases were analysed including all NHL types combined and by four main types separately. We also conducted analyses including diagnosis/disease component in each body system chapter in ICPC-2. For this, to reach enough statistical power we included all NHL cases. Based om the ICPC-2 classification across chapters we present figures grouped into four subgroups: symptoms and complains, infectious diseases, neoplasms and congenital anomalies, and other diseases.

2.3 Ethical considerations

The present project was approved by the Regional Committee for Medical and Health Research Ethics, (REK Sør-Øst: 2016/1305). As this is a register-linked study, the approval also covers exemption from informed consent.

3. Results

A total of 2,224,484 AYA were included in the study whereas 275 were survivors of NHL. The median age of patients at diagnosis was 30 years; 156 (57%) were male and 119 (43%) were female (Table 1). Mature B cell lymphoma was the most frequent type (72%), followed by mature T-cell and NK-cell lymphomas (20%).

Figure 1 and 2 presents mean number consultations for cases and non-cases. For cases. the most common reason for contact with the GP in in the first year of the diagnosis were general and unspecified symptoms with a mean number of consultations at 4.3 per year.

Comparing mean number consultations between cases and non-cases in the first year of the diagnosis, NHL survivors consulted their GP more often than non-cases for symptoms in the blood and immune system ($p<0.001$), digestive ($p<0.001$), musculoskeletal ($p<0.01$), and cardiovascular system ($p<0.05$).

Musculoskeletal complains were the most frequent health problem in the period 2-5 years after diagnosis, with a mean number of consultations at 8.2 in the period. Two to five years after the cancer diagnosis contacts with GP were more often compared with cancer free population for problems in the blood and immune system ($p<0.001$) and digestive system ($p<0.001$). Musculoskeletal (mean, 8.2) and digestive symptoms (mean 8.2) were the most frequents after 6 years of the cancer diagnosis.

Six to ten years after the cancer diagnosis diseases and complaints leading to consultations with the GP more often among NHL survivors compared with the free cancer population were reported in the following code groups: blood and immune system ($p<0.001$), digestive system ($p<0.001$), neurological system ($p<0.001$), skin ($p<0.001$), urological system ($p<0.001$), respiratory system ($p<0.05$), cardiovascular system ($p<0.05$), but also general and unspecified ($p<0.05$) were more often among cases compared to non-cases.

The odds ratios for GP contacts regarding each ICPC-2 chapter are shown Table 2. In the first year after the cancer diagnosis, the risk of consulting GP for having health problems related to related to blood and immune system (related to NHL disease and its treatment) was 32% higher among NHL survivors compared with non-cases (blood and immune system OR=1.32 95% CI:1.27-1.37). Risk of musculoskeletal complains was also higher among NHL survivors compared with cancer free population (OR=1.19 95% CI:1.14-1.23).

Health problems with higher risk of presentation in GP consultation two to five years after the cancer diagnosis were health problems related to blood and immune system (OR=1.50 95% CI:1.45-1.55) and respiratory problems (OR=1.03 95% CI:1.00-1.07).

Analyses of cancer subtypes show that NHL survivor consult their GP for problems related to NHL disease and its treatment in almost all NHL subtypes (Appendix 1). General and unspecified symptoms had higher risk to be observed among precursor cell lymphomas and NHL subtype NOS.

Six to ten years after the cancer diagnosis the risk of consultation for several health problems was statistically significantly higher among NHL survivors than in non-cases. Among these symptoms and complains were urological, blood and immune system, skin, respiratory, neurological, digestive, and general and unspecified symptoms 1.1 to 3.86 fold significantly increased.

Figure 3 and Appendix 2 show diagnosis/disease component in each ICPC-2 body system chapter where NHL had significantly higher risk compared with cancer-free population. In addition to cancer related symptoms (Figure 3a), we observed symptoms related to infections in the respiratory system, urinary infection, skin, Herpes Zoster, and infections in the eye (Figure 3b). Among symptoms/complaints (Figure 3c) a neurological symptom was headache. Fever, weakness/tiredness general, cough, skin symptoms and pregnancy and pelvis symptoms in addition to other NHL lymphoma related symptoms were higher than expected in the general population. Musculoskeletal problems including seropositive rheumatoid arthritis.

4. Discussion

Adolescents and young adults diagnosed with NHL have been an understudied population and there is limited description of late effects after the diagnosis.[91,92] To our knowledge, this is the first large-scale study of GP consultations among adolescents and young adults' survivors of NHL. The present study shows that demand for physician care among these cancer survivors is considerably greater than for the general population, and this need persists many years after the diagnosis. Health problems related to NHL disease and its treatment in almost all NHL subtypes

is still important not only in the first years but also 6-10 years after the cancer diagnosis. We further found that NHL survivors also had significantly more overall GP visits for symptoms and complains related to musculoskeletal system, digestive system, neurological system, respiratory system, psychological, skin, urological system, and general and unspecified symptoms. These health problems were statistically significant in mature B cell lymphoma, mature T-cell and NK-cell lymphomas, and NHL NOS (not otherwise specified).

Excess of contacts with a doctor was greater for infection diseases in the respiratory system, urinary infection, skin, Herpes Zoster, and infections in the eyes. Headache, fever, weakness/tiredness general, cough, skin symptoms, and pregnancy and pelvis complain were higher among these survivors than expected in the general population. Musculoskeletal problems including rheumatoid/seropositive arthritis in addition to others musculoskeletal disease was also overrepresented in NHL survivors.

4.1 Comparison with existing literature

Direct comparison with other large studies into health problems among adolescent and young adults in general practice is not possible because of the absence of similar studies. The only similar study the authors were able to identify was the population-based British Columbia study reported by Andrea C Lo et al, 2021.[93] The study is based on self-reported late effects and included 79 individuals aged 15-24 years NHL survivors and 226 survivors of Hodgkin lymphoma. They report among all lymphoma survivors, significant high risk of hypothyroidism, secondary malignancy, symptomatic pulmonary toxicity, oesophageal complications, xerostomia/dental decay, cardiac disease, and infertility among these survivors. Health problems in the mouth as well as pelvis complain are reported in our study.

Another study by Mellblom and colleagues, 2021 including Norwegian children and AYA survivors of NHL report that 33% of NHL self-reported 5 or more late effects.[94]Among most common health problems were psychological, memory and concentration problems, fatigue, reduced fertility, numbness in hands/feet, muscle cramps, hormonal changes, and dental problems. Some of these health problems are found in our study.

Musculoskeletal complains were the most frequent health problem reported after the first year of the cancer diagnosis. Musculoskeletal symptoms such as leg/thigh symptom/complaint, rheumatoid/seropositive arthritis, and other musculoskeletal disease were higher in NHL survivors compared to the general population. In the past decades, a higher incidence of

lymphomas particularly NHL has been reported in patients with a range of chronic autoimmune and inflammatory rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome (pSS), dermatomyositis, and celiac diseases.[95] Furthermore, Wang and colleagues, 2020 report that the association between NHL and chronic autoimmune and inflammatory diseases can be bidirectional.[96] Among 25,074 patients with NHL, they found that 49 developed pSS. Some possible explanations may be that pSS may develop before NHL, but is late diagnosed, the two entities might have similar genetic factors, may be due effects of cancer treatment, or at lymphoma cells may influence the immune system.

Other studies conducted in adults NHL survivors show also higher relative risks of chronic rheumatic disease. Ocier K et al 2021, show that B-cell non-Hodgkin's lymphoma adult survivors had higher relative risks of chronic rheumatic disease of the heart valves, cardiovascular disease, acute renal failure, pneumonia, and nutritional deficiencies 5 years after cancer diagnosis.[97,98] Our study supports those findings, rheumatoid/seropositive arthritis, cystitis/urinary infection other, acute bronchitis, and other respiratory infections are also higher in NHL survivors than expected in the general population.

4.2 Strengths and limitations

The strengths of this study include a well-defined study population with a large sample size including an entire cohort of individual with minimal selection bias. Another major strength is that the consultation frequency used in this study reflects the true usual GP consultation pattern among cases and cancer-free population in Norway. The use of nationwide data registers has several well-known strengths and limitations: The claims register (KUHR) for Norwegian GP used is nearly complete for the studied years, as >99% of the population
were included in the regular GP scheme and no selection bias was therefore present.
Long follow-up duration of the study period which make possible to analyse health problems in different points after the cancer diagnosis and to identify long-term effects. In the present study was possible to have a control group which can help to ensure the internal validity and strength the findings of the study.

The most important limitation of this study is at in the KUHR registry is a potential variability and lack of specificity of the GPs' diagnoses, which were not formulated for research purposes. However, this problem was reduced by grouping by charter in the regression models. Another limitation was at predictor variables available in the dataset are limited and the study could have

been improved with more information on cancer treatment and possible confounders, especially regarding the social context.

4.3 Contribution/implications for policy and research

In the Nordic countries adolescent and young adults' patients have a relative hight survival rate.[99] This implies that outcomes experienced by NHL survivors translates into increased use of health service resources. From the data presented in this paper, adolescent, and young adults' survivors of NHL face unique medical, psychosocial, and supportive care needs. It is important to understand health care utilisation among cancer survivors for future health planning. New knowledge about these health problems can help to increase awareness on long-term treatment-related toxicities and their impact on the quality of life in survivors. Moreover, physicians need information on the unique health care requirements of this patient group to provide appropriate care.

5. Conclusion

Compared with free-cancer population we found an increased contacts with the GP among NHK survivors for health problems for up to 10 years postdiagnosis related to blood and immune system, digestive system, neurological system, respiratory system, skin, urological system, and general and unspecified symptoms. These health problems may be due to late effects of cancer treatment, increased health complications or both. Our results indicate the need of follow-up programs for possible late effects of cancer treatment, even years after active treatment has finished.

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Ethics approval and consent to participate: This study was approved by the Regional Committees for Medical and Health Research Ethics, (REK South-East: 2016/1305). As this is a register-linked study, the approval also covers exemption from informed consent because that would not be feasible to acquire.

Conflict of Interest: The authors declare no conflict of interest.

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