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A systematic review and meta-analysis of HHV-6 and mortality after hematopoietic cell transplant

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Human herpesvirus-6B (HHV-6B) reactivation has been associated with non-relapse mortality (NRM) and overall mortality (OM) following allogeneic hematopoietic stem cell transplant (HCT). We performed a systematic review and meta-analysis to better quantify the association. Studies were included if they systematically tested a cohort of HCT recipients for HHV-6 infection or reactivation and described mortality for patients with and without HHV-6B. Random effects models were used to assess the pooled effect of HHV-6B positivity on each outcome of interest. Bayesian aggregation was additionally performed if models included 10 or fewer studies. Eight studies were included in the NRM analysis, which demonstrated a significant association between HHV-6 detection and NRM (pooled effect: 1.84; 95% CI: 1.29–2.62) without significant heterogeneity ($I^2 = 0.0\%$, $p = 0.55$). A Bayesian aggregation of the raw data used to construct the NRM random effects model supported these findings (95% credible interval: 0.15–1.13). Twenty-five studies were included in OM analysis, which showed a significant positive association (pooled effect: 1.37; 95% CI: 1.07–1.76), though considerable heterogeneity was observed ($I^2 = 36.7\%$, $p < 0.05$). HHV-6 detection is associated with NRM and OM following HCT. Randomized trials are warranted to evaluate if preventing or treating HHV-6B reactivation improves outcomes.

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INTRODUCTION

HHV-6 is a member of the *Roseolovirus* genus of the beta-herpesvirus subfamily of human herpesviruses [1]. Human herpesvirus 6 (HHV-6) is the collective name of two HHV-6 species, HHV-6A and HHV-6B. The epidemiology of HHV-6A has not been defined. In contrast, HHV-6B infects most individuals in early childhood and the virus reactivates in 30-70% of HCT recipients [2–6]. Because HHV-6B is the pathogenic species known to reactivate in HCT, the current work focuses on evaluating HHV-6B and mortality [7]. Risk factors associated with HHV-6B reactivation include receiving allogeneic (versus autologous) HCT, myeloablative conditioning regimen, transplants from unrelated or human leukocyte antigen (HLA)-mismatched donors, and umbilical cord blood transplants [3, 4, 8–13]. HHV-6B reactivation has been associated with subsequent encephalitis, central nervous system (CNS) dysfunction, bone marrow suppression, acute graft-versus-host-disease (aGVHD), cytomegalovirus (CMV) reactivation, lower respiratory tract disease, and mortality [2, 4, 5, 8–10, 13–29].

While some studies have reported an association between HHV-6B and mortality [20, 22, 30–36], results have been conflicting [37]. To date, no prior work has systematically aggregated data from studies of HHV-6B and mortality. The goal of the current study is to fill this gap and characterize mortality outcomes in HCT recipients documented to have HHV-6B reactivation compared to those without HHV-6B reactivation.

METHODS

A search of the PubMed database was performed using the terms:

(hematopoietic OR stem cell OR cord blood OR bone marrow OR transplant*)

AND

(HHV-6 OR MeSH term: herpesvirus 6 OR HHV6 OR human herpesvirus-6 OR HHV-6B OR HHV6B OR human herpesvirus-6B OR HHV-6A OR HHV6A OR human herpesvirus-6A)

This search was performed according to PRISMA guidelines [38] on 2/1/24 and returned 1,319 results. Manuscripts (or studies) were screened for the following entry criteria (1) inclusion of a cohort of HCT recipients systematically tested for HHV-6 (2) report of the number of patients with HHV-6 infection or reactivation, and (3) report of the number of patients with at least one outcome of interest. Outcomes of interest included non-relapse mortality (NRM), relapse-related mortality (RM), overall survival (OS), treatment-related mortality (TRM), and overall mortality/all-cause mortality (OM/ACM). In instances where raw data describing an outcome of interest by HHV-6B positivity were unclear or not described, the study's authors were contacted to request these data.

Definitions

NRM was defined as any mortality not attributable to relapse. ACM and OM were defined as mortality due to any reason. OS was defined as survival during the follow up period. RM was defined as mortality due to relapse of disease. TRM was defined as mortality attributed to any treatment-related cause. Studies that assessed OS or ACM were converted to OM by

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subtracting the number of patients who survived from the total number of patients whose outcomes were described.

Statistical analysis

Study effect sizes were calculated as odds ratios using the raw data for the number of HHV-6B positive and negative patients who did and did not experience each outcome of interest. Studies that did not include at least 10 patients with and 10 patients without HHV-6B detection were excluded from statistical models. Studies were divided into OM, RM, NRM, and TRM. Random effects models were used to pool the effect sizes using the Mantel-Haenszel method [39], with a Paule-Mandel estimator for τ^2 [40] and Hartung-Knapp adjustments [41]. Models were assessed for heterogeneity using an I^2 test and Cochrane's Q [42]. Subgroup analyses by stem cell source (CBT, non-CBT, CBT and non-CBT, or source unclear), age of cohort (adult, pediatric, or both), and follow up period (less than the median follow-up period of all studies, or greater than or equal to the median follow up period of all studies) were performed. These analyses were included in the main results if all subgroups contained at least 3 studies and were otherwise detailed in the supplementary materials (pages 4-6, and 8-10) due to the limited utility of subgroup analyses with a small number of studies.

In models that contained 10 or more studies, publication bias was assessed with a linear regression of funnel plot asymmetry using the algorithm described by Peters et al. [43] for binary outcome data. In models with 10 or fewer studies, raw data were evaluated with Bayesian aggregation of the treatment effect on the logarithm of the odds ratio (logOR). The rationale for this additional analysis is that Bayesian modeling provides additional context to the results of random effects models that include a small number of studies due to the minimal impact of small datasets on Bayesian inferences. Rubin models with partial pooling and weakly informative priors were used. These models were constructed using the Markov Chain Monte Carlo method using 10 chains set to 20,000 iterations each and were not interpreted if r-hat exceeded 1.05.

RESULTS

Of the 1319 results, 1063 were excluded during screening, leaving 256 articles for full-text review. During full-text review, 185 articles were excluded and 71 articles met inclusion criteria. Among studies that met inclusion criteria, 28 were included in statistical analyses (based on the minimum number of patients required) with a total of 4241 patients included across all studies [2, 20–22, 30, 32–35, 44–62]. A PRISMA flowchart detailing reasons for exclusion is provided in Fig. 1. Characteristics of patients included in analyses are given in Table 1. A full dataset with all included and excluded studies, along with all collected data and all reasons for exclusion, is provided in

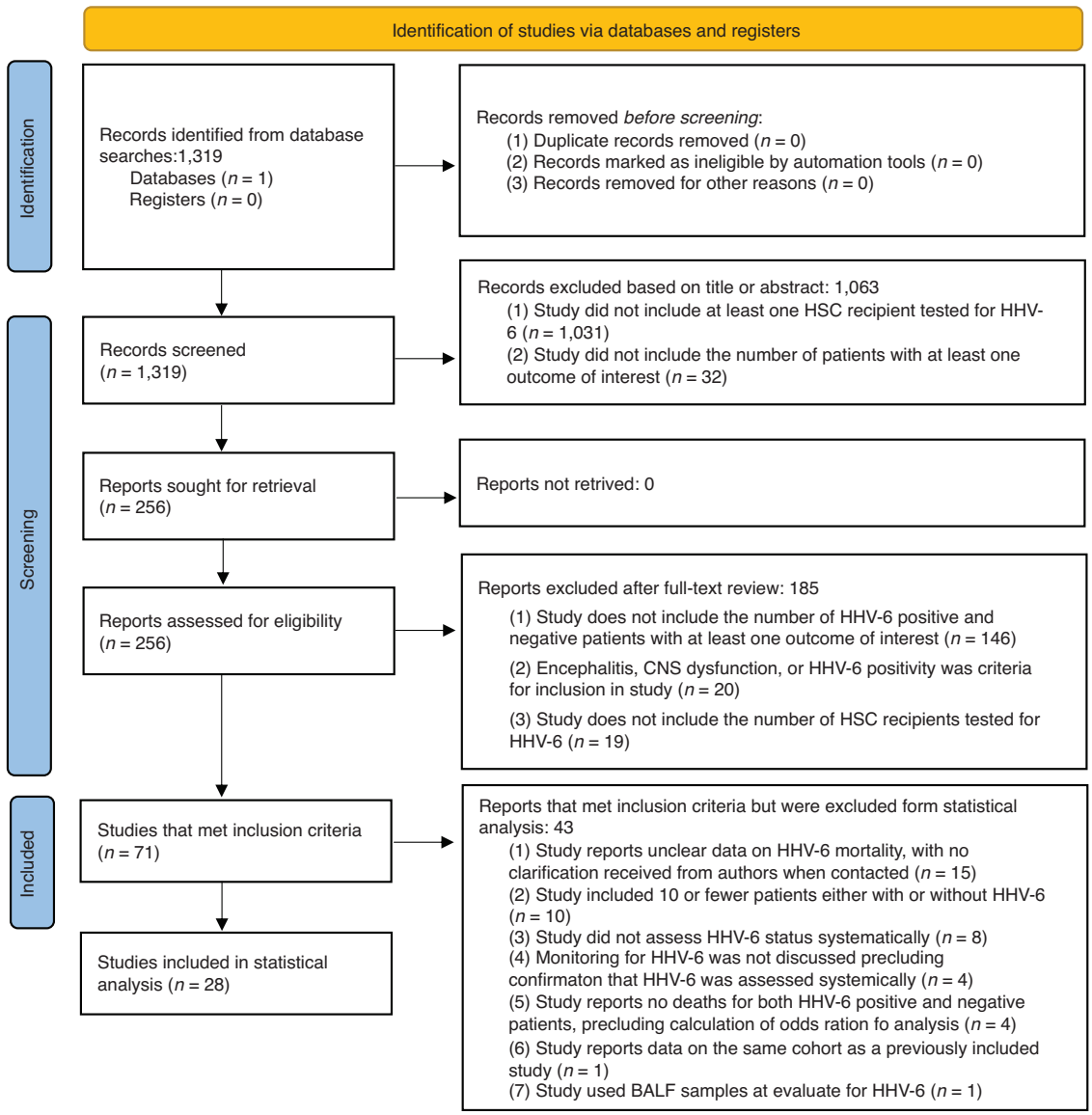

Fig. 1 PRISMA Flowchart.

Table 1. Characteristics of Included Studies.

Characteristics		Included in Statistcal Analysis	Included in OM Meta-Analysis (Fig. 3)	Included in NRM Meta-Analysis (Fig. 2)	Included in RM Meta-Analysis
Total Studies	*N*	28	25	8	7
Average number of patients per study	*N* (range)	151 (25–738)	162 (26–738)	191 (25–738)	229 (26–738)
Adult vs. pediatric studies % (age range)	Adult	9 (32.1%)	7 (28.0%)	3 (37.5%)	3 (42.9%)
	Pediatric	8 (28.6%)	7 (28.0%)	2 (25.0%)	1 (14.3%)
	Both	11 (39.3%)	11 (44.0%)	3 (37.5%)	3 (42.9%)
Study Design	Prospective	16 (57.1%)	15 (60.0%)	5 (62.5%)	4 (57.1%)
	Retrospective	12 (42.9%)	10 (40.0%)	3 (37.5%)	3 (42.9%)
Underlying diseases (N patients across all studies)	ALL	306 (6.2%)	221 (4.4%)	160 (12.5%)	207 (15.5%)
	AML	355 (7.3%)	342 (6.8%)	206 (16.1%)	193 (14.5%)
	CML	85 (1.7%)	78 (1.5%)	9 (0.7%)	12 (0.9%)
	NHL	15 (0.3%)	12 (0.2%)	7 (0.5%)	4 (0.3%)
	AML or MDS	146 (2.9%)	137 (2.7%)	12 (1%)	17 (1%)
	Myeloma	157 (3.1%)	141 (2.8%)	0 (0.0%)	16 (1.2%)
	Unspecified lymphoma	286 (5.8%)	275 (5.4%)	0 (0.0%)	11 (0.8%)
	Unspecified leukemia	1490 (40.0%)	1490 (29.5%)	0 (0.0%)	0 (0.0%)
	Neuroblastoma	7 (0.1%)	7 (0.1%)	0 (0.0%)	0 (0.0%)
	Unspecified malignancy	1274 (32.3%)	1263 (25.0%)	668 (52.2%)	657 (49.3%)
	Non-malignancy	509 (10.8%)	508 (10.0%)	146 (11.4%)	145 (10.9%)
	Unspecified	583 (12.6%)	583 (11.5%)	72 (5.6%)	72 (5.4%)
GVHD prophylaxis	CsA	219 (14.1%)	219 (13.4%)	58 (27.6%)	58 (19.5%)
	TAC	89 (5.3%)	89 (5.4%)	0 (0.0%)	0 (0.0%)
	MTX	22 (1.3%)	3 (0.2%)	19 (9.0%)	0 (0.0%)
	TAC + MTX	9 (0.5%)	9 (0.5%)	0 (0.0%)	0 (0.0%)
	Sirolimus	161 (10.0%)	161 (9.8%)	0 (0.0%)	0 (0.0%)
	Cyclophosphamide	101 (6.0%)	101 (6.2%)	0 (0.0%)	0 (0.0%)
	ATG	136 (8.3%)	136 (8.3%)	0 (0.0%)	0 (0.0%)
	alemtuzumab	34 (2.0%)	34 (2.1%)	0 (0.0%)	0 (0.0%)
	CsA + prednisolone	172 (10.7%)	172 (10.5%)	0 (0.0%)	0 (0.0%)
	CsA + unspecified steroids	26 (1.5%)	26 (1.6%)	26 (12.4%)	26 (8.7%)
	CsA + MTX	436 (32.5%)	431 (26.3%)	5 (2.4%)	0 (0.0%)
	CsA + MMF	82 (4.8%)	82 (5.0%)	0 (0.0%)	0 (0.0%)
	CsA + MMF + TAC	53 (3.1%)	0 (0.0%)	0 (0.0%)	53 (17.8%)
	MMF + MTX	3 (0.2%)	3 (0.2%)	0 (0.0%)	0 (0.0%)
	CsA MMF + MTX	174 (10.9%)	174 (10.6%)	102 (48.6%)	102 (34.2%)
	TAC/MTX/MMF	59 (3.4%)	0 (0.0%)	0 (0.0%)	59 (19.8%)
Conditioning regimen	RIC	1179 (34.7%)	1170 (34.6%)	400 (27.1%)	391 (27.0%)
	MAC	2223 (65.3%)	2207 (65.4%)	1074 (72.9%)	1058 (73.0%)
Studies that administered antiviral prophylaxis (N)	ACY	12 (42.9%)	10 (40.0%)	2 (25.0%)	2 (28.6%)
	GAN	2 (7.1%)	2 (8.0%)	0 (0.0%)	0 (0.0%)
	ACY and GAN	4 (14.3%)	4 (16.0%)	1 (12.5%)	1 (14.3%)
	IVIg	1 (3.6%)	0 (0.0%)	1 (12.5%)	0 (0.0%)
	Unclear or ND	9 (32.1%)	9 (36.0%)	4 (50.0%)	4 (57.1%)
Outcomes reported	(Range of mortality %)	4–65%	7–65%	4–42%	6–30%
Mean follow-up period	(Days and range)	99.9 (28–365)	99.9 (28–365)	87.6 (28–120)	87.6 (28–120)
HHV-6 Monitoring frequency	2x per week	1 (3.6%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
	1x per week	15 (53.6%)	12 (48.0%)	4 (50.0%)	3 (42.9%)
	1x per 2 weeks	1 (3.6%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
	Other	5 (17.9%)	5 (20.0%)	2 (25.0%)	2 (28.6%)
	Unclear or ND	6 (21.4%)	6 (24.0%)	2 (25.0%)	2 (28.6%)
Samples used for testing (N)	Whole blood	5 (17.9%)	5 (20.0%)	0 (0.0%)	0 (0.0%)
	Plasma	17 (60.7%)	16 (64.0%)	7 (87.5%)	6 (85.7%)
	PBMC	3 (10.7%)	2 (8.0%)	1 (12.5%)	0 (0.0%)
	Unclear or ND	3 (10.7%)	2 (8.0%)	0 (0.0%)	1 (14.3%)
Threshold for HHV-6 detection, copies/mL (N)	1000	4 (14.3%)	4 (16.0%)	1 (12.5%)	1 (14.3%)
	500	3 (10.7%)	3 (12.0%)	1 (12.5%)	1 (14.3%)
	200	1 (3.6%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
	125	1 (3.6%)	1 (4.0%)	1 (12.5%)	1 (14.3%)

Table 1. continued

Characteristics		Included in Statistcal Analysis	Included in OM Meta-Analysis (Fig. 3)	Included in NRM Meta-Analysis (Fig. 2)	Included in RM Meta-Analysis
	120	1 (3.6%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
	100	2 (7.1%)	2 (8.0%)	1 (12.5%)	1 (14.3%)
	50	3 (10.7%)	3 (12.0%)	0 (0.0%)	0 (0.0%)
	25	3 (10.7%)	3 (12.0%)	1 (12.5%)	1 (14.3%)
	20	1 (3.6%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
	10	1 (3.6%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
	Unclear or ND	8 (28.6%)	5 (20.0%)	3 (37.5%)	2 (28.6%)
Type of HCT	BMT	921 (16.5%)	850 (15.7%)	154 (11.8%)	914 (76.0%)
	CBT	753 (13.5%)	750 (13.8%)	864 (66.1%)	289 (24.0%)
	PBSC	1382 (24.7%)	1292 (23.8%)	289 (22.1%)	0 (0.0%)
	Unspecified	2538 (45.4%)	2538 (46.7%)	0 (0.0%)	0 (0.0%)

ALL Acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *NHL* Non-Hodgkin lymphoma, *MDS* Myelodysplastic syndrome, *RIC* Reduced-intensity conditioning, *MAC* myeloablative conditioning, *ACY* Acyclovir, *GAN* Ganciclovir, *ND* Not discussed, *OM* Overall mortality, *RM* Relapse mortality, *NRM* Non-relapse mortality.

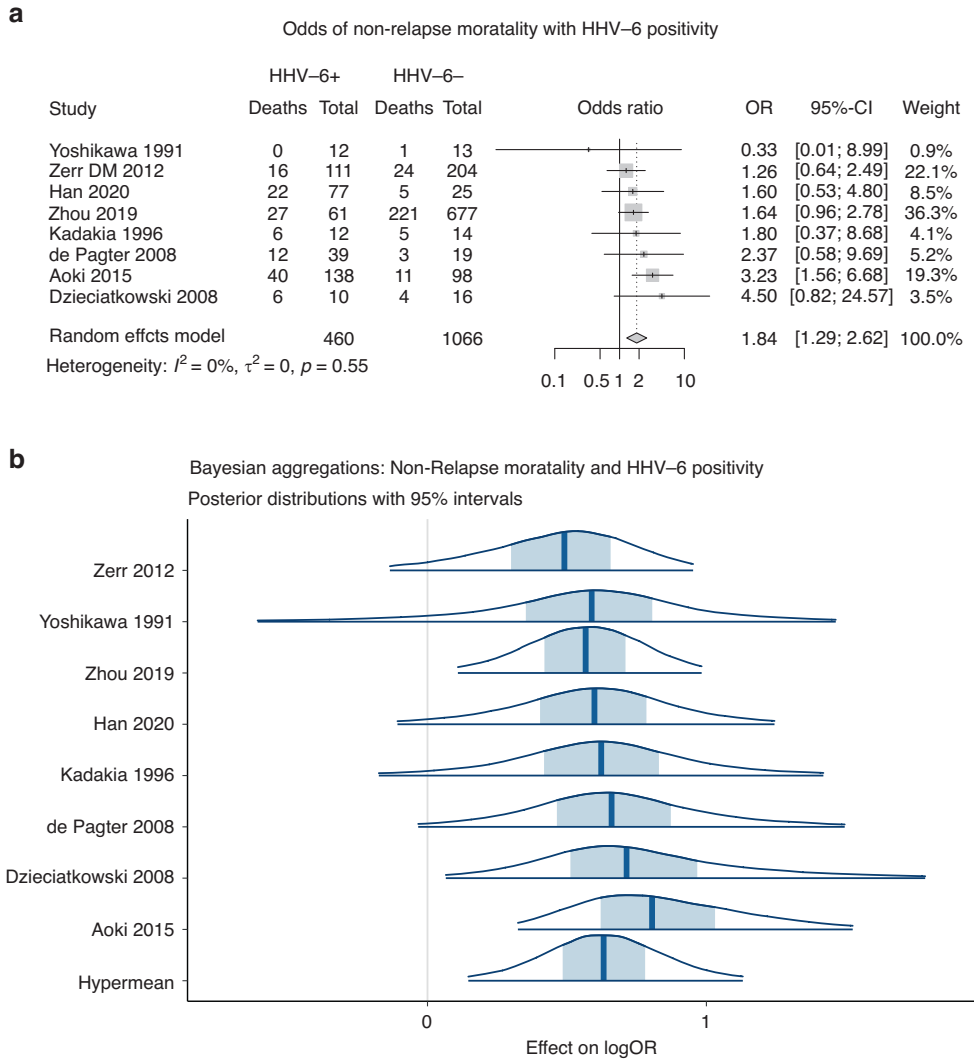

Fig. 2 **a** Non relapse mortality associated with HHV-6 positivity: Random effects model. **b** Non relapse mortality associated with HHV-6 positivity: Bayesian Aggregation.

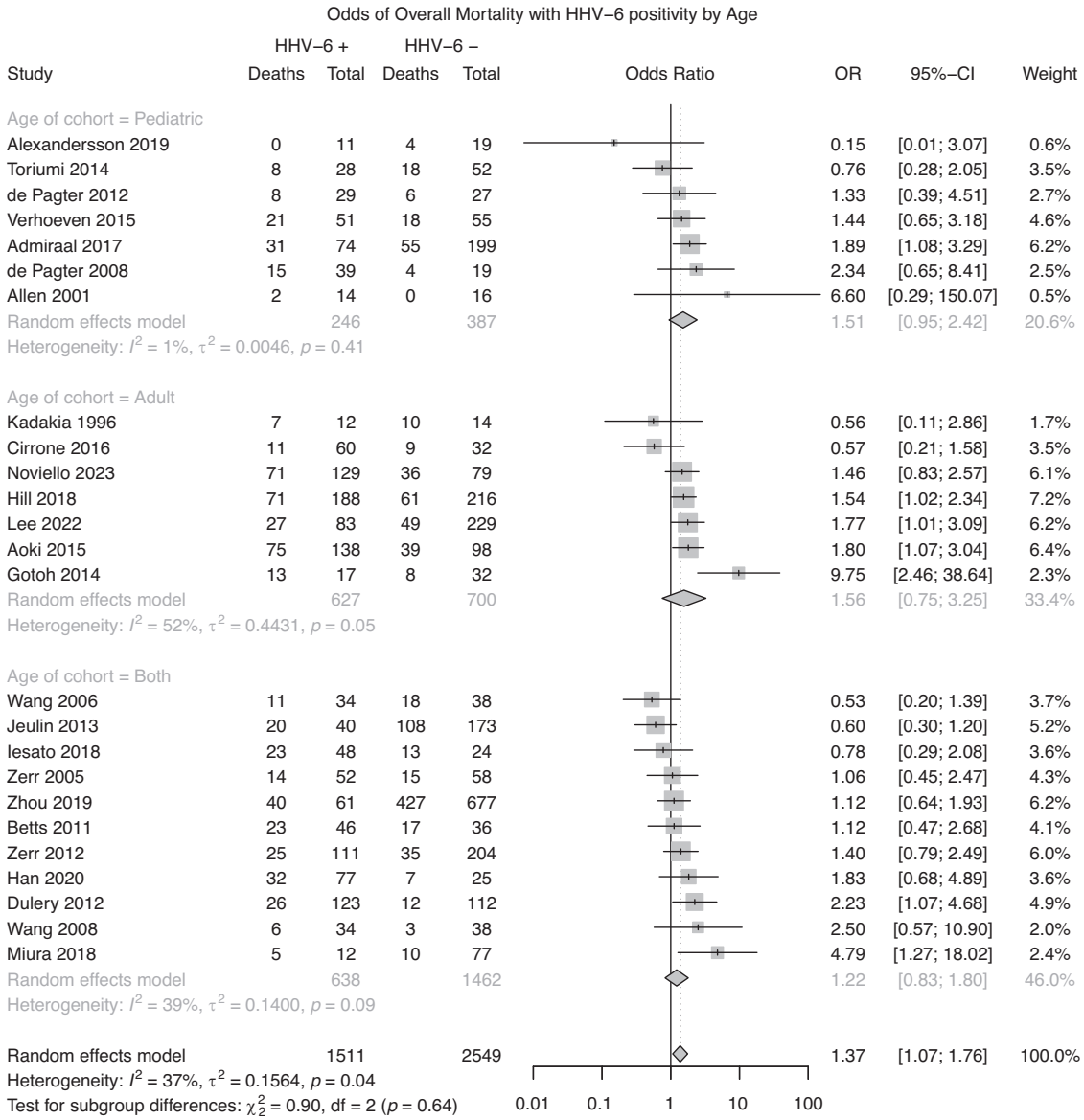

Fig. 3 **a** Risk of Overall Mortality with HHV-6 Positivity, Subgroup analysis by Stem Cell Source. **b** Risk of Overall Mortality with HHV-6 Positivity, Subgroup analysis by Age. **c** Risk of Overall Mortality with HHV-6 Positivity, Subgroup analysis by Follow-up Period.

Supplementary Table 1. Mortality data stratified by HHV-6 status is provided in Supplementary Table 2.

Of the 28 studies included in statistical analyses, 25 provided OM data, 8 provided NRM data, 7 provided RM data, and 1 provided TRM data. Models were not built to assess TRM because only 1 study was identified. Some studies described multiple outcomes of interest and were thus included in multiple analyses. Subgroup analyses for studies assessing OM were included in main results. An insufficient number of studies included the data required for subgroup analyses of RM and NRM; these results are available in the supplementary materials on pages 4-6, and 8-10 for completeness but are not described in the main results.

HHV-6B detection and non-relapse mortality

Eight studies were included in analysis of non-relapse mortality. A random effects model demonstrated a pooled effect size of 1.84 (95% CI: 1.29–2.62, $p < 0.01$), indicating that patients with HHV-6B detection had significantly increased odds of NRM (Fig. 2a). The model did not exhibit significant heterogeneity, with 0% of the observed effects attributed to variation between studies ($I^2 = 0.0\%$, $Q = 5.94$, $p = 0.55$).

Due to the small number of studies assessed, a Bayesian aggregation was performed to understand if the observed association may be influenced by the limited number of studies. The hypermean of the aggregate treatment effect on logOR was 0.63, with a 95% credible interval of 0.15 to 1.13 (Fig. 2b). This model can be interpreted as indicating that there is a 95% probability that patients diagnosed with HHV-6B infection or reactivation were between 15% and 113% more likely to have an outcome of NRM. These results provide reasonable confidence that HHV-6B positivity predicts non-relapse mortality, in support of the random effects model.

HHV-6B detection and overall mortality

Twenty-five studies were included in analysis of overall mortality. A random effects model demonstrated a pooled effect size of 1.37 (95% CI: 1.07–1.76, $p < 0.05$), indicating that patients with HHV-6B detection had significantly increased odds of death due to any cause. Significant heterogeneity was observed in the model, with 37% of the pooled effect attributable to between-study heterogeneity ($I^2 = 36.7\%$, $Q = 37.9$, $p < 0.05$). The heterogeneity

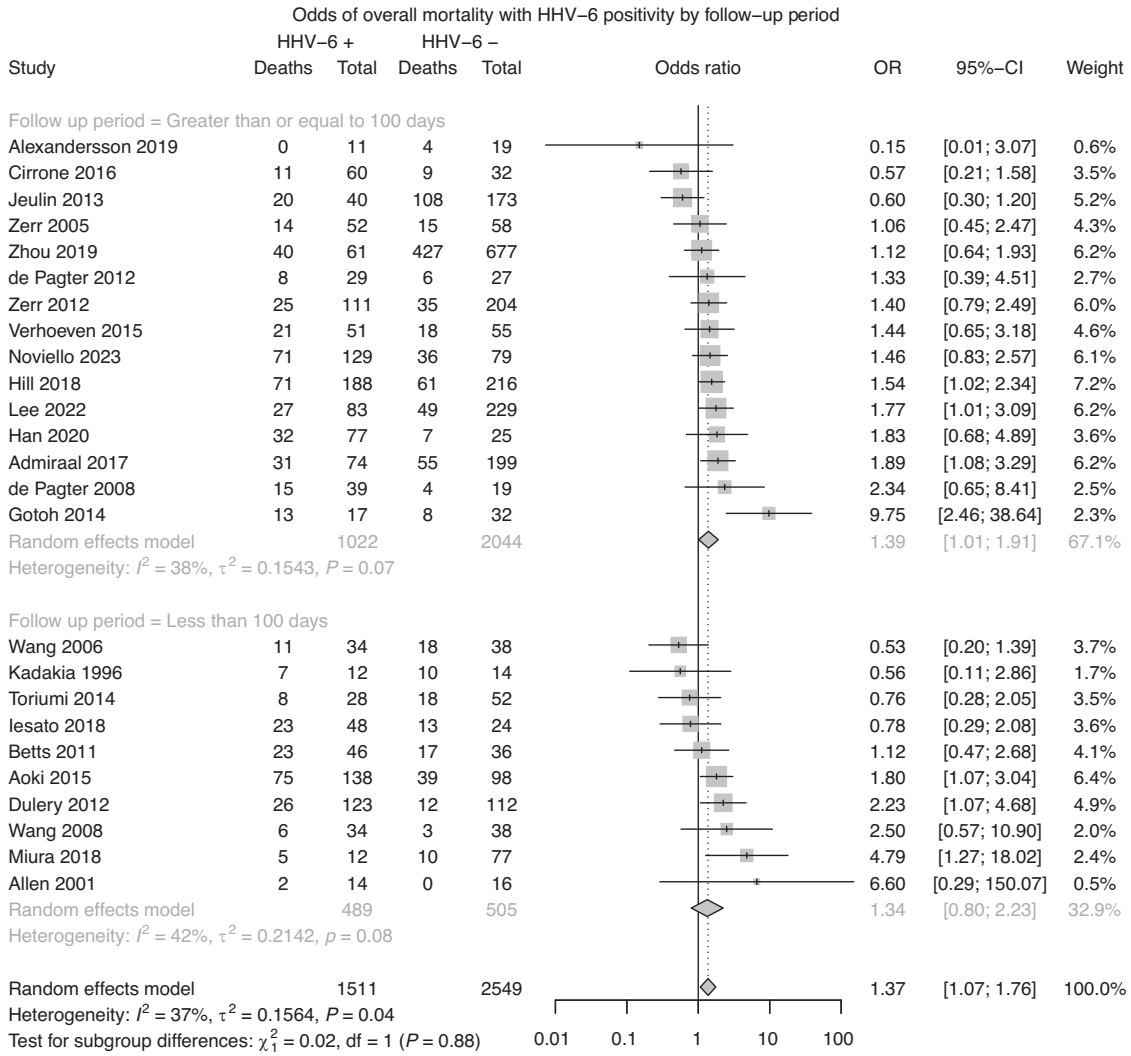

Fig. 3 Continued.

observed in the model suggests that the observed effect may be due to variation between studies, rather than a true pooled effect. Subgroup analyses did not reveal a significant difference between groups based on stem cell source (Q = 0.55, p = 0.91; Fig. 3a), age (Q = 0.90, p = 0.64; Fig. 3b), or follow-up period based on a median follow-up period of 100 days (Q = 0.02, p = 0.88; Fig. 3c). A test of funnel plot asymmetry did not indicate a significant influence of publication bias on the current results (t = −0.18, p = 0.85; Fig. 4).

HHV-6B detection and relapse mortality

Seven studies were included in analysis of relapse mortality and HHV-6B positivity. A random effects model demonstrated a pooled effect size of 0.74 (95% CI: 0.28–1.96) without significant heterogeneity observed (I^2 = 40.1%, Q = 10.0, p = 0.12), indicating that HHV-6B detection did not increase the odds of relapse mortality. A Bayesian aggregation was performed due to the low number of studies included, which supported a lack of association (Credible interval: −1.18 to 0.54).

DISCUSSION

The main objective of the present work was to determine if there was a significant association between HHV-6B reactivation and mortality following HCT. We found that HHV-6B detection is associated with NRM as supported by a significant pooled effect, a lack of heterogeneity, and Bayesian aggregation, while OM is associated with HHV-6B as supported by a pooled effect limited by heterogeneity.

HHV-6B can cause encephalitis [63] and has been associated with pneumonitis [29]. However, these complications do not occur frequently enough to explain the degree of increased NRM we observed. A conjecture that more fully explains our findings is that HHV-6B may be involved in immune dysregulation after HCT, which may explain more frequent adverse events such as acute graft-vs-host disease (aGVHD). HHV-6B reactivation has been associated with delayed reconstitution in NK cells [64], as well as impaired neutrophil [65] and platelet [35] engraftment. Most importantly, HHV-6B can efficiently infect CD4 + T cells [66] and has been shown to decrease T cell reconstitution after HCT [67]. CD4 + T-cell reconstitution after HCT has been associated with improved outcomes [68–71] whereas delayed CD4 + T-cell reconstitution has been associated with increased risk of aGVHD [30] as well as increased mortality [68–71]. Furthermore, some have postulated that HHV-6 may also deplete regulatory CD4 + T cells and increase the likelihood of dysregulated immune responses, like aGVHD [66]. Studies using mouse models potentially support the theory that HHV-6-mediated immune dysregulation causes aGVHD by demonstrating that pretreatment of allografts with inhibition against OX40, the entry receptor for HHV-6B, results in

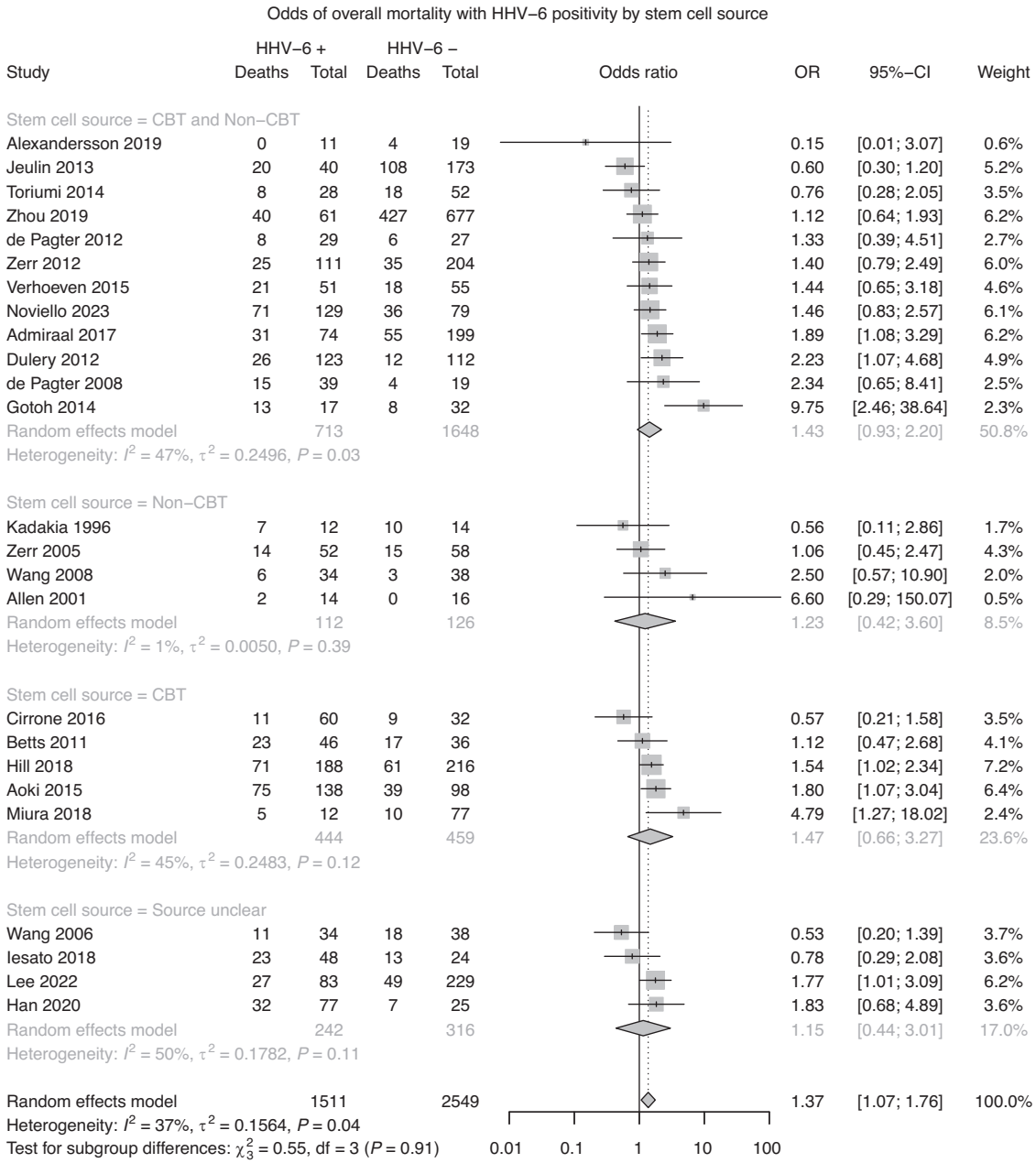

Fig. 3 Continued.

decreased severity of GVHD [72]. aGVHD is a significant source of morbidity and mortality after alloHCT [73] and a 2018 meta-analysis reported that HHV-6 reactivation is independently associated with nearly a 3-fold increased risk of developing grade II to IV acute GVHD [23]. Further investigation of the role of HHV-6 may play in aGVHD is needed.

Approximately 0.3–2.9% of individuals are known to have HHV-6B or HHV-6A integrated into the chromosome of every nucleated cell, which can be passed down to offspring in a mendelian fashion (iciHHV-6). Consequently, these patients have strikingly and continuously high HHV-6 DNA viral levels in whole blood (> 5.5 $\log_{10}$ copies/mL) without necessarily having demonstrated HHV-6 reactivation. It should be noted that antiviral therapy for iciHHV-6 patients in the absence of reactivation is ineffective and would only expose patients to the risk of drug side effects. Thus, it is important to distinguish between active replication and iciHHV-6, which is inconsistently reported in the context of the papers reviewed.

Treatments for HHV-6B disease are limited and there are currently no FDA-approved therapies for HHV-6B disease. Both ganciclovir and foscarnet are used off-label as first line agents for HHV-6 encephalitis [74]. Unfortunately, use of these antivirals is limited by side effects of myelosuppression (ganciclovir) and nephrotoxicity (foscarnet); for this reason, prophylactic use is not recommended [74]. Other agents, such as cidofovir have only anecdotal evidence for use [7, 74]. Clinical trials exploring the efficacy of viral specific T-cell therapies have been previously attempted but were discontinued due to a low probability of meeting the primary endpoints [73, 75]. Artesunate has also recently been studied for its in vitro effect on HHV-6 [76], but it has not been studied in the context of HSCT. Considering our findings of higher mortality associated with HHV-6B reactivation,

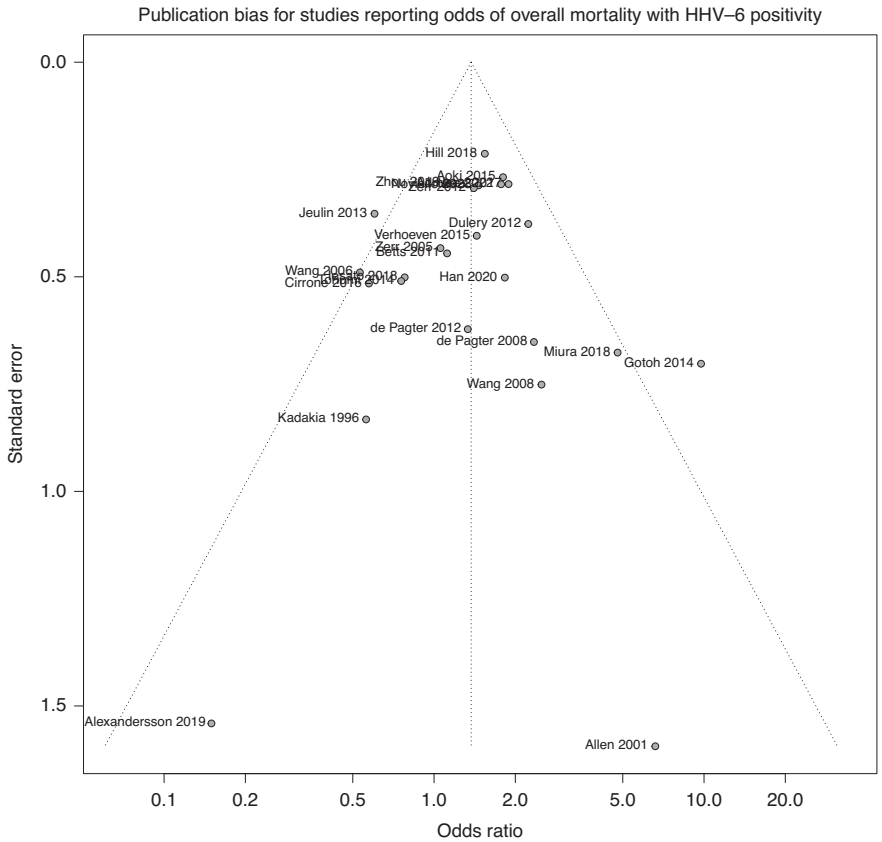

Fig. 4 Funnel Plot of Studies evaluating Overall Mortality.

there is an urgent need for improved antiviral agents specifically against HHV-6.

Our findings are limited by the following considerations: (1) Despite an available HHV-6 PCR international standard [7, 77], this is not widely used to date, and this limits standardization of viral load assessments across studies. (2) Only one database was accessed to perform this systematic review so there may have been literature that was missed including papers with no English translation, poster presentations, abstracts that did not undergo peer review, or other forms of grey literature. (3) Differing treatment methodologies between different hospitals further complicates the analysis due to potential confounding variables not considered such as protocols for the use of foscarnet or ganciclovir for preemptive treatment of HHV-6 or prophylaxis for CMV. (4) The median follow-up period was 100 days, which indicates that many studies have a relatively short follow-up period and highlights the need for studies assessing the effect of HHV-6B on mortality to include longer follow-up periods. Studies with relatively short follow-up periods were included in the interest of gathering comprehensive results. (5) This analysis did not account for viral load, and higher viral loads may be more strongly associated with our outcomes of interest. (6) The analysis did not adjust for confounders that could contribute to HHV-6 detection and/or mortality due to a lack of consistency in covariables across studies. For the purposes of standardization and future meta-analyses, we recommend several covariables be considered when studying outcomes associated with HHV-6B reactivation in this setting, including transplant source, preconditioning regimen, occurrence of GVHD, steroid usage, and CMV reactivation characteristics. Like HHV-6B, CMV is immunomodulatory and independently associated with increased mortality; this could be affecting our analyses, but we are unable to account for the independent contribution of CMV with the available data in the included studies. However, prior work that adjusted for CMV has shown an independent association between HHV-6 and mortality [52]. 7) Specific contributions to NRM were not consistently available for analysis, so we were unable to provide this data. However, beyond GVHD [23], there may be other factors contributing to NRM associated with HHV-6B reactivation worth investigating such as encephalitis, hepatitis, pneumonitis, myelosuppression, neutropenic fever, nephrotoxicity, and rash. 8) Publication bias was evaluated using a regression of funnel plot asymmetry, and it is possible that this method does not account for all sources of publication bias.

In conclusion, we demonstrate that HHV-6B reactivation was associated with increased NRM and weakly associated with OM in a meta-analysis of 28 studies. Due to the biological consequences of HHV-6B, HHV-6B activity might contribute to a higher NRM. These results provide quantitative context for prior work establishing a link between HHV-6B and NRM and suggest the possible need for improved therapeutic strategies to manage HHV-6B reactivation after HCT. It is critical to note that the current results suggest a correlative, but not causative, relationship between HHV-6B and mortality. Future studies must carefully account for variables that could contribute to mortality, such as the reactivation of other herpesviruses.

DATA AVAILABILITY

All scripts used to perform analyses and generate figures and all raw data used in analyses are publicly available at https://github.com/dannytoomey/hhv6-mortality-ma.

CODE AVAILABILITY

Analyses were performed using the R programming language, version 4.3.2. All scripts and raw data used in analysis are publicly available on GitHub [78].

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AUTHOR CONTRIBUTIONS

CS and HZ designed the study, performed data collection, wrote the manuscript, and prepared submission materials. KC designed and reviewed statistical analyses. TP and DT reviewed the data, performed data analysis, and assisted with manuscript revisions. JAH and DMZ provided expert review of all materials and assisted in project design.

COMPETING INTERESTS

CS, HZ, KC, TP, and DT have no conflicts to disclose. JAH provides consulting for Allovir, Gilead, Karius, Symbio, and receives research support from Allovir, Gilead, Karius, and Merck. DMZ received research funding from Merck and served as a consultant for AlloVir by serving on clinical endpoint adjudication committees for two studies.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Our study is exempt from IRB approval as all data is publicly available.

ADDITIONAL INFORMATION

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