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Effect of herpes zoster vaccine on patients after hematopoietic stem cell transplantation: a systematic review and meta-analysis

Xunyi Jiao[1], Jinli Zhu[1], Yangyang Ding[1], Meng Xiao[1] and Zhimin Zhai[1*]

Abstract

Background Herpes zoster(HZ), a severe complication following hematopoietic stem cell transplantation (HSCT), is associated with significant morbidity. The effect of herpes zoster vaccine(HZV) for preventing HZ on patients after HSCT is unclear. We conducted a systematic review and meta-analysis investigating the efficacy and safety of HZV in HSCT recipients.

Methods The databases Pubmed, Embase, and Cochrane Library were searched to identify relevant studies. Random-effects models were used to calculate risk ratios (RRs) and 95% confidence intervals (CIs) for HZ infection and related events.

Results A total of 3048 individuals from five studies (four randomized controlled trials and one retrospective cohort study) were included. The overall incidence of HZ in the HZV group and control group was 6.4% and 18.3% respectively, resulting in a pooled RR of 0.36 (95%CI, 0.29–0.45; $P<0.001$), indicating no heterogeneity ($P=0.88$,$I^2=0$). HZV demonstrated a reduction in the risk of PHN (RR, 0.40; 95% CI, 0.15–1.11), although statistical significance was not reached ($P=0.08$). Furthermore, through two independent RCTs, HZV showed a decrease in the incidence of HZ-related complications compared to placebo administration. The overall incidence of adverse events in the HZV group and control group was found to be 63.6% and 60.2% respectively, with a pooled RR of 1.02 (95% CI, 0.97–1.06, $P=0.51$), indicating no heterogeneity ($P=0.66$, $I^2=0$).

Conclusion The HZV group demonstrated a significant reduction in the risk of HZ among HSCT recipients, without an increase in adverse events. This highlights the positive impact of HZV on decreasing the incidence of PHN and complications associated with HZ. Furthermore, our findings support the effectiveness and tolerability of HZV as a preventive measure against HZ for HSCT recipients.

Keywords Herpes zoster, Herpes zoster vaccine, Hematopoietic stem cell transplantation, Meta-analysis

*Correspondence:
Zhimin Zhai
zzzm889@163.com
[1]Department of Hematology/Hematological Lab, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China

Introduction

Herpes zoster (HZ) is a severe viral infection resulting from the reactivation of latent varicella-zoster virus (VZV). The incidence of HZ is higher in immunocompromised populations compared to immunocompetent individuals [1]. As a frequent complication following HSCT, it occurs in approximately 44% of allogeneic transplant recipients and 28% of autologous transplant recipients [2–4]. The most characteristic feature of HZ is a painful dermatomal rash, with acute pain lasting from 2 weeks to a month [5, 6]. A proportion of patients experience postherpetic neuralgia (PHN), which is neuropathic pain persisting for several months after the resolution of the rash [7]. HZ and HZ-associated pain significantly impact the quality of life (QoL) in affected individuals. HSCT recipients are particularly susceptible to developing severe and prolonged local disease manifestations, as well as potentially life-threatening systemic complications such as encephalitis, pneumonia, hepatitis, and even death [4, 8]. In recent years, there have been advancements in HZV development and clinical trials targeting immunosuppressed populations including older adults, cancer patients, and solid organ transplant recipients [9–16]. However, due to the heterogeneity within this immunosuppressive population along with concerns regarding vaccine safety and incidence rates of HZ infection among HSCT recipients, limited studies have evaluated the immunogenicity and effectiveness of HZV specifically in this population. Consequently, there is currently no consensus on recommendations for HZV usage in HSCT recipients. We conducted a systematic review and meta-analysis aiming to evaluate both efficacy and safety outcomes associated with HZV administration for preventing HZ infection among HSCT recipients. Our analysis compares preventive effects between an intervention group receiving HZV versus a control group receiving either placebo or no prophylaxis.

Materials and methods

The present systematic review and meta-analysis was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [18].

Data sources

A comprehensive search was conducted in the Pubmed, Embase, and Cochrane Library databases from their inception to 10 October 2024 using the Medical Subject Heading (MeSH) terms "herpes zoster" and "hematopoietic stem cell transplantation", combined with entry terms. All included articles were written in English. The full search methods are provided in supplement file 1.

Data extraction and study selection

Eligibility criteria (based on the PICO framework):

Population: HSCT recipients (allogeneic HSCT [allo-HSCT]/autologous HSCT [auto-HSCT] recipients; no age or time post-transplant restrictions).

Intervention: Any approved HZV (type and dose not limited).

Comparison: HSCT recipients who have not received HZV.

Outcome: Effectiveness (infection rate and HZ-related complications), and safety (adverse events).

Study design: Including randomized controlled trials (RCTs), cohort studies, case-control studies, etc.

Exclusion criteria: Non-HSCT populations, non-HZV studies, case reports, non-English language publications, etc.

Two investigators (Xunyi Jiao and Jinli Zhu) independently conducted a comprehensive review of the eligible reports, extracting pertinent information using a standardized extraction sheet encompassing details such as first author, publication year, country, study design, subject demographics and numbers, types of HSCT received, vaccination programs implemented, clinical outcomes assessed, and duration of follow-up. To account for heterogeneity in follow-up durations across studies, we collected data from each study for the longest available period for analysis.

HZV and outcome measures

The study involved the administration of live attenuated vaccine and recombinant zoster vaccine. Some participants in the included studies received antiviral drug therapy, including acyclovir, famciclovir, and valacyclovir. The impact of pre-transplant drug prophylaxis was not considered in this review. Comparisons were made between groups receiving HZV for prophylaxis and a control group.

The primary outcome measures assessed the overall incidence of HZ among HSCT recipients. Secondary outcome measures included the incidence of PHN, HZ-related complications, vaccine-related adverse events, and serious adverse events. HZ was defined according to the criteria established by investigators in the included studies [19–23], which encompassed new rash characteristic of HZ, clinical symptoms and/or signs suggestive of HZ, as well as specific laboratory findings.

Quality assessment

Two writers (Xunyi Jiao and Jinli Zhu) separately assessed the risk of bias and resolved divergence by consensus. The risk of bias in RCTs, including participant selection, confounding variables, exposure measurement, outcome assessment blinding, incomplete outcome data, and selective result reporting, was evaluated using the

Cochrane Risk of Bias Tool [24]. There were three categories for the parameters: low, unclear, and high risk of bias. For observational research, the Newcastle-Ottawa Scale (NOS) [25] was employed. 5 to 6 NOS ratings were regarded as intermediate quality, <5 low quality, and ≥7 as excellent quality.

Statistical analysis

To report the HZ morbidity of HSCT patients in the HZV group compared to those in the control group, the primary indicators employed were risk ratios (RRs) and 95% confidence intervals (CIs). The degree of statistical heterogeneity was evaluated using the I^2 statistic, and heterogeneity was defined as an I^2 value of ≥50% [26]. The random-effects model results were presented because these investigations were carried out in various geographic regions and among HSCT groups with diverse underlying diseases. All HZV, regardless of the type or amount of individual vaccinations, were merged for comparison. The data analysis was carried out using Review Manager 5.4.

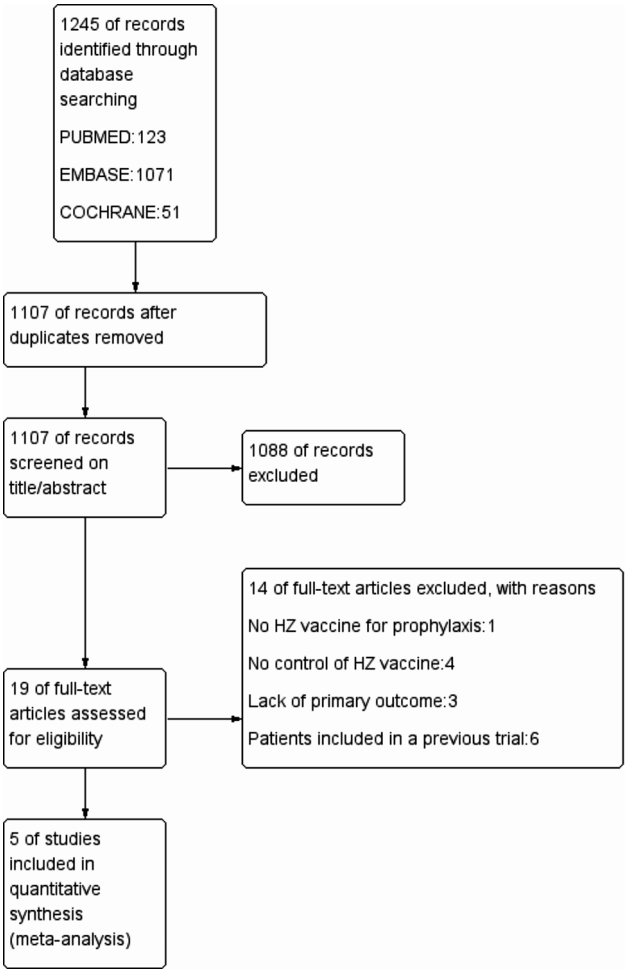

Fig. 1 PRISMA flow diagram of the study selection process

Results

Search results and characteristics of included studies

Two authors (Xunyi Jiao and Jinli Zhu) reviewed 1245 abstracts, from which 19 full-text articles were retrieved and assessed (Fig. 1). The following factors led to the exclusion of 14 publications: (1) no HZV for prophylaxis ($n=1$), (2) no control of HZV ($n=4$), (3) lack of primary outcome ($n=3$), (4) patients involved in a prior trial ($n=6$). The five studies that made up the final meta-analysis included four RCTs [19, 20, 22, 23] and one cohort study [21].

Description of included studies

A total of 3048 patients from the five studies were available for analysis. Of these, 1481 were included as a control group, while 1567 HSCT patients received HZV as a prophylactic. Three studies were single-center studies [21–23] and two were multi-center studies [19, 20]. Two studies were conducted in American adults [22, 23], one study was conducted in Japanese pediatric patients [21], and the other two study involves adult patients from multiple countries including Asia, Europe, America and so forth [19, 20]. One study was designed as retrospective cohort study [21] and the other four RCTs [19, 20, 22, 23]. General characteristics of the included studies are presented in Table 1. All five studies had information on HZV events, and two studies documented safety [19, 20]. One study focused on allo-HSCT recipients [21], while the remaining four were conducted in auto-HSCT recipients [19, 20, 22, 23]. Inactivated HZV was utilized in two studies [20, 23], the recombinant zoster vaccine was employed in two studies [19, 22], and the live attenuated HZV was examined in one study [21].

Influence of HZV on the incidence of HZ

Five studies investigated the HZ outcomes in HZV group compared with controls in HSCT recipients. The overall incidence of HZ in the HZV group and control group was 6.4% and 18.3% respectively, with a pooled RR of 0.36 (95%CI, 0.29–0.45, $P<0.001$), showing no heterogeneity across studies ($P=0.88$, $I^2=0$) (Fig. 2A). The outcome of allo-HSCT subgroup was not presented because only one study contributed to this outcome. In auto-HSCT recipients, HZV group had a lower risk of HZ events in comparison to the control group (RR, 0.37; 95%CI, 0.29–0.45, $P<0.001$) without heterogeneity ($P=0.97$, $I^2=0$) (Fig. 2B).

Effects on PHN

Two studies [19, 20] investigated the risk of PHN in patients with confirmed HZ after vaccination compared to a control group. HZV was associated with a reduced risk of PHN (RR, 0.40; 95%CI, 0.15–1.11), although statistical significance was not achieved ($P=0.08$). There

Table 1 Characteristics of included studies

Study	Country	Sex	Mean/median age (yr)	Study design	Outcome (events/ total number at risk)	Transplantation type	Follow up duration
Aoki (2016)	Japan	HZV group: 41.9% females; Control group: 43.8% females	HZV group:4.8 (median); Control group:7.1 (median)	Retrospective cohort study	HZV group:1/31; Control group:4/16	Allogeneic HSCT	Mean 7.2 years (range,2.9–13.8 years)
Hata (2002)	USA	HZV group: 37.3% females; Control group: 38.3% females	HZV group:44 (median); Control group:44 (median)	Randomized controlled trial	HZV group:7/53; Control group:17/56	Autologous HSCT	Mean 24.2 months (range,0.9-56.0months)
Stadtmauer (2014)	USA	HZV group: 34.4% females; Control group: 36.7% females	HZV group A:56.5 (median); HZV group B:58.0 (median); HZV group C:58.0 (median); Control group:59.5 (median)	Randomized controlled trial	HZV group:2/75; Control group:2/23	Autologous HSCT	4 to 15 months
Winston (2018)	North America, South America, Europe and Asia	HZV group: 37.7% females; Control group: 36.2% females	HZV group A:57.0 (median); HZV group B:56.0 (median); Control group:56.0 (median)	Randomized controlled trial	HZV group:42/538; Control group:113/535	Autologous HSCT	HZV group:2.4 years (mean); Control group:2.3 years (mean)
Bastidas (2019)	North America, South America, Europe, South Africa, Australia and Asia	HZV group: 37.1% females; Control group: 37.4% females	HZV group:54.8 (mean); Control group:55.1 (mean)	Randomized controlled trial	HZV group:49/870; Control group:135/851	Autologous HSCT	HZV group:26.3 months (mean); Control group:23.4 months (mean)

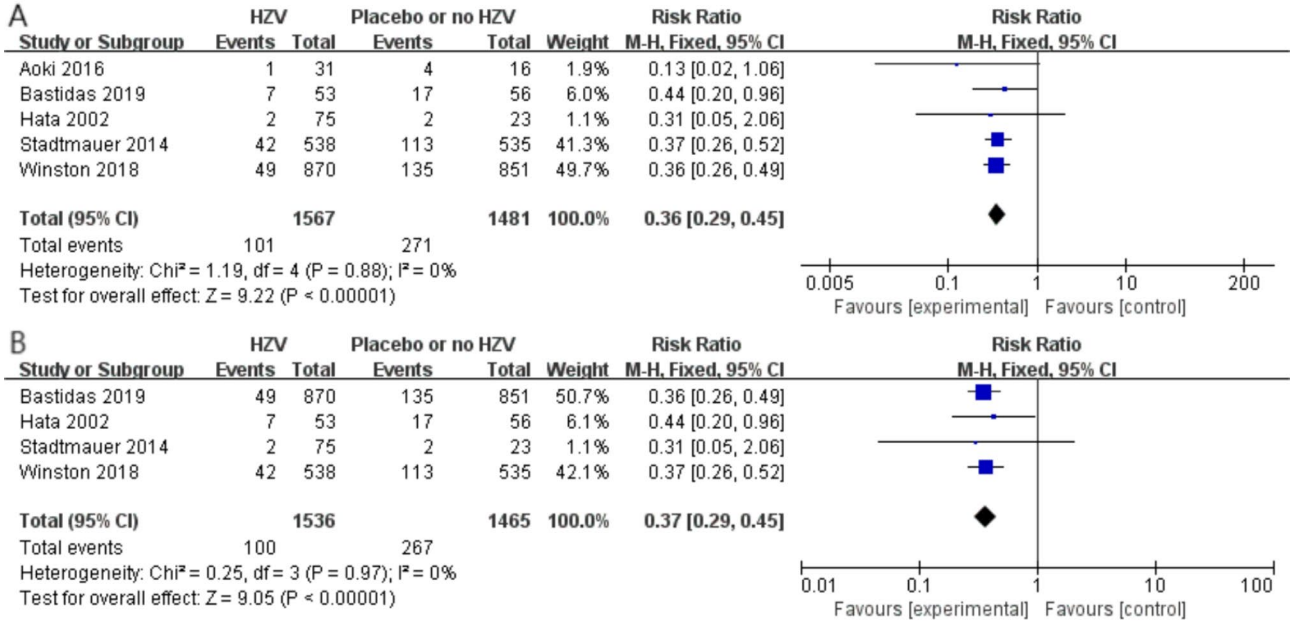

Fig. 2 Forest plot estimating the risk of herpes zoster (HZ) with herpes zoster vaccine (HZV) in HSCT recipients.**A** Forest plot estimating the risk of HZ with HZV in all HSCT recipients; **B** Forest plot estimating the risk of HZ with HZV in autologous HSCT recipients

Fig. 3 Forest plot estimating the risk of postherpetic neuralgia after HZV in HSCT recipients

was no heterogeneity observed in these studies ($P = 0.75$, $I^2 = 0$) (Fig. 3).

Effects on HZ–related complications

Although both studies [19, 20] described the incidence of HZ-related complications, the definition of the event differed, precluding the pooling of results. Bastidas [19] excluded PHN or HZ-related hospitalization. In Bastidas's modified total vaccinated cohort, incidence rate ratios (IRRs) for the vaccine group vs. the placebo group were 0.22 (95%CI, 0.04–0.81; $P = 0.02$; 1.6 vs. 7.1 cases per 1000 person-years) for HZ–related complications. Winston [20] included admission to the hospital or an extended stay in the hospital due to HZ, dissemination of HZ manifested by disseminated rash or varicella zoster viremia, visceral HZ, ophthalmic HZ, neurological impairment due to HZ, or the need for intravenous acyclovir for the treatment of HZ. 12 (2%) of 538 participants in the HZ group were confirmed to have HZ–related complications (9.4 per 1000 person-years) versus 44 (8%) of 535 in the placebo group (35.8 per 1000 person-years). The estimated vaccine efficacy against HZ–related complications was 73.5% (95%CI, 49.8–86.0). Overall, HZV reduced the incidence of HZ–related complications compared with placebo.

Safety of HZV

Two studies [19, 20] examined adverse events and safety outcomes of HZV compared with controls. All adverse events observed from the time of first dose of vaccine through to 28 or 30days after the last dose were recorded. A pooled analysis was conducted for adverse events (Fig. 4A). The total number of adverse events was 1004 (63.6%) in the HZV group and 890 (60.2%) in the control group. No increased risk of adverse events was found (RR, 1.02; 95% CI, 0.97–1.06; $P = 0.51$), without heterogeneity ($P = 0.66$, $I^2 = 0$). The incidence of serious adverse events in the HZV group and control group was 19.3% and 18.2% respectively, with a pooled RR of 1.01 (95% CI, 0.88–1.16), showing no heterogeneity across studies ($P = 0.96$, $I^2 = 0$) (Fig. 4B). There was no significant

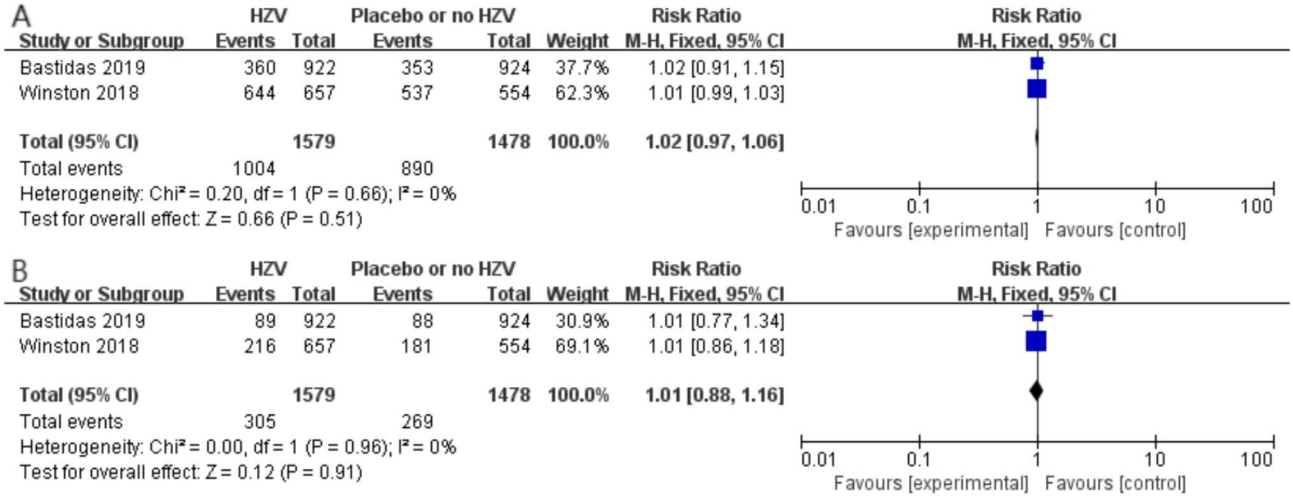

Fig. 4 **A** Forest plot estimating the risk of adverse events after HZV in HSCT recipients; **B** Forest plot estimating the risk of serious adverse events after HZV in HSCT recipients

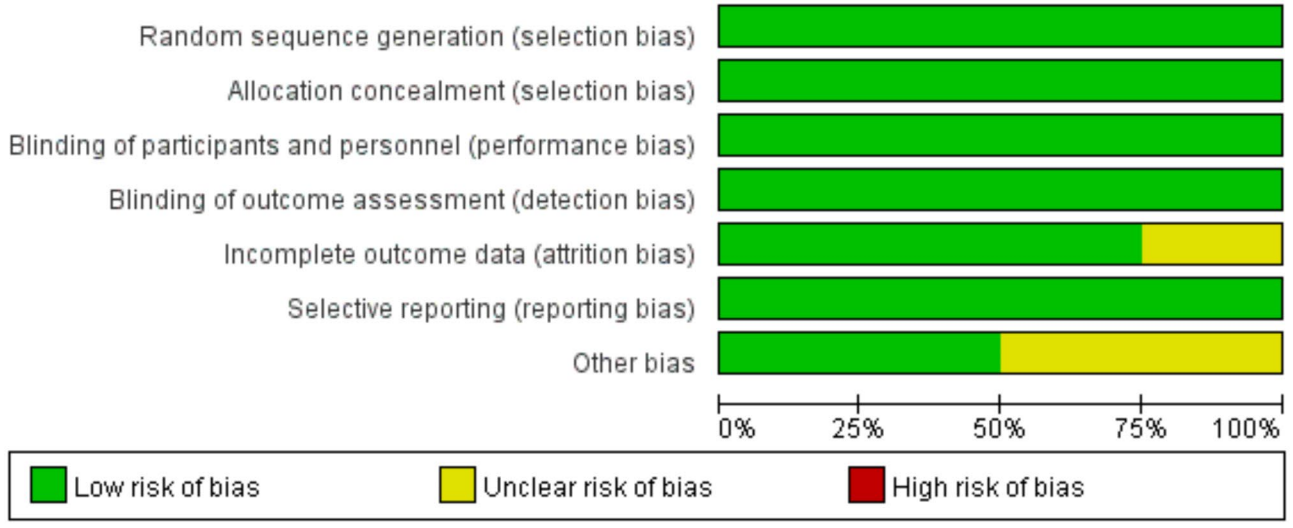

Fig. 5 Risk of bias summary for the randomized controlled trials included

differences between the two groups in the serious adverse events ($P = 0.91$).

Assessment of publication bias and risk of bias

The assessment of publication bias using a funnel plot was not conducted due to the inclusion of fewer than 7 studies.

The biases of observational studies were evaluated using the NOS. Among the included studies, only one was a retrospective cohort study with a score of 8, indicating high quality. The specific evaluation items are provided in supplement file 2. The risk of bias in RCTs showed a low risk in randomization processes, blinding selection, blinding assessment, and reporting bias, but an unclear risk in missing outcome data and other bias. Figure 5 provides an overview as a percentage to present each risk of bias item. Figure 6 presents the risk of bias summary for the four studies included in our meta-analysis.

Discussion

This meta-analysis, comprising 3048 HSCT recipients, represents the first comprehensive evaluation of the efficacy and safety of HZV in this population. Our findings demonstrate a significant reduction in the risk of HZ and no increased risk of adverse events following HZV administration in HSCT recipients during the short follow-up period.

Among the studies included in our meta-analysis, four investigated inactivated vaccines, while one examined a live attenuated vaccine. For immunocompromised individuals, inactivated HZV are considered the mainstream

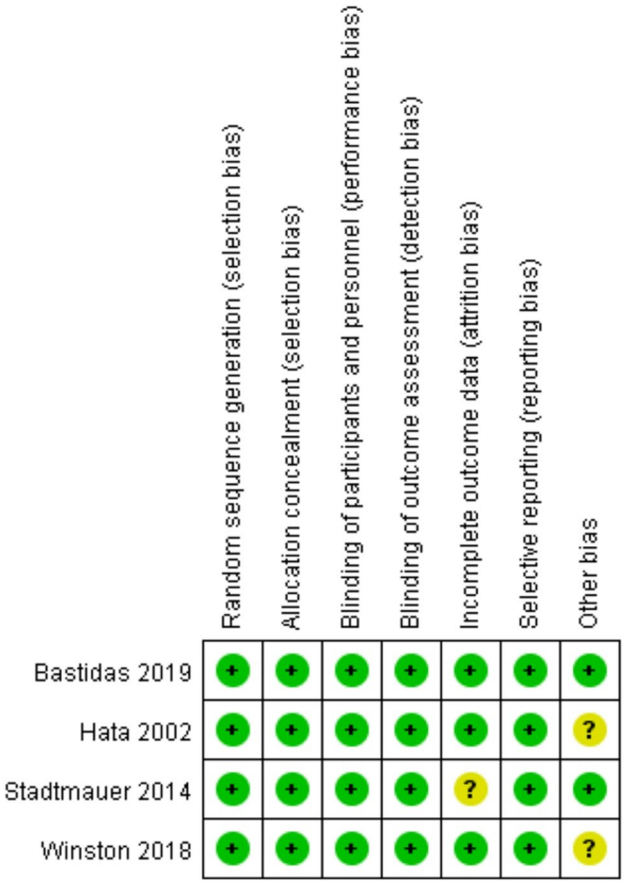

Fig. 6 Risk of bias graph for the randomized controlled trials included

recommendation in guidelines and consensus. Ohfuji [27] and Curtis [28] evaluated the safety of receiving live HZV in immunodeficient patients with underlying diseases and those treated with biologics, respectively, but the current use of live vaccines in the immunodeficient population is limited. An adjuvanted recombinant zoster vaccine (aRZV), recognized as a novel modified inactivated vaccine, has been developed and administered to immunocompetent adults in clinical trials [15, 16, 29]. Due to the absence of more robust clinical evidence, expert recommendations on HZ vaccination for HSCT recipients vary, and the urgency of determining the efficacy of HZV in this population is underscored.

Within the studies included in our meta-analysis, there is a notable bias regarding the type of HSCT due to the absence of RCTs specifically in allo-HSCT recipients. Baumrin [30] reported a lower incidence of HZ in allo-HSCT recipients after receiving aRZV in an observational single-center study. The studies by Issa [31] and Naidus [32] included both allo-HSCT and auto-HSCT recipients but provided limited descriptions of the efficacy and safety of a live attenuated HZV. These results were not included in the meta-analysis due to the small sample size and the use of historical controls.

The duration of humoral and cell-mediated immune response is closely related to the timing of vaccination and the number of doses. Due to the lack of experience in applying HZV to HSCT recipients and the heterogeneity of HZV, our meta-analysis did not discuss the dosage form and timing of vaccination. Some clinical trials presented HZV-induced humoral immunogenicity and cell-mediated immunity, including anti–glycoprotein E antibody concentrations, CD4 T-cell proliferation in response to HZV, and T cell activation-related cytokines, among other indicators. Stadtmauer [33] provided an in-depth description of the humoral and cell-mediated immune responses to HZV, indicating that the immune response induced by the vaccine varied somewhat among different underlying diseases. However, one of the shortcomings of the research is the lack of routine screening for serological antibodies and other indicators before vaccination in clinical trials. Limited data on immune responses were available, precluding a pooled analysis. In addition, the data presented above did not include an analysis correlating immunogenicity results with vaccine efficacy [19, 20]. The prophylactic effects of various types and formulations of vaccines and their associated immune responses in HSCT recipients still require confirmation through larger-scale clinical trials. The heterogeneity arising from different types and formulations of vaccines was not considered in this meta-analysis, representing one of the limitations of our study.

HZ infection often presents as a painful rash. HZ-associated pain can be acute and resolve after recovery from the disease. However, some patients experience PHN, which significantly impacts patients' QoL and interferes with activities of daily living (ADLs). Limited studies on the relationship between HZV and pain were included in this meta-analysis. Curran [34] assessed the impact of HZV on QoL in HSCT patients using a precise scale, revealing that HZV significantly reduced the impact of HZ on patients' QoL who developed breakthrough disease. However, more detailed data on the incidence of PHN, moderate-to-severe HZ-associated pain, HZ-associated pain duration, and pain medication use are still lacking. Kim [35] demonstrated the efficacy of aRZV in reducing HZ-associated pain duration and pain medication use in cases of breakthrough pain, thereby improving the QoL of those with HZ in 2023. This study was excluded from the meta-analysis due to the lack of primary outcome measures. Our results suggest that the risk of PHN is reduced in HSCT recipients following HZV, although this did not reach statistical significance ($P = 0.08$). This indicates that the current sample size may be insufficient to detect a significant difference. With an increased sample size, the statistical power of the test would improve, making it easier to detect a true effect. Studies in the elderly population have shown that HZV

can prevent herpes zoster and its sequelae, including PHN, by enhancing cell-mediated immunity (CMI) and humoral immune responses, with significant preventive effects on PHN [9, 15, 16].

The reduction of HZ-related complications is also considered one of the indicators to evaluate the efficacy of HZV. However, there were differences in the definition of this index among the included RCTs, preventing the conduct of pooled analyses.

Another concern is the safety of HZV. Our meta-analysis indicates no difference in the incidence of adverse events between the vaccine and placebo groups. Adverse events were monitored for one month after vaccination, with a lack of data for longer follow-up periods. The short follow-up period mainly captures immediate adverse events but may miss late-onset or rare reactions, leading to an incomplete safety profile. This could underestimate the long-term safety of HZV, especially in immunocompromised HSCT recipients. For allo-HSCT, the relationship between the greater $CD4^+$ T-cell effector response induced by HZV and the increased incidence of graft-versus-host disease (GVHD) lacked complete and reliable evaluation in the aforementioned studies. The impact of HZV on the incidence of GVHD in HSCT recipients was not assessed, especially in RCTs. Previous studies have demonstrated that in solid organ transplant patients, the onset of viral infection is related to the occurrence of transplant rejection [36]. While there is a case report of local skin GVHD activation and VZV infection in an allo-HSCT recipient after influenza vaccine administration, raising concerns about vaccine-induced GVHD, limited evidence exists, and no association between HZV and GVHD has been reported in the included clinical studies [37]. Baumrin [30] reported that there are no increased rates of chronic GVHD compared with historical controls after HZV in a single-center prospective observational cohort study.

While this study provides valuable insights into the effect of the herpes zoster vaccine in HSCT recipients, several limitations must be considered. Several limitations exist in this study. First, our conclusions are based on a small number of clinical trials, we need more randomized clinical trials with large sample size to verify the efficacy and safety of HZV in HSCT population. Second, the majority of included studies predominantly focus on auto-HSCT recipients, with a notable lack of research on allo-HSCT recipients. This limits the generalizability of our findings to the broader HSCT population, particularly since allo-HSCT recipients are often at a higher risk for complications due to more intensive immunosuppressive therapies. Future studies should focus on allo-HSCT populations to better understand the vaccine's safety, efficacy, and long-term outcomes in this high-risk group. Another limitation is the heterogeneity across the included studies, including differences in study designs, vaccine types, patient characteristics, and follow-up durations. Although we conducted sensitivity and subgroup analyses to explore this heterogeneity, the variability in these factors may still impact the overall findings and reduce the robustness of the conclusions. Additionally, there were variations in vaccine administration schedules and doses, which could influence both the immunogenicity and effectiveness of the vaccine, especially in the context of long-term outcomes like PHN. Future research should standardize vaccine regimens and follow-up periods to allow for more consistent and comparable results. Furthermore, the inclusion of observational studies introduces potential biases, such as selection bias and information bias, which are inherent in non-randomized studies. Although we assessed the quality of included studies, the variability in study quality could affect the overall reliability of our results. Another concern is publication bias, as studies with positive outcomes are more likely to be published, potentially skewing the findings. Overall, future studies should aim to focus on allo-HSCT populations and standardize vaccine regimens and follow-up periods. High-quality RCTs with longer follow-up durations and more detailed subgroup analyses are needed to confirm the long-term benefits of HZV in HSCT recipients.

In conclusion, our analysis demonstrated the effectiveness of HZV for HSCT recipients, reducing the incidence of HZ with a low adverse event profile. However, more detailed RCTs are needed to guide the clinical application of HZV, particularly in terms of vaccine type, dose, and HSCT type.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-025-02670-5.

Supplementary Material 1

Supplementary Material 2

Author contributions

The literature search and study selection were conducted independently by X.J. and J.Z.,with discrepancies reviewed and resolved by consensus(M.X. and Y.D.).The data extraction was retrieved and summarized independently by X.J. and J.Z.The bias risk of all the enrolled experiments was assessed by X.J. and J.Z.The data analysis were performed by X.J. and Y.D.X.J. and Z.Z. wrote, reviewed and edited the manuscript.All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable. This meta-analysis is based on previously published studies, and no new data were collected from human participants.

Consent for publication

This meta-analysis included data from previously published studies. All original studies were conducted in accordance with ethical standards, and informed consent was obtained as required.

Competing interests

The authors declare no competing interests.

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