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RESEARCH ARTICLE

# Factors Affecting Receipt of Expensive Cancer Treatments and Mortality: Evidence from Stem Cell Transplantation for Leukemia and Lymphoma

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**Objective.** To identify factors that affect whether patients diagnosed with either leukemia or lymphoma receive a stem cell transplant and secondly if receipt of stem cell transplantation is linked to improved survival.

**Data.** California inpatient discharge records (2002–2003) for patients with either leukemia or lymphoma linked with vital statistics death records (2002–2005).

**Study Design.** Bivariate Probit treatment effects model that accounts for both the type of treatment received and survival while controlling for nonrandom selection due to unobservable factors.

**Principal Findings.** Having private insurance coverage and residence in a well-educated county increased the chances a patient with either disease received HSCT. Increasing age and travel distance to the nearest transplant hospital had the opposite effect. Receipt of HSCT had a significant impact on mortality. We found the probability of death was 4.3 percentage points higher for leukemia patients who did NOT have HSCT. Receipt of HSCT reduced the chances of dying by almost 50 percent. The likelihood of death among lymphoma patients who underwent HSCT was almost 5 percentage points lower, a 70 percent reduction in the probability of death.

**Conclusions.** The findings raise concern about access to expensive, but highly effective cancer treatments for patients with certain hematologic malignancies.

**Key Words.** Leukemia, lymphoma, stem cell transplantation, survival, bivariate probit, insurance, access

Although hematopoietic stem cell transplantation (HSCT) can be an effective treatment for hematologic malignancies, most notably specific types of leukemia and lymphoma, relatively few patients undergo this procedure. This treatment is technologically complex, requiring administration of high-dose chemotherapy, sometimes in conjunction with radiation therapy, to eradicate

malignant cells. Healthy bone marrow precursor cells are destroyed in the process and replaced with the patient's own cells (autologous transplantation). Alternatively, the stem cells for allogeneic transplants come from the bone marrow, peripheral blood stem cells, or umbilical cord blood of a human leukocyte antigen (HLA) matched donor. About 48,000 new cases of leukemia, 70,000 new cases of non-Hodgkin lymphoma, and 9,300 new cases of Hodgkin lymphoma are diagnosed annually (www.lls.org 2012).

HSCT is expensive. Reported initial hospitalization cost for an autologous transplant ranged from $36,000 to $88,000 (2012 dollars). Allogeneic transplants were even more expensive as the first year costs in 2012 dollars were estimated to range from $100,000 to $200,000 (Khara, Zeliadt, and Lee 2012). According to a 2009 AHRQ report, HSCT was found to experience the most rapid increase in total hospital costs among all inpatient procedures—about 85 percent between 2004 and 2007. Expenditures on HSCT in 2007 totaled $1.3 billion (Stranges, Russo, and Friedman 2009).

This study investigated demographic and socioeconomic factors that may account for the low use of HSCT to treat these hematologic malignancies. We then examined whether receipt of HSCT was associated with improved survival. Prior research did not evaluate the impact of HSCT on survival in comparison to a control group who did not undergo this procedure. Importantly, our methodology recognizes that receipt of HSCT is nonrandom, and failure to account for this endogeneity may bias the effect of receipt of HSCT on survival.

## BACKGROUND

Leukemia is a type of cancer that begins in the bone marrow but quickly moves into the blood prior to spreading to other parts of the body. The disease occurs when blood cells produced in the bone marrow proliferate. There are four main types of leukemia: acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). For acute leukemia, immature cells called blasts crowd out normal cells, whereas with chronic leukemia the cells appear to be mature but are ineffective in fighting infection. The type of cells that are affected

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by leukemia may be myeloid or lymphoid. Allogeneic HSCT is the only known curative treatment for chronic myeloid leukemia (D'Antonio 2005). The best treatment for chronic lymphocytic leukemia is high-dose ablative therapy in conjunction with HSCT (Rizouli and Gribben 2003). Two international clinical trials and a population-based study using Swedish data show better outcomes among patients with acute myeloid leukemia who received either an autologous or allogeneic HSCT in first remission (Juliusson, Karlsson, and Lazarevic 2013; Oran and Weisdorf 2011). For patients with acute lymphocytic leukemia who relapsed following allogeneic HSCT, a second HSCT provides the best chance for long-term survival (Poon et al. 2013).

Lymphoma is a cancer that develops in cells of the lymphatic system, and it can be categorized as either Hodgkin or non-Hodgkin depending on the type of cells present. Most people with non-Hodgkin lymphoma have B-cell type, whereas the other common types include T cell or NK-cell. Hodgkin lymphoma is distinguished by the presence of Reed-Sternberg cells. Autologous HSCT works best for patients with Hodgkin lymphoma who have relapsed after chemotherapy and experience induced complete response duration of less than 1 year (Reece 2002). Retrospective analysis suggests that autologous HSCT resulted in improved response rates and more durable remissions when compared to chemotherapy for patients with Hodgkin lymphoma (Meehan et al. 1995). Thus, autologous transplantation is frequently recommended for patients with Hodgkin disease at time of relapse (Horning et al. 1997). Moreover, patients with intermediate or high-grade non-Hodgkin lymphoma demonstrated improved disease-free and overall survival if autologous HSCT was performed after initial relapse (Meehan et al. 1995).

Only a handful of studies have attempted to investigate factors that may impede access to HSCT using population-based data. For example, whites with certain hematologic malignancies were more likely to undergo HSCT than African Americans and other minorities (Mitchell et al. 1997; Joshua et al. 2010), and men were more likely to receive HSCT than women (Hwang et al. 2004; Joshua et al. 2010). Insurance coverage also matters as one study found that Medicaid, self pay, and HMO enrollees with either leukemia or lymphoma were significantly less likely than those with private coverage to undergo a bone marrow transplant (Mitchell et al. 1997). Mehta et al. (2003) examined the effect of gender among leukemia patients who underwent HSCT and found no significant bias in use for males compared to females. These studies, however, did not evaluate whether receipt of HSCT was associated with improved survival. To our knowledge, only one population-based study investigated survival after receipt of an allogeneic HSCT among persons

with either acute or chronic leukemia. Serna et al. (2003) found that Hispanics had lower 1- and 3-year adjusted survival rates than whites, but such disparities were not evident for whites versus blacks. The major limitation of their survival analysis was the absence of a control group. Thus, research evaluating mortality among patients with hematologic malignancies who underwent HSCT compared to those who did not receive the treatment is nonexistent. Our study addresses this significant gap in knowledge.

## DESCRIPTION OF DATA

The study employs data obtained from the California Office of Statewide Planning and Development (OSHPD). Nonpublic use patient hospital discharge records were obtained for the years 2002–2003. The inpatient discharge data include all hospital stays that occurred during 2002–2003 for cases that met the criteria as having either leukemia or lymphoma. Each record includes patient's age, gender, race/ethnicity, type of insurance coverage, principal and secondary diagnoses, along with principal and secondary procedures/treatments. Hospital characteristics including facility name, address, type of control, count of licensed beds, and teaching status were obtained from OSHPD. We linked the hospital characteristics to the discharge data using the state hospital identification numbers.

We consulted with a hematologist/medical oncologist, who specializes in administering HSCT, to identify the ICD-9-CM codes that distinguish either leukemia or lymphoma; the diagnosis codes are reported in Table 1. OSHPD staff used these ICD-9-CM codes to extract the sample and then linked the patient discharge data to vital statistics death records for the years 2002–2005 with an exact matching algorithm that used Social Security numbers, gender, and date of birth. Less than 0.5 percent of the discharge records could not be matched with the vital statistics death records. Each patient discharge record was then assigned an encrypted identification number. As a patient with either leukemia or lymphoma may experience multiple hospital stays, it was necessary to convert the claim-level file into a patient-level file. This was accomplished by linking claims using the encrypted patient identification number. To ensure patient confidentiality, OSHPD would not release the date of each discharge but only the quarter and year in which each hospitalization occurred. Likewise, OSHPD would not relinquish the exact date of death for patients who expired. Thus, our mortality indicator simply identifies whether the patient died by the end of 2005.

Table 1: Description of Variables

Dependent variables
- HSCT = 1 if the patient received hematopoietic stem cell transplantation (ICD-9-CM procedure codes 41.01, 41.02, 41.03, 41.04, 41.05, 41.07, 41.08, 41.09); = 0 otherwise
- DEATH = 1 if the patient died during the time period; = 0 otherwise

Insurance coverage
- MEDI-CAL = 1 if the patient's insurance coverage is Medi-Cal; = 0 if not
- MEDICARE = 1 if the patient's insurance coverage is Medicare; = 0 if not
- PRIVATE* = 1 if the patient's insurance coverage is private commercial; = 0 if not
- SELF PAY = 1 if the patient has no insurance coverage; = 0 if not
- OTHERINS = 1 if the patient has other insurance coverage such as workers compensation; = 0 if not
- SWITCH = 1 if the patient switched insurance coverage to more generous insurance; = 0 if not

Demographics
- AGE = patient's age measured in years
- FEMALE = 1 if patient is female; = 0 if patient is male
- WHITE* = 1 if patient's race is white; = 0 if not
- BLACK = 1 if patient's race is African American; = 0 if not
- ASIAN = 1 if patient's race is Asian; = 0 if not
- RACEOTHER = 1 if patient's race is other than white, black or Asian; = 0 if not
- RACEMISS = 1 if patient's race is missing; = 0 if not

Disease type—leukemia
- Acute Lymphocytic Leukemia*= 1 if patient's diagnosis is acute lymphocytic leukemia (ICD-9-CM diagnosis codes 204.0, 204.01) = 0 if not
- Acute Myeloid Leukemia = 1 if patient's diagnosis is acute myeloid leukemia (ICD-9-CM diagnosis codes 205.0, 205.01, 205.8, 205.81, 205.9, 205.91); = 0 if not
- Chronic Lymphocytic Leukemia = 1 if patient's diagnosis is chronic lymphocytic leukemia (ICD-9-CM diagnosis codes 204.1, 204.11, 204.8. 204.81. 204.9, 204.91); = 0 if not
- Chronic Myeloid Leukemia= 1 if patient's diagnosis is chronic myeloid leukemia (ICD-9-CM diagnosis codes 205.1, 205.11); = 0 if not
- UNSPECIFIED = 1 if patient's diagnosis is other acute or chronic leukemia (ICD-9-CM diagnosis codes 202.4, 205.20, 205.31, 206.0, 206.01, 206.1, 206.11, 206.8, 206.81, 206.9, 206.91, 207.0, 207.01, 207.1, 207.11, 207.20, 207.21, 207.80, 208.0, 208.01, 208.1, 208.11, 208.80, 208.81, 208.9, 208.91, V10.60, V10.61, V10.62, V10.63, V10.69); = 0 if not

Disease type—lymphoma
- NON-HODGKIN = = 1 if the patient's diagnosis is non-Hodgkin lymphoma (ICD-9-CM diagnosis 200.00–200.08, 200.10–200.18, 200.20–200.28, 200.80–200.88, 202.00–202.08, 202.80–202.88, 202.90–202.98)

  = 0 if Hodgkin lymphoma (ICD-9-CM diagnosis codes 200.00–200.08)

Comorbid conditions†
- ANEMIA = 1 if patient ever had anemia or other diseases of the blood (excluding leukemia and lymphoma; = 0 if not
- CANCER = 1 if patient ever had cancer other than leukemia or lymphoma; = 0 if not
- CIRCULATE = 1 if patient ever had a disease of the circulatory system; = 0 if not
- DIGESTIVE = 1 if patient ever had a disease of the digestive system; = 0 if not
- URINARY = 1 if patient ever had a disease of the urinary or genital system; = 0 if not
- INFECTIOUS = 1 if patient ever had an infectious or parasitic disease; = 0 if not

*continued*

Table 1. *Continued*

| | |
|---|---|
| | INJURY = 1 if patient ever had an injury or poisoning; = 0 if not |
| | MENTAL = 1 if patient ever had a mental disorder; = 0 if not |
| | MUSCLE = 1 if patient ever had a disease of the musculoskeletal system; = 0 if not |
| | NERVOUS = 1 if patient ever had a disease nervous system; = 0 if not |
| | RESPIRATORY =1 if patient ever had a disease of the respiratory system; = 0 if not |
| | DERM = 1 if patient ever had a skin disorder; = 0 if not |
| Hospital characteristics | |
| | HOSPLARGE = 1 if patient was treated at a hospital with more than 475 beds; = 0 if not |
| | HOSPMEDIUM = 1 if patient was treated at a hospital with 200 to 474 beds; = 0 if not |
| | HOSPSMALL* = 1 if patient was treated at a hospital with less than 200 beds; = 0 if not |
| | TEACH* = 1 if patient was treated at a teaching hospital; = 0 if not |
| | GOVERNMENT = 1 if patient was treated at a government (state/local) hospital; = 0 if not |
| | FOR-PROFIT = 1 if patient was treated at a for-profit hospital; = 0 if not |
| | NONPROFIT* = 1 if patient was treated at a nonprofit hospital; = 0 if not |
| Instruments | |
| | DISTLT10* = 1 if distance from the patient's zip code of residence to the nearest hospital that performs HSCT is less than 10 miles; = 0 if not |
| | DIST10-35 = 1 if distance from the patient's zip code of residence is at least 10 miles but less than 35 miles; = 0 if not |
| | DIST35-70 = 1 if distance from the patient's zip code of residence is at least 35 miles but less than 70 miles; = 0 if not |
| | DIST70 = 1 if distance from the patient's zip code of residence is greater than or equal to 70 miles; = 0 if not |
| | MHINCOME = median household income (2002) in the county where the patient resides; expressed in 10,000s of dollars |
| | %BACHDEG = measures the percentage of the population (aged 25 and over) in the county where the patient resides who hold a bachelor's degree (2002) |
| | %UNEMPLOY = measures the unemployment rate (2002) in the county where the patient resides |

*Indicates the category is the reference group in the regression analysis.
†Reference category identifies patients who have no comorbid conditions.

The exact matching yielded 6,788 leukemia patients and 9,898 lymphoma patients. We restricted each sample to patients who resided in California and had both valid age and zip code of residence information. These restrictions resulted in a leukemia sample of 5,722 (84.3 percent) and a lymphoma sample of 9,137 (92.3 percent).

## METHODS

### *Estimation Strategy*

The key difference between experimental and observational data is random assignment. With observational data, the treatment received is not allocated

randomly so the characteristics of those who receive the treatment or intervention of interest are likely to differ from those who do not. This means that the explanatory variable indicating type of treatment received is correlated with the error term in the survival equation. Thus, unobserved factors that influence who receives the treatment and the outcome of interest (survival) may bias the coefficient on treatment received variable. Instrumental variables estimation has been used extensively to reduce or remove the potential bias resulting from unobserved differences between nonrandomized groups.

HSCT is one treatment option for patients diagnosed with either leukemia or lymphoma. We anticipate that the characteristics of patients with either malignancy who received this treatment will differ from those who did not undergo the procedure. If some of these differences are unobservable and affect survival, our analysis may be subject to sample selection bias. We estimated a treatment effects model that accounts for the binary nature of both the type of treatment received and survival, while allowing for the possibility that unobserved selection may influence the estimated impact of treatment received on the probability of dying (Heckman and Hotz 1989; Meyer 1995).

The probability of receiving stem cell transplantation versus an alternative treatment is specified as:

$$\Pr(\text{HSCT} = 1) = \Pr(Z\delta + \upsilon > 0),$$

and the probability of death is specified as:

$$\Pr(\text{DEATH} = 1) = \Pr(X\beta + \alpha\text{HSCT} + \varepsilon > 0),$$

where Z and X represent observable characteristics that are independent of ($\upsilon$, $\varepsilon$) and Z contains at least one variable that is not in X and it must be a statistically significant predictor of receipt of HSCT. $\delta$, $\beta$, and $\alpha$ are parameters to be estimated; and $\upsilon$ and $\varepsilon$ are random error terms. The assumption that $\upsilon$ and $\varepsilon$ are distributed bivariate normal with $\text{E}(\upsilon) = 0$, $\text{E}(\varepsilon) = 0$, $\text{Var}(\upsilon) = 1$, $\text{Var}(\varepsilon) = 1$, and $\text{Cov}(\upsilon, \varepsilon) = \rho$ (rho) allows for the possibility that the residuals of the treatment received equation may be correlated with the residuals from the equation predicting whether a leukemia (lymphoma) patient died. Thus, the bivariate probit IV approach, contrary to propensity score matching methods, directly controls for selection due to unobservables. In this example, controlling for unobservables characteristics (whether a suitable matched donor is available, stage and grade of disease) is important. If rho is negative and significant, this indicates that patients with leukemia (lymphoma) who were more likely to undergo a stem cell transplant were also less likely to die. This could happen, for example, if individuals who received a stem cell transplant were

matched with suitable donors. After controlling for potential nonrandom selection, the coefficient on the HSCT variable measures the treatment effect, that is, the difference in the probability of death that exists between HSCT recipients and those who underwent alternative treatments.

Controlling for nonrandom selection due to unobservable factors is contingent on identifying a set of instruments that predict receipt of stem cell transplantation but at the same time are unrelated to whether the patient died. The instruments are included in the equation predicting receipt of HSCT but are excluded from the mortality equation. We performed two tests to evaluate the relevance and validity of the instruments. Relevance implies the instruments are strong predictors of treatment choice. The first involves estimating the treatment choice equation with and without the set of instruments and then testing whether the set of instruments are jointly significant (Bound, Jaeger, and Baker 1995; Staiger and Stock 1997). Validity requires that the instruments be orthogonal to or uncorrelated with the residuals from the second-stage equation predicting whether the patient died. To test whether this orthogonality condition holds, we regressed the variable indicating death on the dummy variable identifying receipt of HSCT, the other exogenous variables that were hypothesized to influence mortality, and the set of instruments. We then conducted a likelihood ratio test to determine if the instruments are jointly significant (Davidson and MacKinnon 1993). If the instruments jointly have no effect, this means the instruments provided no additional information in predicting death other than what was already explained by receipt of HSCT versus alternative treatment options.

### *Specification of Empirical Model*

Table 1 defines the dependent and independent variables employed in the estimation of the two equation models predicting receipt of HSCT and the probability of death. We estimated separate models for each disease type. The independent variables in the treatment received equation included type of insurance coverage; demographics; disease type; the presence or absence of common comorbid conditions; hospital characteristics; travel distance to the nearest high-volume hospital that performs HSCT; and proxies for educational attainment, household income, and economic conditions. The mortality equation included the same set of patient and hospital characteristics but excluded travel distance and the proxies for educational attainment, household income, and economic conditions. The latter were hypothesized to influence type of treatment received but not survival.

Insurance coverage serves as a proxy for the patient's ability to pay. We anticipated that patients with more generous insurance coverage would be more prone to receive HSCT than patients classified as either self pay or those enrolled in Medi-Cal. Information obtained from discussions with state officials offers some insights into how Medi-Cal and other state Medicaid programs restrict access to HSCT. Nearly all Medi-Cal beneficiaries are enrolled in managed care plans that do not cover HSCT. Assuming a Medi-Cal patient meets the other qualifications for HSCT (failing to be cancer free after multiple round of chemotherapy), he/she must switch to Medi-Cal fee-for-service in order for Medi-Cal to cover the procedure. Essentially, Medi-Cal has established many barriers that may make it difficult for a Medi-Cal patient to undergo HSCT. Furthermore, we hypothesize that more generous insurance coverage is associated with improved survival. Patients with either disease may have experienced multiple hospitalizations. To account for this possibility, insurance coverage was coded as either insurance type at the time of transplant for HSCT recipients or as the most frequent type of coverage for non-HSCT patients. For example, if a patient had four hospital stays and was enrolled in Medi-Cal for three of four hospitalizations, the patient was assigned to Medi-Cal. Some patients may have switched to more generous insurance during the course of treatment, so the regression model included a variable to identify switchers. Switching to more generous insurance coverage is hypothesized to be associated with an increased likelihood of receipt of HSCT, but a reduction in the probability of dying.

Age was expected to have a negative impact on receipt of HSCT given the toxicity of the procedure linked to increasing age. Racial/ethnic minorities and females are less likely than either whites or males to undergo HSCT (Hwang et al. 2004). Although age is associated with an increased risk of dying, we have no priors regarding the effects of race/ethnicity. Type of leukemia or lymphoma is an important determinant of whether HSCT is deemed as a viable treatment option. For example, HSCT remains an investigational treatment for adults with acute lymphocytic leukemia because large-scale trials to confirm its effectiveness have not been conducted. We anticipate that persons with specific comorbid conditions (severe pulmonary disease, heart valve disease, prior solid tumor malignancy, and moderate or severe hepatic) will be less prone to undergo HSCT. To earmark the presence or absence of common comorbid conditions, we employed the algorithm developed by Elixhauser et al. (1998). Finally, hospital characteristics, including size, teaching, and ownership status, are likely to influence both receipt of HSCT and associated death. However, we have no priors regarding the direction of these effects.

We constructed a set of instruments (identifying variables) that predict receipt of HSCT but should not impact mortality. Previous research found that travel distance is a valid instrument that predicted receipt of cardiac catheterization for heart attack patients, but it had no impact on subsequent mortality (McClellan, McNeill, and Newhouse 1994). We identified only 18 hospitals in California that performed at least 10 stem cell transplants on leukemia and lymphoma patients during the time period. Clearly, some of these hospitals are "centers of excellence" for HSCT and many patients may prefer to undergo HSCT at hospitals with an experienced transplant team. We calculated travel distance from each patient's zip code of residence to each of these 18 hospitals. We then assigned the shortest travel distance to each patient to create the variable "travel distance to the nearest hospital that performs HSCT." We hypothesize that patients who live farther from a transplant hospital will be less likely to undergo HSCT. However, there is no reason why travel distance to the nearest transplant hospital should be directly related to mortality. We converted this continuous distance measure into a series of dummy variables with the reference category identifying patients who live within 10 miles of the nearest transplant hospital.

Other instruments control for educational attainment, median household income, and local economic conditions. More highly educated and higher income patients are likely to be more aware of the best available treatments for leukemia and lymphoma and consequently should be more predisposed to undergo HSCT. Unfortunately, hospital discharge records have no information on each patient's educational attainment and income. To mitigate potential bias from omitting such details, we included two proxy variables measured for the patient's county of residence: percentage of the population with a bachelor's degree and median household income. We expect both proxy variables will increase the chances a patient receives HSCT, but there is no reason why such county indicators should impact individual survival. The county unemployment rate is included in the HSCT equation to capture economic conditions, and we hypothesize that it will not affect individual mortality.

## RESULTS

Table 2 reports descriptive statistics for the populations of leukemia and lymphoma patients treated in California hospitals during 2002–2003. About 12 percent of leukemia patients received HSCT, while nearly 9 percent with this

Table 2: Summary Statistics for the Leukemia and Lymphoma Samples

| *Variable Name* | *Leukemia Sample, % (n = 5,721)* | *Lymphoma Sample, %(N = 9,137)* |
|---|---|---|
| HSCT (overall sample) | 12.1 | 7.3 |
| DEATH (overall sample) | 8.8 | 7.1 |
| DEATH (HSCT sample) | 2.5 (*N* = 691) | 1.2 (*N* = 664) |
| DEATH (non-HSCT sample) | 9.7 (*N* = 5,030) | 7.6 (*N* = 8,473) |
| Insurance coverage | | |
| MEDI-CAL | 27.1 | 17.1 |
| MEDICARE | 7.6 | 10.3 |
| PRIVATE | 58.3 | 65.7 |
| SELF PAY | 1.7 | 2.2 |
| OTHERINS | 5.3 | 4.7 |
| SWITCH | 6.4 | 4.4 |
| Demographics | | |
| AGE | 36.7 (20.9) | 47.5 (13.6) |
| FEMALE | 44.0 | 45.2 |
| WHITE | 71.7 | 79.3 |
| BLACK | 6.8 | 6.9 |
| ASIAN | 7.8 | 6.0 |
| RACEOTHER | 13.1 | 7.2 |
| RACEMISS | 0.6 | 0.6 |
| Disease type—leukemia | | |
| Acute Lymphocytic Leukemia | 35.5 | — |
| Acute Myeloid Leukemia | 31.1 | — |
| Chronic Lymphocytic Leukemia | 13.7 | — |
| Chronic Myeloid Leukemia | 10.0 | — |
| UNSPECIFIED Leukemia | 8.1 | — |
| Disease type—lymphoma | | |
| Non-Hodgkin Lymphoma | — | 70.3 |
| Comorbid conditions | | |
| ANEMIA | 71.8 | 48.9 |
| CANCER | 9.3 | 14.3 |
| CIRCULATORY | 48.4 | 50.0 |
| DIGESTIVE | 49.9 | 42.3 |
| URINARY | 33.1 | 27.2 |
| INFECTIOUS | 54.7 | 31.6 |
| INJURY | 35.8 | 22.8 |
| MENTAL | 28.2 | 29.3 |
| MUSCLE | 19.7 | 18.5 |
| NERVOUS | 24.9 | 16.9 |
| RESPIRATORY | 44.7 | 34.4 |
| OTHER CONDITION | 29.8 | 16.0 |
| Hospital characteristics | | |
| HOSPLARGE | 24.3 | 21.5 |
| HOSPMEDIUM | 53.0 | 54.1 |

*continued*

Table 2. *Continued*

| *Variable Name* | *Leukemia Sample, % (n = 5,721)* | *Lymphoma Sample, %(N = 9,137)* |
|---|---|---|
| HOSPSMALL | 22.7 | 24.4 |
| TEACH | 26.0 | 23.0 |
| GOVERNMENT | 17.6 | 19.4 |
| FOR-PROFIT | 6.6 | 9.7 |
| NONPROFIT | 75.8 | 69.7 |
| Instruments | | |
| DISTLT10 | 35.8 | 35.9 |
| DIST10-35 | 40.3 | 42.1 |
| DIST35-70 | 10.6 | 10.9 |
| DIST70 | 13.2 | 11.1 |
| MHINCOME | $48,554 (10,678) | $49,414 (11,072) |
| %BACHDEG | 17.5 (4.9) | 17.7 (4.8) |
| %UNEMPLOY | 7.1 (2.2) | 6.8 (2.2) |

disease died by 2005. Receipt of HSCT appears to be linked to improved survival. Only 2.5 percent of 691 leukemia patients who underwent HSCT died compared to 9.7 percent of the 5,030 patients those who did not have HSCT. Slightly more than 7 percent of the overall lymphoma sample received HSCT, whereas about the same percentage died. Among the 8,473 lymphoma patients who did not receive HSCT, the death rate was 7.6 percent compared to 1.2 percent among the 664 who underwent the treatment.

More than half of leukemia patients had private insurance coverage (58.3 percent); about 27 percent were insured through Medi-Cal, but only 1.7 percent was self pay (uninsured). More than 6 percent of leukemia patients switched to better insurance coverage during the course of treatment. Among the lymphoma sample, almost two thirds had private insurance coverage and 17 percent were enrolled in Medi-Cal. Switchers accounted for a smaller share (4.7 percent) of lymphoma patients, although the fraction that was self pay was slightly higher (2.2 percent). Persons with leukemia were younger than lymphoma patients (36.7 vs. 47.5). Females accounted for less than half of each sample. The majority of both samples were white.

Almost two thirds of leukemia patients had acute lymphocytic leukemia or acute myeloid leukemia, about 36 and 31 percent, respectively. Close to 14 percent of the sample had chronic lymphocytic leukemia and almost 10 percent had chronic myeloid leukemia. Nearly 70 percent of the lymphoma sample had non-Hodgkin disease. For patients with leukemia, the most common comorbid conditions included anemia and blood disorders excluding leukemia (about 72 percent), infectious disease (nearly 55 percent), and diges-

tive problems (50 percent). Circulatory conditions (50 percent) and anemia and blood disorders (48.9 percent), followed by digestive issues at 42 percent, were most common among lymphoma patients.

About 36 percent of both samples live within 10 miles of a hospital which performs a high volume of HSCT procedures. Another 40–42 percent of both samples would need to travel between 10 and 35 miles to obtain care at a high-volume hospital. Close to one-quarter of both samples must travel 35 miles or more to receive care from a high-volume transplant hospital. Educational attainment, median household income, and county unemployment rates were similar for both samples.

Table 3 reports the marginal effects from the bivariate probit predicting receipt of HSCT and mortality for patients with leukemia. Marginal effects measure the absolute change in the probability of the event. Alternatively, one can multiply the actual change by 100 and interpret it as a percentage point (absolute) change in the probability of interest. Type of insurance had a significant impact on access to this expensive technology. Compared to leukemia patients with private insurance, the probability of receiving HSCT was about 1 percentage point lower for Medi-Cal and Medicare patients and almost 2 percentage points lower for self pay (uninsured) patients ($p < .01$). Although age and race/ethnicity had significant negative effects on HSCT receipt, gender differences were negligible. Leukemia type was a significant predictor of HSCT. The likelihood of HSCT receipt was 3.3 percentage points higher for patients with acute myeloid leukemia compared to those with acute lymphocytic leukemia ($p < .01$). For patients with chronic myeloid leukemia the probability of HSCT receipt was 3.4 percentage points higher ($p < .01$).

The set of instruments included in the HSCT equation were all highly significant and with one exception had the correct signs. Increases in travel distance to the nearest transplant hospital had the expected negative effect on receipt of HSCT. The proxy variables for educational attainment and household income were positive and statistically significant ($p < .01$). The county unemployment rate had a positive sign, which was contrary to expectations. One possible explanation is that the unemployment rate is endogenous. Rho, the correlation across the residuals between the treatment received and survival equations, was not statistically significant. This implies that nonrandom selection due to unobservable factors was not a source of bias.

Column 2 of Table 3 reports the marginal effects predicting the probability of death. The chances of dying were 4.3 percentage points higher for leukemia patients who did not undergo HSCT compared to those who did ($p < .01$). As 8.8 percent of leukemia patients died, this means the probability

Table 3: Marginal Impacts from Bivariate Probit Model Predicting Receipt of Hematopoietic Stem Cell Transplantation (HSCT) and Mortality for Patients with Leukemia ($N = 5{,}721$)

| *Variable Name* | *Receipt of HSCT* | *DEATH* |
|---|---|---|
| HSCT | — | −0.043*** |
| Insurance coverage (reference is PRIVATE) | | |
| MEDI-CAL | −0.011*** | 0.034*** |
| MEDICARE | −0.012*** | 0.027*** |
| SELF PAY | −0.019*** | 0.113*** |
| OTHERINS | 0.009*** | 0.025 |
| SWITCH | 0.004 | −0.056*** |
| Demographics (reference is WHITE and MALE) | | |
| AGE | −0.0005*** | 0.0018*** |
| FEMALE | −0.001 | −0.017*** |
| BLACK | −0.009*** | −0.007 |
| ASIAN | −0.003 | 0.001 |
| RACEOTHER | −0.003 | −0.008 |
| RACEMISS | −0.016*** | −0.024 |
| Disease type—leukemia (reference is Acute Lymphocytic Leukemia–ALL) | | |
| Acute Myeloid Leukemia | 0.033*** | 0.043*** |
| Chronic Lymphocytic Leukemia | −0.001 | −0.038*** |
| Chronic Myeloid Leukemia | 0.034*** | −0.010 |
| UNSPECIFIED Leukemia | −0.002 | 0.011 |
| Instruments | | |
| DIST10-35 | −0.007*** | — |
| DIST35-70 | −0.012*** | — |
| DIST70 | −0.012*** | — |
| MHINCOME† | 0.004*** | — |
| %BACHDEG‡ | 0.033*** | — |
| %UNEMPLOY | 0.005*** | — |
| RHO (selection effect) | 0.066 (0.127) | — |

†Median Household income in the patient's county of residence is expressed in $10,000s.
‡Percentage of the population in the patient's county of residence with a bachelor's degree is divided by 10.
***Significant at $p < .01$.
*Source.* http://www.dof.ca.gov/research/demographic/state_census_data_center/products-services.

of death was almost 50 percent lower for leukemia patients who underwent HSCT. Lack of insurance or less generous coverage was associated with increased mortality. The probability of death was about 11 percentage points higher for self pay (uninsured) patients compared to those with private insurance ($p < .01$). Medi-Cal and Medicare patients were, respectively, 3.4 and 2.7 percentage points more likely to die than leukemia patients with private insurance ($p < .01$). Conversely, patients who switched to more generous insurance improved their chances of survival by close to 6 percentage points

($p < .01$). Older leukemia patients were more likely to die, whereas the likelihood of surviving was 1.7 percentage points greater for females relative to males ($p < .01$). In contrast, race/ethnicity had no impact on survival. Compared to patients with acute lymphocytic leukemia, the chances of survival was 4.3 percentage points higher for patient with acute myeloid leukemia, but 3.8 percentage points lower for patients with chronic lymphocytic leukemia ($p < .01$).

Table 4 reports analogous results for lymphoma patients. More than 7 percent of lymphoma patients received HSCT. Patients with limited or no insurance were about 1 percentage point less likely than those with private insurance to receive a stem cell transplant ($p < .01$). In contrast, those who switched to more generous coverage were 1.6 percentage points more likely

Table 4: Marginal Impacts from Bivariate Probit Model Predicting Receipt of Hematopoietic Stem Cell Transplantation (HSCT) and Mortality for Patients with Lymphoma ($N = 9{,}137$)

| *Variable Name* | *Receipt of HSCT* | *Death* |
|---|---|---|
| HSCT | — | −0.049*** |
| Insurance coverage (reference is PRIVATE) | | |
| MEDI-CAL | −0.009*** | 0.038*** |
| MEDICARE | −0.009*** | 0.035*** |
| SELF PAY | −0.008*** | 0.069*** |
| OTHERINS | −0.005*** | 0.019 |
| SWITCH | 0.016*** | −0.052*** |
| Demographics (reference is WHITE and MALE) | | |
| AGE | −0.0002*** | 0.0014*** |
| FEMALE | −0.0004 | −0.010*** |
| BLACK | −0.0019 | −0.006 |
| ASIAN | −0.0034 | −0.008 |
| RACEOTHER | −0.0016 | −0.016 |
| RACEMISS | 0.0168 | −0.022*** |
| Non-HODGKIN Lymphoma | −0.0005 | 0.012*** |
| Instruments | | |
| DIST10-35 | 0.0001 | — |
| DIST35-70 | −0.0038*** | — |
| DIST70 | −0.0042*** | — |
| MHINCOME[†] | 0.0007 | — |
| %BACHDEG[‡] | 0.0156*** | — |
| %UNEMPLOY | 0.0025*** | — |
| RHO (selection effect) | 0.0051 (0.1602) | — |

[†]Median Household income in the patient's county of residence is expressed in $10,000s.
[‡]Percentage of the population in the patient's county of residence with a bachelor's degree is divided by 10.
***Significant at $p < .01$.

to undergo HSCT ($p < .01$). Older persons were less likely to undergo HSCT, but the effects of gender and race/ethnicity were negligible. Disease type did not impact receipt of HSCT.

The set of instruments included in the HSCT equation but excluded from the mortality equation were jointly significantly different from zero ($p < .001$). Greater travel distance to the nearest transplant hospital had the anticipated negative effect on whether a lymphoma patient received HSCT ($p < .001$). The proxy variables used to control for educational attainment and household income had the expected positive signs, but only the education effect was statistically significant ($p < .001$). Here again, the county unemployment rate was statistically significant and had a counterintuitive sign. Rho, which measures the correlation across the residuals in the treatment choice and mortality equations, was not statistically significant, implying the selection effect due to unobservables was nonexistent.

The marginal effects predicting mortality for the lymphoma sample are reported in column 2 of Table 4. Patients who underwent HSCT were 4.9 percentage points less likely to die compared to those who did not receive the procedure ($p < .01$). As 7.1 percent of lymphoma patients died, this implies that receipt of HSCT reduced the probability of death by 69 percent. Patients covered by Medi-Cal or Medicare were about 3.8 and 3.5 percentage points, respectively, more likely to die than their privately insured counterparts ($p < .01$). For self pay (uninsured) lymphoma patients, the risk of dying was 6.9 percentage points higher relative to those with private insurance ($p < .01$). Patients who switched to better insurance coverage improved their chances of survival by more than 5 percentage points ($p < .01$). Age was associated with a greater risk of death as expected. The probability of survival was 1 percentage point higher for females in comparison to males ($p < .01$). In general, race/ethnicity did not influence survival. Finally, patients with non-Hodgkin lymphoma were 1.2 percentage points more likely to die than those with the Hodgkin form of this disease ($p < .01$).

We conducted the appropriate statistical tests to evaluate the validity of the instruments. For both samples, we found the instruments were significant predictors of receipt of HSCT. The $\chi^2 = 121.57$ ($p < .0001$) for the leukemia sample, while the $\chi^2 = 77.21$ ($p < .0001$) for the lymphoma sample. The second condition for instrument validity requires that the instruments are uncorrelated with mortality. The condition was satisfied for both the lymphoma sample ($\chi^2 = 4.18$, $p = .6518$) and the leukemia sample ($\chi^2 = 5.10$; $p = .5315$). For both samples, the instruments were not statistically significant predictors of mortality either individually or jointly as a group.

## DISCUSSION

Our findings revealed several factors that influenced whether a leukemia or lymphoma patient underwent HSCT. Having private insurance coverage and residence in a well-educated county increased the chances a patient with either disease received HSCT. In contrast, increasing age and travel distance to the nearest transplant hospital had the opposite effect. Receipt of HSCT had a significant impact on mortality. We found the probability of death was 4.3 percentage points higher for leukemia patients who did *not* have HSCT compared to those who received this treatment ($p < .01$). Thus, receipt of HSCT reduced the chances of dying by almost 50 percent. The likelihood of death among lymphoma patients who underwent HSCT was almost 5 percentage points lower than those who did not have a transplant, which corresponds to a 70 percent reduction in the probability of death. Type of insurance coverage also had significant independent effects on survival. For example, the probability of death was 11.3 percentage points higher for self pay (uninsured) leukemia patients relative to those with private insurance. The corresponding difference for lymphoma patients was about 7 percentage points.

While our findings highlight the linkages between receipt of expensive medical treatments and improved survival, our study has some limitations. First, the State of California would not release the exact date of receipt of HSCT for each patient who underwent the treatment nor would the state relinquish the exact date of death for patients who expired by the end of 2005. Consequently, we were not able to calculate duration of survival measured in either days or months. Second, we could not control for grade or stage of disease as such information is absent from inpatient claims databases. However, we found no selection bias due to unobservables, suggesting our inability to control for clinical characteristics was not a source of omitted variables bias. Third, the race variable did not distinguish ethnicity so we could not clearly identify Hispanic patients. Finally, the insurance variable lumped different types of private insurance coverage into a single category so we could not differentiate more generous PPO plans from more restrictive HMO coverage. Anecdotal information suggests that HMO plans tend to contract with one or two hospitals in a market area to perform HSCT, whereas PPO plans will contract with multiple providers in the same market area. As HMO plans are likely to adopt more stringent criteria regarding which patients are eligible for HSCT, the findings can be viewed as a lower bound estimate of differences associated with having private insurance coverage.

In conclusion, receipt of HSCT along with having private insurance coverage was associated with substantial improvements in survival. These findings raise concerns about access to expensive cancer treatments for patients who lack insurance or have Medicaid coverage. Some of the initiatives implemented under the Affordable Care Act may have unintended consequences and heighten such access concerns. Many states have refused to expand their Medicaid program under the provisions of the Affordable Care Act, so many lower income persons will remain uninsured. For states that have adopted the Medicaid expansions, this population is expected to grow substantially. In response to higher caseloads, states may be forced to implement even more stringent eligibility criteria for expensive cancer treatments. Private insurance plans offered on the state exchange markets may also adopt strategies designed to limit access to expensive cancer treatments. For example, some of the more affordable plans offered on individual state insurance exchanges may restrict access to HSCT by contracting with only one or two hospitals, neither of which performs HSCT. Only time will tell how access to expensive cancer treatments is affected by evolving health care reforms.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: Author Matrix.