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Health resource utilization and costs associated with multi-virus infection after allogeneic hematopoietic cell transplantation

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Introduction

- Patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) are at higher risk of primary viral infections and frequently reactivate multiple viruses due to preparative conditioning regimens and subsequent immune deficits.[1]
- In a cohort of 404 allo-HCT recipients, 90% had ≥1, 62% had ≥2 and 28% had ≥3 double-stranded (ds) DNA viruses detected within 100 days post allo-HCT.[2]
- DsDNA viral infections after allo-HCT are associated with increased mortality and pose a substantial economic burden on the health care system.[3,4]
- To date, there is little published evidence on the economic burden of multiple dsDNA viral infections during the post-transplant period.

Objectives

- To compare health care reimbursements, HRU and clinical outcomes between allo-HCT patients with no versus multiple dsDNA infections due to CMV, BKV, EBV, JCV, AdV, and HHV-6.

Methods

- Data source: US open source claims database obtained from the Decision Resources Group Real World Evidence Data Repository.[5]
- Baseline: 1-year period prior to the index allo-HCT
  Follow-up: 1-year period post allo-HCT.

DsDNA virus infections

- At least one diagnosis code within 1-year post allo-HCT for: BKV/EBV/JCV (grouped together due to lack of specific diagnosis codes), CMV, AdV, HHV-6,
- Patients were stratified as: 1, 2, ≥3, no dsDNA viral infections.

Study outcomes

- **Total healthcare reimbursement:** estimated from all submitted charges using a reimbursement-to-charge ratio of 0.425; reported in 2019 US dollars.
- **HRU:** Overall length of stay (LOS) and ICU days for index hospitalization and readmissions, readmission rate (per person year).
- **Clinical outcomes:** mortality, renal impairment.

Statistical analyses

- **Adjusted reimbursement:** Multivariable generalized linear model fitted with a negative binomial distribution.
- **All-cause mortality:** Multivariable Cox proportional hazards model with time-dependent and other baseline covariates.

Results

Study population

- 13,363 allo-HCT patients were identified (representing ~22% of allo-HCTs reported to CIBMTR for the study period) (Figure 1);
  - 3,949 (30%) were coded with 1 virus, 1,069 (8%) with 2, 238 (2%) with ≥3, 8,107 (61%) with none
- The median age at index (years) was 52 (IQR: 29—53), 41 (IQR: 17—58), 25 (IQR: 10—49) and 54 (IQR: 36—64) for patients with 1, 2, ≥3 viruses and patients with no viruses respectively.
- The majority of the patients had a malignant underlying disease (84.0%-89.1%) and underwent mobilized peripheral blood stem cell transplant (61.8%-72.4%).

Figure 1. Study population

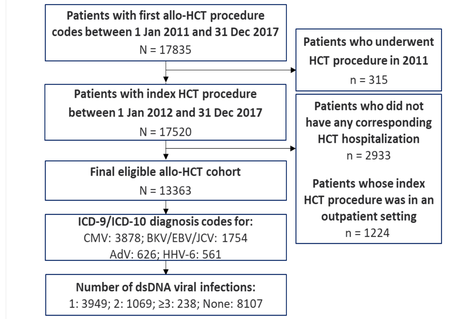


Table 1. Baseline Characteristics

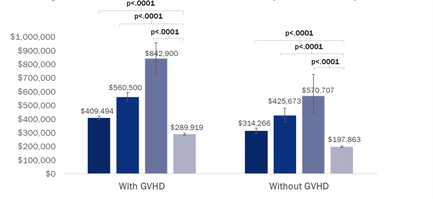
	Number of dsDNA viral infections within 1 year of allo-HCT				P-value
	1 (n=3949)	2 (n=1069)	≥ 3 (n=238)	None (n=8107)	
Age at index, Median [Q1 ; Q3]	52 [29 ; 63]	41 [17 ; 58]	25.0 [10 ; 49]	54 [36 ; 64]	<.0001
Sex, Female	1732 (43.9%)	465 (43.5%)	108 (45.4%)	3419 (42.2%)	0.2810
Underlying disease**					
Malignant	3503 (88.7%)	915 (85.6%)	200 (84.0%)	7224 (89.1%)	<.0001
Non-malignant immunodeficient	67 (1.7%)	27 (2.5%)	*	77 (1.0%)	
Non-malignant immunocompetent	346 (8.8%)	112 (10.5%)	26 (10.9%)	518 (6.4%)	
Inherited metabolic disorders	10 (0.3%)	7 (0.7%)	*	15 (0.2%)	
Unknown	23 (0.6%)	8 (0.8%)	7 (3.0%)	273 (3.4%)	
Stem cell source					
Bone Marrow	549(13.9%)	150 (14.0%)	32 (13.5%)	1066 (13.2%)	<.0001
Peripheral Blood	2858 (72.4%)	712 (66.6%)	147 (61.8%)	5687 (70.2%)	
Cord Blood	276 (7.0%)	128 (12.0%)	40 (16.8%)	351 (4.3%)	
Unknown	266 (6.7%)	79 (7.4%)	19 (8.0%)	1003 (12.4%)	
Number of comorbidities					
0	580 (14.7%)	127 (11.9%)	30 (12.6%)	1573 (19.4%)	<.0001
1-2	1985 (50.3%)	582 (54.4%)	126 (52.9%)	3927 (48.4%)	
≥3	1384 (35.1%)	360 (33.7%)	82 (34.5%)	2607 (32.2%)	

*SD: standard deviation *Cells with ≤5 observations are not reported*
***Non-exclusive categories*
†P-values derived from ANOVA test for continuous variables and Chi-square test for categorical variables to test for significant differences across the four groups

Total healthcare reimbursement

- Unadjusted mean total healthcare reimbursements were: no virus, $266,345; 1, $431,614; 2, $639,097; ≥3, $964,378 (p<.0001).
- Unadjusted mean total healthcare reimbursements per day survived were: no virus, $1,295; 1, $1,768; 2, $2,460; ≥3, $3,373 (p<.0001).
- After adjusting for age, health insurance plan, underlying disease, stem cell source, costs at baseline, and follow-up time (Figure 2):
  - For patients with GVHD, adjusted mean reimbursements were: no virus, $289,919; 1, $409,494; 2, $560,500; ≥3, $842,900 (p<.0001)
  - For patients without GVHD, adjusted mean reimbursements were: no virus, $197,863; 1, $314,266; 2, $425,673; ≥3, $570,707(p<.0001)

Figure 2. Adjusted total reimbursements (2019 USD)



Least square means and 95% CI derived from the adjusted generalized linear model

HRU

- HRU increased with the number of viral infections increased (Table 2).

Table 2. HRU in the first year after allo-HCT, stratified by number of dsDNA viral infections

	Number of dsDNA viral infections within 1 year of allo-HCT				P-value
	1 (n=3949)	2 (n=1069)	≥ 3 (n=238)	None (n=8107)	
Overall LOS (index and readmissions)					
Mean [SD]	61.4 [51.4]	77.0 [59.0]	103.3 [69.7]	41.3 [40.8]	<.0001
Median [Q1: Q3]	46.0 [28.0 ; 79.0]	59.0 [38.0 ; 97.0]	83.0 [54.0 ; 140.5]	29.0 [19.0 ; 49.0]	
Index hospitalization LOS					
Mean [SD]	31.0 [29.6]	37.3 [31.8]	42.8 [34.1]	24.9 [22.7]	<.0001
Median [Q1: Q3]	25.0 [18.0 ; 35.0]	29.0 [21.0 ; 42.0]	32.0 [23.5 ; 48.5]	22.0 [15.0 ; 29.0]	
Patients with any ICU stay	**992 (25.1%)**	**336 (31.4%)**	**80 (33.6%)**	**1757 (21.7%)**	**<.0001**
Number of days in ICU					
Mean [SD]	29.4 [22.3]	33.5 [30.9]	37.9 [39.9]	26.9 [20.8]	<.0001
Median [Q1: Q3]	26.0 [18.0 ; 34.0]	28.0 [19.0 ; 38.5]	27.5 [12.5 ; 45.5]	24.0 [17.0 ; 31.0]	
Patients with any readmission after index LOS after index	**2850 (72.2%)**	**859 (80.4%)**	**211 (88.7%)**	**4214 (52.0%)**	**<.0001**
Mean [SD]	42.1 [45.5]	49.4 [51.3]	68.0 [63.7]	31.6 [39.5]	<.0001
Median [Q1: Q3]	26.5 [11.0 ; 58.0]	33.0 [14.0 ; 66.0]	44.0 [21.0 ; 99.0]	17.0 [7.0 ; 41.0]	
Patients with any ICU stay after index	**1366 (34.6%)**	**443 (41.4%)**	**118 (49.6%)**	**1885 (23.3%)**	**<.0001**
Number of days in ICU					
Mean [SD]	21.4 [26.9]	23.7 [30.4]	27.1 [40.2]	16.0 [21.6]	<.0001
Median [Q1: Q3]	11.0 [4.0 ; 27.0]	14.0 [4.0 ; 34.0]	11.0 [3.0 ; 30.0]	8.0 [3.0 ; 20.0]	
Readmission rate (per person yr) (95% CI)	2.5 (2.5 - 2.6)	3.4 (3.3 - 3.5)	4.7 (4.4 - 4.9)	1.5 (1.5 - 1.5)	<.0001

SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile; CI: confidence interval; LOS: length of stay; ICU: intensive care unit; †P-values derived from ANOVA test for continuous variables, Chi-square test for categorical variables and likelihood ratio test for rate variables to test for significant differences across the four groups

Clinical outcomes

- Among patients with GVHD (Table 3):
  - All-cause mortality rate increased significantly from 16.8% for patients with no viral infections to 21.0%, 21.4%, and 21.1% in patients with 1, 2, ≥3 viral infection respectively (p<.0001)
  - New diagnosis of renal impairment increased significantly from 22.3% for patients with no viral infections to 27.5%, 33.5%, and 35.7% in patients with 1, 2, ≥3 viral infection respectively (p<.0001)
- Among patients without GVHD (Table 3):
  - New diagnosis renal impairment increased significantly from 14.6% for patients with no viral infections to 20.9%, 21.7%, and 30.2% in patients with 1, 2, ≥3 viral infection respectively (p<.0001)
- The multivariable Cox proportional hazards model showed that increasing number of dsDNA viral infections were associated with a higher risk of mortality as compared to patients with no dsDNA viral infection (p<.0001) (Figure 3):
  - 1 infection: HR=1.5; 95% CI=1.3—1.6
  - 2 infections: HR=2.0; 95% CI=1.7—2.3
  - ≥3 infections: HR=2.5; 95% CI=1.8—3.3
- In addition, time-dependent development of GVHD, higher age, type of underlying disease and stem cell source, higher number of comorbidities at baseline were also significant predictors of mortality.
  - Interaction between number of dsDNA viral infections and GVHD was not statistically significant

Figure 3. Cox proportional hazards model (multivariable analysis)

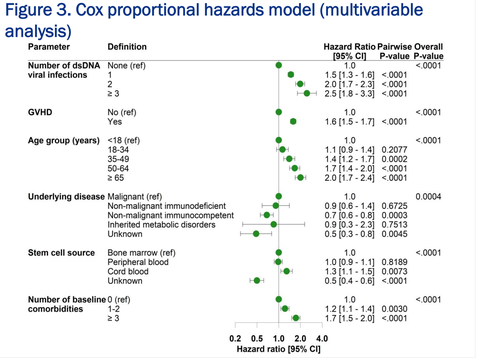


Table 3. Clinical outcomes in the first year after allo-HCT, stratified by number of dsDNA viral infections

	Number of dsDNA viral infections within 1 year of allo-HCT				P-value
	1 (n=3949)	2 (n=1069)	≥ 3 (n=238)	None (n=8107)	
Allo-HCT patients with GVHD	**3063 (77.6%)**	**857 (80.2%)**	**185 (77.7%)**	**4794 (59.1%)**	**<.0001**
All-cause mortality	643 (21.0%)	183 (21.4%)	39 (21.1%)	806 (16.8%)	<.0001
Renal impairment during baseline	682 (22.3%)	170 (19.8%)	30 (16.2%)	1028 (21.4%)	0.1364
New diagnosis of renal impairment	843 (27.5%)	287 (33.5%)	66 (35.7%)	1069 (22.3%)	<.0001
Allo-HCT patients without GVHD	**886 (22.4%)**	**212 (19.8%)**	**53 (22.3%)**	**3313 (40.9%)**	**<.0001**
All-cause mortality	194 (21.9%)	47 (22.2%)	6 (11.3%)	673 (20.3%)	0.2423
Renal impairment during baseline	178 (20.1%)	40 (18.9%)	6 (11.3%)	729 (22.0%)	0.1308
New diagnosis of renal impairment	185 (20.9%)	46 (21.7%)	16 (30.2%)	485 (14.6%)	<.0001

†P-values derived from Chi-square test for categorical variables to test for significant differences across the four groups; Renal impairment was defined through ICD-9 and ICD-10 diagnosis codes for glomerular diseases, renal tubulo-interstitial diseases, acute kidney failure and chronic kidney disease, urolithiasis, other disorders of the kidney and the ureter, kidney injury, and dialysis.

Limitations

- The identification of dsDNA viral infections in a claims database may underestimate the true incidence, as there is a potential for underreporting due to the use of non-specific diagnosis codes and under-coding of identified infections.
- There is also a lack of granularity in the severity of GVHD in the diagnosis codes of GVHD.
- The claims data do not include information for events outside the hospital, such as out-of-hospital deaths.
- The total reimbursed amount in our study was estimated through a reimbursement to charge ratio of 0.425 derived from ~20% of submitted-remitted overlapping claims, which is an estimated reimbursement.

Conclusions

- Allo-HCT patients with multiple dsDNA viral infections have significantly higher health care costs and HRU in the first year after allo-HCT, further amplified by the presence of GVHD.
- After adjusting for baseline characteristics and follow-up time, health care costs were significantly higher in allo-HCT patients with multiple dsDNA viral infections, in patients with or without GVHD.
- Allo-HCT patients with multiple dsDNA viral infections have worse clinical outcomes including greater renal impairment (irrespective of the presence of GVHD) and higher mortality rate for patients with GVHD.
- Patients with increasing number of viral infections had a higher risk of all-cause mortality, after adjusting for GVHD and baseline characteristics.
- Improved dsDNA virus treatment and prevention strategies may reduce costs and improve outcomes.

References

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Disclosures

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- JAH has disclosures for Allogene, AlloVir, Gilead, Karius, Takeda; RTM has disclosures for AlloVir, Artiva Biotherapeutics, Athersys, BMS/ Celgene, RSPR, Fate Therapeutics, Incyte, Kite Therapeutics, Novartis, Omeros, PACT Pharma; SHM is an employee of AlloVir, Inc., where he is also a shareholder; ZZ and AC are employees of Certara, and led the development of study design, implementation of the statistical analyses and reporting of study results as independent contractors for AlloVir, Inc.; MJB has disclosures for AlloVir, EvrysBio (share options), Gilead, GSK, Helocyte, Merck, SymBio, VirBio.