






## BRIEF REPORT

# Active surveillance of serious adverse events following transfusion of COVID-19 convalescent plasma

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## Abstract

**Background:** The reported incidence of adverse reactions following Coronavirus disease 2019 (COVID-19) convalescent plasma (CCP) transfusion has generally been lower than expected based on the incidence of transfusion reactions that have been observed in studies of conventional plasma transfusion. This raises the concern for under-reporting of adverse events in studies of CCP that rely on passive surveillance strategies.

**Materials and Methods:** Our institution implemented a protocol to actively identify possible adverse reactions to CCP transfusion. In addition, we retrospectively reviewed the charts of inpatients who received CCP at Stanford Hospital between May 13, 2020 and January 31, 2021. We determined the incidence of adverse events following CCP transfusion.

**Results:** A total of 49 patients received CCP. Seven patients (14%) had an increased supplemental oxygen requirement within 4 h of transfusion completion, including one patient who was intubated during the transfusion. An additional 11 patients (total of 18, 37%) had increased oxygen requirements within 24 h of transfusion, including 3 patients who were intubated. Six patients (12%) fulfilled criteria for transfusion-associated circulatory overload (TACO).

**Conclusion:** Using an active surveillance strategy, we commonly observed adverse events following the transfusion of CCP to hospitalized patients. It was not possible to definitively determine whether or not these adverse events are

**List of abbreviations:** (AKI), acute kidney injury; (ALL s/p HSCT), acute lymphocytic leukemia status post hematopoietic stem cell transplant; (BNP), N-terminal-prohormone brain natriuretic peptide; (CAD), coronary artery disease; (CCP), Coronavirus disease 2019 convalescent plasma; (COVID-19), Coronavirus disease 2019; (cm H<sub>2</sub>O), centimeters of water; (CVP), central venous pressure; (CXR), chest x-ray; (desat), oxygen desaturation; (EAP), Expanded Access Protocol; (EF), left ventricular ejection fraction; (EUA), Emergency Use Authorization; (FDA), Food and Drug Administration; (FFP), fresh frozen plasma; (FiO<sub>2</sub>), fraction of inspired oxygen; (GA), gestational age; (HFNC), high flow nasal cannula; (HTN), hypertension; (ICU), intensive care unit; (INRs), international normalized ratios; (IRB), Institutional Review Board; (Is/Os), intake/output; (LE), lower extremity; (L/min), liters per minute; (min), minute; (mL), milliliter; (NA), not available; (NC), nasal cannula oxygen; (ND), not determined; (NSTEMI), non-ST segment elevation myocardial infarction; (O<sub>2</sub> sat), oxygen saturation; (PE), pulmonary embolism; (PEEP), positive end-expiratory pressure; (pg), picograms; (resp), respiratory; (RA), room air; (RCTs), randomized controlled trials; (RD), risk difference; (RR), respiratory rate; (SAEs), serious adverse events; (TACO), transfusion-associated circulatory overload; (TRALI), transfusion-related acute lung injury; (TTE), transthoracic echocardiogram; (ULN), upper limit of normal; (wks), weeks.

Erica Swenson and Lisa Kanata Wong contributed equally to this study.

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related to CCP transfusion. TACO was likely over-diagnosed given overlap with the manifestations of COVID-19. Nevertheless, these results suggest that the potential adverse effects of CCP transfusion may be underestimated by reports from passive surveillance studies.

## 1 | INTRODUCTION

Plasma from patients who have recovered from SARS-CoV-2 infection, CCP, has received attention as a potential treatment for COVID-19.<sup>1,2</sup> TACO is the most common severe reaction to plasma transfusion.<sup>3–5</sup> Passive reporting has been shown to underestimate the incidence of TACO.<sup>6,7</sup> In an active surveillance study of unselected patients transfused at a tertiary hospital, the incidence of TACO was found to be 4.8%.<sup>6</sup> Another active surveillance study of 251 emergency department patients with elevated international normalized ratios (INRs) who received plasma reported a TACO incidence of 12%.<sup>8</sup> Other known risks of plasma transfusion include transfusion-transmitted infections, allergic reactions, febrile non-hemolytic reactions, transfusion-related acute lung injury (TRALI), and hemolytic reactions.<sup>3–5</sup>

In the United States, CCP has generally been used outside of randomized controlled trials (RCTs). The United States Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for CCP for hospitalized patients with COVID-19 on August 23, 2020, largely based on data from an uncontrolled national Expanded Access Protocol (EAP) which enrolled 105,717 patients.<sup>9–14</sup> While a primary goal of the EAP was to assess the safety of CCP, the study relied on passive reporting of serious adverse events (SAEs), including TACO, TRALI, and death. No instructions or diagnostic criteria were provided to study sites to guide SAE monitoring or reporting. Of the first 20,000 patients enrolled in this protocol, 141 (1%) were reported to have an SAE that was considered a potential transfusion reaction within 4 h of completion of CCP transfusion.<sup>12</sup> This included 63 fatalities (0.3% of all transfusions), 36 TACO (0.18% of all transfusions), 21 TRALI (0.1% of all transfusions), and 21 severe allergic transfusion reactions (0.1% of all transfusions). In contrast, in an active surveillance study of CCP transfusions, there was a 12.9% incidence of reactions, with 3.1% attributed by the authors to transfusion.<sup>15</sup>

We instituted an active surveillance protocol for transfusion reactions after CCP. The EAP stopped enrollment on August 28, 2020, after the United States FDA

issued the EUA for CCP. We continued our active surveillance strategy for CCP transfused under the EUA.

We then performed a retrospective chart review of patients who received CCP between May 13, 2020 and January 31, 2021.

## 2 | METHODS

The national EAP was approved by the Stanford Hospital Institutional Review Board (IRB). The EAP methods have been described.<sup>11–14</sup> The Stanford IRB approved a retrospective chart review study. Patients were eligible to be transfused under the EAP if they had severe or life-threatening COVID-19 or were at risk for progression to severe or life-threatening illness. Under the EUA, hospitalized adult patients with COVID-19 were eligible to receive CCP.

The on-call transfusion medicine physician was paged when a CCP was ordered. The transfusion medicine team evaluated the potential recipient's volume status and risk factors for volume overload with the treating team. All patients were recommended to receive CCP transfusion over 4 h, and additional TACO mitigation strategies were recommended, if appropriate, including diuresis prior to transfusion. Treating teams were asked to report all suspected transfusion reactions. Approximately 24 h post-transfusion, the transfusion medicine team evaluated the patient's chart for evidence of transfusion reactions. This included a review of the patient's progress notes, vital signs, chest radiology, and discussion with the treating team. For patients with any potential evidence of a transfusion reaction, the transfusion medicine on-call team guided the treating team regarding further evaluation and management.

Transfusion reactions were classified by the 2018 CDC/NHSN Hemovigilance criteria, version 2.5.2.<sup>16</sup> The criteria for TACO are “new onset or exacerbation of 3 or more of the following within 6 h of cessation of transfusion”: acute respiratory distress, elevated brain natriuretic peptide (BNP), elevated central venous pressure, evidence of left heart failure, evidence of positive fluid balance, and radiographic evidence of pulmonary edema.<sup>16</sup> Each case was additionally assigned an imputability category.

In addition, we retrospectively evaluated the charts of all adult patients at Stanford who were transfused with CCP between May 13, 2020 and January 31, 2021 and had been discharged from the hospital at the time of chart review on February 4, 2021, to record outcomes beyond the 24-h time point. We followed patients until they died or were discharged. To facilitate direct comparison with prior published CCP adverse event data, we assessed the incidence of adverse events at 4-h and 24-h following transfusion.<sup>12</sup>

To compare the risk between the Stanford and national EAP cohorts, we calculated the risk difference for adverse events as risk difference (RD) = risk for adverse event (total Stanford cohort) - risk for adverse event (national EAP). We estimated 95% confidence intervals and p values of the RD using the “fmsb” package in R statistical programming language, version 4.0.3.<sup>17</sup>

### 3 | RESULTS

Forty-nine patients received CCP at Stanford Hospital between May 13, 2020 and January 31, 2021. Thirty patients received CCP under the EAP, and 19 under the EUA (Table 1). The mean age was 52.5 years. Fifty-nine percent of CCP recipients were male. Many patients were overweight (33%) or obese (41%). Most patients received CCP in the ICU (70%). Eighty-eight percent of the patients were on supplemental oxygen and 33% were mechanically ventilated prior to transfusion.

Seven patients (14%) had increased oxygen requirements during or within 4 h of completion of CCP transfusion (Table 2). An additional 11 patients had increased oxygen requirements between 4 h and 24 h after CCP transfusion, totaling 18 patients (37%) with increasing oxygen requirements within 24 h of CCP transfusion. One patient (2%) was intubated within 4 h of transfusion. Two additional patients were intubated between 4-h and 24-h following transfusion, for a total of 3 (6%) patients who were intubated within 24 h of transfusion.

Due to significant overlap in clinical manifestations, it was not possible to firmly attribute worsened respiratory status following transfusion to worsening COVID versus TACO. We assessed whether cases fulfilled 2018 CDC/NHSN criteria for “definitive” TACO, bearing in mind that some patients that fulfill these criteria may in fact not have experienced a transfusion reaction. Out of the 18 patients who had increasing oxygen requirements within 24 h of CCP transfusion, 6 (12%) met 2018 CDC/NHSN case definition for “definitive” TACO (Table 3). Of these 6 cases, 5 were assigned an imputability of “probable” and 1 “possible”.<sup>16</sup> Compared to the national EAP cohort, the Stanford cohort had a 12.06% higher reported risk for TACO within 4 h (95% CI: [2.89,

21.24%],  $p = .01$ ). No patients died within 4 h of transfusion and 2 (4%) died within 7 days of transfusion (Table 2). No patient fulfilled the case definition for TRALI or allergic transfusion reaction.

All suspected transfusion reactions were identified via active surveillance by transfusion medicine physicians; none were reported by the treating team.

### 4 | DISCUSSION

Using an active surveillance strategy, we commonly observed adverse reactions following CCP transfusion, with 12% of patients fulfilling the 2018 CDC/NHSN case definition for TACO. This contrasts with the low rate of adverse reactions reported in the national EAP, which relied on passive reporting.<sup>12</sup>

The adverse events captured in our study may have been due to transfusion or to underlying COVID-19 pneumonia. Randomized controlled trials with active surveillance for possible transfusion reactions are required to accurately determine the true incidence of adverse reactions caused by CCP. The incidence of adverse events attributable to CCP is undoubtedly lower than the incidence reported in our study. We strictly defined TACO based on the 2018 CDC/NHSN criteria, following standard methods in the transfusion literature. A limitation of this approach is that a patient with worsening viral pneumonia could also meet the CDC/NHSN TACO criteria.

Out of a total of 18 patients with worsened respiratory status following CCP transfusion, 6 met TACO criteria; 12 did not meet transfusion reaction diagnostic criteria and most likely had progression of underlying COVID-19 pneumonia. In the national EAP study, < 1% of patients were reported to have any adverse event within 4 h following transfusion, and 0.18% of patients were reported to have TACO.<sup>12</sup> In our cohort, 12% of patients fulfilled the CDC/NHSN case definition for TACO.<sup>16</sup> The incidence of TACO in our study is consistent with what has previously been reported in an active surveillance study of fresh frozen plasma (FFP) transfusion to emergency department patients.<sup>8</sup>

When considering why there was a higher reported incidence of TACO in our cohort compared with the national EAP, two important considerations are 1) small sample size and 2) differences between the study populations. Given the substantial differences in the incidence of adverse events between our study and the reported national EAP data, it is possible but less likely that the difference is solely due to small sample size. If our cohort was more ill at baseline, this could potentially be an explanation for a true higher incidence of adverse

**TABLE 1** Demographic information of patients who received COVID-19 convalescent plasma at Stanford under the expanded access protocol (EAP) and FDA emergency use authorization (EUA) compared with data published on the first 20,000 patients enrolled in the national EAP<sup>12</sup>

	Stanford EAP	Stanford EUA	Total Stanford cohort	National EAP data
<i>n</i>	30	19	49	20,000
<b>Age</b>				
Mean age (years)	51.1	54.7	52.5	NR
Age range (years)	23–80	27–79	23–80	NR
Age (18–39 years)	9 (30%)	5 (26%)	14 (29%)	1532 (8%)
Age (40–59 years)	12 (40%)	4 (21%)	16 (33%)	6376 (32%)
Age (60–69 years)	3 (10%)	8 (42%)	11 (22%)	5409 (27%)
Age (70–79 years)	5 (17%)	2 (11%)	7 (14%)	4119 (21%)
Age (80 years and above)	1 (3%)	0 (0%)	1 (2%)	2564 (13%)
<b>Sex</b>				
Male	17 (57%)	12 (63%)	29 (59%)	12,165 (61%)
Female	13 (43%)	7 (37%)	20 (41%)	7761 (39%)
Other	0 (0%)	0 (0%)	0 (0%)	74 (< 1%)
<b>Weight status</b>				
Underweight	0 (0%)	0 (0%)	0 (0%)	310 (2%)
Normal	9 (30%)	3 (16%)	12 (24%)	3322 (18%)
Overweight	9 (30%)	7 (37%)	16 (33%)	5304 (28%)
Obese	12 (40%)	8 (43%)	20 (41%)	9753 (52%)
Unknown	0.00%	1 (5%)	1 (2%)	0 (0%)
<b>Race</b>				
Asian	1 (3%)	2 (11%)	3 (6%)	999 (5%)
Black	1 (3.3%)	0 (0%)	1 (2%)	3916 (20%)
White	27 (90%)	17 (90%)	44 (90%)	9734 (49%)
Other or unknown	1 (3.3%)	0 (0%)	1 (2%)	5351 (27%)
<b>Ethnicity</b>				
Hispanic/Latino	22 (73%)	15 (79%)	37 (76%)	6936 (35%)
Not Hispanic/Latino	8 (27%)	4 (21%)	12 (24%)	13,064 (65%)
<b>Clinical status prior to CCP transfusion</b>				
Mechanically ventilated	11 (37%)	5 (26%)	16 (33%)	6864 (34%)
On supplemental oxygen	26 (90%)	17 (90%)	43 (88%)	NR
Admitted to ICU	24 (80%)	10 (53%)	34 (70%)	11,560 (58%)

Abbreviations: CCP, Coronavirus disease 2019 (COVID-19) convalescent plasma, EAP, Expanded Access Protocol, EUA, Emergency Use Authorization, ICU, intensive care unit, NR, not reported.

events. While our cohort had a somewhat higher percentage of patients admitted to the ICU at the time of CCP transfusion (70% vs 58%), those mechanically ventilated at the time of transfusion (33% vs 34%) were similar. In addition, our cohort was younger than the EAP cohort (16% vs 33% of patients were 70 years of age and older) and had a similar risk of mortality within 4 h or within 7 days of transfusion. Overall, it is unlikely that the differences in rates of adverse reactions could be attributed

either to small sample size or to our cohort being more ill than the national cohort.

A likely explanation for the difference in the reported incidence of adverse events between our study and the national EAP study is that each patient in our cohort was actively surveilled by transfusion medicine physicians. This explanation is in line with the thinking of Nguyen et al, who also performed an active surveillance study of transfusion reactions.<sup>15</sup> EAP study sites may not have

**TABLE 2** Serious adverse events observed at Stanford compared with safety data reported for the first 20,000 patients enrolled in the national EAP<sup>12</sup>

	Stanford EAP (n = 30)	Stanford EUA (n = 19)	Total Stanford cohort (n = 49)	National EAP data (reported) (n = 20,000)	Risk difference (RD) <sup>g</sup> , 95% CI, p value
<b>Increased O<sub>2</sub> requirement</b>					
Within 4 h of transfusion <sup>a</sup>	6 (20%)	1 (5%)	7 (14%)	NR	NR
Within 24 h of transfusion <sup>b</sup>	11 (37%)	7 (37%)	18 (37%)	NR	NR
<b>Intubation</b>					
Within 4 h of transfusion <sup>a</sup>	1 (3%)	0 (0%)	1 (2%)	NR	NR
Within 24 h of transfusion <sup>c</sup>	2 (7%)	1 (5%)	3 (6%)	NR	NR
<b>TACO<sup>d</sup></b>					
Within 4 h of transfusion	4 (13%)	2 (11%)	6 (12%)	36 (0.18%)	12.06% [2.89%, 21.24%] p = .010
Within 24 h of transfusion <sup>e</sup>	4 (13%)	2 (11%)	6 (12%)	NR	NR
<b>TRALI<sup>d</sup></b>					
Within 4 h of transfusion	0 (0%)	0 (0%)	0 (0%)	21 (0.11%)	-0.11% [-0.15%, -0.06%] p < .0001
Within 24 h of transfusion	0 (0%)	0 (0%)	0 (0%)	NR	NR
<b>Severe allergic transfusion reaction<sup>d</sup></b>					
Within 4 h of transfusion	0 (0%)	0 (0%)	0 (0%)	21 (0.11%)	-0.11% [-0.15%, -0.06%] p < .0001
Within 24 h of transfusion	0 (0%)	0 (0%)	0 (0%)	NR	NR
Serious adverse event within 7 days of transfusion	3 (10%)	0 (0%)	3 (6%)	113 (0.56%)	5.56% [-1.16%, 12.3%] p = .105
Thrombotic or thromboembolic complication	5 (17%)	0 (0%)	5 (10%)	457 (2%)	7.92% [-0.56%, 16.4%] p = .067
Sustained hypotension	0 (0%)	1 (5%)	1 (2%)	677 (3%)	-1.34% [-5.31%, 2.62%] p = .507
Cardiac events	1 (3%)	1 (5%)	2 (4%)	1806 (9%)	-4.95% [-10.5%, 0.61%] p = .0808
ICU admission	3 (10%)	0 (0%)	3 (6%)	113 (0.56%)	5.56% [-1.16%, 12.27%] p = .105
<b>Mortality</b>					
Within 4 h of transfusion	0 (0%)	0 (0%)	0 (0%)	63 (0.3%)	-0.32% [-0.39%, -0.24%] p < .001
Within 7 days of transfusion <sup>f</sup>	0 (0%)	2 (11%)	2 (4%)	2592 (13%)	-8.88% [-14.44%, -3.32%] p = .0017
Overall	5 (17%)	3 (16%)	8 (16%)	NR	NR

Abbreviations: CCP, Coronavirus disease 2019 (COVID-19) convalescent plasma; EAP, Expanded Access Protocol; EUA, Emergency Use Authorization; ICU, intensive care unit; NR, not reported; O<sub>2</sub>, supplemental oxygen; Related, related to CCP transfusion; TACO, transfusion-associated cardiac overload; TRALI, transfusion-related acute lung injury.

<sup>a</sup>Data in this row includes patients with TACO.

<sup>b</sup>Data in this row includes patients with increased O<sub>2</sub> requirements within 4 h of transfusion and patients with TACO.

<sup>c</sup>Data in this row includes patients intubated within 4 h of transfusion and patients with TACO.

<sup>d</sup>Diagnosis of TACO, TRALI, and severe allergic transfusion reactions were assigned using CDC/NHSN Hemovigilance definitions for the Stanford cohort.<sup>16</sup>

<sup>e</sup>Data in this row includes patients with who developed TACO within 4 h of transfusion.

<sup>f</sup>Data in this row includes patients who died within 4 h of transfusion.

<sup>g</sup>Reference group = national EAP; risk difference (RD) = risk for adverse event (Stanford) - risk for adverse event (National EAP).<sup>12</sup>

TABLE 3 Characteristics of patients that fulfilled CDC/NHSN criteria for transfusion-associated circulatory overload (TACO)<sup>16</sup>

23F, ALL s/p HSCT, nephrotic syndrome, hypoalbuminemia. Home furosemide held on admission.		42 M HTN, massive bilateral PE, multiple cerebral infarcts.		71 M CAD, h/o NSTEMI.		74 M, HTN.		34F pregnant 12 weeks GA.	
# CCP units transfused	1	2	2	2	1	1	1	1	1
Volume transfused (mL)	206	409	429	242	250				
Transfusion duration (min)	90	105	484 <sup>a</sup>	83	38				
Pre-CCP resp status	O <sub>2</sub> sat 100% RR 20 NC 1 L/min	O <sub>2</sub> sat 98% RR 35 Vent	O <sub>2</sub> sat 95% RR 20 HFNC	O <sub>2</sub> sat 94% RR 33 HFNC	O <sub>2</sub> sat 98% RR 30 HFNC				
Pre-CCP resp support	FiO <sub>2</sub> 99% 30 L/min	FiO <sub>2</sub> 70% PEEP 12	FiO <sub>2</sub> 100% 30 L/min	FiO <sub>2</sub> 60% 30 L/min	FiO <sub>2</sub> 80% 40 L/min				
Post-CCP resp status	O <sub>2</sub> sat 98% RR 18 RA	O <sub>2</sub> sat 90% RR 31 Vent	O <sub>2</sub> sat 91% RR 19 HFNC	O <sub>2</sub> sat 89% RR 38 HFNC	O <sub>2</sub> sat 98% RR 48 HFNC				
Post-CCP resp support	FiO <sub>2</sub> 100% PEEP 10	FiO <sub>2</sub> 80% PEEP 14	FiO <sub>2</sub> 100% 30 L/min	FiO <sub>2</sub> 70% 30 L/min	FiO <sub>2</sub> 80% 40 L/min				
Manifestation of acute respiratory distress	*Dyspnea, cough, increased work of breathing w/in 6 h of transfusion	*Desat and increased ventilatory support w/in 2 h of transfusion	*Desat during transfusion prompting emergent intubation	*Dyspnea, desat during transfusion of 2nd unit. Intubated w/in 7 h of transfusion	*Dyspnea, tachypnea, desat during transfusion. Intubated w/in 9 h of transfusion				*Tachypnea, dyspnea, increased work of breathing w/in 1 h of transfusion
Pre-CCP BNP (pg/mL)	NA	7159	47	283	NA				
<ULN (pg/mL) <sup>b</sup>	<353	<93	<229	<229					
Post-CCP BNP (pg/mL)	*912	*3811	189	*346	*428				
<ULN (pg/mL) <sup>b</sup>	<178	<353	<93	<229	<178				
Post CCP CVP (cm H <sub>2</sub> O)	NA	*12	NA	NA	NA				
TTE <sup>c</sup>	Pre: EF 61%	Pre: Low/normal LV systolic function (EF ND), markedly reduced RV systolic function	Pre: EF 65%, LVH	Post: EF 65%	Pre: EF 50%				

(Continues)

TABLE 3 (Continued)

	23F, ALL s/p HSCT, nephrotic syndrome, hypoalbuminemia. Home furosemide held on admission.	71F, HTN, AKI.	42 M HTN, massive bilateral PE, multiple cerebral infarcts.	71 M CAD, h/o NSTEMI.	74 M, HTN.	34F pregnant 12 weeks GA.
Net Is/Os (mL) <sup>d</sup>	* +259	-717	-740	*+508 <sup>a</sup>	-305	-320
Clinical volume overload	*LE edema	NA	NA	NA	NA	*LE edema
Post-CCP CXR	*Increased bilateral patchy and consolidative opacities in upper and mid lung zones	*Increased bilateral diffuse hazy opacities	*Significantly increased bilateral opacities	*Worsened bilateral multifocal opacities	*Worsened perihilar lung consolidation, with new air bronchograms	*Persistent multifocal patchy and consolidative opacities, increased in the lung bases
Management/outcome	Improved without diuretics, discharged	Deceased	Deceased	Deceased	Improved w/ furosemide, discharged	Improved w/ furosemide, discharged
Imputability	Probable	Probable	Possible	Probable	Probable	Probable

Note: All patients had onset of respiratory distress within 4 h of CCP transfusion. Asterisk indicates CDC/NHSN Hemovigilance TACO diagnostic criteria that were met.<sup>16</sup>

Abbreviations: AKI, acute kidney injury; ALL s/p HSCT, acute lymphocytic leukemia status post hematopoietic stem cell transplant; BNP, N-terminal-prohormone brain natriuretic peptide; CAD, coronary artery disease; CCP, COVID-19 convalescent plasma; CCP, prior to CCP transfusion; cm H<sub>2</sub>O, centimeters of water; CVP, central venous pressure; desat, oxygen desaturation; CXR, chest x-ray; EF, left ventricular ejection fraction; FiO<sub>2</sub>, fraction of inspired oxygen; GA, gestational age; HFNC, high flow nasal cannula; HTN, hypertension; Is/Os, intake/output; LE, lower extremity; L/min, liters per minute; min, minute; mL, milliliter; NA, not available; NC, nasal cannula oxygen; ND, not determined; NSTEMI, non-ST segment elevation myocardial infarction; O<sub>2</sub> sat, oxygen saturation; PE, pulmonary embolism; PEEP, positive end-expiratory pressure (reported in cm H<sub>2</sub>O); pg, picograms; resp, respiratory; RA, room air; RR, respiratory rate (reported in breaths per minute); TTE, trans-thoracic echocardiogram; ULN, upper limit of normal; Vent = mechanical ventilation; wks, weeks.

<sup>a</sup>Patient received 1 unit over 235 min, then 20 h and 5 min later received a second unit over 249 min. Net Is/Os calculated for day during which the second unit was transfused.

<sup>b</sup>Upper limit of normal for BNP adjusted by age and sex, reflecting 95th percentile without congestive heart failure.

<sup>c</sup>TTE findings are indicated as pre- or post- relative to CCP transfusion.

<sup>d</sup>Inns/Outs were measured from the 7 am prior to CCP transfusion to the 7 am following CCP transfusion.

had clinicians familiar with CDC/NSHN criteria actively evaluating all CCP recipients post-transfusion. This could have contributed to the under-reporting of potential transfusion reactions to CCP. The fact that none of the suspected transfusion reactions to CCP at our institution were reported through routine transfusion reaction reporting mechanisms highlights the challenges of relying on passive reporting of transfusion reactions.

Under-reporting of serious adverse events has been highlighted as an issue in other studies.<sup>18,19</sup> For example, a retrospective analysis revealed that the reported incidence of cardiovascular adverse events in studies of experimental oncology treatments was lower than that observed among the general population.<sup>18</sup> Given that a key aim of the EAP was to assess safety, the potential for under-reporting of adverse reactions is very important to consider.

Especially in light of uncertainty regarding whether patients benefit from CCP transfusion, it is paramount that the potential adverse effects are carefully considered.<sup>20–24</sup> Using an active surveillance strategy, adverse events were common following transfusion of CCP to hospitalized patients. The potential adverse effects of CCP may be underestimated in studies relying on passive surveillance strategies.

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## CONFLICT OF INTEREST


The authors have reviewed the AABB's conflict of interest policy and report no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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