Risk Factors for Cytomegalovirus Infection after Haematopoietic Stem Cell Transplantation: A Meta-Analysis

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ABSTRACT

Cytomegalovirus (CMV) infection is the most common viral infection after haematopoietic stem cell transplantation (HSCT). However, studies on related risk factors give different views without any clear conclusion. Therefore, the purpose of this study was to evaluate the risk variables of CMV infection after HSCT in order to provide recommendations for therapeutic treatment. The National Knowledge Infrastructure [CNKI], Chinese Biomedical Literature database [SinoMed], Wanfang Digital Periodicals [WANFANG] and China Science and Technology Journal [VIP] databases, as well as PubMed, Embase, CENTRAL, Web of Science databases were searched. The search keyword was Cumulative Index of Nursing and Related Health Literature (CINAHL). The search time spanned from the time when the database was created to February 2023. Based on inclusion and exclusion criteria, two researchers independently chose the literature, retrieved data, and assessed the bias risk. The methodological quality of the included studies was assessed by the Newcastle Ottawa scale (NOS). A total of 1,038 literatures were retrieved, of which, 18 studies were finally included. The final results of meta-analysis showed that there were seven risk factors as follows: Acute graft-*versus*-host disease (aGVHD) grades II-IV (II-IV) [odds ratio = 3.39, 95% CI (2.13, 5.41), p <0.05]; ant-thymocyte globulin (ATG) administration in treatment [odds ratio = 2.53, 95% CI (1.41, 4.53), p <0.05]; cyclosporine level after transplantation (>300 ng/ml) [OR = 3.79, 95% CI (1.24, 11.65), p <0.05]; age [odds ratio = 1.83, 95% CI (1.06, 3.15), p <0.05]; neutrophil deficiency time [odds ratio = 6.58, 95% CI (2.24, 19.30), p <0.05]; CMV infection in recipients before transplantation [odds ratio = 6.32,95% CI (4.03, 9.90), p <0.05]; fungal infection [odds ratio = 2.63, 95% CI (1.09, 6.34), p <0.05].

This study preliminarily revealed that CMV infection after HSCT is related to aGVHD (II-IV), ATG administration in pretreatment, cyclosporine level (>300 ng/ml) after transplantation, age, neutrophil deficiency time, CMV infection in recipients before transplantation and fungal infection. However, the mechanisms behind the risk variables are unclear. Further research is necessary to understand the risk factors and to enhance the care of patients with these risk factors to prevent or control infection.

Key Words: *Haematopoietic stem cell transplantation, Cytomegalovirus infection, Risk factors, Meta-analysis.*

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INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) has been used extensively in patients with immunodeficiency, malignant tumours, haematological disorders, and other metabolic diseases in recent years. It plays an important role in improving disease-free survival rates.[1] It is the delay in immune reconstitution or the existence of immunodeficiency in patients caused by transplantation that it is easy for them to become a high-risk group for infection.[2]

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Cytomegalovirus (CMV) infection is the most common viral infection after transplantation, which mostly occurs in the first 1-3 months after transplantation with an incidence rate of 37.9 - 81.9%.[3-5] In case of no appropriate treatments, asymptomatic CMV infection may progress to CMV diseases, which not only causes local organ damage, but can also result in secondary bacterial and invasive fungal infection. It can also contribute to post-transplant-*versus*-host diseases, and post-transplant bone marrow failure through indirect effects, thereby increasing mortality, etc.[6,7] CMV infection is paid high attention and is closely monitored in clinical practice due to its high incidence after transplantation. Therefore, the risk factors for CMV infection have attracted increasing attention from researchers. Dozens of studies showed that human leucocyte antigen (HLA) incompatibility, seropositive blood donors, ant-thymocyte globulin (ATG) administration in pretreatment, hormone use after transplantation, and graft-*versus*-host disease (GVHD) are the risk factors for CMV infection.[8-11] In addition, several risk factors for CMV remain

paradoxical, and the failure to recognise the risk factors of CMV may be linked to a lack of awareness of this symptom. For example, Zou *et al.*'s study supported an association between CMV infection and age,[8] whereas others did not.[11] There are discrepancies between the results of the studies without definite conclusions. To give healthcare professionals a greater guidance, this meta-analysis was conducted to compile risk factors for CMV infection.

METHODOLOGY

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The detailed study protocol is available on the PROSPERO website under the registration number CRD42022382046.

A comprehensive search of articles from nine databases during the period from data creation to February 2023, including Chinese databases (National Knowledge Infrastructure [CNKI], China Biomedical Literature Database [SinoMed], Wanfang Digital Journal [Wanfang], China Science and Technology Journal [VIP] Database, PubMed, Embase, CENTRAL, Web of Science, and the Cumulative Index of Nursing and Related Health Literature (CINAHL). During the literature search, MeSH term combinations, Emtree synonyms, and free words were employed. Chinese search terms include as follow: Haematopoietic stem cells, stem cells, cytomegalovirus infection, cytomegalic infection diseases, CMV, cytomegalic inclusion diseases, and transplantation. English search terms include as follow: Haematopoietic stem cell, haematopoietic progenitor cell, cytomegalovirus infection, cytomegalic inclusion disease, inclusion disease, transplant, and graft. Furthermore, no restrictions were placed on the date, country, publication status, or year of publication, but the languages were restricted to English and Chinese.

The details of the search strategy are outlined in Figure 1. In addition, grey literature and the reference Lists included in the identified articles were manually searched. The inclusion criteria were case-control and cohort studies with post-HSCT CMV infection.

The language of the literature was limited to Chinese or English with no restrictions on the age, gender, race, and disease duration of patients in the literature. Outcome indices in the studies included must-have risk factors for CMV infection after HSCT: acute graft-*versus*-host disease (aGVHD), HLA (consanguineous transplantation), the use of ATG, gender, age, neutrophil deficiency time, CMV infection in recipients before transplantation, CMV infection in donors before transplantation, cyclosporine (>300 ng/ml) after transplantation, fungal infection, blood groups, etc. The exclusion criteria were duplicate publications as well as the literature of no original text found; reviews, experience summaries, animal experiments, case reports, conferences, meta-analysis, etc; disease diagnosis not consistent with CMV infection; and studies without a control group.

The Newcastle-Ottawa Scale (NOS) was adopted to evaluate the literature quality of the included studies. A score of 1-4 indicated low quality and a score 5-9 indicated high quality.

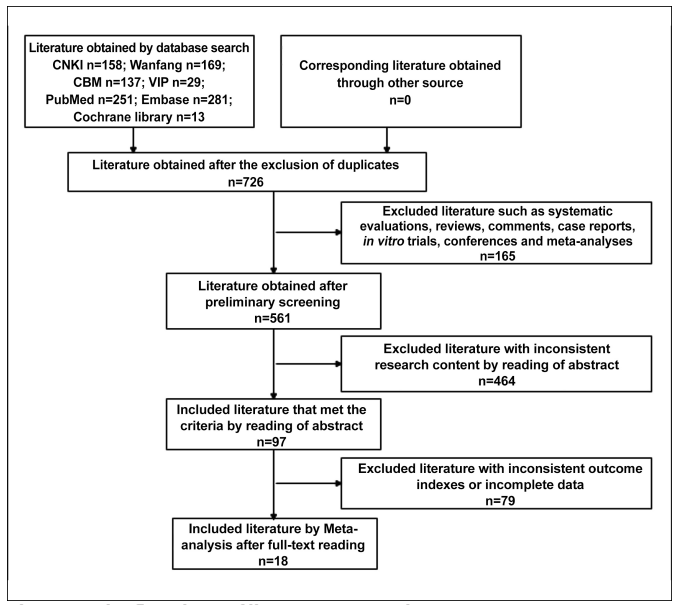

Figure 1: The flowchart of literature screening.

Following the inclusion and exclusion criteria, two reviewers (STW and CLW) looked over each article's title and abstract on their own before retrieving and reading the full-text articles. For inclusion in this systematic review and meta-analysis, each article was subjected to an independent evaluation by both reviewers. Any disagreements regarding the inclusion of an article were settled by consulting a third reviewer (CYZ or LW) and coming to a mutually agreeable decision. STW and CLW, two independent reviewers, also carried out the data extraction. The authors, publication year, baseline status, interventions, and risk factors of the included studies were among the data gathered from the systematic review studies.

Stata 15.0 software (Stata Corporation, College Station, Texas, USA) was used for data analysis. The effect size was expressed as odds ratio (odds ratio, OR) and its 95% confidence interval (CI). When $I^2 \leq 50\%$ and $p > 0.10$, the fixed effect model was adopted to combine the effect size. When $I^2 > 50\%$ and $p < 0.10$, the random effect model was adopted to combine the effect size. When there was great heterogeneity, the one-by-one elimination method was used for sensitivity analysis to explore the source of heterogeneity. When the number of included references for each outcome indicator ranged from 2 to 10, the Egger's test was used to evaluate the publication bias of the included study, and $p > 0.05$ was considered as no publication bias.

RESULTS

A total of 1,038 studies were obtained through systematic search. A total of 726 studies were obtained after deduplication by the Endnote X9 software, and 97 studies were obtained after the exclusion of irrelevant literature and studies with inconsistent research content by reading titles and abstracts. For the remaining literature, after excluding the literature with inconsistent outcome indices or incomplete data by full-text reading is shown in Figure 1.

Table I: Basic characteristics of the selected studies.

Author	Country	Year	Research type	Sample size		Risk factors
				Observation groups	Control groups	
Chenglin *et al.*[12]	China	2020	Case-control	165	104	2,3,8
Ji *et al.*[13]	China	2019	Case-control	21	32	1,3,8,9,1,2
Yongping *et al.*[14]	China	2014	Cohort study	62	18	1,7
Hui *et al.*[15]	China	2019	Case-control	26	14	3
Lieguang *et al.*[16]	China	2014	Case-control	2553	5494	1,3
Xuan *et al.*[17]	China	2016	Cohort study	65	100	1,3,6
Zhixiang *et al.*[18]	China	2012	Case-control	132	51	2,3,5,6,8
Huan *et al.*[19]	China	2015	Cohort study	13	17	1,3
Aizhi *et al.*[20]	China	2014	Cohort study	33	49	2,8,10,11
Jun *et al.*[21]	China	2014	Case-control	57	51	1,2,3,4,13
Chen *et al.*[22]	China	2020	Cohort study	26	96	3,5,7,8,9,13
Yu[23]	China	2017	Case-control	60	173	5
Leling *et al.*[24]	China	2021	Cohort study	229	41	1,2,3
Pinana *et al.*[25]	Spain	2009	Case-control	69	117	2
Jaing *et al.*[26]	Taiwan, China	2019	Cohort study	54	236	2,3,10,11
Lin *et al.*[27]	Taiwan, China	2017	Case-control	32	50	1,2,3,5,8,10
Yoon *et al.*[28]	Korea	2009	Cohort study	28	89	1,2,3,11
Rowe *et al.*[29]	America	2017	Case-control	26	65	3,11

1. ATG administration in pretreatment; 2. HLA; 3. aGVHD (II-IV); 4. cGVHD; 5. Gender; 6. CSA >300 ng/ml after transplantation; 7. Fungal infection; 8. Age; 9. Blood type matching; 10. Positive CMV in donors before transplantation; 11. Positive CMV in recipients before transplantation; 12. Blood type compatibility; 13. Neutrophil deficiency time.

Table II: Literature quality evaluation table.

Author	Year	NOS score (points)								Total score
		a	b	c	d	e	f	g	h	
Chenglin *et al.*	2020	1	1	1	0	2	0	0	0	5
Wu Ji *et al.*	2019	1	1	1	0	1	0	1	0	5
Zhang *et al.*	2014	1	1	1	0	1	0	0	0	4
Hui *et al.*	2019	1	1	1	0	1	0	0	0	4
Chen *et al.*	2014	1	1	1	0	1	1	0	0	5
Xuan *et al.*	2016	1	1	1	0	2	0	0	0	5
Zhixiang *et al.*	2012	1	1	1	0	2	1	0	1	7
Huan *et al.*	2015	1	1	1	0	2	1	0	0	6
Aizhi *et al.*	2014	1	1	1	0	2	1	0	1	7
Jun *et al.*	2014	1	1	1	0	2	1	0	1	7
Chen *et al.*	2020	1	1	1	0	2	1	0	0	6
Lin Yu	2017	1	1	1	0	2	0	0	0	5
Leling *et al.*	2021	1	1	1	0	1	0	0	0	4
Pinana *et al.*	2009	1	1	1	0	1	0	0	0	6
Jaing *et al.*	2019	1	1	1	0	2	1	0	0	6
Lin *et al.*	2017	1	1	1	0	2	1	0	1	7
Yoon *et al.*	2009	1	1	1	0	1	0	1	0	5
Rowe *et al.*	2017	1	1	1	0	2	1	0	0	6

a: Representativeness of the exposed cohort; b: Selection of non-exposed cohort; c: Methods for determining exposure factors; d: Determination of outcome indices that did not yet need to be observed at the beginning of the study; e: Consideration of the comparability between exposed and non-exposed groups in the design and statistical analysis; f: Research on whether the evaluation of the research results was sufficient; g: Research on whether the follow-up was long enough after the results; h: Research on whether the follow-up of exposed and non-exposed groups was complete.

Table III: Pooled risk factors of CMV infection.

Risk factors	Number of included studies	Results of heterogeneity		Effect model	Results of meta-analysis	
		p	I^2 (%)		OR (95% CI)	p
aGVHD (II-IV)	14	<0.10	77.0%	Random	3.39 (2.13, 5.41)	<0.05
ATG administration in pretreatment	9	<0.10	77.8%	Random	2.53 (1.41, 4.53)	<0.05
Serum cyclosporine concentration (>300ng/ml) after transplantation	2	<0.10	63.1%	Random	3.79 (1.24, 11.65)	<0.05
Age	6	<0.10	69.8%	Random	1.83 (1.06, 3.15)	<0.05
Neutrophil deficiency time	2	>0.10	0.0%	Fixed	6.58 (2.24, 19.30)	<0.05
CMV infection in recipients before transplantation	4	>0.10	30.1%	Fixed	6.32 (4.03, 9.90)	<0.05
Fungal infection	2	>0.10	0.0%	Fixed	2.63 (1.09, 6.34)	<0.05

CI = Confidence interval; OR = Odds ratio.

As shown in Table I, the basic information of 18 included articles was extracted, including author, country, year, study type, sample size of the experimental group and the control group, and the extraction of influencing factors. A total of 10,448 participants were included in the 18 cross-sectional studies. Most articles (15/18) were published in the past 10 years, of which most (13/18) were conducted in China, and 2 in Taiwan, with one each in America, Korea, and Spain.

The quality evaluation of the included literature is shown in Table II. The included literature was scored according to the

NOS standard, and most of the scores were 5-7 points, indicating a moderate or higher level of quality.

A total of 13 potential risk factors associated with CMV infection were identified, including ATG administration in pretreatment, HLA, aGVHD (II-IV), cGVHD, gender, CSA>300 ng/ml after transplantation, fungal infection, age, blood type matching, positive CMV in donors before transplantation, positive CMV in recipients before transplantation, blood type compatibility, and neutrophil deficiency time. However, only aGVHD (II-IV), pre-treated ATG administration, cyclosporine level (>300 ng/ml) after transplantation, age, neutrophil deficiency time, CMV infection in recipients before transplantation, and fungal infection had sufficient data and could be synthesised. In the analysis of neutrophil deficiency time, CMV Infection in recipients before transplantation and fungal infection, a fixed effects model was used, as no statistically significant heterogeneity was observed. While the statistical heterogeneity of aGVHD (II-IV), cyclosporine level, ATG administration in pretreatment and age was observed, thus a random effects model was used. Sensitivity analysis was performed to explore the source of heterogeneity. The main source causing the increased heterogeneity was not identified by the one-by-one elimination method. Sensitivity analysis showed that after the exclusion of any literature, the obtained result was consistent with the original one, indicating that the result was relatively stable and reliable, as shown in Table III.

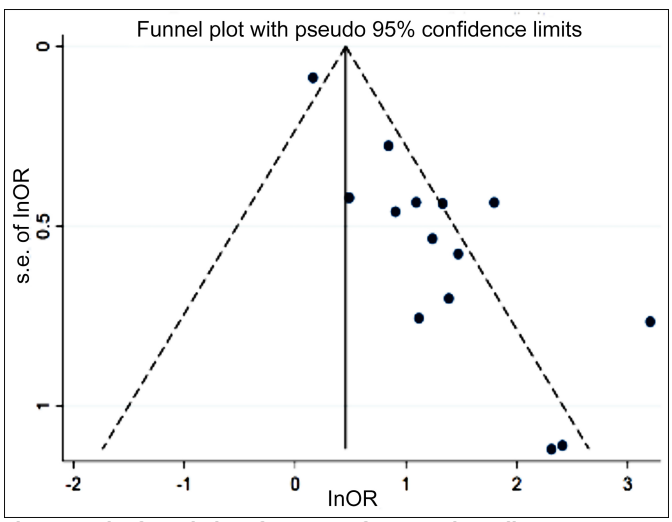

Figure 2: The funnel plot of acute graft-*versus*-host disease.

The number of studies included in aGVHD (II-IV) alone exceeded the amount of 10 and publication bias could be assessed by the funnel plots. Visually, it was found that all points on the funnel plot were diffusely distributed, not completely symmetrical, and there was the possibility of publication bias (Figure 2). Since the number of included studies for such outcome indices as neutrophil deficiency time, cyclosporine level (>300 ng/ml), fungal infection, and blood type matching was 2, respectively, the publication bias could not be evaluated by the funnel plots and Egger's test. The number of included studies for such outcome indices as HLA (consanguineous transplantation), ATG administration pretreatment, age, CMV infection in recipients before transplantation, CMV infection in donors before transplantation was between 2 and 10. Therefore, Egger's test could be used to evaluate publication bias and the result suggested that there was no publication bias ($p > 0.05$).

DISCUSSION

The NOS scores of the 18 pieces of included literature were mostly 5-9, indicating a moderate or higher level of quality. In all included literature, a total of 10,448 patients after HSCT were screened, involving 3,651 with CMV infection. And the overall sample size was relatively high, indicating that this study has high reliability. In all included studies, the source of the research objects and the diagnostic criteria for the results were clarified, but the monitoring time was not unified in most studies, which may have a certain impact on the research results. Finally, seven relevant risk factors were identified in this study.

The results showed that aGVHD (II-IV) increased the risk of CMV infection. In the normal state of human immune function, intracellular CMV usually manifests as a quiescent state of infection clinically. When the body's immune function is suppressed, CMV can be reactivated to replicate at a sustained high level and enter the active phase.[30,31] Recent studies have suggested that GVHD may inhibit the specific immunity of CMV infection by reducing the release of thymus-dependent T cells, thereby causing the destruction of the body's immune status; meanwhile, systemic corticosteroids administration can inhibit the antiviral immune response of the host, which not only made it difficult to remove the virus but caused the spread of the virus.[12,15] In addition, the treatment for aGVHD (II-IV) means that with higher doses and longer duration of systemic hormone administration,[32] there will be an increased risk of CMV infection. Therefore, close attention to the occurrence of aGVHD and timely monitoring of CMV during medication administration can reduce the occurrence of viraemia.

Studies suggested that CMV infection is related to ATG administration in pretreatment. CMV is a DNA-virus from the herpesvirus group, whose immune responses *in vivo* are mainly mediated by T lymphocytes. CMV can generate an immune response after the initial infection, with a long incubation period *in vivo*. The delay of T cell immune reconstruction or T cell immunodeficiency is an important factor in CMV infection.[33] ATG serves as a strong immunosuppressant that inhibits T cell activity and ATG use increases the incidence of CMV infection in the pretreatment scheme, which may be related to the strong scavenging effect of ATG on T cells and long half-life *in vivo*.[34-36] Studies have shown that ATG pretreatment can lead to the increased incidence of CMV reactivation, and the application of antiviral agents for three consecutive weeks after ATG administration can still cause the occurrence

of CMV infection.[37] Therefore, the virus infection should be actively and routinely monitored from the pretreatment, with the administration of antiviral drugs for pretreatment according to the doctor's advice and timely interventional treatment.

Cyclosporine level (>300 ng/ml) is a risk factor for CMV infection. By reviewing the clinical data of 165 patients after HSCT, Xuan *et al*. found that cyclosporine level (>300 ng/ml) is a risk factor for CMV, which is consistent with the findings of Zhixiang *et al*.[17,18] In another study of the relationship between the changes in cyclosporine concentration and CMV infection in patients after HSCT, it was found that the cyclosporine blood concentration in CMV DNA-positive group was significantly higher than that in CMV DNA-negative group.[37] After HSCT, patients need to use immunosuppressants to prevent GVHD. In case of too low cyclosporine concentration, it is not conducive to the prevention of GVHD, while in case of too high concentration, it can aggravate the immunosuppressive status and easily lead to CMV infection. Therefore, immunosuppressive therapy also increases the risk of infection with other opportunistic viruses such as CMV and the two can form a vicious circle, which is not conducive to immune reconstitution after HSCT and further increases the chance of CMV infection.[28,29] Taken together, after HSCT, patients should regularly monitor the cyclosporine level and adjust the dose according to the blood concentration to reduce the incidence of CMV infection. Due to the small amount of literature included in this study, there is no mention of differences in blood levels of cyclosporine by administration method or the number of times it is measured, which may introduce bias into the analysis. Further verification of the above results is required.

Age plays an important role in inducing CMV infection. With increasing age, patients' immunity decreases and they are vulnerable to CMV infection; meanwhile, the older the age, the higher the probability of GVHD after transplantation, which can increase the risk of CMV infection.[38] However, the important role of age in inducing CMV infection remains controversial and relevant studies[14,15] showed that there was no correlation between age and inducing CMV infection, which may be due to the lack of uniform standards for the division of age groups in the literature that met the inclusion criteria. This suggests that further high-quality prospective researches with large samples are still needed in the future. In clinical nursing work, it is necessary to pay attention to older patients and provide health education for them to achieve early prevention, early detection, and early treatment.

Neutrophil deficiency time is an important factor in inducing CMV infection. In another study, Jang *et al.* found by analysing the influence factors of CMV infection after HSCT that neutropenia is a significant factor in the occurrence of CMV infection,[39] which is consistent with the result of this study. Patients with low immune function after transplantation can seriously consume neutrophils in case of bacterial infection. Additionally, due to low immunity, it is very easy to induce GVHD, which can affect the recovery of haematopoietic function or prolong the recovery time of neutrophils. Therefore, clinically, antibiotics and antiviral medicines should be used to prevent infection according to the actual situation, with the prevention of GVHD and the shorter neutrophil deficiency time, so as to reduce the incidence of CMV infection.

Meta-analysis suggested that CMV infection is related to CMV infection in recipients before the transplantation. Studies have shown that almost all viraemias occur in seropositive recipients, with very few coming from CMV transmission of donors.[40] The effect of CMV serological status in donors on post-transplant CMV infection and transplant prognosis depends on the CMV serological status in recipients. Related studies have shown that the positive infection rate of cytomegalovirus serological tests in normal humans is as high as 95%. Cytomegalovirus infection does not cause dangerous consequences in a normal human body. Patients undergoing transplantation have their immune system in a suppressed state, and only a small part of the immune function of cells has resumed operation. The entire body is in a high-risk operating state due to the wide range of cytomegalovirus infections, so the most common postoperative complication for transplant patients is cytomegalovirus infection. In the literature on an exploration of factors for CMV infection, it has been pointed out that pre-transplant CMV seropositive recipients are considered to be an important risk factor for CMV reactivation after HSCT.[41,42] Generally speaking, when the recipient is positive and the donor is negative, the CMV infection of the recipient after transplantation significantly increases compared with when they both are negative. This is mainly because the cellular immunity of the recipient to CMV is destroyed in the pretreatment, and in the donor graft, there are no CMV specific T cells, resulting in the delay of CMV immune reconstruction.[43] Therefore, it is necessary to actively monitor the serological status in clinical work to achieve early prevention and monitoring, which is conducive to improving the prognosis.

In this study, it can be concluded that fungal infection has a significant effect on CMV infection. It has been reported in the literature that the first peak of fungal infection after HSCT is 0-30 days after transplantation, which is earlier than the time of CMV infection.[44] The possible reason is that fungal infection after HSCT can impair immune function and easily induce CMV infection. Therefore, prevention should be carried out for patients with a history of fungal infection, with the selection of effective medicines and the regular performance of fungal tests from the pretreatment stage until the end of the peak period of fungal infection.

This study is the first to evaluate the risk factors for CMV infection after haemodialysis and systematic review. By increasing awareness of CMV infection following HSCT, health-

care professionals may be better able to prevent, assess, diagnose, treat, and monitor CMV infection. Overall, the extensive literature search conducted across nine electronic databases to reduce the possibility of missing research is one of this study's strong points. Furthermore, the studies that were included had a high-to-moderate quality. There were limitations even though this study was carried out in compliance with the meta-analysis criteria. Firstly, there was not much literature on risk factors for site infections, which could have an impact on the findings. Secondly, there was heterogeneity in the analysis results of local infection risk factors, which may be related to the inconsistency of the study population and study objectives included in the study. Thirdly, there may be bias in the results since the majority of the included studies were carried out in China, so care should be taken when interpreting them.

CONCLUSION

Cytomegalovirus infection after HSCT is related to aGVHD (II-IV), ATG administration in pretreatment, serum cyclosporine concentration (>300 ng/ml) after transplantation, age, neutrophil deficiency time, cytomegalovirus infection in recipients before transplantation, and fungal infection. These results imply that more studies with a larger total sample size should be carried out to identify the risk factors that have the greatest impact on CMV infection, as well as the underlying mechanism of the infection and the best ways to treat it.

CLINICAL TRIAL REGISTRATION:
As it is based entirely on previously published studies, this study protocol has been registered on the PROSPERO website (CRD 42022382046).

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
STW: Conceptualisation and writing of the original draft.
STW, CYZ: Data curation.
STW, LW: Methodology.
STW, CLW: Software.
CLW: Supervision.
All authors approved the final version of the manuscript to be published.

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