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TRANSFUSION COMPLICATIONS

TRANSFUSION

Transfusion-associated adverse events incidence and severity after the implementation of an active hemovigilance program with 24 h follow-up. A prospective cohort study

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Abstract

Background: Hemovigilance (HV) is usually based on voluntary reports (passive HV). Our aim is to ascertain credible incidence, severity, and mortality

Abbreviations: ARDS, acute respiratory distress syndrome; AS, additive solution; CIs, confidence intervals; CT, computed tomography; GEE, generalized estimating equations; HEMACUA, HEMovigilancia Activa con CUArentena, active hemovigilance with quarantine; HTR, hemolytic transfusion reaction; HV, hemovigilance; HVN, hemovigilance nurses; IgA, immunoglobulin A; IHN, international hemovigilance network; IQR, interquartile range; MTT, maximum transfusion time; PE, plasma exchanges; RBCs, red blood cells; RR, relative risk; SAG, *Saline, Adenine, Glucose*; SHOT, serious hazards of transfusion; SUT, single unit transfusions; TAAEs, transfusion-associated adverse events; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnea; TRALI, transfusion related acute lung injury; TRS, transfusion-related symptom; TTI, transfusion-transmitted infection.

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of transfusion-associated adverse events (TAAEs) using an active HV program.

Study Design and Methods: Prospective cohort study to estimate transfusion risk after 46,488 transfusions in 5830 patients, using an active HV program with follow-up within the first 24 h after transfusion. We compared these results to those with the previously established passive HV program during the same 30 months of the study. We explored factors associated with the occurrence of TAAEs using generalized estimating equations models.

Results: With the active HV program TAAEs incidence was 57.3 (95% CI, 50.5–64.2) and mortality 1.1 (95% CI, 0.13–2.01) per 10,000 transfusions. Incidence with the new surveillance model was 14.0 times higher than with the passive. Most events occurred when transfusions had already finished (60.2%); especially pulmonary events (80.4%). Three out of five deaths and 50.3% of severe TAAEs were pulmonary. In the multivariate analysis surgical patients had half TAAEs risk when compared to medical patients (OR, 0.53; 95% CI, 0.34–0.78) and women had nearly twice the risk of a pulmonary event compared to men (OR, 1.84; 95% CI, 1.03–3.32). Patient's age, blood component type, or blood component shelf-life were unrelated to TAAEs risk.

Discussion: Active hemovigilance programs provide additional data which may lead to better recognition and understanding of TAAEs and their frequency and severity.

KEYWORDS

RBC transfusion, transfusion complications-non infectious, transfusion practices (adult)

1 | INTRODUCTION

Transfusion-associated adverse events (TAAEs) occur during or after transfusion of any blood component. They are defined as *hyper-acute* when they occur before the transfusion has ended, *acute* when the symptoms appear over the first 24 h, and *delayed* for those occurring subsequently. Delayed transfusion-related infections are a primary concern of healthcare providers, but their incidence and severity are usually low and well defined.[1,2] However, the distinction between hyperacute and acute TAAEs incidence is blurred and probably under-reported with current hemovigilance (HV) programs[3] mainly based on voluntary reporting by transfusion staff. We call these models *passive* HV programs. Newer HV models that pro-actively review the patient's clinical course after the transfusion has ended (*active* HV programs)[4] and during subsequent hours, would enable better TAAEs detection and enhanced knowledge of the risks of transfusion.

Our aims were two-fold. To ascertain the incidence, severity, and imputability of TAAEs using an active HV program with follow-up within the first 24 h after transfusion. Moreover, to compare these incidences to those using a traditional passive HV model. We also explored the relationship between patients and blood component features and the occurrence of TAAEs.

2 | METHODS

2.1 | Study design

This is a prospective cohort study to assess TAAEs incidence, severity, mortality, and imputability in our hospital between January 2017 and June 2019. A new hemovigilance protocol defined as HEMACUA (*HEMovigilancia Activa con CUArentena*, Active Hemovigilance with Quarantine) commenced in January 2017. Before this new program was set up, TAAEs were voluntarily notified by the ward staff involved in the transfusion procedure using an HV form sent back to the blood bank in addition to the empty blood component bag. This report form was only sent to the blood bank when an event occurred during the transfusion. With this system, the TAAEs occurring during transfusion were monitored, but

not those occurring after the transfusion ended. After implementation of the new active HEMACUA program, the passive model was kept active. This enabled us to compare the TAAEs reporting rate between the new active-HEMACUA and the old passive model. TAAEs detected with the active and passive model were included in both groups for incidence comparisons.

The HEMACUA program was included as a clinical practice and the study was reviewed and approved by the hospital Ethics Committee. As multiple factors could determine the TAAEs incidence, we report the blood component features and our transfusion clinical practice in the supplementary annex.

The analysis of transfusion errors, near misses, and delayed adverse events are beyond the scope of this study.

2.2 | Transfusion definition

We define a transfusion as the procedure from medical prescription to 24 h after the end of a single unit component infusion. If a patient required several components, each one was analyzed as a different transfusion procedure with a different HV report.

2.3 | Active hemovigilance with 24 h quarantine

Nurses were trained by Blood Bank hematologists to identify any adverse event that could be related to the transfusion over 24 h after its completion. They were denominated *Hemovigilance nurses* (HVN). When events were undetected, the transfusion process was completed *without event*. If any signs or symptoms were found, these were labeled as a *transfusion-related symptom* (TRS). Any unstandardized relevant information on the TRS was also recorded by the HVN, in addition to the time from onset of transfusion to the event. TRS were then classified by blood bank hematologists as a TAAE according to our standard definitions (Figure 1). When TAAEs occurred after the transfusion of several blood components and we were uncertain as to which was responsible, the TAAEs were assigned to the last component transfused following the rule *"one TAAE to one component."*[5] However, when a single blood component was related to several TAAEs, these were all assigned to that single blood component. After this initial HVN screening, Blood Bank hematologists reviewed the TAAE category, severity, and imputability and reclassified or excluded, if necessary. TRS deemed unrelated to the transfusion after the hematologist's review were excluded and not included as a TAAE. For inconclusive TAAEs, an HV Expert Committee discussed selected cases for final approval. This Committee included Critical Care, Anesthesia, Internal Medicine, Pneumology, Allergology, Blood Bank specialists, and a hematologist from the Regional Transfusion Centre. All pulmonary TAAEs were discussed and classified by majority agreement between the Committee members. Patients with a confirmed allergic or gastrointestinal TAAE were reviewed by an Allergist specialist. In this setting, a retrospective search looking for immunoglobulin deficiencies was also performed with the aim of locating undiagnosed IgA-deficient patients.

2.4 | Patients, transfusions, transfusion practice, and blood component features

Our transfusion chain is highly computerized from prescription to transfusion monitoring, which enables an on-time control of the transfusion process and to know most features of each transfusion[6] *Threshold* for transfusion was set to 7 g dL for red blood cells (RBC) and 10×10^9/L for prophylactic platelet transfusions. We define as *single unit transfusions* (*SUT*) those transfusions prescribed for a single blood component unit. Products were classified as *fresh* when time from the donor's blood collection to transfusion was before 21, three and 60 days for RBC, platelets, and plasma, respectively. *Maximum transfusion time* (*MTT*) was defined to calculate the median transfusion time for each blood component. A broader description of these definitions is given in the supplementary appendix.

Our hospital has a small pediatric unit with very low transfusion requirement. Therefore, our result should only be inferred to the adult population.

Pre-medications were not routinely used prior to transfusion. We do not have reliable information on how many patients received what type of premedication.

2.5 | TAAE classification

TAAEs categories, severity and imputability were defined as in accordance with the *International Hemovigilance Network* (*IHN*) *proposed standard definitions*[7] and the Serious Hazards of Transfusion (SHOT) definitions.[3] Pulmonary TAAEs were classified according to the criteria proposed by Vlaar[8] and also according to the ISBT-IHN-AABB 2018 TACO definition.[9] Vlaar's definition consider TACO when the event onset is during or up to 6 h after transfusion; and the second definition when it occurs up to 12 h. We included a separate new TAAEs category for *Digestive* events (see explanation in the Discussion). Severity was classified as *Death*, *Signs with vital risk*, or *Signs without vital risk and full*

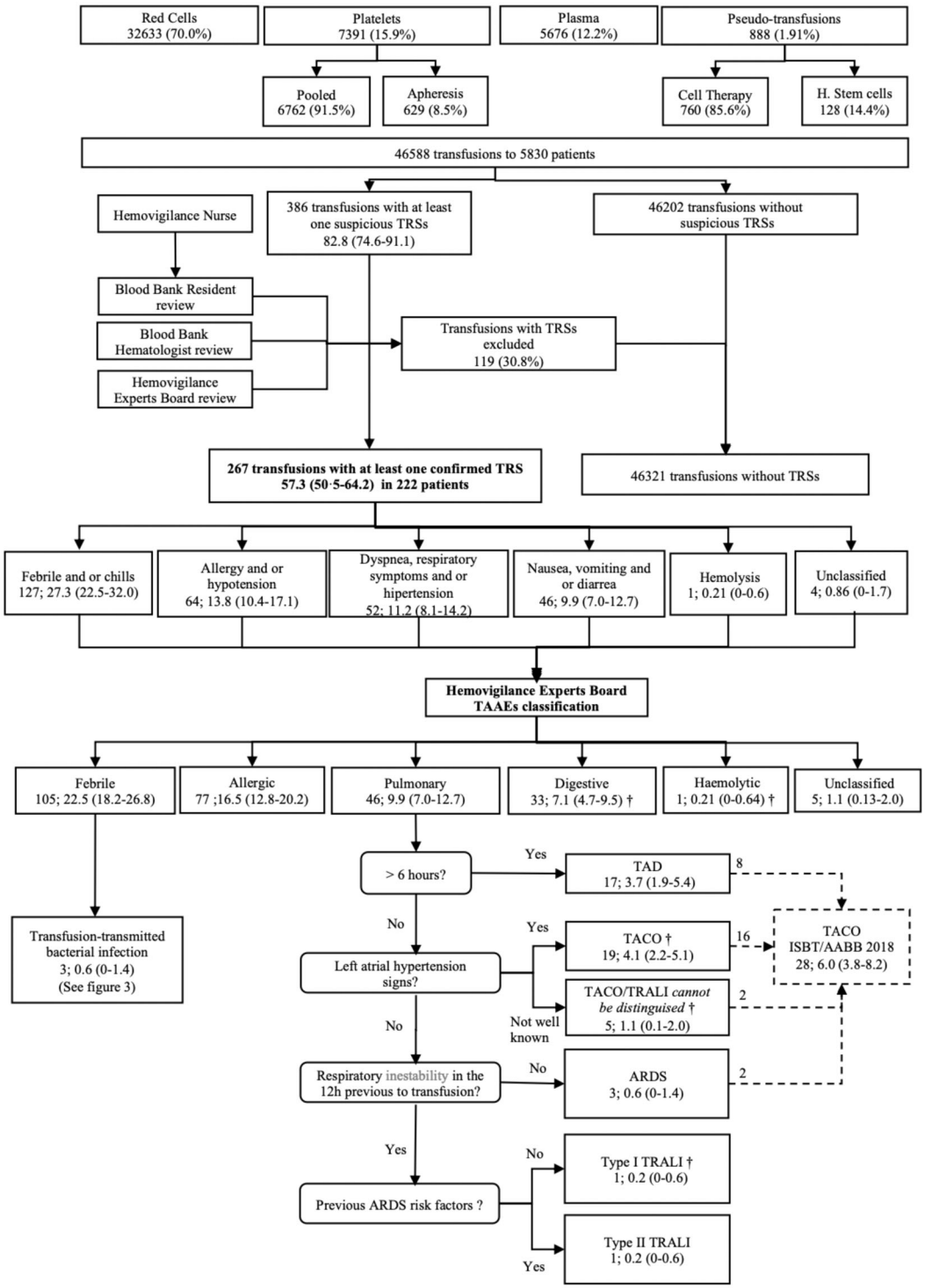

FIGURE 1 Transfusion-associated adverse events (TAAEs) using the active hemovigilance program. Cases, rates per 10,000 transfusions and 95% CI. TACO cases are recorded according to the Vlaar and the ISBT/AABB 2018 (dotted lines) definitions. ARDS, acute respiratory distress syndrome; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnea; TRALI, transfusion-related acute lung injury; TRSs, Transfusion-related symptoms; †, deaths cases.

resolution. Signs with vital risk was used when a patient required intensive care and/or aggressive treatment. Imputability was classified as *certain*, *likely*, and *possible*. TRS with imputability *unlikely* were ruled out as TAAEs.

2.6 | Statistical analysis

The database was unidentified before the analysis. TAAEs incidences were estimated as number of cases per 10,000 transfusions; and number of transfusions

TABLE 1 Univariate and multivariate GEE logistic regression analysis.[a]

Variable explored (reference category)		Any TAAE				Pulmonary TAAE			
		Univariate		Multivariate		Univariate		Multivariate	
		RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value	RR (95% CI)	*p*-Value
Sex (man)	Woman	1.14 (0·87–1.49)	ns	1.12 (0.85–1.46)	ns	1.91 (1.06–3.45)	.032	1.84 (1.03–3.32)	.041
Age (under 60 years)	Over 60 years	0.91 (0.69–1.20)	ns	0.82 (0.62–1.10)	ns	2.27 (1.12–4.62)	.022	1.09 (0.87–3.04)	.08
Blood component shelf-life (fresh)	Old	1.17 (0.91–1.50)	ns	1.23 (0.96–1.58)	ns	1.78 (0.96–3.30)	.066	1.62 (0.87–3.04)	ns
Patient feature (medical department)	Hemato-oncologic	1.21 (0.84–1.76)	ns	1.18 (0.80–1.74)	ns	0.61 (0.21–1.75)	ns	0.73 (0.25–2.15)	ns
	Anesthesia, surgery or solid organ transplant	0.53 (0.36–0.78)	.001	0.53 (0.34–0.78)	.001	0.99 (0.42–2.32)	ns	1.16 (0.49–2.74)	ns
	Emergency & intensive care	0.94 (0.63–1.42)	ns	0.93 (0.62–1.39)	ns	1.41 (0.55–3.64)	ns	1.43 (0.55–3.69)	ns
Blood component (red blood cells)	Platelets	1.15 (0.83–1.58)	ns	1.09 (0.79–1.53)	ns	0.70 (0.29–1.65)	ns	0.99 (0.40–2.43)	ns
	Plasma	0.56 (0.34–0.92)	ns	0.65 (0.39–1.07)	ns	0.30 (0.07–1.26)	ns	0.38 (0.89–1.61)	ns
	Hematopoietic stem cells (HSC)	8.4 (3.58–19.73)		Not included				Not included	
	Cell therapy (CT)	0.23 (0.28–1.82)		Not included				Not included	

Abbreviation: TAAE, Transfusion-associated adverse event.

[a]Sample size in both multivariate analysis included 45,969 transfusions. HSC and CT were excluded from the multivariate analysis by coloniality as all the HSC and most CT were hemato-oncologic patients.

needed to observe one TAAE. Both are estimated according to their corresponding 95% confidence intervals (CIs). Numeric variables are reported as median and interquartile range (IQR). We used a Chi squared to compare TAAEs detection using the passive versus the active HV model. We explored the factors that could be associated with the *occurrence* of a TAAE or a *pulmonary event* using generalized estimating equations (GEE) models.[10] We tested the association between the occurrence of dependent variables *TAAEs* (*yes/no*) and *pulmonary TAAEs* (*yes/no*) and several covariates and interaction variables. (See covariates in Table 1). The association between the proposed variables on the occurrence of a TAAE or a pulmonary event was analyzed by univariate and logistic regression analysis. As each patient can receive more than one blood component, a correlation appears between the different transfusions over the same patient. GEE takes into account this design and we selected a binomial family and a logit as the link function. Effect measurements are expressed by relative risk (RRs) with their corresponding 95 percent confidence intervals (95% CIs). We performed statistical analysis using SPSS Statistics for Windows, version 14.0 (SPSS Inc., Chicago, Ill., USA) and Stata v16. (College Station, TX; StataCorp LLC). Missing data analysis is reported in Table S1. We used the STROBE cohort reporting guidelines.[11]

3 | RESULTS

We examined a total of 46,588 transfusions in 5830 patients over 30 months of routine clinical practice. Median patient age was 72.02 years; range (0–103.5) and 18,778 transfusions (40.3%) were for women.

3.1 | TAAE incidence with the active and passive hemovigilance models

We compared the results obtained with the new active HV procedure to those obtained with the passive model (see Table 2). Under the passive HV procedure, we received a total of 19 TAAE reports; 4.08 per 10,000 transfusions (95% CI 2.24 to 5.91) or one TAAE per 2452 transfusions (95% CI 1692 to 4455). Most TAAEs were febrile, 14 (77.8%) and 4 (22.2%) allergic. Respiratory symptoms were also reported for two febrile TAAEs (5.5%) as one TACO and one TACO/TRALI. A hyperhemolysis event was also reported passively. Regarding severity, all cases were classified as *Signs without vital risk and full resolution*; except one platelet transfusion that developed a TACO/TRALI with fever and was classified *as Signs with vital risk*, and the hyperhemolysis case as *Death*. Imputability was *certain* for the hyperhemolysis and TACO events, *likely* in three and *possible* in 14 of the cases. All these events detected with the passive system were also analyzed and included in the active system's (HEMACUA) results.

TABLE 2 TAAEs detected using the passive or the active models.

	Passive model	Active model
Febrile	14	105
Allergic	4	77
Pulmonary	2	46
Digestive		33
Hemolytic	1	1
Unclassified		5
Events	**19**	**267**
No events	46,569	46,321
Rate per 10,000 transfusions*	**4.08**	**57.64**
Transfusions	46,588	46,588

Note: Bold values indicate p <.0001.
Abbreviation: TAAE, Transfusion-associated adverse event.
*Chi-square p value <.0001.

With the HEMACUA protocol, we detected a total of 267 confirmed TAAEs in 222 patients. The 19 TAAEs reported in the passive model were also detected and recorded with the active program. TAAEs incidence was 57.3 per 10,000 transfusions (95% CI 50.5–64.2); or one TAAE per 174 transfusions (95% CI 156 to 199). The new HEMACUA program reported 14.0-fold more TAAEs than the passive HV procedure over the same period (95% CI, 10.9–22.5; $p < .0001$; Table 2; Figures 1 and 2). The number of transfusions with TAAEs per patient ranged from one to six, with a median of one. Transfused patients with at least one TAAE was 3.8% (95% CI, 3.33–4.29). This means that one for every 26.1 patients transfused (95% CI, 23.2–30.0) underwent TAAEs.

3.2 | Fevers and bacterial transfusion transmitted infections

Fever was the most common adverse event but mild, without vital risk and full resolution and low imputability. Three suspected cases were defined as likely bacterial/fungal *transfusion-transmitted infection* (*TTI*) because the pathogen was not confirmed in the blood component culture. A summary of the process to identify bacterial TTI is reported in Figure 3.

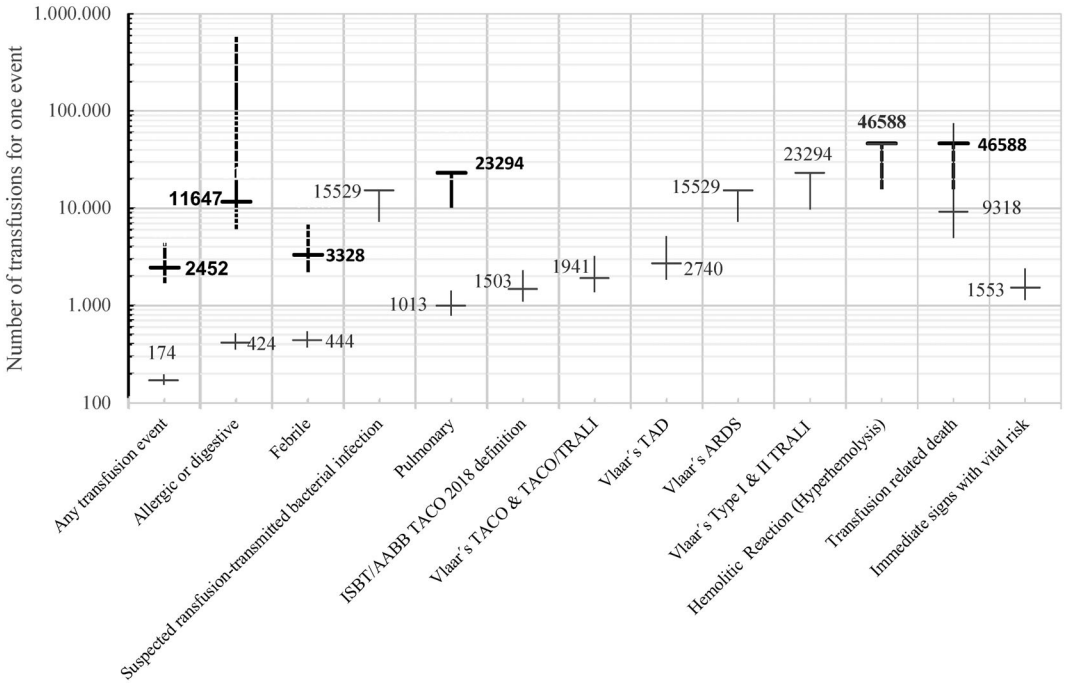

FIGURE 2 Number of transfusions for one event (95% CI) using the Passive (bold) or Active Hemovigilance procedure. ARDS, acute respiratory distress syndrome; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnea; TRALI, transfusion-related acute lung injury.

3.3 | Allergic and gastrointestinal events

Allergic reactions were mild and with high imputability. Gastrointestinal events defined as nausea, vomiting, or diarrhea were usually difficult to define as a single TAAE, although allergic digestive symptoms were suspected in most of them. Their severity was mild, except for one single case in a patient who died after vomiting and a subsequent broncho-aspiration (see clinical description in the supplementary appendix). From 125 allergic and gastrointestinal TRS investigated, 110 cases in 87 patients were confirmed as TAAEs. Of these, 52 (60%) had a previous IgA test performed, but none was confirmed as IgA deficient.

3.4 | Pulmonary events (Figure 1).

We detected 46 pulmonary events that revealed a rate of 9.9 per 10,000 (7.0–12.7). These were the third most common TAAEs, but the most severe; as 31 out of 46 (67%), had immediate signs which were life-threatening or led to death (Figure S1). Twenty four (52.2%) were transfusion-associated circulatory overload (TACO or TACO/TRALI) and 17 (37.0%) transfusion-associated dyspnea (TAD). According to the revised ISBT-IHN-AABB TACO case surveillance definition, 2018,[9] 28 out of 46 pulmonary TAAEs (68.8%) were defined as TACOs, which reveals an incidence of 6.0 (3.8–8.2) cases per 10,000. TRALI were rare. Only one *Type I* and one *Type II* TRALIs were reported. Both were severe and with a *certain* imputability. A clinical description of both cases is reported in the supplementary appendix.

Imputability for TACO was certain in 19 out of 24 (79.2%) and defined as *possible* for ARDS and TAD.

Pulmonary TAAEs were more common in patients that shared some characteristics: Postsurgical patients with cancer (39.1%) or an inflammatory context (65.2%), previously or currently intubated (34.8%), transfused with more than five blood components in the previous 12 h (47.8%) and with simultaneous fluid overload (36.9%).

3.5 | Rare and unclassifiable events

One patient died after multiple transfusions with a diagnosis of *hyperhemolysis* after an allogenic stem cell transplantation.[12] This patient was reported in both the active and passive hemovigilance systems. We have not reported acute HTR due to ABO or other RBC incompatible transfusions in this timeframe. Unclassifiable events include two cases of severe hypotensive shock; one with a cardiorespiratory arrest who fully recovered. Another patient referred headache, abdominal pain, and cramps after a RBC transfusion with full resolution. Two others revealed hypertension. All five unclassified TAAEs occurred the first 2 h after onset of transfusion. A summary of TAAE frequency is shown in Figure S1.

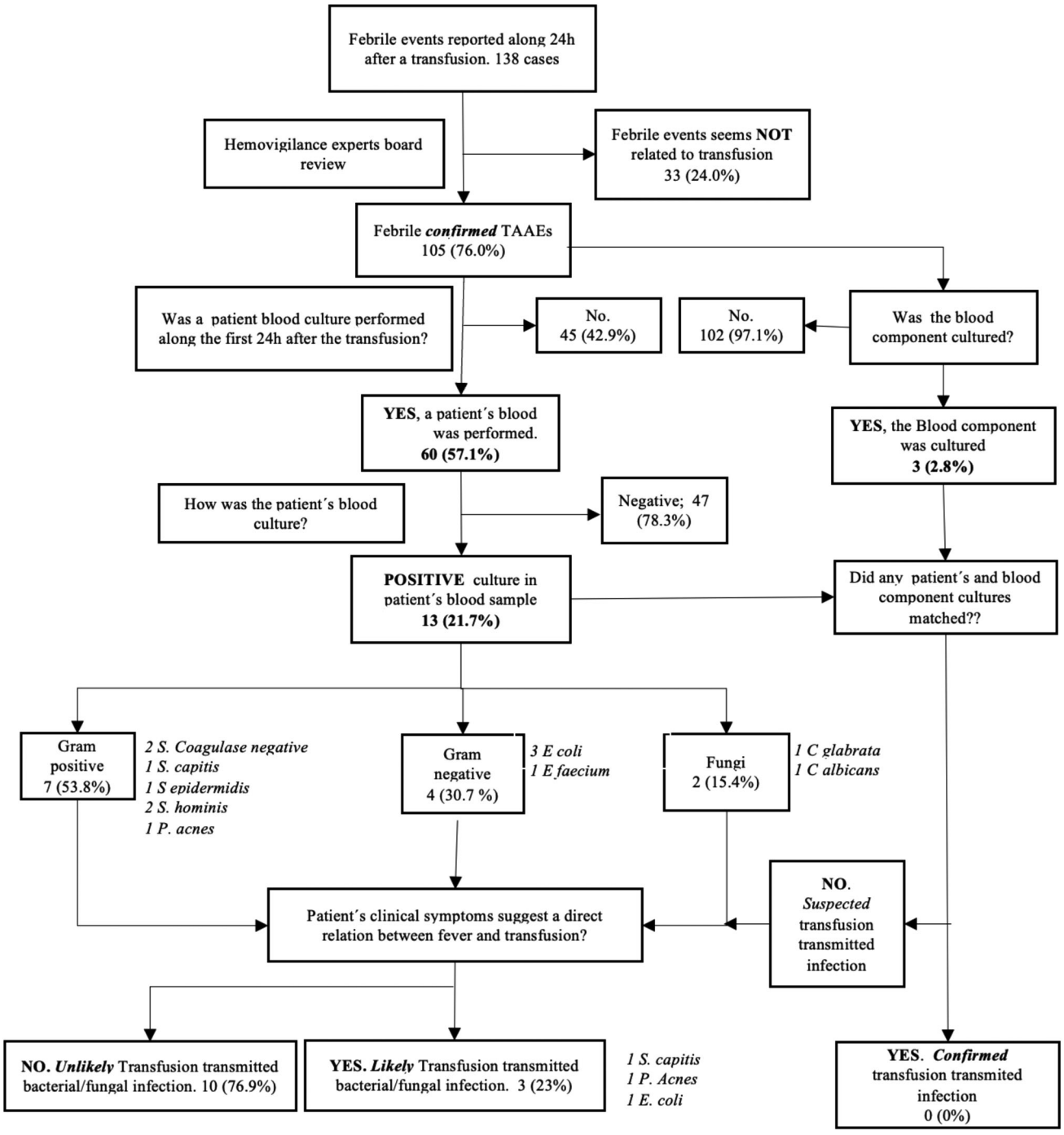

FIGURE 3 Suspected bacterial/fungal transfusion-transmitted infections (TTIs). *Confirmed* TTI requires a match between the microbe identified in the blood component and that identified in the patient culture. *Likely* TTI requires a positive microbe culture in the patient without component positive culture, and a clinical relationship between the patient fever and the transfusion. We classified *Unlikely* TTI when positive microbe culture in the patient did not suggest a clinical relationship with the transfusion.

3.6 | Mortality, severity, and imputability

Only one transfusion-related death was reported with the passive system; 0.21 per 10,000 (95% CI, 0.17–0.25) compared to five cases in the HEMACUA protocol; 1.1 per 10,000 (95% CI, 0.13–2.01; *p* value: ns). Three (60%) out of five deaths were associated with pulmonary TAAEs, 35 out 252 events (13.9%) were fatal or severe; of these, 28 (80%) were lung-related. A full clinical description of the deaths and TRALI cases is outlined in the supplementary appendix. Imputability was *certain* or *likely* in

TABLE 3 TAAEs severity and imputability in the active HV model.

	Severity					Imputability		
TAAEs	Death	Signs with vital risk	Signs without vital risk and full resolution	Death or vital risk; *n* (%)	Certain	Likely	Possible	Certain or likely; *n* (%)
Febrile	0	0	105	0 (0)	0	23	82	23 (21·9)
Allergic	0	0	77	0 (0)	15	20	42	35 (45·5)
Nausea/vomiting	1	0	26	1 (3·7)	1	5	21	6 (22·2)
TAD	0	12	5	12 (70·6)	0	4	13	4 (23·5)
Other	0	2	3	2 (40·0)	0	0	5	0 (0)
Diarrhea	0	0	6	0 (0)	0	2	4	2 (33·3)
HTR	1	0	0	1(100)	1	0	0	1 (100)
TACO	1	9	9	10 (52·6)	17	1	1	18 (94·7)
TACO/TRALI	1	3	1	4 (80)	2	3	0	5 (100)
Type II TRALI	0	1	0	(1100)	1	0	0	1 (100)
Type I TRALI	1	0	0	1 (00)	1	0	0	1 (100)
ARDS	0	3	0	3 (100)	1	1	1	2 (66·7)
TOTAL	5	30	232	35 (13·1)	39	59	169	98 (36·7)

Abbreviations: HTR, hemolytic transfusion reaction; TAAEs, transfusion-associated adverse events; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnea; TRALI, transfusion-related acute lung injury.

98 out of 267 (36.7%) cases and higher in the 31 pulmonary out of 46 (67.4%) cases. A detailed description of severity and imputability is shown in Table 3.

3.7 | Time from onset of transfusion and other factors related to the events

Most TAAEs occurred when the transfusion had already finished (Figure 4). Overall, 161 (60.2%) and 215 (80.4%) of pulmonary events occurred more than 2 h after the onset of transfusion. Regarding factors associated with TAAEs occurrence, we found in the multivariate analysis (Table 1) that surgical patients had approximately half the TAAE risk compared to medical-ward patients (RR, 0.53; 95% CI, 0.34–0.78) and women had nearly twice the risk of a pulmonary event compared to men (RR, 1.84; 95% CI, 1.03–3.32). *Patient age, blood component shelf-life, or blood component type* were unrelated to TAAEs risk during multivariate analysis. Raw incidences by blood component and patient features are shown in Table S2.

4 | DISCUSSION

Hemovigilance (HV) is the procedure to monitor any adverse event occurring from blood donation until after the end of transfusion. This holistic approach is managed with disparate frameworks and results in current HV programs.[3,5,13–16] However, most share a model based on the passive reporting of events that tends to underestimate TAAEs incidence.[17]

4.1 | Statement of principal findings

Our main finding in this study is that the implementation of an active HV program markedly increases the detection of TAAEs compared to the passive HV model (Table 2). This increase is especially attributable to those TAAEs occurring when the transfusion has already finished, and especially to the pulmonary events found to be the most severe (Figure S1).

Our multivariate analysis revealed a limited relationship between the blood component or patient's features and the risk of onset of a TAAE.[18] However, we found a lower risk of onset of TAAEs in patients transfused after a surgical procedure and a higher risk of developing pulmonary events in women. We do not have a clear explanation for the lower risk for surgical patients compared to medical patients and this finding should be confirmed and explored in other studies. The higher female risk of pulmonary events could be accounted for by alloimmunization during pregnancies, but unfortunately, we do not have information on patients' pregnancy antecedents which could help to understand this finding.

We observed a dichotomous profile for TAAEs in our study. On the one hand, common febrile, allergic, or

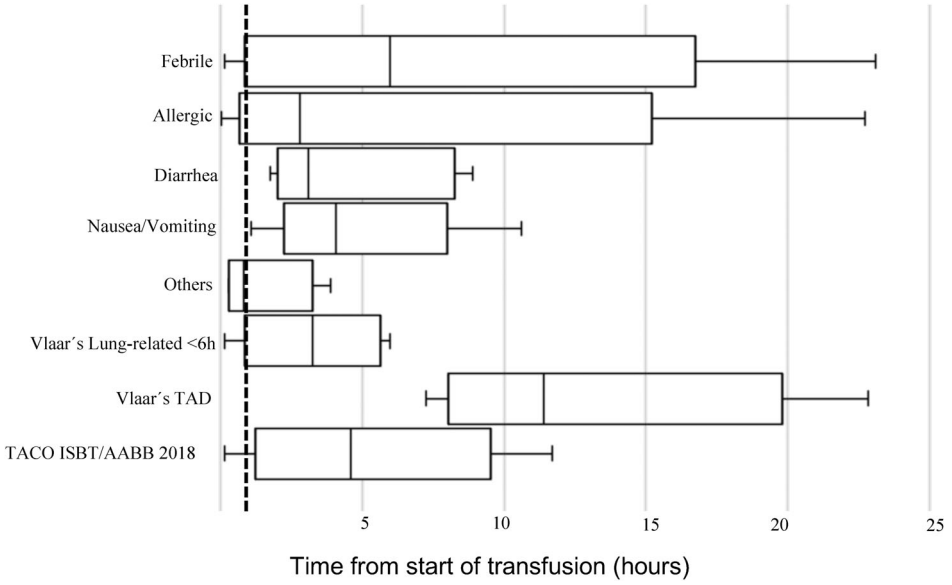

FIGURE 4 Time to transfusion adverse event from the transfusion onset. Box plots show median 25% and 75% percentiles. Whiskers show minimum and maximum values. Pulmonary events have been grouped as those occurring before or after 6 h (TAD). The dotted line denotes the median time for a RBC transfusion that was 1.1 h. TAD, Transfusion-associated dyspnea.

gastrointestinal TAAEs that are usually mild. On the other hand, belated and severe pulmonary TAAEs that went unnoticed for the passive HV model (Figure 4). Only two out of 46 pulmonary events were found in the passive model. This reinforces the importance of an active HV model to detect pulmonary events; the most severe.

Fever was very common but severity and imputability was low without evidence of transfusion transmitted infections (Figure 3). Allergic events including digestive symptoms, were also common and mild. We explored patient IgA levels looking for a possible relationship between allergic symptoms and IgA deficiency without drawing definitive conclusions.

4.2 | Strengths and weaknesses of the study

The implementation of effective Patient Blood Management policies and optimizing software integration in our hospital during the last few years[6] has enabled a huge data compilation and further analysis of our transfusion practice. Our Expert Board review for an accrued events classification supports our results that uncover a higher transfusion risk than previously recognized. The implementation of an effective SUT policy[19] also optimizes identifying the correct component that causes each TAAE; as most TAAEs are linked to a single blood component transfusion. We believe these are the main strengths of our study.

However, we acknowledge a single-center study as the main weakness. Since transfusion practice varies among hospitals, this compromises our study's external validity. Only 56 (0.2%) transfusions were performed to children under 16 in this study, so our conclusions cannot be deemed applicable to the pediatric population. Most blood components were not cultured after a febrile event, and this limited the confirmation of fungal/bacterial transfusion-transmitted infections. Moreover, as reliable information on premedication was unavailable, fever and allergic TAAEs should be interpreted cautiously. Finally, we cannot rule out missed or over-reporting in our new HV model. We are aware of these weaknesses in our study.

4.3 | Strengths and weaknesses in relation to other studies

Comparing our result to National HV reports studies shows that TAAEs incidence, mortality, and severity in our study is high.[3,5,13–16,20,21] However, our incidence is quite similar to that found in one of the infrequent prospective, active, 24-h follow-up hemovigilance studies published.[4] In this selective study designed to assess the safety of inactivated platelets, Knutson et al. reported one TAAE every 156 transfusions. This is similar to our one per 174 incidence and could reveal the actual incidence of transfusion risk. We agree with the SHOT report: *low reporting should not be interpreted as a safe organization, as this may represent under-reporting; and similarly, high reporting should not be interpreted as an unsafe organization, as this may actually represent a culture of greater openness*.[3]

However, we concur with updated HV national reports[3,15] to establish TACO as the most severe TAAE with TRALI relegated as a rare event. The low incidence of TRALI could be accounted for by the implementation of preventive measures on blood donor selection[22] but

also due to the accepted TRALI definition that restricts this diagnosis to a timeframe of 6 h at the end of transfusion[7–23] forcing us to label *delayed TRALIs*[24] as TADs with Vlaar's classification. The TRALI definition could be revised to extend this event beyond 6 h, especially when specific antibodies were reported.

The definition of TACO is still unclear. In our study we explored comparison of TACO incidence according to the traditional ISBT/AABB 2018 definition[9] (6.0 per 10,000; 95% CI 3.8–8.2) or the new Vlaar's classification[23] (4.1 per 10,000; 95% CI 2.2–5.1). Furthermore, we have labeled two hypertension events as *unclassifiable* because those patients did not show respiratory symptoms, although TACO diagnosis was highly suspected. Our TACO incidences using both classifications are still lower compared to reports in intensive care unit patients that attain 5.8%.[25] These discrepancies suggest that new consensus definitions are desirable for pulmonary TAAEs. In any case, a clear conclusion to draw is that TACO is recognized as the most worrying TAAE and the frontline intervention in the future to reduce transfusion risk.

Even as bacterial transfusion-transmitted infections have been reduced in the last few years due to the implementation of safer practices during blood donation[26] they still occur, although this is difficult to confirm (Figure 3). Hemolytic transfusion reactions (HTR) due to ABO errors have fortunately decreased after the implementation of effective patient identification[6] and we do not report any cases during the study period. Interestingly, some *hyperhemolysis* cases have recently been referred to in international HV reports.[3] Here we report one of these (supplementary case 5 in the clinical description of deaths), although we have identified at least four cases in the last few years (outside the scope of this study's timeframe) with a profile linked to stem cell transplanted patients.[27] This unknown severe event warrants future monitoring and research.

Digestive events are not recognized as a category of transfusion event in HV reports. However, we detected 12.4% of TAAEs with specific digestive symptoms, predominantly nausea, or vomiting. Even if these TAAEs appear to have an allergic background, we believe that a different category classification as *digestive TAAEs* could be helpful to better define these symptoms in the future.

4.4 | Meaning of the study: Possible explanations and implications for clinicians, policymakers

Our study suggests that transfusion risk could be higher than previously reported, as most TAAEs occur when the transfusion has already ended. This is remarkable for pulmonary events, especially TACOs that emerge as the most worrying and preventable TAAE. Our findings support the implementation of active HV programs, TAAEs definition agreement and further staff education to improve report accuracy and concordance.[28,29] As transfusion is one of the more overused medical practices,[30] SUT promotion and restrictive transfusion policies[31] should be considered as the primary aim of policymakers to reduce transfusion risk.

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CONFLICT OF INTEREST STATEMENT

José L Bueno declares consulting fees on a National PBM program from the Turkish Health Ministry, Honoraria for lectures from Grifols, Macopharma, Terumo BCT, and Sanofi. He is also the inventor and main holder of patent EP 3272373 B1 on a transfusion safety device that has been licensed in several European countries since August 2019. JAGE declares honoraria for lectures from Vifor-Uriach, Zambon, Sandoz, Octapharma, BSL-Behring, and Fresenius. Other authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

DATA AVAILABILITY STATEMENT

Data necessary for the replication of our results, tables, and figures are available in .xls, .sav, and .mdb de-identified files for editors and reviewers without restrictions. These files are structured by means of a data dictionary included in the supplementary material (missing data table). Data will also be available for readers "with publication" after approval of a proposal and with a signed data access agreement.

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