Virology Journal

REVIEW

Open Access

Impact of antiviral prophylaxis on EBV viremia and posttransplant lymphoproliferative disorders in solid organ transplant recipients: a systematic review and meta-analysis

Marjan Moghadamnia[1,2], Khadijeh Delroba[3], Shima Heidari[3], Zahra Rezaie[3] and Simin Dashti-Khavidaki[3,4*]

Abstract

Introduction Organ transplant recipients face a substantial risk of developing posttransplant lymphoproliferative disorders (PTLD). In over 90% of cases with B-cell PTLD following solid organ transplantation, the Epstein-Barr virus (EBV) genome is promptly identified, usually within the initial year. A continuing discussion revolves around the efficacy of antiviral prophylaxis in mitigating the incidence of PTLD in solid organ transplant (SOT) patients. This study aimed to conduct a systematic review and meta-analysis to investigate this issue.

Method A comprehensive search was conducted up to December 31, 2023, in databases including PubMed, Embase, and the Cochrane Library for retrospective and prospective studies comparing antiviral prophylaxis effects on EVB viremia and PTLD incidence in SOT recipients. Fixed or random effect models were applied based on the heterogeneity assessed via the I^2 statistic, using Stata 16.0 software for data analysis.

Results In total, 22 eligible studies involving 13,498 patients were analyzed. Antiviral prophylaxis was associated with a significant reduction in EBV viremia incidence in SOT recipients, as demonstrated in 10 studies (relative risk (RR) 0.69, 95% CI 0.54 to 0.88). The rate of PTLD was significantly lower among those who received antiviral prophylaxis compared to those who did not, as reported in 18 studies (RR 0.77, 95% CI 0.63 to 0.94). No significant difference was observed in the subgroup of high-risk recipients based on EBV serology (RR 1.13, 95% CI 0.72 to 1.78). Additionally, a notable reduction in PTLD incidence was seen in the pediatric subgroup (RR 0.58, 95% CI 0.43 to 0.79) using antiviral prophylaxis, while no significant differences were observed in the subgroup of adults (RR 0.88, 95% CI 0.64 to 1.21). Administration of antiviral prophylaxis can significantly reduce the incidence of PTLD among kidney (RR 0.63, 95% CI 0.46 to 0.87) and heart transplant patients (RR 0.61, 95% CI 0.39 to 0.96). PTLD incidence was significantly reduced among recipients of T-cell depletion or steroid-based immunosuppression using antiviral prophylaxis (RR 0.54, 95% CI 0.39–0.74 and RR 0.55, 95% CI 0.41–0.73, respectively).

Conclusion This meta-analysis revealed that administering antiviral prophylaxis to patients after solid organ transplantation reduces PTLD and EBV viremia occurrences, especially among pediatric recipients, individuals undergoing kidney or heart transplantation, and those receiving high-intensity immunosuppression regimens.

*Correspondence:
Simin Dashti-Khavidaki
dashtis@sina.tums.ac.ir; simindashtikh@gmail.com
Full list of author information is available at the end of the article

Key Summary Points

- Post-transplant lymphoproliferative disorders (PTLD) and other EBV syndromes are among the most serious complications following solid organ transplantation (SOT), primarily due to the necessity for prolonged immunosuppressive therapy.
- Among the strategies for preventing EBV-related complications, the use of antiviral prophylaxis is a subject of ongoing debate.
- This systematic review and meta-analysis found that antiviral prophylaxis significantly reduced EBV viremia incidence (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.54 to 0.88) compared to those without prophylaxis.
- In the sub-analysis related to high-risk EBV serologically mismatched SOT recipients (EBV D+/R-), the result did not show a significant difference in terms of PTLD incidence (RR 1.13, 95% CI 0.72 to 1.78).
- Antiviral prophylaxis significantly impacted the occurrence of PTLD events among pediatric SOT patients (RR 0.58, 95% CI 0.43 to 0.79), but not among adult patients (RR 0.88, 95% CI 0.64 to 1.21).
- Antiviral prophylaxis significantly impacted the occurrence of PTLD events among kidney/simultaneous pancreas and kidney (RR 0.63, 95% CI 0.46 to 0.87) and heart (RR 0.61, 95% CI 0.39 to 0.96) transplant patients but not liver (RR 0.5, 95% CI 0.23 to 1.08) transplant recipients.

Keywords Antiviral, EBV viremia, PTLD, Solid organ transplantation

Introduction

Epstein–Barr virus (EBV) syndrome can present with a wide spectrum of clinical manifestations, ranging from asymptomatic infection to EBV viremia, EBV disease, and various malignancies including lymphoma [1]. Post-transplant lymphoproliferative disorders (PTLD) and other EBV syndromes are among the most serious complications following solid organ transplantation (SOT), primarily due to the necessity for prolonged immunosuppressive therapy [2].

The incidence of EBV-associated PTLD varies from 1.2% in adults to 8.4% in pediatric patients [3], and is influenced by factors such as the post-transplant period, type of allograft, induction therapy, intensity of immunosuppression, and the recipient's EBV serological status [4]. The increased incidence of EBV-induced PTLD in younger patients is likely due to their limited prior exposure to EBV, and consequently, lower immunity [5].

Among the strategies for preventing EBV-related complications, the use of antiviral prophylaxis is a subject of ongoing debate. Although this notion is supported by many studies [6–8], others have found no significant benefit [9–11]. Some of the observations reported in the mentioned studies are provided below for better clarification.

For instance, the correlation between prophylactic antiviral administration and PTLD reduction incidence was estimated about 83% by Funch et al. [6]. This finding was confirmed by Ville et al. [7] indicating that antiviral prophylaxis may serve to avert the occurrence of late-onset PTLD. In addition to PTLD prevention, antiviral utilization has indicated its role in EBV viremia prohibition. The study by Höcker et al. [8] revealed that (val-)ganciclovir use was associated with lower EBV viral load in pediatric kidney allograft recipients.

In contrast to the discussed findings, other research studies have questioned the antiviral therapies efficacy in prevention of EBV-associated complications in transplantation. Due to the results of a Switzerland cohort study published in 2021 [10], no significant correlation was found between the use of antiviral prophylaxis and early or late EBV and PTLD occurrence. Accordingly, two years later, Cheyssac et al. [9] stated that irrespective of EBV status, valganciclovir prophylaxis has no effect for EBV infection prevention in organ transplant recipients.

Although a systematic review and meta-analysis on this topic was conducted in 2016 [3], numerous studies with substantial sample sizes have been published since then (2016–2023). The previous review focused exclusively on high-risk SOT recipients that is seropositive donors and seronegative recipients (D+/R−), leaving the role of antiviral prophylaxis in other EBV serological statuses unclear. Given the importance of this issue and the potential for new insights, we aimed to conduct the present study to further elucidate the role of antiviral prophylaxis in preventing post-transplant EBV viremia, disease and PTLD in patients across different age ranges, both pediatric and adults.

Method

Study design

To guarantee a comprehensive and systematic analysis of the data, we adhered completely to the Preferred Reports for Systematic Reviews and Meta-Analyses (PRISMA) standards throughout our research procedure [12].

Data source and search strategy

A complete search of electronic databases, including PubMed, Cochrane, and Embase, was carried out until December 31, 2023. The search adopted MeSH terms, Emtree terms and related keywords. In addition, the references of included articles and previous relevant systematic reviews were screened to thoroughly identify relevant studies [13]. We followed the PICO (population, intervention, comparison, and outcome) structure to frame our research questions [14, 15]. Solid organ recipients were identified as the population could be studied. The use of antiviral prophylaxis or preventive therapy made up the intervention studied. The outcomes of interest were EBV infection or viremia, EBV disease, and PTLD. No particular group was used for comparison in this framework.

Study selection and data extraction

Two researchers independently screened the titles and abstracts of identified records and resolved any disagreements through discussion. Randomized controlled trials (RCTs) and observational studies that investigated the effects of antiviral prophylaxis or preemptive treatment in preventing EBV-related diseases and complications were included. Researches involving nonhuman subjects, abstracts for conferences, reviews without original data, case reports, and studies published in languages other than English were excluded. The studies that compared the efficacy of two antivirals were also excluded from the meta-analysis. Full-text articles meeting the inclusion criteria were retrieved and the data were extracted using a specific custom Microsoft Excel form. The key data extracted were study details, population demographics, baseline EBV serology, intervention features, and patients' outcomes. If a study utilized two or more different antivirals or reported outcomes separately across different time frames, it was included in the meta-analysis separately, provided that the populations did not overlap and the results were distinctly separated.

Statistical analysis

The Cochran Q test and the I^2 statistic were applied for the heterogeneity investigation of the studies [16]. I^2 statistics of 25%, 50%, and 75% are determined as low, medium, and high heterogeneity levels of studies, respectively. The Q test was supported statistically to be significant with a *P*-value of less than 0.1. The choice of fixed and random models was depended on the level of heterogeneity. A random model was used when the heterogeneity was significantly different ($P < 0.1$ for Q test or $I^2 \geq 50\%$). On the other hand, if heterogeneity of studies was not significant, a fixed effect model was used [17].

Univariate meta-regressions using random-effects models were performed to explore potential sources of heterogeneity for both EBV viremia and PTLD outcomes. The following categorical variables were assessed as potential moderators: patient age (adult, pediatric, mixed); transplant type (kidney, heart, liver, other); serostatus (high risk, non-high risk, mixed); antiviral agent ((val-)ganciclovir, (val-)acyclovir, (val-)ganciclovir or (val-)acyclovir, mixed); intervention duration (0–1 month, 1–6 months, > 6 months); induction immunosuppression (T-cell depleting, T-cell non-depleting, none, mixed); maintenance immunosuppression (excluding calcineurin inhibitors and antimetabolites: with mTOR inhibitor, with steroids, without steroids); and publication decade (before 2010, 2010 or later).

Funnel plots and Egger's test were the methods used for assessing publication bias. Sensitivity analysis was done to check the consistency of the results. All analyses were performed using Stata version 16, and a *P* value of ≤ 0.05 was accepted as statistically significant for the primary outcomes.

Quality assessment

Two reviewers independently evaluated the methodological quality and risk of bias of the included studies using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) tool for RCTs [18] and the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool for observational studies [19]. Any disagreements were solved by discussion.

Result

Study identification

Researchers retrieved a total of 1,868 publications, including 1,150 from Embase, 715 from PubMed, and three studies from Cochrane database. Also references from recovered articles and related reviews were evaluated. After excluding duplicate articles and filtering based on title and abstract, a total of 142 full text articles underwent review. Ultimately, 120 articles were excluded due to reasons such as unavailability of full text, case reports, overlapping data, the absence of a control group, and the comparison of different antivirals within each study arm. Finally, 22 articles with 13,498 patients were identified based on inclusion and exclusion criteria for further analysis (Fig. 1).

Study characteristics

The studies included in this analysis spanned publication years from 1993 to 2023. The USA [6, 20, 21] and France [7, 9, 22] each conducted three studies, and Australia [23, 24], Canada [25, 26], Germany [8, 11], and

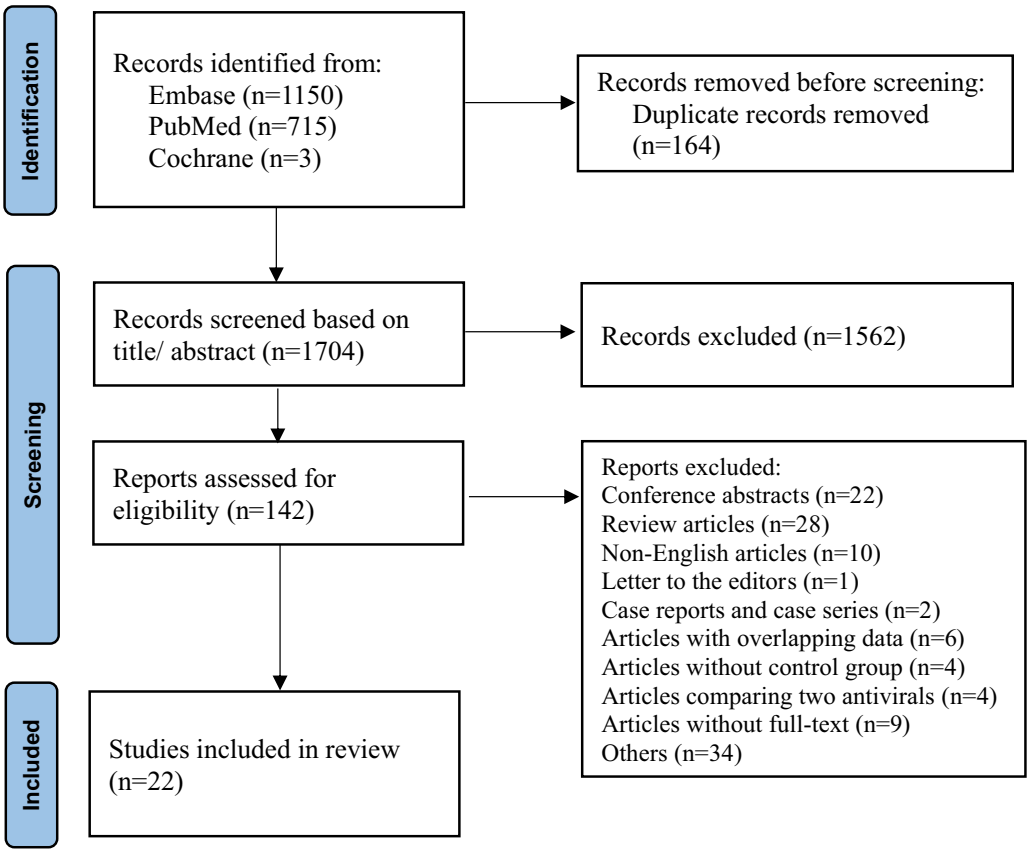

Fig. 1 PRISMA diagram showing study selection process. Legend: The flowchart shows the number of studies that were found, reviewed, and excluded, and the reasons for exclusion at each step of the process

Switzerland [10, 27] each conducted two. Additional studies were carried out in Belgium [28], Denmark [29], England [30], Iran [31], Italy [32], Korea [33], and Spain [34]. One study had multicenter populations across continents [35]. Participant numbers varied, ranging from 16 to 4,765 participants in multicenter nationwide observational prospective study from Switzerland [10]. Only one study was RCT [22]. Pediatric patients [6, 8, 9, 25, 26, 29, 31–33] and adults (7, 10, 11, 20, 22–24, 28, 30, 34) were evaluated in 8 and 10 studies, respectively, with three studies involving both children and adults [35]. In one study, the population remained unidentified [21]. Kidney or liver transplants were the focus of eight [6, 8, 9, 11, 20, 22, 27, 29] and four studies [30–33], respectively. Heart transplant patients were investigated in three studies [26, 28, 34] and pancreas or simultaneous pancreas and kidney transplantation (SPK) recipients in one study [7]. Furthermore, six studies included a broader population covering various types of solid organ transplantation [21, 23–25, 35]. Antivirals such as ganciclovir, valganciclovir, acyclovir, and valacyclovir were used in studies, with durations ranging from two weeks to up to two years post-transplantation [33]. The evaluated primary outcomes included the incidence of EBV infection or viremia, EBV disease, and PTLD across 10 [7–9, 11, 20, 24, 25, 28–30], 3 [8, 9, 22], and 17 studies [6–10, 20–24, 26–28, 31–34], respectively (Table 1). The median follow-up period varied from two weeks to nine years.

Risk of bias

The risk of bias for primary outcomes was assessed using the ROBINS-I tool for 20 studies [1, 2, 5, 8, 12, 13, 16–18, 20, 21, 24, 27–29, 33–35, 38, 43] the RoB 2 tool for one RCT [22]. The results of bias are reported in Fig. 2 and Fig. 3, respectively.

Publication bias

Publication bias was not detected in studies evaluating PTLD (Egger's test $P=0.355$); however, it was detected in studies evaluating EBV viremia (Egger's test $P=0.018$). The funnel plots are displayed in Fig. 4.

Table 1 Summary of studies included in the analysis

First author/ Year/ Reference number	Study design	Population	Type of transplant	Number of patients (Int/Con)	EBV serology	Antiviral prophylaxis used and doses		Duration of prophylaxis		Duration of follow-up		Outcome measures	Outcome		Limitations
						Int	Con	Int	Con	Int	Con		Int	Con	
Schlech et al. 1993 [22]	Randomized controlled trial	Adult	Kidney	50 (25/25)	R+	A (PO): 800 mg four times daily	Placebo	84 days	–	60 mo		EBV disease PTLD	0 0	0 0	Small sample size
Darenkov et al. 1997 [21]	Retrospective observational	Unknown	Kidney, pancreas, and liver	377 (198/179)	R+ (95%)	G (IV):5 mg/kg/day or A (PO): 800 mg four times daily	No antiviral prophylaxis	Limited to the period of antilymphocyte antibody administration	–	4 mo		PTLD	01 $P=0.03$	7	Use of a historical control group, short follow-up period (antiviral therapy might reduce the sensitivity of peripheral blood monitoring for B lymphoproliferation, potentially delaying the diagnosis of PTLD)
Birkeland et al. 1999 [29]	Retrospective consecutive clinical study with historical controls	Adult and pediatric	Kidney	267 (207/60)	21 R-, 241R+	A: 3200 mg/day	No antiviral prophylaxis	3 mo	–	Range from 273 days up to 7 years		EBV infection	60 primary EBV infection ($P=0.02$) reactivated EBV infections ($P=0.0002$)	39	Use of a historical control group, small sample size
Malouf et al. 2002 [24]	Retrospective	Adult	Lung, heart–lung	18 (15/3)	R-	A (n = 7, 4 of these 7 patients were later switched to VA): 400 to 600 mg daily, VA (n = 8): 500 to 1000 mg daily. G (n = 3): 1 g three times a week	No antiviral prophylaxis	Unknown	–	806 ± 534 days		EBV infection PTLD	10 0	3 2	retrospective nature, lack of routine pre-transplant EBV serology, small sample size, variations in the types and doses of antiviral prophylaxis
Wong et al. 2004 [23]	Retrospective cohort	Adult	Lung, heart–lung	16 (12/4)	D+\R-	G	No antiviral prophylaxis	8 to 12 weeks	–	1124 days		PTLD	4	1	Small sample size, retrospective design
Funch et al. 2005 [6]	Multicenter case–control	Adult and pediatric	Kidney	475 (310/165)	58% reported (R- = 25%)	G (n = 111) A (n = 146) patients), both G and A (n = 53)	No antiviral prophylaxis	53 ± 68 days	–	Up to the development of PTLD or the end of the study period (December 31, 2001)		PTLD	54 OR:0.56, 95% CI: 0.35–0.86	46	Lack of dosage data, variations in the use of antiviral prophylaxis, absence of donor/recipient serology data

Table 1 (continued)

First author/ Year/ Reference number	Study design	Population	Type of transplant	Number of patients (Int/Con)	EBV serology	Antiviral prophylaxis used and doses		Duration of prophylaxis		Duration of follow-up		Outcome measures	Outcome		Limitations
						Int	Con	Int	Con	Int	Con		Int	Con	
Crespo-Leiro et al. 2007 [34]	Retrospective	15 years and older	Heart	3,393 (1816/157)	Unknown	A (n = 1,369) or/ and G (n = 1,017)	No antiviral prophylaxis	A: 3 mo G: 1 mo	–	5.8 ± 4.1 years		PTLD (Lymphoma)	28	34	Scarcity of data on EBV serology, retrospective design
													RR:0.7 95% CI: 0.4–1.2 $P = 0.1921$		
Li et al. 2007 [20]	Prospective	Pediatric and young adult	Kidney	102 (91/11)	Mix	G (IV) (n = 83): 5 mg/kg/day or A(n = 8): 10 mg/kg/dose four times daily	No antiviral prophylaxis	G: first 100 days post-transplantation A: not mentioned	–	79.8 ± 21.1 mo		EBV infection	30	9	Small sample size, variations in the use of antiviral prophylaxis
												PTLD	4	0	
Manuel et al. 2007 [27]	Retrospective cohort	Adult	Kidney	143 (78/65)	Unknown	VA (n = 16): 8 g daily or 1 g daily, VG (n = 62): 450 mg daily	No antiviral prophylaxis	3 mo	–	At least 12 mo		PTLD	1	0	Variability in antiviral prophylaxis, small number of PTLD cases, lack of specific focus on PTLD, retrospective design, lack of data on EBV serology
Opelz et al. 2009 [35]	Retrospective cohort	Adult and pediatric	Kidney, heart, and liver	2227 (882/1345)	R-	Unknown	No antiviral prophylaxis	Unknown	–	Up to 3 years		PTLD (NHL)	24	26	retrospective design and reliance on registry data may introduce biases related to underreporting or incomplete data on post-transplant tumors The lack of data on the impact of different immunosuppressive regimens across transplant types, Insufficient information on the antivirals used
													$P = 0.09$		
Kim et al. 2010 [33]	Retrospective cohort	Pediatric	Liver	38 (26/12)	R-	G (IV) followed by A (PO)	No antiviral prophylaxis	G: 2 weeks, A: 2 years	–	69.3 ± 34.2 mo		PTLD	5	4	Retrospective design, small sample size
													$P = 0.289$		

Table 1 (continued)

First author/ Year/ Reference number	Study design	Population	Type of transplant	Number of patients (Int/Con)	EBV serology	Antiviral prophylaxis used and doses		Duration of prophylaxis		Duration of follow-up		Outcome measures	Outcome		Limitations
						Int	Con	Int	Con	Int	Con		Int	Con	
Manlhiot et al. 2010 [26]	Retrospective cohort	Pediatric	Heart	173 (53/120)	Mix	G or VG	No antiviral prophylaxis	12 weeks	–	Median: 4.1 years		PTLD	3	20	retrospective design, variability in immunosuppressive regimens and antiviral protocols over time
													HR: 7.6 with antiviral prophylaxis vs. 15.4 without antiviral prophylaxis, $P=0.02$		
Höcker et al. 2012 [8]	Prospective, multicenter cohort	Pediatric	Kidney	28 (20/8)	D+/R-	VG (n = 13): mean dose of 473 ± 49 mg/m^2/day or G (n = 7): mean dose of 42.2 ± 6.9 mg/kg/day	No antiviral prophylaxis	VG: 102 ± 3 days and G: 101 ± 2 days	–	1-year		EBV infection	9	8	small sample size,Observational design, co-administration of CMVIG with antiviral therapy
													$P<0.0001$		
												EBV disease	4	4	
													P = 0.09		
												PTLD	1	1	
													P = 0.5		
Aliakbarian et al. 2014 [31]	Retrospective cohort study with a historical control group	Pediatric	Liver	204 (87/117)	Unknown	G (IV): 10 mg/kg/day in 2 divided doses followed by VG (PO): [7× body surface area × creatinine clearance]/d	No antiviral prophylaxis	**G**: during hospitalization, continued with **VG** until the end of the first mo post-transplantation, and extended for 2 weeks after a negative EBV PCR result	–	−20 ± 5.6 mo	34 ± 12 mo	PTLD	5	12	Use of a historical control group,relatively short follow-up period in the case group compared to the control group, absence of detailed EBV serology data
													$P=0.24$		
Halliday et al. 2014 [30]	Retrospective cohort	Adult	Liver	A: 98 (23/85) G: 98 (16/82)	R+	G or A or both	No antiviral prophylaxis	A: Unknown G: until two consecutive samples showed undetectable CMV DNA, with an assay cut-off of 200 genomes/mL	–	Median: 249 days (range 13– 930 days)		EBV infection	A	17	49Retrospective design, short follow-up period, variability in monitoring, small sample size, and lack of specification regarding which patients received both antivirals
														HR:1.57, $P=0.12$	
													G	8	58
														HR:0.56 $P=0.13$	

Table 1 (continued)

First author/ Year/ Reference number	Study design	Population	Type of transplant	Number of patients (Int/Con)	EBV serology	Antiviral prophylaxis used and doses		Duration of prophylaxis		Duration of follow-up		Outcome measures	Outcome		Limitations
						Int	Con	Int	Con	Int	Con		Int	Con	
Nicastro et al. 2017 [32]	Retrospective cohort with historical control	Pediatric	Liver	116 (16/100)	Mix	G (IV): 5 mg/kg per dose every 12 h	Preemptive VG (IV): 5 mg/kg per dose every 12 h upon detection of CMV viremia reaching 100,000 copies/mL, followed by VG (PO): 15 mg/kg per dose every 12 h	4 weeks	G for at least 2 weeks, followed by VG until two consecutives negative CMV PCR results	94.9 ± 30 mo	42.7 ± 23 mo	PTLD	0 8 OR = 0.29 95% CI 0.06 – 1.31 $P = 0.11$		Retrospective design, small comparative cohort, different follow-up periods between the two groups
Ville et al. 2018 [7]	Retrospective cohort	Adult	Kidney, simultaneous pancreas and kidney	73 (37/36)	R-	VA: 1500 mg three times a day or VG: 450 mg twice daily	No antiviral prophylaxis	3 or 6 mo	–	69.3 ± 7.2 mo	91.5 ± 10.3 mo	EBV infection PTLD	16 30 $P = 0.02$ 4 10 $P = 0.06$		Retrospective design, small sample size, differences in the follow-up duration between the two groups, variability in antiviral treatment duration
Albatati et al. 2020 [25]	Retrospective cohort	Pediatric	Heart and kidney	44 (25/19)	D + \R-	VG: 7 mg × body surface area × creatinine clearance	No antiviral prophylaxis	3 to 6 mo	–	at least 12 mo		EBV infection	6	12	Retrospective design, small sample, variability in dosing and duration of VG, differences in the frequency of laboratory testing and immunosuppressive protocols, short follow-up period for assessing long-term outcome such as PTLD

Table 1 (continued)

First author/ Year/ Reference number	Study design	Population	Type of transplant	Number of patients (Int/Con)	EBV serology	Antiviral prophylaxis used and doses		Duration of prophylaxis		Duration of follow-up		Outcome measures	Outcome		Limitations
						Int	Con	Int	Con	Int	Con		Int	Con	
Blazquez-Navarro et al. 2021 [11]	Retrospective analysis (sub-study within the randomized, multi-center, investigator-initiated retrospective cohort)	Adult	Kidney	540 (308/232)	Mix	Prophylaxis G (IV) (n = 32) or VG (n = 276): average daily dose 277 mg/day	Preemptive G (IV) (n = 8) or VG (51): average daily dose 450 mg/day	Median:118 days	Median: 92 days	1 year		EBV infection	62	47	Non-randomized groups; lack of power calculation, Choice of antiviral strategy based on center or physician, Variability of antiviral dose and duration
													P = 1.000 OR [95% CI]: 1.01 [0.64–1.57]		
Walti et al. 2021 [10]	Switzerland nationwide, multicenter, observational cohort	Adult	Kidney, liver, lung, heart, and combined transplants	4765 (2127/263)	R-:6% R + :94%	(V)G (n = 1895) or (V)A (n = 232)	No antiviral prophylaxis	Median: 97 days (IQR 79–173)	–	Median: 4.61 years (IQR 2.22– 7.62)		PTLD	30	27	Observational design, the duration of antiviral prophylaxis was not available for all patients
													Early EBV + PTLD: SHR 0.535, *P* = 0.264; late EBV + PTLD: SHR 2.213, *P* = 0.150		
Cheyssac et al. 2023 [9]	Retrospective multicenter cohort	Pediatric	Kidney	79 (57/22)	Mix	VG: 7 × glomerular filtration rate × body surface area	No antiviral prophylaxis	6 mo	–	12 mo		EBV infection	57	22	Retrospective design, variability in EBV viral load monitoring, small sample Ssze, short follow up period for assessing the long-term outcomes
													P = 0.99		
												EBV disease	33	9	
													P = 0.17		
												PTLD	2	0	
Van Aelst et al. 2023 [28]	Retrospective cohort	Adult	Heart	272 (61/211)	Unknown	G (IV): 5 mg/kg twice daily, followed by VG (PO): 450–900 mg daily	No antiviral prophylaxis	3–6 mo	–	Unknown		EBV infection	1	7	Retrospective design, variation in prophylaxis duration, co-administration of MVIG with antiviral therapy
												PTLD	1	7	

A Acyclovir, *CI* confidence interval, *CMV* cytomegalovirus, *CMVIG* Cytomegalovirus immunoglobulin, *Con* Control, *D* donor, *EBV* Epstein-Barr virus, *G* ganciclovir, *HLA* human leukocyte antigen, *HR* hazard ratio, *Int* intervention, *IQR* interquartile rang, *IV* intravenous, *MMF* mycophenolate mofetil, *mo* month(s), *n* number, *NHL* Non-hodgkin lymphoma, *OR* odds ratio, *PO* orally, *PTLD*: Post-transplant lymphoproliferative disorders, *R* recipient, *RR* relative risk, *SHR* Sub-distribution hazard ratio, *VA* valacyclovir, *VG* valganciclovir

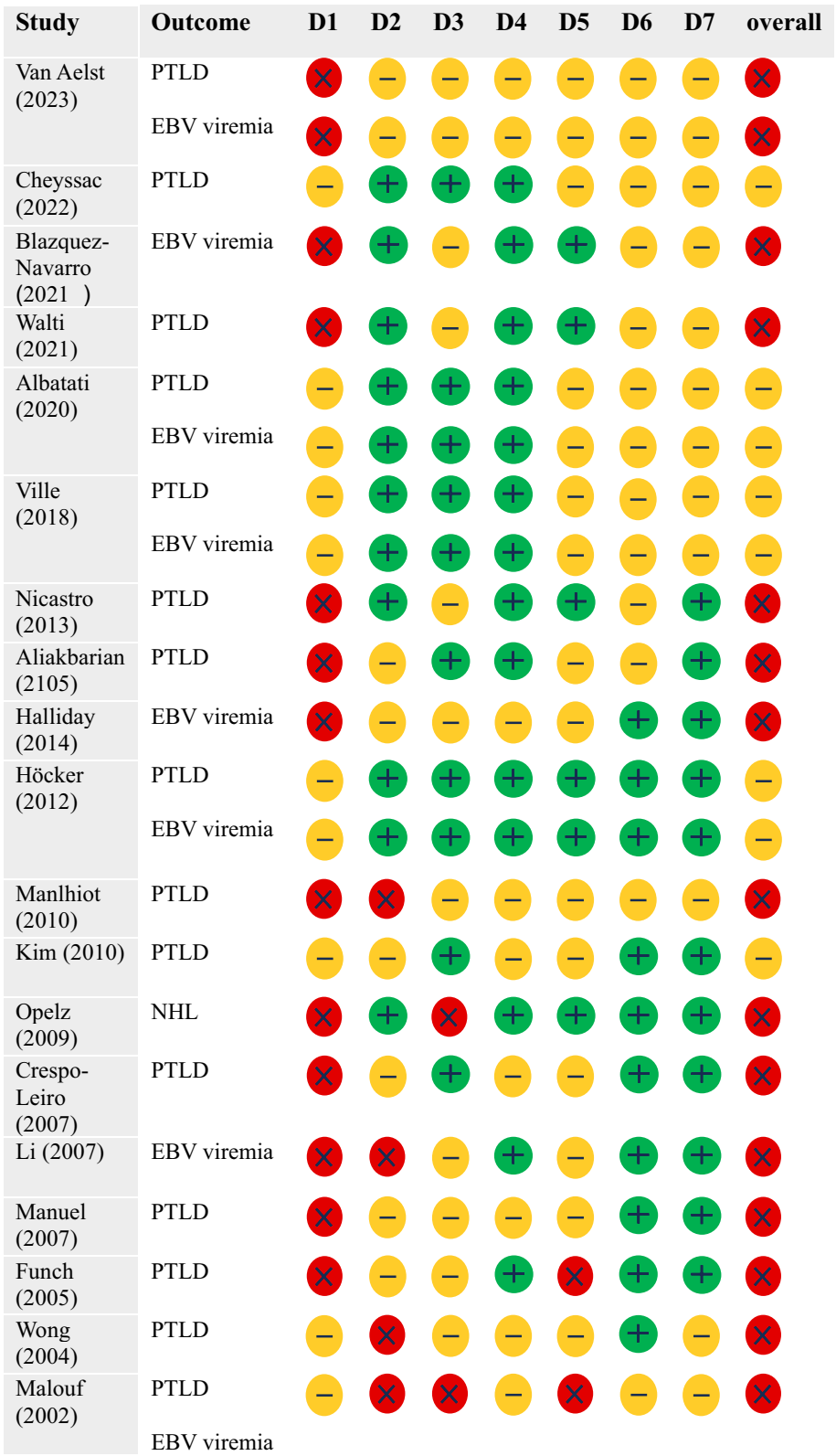

Fig. 2 Traffic light plot for risk of bias assessment using the ROBINS-I tool for non-randomized studies. Legend: ROBINS-I tool for the assessment of risk of bias in non-randomized studies presented in the form of a traffic light plot. Studies are presented with color-coded assessments indicating their risk levels, allowing for easy visualization of their internal validity

Data analysis

Due to the small number of articles for EBV disease (3 articles) and the different definitions of EBV disease, we performed meta-analysis only for two outcomes: EBV-viremia and PTLD.

Effect of antiviral prophylaxis on the incidence of EBV viremia

As mentioned above, different antivirals were used with varying duration across the included studies. Figure 5 shows that in 10 studies consisting a total of 1,521 patients, regardless of the prophylactic agent and type of SOT, antiviral prophylaxis significantly reduced EBV viremia incidence (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.54–0.88) compared to those without prophylaxis. It should be mentioned that in Ville et al.'s study, the analysis was conducted separately for early EBV viremia incidence (within the first 100 days of transplantation) and late EBV viremia incidence (after one year of transplantation) [7]. Similarly, regarding the study of Halliday et al., that patients received two different antivirals, each group was analyzed separately [30].

Effect of antiviral prophylaxis on the incidence of PTLD

Excluding the prophylactic agent and type of SOT, there was a notable difference in the rate of PTLD as indicated by Fig. 6 among 12,227 patients of 18 studies (RR 0.77, 95% CI 0.63–0.94).

Subgroup analysis

In the sub-analysis related to 2,327 high-risk EBV serologically mismatched SOT recipients (EBV D + /R−), the result of the analysis of five studies did not show a significant difference in terms of PTLD (RR 1.13, 95% CI 0.72–1.78) (Fig. 6).

All eight studies on pediatric patients, comprising a total of 1,215 SOT recipients, evaluated the antiviral efficacy in preventing PTLD. In this subgroup, antiviral prophylaxis significantly impacted the occurrence of PTLD events (RR 0.58, 95% CI 0.43–0.79) (Fig. 7). However, the analysis of 8 studies encompassing 8,732 adults did not show this effectiveness (RR 0.88, 95% CI 0.64–1.21) (Fig. 7).

The studies were also analyzed for the effect of antiviral prophylaxis on the occurrence of PTLD, based on the type of solid organ transplanted. The analysis of seven studies conducted on 952 kidney or SPK transplant patients showed that the use of antiviral prophylaxis regimen can significantly reduce the incidence of PTLD with RR of 0.63 (95% CI 0.46–0.87) (Fig. 8). Additionally, based on data from three studies involving 3,806 heart transplant patients, administration of antiviral prophylaxis regimens demonstrated significant effectiveness in reducing the incidence of PTLD (RR 0.61, 95% CI 0.39–0.96) (Fig. 8). The occurrence of PTLD remained unchanged in 358 liver transplant recipients, as the PTLD rate was comparable regardless of whether prophylaxis was administered or not (RR 0.50, 95% CI 0.23–1.08) (Fig. 8).

The impact of antivirals on the incidence of PTLD, considering the induction regimen, was evaluated as follows: six studies used T-cell depleting agents [6, 21, 22, 26, 28, 29], four studies used T-cell non-depleting agents [8, 20, 30, 33], six studies utilized both types of agents [9, 10, 25, 27, 34, 35], and four studies did not involve any induction regimen [23, 24, 31, 32]. Two studies also did not mention the type of induction regimen [7, 11]. Analysis of these studies indicated that administering antivirals to patients on induction regimens with depleting agents like Anti-thymocyte globulin *(*ATG*)* and OKT3 significantly lowered the incidence of PTLD (RR 0.54, 95% CI 0.39–0.74). However, this effect was not significant in other groups. (Fig. 9).

When examining maintenance regimens, studies were categorized based on the use of steroids. An analysis of 12 studies, including 1939 individuals receiving steroids, indicated that antiviral treatment was significantly linked to a lower incidence of PTLD (RR 0.55, 95% CI 0.41–0.73). Conversely, this significant association was not observed in patients on maintenance regimens without steroids. (Fig. 10).

The analysis of patients in two subgroups, categorized by the antiviral therapy they received (either acyclovir and valacyclovir, or ganciclovir and valganciclovir), showed a significant reduction in the incidence of EBV-associated PTLD in both groups (RR 0.65, 95% CI 0.45–0.95 and RR 0.51, 95% CI 0.35–0.74, respectively). However, the RR was found to be lower in the group receiving ganciclovir and valganciclovir.

Meta-regression analysis

For the PTLD outcome, univariate meta-regression analyses identified transplant type, induction immunosuppression, and maintenance immunosuppression as significant moderators of the observed heterogeneity ($P < 0.05$). In contrast, patient age, serostatus, antiviral agent, intervention duration, and publication decade did not significantly explain the observed heterogeneity ($P > 0.05$). For the EBV viremia outcome, none of the tested moderators significantly explained the observed heterogeneity ($P > 0.05$) (Table 2).

Discussion

This meta-analysis indicates that antiviral prophylaxis strategies can effectively reduce the incidence of EBV viremia and PTLD. The EBV life cycle consists of two

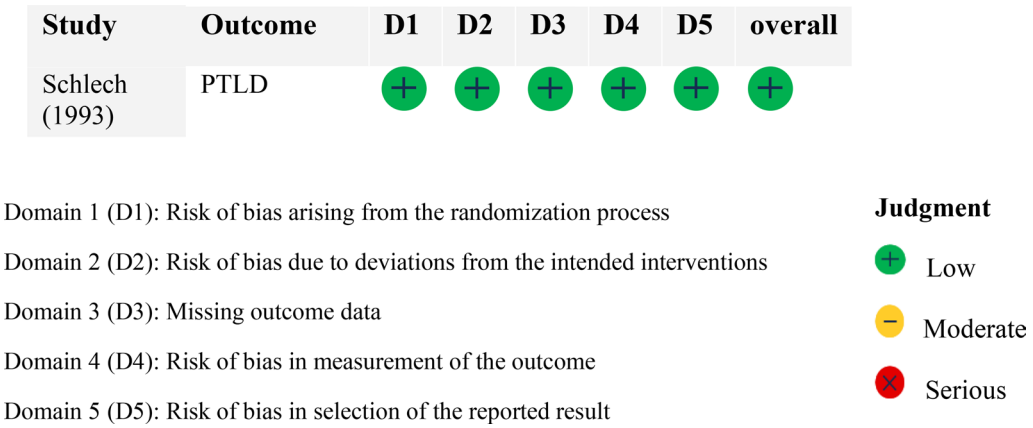

Fig. 3 Traffic light plot for risk of bias assessment using ROB 2.0 for randomized controlled studies. Legend: Traffic light plot for risk of bias assessment using the ROB 2.0 tool for randomized controlled trials. Studies are presented with color-coded assessments indicating their risk levels, allowing for easy visualization of their internal validity

distinct phases: lytic and latent. During the lytic phase, EBV actively replicates and produces infectious virions, a process crucial for initial infection or viral reactivation [36, 37]. Nucleoside analogues such as acyclovir and ganciclovir inhibit lytic EBV replication by targeting key viral and cellular enzymes. Nucleoside analogues acyclovir and ganciclovir undergo initial phosphorylation by the viral protein kinase during the lytic phase, subsequently receiving additional phosphorylation from cellular enzymes guanosine monophosphate (GMP) and nucleoside diphosphate (NDP) kinase, which transform them into their active triphosphate forms. These active forms inhibit EBV DNA polymerase by acting as competitive inhibitors or alternative substrates, halting DNA replication [38]. As a result, antiviral prophylaxis during the lytic phase effectively decreases episodes of EBV viremia [39]. On the other hand, the latent phase of EBV enables the virus to remain undetected within B lymphocytes by expressing a limited number of viral genes, thereby evading immune surveillance. Latent EBV proteins exhibit diverse functions that facilitate cell proliferation, immune evasion, and resistance to apoptosis, thereby contributing to the development of lymphoproliferative diseases [40]. The viral enzyme, porin kinase, which is targeted by nucleoside analogs such as ganciclovir and acyclovir, is expressed solely during the lytic phase of the virus. Consequently, Prophylactic antiviral therapy, is unable to directly target latently infected cells or prevent EBV-driven B-cell transformation linked to PTLD [41]. Nevertheless, Antiviral prophylaxis during the lytic phase of EBV may significantly diminish the viral load and impede the latency transition of infected cells, thereby reducing the reservoir of latently infected B cells and decreasing the risk of sequelae from EBV, particularly in immunocompromised individuals. Furthermore, recent evidence indicates that EBV lytic reactivation is pivotal in oncogenesis by facilitating immune evasion, genomic instability, apoptosis resistance, and enhancing tumorigenesis and invasiveness. Therefore, despite the limited efficacy of antiviral drugs in treating EBV-associated malignancies, preliminary studies have shown promise in combining these agents with histone deacetylase inhibitors, such as arginine butyrate. This approach aims to stimulate lytic gene expression and enhance tumor sensitivity to treatment [38, 41].

PTLD represents a heterogeneous spectrum of predominantly B-cell disorders and is a life-threatening complication after SOT. In most cases, PTLD is associated with active replication of EBV following either primary infection or reactivation [2, 4]. The American Society of Transplantation guideline does not recommend the use of chemoprophylaxis for the early prevention of PTLD in patients with high-risk EBV serology [2]. This recommendation is supported by the findings of a prior meta-analysis [3]. Our systematic review and meta-analysis may change this recommendation and provide important information on the use of antiviral prophylaxis or pre-emptive therapy in preventing PTLD in solid organ transplant recipients. We included all studies that used antiviral drugs, regardless of EBV serology. In the subgroup analysis of patients with high-risk serology, antiviral prophylaxis did not lower the risk of PTLD. This finding aligns with previous meta-analyses that included only studies with high-risk serology patients, concluding that the evidence is insufficient to support the routine use of antivirals in solid organ transplant recipients to decrease the incidence of PTLD [3]. Recipient's EBV seronegativity is one of the known risk factors for early

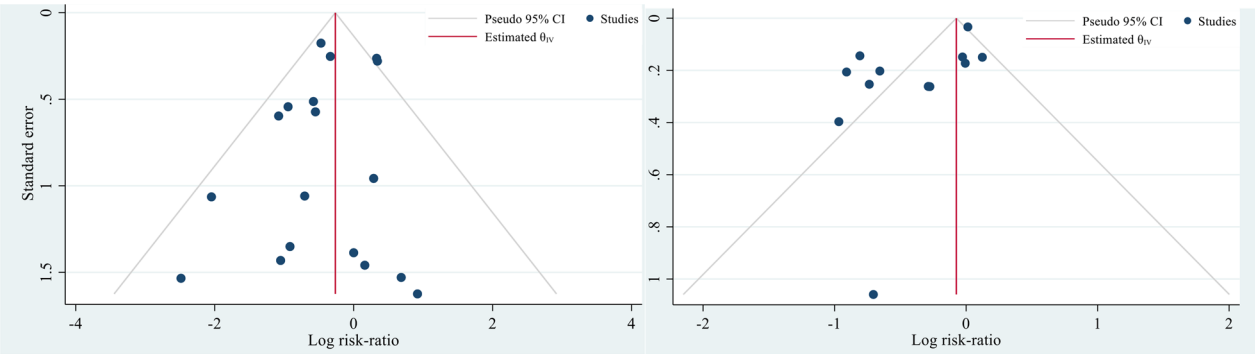

Fig. 4 Funnel plot illustrating the effect of antiviral prophylaxis on the incidence of PTLD (left) and EBV viremia (right). Legend: The funnel plot of the log risk ratio against the standard error for antiviral prophylaxis on the incidence of PTLD (left) and EBV viremia (right). The asymmetry of the plots observed indicates the possibility of publication bias

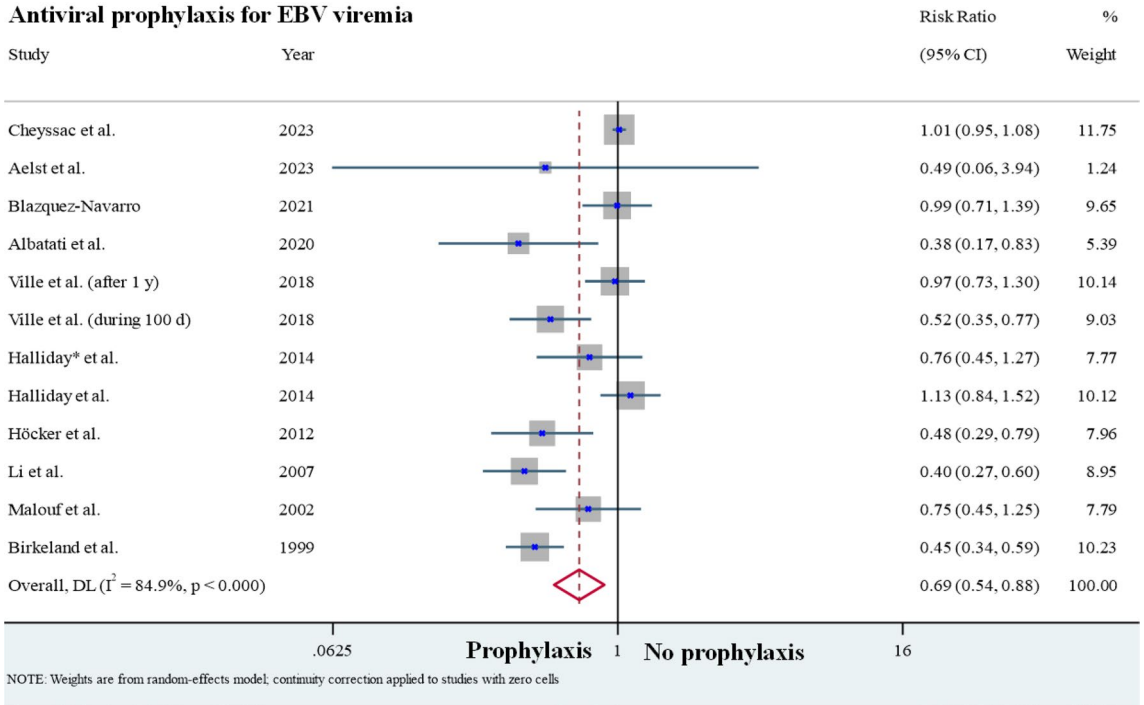

Fig. 5 Effect of antiviral prophylaxis on the incidence of EBV viremia. Legend: Forest plot showing the impact of antiviral prophylaxis on the occurrence of EBV viremia. The plot summarizes effect estimates and confidence intervals, demonstrating the protective effect of prophylaxis

PTLD, which is typically associated with EBV-positive PTLD [36, 37]. However, this finding is not consistent with our results. This could be due to the limited number of studies and patients included in this sub-analysis, as most of the included studies analyzed mixed serology status of the patients. Therefore, larger and stronger studies are required to make conclusions in this patient population. It should be noted that one of the studies included in the previous meta-analysis was not included in our study because the full text of the publication was not available to the authors of the present work [38]. Additionally, three studies from the previous meta-analysis did not meet our inclusion criteria [42–44].

When pediatric patients were separated from the adult SOT recipients, it was observed that antiviral prophylaxis did not lower the risk of PTLD in adults, while, the risk reduction in pediatric patients became more significant. This finding is expected because

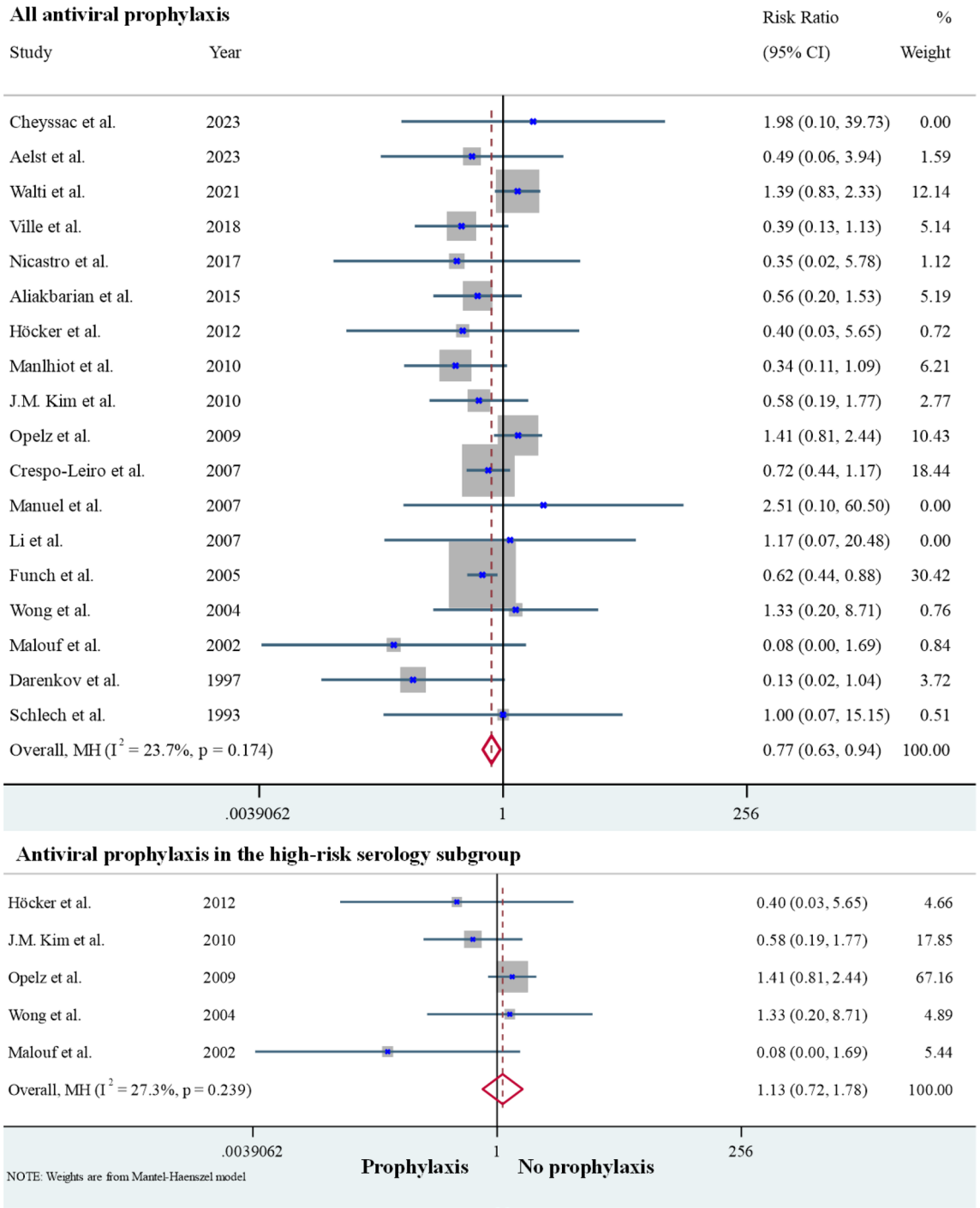

Fig. 6 Effect of antiviral prophylaxis on the incidence of PTLD and subgroup of high-risk EBV serology. Legend: Forest plot showing the effect of antiviral prophylaxis on the incidence of PTLD, including a subgroup analysis for patients with high-risk EBV serology. Results indicate how prophylaxis impacts different risk categories

EBV DNA is detected in the majority of B-cell PTLD developing within the first year after solid organ transplantation [45]. However, in adult populations, PTLD that occurs later after transplantation is increasingly reported to be EBV-negative [46].

In the analysis by induction and maintenance immunosuppression regimen, a significant reduction in the risk of

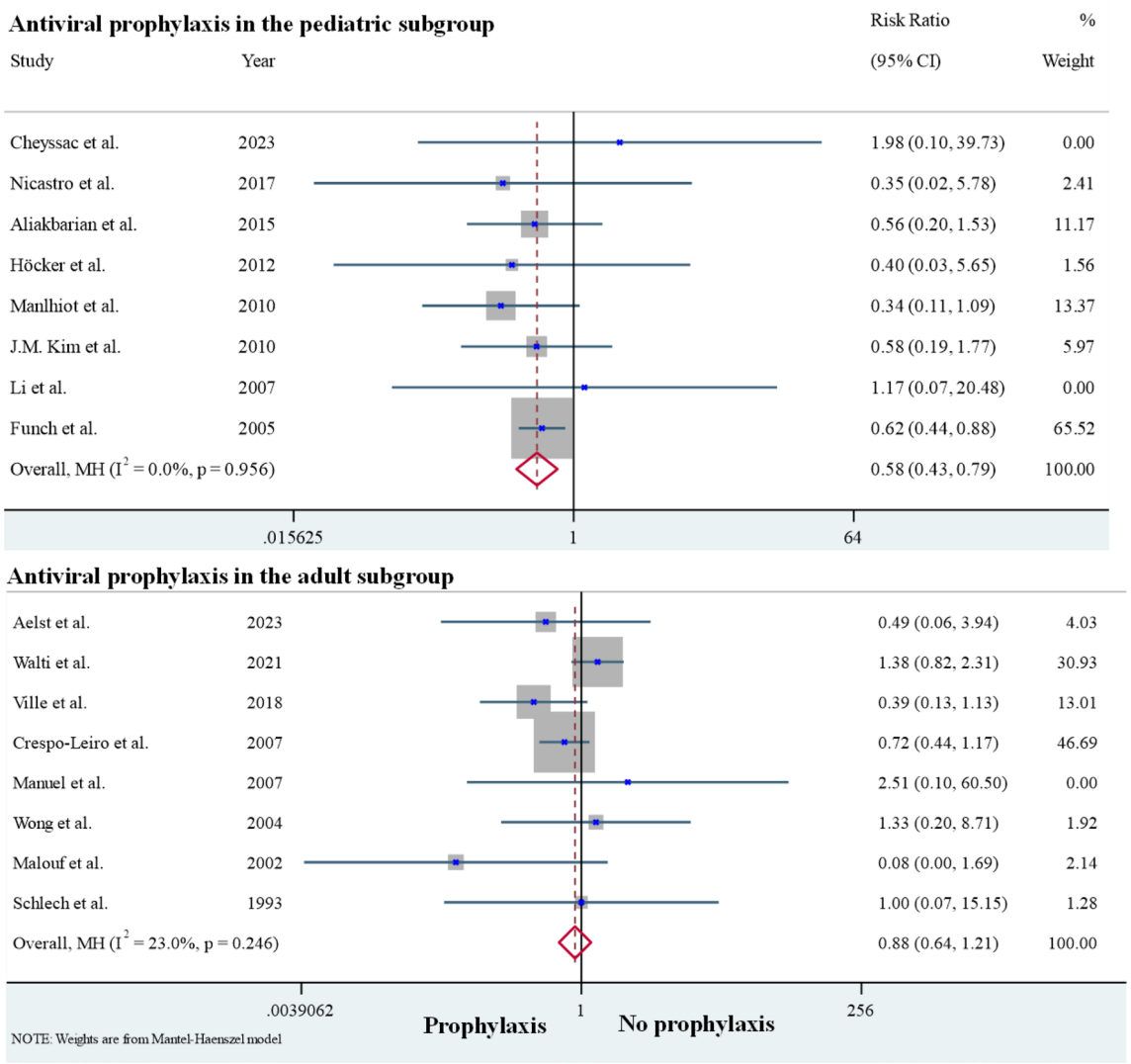

Fig. 7 Effect of antiviral prophylaxis on the incidence of PTLD by subgroups of age. Legend: Forest plot presenting the effect of antiviral prophylaxis on the incidence of PTLD by age subgroups. This analysis highlights age-related differences in prophylaxis efficacy, providing insights into tailored approaches

PTLD is observed in patients receiving T-cell-depleting agents and in patients receiving steroids in maintenance immunosuppression other than CNIs and antimetabolites. The use of T-cell-depleting agents in the induction regimen is a significant risk factor for early PTLD [2]. Therefore, in these patients, antiviral prophylaxis may be particularly beneficial in reducing the risk of PTLD.

In the analysis by organ transplant type, a notable reduction in the risk of PTLD is observed in the kidney and heart transplant subgroups; while, this reduction is not significant for liver transplantation. This may be attributable to more potent immunosuppressive regimens employed in heart and kidney transplantation. The limited number of studies on liver transplantation with the small total patient population make it difficult to draw reliable conclusion.

Antiviral prophylaxis significantly reduced the incidence of EBV-associated PTLD in both patient subgroups, regardless of whether they received (val-) acyclovir or (val-) ganciclovir. Notably, a more pronounced reduction in PTLD risk was observed in the (val-) ganciclovir group, suggesting a potential advantage of this antiviral class. However, significant variability existed in antiviral regimens, including drug choice, dosage, and prophylaxis duration, across the study population. This heterogeneity limits our ability to draw definitive

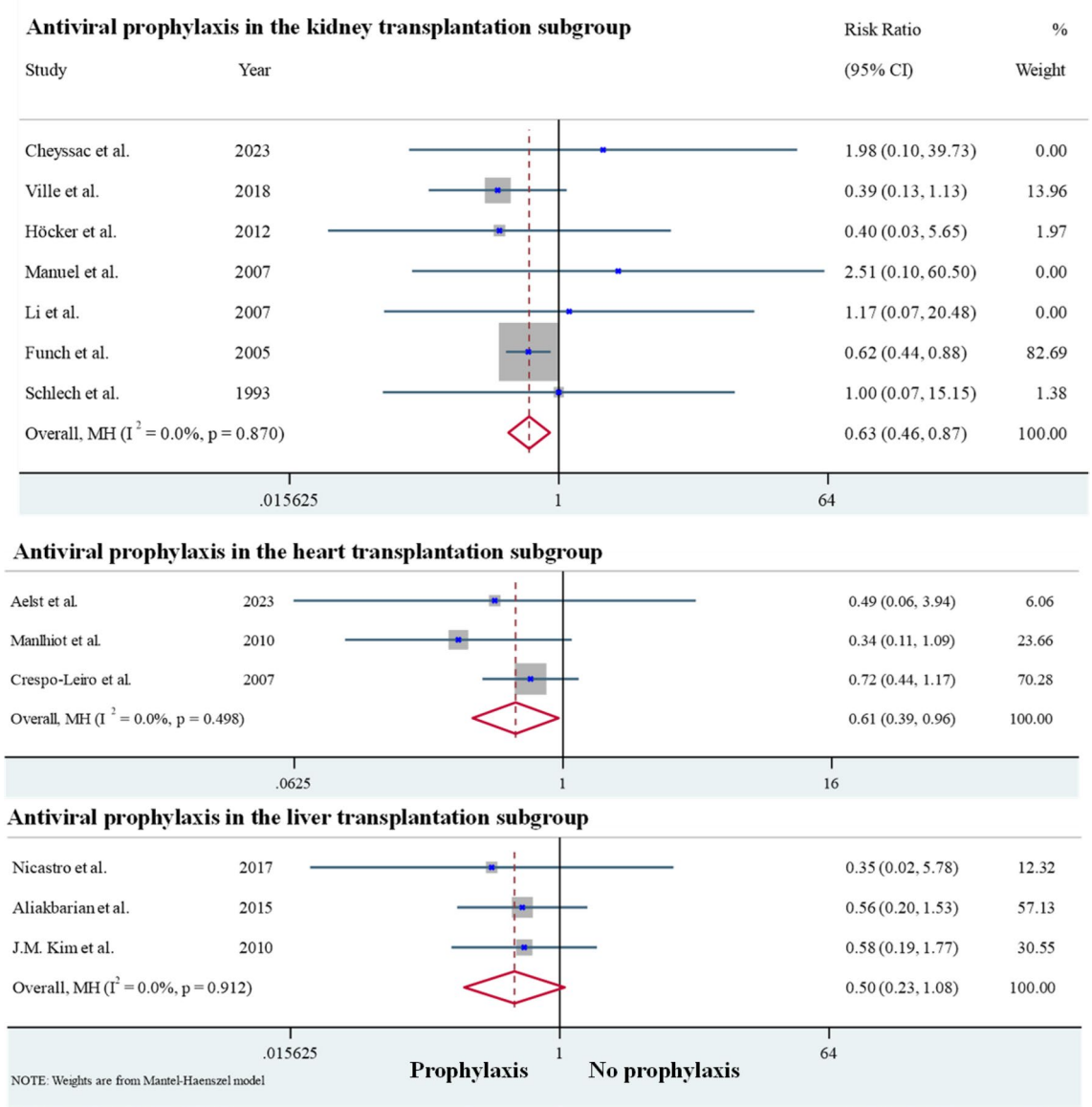

Fig. 8 Effect of antiviral prophylaxis on the incidence of PTLD by subgroups of organ transplantation. Legend: Forest plot illustrating the effect of antiviral prophylaxis on the incidence of PTLD across various organ transplantation subgroups. Results indicate variations in protective effects based on the type of organ transplanted

conclusions regarding the most effective antiviral drug, dose, or prophylaxis duration for preventing EBV-related post-transplant complications. To address this limitation, head-to-head randomized controlled trials are needed to directly compare the efficacy and safety of different antiviral agents. Notably few studies comparing two antiviral regimens were excluded from the final analysis. In the research conducted by Razonable and colleagues, the rates of EBV DNAemia were found to be quite similar among patients taking oral ganciclovir and those on oral valganciclovir. However, high-level EBV DNAemia was detected in 6.3% of patients receiving oral ganciclovir compared to only 1.2% of those receiving oral valganciclovir. Notably, there was no reported case of PTLD in either group during 12 months after transplantation [47]. An older RCT compared the sequential use of 2 weeks of intravenous ganciclovir followed by 50 weeks of high-dose oral acyclovir with 2 weeks of intravenous ganciclovir alone as prophylaxis for CMV and EBV disease after pediatric liver transplantation. The rate of EBV disease among patients treated with the combination regimen was similar to that of patients receiving ganciclovir alone

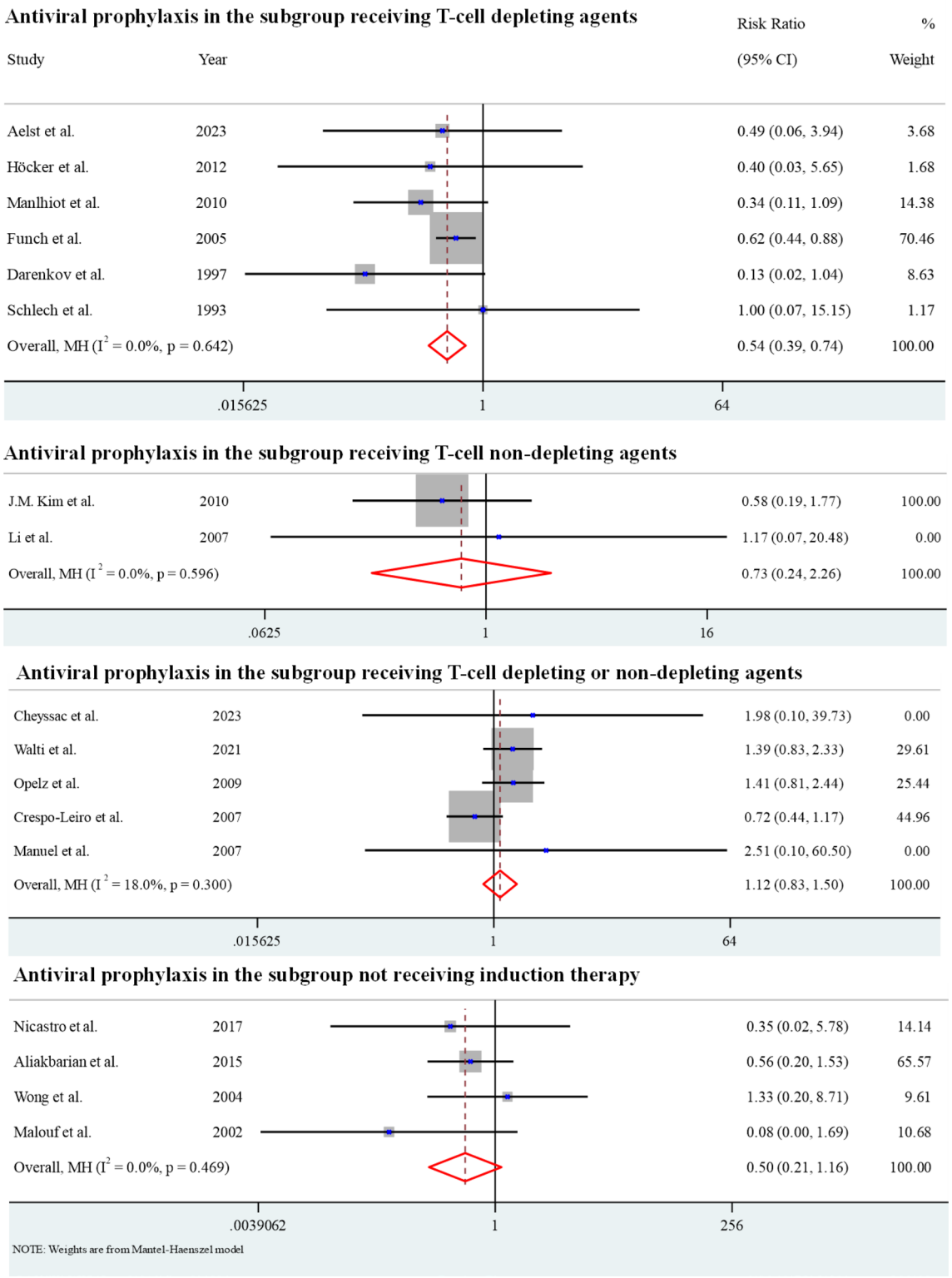

Fig. 9 Effect of antiviral prophylaxis on the incidence of PTLD by subgroups of induction immunosuppression Legend: Forest plot illustrating the effect of antiviral prophylaxis on the incidence of PTLD across different subgroups of induction immunosuppression. Results suggest varying levels of protection offered by antiviral prophylaxis depending on the specific induction immunosuppression regimen

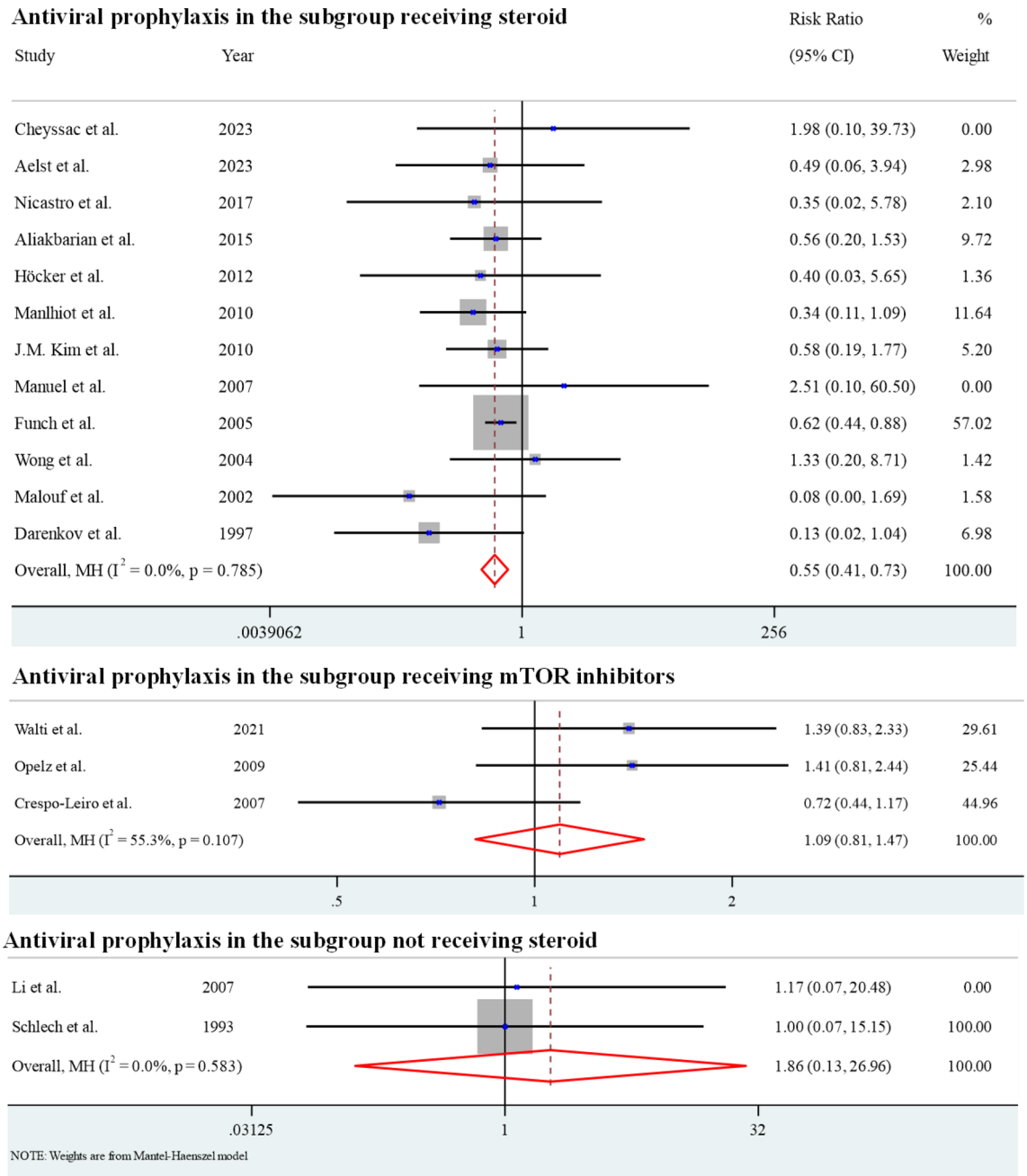

Fig. 10 Effect of antiviral prophylaxis on the incidence of PTLD by subgroups of maintenance immunosuppression Legend: Forest plot illustrating the effect of antiviral prophylaxis on the incidence of PTLD across different subgroups of maintenance immunosuppression. Results suggest varying levels of protection offered by antiviral prophylaxis depending on the specific maintenance immunosuppression regimen

[48]. In another study, researchers compared two groups of patients, one group receiving intravenous ganciclovir for 100 days (group 1: high-risk serology) and the other group receiving intravenous ganciclovir for 2 weeks (group 2: low-risk serology). Both groups were then transitioned to oral acyclovir. No cases of PTLD and only one case of EBV disease which resolved later were reported in group 1. In contrast, in group 2 two cases of PTLD were reported [49]. Overall, it appears that more comprehensive, controlled clinical trials with adequate sample sizes are needed to determine the optimal prophylaxis regimen.

There are several limitations to this meta-analysis. The majority of the studies included were cohort and

Table 2 The result of meta-regression

Variables	outcome	beta with 95% CI	Standard error	*P*-value
Age	PTLD	0.21 (−0.35, 0.78)	0.29	0.461
	EBV viremia	0.28 (−0.19, 0.77)	0.24	0.244
Transplant type	PTLD	0.17 (0.05, 0.29)	0.06	0.003
	EBV viremia	−0.04 (−0.25, 0.17)	0.10	0.708
Serostatus	PTLD	−0.04 (−1.15, 1.05)	0.56	0.930
	EBV viremia	0.04 (−0.57, 0.66)	0.31	0.894
Antiviral agent	PTLD	0.02 (−0.08, 0.14)	0.05	0.648
	EBV viremia	0.04 (−0.23, 0.13)	0.09	0.606
Intervention duration	PTLD	−0.09 (−0.44, 0.24)	0.17	0.582
Induction immunosuppression	PTLD	0.16 (0.00, 0.31)	0.08	0.045
	EBV viremia	0.14 (−0.11, 0.40)	0.13	0.282
Maintenance immunosuppression	PTLD	−0.53 (−0.97, −0.09)	0.22	0.017
	EBV viremia	−0.23 (−0.76, 0.29)	0.27	0.386
Decade of publication	PTLD	−0.01 (−0.43, 0.41)	0.21	0.958

EBV Epstein-Barr virus, *PTLD* Post-transplant lymphoproliferative disorders

observational in design, with only one RCT in the final analysis. A high risk of bias was observed in some of the studies and there was notable clinical heterogeneity among them due to the variations in study methodologies. Some studies focused on CMV prophylaxis and reported its effects on the incidence of PTLD as side findings. The follow-up periods were also different and ranged from several weeks to several years. Moreover, data regarding specific antiviral agents and their duration of administration were insufficient to make specific recommendations regarding the best prophylactic strategy. Furthermore, the induction and maintenance immunosuppression, as well as other concurrent medications, showed significant variations across studies, which may directly influence the incidence of PTLD.

In addition, EBV serology varied among the studies, with most studies were not restricted to the high-risk patients. The definitions of EBV viremia and the methods of EBV viral load detection also varied among studies. Finally, we could not distinguish between early PTLD (within the first year after transplantation) and late PTLD (after the first year of transplantation) as our analysis focused on the overall incidence of PTLD.

Conclusion

This meta-analysis demonstrates that antiviral prophylaxis has a beneficial effect on the prevention of EBV viremia and PTLD after SOT. Notably, pediatric recipients, those undergoing kidney or heart transplantation, and patients receiving T-cell depletion or steroid-based immunosuppression appear to benefit significantly from universal antiviral strategies. While the effectiveness of prophylaxis in adults remains debated, these findings underscore the importance of personalized approaches considering patient age and the unique characteristics of PTLD in different populations. However, further randomized clinical trials with standardized protocols in different populations are needed to clarify several gray areas, such as identifying which populations would benefit most from prophylaxis, the most effective antiviral regimen, and the optimal dose and duration of antiviral therapy.

Acknowledgements
We do not have anyone to acknowledge.

Author contributions
MM and SD-K had the idea and conceptualized the work. MM, KD, SH, and ZR performed the literature search and data analysis. All authors drafted the manuscript. MM and SD-K critically revised the work. All authors read and approved the final manuscript.

Funding
No funding support.

Availability of data and material
All data have been presented in this article and there is no more data or material.

Declarations

Declarations
Ethical approval and consent to participate.
Not applicable.

Consent for publication
This article is authors' own work and does not need consent for publication from third party. All authors agree with its publication.

Competing interest
All authors declare no competing interest.

Author details
[1]Department of Pharmacotherapy, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran. [2]Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran. [3]Department of Pharmacotherapy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. [4]Liver Transplantation Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Received: 10 October 2024 Accepted: 3 January 2025
Published online: 15 January 2025

References

1. Gross TG, Rubinstein JD. Post-transplant lymphoproliferative disease in children, adolescents, and young adults. Hematol Oncol. 2023;41:48–56.
2. Allen UD, Preiksaitis JK. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: guidelines from the American Society of Transplantation infectious diseases community of practice. Clin Transplant. 2019;33(9):e13652. https://doi.org/10.1111/ctr.13652.
3. AlDabbagh M, Gitman M, Kumar D, Humar A, Rotstein C, Husain S. The role of antiviral prophylaxis for the prevention of epstein–barr virus–associated posttransplant lymphoproliferative disease in solid organ transplant recipients: a systematic review. Am J Transplant. 2017;17(3):770–81.
4. Yamada M, L'Huillier AG, Green M. A focused review of epstein-barr virus infections and PTLD in pediatric transplant recipients: guidance from the IPTA and ECIL guidelines. J Pediatr Infect Dis Soc. 2024;13(Supplement_1):S31–8. https://doi.org/10.1093/jpids/piad097.
5. Fulchiero R, Amaral S. Post-transplant lymphoproliferative disease after pediatric kidney transplant. Front Pediatr. 2022;10:1087864.
6. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant. 2005;5(12):2894–900.
7. Ville S, Imbert-Marcille BM, Coste-Burel M, Garandeau C, Meurette A, Cantarovitch D, et al. Impact of antiviral prophylaxis in adults Epstein-Barr virus-seronegative kidney recipients on early and late post-transplantation lymphoproliferative disorder onset: a retrospective cohort study. Transpl Int. 2018;31(5):484–94.
8. Höcker B, Böhm S, Fickenscher H, Küsters U, Schnitzler P, Pohl M, et al. (Val-) Ganciclovir prophylaxis reduces Epstein-Barr virus primary infection in pediatric renal transplantation. Transpl Int. 2012;25(7):723–31.
9. Cheyssac E, Savadogo H, Lagoutte N, Baudouin V, Charbit M, Novo R, et al. Valganciclovir is not associated with decreased EBV infection rate in pediatric kidney transplantation. Front Pediatr. 2023;10:1085101.
10. Walti LN, Mugglin C, Sidler D, Mombelli M, Manuel O, Hirsch HH, et al. Association of antiviral prophylaxis and rituximab use with posttransplant lymphoproliferative disorders (PTLDs): a nationwide cohort study. Am J Transpl. 2021;21(7):2532–42.
11. Blazquez-Navarro A, Dang-Heine C, Wehler P, Roch T, Bauer C, Neumann S, et al. Risk factors for Epstein-Barr virus reactivation after renal transplantation: results of a large, multi-centre study. Transpl Int. 2021;34(9):1680–8.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021. https://doi.org/10.1136/bmj.n71.
13. Jpt H. Cochrane handbook for systematic reviews of interventions. http://www.cochrane-handbook.org. 2008.
14. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995;123(3):A12–3.
15. Eriksen MB, Frandsen TF. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. J Med Lib Assoc: JMLA. 2018;106(4):420.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019. https://doi.org/10.1136/bmj.l4898.
19. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016. https://doi.org/10.1136/bmj.i4919.
20. Li L, Chaudhuri A, Weintraub LA, Hsieh F, Shah S, Alexander S, et al. Subclinical cytomegalovirus and Epstein-Barr virus viremia are associated with adverse outcomes in pediatric renal transplantation. Pediatr Transplant. 2007;11(2):187–95.
21. Darenkov IA, Marcarelli MA, Basadonna GP, Friedman AL, Lorber KM, Howe JG, et al. REDUCED INCIDENCE OF EPSTEIN-BARR VIRUS-ASSOCIATED POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER USING PREEMPTIVE ANTIVIRAL THERAPY1. Transplantation. 1997;64(6):848–52.
22. Schlech WF III, Meagher N, Cohen AD, Belitsky P, MacDonald A, LeBlanc JC. A randomized double-blind placebo controlled trial of oral acyclovir in renal allograft recipients. Can J Infect Dis Med Microbiol. 1993;4(2):84–8.
23. Wong JY, Tait B, Levvey B, Griffiths A, Esmore DS, Snell GI, et al. Epstein-Barr virus primary mismatching and HLA matching: key risk factors for post lung transplant lymphoproliferative disease. Transplantation. 2004;78(2):205–10.
24. Malouf MA, Chhajed PN, Hopkins P, Plit M, Turner J, Glanville AR. Anti-viral prophylaxis reduces the incidence of lymphoproliferative disease in lung transplant recipients. J Heart Lung Transplant. 2002;21(5):547–54.
25. Albatati S, Sharma A, Haubrich K, Wright A, Gantt S, Blydt-Hansen TD. Valganciclovir prophylaxis delays onset of EBV viremia in high-risk pediatric solid organ transplant recipients. Pediatr Res. 2020;87(5):892–6.
26. Manlhiot C, Pollock-BarZiv SM, Holmes C, Weitzman S, Allen U, Clarizia NA, et al. Post-transplant lymphoproliferative disorder in pediatric heart transplant recipients. J Heart Lung Transplant. 2010;29(6):648–57.
27. Manuel O, Venetz JP, Sturzenegger N, Fontana M, Meylan PR. Efficacy and safety of universal valganciclovir prophylaxis combined with a tacrolimus/mycophenolate-based regimen in kidney transplantation. Swiss Med Wkly. 2007;37:669. https://doi.org/10.4414/smw.2007.11961.
28. Van Aelst LN, Droogné W, Vörös G, Van Cleemput J. Combination prophylaxis in CMV high risk heart transplant recipients: a single center experience. Clin Transplant. 2023;37(3):e14848.
29. Birkeland S, Andersen H, Hamilton-Dutoit SJ. PREVENTING ACUTE REJECTION, EPSTEIN-BARR VIRUS INFECTION, AND POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS AFTER KIDNEY TRANSPLANTATION: USE OF ACICLOVIR AND MYCOPHENOLATE MOFETIL IN A STEROID-FREE IMMUNOSUPPRESSIVE PROTOCOL1. Transplantation. 1999;67(9):1209–14.
30. Halliday N, Smith C, Atkinson C, O'Beirne J, Patch D, Burroughs AK, et al. Characteristics of Epstein-Barr viraemia in adult liver transplant patients: A retrospective cohort study. Transpl Int. 2014;27(8):838–46.
31. Aliakbarian M, Dehghani SM, Geramizadeh B, Nikeghbalian S, Kasiri K, Kazemi K, et al. Prevention of posttransplant lymphoproliferative disorder in pediatric patients with a liver transplant. Exp Clin Transplant. 2015;13:426–9.
32. Nicastro E, Giovannozzi S, Stroppa P, Casotti V, Callegaro AP, Tebaldi A, et al. Effectiveness of preemptive therapy for cytomegalovirus disease in pediatric liver transplantation. Transplantation. 2017;101(4):804–10.
33. Kim JM, Lee SK, Kim SJ, Joh JW, Kwon CH, Choe YH, Shin M, Kim EY, Moon JI, Jung GO, Choi GS. Risk factors for posttransplant lymphoproliferative disorder in pediatric liver transplant recipients with cytomegalovirus antigenemia. InTransplantation proceedings 2010 Apr 1 (Vol. 42, No. 3, pp. 895-899). Elsevier.
34. Crespo-Leiro MG, Alonso-Pulpón L, Arizón JM, Almenar L, Delgado JF, Palomo J, et al. Influence of induction therapy, immunosuppressive regimen and anti-viral prophylaxis on development of lymphomas after heart transplantation: data from the spanish post–heart transplant tumour registry. J Heart Lung Transplant. 2007;26(11):1105–9.
35. Opelz G, Daniel V, Naujokat C, Döhler B. Epidemiology of pretransplant EBV and CMV serostatus in relation to posttransplant non-Hodgkin lymphoma. Transplantation. 2009;88(8):962–7.
36. Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in US kidney recipients. Am J Hematol. 2011;86(2):206.
37. Sprangers B, Riella LV, Dierickx D. Posttransplant lymphoproliferative disorder following kidney transplantation: a review. Am J Kidney Dis. 2021;78(2):272–81.

38. Pociupany M, Snoeck R, Dierickx D, Andrei G. Treatment of Epstein-Barr Virus infection in immunocompromised patients. Biochem Pharmacol. 2024;10:116270.
39. Zangwill SD, Hsu DT, Kichuk MR, Garvin JH, Stolar C, Haddad J Jr, et al. Incidence and outcome of primary Epstein-Barr virus infection and lymphoproliferative disease in pediatric heart transplant recipients. J Heart Lung Transplant. 1998;17(12):1161–6.
40. Cao Y, Xie L, Shi F, Tang M, Li Y, Hu J, Zhao L, Zhao L, Yu X, Luo X, Liao W. Targeting the signaling in Epstein-Barr virus-associated diseases: mechanism, regulation, and clinical study. Signal Transduct Target Ther. 2021;6(1):15.
41. Toner K, Bollard CM. EBV+ lymphoproliferative diseases: opportunities for leveraging EBV as a therapeutic target. Blood J Am Soc Hematol. 2022;139(7):983–94.
42. Kogan DL, Burroughs M, Emre S, Fishbein T, Moscona A, Ramson C, et al. Prospective longitudinal analysis of quantitative Epstein-Barr virus polymerase chain reaction in pediatric liver transplant recipients. Transplantation. 1999;67(7):1068–70.
43. Holmes RD, Orban-Eller K, Karrer FR, Rowe DT, Narkewicz MR, Sokol RJ. Response of elevated Epstein-Barr virus DNA levels to therapeutic changes in pediatric liver transplant patients: 56-month follow up and outcome. Transplantation. 2002;74(3):367–72.
44. Özçay F, Arslan H, Bilezikçi B, Sevmiş Ş, Moray G, Haberal M. The role of valacyclovir on Epstein–Barr virus viral loads in pediatric liver transplantation patients. InTransplantation proceedings 2009 Sep 1 (Vol. 41, No. 7, pp. 2878-2880). Elsevier.
45. Nijland ML, Kersten MJ, Pals ST, Bemelman FJ, Ten Berge IJ. Epstein-Barr virus–positive posttransplant lymphoproliferative disease after solid organ transplantation: pathogenesis, clinical manifestations, diagnosis, and management. Transplant Direct. 2016;2(1):e48.
46. Peters AC, Akinwumi MS, Cervera C, Mabilangan C, Ghosh S, Lai R, et al. The changing epidemiology of posttransplant lymphoproliferative disorder in adult solid organ transplant recipients over 30 years: a single-center experience. Transplantation. 2018;102(9):1553–62.
47. Razonable RR, Brown RA, Humar A, Covington E, Alecock E, Paya CV. Herpesvirus infections in solid organ transplant patients at high risk of primary cytomegalovirus disease. J Infect Dis. 2005;192(8):1331–9.
48. Green M, Kaufmann M, Wilson J, Reyes J. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for prevention of cytomegalovirus and Epstein-Barr virus disease after liver transplantation in children. Clin Infect Dis. 1997;25(6):1344–9.
49. McDiarmid SV, Jordan S, Lee GS, Toyoda M, Goss JA, Vargas JH, et al. Prevention and Preemptive Therapy of Posttransplant Lymphoproliferative Disease in Pediatric Liver Recipients1. Transplantation. 1998;66(12):1604–11.

Publisher's Note