



RISK FACTORS, CLINICAL CHARACTERISTICS, AND OUTCOMES OF TRANSFUSION-RELATED ACUTE LUNG INJURY: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction: Transfusion-related acute lung injury (TRALI) remains a leading cause of transfusion-associated morbidity and mortality. Evidence on its risk factors, clinical phenotype and prognosis is fragmented across heterogeneous definitions, clinical settings and surveillance systems, and has not been synthesised since the 2019 consensus redefinition (TRALI type I/type II). This review aimed to quantify patient-, donor- and transfusion-related risk factors, describe clinical, laboratory and radiological characteristics and underlying mechanisms, compare TRALI with transfusion-associated circulatory overload (TACO), and estimate clinical outcomes.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Randomised controlled trials (RCTs), prospective and

retrospective cohort, nested case-control, cross-sectional and haemovigilance studies were eligible. Risk of bias was appraised with the Newcastle-Ottawa Scale (NOS) and Cochrane RoB 2. Odds ratios (OR), risk ratios (RR), mean differences (MD) and logit-transformed proportions were pooled using DerSimonian-Laird random-effects models with 95% prediction intervals, leave-one-out, cumulative and small-study-effect analyses; certainty was graded with GRADE.

Results: Thirty-nine studies (37 observational, 2 RCTs) from 14 countries were included, covering more than 16.8 million transfused patients or hospitalisations and more than 144 million blood components; 30 studies contributed to quantitative synthesis. Pooled TRALI incidence was 4.47% (95% CI 2.29–8.56) in high-risk/critical-care cohorts, 0.41% (0.11–1.47) in general peri-operative cohorts and 0.017% (0.007–0.045) in coded administrative databases, and 1.88 per 100,000 components (0.46–7.66). Exposure to high-risk donor plasma or leukocyte antibodies (OR 4.91, 2.43–9.94; $I^2 = 0\%$), chronic lung disease (OR 2.72, 1.46–5.08), shock or sepsis (OR 2.54, 1.05–6.09), platelet exposure (OR 1.74, 1.08–2.78), female recipient sex (OR 1.24, 1.14–1.35) and each additional component transfused (OR 1.20, 1.12–1.29) were associated with TRALI. An antibody-mediated mechanism was confirmed in 68.7% (56.1–79.1) of investigated cases, and 69.2% of recent cases were TRALI type II. TRALI presented with fever (OR 4.84), hypotension and new mechanical ventilation (OR 32.2); 53.6% (28.2–77.2) of patients required invasive ventilation. In-hospital mortality was higher than in transfused controls (OR 5.22, 2.68–10.17; $I^2 = 84\%$), with a pooled case-fatality of 27.3% (19.5–36.8), more ICU admissions (OR 3.16, 1.91–5.24) and longer hospital (MD +6.9 days) and ICU

stay (MD +5.2 days). Compared with TACO, TRALI carried higher mortality (OR 2.48, 2.20–2.80), longer stay (MD +4.8 days), lower natriuretic peptide levels and fewer cardiovascular comorbidities. Mitigation strategies showed a non-significant reduction in incidence (RR 0.57, 0.28–1.18).

Discussion: The findings support a threshold two-hit model in which recipient inflammatory priming (shock, sepsis, chronic lung and liver disease, alcohol and tobacco exposure) interacts with donor leukocyte antibodies and non-antibody biological response modifiers in plasma-rich components. Recipient factors predominate in TRALI type II and possible TRALI, whereas donor antibodies drive type I disease. TRALI is clinically and prognostically distinct from TACO.

Conclusion: TRALI is not rare in high-risk patients and carries roughly a five-fold excess in-hospital mortality. Prevention should combine donor-based mitigation (male-predominant or antibody-screened plasma and platelets), restrictive patient blood management in primed recipients, early recognition using natriuretic peptides and imaging, and systematic haemovigilance reporting.

Keywords: transfusion-related acute lung injury; TRALI; transfusion-associated circulatory overload; risk factors; HLA antibodies; mortality; haemovigilance; meta-analysis

INTRODUCTION

Background

Transfusion-related acute lung injury (TRALI) is a syndrome of acute hypoxaemic respiratory failure with bilateral non-cardiogenic (permeability) pulmonary oedema that develops during or within 6 hours of the transfusion of a blood component. Once regarded as an exceptional complication, TRALI has been recognised for more than two decades by haemovigilance agencies and the United States Food and Drug Administration as one of the leading causes of transfusion-related death, and it continues to account for a substantial proportion of transfusion fatalities despite major advances in donor management.^{1–3}

The diagnostic framework has evolved considerably. The 2004 Canadian Consensus Conference introduced the categories TRALI and possible TRALI, the latter denoting acute lung injury temporally related to an alternative acute respiratory distress syndrome (ARDS) risk factor. In 2019, an international Delphi panel redefined the syndrome by aligning it with the Berlin ARDS criteria, abandoning the term possible TRALI and introducing TRALI type I (no ARDS risk factor) and TRALI type II (ARDS risk factor present or mild ARDS with stable respiratory status during the 12 hours before transfusion), together with the categories ARDS and TRALI/TACO for cases that cannot be distinguished. Validation in a national haemovigilance database suggested that the revised definition captures a similar number of TRALI cases while improving the classification of circulatory overload.^{4–6}

Pathophysiologically, TRALI is best explained by a threshold or two-hit model. A first hit — an inflammatory condition of the recipient such as sepsis, shock, major surgery or liver disease — primes neutrophils and activates the pulmonary endothelium; a second hit delivered by the transfused component, either passively transfused donor antibodies against human leukocyte antigens (HLA) class I/II or human neutrophil antigens (HNA), or non-antibody biological response modifiers accumulating during storage, triggers neutrophil activation, endothelial injury and capillary leak.^{7–10}

Epidemiological estimates vary widely. Active surveillance, electronic screening and expert adjudication identify far more cases than passive reporting, and an electronic-algorithm study found that only about 14% of true TRALI cases had been reported to the blood bank by clinicians. Reported incidences therefore depend heavily on the denominator (per unit, per patient or per transfusion episode), the case definition and the clinical population.^{11–14}

Because most antibody-mediated TRALI is caused by plasma from alloimmunised, mostly multiparous, female donors, blood services worldwide have introduced male-predominant plasma, deferral or HLA-antibody testing of previously pregnant platelet donors, and pooled solvent/detergent-treated plasma. These measures reduced plasma-associated TRALI substantially, but residual risk persists, especially with apheresis and pooled platelets, group AB plasma and in highly primed recipients.^{15–18}

Clinically, TRALI must be distinguished from transfusion-associated circulatory overload (TACO), the most frequent pulmonary transfusion reaction, which results from hydrostatic pulmonary oedema. Both syndromes present with dyspnoea, hypoxaemia and bilateral infiltrates within hours of transfusion, and they may coexist. Accurate differentiation is essential because management (diuresis versus avoidance of fluid removal), donor investigation and prognosis differ.^{6,19,20}

Research gap

Previous systematic reviews addressed only fragments of this evidence. Hu and colleagues pooled risk factors in critically ill patients from 13 studies published before March 2020 but did not analyse clinical outcomes, phenotype or the comparison with TACO; White and colleagues estimated incidence per blood component from active surveillance; and two meta-analyses published in 2015 examined only the effect of low-risk donor strategies. None of these reviews applied the 2019 redefinition, separated TRALI from possible TRALI when pooling donor factors, or incorporated the large administrative, haemovigilance, paediatric, obstetric and low- and middle-income country cohorts published since 2020.^{12,16,17,21}

Consequently, clinicians still lack an integrated, quantitative synthesis that links who develops TRALI (patient and donor risk), how it presents (clinical, laboratory and radiological phenotype), why it develops (immune versus non-immune mechanisms), how it differs from TACO, and what it costs patients in terms of mortality, mechanical ventilation and length of stay. This gap is particularly relevant for countries such as Indonesia, where national haemovigilance is still developing and where our search did not identify any eligible primary Indonesian study.

Novelty

- First systematic review and meta-analysis to integrate recipient, donor and transfusion risk factors, clinical/laboratory/radiological characteristics, mechanisms, TRALI–TACO differentiation and clinical outcomes within a single quantitative framework.
- Incorporates evidence published after the 2019 consensus redefinition (TRALI type I/II), including studies from 2021–2026 not covered by earlier reviews.

- Stratifies incidence by clinical setting and surveillance mode and reports prediction intervals, leave-one-out, cumulative and small-study-effect analyses to explain heterogeneity.
- Separates TRALI from possible TRALI/transfused ARDS when synthesising donor factors, avoiding double counting of shared control groups.
- Includes randomised controlled trials of prevention (washed red blood cells) and treatment (high-dose ascorbic acid), paediatric and obstetric cohorts, and data from Asia, Africa and Oceania.
- Translates pooled estimates into a mechanistic framework, a bedside diagnostic approach and tiered prevention recommendations.

Objectives

General objective: to systematically identify, appraise and quantitatively synthesise the evidence on risk factors, clinical characteristics, mechanisms and outcomes of TRALI.

Specific objectives: (1) to quantify patient-, donor- and transfusion-related risk factors associated with TRALI; (2) to describe the clinical, laboratory and radiological characteristics of patients with TRALI; (3) to summarise the evidence for immunological and non-immunological mechanisms; (4) to compare TRALI with other transfusion-related conditions, particularly TACO; (5) to estimate clinical outcomes, including mortality, need for mechanical ventilation, intensive care unit (ICU) and hospital length of stay and complications; (6) to estimate the magnitude of associations between risk factors and TRALI and identify factors associated with poor outcome; and (7) to derive implications for TRALI prevention and transfusion safety.

Expected benefits

- **Clinical practice:** identification of high-risk recipients in whom restrictive transfusion, component selection and post-transfusion monitoring should be intensified, and an evidence-based approach to distinguishing TRALI from TACO.
- **Transfusion services and haemovigilance:** quantitative support for donor-based mitigation policies, component-specific risk awareness and standardised reporting using the 2019 definitions.
- **Research:** a transparent evidence map highlighting gaps in biomarkers, therapy, paediatric and low- and middle-income settings.
- **Health policy (including Indonesia):** a basis for national guidelines on plasma and platelet donor selection, hospital transfusion committees and haemovigilance development.

Hypotheses

- **H1:** Recipient inflammatory and organ-dysfunction conditions (shock, sepsis, chronic lung disease, liver disease, chronic alcohol use, smoking and mechanical ventilation) are associated with increased odds of TRALI.
- **H2:** Exposure to high-risk donor plasma (female or alloimmunised donors, HLA/HNA antibody-positive components), plasma-rich components and a greater number of components is associated with increased odds of TRALI.
- **H3:** TRALI is associated with higher in-hospital mortality, greater need for mechanical ventilation, more ICU admissions and longer length of stay than transfusion without TRALI.
- **H4:** TRALI has a clinical and prognostic profile distinct from TACO (lower natriuretic peptides, fewer cardiovascular comorbidities and higher mortality).
- **H5:** Antibody-mediated mechanisms account for most investigated TRALI cases, and donor-based mitigation strategies reduce TRALI incidence.

METHODS

Protocol and reporting standard

This systematic review and meta-analysis was designed and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, outcomes and analysis plan were specified a priori by the authors.²²

Eligibility criteria

Eligibility was defined using the PECOS framework. Studies were included if they enrolled recipients of allogeneic blood components (or analysed implicated donors/components) and reported extractable data on TRALI incidence, risk factors, clinical, laboratory or radiological characteristics, mechanisms, comparison with TACO, clinical outcomes, or the effect of mitigation strategies. Only randomised controlled trials, prospective or retrospective cohort studies, (nested) case-control studies, cross-sectional studies and haemovigilance/registry analyses were eligible.

Table 1. Eligibility criteria (PECOS framework)

Element	Inclusion criteria	Exclusion criteria
Population	Recipients of allogeneic RBC, plasma, platelets, cryoprecipitate or whole blood of any age and clinical setting (ICU,	Autologous transfusion only; animal or in-vitro models

	surgery, obstetrics, paediatrics, haematology, general wards); implicated donors/components for donor analyses	
Exposure	Recipient factors (shock, sepsis, alcohol, smoking, liver or lung disease, mechanical ventilation, sex, age); donor factors (sex, parity, HLA/HNA antibodies); transfusion factors (component type, number/volume, storage, processing)	Exposures not related to transfusion
Comparator	Transfused patients without TRALI; recipients of low-risk components; pre-mitigation periods; patients with TACO; control arms of RCTs	No comparator required for incidence, phenotype and case-fatality outcomes
Outcomes	Incidence; association measures (OR/RR/HR); clinical, laboratory and radiological features; mechanism (immune/non-immune); mortality, mechanical ventilation, ICU admission, length of stay, complications; TRALI–TACO differences; effect of mitigation	No TRALI-specific extractable data
Study design	RCTs; prospective/retrospective cohort; nested case–control; cross-sectional; haemovigilance/registry studies with ≥ 3 TRALI cases	Narrative/systematic reviews and meta-analyses (discussion only); case reports/series < 3 patients; editorials, letters, conference abstracts, preprints; retracted articles; duplicate/overlapping data without unique information
Time/language	Peer-reviewed full texts published 1 January 2011 – 6 October 2026 (≤ 15 years); English	Publications before 2011; non-English

Search Strategy

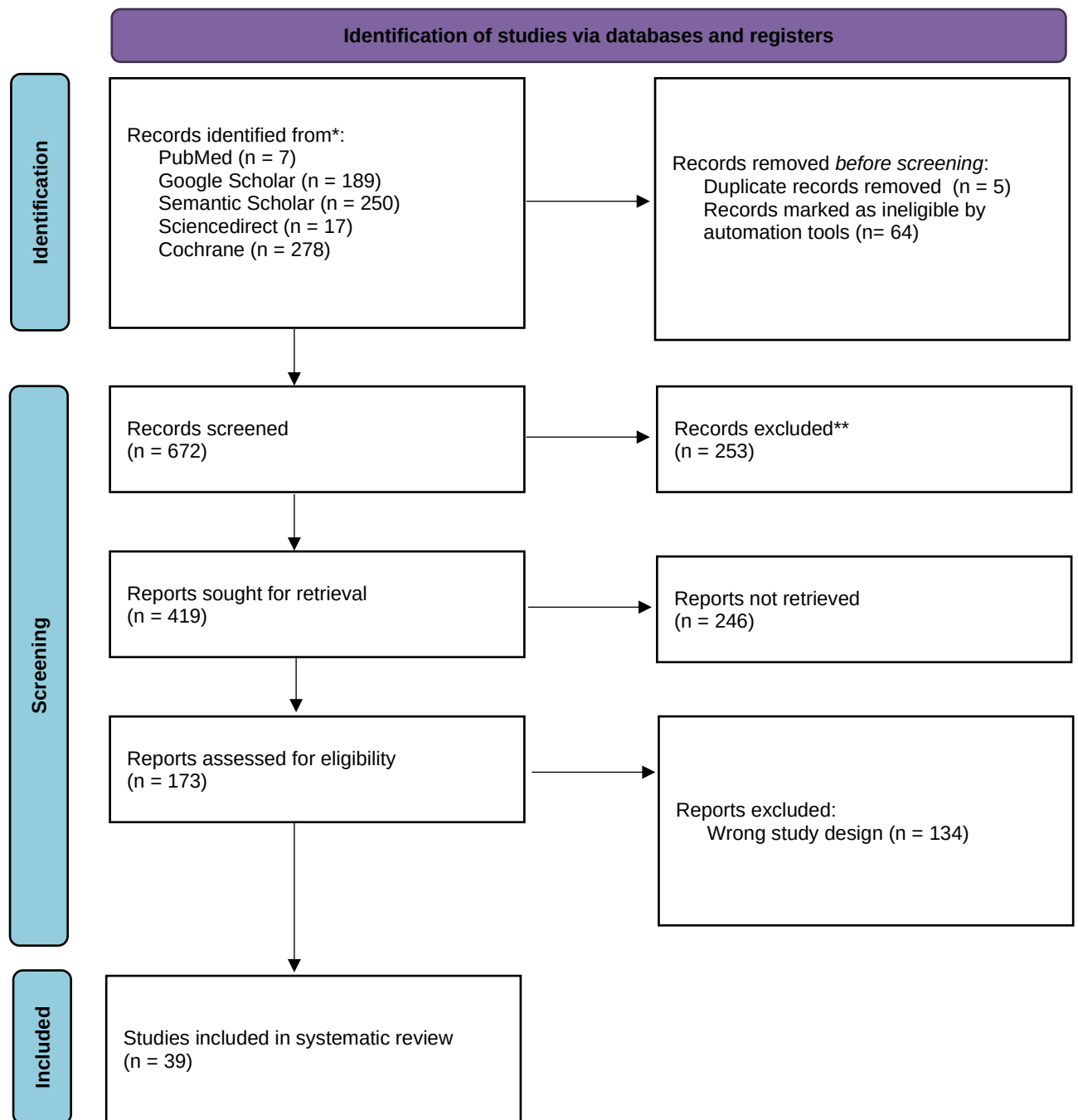
The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P — Population	Transfusion recipients	Critically ill patients	High-risk transfusion recipients
I — Intervention/Exposure	Blood component transfusion	Donor leukocyte antibodies	Plasma-rich components
C — Comparison	Transfusion-associated circulatory overload (TACO)	Transfused controls without TRALI	Low-risk donor strategies
O — Outcome	TRALI incidence	In-hospital mortality	Mechanical ventilation

The Boolean MeSH keywords inputted on databases for this research are:
 ("Transfusion recipients" OR "Critically ill patients" OR "High-risk transfusion recipients")
 AND ("Blood component transfusion" OR "Donor leukocyte antibodies" OR "Plasma-rich components") AND ("Transfusion-associated circulatory overload (TACO)" OR "Transfused controls without TRALI" OR "Low-risk donor strategies") AND ("TRALI incidence" OR "In-hospital mortality" OR "Mechanical ventilation")

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Transfusion recipients") AND ("Blood component transfusion" OR "Donor leukocyte antibodies" OR "Plasma-rich components" AND "Transfusion-associated circulatory overload (TACO)" OR "Transfused controls without TRALI" AND "TRALI incidence" OR "In-hospital mortality" OR "Mechanical ventilation")	7
Google Scholar	("Transfusion recipients" OR "Critically ill patients" OR "High-risk transfusion recipients") AND ("Blood component transfusion" OR "Donor leukocyte antibodies" OR "Plasma-rich components") AND ("Transfusion-associated circulatory overload (TACO)" OR "Transfused controls without TRALI" OR "Low-risk donor strategies") AND ("TRALI incidence" OR "In-hospital mortality" OR "Mechanical ventilation")	189
Semantic Scholar	("Transfusion recipients" OR "Critically ill patients" OR "High-risk transfusion recipients") AND ("Blood component transfusion" OR "Donor leukocyte antibodies" OR "Plasma-rich components") AND ("Transfusion-associated circulatory overload (TACO)" OR "Transfused controls without TRALI" OR "Low-risk donor strategies") AND ("TRALI incidence" OR "In-hospital mortality" OR "Mechanical ventilation")	250
Science-direct	("Transfusion recipients") AND ("Blood component transfusion" OR "Donor leukocyte antibodies" OR "Plasma-rich components") AND ("Transfusion-associated circulatory overload (TACO)" OR "Transfused controls without TRALI") AND ("TRALI incidence" OR "In-hospital mortality" OR "Mechanical ventilation")	17
Cochrane	("Transfusion recipients" AND "Blood component transfusion" OR "Donor leukocyte antibodies" OR "Plasma-rich components" AND "Transfusion-associated circulatory overload (TACO)" OR "Transfused controls without TRALI" AND "TRALI incidence" OR "In-hospital mortality" OR "Mechanical ventilation")	278



Article search flowchart

Study selection

Records were de-duplicated by PubMed identifier and digital object identifier. Screening proceeded in two stages. First, publication-type filters and title rules removed reviews, guidelines, case reports, editorials/letters/errata, animal and in-vitro studies, preprints, conference abstracts and non-English records; automated decisions were verified by a reviewer and misclassified primary studies (for example, retrospective haemovigilance series with the word "review" in the title) were restored. Second, two reviewers (NKODP and

IAYP) independently screened the remaining titles and abstracts and then assessed full texts or complete structured abstracts against the eligibility criteria. Disagreements were resolved by discussion with a third reviewer (PPAD). Reasons for full-text exclusion were recorded.

Data collection process and data items

Data were extracted into a piloted spreadsheet by one reviewer and checked by a second. Whenever possible, full texts were retrieved from PubMed Central or Europe PMC and numerical data were taken directly from the published tables rather than from abstracts. Adjusted estimates were preferred; when only percentages were reported, counts were reconstructed from the reported denominators and verified against the published confidence intervals, and these derivations are flagged in the figures. Four groups of publications arose from shared populations (the UCSF/Mayo Clinic TRALI Study Group cohort; the Amsterdam cardiac surgery cohort; American Red Cross haemovigilance; Canadian Blood Services haemovigilance). Each publication was used only for the outcome it uniquely contributed, and overlapping publications were never pooled within the same meta-analysis.

Table 2. Data items extracted and analysis plan by outcome domain

Domain	Data items	Effect measure / model	Minimum k
Study identifiers	First author, year, country, centre(s), period, design, funding	—	—
Population	Setting, age group, sample size (transfused patients, components), number of TRALI/possible TRALI/TACO cases, TRALI definition (2004 CCC, 2019 redefinition, ICD coding)	—	—
Incidence	Cases per transfused patient; cases per component	Logit proportion; log rate per 10 ⁵ units; random effects	2
Risk factors	Recipient, donor and transfusion exposures; adjusted/crude OR with 95% CI or 2×2 counts	OR (generic inverse variance); random effects; subgroups by exposure definition	2
Phenotype	Vital signs, fever, hypotension,	Narrative + OR	1–2

	oxygenation, imaging, leukocytes, platelets, cytokines, BNP/NT-proBNP, NET markers, TRALI type	(single-study profile plots); pooled proportions	
Mechanism	Donor HLA/HNA antibody results, cognate testing, immune vs non-immune classification	Pooled proportion	2
Outcomes	In-hospital/ICU mortality, mechanical ventilation, ICU admission, ICU and hospital LOS	OR, pooled proportion, MD (medians converted by Wan et al.)	2
TRALI vs TACO	Mortality, LOS, comorbidities, BNP, fluid balance	OR, MD	1–2
Mitigation	Incidence before/after or intervention/control	RR, random effects	2

Outcome and exposure definitions

TRALI was accepted as defined by the primary studies, provided that the definition corresponded to the 2004 Canadian Consensus Conference/NHLBI criteria, the 2019 consensus redefinition, expert-panel adjudication, haemovigilance imputability criteria, or validated diagnostic codes (for administrative databases). Possible TRALI (2004) was considered equivalent to TRALI type II or transfused ARDS and was analysed separately when reported separately. TACO was defined according to the primary studies (ISBT 2018 or NHSN criteria). When a study reported a composite TRALI/possible TRALI outcome, it was included in the composite and explored in sensitivity analyses.^{4,6}

Risk-of-bias assessment

Observational studies were appraised with the Newcastle–Ottawa Scale (NOS), using the cohort or case–control version as appropriate and an adapted version for cross-sectional and haemovigilance analyses (selection, four items; comparability, up to two stars; outcome/exposure, three items; maximum nine stars). Studies scoring 7–9 were classified as good quality (low risk of bias), 5–6 as fair (moderate risk) and ≤ 4 as poor (high risk). Randomised trials were appraised with the Cochrane Risk of Bias 2 tool across five domains. Two reviewers performed the assessments independently, resolving disagreements by consensus.²³

Effect measures

Associations between exposures and TRALI and between TRALI and mortality, mechanical ventilation and ICU admission were expressed as odds ratios (OR) with 95% confidence intervals (CI). Before–after and intervention comparisons were expressed as risk ratios (RR). Length of stay was expressed as mean difference (MD) in days. Incidence, case-fatality, the proportion requiring mechanical ventilation, the proportion of immune-mediated cases and the proportion of TRALI type II were expressed as proportions; incidence per component was expressed per 100,000 units.

Synthesis methods

Random-effects meta-analyses using the DerSimonian–Laird estimator of between-study variance (τ^2) were performed for all outcomes with at least two independent studies. Adjusted ORs were pooled on the log scale by the generic inverse-variance method, with standard errors derived from the reported confidence limits [$SE = (\ln \text{upper} - \ln \text{lower})/3.92$]; when the published interval was asymmetric (for example, from penalised regression), this approach yields a conservatively wide interval and lower weight. Crude ORs and RRs were computed from 2×2 tables, adding 0.5 to all cells when a zero count was present. Proportions were pooled after logit transformation and back-transformed; rates per unit were pooled on the log scale with Poisson standard errors. Medians and interquartile ranges were converted to means and standard deviations by the method of Wan and colleagues.²⁴

Statistical heterogeneity was quantified with Cochran's Q (significance $p < 0.10$), I^2 (25%, 50% and 75% indicating low, moderate and high heterogeneity) and τ^2 , and a 95% prediction interval was calculated for analyses with at least three studies. Pre-specified subgroup analyses were performed by clinical setting and surveillance mode (incidence), study design/data source (mortality, case-fatality), exposure definition (shock versus sepsis; plasma versus platelets) and case definition (TRALI versus possible TRALI). Sensitivity analyses comprised leave-one-out analysis, substitution of adjusted for crude estimates and cumulative meta-analysis by publication year. Small-study effects were explored with funnel plots, Egger's regression test, Begg's rank-correlation test and Duval–Tweedie trim-and-fill when at least five studies were available. All tests were two-sided with $\alpha = 0.05$.

Analyses were implemented in Python 3 (NumPy 2.4, SciPy 1.17 and Matplotlib 3.10) using the inverse-variance DerSimonian–Laird algorithms of Review Manager 5.4, and forest plots were formatted in Review Manager style. Certainty of evidence for the main outcomes was rated with the GRADE approach (risk of bias, inconsistency, indirectness, imprecision, publication bias; upgrading for large effects and dose–response).

Ethical considerations

This review used published aggregate data only; ethical approval and informed consent were therefore not required.

Table 3. Risk of bias of observational studies (Newcastle–Ottawa Scale, item-level)

Study	S1 Representativeness / case definition	S2 Selection of controls / non-exposed	S3 Ascertainment of exposure	S4 Outcome absent at start / control definition	C Comparability (0–2)	O1 Outcome assessment	O2 Same method / follow-up length	O3 Adequacy of follow-up / non-response	Total (0–9)	Quality
Toy 2012 ²⁵	★	★	★	★	★★	★	★	★	9	Good (low risk)
Looney 2014 ²⁶	★	★	★	★	★	★	★	★	8	Good (low risk)
Toy 2015 ²⁷	★	★	★	★	★★	★	★	—	8	Good (low risk)
Roubinian 2017 ²⁸	★	—	★	★	★★	★	★	—	7	Good (low risk)
Roubinian	★	★	★	★	★	★	★	—	7	Good

2020 ²⁹										(low risk)
Vlaar 2011 ³⁰	★	★	★	★	★★	★	★	—	8	Good (low risk)
Vlaar 2012 ³¹	★	★	★	★	★	★	★	—	7	Good (low risk)
Mulder 2015 ³²	★	★	★	★	★★	★	—	—	7	Good (low risk)
Clifford 2015 ³³	★	★	★	★	—	★	★	—	6	Fair (moderate risk)
Menis 2014 ³⁴	★	★	★	—	★★	—	★	—	6	Fair (moderate risk)
Benson 2011 ³⁵	★	★	★	★	—	★	★	—	6	Fair (moderate risk)
Kleinman	★	★	★	★	★★	★	★	—	8	Good

2011 ³⁶										(low risk)
Teofili 2014 ³⁷	–	★	★	★	★	★	★	–	6	Fair (moderate risk)
Xing 2014 ³⁸	★	★	★	–	–	★	★	–	5	Fair (moderate risk)
Zah-Bogović 2014 ³⁹	★	★	★	★	★	★	★	–	7	Good (low risk)
Kumar 2016 ⁴⁰	★	–	★	–	–	★	★	–	4	Poor (high risk)
Jamil 2017 ⁴¹	★	★	★	–	–	★	★	–	5	Fair (moderate risk)
Thalji 2018 ⁴²	★	★	★	★	–	★	★	★	7	Good (low risk)
Meyer 2018	★	–	★	–	–	★	★	★	5	Fair

⁴³										(moderate risk)
Vossoughi 2019 ⁴⁴	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Yokoyama 2021 ⁴⁵	★	★	★	★	★★	—	★	—	7	Good (low risk)
McVey 2021 ⁴⁶	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Klanderman 2022 ⁴⁷	★	★	★	★	—	★	★	★	7	Good (low risk)
Sivakaanthan 2022 ⁴⁸	★	—	★	—	—	★	★	★	5	Fair (moderate risk)
Kazakova 2025 ⁴⁹	★	★	★	—	★	—	★	★	6	Fair (moderate risk)
Liu 2025 ⁵⁰	★	★	★	—	—	★	★	—	5	Fair

										(moderate risk)
Young 2025 ⁵¹	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Wang 2026 ⁵²	★	★	★	★	★	★	★	—	7	Good (low risk)
Wiersum-Osselton 2011 ⁵³	★	★	★	—	★	★	★	—	6	Fair (moderate risk)
Funk 2012 ⁵⁴	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Ozier 2011 ⁵⁵	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Eder 2013 ⁵⁶	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Lieberman	★	—	★	—	—	★	★	★	5	Fair

2014 ⁵⁷										(moderate risk)
Peters 2019 ⁵⁸	★	★	★	★	—	★	★	—	6	Fair (moderate risk)
Lee 2019 ⁵⁹	★	—	★	—	—	★	★	—	4	Poor (high risk)
Arinsburg 2012 ⁶⁰	★	★	★	—	—	★	★	★	6	Fair (moderate risk)
Lin 2012 ⁶¹	★	—	★	—	—	★	★	★	5	Fair (moderate risk)

★ = star awarded; — = no star. Total 7–9 = good (low risk of bias); 5–6 = fair (moderate); ≤4 = poor (high). Cross-sectional and haemovigilance analyses were appraised with an adapted NOS.

Table 4. Risk of bias of randomised controlled trials (Cochrane RoB 2)

Trial	D1 Randomisation	D2 Deviations from intended interventions	D3 Missing outcome data	D4 Measurement of outcome	D5 Selection of reported result	Overall	Main rationale
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Kor et al. 2025 ⁶²	Low	Some concerns	Low	Some concerns	Low	Some concerns	Two-centre, non-blinded phase II trial analysed by modified intention-to-treat; objective biomarkers but clinician-adjudicated TRALI/TACO without blinding; TRALI a secondary outcome with very few events
Kassem et al. 2022 ⁶³	Some concerns	Low	Low	Low	Some concerns	Some concerns	Placebo-controlled; laboratory primary outcomes objectively measured; limited reporting of allocation concealment and of pre-specified clinical secondary outcomes

Risk of bias

Of the 37 observational studies, 14 (38%) were of good quality (NOS 7–9), 21 (57%) of fair quality (NOS 5–6) and 2 (5%) of poor quality (NOS ≤ 4). The main sources of bias were the absence of adjustment for confounding (comparability) in haemovigilance, case-series and before–after designs, reliance on passive reporting or diagnostic codes for outcome ascertainment in administrative studies, and incomplete follow-up or reporting of denominators. Prospective active-surveillance and nested case–control studies with expert adjudication scored highest. Both RCTs were judged to have some concerns, related to the lack of blinding in one trial and to incomplete reporting of allocation concealment and clinical outcomes in the other.

Risk of bias of observational studies - Newcastle-Ottawa Scale (traffic-light plot)

	S1	S2	S3	S4	C	O1	O2	O3	Total
Toy 2012	★	★	★	★	★★	★	★	★	9
Looney 2014	★	★	★	★	★	★	★	★	8
Toy 2015	★	★	★	★	★★	★	★	★	8
Roubinian 2017	★	★	★	★	★★	★	★	★	7
Roubinian 2020	★	★	★	★	★	★	★	★	7
Vlaar 2011	★	★	★	★	★★	★	★	★	8
Vlaar 2012	★	★	★	★	★	★	★	★	7
Mulder 2015	★	★	★	★	★★	★	★	★	7
Clifford 2015	★	★	★	★	★	★	★	★	6
Menis 2014	★	★	★	★	★★	★	★	★	6
Benson 2011	★	★	★	★	★	★	★	★	6
Kleinman 2011	★	★	★	★	★★	★	★	★	8
Teofil 2014	★	★	★	★	★	★	★	★	6
Xing 2014	★	★	★	★	★	★	★	★	5
Zah-Bogović 2014	★	★	★	★	★	★	★	★	7
Kumar 2016	★	★	★	★	★	★	★	★	4
Jamil 2017	★	★	★	★	★	★	★	★	5
Thalji 2018	★	★	★	★	★	★	★	★	7
Meyer 2018	★	★	★	★	★	★	★	★	5
Vossoughi 2019	★	★	★	★	★	★	★	★	6
Yokoyama 2021	★	★	★	★	★★	★	★	★	7
McVey 2021	★	★	★	★	★	★	★	★	6
Klanderman 2022	★	★	★	★	★	★	★	★	7
Sivakaanthan 2022	★	★	★	★	★	★	★	★	5
Kazakova 2025	★	★	★	★	★	★	★	★	6
Liu 2025	★	★	★	★	★	★	★	★	5
Young 2025	★	★	★	★	★	★	★	★	6
Wang 2026	★	★	★	★	★	★	★	★	7
Wiersum-Osselton 2011	★	★	★	★	★	★	★	★	6
Funk 2012	★	★	★	★	★	★	★	★	6
Ozier 2011	★	★	★	★	★	★	★	★	6
Eder 2013	★	★	★	★	★	★	★	★	6
Lieberman 2014	★	★	★	★	★	★	★	★	5
Peters 2019	★	★	★	★	★	★	★	★	6
Lee 2019	★	★	★	★	★	★	★	★	4
Arinsburg 2012	★	★	★	★	★	★	★	★	6

S1 representativeness/case definition; S2 selection of controls/non-exposed; S3 ascertainment of exposure; S4 outcome absent at start/definition of controls; C comparability (0-2 stars); O1 outcome at least once; O2 same method/adequate follow-up; O3 adequacy of follow-up/non-response. Green = star awarded/low risk; amber = partial (one comparability star) or fair quality (5-6); red = no star/high risk or poor quality (≤ 4). Total ≥ 7 = good quality.

Figure 1. Item-level risk-of-bias (Newcastle–Ottawa Scale) traffic-light plot of the 37 observational studies.

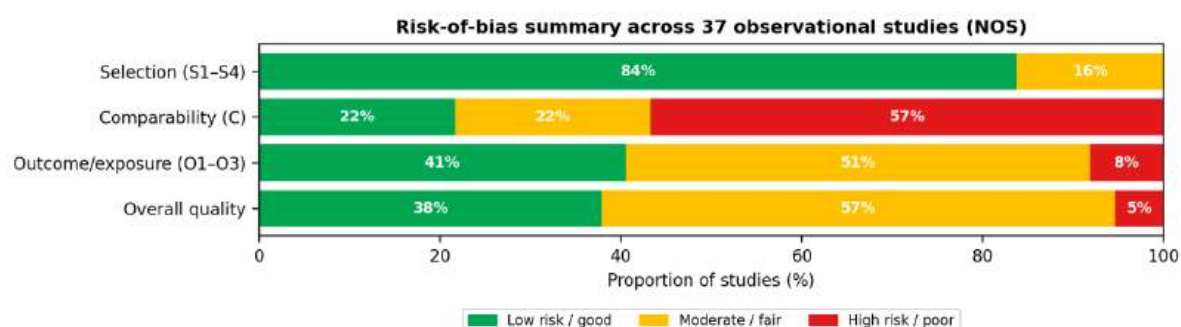


Figure 2. Summary of risk of bias across Newcastle–Ottawa domains and overall quality.

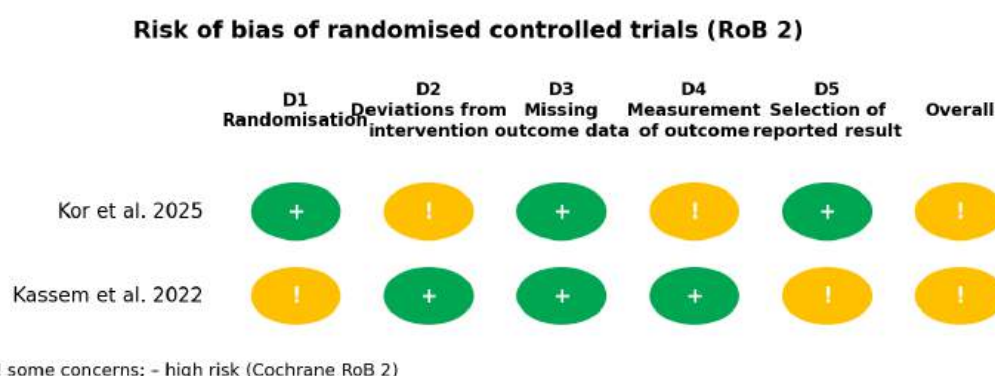


Figure 3. Risk of bias of the randomised controlled trials (Cochrane RoB 2)

RESULTS

Characteristics of included studies

The 39 included studies comprised 13 retrospective case series or haemovigilance analyses, 11 retrospective clinical cohorts, two retrospective administrative cohorts, eight nested case–control studies, three prospective cohort or prospective case–control studies and two randomised controlled trials. They were conducted in 14 countries: 20 in North America, 10 in Europe, 7 in Asia (China, Japan, South Korea, Pakistan and Kuwait), and one each in Oceania and Africa; 22 (56%) were published in 2015 or later and 11 (28%) in 2020 or later. Populations included general hospitalised recipients, adult and paediatric intensive care, cardiac, non-cardiac and liver-transplant surgery, post-partum haemorrhage, acute massive haemorrhage, elderly Medicare beneficiaries, and national or regional blood-supply systems. Collectively, the studies covered more than 16.8 million transfused patients or hospitalisations and more than 144 million distributed or transfused blood components, with over 5,900 TRALI events.

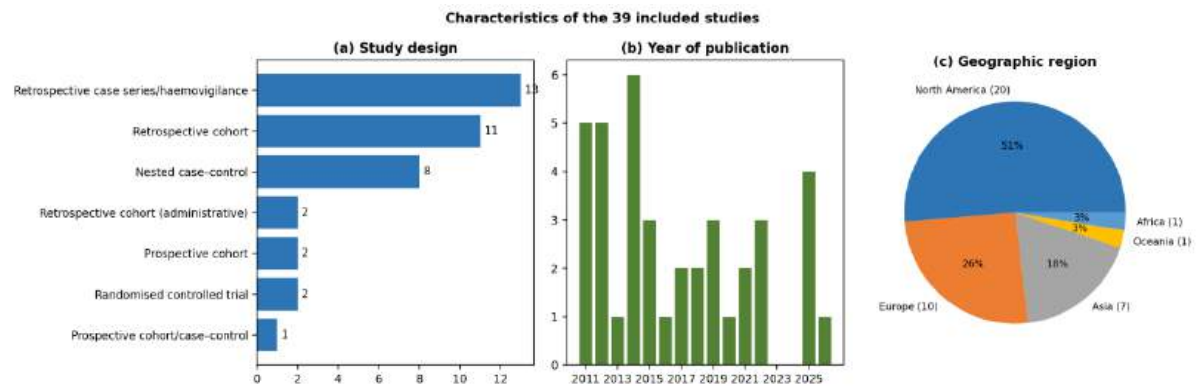


Figure 4. Distribution of the 39 included studies by (a) design, (b) year of publication and (c) geographic region.

Table 5. Characteristics of the 39 included studies

No.	Study	Country	Design (period)	Population / setting	Sample	TRALI cases (definition)	Main data contributed	Quality
1	Toy et al. 2012 ²⁵	USA	Prospective active surveillance + nested case–control (2006–2009)	Transfused inpatients, 2 academic centres	89 TRALI vs 164 transfused controls	89 (2004 CCC; expert panel)	Recipient and donor risk factors; incidence 2.57→0.81 per 10 ⁴ units after mitigation	NOS 9 (good)
2	Looney et al. 2014 ²⁶	USA	Prospective case study with controls (2006–2009)	Same surveillance cohort	89 TRALI, 145 possible TRALI, 164 controls	89 (2004 CCC)	Clinical course, vital signs, cytokines, ventilation, mortality	NOS 8 (good)
3	Toy et al. 2015 ²⁷	USA	Nested case–control (2006–2009)	Same surveillance cohort	145 possible TRALI vs 163 controls	Possible TRALI	Recipient vs transfusion factors in possible TRALI	NOS 8 (good)
4	Roubinian et al. 2017 ²⁸	USA	Post hoc case–control	Subset with stored samples	TRALI 21, pTRALI 26, TACO 22, controls 24	21	BNP and clinical discriminators TRALI vs TACO	NOS 7 (good)
5	Roubinian et	USA	Case–control,	4 academic	TACO 160,	12 (+7	Pre-/post-transfusion	NOS 7

	al. 2020 ²⁹		secondary analysis	hospitals	transfused ARDS 51, TRALI 12, TACO/TRALI 7, controls 335	TACO/TRALI)	NT-proBNP	(good)
6	Vlaar et al. 2011 ³⁰	Netherlands	Prospective nested case–control	Cardiac surgery cohort	668 patients	16 (2.4%; 2004 CCC)	Incidence, transfusion risk factors, donor antibodies, mortality	NOS 8 (good)
7	Vlaar et al. 2012 ³¹	Netherlands	Prospective nested case–control (same cohort)	Cardiac surgery	16 TRALI; transfused and non-transfused controls (1:2)	16	Plasma and BAL inflammation, coagulation and fibrinolysis markers	NOS 7 (good)
8	Mulder et al. 2015 ³²	Netherlands	Retrospective cohort (2009–2012)	Paediatric ICU	2294 admissions; 304 transfused	21 (6.9%)	Risk factors (ventilation, sepsis, PRISM III); outcomes	NOS 7 (good)
9	Clifford et al. 2015 ³³	USA	Retrospective cohort, before–after (2004, 2011)	Adult non-cardiac surgery	3379 transfused	45 TRALI/possible TRALI	Incidence by volume/specialty; mortality; LOS; mitigation	NOS 6 (fair)

10	Menis et al. 2014 ³⁴	USA	Retrospective claims cohort (2007–2011)	Medicare inpatients ≥ 65 y	11,378,264 transfusion stays	2556 (ICD-9-CM)	Recipient risk factors (sex, age, race, fibrosis, tobacco)	NOS 6 (fair)
11	Benson et al. 2011 ³⁵	USA	Retrospective cohort	Liver transplantation	525	7 (1.3%)	Plasma/platelet per-unit risk; mortality; ICU LOS	NOS 6 (fair)
12	Kleinman et al. 2011 (LAPS-II) ³⁶	USA	Retrospective cohort, matched donor arms	Recipients of 2596 high-plasma-volume components	Anti-HLA-positive vs negative donor arms	7 vs 2 (blinded panel)	Effect of donor HLA antibodies; TACO by arm	NOS 8 (good)
13	Teofili et al. 2014 ³⁷	Italy	Retrospective cohort	Post-partum haemorrhage (≥ 3 RBC)	71	13 TRALI + 1 possible	Obstetric risk factors; ICU; outcome	NOS 6 (fair)
14	Xing et al. 2014 ³⁸	China	Retrospective cohort (2008–2011)	Paediatric surgery	1495	2	Incidence; transfusion duration; donor sex	NOS 5 (fair)
15	Zah-Bogović et al. 2014 ³⁹	Croatia	Prospective cohort (2009–2010)	Cardiac surgery	262	32 possible TRALI (12.2%)	Units transfused, CPB duration, respiratory comorbidity	NOS 7 (good)
16	Kumar et al.	Kuwait	Retrospective	All recipients	170,871	9	Incidence 1:19,000;	NOS 4

	2016 ⁴⁰		single-institution (15 years)		transfusions		ventilation; no deaths	(poor)
17	Jamil et al. 2017 ⁴¹	Pakistan	Retrospective cohort (2012–2016)	Paediatric ICU	1066 transfused	11 (1.03%)	Incidence; case-fatality	NOS 5 (fair)
18	Thalji et al. 2018 ⁴²	USA	Retrospective cohort (2010–2014)	Paediatric non-cardiac surgery	411	1.2% TRALI; 3.4% TACO	Incidence of pulmonary complications	NOS 7 (good)
19	Meyer et al. 2018 ⁴³	USA	Retrospective blood-bank registry (2002–2013)	Urban tertiary/trauma centre	714,757 units	7 (probable)	Incidence per unit; symptom duration	NOS 5 (fair)
20	Vossoughi et al. 2019 ⁴⁴	USA	Retrospective multicentre haemovigilance (2007–2017)	5 blood centres, 9 states	10,012,707 components	104	Rates by donor sex and year	NOS 6 (fair)
21	Yokoyama et al. 2021 ⁴⁵	Japan	Nested case–control (2010–2015)	Nationwide DPC inpatients	2,019,501 transfused; 72 vs 288 matched	72 (coded)	Lung disease, BMI, plasma; treatments; mortality	NOS 7 (good)

22	McVey et al. 2021 ⁴⁶	Canada	Retrospective haemovigilance cohort (2013–2016)	Tri-hospital network	1144 suspected reactions	19 (possible–definite)	Mortality and time-to-death by reaction type	NOS 6 (fair)
23	Klanderman et al. 2022 ⁴⁷	Netherlands	Retrospective before–after cohort (2014 vs 2015)	Multicentre ICUs, plasma recipients	8944 admissions; 772 plasma recipients	19 (6 type I, 13 type II)	qFFP vs SDP; phenotype; mortality; LOS	NOS 7 (good)
24	Sivakaanthan et al. 2022 ⁴⁸	Australia	Retrospective haemovigilance (1999–2019)	Queensland referrals	91 referred cases	30 TRALI + 18 possible	Onset, severity, antibody vs non-antibody cases	NOS 5 (fair)
25	Kazakova et al. 2025 ⁴⁹	USA	Retrospective administrative cohort (2016–2020)	999 acute-care hospitals	3,450,698 transfusion hospitalisations	2237 (coded)	Mortality, LOS; TRALI vs TACO	NOS 6 (fair)
26	Liu et al. 2025 ⁵⁰	China	Retrospective cohort	Intra-/post-operative transfusion	5846	4	Component-specific rates; donor antibodies; clinical course	NOS 5 (fair)
27	Young et al. 2025 ⁵¹	USA	Retrospective national	American Red Cross	≈133.2 million components	393 (high probability)	Component-specific TRALI rates	NOS 6 (fair)

			haemovigilance (2006–2023)	distributions				
28	Wang et al. 2026 ⁵²	China	Prospective multicentre cohort (2020– 2025)	Acute massive haemorrhage	513	42 (8.2%)	Smoking, transfusion burden, NET biomarkers; prediction model	NOS 7 (good)
29	Kor et al. 2025 ⁶²	USA	Phase II RCT (2 centres)	Cardiac surgery with RBC transfusion	154 (81 washed vs 73 standard)	1 (0 vs 1)	Washed RBC; lung- injury biomarkers; TRALI/TACO	RoB 2: some concerns
30	Kassem et al. 2022 ⁶³	Egypt	Placebo- controlled RCT	Critically ill patients with TRALI	80	80 (all TRALI)	High-dose IV ascorbic acid; inflammatory and oxidative markers	RoB 2: some concerns
31	Wiersum- Osselton et al. 2011 ⁵³	Netherlands	National before–after haemovigilance (2002–2009)	Reported TRALI	110 cases	110	Effect of male-only quarantine FFP (–33%)	NOS 6 (fair)
32	Funk et al. 2012 ⁵⁴	Germany	National haemovigilance before–after	Confirmed TRALI	80 cases	80 (60 immune, 20 non-immune)	Immune vs non- immune; FFP-related rates	NOS 6 (fair)

			(2006–2010)					
33	Ozier et al. 2011 ⁵⁵	France	National haemovigilance (2007–2008)	Notified cases	85 cases	62 TRALI + 23 possible	Immune mechanism; per-component risk; mortality	NOS 6 (fair)
34	Eder et al. 2013 ⁵⁶	USA	Before–after haemovigilance (2006 vs 2008– 2011)	American Red Cross plasma	National distributions	Suspected TRALI	Residual risk; group AB plasma	NOS 6 (fair)
35	Lieberman et al. 2014 ⁵⁷	Canada	Retrospective case series (2001–2011)	Canadian Blood Services reports	284 cases (17 paediatric)	284	Paediatric vs adult presentation and outcome	NOS 5 (fair)
36	Peters et al. 2019 ⁵⁸	Netherlands	Secondary analysis of two case–control cohorts	ICU and cardiac surgery	TRALI vs transfused controls	—	Donor sex, age and ABO group	NOS 6 (fair)
37	Lee et al. 2019 ⁵⁹	South Korea	Retrospective case series (2013–2019)	Tertiary hospital	7	7 (5 type II)	Onset time; reclassification by 2019 criteria	NOS 4 (poor)
38	Arinsburg et al. 2012 ⁶⁰	USA	Before–after cohort (16 + 16 months)	Three hospitals	461,598 components	TRALI/possible TRALI	Conversion to low- risk plasma	NOS 6 (fair)

39	Lin et al. 2012 ⁶¹	Canada	National haemovigilance (2001–2009)	Canadian Blood Services	Suspected TRALI reports	Definite/possible	Impact of prevention measures	NOS 5 (fair)
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Abbreviations: BAL, bronchoalveolar lavage; CCC, Canadian Consensus Conference; CPB, cardiopulmonary bypass; DPC, Diagnosis Procedure Combination; FFP, fresh frozen plasma; ICD, International Classification of Diseases; LOS, length of stay; NET, neutrophil extracellular trap; NOS, Newcastle–Ottawa Scale; pTRALI, possible TRALI; qFFP, quarantine FFP; RCT, randomised controlled trial; SDP, solvent/detergent-treated pooled plasma; TACO, transfusion-associated circulatory overload.

Incidence of TRALI

Sixteen studies reported TRALI per transfused patient. Incidence differed markedly by setting (test for subgroup differences, $p < 0.001$): the pooled incidence was 4.47% (95% CI 2.29–8.56; $I^2 = 94\%$) in high-risk or critical-care populations (cardiac surgery, liver transplantation, post-partum haemorrhage, paediatric and adult ICU, and acute massive haemorrhage), 0.41% (0.11–1.47; $I^2 = 90\%$) in general peri-operative and hospital cohorts, and 0.017% (0.007–0.045) in coded administrative databases. The highest incidences were reported in post-partum haemorrhage (19.7%), cardiac surgery with a 24-hour broadened definition (12.2%), acute massive haemorrhage (8.2%) and paediatric intensive care (6.9%).^{32,37,39,52}

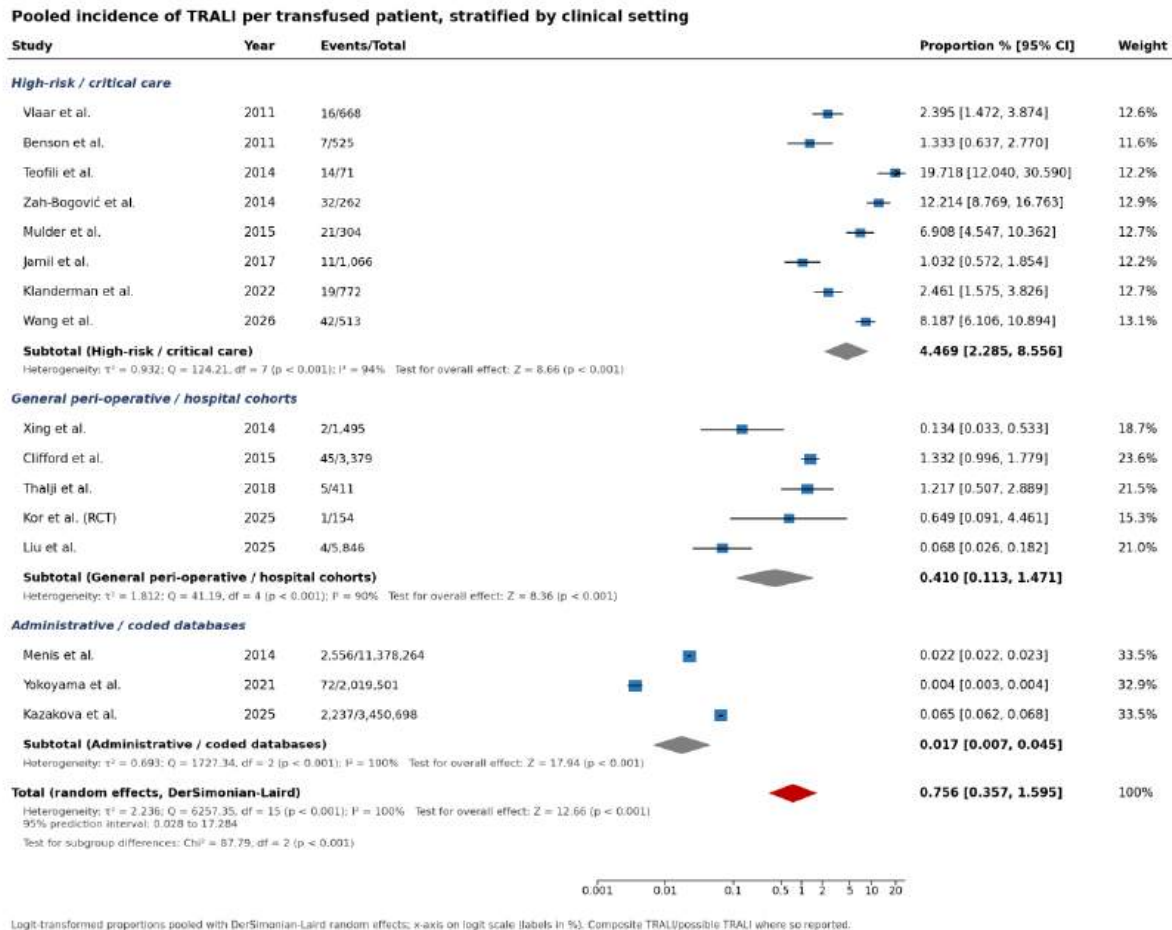


Figure 5. Forest plot of pooled TRALI incidence per transfused patient, stratified by clinical setting (logit-transformed proportions, random effects).

Five studies reported TRALI per blood component (Figure 7). The pooled rate was 1.88 per 100,000 components (95% CI 0.46–7.66; $I^2 = 99\%$), ranging from 0.30 per 100,000 in the 18-year American Red Cross programme to 15.5 per 100,000 in prospective active surveillance at two academic centres, illustrating the large under-ascertainment inherent in passive surveillance.^{25,40,43,44,51}

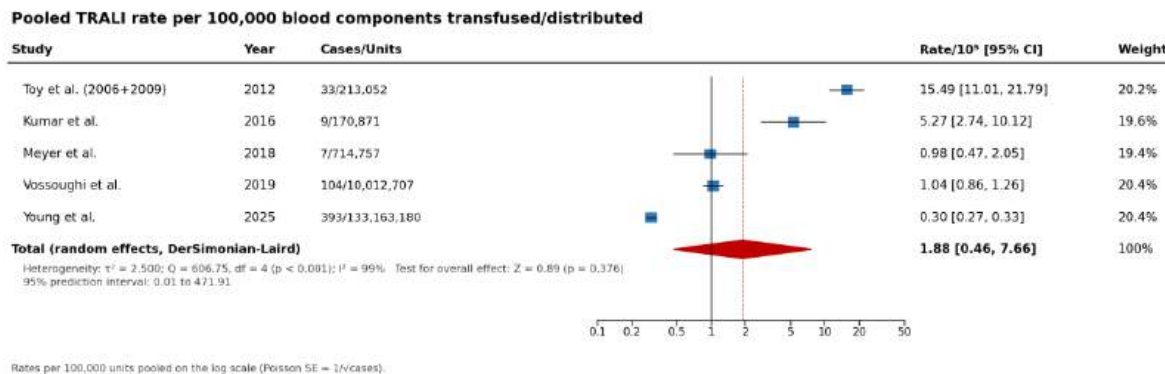


Figure 6. Forest plot of pooled TRALI rate per 100,000 blood components transfused or distributed.

Patient-related risk factors

Shock and sepsis. Four studies examined a systemic inflammatory first hit. Shock or sepsis before transfusion was associated with TRALI (pooled OR 2.54, 95% CI 1.05–6.09; $p = 0.037$; $I^2 = 72\%$), with no difference between the shock and sepsis subgroups ($p = 0.79$). The largest adjusted estimates came from the prospective UCSF/Mayo cohort (shock, OR 4.2) and the paediatric ICU cohort (sepsis, OR 7.20).^{25,32,45,52}

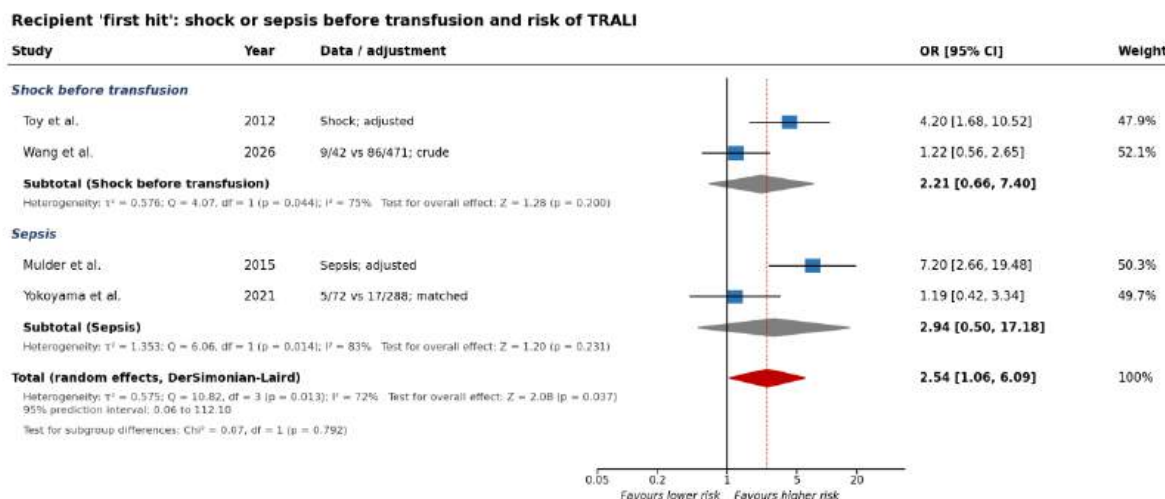


Figure 7. Forest plot of shock or sepsis before transfusion and risk of TRALI.

Chronic alcohol use and smoking. Chronic alcohol abuse was an independent risk factor in the primary multivariable model of the UCSF/Mayo cohort (OR 5.9, 1.22–28.3), but the pooled

estimate including crude data from a massive-haemorrhage cohort was not statistically significant (OR 2.41, 0.64–9.11; $I^2 = 62\%$) (Figure 9). Similarly, current smoking was independently associated with TRALI in the UCSF/Mayo cohort (OR 3.4) and in massive haemorrhage (crude OR 3.84), and tobacco use modestly increased odds in elderly Medicare beneficiaries (OR 1.16), but the pooled estimate across five studies did not reach significance (OR 1.61, 0.91–2.85; $p = 0.099$; $I^2 = 76\%$).^{25,34,37,45,52}

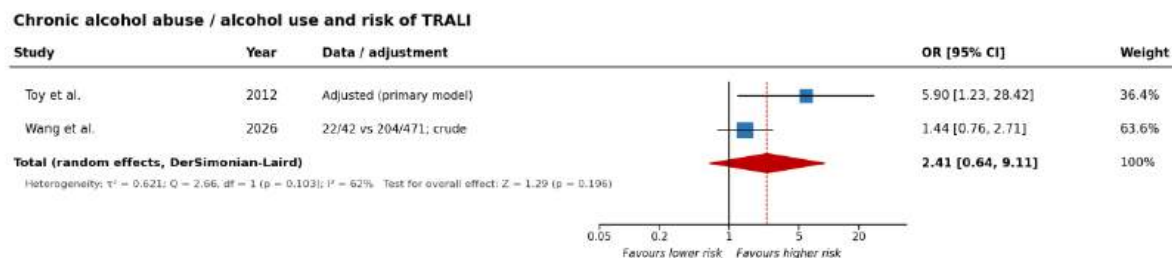


Figure 8. Forest plot of chronic alcohol use and risk of TRALI.

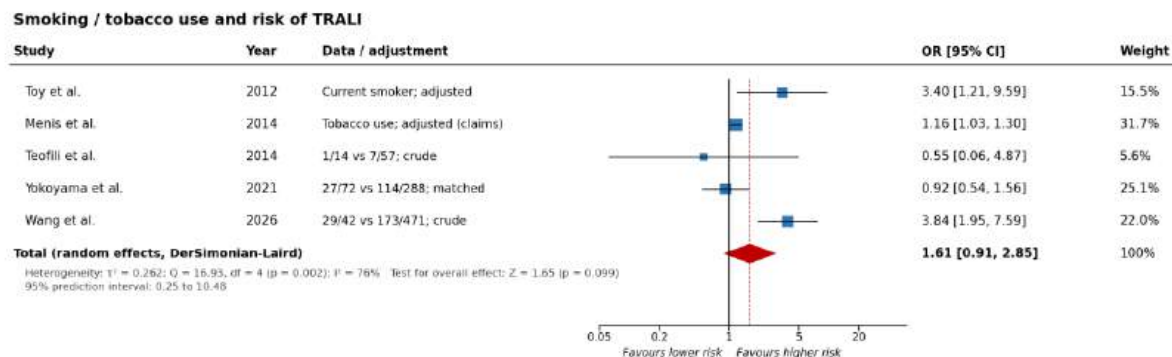


Figure 9. Forest plot of smoking/tobacco use and risk of TRALI.

Mechanical ventilation. Being mechanically ventilated at the time of transfusion was not associated with TRALI in pooled analysis (OR 1.26, 0.75–2.13; $I^2 = 25\%$). However, the paediatric ICU cohort reported a strong adjusted association (OR 18.94) and, in the UCSF/Mayo cohort, a peak airway pressure above 30 cmH₂O within 12 hours of intubation independently predicted TRALI (OR 3.6, 1.01–13.1), suggesting that injurious ventilation rather than ventilation per se constitutes the first hit.^{25,26,32,52}

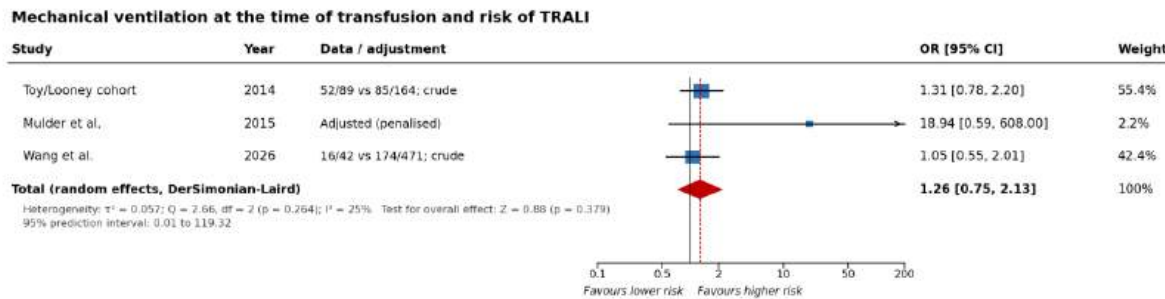


Figure 10. Forest plot of mechanical ventilation at the time of transfusion and risk of TRALI.

Liver disease and hepatic/transplant surgery. Liver surgery (predominantly transplantation) was an independent risk factor in the UCSF/Mayo model (OR 6.7, 1.25–35.7), and severe liver disease doubled the odds in univariate analysis (OR 2.9). Pooling with transplant surgery in non-cardiac surgical patients and coded liver dysfunction in Japan produced a non-significant estimate (OR 1.80, 0.64–5.10; $I^2 = 56\%$). In liver transplantation specifically, only high-plasma-volume components were associated with TRALI.^{25,33,35,45}

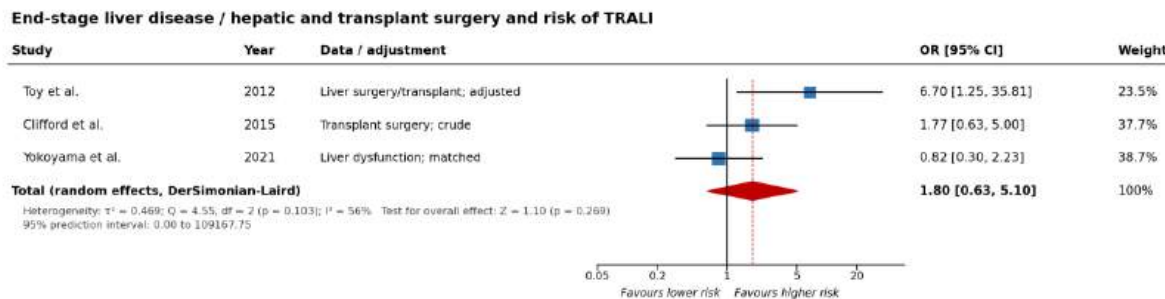


Figure 11. Forest plot of liver disease or hepatic/transplant surgery and risk of TRALI.

Chronic lung disease. Pre-existing chronic lung disease was consistently associated with TRALI (pooled OR 2.72, 1.46–5.08; $p = 0.002$; $I^2 = 60\%$), including interstitial lung disease in the Japanese nationwide study (adjusted OR 3.88), post-inflammatory pulmonary fibrosis in elderly Medicare beneficiaries (OR 1.89) and respiratory comorbidity in cardiac surgery (crude OR 4.25). Obstructive airway disease and infectious lung disease were not associated with TRALI.^{34,39,45}

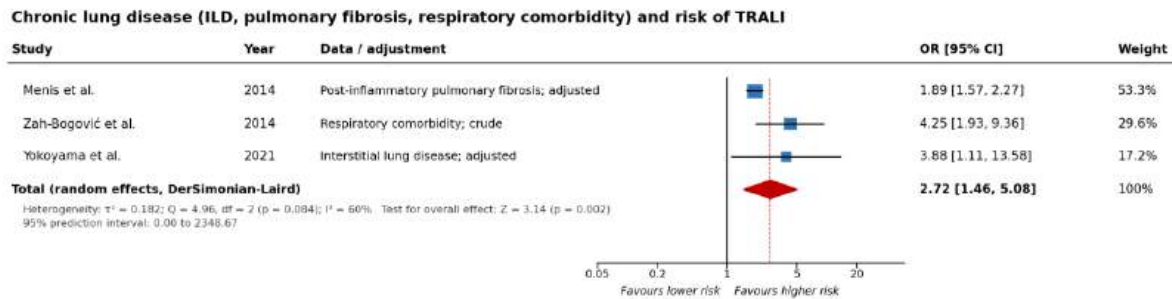


Figure 12. Forest plot of chronic lung disease and risk of TRALI.

Haematological malignancy and other comorbidities. Findings for haematological malignancy were contradictory and could not be reconciled by pooling (OR 0.86, 0.13–5.69; $I^2 = 90\%$) : leukaemia/lymphoma appeared protective in the UCSF/Mayo cohort (OR 0.32), possibly reflecting neutropenia and immunosuppression, whereas haematological malignancy was over-represented among Japanese cases (crude OR 2.20) and accounted for 21–27% of haemovigilance cases in France and Australia. Body mass index ≥ 25 kg/m² (OR 2.10), hypertensive disorders of pregnancy in post-partum haemorrhage (OR 27.7), higher Pediatric Risk of Mortality III score (OR 1.05 per point), cardiopulmonary bypass duration (OR 1.08 per unit time) and pre-transfusion positive fluid balance (OR 1.15 per litre) were additional single-study risk factors.^{25,32,37,39,45,48,55}

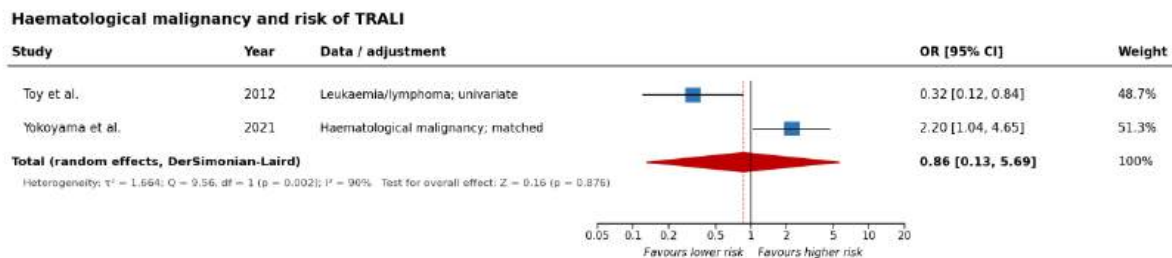


Figure 13. Forest plot of haematological malignancy and risk of TRALI.

Recipient sex and age. Female recipient sex was associated with a small but precise increase in odds (pooled OR 1.24, 1.14–1.35; $I^2 = 0\%$), driven by the Medicare cohort, whereas the three clinical cohorts were individually non-significant. Age effects were non-linear: TRALI was more frequent at ages 65–79 than above 79 years among Medicare beneficiaries (OR 1.19), and both the youngest (0–17 years) and oldest (≥ 75 years) groups had lower odds than those aged 55–64

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in the US hospital database, whereas older age favoured TACO or possible TRALI over TRALI.^{28,33,34,49,52}

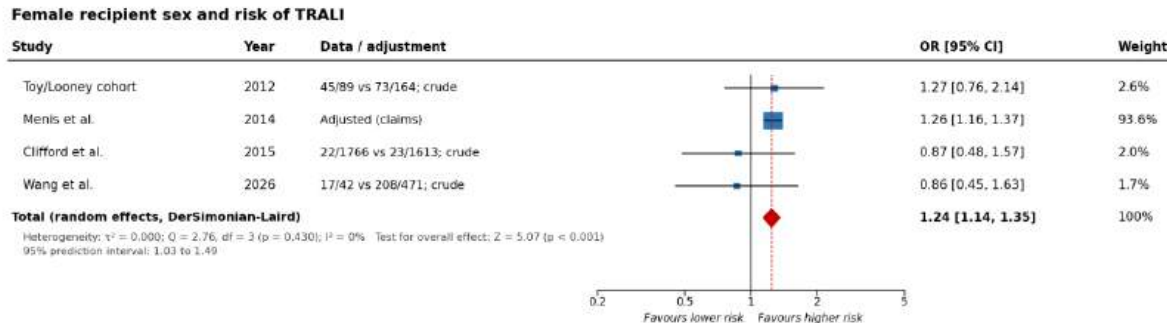


Figure 14. Forest plot of female recipient sex and risk of TRALI.

Table 6. Study-level estimates for patient-related risk factors (as entered into meta-analysis)

Risk factor	Study	OR (95% CI)	Adjustment / data source
Shock before transfusion	Toy et al. 2012 ²⁵	4.20 (1.69–10.6)	Multivariable (primary model)
	Wang et al. 2026 ⁵²	1.22 (0.56–2.65)	Crude 2×2 (9/42 vs 86/471)
Sepsis	Mulder et al. 2015 ³²	7.20 (2.69–19.69)	Multivariable
	Yokoyama et al. 2021 ⁴⁵	1.19 (0.42–3.34)	Matched 2×2 (5/72 vs 17/288)
Chronic alcohol use	Toy et al. 2012 ²⁵	5.90 (1.22–28.3)	Multivariable
	Wang et al. 2026 ⁵²	1.44 (0.76–2.71)	Crude (drinking history)
Smoking / tobacco	Toy et al. 2012 ²⁵	3.40 (1.22–9.7)	Multivariable (current smoker)
	Menis et al. 2014	1.16 (1.00–	Multivariable (claims)

	³⁴	1.26)	
	Teofili et al. 2014 ³⁷	0.55 (0.06–4.87)	Crude
	Yokoyama et al. 2021 ⁴⁵	0.92 (0.54–1.56)	Matched (smoking history)
	Wang et al. 2026 ⁵²	3.84 (1.95–7.59)	Crude
Mechanical ventilation	Looney et al. 2014 (UCSF/Mayo) ²⁶	1.31 (0.78–2.20)	Crude (ventilated before oedema)
	Mulder et al. 2015 ³²	18.94 (2.38–2452.56)*	Multivariable, penalised
	Wang et al. 2026 ⁵²	1.05 (0.55–2.01)	Crude
Liver disease / surgery	Toy et al. 2012 ²⁵	6.70 (1.25–35.7)	Multivariable (liver surgery/transplant)
	Clifford et al. 2015 ³³	1.77 (0.63–5.00)	Crude (transplant surgery)
	Yokoyama et al. 2021 ⁴⁵	0.82 (0.30–2.23)	Matched (liver dysfunction)
Chronic lung disease	Menis et al. 2014 ³⁴	1.89 (1.52–2.20)	Multivariable (pulmonary fibrosis)
	Zah-Bogović et al. 2014 ³⁹	4.25 (1.93–9.36)	Crude (respiratory comorbidity)
	Yokoyama et al. 2021 ⁴⁵	3.88 (1.11–13.6)	Multivariable (interstitial lung disease)
Haematological	Toy et al. 2012 ²⁵	0.32 (0.12–	Univariate

malignancy		0.83)	(leukaemia/lymphoma)
	Yokoyama et al. 2021 ⁴⁵	2.20 (1.04– 4.65)	Matched
Female recipient	Looney et al. 2014 (UCSF/Mayo) ²⁶	1.27 (0.76– 2.14)	Crude
	Menis et al. 2014 ³⁴	1.26 (1.16– 1.38)	Multivariable (claims)
	Clifford et al. 2015 ³³	0.87 (0.48– 1.57)	Crude
	Wang et al. 2026 ⁵²	0.86 (0.45– 1.63)	Crude

**Published asymmetric interval from penalised regression; in the meta-analysis the standard error was derived from the full interval width, which down-weights this estimate.*

Donor- and transfusion-related risk factors

High-risk donor exposure. Exposure to plasma from female donors or to components containing donor leukocyte antibodies was strongly and homogeneously associated with TRALI (pooled OR 4.91, 2.43–9.94; $p < 0.001$; $I^2 = 0\%$). In the Amsterdam cardiac surgery cohort, the presence of antibodies in donor plasma remained the only independent risk factor after adjustment for patient factors (OR 14.2, 1.5–132). In the UCSF/Mayo cohort the risk was dose-dependent and antibody-specific: each ten-fold increase in cognate anti-HLA class II (MFI > 1500) tripled the odds (OR 3.2, 1.52–6.7) and each 100 mL of anti-HNA-positive plasma increased odds by 71% (OR 1.71, 1.18–2.5), whereas non-cognate or weak class II and class I antibodies carried little or no risk. By contrast, female-donor plasma was not associated with possible TRALI (OR 0.82, 0.29–2.3), indicating that donor factors operate predominantly in TRALI type I.^{25,27,30,36}

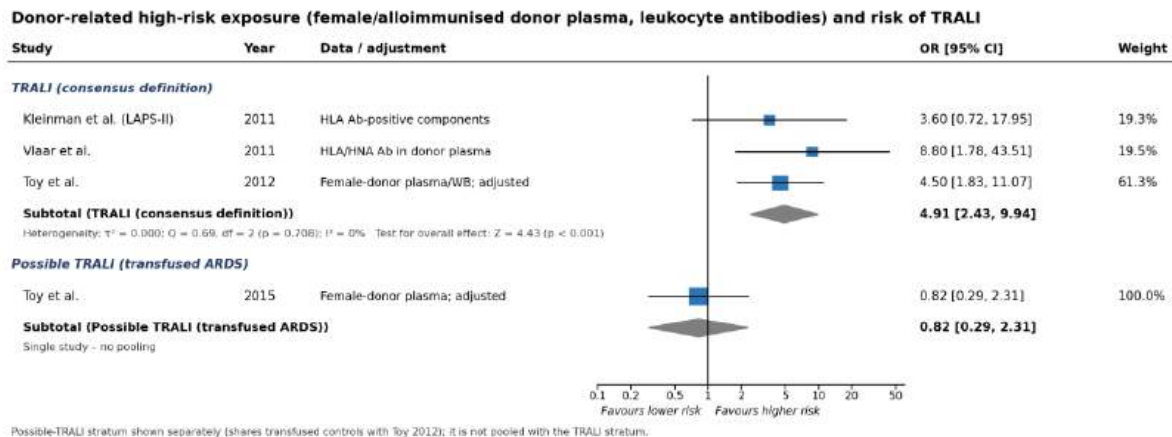


Figure 15. Forest plot of high-risk donor exposure (female or alloimmunised donor plasma, leukocyte antibody-positive components) and risk of TRALI; the possible-TRALI stratum is shown separately and not pooled.

Transfusion burden. Each additional blood component increased the odds of TRALI by 20% (pooled OR 1.20, 1.12–1.29; $I^2 = 0\%$). In non-cardiac surgery, incidence rose from 0.5% with ≤ 350 mL to 4.2% with ≥ 1401 mL transfused, and in the UCSF/Mayo cohort receiving 3–9 rather than 1–2 units was associated with an OR of 4.5; notably, after adjustment for antibody exposure and recipient factors, the residual effect of receiving more than nine units was small (OR 1.05, 0.91–1.20), indicating that the number of units acts largely as a carrier of antibody and biological-response-modifier exposure.^{25,30,33,39}

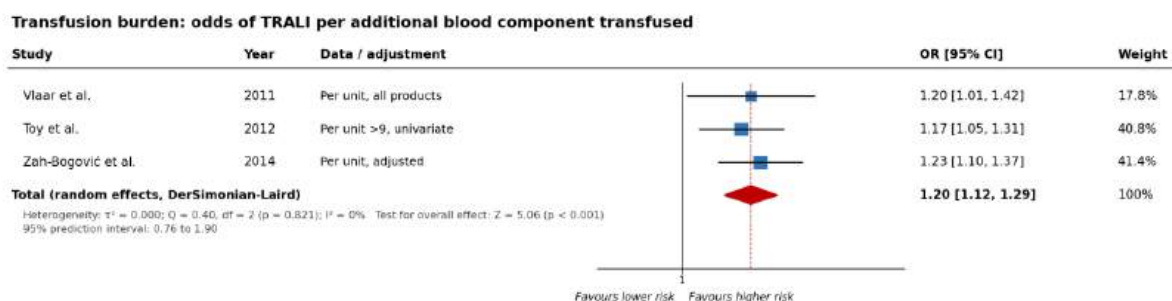


Figure 16. Forest plot of odds of TRALI per additional blood component transfused.

Plasma and platelets. Platelet exposure was associated with TRALI (pooled OR 1.74, 1.08–2.78; $I^2 = 61\%$), and any plasma-containing component increased the odds in Japan (adjusted OR 1.94, 1.10–3.42); the per-unit association for plasma was of borderline significance (OR 1.10, 0.98–1.23). In the American Red Cross programme (2006–2023), relative to red cells, the TRALI rate was approximately two-fold higher for male-predominant plasma (RR 2.13, 1.69–2.70) and plasma-suspended apheresis platelets (RR 2.72, 2.06–3.58) and more than six-fold higher for pooled whole-blood-derived platelets (RR 6.48, 3.62–11.61), whereas platelets in additive solution (RR 1.26, 0.47–3.39) and pathogen-reduced platelets in additive solution (RR 0.49, 0.16–1.52) were not associated with excess risk.^{30,35,45,51}

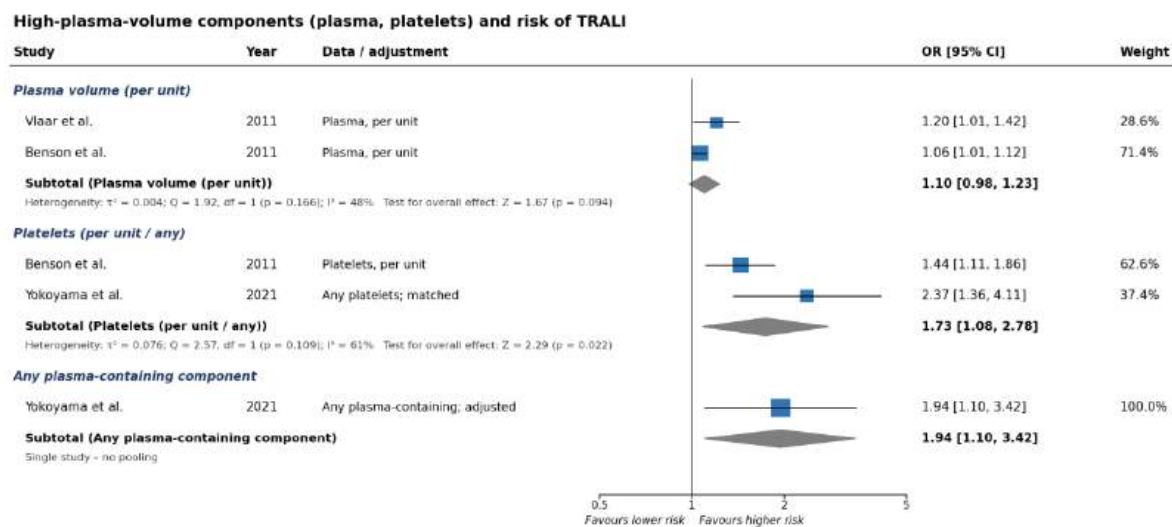


Figure 17. Forest plot of high-plasma-volume component exposure (plasma, platelets) and risk of TRALI.

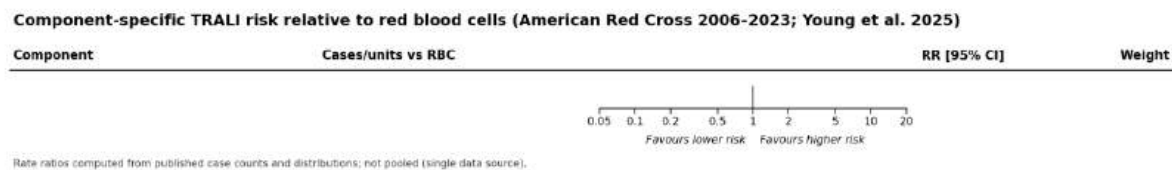


Figure 18. Component-specific TRALI risk relative to red blood cells in the American Red Cross haemovigilance system, 2006–2023.

Donor sex, storage and other donor characteristics. Across five US blood centres, the TRALI rate was 2.25 per 100,000 for female-donated versus 1.08 per 100,000 for male-donated components; between 2007 and 2013 the rate for female plasma was 33.85 versus 1.59 per 100,000 for male plasma, and after mitigation a significantly higher rate persisted only for female-donated plateletpheresis products. Group AB plasma, still partly collected from female donors, carried a 14.5-fold higher risk than group A, B and O plasma after male-predominant policies. Red cells stored for more than 14 days were associated with TRALI in cardiac surgery (OR 1.6, 1.04–2.37), but older leukoreduced red cells carried no excess risk in the UCSF/Mayo cohort, and a secondary analysis of two Dutch cohorts found no association with donor sex, age or ABO group once male-only plasma was in place.^{25,30,44,56,58}

Table 7. Donor- and transfusion-related factors: study-level evidence

Factor	Study	Effect estimate (95% CI)	Comment
Female-donor plasma/whole blood	Toy et al. 2012 ²⁵	OR 4.5 (1.85–11.2)	Adjusted for recipient factors
Cognate anti-HLA class II (MFI >1500)	Toy et al. 2012 ²⁵	OR 3.2 (1.52–6.7) per 10-fold	Dose-dependent; class I not significant
Anti-HNA (GIFT-positive) volume	Toy et al. 2012 ²⁵	OR 1.71 (1.18–2.5) per 100 mL	Dose-dependent
Donor HLA/HNA antibodies present	Vlaar et al. 2011 ³⁰	OR 8.8 (1.8–44); adjusted 14.2 (1.5–132)	Only independent factor after adjustment
HLA antibody-positive components	Kleinman et al. 2011 ³⁶	OR 3.6 (0.7–17.4)	TRALI 0.59% vs 0.16%; TACO identical (1.17 vs 1.22%)
Female-donor	Toy et al. 2015 ²⁷	OR 0.82 (0.29–	No effect in transfused

plasma (possible TRALI)		2.3)	ARDS
Total blood products, per unit	Vlaar et al. 2011 ³⁰	OR 1.2 (1.03–1.44)	Cardiac surgery
Total units, per unit	Zah-Bogović et al. 2014 ³⁹	OR 1.23 (1.10–1.37)	Possible TRALI; plus CPB duration OR 1.08
Plasma, per unit	Benson et al. 2011 ³⁵	OR 1.06 (1.00–1.11)	Liver transplantation
Platelets, per unit	Benson et al. 2011 ³⁵	OR 1.44 (1.12–1.87)	Liver transplantation
Any plasma-containing component	Yokoyama et al. 2021 ⁴⁵	OR 1.94 (1.10–3.42)	Adjusted, nationwide
RBC stored >14 days	Vlaar et al. 2011 ³⁰	OR 1.6 (1.04–2.37)	Not confirmed in UCSF/Mayo cohort
Group AB vs A/B/O plasma	Eder et al. 2013 ⁵⁶	OR 14.5 (6.8–30.9)	AB plasma from antibody-positive female donors
Female vs male donated components	Vossoughi et al. 2019 ⁴⁴	2.25 vs 1.08 per 10 ⁵	Residual risk with female plateletpheresis
Pooled WB platelets vs RBC	Young et al. 2025 ⁵¹	RR 6.48 (3.62–11.61)	No mitigation required for pooled platelets in USA
Donor sex, age, ABO	Peters et al. 2019 ⁵⁸	No association	Male-only plasma era

Clinical, laboratory and radiological characteristics

In the largest prospective cohort, patients with TRALI developed new fever ($\geq 38^\circ\text{C}$) more often than transfused controls (32.5% vs 9.0%; OR 4.84, 2.30–10.19), a temperature rise of at least

1 °C (OR 2.79), tachycardia, tachypnoea, lower systolic and diastolic blood pressure and higher central venous pressure; 78% of previously unventilated patients required new mechanical ventilation (OR 32.2, 11.0–93.9), 32% received non-invasive ventilation and 25% needed new vasopressors (Figure 20). The mean PaO₂/FiO₂ ratio fell to 154 ± 74 mmHg at oedema onset and improved partially at 24–48 hours. Symptoms began within one hour of transfusion in 87% of confirmed Australian cases, mean onset was 117 minutes in a Korean series, and symptoms resolved after a mean of 1.4 days with supportive care in a US trauma centre.^{26,43,48,59}

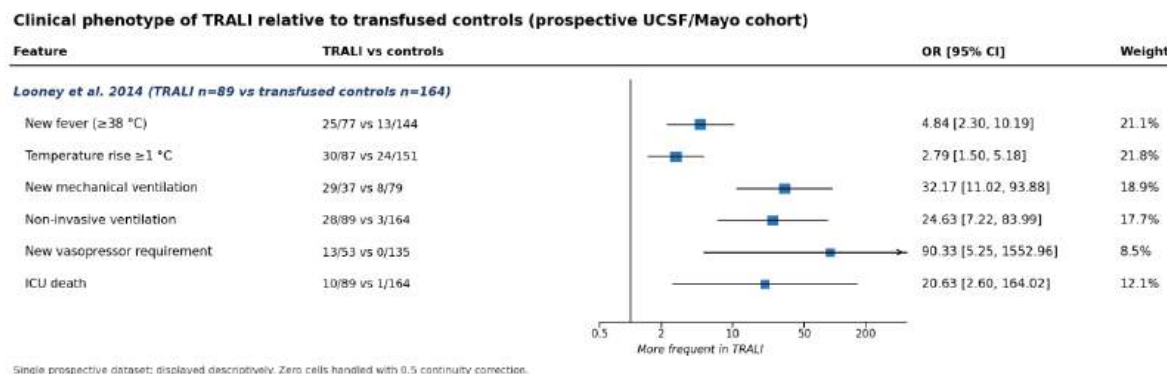


Figure 19. Clinical phenotype of TRALI relative to transfused controls in the prospective UCSF/Mayo cohort (descriptive single-study forest plot).

Radiologically, new bilateral infiltrates were documented in all cases by definition and in 100% of adjudicated cases in the Dutch ICU, Australian and Korean series. Laboratory findings included a rise in neutrophils at 24–48 hours with a fall in platelet count, occasional transient leukopenia, elevated pre-transfusion interleukin-8 (OR 3.0 per ten-fold increase), post-transfusion increases in IL-8, IL-10 and IL-1 receptor antagonist, and in cardiac surgery, elevated bronchoalveolar lavage IL-6, IL-8, elastase- α 1-antitrypsin and thrombin-antithrombin complexes with suppressed fibrinolysis due to increased plasminogen activator inhibitor-1. In acute massive haemorrhage, neutrophil extracellular trap markers (citrullinated histone H3, myeloperoxidase, neutrophil elastase) were independent predictors, and a combined model achieved an area under the curve of 0.85 (Table 10). Under the 2019 redefinition, the majority of recently reported cases were TRALI type II (pooled 69.2%, 49.4–83.8).^{25,26,31,47,48,52,59}

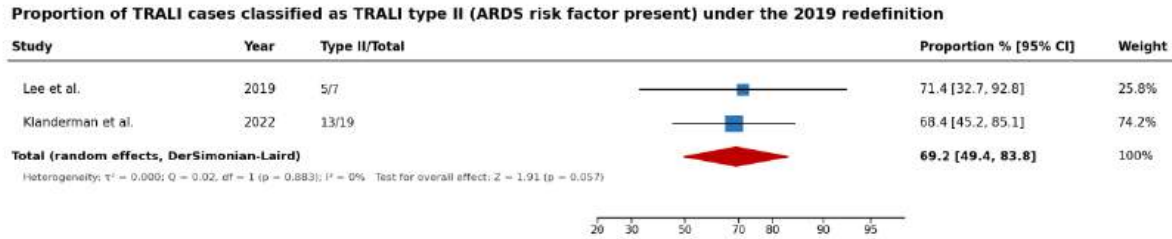


Figure 20. Proportion of TRALI cases classified as TRALI type II under the 2019 consensus redefinition.

Table 8. Clinical course and outcomes of patients with TRALI across studies

Study	TRALI n	Mortality	Mechanical ventilation	ICU	Hospital LOS	Other features
Vlaar 2011 ³⁰	16	13% vs 0% (transfused) and 3% (non- transfused)	—	—	—	Older age, longer CPB
Looney 2014 ²⁶	89	15/89 (17%) vs 7/164 (4%); ICU death 10/89	New MV 29/37 (78%); NIV 28/89	—	—	Fever 32.5%; new vasopressors 13/53
Clifford 2015 ³³	45	13/45 (28.9%) vs 81/3193 (2.5%)	—	ICU LOS 11.2 vs 5.9 d	12.3 vs 6.6 d	Risk rises with volume
Benson 2011	7	2/7 (28.6%)	—	ICU	—	Plasma/platelets

³⁵		vs 15/518 (2.9%)		LOS 2 vs 0 d		implicated
Teofili 2014 ³⁷	14	0/14	None >96 h	ICU 5/14 vs 5/57	Longer post- partum stay	Hypertensive disorders
Mulder 2015 ³²	21	Higher than controls	Longer duration	PICU	—	Sepsis, ventilation
Kumar 2016 ⁴⁰	9	0/9	6/9	—	—	Off-label hydrocortisone in all
Jamil 2017 ⁴¹	11	7/11 (63.6%)	—	PICU	—	Onset 2.73 ± 1.67 h
Yokoyama 2021 ⁴⁵	72	15/72 (20.8%) vs 48/288 (16.7%)	Intubation 19/72 vs 24/288	33/72 vs 65/288	—	Corticosteroids 77.8%
McVey 2021 ⁴⁶	19	6/19 (32%); median time to death 3 d	—	—	—	TACO mortality 18%
Klanderman 2022 ⁴⁷	19	ICU death 13/19 (68%) vs 22% of plasma recipients	All ICU	ICU LOS 8 vs 3 d	11–14 d	Type II 68%

Sivakaanthan 2022 ⁴⁸	30	0/30	Invasive ventilation 10/30	6/30	—	Onset <1 h 87%
Kazakova 2025 ⁴⁹	2237	32.3% vs 11.4% all transfused; TACO 16.1%	—	—	16.5 ± 17.2 vs 9.6 ± 13.5 d	Highest mortality among reactions
Liu 2025 ⁵⁰	4	1/4	3/4 (40–105 h)	—	—	Hypotension, temperature rise

Table 9. Laboratory, biomarker and radiological characteristics of TRALI

Domain	Study	Principal finding
Oxygenation	Looney 2014 ²⁶ ; Roubinian 2017 ²⁸	PaO ₂ /FiO ₂ 154 ± 74 at onset vs 413 ± 73 in controls; similar to TACO (143 ± 72 vs 139 ± 64)
Chest imaging	Klanderman 2022 ⁴⁷ ; Sivakaanthan 2022 ⁴⁸ ; Lee 2019 ⁵⁹	Bilateral infiltrates in 100% of adjudicated cases
Haematology	Looney 2014 ²⁶	Neutrophilia at 24–48 h; platelet fall; transient leukopenia in 2 cases
Inflammatory cytokines	Toy 2012 ²⁵ ; Looney 2014 ²⁶	Pre-transfusion IL-8 OR 3.0 per 10-fold; post-transfusion ↑ IL-8, IL-10, IL-1Ra
Alveolar inflammation, coagulation	Vlaar 2012 ³¹	Pre-onset systemic IL-6/IL-8 ↑; BAL IL-6, IL-8, elastase-α1-AT, TATc ↑; PAI-1 ↑ with suppressed fibrinolysis
Natriuretic	Roubinian 2017 ²⁸ ;	BNP 271 (137–638) pg/mL in TRALI vs

peptides	Roubinian 2020 ²⁹	1934 (1552–3000) in TACO; cut-off 750 pg/mL: sensitivity 88%, specificity 81%; pre-transfusion NT-proBNP not elevated in TRALI (p = 0.31)
Neutrophil extracellular traps	Wang 2026 ⁵²	citH3 (OR 1.142), MPO (OR 5.017), NE (OR 1.014) independent predictors; IL-6, IL-1 β , TNF- α , IL-8 $\uparrow$; AUC 0.85
Echocardiography, fluid balance	Klanderman 2022 ⁴⁷ ; Roubinian 2017 ²⁸	Impaired LV function in 20–33% of examined patients; median pre-oedema fluid balance 1.5 L (TRALI) vs 2.0 L (TACO)
Donor serology	Funk 2012 ⁵⁴ ; Ozier 2011 ⁵⁵ ; Liu 2025 ⁵⁰	Immune (HLA class I/II, HNA) mechanism in 60–75%; reverse TRALI by recipient antibody described

Immunological and non-immunological mechanisms

Among investigated cases with complete donor serology, an antibody-mediated mechanism was identified in a pooled 68.7% (95% CI 56.1–79.1; $I^2 = 39\%$): 75% of 80 confirmed German cases, 60% of 50 French cases with complete serology and three of four Chinese surgical cases, one of which was attributed to recipient antibodies against donor HLA-A*24 (reverse TRALI). Implicated donors were overwhelmingly women (64 of 68 in Germany). Non-immune TRALI accounted for one-quarter of German cases and for an increasing proportion of recent Australian cases after donor mitigation, consistent with a residual role for storage-related biological response modifiers and recipient priming.^{48,50,54,55}

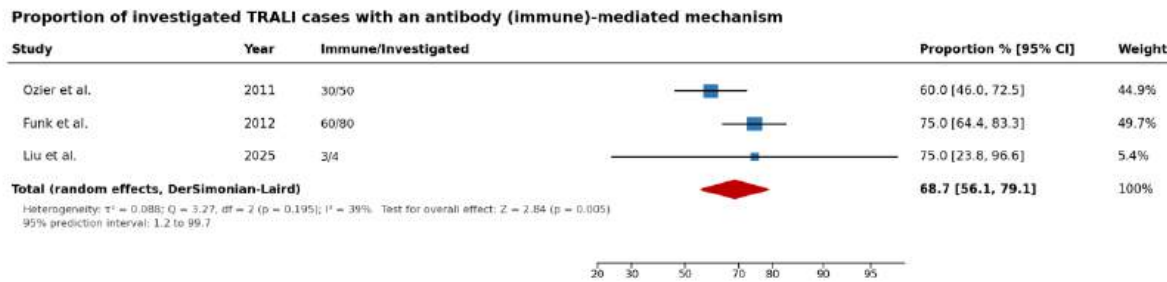


Figure 21. Pooled proportion of investigated TRALI cases with an antibody (immune)-mediated mechanism.

Table 10. Evidence for immunological and non-immunological mechanisms of TRALI

Mechanism	Clinical evidence from included studies	Interpretation
Donor anti-HLA class II and anti-HNA (cognate)	Dose-dependent ORs 3.2 per 10-fold (class II) and 1.71 per 100 mL (HNA) ²⁵ ; antibody presence OR 14.2 adjusted ³⁰ ; antibody-positive components OR 3.6 ³⁶	Strongest single 'second hit'; drives TRALI type I
Donor anti-HLA class I	Little or no independent risk ²⁵	Lower clinical relevance than class II/HNA
Immune proportion in haemovigilance	75% ⁵⁴ ; 60% ⁵⁵ ; 3/4 ⁵⁰	Majority of investigated cases remain antibody-associated
Residual risk after mitigation	Female plateletpheresis ⁴⁴ ; AB plasma ⁵⁶ ; pooled WB platelets ⁵¹	Plasma-rich products from alloimmunised donors still implicated
Non-antibody (storage, BRMs)	RBC >14 days OR 1.6 ³⁰ but no effect of older leukoreduced RBC ²⁵ ; washed RBC did not reduce	Inconsistent; likely relevant only in heavily primed recipients

	lung-injury biomarkers ⁶² ; TRALI still occurs with SDP ⁴⁷	
Recipient priming	Pre-transfusion IL-8 ²⁵ ; systemic inflammation and neutrophil sequestration before onset ³¹ ; NET markers ⁵² ; shock/sepsis OR 2.54 (this review)	Essential first hit, dominant in type II/possible TRALI ²⁷

Comparison of TRALI with TACO

In a case-control comparison, TACO patients more often had chronic heart failure (45% vs 24%), coronary artery disease (36% vs 14%) and age ≥ 70 years (32% vs 19%), whereas 38% of TRALI patients versus none of the TACO patients had received plasma or whole blood from female donors (Figure 23). Post-transfusion BNP was markedly lower in TRALI (median 271 vs 1934 pg/mL), and a multivariable model including age >70 years, BNP >1000 pg/mL and a fluid balance >3 L in the 24 hours before transfusion distinguished TACO or possible TRALI from TRALI (OR 14.1, 40.3 and 64, respectively; area under the curve 0.88; negative predictive value 91%). Pre-transfusion NT-proBNP was elevated in TACO and transfused ARDS but not in TRALI. In recipients of HLA-antibody-positive versus antibody-negative components, TACO incidence was identical (1.17% vs 1.22%), underlining its non-immune nature.^{28,29,36}

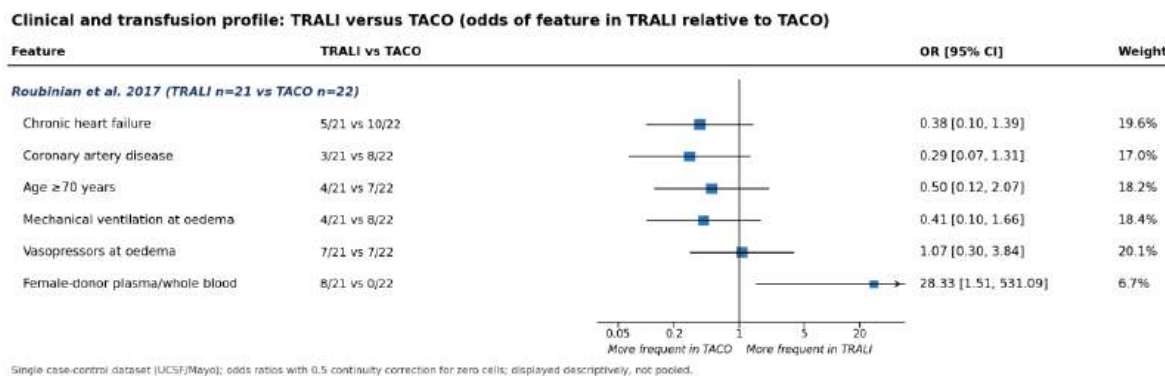


Figure 22. Clinical and transfusion profile of TRALI versus TACO (descriptive single-study forest plot).

Prognostically, TRALI carried higher in-hospital mortality than TACO (pooled OR 2.48, 2.20–2.80; $I^2 = 0\%$) : 32.3% versus 16.1% in 3.45 million US transfusion hospitalisations and 32% versus 18% in a Canadian haemovigilance network, where deaths after TRALI also occurred earlier (median 3 vs 16 days). Hospital length of stay was 4.8 days longer after TRALI than after TACO (MD 4.80, 3.98–5.62). In paediatric non-cardiac surgery, however, TACO (3.4%) was more frequent than TRALI (1.2%).^{42,46,49}

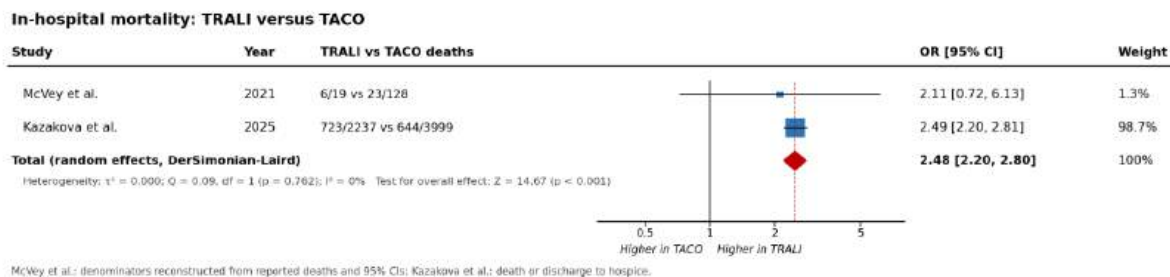


Figure 23. Forest plot of in-hospital mortality in TRALI versus TACO.

Table 11. Distinguishing features of TRALI and TACO synthesised from the included studies

Feature	TRALI	TACO
Mechanism	Permeability (non-hydrostatic) oedema; immune or non-immune two-hit ²⁵	Hydrostatic oedema from volume/left-atrial hypertension; not antibody-related ³⁶
Typical recipient	Younger; inflammatory first hit (shock, sepsis, liver/lung disease) ^{25,45}	Older; heart failure, coronary disease, renal failure; positive fluid balance ²⁸
Blood pressure, temperature	Hypotension, fever in about one-third ²⁶	Hypertension typical; fever may occur
Natriuretic peptides	BNP median 271 pg/mL; NT-proBNP not elevated pre-transfusion ^{28,29}	BNP median 1934 pg/mL; >1000 pg/mL in 84% ²⁸
Donor factors	Female/alloimmunised plasma	None (0%) ²⁸

	in 38% ²⁸	
Mortality	32% (OR 2.48 vs TACO) ^{46,49}	16–18% ^{46,49}
Hospital LOS	16.5 ± 17.2 days ⁴⁹	11.7 ± 13.4 days ⁴⁹
Management	Supportive, lung-protective ventilation; avoid diuretics if hypovolaemic; donor work-up	Diuretics, slower transfusion, reduced volume

Clinical outcomes

Mortality. Six studies compared in-hospital mortality between TRALI patients and transfused controls. TRALI was associated with a five-fold increase in the odds of death (pooled OR 5.22, 2.68–10.17; $p < 0.001$; $I^2 = 84\%$; 95% prediction interval 0.58–46.8). The association was strongest in retrospective clinical cohorts (OR 12.75, 7.49–21.71; $I^2 = 0\%$), intermediate in prospective active surveillance (OR 4.55, 1.78–11.62) and weakest in administrative databases (OR 2.33, 0.85–6.41), and the subgroup difference was significant ($p = 0.007$). Substituting the APACHE II-adjusted estimate (OR 3.4) for the crude estimate of the prospective cohort did not materially change the result (OR 4.99, 2.55–9.75).^{26,33,35,45,47,49}

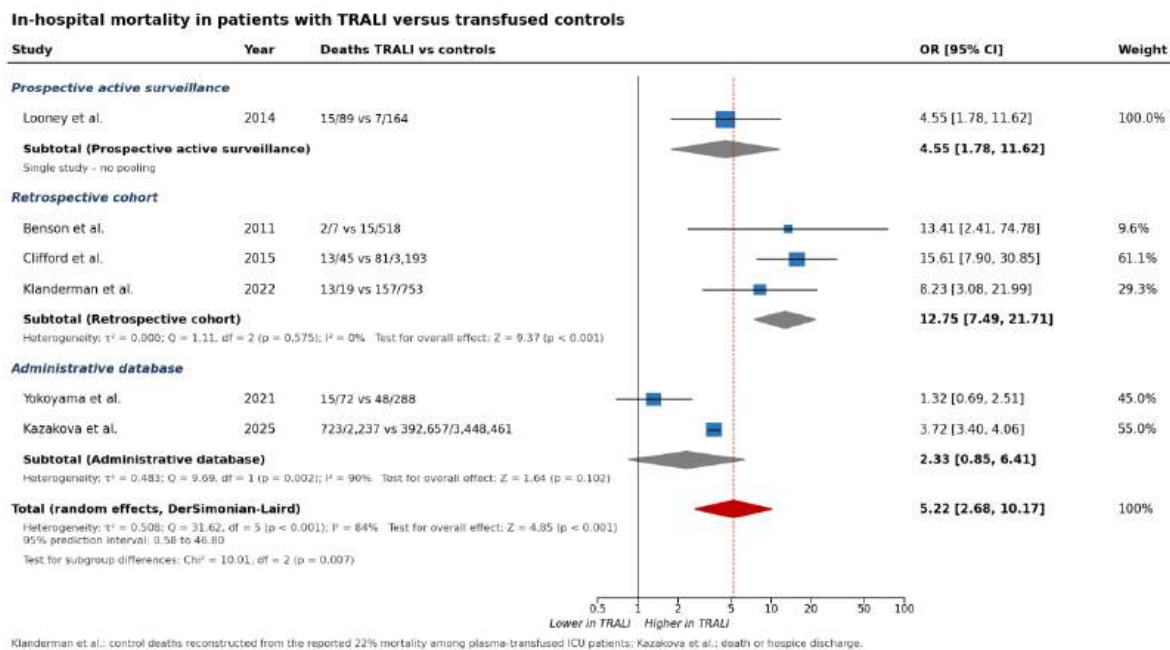


Figure 24. Forest plot of in-hospital mortality in patients with TRALI versus transfused controls, stratified by data source.

The pooled in-hospital case-fatality among 2,572 patients with TRALI from 13 studies was 27.3% (19.5–36.8; $I^2 = 71\%$) (Figure 26), ranging from 16.3% in prospective active surveillance to 38.3% in retrospective clinical cohorts, 27.5% in administrative databases and 9.2% in haemovigilance series (subgroup $p = 0.090$). Case-fatality was highest in critically ill populations, reaching 68% in Dutch ICUs and 63.6% in a Pakistani paediatric ICU, whereas no deaths occurred among confirmed cases in Kuwaiti, Australian and Italian obstetric series.^{37,40,41,47,48}

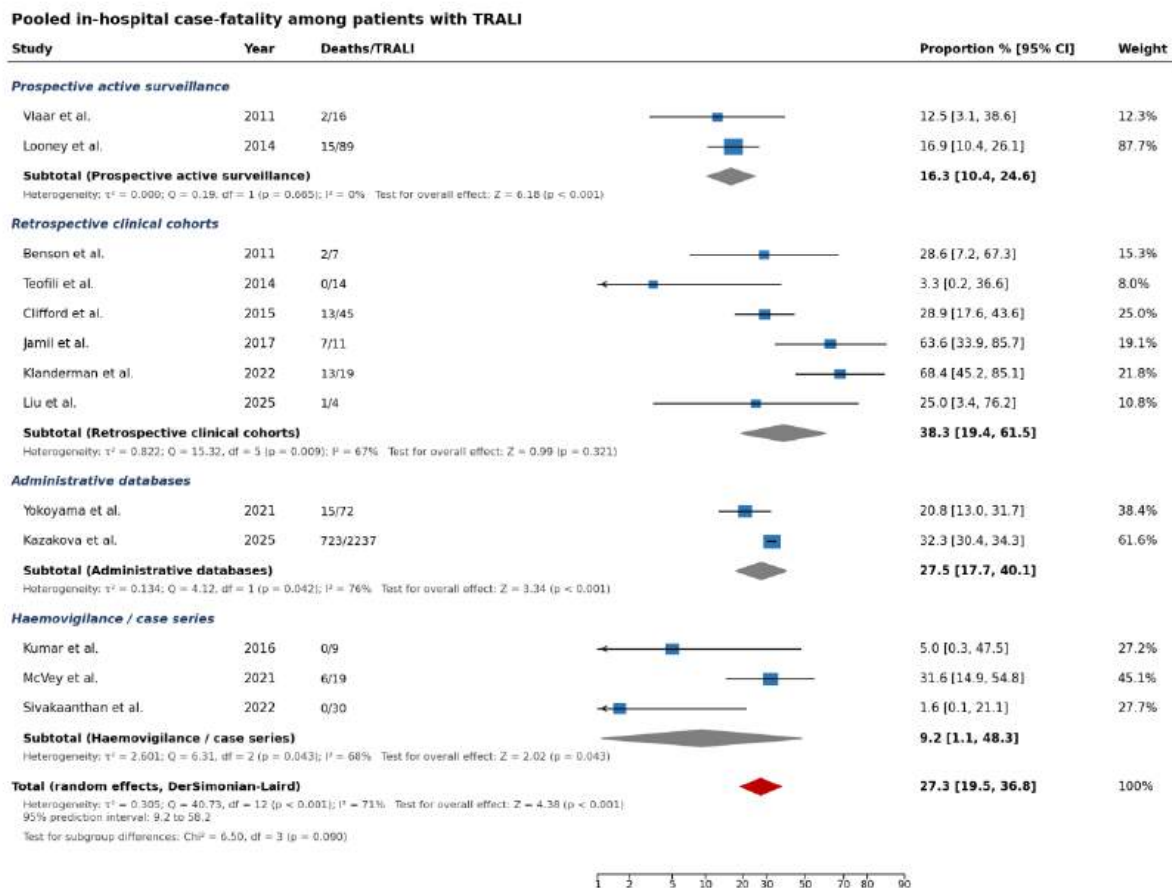


Figure 25. Forest plot of pooled in-hospital case-fatality among patients with TRALI, stratified by data source.

Mechanical ventilation and ICU care. A pooled 53.6% (28.2–77.2; $I^2 = 86\%$) of patients with TRALI required invasive mechanical ventilation, and the odds of requiring ventilation were substantially higher than in transfused controls (OR 10.8, 1.38–84.2; $I^2 = 91\%$). ICU admission was three-fold more likely (OR 3.16, 1.91–5.24; $I^2 = 0\%$). In Japan, 77.8% of TRALI patients received systemic corticosteroids and 36.1% received sivelestat, reflecting the absence of an evidence-based specific therapy.^{26,37,40,45,48,50}

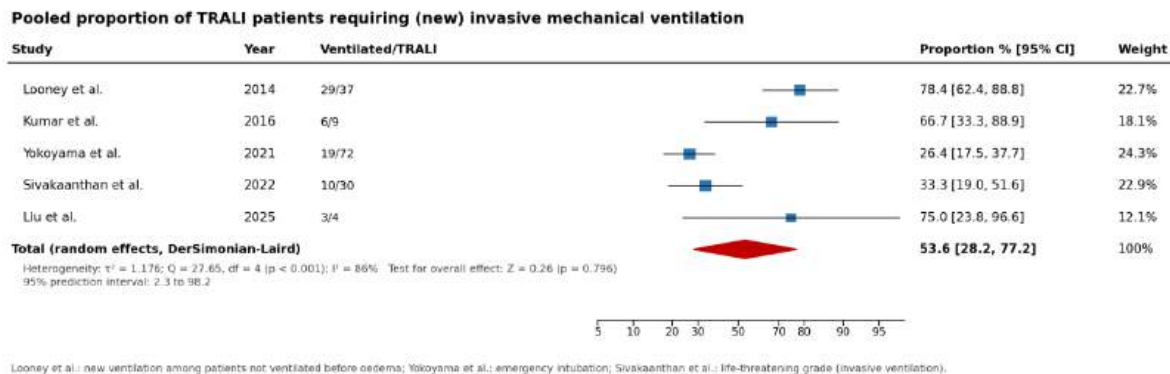


Figure 26. Pooled proportion of patients with TRALI requiring (new) invasive mechanical ventilation.

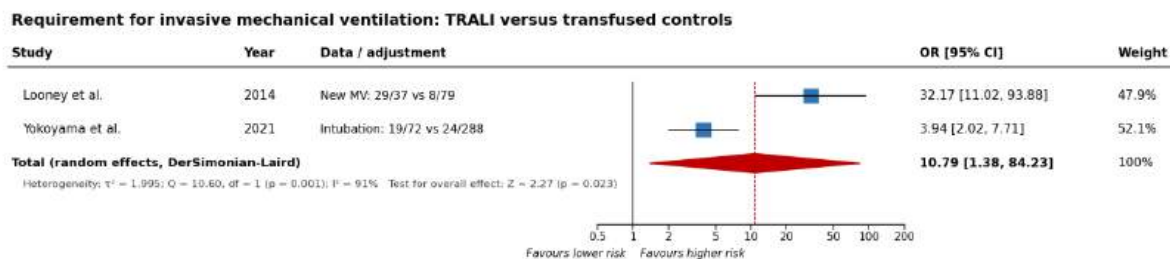


Figure 27. Forest plot of the requirement for invasive mechanical ventilation in TRALI versus transfused controls.

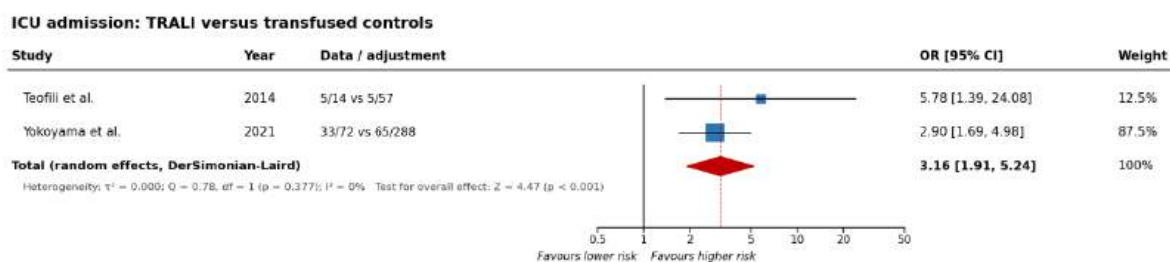


Figure 28. Forest plot of ICU admission in TRALI versus transfused controls.

Length of stay. TRALI prolonged hospital stay by a mean of 6.9 days (MD 6.89, 6.20–7.59; $I^2 = 0\%$) and ICU stay by 5.2 days (MD 5.16, 1.60–8.72; $I^2 = 0\%$) relative to transfused controls. Within TRALI patients, liver transplantation and higher pre-transfusion fluid balance were

associated with shorter ICU stay and ventilation, whereas the quantity of cognate anti-HLA class II antibody was associated with longer ICU stay.^{26,33,35,47,49}

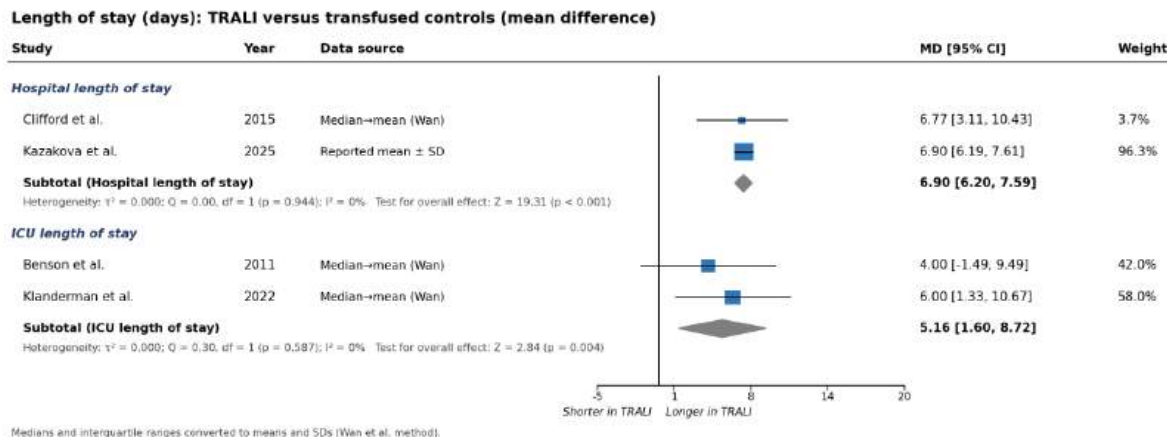


Figure 29. Forest plot of hospital and ICU length of stay (mean difference in days) in TRALI versus transfused controls.

Treatment. In the only treatment RCT, 80 critically ill patients with TRALI were randomised to high-dose intravenous ascorbic acid (2.5 g every 6 hours for 96 hours) or placebo; ascorbic acid increased IL-10 and superoxide dismutase and reduced IL-8 (11.8 ± 7.3 vs 35.5 ± 19.8 pg/mL), C-reactive protein and malondialdehyde, but clinical end points could not be pooled.⁶³

Effect of mitigation strategies

Four comparisons evaluated risk-mitigation strategies. Overall, mitigation was associated with a 43% non-significant reduction in TRALI incidence (pooled RR 0.57, 0.28–1.18; $I^2 = 60\%$). Male-predominant plasma reduced TRALI per unit by 69% at two academic centres (RR 0.31) but not the combined TRALI/possible TRALI incidence in non-cardiac surgery (RR 1.11), solvent/detergent pooled plasma halved the per-unit incidence in Dutch ICUs without reaching significance (RR 0.53, 0.21–1.29), and point-of-care washed red cells were tested in only 154 cardiac surgical patients (RR 0.30, 0.01–7.27). Haemovigilance data were consistent with a substantial benefit: male-only quarantine plasma reduced Dutch TRALI cases by 33%, the German FFP-related immune TRALI rate fell from 12.71 to 0 per million units, plasma-associated TRALI at

the American Red Cross fell from 18.6 to 4.2 per million units, and conversion to low-risk plasma eliminated plasma-associated TRALI in three US hospitals (0.0084% to 0).^{25,33,47,53,54,56,60–62}

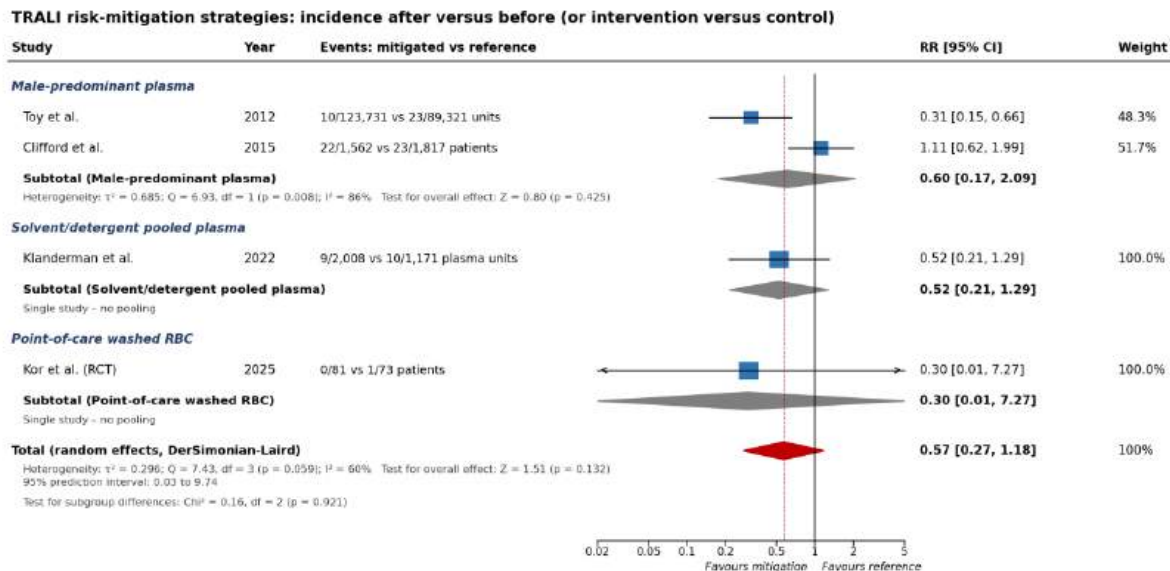


Figure 30. Forest plot of TRALI risk-mitigation strategies (incidence after vs before, or intervention vs control).

Overview, heterogeneity, sensitivity analyses and publication bias

Heterogeneity was high for incidence, mortality and the proportion requiring ventilation, moderate for shock/sepsis, smoking and lung disease, and absent for donor antibody exposure, transfusion burden, female recipient sex, ICU admission and length of stay. In leave-one-out analysis, the pooled mortality OR ranged from 3.88 (omitting Clifford et al.) to 7.16 (omitting Yokoyama et al.) and always remained significant; the cumulative meta-analysis showed that the association had been significant since the first study in 2011 and stabilised at an OR of 5–6 from 2014 onwards. There was no evidence of small-study effects for mortality (Egger intercept 1.02, $p = 0.49$; Begg $p = 0.47$; trim-and-fill imputed no studies) or for case-fatality (Egger $p = 0.23$). Funnel-plot asymmetry for incidence (Egger $p = 0.012$) reflects the systematically higher incidence in small, high-risk active-surveillance cohorts rather than publication bias.^{33,45}

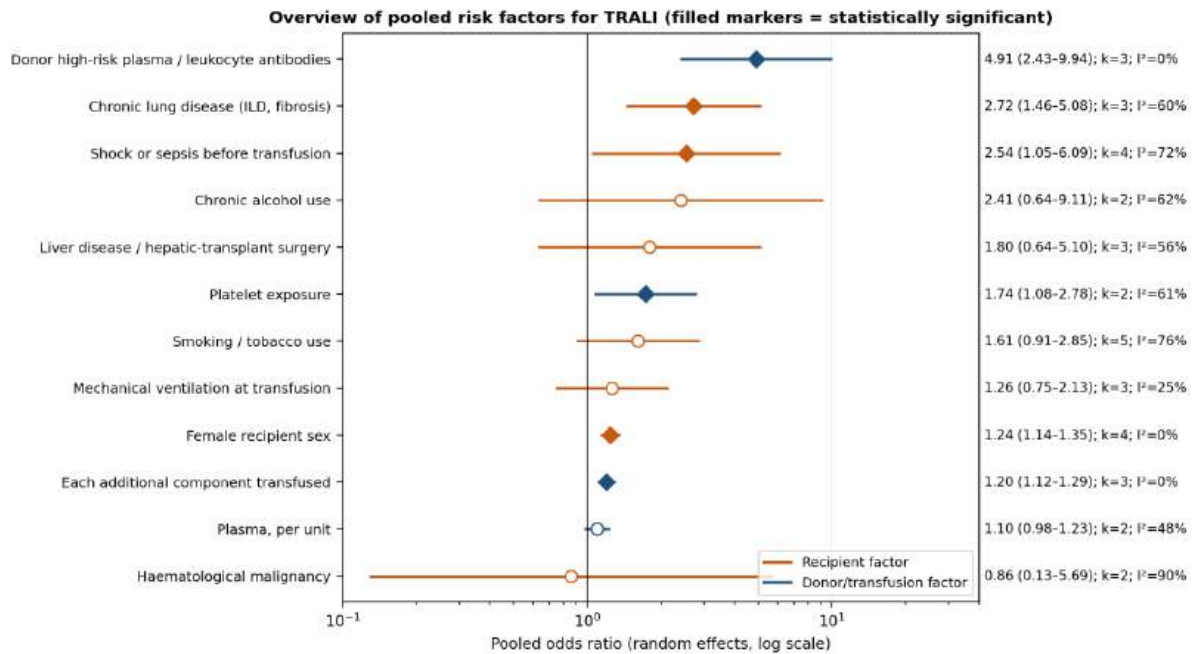


Figure 31. Overview of pooled odds ratios for recipient and donor/transfusion risk factors for TRALI.

Table 12. Summary of all meta-analyses (DerSimonian–Laird random effects)

Outcome / exposure	k	Measure	Pooled estimate (95% CI)	p	I ² (%)	τ ²	95% prediction interval
Incidence – high-risk/critical care	8	%	4.47 (2.29–8.56)	—	94	0.932	0.38 to 36.68
Incidence – general peri-operative/hospital	5	%	0.410 (0.113–1.471)	—	90	1.812	0.004 to 32.621
Incidence – administrative databases	3	%	0.017 (0.007–0.045)	—	100	0.693	0.000 to 97.260
Rate per 10 ⁵	5	rate	1.88 (0.46–	—	99	—	—

components			7.66)				
Shock or sepsis	4	OR	2.54 (1.05–6.09)	0.037	72	0.575	0.06 to 112.11
Chronic alcohol use	2	OR	2.41 (0.64–9.11)	0.196	62	0.621	—
Smoking / tobacco	5	OR	1.61 (0.91–2.85)	0.099	76	0.262	0.25 to 10.48
Mechanical ventilation at transfusion	3	OR	1.26 (0.75–2.13)	0.379	25	0.057	0.01 to 119.32
Liver disease / hepatic-transplant surgery	3	OR	1.80 (0.64–5.10)	0.269	56	0.469	0.00 to 109167.75
Chronic lung disease	3	OR	2.72 (1.46–5.08)	0.002	60	0.182	0.00 to 2348.67
Haematological malignancy	2	OR	0.86 (0.13–5.69)	0.876	90	1.664	—
Female recipient sex	4	OR	1.24 (1.14–1.35)	<0.001	0	0.000	1.03 to 1.50
High-risk donor plasma / leukocyte antibodies	3	OR	4.91 (2.43–9.94)	<0.001	0	0.000	0.05 to 474.09
Each additional component	3	OR	1.20 (1.12–1.29)	<0.001	0	0.000	0.76 to 1.90
Plasma, per unit	2	OR	1.10 (0.98–1.23)	0.094	48	0.004	—
Platelet exposure	2	OR	1.74 (1.08–2.78)	0.022	61	0.076	—

Antibody-mediated mechanism	3	%	68.73 (56.07–79.11)	—	39	0.088	1.24 to 99.74
TRALI type II (2019 definition)	2	%	69.21 (49.42–83.80)	—	0	0.000	—
In-hospital mortality vs transfused controls	6	OR	5.22 (2.68–10.17)	<0.001	84	0.508	0.58 to 46.80
Case-fatality	13	%	27.26 (19.46–36.77)	—	71	0.305	9.16 to 58.20
Invasive ventilation (proportion)	5	%	53.56 (28.16–77.24)	—	86	1.176	2.35 to 98.22
Invasive ventilation vs controls	2	OR	10.79 (1.38–84.23)	0.023	91	1.995	—
ICU admission vs controls	2	OR	3.16 (1.91–5.24)	<0.001	0	0.000	—
Hospital length of stay	2	MD (days)	6.89 (6.20–7.59)	<0.001	0	0.000	—
ICU length of stay	2	MD (days)	5.16 (1.60–8.72)	0.004	0	0.000	—
Mortality: TRALI vs TACO	2	OR	2.48 (2.20–2.80)	<0.001	0	0.000	—
Mitigation strategies	4	RR	0.57 (0.28–1.18)	0.132	60	0.296	0.03 to 9.74

Proportions in %, rates per 100,000 components; prediction intervals only for $k \geq 3$.

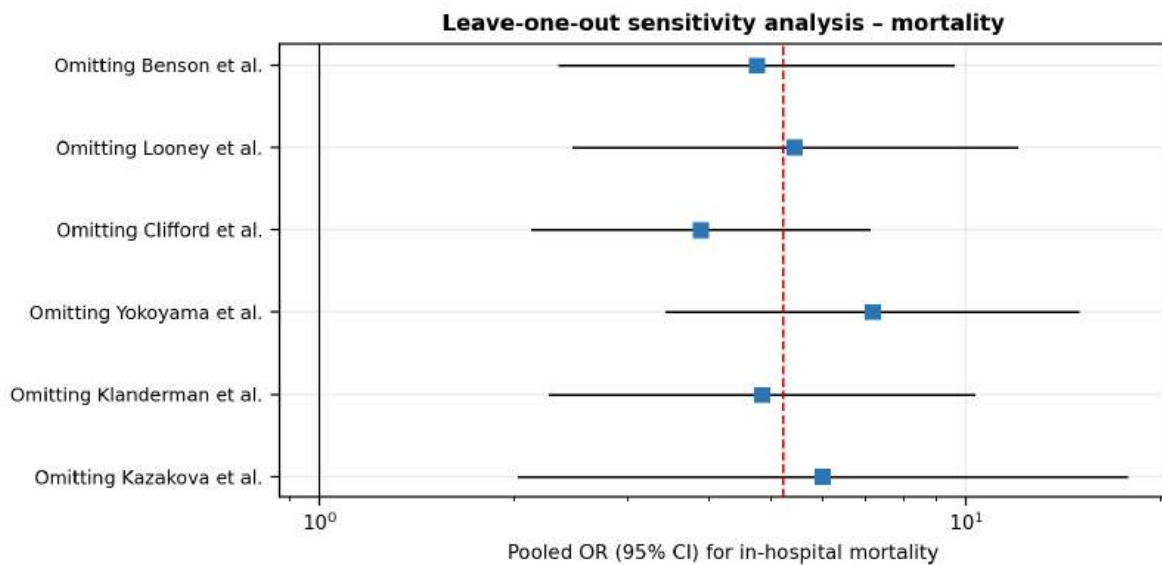


Figure 32. Leave-one-out sensitivity analysis of the pooled mortality odds ratio.

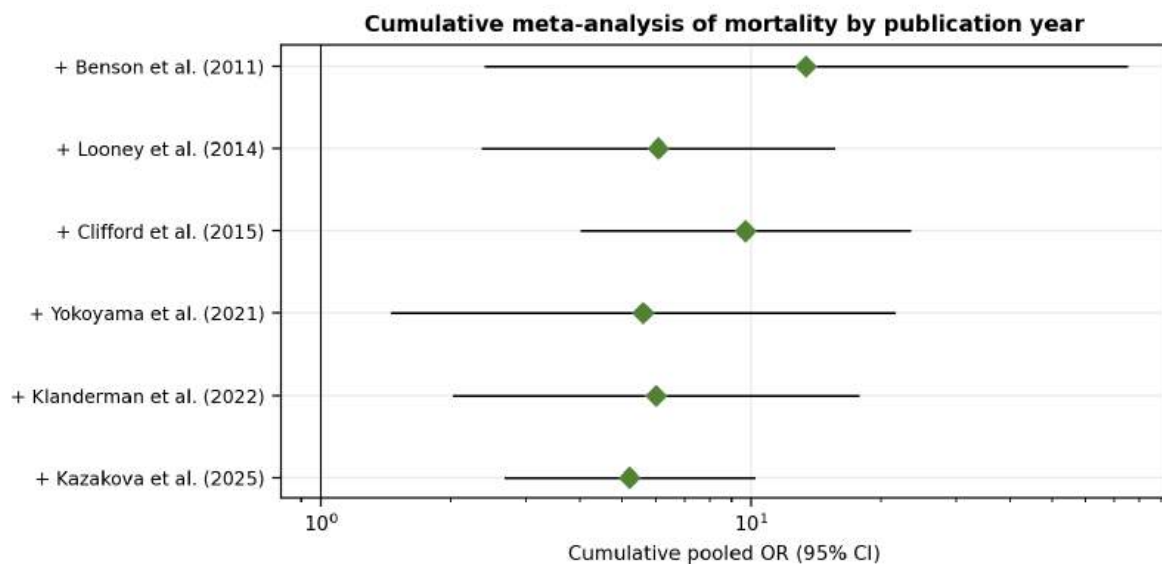


Figure 33. Cumulative meta-analysis of mortality by year of publication.

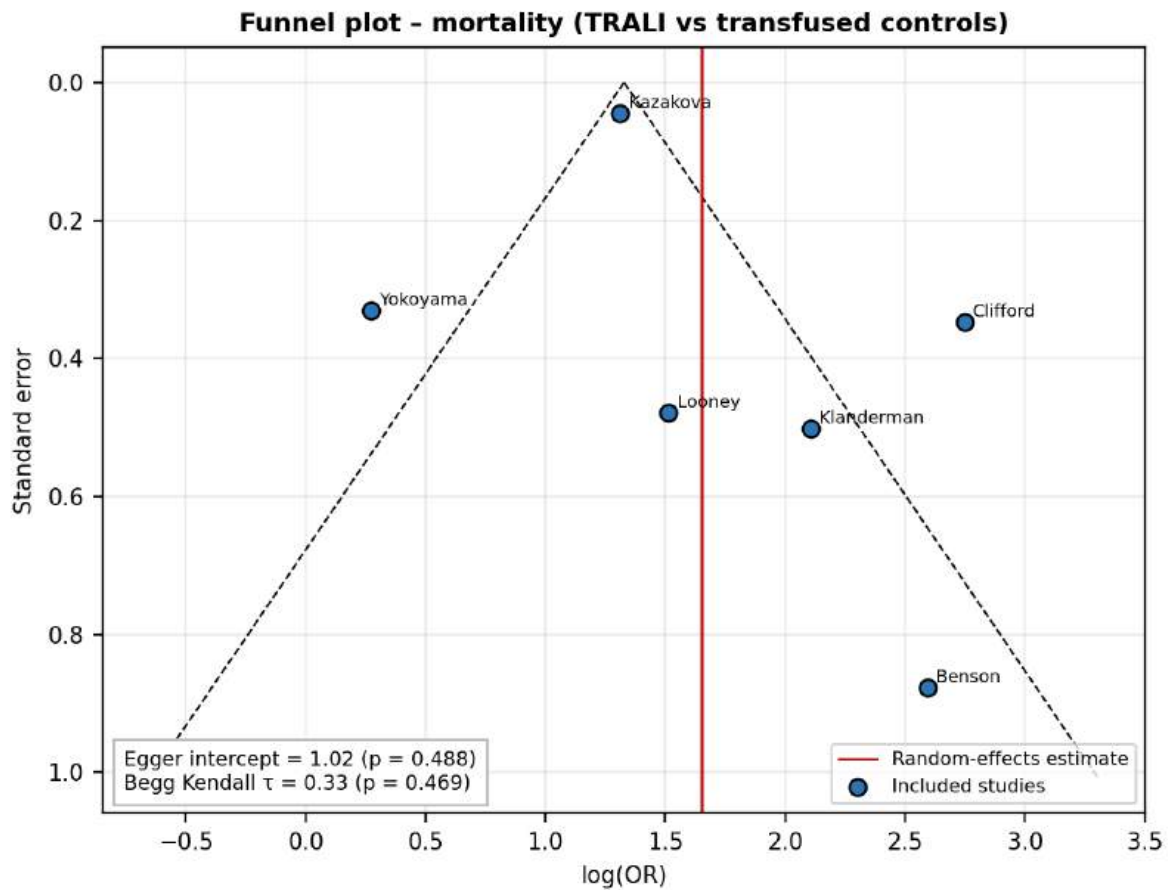


Figure 34. Funnel plot with Egger and Begg tests and trim-and-fill for mortality (TRALI vs transfused controls).

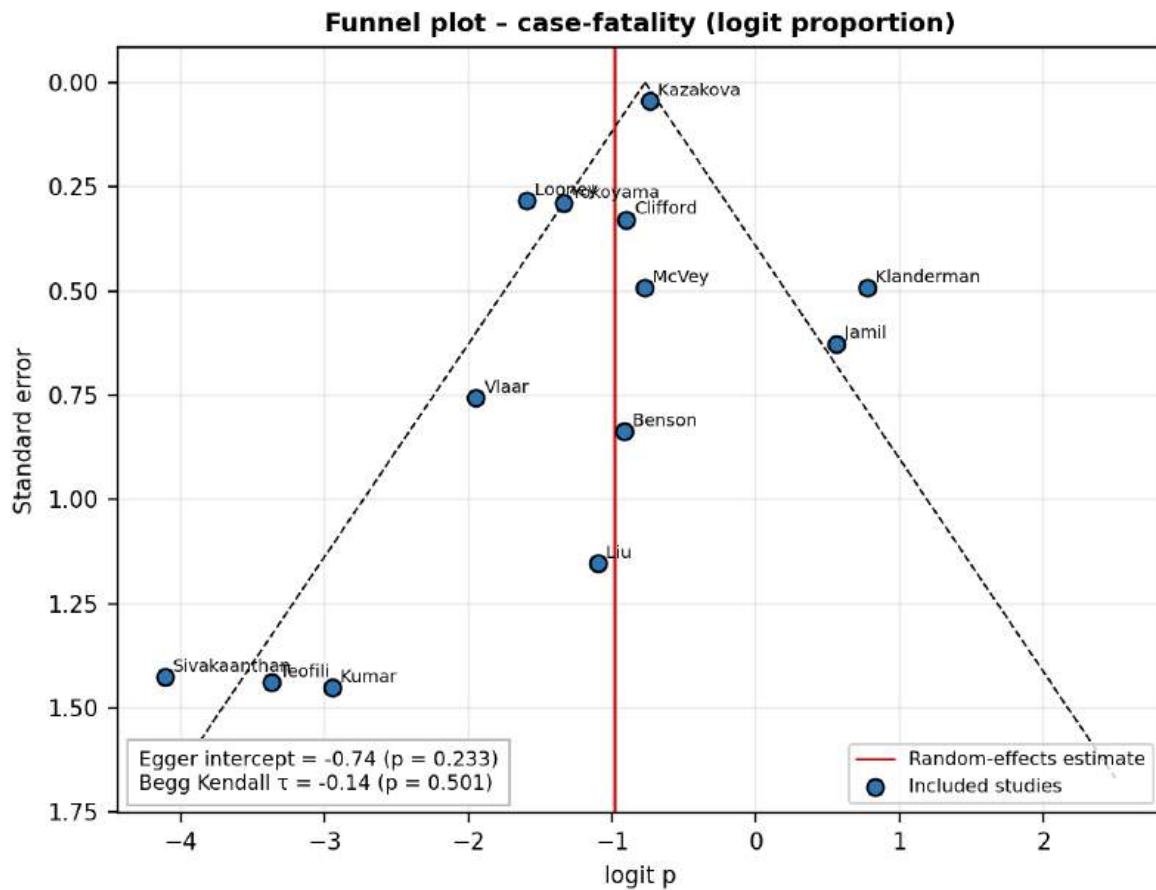


Figure 35. Funnel plot for pooled case-fatality (logit proportions).

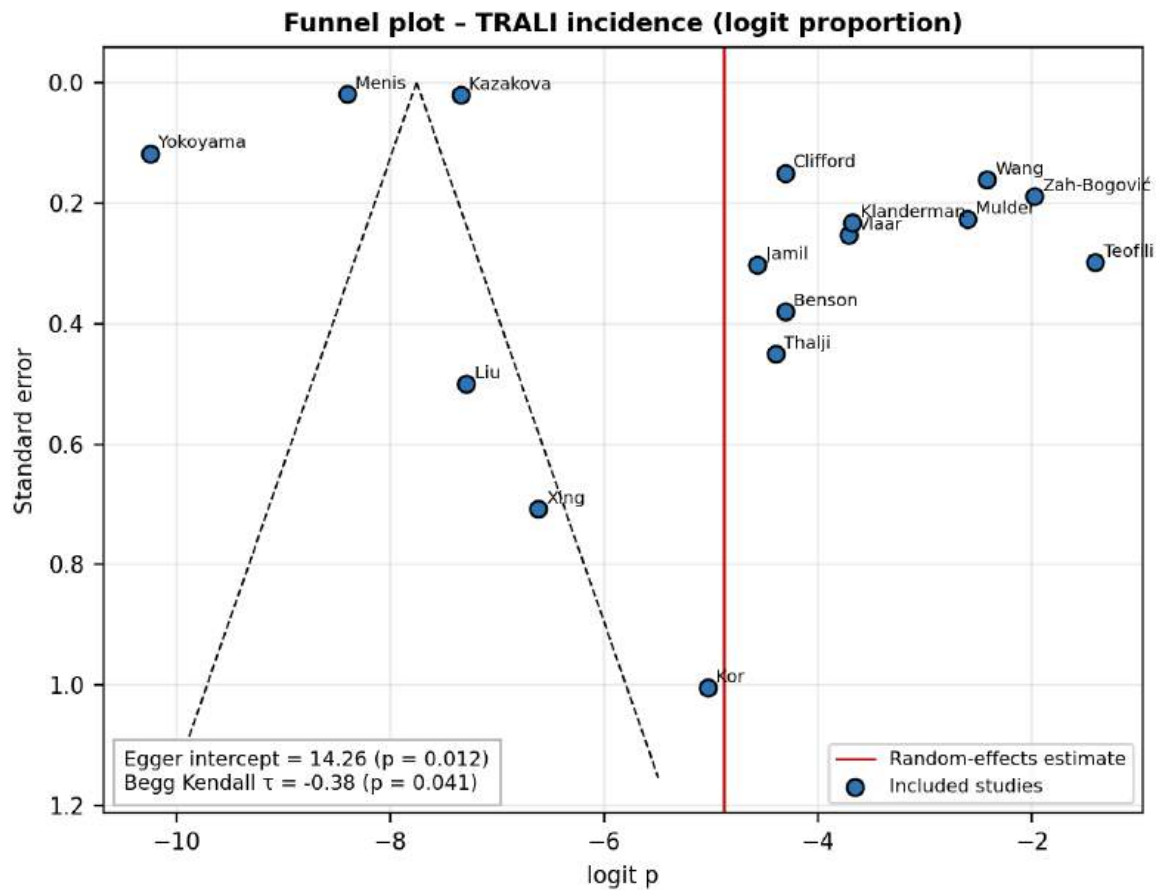


Figure 36. Funnel plot for TRALI incidence (logit proportions).

Table 13. Sensitivity, subgroup and small-study-effect analyses

Analysis	Method	Result	Interpretation
Mortality vs controls	Leave-one-out	OR range 3.88 (omitting Clifford et al.) to 7.16 (omitting Yokoyama et al.); all significant	Robust
Mortality vs controls	Adjusted estimate substituted (Looney: OR 3.4, APACHE II-	OR 4.99 (2.55–9.75)	Robust

	adjusted)		
Mortality vs controls	Cumulative meta-analysis	Significant from 2011; stable OR 5–6 since 2014 (final 5.22)	Stable over time
Mortality vs controls	Subgroups by data source	Retrospective 12.75; prospective 4.55; administrative 2.33; p 0.007	Effect modification by baseline risk
Mortality vs controls	Egger / Begg / trim-and-fill	Egger intercept 1.02 (p 0.488); Begg p 0.469; 0 studies imputed	No small-study effect
Case-fatality	Egger / Begg	Egger p 0.233; Begg p 0.501; subgroup p 0.090	No small-study effect
Incidence per patient	Egger / Begg; subgroups by setting	Egger p 0.012; Begg p 0.041; setting subgroup p <0.001	Asymmetry explained by setting
Shock vs sepsis	Subgroup difference	p 0.792	Comparable first hits
Donor exposure	Case definition (TRALI vs possible TRALI)	TRALI OR 4.91; possible TRALI OR 0.82	Donor effect confined to TRALI
Mitigation	Subgroups by strategy	p 0.921	Imprecise

Certainty of evidence

Certainty of evidence was moderate for the associations of high-risk donor exposure and transfusion burden with TRALI (large or dose-dependent effects with no heterogeneity), low for mortality, case-fatality, chronic lung disease, female recipient sex, ICU admission, length of stay and the TRALI–TACO mortality difference, and very low for shock/sepsis, mechanical ventilation

requirement, mitigation and incidence, mainly because of inconsistency, imprecision and reliance on observational or before–after designs.

Table 14. GRADE summary of findings for the main outcomes

Outcome	Studies (participants)	Pooled effect (95% CI)	Certainty	Main reasons
High-risk donor plasma/antibody exposure	3 ($\approx$ 3,500 recipients)	OR 4.91 (2.43–9.94)	⊕⊕⊕○ Moderate	Observational; upgraded for large effect and dose–response; I^2 0%
Transfusion burden (per unit)	3 ($\approx$ 1,200)	OR 1.20 (1.12–1.29)	⊕⊕⊕○ Moderate	Consistent dose–response; partly mediated by antibody exposure
Chronic lung disease	3 ($>$ 11 million stays)	OR 2.72 (1.46–5.08)	⊕⊕○○ Low	Observational; moderate heterogeneity; coded exposures
Shock or sepsis	4 ($\approx$ 1,400)	OR 2.54 (1.05–6.09)	⊕○○○ Very low	Inconsistency (I^2 72%); crude estimates in two studies
Female recipient sex	4 ($>$ 11 million stays)	OR 1.24 (1.14–1.35)	⊕⊕○○ Low	Dominated by claims data; small effect
In-hospital mortality vs controls	6 (2,469 TRALI; 3.45 million controls)	OR 5.22 (2.68–10.17)	⊕⊕○○ Low	Inconsistency (I^2 84%) offset by large, consistent effect; no small-study effect

Case-fatality	13 (2,572 TRALI)	27.3% (19.5–36.8)	⊕⊕○○ Low	Heterogeneity by data source
Mechanical ventilation vs controls	2 (≈480)	OR 10.8 (1.38–84.2)	⊕○○○ Very low	Inconsistency, imprecision
ICU admission vs controls	2 (431)	OR 3.16 (1.91–5.24)	⊕⊕○○ Low	Few studies
Hospital LOS vs controls	2 (≈3.45 million)	MD +6.9 days (6.2–7.6)	⊕⊕○○ Low	Median-to-mean conversion; administrative data
Mortality TRALI vs TACO	2 (6,383)	OR 2.48 (2.20–2.80)	⊕⊕○○ Low	Coded diagnoses; indirectness
Mitigation strategies	4 (incl. 1 RCT)	RR 0.57 (0.28–1.18)	⊕○○○ Very low	Before–after designs, imprecision, heterogeneous interventions
Incidence per transfused patient	16	0.017–4.47% by setting	⊕○○○ Very low	Extreme heterogeneity by setting/surveillance

DISCUSSION

Principal findings

This systematic review and meta-analysis of 39 studies published between 2011 and 2026 provides an integrated quantitative picture of TRALI. Five principal findings emerge. First, TRALI is far from rare in primed recipients: almost one in twenty transfused patients in critical-care and high-risk surgical or obstetric settings developed TRALI, compared with fewer than 1 in 200 in general peri-operative cohorts and fewer than 1 in 5,000 when ascertained by diagnostic codes.

Second, the strongest and most consistent risk factor was exposure to plasma from female or alloimmunised donors containing leukocyte antibodies (OR 4.91, with no heterogeneity), followed by chronic lung disease, shock or sepsis, platelet exposure and the cumulative number of components. Third, roughly two-thirds of investigated cases remain antibody-mediated even in the mitigation era, while most recently reported cases fulfil the 2019 definition of TRALI type II. Fourth, TRALI is associated with a five-fold excess in-hospital mortality, a case-fatality of about 27%, frequent need for invasive ventilation and nearly a week of additional hospitalisation. Fifth, TRALI is clinically and prognostically distinct from TACO, with lower natriuretic peptides, a different comorbidity and donor-exposure profile and approximately 2.5-fold higher mortality. Hypotheses H1 (partly), H2, H3, H4 and H5 (for the immune proportion; not statistically for pooled mitigation) were therefore supported.^{25,28,30,49}

Patient-related risk factors: the first hit

The association with shock and sepsis is consistent with the concept that systemic inflammation primes neutrophils and activates the pulmonary endothelium before transfusion. In cardiac surgery, systemic IL-6 and IL-8 were already elevated before TRALI onset, and in the UCSF/Mayo cohort pre-transfusion IL-8 independently predicted TRALI. Experimental work indicates that circulating mitochondrial DNA and other damage-associated molecular patterns, which are abundant after trauma and in stored blood products, can act as a first hit through Toll-like receptor 9, and a recent clinical study of aortic dissection surgery found that high C-reactive protein and platelet transfusion interacted synergistically to produce refractory post-operative hypoxaemia.^{25,31,64,65}

The heterogeneity of the shock/sepsis estimate ($I^2 = 72\%$) is informative rather than merely statistical. In populations in which sepsis or shock is nearly universal or in which TRALI is ascertained from codes, the contrast between cases and controls is attenuated, and the 2019 redefinition reclassifies patients whose respiratory status was deteriorating before transfusion as ARDS rather than TRALI. Importantly, the UCSF/Mayo investigators showed that recipient ARDS risk factors — chronic alcohol abuse, current smoking, shock and positive fluid balance — rather

than transfusion factors predominate in possible TRALI, which supports the conceptual shift towards the term transfused ARDS for many of these cases.^{4,27}

Chronic alcohol use and smoking were independent predictors in the best-adjusted cohort but did not reach significance when pooled with crude estimates. Biologically, chronic alcohol exposure impairs alveolar epithelial barrier function and glutathione homeostasis, and tobacco smoke primes alveolar macrophages and neutrophils; both are established ARDS risk modifiers. Our findings confirm the direction reported by Hu and colleagues (pooled ORs 3.82 for both factors) but indicate that the magnitude is smaller and less certain when larger, more heterogeneous cohorts are included.^{21,25,52}

Chronic lung disease emerged as a novel and consistent risk factor (OR 2.72). Interstitial lung disease and post-inflammatory pulmonary fibrosis are characterised by endothelial dysfunction, reduced alveolar reserve and a pro-inflammatory milieu, which may lower the threshold for clinically overt permeability oedema after an otherwise sub-threshold transfusion insult. This finding has practical relevance because patients with fibrotic lung disease frequently receive transfusions during exacerbations, surgery or haematological complications.^{34,39,45}

Liver disease and liver surgery appear to be important risk states, as end-stage liver disease combines a high plasma requirement, endotoxaemia, complement and endothelial activation and, during transplantation, ischaemia–reperfusion injury. The pooled estimate was not significant because one of the three studies used coded liver dysfunction in a nationwide database. In liver transplantation, only plasma and platelets — not red cells — were associated with TRALI, supporting the use of viscoelastic-guided haemostatic therapy to minimise plasma exposure.^{25,35,45}

The contradictory findings for haematological malignancy illustrate the complexity of the two-hit model. Profound neutropenia may protect against neutrophil-dependent TRALI, which is consistent with the lower odds observed in the UCSF/Mayo cohort among patients with leukaemia or lymphoma, low platelet counts or immunosuppression. Conversely, haematology patients receive large numbers of plasma-rich platelet concentrates and are over-represented in haemovigilance reports. The net effect probably depends on neutrophil count, inflammatory status and platelet exposure, and should be examined in dedicated haematology cohorts.^{25,45,48,55}

Mechanical ventilation per se was not associated with TRALI, but high peak airway pressure was. Experimental data show that injurious ventilation lowers the antibody titre required to induce lung injury, and clinical guidance for transfusing ventilated patients emphasises lung-protective ventilation and avoidance of hypervolaemia. The small excess risk in female recipients was driven by Medicare claims and may reflect recipient alloimmunisation from pregnancy, which can also underlie reverse TRALI caused by recipient antibodies against donor leukocytes.^{25,34,66,67}

Donor- and transfusion-related factors: the second hit

The homogeneous five-fold association with high-risk donor exposure, together with the dose-response relationship for cognate anti-HLA class II and anti-HNA antibodies, provides the strongest causal evidence in the TRALI literature. Antibodies against HLA class II and HNA-3a are clinically more relevant than those against HLA class I, which explains why a Norwegian lookback of 2,562 platelet transfusions from donors with HLA class I antibodies found no TRALI cases and why the LAPS-II study, which selected donors on the basis of HLA antibody screening, observed only a non-significant 3.6-fold difference. HLA antibodies are found mainly in women sensitised by pregnancy, which explains the success of male-predominant plasma strategies.^{8,25,36,68–70}

The per-unit gradient (OR 1.20 per component) and the higher risk with plasma-rich components are consistent with a cumulative-dose model in which each unit contributes a probability of carrying a pathogenic antibody or biological response modifier. That the residual effect of the number of units largely disappeared after adjustment for antibody and recipient factors in the UCSF/Mayo cohort supports this interpretation. Component-level haemovigilance data indicate that, after plasma mitigation, residual risk has shifted towards platelets: apheresis platelets suspended in plasma carried a higher risk than red cells, and selective HLA-antibody testing of previously pregnant female plateletpheresis donors was predicted to prevent about 60% of platelet-associated cases. Pooled whole-blood-derived platelets, which are not subject to mitigation requirements in the United States, had the highest risk, whereas platelets stored in additive solution or pathogen-reduced additive-solution platelets did not differ from red cells.^{18,25,44,51}

Evidence for storage-related, non-antibody TRALI is inconsistent. Red cells stored for more than 14 days were associated with TRALI in cardiac surgery, but not in the larger UCSF/Mayo

cohort with leukoreduced units, and point-of-care washing of red cells did not attenuate lung-injury biomarkers in a randomised trial. A recent cardiac surgery study linked exposure to stromal-cell-derived factor-1 α in red-cell supernatants — highest in units from female donors and in whole-blood-filtered units — to post-transfusion lung injury through natural killer cell cytotoxicity, suggesting that non-antibody mechanisms may involve specific mediators rather than storage duration per se.^{9,25,30,62,71}

Mechanisms: integrating immune and non-immune pathways

In antibody-mediated TRALI, donor antibodies bind cognate antigens not only on neutrophils and monocytes but also on the pulmonary endothelium. Conditional knockout studies showed that endothelial MHC class I is the critical antigen source for anti-leukocyte antibodies, that complement fixation on the endothelium initiates platelet retention and neutrophil extracellular trap (NET) release, and that complement activation is increased in clinical TRALI, reframing TRALI as a rapid-onset pulmonary vasculitis. Anti-HNA-3a antibodies can directly disturb lung endothelial cells through the choline transporter-like protein 2, causing barrier dysfunction even after neutrophil depletion.^{8,72–74}

Downstream, primed neutrophils release reactive oxygen species, proteases and NETs; platelets form heterotypic aggregates with neutrophils and promote NET formation, and dismantling NETs or inhibiting platelet activation protects against experimental lung injury. The clinical observation that NET markers predicted TRALI in massive haemorrhage and the increase in alveolar thrombin generation with suppressed fibrinolysis in cardiac surgery are consistent with this effector phase. Regulatory mechanisms also matter: low IL-10 levels have been reported in TRALI patients, and IL-10, complement inhibition and osteopontin blockade are among the most promising experimental therapies.^{31,52,74–77}

The threshold model explains why strong cognate antibodies may cause TRALI type I in otherwise stable recipients, whereas weak antibodies or non-antibody mediators require substantial priming and therefore produce TRALI type II; why mitigation has reduced type I disease but left a residue of type II and non-immune cases; and why the proportion of non-antibody cases has

increased in recent haemovigilance series. A three-step model of priming, pulmonary reaction and effector phase has also been proposed to guide stage-specific prevention and therapy.^{10,48,54,78}

Pathophysiological framework of TRALI: threshold (two-hit) model integrating the evidence of this review

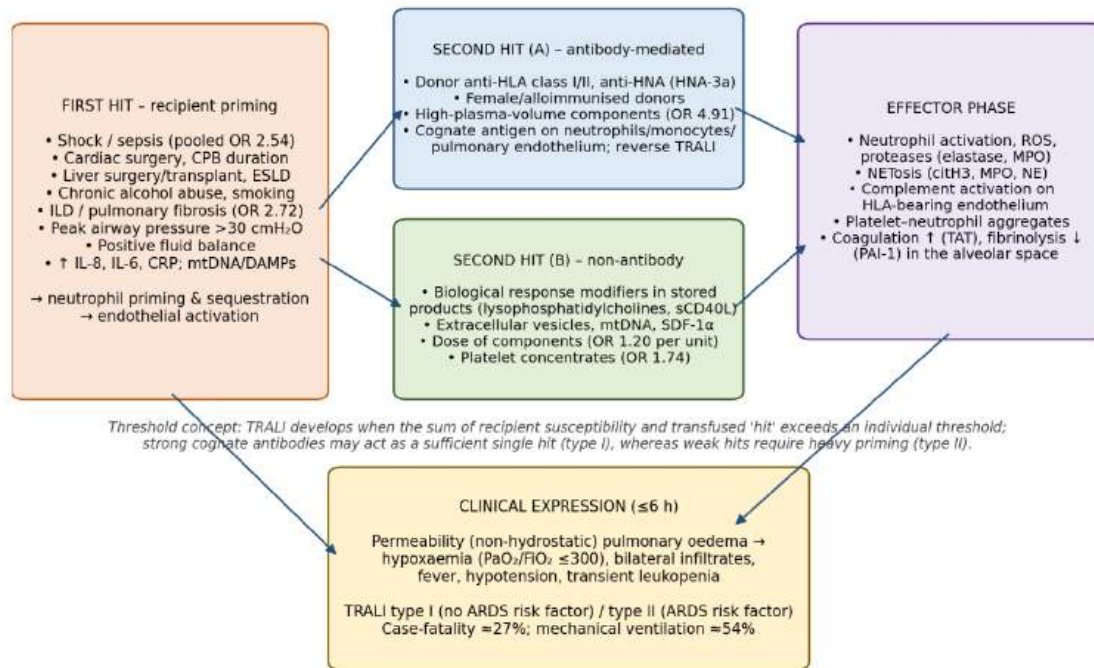


Figure 37. Integrated pathophysiological framework of TRALI (threshold two-hit model) annotated with pooled estimates from this review.

Clinical phenotype, diagnosis and differentiation from TACO

The clinical phenotype of TRALI resembles the systemic inflammatory response syndrome: fever in about one-third of cases, tachycardia, hypotension often requiring new vasopressors, and profound hypoxaemia with bilateral infiltrates developing mostly within the first hour after transfusion and resolving within 48–96 hours in survivors. These features, together with low natriuretic peptides, are the most useful discriminators from TACO, in which hypertension, older age, cardiac and renal comorbidity, positive fluid balance and high BNP predominate. A simple model combining age, BNP and fluid balance achieved a negative predictive value of 91% for TRALI, and pre-transfusion NT-proBNP was not elevated in TRALI. Nonetheless, fever and

bilateral infiltrates also occur in TACO, and both syndromes may coexist, so that diagnosis requires integrated assessment by clinicians with critical care expertise.^{2,26,28,29}

Under-recognition is the main diagnostic challenge. Electronic screening algorithms based on post-transfusion chest radiographs and oxygenation identified many unreported cases, and a survey of Dutch clinicians showed that the presence of sepsis or another ARDS risk factor reduced the inclination to report TRALI — precisely the patients at highest risk. The 2019 redefinition, which explicitly accommodates type II TRALI and introduces the TRALI/TACO category, should improve reporting of these cases. Figure 39 summarises a bedside approach derived from the pooled evidence.^{4,5,13,14}

Evidence-informed bedside approach to post-transfusion respiratory distress (2019 TRALI redefinition; ISBT 2018 TACO criteria)

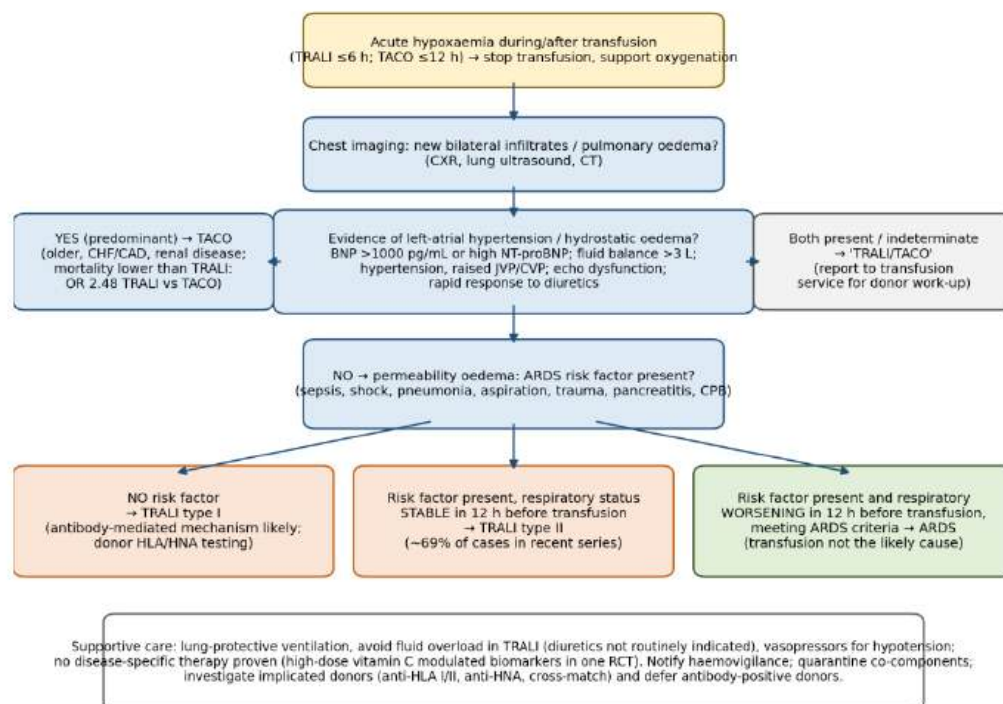


Figure 38. Evidence-informed bedside approach to post-transfusion respiratory distress distinguishing TRALI type I/II, ARDS and TACO.

Outcomes and prognosis

The pooled five-fold excess mortality is clinically important but must be interpreted carefully. The wide prediction interval and the gradient across data sources indicate that the attributable mortality of TRALI depends on the underlying illness. The highest relative effects were found in surgical and transplant cohorts with low baseline mortality, whereas in critically ill and administrative populations the contrast was smaller because controls also had substantial mortality. In the prospective UCSF/Mayo cohort, adjustment for APACHE II attenuated but did not abolish the association (OR 3.4), and patients with possible TRALI had even higher mortality (42%) than those with TRALI (17%), indicating that much of the death burden in type II disease is driven by the underlying ARDS risk factor.^{26,33,47,49}

Case-fatality also varied with surveillance mode, from about 9% in passive haemovigilance series to 38% in retrospective clinical cohorts and 68% among ICU patients. These figures exceed the 6–12% mortality commonly cited in reviews, which largely derives from haemovigilance data, and they highlight that TRALI in the ICU is a life-threatening event. The marked burden on ventilatory support, ICU admission and length of stay also implies substantial resource use.^{41,46,47,78}

Comparison with previous systematic reviews

Our donor- and transfusion-related estimates are directionally consistent with those of Hu and colleagues, but our patient-related estimates are generally smaller and less certain, owing to the inclusion of larger and more diverse cohorts and the separation of TRALI from possible TRALI. Our per-component rate (1.88 per 100,000) is compatible with the active-surveillance estimates of White and colleagues once differences in component mix are considered, and our pooled RR for mitigation (0.57) agrees closely with the OR of 0.61 reported by Müller and colleagues, although the effect restricted to plasma-associated TRALI in the review by Schmickl and colleagues was larger (RR 0.27). No previous review quantified clinical outcomes or the TRALI–TACO prognostic difference.^{12,16,17,19,21}

Table 15. Comparison of the present findings with previous systematic reviews and meta-analyses

Review	Scope	Key pooled findings	Present review
Hu et al. (Respir Care) ²¹	13 studies, critically ill, to March 2020; risk factors only	Shock OR 4.41; alcohol 3.82; smoking 3.82; ventilation 4.13; FFP units 1.21; female sex 1.26	Shock/sepsis 2.54; alcohol 2.41 (NS); smoking 1.61 (NS); ventilation 1.26 (NS); donor antibody 4.91; outcomes and TACO added
White et al. (Transfusion) ¹²	80 studies; incidence per component	Active surveillance: RBC 0.17, PLT 0.31, plasma 3.19 per 10 ⁴ units	1.88 per 10 ⁵ units overall; per patient 0.017–4.47% by setting
Müller et al. (Transfusion) ¹⁶	10 studies; low-risk donor strategies	OR 0.61 (0.42–0.88)	RR 0.57 (0.28–1.18) across strategies incl. SDP and washed RBC
Schmickl et al. (Crit Care Med) ¹⁷	45 studies; male-predominant plasma	Plasma-related TRALI RR 0.27; mortality RR 0.89	Mortality of TRALI vs controls OR 5.22
White et al. (Transfusion) ¹⁹	22 studies; TACO incidence	TACO 22.2 per 1000 patients	TACO more frequent but less lethal than TRALI (OR 2.48 for death)

Implications for prevention and transfusion safety

Prevention must address both hits. At the blood-service level, the most robust strategy remains the use of plasma-rich components from donors at low risk of leukocyte alloimmunisation: men, never-pregnant women or women who test negative for HLA antibodies since their last

pregnancy, as required by AABB standards. Our data highlight three residual gaps — group AB plasma, apheresis platelets from previously pregnant women and pooled whole-blood platelets — that can be addressed by HLA/HNA antibody screening, suspension of pooled platelets in male plasma or additive solution, pathogen-reduced additive-solution platelets and pooled solvent/detergent plasma. Donors implicated in TRALI should be investigated for cognate HLA class II and HNA antibodies and deferred when positive.^{15,44,47,51,56}

At the hospital level, patient blood management is the most effective way to reduce exposure, particularly in recipients with an active first hit (sepsis, shock, liver surgery or transplantation, chronic lung disease, cardiac surgery with prolonged bypass, massive haemorrhage and post-partum haemorrhage with hypertensive disorders). Restrictive haemoglobin thresholds, goal-directed haemostatic therapy guided by viscoelastic testing, avoidance of prophylactic plasma for minor coagulation abnormalities, preference for factor concentrates where appropriate, lung-protective ventilation and avoidance of positive fluid balance are pragmatic measures supported by the risk factors identified here.^{25,35,37,66}

At the bedside, every new hypoxaemia within six hours of transfusion should prompt cessation of the transfusion, chest imaging, natriuretic-peptide measurement, fluid-balance review and reporting to the transfusion service, irrespective of the presence of sepsis or another ARDS risk factor. Systematic active surveillance, ideally supported by electronic screening algorithms, is needed to overcome under-reporting. For countries with developing haemovigilance systems, including Indonesia, the absence of local primary data identified in this review is itself an actionable finding: national TRALI surveillance using the 2019 definitions, donor HLA-antibody screening capacity in regional blood centres and hospital transfusion committees are priorities.^{4,13,14}

Table 16. Evidence-based recommendations for TRALI prevention and transfusion safety

Level	Recommended action	Supporting evidence from this review
Blood service	Male-predominant/never-pregnant or HLA-antibody-negative donors for	Donor exposure OR 4.91; AB plasma OR 14.5; pooled WB

	plasma, whole blood and apheresis platelets; screen group AB plasma donors; prefer additive-solution or pathogen-reduced platelets; consider SDP	platelets RR 6.48; PAS platelets no excess risk
Donor management	Investigate implicated donors for cognate HLA class II and HNA antibodies; defer positive donors; look back at co-components	Dose-dependent class II/HNA risk; 69% immune-mediated
Hospital transfusion committee	Patient blood management; restrictive thresholds; viscoelastic-guided haemostasis; minimise plasma and platelet use	Per-unit OR 1.20; plasma/platelet associations
High-risk recipients	Heightened indication review and monitoring in shock/sepsis, chronic lung disease, liver disease/transplant, cardiac surgery, massive and post-partum haemorrhage, alcohol use, smoking	ORs 2.54 (shock/sepsis), 2.72 (lung disease); incidence 4.5% in high-risk settings
ICU/anaesthesia	Lung-protective ventilation (peak pressure <30 cmH ₂ O); avoid positive fluid balance; monitor 6 h after transfusion	Peak airway pressure OR 3.6; fluid balance OR 1.15 per L
Diagnosis	Stop transfusion; imaging; BNP/NT-proBNP; fluid balance; classify as TRALI type I/II, ARDS, TACO or TRALI/TACO	BNP 271 vs 1934 pg/mL; NPV 91% for model

Haemovigilance and research	Active electronic surveillance; national reporting with 2019 definitions; trials of IL-10, complement or NET inhibition	Under-reporting; no proven therapy; vitamin C modulates biomarkers only
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Strengths

The strengths of this review include a comprehensive, transparent search of two bibliographic databases and a semantic engine with verification of every citation; extraction of numerical data from full-text tables where available; inclusion of the 2019 redefinition and studies up to 2026; explicit handling of overlapping cohorts; separation of TRALI from possible TRALI; extensive subgroup, sensitivity and small-study-effect analyses; and GRADE assessment.

Implications for research

- Prospective, multicentre active-surveillance cohorts using the 2019 TRALI and 2018 TACO definitions, with standardised denominators, in Asia, Africa and Latin America.
- Individual-patient-data meta-analysis to estimate adjusted effects of recipient factors, to separate TRALI type I from type II and to quantify attributable mortality.
- Validation of composite diagnostic tools combining BNP/NT-proBNP, fluid balance, echocardiography or lung ultrasound, and NET or complement biomarkers.
- Randomised trials of targeted therapies (IL-10, complement inhibition, NET-directed therapy) and of component-processing strategies in high-risk recipients.
- Cost-effectiveness analyses of HLA/HNA donor screening for platelets and AB plasma in resource-limited blood services.

CONCLUSION AND RECOMMENDATIONS

Conclusion

TRALI remains a frequent and serious complication of transfusion in primed recipients, affecting about one in twenty transfused patients in high-risk settings. Its development is best explained by a threshold two-hit model: recipient inflammatory and organ-dysfunction states (shock or sepsis, chronic lung disease, liver disease, alcohol and tobacco exposure, injurious ventilation)

lower the threshold, and donor leukocyte antibodies in plasma-rich components — the strongest and most consistent risk factor — together with cumulative transfusion burden and non-antibody mediators provide the second hit. About two-thirds of investigated cases are antibody-mediated, and most recent cases are TRALI type II. TRALI presents with hypoxaemia, bilateral infiltrates, fever and hypotension, low natriuretic peptides and frequent need for invasive ventilation, and it carries a roughly five-fold excess in-hospital mortality, a case-fatality of about 27%, more ICU admissions and nearly one week of additional hospitalisation. It is clinically distinct from, and more lethal than, TACO.

Recommendations

- **For clinicians:** apply restrictive, indication-based transfusion in recipients with an active first hit; avoid unnecessary plasma and platelets; use lung-protective ventilation and avoid positive fluid balance; monitor oxygenation for 6 hours after transfusion; and stop the transfusion, image the chest and measure BNP/NT-proBNP whenever hypoxaemia develops.
- **For diagnosis and reporting:** classify post-transfusion pulmonary oedema according to the 2019 TRALI and 2018 TACO definitions and report every suspected case — including those with sepsis or other ARDS risk factors — to the transfusion service and haemovigilance system.
- **For blood services:** maintain male-predominant or antibody-screened plasma, extend HLA/HNA screening to previously pregnant apheresis-platelet and group AB plasma donors, favour additive-solution, pathogen-reduced or male-plasma-suspended platelets, and consider pooled solvent/detergent plasma where available.
- **For health policy in Indonesia and similar settings:** develop national TRALI surveillance, strengthen hospital transfusion committees and patient blood management programmes, and build regional capacity for donor leukocyte-antibody testing.
- **For researchers:** conduct prospective multicentre studies with standardised definitions, individual-patient-data syntheses and randomised trials of targeted preventive and therapeutic strategies.

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Data availability: The extracted dataset, analysis code and complete search outputs are available from the corresponding author on reasonable request.

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ABBREVIATIONS

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; BNP, B-type natriuretic peptide; BRM, biological response modifier; CI, confidence interval; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HLA, human leukocyte antigen; HNA, human neutrophil antigen; ICU, intensive care unit; IL, interleukin; LOS, length of stay; MD, mean difference; MV, mechanical ventilation; NET, neutrophil extracellular trap; NOS, Newcastle–Ottawa Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PAS, platelet additive solution; PLT, platelets; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RBC, red blood cells; RCT, randomised controlled trial; RR, risk ratio; SDP, solvent/detergent-treated pooled plasma; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; WB, whole blood.

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