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Cytomegalovirus Infection in Allogeneic Hematopoietic Cell Transplantation Managed by the Preemptive Approach: Estimating the Impact on Healthcare Resource Utilization and Outcomes

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A B S T R A C T

We quantified cytomegalovirus (CMV) antiviral use and hospital length of stay (LOS) associated with CMV infection in a contemporary cohort of conventional (CONV) and CD34-selected (T cell–depleted) hematopoietic cell transplantation (HCT) recipients managed by preemptive therapy (PET) in a single US center. Adults who received first allogeneic HCT at Memorial Sloan Kettering Cancer Center from June 2010 through December 2014 were analyzed. Days on PET, number of readmissions, and readmission LOS by day 180 post-HCT were summarized. Estimated unit value (EUV) was defined as the expected number of PET days for a cohort of 100 HCT with characteristics as the analyzed cohort. Standardized incidence ratio was calculated as the ratio of observed outcomes of patients with CMV viremia over the outcomes of patients without CMV viremia. Of 318 patients, 88 received CONV and 230 CD34-selected HCT. Rates of CMV viremia were 26.3% for CONV and 41.9% for CD34-selected ($P = .003$). Among patients with viremia 68.2% CONV and 97.9% CD34-selected received PET. EUV for PET was 852 days and 2821 days for CONV and CD34-selected, respectively. The standardized incidence ratios for number of readmission and readmission LOS were 1.7 (95% confidence interval [CI], 1.4 to 2.1) and 1.2 (95% CI, 1.1 to 1.3), respectively, for CONV HCT and 1.7 (95% CI, 1.3 to 2.1) and 1.6 (95% CI, 1.5 to 1.7), respectively, for CD34-selected HCT. Overall survival was similar between patients with and without CMV viremia by HCT type. CMV end-organ disease was associated with lower overall survival only in CD34-selected HCT ($P = .0007$). CMV infection managed by PET requires substantial antiviral use and is associated with longer readmission LOS more, particularly among CD34-selected HCT.

INTRODUCTION

Cytomegalovirus (CMV) viremia occurs in 40% to 90% of CMV-seropositive recipients (R^+) [1–3] and is associated with increased overall mortality after hematopoietic cell transplantation (HCT) [4]. Risk factors for CMV reactivation after HCT are well established and include T cell depletion, allograft from HLA-mismatched or CMV-seronegative donor (D^-), and graft-versus-host disease (GVHD) [1,4]. Preemptive therapy (PET) has reduced the rates of CMV end-organ disease to less than 5% [5], the trade-off being increased use of CMV antivirals with their associated toxicities and potentially prolonged hospital length of stay (LOS).

By our institutional algorithm, ex vivo T cell depletion by CD34 selection is the first choice for patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). T cell depletion is an effective strategy for GVHD prophylaxis, alleviating the need for additional pharmacologic immunosuppression [6–9]. Higher rates of viral infections have been reported in CD34-selected HCT because of delayed immune reconstitution [2,10,11]. We analyzed a contemporary cohort of conventional (CONV) and CD34-selected HCT managed preemptively for CMV. Our objectives were to quantify the use of PET and to assess the impact of CMV viremia on hospital LOS by day +180 after HCT.

METHODS

Study Cohort

Consecutive adults with acute leukemia, chronic leukemia, MDS, myeloproliferative disease, Hodgkin disease, and non-Hodgkin lymphoma who underwent first CONV or CD34-selected HCT at Memorial Sloan Kettering between June 1, 2010 and December 31, 2014 were included in the study.

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Patients were followed until death, second HCT, or 1 year after HCT, whichever occurred first. Data were extracted from medical records and hospital and research databases. The study was reviewed by the Memorial Sloan Kettering Institutional Review Board and was granted a waiver of authorization (IRB no. 16-920).

Graft Manipulation and Conditioning Regimens

Ex vivo CD34 selection was performed by the CliniMACS CD34$^+$ Reagent System (Miltenyi, Biotec, Gladbach, Germany). All patients received peripheral blood stem cell allografts after myeloablative (CD34-selected) or reduced-intensity (CONV) conditioning regimens. Per institutional algorithm, patients with AML or acute lymphocytic leukemia in first complete remission and MDS received CD34-selected HCT unless they were deemed ineligible or refused by insurance. In general, eligibility for CD34-selected HCT included low disease burden if present or remission, availability of ≥8/10 HLA matched donor, Karnofsky performance status ≥ 70, no active infection or extramedullary disease, and no significant organ dysfunction that would preclude safe administration of myeloablative cytoreductive regimens [12]. Patients with lymphoma or chronic lymphocytic leukemia received conventional HCT after reduced-intensity conditioning regimens with low-dose total body irradiation [13] or busulfan and fludarabine. Patients with AML included in the CONV cohort were in remission at the time of HCT.

Supportive Care

All patients received acyclovir prophylaxis for herpes simplex virus and varicella-zoster virus per institutional standards of care [2]. CMV R$^+$ or CMV-seropositive donors (D$^+$) were routinely monitored by CMV quantitative PCR (qPCR) assays starting on day +14 post-HCT. Initiation of PET was at the discretion of the treating physician. Per institutional standards of care ≥2 consecutive PCR > 500 copies/mL in whole blood or >300 IU/mL in plasma for CONV HCT and ≥2 consecutive quantifiable PCR at any value for CD34-selected HCT were the recommended thresholds for initiation of PET. Valganciclovir or ganciclovir was the preferred first-line therapy. Foscarnet was used preferentially in patients with cytopenias (particularly before engraftment) or other contraindications to valganciclovir or ganciclovir. Timing for initiation and choice of antiviral was at the discretion of the treating physician. PET continued until >2 consecutive PCR below the limit of detection for CONV HCT off steroids. CD34-selected recipients on steroids continued maintenance therapy at the discretion of the treating physician.

Laboratory Methods

CMV IgG levels were determined using an automated semiquantitative ELISA (VIDAS; Biomerieux Inc., NC). qPCR for CMV was performed by the Clinical Microbiology Laboratory at Memorial Sloan Kettering using Roche analyte specific reagent (Roche Diagnostics, Branchburg, NJ) before March 2013 and the Cobas Ampliprep/Cobas Taqman CMV qPCR in plasma (Roche Molecular Diagnostics, NJ) from March 2013 onward. The lower limit of quantification and linear range were >500 to 1.0×10^6 copies/mL for blood and >137 to 9.1×10^6 IU/mL for plasma [14].

Definitions

CMV viremia was defined as ≥1 CMV qPCR > 500 copies/mL for whole blood or >137 IU/mL for plasma. CMV disease was diagnosed using standard definitions [15]. GVHD scoring was based on consensus guidelines [16]. PET days were the total number of days on a given antiviral(s) by day +180 after HCT. LOS was defined as the number of days in the hospital from the day of HCT through day +180 after HCT. Readmission LOS was the number of days in the hospital after discharge from the incident admission for HCT through day +180 after HCT. Number of readmissions was defined as the number of admissions after the admission for HCT through day +180 after HCT. "Well days" were defined as the number of days alive and out of the hospital. The number of well days was used to account for early mortality that may have explained shorter hospitalizations [17].

Statistical Analysis

The incidence for CMV viremia and CMV end-organ disease were estimated by the cumulative incidence analysis, with second HCT, relapse, death, and last follow-up before the event of interest treated as competing risks. Categorical and continuous variables were compared using the chi-square and Mann-Whitney rank sum tests (Kruskal-Wallis tests), respectively.

The estimated unit value (EUV) provides the number of PET days by day +180 for a hypothetical cohort of 100 patients based on our observed rates. EUV was calculated as $a \times b \times c \times 180$, where a is the observed cumulative incidence of CMV viremia, b is the observed proportion of patients with CMV

Table 1
Baseline Characteristics of the Cohort (N = 318)

Characteristic	Total (N = 318)	CONV (n = 88)	T Cell Depleted (n = 230)
Age			
Mean (standard deviation), yr	53.8 (13.0)	53.4 (12.4)	53.9 (13.2)
Median (IQR), yr	56.2 (46.5-64.6)	54.7 (47.3-63.3)	56.9 (45.6-64.8)
Sex			
Female	138 (43.4)	31 (35.2)	107 (46.5)
Male	180 (56.6)	57 (64.8)	123 (53.5)
R and D CMV serostatus			
R$^+$/D$^+$	108 (34.0)	31 (35.2)	77 (33.5)
R$^+$/D$^-$	79 (24.8)	15 (17.0)	64 (27.8)
R$^-$/D$^+$	40 (12.6)	15 (17.0)	25 (10.9)
R$^-$/D$^-$	91 (28.6)	27 (30.7)	64 (27.8)
Underlying disease			
Acute lymphoblastic leukemia	30 (9.4)	0	30 (13.0)
AML	159 (50.0)	32 (36.4)	127 (55.2)
MDS	78 (24.5)	5 (5.7)	73 (31.7)
Chronic lymphocytic leukemia	12 (3.8)	12 (13.6)	0
Hodgkin disease	12 (3.8)	12 (13.6)	0
Non-Hodgkin lymphoma	27 (8.5)	27 (30.7)	0
Donor type			
Matched related	114 (35.8)	39 (44.3)	75 (32.6)
Matched unrelated	149 (46.9)	41 (46.6)	108 (47.0)
Mismatched related	3 (.9)	1 (1.1)	2 (.9)
Mismatched unrelated	52 (16.4)	7 (8.0)	45 (19.6)
Conditioning regimen			
Myeloablative	230 (72.3)	0	230 (100.0)
Busulfan/melphalan/fludarabine	153 (48.1)	0	153 (66.5)
Clofarabine/thiotepa/melphalan	13 (4.1)	0	13 (5.7)
Total body irradiation/thiotepa/cyclophosphamide or fludarabine	64 (20.1)	0	64 (27.8)
Reduced intensity	88 (27.7)	88 (100.0)	0
Fludarabine/busulfan*	67 (21.1)	67 (76.1)	0
Melphalan	1 (0.3)	1 (1.1)	0
Total body irradiation/cyclophosphamide/fludarabine/thiotepa	20 (6.3)	20 (22.7)	0

Values are n (%) unless otherwise defined.
* Three patients also received rituximab.

viremia who received PET, and c is the number of PET days per 100 patient-days among patients treated with PET [18]. Standardized incidence ratio (SIR) and 95% confidence intervals (CIs) were defined as the observed outcome of interest (number of readmissions, readmission LOS, and total LOS) for patients with CMV viremia over the observed outcome for patients without CMV viremia. Patients were followed through day +180, relapse, or second HCT, whichever occurred first. CIs were calculated by applied approximation for chi-square percentiles.

Overall survival (OS) was estimated using the Kaplan-Meier method. The log-rank test was used for time-to-event analyses. Univariate and multivariate analyses, including logistic regression, Poisson regression, and linear regression, were performed for CMV viremia incidence, number of readmission, and readmission LOS, respectively. The forward stepwise method was used for model selection. Variables with $P < .3$ entered the multivariate models, and variables with $P < .1$ stayed in the final models. Statistical analyses were performed with R, version 3.5.1 (R foundation for Statistical Computing, Vienna, Austria. URL: https://www.r-project.org/).

RESULTS

Incidence of CMV Infection

Three hundred eighteen patients, including 88 CONV and 230 CD34-selected HCT recipients, were analyzed. Table 1 shows the baseline characteristics by HCT type. The differences in underlying disease, HLA mismatch, and conditioning regimen intensity between the 2 groups are inherent to our institutional algorithm. The overall incidence of CMV viremia was 26.3% in CONV and 41.9% in CD34-selected HCT (Figure 1A). Among CMV R^+ the incidence of CMV viremia was 46.6% in CONV and 66.3% in CD34-selected HCT (Figure 1B). The onset of CMV viremia from HCT was a median of 41 days (interquartile range [IQR], 35 to 49) and 28 days (IQR, 25 to 33) for CONV and CD34-selected HCT, respectively. CD34-selected HCT had a higher rate ($P = .0033$) and earlier onset of CMV viremia ($P < .0001$) compared with CONV HCT.

To identify predictors for CMV viremia, patient and transplant characteristics from Table 1 and acute GVHD (grades II to IV) were examined in univariate logistic models. Female sex, CD34 selection, CMV R^+, and CMV D^+ were associated with CMV viremia. In multivariate logistic model CD34 selection and CMV R^+ remained significant (Supplementary Table S1). The incidence of CMV viremia of CD34-selected HCT was 2.7 times more compared with CONV HCT (95% CI, 1.4 to 5.5) after adjusting for CMV R or D serostatus and HLA match.

CMV Disease

At 1 year the cumulative incidence of CMV end-organ disease was 2.3% in CONV and 6.1% in CD34- selected HCT (Figure 2). Thirteen of 230 CD34-selected HCT recipients developed CMV disease at a median of 134 days (IQR, 98 to 182) after HCT compared with 2 of 88 CONV HCT recipients who developed CMV disease at 19 and 44 days after HCT.

PET Use

Figure 3 shows the distribution of PET duration by specific cut-offs (top) and the number of PET days (bottom). Mean (standard deviation) and median (IQR) of PET days among patients who received PET are shown. A higher proportion of CD34-selected HCT recipients received > 60 days of PET.

Next, we estimated the number of PET days per 100 patient-days and the EUV (Table 2). Of 22 CONV HCT recipients with CMV viremia, 15 (68.2%) received PET. Of 96 CD34-selected HCT recipients with CMV viremia, 94 (97.9%) received PET. The EUV for PET was 852 days for CONV HCT and

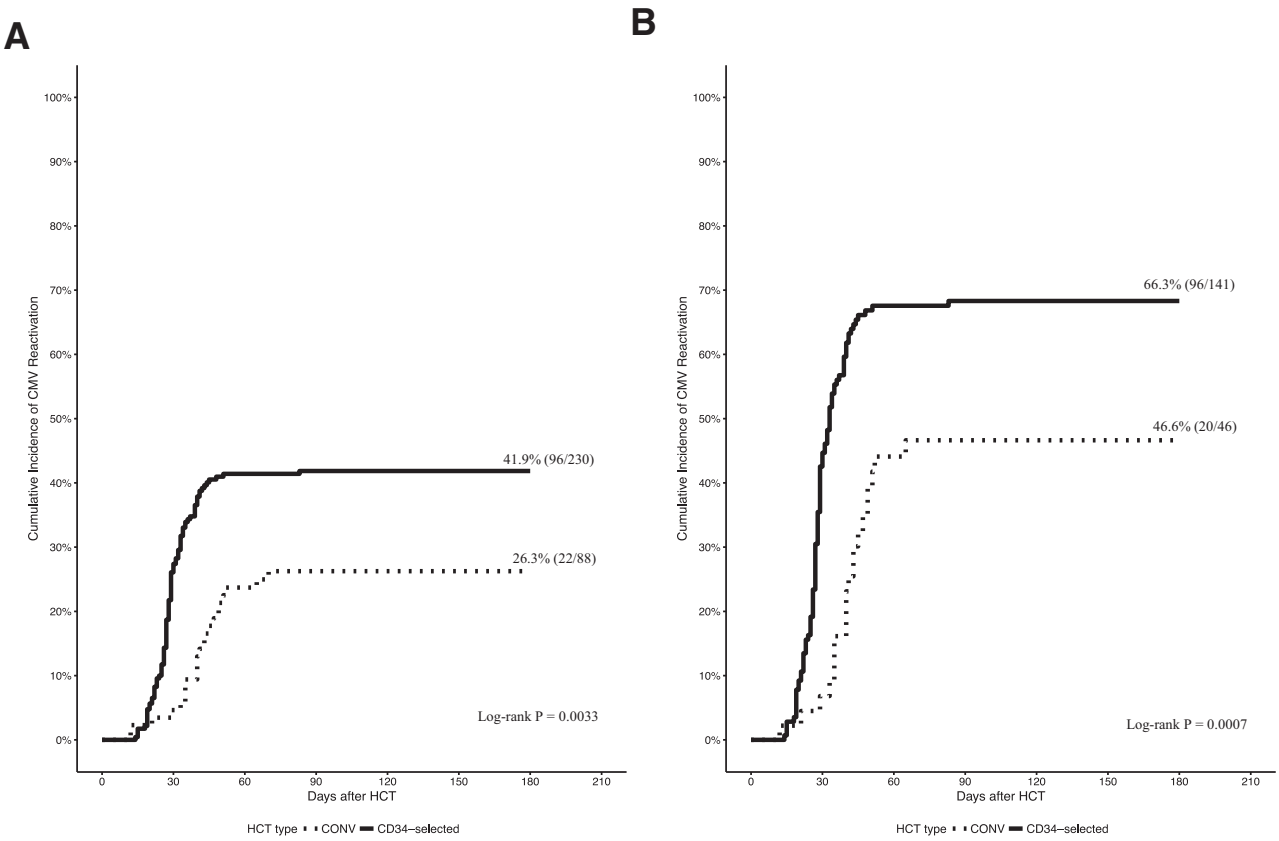


Figure 1. Cumulative incidence of CMV viremia. (A) Cumulative incidence of CMV viremia in CONV and CD34-selected HCT through day +180 after HCT. CMV viremia occurred at a median of 41 days (IQR, 35 to 49) after CONV HCT and 28 days (IQR, 25 to 33) after CD34-selected HCT. (B) Cumulative incidence of CMV viremia among CMV R+ CONV HCT and CD34-selected HCT through day +180 after HCT.

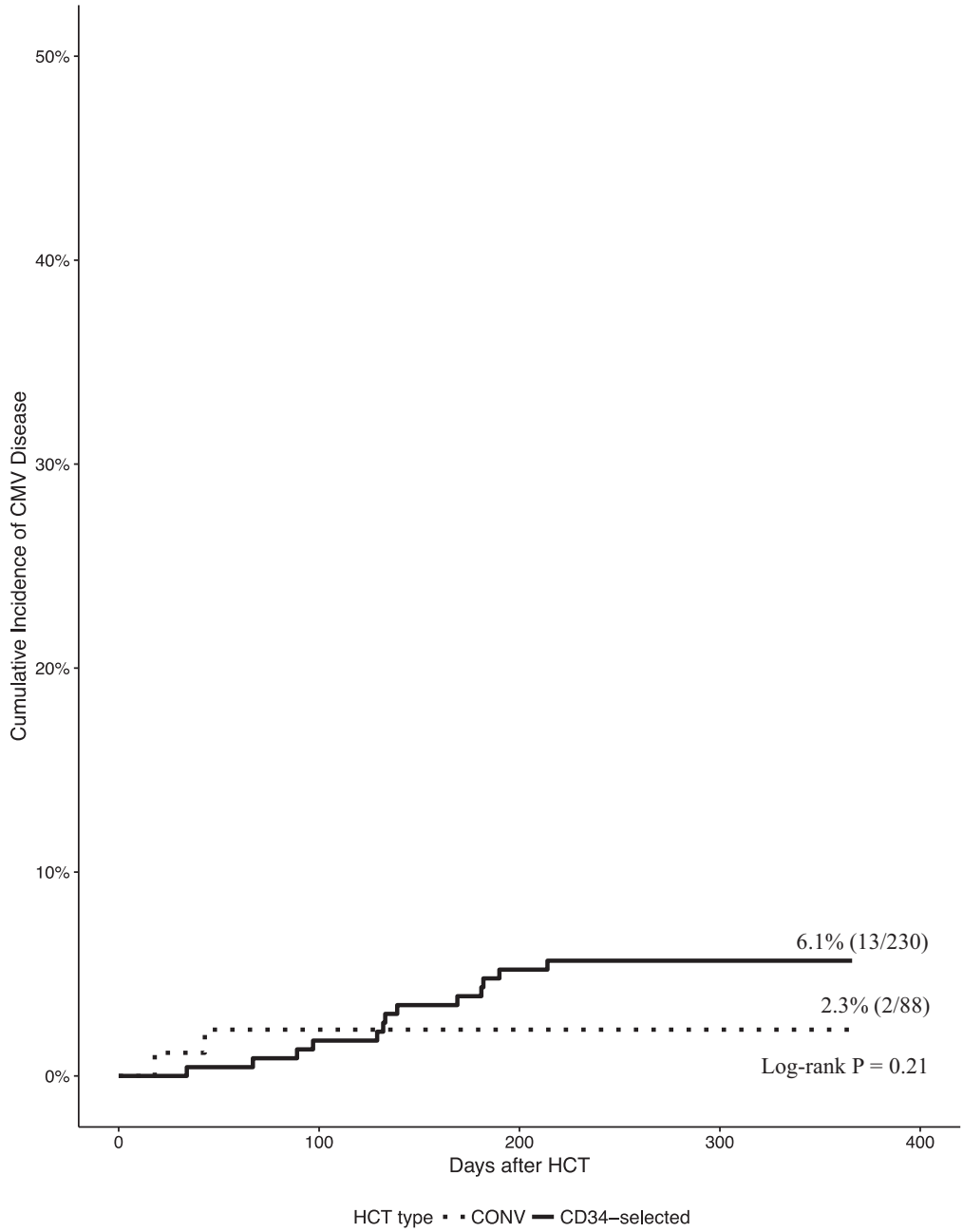


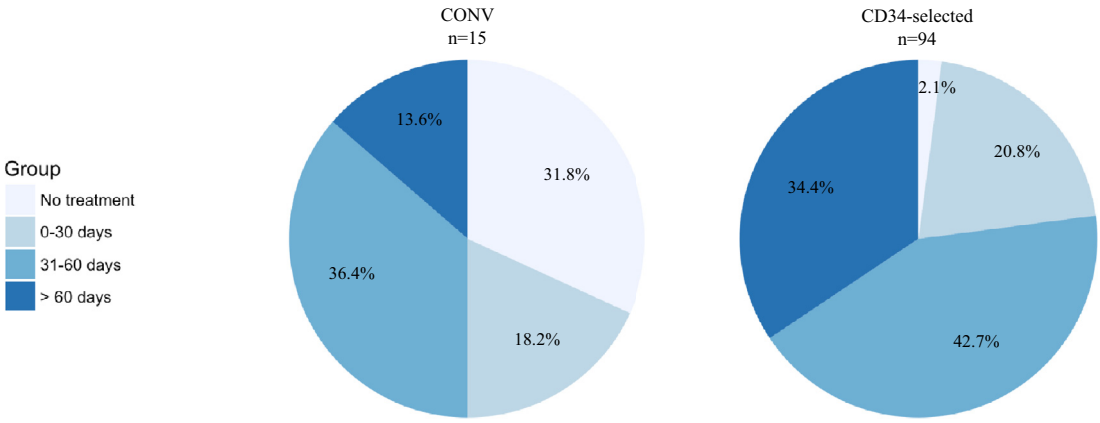
Figure 2. Cumulative incidence of CMV end-organ disease for CONV and CD34-selected HCT at 1 year after HCT. Two of 88 CONV HCT recipients developed CMV disease at 19 and 44 days after HCT. Thirteen of 230 CD34-selected HCT recipients developed CMV disease at a median of 134 days (IQR, 98 to 182) after HCT.

2821 days for CD34-selected HCT. The EUV for CD34-selected HCT was 3-fold higher compared with CONV HCT.

Healthcare Use

Table 3 shows a comparison of hospitalization metrics by day +180 among CMV R^-, CMV R^+ with CMV viremia, and CMV R^+ without CMV viremia. Next, we compared CMV R^+ with viremia with all patients without viremia (including R^- and R^+ without viremia). Among CD34-selected HCT, patients with CMV viremia had more readmissions, longer readmission LOS, and total LOS compared with patients without CMV viremia. In contrast, among CONV HCT the hospitalization metrics were similar between patients with viremia and without viremia.

Reasons for readmission were categorized as related to CMV, viral infection (not CMV), infection (nonviral), GVHD, or other. Among CONV HCT, CMV accounted for 9.6% and viral infection (not CMV) for 0% of readmissions. In contrast, GVHD and nonviral infections accounted for 35% of readmissions. Among CD34-selected HCT, CMV accounted for 34.5% and viral infections (non-CMV) for 13% of readmissions, whereas GVHD and nonviral infections combined accounted for 9.8% of all readmissions. Supplementary Table S2 shows number of readmission, readmission LOS, and total LOS by HCT type and CMV viremia by day +180. We also report the number of well days as a measure of days alive and not hospitalized.



PET duration, days	Antiviral	CONV	CD34-selected
Mean (sd)	Val(GVC)	34.7 (19.2)	56.5 (48.2)
	Foscarnet	30.2 (21.6)	29.3 (24.6)
Median (IQR)	Val(GVC)	37 (21-45)	41 (26-68)
	Foscarnet	29 (15.3-36)	23(10-39.3)

Figure 3. PET use by day 180 among CONV and CD34-selected HCT. (Top) Percentage of patients with CMV viremia by cut-off for PET duration (no PET, <30 days, 31 to 60 days, and >60 days). Fifty percent of CONV HCT recipients and 10% of CD34-selected HCT recipients received PET for <30 days. In contrast, 13.8% and 34.4% of CONV HCT recipients and CD34-selected HCT recipients, respectively, received PET for >60 days. (Bottom) Mean (standard deviation) and median (IQR) number of antiviral days among patients who received PET.

Table 2
Treatment Days among Patients Receiving PET Through Day +180

	CONV (n = 22)	TCD (n = 96)
No. (%) of PET among patients with CMV viremia		
Val(GVC)	15 (68.2)	87 (90.6)
Foscarnet	6 (27.3)	40 (41.7)
Total	15 (68.2)	94 (97.9)
Total duration per 100 patient-days		
Val(GVC)	19.6	33.1
Foscarnet	17.5	18.1
Total*	26.4	38.2
EUV,† days		
Val(GVC)	633	2262
Foscarnet	226	569
Total	852	2821

Val(GVC) indicates valganciclovir or ganciclovir.
* Adjusted for overlap.
† EUV provides the number of PET days by day +180 for a hypothetical cohort of 100 patients based on our observed rates.

To estimate the impact of CMV on hospitalization metrics we estimated SIR. In CONV HCT the SIR for number of readmissions, readmission LOS, and total LOS was increased for patients with CMV viremia compared with patients without CMV viremia (Figure 4, top). CONV patients without viremia had similar well days (days alive and out of the hospital by day +180; median, 150 days; IQR, 78 to 160) compared with patients with CMV viremia (median, 142 days; IQR, 75 to 156; $P = .60$).

In CD34-selected HCT the SIR for number of readmissions, readmission LOS, and total LOS was increased for patients with CMV viremia compared with no viremia (Figure 4, bottom). CD34-selected HCT recipients without viremia had more well days (median, 155 days; IQR, 138 to 162) compared with CD34-selected with HCT recipients CMV viremia (median, 145 days; IQR, 116 to 158; $P = .0003$).

Next, we tried to identify predictors for the number and LOS of readmissions. In univariate Poisson models CMV viremia, CMV R^+, HLA mismatch, and presence of GVHD (grades II to IV) were associated with more readmissions. In univariate models CMV viremia and HLA mismatch were associated with

Table 3
Hospitalization Metrics for CMV R^-, CMV R^+ with CMV Viremia, and CMV R^+ without CMV Viremia

	R^-	R^+ with Viremia	R^+ without Viremia	P*
No. of readmissions†				
CONV	0 (0-1)	1 (0-2)	0 (0-2)	.276
T cell depleted	0 (0-1)	1 (0-2)	0 (0-1)	.001
Readmission LOS,‡ days				
CONV	0 (0-8.8)	5 (0-19.3)	0 (0-12.8)	.375
T cell depleted	0 (0-9)	8 (0-22)	0 (0-9)	.001
Total LOS,§ days				
CONV	23 (18.3-34.5)	32.5 (25.5-61.5)	31 (20.5-38.3)	.090
T cell depleted	21 (17-32)	27 (21.8-48.3)	25 (18-31)	.002

Values are median (IQR).
* P value of Kruskal-Wallis test for comparison of medians of outcomes of interest among group.
† Number of readmissions after HCT to Day+180 or last follow-up.
‡ LOS from first readmission after HCT to Day+180 or last follow-up.
§ LOS from HCT infusion to Day+180 or last follow-up.

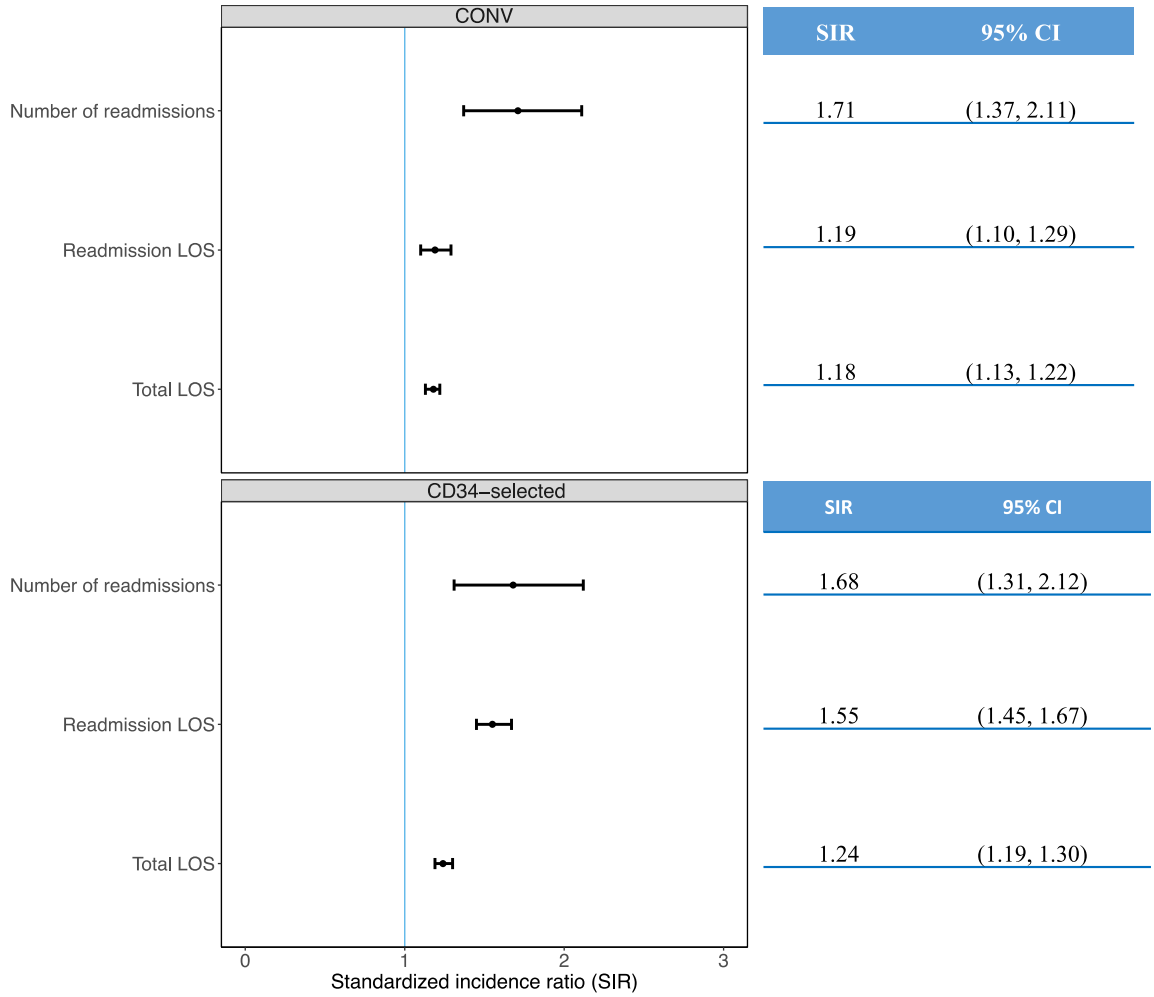


Figure 4. SIR (*dots*) with 95% CIs (*whiskers*) for number of readmissions, readmission LOS, and total LOS by day 180 after HCT. (Top) CONV HCT. (Bottom) CD34-selected HCT.

longer readmission LOS. The limited sample size and inflated zeros for number or readmissions and the non-Gaussian distribution of readmission LOS precluded multivariate analyses.

Overall Survival

Sixty-eight percent of CONV HCT recipients were alive at 1 year post-HCT. OS was 72.7% (16/22) and 65.2% (43/66) for CONV HCT recipients with and without CMV viremia, respectively ($P = .47$) (Figure 5, left).

Seventy-seven percent of CD34-selected HCT recipients were alive at 1 year. OS was 72.9% (69/96) and 79.4% (106/134) for CD34-selected HCT recipients with and without CMV viremia, respectively ($P = .19$) (Figure 5, right). Thirteen CD34-selected HCT recipients developed CMV end-organ disease. OS was 38.5% (5/13) and 78.3% (170/217) for CD34-selected with and without CMV end-organ disease, respectively ($P = .0007$) (Figure 6).

DISCUSSION

The impact of PET on reducing rates of CMV disease and associated mortality in HCT is well defined. In contrast, real-world studies quantifying PET and healthcare resource use in HCT managed with the preemptive approach are limited.

We analyzed a contemporary cohort of CONV and CD34-selected HCT from a major US institution. CD34 selection was the preferred HCT type for patients with AML in remission and MDS. Because of the stringent T cell depletion achieved by CD34 selection, recipients of CD34-selected HCT had higher rates of CMV compared with CONV HCT recipients. The higher incidence of CMV viremia and longer duration of PET in CD34-selected HCT contributed to the observed differences in use of PET and healthcare resources among the 2 HCT types. We have shown that delay of PET initiation in CD34-selected HCT is associated with persistent CMV viremia, antiviral resistance, and CMV end-organ disease [2,19]. Low viral thresholds for initiating PET in high-risk HCT (including CD34-selected) are used by other institutions [20]. We used the EUV to report the expected number of PET days for a cohort of 100 HCT and enable comparison between HCT types. The EUV for PET duration was 3-fold higher in CD34-selected HCT compared with CONV HCT.

Next, we examined healthcare resource use by the presence or absence of CMV viremia. The median LOS for readmissions for patients without CMV viremia and with CMV viremia was similar for CONV HCT. In contrast, among CD34-selected HCT, patients with CMV viremia had significantly longer readmission LOS compared with those without CMV viremia. Importantly, among CD34-selected HCT approximately one-third of readmissions were for management of CMV. Using SIR we showed increased number of readmissions, readmission LOS, and total LOS for both HCT types with CMV viremia. Effective CMV prevention has the potential of reducing LOS, and savings from

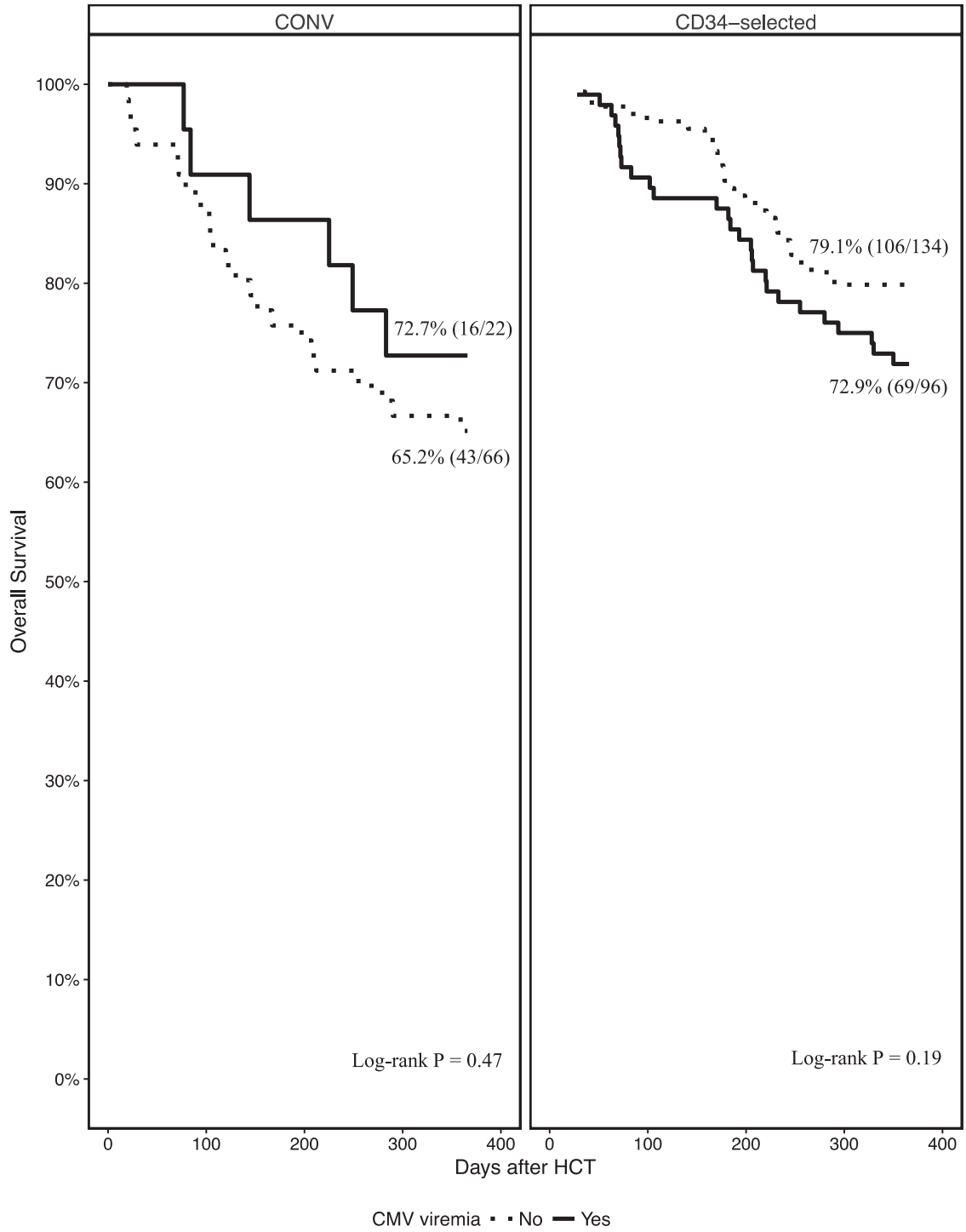


Figure 5. One-year OS at after HCT by CMV viremia. OS was similar for CONV HCT with and without CMV viremia ($P = .53$) (left) and CD34-selected HCT with and without CMV viremia ($P = .14$) (right).

reduced LOS need to be taken into consideration in cost–benefit analyses of prophylaxis, specifically in CD34-selected HCT. Although economic analyses were beyond the scope of our study, the currently ongoing randomized study PROGRESS II, BMT Clinical Trials Network 1301 (ClinicalTrials.gov Identifier: NCT02345850) comparing outcomes between CD34-selected and CONV HCT will provide data for such analyses.

Rates of CMV end-organ disease were similar across HCT types, confirming the effectiveness of PET in preventing CMV end-organ disease. Later occurrence of CMV end-organ disease in CD34-selected HCT recipients reflects delayed immune reconstitution. Persistent CMV viremia typically precedes CMV end-organ disease [2,19]. CMV end-organ disease was associated with decreased survival in CD34-selected HCT. In the pivotal phase III study patients who received letermovir prophylaxis in the first 100 days post-HCT had lower rates of CMV infection and a survival advantage through week 24 compared with patients treated preemptively [21]. Given the late

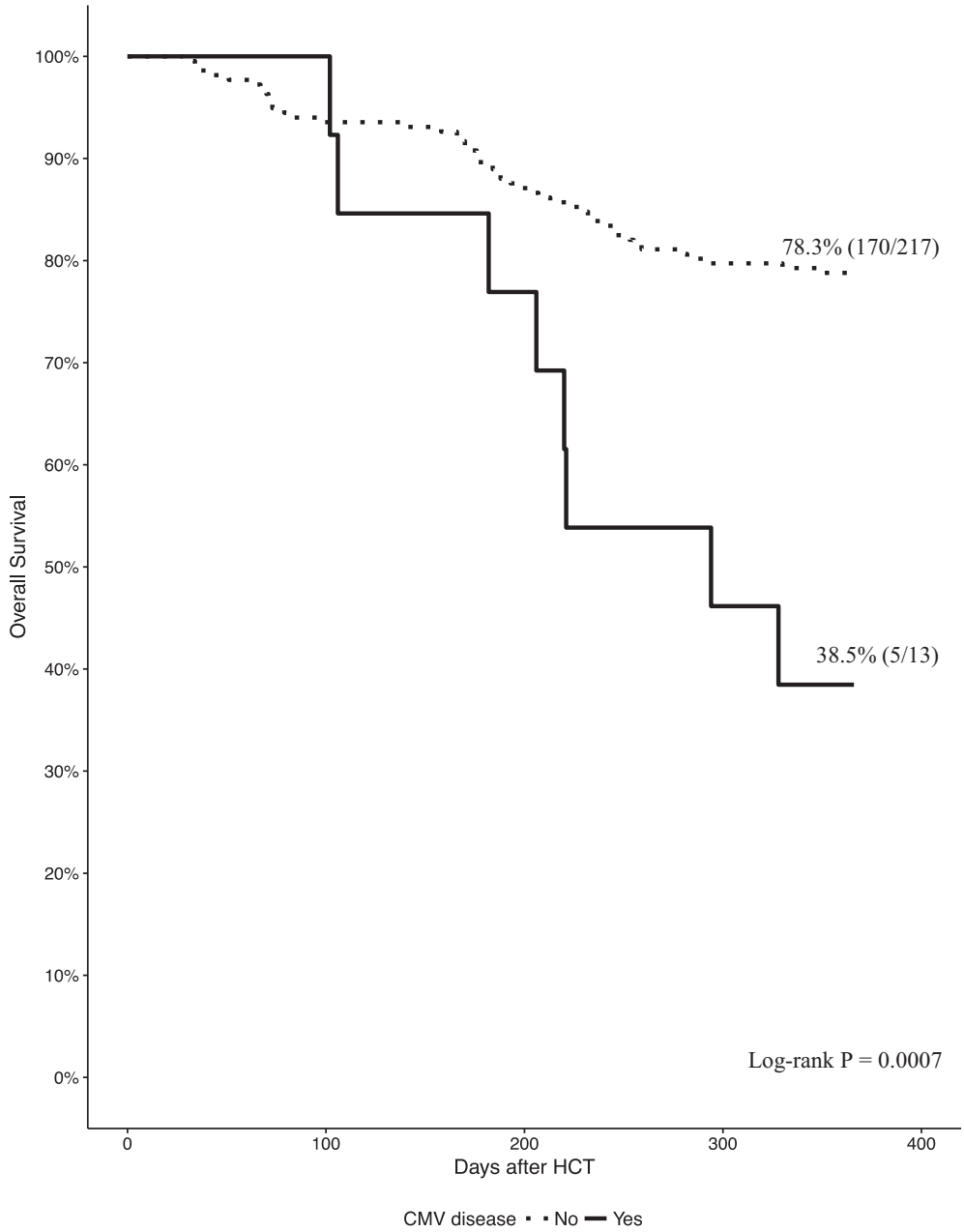


Figure 6. One-year OS by CMV end-organ disease in CD34-selected HCT. CMV end-organ disease was associated with lower OS ($P = .00069$).

onset of CMV disease in CD34-selected HCT, extended CMV prophylaxis beyond 100 days after HCT or other strategies to restore long-term CMV immunity may be warranted [22–24].

Our study has several limitations. First, CMV viremia was treated according to the standards of care at our institution. Because of inherent differences in types and stage of underlying disease between CONV and CD34-selected HCT, the risk for CMV infection is likely different. Although our standards for CMV management are in accordance with currently published guidelines endorsed by professional societies, variability exists across centers. As a result, our findings may not be applicable to centers with a different population mix or when new CMV antivirals and other modalities become available [25]. Our methodology may be used to generate center-specific data. Future studies in larger cohorts may enable development of integrative predictive algorithms for PET use after controlling for differences in patient characteristics and practice patterns.

In summary, we show differential PET use between 2 different HCT types; CD34-selected HCT had a 3-fold higher PET use compared with CONV HCT. CMV infection was associated with more frequent and prolonged readmissions. Among CD34-selected HCT management of CMV was the main reason for readmission (in approximately one-third of all readmissions). Our data provide a strong impetus for implementation of effective strategies for the management of CMV infection after HCT.

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Authorship statement: Y.-T.H. and Y.S. equally contributed to the work. Y.-T.H. and G.A.P. designed the research. Y.-T.H., S.J.K., P.N., D.B., and M.M. collected the data. Y.-T.H. and Y.S. performed analyses. Y.-T.H., Y.S., and G.A.P. prepared the figures and tables and wrote the manuscript with input from S.A.G., M.-A.P., and A.A.J.

SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.11.012.

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