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Review Article

Transfusion-Related Acute Lung Injury (TRALI) Risk Reduction Measures and The Impact on Preventing TRALI: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related morbidity and mortality. Efforts to reduce TRALI incidence primarily relied on preventive strategies, including male-only or predominantly-male only donor policy for plasma-containing transfusion components. We conducted a systematic review and meta-analysis to assess the effectiveness of TRALI risk reduction measures for preventing TRALI and related-mortality.

Study design and Methods: We searched MEDLINE, EMBASE, and Cochrane library of observational and interventional studies from January 1, 2000, through January 1, 2020. Primary and secondary outcome measures were the onset of TRALI and the 30-day mortality among TRALI patients, respectively.

Results: Fifteen articles were included. Using a random-effects model, meta-analysis based on studies involving only fresh frozen plasma (FFP) suggested a significant reduction for TRALI risk after intervention of male-only plasma donor policy (relative risk [RR], 0.28; 95% confident interval [CI], 0.21-0.38). Pooled data of all studies showed a tendency toward reduced 30-day mortality among TRALI patients in male-only plasma group (RR, 0.71; 95% CI, 0.54-0.94).

Conclusion: The implementation of TRALI risk reduction strategy, male-only or predominantly male-only donor transfusion policy, results in a reduction of TRALI incidence, and possibly mortality.

Keywords: TRALI; Blood transfusion; Male-only plasma; ALI

INTRODUCTION

Transfusion-related acute lung injury (TRALI), a particular form of acute lung injury (ALI), is characterized by the onset of acute respiratory distress typically within 6 hours of blood transfusion without an additional risk factor for ALI [1]. Clinical presentation of TRALI commonly included rapid onset of hypoxemia, dyspnoea, and tachypnoea, which may be accompanied by rigors, fever, tachycardia, and hypotension. Physical examination may reveal decreased breath sounds and diffuse crackles by auscultation of lungs, and bilateral infiltrates consistent with pulmonary oedema on chest radiograph without other evidence of circulatory overload [2]. Upon the development of the definition of TRALI by the Canadian Consensus Conference in 2004 and subsequent increased recognition of this syndrome, cardiac surgery, septic and critical ill patients are significantly recognised as being at risk for the onset of TRALI. Consequently, TRALI has become the leading cause of transfusion-related morbidity and mortality [3-5]. However, this adverse event of transfusion is still underdiagnosed and underreported due to reduced awareness of TRALI among clinicians.

TRALI is a clinical diagnosis for which no definitive laboratory tests are available, the clinical finding of TRALI is indistinguishable from other forms of ALI, including transfusion-associated circulatory overload (TACO), acute respiratory distress syndrome (ARDS), sepsis, and anaphylaxis. Unlike TRALI, TACO is characterized by pulmonary oedema primarily related to circulatory overload, patient suffering TACO is more likely to be associated with hypertension, and response to diuretic administration. Differentiation of TRALI

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and TACO is generally based on patient history and circulatory overload status [2, 6]. The term possible TRALI was established to identify the patient with an underlying risk factor for ALI such as septic reaction and aspiration within 6 hours of blood transfusion, while the term delayed TRALI is described by the onset of acute respiratory distress within 6-72 hours of blood transfusion. These conventional definitions of TRALI subsequently rule out the possibility of diagnosing TRALI in patients implied with other causes of ALI, which lead to diagnosing TRALI by exclusion [1].

Generally, a two-event model (equivalent to the two-hit hypothesis) is presumed to underlie the development of TRALI. In this pathophysiological model, the priming event corresponds to the clinical condition of the patient including surgery, cardiovascular disease, sepsis, mechanically ventilated, and massive transfusion [7]. Such pre-existing "first-hit" risk factors present in the transfused patient cause the activation of pulmonary endothelium and the sequential release of cytokines and production of adhesion molecule, which trigger the sequestration and priming of polymorphonuclear leucocytes (PMNs), especially neutrophils, in the activated pulmonary endothelium [8]. The second event is the passive transfusion of donor leucocyte antibodies directly against antigens on PMNs and/or physiological mediators present in transfused component, which activate the primed PMNs and trigger the release of oxidases and proteases, inducing endothelial damage, capillary leak and ALI [9-10].

The transfusion factors of "second-hit" can be divided into antibody and non-antibody-mediated TRALI. Infusion of human leucocyte antigens (HLA) class I and II and/or the human neutrophil alloantigen (HNA) with corresponding antibodies present in the plasma fraction of the transfused unit, directly against antigens of the recipient was recognized as a causative factor in antibody-mediated TRALI [11]. Neutrophil activation initiates directly upon binding of HNA antibodies to the neutrophil surface or indirectly, mainly upon binding of HLA class I antibodies to the vascular endothelial cells, or HLA class II antibodies to the circulating monocytes, leading to initiation of the inflammatory cascade [12]. Although the role of HLA and HNA antibodies from the transfused component has been confirmed in other studies, recipients of a transfused component containing leucocyte antibodies do not always result in TRALI, even when a cognate recipient antigen is present [13]. Alternatively, TRALI can also occur in the setting of pooled platelets (PLTs), red blood cells (RBCs) transfusion, and following infusion of fractionated derivatives [13]. These findings have led to the development of an alternative hypothesis for the pathogenesis of TRALI, termed non-antibody mediated TRALI.

Non-antibody mediated TRALI appears to result from the accumulation of proinflammatory mediators during storage of plasma layer of cell-containing blood products or by prolonged RBCs and PLTs storage. In vitro evidence showing proinflammatory mediators including bioactive lipids, cytokines, CD40 ligand (CD40L), and RBC-derived microparticles, are involved in the "second-hit" in place of leucocyte antibodies [13]. Accumulation of bioactive lipids in the plasma unit has been identified as the risk factor which triggers neutrophil activation through the G-protein coupled receptor on the neutrophil [13-14]. Infusion of CD40L is thought to be responsible for the macrophage activation through CD40 receptor, leading to the expression and release of multiple pro-inflammatory cytokines, and thus mediating TRALI. However, the involvement of such CD40-CD40L interaction and the inflammatory role of PLTs has not been widely accepted [13,15].

Other than plasma-containing blood products, studies suggested prolonged RBCs storage is contributed to the occurrence of TRALI. During storage, RBCs experience progressive morphological deterioration, which compromises Duffy antigen expression and ability to release adenosine-5'-triphosphate (ATP) [13]. Duffy antigen is responsible to make RBCs-bound chemokines inaccessible to circulating neutrophils, the loss of Duffy antigen on aged-RBCs reduces chemokine scavenging function, thus increased neutrophil activation and results in ALI [16]. Additionally, storage-induced deficiency in ATP release from transfused RBCs may promote adhesion of the RBC to the endothelial cells and resulted in hypoxemia and sequestration of RBCs in the lung [17]. However, the role of aged blood in TRALI remains controversial due to the lack of supportive clinical evidence.

A threshold model has been proposed to offer alternative ways to describe the development of TRALI in susceptible patients. Factors implicated in this model include the systemic inflammation of the recipient and the antibody exposure from transfusion unit, in which TRALI evolves once the priming or activating capacity of pulmonary endothelial and/or neutrophils has overcome a threshold. Recipients with poor clinical state including surgery, infection or other inflammatory responses who have priming of pulmonary neutrophils are susceptible to develop TRALI, even in the absence of antibody exposure during transfusion. Alternatively, sufficient quantity of antibody present in the transfused unit against antigens of the recipient can cause severe TRALI in patients without predisposition [18-19].

Despite great efforts have been made in TRALI research, no specific treatment is available for TRALI yet. Current management options are primarily supportive, with most cases requiring oxygen supplementation, and mechanical ventilation based on clinical severity. Therefore, reduction of TRALI incidence is predominantly achieved by preventive strategies [20]. The risk of specific blood components (BCs) implicated in TRALI had been identified in the haemovigilance report in the United Kingdom (UK) during the period 1996-2002. It was concluded that transfusion components containing higher content of plasma such as fresh frozen plasma (FFP) and pooled PLTs carry higher risk of developing TRALI among all BCs [21]. The prevalence of HLA and/or HNA antibodies implicated in antibody-mediated TRALI are occurring more frequently in multiparous female plasma donors who have been allo-immunised to leucocyte antigens from the foetus during pregnancy, or donor who had previous transfusions. The clinical significance of female plasma donor with history of pregnancy was confirmed by the randomised trial published in 2001 [22]. Consequently, a male-predominant plasma transfusion policy has been applied to the production of FFP in the UK National Blood Service since 2003, which showed a significant reduction of FFP-related TRALI cases in the UK [21]. This convincing outcome has led to various preventive strategies throughout the world, including exclusion of donors who had history of pregnancy and history of transfusion by HLA and/or HNA antibodies screening, preferential use of FFP and pooled PLTs from male donors or exclusion of all female donors [20-21]. So far, several observational studies have been published to elucidate the effects of these preventive strategies [7, 21-35].

Despite widespread adoption of the TRALI risk reduction measures, the effectiveness and clinical impact of the TRALI preventive strategy has yet been systematically addressed. We hypothesize that the implementation of male-predominant

plasma transfusion policy with or without application of other risk reduction measures in clinical practices is associated with reduction on both the incidence and mortality of TRALI across different population. To inform transfusion policy and address the evidence gap, we conducted a comprehensive systematic evaluation and meta-analysis of 15 observational studies.

METHODS

In this study, the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocols were used for this meta-analysis [36].

Search Strategy

To identify literature in electronic databases, MEDLINE, EMBASE, and Cochrane library (including the Central Database of Controlled Trials, the Database of Abstracts of Reviews of Effects, and the Cochrane Database of Systematic Reviews, respectively) were systematically searched from January 1, 2000, through January 1, 2020 by using the following medical subject heading (MeSH; or EMTREE equivalent) terms reflecting ''TRALI,'' AND ''blood transfusion,'' AND ''plasma,'' OR ''ALI,''. To identify observational and interventional studies, the following free-text terms: ''case-control study,'', ''controlled trial,'' were added. Furthermore, we performed manual screen on the reference lists and related literature from retrieved articles to ensure sensitive search strategy.

Eligibility Criteria

All titles and abstracts of articles retrieved by our search strategy are screened using prespecified inclusion and exclusion criteria to confirm eligibility. Eligible studies evaluated the effect of TRALI preventive strategies on the incidence and mortality of TRALI. TRALI preventive strategies is referred to 1) Male-only donor or predominantly male-only donor policy for plasma and/or platelet products; 2) HLA and/or HNA antibodies screening of donors and subsequent deferral of positive-donors; 3) The exclusion of female donor with history of pregnancy or donor with previous transfusion. Studies meeting the following criteria were considered eligible 1) Study design: observational and interventional trials including randomized controlled trial, cohort study, case-control study or cross-sectional study; 2) Population; no restrictions; 3) Intervention (exposure): transfusion of plasma-containing components (preferably FFP, but cryosupernatant cannot be excluded) from male-only, predominantly-male only or never pregnant HLA-negative female donors versus transfusion of plasma-containing components from unisexual donors. (''control plasma''); 4) Outcome, setting and timeframe: the primary outcome measure was the effect of the intervention of TRALI preventive strategies for transfusion on the incidence of TRALI. The secondary outcome measure was the effect of the intervention of TRALI preventive strategies for transfusion on all-cause short-term (30-day) mortality among patients of TRALI.

Exclusion Criteria

Studies with the following criteria were excluded 1) Study type: review, meta-analysis, letters, or conference proceedings; 2) Not in English language; 3) Timeframe: publication date prior to 2000; 4) Lack of control group; 5) No outcome measurement; 6) Duplicates or ''sub-cohorts'' data of previous published studies; 7) Case report that included with less than or equal to 2 cases.

Study Synthesis and Assessment of Methodological Quality

For each eligible study, we addressed the general information including country, study period, population, intervention specifics, and design characteristic (retrospective, prospective, passive surveillance, active surveillance etc).

The methodologic quality of retrieved studies in this systematic review was assessed using the published standards for qualifying observational studies by Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [37].

Statistical Analysis

We provided a description of the observational data from each study, including 1) type of transfused blood product (FFP-only or any BCs), 2) total number of transfusion (units), 3) total number of TRALI or possible TRALI cases, 4) total number of fatal TRALI or possible TRALI cases, and 5) total number of non-fatal TRALI cases, before and after intervention of TRALI preventive strategies, respectively.

Data on TRALI incidence before and after intervention were expressed as odd ratios (OR) for case-control studies and incidence rate ratios (IRR) for cohort studies. We assumed there were constant numbers of transfusion during the study period, when reviewing studies without clear addressment of total transfusion units across the study period, the distributed units of pre- and post-intervention period in the denominators of IRR was used. Given the low prevalence of TRALI cases (incidence in pre-intervention group of cohort studies = 1.5 per 105 transfusion), the value of IRR obtained from cohort studies and OR obtained from case-control studies were assumed to be approximated and thus pooled OR and IRR in the analysis were expressed as relative risk (RR). Primary observational data on TRALI-related 30-day mortality were expressed as OR and hazard ratios (HR), by assuming they approximated each other. The pooled OR and HR in the analysis were also expressed as RR [38].

Using the binary data obtained from retrieved studies, we used the random effect model to estimate 1) the estimates of pooled effect size as pooled RRs with 95% confidence intervals (CI) using the method of DerSimonian & Laird [39], and 2) the estimates of heterogeneity using the Mantel-Haenszel modelling approach [40]. For all analyses, I2 statistics were expressed to assess the consistency of the results (i.e. variance) between studies as low (1-30%), moderate (30-50%), or high (>50%) heterogeneity with Cochran's Q test determine the p value ($p < 0.05$ referred to as significant heterogeneity) [41]. Statistical significances for all studies were addressed as z-score and p value ($p < 0.05$ referred to as statistically significant) [38]. All statistical analyses were performed using STATA version 13.0. (StataCorp. 2013. College Station, TX).

RESULTS

Study selection

Our predefined search strategy yielded 1179 citations from electronic searches in databases and other sources. After removing duplicate citations, 859 records were subjected for title and abstract screen. A further 824 citations considered as ''non-relevant'' were excluded. Of the remained 35 citations, we performed a full-text screening and further excluded 20 citations based on our predefined exclusion criteria. Overall, 15 citations were considered as eligible and included for the systematic review (Figure 1).

Study characteristics

Overall, 15 observational studies were found on the effect of TRALI preventive strategy on the incidence of TRALI across 7 countries [7,21-35] (Table 1 and Table 2). No randomized controlled trials

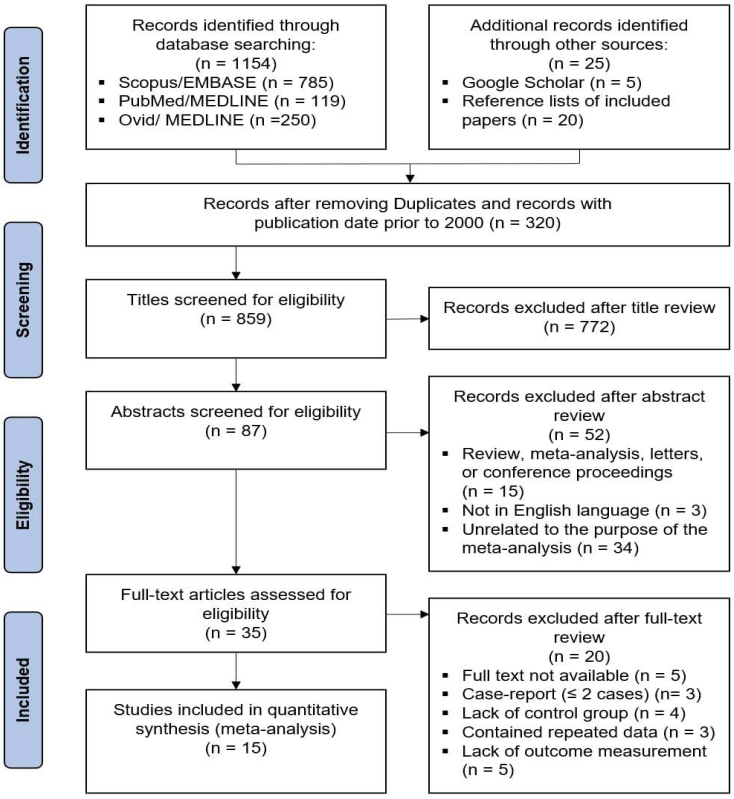

Figure 1. PRISMA flow diagram of article identification, screening, eligibility, and inclusion for systematic review on TRALI risk reduction measures impacts on preventing TRALI.

were included. Of the included observational studies, 3 studies were prospective [7,24,26], the remaining 12 studies had a retrospective design. Eight studies were carried out with national registries using passive surveillance of TRALI [23,21,27,29,31-33,35]. Five studies were carried out in high-risk population including surgery and intensive care unit (ICU), TRALI cases were activated screened in these studies [24-26,28,34]. The remaining 2 studies had general hospital population with an active reporting of TRALI [7,30]. The Canadian Consensus Criteria were used in all included studies to diagnose TRALI and/or possible TRALI [1]. In four studies, data were collected before the international establishment of Canadian Consensus Criteria on reporting TRALI [21,23-25]. Of these studies, two defined TRALI cases by American-European consensus criteria for ALI within 6 hours of transfusion [24-25], and one reported TRALI according to the UK haemovigilance scheme Serious Hazards of Transfusion (SHOT) recommendation and retrospectively applied the Canadian Consensus Criteria when it is established in 2004 [23]. The remaining one study defined TRALI cases as ''dyspnoea, hypotension with hypoxia and bilateral pulmonary oedema develops within 4 hours of transfusion'' [21]. The majority of studies were able to implement 100% male-only plasma transfusion policy, only 3 studies used male-predominantly plasma transfusion policy [21,32-33]. Four studies used, in combination with male-only plasma transfusion policy, plasma from female donors without history of pregnancy or shown negative result on HLA and/or HNA antibodies screening [7,23,30-31].

Methodologic quality

The 15 eligible studies greatly fulfilled the crucial STROBE standards (Table 3) [37]. Thirteen out of fifteen studies clearly defined objective, study population, setting, all outcomes and number of exposures. However, the potential confounders and lost to follow-up remained undefined in studies carried out with national registries [21,23,27,29,31-35]. Overall, quality assessment revelated that risk of bias of study selection was low and quality of evidence obtained from included studies was considered as ''high quality''.

Meta-analysis on TRALI incidence

The effect of TRALI preventive strategy for plasma-containing transfusion components on the incidence of TRALI for studies involving only FFP and studies involving any BCs are summarized in Figure 2. The meta-analysis based on 15 studies (725 TRALI cases reported) demonstrated there is an association between the intervention of TRALI preventive strategy and a reduction on TRALI risk. Of the nine studies involving only FFP (314 TRALI cases), there was a significant difference in the TRALI risk between male-only plasma and control plasma (RR, 0.28; 95% CI, 0.21-0.38; p = 0.000; I2 = 32%) [21,25,27,29-33,35]. In the subset of cohort studies involving any BCs (10 studies; 411 TRALI cases), there was a mitigation of TRALI risk in male-only plasma group compared to control plasma group (RR, 0.57; 95% CI, 0.46-0.70; p = 0.000; I2 = 60%) [7,21,23-24,26-28,30,34-35]. Of the ten studies, seven showed TRALI preventive strategy for plasma-containing components had a protective effect on TRALI risk [7,23,27,30,35], one showed unchanged effect [28] and two studies showed opposite effect [24,34]. Pooled data of all studies suggested there was significant reduction of TRALI incidence after the introduction of male-only or predominately-male FFP transfusion strategy across population (RR, 0.44; 95% CI, 0.37-0.52; p = 0.000; I2 = 62%). Heterogeneity was high for all studies combined (I2 = 62%; p = 0.000) and studies involving all BCs (I2 = 60%; p = 0.008), and moderate for studies involving only FFP(I2 = 32%; p = 0.160). However, the observed moderate heterogeneity for studies involving only FFP was insignificant (p > 0.1).

Table 1: List of States with no self-supported Blood Bank districtwide.

Reference, country	Design	Study period	Population	Outcome	Risk reduction strategy	Effect on TRALI risk
Insunza 2004, Spain [23]	Pro. Passive	2001-2002	National	TRALI*	Male-only & Never-pregnant or HLA-negative females	↓ OR 0.35 (95%CI 0.02-6.69)
Gajic 2007, US [24]	Pro. Active	1999-2005	ICU	TRALI* & Mortality	Male-only	↑ OR 1.33 (95%CI 0.72-2.47)
Wright 2008, UK [25]	Retro. Active	1998-2006	Surgery	TRALI* & Mortality	Male-only	OR 0.63 (95%CI 0.34-1.15)
Chapman 2009, UK [21]	Retro. Passive	1999-2004 vs 2004-2006	National	TRALI*	Predominantly male-only	↓ OR 0.20 (95%CI 0.05-0.85)
Nakazawa 2009, Japan [26]	Pro. Active	2007-2008	Surgery	TRALI*	Male-only	↓ OR 0.72 (95%CI 0.12-4.30)
Eder 2010, US [27]	Retro. Passive	2006-2008	National	TRALI & Mortality	Male-only	OR 0.26 (95%CI 0.11-059)
Vlaar 2010, Dutch [28]	Retro. Active	2006-2007	ICU	TRALI*	Male-only	↓ OR 0.98 (95%CI 0.39-2.48)
Wiersum 2011, Dutch [29]	Retro. Passive	2005-2007 vs 2007-2009	National	TRALI	Male-only	↓ OR 0.79 (95%CI 0.36-1.73)
Arinsburg 2012, US [30]	Retro. Active	2005-2008	Hospitals	TRALI*	Male-only & Never-pregnant or HLA-negative females	↓ OR 0.11 (95%CI 0.01-0.86)
Funk 2012, Germany [31]	Retro. Passive	2006-2009 vs 2010	National	TRALI	Male-only & Never-pregnant or HLA-negative females	↓ OR 0.05 (95%CI 0.00-0.76)
Lin 2012, Canada [32]	Retro. Passive	2004-2007 vs 2008-2009	National	TRALI*	Predominantly male-only	↓ OR 0.38 (95%CI 0.11-1.32)
Toy 2012, US [7]	Pro. Active	2006 vs 2009	Hospitals	TRALI	Male-only & Never-pregnant females	↓ OR 0.31 (95%CI 0.15-0.66)
Eder 2013, US [33]	Retro. Passive	2006 vs 2008-2011	National	TRALI*	Predominantly male-only	↓ OR 0.22 (95%CI 0.13-0.37)
Clifford 2015, US [34]	Retro. Passive	2004 vs 2011	Surgery	TRALI*	Male-only	↑ OR 1.11 (95%CI 0.62-1.99)
Vossoughi 2019, US [35]	Retro. Passive	2007-2013 vs 2014-2017	National	TRALI	Male-only	↓ OR 0.16 (95%CI 0.05-0.52)

Pro: Prospective; Retro: Retrospective; ICU: intensive care unit; TRALI*: possible TRALI; OR: Odd ratio; CI: confident interval

Table 2. Observational data of included studies reporting total transfused/distributed units and TRALI cases before and after intervention.

Reference	TRALI cases reported		Total transfused/distributed units	
	Before	After	Before	After
Studies involving FFP only				
Wright 2008 [25]	37	14	6,730	6,536
Chapman 2009 [21]	29	2	1,874,000	634,000
Eder 2010 [27]	26	7	1,638,055	1,729,128
Wiersum-Osselton 2011 [29]	30	8	583,250	195,750
Arinsburg 2012 [30]	4	0	47,756	52,230
Funk 2012 [31]	46	0	4,710,000	1,080,000
Lin 2012 [32]	16	3	982,061	479,050
Eder 2013 [33]	31	28	1,664,598	6,695,037
Vossoughi 2019 [35]	30	3	1,166,924	733,571
Studies involving any BCs				
Insunza 2004 [23]	3	0	74,741	30,883
Chapman 2009 [21]	58	12	16,550,000	5,897,000
Gajic 2007 [24]	15	20	97	92
Nakazawa 2009 [26]	3	2	1,596	1,480
Eder 2010 [27]	30	10	1,638,055	1,729,128
Vlaar 2010 [28]	17	6	1,350	485
Arinsburg 2012 [30]	9	1	227,913	233,685

Toy 2012 [7]	23	10	89,321	123,731
Clifford 2015 [34]	23	22	1,817	1,562
Vossoughi 2019 [35]	111	36	5,959,073	4,053,634
Studies reporting all-causes 30-day Mortality				
Gajic 2007 [24]	27 [a]	16 [a]	85 [b]	96 [b]
Wright 2008 [25]	56 [a]	29 [a]	73 [b]	53 [b]
Eder 2010 [27]	19 a	9:00 AM	50 [b]	42 [b]

[a]Number represents fatal-TRALI cases
[b]Number represents non-fatal TRALI cases instead of transfusions

Table 3. Observational data of included studies reporting total transfused/distributed units and TRALI cases before and after intervention.

Item	Recommendation	References														
Abstract		7	21	23	24	25	26	27	28	29	30	31	32	33	34	35
1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	(b) Provide in the abstract an informative and balanced summary	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Introduction															
2	Explain the scientific background and rationale	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	State specific objectives and prespecified hypotheses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods																
4	Present key elements of study design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Describe the setting, locations, and relevant dates	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Give the eligibility criteria, sources and methods of selection of participants or case ascertainment. Describe methods of follow-up	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Give matching criteria and number of exposed and unexposed or control per case	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Yes	No
7	Define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	For each variable of interest, give sources of data and details of methods of assessment. Describe comparability of assessment methods.	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Describe any efforts to address potential sources of bias	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
10	Explain how the study size was arrived at	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Explain how quantitative variables were handled in the analyses.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	(a) Describe all statistical methods	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	(b) Describe any methods used to examine subgroups and interactions	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	(c) Explain how missing data were addressed	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	Yes	No
	(d) If applicable, explain how loss to follow-up or matching of cases and controls was addressed	Yes	Yes	N/A	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No
	(e) Describe any sensitivity analyses	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results																
13	(a) Report numbers of individuals at each stage of study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	(b) Give reasons for non-participation at each stage	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No

	(c) Consider use of a flow diagram	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No
14	(a) Give characteristics of study participants and information on exposures and potential confounders	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
	(b) Indicate number of participants with missing data	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No
	(c) Summarise follow-up time	Yes	No	No	N/A	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
15	Report numbers of outcome events or summary measures over time	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision.	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
	(b) Report category boundaries when continuous variables were categorized	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	(c) If relevant, translating estimates of relative risk into absolute risk	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
17	Report other analyses done	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Discussion															
18	Summarise key results with reference to study objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19	Discuss limitations of the study, sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
20	Give interpretation of results considering objectives, limitations, multiplicity, results from similar studies, and relevant evidence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes
21	Discuss the generalisability of the results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
	Other Information															
22	Give the source of funding and the role of the funders for the present study	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

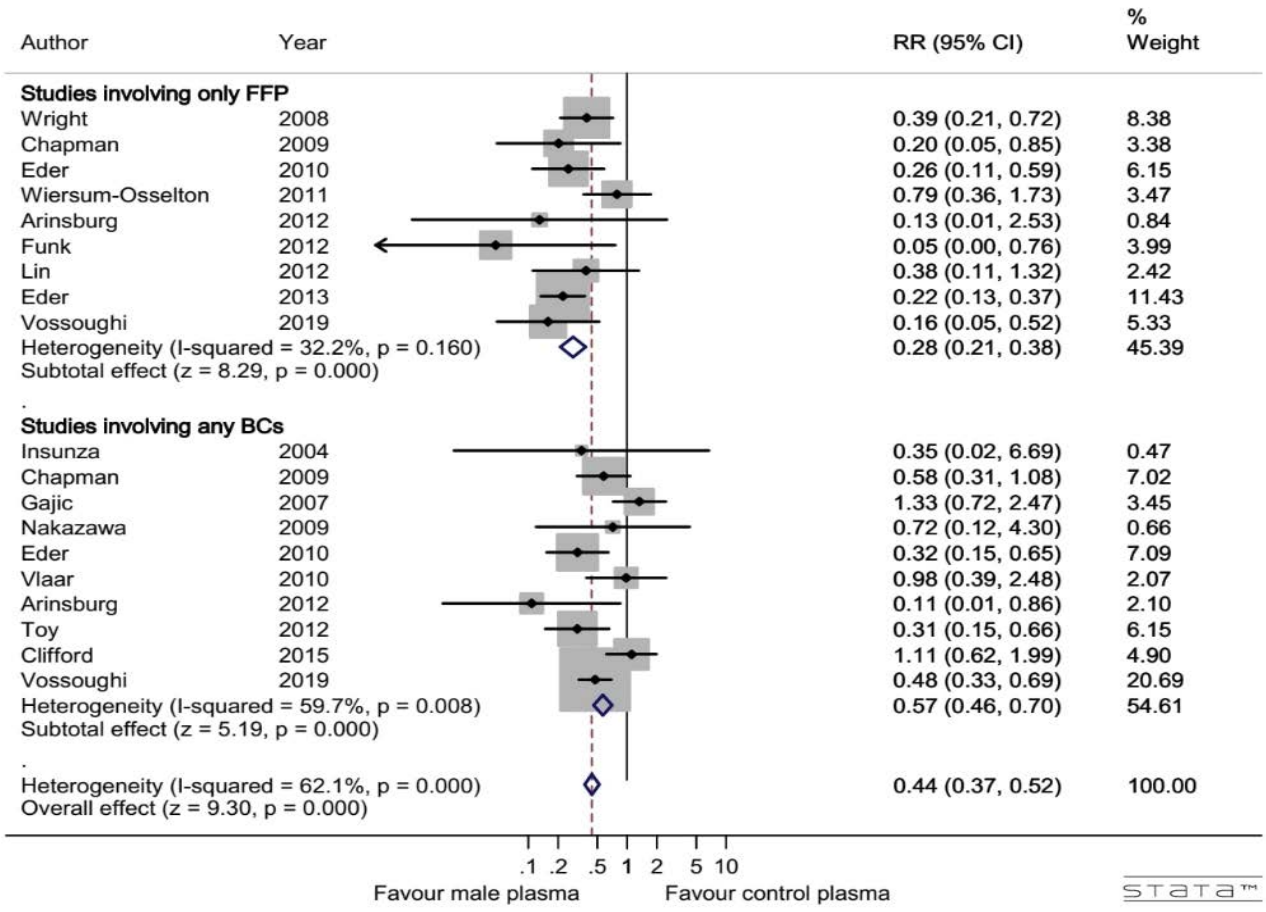

Figure 2. TRALI incidence: forest plot. Data on TRALI incidence before and after intervention were expressed as relative risk ratio (RR) with pooled effect size estimated as RRs with 95% confidence intervals (CI). Statistical significances for all studies were expressed as z-score and p value. Heterogeneity of studies was expressed as I-squared value with respective p value. % Weight was expressed according to the sample size in each study

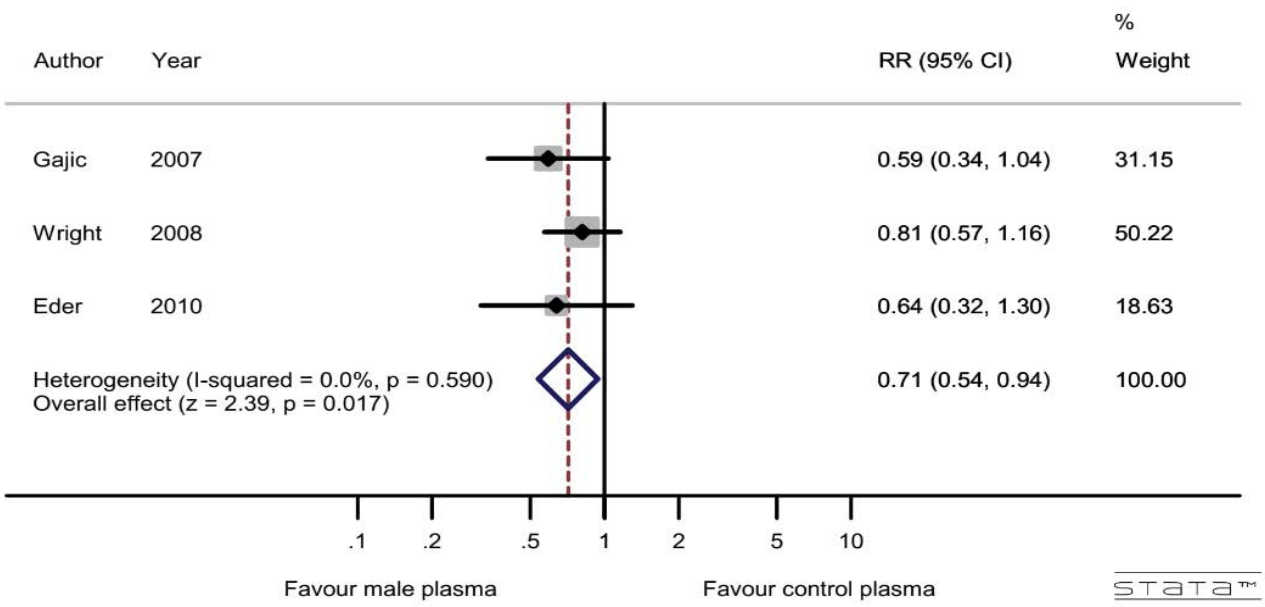

Figure 3. TRALI-related mortality: forest plot. Data on TRALI incidence before and after intervention were expressed as relative risk ratio (RR) with pooled effect size estimated as RRs with 95% confidence intervals (CI). Statistical significances for all studies were expressed as z-score and p value. Heterogeneity of studies was expressed as I-squared value with respective p value. % Weight was expressed according to the sample size in each study.

Meta-analysis on TRALI-related mortality

Data on 30-day TRALI-related mortality of total cohort were only available from three studies [24-25,27], none of the studies demonstrated a significant reduction of short-term mortality among patients with TRALI after the intervention of TRALI preventive transfusion strategy (Figure 3). Pooled data of all studies suggested there was a tendency to reduced TRALI-related mortality after implementation of male-only donor policy for plasma-containing transfusion components (RR, 0.71; 95% CI, 0.54-0.94; p = 0.017; I2 = 0%), there was no evidence of heterogeneity or effect modifications. However, the differences between male-only or predominantly-male plasma group and control plasma group on the effect of reduction 30-day mortality was insignificant (p > 0.05).

DISCUSSION

Over the past 16 years, efforts to reduce the risk for TRALI have primarily focused on antibody-mediated TRALI. It was clear that plasma-rich transfusion components linked to female donor with HLA and/or HNA antibodies were responsible for the majority of TRALI-related mortalities [42]. Several strategies have been implemented across many countries to mitigate the risk of TRALI from these components. The most commonly used TRALI risk reduction measure was increasing collections from male donors followed by HLA and/or HNA antibody testing [43]. The main findings of this systematic review are: 1) Introduction of TRALI risk reduction measures of deferring donors at high-risk of having HLA-antibodies from the donor pool, mainly male-only donor policies, results in significant reduction of TRALI incidence (RR, 0.28; 95% CI, 0.21-0.38). 2) Implementation of TRALI risk reduction measures for plasma-rich transfusion components shows a reduction of 30-day mortality among TRALI patient (RR, 0.71; 95% CI, 0.54-0.94), however, the observed reduction was only a trend due to small number of studies and patient included.

Our study is able to confirm that the introduction of TRALI risk reduction measure such as male-only donor policies for plasma-rich transfusion components indeed reduces the onset of TRALI by 72% (95% CI, 62-79%). This finding is consistent with the conclusion by Middelburg et al [44] that the majority of TRALI cases, up to 80%, are antibody-mediated TRALI, induced by the passive transfer of donor leukocyte antibodies, present in the plasma fraction of the transfused unit. Notably, studies by Gajic et al [24] and Clifford et al [34], which comparing critically ill and surgical patients who received either only male or female donor plasma, supported an opposite conclusion among TRALI incidence (RR, 1.33; 95% CI, 0.72-2.47; RR, 1.11; 95% CI, 0.62-1.99, respectively), while TRALI risk was unaffected in study by Vlaar et al [28], which included only critically ill patients. This observation can be explained by the respective study population, because these studies were carried out in high-risk patient populations, in which critically ill and surgical patients are more likely to have additional risk of ALI and develop pulmonary oedema after transfusion [5], patient with TACO or combined TACO and TRALI may have actually reported as TRALI cases (i.e. possible TRALI), which would overestimate TRALI incidence and eventually attenuate any preventive effect from the male-only donor transfusion strategy. Two other studies in this review that included only surgical patient, conducted by Wright et al [25] and Nakazawa et al [26], however, suggested a protective effect of TRALI risk reduction strategy, not only on the reduction of TRALI incidence [25-26], but also trend toward lower TRALI-related mortality [25].

Heterogeneity of effects was high for all studies combined (I2 = 62.1%) and low for subgroup analysis of studies involving only FFP (I2 = 32.2%), which can be explained by differences in the population, observation period, proportion of female donor and number of involved transfusions of included studies. In this study, the random effect model was used to estimate an average effect which accounts for heterogeneity among study results. From this perspective, we believed that the observed high heterogeneity in the combined group analysis has no or limited effect on our results and conclusion.

Implementation of TRALI risk reduction transfusion policy can be challenging [45]. Study by Triulzi et al [46] demonstrated that the prevalence of leukocyte antibodies alloimmunisation in donors increases with the number of pregnancies and blood transfusion.

This finding has led to the hypothesis that the risk of antibody-mediated TRALI can be minimized by excluding or screening donors based on their gender, leukocyte antibodies screening results, history of pregnancies and/or transfusions. However, such implementation of donor deferral policy does not completely prevent antibody-mediated TRALI and has multiple implications for transfusion practice: 1) deferral of all female donor carries the risk of unnecessary loss of potential donors and blood products that would be safe for most recipients. The American Red Cross estimated that the implementation of male-only FFP is accompanied by a loss of approximately 50% of whole blood units available for plasma manufacturing, however, the loss of female-derived plasma units is expected to be compensated [42]. 2) There is approximately 1% for the frequency of HLA antibodies in male population [46]. 3) Other than FFP, pooled PLT products are also recognized as plasma-rich transfusion components and can lead to the onset of TRALI. 4) Despite the volume of residual plasma in RBCs products is limited, with a mean volume of 10-20 mL, the risk of TRALI remains in RBCs transfusion [47]. 5) Male-only FFP is introduced to mitigate antibody-mediated TRALI, while the risk of non-antibody mediated TRALI remained unchanged [20]. The above-mentioned implications also partly explain residual TRALI cases observed in included studies.

The main alternative strategy to mitigate plasma-related TRALI incidence is the use of pooled solvent/detergent plasma (S/D plasma). By pooling plasma from unselected donors, possible leucocyte antibody load are reduced by an at least 500-fold dilution of single plasma unit and by neutralizing HLA antigens or residual leucocytes in the plasma pool, in which neither HNA nor HLA antibodies are detectable in S/D plasma, thus minimising the risk of TRALI [48]. So far, the countries that use pooled S/D plasma have not reported any TRALI cases associated with S/D plasma transfusion [49]. However, there are several limitations of this strategy: 1) concern of the use of pooled S/D plasma has been the transmission of viruses and prion disease due to exposure of a patient to multiple donors [20]. 2) the replacement of standard FFP by S/D plasma imposes a constant extra cost onto the healthcare system. In UK, it was deemed the institution of S/D plasma may not be cost-effective compared to male-only plasma transfusion policy [50]. 3) In critically ill patients who have predisposition, low titre or volume of leucocyte antibody from pooled S/D plasma may still be sufficient to introduce TRALI [20]. Another alternative approach would be to screen and exclude all donors or at-risk donors for HLA antibodies. Besides the high labour and costs involved, the cut-off titre for HLA antibody is unclear and the risk of HNA antibody would remain [51].

The main limitation of this study is the lack of randomized controlled trails on the effect of TRALI risk reduction measures on TRALI incidence. The observational nature of all included studies may have introduced bias. Notably, most included studies relied on spontaneous reporting to the national/regional haemovigilance systems which may be far from complete and therefore, underestimate the actual incidence of TRALI. Another limitation of this study include 1) There are differences between implemented donor policies across different countries. Countries which have less availability of plasma supplies adopted predominantly male-only plasma policy [21,32-33], while some countries used, in addition to male-only plasma policy, plasma from never-pregnant female donors without HLA and/or HNA antibodies. 2) Diagnostic criteria for TRALI were not standardized across countries. Some studies reported TRALI cases before the international establishment of Canadian Consensus Criteria on reporting TRALI [21,23-25], in which TRALI was most likely underreported. 3) Observational data on TRALI-related mortality were only available from three studies, The observed reduction on 30-day mortality after intervention is insignificant ($p > 0.05$) and considered to be less conclusive due to the small sample size.

Other potential confounders of this study are: 1) Increased reporting of TRALI due to increased awareness of TRALI by physician after the intervention and relative underestimation of TRALI cases in the control groups may attenuate the protective effect from the male-only donor transfusion strategy. 2) Improvement in healthcare delivery in the ICU overtime which minimizes the occurrence of risk factor for TRALI (e.g. sepsis, positive fluid balance, high peak airway pressure) [7], would result in an overestimation of the policy effect. 3) Possible TRALI cases (e.g. TACO, combined TACO and TRALI) that had an additional risk factor for ALI are reported in some studies [21,23-26,28,30,32-34], which would lead to an underestimation of the policy effects.

To further mitigate the incidence of TRALI, further research should focus on 1) Identification of population with different policy effect on reducing TRALI risk and/or mortality. 2) Addressing strategies and evaluating the effect of these strategies on preventing PLT- and RBC-related TRALI. 3) Evaluating the effectiveness of S/D plasma and donor deferral based on HLA antibodies screening. 4) Evaluating the effect of storage time on blood products in TRALI for developing novel strategies to prevent non-antibody mediated TRALI. 5) Establishment of promising therapeutic approaches targeting TRALI.

CONCLUSION

On the basis of most included studies, deemed to be high quality, we conclude that TRALI risk reduction strategy, male-only or predominantly male-only donor transfusion policy, reduces the onset of TRALI. There is low evidence that effect of preventing TRALI differs across population, implementation of male-only or predominantly male-only donor policy should yield similar results if introduced in other countries. Additionally, there is a tendency that intervention of TRALI risk reduction strategy results in a lower short-term mortality rate among TRALI patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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