Incidence of Transfusion-Related Acute Lung Injury Temporally Associated With Solvent/Detergent Plasma Use In The ICU - A Retrospective Before and After Implementation Study

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Abstract

Background:

Transfusion-related acute lung injury (TRALI) is a severe complication of plasma transfusion, though use of solvent/detergent pooled plasma (SDP) has nearly eliminated reported TRALI cases. The goal of this study was to investigate TRALI incidence in the intensive care unit (ICU) following replacement of quarantined, male-only, fresh frozen plasma (qFFP) by SDP for routine use.

Methods:

We conducted a retrospective multicenter observational before-after cohort study during two six-month periods, before (April to October 2014) and after introduction of SDP (April to October 2015), taking into account a six-month wash-out period. One secondary and four tertiary academic hospitals participated.

Results:

Admitted to the ICU were 8944 patients during both inclusion periods. 1171 qFFP units were transfused in 376 patients in the qFFP, and 396 during the before and after periods respectively in the SDP period. A full patient chart review was performed in 300 patients that received ≥1 units of plasma and had a PaO_2/FiO_2-ratio (P/F-ratio) <300 within 24 hours. Ten cases of TRALI occurred during the qFFP and nine cases during the SDP period, in which plasma was transfused concomitantly with other products, or alone. The incidence was 0.85% (CI95%: 0.33% – 1.4%) per unit qFFP and 0.45% (CI95%: 0.21% - 0.79%, p = 0.221) per SDP-unit. One instance of TRALI occurring after a single SDP unit. Mortality was 70% for patients developing TRALI in the ICU compared to 22% in all patients receiving at least one plasma transfusion.

Conclusion:

Implementation of SDP lowered the incidence of TRALI in which plasma products were implicated, though not significantly. TRALI can still occur as a result of SDP transfusion. Developing TRALI in the ICU was associated with high mortality rates, therefore clinicians should remain vigilant.

Background

Transfusion-related acute lung injury (TRALI) is a severe adverse transfusion reaction, defined as acute onset of pulmonary permeability edema and respiratory compromise within 6 hours after transfusion. TRALI develops following a 'two-hit' event, threshold model [1, 2]. Neutrophils in the lungs are primed by a first hit, e.g. cardiac surgery, sepsis or trauma. In TRALI, these cells are subsequently activated (second hit) by antibodies stored specifically in plasma containing blood products. TRALI develops if the sum of the first- and second-hit are large enough to pass the threshold. Therefore, depending on the patient's predisposition (severity of the first hit), the second hit can be at a lower antibody titer. Patients in the intensive care unit (ICU) are especially at risk of TRALI, as their underlying condition often primes neutrophils, and up to 40% receives at least one blood transfusion during their ICU stay [3].

Over the past decades, mitigation strategies have lowered the incidence of TRALI. After introduction of quarantined, single donor, male-only, fresh frozen plasma (qFFP) the incidence decreased by more than 50% [4, 5], to approximately 5.5% of patients transfused in the ICU [6, 7]. The most recent mitigation step has been the implementation of solvent/detergent treated pooled plasma (SDP) [8–10]. SDP is produced by pooling plasma from hundreds of donors, diluting harmful antibodies to below detectable levels [11]. It is further postulated that harmful antibodies may also be neutralized by soluble antigens during pooling. Nevertheless, undetectable antibody titers are not evidence of absent antibodies.

Since SDP replaced qFFP in 2014 in the Netherlands, the incidence of TRALI has dramatically fallen. Until 2020 there have been no cases reported of TRALI due to SDP, which is now widely seen as the safer alternative concerning TRALI [9]. One study even heralded SDP as to have 'abolished' TRALI from plasma transfusions [12]. The Dutch national hemovigilance network recently reported a case of TRALI, though transfusion-associated circulatory overload could not be ruled out [13]. We hypothesize that the incidence of TRALI after plasma transfusion has decreased since implementation, however that TRALI can still occur after SDP considering the threshold model. A retrospective before and after implementation study was performed to investigate whether the introduction of SDP has reduced the incidence of TRALI in ICU-patients compared to qFFP.

Methods

This study was approved by the medical ethics committee (Amsterdam University Medical Centers – location AMC – *Amsterdam, The Netherlands*) and informed consent was waived due to the retrospective nature of the study. We performed a multicenter retrospective observational before and after implementation cohort study employing a retrospective surveillance strategy to identify episodes of TRALI following plasma transfusions. Transfusion episodes of all patients, either already admitted to the ICU or newly admitted, were reviewed during two 6-month periods: 1) between April 1st until October 1st, 2014; and 2) between April 1st until October 1st, 2015. Excluded were patients readmitted to the ICU and < 18 years of age. The 2014 inclusion window was prior to implementation of SDP and all plasma transfusions were units of qFFP. In November 2014 all blood banks nationwide switched to SDP; the second inclusion period was chosen after a six-month washout phase.

Plasma products

Male only, qFFP (310 mL) was the standard plasma product available nationwide (Q-Plasma, Sanquin Blood Bank – *The Netherlands*). It is produced from apheresis plasma of a single, non-paid, volunteer donor. Implementation of SDP has advantages including an improved safety profile with regards to

pathogen reduction as well as limiting the quantity of harmful antibodies per unit of plasma. The Netherlands only uses Omniplasma® (200 mL)(Octapharma GmbH – *Germany*) which follows the same production process as Octaplas® (Octapharma GmbH – *Germany*). However, the plasma is from all Dutch, non-paid, volunteer donors. They are produced from the pooling of 300–500 apheresis plasma donations. Keeping in mind the threshold model for TRALI, rather than exposing one patient to the entire volume of a plasma unit that may have harmful antibodies, pooling of plasma limits the total quantity of antibodies per unit, preventing patient exposure to high antibody titers.

Case selection

Selection of TRALI patients was through a multitiered approach, 1) potential TRALI cases were identified based on electronically recorded patient data; 2) a full chart review was performed for these patients. Data was collected from all patients with evidence of respiratory decline which was temporally-associated with a plasma transfusion (< 6 hours); 3) a panel with transfusion experts made the final determination of whether cases fulfilled TRALI criteria (Table 1) and assigned imputability (eTable 1).

Table 1
Revised 2019 consensus redefinition for transfusion-related acute lung injury

TRALI Type I	
a.	Acute onset
	Hypoxemia (P/F-ratio ≤ 300 or SpO_2 < 90% on room air)
	Clear evidence of bilateral pulmonary edema on imaging (CXR, Chest-CT, ultrasound)
	No evidence of LAH or, if LAH is present it is judged to not be the main contributor to the hypoxemia
b.	Onset during or within 6 hours of transfusion
c.	No temporal relationship to an alternative risk factor for ARDS
TRALI Type II	
-	Findings as described in categories *a and b* of TRALI Type I, and
-	Stable respiratory status in the 12 hours before transfusion
Adapted from Vlaar, Transfusion (2019) [14]. Abbreviations: *P/F-ratio*: PaO_2/FiO_2-ratio; *CXR*: Chest x-ray; *LAH*: left-atrial hypertension; *ARDS*: acute respiratory distress syndrome.	

Patients with new or worsening respiratory deterioration temporally associated (< 24 hours) with qFFP (before introduction) and SDP (after introduction) were identified based on retrospective electronic patient data and were subjected to a full chart review. The initial identification was performed based on data supplied from participating centers during the two inclusion periods. All Dutch ICUs participate in collating and reporting of anonymized patient data to the NICE foundation for monitoring and optimizing quality of ICU care nationally (*Stichting NICE* – Amsterdam, the Netherlands), from which patient characteristics, as well as admission diagnosis, APACHE-II and SAPS scores, type of admission (medical/planned surgical/emergency surgical), referring specialty, major comorbidities including heart, lung or liver disease and malignancies were derived. Minute-to-minute ventilator data were collected, including ventilation mode, as well as FiO_2 and PaO_2 values from arterial blood gas analyses of all patients in ICU during the inclusion periods. In case no FiO_2 was available it was assumed to be 21% and PaO_2/FiO_2-ratio's (P/F-ratio) were calculated accordingly. An overview of all transfused blood products and the time they were administered were queried from the electronic records.

Patients were electronically identified as a potential case if they 1) received at least one plasma transfusion and 2) had a P/F-ratio < 300 within 24 hours pre- or post-transfusion of the plasma unit. A wide interval prevented exclusion of cases in which the electronically recorded transfusion time, mechanical ventilation data and blood gas analysis times and dates were not perfectly synchronized. Patients excluded from review were those extubated within nine hours of the plasma transfusion or discharged from the ICU within 48 hours of admission and were therefore unlikely to have TRALI, unless they died.

A full chart review was performed on all electronically identified patients. Data was collected from all patients that showed respiratory worsening, temporally associated (< 6 hours) to a plasma transfusion. Respiratory worsening was defined as: increased oxygen requirements, intubation, decreased P/F-ratios compared to pre-transfusion or worsening ventilatory parameters (including a decrease in compliance, increase in FiO_2, positive-end expiratory pressure or driving pressure). Data included: doctor and nurse notes, respiratory parameters, oxygen requirements, hemodynamic variables (e.g., heart-rate, blood pressure and central venous pressure, fluid balance), medication where relevant, start and end times of transfusion, other units transfused and laboratory data including complete blood counts and blood gas results. Additionally, chest X-rays and chest CT's along with the radiology report, and echocardiography results where available were collected.

A panel of transfusion experts and researchers (N.M, A.P, and A.V) reviewed the cases and made the final determination on whether patients had developed TRALI according to the 2018 revised TRALI definition (Table 1) [14]. Patients already mechanically ventilated were required to have stable ventilatory parameters for at least 12 hours prior to transfusion. The panel excluded patients on extracorporeal life support, since no reliable P/F-ratios could be determined, and patients that died before any further investigations could be performed (e.g., P/F-ratio determination or a chest x-ray performed) combined with an alternate clinical explanation. Imputability for each case of TRALI was scored as either definite, probable or possible, following the international society for blood transfusion 2011 definitions (eTable 1) [15]. Cases with imputability scored as doubtful were not included.

Outcomes:

The primary outcome of our study was the incidence of TRALI after implementation of SDP compared to pre-implementation. Secondary outcomes included risk factors for TRALI, the number of cases that received plasma only and imputability of TRALI for these cases. Patient outcomes including mortality, hospital and ICU length of stay (LOS) which were compared between TRALI patients, transfused patients (any transfusion) and plasma transfused patients (receiving at least one unit of plasma, concomitantly with other products or alone).

Sample-size calculation:

Prior implementation of qFFP led to an approximate risk reduction of up to 66% [4, 5, 16], with an incidence thereafter reported in the ICU of 2.4–8.2% [7, 17, 18]. Using a weighted mean incidence, approximately 5.5% of the transfused patient develop TRALI in the ICU due to qFFP. Considering only one case of TRALI due to SDP has been reported to date, we assumed implementation of SDP dramatically reduced the risk of TRALI. Using a chi-square test with an alpha 0.05 and 80% power, at least 302 patients transfused per group are required to show a 75% relative risk reduction for the incidence of TRALI. Inclusion of centers continued until the number of patients receiving plasma transfusions was fulfilled.

Statistical analysis

Data was inspected for normality. Binary outcomes were compared using a chi-square test. To compare continuous data from patients between the qFFP and SDP period we used a Mann-Whitney U test or unpaired student-T test where appropriate. The statistical analysis was performed in R-statistics (version 3.3.2) using the R-studio package. Statistical significance was considered at $p < 0.05$.

Results

A total of 8944 patients were included, from a total of five Dutch ICUs of which four tertiary academic centers and one secondary teaching hospital. A total of 2068 patients received 12804 blood products. Baseline characteristics and transfusion data of all ICU patients before and after implementation of SDP are shown in Table 2. During the SDP period, the number of plasma products transfused was significantly higher. This remained significantly higher after correction of plasma units for volume ($p = 0.013$). Post-hoc analysis showed that this was the result of outliers, the upper range of qFFP transfused in a single patient was 29 units while for SDP this was 564 units as part of plasmapheresis. When excluding the four patients that received the highest number of plasma transfusions in the SDP group (total: 741 units, range: 35–564), the number of plasma units transfused was not significantly different between groups ($p = 0.052$); all patients were included in subsequent analyses.

Table 2
Baseline characteristics

Characteristics	Period		p-value:
	qFFP	SDP	
ICU admissions, n	4563	4381	
Age, years	65 (54–74)	65 (54–73)	0.655
Male, n (%)	2896 (63.5%)	2855 (65.2%)	0.085
BMI	26.4 ± 5.0	26.5 ± 5.1	0.184
APACHE-II Score	15 (12–21)	15 (12–21)	0.396
SAPS	33 (25–45)	33 (26–46)	0.081
Products transfused, n	5985	6819	< 0.001
- **RBC units**	3694	3765	0.160
- **PLTs units**	1023	1141	0.011
- **Plasma products**	1171	2008	< 0.001
- **qFFP**	1171	0	"
- **SDP**	0	2008	"
- **Plasma units (vol. corrected)***	1171	1294	0.013
Patients transfused, n (%)	1068 (23.4)	1000 (22.8)	0.516
- Units per patient transfused	3 (1–6)	3 (1–6)	0.269
- RBC units	2 (1–4)	2 (1–5)	0.742
- PLT units	1 (1–2)	1 (1–2)	0.057
- Plasma units	2 (1–4)	2 (1–4)	0.255
- Plasma volume (L/patient)†	1.2 (0.6–3.1)	1.2 (0.6–5.0)	< 0.001
Type of admission, n (%)			< 0.001
- Medical	1666 (36.5%)	1664 (38.0%)	
- Emergency surgery	762 (16.7%)	832 (19.0%)	
- Planned surgery	2130 (46.7%)	1885 (43.0%)	
Comorbidities, n (%)			
- Chronic renal disease	279 (6.1)	244 (5.6)	0.272
- COPD	359 (7.9%)	355 (8.1%)	0.698
- Hematological malignancy	104 (2.3%)	109 (2.5%)	0.521
- Immunological insufficiency	316 (6.9%)	358 (8.2%)	0.032
- Diabetes	749 (16.4%)	720 (16.4%)	1.000
- History of heart failure	356 (7.8%)	273 (6.2%)	0.006
- Cirrhosis	83 (1.8%)	57 (1.3%)	0.044
Risk factors, n (%)			
- Direct			
- Pneumonia	133 (2.9%)	129 (2.9%)	0.954
- Aspiration	35 (0.8%)	27 (0.6%)	0.461
- Inhalation: smoke/drowning	7 (0.2%)	3 (0.1%)	0.352
- Indirect			
- Sepsis	187 (4.1%)	190 (4.3%)	0.596

Data presented as mean ± SD or median (IQR); *Calculated plasma volume transfused per patient †The number of SDP units transfused when correcting for volume (qFFP 310mL vs. SDP 200mL). Abbreviations: *SAPS*: simplified acute physiology score; *RBC*: red blood cells; *PLT*: platelet transfusion; *qFFP*: quarantine single unit fresh frozen plasma; *SDP*: solvent/detergent treated pooled plasma; *COPD*: chronic obstructive pulmonary disease; *CVA*: cerebrovascular accident; *ALI*: acute lung injury; *LOS*: length of stay.

Characteristics	Period		p-value:
	qFFP	SDP	
- Trauma	182 (4.0%)	176 (4.0%)	0.951
- Pancreatitis	8 (0.2%)	11 (0.3%)	0.496
- Drug overdose	87 (1.9%)	97 (2.2%)	0.325
- Other			
- Cardiac surgery	1702 (37.3%)	1621 (37.0%)	0.767
- CVA	195 (4.3%)	187 (4.3%)	1.000
- Cardiac arrest	216 (4.7%)	212 (4.8%)	0.842
Hospital LOS (days)	9 (5–18)	10 (6–26)	0.000
ICU LOS (days)	2 (1–3)	2 (1–3)	0.026
Died in ICU, n (%)	437 (9.6%)	421 (9.6%)	0.972

Data presented as mean ± SD or median (IQR); *Calculated plasma volume transfused per patient †The number of SDP units transfused when correcting for volume (qFFP 310mL vs. SDP 200mL). Abbreviations: *SAPS*: simplified acute physiology score; *RBC*: red blood cells; *PLT*: platelet transfusion; *qFFP*: quarantine single unit fresh frozen plasma; *SDP*: solvent/detergent treated pooled plasma; *COPD*: chronic obstructive pulmonary disease; *CVA*: cerebrovascular accident; *ALI*: acute lung injury; *LOS*: length of stay.

At least one unit of plasma was transfused to 376 patients in the qFFP period and 396 patients in the SDP group. A total of 300 patients were identified to have at least one episode in which patients received a plasma transfusion and had a P/F-ratio < 300 within 24 hours pre- or post-transfusion. A total of 33 cases were selected to be reviewed by the expert panel and 19 were classified as TRALI (Fig. 1).

Incidence and characteristics of TRALI in patients receiving plasma transfusions:

Characteristics of TRALI patients are shown in Table 3. A total of nineteen patients developed TRALI, with two cases involving qFFP recognized and documented in the patient's chart. A total of 10 patients in the qFFP group developed TRALI after 1171 plasma transfusion (0.85% per unit transfused CI95%: 0.33% – 1.4%), and 9 patients in the SDP developed TRALI out of 2008 units of plasma transfused (0.45% - CI95%: 0.21% – 0.79%), which was not significantly different (p = 0.15).

Table 3
TRALI patient characteristics

Characteristics:	Period		p-value:
	qFFP	SDP	
TRALI patients (n)	10	9	
- Type I	4 (40%)	2 (22%)	0.405
- Type II	6 (60%)	7 (78%)	"
Age (years)	67 (65–73)	62 (41–72)	0.225
Male (n, %)	4 (40%)	6 (67%)	0.365
BMI	24.2 ± 3.9	25.2 ± 3.0	0.519
Apache-II Score	25 (21–27)	23 (21–32)	0.485
SAPS	51 (41–61)	54 (52–79)	0.253
Transfusion data (n, %)			0.930
- Plasma only	2 (20%)	1 (11%)	
- Addition RBC units	6 (60%)	5 (56%)	
- Addition PLT units	7 (70%)	5 (56%)	
Imputability (n, %)			0.084
- Definite	2 (20%)	0 (0%)	
- Possible	2 (20%)	6 (67%)	
- Probable	6 (60%)	3 (33%)	
Diagnosis (n,%)			0.081
- Cardiac arrest	2 (20%)	1 (11%)	
- Major thoracic surgery	2 (20%)	1 (11%)	
- Acute abdominal aortic dissection	1 (10%)	1 (10%)	
- Pneumosepsis	0 (0%)	2 (22%)	
- Sepsis (other)	2 (20%)	0 (0%)	
- Pancreatitis	0 (0%)	2 (22%)	
- Massive hemorrhage	3 (30%)	0 (0%)	
- Other:	0 (0%)	3 (33%)	
Presentation			
- P/F-ratio $_{\text{pre-transfusion}}$	245 (205–306)	216 (171–339)	0.897
- P/F-ratio $_{\text{post-transfusion}}$	192 (158–243)	207 (164–365)	0.447
- ΔStatic compliance (mL/cmH_2O)*	-6.7 (-23 – -0.3)	-7.5 (-14 – -2.5)	1.000
- Chest X-ray (n, bilateral infiltrates (%))	10 (100%)	9 (100%)	1.000
- ΔLeukocytes	-0.5 (-6.8–3.6)	3.2 (2.5–8.3)	0.194
- ΔTemperature (°C)	-0.0 (-0.8–0.5)	-0.2 (-0.7–0.3)	0.870
- Fluid balance, past 72 hrs (L)	4.1 (2.9–8.2)	6.0 (2.6–9.9)	0.807
- Echocardiography (n), impaired (%)†	8 (20%)	6 (33%)	0.276
Outcomes:			
- Hospital LOS (days)	11 (6–22)	14 (3–27)	1.000
- ICU LOS (days)	5 (4–10)	11 (3–28)	0.253

Data presented as mean ± SD or median (IQR); *SAPS*: Simplified acute physiology score; *RBC*: red blood cells; *PLT*: platelet transfusion; *qFFP*: quarantined fresh frozen plasma; *SDP*: solvent/detergent treated pooled plasma; *P/F-ratio*: PaO_2-FiO_2-ratio; *LOS*: length of stay. *Static compliance: calculated as tidal volume (mL) / driving pressure (cmH_2O). † Shown as number of patients with a recent echocardiogram performed and percentage of patients with an impaired LV-function (moderate or worse).

Characteristics:	Period		p-value:
	qFFP	SDP	
- Died in ICU (n, %)	7 (70%)	6 (67%)	1.000

Data presented as mean ± SD or median (IQR); *SAPS*: Simplified acute physiology score; *RBC*: red blood cells; *PLT*: platelet transfusion; *qFFP*: quarantined fresh frozen plasma; *SDP*: solvent/detergent treated pooled plasma; *P/F-ratio*: PaO_2-FiO_2-ratio; *LOS*: length of stay. *Static compliance: calculated as tidal volume (mL) / driving pressure (cmH_2O). † Shown as number of patients with a recent echocardiogram performed and percentage of patients with an impaired LV-function (moderate or worse).

Type I TRALI was present in 40% of the qFFP group and in 30% of the SDP period (p = 0.63), shown in Table 4. There were no significant differences between age, gender or severity of illness i.e., APACHE-II and SAPS scores. Patients that developed TRALI received significantly more blood products – median 22 (12–43), compared to transfused patients (without TRALI), median 3 (IQR: 1–6, p < 0.001) and plasma transfused patients: 6 (IQR: 3–12, p < 0.001).

Table 4
TRALI cases

	Case:	Age (years)	Sex	Plasma Only	Imputability	TRALI Classification	Diagnosis	ALI risk factors	Bilateral infiltrates	Units transfused*		
										Plasma	RBCs	PLTs
qFFP	Case 1	70	F	Yes	Probable	Type I	Abdominal aortic aneurysm rupture	-	Yes	3	-	-
	Case 2	68	F	Yes	Possible	Type II	Sepsis, GI	Shock (non-cardiogenic)	Yes	2	-	-
	Case 3	66	F	-	Definite	Type I	Myasthenia gravis	-	Yes	2	3	1
	Case 4	61	M	-	Definite	Type I	Aorto-iliac bypass graft	-	Yes	2	1	1
	Case 5	74	M	-	Possible	Type I	CABG with aortic valve replacement	Shock (non-cardiogenic)	Yes	1	1	-
	Case 6	53	F	-	Probable	Type II	Upper GI bleeding	Shock (non-cardiac)	Yes	3	1	2
	Case 7	66	F	-	Probable	Type II	Surgery for pelvic trauma	Shock (non-cardiogenic)	Yes	2	-	1
	Case 8	76	F	-	Probable	Type II	Pericardial tamponade	Shock (non-cardiogenic)	Yes	5	7	1
	Case 9	65	M	-	Probable	Type II	Cardiac arrest	Trauma	Yes	3	3	1
	Case 10	83	M	-	Probable	Type II	CABG with aortic valve replacement	Cardiac surgery	Yes	2		2
SDP	Case 11	27	M	Yes	Probable	Type I	Acute renal failure	-	Yes	1	-	-
	Case 12	81	F	-	Probable	Type I	Cardiac arrest	-	Yes	4	3	1
	Case 13	61	M	-	Probable	Type II	Abdomen/pelvis trauma	Shock (non-cardiogenic)	Yes	2	2	1
	Case 14	73	M	-	Possible	Type II	Sepsis, GI	Shock (non-cardiogenic)	Yes	1	-	1
	Case 15	38	M	-	Possible	Type II	Sepsis, GI	Pancreatitis	Yes	4	2	-
	Case 16	41	M	-	Possible	Type II	Thoracic aortic aneurysm dissection	Shock (non-cardiogenic)	Yes	1	1	-
	Case 17	66	F	-	Possible	Type II	Pneumonia, other	Pneumonia	Yes	2	-	2
	Case 18	62	F	-	Possible	Type II	Pneumonia, fungal	Pneumonia	Yes	2	-	1
	Case 19	88	M	-	Possible	Type II	Abdominal aortic aneurysm rupture	Shock (non-cardiogenic)	Yes	2	2	-

*Units transfused within window for developing TRALI. Abbreviations: *GI*: gastrointestinal, *CABG*: coronary artery bypass graft (surgery)

Imputability of SDP as cause for TRALI:

Three patients developed TRALI after receiving only plasma units. In the qFFP group two cases, a type I and type II TRALI scored an imputability of respectively probable and possible (Table 4). One patient receiving only SDP plasma, developed TRALI after a single unit with imputability scored as probable. There were no definite cases of TRALI in the SDP group.

Risk factors and outcomes for TRALI:

ALI risk factors were not significantly different between qFFP and SDP TRALI patients (eTable 2). Hospital LOS did not differ between TRALI patients and patients receiving any transfusion. ICU LOS was longer in TRALI patients with a median of 8 days (IQR 4–18) compared to transfused patients, 3 days (IQR 2–8, $p = 0.003$), and also plasma transfused patients 3 days (IQR: 2–7, $p < 0.01$). Mortality in the TRALI group (70%) was significantly higher than both the transfused patient group (17.2%, $p < 0.001$) and the plasma transfused patients (22.0%, $p < 0.001$).

Discussion

In this before and after implementation study of SDP, we investigated the incidence of TRALI through a retrospective chart review of all patients developing acute lung injury, temporally associated with plasma transfusions. The main findings of our study are: 1) the incidence of TRALI was 1:220 units, or 0.45% (CI95%: 0.19% – 0.81%), in which SDP was transfused alone, or concomitantly with other transfusion products; 2) a single case of TRALI following transfusion of one unit of SDP was identified with probable imputability, demonstrating another case of SDP induced TRALI; and 3) the overall 70% mortality of TRALI connected to plasma transfusion in the ICU is extremely high compared to 22% in all patients receiving plasma who did not develop TRALI.

To our knowledge, only one TRALI case has been reported very recently by hemovigilance systems as a result of SDP [13]. The absence of reported cases following SDP transfusion, may have calmed clinicians concerns of TRALI as potential complication. However, development of TRALI follows a two-hit event, threshold model [1, 2]. In our clinical practice with critically ill patients whose underlying condition often constitutes a severe first-hit, we did not expect TRALI to disappear since only a minor second-hit may be required to pass the threshold and activate primed neutrophils. Our study found that the incidence of TRALI in which plasma was (concomitantly) administered did decrease from 0.85–0.45% per transfused unit. Nine patients developed TRALI in which SDP was concomitantly administered and cannot be ruled out as contributor, and finally one patient developed TRALI after a single unit of SDP, proving again that SDP transfusion is not completely 'TRALI safe'.

TRALI is a clinical diagnosis, and positive alloantibody titers are neither required for diagnosis nor confirmation of cases [14]. In suspected cases of TRALI, laboratory analysis confirming the presence of alloantibodies can strengthen or validate clinician's and hemovigilance officer's belief that this is a true case. Manufacturers correctly state that tested SDP plasma products have titers of anti-HLA and anti-HNA antibodies that are below the detection limit, however this does not exclude the presence of these antibodies, nor preclude activation of neutrophils. The findings of our study show that TRALI can still occur, and clinicians must therefore remain alert, and report suspected cases. Reliance on antibody titers to confirm cases should be avoided.

Our study found a 70% ICU mortality rate in TRALI patients, much higher compared to the conventional TRALI mortality rate of 5–20% [19, 20]. It should be noted that our population of critically ill patients developed TRALI on top of their underlying condition. The high mortality rates may be further explained by an indication bias of plasma transfusion, where outcomes of patients receiving plasma in context of for example hemorrhage or spontaneous coagulopathy are likely to be worse than patients not requiring transfusion. The subgroup of patients receiving plasma transfusion had a mortality rate of 22%, similar to a previous study [21]. Developing TRALI on top of this, appears to sharply increase the risk of death to 70%, however this is compared to an unmatched cohort. Other ICU studies have reported similar or lower mortality rates of 41% and 67% [6, 7] in medical ICU patients developing TRALI.

Our study does have a number of limitations, first the incidence of TRALI reported is not the true incidence of TRALI in the ICU. Only patients receiving plasma were reviewed, thereby excluding TRALI cases due to other blood products. Second, this was a database study where imprecise registration of the transfusion start and end times could have led us to underestimate the number of cases as TRALI. The diagnosis of TRALI was ruled-out beyond the six-hour post-transfusion window. On the other hand, a retrospective study of cases has the potential for confirmation bias and over estimation of the number of TRALI cases. Also, there is a risk of misdiagnosing TRALI as TACO, which can be difficult to differentiate retrospectively. We minimized this by utilizing an expert panel to adjudicate cases and which was blinded to the year the case occurred, and to which plasma product was transfused. Furthermore, due to the retrospective nature of the study, antibody measurements in the suspected products were not performed and a causal relationship cannot be determined. Moreover, donor antibody screening is not feasible when implicated products contain between 300 and 500 donors. Finally, in cases where more than one blood product was transfused within the six-hour TRALI window, it was impossible to discern a single unit as the culprit. Whether these cases were due to SDP, or whether SDP was an innocent bystander remains unclear.

Based on our findings we advocate that clinicians remain vigilant when transfusing SDP. Cases of TRALI can still occur, and early recognition and supportive care for these patients is critical.

Unrecognized cases of TRALI will certainly not help combat the extremely high mortality seen. Furthermore, additional investigation is needed to understand whether diluted HLA or HNA antibodies are still able to induce TRALI in the presence of a first hit, or that other substances in SDP are causative. Sources labelling SDP as safe, 'TRALI free', or TRALI as abolished in the setting of plasma transfusion may lull clinicians into a false sense of security, which may delay recognition and prompt stabilization of these patient. Suspicion should remain high and laboratory work-ups should be performed according to hospital protocol.

Conclusions

Implementation of SDP has decreased the incidence of TRALI, though it can still occur as a result of SDP. Clinicians should remain vigilant and continue to report cases. TRALI cases involving plasma transfusion in the ICU are associated with a very high mortality.

Declarations

Ethical approval and consent to participate:

This study was approved by the medical ethics committee (Amsterdam University Medical Centers – location AMC – *Amsterdam, The Netherlands*) and informed consent was waived due to the retrospective nature of the study (reference number: W16_038 # 16.053).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request in combination with a statistical analysis plan.

Competing interests

The authors declare they have no competing interests

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Authors' contributions

The study was designed by R.K, A.P and A.V. Electronic patient data was collated and provided by P.T., H.E., O.C., S.A. and A.V. An individual chart review and retrieval of the data performed by R.K., N.M., D.E. and A.P. Selection of cases was made by N.M., A.P. and A.V. The manuscript was written by R.K., N.M. and A.V and critically evaluated by all authors which approved the final manuscript.

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Figures

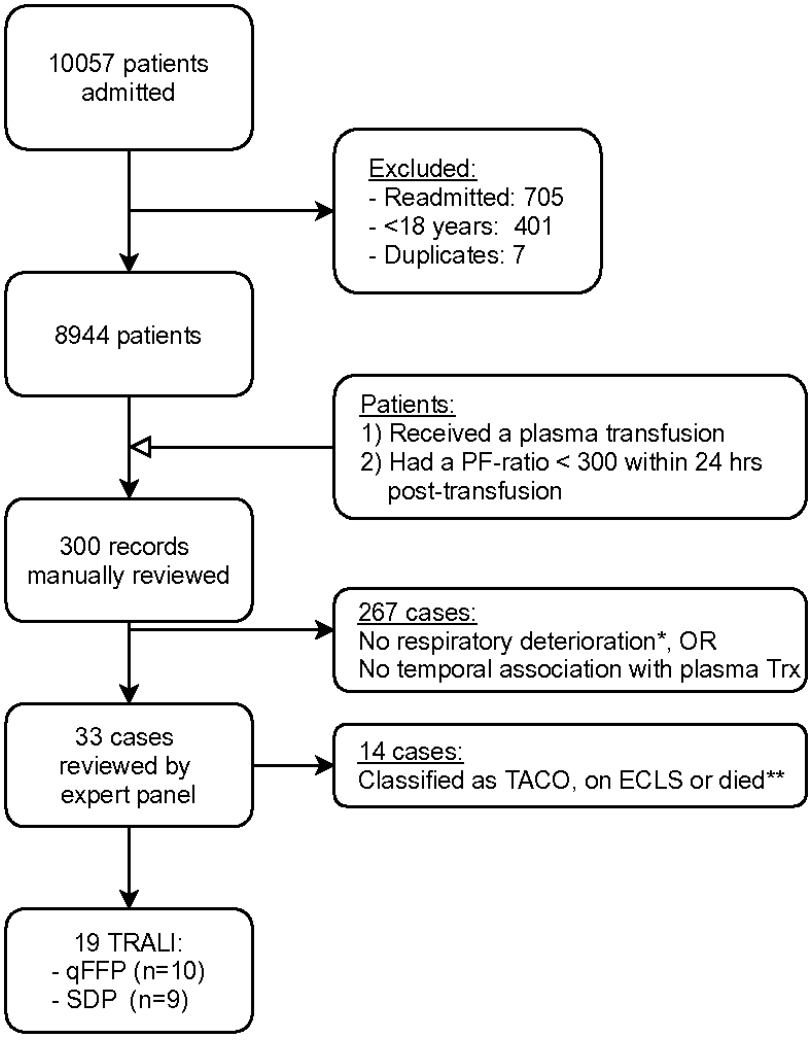

Figure 1

TRALI case identification and classification Flow diagram detailing TRALI patient selection. *Respiratory deterioration defined as: increased oxygen requirements, intubation, decreased PF-ratio or worsening ventilatory parameters (i.e. decreased compliance, increase in FiO2, PEEP or driving pressure). **Patients that died before investigations could be performed and that had an alternate clinical explanation for deterioration were excluded. Abbreviations:

TRALI: transfusion-related acute lung injury; PF-ratio: PaO2/FiO2-ratio; TACO: transfusion-associated circulatory overload; ECLS: extracorporeal life support; qFFP: quarantined fresh frozen plasma; SDP: solvent-detergent pooled plasma.

Supplementary Files

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