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Elizabeth Burns Date

Chronic Myelogenous Leukemia: Poverty Based Disparities in Survival

By

Elizabeth Burns
Master of Public Health

Epidemiology

_____

Kevin Ward, PhD
Committee Chair

Chronic Myelogenous Leukemia: Poverty Based Disparities in Survival

By

Elizabeth Burns

B.S., Georgia Institute of Technology, 2015
MD, Emory University, 2021

Thesis Committee Chair: Kevin Ward, PhD

An abstract of
A thesis submitted to the Faculty of the
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Abstract

Chronic Myelogenous Leukemia: Poverty Based Disparities in Survival
By Elizabeth Burns

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm characterized by a pathogenic gene known as the Philadelphia or Ph chromosome which results in oncogene BCR-ABL1. The Philadelphia chromosome provides a great target for treatment, and tyrosine kinase inhibitors introduced in the early 2000s have brought 5-year survival of CML to nearly 90% in clinical trials. However, epidemiologic studies place 5-yr relative survival of CML in the US at 70% for 2010–2016 calendar period. There is currently little published data on what role poverty or SES plays in CML disparities. As research has shown that not all individuals receive therapy equally, individuals in poverty with limited access to care may not be benefiting as fully from the availability of TKI treatment and therefore experience worse outcomes. This analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program found that there is a negative correlation between living in high poverty rate areas (greater than 20% of individuals under the poverty line) and CML survival time compared to cases living in low poverty areas (HR = 1.52; 95% CI 1.13-2.05). This is consistent with prior studies demonstrating increased cancer mortality in high poverty areas. Survival disparities in CML between low and high poverty areas may be mediated by limited access to tyrosine kinase inhibitors: an effective and well tolerated targeted treatment for CML. Cost and inaccessibility may lead to lower rates of TKI utilization in low SES patients.

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Chapter I: Background/ Literature Review

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm characterized by a pathogenic gene translocation from chromosome 9 to chromosome 22 [t(9;22)(q34;q11)], known as the Philadelphia or Ph chromosome, which results in oncogene BCR-ABL1. This creates a constitutively active protein, BCR-ABL tyrosine kinase, which in the case of CML allows unchecked proliferation of myeloid cells and enhanced protein kinase activity (1). This disease has an incidence of 1-2 per 100,000 adults (2). In the year 2021 within the United States, there are predicted to be 9110 new CML cases and 1220 CML-related deaths (3).

Reports from US and European CML registries indicate CML incidence is higher in older individuals, with a median age of diagnosis between 57 and 60 years (4, 5). Incidence is also higher in males, with an approximately 1.2-1.7 times higher incidence relative to females (4, 5). Incidence has remained steady over time and has not shown significant variance between databases or geographic areas (4, 5). No differences in incidence between races has been observed (4, 5). The only known environmental risk factor for development of CML is high-dose radiation (6). Some epidemiological research suggests smoking and increased body mass is associated with higher risk of CML development, but this has not been proven (6). Heredity, diet, chemical exposure, and infections do not appear to influence risk of CML development (6).

Prior to the year 2000, CML treatment consisted of non-targeted agents such as hydroxyurea, interferon alfa (IFN-a) and allogenic stem-cell transplant (2). 5-year overall survival of CML patients at this time within clinical trials was 68 to 70% (7). Survival time following a diagnosis of CML made large gains during the early 2000s, due mostly to the introduction of tyrosine kinase inhibitors (TKI) such as imatinib (7). These are oral drugs taken

daily, with highly tolerable side effects relative to other chemotherapies (8). These drugs offer targeted inhibition of BCR-ABL tyrosine kinase produced by the Philadelphia chromosome and prevent cellular proliferation of malignant cells with relatively little effect on healthy tissue (7). In clinical trials, TKIs were shown to be significantly superior to traditional interferon alfa plus cytarabine treatment with 5-yr survival following imatinib documented at 89% (7). More recently, second and third generation TKIs demonstrated similar efficacy in clinical trials (2). However, real world effectiveness has not approached the efficacy observed in trials. The United States SEER database places 5-yr relative survival of CML at 56% for the 2001–2008 calendar period and 70.6% for the 2011–2017 calendar period (5, 9). Cancer clinical trials often have strict inclusion criteria resulting in exclusion or underrepresentation of elderly and low socioeconomic populations or patients with comorbid conditions, sometimes overestimating mortality benefit for those excluded groups (10).

CML phase greatly influences management of disease and is a significant prognostic factor. CML is graded or staged into three phases: Chronic, accelerated and blast phase. Chronic phase is the initial stage and is the phase at diagnosis for the majority of patients; 93% of patients within the Swedish CML registry presented in chronic phase (11). With modern medical management, only 1 to 1.5% of patients progress to more accelerated or blast phases per year (12). Though few patients progress or present in advanced phases, they are significantly more difficult to treat and have median survival time of 7-11 months (12). Advanced phases may also be indications for allogenic stem cell transplant, which has a more severe adverse event profile than TKIs and has been phased out at first line treatment for chronic phase CML (12). Despite this, the SEER database within the United States does not record CML phase at diagnosis,

preventing its inclusion analyses. This limitation is equally present in other studies relying exclusively on SEER data.

Risk Factors for CML Survival Outcomes

The success of TKI inhibitors and subsequent improved survival in CML has overshadowed continued disparities in CML outcomes. Though survival for all ages and races increased significantly from 1975 to 2014 in the United States, African Americans and patients over 75 years of age have experienced small increases relative to other groups (13).

Age has frequently been shown to be a strong prognostic factor in CML. Based on SEER data from 1975 to 2009, individuals age 65+ had 5-year relative survival half that of individuals age 30-49 and 10 year relative survival of only a third (5). Analysis of the Swedish CML registry showed comparable 5-year relative survival between ages <60 and 60-80, but reduced relative survival for ages >80 (11). In both the United States and England, excess hazard ratios for CML mortality for patients age 65-74 and 75+ were 2 and 3-4, respectively, compared to patients age 45-64 (14).

In addition to a higher incidence in males, males have shown slightly worse CML outcomes than females in some studies. Studies utilizing SEER data from 2000 and later have shown modest decreased hazard ratios for females compared to males (15, 16). However, a separate review of the SEER database between the years of 1975 and 2009 by Chen et al. did not show differences in relative survival between men and women with CML (5).

Disparities in adult-onset CML outcome by race appear to be minimal or disfavoring nonhispanic white prior to and during early imatinib introduction (5, 17). Chen et al did not show relative survival differences between Caucasians and African Americans within the SEER database between the years of 1975 and 2009, but did show significantly higher 10-year relative

survival for Asian Americans (5). Looking at CML cases 1992-2006 with follow-up through 2011, the SEER database showed significantly worse 5-year relative survival in adult non-Hispanic whites with CML compared to adult Hispanic whites and blacks (17). In children <18 however, blacks have significantly worse 5-year relative survival (17).

Following introduction of imatinib, racial disparities appeared to worsen for African American women while improving for African American males, relative to their white counterparts (15). SEER data from the post-imatinib era has shown lower relative survival in young (<50) African American women compared to young Caucasian women. Looking at SEER data from 1973-1998, relative survival was significantly lower for African American males compared to Caucasian males prior to the imatinib era (prior to May 2001), but this difference became non-significant post-imatinib.

Improvement in survival post-TKI introduction has been modest in older patients compared to younger patients (13, 15). Wiggins et al. noted that Imatinib use is significantly less in older patients; 90% of patients 20-59 years of age received imatinib treatment for CML while only 46% of patients greater than 80 years of age received imatinib treatment (18). As elderly patients who use imatinib do have significantly improved survival time, lower rates of imatinib use have been proposed as a reason for limited survival improvement post-imatinib for elderly patients. Rates of imatinib use have not been shown to vary based on race, sex, urban/rural residence, or insurance status.

Insurance status at diagnosis may also affect survival in CML. Insurance status has previously been associated with later stage at diagnosis and higher cancer-specific mortality for solid tumors (16). Based on SEER data from 2007 to 2012, both uninsured and Medicaid insurance was associated with worse overall survival in CML compared to other insurance

coverage in patients 18-64 years old (16). When controlling for confounders, within the 15 to 64 age group, uninsured patients and Medicaid patients had hazard ratios of 1.93 and 1.83 respectively compared to an insured comparator group (16). After age 65, there was not a significant difference in overall survival between CML patients with Medicaid and Medicare or other forms of insurance (16). For those with insurance, higher overall out of pocket costs has been shown to be associated with significantly higher rates of TKI nonadherence and discontinuation (8).

Marital status has been weakly associated with CML outcomes. Perry et al. noted that in patients under 15-64 years of age, single persons had significantly worse outcomes than married individuals; divorced/widowed patients in that age group had comparable outcomes to married patients (16). Over 65 years of age, the opposite appeared to be true: divorced/widowed/separated patients had worse survival than married patients, while single patients in this age group had comparable outcomes to married patients (16).

Rural-urban disparities in overall survival and life expectancy have increased over the past three decades (19). From systematic review of rural cancer survival in high-income counties, most studies showed worse cancer survival in rural areas compared to metropolitan or urban areas (20). This rural-urban disparity has been attributed to later stage at diagnosis and less utilization of aggressive treatment modalities in rural areas (20, 21). This disparity may be mediated by socioeconomic status, which tends to be lower in more rural areas (20, 21). There is little knowledge on what role rurality plays specifically on CML outcomes.

Poverty Level and Cancer Outcomes

Socioeconomic status (SES) is known to play an important role in mediating an individual's health, including incidence and outcomes of cancer (19, 21). Survival differences in

leukemia mortality have previously been attributed to less aggressive treatment for low SES individuals (22). Looking directly at income, men living below the poverty line have been shown to have 80% higher overall cancer mortality than men with incomes greater than 600% of the poverty level (19). Individuals with family income below the poverty level are significantly more likely to forgo medical care due to cost (19) and be diagnosed with cancer at later stages (21). Low-income patients often report difficulties in finding physicians, traveling long distances to care, and unaffordable healthcare with and without insurance (23). Prescriptions are less likely to be filled in areas with high-poverty and low vehicle access within the United States (24).

Another way to indirectly measure SES is local poverty rate, which is has been shown to correlate well with other area-level measurements of SES (21). This is an area based measure which is captured in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program calculated from the address of the patient at the time of diagnosis(25). The US Census Bureau defines "poverty areas" as those with a greater than 20% poverty rate(26). Overall cancer mortality in these poverty areas compared to low poverty areas increased significantly between 1975 and 1999, attributed partially to increased relative rate of cancer risk factors in low poverty areas such as smoking and obesity (21). This disparity is also attributed to survival differences. Individuals living in these poverty areas have overall five-year cancer survival 10% lower than individuals living in low poverty areas with less than 10% poverty rate (21).

There is currently little published data on what role poverty or SES plays in CML disparities. As CML is a disease with a relatively recent effective oral treatment and very few modifiable risk factors, clarifying current disparities in outcomes may guide toward targets for intervention. As research has shown that not all individuals receive therapy equally, individuals

in poverty with limited access to care may not be benefiting as fully from the availability of TKI treatment and therefore experience worse outcomes. We are unable to determine who in SEER receives targeted TKI treatment, as TKIs and other chemotherapy are captured in the same field and may be underascertained (27). Limiting the analysis to CML diagnosed 2010 and forward, when recommendations for TKI treatment have been well established within the medical community, will ensure results are most applicable to the post-TKI era (28). If trends for other cancers hold true for CML, it would be expected that high poverty is correlated with increased mortality in CML when controlling for other factors.

Chapter II: Manuscript

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm characterized by a pathogenic gene translocation from chromosome 9 to chromosome 22 [t(9;22)(q34;q11)], known as the Philadelphia or Ph chromosome, which results in oncogene BCR-ABL1. This creates a constitutively active protein, BCR-ABL tyrosine kinase, which in the case of CML allows unchecked proliferation of myeloid cells and enhanced protein kinase activity (1). This disease has an incidence of 1-2 per 100,000 adults (2). In the year 2021 within the United States, there are predicted to be 9110 new CML cases and 1220 CML-related deaths (3).

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There is currently little published data on what role poverty or SES plays in CML disparities. As CML is a disease with a relatively recent effective oral treatment and very few modifiable risk factors, clarifying current disparities in outcomes may guide toward targets for intervention. As research has shown that not all individuals receive therapy equally, individuals in poverty with limited access to care may not be benefiting as fully from the availability of TKI treatment and therefore experience worse outcomes. We are unable to determine who in SEER receives targeted TKI treatment, as TKIs and other chemotherapy are captured in the same field and may be underascertained (27). Limiting the analysis to CML diagnosed 2010 and forward, when recommendations for TKI treatment have been well established within the medical community, will ensure results are most applicable to the post-TKI era (28). If trends for other cancers hold true for CML, it would be expected that high poverty is correlated with increased mortality in CML when controlling for other factors.

Methods

Study Population

11,013 cases of chronic myelogenous leukemia (ICD-O-3 histology codes 1863, 1875, 1876) diagnosed from 2010-2015 with follow up through December 31st, 2016 were identified from the SEER 18 Region custom data, Nov 2018 submission. The SEER 18-region coverage system includes approximately 36% of the United States population (29). Individuals were removed who were under 18, diagnosed by autopsy or death certificate only, diagnosed with multiple primary cancers, alive with no follow up time (i.e., immediately lost to follow up), diagnosed with chronic myelomonocytic leukemia (CMML), unknown rural-urban continuum value, unknown race, and unknown cause of death resulting in a final analytic dataset of n=5515 (Figure 1). Though CML and CMML are both included under the "Chronic Myelogenous Leukemia" SEER site recode, they are distinct disease types with different ICD-O-3 morphology codes and natural history of disease (30, 31). Notably CMML does not have the Philadelphia chromosome and is not treated with TKIs (30, 31). In interest of making results most applicable to disease that can be treated with TKIs, CMML was removed from this analysis. Removal of CMML varies among other epidemiological studies using SEER to analyze CML (17).

Exposure Variable

The exposure variable of interest was county poverty rate, defined as the percentage of persons below poverty in the patient's county of residence at the time of diagnosis. This value is calculated based on county level data from the Census American Community Survey (ACS) 2010-2014 for cases diagnosed 2012 or earlier and ACS 2013-2017 for cases diagnosed 2013 or later (25). Poverty level was grouped into three categories for analysis: low 0.0-9.9%, moderate 10.0-19.9%, and high 20%-100%. No cases were missing values for poverty level.

Covariates

Other variables controlled for in the analysis include sex, race, rural-metropolitan continuum, age at diagnosis, marital status at diagnosis, insurance status at diagnosis, chemotherapy status and year of diagnosis. Race was categorized in four categories: White, Black, Hispanic, and other with other including non-Hispanic American Indian/Alaska Native and Non-Hispanic Asian or Pacific Islander. Individuals with unknown race (n=127) were removed from analysis. Rural-metropolitan continuum was categorized into two groups: metropolitan and rural/urban. Age at diagnosis was categorized as 18-49, 50-64, and 65+. Marital status at diagnosis was categorized as Unmarried (including never married, separated, divorced, and widowed), Married (including Married and unmarried or domestic partners), or unknown. Insurance status was categorized into Uninsured/Any Medicaid, Insured, and unknown. Chemotherapy Status, which includes TKI therapy as well as other forms of chemotherapy, is categorized as Yes or No/Unknown (27).

Outcome of Interest

The outcome of interest was 5-year mortality of CML. Survival time was defined in months from the date of diagnosis to death, end of follow up period (December 31st, 2016) or last known date alive. Cases were censored for deaths not due to CML, individuals lost to follow-up, and the study endpoint. Cases with unknown causes of death were excluded from analysis. Cause of death and vital status as listed in the SEER registry is gathered from a combination of state vital records and the National Death Index (NDI) within National Center for Health Statistics (NCHS).

Statistical Analysis

Descriptive statistics for the study population were calculated as frequencies and percentages, with differences in covariates by poverty category determined with a Chi-Square test. Survival across poverty rate categories was compared using unadjusted Kaplan-Meier survival curves. Multivariate analysis was conducted using a Cox proportional-hazards model to calculate adjusted hazard-ratios, with survival time as the outcome of interest and poverty rate as the main predictive variable of interest. The multivariable cox regression model controlled for poverty level, sex, race, rural-metropolitan continuum, age, marital status, insurance status, chemotherapy status and year of diagnosis. All variables satisfied the proportional hazards assumption as assessed graphically via log-log survival curves. Interaction between main exposure variable of poverty and other covariates was assessed and determined to be nonsignificant. Sensitivity analysis was also performed, comparing model performance with and without individuals with unknowns for marital status and insurance status.

The study dataset was pulled from Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database (Incidence - SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Submission) using SEER*Stat Version 8.3.6. (National Cancer Institute) (32). All data analyses were performed with SAS Version 9.4 and SAS Studio Version 3.8. (SAS Institute, Cary, NC). This study did not undergo IRB review as the SEER data used is publicly available and in a deidentified format.

Results

Among the 5515 individuals in the study population, 942 (17.3%) lived in counties with low poverty rates, 3634 (65.7%) lived in counties with moderate poverty rates, and 939 (17.0%) lived in counties with high poverty rates. The overall cohort was 57% male, with 88% living in metropolitan areas. 51% of the cohort was married, 73% was insured and 80% was known to have received some form of chemotherapy. The cohort was 65% white, 12% black, 15% Hispanic and 8% other race. Age of the cohort was 36% 18 to 49 years of age, 31% 50 to 64 years of age and 33% over 65 years of age. At the end of the study period, 81% of the cohort was alive, 10% had deaths attributable to CML and 9% had died from other causes.

The distribution of sex was not significantly different between poverty groups, but race, rural-metropolitan continuum, age, marital status, insurance status, year of diagnosis and SEER specific cause of death all varied significantly (Table 1). Greater numbers of white and 'other' race individuals lived in low poverty rate counties while greater number of black and Hispanic individuals lived in moderate and high poverty rate counties. The highest proportion of rural/urban counties was seen in the highest poverty group, though the majority of persons in all poverty groups resided in metropolitan counties. A higher proportion of individuals age 18-49 were present in the moderate and high poverty groups, while individuals age 65+ most often resided in low poverty counties. The low poverty group had the greatest proportion of married individuals while the high poverty group had the lowest proportion of married individuals; the proportion of people with unknown marriage status was consistently about 10% between all groups. The low poverty group had the greatest proportion of insured individuals while the high poverty group has the greatest proportion of uninsured/Medicaid individuals; those with unknown insurance status represented a slightly higher proportion in the low poverty group

(10.5%) compared to middle (7.4%) and high poverty groups (7.7%). The high poverty group had a lower proportion of individuals known to have received chemotherapy compared to the low and moderate poverty groups. The low and high poverty groups had a greater proportion of individuals diagnosed from 2013-2015 compared to 2010-2012, while the moderate poverty group had a more equivalent proportion diagnosed between all years. In univariate analysis, the low poverty group had the lowest proportion of deaths due to CML or other causes while the high poverty group had the greatest proportion of deaths due to CML or other causes.

Unadjusted Kaplan-Meier survival curves differed significantly by poverty level (Log-Rank x=10.19; p = 0.0061) (Figure 2). The curves showed comparable survival for low and moderate poverty groups with the high poverty group consistently showing the lowest survival.

The multivariable analysis showed a significantly increased risk of death from CML for patients living in high poverty rate counties, as compared to both low poverty (HR = 1.52; 95% CI 1.13-2.05) and moderate poverty counties (HR = 1.31; 95% CI 1.05-1.63) (Table 2). There was not a significant difference in risk of death from CML between lowest and moderate poverty counties (HR 1.16; CI 0.91-1.48).

Cases ages 50-64 had a 66% increased risk of death from CML compared to ages 18-49 (HR=1.66;95% CI 1.22-2.24), and cases age 65+ had a risk of death from CML over 7 times that compared to ages 18-49 (HR=7.14, 95% CI 5.53-9.21). Females had a 36% lower risk of death from CML compared to males (HR=0.74; 95% CI 0.62-0.88). Married cases had a 43% reduced risk of death from CML compared to unmarried cases (HR=0.57; 95% CI 0.48-0.68). Cases with insurance had a 25% reduced risk of death from CML compared to uninsured/Medicaid patients (HR=0.75; 95% CI 0.60-0.94). Individuals who received chemotherapy had a 48% reduced risk of death from CML compared to individuals who did not receive chemotherapy or had unknown

chemotherapy status (HR=0.52; CI 0.43-0.62). There was not a significantly different risk of death from CML based on rural-metropolitan continuum values, race, or diagnosis year.

Sensitivity Analysis

Sensitivity analysis was performed to determine if the hazard ratio of poverty groups was affected by the inclusion in multivariate models of unknowns within the marriage and insurance variables. In primary analyses, cases with unknown values in these covariates were kept in the dataset. Unknowns comprised approximately 10% of the overall population and were evenly distributed as approximately 10% of each poverty rate category. When multivariate analysis was rerun excluding cases with unknown marriage or insurance status (n=4767), the hazard ratios between poverty groups remined significant in the same direction (Table 3).

Discussion

Results from this study suggest that cases living in high poverty areas (>20% of individuals under the poverty line) are at an increased risk of death from CML compared to cases living in moderate or low poverty areas. Cases in high poverty areas had a 50% increased risk of death from CML compared to cases in low poverty counties, and 30% increased risk compared to cases in moderate poverty counties. This was consistent with prior studies from the SEER database demonstrating increased risk of death from cancer overall in high poverty areas (19-21).

Looking at case-specific survival of the poverty groups, the low poverty group had a cause-specific survival estimate of 90% at five years, rivaling that seen in modern clinical trials (7). The high poverty group had a cause-specific survival estimate of 83% in cause-specific survival, not reaching the efficacy seen in clinical trials. This overall discrepancies between clinical trials' and epidemiologic studies' measurement of CML survival may be primarily driven by factors of inclusion and exclusion in trials.

CML is now primarily treated with tyrosine kinase inhibitors (TKI) such as imatinib. These are oral drugs taken daily, with highly tolerable side effects relative to other chemotherapies (8). These drugs offer targeted inhibition of BCR-ABL tyrosine kinase and prevent cellular proliferation of malignant cells with relatively little effect on healthy tissue (7). In clinical trials, 5-yr survival with imatinib was about 89% (7). More recently, second and third generation TKIs have had clinical trials with similar efficacy (2). Prior to the year 2000, CML treatment consisted of non-targeted agents such as hydroxyurea, interferon alfa (IFN-a) and allogenic stem-cell transplant and 5-year overall survival of CML patients at this time within clinical trials was 68 to 70% (2, 7).

As TKIs are such an effective treatment, this discrepancy may be due to reduced healthcare access in high-poverty counties (7, 20). Low-income patients often report difficulties in finding physicians, traveling long distances to care, and unaffordable healthcare with and without insurance (23). Individuals living in poverty are more likely to delay healthcare because of transportation difficulties, arising from poor public transit infrastructure and low vehicle access (20, 33). Prescriptions are less likely to be filled in areas with high-poverty and low vehicle access within the United States (24).

Cost and inaccessibility may lead to lower rates of TKI utilization in low SES patients. Survival differences in leukemia mortality have previously been attributed to less aggressive treatment for low SES individuals (22). Firstline approved TKIs cost approximately $100,000 each year and the actual out of pocket cost paid depends on the individual insurance plan and access to financial assistance programs (16). The hypothesis of lower TKI utilization is supported by my finding that in univariate analysis chemotherapy utilization was significantly different between poverty groups, with 4% fewer cases receiving chemotherapy in the high poverty area; though this chemotherapy variable does not have a high enough sensitivity to draw any definitive conclusions.

Fewer individuals in the high poverty areas were insured compared to those in low poverty areas, which could contribute to TKI nonadherence. Although imatinib use has not been previously seen to vary with insurance (18) and insurance was controlled for in the multivariate model, these insurance variables do not account for quality of insurance or the amount an individual would pay for TKIs on their specific plan. For instance, the vast majority of Part D Medicare plans require coinsurance rather than a copayment for imatinib with average coinsurance rates of 29.8% per fill (8), which could mean out of pocket costs of over $29,000 a

year for imatinib even with Medicare. It is known higher out of pocket costs lead to greater rates of discontinuation and nonadherence to imatinib (8). Higher out of pocket costs are associated with unstable insurance coverage (34) and are frequent barriers to care for low-income families who do have insurance (23). Lack of insurance or high out of pocket costs for individuals living in poverty could result in greater rates of nonadherence or discontinuation of TKIs in that population.

There was no difference in CML survival between races in the adjusted model, which is most similar to prior studies of CML epidemiology in the pre-imatinib era and early 2000s (5, 17). African Americans and especially African American women have had lower survival gains between the pre- and post-imatinib era (13), but overall post-imatinib there were not significant differences in relative survival based on race (15). Interpretations of racial disparities vary between studies using the same SEER database – this may be due to varying years of coverage (including years pre-TKIs, early TKI use, and post-TKIs), consideration of individuals under 18, and varying definitions of CML to include CMML as is default in the SEER database (17).

Lack of disparity between race does however differ from studies which have shown overall cancer survival to vary significantly between different races (13). Ward et al. 2004 found that even after controlling for county poverty rate, there are higher death rates from cancer in African American and American Indian/Alaskan Native men and women compared to non-Hispanic Whites (21). These differences may be present because of differing prominence of environmental risk factors between races, such as obesity and smoking, or greater utilization of screening tests in non-Hispanic Whites (21). However, there are no screening tests and minimal environmental risk factors for CML development or progression. This difference may also be

reflective of differences between 1975-1999 and 2010-2016 data and lessening survival disparities over time.

This study found that patients who were younger, female, married, insured, and known to be receiving chemotherapy had lower risk of death from CML. These findings are all consistent with prior studies of CML. Younger patients have consistently shown better outcomes after CML diagnosis, especially compared to elderly cases (11, 14). Studies utilizing SEER data from 2000 and after have shown modest decreased hazard ratios for females compared to males (15, 16). Marital status has been weakly associated with CML outcomes, with single and divorced/widowed patients having worse outcomes than married patients for some age groups (16). Precious study utilizing SEER demonstrated worse overall survival for uninsured and Medicaid patients with CML (16).

Strengths and Limitations

The SEER database has multiple strengths as large population-based dataset. This dataset covers 36% of the United States population and is the most comprehensive cancer database in the United States(29). This coverage offers representability and generalizability to the overall United States population and enables a decently large sample size for the study despite the relatively low incidence of CML. The large sample size will also allow any errors in pathologic diagnosis, which are still present with current medical practices, to have a minimal effect on results via regression toward the mean. The database compiles demographic data from multiple source registries which leads itself easily to consideration of determinants of health such as poverty while accounting for possible confounders.

There are multiple limitations to the chemotherapy variable in SEER(27). This variable is gathered from Medicare records that may be incomplete and sensitivity for chemotherapy data is

estimated to be about 68%. It is unlikely that treatment is captured completely as more patients have treatment in an outpatient setting and results in under-ascertainment of patients receiving chemotherapy. As this variable is incomplete, we cannot accurately distinguish between “no treatment” and unknown treatment.” This variable also does not differentiate between TKIs or other chemotherapy, which is sometimes still used for treatment of CML. This variable cannot not assess length of time chemotherapy was used prior to discontinuation or level of adherence to treatment. A future study could more accurately capture TKI use and adherence via direct chart review.

The variable used to assess poverty within the SEER database is at the county level(25). This variable is used in the SEER dataset because it is non-identifying and easily accessible, but this does not consider variation of wealth or income within a county. Ideally, individual level data on income or poverty would be more precise as to an individual’s SES, which could be collected in a prospective research. It is unlikely a specific variable such as individual income would be included in the SEER database due to privacy concerns.

CML phase greatly influences management of disease and is a significant prognostic factor. CML is graded or staged into three phases: Chronic, accelerated and blast phase. Chronic phase is the initial stage and is the phase at diagnosis for the majority of patients; 93% of patients within the Swedish CML registry presented in chronic phase (11). With modern medical management, only 1 to 1.5% of patients progress to more accelerated or blast phases per year (12). Though few patients progress or present in advanced phases, they are significantly more difficult to treat and have median survival time of 7-11 months (12). Advanced phases may also be indications for allogenic stem cell transplant, which has a more severe adverse event profile than TKIs and has been phased out at first line treatment for chronic phase CML (12). Despite

this, the SEER database within the United States does not record CML phase at diagnosis, preventing its inclusion in this analysis. Cancer cases living in high poverty areas have previously been seen to present at later stages compared to cases in low poverty areas (21, 35). If this also holds true for CML, phase at diagnosis could be confounding CML survival time between poverty levels. This limitation is equally present in other studies relying exclusively on SEER data.

In summary, cases residing in high poverty areas have decreased 5-year survival from CML compared to cases residing in low or moderate poverty areas. There is a graded increase in risk as county poverty rate increases, however risk between low and moderate poverty areas was not significantly different. This is consistent with prior studies demonstrating increased cancer mortality in high poverty areas. Survival disparities in CML between low and high poverty areas may be mediated by limited access to tyrosine kinase inhibitors: an effective and well tolerated targeted treatment for CML.

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County Poverty Rate	Total		0-9.99%		10-19.99%		20-100%		Chi-Square
	n=5515		n=942		n=3634		n=939		
Demographic Characteristic	N	%	n	%	N	%	N	%	
Sex									0.6006
Male	3142	57.0%	549	58.3%	2067	56.9%	526	56.0%	
Female	2373	43.0%	393	41.7%	1567	43.1%	413	44.0%	
Race									<.0001
White	3584	65.0%	661	70.2%	2319	63.8%	604	64.3%	
Black	648	11.7%	67	7.1%	419	11.5%	162	17.3%	
Hispanic	837	15.2%	77	8.2%	628	17.3%	132	14.1%	
Other	446	8.1%	137	14.5%	268	7.4%	41	4.4%	
Rural-Metropolitan Continuum									<.0001
Metropolitan	4862	88.2%	884	93.8%	3381	93.0%	597	63.6%	
Rural/Urban	653	11.8%	58	6.2%	253	7.0%	342	36.4%	
Age									0.0263
18-49	1996	36.2%	315	33.4%	1343	37.0%	338	36.0%	
50-64	1694	30.7%	306	32.5%	1071	29.5%	317	33.8%	
65+	1825	33.1%	321	34.1%	1220	33.6%	284	30.2%	
Marital Status									0.0012
Unmarried	2154	39.1%	316	33.5%	1440	39.6%	398	42.4%	
Married	2801	50.8%	525	55.7%	1834	50.5%	442	47.1%	
Unknown	560	10.2%	101	10.7%	360	9.9%	99	10.5%	
Insurance Status									<.0001
Uninsured/Any Medicaid	1062	19.3%	121	12.8%	696	19.2%	245	26.1%	
Insured	4014	72.8%	722	76.6%	2670	73.5%	622	66.2%	
Unknown	439	8.0%	99	10.5%	268	7.4%	72	7.7%	
Chemotherapy Status									0.011
No/Unknown	1124	20.4%	188	20.0%	711	19.6%	225	24.0%	
Yes	4391	79.6%	754	80.0%	2923	80.4%	714	76.0%	
Year of Diagnosis									0.0003
2010	852	15.4%	138	14.6%	569	15.7%	145	15.4%	
2011	882	16.0%	120	12.7%	619	17.0%	143	15.2%	
2012	898	16.3%	130	13.8%	631	17.4%	137	14.6%	
2013	954	17.3%	184	19.5%	598	16.5%	172	18.3%	
2014	980	17.8%	200	21.2%	617	17.0%	163	17.4%	
2015	949	17.2%	170	18.0%	600	16.5%	179	19.1%	
SEER Specific Cause of Death (Capped at 60mo f/u)									0.0018
Alive	4465	81.0%	796	84.5%	2942	81.0%	727	77.4%	
Dead (Attributable CML)	568	10.3%	83	8.8%	364	10.0%	121	12.9%	
Dead (Attributable Other)	482	8.7%	63	6.7%	328	9.0%	91	9.7%	

Table 1. Demographic characteristics by poverty status for cases of primary chronic myelogenous leukemia, Adults aged ≥18 years, SEER Registry, 2010-2015

Poverty Rate (%)	Hazard Ratio	95% CI Lower	Upper
0-9.99	1.00		
10-19.99	1.16	0.91	1.48
20+	1.52	1.13	2.05
10-19.99	1.00		
20+	1.31	1.05	1.64
Sex			
Male	1.00		
Female	0.74	0.62	0.88
Race			
White	1.00		
Black	0.96	0.73	1.27
Hispanic	0.77	0.58	1.04
Other	1.00	0.72	1.39
Rural-Metropolitan Continuum			
Metropolitan	1.00		
Rural/Urban	1.13	0.88	1.45
Age			
18-49	1.00		
50-64	1.66	1.22	2.24
65+	7.14	5.53	9.21
Marital Status			
Unmarried	1.00		
Married	0.57	0.48	0.68
Unknown	0.35	0.24	0.50
Insurance Status			
Uninsured/Any Medicaid	1.00		
Insured	0.75	0.60	0.94
Unknown	0.89	0.61	1.28
Chemotherapy Status			
No/Unknown	1.00		
Yes	0.52	0.43	0.62

Table 2. Adjusted* hazard ratios for Cox multivariable 5-year survival analysis for cases of primary chronic myelogenous leukemia, adults aged >=18, SEER Registry, 2010-2016. Adjusted for all listed variables and year of diagnosis.

Poverty Prevalence (%)	Hazard Ratio	95% CI Lower	Upper
0-9.99	1.00		
10-19.99	1.10	0.85	1.43
20+	1.51	1.09	2.07
10-19.99	1.00		
20+	1.37	1.08	1.74

Table 3. Sensitivity Analysis. Adjusted* hazard ratios for Cox multivariable 5-year survival analysis for cases of primary chronic myelogenous leukemia, adults aged >=18, SEER Registry, 2010-2016. Adjusted for all listed variables and year of diagnosis, with individuals removed with unknown insurance and marriage values.

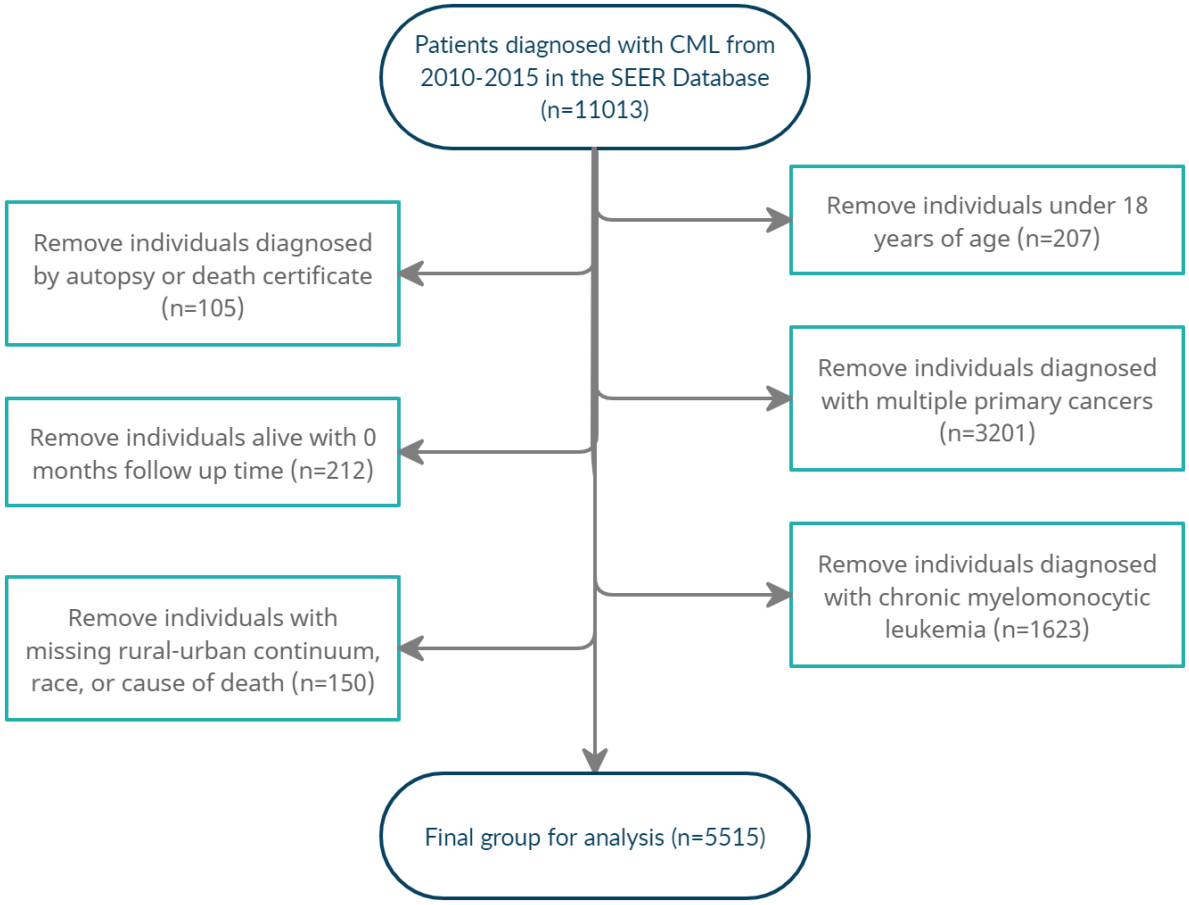

Figure 1. Inclusion and Exclusion Criteria. Inclusion criteria included patients diagnosed with CML from 2010-2016 in the SEER 18 Region, Nov 2018 submission database. Removal of individuals under 18, those diagnosed by autopsy or death certificate, those with multiple primary cancers, individuals alive with 0 months follow up time, CMML histology, and persons missing values for rural-urban continuum, race or cause of death left a final study population of 5515 individuals.

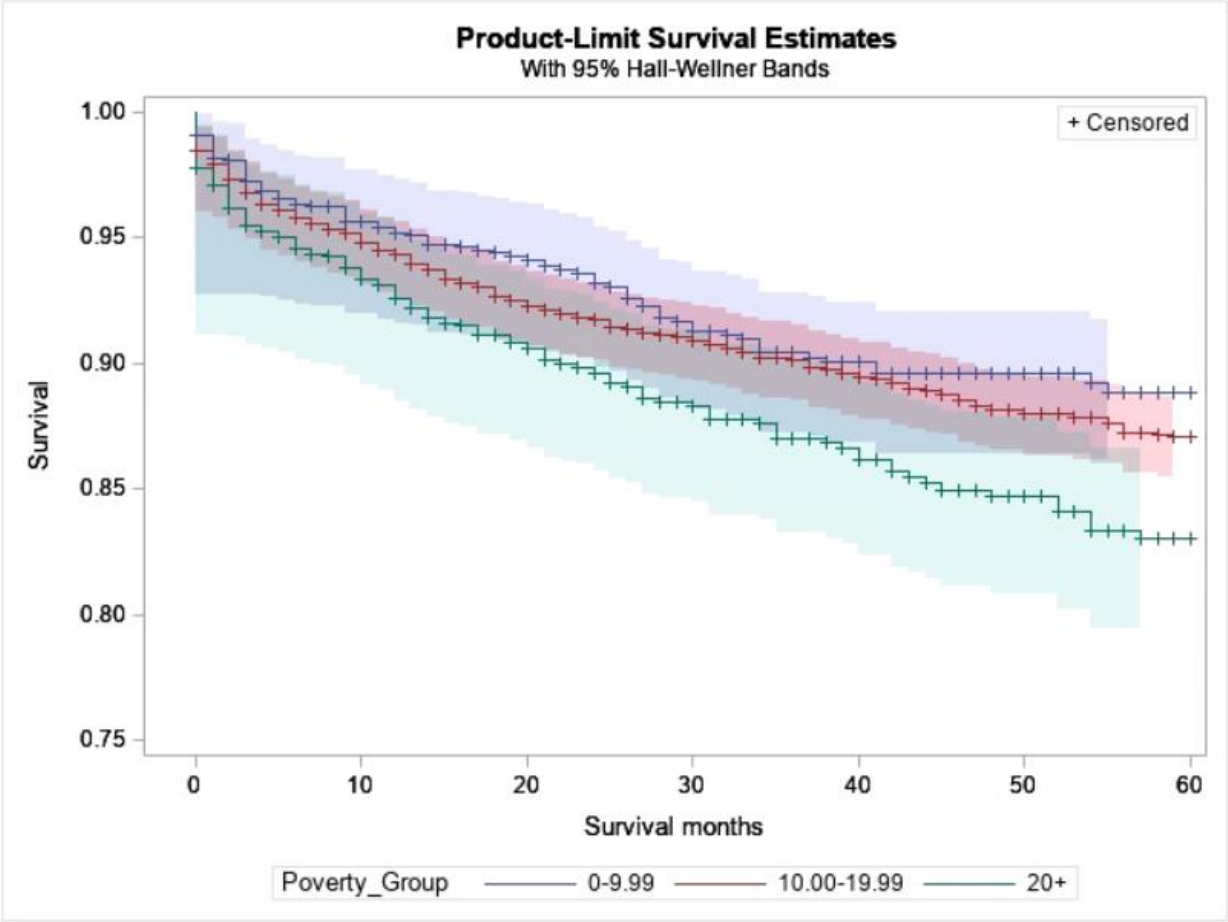

Figure 2. Unadjusted Kaplan-Meier Curve for Poverty Groups with 95% Hall-Wellner Bands. (Log-Rank x=10.188; p = 0.0061). Cases in counties with low poverty (0-9.99% poverty rate) are represented in blue, cases in counties with moderate poverty (10-19.99% poverty rate) are represented in red, and cases in counties with high poverty (20%+ poverty rate) are represented in green.

Chapter III: Future Directions

Overall, further research is needed to explore the underlying reasons for survival disparities between CML cases living in high and low poverty areas. Following the hypothesis that TKI utilization is lower for individuals in poverty, a future study would ideally a.) more accurately reflect individual TKI use via a more reliable measure such as direct chart review and b.) more accurately reflect individual's personal income and if they are personally living under the poverty line. It may also be helpful to consider patients' adherence and access to TKIs after initial prescription. Qualitative analysis could elaborate on patients' reasons for not starting or not adhering to TKI therapy, be those medical, personal, or financial reasons.