Male-Predominant Plasma Transfusion Strategy for Preventing Transfusion-Related Acute Lung Injury: A Systematic Review

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Objectives: To assess 1) the effectiveness of male-predominant plasma transfusion strategy for preventing transfusion-related acute lung injury and related mortality; and 2) whether this effect varies across different patient subgroups.

Design: Systematic Review and meta-analysis: Data were identified by querying MEDLINE and EMBASE (including proceedings of major conferences on blood transfusions), searching the Internet for hemovigilance reports, reviewing reference lists of eligible articles and contacting experts in the field. Eligible were all studies reporting transfusion-related acute lung injury incidence, all-cause mortality (primary outcomes), hospital length of stay, time to extubation, Pao_2/Fio_2-ratio or blood pressure changes (secondary outcomes) in recipients of plasma transfusions containing relatively more plasma from individuals at low risk of carrying leukocyte-antibodies ("male plasma") than those receiving comparator plasma ("control plasma"). No limits were placed on study design, population or language. The only exclusion criteria were non-human subjects and lack of control group. Prespecified study quality indicators (including risk of bias assessment) and potential effect modifiers were tested using Cochran's Q Test. Final analyses using random-effects models and I_2 to assess heterogeneity were performed in the subset of studies judged to provide the best evidence and separately for significantly different subgroups using STATA 12.1 (StataCorp, College Station, TX).

Setting: As per primary studies.

Patients/Subjects: As per primary studies.

Interventions: As per primary studies (generally: exposure to plasma containing relatively more male plasma than comparator plasma).

Measurements and Main Results: From a total of 850 retrieved records, we identified 45 eligible studies. For transfusion-related acute lung injury incidence, final analysis was restricted to 13 cohort studies and one randomized controlled trial in which transfusion-related acute lung injury cases only involved plasma transfusions. Risk of transfusion-related acute lung injury and mortality in plasma recipients exposed to men when compared with control plasma were 0.27 (95% CI, 0.20–0.38; $p < 0.001$; $I^2 = 0\%$; $n = 14$; 286 events) and 0.89 (95% CI, 0.80–1.00; $p = 0.04$; $I^2 = 79\%$; $n = 7$; 5, 710 events), respectively. No other significant interactions were found. Secondary outcomes showed similar results but were less reported and the studies were more heterogeneous. Sensitivity analyses did not alter the results. There was no evidence of publication bias.

Discussion: More than 800 million people in 17 countries are subject to male-predominant plasma transfusion policy and at least three more countries are planning or considering adoption

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of this strategy. On the basis of most observational data, judged to be of high quality, male-predominant plasma transfusion strategy reduces plasma-related transfusion-related acute lung injury incidence and possibly mortality. There was no evidence that the effect differs across patient subgroups, but power to detect such differences was low. (*Crit Care Med* 2015; 43:205–225)

Key Words: acute lung injury; blood transfusion; donor selection; hla antigens; metaanalysis; plasma; primary prevention; policy

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality in the United States (1) and defined as new acute lung injury (ALI) (2) during or within 6 hours of transfusion without temporal relationship to an alternative risk factor for ALI (3, 4). Because treatment options are limited and mainly supportive (5), great efforts have been made to develop effective prevention strategies (6).

Among all blood products, plasma-rich components such as fresh frozen plasma (FFP) and platelet units carry the greatest per unit risk of causing TRALI (7–9). Most cases are because of donor antibodies against cognate recipient leukocyte antigens (human-leukocyte-antigen [HLA] or rarely human-neutrophil-antigen [HNA]) (10–12). It has been shown that, likely because of exposure to fetal alloantigens during pregnancy, female plasma donors have a higher prevalence of anti-HLA-antibodies than male donors (13, 14). During the past decade, this triggered the implementation of several TRALI risk mitigation policies throughout the world, in which transfusable plasma units were predominantly (generally > 80%) obtained from male donors ("male-predominant plasma transfusion strategy/policy") (7, 15–19).

Some countries further excluded previously transfused individuals from the plasma donor pool (19). Recent evidence, however, suggests that men, and women without history of pregnancy, have approximately the same prevalence of HLA-antibodies, independent of transfusion history (1–2%) (20, 21), whereas a dose-dependent increase in prevalence was found with increasing number of prior pregnancies (11–32% for one and more than four pregnancies, respectively) (20). Thus, it may be unnecessary to exclude never-pregnant women and donors with history of transfusion from plasma donor pools (15).

Several observational studies reported that male-predominant plasma transfusion strategies decreased TRALI incidence (7, 16, 17, 22). In a study of patients undergoing cardiac surgery, however, men when compared with women plasma transfusions were significantly associated with worse pulmonary function and short-term mortality, raising concerns that male-predominant transfusion strategies may not be beneficial for all patient subgroups (23). Therefore, it is not clear whether this strategy should generally be adopted (24).

Despite widespread adoption of the male-predominant plasma transfusion strategy (25), the effectiveness of this policy has not been systematically evaluated so far. The goal of our study is to fill this evidence gap.

The objectives of this systematic review and metaanalysis are to assess 1) the effectiveness of male-predominant plasma transfusion strategy for preventing TRALI and related mortality and 2) whether this effect varies across different patient subgroups.

METHODS

Data Sources

In accordance with a prespecified study protocol (e-Appendix 1, Supplemental Digital Content 1, http://links.lww.com/CCM/B85), MEDLINE and EMBASE (which include the proceedings from annual conferences by the American Association of Blood Banks and International Society of Blood Transfusion [ISBT]) were systematically searched with the assistance of a reference librarian from inception to April 16, 2013. The final search strategies used for each database included Medical Subject Heading/ EMTREE terms reflecting "TRALI," "transfusion," "plasma," and "sex-selection" (**e-Appendix 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/B86). Furthermore, we manually screened reference lists of retrieved articles, extensively searched the Internet for available hemovigilance reports and contacted all members of the International Hemovigilance Network and ISBT working party on hemovigilance, as well as multiple experts in the field regarding unpublished data. This was a systematic review only summarizing study-level data from available reports, thus no institutional review board approval was required.

Eligibility Criteria

Studies meeting the following criteria were included 1) study design: case–control studies, cohort studies, and randomized controlled trials (RCTs); 2) population: no restrictions; 3) intervention: transfusion of plasma (preferably FFP, but may include plasma frozen within 24 hr and cryosupernatant) from donor-pool containing relatively more plasma from individuals at low risk of having HLA-antibodies (men, never-pregnant women, ever-pregnant women tested negative for HLA-antibodies; in the following "male plasma") than the donor-pool of comparator plasma ("control plasma"); 4) Outcome: primary outcome measures were TRALI incidence (3, 4) and all-cause mortality (short term [≤ 1 mo] vs long term [> 1 mo]). Secondary outcome measures included hospital length of stay (HLOS), change in Pao_2/Fio_2-ratio or blood pressure before versus after transfusion (within 1 d). Beyond these prespecified outcomes, we evaluated two other clinically relevant outcomes reported in the studies (Pao_2/Fio_2-ratio < 300 and time to extubation). No limits were placed on publication status or language. Exclusion criteria were nonhuman subjects and lack of control group.

Data Extraction and Assessment of Study Quality

After removing duplicate records, all references retrieved from databases were independently evaluated for eligibility by at least two different reviewers (C.S., S.M., F.F., S.S., J.R.), using prespecified criteria. Discordant results were resolved by consensus. Data extraction and bias assessment were done in the same manner using a piloted Microsoft Access form. For

TABLE 1. Criteria Used for Risk of Bias Assessment in Observational Studies

Confounding	Low risk	If probably no substantial confounders exist or they were adjusted for (e.g., regression, standardization, and matching)
	High risk	if any of the above was grossly violated
Selection bias	Low risk	If no "conditioning on common effects" (i.e., case–control studies: appropriate selection of controls; cohort studies: no large loss to follow-up)
	High risk	if any of the above was grossly violated
Measurement bias	Low risk	If exposure and outcome assessment (especially transfusion-related acute lung injury) was done based on standard criteria, blinded to outcome or exposure, respectively, by more than one expert(s)
	High risk	If any of the above was grossly violated

Note: Confounding by "increased reporting over time because of greater physician awareness" was not considered for the bias assessment because 1) it is a potential problem in all cohort studies and 2) is expected to have an effect "toward the null" rendering the metaanalysis more conservative.

feasibility reasons, eligibility screening, data abstraction, and bias assessment for records obtained from other sources were undertaken by one author (C.S.) and carefully checked by another (S.M.).

Authors of included studies were contacted when additional information was needed. The extracted data included general study information, outcome data and data on prespecified, potential effect modifiers (full list of variables and definitions in **e-Table 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/B87). In cohort studies with unclear timing of intervention, the transition period was counted as part of the preimplementation period (control group) to maximize data while being conservative. If there was strong evidence that the first years after the introduction of hemovigilance databases did not represent valid estimates of preintervention risk (e.g., healthcare providers first had to learn about these central databases or standardized work-up procedures for TRALI determination were introduced only after a few years), data from these periods were omitted.

For observational studies, the risk of bias for each outcome was assessed as "high/unclear" or "low" separately for three domains using a modified version of the Newcastle-Ottawa Scale (**Table 1**) (26, 27). Potential confounding by increased reporting over time because of greater physician awareness, which affected all cohort studies, was not considered for bias assessment because it is expected to bias the results toward the null rendering the metaanalysis more conservative. For bias assessment of RCTs, we used the Cochrane Collaboration risk of bias instrument (28). To evaluate the potential impact of "any high/unclear risk of bias" on the results, a formal interaction test was done.

Statistical Analysis

All statistical analyses were conducted using STATA version 12.1 (StataCorp, College Station, TX).

Data on TRALI incidence were expressed as odds ratios (OR) for case–control studies and incidence rate ratios (IRR; number of new TRALI cases per number of transfusions in post- vs preintervention period) for cohort studies and RCT. If number of transfusions were not available, we used the duration of pre- and postimplementation periods in the denominators of the IRR, thus assuming constant numbers of transfusions across the whole study period. ORs reflecting the odds of TRALI in patients exposed to control plasma when compared with male-predominant plasma were inverted. Given the very low incidence of TRALI (median prevalence in the control groups of cohort studies = 1.8 per 10^5 transfusions; range from 2 per 10^6 to 6 per 100 transfusions), we assumed IRR ≈ OR and thus pooled OR and IRR in the analysis (in the following referred to as "relative risk" [RR] (29). Using the median and range of the TRALI incidence as the assumed control risks, we further calculated the absolute risk difference (RD).

Primary data for mortality were expressed as ORs, rate ratios, and hazard ratios and, assuming that they approximate each other, were also combined together into a "RR" measure.

For secondary outcomes, weighted mean differences and ORs were used as effect measures for continuous and nominal variables, respectively.

Whenever available the (most) adjusted effect estimate reported was preferred over crude data for the analysis of all outcomes. If crude data for ORs or IRRs contained "zero cells," then 0.5 was added to all cells to allow computation of the variance (30). Anticipating substantial heterogeneity, random-effects models (DerSimonian–Laird method) were used for all analyses (31).

For each outcome, an initial analysis was performed based on data from all eligible studies. If there was evidence of significant heterogeneity by a study quality indicator, then subsequent analyses were restricted to the subset of studies considered to be the better source of evidence. Within this subset, the final analysis was performed separately in subgroups defined by significant effect modifiers (other than study quality indicators). For all analyses, I^2 statistic was used to quantify heterogeneity between studies as "low" (1–30%), "moderate" (30–50%), or "high" (> 50%) (32).

Using single and multivariable metaregression, the following prespecified characteristics were formally examined as sources of heterogeneity based on Cochran's Q Test ($p < 0.05$ defining significant heterogeneity): indicators of study quality including study design, risk of bias, and outcome features (definition, assessment [for TRALI incidence

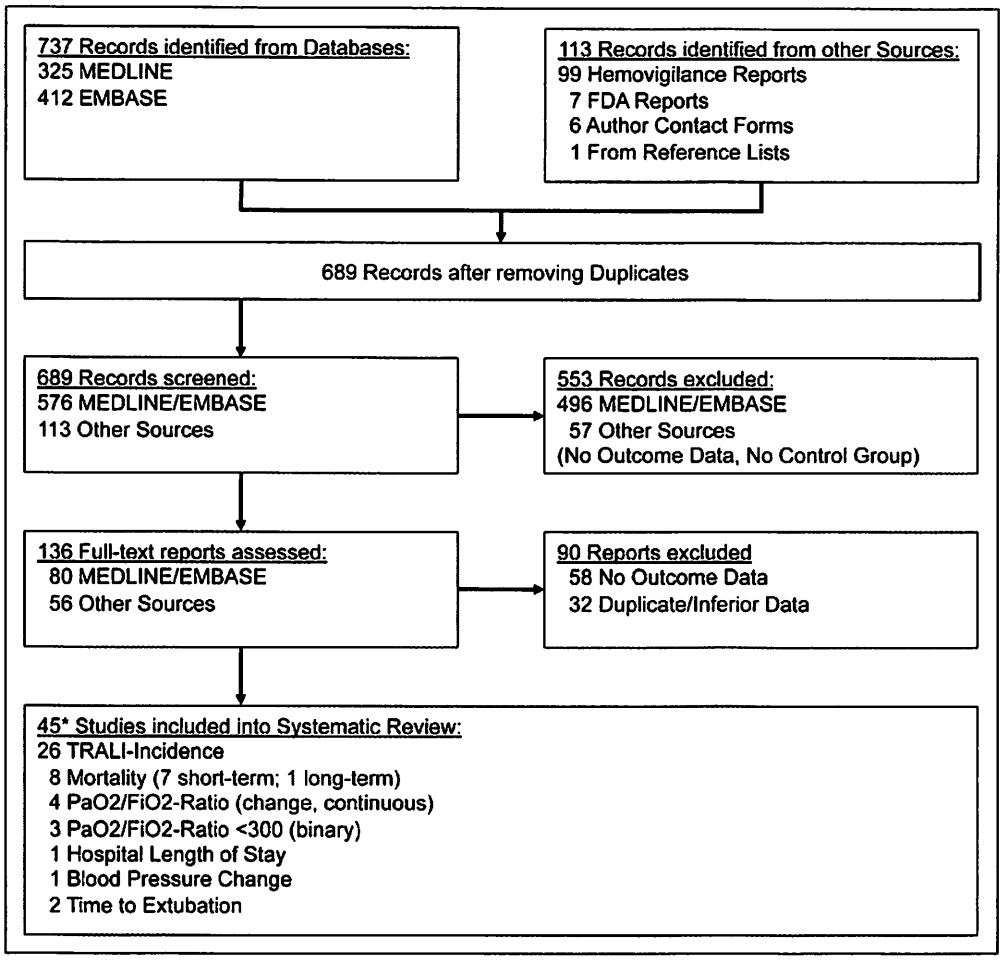

Figure 1. Flow chart. *Some reports include data on several outcomes, whereas some studies are based on the information from several hemovigilance reports from different years. FDA = Food and Drug Administration, TRALI = Transfusion-related acute lung injury.

only], surveillance, type of involved blood components [BCs], involved BCs issued vs transfused); intervention specifics (exact donor selection criteria); population characteristics (severity of illness, medical vs surgical, mean age, percentage of women, average number of transfusions, and region).

Effect modification by exact type of intervention was further assessed in a dose–response fashion. On the basis of expected percentage of contained male plasma, we assigned the following values based on the exposure of plasma from different donor-pools: female-only 0, mixed 50, male-predominant 85, and male-only 100. The "gradient" between the male plasma percentage before versus after the policy (or between cases and controls) was then calculated as the absolute numeric difference between the values assigned to the two groups. We tested our hypothesis of an inverse linear relationship between the gradient of the intervention and the RRs on the log scale through metaregression.

Galbraith plots were used to explore the existence of other potential sources of heterogeneity for possible inclusion into a post hoc analysis. Sensitivity analyses (using random-effect models) were performed to test robustness of results (for details see *Results* section).

For primary outcomes, publication bias was assessed using funnel plots and Egger's regression test ($p < 0.05$ used to judge significance) (33, 34).

RESULTS

Literature Search and Author Contacts

We retrieved 737 and 113 records from databases and other sources, respectively. Agreement between reviewers regarding eligibility of records from databases was excellent ranging from 91% to 96% (**Fig. 1**). Through author contact, we identified six studies (D. Dinesh, personal communication, October 17, 2013; L. Porretti, personal communication, November 06, 2013; H. Okazaki, personal communication, November 10, 2013; M. Palfi and G. Berlin, personal communication, November 20, 2013; M. Jutzi, personal communication, October 17, 2013; M. Li, personal communication, December 13, 2013) and obtained additional information on three studies (35–37). After detailed review, we identified 45 studies (D. Dinesh, personal communication, October 17, 2013; L. Porretti, personal communication, November 06, 2013; H. Okazaki, personal communication, November 10, 2013; M. Palfi and G. Berlin, personal communication, November 20, 2013; M. Jutzi, personal communication, October 17, 2013; M. Li, personal communication, December 13, 2013) (1, 7, 16, 19, 23, 35–52) meeting the eligibility criteria, including a total of 11 studies (D. Dinesh, personal communication, October 17, 2013; L. Porretti, personal communication, November 06, 2013; H. Okazaki, personal communication, November 10, 2013; M. Palfi and G. Berlin, personal communication, November 20, 2013; M. Li, personal communication, December 13, 2013) (1, 19, 44, 48, 49, 53) for which data were obtained exclusively from nondatabase sources (**Table 2**).

On the basis of our literature review, 17 countries implemented, in part, or nationwide a male-predominant plasma transfusion strategy. Data from 13 of these countries are included in this review (**Fig. 2**).

TRALI Incidence

The initial analysis based on 25 studies (647 TRALI events; D. Dinesh, personal communication, October 17, 2013; L.

Porretti, personal communication, November 06, 2013; H. Okazaki, personal communication, November 10, 2013; M. Palfi and G. Berlin, personal communication, November 20, 2013; M. Jutzi, personal communication, October 17, 2013; M. Li, personal communication, December 13, 2013) (7, 16, 19, 23, 35–51) demonstrated a reduced risk of TRALI in men versus control plasma, but a moderate amount of heterogeneity was present (RR, 0.48; 95% CI, 0.37–0.64; $p < 0.001$; $I^2 = 38\%$), which was explained by (the study quality indicators) study design and type of involved BC. In the subset of cohort studies and the one RCT in which the involved BC was FFP only ($n = 14$; 286 TRALI events; D. Dinesh, personal communication, October 17, 2013; L. Porretti, personal communication, November 06, 2013; H. Okazaki, personal communication, November 10, 2013; M. Palfi and G. Berlin, personal communication, November 20, 2013; M. Jutzi, personal communication, October 17, 2013; M. Li, personal communication, December 13, 2013) (7, 16, 35, 37, 40, 42, 45, 46, 50, 51), there was no evidence of effect modification by any other variable (**Table 3**). Thus, the final analysis was performed in this subset, in which the RR for developing TRALI in the men versus control plasma group was 0.27 (95% CI, 0.20–0.38; $p < 0.001$; $I^2 = 0\%$; **Fig. 3**), corresponding to 1.18 fewer TRALI cases per 100,000 plasma transfusions (RD ranging from 0.145 to 4,370 fewer TRALI cases per 100,000 plasma transfusions; e-Table 2, Supplemental Digital Content 4, http://links.lww.com/CCM/B88).

In sensitivity analyses, results remained unchanged when including the Food and Drug Administration report (1) (RR, 0.26; 95% CI, 0.20–0.34; $I^2 = 0\%$; rationale: excluded from primary analysis because of ≈40% overlap with at least one other report) (46), excluding the most influential study (46) (RR, 0.31; 95% CI, 0.21–0.47; $I^2 = 0\%$) or including only studies identified from database search (RR, 0.26; 95% CI, 0.19–0.38; $I^2 = 0\%$; $n = 8$; rationale: less risk of selection bias because of screening and data abstraction by reviewers blinded to each other).

Inspection of Galbraith plots did not suggest additional sources of heterogeneity (**e-Appendix 3**, Supplemental Digital Content 5, http://links.lww.com/CCM/B89). There was no evidence of publication bias ($p = 0.78$; e-Appendix 3, Supplemental Digital Content 5, http://links.lww.com/CCM/B89).

Mortality

The metaanalysis based on seven studies (5,710 deaths) (23, 39, 40, 52) demonstrated a significantly reduced risk of mortality in men versus control plasma, but heterogeneity was high (RR, 0.89; 95% CI, 0.80–1.00; $p = 0.04$; $I^2 = 79\%$; **Fig. 4**). Among the prespecified variables, no significant source of heterogeneity was identified (e-Appendix 3, Supplemental Digital Content 5, http://links.lww.com/CCM/B89).

Inspection of Galbraith and funnel plot ($p = 0.36$) did not imply additional sources of heterogeneity or publication bias, respectively (e-Appendix 3, Supplemental Digital Content 5, http://links.lww.com/CCM/B89).

Results did not change when excluding the "outlying" study by Welsby et al (23) in a sensitivity analysis (RR, 0.88; 95% CI, 0.79–0.99; $p = 0.03$; $I^2 = 81\%$; interaction test for mean number of transfusions $p = 0.07$).

For long-term mortality only one study (23) was identified (rate ratio, 1.11; 95% CI, 0.83–1.49; $p = 0.47$; high/unclear risk of bias).

Secondary Outcomes

Data on secondary outcomes generally favored men over control plasma but were less reported and more heterogeneous (**Table 4**; e-Appendix 3, Supplemental Digital Content 5, http://links.lww.com/CCM/B89).

DISCUSSION

More than 800 million people in 17 countries are affected by a male-predominant plasma transfusion policy (54), and at least three more countries are planning or considering adoption of this strategy. The main finding of this metaanalysis is that this strategy of excluding individuals at high risk of having HLA-antibodies from the donor pool reduces plasma-related TRALI incidence by 73% (95% CI, 80–62%). This is consistent with the conclusion by Middelburg et al (12) that about 80% of TRALI cases are likely because of an antibody-mediated immune mechanism. This strategy was also associated with significant reduction in mortality although this latter evidence was quite heterogeneous.

Most notably, the study by Welsby et al (23), comparing 390 matched pairs of patients who underwent cardiac surgery and received either only male or female donor plasma, supported opposite conclusions across various outcomes (TRALI incidence, mortality, HLOS). There are several possible explanations for this observation: 1) because patients undergoing cardiac surgery are more likely to develop pulmonary edema from fluid overload that may occur with transfusion, some TRALI cases may have actually had Transfusion Associated Circulatory Overload (TACO; or TRALI + TACO), which would attenuate any preventive effect from a male plasma strategy; 2) although patients were matched by surgery date and number of transfusions (mortality was further adjusted by several other variables), the results of this study may be (partly) confounded by the much higher number of major postoperative infections among recipients of male donor plasma (14 vs 3; $p = 0.01$). One could argue that infections are rather an effect mediator through which male-transfusions "cause harm," but this has not been observed elsewhere and it is hard to imagine a plausible underlying pathophysiologic mechanism; 3) the findings may be because of chance, but given the consistency across different outcomes this is not an entirely satisfactory explanation; 4) As Welsby et al caution (23), patients undergoing cardiac surgery may constitute a subgroup in which the effect of male-predominant plasma differs when compared with the general hospital population underlying most other study reports: e.g., in these patients, the higher concentration of Factor V in female plasma (55) with its procoagulation effect may outweigh the benefits of a lower HLA concentration in male plasma. The two

TABLE 2. Characteristics of Included Studies for Each Outcome

	TRALI Incidence			
Study Characteristic	**Palfi et al (35)**	**Insunza et al (38)**	**Gajic et al (39)**	**Wright et al (40)**
Country-institution	Sweden-SC	Spain-RHV	USA-SC	UK-SC
Study design	RCT	CS	CC	CS
Study period(s)	03/1995 to 11/1997	2000–01/2002 vs 02-12/2002	1999 to 2005	1998–2006/2003 vs 08/2003–2006
Events, male	0	0	20	Adj. OR = 0.39 (95% CI, 0.16–0.9)
Transfusions, male	100	30,883	92[a]	
Events, control	1	3	15	
Transfusions, control	100	74,741	97[a]	
Outcome definition	Poss. T.[b]	Other	Other	Poss. T.
Involved transfusions	FFP	Any BC	FFP + other BC	FFP
Transfusion type	Transfused	Issued	Transfused	Transfused
TRALI assessment	Other/uncl.	Other/uncl.	Other/uncl.	Other/uncl.
Surveillance	Active	Passive	Active	Active
Hospital setting	ICU	General	ICU	Intra/post-OP
Medical vs surgical	M + S/uncl.	M + S/uncl.	M + S/uncl.	Surgical
Population, mean age (yr)	66		69	74.8
% Female	46.7		63	18.6
Mean transfusion	1		4	5.2
Intervention details	Male-only	Male + NPF + AB-EPF	Male-only	Male-predominant
Transfused donors	Excluded	Allowed	Allowed	Allowed
Gradient	100	50	50	35
Risk of any bias	Low	Low	Low	High/uncl (C)

Nakazawa et al (41)	Price et al (42)	Vlaar et al (36)	Welsby et al (23)	Wiersum-Osselton et al (43)
Japan-SC	USA-RHV	Dutch-SC	USA-SC	Dutch-NHV
CS	CS	CS	CC	CS
10/2007–2001/2008 vs 02/2008–05/2008	2002–05/2007 vs 06/2007–2009	06–10/2006 vs 06–10/2007	1995 to 2007	2005–11/2007 vs 12/2007–11/2009
2	2	6	4	8
1,480	26 mo	485[b]	386[a]	195,750
3	6	17	2	30
1,596	65 mo	1,350[b]	388[a]	583,250
Poss. T.	Poss. T.	Poss. T.	Other	TRALI
Any BC	FFP	Any BC	Any BC	FFP + other BC
Transfused	Issued	Transfused	Transfused	Issued
Other/uncl.	Other/uncl.	Expert panel	Other/uncl.	Expert panel
Active	Passive	Active	Active	Passive
Intra/post-OP	General	ICU	Intra/post-OP	general
Surgical	M + S/uncl.	M + S/uncl.	Surgical	M + S/uncl.
67.2			65.5	
54.9			31.5	
37.5		5.1	5.9	
Male-only	Male + NPF + AB-EPF	Male-only	Male-only	Male-only
Allowed	Allowed	Excluded	Allowed	Excluded
50	50	50	100	50
Low	High/uncl (M)	High/uncl (C)	High/uncl (C)	Low

(*Continued*)

TABLE 2. (*Continued*). Characteristics of Included Studies for Each Outcome

	TRALI Incidence			
Study Characteristic	**Quebec HV (44)**	**Funk et al (16)**	**Arinsburg et al (45)**	**Eder et al (46)**
Country-institution	Canada-RHV	Germany-NHV	USA-MC	USA-NHV
Study design	CS	CS	CS	CS
Study period(s)	2005–2008 vs 2009	2006–2009 vs 2010	01/06–04/07 vs 05/07–08/08 and 08/05–11/06 vs 12/06–03/08	2006 vs 2008–2011
Events, male	3.04[d]	0	0	28
Transfusions, male	338,005	1,080,000	52,230	6,695,037
Events, control	24.7[d]	46	3	31
Transfusions, control	1,352,020	4,710,000	47,756	1,664,598
Outcome definition	TRALI	Other/uncl.	TRALI	Poss. T.
Involved transfusions	Any BC	FFP	FFP	FFP
Transfusion type	Issued	Issued	Transfused	Issued
TRALI assessment	Other/uncl.	Other/uncl.	Expert panel	Expert panel
Surveillance	Passive	Passive	Active	Passive
Hospital setting	General	General	General	General
Medical vs surgical	M + S/uncl.	M + S/uncl.	M + S/uncl.	M + S/uncl.
Population, mean age				
% Female				
Mean transfusion				
Intervention details	Male-only	Male + NPF +AB-EPF	Male + NPF +AB-EPF	Male-predom.
Transfused donors	Allowed	Allowed	Allowed	Allowed
Gradient	50	50	50	35
Risk of any bias	Low	Low	Low	Low

TRALI Incidence				
Lin et al (37)	**Toy et al (47)**	**Reesink et al (19)**	**French HV (48)[c]**	**Danish HV (49)**
Canada-NHV	USA-MC	Australia-NHV	France-NHV	Denmark-NHV
CS	CS	CS	CS	CS
2004–2007 vs 2008–2009	2006 vs 2009	2006–2007 vs 2008–06/2011	2007–2009 vs 2010–2011	2001–2005 vs 2006–2011
3	10	26	33	11
479,050[b]	123,731	42 mo	6,157,134	3,175,008
16	23	21	88	11
982,061[b]	89,321	24 mo	8,599,362	2,374,291
Poss. T.	TRALI	TRALI	TRALI	Other/uncl.
FFP	Any BC	Any BC	Any BC	Any BC
Issued	Transfused	Issued	Issued	Issued
Expert panel	Expert panel	Other/uncl.	Expert panel	Other/uncl.
Passive	Active	Passive	Passive	Passive
General	General	General	General	General
M + S/uncl.	M + S/uncl.	M + S/uncl.	M + S/uncl.	M + S/uncl.
Male-predom.	Male + NPF	Male-only	Male + NPF +AB-EPF	Male-only
Allowed	Allowed	Allowed	Allowed	Excluded
35	50	50	50	50
Low	Low	Low	Low	Low

(*Continued*)

TABLE 2. (*Continued*). Characteristics of Included Studies for Each Outcome

	TRALI Incidence			
Study Characteristic	**Chapman et al (7, 50, 51)**	**Jutzi (Personal Communication, October 17, 2013)[b]**	**Dinesh (Personal Communication, October 17, 2013)[b]**	**Porretti (Personal Communication, November 06, 2013)[b]**
Country-institution	UK-NHV	Switzerland-NHV	New Zealand-NHV	Italy-NHV
Study design	CS	CS	CS	CS
Study period(s)	10/1999–2004 vs 2004–2011[d]	2002–2007 vs 2008–2012	2005–2007 vs 2008–2011	2010 vs 2011
Events, male	7	1	2	1
Transfusions, male	2,123,395	298,000	73,735	338,950
Events, control	29[d]	7	9	5
Transfusions, control	1,874,000[f]	435,000	62,878	395,602
Outcome definition	Other/uncl.	TRALI	Poss. T.	TRALI
Involved transfusions	FFP	FFP	FFP	FFP
Transfusion type	Issued	Issued	Issued	Issued
TRALI assessment	Expert panel	Expert panel	Expert panel	Other/uncl.
Surveillance	Passive	Passive	Passive	Passive
Hospital setting	General	General	General	General
Medical vs surgical	M + S/uncl.	M + S/uncl.	M + S/uncl.	M + S/uncl.
Population, mean age (yr)				
% Female				
Mean transfusion				
Intervention details	Male-predom.	Male + NPF + AB-EPF	Male-only	Male-only
Transfused donors	Excluded	Allowed	Excluded	Excluded
Gradient	35	50	50	50
Risk of any bias	High/uncl (M)	Low	Low	Low

TRALI Incidence			
Okazaki (Personal Communication, November 10, 2013)[b]	**Palfi and Berlin (Personal Communication, November 20, 2013)[b]**	**Li (Personal Communication, December 13, 2013)[b]**	**FDA Report (1)[e]**
Japan-NHV	Sweden-NHV	USA-RHV	USA-NHV (fatalities)
CS	CS	CS	CS
2004–2011 vs 2012	2004–2007 vs 2009–2010	2004–2006 vs 2007–2013	2005–2007 vs 2008–2012
0	3	3	19
756,756	193,800	1,296,779	5 yr
13	16	3	51
6,526,917	469,000	644,861	3 yr
TRALI	TRALI	Poss. T.	Poss. T.
FFP	FFP	FFP	FFP
Issued	Issued	Issued	Issued
Expert panel	Expert panel	Expert panel	Expert panel
Passive	Passive	Passive	Passive
General	General	General	General
M + S/uncl.	M + S/uncl.	M + S/uncl.	M + S/uncl.
Male-only	Male-predom.	Male + NPF	Male-predom.
Allowed	Allowed	Allowed	Allowed
20	35	50	35
Low	Low	Low	Low

(*Continued*)

TABLE 2. (*Continued*). Characteristics of Included Studies for Each Outcome

	Mortality					
Study Characteristic	**Gajic (39)**	**Wright et al (40)**	**Welsby et al (23)**	**Welsby et al (23)[c]**	**Tynell et al 1Tx (52)**	**Tynell et al 2Tx (52)**
Country-institution	USA-SC	UK-SC	USA-SC		Sweden/ Denmark-NHV	
Study design	CC	CS	CC		CS	
Study period(s)	1999–2005	1998–2006/ 2003 vs 08/ 2003–2006	1995–2007		1990–2002	
Events/change (SD) n, male	16	29	18	Adj $RR_{inverted}$ = 1.11 (95% CI, 0.83–1.49)	Adj $HR_{inverted}$ = 0.99 (95% CI, 0.94–1.05)	Adj $HR_{inverted}$ = 1.0 (95% CI, 0.93 to 1.08)
Transfusions, male	96[a]	53[a]	372[a]			
Events/change (SD) n, control	27	56	11			
Transfusions, control	85[a]	73[a]	379[a]			
Outcome definition	Short-term M.	Short-term M.	Short-term M.	Long-term M.[g]	Short-term M.	
Involved transfusions	FFP + other BC	Any BC	Any BC		FFP	
Transfusion type	Transfused	Transfused	Transfused		Transfused	
TRALI assessment	Na	NA	NA		NA	
Surveillance	Active	Active	Active		Active	
Hospital setting	ICU	Intra/post-OP	Intra/post-OP		General	
Medical vs surgical	M + S/uncl.	Surgical	Surgical		M + S/uncl.	
Population, mean age (yr)	69	74.8	65.5		70	
% Female	63	18.6	31.5		44.6	
Mean transfusion	4	15.6	5.9		1	2
Intervention details	Male-only	Male-predom.	Male-only		Male-only	
Transfused donors	Allowed	Allowed	Allowed		Allowed	
Gradient	50	35	100		100	
Risk of any bias	Low	High/uncl (C)	High/uncl (C)	High/uncl (C)	Low	

		Pao_2/FiO_2-Ratio			
Tynell et al 3.5Tx (52)	**Tynell et al 5 + Tx (52)**	**Palfi et al (35)**	**Gajic et al (39)**	**Wright et al (40)**	**Nakazawa et al (41)**
Sweden/ Denmark-NHV CS 1990 - 2002		Sweden-SC	USA-SC	USA-SC	Japan-SC
		RCT	CC	CS	CS
		03/1995–11/1997	1999–2005	1998-2006/2003 vs 08/2003–2006	10/2007–01/2008 vs 02/2008–05/2008
Adj $HR_{inverted}$ = 0.86 (95% CI, 0.79–0.94)	Adj $HR_{inverted}$ = 0.76 (95% CI, 0.67–0.85)	1 (141) $n = 100$[b]	−41 (240) $n = 88$	−167 (179) $n = 68.5$	−62 (143) $n = 55$
		NA	NA	NA	
		−20 (137) $n = 100$[b]	−84 (210) $n = 88$	−158 (184) $n = 98.5$	−69 (147) $n = 27$
		NA	NA	NA	
Short-term M.		PFR cont.	PFR cont.	PFR cont.	PFR cont.
FFP		FFP	FFP + other BC	any BC	Any BC
Transfused		Transfused	Transfused	Transfused	Transfused
NA		NA	NA	NA	NA
Active		Active	Active	Active	Active
General		ICU	ICU	Intra/post-OP	Intra/post-OP
M + S/uncl.		M + S/uncl.	M + S/uncl.	Surgical	Surgical
70		66	69	74.8	67.2
44.6		46.7	63	18.6	54.9
3.5	5		4	15.6	37.5
Male-only		Male-only	Male-only	Male-predom.	Male-only
Allowed		Excluded	Allowed	Allowed	Allowed
100		100	50	35	50
Low	Low	Low	Low	High/uncl (C)	Low

(*Continued*)

TABLE 2. (*Continued*). Characteristics of Included Studies for Each Outcome

Study Characteristic	Pao_2/Fio_2-Ratio < 300 (binary)		
	Gajic et al (39)	Wright et al (40)	Nakazawa et al (41)
Country-institution	USA-SC	UK-SC	Japan-SC
Study design	CC	CS	CS
Study period(s)	1999–2005	1998–06/2003 vs 08/2003–2006	10/2007–01/2008 vs 02/2008–05/2008
Events/change (SD) n, male	49	26	9
Transfusions, male	63[a]	42[a]	46[a]
Events/change (SD) n, control	58	13	10
Transfusions, control	54[a]	85[a]	17[a]
Outcome definition	PFR < 300	PFR < 300	PFR < 300
Involved transfusions	FFP + other BC	Any BC	Any BC
Transfusion type	Transfused	Transfused	Transfused
TRALI assessment	NA	NA	NA
Surveillance	Active	Active	Active
Hospital setting	ICU	Intra/post-OP	Intra/post-OP
Medical vs surgical	M + S/uncl.	Surgical	Surgical
Population mean age (yr)	69	74.8	67.2
% Female	63	18.6	54.9
Mean transfusion	63	18.6	54.9
Intervention details	Male-only	Male-predom.	Male-only
Transfused donors	Allowed	Allowed	Allowed
Gradient	50	35	50
Risk of any bias	Low	High/uncl (C)	Low

TRALI = transfusion-related acute lung injury, SC = single center, RHV = regional hemovigilance, NHV = National Hemovigilance, RCT = randomized controlled trial, CS = cohort study, CC = case–control study, Tx = transfusions, adj. = adjusted, OR = odds ratio, poss. T. = possible TRALI, FFP = fresh frozen plasma (may include small numbers of FP24 and cryosupernatant transfusions), BC = blood component, uncl. = unclear; If risk of bias is high/unclear the letter in parenthesis denotes the corresponding domain (C = confounding, S = selection bias, M = measurement bias), post-OP = postoperative, M + S = medical and surgical, NPF = never-pregnant females, AB-EPF = HLA-antibody–negative ever-pregnant females, PFR = Pao_2/Fio_2-ratio (pressure of arterial oxygen over fraction of inspired oxygen), HLOS = hospital length of stay, BP = blood pressure, cont. = continuous, TTE = time to extubation, HR = hazard ratio, RR = rate ratio, MC = multicenter, *n* = sample size, NA = not applicable, FDA = Food and Drug Administration.

[a]Number represents nonevents instead of transfusions.

[b]Data based on personal communication with the author.

[c]Data based on hemovigilance reports.

[d]Numbers are noninteger because they were estimated from reported "Incidence per 100,000 transfusions."

[e]Due to an estimated overlap of about 40% (19) with (at least) one other study (46) the Food and Drug Administration report on transfusion-related acute lung injury–related fatalities was excluded from the primary analysis but later entered into the sensitivity analysis.

[f]Postimplementation data reported by Chapman et al 2013 (7, 50, 51) were updated with data from UK hemovigilance reports 2007–2011.

[g]As prespecified, short- and long-term mortality were treated as separate outcomes.

For details about variable definitions see e-Table 1, Supplemental Digital Content 3, http://links.lww.com/CCM/B87.

Units of change were mm Hg for blood pressure change and days for time to extubation. The event for hospital length of stay was a duration of ≥ 10 days.

HLOS	BP-Change	Time to Extubation	
Welsby et al (23)	Palfi et al (35)	Gajic et al (39)	Wright et al (40)
USA-SC	Sweden-SC	USA-SC	UK-SC
CC	RCT	CC	CS
1995–2007	03/1995–11/1997	1999–2005	1998–06/2003 vs 08/2003–2006
52	3.2 (20.4) $n = 100$	0 (1.5) $n = 112$	1 (5.2) $n = 59$
338[a]			
26	−0.8 (20.3) $n = 100$	1 (1.5) $n = 112$	1 (2.2) $n = 85$
364[a]			
HLOS binary	BP cont.	TTE cont.	TTE cont.
Any BC	FFP	FFP + other BC	Any BC
Transfused	Transfused	Transfused	Transfused
NA	NA	NA	NA
Active	Active	Active	Active
Intra/post-OP	ICU	ICU	Intra/post-OP
Surgical	M + S/uncl.	M + S/uncl.	Surgical
65.5	66	69	74.8
31.5	46.7	63	18.6
5.9	1	4	5.2
Male-only	Male-only	Male-only	Male-predom.
Allowed	Excluded	Allowed	Allowed
100	100	50	35
High/uncl (C)	Llow	Low	High/uncl (C)

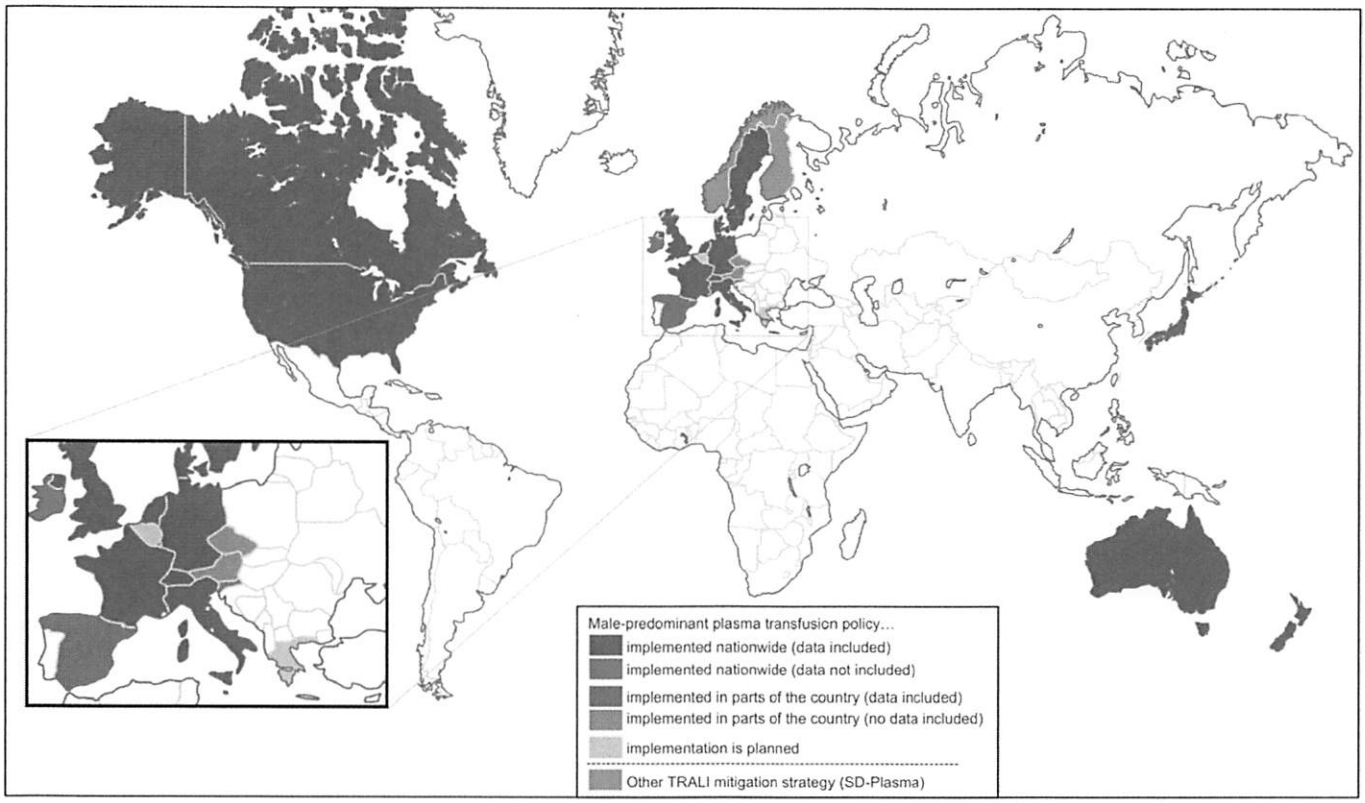

Figure 2. Transfusion-related acute lung injury (TRALI)-mitigation strategies for plasma transfusions adopted by different countries. A male-predominant plasma transfusion strategy has been implemented nationwide in the United States, Canada, United Kingdom, Ireland, France, Netherlands, Switzerland, Italy, Slovenia, Denmark, Sweden, Japan, Australia, New Zealand, and locally in Hong Kong, as well as in a blood center in Moscow (Russia). Spain, Austria, and Czech Republic implemented this strategy in major parts of the country, whereas Greece and Belgium are planning to adopt this policy (Poland is considering this step). Norway, Finland, and Luxembourg use exclusively solvent detergent plasma to prevent TRALI. In Ireland and France, this alternative strategy is used complementary.

other studies in this review that included only surgical patients (Wright et al [40] abdominal aortic surgery and Nakazawa et al [41] 2/3 cardiac and 1/3 abdominal surgery), however, do not suggest any harmful effect of male donor plasma, but on the contrary report better pulmonary function (40, 41), decrease in TRALI incidence (40), and trend toward lower mortality (40). When formally evaluated, there was no effect modification by medical versus surgical subgroups in our analysis.

The only other study showing a trend toward increased TRALI incidence, by Gajic et al (39), favored male donor plasma across all other outcomes, suggesting that this trend was a chance finding.

On the basis of prespecified interaction testing (Cochran's Q), we did not identify any subgroups of patients for which the effect of male-predominant plasma transfusion strategy on TRALI incidence is significantly different. In the primary analysis, the exact type of intervention (restriction to men-only vs men + never-pregnant women vs men + never-pregnant women + ever-pregnant women tested negative for HLA-antibodies vs men-predominant) and the related "gradient" of male plasma increase both reached significance but the direction of the effect estimates was scientifically implausible (suggesting less effect with increased strictness of high-risk donor exclusion) and disappeared completely when tested in the final analysis subset. Given that we performed several (prespecified) tests, these initial findings were thus most likely false positives. On the other hand, metaregression is known to have low power to identify true effect modification. When tested in the full dataset, there was a statistical trend toward a more pronounced reduction of TRALI incidence in older and male patients (e-Appendix 3, Supplemental Digital Content 5, http://links.lww.com/CCM/B89). Although sample size was small and subgroup analysis using study-level data is prone to ecologic fallacy, these findings could still be interesting for hypothesis-generating purposes.

Of note, there was little evidence that exclusion of previously transfused individuals from the donor pool resulted in a smaller effect estimate. This is consistent with observations that there are no-to-minimal differences in HLA-antibody prevalence in transfused when compared with untransfused individuals (20, 21). The absence of effect modification by different regions indicates that 1) there is little variation in HLA-antibody prevalence across populations and 2) male-predominant plasma transfusion strategy should yield similar results if implemented in other countries (an exception may be places where the average number of pregnancies per women and thus the HLA-prevalence is substantially different).

Introduction of a male-predominant plasma transfusion policy may be a challenge although (19, 38). The American Red Cross supplying ≈40% of U.S. transfusions was not able to provide more than 60% of AB-blood group plasma from men (17). This "universal donor plasma," however, is mostly used in emergency situations in which the risk of TRALI may be of less practical relevance and

TABLE 3. Transfusion-Related Acute Lung Injury Incidence: Results From Heterogeneity Testing

	Initial Dataset Based on All Eligible Studies, $n = 25$				Final Subset Restricted to Cohort Studies + one Randomized Controlled Trial Involving Fresh Frozen Plasma only, $n = 14$			
Study Characteristic	*n*	β	95% CI	*p*	*n*	β	95% CI	*p*
Indicators of study quality								
Risk of bias		1.16	0.54–2.5	0.70		1.27	0.60–2.7	0.50
Study design		0.31	0.13–0.75	0.01[a]		NA		
TRALI definition		1.10	0.74–1.63	0.63		0.77	0.40–1.47	0.40
TRALI assessment		0.57	0.33–1.0	0.049[a]		0.68	0.29–1.60	0.34
Surveillance		1.57	0.82–3.0	0.17		1.36	0.52–3.6	0.50
Type of involved blood component		1.45	1.08–1.93	0.02[a]		NA		
Transfusion type	23	1.73	0.88–3.4	0.11	13	1.44	0.54–3.8	0.44
Potential effect modifiers								
Intervention: sex selection		0.73	0.62–0.86	0.001		0.99	0.68–1.46	0.97
Intervention: transfusion history		1.03	0.52–2.0	0.94		0.73	0.31–1.70	0.43
Gradient, per 10-unit increase		1.36	1.08–1.71	0.01		1.03	0.69–1.54	0.87
Population: severity of illness[b]			NA	0.049			NA	0.70
Population: medical vs surgical vs both patients[b]		1.39[c]	0.50–3.9	0.52[c]		1.50[c]	0.53–4.2	0.41[c]
Mean age, per 10-yr increase	5	0.21	0.02–2.5	0.14			Insufficient *n*	
Percentage of women, per 10% points increase	5	1.28	0.86–1.91	0.15			Insufficient *n*	
Mean no. of involved transfusions, per 1-unit increase	6	0.99	0.91–1.09	0.86			Insufficient *n*	
Region[b]			NA	0.97			NA	0.93

n = sample size, TRALI = transfusion-related acute lung injury, NA = applicable.

[a]When entering the three significant quality indicators into metaregression together, only study design and type of involved blood component remained significance.

[b]Entered as a categorical variable (joint F test for dummy variables).

[c]No study had exclusively medical patients, thus the *p* value reflects interaction test of surgical vs medical + surgical/unclear.

For definitions and coding see Table 2 and e-Table 1, Supplemental Digital Content 3, http://links.lww.com/CCM/B87. Unless stated otherwise, *n* was 25 and 14 for the primary and for the final analysis, respectively.

represents only 4–10% of all plasma transfusions (17). In addition, it has been suggested that for emergency transfusions it may be safe to administer group A in lieu of AB plasma (25, 56, 57).

The main alternative strategy to prevent plasma-related TRALI adopted by some countries (Fig. 2) is the use of solvent detergent (SD) plasma: by pooling plasma from many, unselected donors HLA-antibodies (and other pathogenic substances) are diluted below detection thresholds of assay methods (58). So far, no TRALI case could definitely be linked to SD-plasma transfusion (8, 59). Although the implementation of male-predominant plasma transfusion strategy requires an initial investment into blood centers' infrastructure (19) and poses an organizational challenge on blood center staff (with an unclear effect on running costs), the usage of SD-plasma imposes a constant extra-cost onto the healthcare system (standard FFP = $100 vs SD-plasma = $140) and may thus not be cost-effective (60). Another alternative would be to (regularly) test female donors for HLA-antibodies using plasma from test-negative women for transfusion, but the cost-effectiveness of this strategy is unknown and the risk of human neutrophil antigen-antibodies would remain.

Strengths of our study include the substantial efforts taken to identify all relevant data. Furthermore, the estimates of TRALI incidence are very precise because of the large number of events (final analysis: 222 and 64 TRALI cases based on 17.8 and 13.4 million plasma transfusions in pre- and postimplementation period, respectively). The inclusion of data from 13 of 17 countries that have adopted a male-predominant plasma transfusion

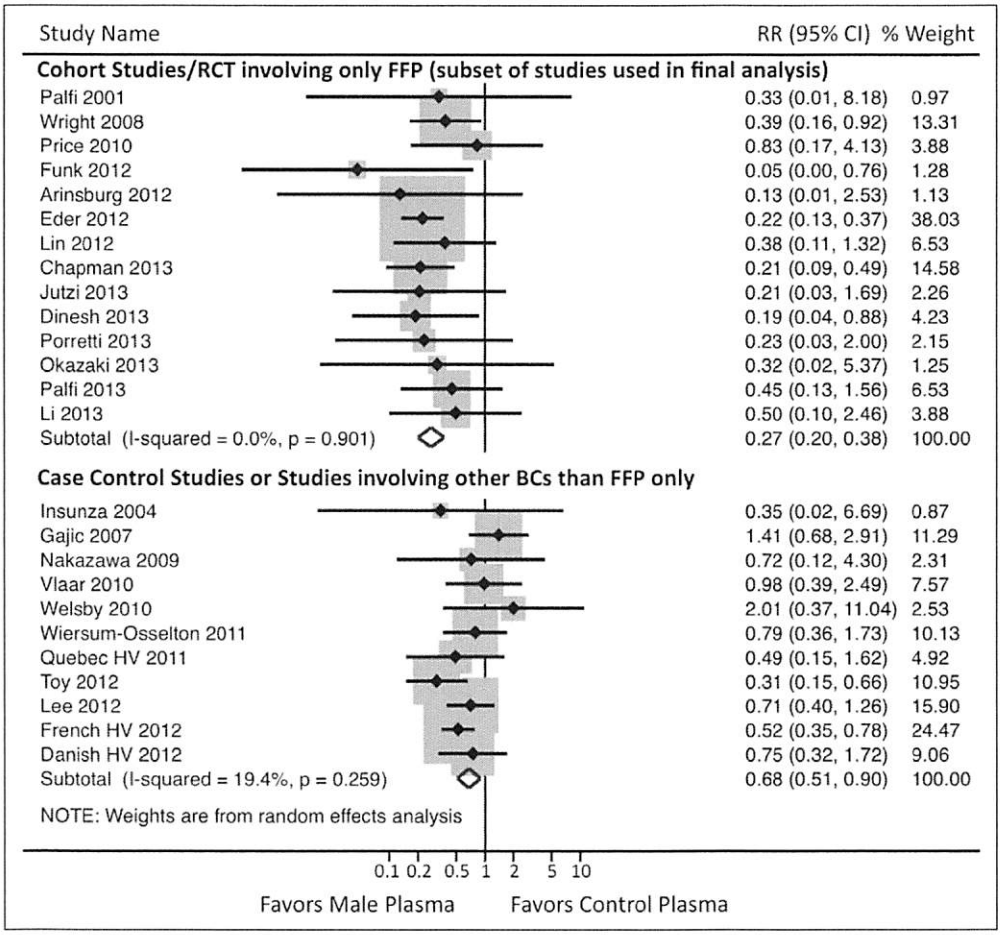

Figure 3. Transfusion-related acute lung injury (TRALI) incidence: forest plot. All 25 studies included into the primary analysis are shown. Because of significant interaction by the quality indicators study type and type of involved transfusions, the final analysis was restricted to the subset of studies expected to be the better source of evidence: 13 cohort studies and one randomized controlled trial (RCT) in which TRALI cases involved only fresh frozen plasma (FFP) transfusions (*top*). In the final analysis, risk of TRALI was significantly reduced in the male plasma group ($p < 0.001$) and there was no evidence of effect modification (Table 3) or heterogeneity. BC = blood component, HV = hemovigilance, RR = relative risk.

strategy and the large spectrum of populations covered across four continents makes our results well generalizable. And, the inclusion of multiple, clinically important outcomes facilitates decision making using a patient-centered approach.

The main limitation is the observational nature of most studies, which are inherently prone to bias. We evaluated the risk of bias and conducted interaction testing to determine the impact of the risk of bias on the estimates. With the majority of data stemming from hemovigilance systems collecting longitudinal data before and after the policy implementation, increased reporting over time because of raised physician awareness (of TRALI and hemovigilance systems) is the main potential confounder. Its effect is a relative underestimation of TRALI incidence in the control groups thus biasing the estimates of TRALI incidence toward the null. Other potential confounders are institutional improvements in critical care delivery (61), reducing the prevalence of risk factors for TRALI (e.g., septic shock, high peak airway pressures) (47), which would lead to an overestimation of the policy effects. This should also decrease the number of TRALI cases involving BCs not affected by the policy (RBCs, platelets). However, in several studies, the opposite happened (17, 43), indicating that increased reporting by far outweighed any possible confounding because of medical progress. Finally, some studies included cases of possible TRALI that had an alternate ALI risk factor in which male-predominant plasma strategy may have a smaller effect (47). This and the fact that we included the transition period in some studies in the control group could have led to a further underestimation of the policy effects, rendering our results overall rather conservative.

The majority of studies reported the use of standard definitions for TRALI ascertainment, and many studies had standardized work-up plans involving multiple experts. To our knowledge, in none of the studies were the case reviewers aware of donor sex at the time of TRALI ascertainment. The risk of differential measurement bias was thus overall low. In all included studies, we judged that controls were chosen appropriately and thus found no indication of selection bias. The one included RCT was assessed to be at low risk of bias across all five domains of the Cochrane bias assessment instrument. We were not alerted by any of the reported funding sources or conflicts of interests by any of the primary study authors. Overall, we consider the quality of included studies as high and highly relevant for policy makers. In fact, intentional randomization of patients to female donor plasma appears unethical given the current state of knowledge, precluding further RCTs on this topic.

Another limitation is that for reports identified from nondatabase sources investigators were not blinded to each other during eligibility screening, data abstraction, and bias assessment. This was because of feasibility reasons and based on sensitivity analysis did not impact our results. For records identified from databases, we did not log the exact number of discordant results during data abstraction, but overall there were only few disagreements and investigators reached unanimous consensus in all cases.

We failed to demonstrate a dose–response effect in the sense that a large increase in the male plasma proportion

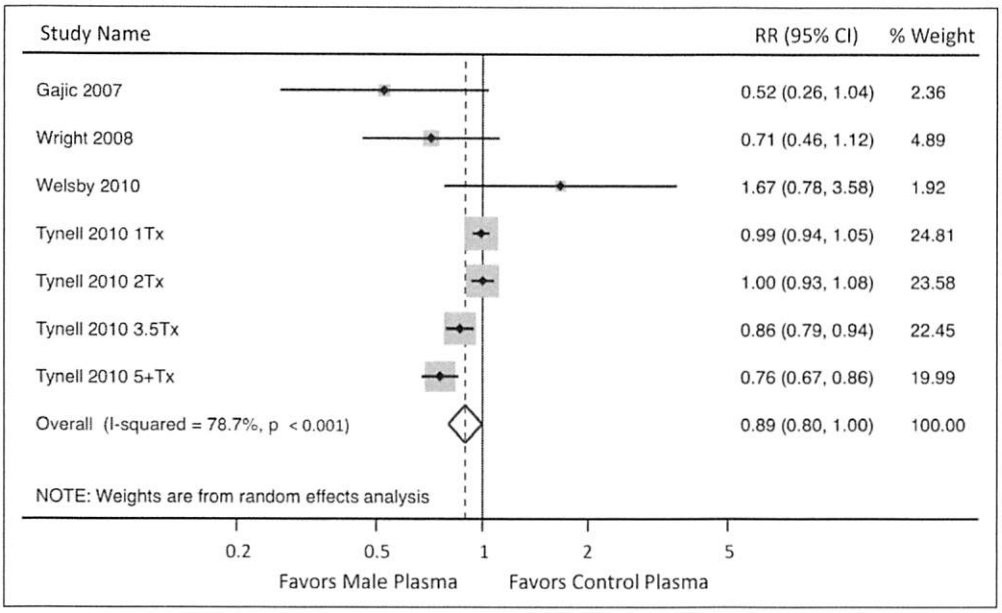

Figure 4. Mortality: forest plot. There was no significant interaction by quality indicators or potential, prespecified effect modifiers. Risk of mortality was significantly reduced in the male plasma group ($p = 0.04$), but heterogeneity was high.

should elicit a larger protective effect. This was probably because of little variation in gradients (four levels, two levels only in one study) and sample size ($n = 14$). Visually, there was some indication that for mortality there is a dose–response effect, in that recipients of many transfusions benefit more from the policy (e-Appendix 3, Supplemental Digital Content 5, http://links.lww.com/CCM/B89); however, formal testing was negative. Overall, most subgroup analyses and the metaanalyses for all outcomes except TRALI incidence were somewhat limited by small sample sizes. Thus, although we did not find evidence that the effect of male-predominant plasma policy varies across different patients subgroups, we cannot exclude this possibility.

Future research should focus on 1) the identification of patient subgroups in whom the effect of a male-predominant plasma transfusion strategy may differ; 2) evaluating the effect of similar strategies increasingly adopted to prevent TRALI cases related to platelet transfusion; 3) the identification of strategies to prevent TRALI cases related to RBC transfusion; 4) comparing cost-effectiveness of this policy when compared with the usage of SD-plasma or HLA-screening; and 5) evaluating the effectiveness of platelet additive solutions for preventing TRALI.

CONCLUSIONS

On the basis of most observational data, judged to be of high quality, we conclude that male-predominant plasma transfusion strategy reduces plasma-related TRALI incidence and possibly mortality. There was no evidence that the effect differs across patient subgroups but power to detect such differences was low. Other outcomes generally supported a protective effect of this strategy, but sample sizes were small, heterogeneity high, and thus results less conclusive.

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TABLE 4. Results for Secondary Outcomes

Outcome	Studies	Events	Effect Estimate[a] (95% CI)	p	I^2	Favors
Pa_{O_2}/F_{IO_2}-ratio change (23, 35, 39, 41)	4	NA	WMD = 16 (−11 to 42)	0.25	0%	Men
Pa_{O_2}/F_{IO_2}-ratio < 300 (respiratory failure) (23, 39, 41)	3	253	RR = 0.39 (0.18 to 0.83)	0.01	81%	Men
Hospital length of stay, continuous	0					
Hospital length of stay ≥10 d (23)	1[b]	78	OR = 2.2 (1.3 to 3.5)	< 0.05	NA	Control
Change in mean arterial blood pressure (35)	1[c]	NA	+3.2 mm Hg (male plasma) vs −0.8 mm Hg (multiparous plasma)	< 0.01[d]	NA	Men
Time to extubation (d)	2	NA	WMD = −0.74 (−1.6 to 0.12)	0.09	44%	Men

NA = not applicable, WMD = weighted mean differences, RR = relative risk, OR = odds ratio.
[a]Based on the comparison men vs control plasma.
[b]High/unclear risk of bias.
[c]Low risk of bias.
[d]Paired-sample Wilcoxon signed rank test.

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