ETHNICITY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION OUTCOMES IN BRITISH COLUMBIA, CANADA

by

Maryam Noparast

MPhil, University of Bergen, 2006

MD, Tehran University of Medical Sciences, 1998

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate Studies

(Interdisciplinary Oncology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

January 2012

Abstract

Background

There are documented ethnic disparities in cancer care access, use and clinical outcomes in North America. Hematopoietic stem cell transplantation (HSCT) is an established treatment for many hematological and non-hematological malignancies. The effect of ethnicity on unrelated-donor HSCT outcomes has not been studied in Canadian patients.

Objective

To determine whether ethnicity is associated with unrelated donor HSCT outcomes in patients with hematologic malignancies in British Columbia, Canada.

Design

Retrospective medical chart review

Materials and Methods

We reviewed the registry data of 395 patients receiving first time unrelated donor HSCT for hematological malignancies at the leukemia/BMT center of British Columbia (BC) between 1988 and 2008. A patient's ethnicity was reported to be white (N=340), Asian (N=32), native (N=8), Hispanic (N=3), black (N=2), mixed (N=9) or other- not specified (N=1). For my analysis, ethnicity was further categorized as white (N=340) and non-white (N=55). HSCT outcomes were compared using log-rank test and Cox proportional hazard regression analysis adjusting for statistically-significant patient, disease and transplant-related factors.

Results

No statistically significant difference for overall survival, non-relapse survival, grade II-IV acute graft versus host disease (aGVHD) and chronic graft versus host disease (cGVHD) rates were found between whites and non-whites. Analyzing a subset of 115 cases (88 whites and 27 non-whites) who received their transplant after June 2001 (the start of high resolution DNA-based

human leukocyte antigen (HLA) matching in the study center) and had an underlying diagnosis of acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia or myelodysplastic syndrome didn't show any statistically significant difference for HSCT outcomes between whites and nonwhites either.

Conclusion

According to our data, unrelated-donor HSCT clinical outcomes are comparable between patients having white and non-white ethnicity in BC. This finding contrasts with those of US studies. This might be due to: This might be due to: 1) different ethnic compositions of the BC and US populations 2) different access to health care for ethnic minorities in the BC and US populations 3) my analysis using a heterogeneous non-white ethnic group, and thereby potentially masking ethnic differences.

Preface

This study was approved by the UBC/BCCA Ethics Board (certificate number H09-00248).

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Acknowledgements

First and foremost I offer my sincerest gratitude to my supervisor, Dr. Chris Bajdik, who has supported me throughout my thesis with his motivation, patience and knowledge. I appreciate all his contributions of time, ideas and understanding.

I would like to gratefully acknowledge the supervision of my thesis committee members: Dr. Donna Hogge, Dr. Carolyn Gotay and Dr. John Spinelli; who have been abundantly helpful and have assisted me in numerous ways.

I have to specially thank Dr. Victor Ling, the director of IOP, who has been providing me with insightful comments, guidance and support during my ups and downs.

I would like to kindly mention Ms. Janet Nitta, the senior data coordinator at the Leukemia/BMT Program of BC, for her continuous help and collaboration.

My final words go to my family. I want to thank my family, whose love and guidance is with me in whatever I pursue.

Dedication

I honor the memory of my beloved grandmother whom I lost in the first year of my Master studies and I couldn't be present at her death-bed.

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1. Introduction

1.1 Background

There are ethnic disparities in healthcare access, healthcare use and clinical health outcomes in North America. Poor prognoses for patients from ethnic minority groups have been correlated with factors that are both intrinsic and extrinsic to the patient. These factors may include age at onset, cancer cell biology, disease stage at diagnosis, comorbidities, patient socioeconomic status (SES), healthcare access and delivery (compliance and treatment options received), and psychosocial and cultural factors. Identifying and modifying these factors may reduce health disparities (1), however realizing if any problem exists is an important first step.

Hematopoietic stem cell transplantation (HSCT) is an established curative therapy for a variety of cancers and non-malignant conditions.(2) There is only a 30% chance of finding a suitable donor among a patient's siblings; so many patients must find unrelated donors in national and international registries. Someone's best chance of finding a suitable donor is within his or her own ethnic group. Unfortunately, non-white donors are under-represented in the Canadian and international donor registries.(3) This is hypothesized to affect the likelihood of obtaining a matched donor and achieving desirable outcomes such as survival for ethnic minority groups.

So far, a number of studies examining race/ethnicity in the US HSCT patients indicate substantial and as yet unexplained racial differences in outcomes (4); however no study has evaluated the effect of ethnicity in Canadian patients, where the multi ethno-cultural structure is different from that of the US population.(3) My study addresses this issue for the first time in the population of British Columbia, Canada based on the hypothesis that ethnicity affects the outcomes of HSCT. The findings could be applied to improve the care and outcomes of HSCT at individual patient and public health level by targeting the vulnerable ethnic groups.

1.2 HSCT

1.2.1 What is Hematopoietic Stem Cell Transplantation (HSCT)?

Hematopoietic stem cells (HSC) are long-lived reconstituting cells that have the potential for self-renewal and giving rise to the other more mature cells of the various hematopoietic lineages (5) (Illustration1). These cells are normally found in bone marrow of adults, although a small number circulate in the blood stream. They could also be isolated from umbilical cord blood at the time of delivery.(5,6)

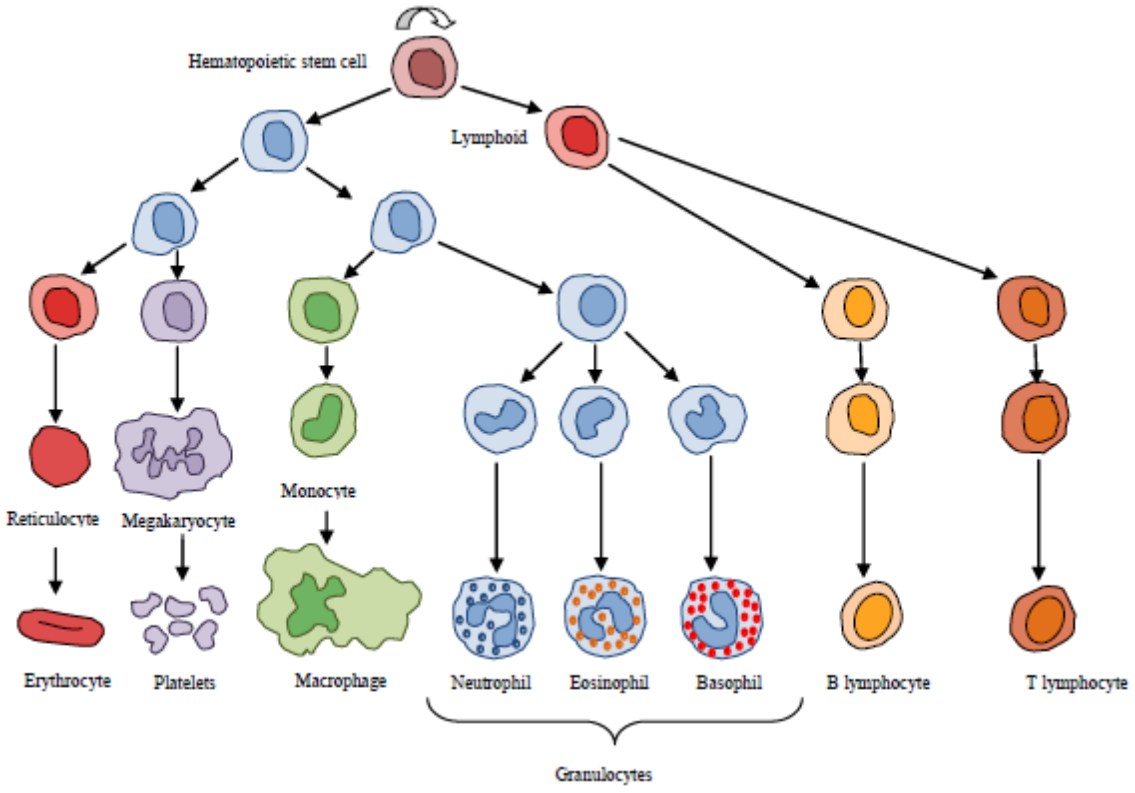

Illustration 1. Formation of blood cells, based on reference (7)

Hematopoietic stem cell transplantation (HSCT) is defined as: *the intravenous infusion of HSCs to restore normal blood cell formation function in patients with damaged or diseased bone marrow or immune systems*.(8)

The human bone marrow transplant was first attempted to cure a patient with aplastic anemia in 1939. Since then, HSCT has become a standard treatment for many malignant and non-malignant conditions.(6)

HSCT can be performed with HSCs from a family member (***related allogeneic***) or unrelated volunteer (***unrelated allogeneic***) or with stem cells previously collected from the patient (***autologous***). The choice between the more risky allogeneic transplant and an autologous procedure depends on the patient's age, the underlying disease, donor availability and institutional preference.(6)

My study and this review focuses on **unrelated allogeneic** HSCT so that the effect of immunologic differences between recipients and donors on outcomes can be addressed.

1.2.2 Indications for HSCT

HSCT can normalize hematopoietic function after high dose (myeloablative) cytotoxic therapy of malignancies and/or induce potent anti-malignancy immunologic effect. It can also be used to correct congenital or acquired immunologic/hematologic dysfunctions.(9) Some of the common indications for HSCT are shown in Illustration 2.

My study addresses HSCT for treating **hematologic malignancies** (i.e., leukemia, lymphoma, myelodysplastic syndrome, and multiple myeloma) which are the most common indications for allogeneic HSCT.(9)

Allogeneic	• Acute leukemia • Myelodysplastic syndrome • Chronic myeloid leukemia • Severe aplastic anemia • Indolent lymphoma • Chronic lymphocytic leukemia • Severe immunodeficiency syndrome • Hemoglobinopathies
Autologous	• Progressive large-cell lymphoma • Progressive Hodgkin disease • Multiple myeloma • Relapsed germ cell tumor

Illustration 2. Common indications for HSCT, based on reference (6)

1.2.3 Allogeneic HSCT procedure

Traditionally, stem cells for HSCT were collected from pelvic bone marrow - referred to as bone marrow transplant (BMT). However, currently peripheral blood is the preferred source for HSCs in most transplant centers.

To help mobilize bone marrow stem cells into peripheral blood, donors are treated with colony stimulating factors (CSF). The donor's blood is then collected by leukapheresis so that HSCs could be isolated in sufficient quantity for transplantation. In preparation for allogeneic stem cell transplantation, the recipient undergoes a conditioning regimen of high-dose chemotherapy and, in some cases, radiotherapy to eradicate the underlying malignant disease and to suppress the recipient's immune system so that it will not reject the donor's stem cells. The first conditioning regimen to be developed - high dose cyclophosphamide combined with total body irradiation (TBI) - remains in common use, and a variety of other TBI and non-TBI preparative regimens

have also been developed. Conditioning is administered over approximately one week and produces both hematologic (pancytopenia) and non-hematologic side effects. The latter, referred to collectively as regimen-related toxicity, can affect many organ systems.

The actual transplantation of the cells is a simple process involving intravenous infusion of a liquid stem cell product through a large-bore central venous catheter over 1 to 2 hours. The stem cells are then able to travel or "home" to the bone marrow cavity to re-establish hematopoiesis over the next two weeks (engraftment). Engraftment is the process whereby the donor cells begin to produce new blood components within the recipient's bone marrow cavity. In practice, engraftment is said to have occurred when the absolute neutrophil count (ANC) consistently measures 0.5×10^9/L. Platelet and red blood cell engraftment generally follows. Until engraftment, the patient's protective immunity is reduced and he or she is vulnerable to infection. To reduce opportunistic infections all patients routinely receive antifungal and antiviral prophylaxis throughout the neutropenic period and the patient is confined to a single room equipped to provide the safest possible environment.

The average length of hospital stay for allogeneic transplantation is 5 weeks, but the stay can be much longer if complications develop. Restoration of T-cell and B-cell immunity, which may take months or longer, is critical to the recipient's recovery process.(6)

1.2.4 Prognostic factors for allogeneic HSCT

Factors that predict the outcome of HSCT can be divided into 3 groups: *recipient's factors* (such as age, race, type of underlying disease, stage of disease at diagnosis, time to transplant, co-morbidities); *donor's factors* (such as age, sex, Cytomegalovirus (CMV) sero-positivity) and *transplant factors* (such as stem cell source, conditioning regimen, degree of HLA matching).(10-12)

1.2.4.1 HLA matching

Advancement in understanding the HLA system is one of the most important reasons for improved HSCT outcomes in recent years.(11)

The HLA system is comprised of molecules in the immune system that are essential to T-cell mediated adaptive immunity. HLA antigens are coded by a series of closely linked genes located at position p21.3 on the short arm of chromosome 6. The HLA molecules are split into 3 main regions based on their structure and function in the immune response: class I, class II and class III (Illustration 3). Of great interest in transplantation are six classic HLA genes which encode the highly polymorphic loci: (1) HLA-A, B and C (class I region) and (2) HLA-DR, DQ and DP (in the class II region).(9,11,13)

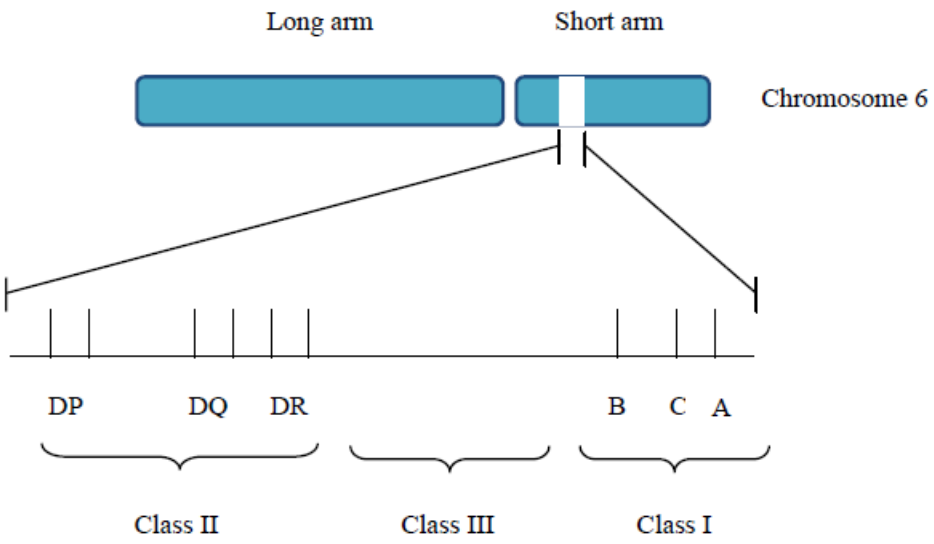

Illustration 3. Gene map of HLA region on chromosome 6, based on reference (14)

A characteristic feature of HLA genes is their extreme polymorphism.(9) According to the international ImMunoGeneTics **(**IMGT)/HLA database, there are currently 6534 HLA and related alleles described by the HLA nomenclature and included in the database (4946 variant alleles at Class I loci and 1457 variant alleles at HLA Class II loci).(15)

The polymorphism displayed by HLA genes, coupled with the tendency to be strongly linked to one another, have important implications in donor-recipient HLA matching for HSCT.
With technical advances made in the past couple of decades, the level of HLA typing has upgraded from antigen level (serological methods) to allele level (DNA based methods).(9) Using high resolution techniques to find a donor matched at the HLA-A, HLA-B, HLA-C and DRB1 loci is important for a successful unrelated donor HSCT, as each HLA mismatch reduces the overall survival about 10% in patients with early stage disease.(16) By introduction of DNA-based methods for HLA typing, the importance of correlating previous serologic designations with new allele designations - especially for unrelated donors- has emerged as major issue (9) as some donor-recipient pairs which were matched by serologic methods are not matched at the molecular level.

Although the preferred type of donor is an HLA-identical sibling; there is only a 30% chance of finding such a donor in someone's family and the rest of the patients must depend on alternative donor sources.(6,16) More than 14 million volunteer donors or cord blood units from the many registries worldwide provide stem cells for patients without family donors.(17)

The likelihood of identifying a donor is increased if donor and patient share the same ethnic or racial background.(9) At present, about 80% of Caucasian patients have the chance of finding an acceptable matched unrelated donor while this rate is lower for patients of other ethnicities.(6) For example, blacks have a 50% chance of finding a serologically matched donor and 6% chance of finding a molecular matched donor. Given the high frequency of rare and uncommon polymorphisms in the African-American population, increasing the donor pool seems unlikely to enhance the odds of finding a suitable adult unrelated donor for this group of people.(16)

1.2.4.2 Stem cell source

HSCs could be acquired from three different sources: *bone marrow* (BM), *peripheral blood* (PB) and *umbilical cord blood* (UCB).

The recovery of neutrophils and platelets (engraftment) occurs faster when PB stem cells are used for HSCT but the incidence of some complications (e.g., chronic graft versus host disease) seems to increase after PB HSCT compared to BMT. Some argue lower relapse and mortality rates after PB HSCT compared to BMT, however this is not supported by large randomized trials and the current evidence shows that the overall survival after these two types of transplant is comparable.(9)

Umbilical cord blood harvested at the time of delivery is also used for HSCT. The successful transplantation of unrelated umbilical cord blood cells from central storage facilities was one of the most exciting developments of the 1990s. Cord blood provides an essentially unlimited supply of donors, and these donors appear to possess an immature (and therefore more tolerant) immune system, which allows for a greater degree of mismatching between donor and recipient. A drawback to cord blood transplantation is that the number of stem cells in the product is relatively low for a large recipient (e.g., an older child or an adult). As a result, the vast majority of successful cord blood transplants have been done in small children; nonetheless, some adults have become long-term survivors.(6)

1.2.5 HSCT outcomes

1.2.5.1 Graft failure

Engraftment usually takes place about 10-20 days after HSCT depending on the source of stem cells used (earlier in PB, followed by BM and UCB stem cells). Lack of initial engraftment (primary graft failure or graft rejection) and subsequent irreversible drop of blood counts

(secondary graft failure) are serious complications; however, the risk is less than 5% and it is particularly rare after matched-sibling transplants.(6,11)

1.2.5.2 Graft versus host disease (GVHD)

GVHD is one of the most common causes of overall mortality and morbidity after allogeneic HSCT.(11,18) This syndrome occurs when the immuno-competent T cells in the donor graft recognize recipient's antigens as foreign targets and cause a reaction.(2) It can be the direct cause of death through organ failure or an indirect cause by development of life-threatening infections. GVHD is accounted as the primary cause of mortality in 13% and 14% of deaths occurring after HLA-matched sibling and unrelated donor transplants respectively. However, its presence also decreases the risk of disease relapse and thus might affect post-transplant outcomes.(18)

The clinical syndrome of GVHD is heterogeneous and classically divided into acute and chronic varieties; however the time cut-off of 100 days post-HSCT which has traditionally been used to classify this clinical syndrome into acute and chronic is currently being challenged.(18)
The recent NIH Consensus conference suggested recognition of two categories of GVHD: " *1) acute GVHD (absence of features consistent with chronic GVHD) comprising a) classic acute GVHD (before day 100), and b) persistent, recurrent or late acute GVHD (after day 100, often upon withdrawal of immunosuppression); and 2) chronic GVHD comprising a) classic chronic GVHD (no signs of acute GVHD), and b) an overlap syndrome, in which features of both acute and chronic GVHD are present*".(19)

1.2.5.2.1 Acute graft versus host disease (aGVHD)

The incidence of aGVHD varies from 40-60% in HLA-identical sibling transplants to 60-80% in unrelated donor transplants.(11)

aGVHD develops through a process of direct allo-recognition when donor T cells encounter recipient HLA antigens. HLA matching is therefore of prime importance in order to minimize the risk of developing aGVHD. Recipient pre-transplant conditioning involving chemotherapy /radiotherapy initiates a cascade of cytokine release including tumor necrosis factor (TNF) α and interleukin1 (IL1) in the so-called 'cytokine storm'. Donor T cells contained within the graft encounter recipient HLA and proliferate, initiating a complex multifactorial effector phase involving direct cytokine action and cellular attack, ultimately resulting in tissue damage. The major target organs are primarily the skin, gastrointestinal tract and the liver.

aGVHD is graded according to severity from I to IV, with grades III-IV being termed severe and associated with patient mortality.(12)

1.2.5.2.2 Chronic graft versus host disease (cGVHD)

cGVHD incidence varies between 30 to 50% in HLA-matched sibling transplants and at least 60 to 70% of unrelated donor HSCTs. It is also the most common cause of impaired long-term outcome and quality of life after allogeneic HSCT.(20)

This syndrome, which resembles connective tissue disorders like scleroderma, may develop when active aGVHD progresses gradually into cGVHD (progressive), after favorable resolution of aGVHD (quiescent), or with no evidence of prior aGVHD (de novo).(2)

The immunology of the condition is not completely understood but involves allo-activated donor CD4+ and CD8+ T cells, and autoantibody production leading to tissues damage, fibrosis and immune incompetence. The organ involvement is more extensive than aGVHD and contains skin, exocrine glands, lungs and musculoskeletal system.(11) A grading system based on the degree of involvement of skin, liver, or other affected organs, divides cGVHD into limited or

extensive forms which correlates with prognosis. Development of cGVHD may also decrease the risk of post transplant relapse, suggestive of a graft-versus-tumor effect.(2)

1.2.5.3 Relapse

Recurrence of the underlying malignant disease is the most common cause of treatment failure after allogeneic HSCT. Although it mostly happens by the second year after HSCT, it could occur years later too. The risk of relapse varies between 10% and 60% and depends on the type and stage of disease at the time of transplantation.(6,11) It is the cause of 38% of deaths after matched related transplant and 32% of deaths after matched unrelated transplants.(11)

1.2.5.4 Secondary malignancies

Secondary malignancy is a common complication of conventional chemotherapy and radiotherapy - which are applied before HSCT- and its risk in HSCT recipients varies between 4 to 11 folds that of the general population**.**

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are common problems after autologous transplant. In allogeneic transplant recipients, lymphoma is the most common malignancy occurring in the first year after HSCT. The risk of solid tumors in allogeneic and autologous setting increases gradually with time post transplant. Regular screening of all HSCT survivors for early detection of a second malignancy is advised.(6,11)

1.2.5.5 Veno-occlusive disease (VOD)

Veno-occlusive disease (VOD) of liver, also known as Sinusoidal Obstruction Syndrome (SOS), is a distinct clinical syndrome seen in 5-55% of patients receiving high dose chemotherapy with HSCT. It consists of fluid retention and liver dysfunction. In severe cases, VOD results in renal

dysfunction, encephalopathy, and multi-organ failure. Severe VOD is associated with high mortality.(21)

1.2.5.6 Death

Treatment-related mortality (TRM) in the first 12 months after matched-sibling stem cell transplantation is about 20% to 30%. The figure is higher among recipients of unrelated donor transplants, reaching almost 50% at most adult transplant centres.(6) TRM rates depends on a number of factors related to the patient (e.g., age, sex, comorbid diseases), the disease (e.g., stage, extent of involvement, intrinsic disease characteristics), or the transplantation procedure (e.g., time from diagnosis to transplantation, type of graft, HLA compatibility of the donor).(1)

1.2.6 HSCT worldwide

HSCT has been increasingly used during the last few decades.(1) According to the Worldwide Network for Blood and Marrow Transplantation (WBMT) a total of 50,417 first time HSCTs were reported in 2006; of which 43% were allogeneic and 57% were autologous. The median HSCT rates per 10 million inhabitants in continental regions and participating countries were 48.5 in the Americas (North and South America), 184 in Asia, 268.9 in Europe, and 47.7 in the Eastern Mediterranean and Africa. Globally, the main reasons for HSCT were lympho-proliferative disorders (54.5%) and the main reason for allogeneic HSCT was leukemia (71%). In Americas 42% of HSCTs were allogeneic and 58% were autologous. There were higher proportions of unrelated donor HSCTs in the Americas, Asia, and Europe than in the Eastern Mediterranean and Africa.(17)

According to the Canadian Blood and Marrow Transplant Group (CBMTG) statistics for the year 2010, a total of 739 HSCTs were performed for all age groups across Canada of which 459 were

Autologous (62%), 149 were related allogeneic (20%) and 131 were unrelated allogeneic transplants (18%).(22)

1.2.7 HSCT in British Columbia

HSCT has been available as a therapeutic modality for selected adult patients in Vancouver, BC since 1981. The Leukemia/Bone Marrow Transplantation Program of BC is the only facility in the province responsible for adult HSCT. The program is funded by the provincial government and located at the Vancouver General Hospital (VGH) and performs both autologous and allogeneic HSCTs. Illustration 4 shows the increasing number of HSCT procedures at this center between 1981and 2000.(23)

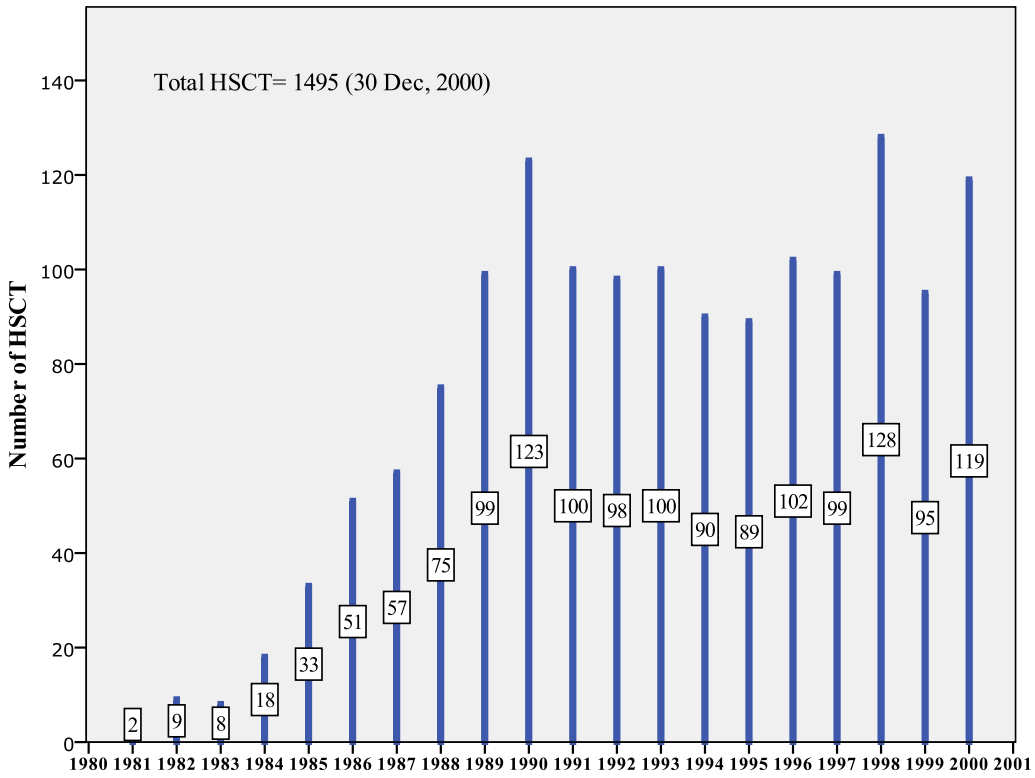

Illustration 4. HSCT per year and cumulative number of survivors at Leukemia/Bone marrow transplantation center of British Columbia, based on reference (23)

In 2009 about 192 transplants were performed at Leukemia/BMT center of BC of which 121 were *autologous* (63%), 29 were *related* (15%) and 42 were *unrelated* donor transplants (22%).(22)

1.3 Ethnicity and HSCT

1.3.1 What is ethnicity?

Ethnicity is derived from a Greek word meaning a people or tribe.(24) According to "A dictionary of epidemiology" ethnicity or ethnic group is defined as:" *a social group characterized by a distinctive social and cultural tradition maintained within the group from generation to generation, a common history and origin, and a sense of identification with the group. Members of the group have distinctive features in their way of life, shared experiences, and often a common genetic heritage. These features may be reflected in their health and disease experience*" and "*the social group a person belongs to and either identifies with or is identified with by others as a result of a mix of cultural and other factors, including language, diet, religion, ancestry, and physical features traditionally associated with race. Increasingly the concept is being used synonymously with race, but the trend is pragmatic rather than scientific*."(25)

The concept of ethnicity is neither simple nor precise and there are no consistent standard definitions of race or ethnicity in the context of health-related studies. Definitions are usually study specific and they must be made explicit before research can be done.(24,26)

1.3.2 Ethnicity and race

The terms of ethnicity and race are often used interchangeably; however, ethnicity should be distinguished from race, which in the biological sciences means "*one of the divisions of humankind as differentiated by physical characteristics"*.(24) No race possesses a discrete

package of genetic characteristics. There is more genetic variation, that is, variations in allele frequencies, within races (85 percent within races) than there is between races (15 percent between races), and the genes responsible for morphological features such as skin color (which are the basis of racial groupings) are few, atypical, and not associated with genes responsible for diseases.(24,27)

1.3.3 Measures of ethnicity

Ethnicity and race, unlike age and sex, are less objective and therefore more difficult to conceptualize and measure.(27) Because of a lack of biologic basis and standardization of wording and assessment for our current racial/ethnic classifications, these variables have been inconsistently measured and neither the validity nor the reliability of racial/ethnic assignment can be assumed.(27,28) The racial/ethnic categories commonly used in biomedical sciences and epidemiology are broad and overlapping. Individuals do not fit neatly into these categories and these broad groupings can mask significant within-group heterogeneity. As there is no agreement among researchers on how categories should be defined or how individuals should be assigned to them, they vary from study to study and from data set to data set. The optimal way to assess race/ethnicity depends on the purpose for which data are being collected.(28)
Conventional measures of ethnicity include:

1. Skin color, which is genetically determined, is clearly based on race, and observers classify subjects' ethnicity by means of skin color. This method is subjective, imprecise, and unreliable. For example, an observer could not accurately distinguish by observation alone between Muslim and Hindu Punjabis, who are in several important respects culturally distinct. Given an opportunity to define their own ethnicity in health studies, they would probably not place themselves in the same ethnic group. They are, however, likely to be in the same racial group.

2. Country of birth, as coded on birth and death certificates, has commonly been used as an objective index of ethnicity. For example, India is culturally diverse with innumerable distinct ethnic groups, a complex caste system, at least eight major religions and 15 official languages. Yet Indians are grouped as one by this method, a classification comparable to European. On the other hand, immigrants' children could not be identified by this method.(24)

3. Ethnic or cultural origins of the respondent's ancestors is another method which has been used in 2006 Canadian census to determine ethnic origin of Canadian population. An ancestor is someone from whom a person is descended and is usually more distant than a grandparent. Multiple responses occur when a respondent provides two or more ethnic origins. Ethnic origin responses are a reflection of each respondent's perception of their ethnic ancestry and, consequently, the measurement of ethnicity could be affected by changes in the social environment in which the question is asked and changes in the respondent's understanding or views about the topic. Awareness of family background or length of time since immigration can affect responses to the ethnic origin question as well.(29) It also ignores current lifestyle or self perception of the individual.(24)

4. Surname analysis uses an individual's last name to estimate the likelihood that the individual belongs to a particular racial or ethnic group. Surname analysis is more reliable for identifying Hispanics and Asians than African Americans because of more distinctive last names among the former groups. The method has shown a reasonable accuracy for identifying Asians and Hispanics across diverse populations, however, errors also occur because of intermarriage, name change, and adoption. The accuracy of the method could be increased by using race data when available. For example, in US -where many Filipino and Hispanic surnames overlap- availability of Asian race data can be used to distinguish Filipinos from Hispanics. The 1990 US Census Spanish list (containing fewer than 1,000 Spanish surnames) showed an overall sensitivity of 79

percent and a specificity of 90 percent compared with self-reported ethnicity in a national sample and Asian surnames yield similar overall accuracy. Lauderdale and Kestenbaum's name list, derived from Social Security records, and validated using the 1990 US Census, showed sensitivities ranging from 74 percent for Vietnamese to 29 percent for Filipinos and positive predictive values ranging from 92 percent for Japanese to 76 percent for Chinese.(30)

5. Some have argued *self-report* as the optimal method for collecting racial/ethnic data.(31,32) However, self assessed ethnicity is changeable over time (24,28,33) and is not subject to the control of the investigator, characteristics that are counter to the principles of scientific measurement.(24)

1.3.4 Ethnic portrait of British Columbia

According to the 2006 Canadian census an estimated 5,068,100 individuals (16.2% of Canada total population) identified themselves as a member of the visible minority population (34) based on the question: "What were the ethnic or cultural origins of this person's ancestors?".(29) Three out of 10 of visible minorities were born in Canada.(35) This rate of visible minority report was the highest in the province of British Columbia (24.8% of BC population). The province's largest visible minority group was Chinese (40.4% of the visible minority population) followed by south Asian and Filipino (Table 1).(36)

In Canada, the visible minority population has been growing steadily over the last 25 years; however its growth has speeded-up in recent years. The main reason is the increasing number of recent immigrants who mostly belong to visible minority groups. If current immigration trends continue, Canada's visible minority groups could account for roughly one-fifth of the total population by 2017.(35)

Table 1. Distribution of visible minority groups in Canada and BC, 2006 (34)

Ethnicity	**2006 Canada population (%)**	**2006 BC population (%)**
South Asian	1,262,865 (4%)	262,290 (6.4%)
Chinese	1,216,570 (3.9%)	407,225 (10%)
Black	783,795 (2.5%)	28,315(0.7%)
Filipino	410,695 (1.3%)	88,080 (2.2%)
Latin American	304,245 (1%)	28,960 (0.7%)
Southeast Asian	239,935 (0.8%)	40,690 (1%)
Total visible minority	5,068,090 (16.2%)	1,008,855 (24.8%)

1.3.5 Ethnicity and health studies

There are several reasons that public health professionals may use information on race and ethnicity in their research:

1. To generate etiological hypotheses.

2. To consider whether biology (e.g., disease mechanisms, drug metabolism) may be different within racial or ethnic groups.

3. To describe the roles of, and interactions between, genetic, environmental, cultural and lifestyle factors in etiology of diseases.

4. To recognize groups that may receive unequal prevention, screening, or treatment, so that public health programs may be better targeted.

5. To assess how the conceptualization of risk factors, symptoms, and disease may differ by race or ethnicity, so that public health interventions may be better tailored to specific groups and those in clinical practice make better informed decisions.(27)

Indeed, several studies have shown variations between races/ethnic groups for health care access, utility and outcomes in a wide setting of various medical conditions. For example, in the US, blacks have a lower chance of receiving medical modalities such as HSCT.(1) Also renal transplants by HLA-identical siblings have a lower graft survival and overall survival in black Americans compared to whites.(4,37)

Higher mortality for ethnic minorities has been reported for many solid tumors (colorectal, genitourinary, breast, lung) and hematological malignancies (leukemias, lymphomas).(38)
The poor outcome of ethnic minority cancer patients could be attributed to intrinsic or extrinsic variables. By identifying and modification for adjustable factors, we can reduce the ethnicity associated disparity in cancer care outcomes.(1,26,38) For instance, evidence shows the difference between cancer-specific mortality of blacks and whites disappears if adjusted for cancer stage at diagnosis and we can conclude that cancer cell biology has little role in survival disparities (1) and targeting at early cancer diagnosis in blacks could result in better outcomes in this group.

1.3.6 Ethnicity and HSCT outcomes

The importance of many patient and donor related demographic variables on outcomes of HSCT has been studied; however there is limited research on the effects of ethnicity.(4)
The existing studies, mostly based on US transplant cases, have shown different HSCT outcomes for ethnic minorities (e.g., blacks and Hispanics) compared to whites.(1,4,37,39,40)

The reasons for this outcome disparity could consist of both *biological* and *non-biological* factors associated with ethnicity.(26)

The degree of HLA-matching between donors and recipients is one of the main *biological* prognostic factors in HSCT, however the degree to which this factor contributes to diverse outcomes in different ethnicities is not well understood.(26) Other effective *biological* factors could include higher frequency of cytokine gene polymorphisms or greater prevalence of cancer drug metabolism pharmacogenetic variants in ethnic minorities like blacks.(4)

Several ethnicity related *non-biologic* factors such as patients' SES, insurance coverage, residential distance to transplant center, language barriers, cultural beliefs about health/disease and compliance with treatment/follow-up care could also determine the outcomes of HSCT. The importance of these factors is emphasized in a complex treatment such as HSCT because most of the recovery and also complications happen after discharge from the transplant center and over a long period of time. Dealing with these factors and improving them is complex and demanding because most are more psycho-social than clinical issues. However, identifying the problem allows health policy makers to allocate enough resources, and clinicians to tailor their approaches to the specific high risk recipients of HSCT.(4)

1.3.6.1 Current literature on ethnicity and HSCT outcomes

The summary of the literature review is presented in Table2.

A study from the Center for International Blood and Marrow Transplant Research (CIBMTR) compared trends in survival rates for ethnic minorities and whites in 6443 patients who received HSCT from HLA identical siblings in US and Canada between 1985 and 1999. All patients had leukemia and none received reduced intensity conditioning regimens. The patient's ethnicity was abstracted from data submitted by transplant centers to CIBMTR. The study found that Hispanics

compared with whites had lower 1-year (53% vs. 65%; *P*<0.001) and 3-year (38% vs. 53%; *P*<0.001) adjusted survival rates between 1995 and1999, whereas no differences were identified between whites and African Americans or Asians.(1)

Another study based on CIBMTR data examined the relationship between ethnicity and different HSCT outcomes and their net effect on survival. 3028 patients with leukemia who received HLA-identical sibling HSCT after myeloablative conditioning in the United States between 1990 and 2000 were analyzed. (Some or all of these patients might have been included in the study mentioned above.) The patient's ethnicity was abstracted from data submitted by transplant centers to CIBMTR. No statistically significant differences in the risk of acute or chronic GVHD, TRM, or relapse were found between whites and any ethnic minority group. However, Hispanics had higher risks of treatment failure (HR: 1.30, P=0.004) and overall mortality (HR: 1.23, P=0.02). The higher risks of treatment failure and mortality among Hispanics may be the net result of modest but not statistically significant increases in both relapse and TRM and cannot be accounted for by any single transplantation-related complication.(40)

To assess post- HSCT race/ethnicity specific survival a retrospective study was conducted on 3587 cases who received a myeloabtalive autologous or allogeneic HSCT (HLA-matched related or unrelated donor) for hematologic diseases (malignant or non-malignant) at the Fred Hutchinson Cancer Research Center (FHCRC) or the affiliated Seattle Veterans Administration Puget Sound Health Care Center, US, between 1992 and 2000. The method of verifying ethnicity wasn't mentioned in the article. Race or ethnicity was not significantly associated with survival for 1366 patients who received autologous HSCT (*P*=0.55). Among 2221 patients who received allogeneic HSCT, blacks had a significantly greater mortality than whites (HR: 1.71; 95% CI, 1.25-2.34) which could be attributed to the higher relapse mortality and non-relapse mortality detected among blacks. Mortality hazard among other racial/ethnic groups was not significantly

different from that of whites. Blacks had higher incidence of "severe aGVHD" after HLA-matched sibling transplant (P=0.047) and unrelated donor HSCT (P=0.014) compared to whites; however, no significant difference for hazard of "extensive cGVHD" was observed between two groups. The higher mortality among blacks could not be explained by obvious socioeconomic differences.(37)

A CIBMTR study among 1675 recipients of sibling donor HSCT for leukemia performed in collaboration with transplant registries in Japan, Scandinavia, and Ireland between1990 and 1999 showed that white Americans, African Americans, and Irish cohorts were at significantly higher adjusted risk for aGVHD than Japanese or Scandinavian cohorts (HR: 1.77, $P < 0.001$; HR: 1.84, $P < 0.006$; HR: 2.22, $P < 0.001$, respectively). White Americans, African Americans and Irish, but not Scandinavians, were at significantly higher risk for early (within 3 months of transplant) TRM compared with Japanese (HR: 2.99, $P < 0.001$; HR: 5.88, $P < 0.001$; HR: 2.66, P <0 .009, respectively). No differences in the risk for cGVHD, relapse, and overall survival were noted.(39)

Another retrospective CIBMTR study to explore the effect of race on outcomes of unrelated donor HSCT for acute or chronic leukemia or myelodysplastic syndrome (MDS) used data on 6207 patients who received their transplant after myeloablative conditioning therapy in affiliated CIBMTR US centers between 1995 and 2004. Information about patients' race was reported by transplant centers. The results showed no difference in the risk of aGVHD grade II-IV, relapse or graft failure between different races. In a multivariate analysis adjusting for other prognostic variables (including annual income), African American race was associated with significantly worse overall survival (RR: 1.47, P<0.01) and disease free survival (RR: 1.48, P<0.01) and higher TRM (RR: 1.56, P<0.01) than whites. Risk of TRM was also increased in Hispanics (RR: 1.30, P<0.01), but overall survival and disease free survival were comparable with that of whites.

Survival was lower in those with the lowest income, even after adjustment for race and measured comorbidities, and the excess mortality was treatment related.(4)

Table 2. Summary of literature about HSCT outcomes and ethnicity

Study No.	Type of transplant	Disease	Study population	Study year	Results
1	HLA-identical sibling donor	Acute or chronic leukemia	CIBMTR: US and Canada	1985-1999	Hispanics had lower 1 year and 3 year adjusted survival than whites between 1995 and 1999. No difference in survival rates between whites and blacks or with Asians.(1)
2	HLA-identical sibling donor	Leukemia	CIBMTR: US	1990-2000	No difference between whites and ethnic minorities for acute and chronic GVHD, relapse, and TRM. Hispanics had increased overall risk of treatment failure (death or relapse) and overall mortality compared to whites.(40)
3	Autologous or allogeneic HSCT	Malignant or non-malignant conditions	US	1992-2000	No difference between ethnicities for autologous transplants. For allogeneic transplant, blacks had higher mortality, aGVHD and non-relapse mortality than whites.(37)
4	Sibling donor	Leukemia	CIBMTR: US/ Ireland/Scandinavian countries and JHCT/JALSG: Japan	1990-1999	GVHD risk is lower in Japanese and Scandinavians than white Americans and African Americans Same risk in Irish, white-Americans and African – Americans.(39)
5	Unrelated donor	Acute or chronic leukemia and myelodysplastic syndrome	CIBMTR: US	1995-2004	African Americans had worse overall survival and disease free survival than whites. African Americans and Hispanics had higher treatment related mortality than whites.(4)

1.4 Objectives

1.4.1 Goal

To determine whether patients' ethnicity affects HSCT outcomes in BC.

1.4.2 Main objective

To determine the relationship between patients' ethnicity and unrelated donor HSCT outcomes at the Leukemia/BMT program of BC facility, Vancouver General Hospital (VGH).

1.4.3 Specific aims

- To assess how ethnicity is related to overall survival after unrelated donor HSCT at the Leukemia/BMT program of BC facility, Vancouver General Hospital (VGH).
- To assess how ethnicity is related to non-relapse survival after unrelated donor HSCT at the Leukemia/BMT program of BC facility, Vancouver General Hospital (VGH).
- To assess how ethnicity is related to aGVHD grade II-IV after unrelated donor HSCT at the Leukemia/BMT program of BC facility, Vancouver General Hospital (VGH).
- To assess how ethnicity is related to cGVHD after unrelated donor HSCT at the Leukemia/BMT program of BC facility, Vancouver General Hospital (VGH).

1.5 Hypothesis

We hypothesized that patient's ethnicity significantly affects survival outcomes (after adjusting for patient, donor and transplant related characteristics) of unrelated donor HSCT for hematological malignancies in BC during 1988-2008.

2. Materials and methods

The study was designed as a retrospective medical electronic/paper chart review. The study environment was “The leukemia/bone marrow transplant program of BC” centre at Vancouver general hospital (VGH) which is the only facility performing adult HSCT in BC. The data related to transplant patients is recorded in their electronic database (BMTserve) as well as their paper chart registry. Study patients were individuals who underwent “unrelated donor” allogeneic HSCT at the center between 1988 (the time first unrelated donor transplant was performed at the study center) and the end of 2008. These patients were further refined by the following inclusion criteria: a) first time transplant patients b) cases with hematological malignancies as underlying disease c) patients with non-missing ethnicity data (Figure1).

The data regarding HSCT patients’ *demographics* (age, gender, ethnicity, etc.), *underlying disease* (cancer type and stage, etc), *donors* (age, sex, parity, CMV status, etc.), *treatments* (date and type of transplant, stem cell source, time from start date of unrelated donor search to transplant, etc.), and *outcomes* (follow up time, engraftment, acute and chronic GVHD, relapse, mortality, etc.) was abstracted from the BMTserve database.

Information in the database about patient’s ethnicity was determined in two ways: (1) during the initial phone call by the transplant coordinator, patients were asked "what is your ethnic background?" and (2) patients were given a "Health Assessment Form" with the question “To which ethnic or culture group do you belong?” The form provided predefined multiple-choice responses and an open-ended “other” option. As the ethnicity for half of the cases was not recorded in BMTserve, additional information about patient’s ethnicity was retrieved from various sources: BMT center oncologists, BCCA paper charts, BMT center paper charts and a file provided by the Canadian Blood Services organization (which facilitates unrelated donor HSCT in Canada) upon our request. The ethnicity categories were determined according to the

BMTserve database (Whites, Blacks, Asians, Hispanics, and Natives) and were further reclassified as white and non-white ethnic groups (Table3).

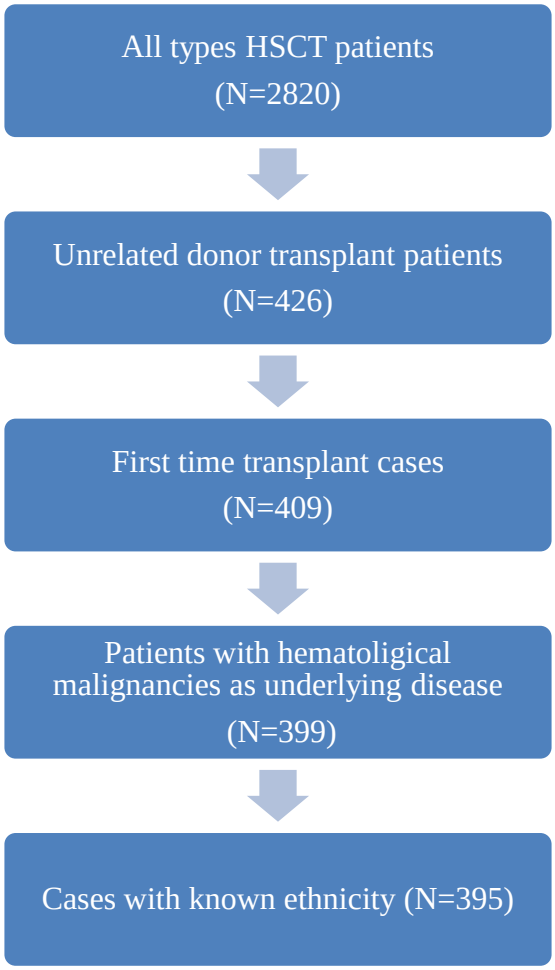

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Figure 1. Selection process of study patients

Table 3. Ethnicity classification of study patients

Database categories(N)		Study categories(N)
Caucasian (331) European or Western Russian (7) Middle East or North Coast of Africa (2)	**White (340)**	**White (340)**
Asian (1) Asian Indian (8) Chinese NOS* (10) Filipino (5) Korean (2) Northern Chinese (1) Southeast Asian/Southern Chinese (5)	**Asian (32)**	**Non-white (55)**
Native American (3) Native American NOS (5)	**Native (8)**	
Black (1) Caribbean Black (1)	**Black (2)**	
Hispanic NOS (3)	**Hispanic (3)**	
Other (1)	**Other (1)**	
Southeast Asian/Southern Chinese & European or Western Russian (1) Native American & Caucasian (6) Mexican or South-western USA Hispanic & Caucasian (1) Black NOS & Caucasian (1)	**Mixed (9)**	

* Not otherwise specified

Overall survival was the primary outcome and defined as the interval between transplant and death. Surviving patients were censored at the date of last contact.

Descriptive statistics were presented as mean ± standard deviation and median along with number and percentage (frequency distributions). We used the χ^2 test for categorical variables and t-test for continuous variables to compare patient, disease, donor and transplant related

characteristics among the two ethnic cohorts. Kaplan-Meier estimates were used to evaluate probabilities of overall survival, non-relapse survival, aGVHD grade II-IV and cGVHD; the log-rank test was used for univariate comparisons. Cox proportional hazards regression technique was used to compare the hazard rates of different outcomes among ethnicities (with whites used as the reference group) while adjusting for confounders. Proportional hazards assumptions were assessed and determined to be valid.

Confounders were assessed based on their effect on other parameter estimates and statistical significance. Potential confounders tested were patient, donor and transplant related factors which were proven to be clinically associated with HSCT outcomes (Table 4, 5, 6). The confounders selected were recipient's age, donor's sex, donor's registry country, year of transplant, patient/donor CMV status, stem cell source and HLA match status of recipient and donor. Two-sided *P* values <0.05 were considered statistically significant.

3. Results

3.1 Descriptive results

395 patients who met our selection criteria were included in the study of which 340 (86%) were classified as white and the other 55 (14%) were categorized as non-white.

Over two decades (1988-2008), the number of unrelated donor transplants has increased in Leukemia/BMT center of BC for both white and non-white patients (Figure 2), however the relative increase has been greater for non-white patients (575%) compared to whites (70%). 49% of non-whites and 33% of whites received their transplant between 2003 and 2008.

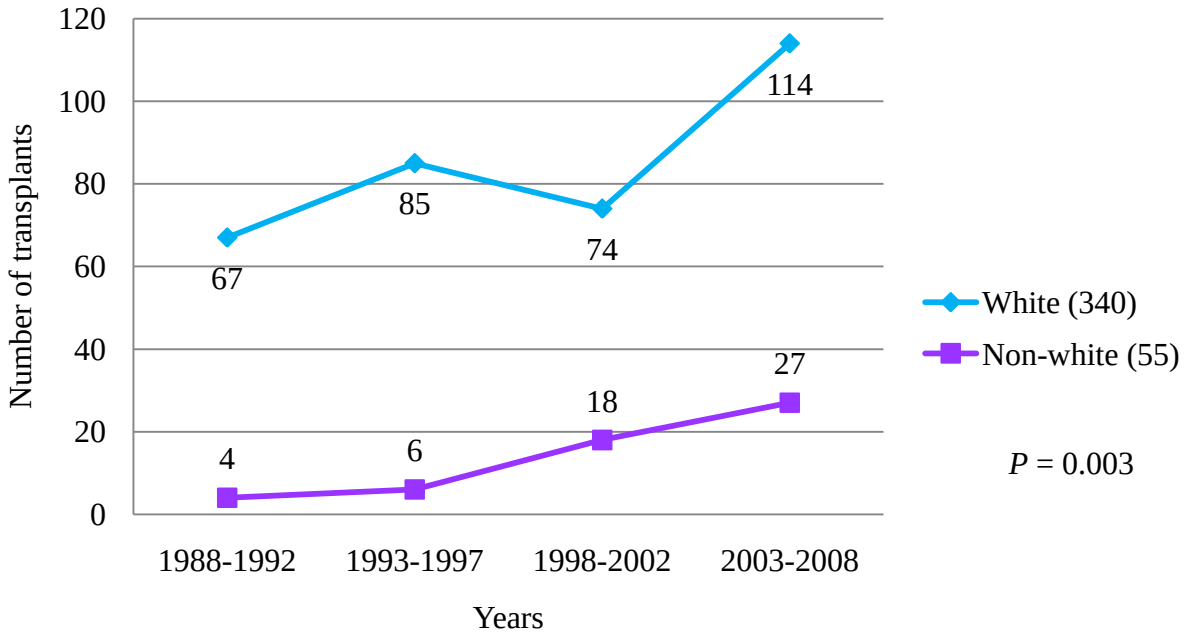

Figure 2. Number of unrelated donor HSCTs for each ethnic category by time period (N=395)

3.1.1 Patients' characteristics

Table 4 shows selected demographic and baseline characteristics of transplant patients by ethnicity. The mean age of white patients at transplant was 40.2 years ± (SD=11) and for non-

white patients was 35.6 years ± (SD=11.6). In general, non-white patients received their HSCT significantly at a younger age than whites (*P*=0.02).

About 60% of whites and 50% of non-whites were males; the sex distribution in whites and non-whites didn't differ significantly (*P*=0.2).

The most common type of underlying disease for both whites and non-whites was AML (26% and 40% respectively) followed by CML (23% and 25% respectively). There was no significant difference among ethnicities according to the type of underlying disease (*P*=0.15).
More than 80% of whites and about 90% of non-whites received their transplant in early or intermediate stages of disease and there was no statistically significant difference between the two groups in this regard (*P*=0.5).

3.1.2 Donors' characteristics

Table 5 shows the characteristics of donors by recipients' ethnicity. The highest proportion of whites (33%) found their donors in the Canadian registry, while the highest proportion of non-whites (49%) received their transplant from US registry donors. 67% of whites and 77% of non-whites received their transplant from non-Canadian donor registries and the difference between two groups was significant (*P*=0.004).

78% of white recipients received their transplant from a male donor, while 60% of non-white patients had a male donor (*P*=0.04); however, taking recipient-donor sex matching, there were no significant differences between whites and non-whites (*P*=0.14).

For non-whites compared to whites, there was a higher chance that both members of a donor-recipient pair were CMV positive, and a lower chance that both members were CMV negative (*P*<0.005).

3.1.3 Transplant characteristics

Table 6 shows characteristics of HSCTs performed by patients' ethnicity. Bone marrow was the most common source for HSCT in both ethnicities. The next most frequent type of HSCT was the combination of bone marrow and peripheral blood in non-whites (33%) and peripheral blood in whites (22%). The two umbilical cord blood HSCTs were performed in white patients. There was a significant difference between whites and non-whites regarding HSCT source ($P<0.005$).

Two-thirds of whites and about half of non-whites had fully matched transplants. Overall, whites were significantly better matched for HLA antigens ($P<0.005$).

For most patients, the time from the start of donor search to transplant was about 3-6 months and the majority of them received their transplants less than 6 months after diagnosis. No significant difference between whites and non-whites was observed for these two variables ($P=0.09$ and $P=0.9$ respectively).

Median follow-up time of survivors after transplant was 70.1 months for whites and 62.1 months for non-whites, and there was no significant difference between two groups in this regard ($P=0.49$).

3.1.4 Transplant outcomes

Table 7 shows cross-tabulations for whites and non-whites regarding the incidence of some transplant outcomes. The incidence of graft failure, aGVHD grade II-IV, cGVHD, VOD, relapse and secondary malignancy for the whole study population was 8.1%, 62.5%, 77%, 26.1%, 22.3% and 8.6% respectively. Generally, no statistically significant difference in the incidence of transplant outcomes was found between two ethnic groups except for the incidence of cGVHD ($P=0.03$) which was more frequent in non-whites (91.4%) compared to whites (74.9%).

The most common primary causes of death in the whole cohort were GVHD (31.7%), relapse (30.4%) and regimen related toxicity (15.4%) and there was no significant difference between two ethnic groups in this regard (P=0.1).

Table 4. Characteristics of unrelated donor transplant patients by ethnicity (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Age at transplant (years)				
<20	11(3.2)	6(10.9)	17(4.3)	**0.02**
20-39	156(45.9)	27(49.1)	183(46.3)	
≥40	173(50.9)	22(40)	195(49.4)	
Sex				
Male	198(58.2)	27(49.1)	225(57)	0.20
Female	142(41.8)	28(50.9)	170(43)	
Underlying disease				
Myelodysplastic Syndrome (MDS)	37(10.9)	7(12.7)	44(11.1)	0.15
Acute Myeloid Leukemia (AML)	89(26.2)	22(40)	111(28.1)	
Acute Lymphoblastic Leukemia (ALL)	41(12.1)	6(10.9)	47(11.9)	
Chronic Myeloid Leukemia (CML)	78(22.9)	14(25.5)	92(23.3)	
Non-Hodgkin Lymphoma (NHL)	51(15)	2(3.6)	53(13.4)	
Multiple Myeloma(MM)	16(4.7)	1(1.8)	17(4.3)	
Other hematological malignancies	27(7.9)	3(5.5)	30(7.6)	
Missing	1(0.3)	0(0)	1(0.3)	
Pre-transplantation risk category*				
Early	153(45)	28(50.9)	181(45.8)	0.5
Intermediate	129(37.9)	21(38.2)	150(38)	
Advanced	58(17.1)	6(10.9)	64(16.2)	

† Chi-Square test for categorical variables

*Early disease, first complete remission or chronic phase; intermediate, second or more complete remission of chronic phase or accelerated phase; advanced, all relapse, primary refractory, or blast phase.

Table 5. Characteristics of unrelated donors by patients' ethnicity (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Donor registry country				
Canada	112(32.9)	13(23.6)	125(31.6)	**0.004**
USA	98(28.8)	27(49.1)	125(31.6)	
Germany	79(23.2)	7(12.7)	86(21.8)	
UK	34(10)	2(3.6)	36(9.1)	
Other countries	15(4.4)	6(10.9)	21(5.3)	
Missing	2(0.6)	0(0)	2(0.5)	
Donor's age				
<30y	88(25.9)	16(29.1)	104(26.3)	0.60
30-39	137(40.3)	24(43.6)	161(40.8)	
≥40	114(33.5)	14(25.5)	128(32.4)	
Missing	1(0.3)	1(1.8)	2(0.5)	
Donor's sex				
Male	244(71.8)	32(58.2)	276(69.9)	**0.04**
Female	96(28.2)	23(41.8)	119(30.1)	
Donor's parity (If female, N= 119)				
Parous	79(82.3)	3(13)	99(83.2)	0.60
Non-parous	17(17.7)	20(87)	20(16.8)	
Recipient/Donor sex match				
Male/Male	157(46.2)	17(30.9)	174(44.1)	0.14
Female/Male	87(25.6)	15(27.3)	102(25.8)	
Female/Female	55(16.2)	13(23.6)	68(17.2)	
Male/Female	41(12.1)	10(18.2)	51(12.9)	

Table 5. Characteristics of unrelated donors by patients' ethnicity (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Donor/Recipient CMV status				
-/-	134(39.4)	9(16.4)	143(36.2)	**<0.005**
-/+	102(30)	14(25.5)	116(29.4)	
+/-	47(13.8)	6(10.9)	53(13.4)	
+\+	50(14.7)	23(41.8)	73(18.5)	
Unknown/other	7(2.1)	3(5.5)	10(2.5)	

† Chi-Square test for categorical variables

Table 6. Transplantation characteristics by patients' ethnicity (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Transplant year				
1988-1992	67(19.7)	4(7.3)	71(18)	**0.003**
1993-1997	85(25)	6(10.9)	91(23)	
1998-2002	74(21.8)	18(32.7)	92(23.3)	
2003-2008	114(33.5)	27(49.1)	141(35.7)	
Stem cell source				
Bone marrow	233(68.5)	32(58.2)	265(67.1)	**<0.005**
Peripheral blood	75(22.1)	5(9.1)	80(20.3)	
Bone marrow & Peripheral blood	30(8.8)	18(32.7)	48(12.2)	
Umbilical cord blood	2(0.6)	0(0)	2(0.5)	
Recipient/Donor HLA matching				
Fully matched	248(72.9)	26(47.3)	274(69.4)	**<0.005**
1 HLA antigen mismatch	69(20.3)	18(32.7)	87(22)	
≥ 2 HLA antigen mismatched	23(6.8)	11(20)	34(8.6)	
Interval from start of donor search to transplant				
<3months	86(25.3)	7(12.7)	93(23.5)	0.09
3-6 months	131(38.5)	22(40)	153(38.7)	
6-12 months	62(18.2)	10(18.2)	72(18.2)	
1-2 years	34(10)	6(10.9)	40(10.1)	
>2 years	17(5)	7(12.7)	24(6.1)	
Missing	10(2.9)	3(5.5)	13(3.3)	

Table 6. Transplantation characteristics by patients' ethnicity (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Interval from diagnosis to transplant				
<6 month	131(38.5)	24(43.6)	155(39.2)	0.9
6-12 month	59(17.4)	8(14.5)	67(17)	
1-2 years	73(21.5)	11(20)	84(21.3)	
>2 years	77(22.6)	12(21.8)	89(22.5)	
Total body irradiation(TBI)				
Yes	317(93.2)	53(96.4)	370(93.7)	0.38
No	23(6.8)	2(3.6)	25(6.3)	
Conditioning regimen*				
Busulfan + Cyclophosphamide ± others	11(3.2)	1(1.8)	12(3)	0.63
Cyclophosphamide + TBI ± others	316(92.9)	53(96.4)	369(93.4)	
Others	13(3.8)	1(1.8)	14(3.5)	
Follow up time of survivors, median range (months)	70.1 (5.5-225.4)	62.1 (8.7-230.2)	68.3 (5.5-230.2)	0.49

† Chi-Square test for categorical variables and unpaired t-test for continuous variables among patients with data available.

* High dose chemotherapy and/or radiotherapy applied before transplant to eradicate malignancy and suppress recipients' immune system.(6)

Table 7. Incidence of transplant outcomes in whites and non-whites (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Absolute Neutrophil Count (ANC) engraftment				
Yes	299(87.9)	47(85.5)	346(87.6)	0.99
No	19(5.6)	3(5.5)	22(5.6)	
Missing	22(6.5)	5(9.1)	27(6.8)	
Graft failure				
Yes	30(8.8)	2(3.6)	32(8.1)	0.18
No	300(88.2)	52(94.5)	352(89.1)	
Missing	10(2.9)	1(1.8)	11(2.8)	
Acute graft versus host disease (aGVHD) grade				
0	44(12.9)	8(14.5)	52(13.2)	0.89
I	44(12.9)	7(12.7)	51(12.9)	
II	108(31.8)	13(23.6)	121(30.6)	
III	65(19.1)	10(18.2)	75(19)	
IV	43(12.6)	8(14.5)	51(12.9)	
Not determined	36(10.6)	9(16.4)	45(11.4)	
aGVHD grade II-IV				
Yes	216(63.5)	31(56.4)	247(62.5)	0.61
No	88(25.9)	15(27.3)	103(26.1)	
Not determined	36(10.6)	9(16.4)	45(11.4)	
cGVHD (alive ≥ 100 days, N= 278)				
Yes	182(74.9)	32(91.4)	214(77)	**0.03**
No	61(25.1)	3(8.6)	64(23)	

Table 7. Incidence of transplant outcomes in whites and non-whites (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Veno-occlusive hepatic Disease (VOD)				
Yes	90(26.5)	13(23.6)	103(26.1)	0.62
No	240(70.6)	41(74.5)	281(71.1)	
Missing	10(2.9)	1(1.8)	11(2.8)	
Maximum grade regimen related toxicity *				
0	6(1.8)	2(3.6)	8(2)	0.67
1	33(9.7)	4(7.3)	37(9.4)	
2	215(63.2)	26(47.3)	241(61)	
3	46(13.5)	8(14.5)	54(13.7)	
4	16(4.7)	3(5.5)	19(4.8)	
Missing	24(7.1)	12(21.8)	36(9.1)	
Subsequent HSCT				
Yes	18(5.3)	4(7.3)	22(5.6)	0.55
No	322(94.7)	51(92.7)	373(94.4)	
Relapse				
Yes	78(22.9)	10(18.2)	88(22.3)	0.43
No	262(77.1)	45(81.8)	307(77.7)	
Secondary malignancy				
Yes	32(9.4)	2(3.6)	34(8.6)	0.16
No	308(90.6)	53(96.4)	361(91.4)	
Status at last follow-up date				
Alive	134(39.4)	21(38.2)	155(39.2)	0.86
Dead	206(60.6)	34(61.8)	240(60.8)	

Table 7. Incidence of transplant outcomes in whites and non-whites (N=395)

Characteristics	**N (%)**			**P value†**
	White	Non-white	Total	
	340(86)	55(14)	395(100)	
Primary cause of death (N=240)				
Relapse	65(31.6)	8(23.5)	73(30.4)	0.10
Graft failure	4(1.9)	1(2.9)	5(2.1)	
GVHD	64(31.1)	12(35.3)	76(31.7)	
Regimen related toxicity	27(13.1)	10(29.4)	37(15.4)	
Infection	32(15.5)	1(2.9)	33(13.8)	
Others	14(6.8)	2(5.9)	16(6.7)	

†Chi-Square test for categorical variables among patients with non-missing values.

*The grading system estimates the non-hematologic toxicities directly caused by a given transplant treatment. It is graded on a 0-4 scale with grade 4 being fatal and grade 3 being life threatening.(9)

3.2 Comparison of HSCT outcomes between whites and non-whites

3.2.1 Kaplan-Meier estimates of survival rates

3.2.1.1 Overall survival

The *minimum follow-up time* for the living patients was 165 days and there was no significant difference between whites and non-whites for this variable. The median survival time for whites was 1.22 ± 0.47 years and for non-whites was 0.85± 1.27 years.

The overall survival rate in white patients was 0.30 and for non-white patients was 0.35 (Figure 3) and no significant difference between survival of the two groups was detected (log rank test P= 0.67).

3.2.1.2 Non-relapse survival

Non-relapse survival rate in white patients was 0.44 and for non-white patients was 0.47 (Figure 4) and no significant difference between non-relapse survival of the two groups was detected (log rank test P= 0.36).

3.2.1.3 Acute graft versus host disease (aGVHD)

The probability of aGVHD grade II-IV in the first 100 days after transplant for white patients was 0.74 and in non-whites was 0.69 (Figure 5) and there was no significant difference between cumulative incidences of aGVHD in the two groups (log rank test P=0.59).

3.2.1.4 Chronic graft versus host disease (cGVHD)

The probability of cGVHD (after day 100 post transplant) for white patients was 0.86 and for non-whites was 0.94 (Figure 6) and there was no significant difference between cumulative incidences of cGVHD in the two groups (log rank test P=0.1).

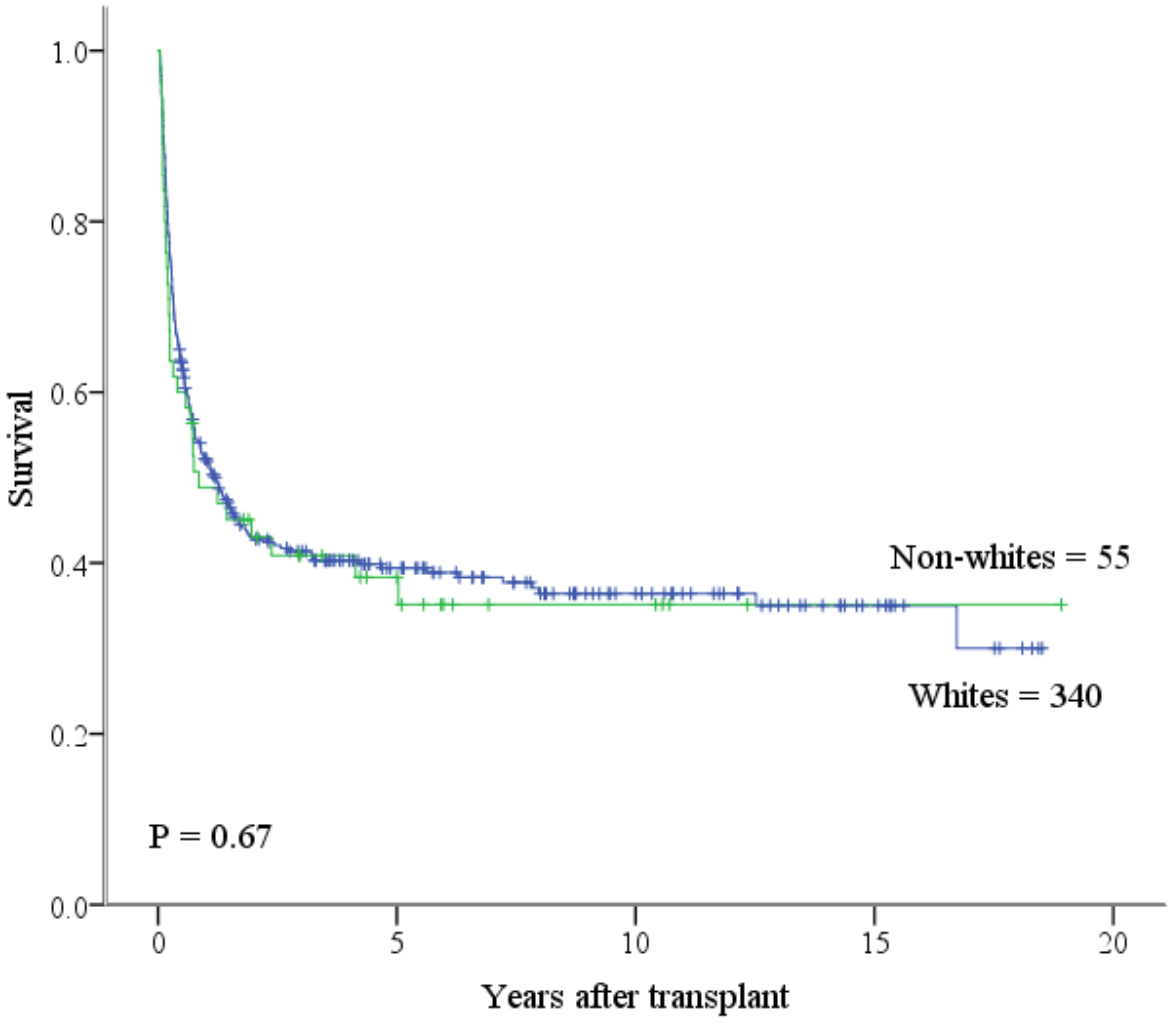

Figure 3. Kaplan-Meier curves for *overall survival* in white and non-white patients

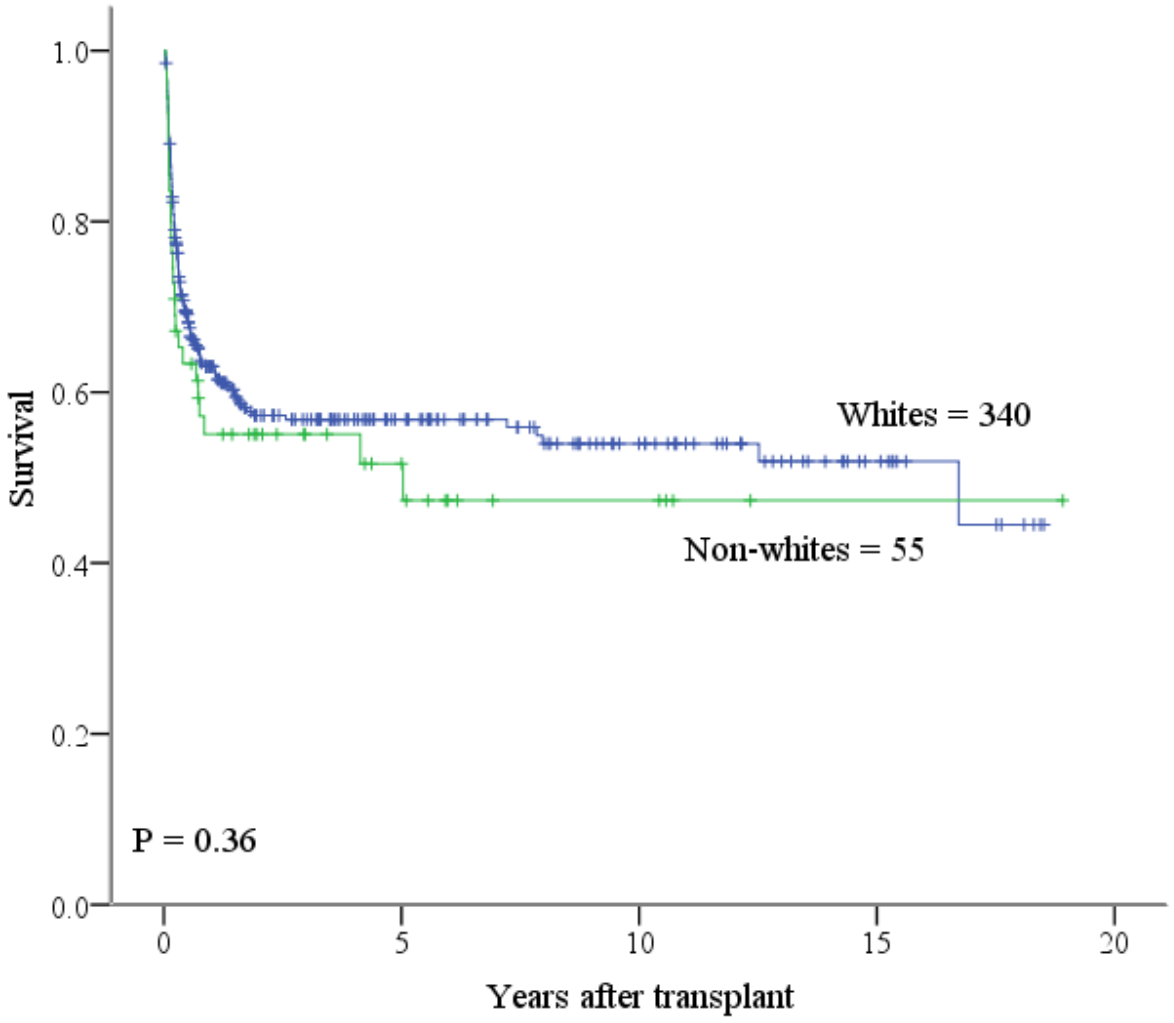

Figure 4. Kaplan-Meier curves for *non-relapse survival* in white and non-white patients

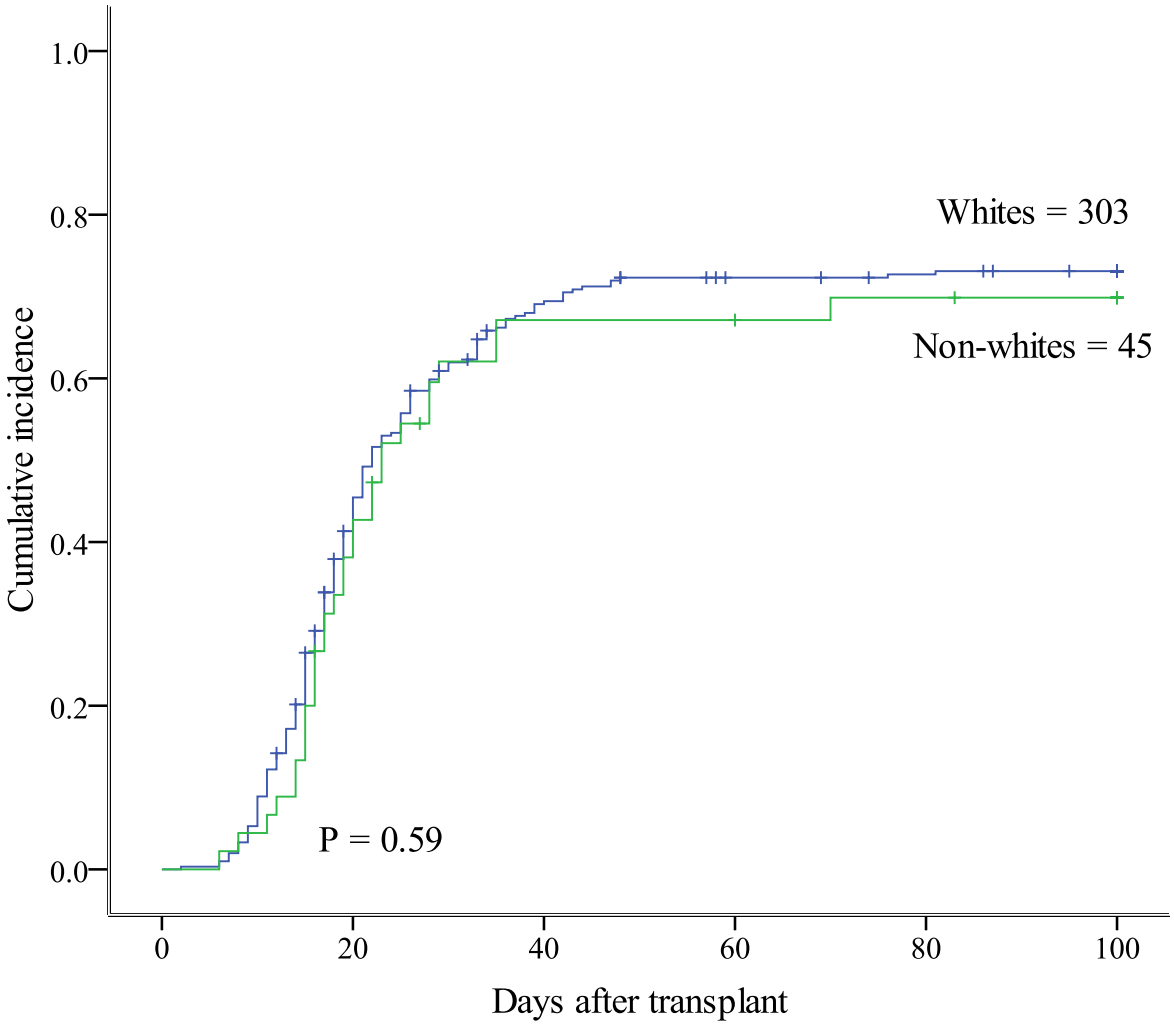

Figure 5. Cumulative incidence curves of *aGVHD grade II-IV* in white and non-white patients

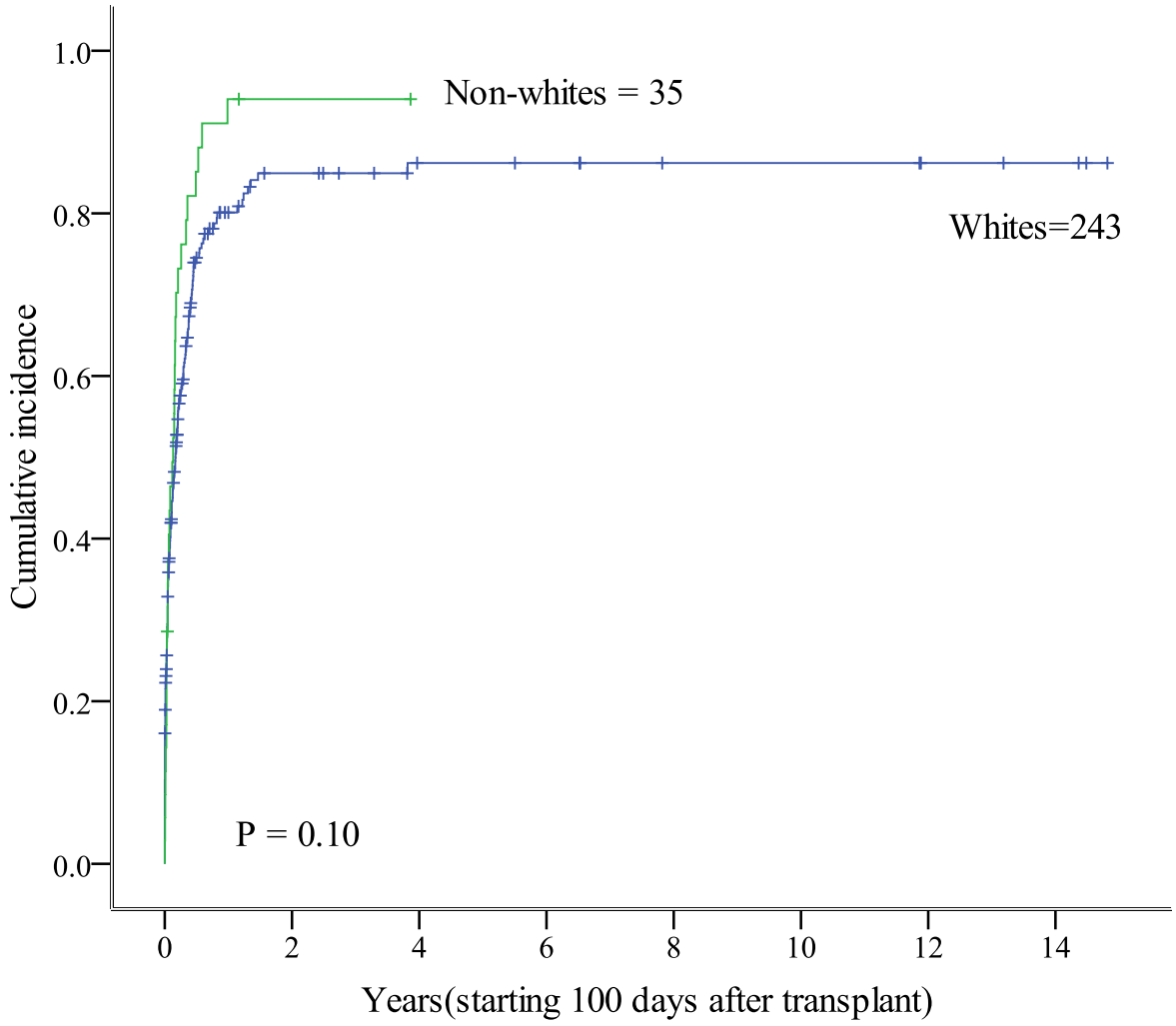

Figure 6. Cumulative incidence curves of *cGVHD* in white and non-white patients

3.2.2 Cox regression analysis for HSCT outcomes

The adjusted hazard ratios of overall mortality, TRM and cGVHD were higher in non-whites and the adjusted hazard ratio of aGVHD was lower in non-whites, however none of these differences were statistically significant (Tables 8).

Table 8. Multivariate analysis of different HSCT outcomes by ethnicity

Outcome	N	HR†	95% CI	P*
Overall survival	395	1.15	0.75-1.78	0.52
Non-relapse survival	395	1.29	0.77-2.15	0.33
aGVHD (grade II-IV)	348	0.80	0.51-1.26	0.34
cGVHD	278	1.09	0.70-1.69	0.71

†White as reference group

*Adjusted for recipient's age, donor's sex, donor's registry country, year of transplant, patient/donor CMV status, stem cell source and HLA match status of recipient and donor.

3.2.3 Subset analysis

To eliminate the possible effect of HLA-match misclassification, we repeated the analysis on a subset of patients whom were matched by DNA- based high resolution HLA matching after June 2001. Before that date, serological based methods were used at the Leukemia/BMT program of BC center to match recipients and donors for HLA antigens. We also limited our analysis to those patients with leukemia or myelodysplastic syndrome as underlying disease (a homogenous

group according to relapse and response to treatment). The subset was composed of 115 patients, 88 of them were white (76%) and 27 were non-white (24%). The results are presented in Table 9.

Table 9. Multivariate analysis of different HSCT outcomes by ethnicity in a subset of patients

Outcome	N	HR†	95% CI	P
Overall survival	115	0.64	0.27-1.50	0.30
Non-relapse survival	115	0.94	0.32-2.77	0.91
aGVHD (grade II-IV)	89	0.58	0.25-1.32	0.19
cGVHD	88	2.10	0.90-4.89	0.09

†White as reference group

*Adjusted for recipient's age, donor's sex, donor's registry country, year of transplant, patient/donor CMV status, stem cell source and HLA match status of recipient and donor.

The adjusted hazard ratios of overall mortality, TRM and aGVHD were lower in non-whites and the adjusted hazard ratio of cGVHD was about 2 times higher in non-whites, however none of these differences were statistically significant

4. Discussion

HSCT as a treatment modality to cure many malignant and non-malignant conditions has been increasingly used in Canadian patients during the past 2 decades. My study investigated the effect of ethnicity on outcomes of unrelated donor HSCT for hematological malignancies in the province of British Columbia between 1988 and 2008. The findings didn't show any statistically significant difference in HSCT outcomes between whites and non-whites.

Some **strengths** of this study are:

- It was the first HSCT outcomes and ethnicity study which was exclusively done in Canada (and in the BC population specifically). Canada has a very diverse ethno-cultural population, with more than 200 ethnic origins reported in the 2006 census (35). My study population differed from that of US studies where most emphasis is put on Hispanic/non-Hispanic ethnicities or black /white as major races while Asians were the majority (58%) of non-white group in the BC series.
- It was based on population-based data for all unrelated HSCT cases performed in BC (about 4 million people) over 2 decades, so even if my study population was relatively small and the power for comparing some main outcomes was low, the external validity of the findings for BC and Canada is high.
- This single centered study removed biases caused by disparities in patient treatment and follow up protocols in multicentre studies.

There are a number of **limitations** for this study:

- The number of patients compared to other ethnicity and HSCT outcomes studies based on multicenter CIBMTR data (1,4,39,40) was small and the power of my study to detect outcome differences based on previous studies' findings was low.

- As explained earlier, ethnicity information was obtained from the BMTserve database. In our study center, patient ethnicity was self reported during a transplant coordinator's phone call or in the Health Assessment Form at the time of admission. The first method is subject to interviewer bias based on the way the ethnicity question was asked by coordinators. Also, language barriers for many non-white minorities could lead to participation bias in both methods. Sensitivity about the issue could cause members of ethnic minorities to be reluctant about answering the question. This might produce under-reporting bias in both methods. These and other biases pertain to how information was collected for BMTserve, but my analysis assumed BMTserve data are accurate.
- The number of cases in each of the ethnic minority subgroups was small so we classified them together as the non-white group. The white (Caucasian) group also consisted of people from different European or North American backgrounds. Many other studies analyzing association of ethnicity and health related outcomes face the same problem and these heterogeneous groups may mask important variations by country of origin, language, diet and other factors relevant to health and disease. (24)
- The recorded ethnicity in the BMTserve database was missing in half of the cases and we tried to fill in the blanks using different sources such as the BC Cancer Agency database, the Canadian Blood Services database and the Leukemia/BMT center physician's recall. The multiple sources of information used to determine ethnicity might have created information bias.
- Finally, we studied those patients who had received an unrelated donor transplant. Patients who had the indication for HSCT but didn't find a matched donor (or refused the transplant because of cultural beliefs, etc.) might have had different characteristics and outcomes. If the likelihood of receiving unrelated HSCT is different among whites and

non-whites, it may result in selection bias. No study in Canada has investigated someone's chance of receiving unrelated HSCT by ethnicity, and my study didn't explore this either. However, ethnic group proportions in my study differed from those of the BC population.

A number of studies of ethnicity and HSCT outcomes based on the US population have shown inferior survival benefits for blacks and/or Hispanic minorities compared to whites (1,4,37,40) ; however my study didn't find any differences in HSCT outcomes between whites and non-white ethnic minorities. The reason for these inconsistent results could be:

1) Canada has a completely different ethnic minority structure (Table1) than the US racial/ethnic layout, where black Americans are the largest racial minority (12.6 % of the US population) and Hispanics are the largest ethnic minority (16.3% of the US population).(41) In my study there were only two blacks and three Hispanics, constituting 3.6% and 5.4% of the non-white population.

Asians composed 58.2% of our non-white group, so our main comparison was between whites and Asians. None of the US studies showed any significant differences in HSCT outcomes between Asian minorities and whites (1,4,37,40). The only study that compared transplant data from Japan to that of the US showed a lower incidence of GVHD in Japanese compared to white and black Americans. However, Japan is different from many other Asian countries by being geographically isolated for long periods of time and having a restricted migration pattern, so Japanese people have less genetic diversity of transplant related genes (e.g., HLA, cytokine genes) and lower chance of developing GVHD after HSCT.(39)

2) The evidence shows that low socioeconomic status is associated with worse health related outcomes and it is not easy to separate its effect from those of ethnicity/racial background. Some studies have shown that the racial/ethnic discrepancy in outcomes will disappear after adjustment

for SES of the groups.(27) In theory, socioeconomic factors may influence whether HSCT is available to patients, whether patients are referred for transplantation in a timely fashion, and whether adequate medical care is provided/used after discharge from the transplant center. Quality medical care after allogeneic HSCT seems to be of particular importance because morbidity and mortality associated with GVHD, delayed immune reconstitution and infections may occur months to years after transplantation. Therefore, these complications have to be interpreted in the context of patients' socioeconomic and cultural backgrounds, which may influence the recognition and treatment of them.(37)

In British Columbia, the universal coverage provided under *Medical Service Plan (MSP)* has made equitable access to an expensive treatment like HSCT available for people with any socio-economic background. However, in the US an average of 16% of the population was uninsured in the period of 2008-2009 and this rate for Hispanics (31%) and blacks (20%) was higher than non-Hispanic whites (11%).(42) This difference in insurance coverage can affect their timely access to care. For example, I found no difference between whites and non-whites in regard to time from diagnosis to transplant, however US studies have shown significant difference between whites and other races for this variable.(1,40) Also, low SES of the US black and Hispanic patients and their limited access to free medical care can influence the long-term care and follow up after HSCT and it may result in the higher TRM reported in these groups.(4,37)

In conclusion, my study considers associations between ethnicity and HSCT outcomes in Canada. As no ethnic disparity in outcomes of HSCT is observed between whites and non-whites in BC, it seems that special attention to ethnic minorities (e.g., stricter follow up) for this treatment is not a priority at this time.

However, with the increasing number of immigrants and progressive use of HSCT for many hematological and non-hematological health issues (e.g., solid tumors, immunodeficiency

syndromes), a multicenter study is recommended because it would allow us to estimate effects for individual non-white subsets of the larger visible minority, and subsequently identify populations where interventions may be useful. Also, studying specific aspects of ethnicity (e.g., pharmaco-genetics, behavioral characteristics, diet, SES) and HSCT outcomes is recommended.

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