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Comparison of vital status, cause of death, and follow-up after HCT in linked CIBMTR and California Cancer Registry data, 1991–2018

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AUTHORSHIP CONTRIBUTIONS

B.V., S.J.S., and L.M.M. conceptualized and designed the study; B.V. performed the analysis; B.V., S.J.S., and L.M.M. drafted the manuscript; C.L.M., A.B., and J.J.P.C. curated the data; L.M., T.H.M.K., and L.M.M. contributed to data acquisition; T.W., J.J.A., L.M., T.H.M.K., and L.M.M. acquired funding; L.M., T.H.M.K., and L.M.M. supervised and administered the study; S.J.S., C.L.M., A.B., J.J.P.C., R.A., T.W., J.J.A., S.M.G., E.E., P.S.A., S.R.S., J.D.R., B.E.S., L.M., T.H.M.K., and L.M.M. provided valuable edits to the manuscript and approved the final version of the manuscript.

CONFLICT OF INTEREST DISCLOSURES

Declarations of interest: none.

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Abstract

Background: Assessing outcomes following hematopoietic cell transplantation (HCT) poses challenges due to the necessity for systematic and often prolonged patient follow-up. Linking the HCT database of the Center for International Blood and Marrow Transplant Research (CIBMTR) with cancer registry data may improve long-term outcome ascertainment, but the reliability of mortality data in death certificates from cancer registries among HCT recipients remains unknown.

Objectives: We compared the classification of vital status and primary cause of death (COD), as well as the length of follow-up between the CIBMTR and California Cancer Registry (CCR) to assess the feasibility of supplementing the CIBMTR with cancer registry data.

Study design: This retrospective study leveraged a linked CIBMTR-CCR dataset. We included patients who were California residents at the time of HCT and received a first allogeneic (alloHCT) or autologous (autoHCT) HCT for a hematologic malignancy diagnosed during 1991–2016. Follow-up was through 2018.

Results: We analyzed 18,450 patients (alloHCT, n=8,232; autoHCT, n=10,218). Vital status agreement was 97.7% for alloHCT and 97.2% for autoHCT. Unknown COD was higher in CIBMTR (12.9%) than CCR (1.6%). After excluding patients with unknown COD information, the overall agreement of primary COD (cancer vs. noncancer) was 53.7% for alloHCT and 83.2% for autoHCT. This agreement was lower within the first 100 days following HCT (alloHCT=31.0%, autoHCT=54.6%). Compared with CIBMTR, deaths due to cancer were higher in CCR (alloHCT=90.0%, autoHCT=90.1% vs. alloHCT=47.3%, autoHCT=82.5% in CIBMTR). CIBMTR reports more frequently noncancer-related deaths, including graft-versus-host disease and infections. Cumulative incidence of cancer-specific mortality at 20 years differed particularly for alloHCT (CCR=53.7%, CIBMTR=27.6%). Median follow-up among alive patients was longer in CCR (alloHCT=6.0, autoHCT=4.7 years) than in CIBMTR (alloHCT=5.0, autoHCT=3.8 years).

Conclusion: Our findings highlight the completeness of vital status data in CIBMTR but reveal substantial disagreement in primary COD. Consequently, caution is required when interpreting HCT studies that only use death certificates to estimate cause-specific mortality outcomes. Improving the accuracy of COD registration and follow-up completeness by developing communication pathways between cancer registries and hospital-based cohorts may enhance our understanding of late effects and long-term outcomes among HCT survivors.

Keywords

Hematopoietic cell transplantation; Cancer registry; Cause of death; Follow-up

INTRODUCTION

Hematopoietic cell transplantation (HCT) is an important treatment option for managing many types of hematologic malignancies.[1] The advancements in clinical approaches have expanded the eligibility criteria for HCT and improved survival outcomes.[1–4] In the last two decades, the annual number of HCTs in the US has more than doubled, with >8,000 allogeneic (alloHCT) and >12,000 autologous (autoHCT) HCTs performed in 2021.[5] Because of the increased number of recipients and survivors, there is a greater focus on understanding long-term outcomes and late effects following HCT to improve clinical care.[6]

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a hospital-based data source for studying treatment outcomes after HCT. CIBMTR collects patient data from all alloHCT recipients (by law since 2005) and >85% of autoHCT recipients in the US.[7,8] The CIBMTR is the most comprehensive registry of HCT patients in the US but the completeness of follow-up data may decline with increasing time since transplantation, often attributed to patients' reduced number of visits to transplant centers for medical care.[9] While linking CIBMTR clinical data with national or state cancer registries might improve follow-up ascertainment, previous research has questioned the reliability of available mortality data abstracted from death certificates in cancer registries when compared with transplant registries.[10–13]

Previous studies comparing primary cause of death (COD) between transplant registries and death certificates have predominantly centered on non-hematologic cancer populations.[10–12] The reliability of COD data among HCT recipients diagnosed with hematologic malignancies remains uncertain. To address this knowledge gap, we compared the classification of vital status and primary COD, and the length of follow-up between the CIBMTR and the California Cancer Registry (CCR) using our previously linked database.[14] More specifically, we estimated the percentage agreement of vital status and primary COD and described patient follow-up and cause-specific mortality outcomes within our linked database. Factors associated with vital status and primary COD agreement were explored using polytomous regression analyses.

MATERIALS AND METHODS

Study design and population

We included patients who underwent a first alloHCT or autoHCT for a hematologic malignancy diagnosed during 1991–2016, with follow-up through December 2018, within our linked database. The calendar period aligns with the data sources completeness in our broader project, which involves linking CIBMTR with cancer registry and hospital discharge data, as described previously.[14] In brief, we linked California patients reported to the CIBMTR and the CCR using 9 factors (date of birth, sex, social security number, residence zip code, date and type of hematologic malignancy diagnosis, transplant center, and the date and type of HCT). We excluded those who had a missing last follow-up date (n=88), had a last follow-up date (CIBMTR or CCR) before the transplant date in CIBMTR (n=111), or received a first HCT before 1991 (n=237) (Figure 1).

Data sources

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program / Be The Match that maintains an outcome registry of patients receiving an HCT. Participating centers in the US are required to report data from all alloHCTs performed since 2005. Reporting for autoHCT is voluntary, with >85% reported to the CIBMTR.[7,8] Participating centers submit clinical data at baseline pre-HCT and at specific time points after HCT: 100 days, 6 months, and annually until 6 years and biannually thereafter or until death. The CCR collects approximately 99% of the incident invasive cancer cases in California. Collected data includes sociodemographic factors, tumor characteristics, initial treatment, and survival data through passive and active follow-up.[15]

Vital status and mortality data

In this report, primary COD refers to the ‘underlying’ or ‘primary’ event leading to mortality.[16,17] The CIBMTR collects primary and secondary/contributory CODs in standardized reporting forms, determined through a comprehensive review of medical records and autopsy reports when available. The forms also include free text fields for specifying COD.[17] For unclear CODs, a physician is contacted to recommend coding. Additionally, CIBMTR conducts data quality audits in 4-year cycles comparing data on the reporting forms with the medical records of the recipients to ensure completeness and accuracy of clinical data, including COD.

CCR obtains primary COD based on death certificates using the codes of the 9th (before 1999) and 10th editions (1999 and onwards) of the International Classification of Diseases (ICD). Death certificates are coded by the National Center for Health Statistics (NCHS). The California Department of Public Health obtains these data via linkage with the NCHS. The NCHS can automatically code 70–80% of death certificates. An additional 20–30% require manual review. In contrast to CIBMTR, CCR does not conduct audits for the COD data and relies on the information in death certificates.[18]

This study focuses on the primary COD because our database lacks information on the contributing or secondary CODs. We classified COD into 3 broad categories (cancer, noncancer, and unknown; Supplementary Table 1) to create comparable groups between CIBMTR and CCR. In CIBMTR, cancer mortality was subdivided into relapse and ‘other cancers’ (subsequent neoplasms and prior malignancies not associated with HCT indication). In CCR, we subdivided cancer mortality into hematologic malignancies and ‘other cancers’ (solid cancers), as relapse mortality was not easily identifiable in ICD codes. Noncancer CODs included infections, respiratory diseases, cardiovascular conditions, hemorrhages, accidental/suicide, graft-versus-host disease (GVHD), and other causes.

Follow-up and vital status harmonization

To account for the difference in reporting time between CIBMTR and CCR, we harmonized the follow-up (observation time). Specifically, the end of follow-up was defined as the earliest of last follow-up date between CIMBTR and CCR, or at the second HCT (when applicable), whichever comes first. If the last follow-up dates in CIBMTR and CCR were within 90 days (consistent with our previous linkage methods)[14], we considered them

concordant and used the earliest date (i.e., the date closest to HCT). Vital status was re-classified based on this harmonized date.

Data analysis

We evaluated the vital status (alive or deceased) percentage agreement between CIBMTR and CCR after harmonizing the follow-up data. Factors associated with vital status disagreement were explored in a polytomous multivariable logistic regression analysis by defining three subgroups (vital status agrees alive, vital status agrees deceased, and vital status disagrees). Variables in the models included age at HCT, sex, period of HCT, race and ethnicity, center volume, time since HCT, and HCT indication. These variables were selected to explore the effect of sociodemographic and healthcare factors on the vital status or COD agreement based on their previous association with survival outcomes or healthcare access in the HCT population.[9,19] HCT volume was defined as in our previous methods by the number of alloHCTs performed at each center during the study period using the information in the CIBMTR database and grouped into tertiles (low, <140; medium, 140–459; high, ≥460).[14] We report the logistic regression analyses with odds ratios (ORs) and 95% confidence intervals (CIs). All P-values are two-sided and were estimated with the Wald test. $P<0.05$ was considered statistically significant.

We compared COD agreement among patients with a known COD in both sources (n=6,337). As with vital status, we estimated the percentage agreement using our broad classification (cancer or noncancer). We fitted polytomous multivariable logistic regression models adjusted for the abovementioned variables to identify factors associated with a discordant COD by establishing three subgroups (COD agreement, cancer in CIBMTR & noncancer in CCR, and noncancer in CIBMTR & cancer in CCR). We estimated the cumulative incidence of cause-specific mortality, considering cancer and noncancer CODs as competing events. Patients were followed from the date of the first HCT until the harmonized end-of-follow-up date. Cumulative incidence curves for detailed CODs by data source are available in Supplementary Figures 1 and 2.

Lastly, we compared the non-harmonized follow-up time from CIBMTR and CCR among individuals with a concordant vital status of alive (n=10,600) to evaluate whether there were any patient-level differences in observation time at the patient level between the two data sources. To assess variations in observation times from each dataset, we used the last follow-up date in each source independently. All analyses were stratified by HCT type and were performed in R version 4.1.1.

Ethical statement

The protocol for this study was approved by the Institutional Review Boards of the University of California, Davis, California Committee for the Protection of Human Subjects, and National Marrow Donor Program and determined not to be human subjects research by the National Cancer Institute.

RESULTS

Population characteristics

The cohort included a total of 18,450 recipients who underwent alloHCT (n=8,232) or autoHCT (n=10,218). Supplementary Table 2 describes the baseline demographic and clinical features at HCT. The median age at alloHCT was 42 years (range 0.4–78.6), and acute myeloid leukemia (45.8%) and acute lymphoid leukemia (26.9%) were the most common indications. The median age at autoHCT was 55 years (range 0.4–84.0), and plasma cell neoplasms (42.5%) and diffuse large B-cell lymphoma (17.2%) were the main indications. For both HCT types, most recipients were male (alloHCT 57.7%, autoHCT 59.4%), non-Hispanic White (alloHCT 52.0%, autoHCT 62.4%), and treated in high-volume centers (alloHCT 80.1%, autoHCT 77.1%).

Vital status

The vital status agreement was 97.7% for alloHCT and 97.2% for autoHCT recipients (Table 1). A total of 50.3% of alloHCT and 31.6% of autoHCT patients were classified as deceased in both sources, while 47.4% of alloHCT and 65.5% of autoHCT patients were classified as alive. Although the percentage of disagreement (alloHCT=2.3%, autoHCT=2.8%) remained low across most demographic and transplant-related characteristics, several factors were significantly associated with vital status disagreement within the multivariable model (Supplementary Table 3). For alloHCT, the highest odds of disagreement were among patients transplanted outside California (vs. high-volume center; OR=5.10, 95%CI=2.52–10.34) and with increasing time after transplantation (1–5 years OR=2.19, 95%CI=1.38–3.48; 6–10 years OR=4.35, 95%CI=2.27–8.33; vs. within 100 days). Other factors associated with disagreement were male sex (vs. females; OR=1.63, 95%CI=1.18–2.24), and Hispanic ethnicity (vs. non-Hispanic White; Hispanic: OR=1.54, 95%CI=1.08–2.19). For autoHCT, demographic characteristics, volume center, and time since HCT were not associated with vital status disagreement.

Cause of death and outcomes

A total of 7,371 patients (alloHCT, n=4,139; autoHCT, n=3,232) were reported as deceased and had concordant mortality dates (Figure 1 and Table 1). Of them, a higher percentage had unknown COD in CIBMTR (alloHCT=7.5%, autoHCT=19.8%) compared to CCR (alloHCT=1.4%, CCR=1.8%) (Table 2). Unknown COD decreased over time by calendar period of HCT in CIBMTR for alloHCT (from 20% in 1991–1994 to 5.1% in 2015–2016) and autoHCT (from 37.4% in 1991–1994 to 10.7% in 2015–2016), whereas in CCR, unknown COD remained below 3% for alloHCT and autoHCT during all HCT periods (Supplementary Table 4). Among the 950 patients with unknown COD in CIBMTR, most were assigned a hematologic malignancy COD in CCR (alloHCT: n=222/311, 71.4%; autoHCT: n=486/650, 76.1%). Similarly, patients with unknown COD in CCR (n=115) were mostly classified as deceased due to relapse in CIBMTR (alloHCT: n=24/58, 41.4%; autoHCT: n=30/57, 52.6%) (Supplementary Table 5).

We excluded patients with unknown COD to evaluate the agreement between sources, yielding 6,337 recipients (alloHCT, n=2,553; autoHCT, n=3,784). Cancer COD was

more frequently reported by CCR (alloHCT=90.0%, autoHCT=90.1%) than CIBMTR (alloHCT=47.3%, autoHCT=82.5%) (Figure 2). For both alloHCT and autoHCT, more patients with noncancer CODs in CIBMTR were classified as having died from cancer in CCR (alloHCT=44.5%, autoHCT=12.2%) compared with the small percentage of patients who were classified as cancer in CIBMTR and had a noncancer COD in CCR (alloHCT=1.8%, autoHCT=4.6%).

The percentage agreement for COD (cancer vs. noncancer) was 53.7% for alloHCT and 83.2% for autoHCT (Supplementary Table 6), with a lower agreement for deaths occurring during the first 100 days after HCT (alloHCT=31.0%, autoHCT=54.6%) (Supplementary Table 7). We then performed polytomous logistic regression to identify factors associated with COD disagreement, focusing on the 'noncancer in CIBMTR & cancer in CCR' subgroup given the abovementioned patterns. Mortality within 100 days after HCT was the only factor associated with COD disagreement for both alloHCT (OR=8.10, 95%CI=4.03–16.29) and autoHCT (OR=10.28, 95%CI=3.57–29.66), using deaths over 10 years as the referent group (Supplementary Table 7). For alloHCT recipients, other factors associated with COD disagreement included older age (vs. ages 0–14 years), non-Hispanic Black (vs. non-Hispanic White) race and ethnicity, chronic myeloid leukemia, and acute lymphoblastic leukemia (vs. acute myeloid leukemia/myelodysplastic syndrome). For autoHCT recipients, other factors included low center volume (vs. high) and Hodgkin lymphoma (vs. plasma cell neoplasms).

Cumulative incidence of mortality, accounting for primary CODs (cancer vs. noncancer) as a competing risk, was estimated among patients with concordant vital status (N=17,971, Figure 1). Figure 3 shows the cumulative mortality curves for alloHCT (Figure 3A) and autoHCT (Figure 3B) by data sources. Following alloHCT, the cancer-specific mortality at 20 years was 53.7% in CCR and 27.6% in CIBMTR, while for noncancer, it was 9.5% in CCR and 29.9% in CIBMTR. Following autoHCT, cumulative incidence at 20 years for cancer-specific mortality was 52.9% in CCR and 38.7% in CIBMTR, while for noncancer, it was 13.4% in CCR and 10.5% in CIBMTR.

Consideration of more detailed COD categories revealed differences in the frequency of noncancer CODs between sources by HCT type (Table 2). For alloHCT recipients, the most common noncancer CODs in CIBMTR were infections (13.5%) and GVHD (10.3%), whereas infections in CCR accounted for only 3.7% of deaths and GVHD was not reported. For autoHCT recipients, infections (4.2%) and respiratory conditions (2.4%) were the most frequent noncancer CODs in CIBMTR, while cardiovascular conditions (3.7%) and infections (3.1%) were the most common in CCR. Supplementary Figures 1 and 2 show the cumulative incidence curves for detailed cause-specific outcomes for alloHCT and autoHCT, respectively. In both HCT types, CIBMTR demonstrated higher cumulative incidence compared to CCR for infections, respiratory conditions, hemorrhage, and other/external causes.

Lastly, we examined the distribution of detailed CODs among patients with discordant COD based on the broad category (cancer and noncancer; Supplementary Table 8). Among patients with discordant COD, the most frequent CODs reported by CIBMTR

were infections (26.4%) and GVHD (21.2%) for alloHCT and infections (24.7%) for autoHCT (Supplementary Table 8). Supplementary Table 9 suggests that most deaths due to GVHD (n=368/426, 86.4%) and infections (n=458/557, 82.2%) in CIBMTR for alloHCT were classified as death due to hematologic malignancy in CCR. Similarly, deaths due to infections (n=106/136, 77.9%) in CIBMTR were generally classified as mortality due to hematologic malignancies in CCR (Supplementary Table 9).

Follow-up

Among patients who were recorded as alive in both CIBMTR and CCR, we analyzed the length of available follow-up time from each source (Table 3 and Figure 4). The median follow-up was longer in CCR than in CIBMTR following alloHCT (6.0 vs. 5.0 years) and autoHCT (4.7 vs. 3.8 years). Patients with longer follow-up time in CCR (alloHCT, n=958; autoHCT, n=1,928) had a median of 4.0 (range, 0.2–26.3) additional years of follow-up, whereas those with longer follow-up time in CIBMTR (alloHCT, n=991; autoHCT, n=1,304) had a median of 1.0 (range, 0.2–16.3) additional year of follow-up (Table 3). These differences were more pronounced in the subgroup of patients transplanted before 2005 compared to patients transplanted in more recent years (Table 3). Notably, allowing for the non-harmonized length of follow-up, CCR identified 620 patients who died after their last known follow-up in CIBMTR, while CIBMTR only captured an additional 22 patients who died after their last known follow-up in CCR.

DISCUSSION

In this large-scale study linking the CIBMTR with a statewide population-based cancer registry, we found a high concordance in vital status, but substantial disagreement in the primary COD classification. As a result, the estimated cumulative incidence of cancer-related mortality was higher using CCR data compared to CIBMTR, while the opposite pattern was observed for noncancer mortality. Although we identified a longer follow-up in CCR, our analyses suggest that this advantage is offset by less reliable COD data in CCR. These results highlight the complementary strengths and limitations of two comprehensive data sources and raise awareness of the limitations of using death certificate data for evaluating cause-specific mortality outcomes among HCT survivors.

The high vital status agreement for alloHCT and autoHCT suggests reliable information from each source. Although based on small numbers, receiving a transplant outside of California and a prolonged time since HCT was associated with vital status disagreement in the alloHCT group. These findings imply difficulties in patient follow-up after transplantation. For autoHCT, we observed similar patterns, but the results were not statistically significant. As reporting for autoHCT is voluntary, our findings may indicate that centers report data from recipients with more complete follow-up information. Because of our harmonization procedures, the results for the vital status are not driven by differences in the reporting schedules between CIBMTR and CCR.

Unlike vital status, the COD disagreement was substantial and more pronounced within 100 days after HCT, a period associated with significant non-relapse mortality such as GVHD and infections.[4,19–22] The higher discrepancies in cumulative incidence of cancer mortality

among alloHCT than autoHCT recipients may reflect the elevated percentage of relapse mortality in the autoHCT population. The COD disagreement is consistent with previous comparisons between transplant and vital statistics registry data in Europe and Australia,[10–12] but contrasts with comparisons between medical records and death certificates in other cancer patient populations, such as breast or prostate cancer, which have reported >90% agreement.[23–25]

This COD disagreement may reflect the mortality data curation process in CIBMTR compared to CCR. Specifically, CIBMTR offers training for standard data collection practices and often relies on clinicians who have access to medical records to assign the primary COD. Although the ICD coding in the CCR data provides a more detailed classification of primary COD than the CIBMTR categories, the disagreement between the two sources indicates the need to improve COD collection practices in the registry setting. Potential approaches could include designing coding recommendations for patients with hematological malignancies who received HCT and reinforcing training on death certificate completion in this setting. Implementing these strategies could enhance the effective supplementation of clinical data with registry information.

Our study raises awareness regarding the validity of registry-based studies using death certification to identify primary COD for assessing outcomes among HCT recipients. Identifying the primary COD is essential for evaluating the effectiveness of therapeutic interventions on cause-specific mortality outcomes and monitoring late effects among transplant survivors. Because of the rarity of some hematologic malignancies and a lack of standard of care in post-progression settings,[26–28] the supplementation of trials with real-world data is increasingly becoming a common approach to evaluate the effect of novel interventions on clinical outcomes.[28–31] The poor COD agreement between two comprehensive real-world data sources underscores the difficulties in using death certification to evaluate and monitor the effect of novel therapies on cause-specific mortality outcomes among HCT recipients, although analyses of overall survival are appropriate.

The percentage of unknown COD in CIBMTR declined over calendar periods in our study, with 5.1% for alloHCT and 10.7% for autoHCT during 2015–2016, which is similar to the 9% during 2018–2020 documented in the latest CIBMTR report for all types of HCT.[5] However, the higher proportion in CIBMTR compared to CCR suggests difficulties in COD identification. Typically, unknown COD is reported to CIBMTR when the available information is insufficient to determine the primary event leading to mortality, suggesting that mortality likely occurred outside of a cancer center. In CCR, the lower percentage of unknown COD may indicate a potential bias toward assigning cancer as the primary COD on a death certificate in the absence of other clinical information.[32,33]

The median non-harmonized follow-up among alive patients was longer in CCR than CIBMTR, with differences more pronounced among patients who underwent HCT before 2005. This reduced difference between sources after 2005 may be attributed to the 2005 Stem Cell Therapeutic and Research Act,[7] allowing for a more complete patient follow-up reporting mandated by law. Similarly, the Security Rule of the Health Insurance Portability and Accountability Act may have contributed to the improvement of follow-up

ascertainment by providing a safe environment for confidentiality data sharing and reporting to CIBMTR.[34,35]

While slight variations in follow-up time are expected given the different reporting processes (CIBMTR follows patients biannually after 6 years, while CCR gathers data yearly), these findings may also indicate loss of follow-up by CIBMTR. Consistent with this result, previous research has shown a decline in the completeness of follow-up post HCT.[9] Although linking CIBMTR to population-based registry data may improve follow-up, the observed discrepancies in COD suggest this approach could be more beneficial for studying other conditions such as second primary malignancies.

This study has several limitations. We grouped mortality as cancer and noncancer to account for the difference in COD coding approaches between data sources. Additionally, CIBMTR utilizes the comprehensive clinical data in medical records to code COD, whereas death certificates often do not account for the entire patient history. Contributing CODs were not available for both datasets, which limits further comparison. For instance, a clinician might record treatment-related mortality as a contributing COD on a death certificate for a case classified as HCT-related by CIBMTR. Cohen's kappa statistic was not estimated because the CIBMTR and CCR may use some of the same records for assigning the primary COD, which violates the assumption of independence.

This study represents one of the largest cohorts of HCT recipients with linked clinical and registry data, improving our understanding of the variability in outcomes and follow-up data between CIBMTR and a cancer registry. The population-based design of this cohort allowed for a rigorous assessment of associated factors with vital status or COD disagreement in multivariable analyses. Our findings may be applicable to other states with similar population demographics.

In conclusion, this study highlights the challenges of assessing outcomes following HCT in the growing population of transplant survivors. Our comparison of two comprehensive real-world data sources identified robust vital status agreement, but reveals considerable disagreement in primary COD data, impacting cause-specific mortality estimates. Specifically, CCR tends to overestimate cancer-related mortality and underestimate noncancer mortality compared to CIBMTR. These findings emphasize the need for careful interpretation of cause-specific mortality outcomes in HCT studies using death certification for COD identification. Nonetheless, the longer follow-up time afforded by CCR could be leveraged to quantify deaths not captured in CIBMTR, suggesting that overall survival may be a reliable endpoint when linking CIBMTR with registry data. Additionally, the longer follow-up time in CCR data could be leveraged to increase the ascertainment of other late effects such as second primary malignancies. Improving the accuracy of COD registration and completeness of follow-up among HCT recipients by developing communication pathways between cancer registries and hospital-based cohorts may improve our understanding of late effects and long-term outcomes among HCT survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

The data that support the findings of this study are available from the California Cancer Registry and Information and Center for International Blood and Marrow Transplant Research. Access to data is granted through an application process by the management or data custodians for each data resource.

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HIGHLIGHTS

- Cause of death disagreement was substantial between CIBMTR and CCR.
- The median follow-up time among alive patients was longer in CCR.
- Careful interpretation of HCT studies using death certificates should be exercised.
- Future initiatives should develop mechanisms for integrating CIBMTR and CCR data.

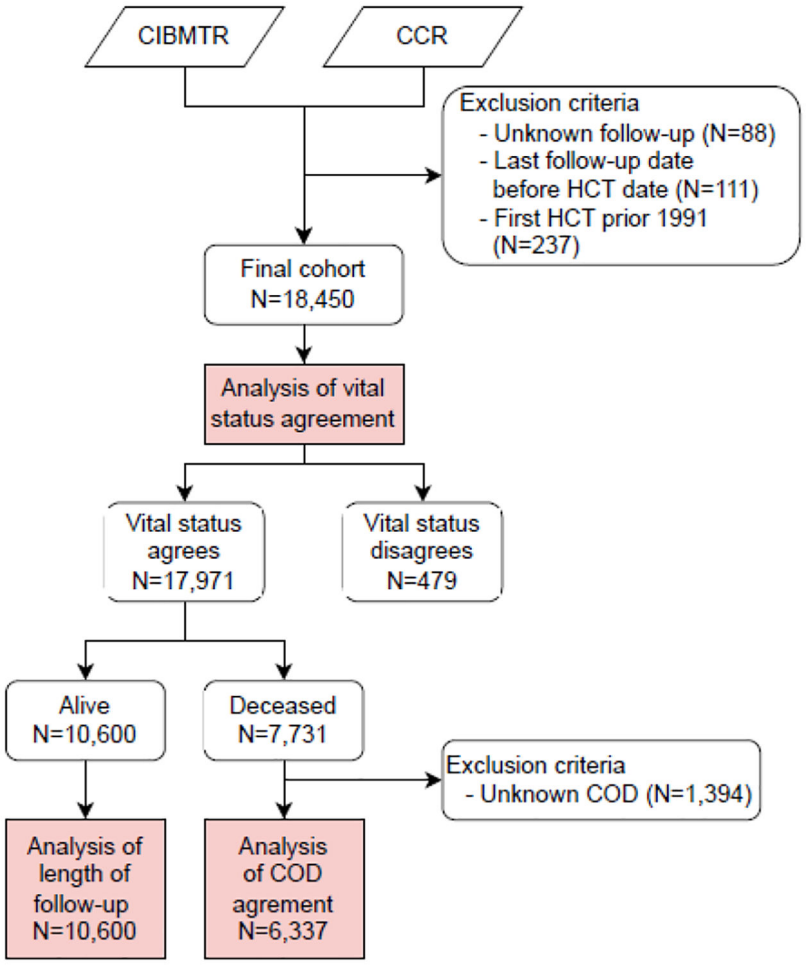

Figure 1. Study cohort.

A total of 18,450 patients diagnosed with hematologic malignancies who received alloHCT or autoHCT were included in the analytic cohort. We compared the vital status, cause of death, and follow-up data between the CIBMTR and the CCR (red boxes). CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry; COD, cause of death; HCT, Hematopoietic cell transplantation.

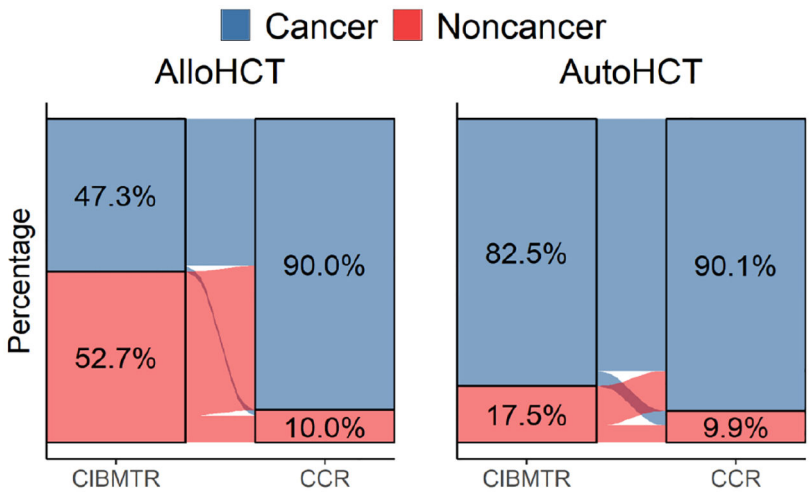

Figure 2. Parallel plot of the cause of death comparison.

We evaluated the agreement of broad cause of death between CIBMTR and CCR by HCT type among patients with a known cause of death, N=6,337. The shades connecting the bar charts represent the distribution of cause of death coding between data sources. AlloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry.

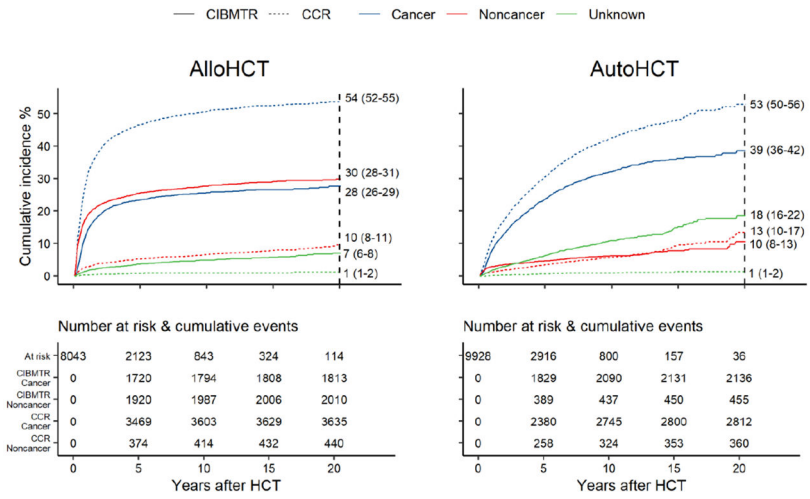

Figure 3. Cumulative incidence of cause-specific outcomes.

Competing risk analyses for each HCT type identified a high incidence of cancer-specific mortality using CCR data compared to CIBMTR among patients with a vital status agreement, N=17,971. AlloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry; HCT, hematopoietic cell transplantation.

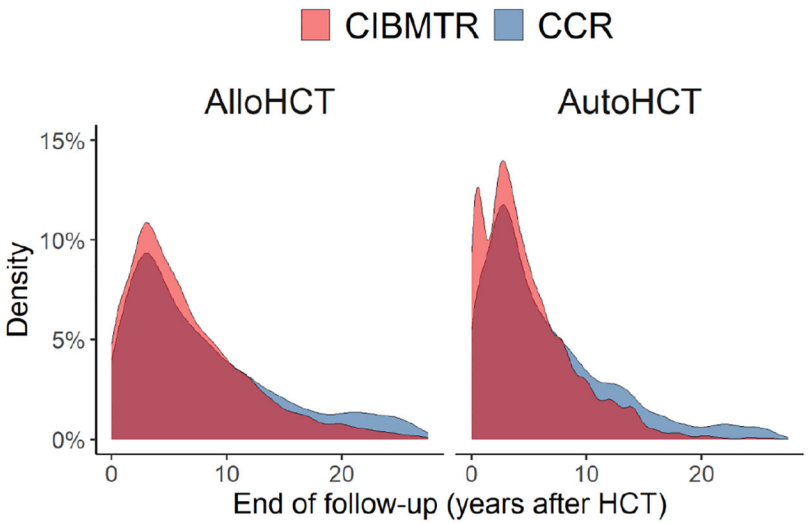

Figure 4. Density plot of follow-up distribution.

We compared the follow-up distribution between CIBMTR and CCR by HCT type among patients classified by both sources as alive at the end of follow-up, N=10,600. AlloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry; HCT, hematopoietic cell transplantation.

Table 1.

Vital status distribution between CIBMTR and CCR by HCT type in the total population, N=18,450.

Vital status	CCR					
	AlloHCT, N (%)			AutoHCT, N (%)		
CIBMTR	Alive	Dead	Total	Alive	Dead	Total
Alive	3904 (47.4)	69 (0.8)	3973 (48.3)	6696 (65.5)	172 (1.7)	6868 (67.2)
Dead	120 (1.5)	4139 (50.3)	4259 (51.7)	118 (1.2)	3232 (31.6)	3350 (32.8)
Total	4024 (48.9)	4208 (51.1)	8232 (100.0)	6814 (66.7)	3404 (33.3)	10218 (100.0)

Vital status is reported at the harmonized end of follow-up (i.e., CCR and CIBMTR vital status assessed at same time point).

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry; HCT, hematopoietic cell transplantation.

Table 2.

Distribution of primary causes of death for CIBMTR and CCR by HCT type among deceased patients, N=7,371.

Cause of death	Total, N=7371 (%)		AlloHCT, N=4139 (%)		AutoHCT, N=3232 (%)	
	CIBMTR	CCR	CIBMTR	CCR	CIBMTR	CCR
Cancer	3953 (53.6)	6452 (87.5)	1815 (43.9)	3637 (87.9)	2138 (66.2)	2815 (87.1)
Relapse	3782 (51.3)	-	1754 (42.4)	-	2028 (62.7)	-
Hematologic malignancies	-	6281 (85.2)	-	3565 (86.1)	-	2716 (84.0)
Other neoplasms *	171 (2.3)	171 (2.3)	61 (1.5)	72 (1.7)	110 (3.4)	99 (3.1)
Noncancer	2468 (33.5)	804 (10.9)	2013 (48.6)	444 (10.7)	455 (14.1)	360 (11.1)
Infection	696 (9.4)	253 (3.4)	559 (13.5)	154 (3.7)	137 (4.2)	99 (3.1)
GVHD	431 (5.8)	-	428 (10.3)	-	3 (0.1)	-
Respiratory	373 (5.1)	91 (1.2)	294 (7.1)	61 (1.5)	79 (2.4)	30 (0.9)
Cardiovascular	114 (1.5)	180 (2.4)	72 (1.7)	62 (1.5)	42 (1.3)	118 (3.7)
Hemorrhage	108 (1.5)	14 (0.2)	85 (2.1)	6 (0.1)	23 (0.7)	8 (0.2)
Other	732 (9.9)	179 (2.4)	566 (13.7)	107 (2.6)	166 (5.1)	72 (2.2)
Accidental/Suicide	14 (0.2)	87 (1.2)	9 (0.2)	54 (1.3)	5 (0.2)	33 (1.0)
Unknown	950 (12.9)	115 (1.6)	311 (7.5)	58 (1.4)	639 (19.8)	57 (1.8)

Subgroup of patients with a concordant deceased vital status between CIBTMR and CCR after follow-up and data harmonization procedures.

* "Other neoplasms" included secondary neoplasm and prior neoplasms for CIBMTR and solid neoplasms for CCR (see Supplementary Table 1).

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry; HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease.

Table 3.

Follow-up time (in years) comparison between CIBMTR and CCR by HCT type among patients with concordant alive vital status, N=10,600.

	AlloHCT			AutoHCT		
	Concordant dates*	**>Follow-up in CIBMTR**	**>Follow-up in CCR**	**Concordant dates***	**>Follow-up in CIBMTR**	**>Follow-up in CCR**
N (%)	1955 (50.1)	991 (25.4)	958 (24.5)	3464 (51.7)	1304 (19.5)	1928 (28.8)
CIBMTR Follow-up, median (range)	4.7 (0–27.4)	6.1 (0.4–27.1)	5.3 (0–26.1)	3.5 (0.1–26.4)	4.9 (0.6–25.7)	3.1 (0–26)
CCR Follow-up, median (range)	4.6 (0–27.4)	4.6 (0–26.2)	12.8 (0.5–27.5)	3.5 (0.1–26.4)	3.7 (0–24.5)	10.4 (0.5–27.4)
Individual-level difference in follow-up, median (range)	0 (0–0.2)	1 (0.2–16.3)	4 (0.2–26.3)	0 (0–0.2)	1 (0.2–12.4)	4.4 (0.2–24.6)
Difference by calendar year at HCT, median (range)						
1991–1994	0 (0–0.1)	1.7 (0.5–16.3)	18.1 (0.3–26.3)	0 (0–0.1)	5.5 (0.7–12.4)	17.2 (0.3–24.6)
1995–1999	0 (0–0.2)	1.4 (0.3–4.3)	10.7 (0.3–23.5)	0 (0–0.2)	1.1 (0.5–2.1)	12.2 (0.3–23.7)
2000–2004	0 (0–0.2)	1 (0.3–9.5)	4.5 (0.3–17.6)	0 (0–0.2)	1 (0.3–2.1)	7.8 (0.3–18.7)
2005–2009	0 (0–0.2)	1 (0.2–9.5)	2.8 (0.2–12)	0 (0–0.2)	1 (0.2–9.1)	3.8 (0.3–13.5)
2010–2014	0 (0–0.2)	1 (0.2–6.8)	1.6 (0.3–7.1)	0 (0–0.2)	1 (0.2–6.7)	1.8 (0.2–8.6)
2015–2018	0 (0–0.2)	1 (0.3–3.8)	0.9 (0.3–2.3)	0 (0–0.2)	0.9 (0.3–3.3)	1.4 (0.2–3.6)

Patient-level follow-up time was calculated separately, for CCR and CIBMTR based on the date of HCT until the earliest of the second HCT or last known follow-up according to the respective source.

* Last known alive dates within 90 days apart between CIBMTR and CCR were considered concordant dates.

Abbreviations: AlloHCT, allogeneic hematopoietic cell transplantation; autoHCT, autologous hematopoietic cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CCR, California Cancer Registry; FU, follow-up.