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Effect of post-storage filters vs. pre-storage filters for leukoreduction of blood components on clinical outcomes: a systematic review and meta-analysis

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Abstract

Background Leukoreduction has been used to limit the risk of adverse events. The most commonly used methodology is filtration (pre- or post-storage). However, whether pre-storage filtration is better than post-storage filtration needs to be clearly defined, particularly for countries that still use post-storage filtration. This study aimed to synthesize the best available evidence on the effectiveness of pre-storage filters compared with post-storage filters for transfusion reactions, for the occurrence of infections, for the length of hospital stay, and for the death of patients undergoing leukoreduced transfusion.

Methods We searched the MEDLINE (PubMed), CINAHL (EBSCO), PsycINFO (APA), Scopus (Elsevier), The Cochrane Library (J. Wiley), Web of Science Core Collection (Clarivate Analytics), Embase (Elsevier), and LILACS (VHL) databases and gray literature for eligible studies in August 2020 and updated the search in October 2023. The Joanna Briggs Institute critical assessment tools were applied to analyze the quality appraisal of the studies. GRADE was used to determine the certainty of the evidence.

Results The meta-analysis showed that pre-storage filtration was a protective factor for the occurrence of febrile non-hemolytic transfusion reaction in red blood cells (RR 0.49, 95% CI 0.41–0.59) and platelet concentrate transfusions (RR 0.16, 95% CI 0.12–0.22). The same did not occur for post-surgical infection after platelet concentrate transfusions (RR 0.82, 95% CI 0.65–1.04). Only one study analyzed the length of hospital stay and showed no significant difference between patients who received leukoreduced transfusions according to the type of filter used. According to the GRADE criteria, the certainty of the evidence for febrile non-hemolytic transfusion reactions was low for red blood cells and very low for platelet concentrate due to the high risk of bias. Infection was a low risk due to imprecision.

Conclusions The results of this review showed that the certainty of recommending the best type of filter (pre- or post-storage) for the benefit of the outcomes analyzed is still fragile; therefore, more robust evidence is needed.

Systematic review registration PROSPERO CRD42020192202.

Keywords Effectiveness, Post-storage filter, Pre-storage filter, Leukoreduction, Meta-analysis

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Background

Transfusion is a relevant therapy for treating patients, especially those in critical condition, to obtain biological responses such as increased tissue oxygenation or to prevent or cease bleeding [1–4]. Alloantigens and metabolically active cells capable of proliferating and producing response modifiers that affect the recipient are introduced during transfusion. In addition, inflammatory mediators, such as cytokines, interleukins [1–6], and tumor necrosis factor, are released by the degradation of leukocytes as blood components are collected, processed, and stored. At the same time, the recipient will respond to transfusion by producing immunological mediators that further influence the recipient's clinical response [5].

Despite advances in transfusion medicine, this therapy can still cause adverse events due to the risks related to the procedure, such as failures during the blood cycle due to incorrect indication of the need for transfusion, inappropriate use of blood components, or aspects inherent to the receiver itself [1–4]. Transfusion reactions (TRs) are among the main adverse events related to using blood products. According to the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM), it is estimated that the expected TR rate is three to five reactions per 1000 transfusions performed [6]. Moreover, red blood cell (RBC) and platelet concentrate (PC) transfusions are responsible for most TRs [7, 8]. The main TR associated with the presence of mediators released by leukocyte degradation is the febrile non-hemolytic transfusion reaction (FNHTR). In addition, alloimmunization (ALO), transfusion-related acute lung injury (TRALI), graft versus host disease (GVHD), and communicable diseases, including cytomegalovirus (CMV), have been found in the literature; however, these infections occur less frequently [6–9]. Transfusional immunomodulation can also cause adverse events, such as increased bacterial infections in the postoperative period and the recurrence of malignancies (i.e., intestinal neoplasia); the reactivation of latent and asymptomatic infections; and increased morbidity and mortality [10–12].

Leukoreduction is one of the procedures used to remove leukocytes through filters to avoid TRs and transfusion-related immunomodulation (TRIM). The pre-storage filter is used during donation (in-line) or to separate blood components (bench) within 48 h after collection. A post-storage filter is used at the bedside during transfusion.

Several studies suggest other clinical benefits of reducing leukocyte counts, such as decreasing the length of hospital stay and the use of antibiotics, in addition to improving the efficiency of platelet transfusion [10, 13, 14]. European countries such as Germany, the United Kingdom, Ireland, and Portugal have adopted leukoreduction since 1990 to prevent complications such as TRs and Creutzfeldt–Jakob Disease Variant transmission [15, 16]. Canada has implemented the same method to avoid TRIM [17]. Leukoreduction is not widely used in Brazil, especially in public health services. Brazilian legislation guides prioritization in recommending leukoreduction for some groups of patients but does not determine the filtration time, whether pre or post-storage [18].

Although the benefits of leukoreduction are recognized, pre-storage leukoreduction has advantages over post-storage, including preventing the accumulation of cytokines that are synthesized during cell storage, preventing RBC hemolysis, and interruption of filtration by cell debris resulting from the storage of RBCs and ensuring quality control of the leukoreduction of products intended for transfusion [6, 10, 19].

Some studies comparing the use of blood components subjected to pre and post-storage filtration have shown that pre-storage leukoreduction is more advantageous for reducing TRs, infection, and postoperative mortality, especially in patients with cancer, transplants, or hematological diseases [19–21]. However, other studies have not shown a difference between the filtration time (before and after storage) and the clinical outcome of transfusion patients [22, 23]. This controversy justifies the need for this review.

Preliminary searches performed in PROSPERO, the Cochrane Library, and the Joanna Briggs Institute (JBI) Evidence Synthesis did not identify reviews that compared pre and post-storage leukoreduction filters on patient outcomes. Considering the knowledge gap about the ideal filter (pre- or post-storage) for performing leukoreduction, it is essential to find the best available evidence about this filter, which in turn will contribute to clinical decisions that promote safety for patients who need transfusions and will also help elaborate public policies on the subject. Therefore, this systematic review aimed to synthesize the best available evidence on the effectiveness of pre-storage filters compared with post-storage filters on the following clinical outcomes: TRs, the occurrence of infections, length of hospital stay, and hospital death in patients receiving leukoreduced transfusion.

Methods

This systematic review had the protocol published a priori [24] and registered in the PROSPERO database (CRD42020192202). Considering that the post-storage filter (bedside) has been the oldest and most widely used technology for decades, the PICO structure presented in the review protocol [24] was changed with regard to the intervention and the comparator by consensus among

the authors of this review. Thus, the pre-storage filter (bench or inline) was considered for intervention, and the post-storage filter (bedside) was considered for the comparator.

Information sources and search strategy

The sources included were MEDLINE (PubMed), CINAHL (EBSCO), PsycINFO (APA), Scopus (Elsevier), The Cochrane Library (Wiley), the Web of Science Core Collection (Clarivate Analytics), Embase (Elsevier) and LILACS (VHL). The search for unpublished studies (gray literature) included regulatory bodies such as the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária-Anvisa*) of Brazil, the Pan American Health Organization (PAHO) and the World Health Organization (WHO); representative entities, such as the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular-ABHH); and the American Association of Blood Banks (AABB), as well as records from the Digital Library of Theses and Dissertations and All Trials and Restoring Invisible and Abandoned Trials (RIAT). The full search strategy is provided in Additional file 1: Appendix 1 and the structured searches were conducted in August 2020 and updated in October 2023.

These references were grouped and imported into EndNote, a web version (Clarivate Analytics, PA, USA), and duplicate articles were removed. The Rayyan platform (https://rayyan.qcri.org/) was used for study screening and selection. The titles and abstracts of the studies were examined, and those relevant to the review question were selected for full-text retrieval. The evaluation was based on the inclusion criteria and was independently conducted by pairs of reviewers (NDMS and LSN, YN and DALMC; JT and NDMS; LSN and YN). Any divergences between reviewers in the study selection process were resolved by consensus or consultation with a third reviewer.

Eligibility criteria

Participants

Patients of any age, sex, or race who received a leukoreduced blood transfusion.

Intervention(s)

Pre-storage filter of any brand and type to remove leukocytes.

Comparator(s)

Post-storage filter of any brand and type to remove leukocytes.

Outcomes

TRs, infections, length of hospital stay, and hospital death. The length of hospital stay was regarded as the number of days the patient stayed there. TRs were considered by the type of reaction and by the diagnosis of the confirmed reaction (ALO, FNHTR, or TRALI), according to internationally adopted definitions. Infections were considered those confirmed by laboratory examination and not associated with contamination of the blood component. In-hospital death was identified as the patient's death during hospitalization from any cause after receiving a leukoreduced transfusion.

Types of studies

Experimental or quasi-experimental studies, including randomized or nonrandomized clinical trials; observational cohort, prospective or retrospective, case–control and cross-sectional studies; and case reports or case series. Studies published in Portuguese, English, or Spanish were included. No time limit was considered for the review.

Quality assessment

Pairs of reviewers (NDMS and LSN; YN and DALMC; JT and NDMS; LSN and YN) assessed eligible studies for methodological quality using standardized JBI critical appraisal tools [25] for quasi-experimental studies and randomized controlled trials after they had been imported into the JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI) software [26]. The purpose of the critical appraisal tool is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct, and analysis [25]. Answers rated as "yes", "no", "unclear" or "not applicable" were assigned for each question (13 for randomized controlled trial studies and 9 for quasi-experimental studies). Any disagreements between reviewers were resolved by consensus among all the reviewers. No studies were excluded based on methodological quality.

Data extraction and statistical analysis

The JBI template form was used for data extraction and is presented in Additional file 2: Appendix 2. The extracted data included the study location, participant details, storage filters used, and relevant results for the review question. The studies included reported RBC units or PC pools. We converted units and pools into the number of transfusions. For RBC, we considered one unit equal to one transfusion. For PC, we considered one pool (4 to 5 units of PC) equal to one transfusion. The frequency of

outcomes was absolute in some studies and percentages in others. It was possible to calculate the quantity of the outcomes in absolute numbers in all cases. Two independent reviewers (DALMC and LSN) performed these calculations, and even if they agreed, they were redone and confirmed by all the reviewers. Any disagreements were resolved by consensus among all the reviewers. It was necessary to contact the main author [22, 23] to request additional information in two cases.

The study results were pooled in a meta-analysis using the JBI SUMARI [26] to estimate a summarized mean effect according to the selected outcomes. Effect sizes are expressed as relative risk (RR) for dichotomous data, with a 95% confidence interval (CI). The random effect model was used due to clinical and methodological variability between studies. Statistical heterogeneity was assessed by visual inspection of the forest plot distribution, Pearson's chi-squared test pattern, and I^2 statistics. We chose to present the results of the meta-analysis, regardless of the degree of heterogeneity, to facilitate follow-up of the interpretations.

A funnel plot was not performed to assess publication bias due to the low number of studies included in each meta-analysis, but a sensitivity analysis was conducted.

Assessing certainty in the findings

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [27] approach to assessing evidence was followed, and a summary of the findings was presented with the following information: absolute effect for the pre and post-storage groups, relative effect estimates considering the RR and 95% CI (dichotomous variables: occurrence of FNHTR and infection) or mean (continuous variable: length of hospital stay). The evidence quality was classified according to the design, execution, and publication limitations (risks of bias), directivity, heterogeneity, and precision of the included studies, as established by GRADE [27].

Results

Results of the search and selection process

The initial literature search identified 1286 records, totaling 821 records after removing duplicates. A total of 796 records were excluded from screening the titles and abstracts because they were clearly ineligible for review. The remaining 26 reports were read in full to confirm their relevance for the review, and 17 were excluded for failing to meet the inclusion criteria [22, 28–43]; thus, nine studies [19–21, 23, 44–48] were included in this review.

The selection results are presented as a flowchart (Fig. 1), as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [49].

Additional file 3:Appendix 3 provides the list of studies excluded after reading the full texts and the reasons for their exclusion.

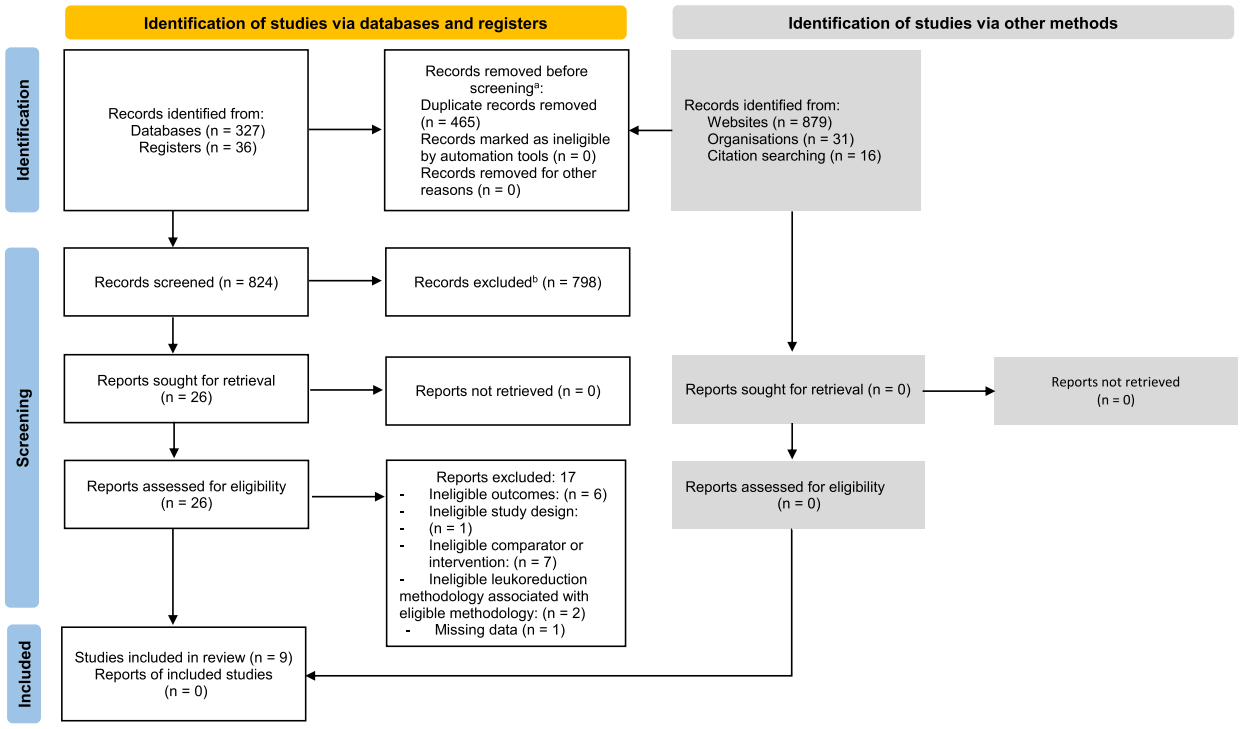
Characteristics of the included studies

One of the included studies was a randomized clinical trial [23], and the others were quasi-experimental [19–21, 44–48]. The characteristics and primary results of the studies are reported in Additional file 2: Appendix 2.

Of the studies included in the review, five (55.6%) [20, 21, 23, 47, 48] were conducted in Europe, three (33.3%) in North America [19, 44, 46] and one (11.1%) in Asia [45]. Most of the publications (n = 7; 77.8%) occurred between 2000 and 2018 [19–21, 44–47], mainly between 2000 and 2005 (n = 4; 44.4%) [20, 44, 46, 47], with the most recent and oldest studies dating from 2018 [45] and 1998 [23], respectively. The most common outcome was TR, mainly FNHTR (n = 7; 77.8%) [19, 20, 44–48]. The study participants were diverse: they were immunocompromised [44, 45] or had oncological [19–21, 46, 48], hematological [19, 48] or cardiac diseases [19, 23]; had undergone different transplants [45] or had an indication for colorectal resection [21]; were candidates for long-term transfusion therapy [47]; or had already presented FNHTR in previous transfusions [19, 45, 46]. The population included in the two studies was any patient who underwent allogeneic transfusion [44, 47].

Importantly, four studies [20, 44, 46, 47] analyzed data from patients who were transfused before and after universal leukoreduction was adopted. All transfused patients who received filtered blood components before universal leukoreduction were selectively indicated, and the predominant type of filtration was post-storage. In the universal leukoreduction phase, all patients received transfusions pre-storage filtered [20, 44, 46, 47]. Therefore, it can be assumed that patients who received post-storage filtered transfusions had a greater risk of reactions than did those who received pre-storage filtered blood components, leading to the risk of equivocally increasing the benefit of pre-storage filtration according to the results of these studies [20, 44, 46, 47], which contributed 78% (269,537 of 345,750) of the transfusions analyzed.

The patient sample sizes described in 6 studies ranged from 32 to 17,475 transfused patients [20, 21, 23, 45, 46, 48], in which the blood components used were RBC and PC. The total number of transfusions (RBC and PC) in the included studies was 345,750 (180,655 pre; 165,095 post-storage filtered), ranging from 161 to 174,856 transfusions [19, 20, 23, 44–48]. Some studies did not present demographic data (age and sex) from the samples [19,



[a]Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
[b]If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig. 1 PRISMA study selection and inclusion criteria.

44, 46, 47]; others only presented the age group [20, 48]. The follow-up time of the patients was reported in only 5 studies and ranged from 1 h to 60 days after transfusion [20, 23, 45, 47, 48]. Notably, FNHTRs were identified in RBC [20, 44–47] transfusions in 5 studies and in patients treated with PC in four studies [19, 45, 46, 48]. Most of the studies evaluated other TRs in addition to FNHTRs, such as allergic reactions [19, 20, 44–47]. One patient can receive more than one transfusion, but only two studies [20, 23] have reported the mean number of transfusions per patient. Only two studies evaluated infection [21, 23], and one analyzed the length of hospital stay [23]. Although one study evaluated mortality [23] within 60 days after transfusion, it was unclear whether death occurred during hospitalization. The main author did not return contact information upon request.

Methodological quality

At least 60% of the studies had positive responses to the applicable questions of the critical evaluation tools. The results of specific scores for each study included in this review using the evaluation criteria associated with the type of study design are provided in Tables 1 and 2.

The greater the number of "yes" responses on the evaluation forms used in this review, the lower the risk of bias. Table 1 shows that the total number of positive

Table 1 Critical appraisal results of the randomized controlled trial study

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% Yes
van Watering et al. 1998 [23]	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	Y	Y	**84.6**

Y = yes, *N* = no, *U* = unclear

JBI critical appraisal checklist for randomized controlled trials: *Q1* was true randomization used for the assignment of participants to treatment groups? *Q2* was allocation to treatment groups concealed? *Q3* were treatment groups similar at baseline? *Q4* were participants blind to treatment assignment? *Q5* were those delivering treatment blind to treatment assignment? *Q6* were outcome assessors blind to treatment assignment? *Q7* were treatment groups treated identically other than the intervention of interest? Q8 = Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized? *Q9* were participants analyzed in the groups to which they were randomized? *Q10* were outcomes measured in the same way for treatment groups? *Q11* were outcomes measured in a reliable way? *Q12* was appropriate statistical analysis used? *Q13* was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 2 Critical appraisal results of quasi-experimental studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	% Yes
Chalandon et al. 1999 [48]	Y	Y	U	Y	N/A	Y	Y	Y	Y	**87.5**
Chang et al 2018 [45]	Y	N	Y	Y	N/A	Y	Y	Y	Y	**87.5**
Da Ponte et al. 2005 [20]	Y	Y	N	Y	N/A	Y	Y	Y	Y	**87.5**
Garancini et al. 2013 [21]	Y	U	Y	Y	N/A	U	Y	Y	Y	**75.0**
Paglino et al 2004[46]	Y	N	U	Y	N/A	U	Y	Y	Y	**62.5**
Pruss et al 2004[47]	Y	N	U	Y	N/A	Y	Y	Y	Y	**75.0**
Uhlmann et al. 2001[44]	Y	N	U	Y	N/A	U	Y	Y	Y	**62.5**
Wang et al 2012[19]	Y	N	U	Y	N/A	U	Y	Y	Y	**62.5**
Total %	**100.0**	**25.0**	**25.0**	**100.0**	**N/A**	**50.0**	**100.0**	**100.0**	**100.0**	

Y yes, *N* no, *U* unclear, *NA* not applicable

JBI critical appraisal checklist for quasi-experimental studies (nonrandomized experimental studies): *Q1* is it clear in the study what is the 'cause' and what is the "effect" (i.e., there is no confusion about which variable comes first)? *Q2* were the participants included in any comparisons similar? *Q3* were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? *Q4* was there a control group? *Q5* were there multiple measurements of the outcome both pre and post the intervention/exposure? *Q6* was follow-up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? *Q7* were the outcomes of participants included in any comparisons measured in the same way? *Q8* were outcomes measured in a reliable way? *Q9* was appropriate statistical analysis used?

responses was 84.6%, with questions 4 and 6 indicating a possible risk of bias considering that there was no information about the blinding of participants and outcome raters. Table 2 shows that the minimum percentage of positive responses in each study was 62.5%, the maximum was 87.5%, and questions 1, 4, 7, 8, and 9 had positive responses in all the included studies. The answers to questions 2 and 3 show the most frequent risk of bias among the studies. The characteristics of the samples of patients in both groups were not presented in six of the eight studies included [19, 20, 44, 46–48], which limited the evaluation of the risk of selection bias relevant to question 2. It is important to note that the risk of selection bias is important in studies that analyzed data from before and after the adoption of pre-storage leukoreduction in all transfusions since the sample of patients who received transfusions with post-storage leukoreduction was more restricted and had a higher risk of TR, as already mentioned [20, 44, 46, 47]. The answers to question 6 were unclear in four studies [19, 21, 44, 46], as there was no report on the follow-up time for evaluating the outcomes. Question 5 was considered not applicable to the quasi-experimental studies of interest for this review because TRs are only transfusional if they occur after the intervention (transfusion), and there is no reason to evaluate them before transfusions.

Review findings and certainty of the evidence

The studies included in this review provided evidence of the effectiveness of the type of filtration of RBCs or PCs on FNHTR [19, 20, 44–48] infection [21, 23] and length of hospital stay [23]. The evidence could be synthesized in meta-analysis for FNHTRs (RBCs and PCs) and infection (PCs). The length of hospital stay was only reported in one study for patients who underwent PC transfusions [23].

A meta-analysis synthesizing evidence on the occurrence of FNHTRs showed that pre-storage filtration was a protective factor against RBC (0.49, 95% CI 0.41 to 0.59) and PC transfusions (RR 0.16, 95% CI, 0.12 to 0.22) (Figs. 2 and 3). However, the heterogeneity between the studies included in the meta-analysis was noteworthy. The I^2 was 66% in the meta-analysis for RBC and 93% for PC (Figs. 2 and 3). The heterogeneity was reduced ($I^2=0$) after repeating the analysis and excluding a very large study [46] to establish how much it dominated the results, and the effect continued to be favorable for the prestorage filter (Fig. 4). Moreover, the effect size increased and the 95% CI increased (from RR = 0.16 [95%CI 0.12–0.22]) to RR = 0.54 [95%CI 0.36–0.82].

The findings on the role of filtration type in preventing infection (Fig. 5) after PC transfusion are inconclusive. Although the RR (0.82) suggested a protective effect of the pre-storage filtration, this estimate was not statistically significant (95% CI 0.65 to 1.04), and the I^2 statistic was 75%. The only study identified for which the length of hospital stay was an outcome showed no statistically significant difference between patients who received leukoreduced PC transfusion according to the filter type used. The certainty in the final set of evidence was low

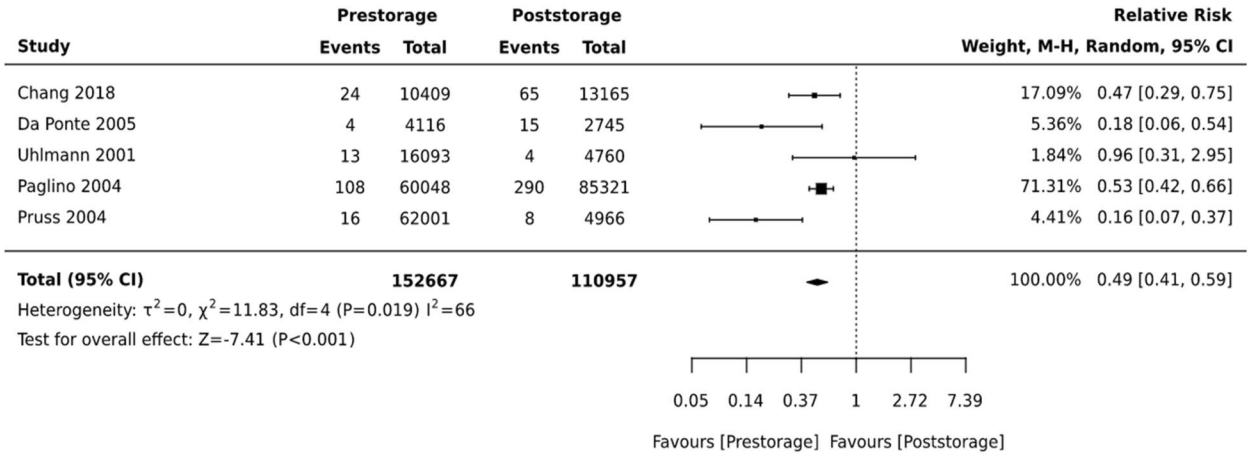


Fig. 2 Forest plot for the occurrence of FNHTRs after RBC transfusions according to the type of filter (pre or post-storage). CI: Confidence interval; M-H: Mantel–Haenszel

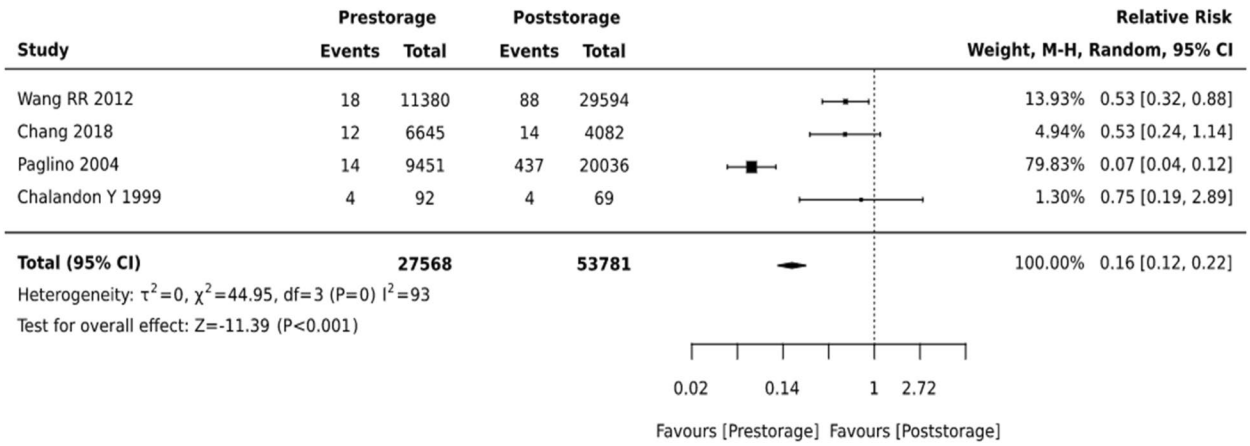


Fig. 3 Forest plot for the occurrence of FNHTRs after PC transfusions according to the type of filter (pre or post-storage). CI: Confidence interval; M-H: Mantel–Haenszel

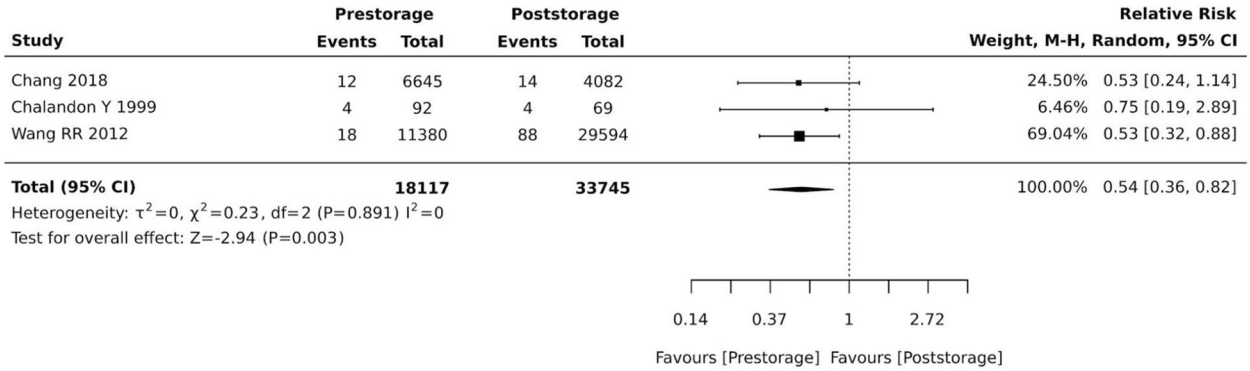


Fig. 4 Forest plot for the occurrence of FNHTRs after PC transfusions according to the type of filter (pre or post-storage), excluding one large study. CI: Confidence interval; M-H: Mantel–Haenszel

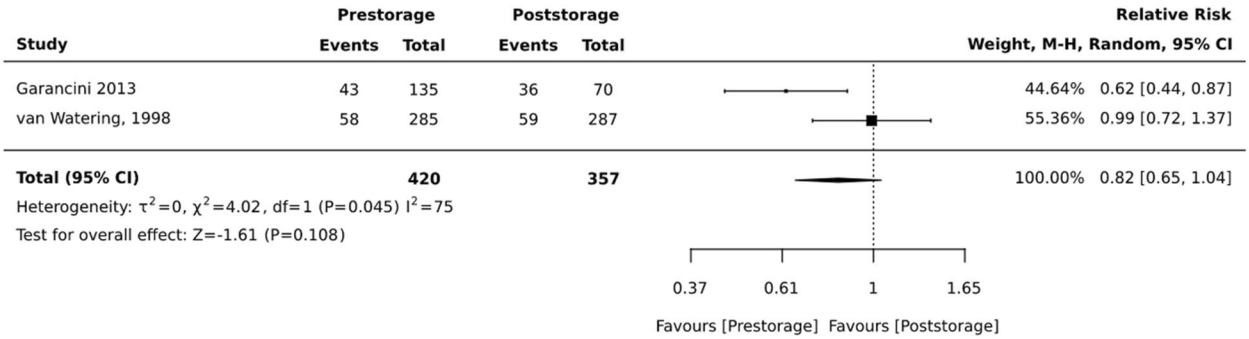


Fig. 5 Forest plot for the occurrence of infection after PC transfusions according to the type of filter (pre or post-storage). CI: Confidence interval; M-H: Mantel–Haenszel

due to the risk of bias, sample size, heterogeneity, and imprecision reflected in the wide CI. A summary of the findings is reported in Additional file 4: Appendix 4.

Discussion

The results showed that the certainty of recommending one type of filter or another is still fragile. The limited number of robust studies evaluating relevant outcomes for this review contributed to this fragility.

Most studies [19–21, 44–48] included in the review were quasi-experimental studies designed as time series to evaluate the impact of adopting universal leukoreduction. In these studies, the outcomes of patients who received leukoreduced blood components before universal leukoreduction were compared to those of all transfused patients after universal leukoreduction. The data sources included existing data from blood centers and patients' health records. Despite the advantages of using existing data [50], controlling for extraneous factors in this kind of data source is not possible, as is the case for randomized controlled trials, increasing the risk of bias in such studies [51]. In studies using existing data sources, changes in clinical practices, professionals involved, or filter models with varying filtration capacities over time cannot be strictly controlled.

Although ALO and TRALI are also related to the presence of inflammatory mediators and have been relevant outcomes in studies that compared leukoreduced and nonleukoreduced transfusions [6–8], only FNHTRs were found in this review. An allergic reaction was found in 75% of the studies analyzed [19, 20, 45–47], but it was not considered an outcome in this review because leukoreduction is not an indication for preventing it since its pathophysiology is different from that of FNHTRs and is related to the presence of anti-IgE antibodies in the receptor [4]. Two studies [21, 23] analyzed the presence of postsurgical infection for immunomodulation, but one study showed that surgery had a high potential for contamination (colorectal resection) [21].

An important aspect to be discussed is the lack of identification of recent primary studies and the greater frequency of studies carried out in developed countries. Most of the included studies were published between 1998 and 2005 [19, 20, 23, 44, 46–48] and originated in Europe and North America. Universal leukoreduction, which presupposes the exclusive use of the pre-storage filter, is adopted in some countries in these regions [15–17]. It can be admitted that, in this case, the use of the pre-storage filter is more appropriate from a practical point of view than the post-storage filter is, which would explain the lack of more recent studies comparing pre and post-storage filtration and, therefore, the possible lack of relevance of this review question for these contexts. However, in contexts with limitations of any nature for adopting universal leukoreduction and in which selective leukoreduction is considered, answering the central question of this review is important to support the recommendations on the type of filter to use. Although it may seem implicit in this comment that universal leukoreduction is based on robust evidence, this is not the case. A systematic review evaluating the use of leukoreduction did not find robust evidence to support or reject the routine use of leukoreduction in all patients transfused with RBCs to prevent TRALI, death, infection, non-infection complications, or other adverse events because the quality of evidence was also very low [52]. As with this review, the different scenarios and the high heterogeneity between studies contributed to the high risk of bias, inconsistency, and imprecision.

The characteristics of the population/sample, blood components, filters, and follow-up time according to the outcomes impacted the assessment of methodological quality and synthesis of the results. These characteristics deserve to be discussed so that they can be considered in primary studies. Some studies presented information

about people's illnesses but lacked demographic data, such as sex or age [19, 20, 44, 46, 47], making it impossible to compare the studied samples. In addition, there was little information, such as a previous history of TR or concomitant use of other nonleukoreduced blood components, constituting factors that may mask the results found since alloimmunized patients have an increased risk of developing TR and because the simultaneous use of a nonleukoreduced blood component leads to a greater chance of developing TR.

Another impacting factor was the length of follow-up of the patients, which was reported in only 5 studies [20, 23, 45, 47, 48]; this factor is relevant for determining whether the time interval was sufficient for the occurrence of the assessed outcome. Notably, only one study raised the issue of premedication, in this case, for anesthetized patients, and discarded premedication in patients with a history of previous reactions [20]. TR identification is more complicated in anesthetized patients, mainly due to the possibility of developing an adverse reaction to the drugs used [53] and even hypothermia associated with exposure during surgical procedures [54, 55]. Pre-transfusion medication to minimize some TR symptoms is still used but is controversial and may mask the side effects of transfusion [56, 57].

A lack of information on storage time regarding blood components and the average number of transfused bags per patient was identified. It is known that bags with longer storage times have a greater number of leukocyte degradation components, increasing the chance of developing adverse events. Additionally, the risk of TR and other adverse events is directly proportional to the number of transfusions received [58]. We know that type of filter equipment may differ between studies and impact the results. Few studies have presented relevant information about the filters used in leukoreduction processes and their filtration capacity. In some cases, it was possible to retrieve data from catalogs available on the internet, but in others, the information was incomplete. These methodological limitations impacted the results of this review and need to be overcome in further primary studies on the effectiveness of pre and post-storage leukoreduction filters. These characteristics of the reports are probably associated with the times of their publication, as consensuses for reports of primary studies did not exist or were not so widespread, such as the CONSORT [59].

Given the points highlighted above and the reduced number of studies found, the certainty of recommending using the pre-storage filter is weak. In addition, this review identified the need for primary studies that comparatively evaluate pre and post-storage leukoreduction filters in the overall population, which limits the recommendation of the best type of filter to prevent the analyzed outcomes. Even so, this review provides essential information for clinical, managerial, and political decisions about the types of filters to be used when leukoreduction of blood components is desired, especially in countries with medium or low income or in situations where universal leukoreduction is not yet an option. Notably, the choice to adopt pre-storage leukoreduction should also consider other factors not discussed in this review, such as logistics, human resources involved, and the restructuring process. According to van de Watering et al. [60], "universal leukoreduction is a step toward maximum safety, but it goes beyond ideal safety".

Conclusions

The results of this systematic review revealed that although the meta-analysis indicated that using a pre-storage filter is a protective factor against FNHTR after RBC and PC transfusions, there was great statistical heterogeneity among the studies. The results for infection were inconclusive. We identified only one study that analyzed the length of hospital stay and none that investigated hospital death. Therefore, the results showed that there needs to be more robust evidence to recommend the best type of filter (pre or post-storage) to prevent the analyzed outcomes.

Abbreviations

ALO	Alloimmunization
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
CI	Confidence interval
CMV	Cytomegalovirus
FNHTR	Febrile nonhemolytic transfusion reaction
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GVHD	Graft versus host disease
M-H	Mantel–Haenszel
PC	Platelet concentrate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RBC	Red blood cells
RR	Relative risk
TR	Transfusion reaction
TRALI	Transfusion-related acute lung injury
TRIM	Transfusion-related immunomodulation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02615-z.

Additional file 1: Appendix 1. Search strategy.

Additional file 2: Appendix 2. Characteristics of included studies.

Additional file 3: Appendix 3. Studies ineligible following full-text review.

Additional file 4: Appendix 4. Summary of Findings.

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Authors' contributions
All the authors: study conception and protocol, literature search, title/abstract and full-text screening, data extraction, quality assessment, statistical analyses, data interpretation, and manuscript writing. DALMC, LSN, and YN: supervision. All the authors read and approved the final manuscript.

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Availability of data and materials
The data we used for this study are available within the review and its additional files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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