Reporting transfusion-related acute lung injury by clinical and preclinical disciplines

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Background. Disciplines involved in diagnosing transfusion-related acute lung injury (TRALI) report according to a "one-hit" theory. However, studies showed that patients with an underlying condition are at increased risk of the development of TRALI. We investigated whether accumulating evidence on the "two-hit" theory has changed the practice of reporting TRALI.

Materials and methods. Departments of haematology, haemovigilance, transfusion medicine, intensive care and anaesthesiology from all Dutch hospitals with at least five beds equipped for mechanical ventilation were invited to participate in an online survey. Using clinical vignettes with conjoint analysis we investigated the effect of patients' age, admission diagnosis, type and number of transfusions and presence of risk factors for acute lung injury on TRALI reporting. A positive β-coefficient indicated a higher likelihood of reporting TRALI.

Results. We received 129 questionnaires (response rate 74%). Respondents were more likely to report TRALI in younger patients, if symptoms developed within 2 hours of transfusion and if patients had received multiple transfusions. Sepsis and the presence of a risk factor for acute lung injury reduced the inclination to report. Transfusion medicine physicians and haemovigilance staff no longer took the age of transfusion products into account in their diagnostic considerations on TRALI.

Discussion. We conclude that the multidisciplinary team involved in TRALI reporting, still considers TRALI a "one-hit" event, despite accumulating evidence that supports the "two-hit" theory. These results suggest that the patients most at risk of developing TRALI are not reported to the blood bank.

Keywords: haemovigilance, reporting, transfusion-related acute lung injury, two-hit model, vignette study.

Introduction

Transfusion-related acute lung injury (TRALI) is a respiratory syndrome caused by blood transfusion. Patients suffer symptoms of dyspnoea, fever, hypotension or sometimes hypertension, and hypoxia. In the absence of biomarkers, TRALI is a clinically diagnosed syndrome and is defined as new acute lung injury (ALI) developing within 6 hours of receiving a blood transfusion (Table I). Possible TRALI has the same definition, but in these cases other risk factors for ALI are also present[1-4]. Approximately 80% of TRALI cases have been related to the presence of antibodies to human leucocyte antigens or human neutrophil antigens, predominantly in female donor blood[5,6].

The reported incidence of TRALI varies widely, ranging from 0.0008 to 1.2% per blood product and from 0.08 to 8% per transfused patient[7]. This 100- to 1000-fold difference in incidences can be explained by differences in study design and patient population but also by underreporting by treating physicians[8-10]. A study in which 36 recipients of a transfusion product from a donor implicated in TRALI were retraced, identified 15 TRALI reactions of which only seven were reported in the hospital and none was reported to the Blood Bank[11].

A multidisciplinary team is usually involved in reporting TRALI. The bedside physician reports a TRALI case to the hospital's haemovigilance

representative. In turn, the haemovigilance officer reports the case to a transfusion medicine specialist at the national Sanquin Blood Bank. Reports of TRALI are important for identifying and excluding involved donors with antibodies in order to prevent future TRALI reactions. In 2008 a survey was conducted to identify what factors influenced reporting of TRALI. This survey showed that the presence of sepsis was a reason for not reporting TRALI. This indicates that physicians suspect TRALI according to the "single-hit" theory, in which antibodies in donor plasma are thought to induce activation of the pulmonary neutrophils in the absence of a priming "first-hit". However, studies in the past decade have indicated that even though TRALI can occur after a "single hit", for example in response to a transfusion product with high levels of cognate antigens (threshold model)[12], it usually follows a "two-hit" model in which a clinical condition (e.g., sepsis, cardiac surgery) primes neutrophils. The "second hit", formed by the transfusion products, activates primed neutrophils and causes TRALI[13-22]. In this follow-up study we investigated whether the improved knowledge on the pathogenesis of TRALI has induced a shift in focus from reporting TRALI according to the "single-hit" theory to the "two-hit"-model among anaesthesiologists, haematologists, intensive care physicians, haemovigilance staff and transfusion physicians. Moreover, we investigated whether the introduction of TRALI mitigation strategies, such as male only plasma and pooled plasma, has influenced TRALI reporting.

Materials and methods

Potential participants

We used an e-mail invitation to request participation in our online survey. We contacted the heads of the department of intensive care medicine, haematology, anaesthesiology and haemovigilance of all Dutch hospitals with five or more beds equipped for mechanical ventilation in their intensive care units (n=68). The chairs of the departments that were willing to participate provided the name and e-mail address of the intensivist, haematologist, anaesthesiologist or haemovigilance officer who was most experienced with transfusion medicine. All transfusion physicians of Sanquin blood supply were also invited to participate (n=23).

Survey

The survey was sent out with Survey Monkey, a web-based survey programme (Survey Monkey, Palo Alto, CA, USA). The first part of the survey inventoried basic demographic characteristics: sex, age, specialisation, work experience, academic- or non-academic hospital setting and, for non-physicians, educational background. This was followed by 16 vignettes and 10 questions on additional factors influencing TRALI reporting. The survey was introduced with a cover letter providing the definition of TRALI according to the Canadian Consensus Conference (Table I) and a description of the vignettes. As the Dutch Blood Bank replaced male-donor only plasma with solvent/detergent-treated plasma in 2015, all vignettes were designed with transfusion of standard red blood cell products, standard pooled platelet concentrates of five buffy coats in male-only plasma and solvent/detergent-treated plasma. All participants were sent up to four reminders if the survey had not been completed after which all uncompleted surveys were regarded as drop-outs. Reminders were sent out every 2 weeks.

Vignettes

We used vignettes to investigate which factors influenced the decision of attending physicians and haemovigilance staff to report a case of TRALI. A vignette is a brief, written case history of a fictitious patient based on a realistic clinical situation. The description is followed by a question to explore what a physician would do if presented with the actual patient. Factors, such as setting, patient's age, and disease, are varied in the vignette to investigate how these changes influence physicians' decision-making. To enhance comparability with our baseline study from 2008, we used the same factors for the vignettes[23]. These factors were selected based on observational, retrospective and prospective studies which indicated that higher patients' age, a severe underlying clinical disease, for example sepsis, multiple transfusions and the presence of a risk factor for ALI, are risk factors for developing TRALI[13,15,22,24-28]. Our previous study indicated that in the Dutch population these variables influenced the decision to report a suspected case of TRALI. We included these five factors and the time of onset of ALI after transfusion

Table I - Definition of transfusion-related acute lung injury.

TRALI	Acute onset within 6 hours of blood transfusion PaO_2/FIO_2 <300 mmHg, or worsening of the PaO_2 to FIO_2 ratio Bilateral infiltrative changes on chest radiograph No sign of hydrostatic pulmonary oedema (pulmonary arterial occlusion pressure ≤18 mmHg or central venous pressure ≤15 mmHg) No other risk factor for acute lung injury
Possible TRALI	Same as for TRALI, but another risk factor present for acute lung injury

PaO_2: partial pressure of oxygen in arterial blood; FIO_2: fraction of inspired oxygen; TRALI: transfusion-related acute lung injury.

as factors in the vignettes (Table II) to explore whether additional scientific evidence on TRALI pathogenesis has influenced how physicians report TRALI. A total of 144 vignettes presented all possible combinations of the six factors and their (3×3×2×2×2×2) factor levels. The number of representative clinical vignettes was reduced to 16 using an orthogonal main effects design[29]. This approach enables statistical testing by conjoint analysis of a suitable fraction of all possible combinations of the factors and their levels. Respondents were asked to rate the degree to which they would consider reporting each of the 16 patients described in the clinical vignettes as suspected of having TRALI and initiating a diagnostic work-up for the condition. A seven-point Likert scale was used ranging from 1 (totally disagree) to 7 (totally agree) to answer the question: "Would you report this case as suspected TRALI?" (Table III).

Determinants of transfusion-related acute lung injury

The third part of the survey included an additional ten questions on how patients' variables influenced the respondent's decision to suspect TRALI or an alternative diagnosis. We asked the respondents whether they took parameters of cardiac function, fluid balance, culture results and transfusion product metrics into account in their decision to report a suspected case of TRALI. These questions were rated on a scale from 0-100 in which 0 corresponded to "I do not take this factor into account in my diagnostic considerations in a suspected case of TRALI" and 100 with "I take this factor fully into account in my diagnostic considerations in a suspected case of TRALI".

Statistical analysis

Conjoint analysis was performed to calculate the relative weights for each level of the factor levels. This results in a utility score (common unit) for each factor level, expressed as β with a 95% confidence interval between brackets. Higher utility values indicate greater preference. Negative β values indicate preferences against the positive direction of the statement, i.e. against reporting a case suspected of being TRALI. The utility for a particular factor level is determined by multiplying the β with the defined factor category, i.e., one times β, two times β, depending on the number of levels per factor.

Data were inspected for normality. As none of the responses of the influence of factors on the decision-making process to report TRALI followed a normal distribution, these factors were investigated with R using a Kruskal-Wallis test. If the Kruskal-Wallis test produced a $p<0.05$, a post-hoc Dunn test was performed. A $p<0.05$ was considered statistically significant.

Table II - Factors incorporated in the clinical vignettes.

Factor	Level
Age of the patient	20 years 80 years
TRALI risk factor	Sepsis Ischaemic cerebrovascular accident
Onset of symptoms	Within 2 hours after transfusion Within 5 hours after transfusion
Type and amount of transfusion	One red blood cell transfusion One platelet transfusion One S/D plasma transfusion One red blood cell transfusion and one S/D plasma transfusion Six red blood cell transfusions and four S/D plasma transfusions
ALI before transfusion	Present Absent

TRALI: transfusion-related acute lung injury; S/D: solvent/detergent; ALI: acute lung injury.

Table III - Example vignettes.

Vignette structure	Vignette A	Vignette B
A (1)-year old patient is treated in the ICU for (2). Within (3) hour(s) of transfusion of (4) the patient develops ALI. The patient had (5) ALI risk factor before transfusion.	A 20-year old patient is treated in the ICU for sepsis. Within 1 hour of transfusion of 1 unit of red blood cells and 1 unit S/D plasma the patient develops ALI. The patient had an ALI risk factor before transfusion.	An 80-year old patient is treated in the ICU for an ischaemic cerebrovascular accident. Within 1 hour of transfusion of 1 unit of platelets the patient develops ALI. The patient had no ALI risk factor before transfusion.
Would you report this case as TRALI?	Would you report this case as TRALI?	Would you report this case as TRALI?

ICU: intensive care unit; TRALI: transfusion-related acute lung injury; S/D: solvent/detergent; ALI: acute lung injury.

Conjoint analysis was performed in SPSS for Windows version 22.0 (IBM Corp., Armonk, NY, USA). R was used to produce figures with the most recent version of the ggplot2 package and to perform Kruskal-Wallis testing (R-core Team, Vienna, Austria).

Results

In total 173 heads of departments from 63 hospitals agreed to participate in our study. We sent out the online questionnaire to 38 intensive care physicians, 38 anaesthesiologists, 19 haematologists, 22 transfusion physicians and 56 haemovigilance officers. Of the invited respondents, 31 intensive care physicians (81.6%), 26 anaesthesiologists (68.4%), 19 haematologists (100%), 43 haemovigilance officers (76.8%) and 10 transfusion medicine physicians (52.6%) returned the questionnaire, which amounted to a total of 129 responses (74%). One respondent did not fill in his specialisation. This response was included in the analysis of the vignettes but was excluded from the sub-analysis per speciality. Table IV summarises the demographic data of the respondents.

Vignettes on reporting transfusion-related acute lung injury

Our analysis revealed that respondents were more likely to report TRALI in 20-year old patients developing lung injury than in 80-year old patients (β-coefficient 0.26 [0.05-0.47]). Respondents were less likely to report a TRALI case if the patient was admitted with sepsis than if the patient was admitted with a cerebrovascular accident (β-coefficient –0.28 [–0.49 to –0.07]). Reporting of TRALI was also dependent on the time of onset of ALI symptoms. Participants were more likely to report the case if pulmonary deterioration occurred within 1 hour after transfusion than when symptoms occurred within 5 hours (β-coefficient 0.41 [0.20-0.62]). The number and type of transfusion products modulated TRALI reporting. Transfusion of platelets or plasma increased the chance of reporting compared to transfusion of red blood cells (platelets: β-coefficient 0.15 [–0.08-0.39]; plasma: β-coefficient 0.08 [–0.08-0.24]). Respondents were most likely to report a TRALI case when multiple transfusion products were administered (β-coefficient 0.31 [–0.09-0.71]). Finally, participants were less inclined to report patients who already had a risk factor for ALI (β-coefficient –0.98 [–0.77 to –1.19]). Figure 1 illustrates the preferences for each variable. Sub-analysis of the response pattern per specialisation, sex, clinical *vs* non-clinical specialisation or work experience did not influence the results.

Questionnaires

Additional determinants that may influence reporting TRALI were measured on a scale of 0-100. Our results show that the 24-hour fluid balance, the presence of an ALI risk factor, and administration of multiple

Table IV - Demographic characteristics of respondents.

		Intensive care physician*	Anaesthesiologist	Haematologist	Haemovigilance officer†	Transfusion medicine physician
N (% of total respondents)		31 (23.8)	26 (20.0)	23 (17.7)	39 (30.0)	10 (7.7)
Sex (%)	Female	29	27	39	66	50
Age (%)	<29 years	0	0	0	0	0
	30-39 years	19.4	15.4	12.8	12.8	30
	40-49 years	71	34.6	25.6	25.6	0
	50-59 years	6.5	38.5	38.5	38.5	70
	>60 years	3.2	11.5	23.1	23.1	0
Years of experience (%)	0-5 years	25.8	7.7	17.4	2.6	30
	6-10 years	41.9	23.1	8.7	18.0	10
	11-15 years	25.8	15.4	26.1	23.1	10
	16-20 years	0	7.7	21.7	12.8	10
	>21 years	6.5	46.2	26.1	41.0	40
Hospital (%)	Academic	19.4	23.0	30.4	7.7	0
	Non-academic	80.6	76.9	69.6	89.6	100
TRALI-cases reported last year (median with range)		0 (0-5)	0 (0-2)	1 (0-5)	0 (0-5)	0.5 (0-3)

The total of the percentages does not reach 100% in all columns because of missing responses from two respondents. *Of the total of 31 intensive care physicians, 18 originated from internal medicine, 12 from anaesthesiology and 1 from cardiology. †Of the total of 39 haemovigilance officers, 22 studied biomedical sciences, medicine or medical pharmacy and 14 were qualified laboratory analysts with additional haemovigilance training. Four respondents did not specify their training. TRALI: transfusion-related acute lung injury.

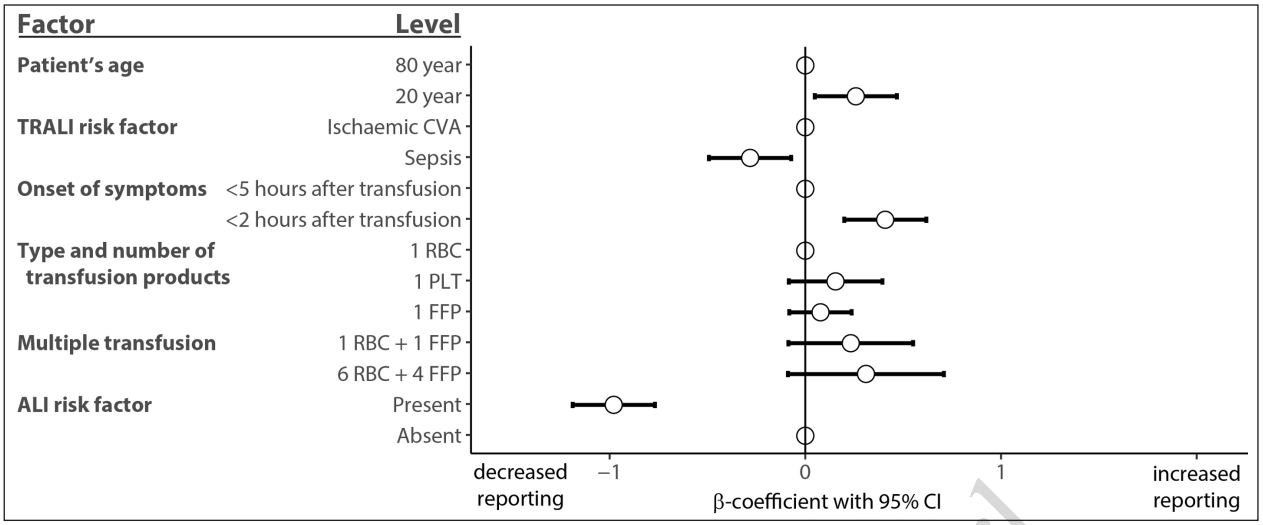

Figure 1 - Preferences of respondents for determinants on reporting TRALI. A positive b-coefficient indicates a higher likelihood of reporting TRALI.
TRALI: transfusion-related acute lung injury; CVA: cerebrovascular accident; RBC: red blood cells; PLT: platelets; FFP: fresh-frozen platelets; ALI: acute lung injury; 95% CI: 95% confidence interval.

transfusions products influence the decision to suspect TRALI. The storage time of the transfused product, on the other hand, has limited influence on the decision to report a case (Figure 2). Of note, however, intensivists and anaesthesiologists are more likely to take the storage time of transfused products into account than transfusion medicine physicians and haemovigilance officers ($p<0.02$). Additional analysis of the questionnaire per speciality shows that compared to the other specialists, haemovigilance staff are less likely to weigh parameters of cardiac performance in the decision to report, including systolic and diastolic ventricular function. Transfusion medicine physicians are more likely to take blood culture results into account than the other specialists ($p<0.05$). Haematologists, transfusion medicine physicians and haemovigilance officers are more likely to take the presence of an ALI risk factor into account than intensivists and anaesthesiologists ($p<0.02$; Figure 2). Overall, the clinical specialties are more focused on patient-related factors while the haemovigilance staff and transfusion specialists are more focused on transfusion-related factors in their differential diagnostic considerations on post-transfusion pulmonary complications (Figure 2).

Discussion

In this study we investigated the practice of reporting TRALI. The results of the present survey are strikingly similar to the findings of 8 years ago. The survey from 2008, which was conducted among intensive care physicians, haematologists, haemovigilance staff and transfusion medicine physicians in the Netherlands showed that the presence of an underlying condition, for example sepsis ("first hit"), was a reason for not reporting TRALI[23]. This indicated that reporting physicians notified TRALI according to the "single-hit" theory. Since 2008 several studies have been published that support the "two-hit" pathogenesis of TRALI[13-22]. There is also evidence supporting the concept that increasing severity of the "first hit" causes more severe TRALI for both the forms mediated by antibodies and those not mediated by antibodies[16,17,22,30,31]. Clinical studies have confirmed these findings and shown that patients with more severe underlying disease are at higher risk of developing lung injury after transfusion[13,14,22,26]. In this study we investigated whether the determinants that influence TRALI reporting have changed accordingly. However, our study demonstrates that the factors influencing reporting of TRALI are similar to those in 2008. The chance that the multidisciplinary team involved in TRALI reporting will designate a case as (possible) TRALI decreases in younger patients, decreases after transfusion of a single red blood cell, fresh-frozen plasma or platelet product, and decreases in patients with an additional ALI risk factor or sepsis - the patients most at risk of developing TRALI. In other words, respondents are still most likely to report "the young and fast" ALI-developers.

There are several possible explanations for the observation that the tendency to report follows the "one-hit" theory and has not shifted to the "two-hit" model. It could indicate that physicians are unaware of the "two-hit" theory on TRALI. Possibly the disciplines involved in TRALI reporting do not realise that elderly patients, patients with an ALI factor, and patients with

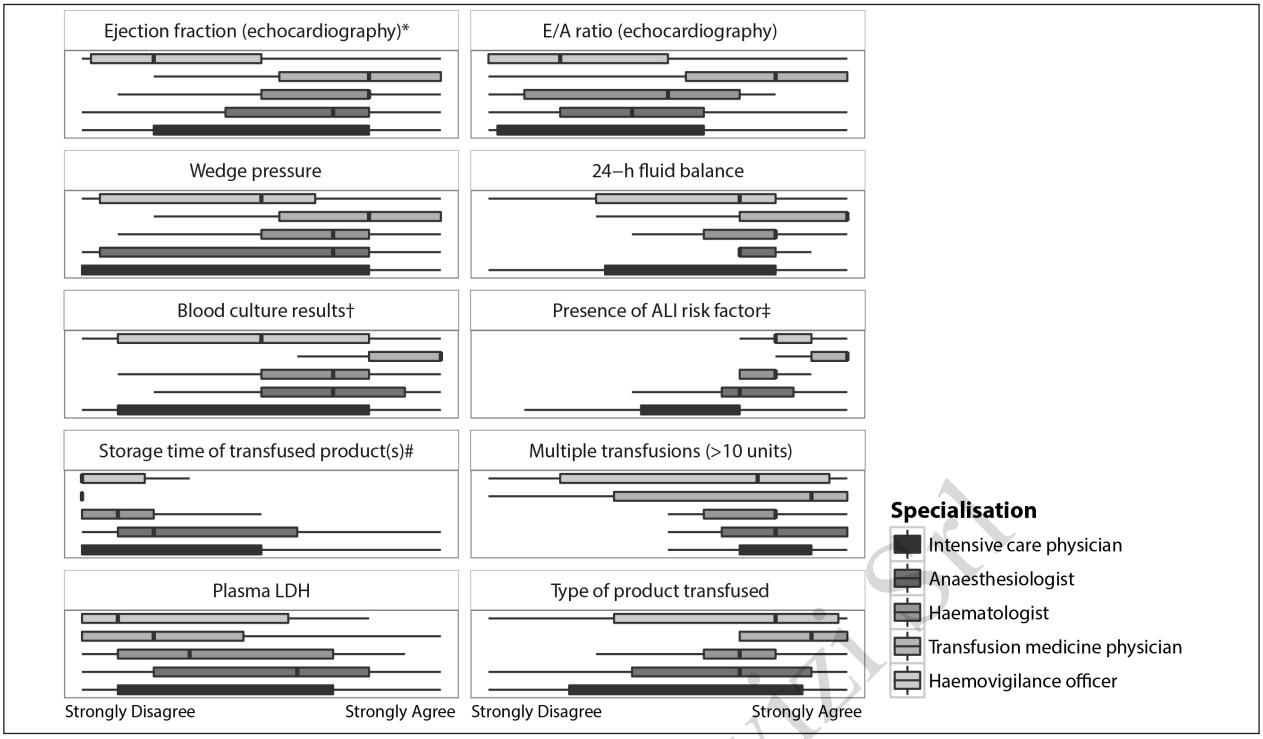

Figure 2 - Analysis by specialty of the influence of blood product and patient-related factors on the decision to suspect TRALI. *, #, †, and ‡ = $p<0.05$. Haemovigilance officers were less likely than the other specialists to take ejection fraction into account. Haemovigilance officers and transfusion medicine physicians were more likely than the other specialists to take blood culture results into account. Intensivists and anaesthesiologists were more likely than transfusion medicine physicians and haemovigilance officers to take the storage time of transfused products into account. Haematologists, transfusion medicine physicians and haemovigilance officers were more likely than intensivists to take the presence of an ALI risk factor into account. LDH: lactate dehydrogenase; ALI: acute lung injury.

more severe underlying disease, such as sepsis, are most at risk of developing TRALI[14,32]. However, it also possible, although this cannot be easily tested with vignettes, that physicians are unaware of a patient's medical history or are unable to evaluate the patient's medical history for the presence of a "two-hit" event resulting in TRALI. It may be particularly difficult for specialists involved in reporting, but who are not at the bedside, to gain insight into a patient's medical history.

Another factor that might influence reporting is that the presentation of TRALI is similar to that of acute respiratory distress syndrome or pulmonary oedema, including transfusion-associated cardiac overload. The differential diagnosis for acute (worsening) lung injury is extensive, especially in patients with acute respiratory distress syndrome risk factors. This can result in the physician overlooking TRALI or deciding that another factor may have caused lung injury and not the transfusion. The Dutch haemovigilance system uses a TRALI score system including imputability of symptoms to the transfused blood product[33]. This can influence the decision to diagnose possible TRALI in patients with diseases presenting in a similar fashion not in line with the international consensus definition of TRALI.

Our results are consonant with those of studies in which TRALI and possible TRALI were under-recognised and under-reported[8,9,11,22,34-37]. The under-recognition of this condition has several implications: if TRALI in patients with more severe underlying disease or acute respiratory distress syndrome risk factors remains unrecognised, no immunological work-up will be performed at the hospital and/or blood bank and donors related to (possible) TRALI cases will no longer be excluded[32].

In the previous survey, plasma transfusion was the most influential factor for reporting TRALI. However, in our present follow-up study, plasma transfusion had almost no effect on the likelihood of respondents reporting a suspected case. We hypothesise that the implementation of male-only quarantine plasma in 2007 and addition of male-only plasma to platelet concentrates in 2009 initiated a general understanding of the potential side-effects of transfusion and that implementation of these policies increased the realisation that the safety of plasma transfusion has increased in the past years. In 2014 quarantine plasma was replaced by solvent/detergent-treated plasma nationwide, to further increase the safety of plasma transfusion. The reduction in the

effect of plasma transfusion on TRALI reporting in the vignettes may reflect the realisation that implementation of these new types of plasma - at least of male-only quarantine plasma - has reduced the incidence of TRALI[38].

The influence of some of the additional determinants that condition reporting of TRALI has changed between our two studies. The respondents' reported influence of echocardiographic estimation of cardiac function was graded similarly, but the 24-hour fluid balance and massive transfusion had more influence on the diagnostic considerations to report TRALI. This might reflect the enhanced focus on transfusion-associated cardiac overload in the recent years[39].

Our results lead us to speculate whether the disciplines familiarise themselves enough with each other's literature: on the one hand, anaesthesiologists and intensive care physicians tend to focus on patient-related factors when they suspect TRALI, confirming the findings of a recent study in which clinical risk factors in recipients predominated in possible TRALI[14]. On the other hand, haematologists, haemovigilance officers and transfusion specialists are more focused on factors related to the transfusion products. Nevertheless, the storage time of transfusion products influenced the decision-making process considerably less than in the previous study. Storage of red blood cells has been implicated in transfusion-induced adverse events. However, in line with evidence from recent, large trials in which storage time of transfusion products was unrelated to transfusion-induced morbidity and mortality, the respondents take storage time of the transfusion products less into account in their diagnostic considerations[40-42]. Disciplines that are more closely in contact with the Dutch Blood Bank - the haemovigilance staff, haematologists and transfusion medicine physicians - seem to be most informed about the lack of evidence on storage time-mediated risk. Our results suggest that a number of intensive care medicine physicians and anaesthesiologists still believe that the age of the transfused products is related to transfusion complications. Hence, knowledge on patient-related risk factors on the one hand and transfusion-related risk factors for TRALI on the other hand may be limited to specialty areas in medicine and for this reason result in under-diagnosing and under-reporting. Integration of this knowledge in all disciplines involved in reporting TRALI may be warranted to increase the diagnosis and reporting of TRALI.

Our study has several limitations. Our overall response rate was good, but we were not able to reach all Dutch hospitals with at least five beds equipped for mechanical ventilation. However, we believe that the high rate of respondents of all disciplines from academic hospitals, large teaching hospitals and small regional hospitals ensures that our study results are representative of current TRALI reporting practice.

Conclusions

As in previous studies, Dutch physicians tend to report TRALI according to a "one-hit" theory. Physicians refrain from reporting the "possible" two-hit TRALI in patients with additional pre-existent lung injury or other severe underlying disease. In this respect, a diagnosis of TRALI is withheld from patients with the highest risk of this severe transfusion-mediated complication. This suboptimal awareness hampers prophylactic treatment measures and identification and exclusion of relevant donors.

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Authorship contributions

ALP, JMB, JJZ, EAMB, SSZ, MGJvK, NPJ and APJV designed the investigation; ALP, EJG and EKvdW performed the research; ALP analysed the data; APJV supervised the conduct of the study; ALP, JMB and APJV wrote the paper. All Authors read and corrected the paper.

The Authors declare no conflicts of interest.

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