SENTINEL PROTOCOL BASED ASSESSMENT REPORT

TRANSFUSION RELATED ACUTE LUNG INJURY AFTER RED BLOOD CELL, PLASMA, AND PLATELET ADMINISTRATION 2013-2015

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. This project was funded by the FDA through HHS Mini-Sentinel contract number HHSF223200910006I.

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I. EXECUTIVE SUMMARY OF KEY FINDINGS

A. BACKGROUND

Transfusion-Related Acute Lung Injury (TRALI) is an adverse event, broadly defined as the onset of respiratory distress during or within 6 hours of blood transfusion. TRALI is a leading cause of transfusion-associated fatalities reported to the U.S. Food and Drug Administration. In 2016, FDA expanded the data within Sentinel to include inpatient electronic medical record (EMR) data from HCA Healthcare (HCA). This assessment of TRALI after blood component exposure is the first Sentinel utilization of this new inpatient data source.

B. OBJECTIVES

This project focused on data exploration and assessed the feasibility of utilizing Sentinel inpatient EMR data to capture exposure to blood components and TRALI. We described the occurrence of TRALI subsequent to blood component exposure and determined the positive predictive value (PPV) of an algorithm for identifying TRALI, as well as reported transfused product exposure in identified TRALI cases. Exploratory analyses focused on feasibility of examining patient and TRALI associated transfusion risk factors, as well as identification of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated). Where possible, we used information derived from medical chart review to inform these explorations.

C. METHODS

1. Electronic data, primary analyses

We utilized a retrospective cohort study design to examine TRALI occurrence among patients transfused in a hospital inpatient setting from September 2013 through September 2015. Within this cohort, capture of potential TRALI cases, potential risk factors for TRALI, and relevant transfusion exposures were described. Inpatient stays with at least one blood component transfused, were used as the study's main unit of analysis. Potential TRALI cases were identified with ICD-9-CM codes. As TRALI is likely under-diagnosed, we focused not only on the TRALI specific ICD-9-CM code (Criterion A: 518.7; potential-TRALI$_A$), but also on specific respiratory failure codes (Criterion B: 518.81, acute respiratory failure; Criterion C: 518.82, Other pulmonary insufficiency, not elsewhere classified) in combination with an ICD-9-CM code for a transfusion reaction (ICD-9-CM codes: 999.80, 999.89, E934.7), hereafter referred to as potential-TRALI$_A$, potential-TRALI$_B$, potential-TRALI$_C$, or potential-TRALI$_{A,B,C}$
Univariate and bivariate descriptive analyses were implemented to characterize transfusion and potential-TRALI as defined with all TRALI criteria (potential-TRALI$_{A,B,C}$) in the HCA Sentinel inpatient database. Unadjusted potential TRALI occurrence rates (OR) after any transfusion were calculated by dividing the number of potential TRALI cases by the number of inpatient transfusion stays during the study time-period. We also calculated 95% confidence intervals and corresponding chi-square tests. All transfusions were identified utilizing the Sentinel inpatient transfusion data. Unadjusted potential TRALI occurrence rates (per 100,000 inpatient transfusion stays) were stratified by year, blood component groups (i.e., plasma, platelets, and red blood cells (RBCs)), age, sex, race, discharge disposition, and quantified units.

2. Electronic data, exploratory analyses

In exploratory analyses, we focused on potential $TRALI_A$ and compared unadjusted TRALI rates (per 100,000 inpatient transfusion stays) by year (reference=2013), sex (reference=male), age (reference=age category 20-34 years), race (reference=white), mechanical ventilation during the inpatient stay (reference =none), discharge disposition (reference =discharged alive), blood component groups (reference =RBCs only), and quantified units during the inpatient stay (reference =1 unit). We calculated unadjusted rate ratios and 95% confidence intervals in analyses focused on comparisons of TRALI rates. With descriptive analyses, we examined feasibility of examining patient and TRALI associated transfusion risk factors, as well as identification of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated) in both electronic data and in medical charts. A qualitative summary describing data elements that are useful/relevant for studying TRALI was created, and potential areas for future data expansion were highlighted.

3. Medical record review

Medical record reviews were conducted to confirm the outcome (TRALI) and transfusion exposure, and the PPV of each electronic algorithm was evaluated. We also validated mechanical ventilation in potential TRALI cases. The gold standard was medical record confirmed outcomes and transfusion exposures.

D. RESULTS

4. Electronic data, primary analyses

We identified 208 potential TRALI-related inpatient stays among 3,945,217 inpatient stays (with and without transfusions) at 169 US hospitals in the HCA Sentinel database [potential-$TRALI_A$ =118 (57%), potential-$TRALI_B$ only=85 (41%), potential-$TRALI_C$ only=5 (2%)]. A transfusion was recorded in electronic data during 92% of these stays (n=192). There were 62 inpatient stays that met potential-$TRALI_A$, as well as potential-$TRALI_B$ and/or potential-$TRALI_C$ [potential-$TRALI_{A,B,C}$]; a transfusion was recorded in 95% of these stays.

After restricting analyses to the 353,749 inpatient stays with a transfusion that occurred during the study period (i.e., transfused inpatient stays), we observed 1,287,763 units of blood products transfused to 285,774 patients in Sentinel inpatient electronic data. Among transfused inpatient stays, the overall unadjusted occurrence rate (OR) of potential-$TRALI_A$ in Sentinel inpatient electronic data was 30.8 potential cases per 100,000 transfused inpatient stays (95% CI: 25.0- 36.6). When TRALI was defined as potential-$TRALI_{A,B,C}$ in electronic data, there were 0.75 TRALI cases per 5,000 units of blood products (0.15 potential cases per 1,000 units; 1.49 potential cases per 10,000 units). When defined only as potential-$TRALI_A$, there were 0.42 potential TRALI cases per 5,000 units of blood products (0.08 potential cases per 1,000 units; 0.85 potential cases per 10,000 units).

Unadjusted analyses focusing on potential-$TRALI_A$ occurrence, found occurrence rates were highest among patients who expired [117.4 per 100,000 transfused inpatient stays (95% CI: 73.1-161.6)] or who were mechanically ventilated during their inpatient stay [123.8 per 100,000 transfused inpatient stays (95% CI: 94.0-153.7)]. While it was not possible to distinguish whether or not units were administered before or after potential-TRALI occurrence in analyses focused only on electronic data, rates increased as number of units recorded during an inpatient stay increased, and patients exposed to greater than 9 units of blood during their hospital stay had the highest rates [191.9 per 100,000 transfused inpatient stays (95% CI, 130.9-252.9)]. Unadjusted rates of TRALI per 100,000 transfused inpatient stays were

similar in all study years [Year 2013=33.7 (95% CI: 17.2-50.1), 2014=28.1 (95% CI: 20.4-35.9), 2015=33.6 (95% CI: 23.5-43.8)]. When examining age categories, the largest rate was observed in the 20-34 year age category, and smaller ORs were observed in the 65+ year age categories [Age 0-19= 44.3 (95% CI: 8.9-79.8); Age 20-34=45.7 (95% CI: 20.9-70.5); Age 35-49=44.5 (95% CI: 23.4-65.7); Age 50-64=35.8 (95% CI: 22.8-48.9); Age 65-79=23.5 (95% CI: 14.6-32.4); Age 80+=21.9 (95% CI: 11.5-32.3)].

5. Electronic data, exploratory analyses

In comparative exploratory analyses, we focused on potential-$TRALI_A$. Significantly higher rates of potential-$TRALI_A$ were observed for the following conditions: patients who expired as compared to those discharged alive [RR=4.7 (95% CI: 3.1-7.3)], and patients mechanically ventilated as compared to those who were not ventilated during their stay [RR=8.7 (95% CI: 5.9-12.7)]. While it was not possible to distinguish whether or not units were administered before or after potential TRALI occurrence in analyses focused only on electronic data, higher rates of potential-$TRALI_A$ were observed in patients who received greater than 1 unit of blood during their inpatient stay. Potential $TRALI_A$ rates increased as number of units increased, with patients exposed to 5 or more units having significantly higher rates of potential $TRALI_A$ than those exposed to one unit [RR 2-4 units=2.3 (95% CI: 1.0-5.1); RR 5-9 units= 6.7 (95% CI: 2.9-15.6); RR >9 units=22.8 (95% CI: 10.2-51.0)]. Similarly, significantly higher rates of potential $TRALI_A$ were observed in patients who were exposed to multiple blood components, as compared to those only exposed to RBCs [RR RBCs and Plasma only=2.7 (95% CI: 1.3-5.5), RR RBCs and Platelets only=4.0 (95% CI: 2.3-7.2), RR RBCs and Plasma and Platelets only=7.0 (95%CI: 3.7-13.2), RR Other transfusion combination=13.0 (95% CI: 7.5-22.6). As compared to patients ages 20 to 34 years, significantly lower rates of TRALI were observed in patients that were over 65 years of age on admission [RR 65-79 years=0.51 (95% CI: 0.27-1.00), RR 80+years=0.48 (95% CI, 0.23-0.99)].

6. Medical record review, TRALI outcome validation

Of 195 potential-$TRALI_{A,B,C}$ inpatient encounters with available medical charts, 68 (35%) met clinical definitions for TRALI, [26 (38%) definitive TRALI, 15 (22%) possible TRALI, 27 (40%) delayed TRALI], 79 (41%) were not cases of TRALI, 36 (18%) were determined to be acute lung injury (ALI) not associated with a transfusion, and 12 (6%) were adjudicated as unable to determine (e.g., complex cases, chart lacking critical information often due to hospital transfers, or incompleteness or ambiguity). To compare to the literature, we calculated a crude OR of TRALI utilizing only cases meeting clinical definitions for definitive, possible, or delayed TRALI, and found a crude TRALI OR of 0.02% per transfused patient, and 0.26 TRALI cases per 5,000 units of blood products (0.05 cases per 1,000 units; 0.53 cases per 10,000 units). There were 19.2 (95% CI: 14.7-23.8) cases meeting clinical definitions for definitive, possible, or delayed TRALI per 100,000 inpatient transfusion stays. When we restricted our analyses to only definitive TRALI cases (n=26), the TRALI OR was 0.001% per transfused patient, and 0.10 TRALI cases per 5,000 units of blood products (0.02 cases per 1,000 units; 0.20 cases per 10,000 units). There were 7.3 cases meeting the clinical definition for definitive TRALI per 100,000 inpatient transfusion stays (95% CI: 4.5-10.2).

The PPV for all inpatient TRALI diagnoses recorded in the Sentinel electronic data (potential-$TRALI_{A,B,C}$) was 35% overall (95% CI: 28-42). The PPV for the potential-$TRALI_A$ criterion was 44% (95% CI: 35-54) and the potential-$TRALI_B$ criterion was 24% (95% CI: 15-33). There were no TRALI cases meeting clinical definitions for definitive, possible, or delayed TRALI identified by the potential-$TRALI_C$ criterion (0/5). The overall PPV when the electronic algorithm was compared to definitive TRALI cases was 13% (95% CI: 9-19). PPV results for the electronic algorithm as compared to possible or delayed TRALI were similar to definitive TRALI comparisons [Possible=8% (95% CI: 4-12), Delayed=14% (95% CI: 9-20)].

7. Medical record review, transfusion exposure validation

When comparing transfusions noted in the Sentinel electronic transfusion data to transfusion of interest as abstracted by adjudicators, the PPV of Sentinel electronic transfusion data was 98.4%. When no or incomplete transfusion data existed in the Sentinel database for potential-TRALI inpatient stays, adjudicators noted that nearly all were hospital transfers in which the transfusion of interest was administered at a different facility. In one case, the exposure of interest was Intravenous Immunoglobulin (IVIg) administered in an outpatient setting (IVIg administrations are not captured in blood transfusion data).

Of 182 potential-TRALI inpatient stays with available charts and recorded transfusions in the Sentinel database, adjudicators were able to find a specific blood component type for 179 TRALI inpatient stays with transfusions in charts of which, RBCs were confirmed in 143 (80%), platelets were confirmed in 43 (24%), and plasma in 36 (20%). Cryoprecipitate was also confirmed in 10 (6%). Perfect concordance was observed between blood components as identified in the Sentinel database as compared to transfusions of interest located by adjudicators in medical charts (PPVs=100%). When transfusion dates and times in medical charts and Sentinel data were compared, concordance was generally observed.

Processing and collection information was typically available in electronic transfusion data and corresponded to information collected by adjudicators, but lack of consistent access to blood bank portions of the EMR across hospitals limited sample sizes available for examining processing and collection methods. When comparing Sentinel electronic information on processing methods or specific component to information gathered by adjudicators, PPVs were below 61%. However, when processing or collection methods were located by adjudicators there was perfect concordance between Sentinel electronic data and information abstracted by adjudicators.

In addition, lack of consistent access to blood bank records limited the sample sizes available to examine the following: Pathogen-reduction methods (N=2) whether or not a blood product was whole blood derived (N=11), blood product age (N=0), and whether the product was derived from a single donor or pooled (N=13). Information about volume transfused was often located by abstractors and in 25 instances information was listed about halted transfusions. Of note, although blood product age itself was not located by adjudicators, notes about expiration dates existed by unit on some medical chart transfusion records and would also likely exist in blood bank records.

8. Medical record review, validation of mechanical ventilation

Of the 195 charts reviewed, 112 (57%) also had a code for mechanical ventilation in Sentinel inpatient data. Adjudicators found evidence of mechanical ventilation in 95 [PPV=85% (95% CI: 77-91%)] of these encounters. We reviewed the 17 cases in which mechanical ventilation was not confirmed by adjudicators. Adjudicators noted 4 (24%)of these patients were placed on Bilevel Positive Airway Pressure (BiPAP) during their inpatient stay, 1 (5%) was transferred from another hospital and placed on a non-rebreather O2 mask, and 3 (18%) were hospital transfers. Other reasons cited for not being able to locate specific mechanical ventilation in charts included extremely long inpatient stays with lengthy charts.

E. CONCLUSIONS

This data exploration study established the feasibility of utilizing electronic Sentinel inpatient EMR data from 169 US hospitals to capture potential-TRALI cases, exposure to blood component type and processing method (e.g., leukocyte-reduced, irradiated), transfusion dates and times. Electronic inpatient transfusion data, corresponded well with medical charts (PPV>98%), but the PPV for $TRALI_{A,B,C}$ was poor. Identified areas for data improvement and expansion include strategies for understanding and reducing missing data in Sentinel inpatient transfusion data and understanding the potential for expanding the Sentinel electronic database to include procedure and diagnosis dates and times.

Capture of potential TRALI cases and potential patient and TRALI associated transfusion risk factors was also feasible, but during medical record review of potential TRALI cases we found the PPV of the TRALI electronic algorithm was poor in all analyses conducted (<50%). Review of medical records associated with 195 potential TRALI cases identified with diagnosis codes for TRALI or ALI and a transfusion reaction in electronic data, yielded 68 TRALI cases meeting clinical definitions for definitive TRALI, possible TRALI or delayed TRALI. Complexity of the diagnosis and the considerable number of codes available in Sentinel inpatient EMR databases may explain the observed low PPV of the electronic TRALI algorithm. In addition, diagnosis codes used to identify potential-TRALI cases may have represented differential diagnoses. While the PPV of diagnosis codes for ALI and a transfusion reaction was <50%, use of these codes yielded TRALI meeting clinical definitions for definitive, possible, or delayed TRALI cases (19 of 68 cases), and may be considered in future studies wishing to use diagnosis codes to capture as many potential TRALI cases as possible. However, most studies implementing this approach would require confirming diagnoses with medical records given the low PPVs for the $TRALI_{A,B,C}$ algorithm.

This study focused on calculating potential-TRALI occurrence rates with electronic inpatient data, and found lower potential-TRALI occurrence rates than have been previously reported in the literature, but also some correspondence with a recent study which examined TRALI as defined with diagnosis codes in the Medicare population.[1] Given the low PPV of the TRALI algorithm, further investigation of results within validated TRALI cases is warranted. Specifically, future work should focus on describing occurrence rates, transfusion exposures, as well as patient and TRALI associated transfusion risk factors within validated TRALI cases.

Important considerations and limitations: Data included in this report are derived from medical files, and should be treated as such. These results should not be published, presented, or shared outside of FDA or the SOC, without prior written consent of relevant the Sentinel inpatient Data Partner(s). In addition, small cell sizes are included in this report and should not be published, presented or shared outside of FDA or the SOC without prior written consent of the Sentinel inpatient Data Partner(s).

II. INTRODUCTION

The Blood Safety Continuous Active Surveillance Network (BloodSCAN), is a component of the Sentinel System initiated by the Center for Biologics Evaluation and Research (CBER) as an active surveillance system that focuses on evaluating recipient safety of FDA-regulated blood components and plasma-derived products. The BloodSCAN framework utilizes billing and other electronic health data within the Sentinel System to assess the risk of adverse health outcomes of interest following exposure to blood products among large populations. The ability to assess population risk of blood-product related adverse events complements spontaneous reporting of adverse events to FDA and other existing FDA safety surveillance programs.

In 2016, FDA expanded the data within Sentinel to include inpatient electronic medical record (EMR) data from Hospital Corporation of America (HCA). This assessment, which is the first Sentinel utilization of this new inpatient data source, examined the feasibility of utilizing HCA's Sentinel database to capture exposure to blood components and the outcome of transfusion-related acute lung injury (TRALI). The assessment also described incidence rates of TRALI subsequent to blood component exposure.

III. BACKGROUND

A. PUBLIC HEALTH SIGNIFICANCE AND STUDY MOTIVATION

Although blood transfusions are administered in many hospitals on a daily basis, patient and exposure associated risk factors for many non-infectious adverse events are poorly understood. Transfusion-related Acute Lung Injury (TRALI) is a rare but serious life threatening adverse event which occurs during or within 6 hours of transfusion. TRALI is characterized by respiratory distress and pulmonary edema and is a leading cause of reported transfusion-related mortality in the United States. Despite voluntary measures taken by the transfusion community to reduce the risk of TRALI, 41% of transfusion-related fatalities reported to the U.S. Food and Drug Administration between years 2010 and 2014 were attributed to TRALI.[2] TRALI is difficult to diagnose and relies on clinician case recognition, and commonly accepted case definitions have varied over time, likely resulting in under- or inconsistent recognition. Reporting of TRALI is not universally required in the United States, although blood transfusion services are required to report fatal complications of blood transfusions to the FDA. These challenges leave us with an incomplete understanding of the epidemiology and attributable burden of these serious transfusion-related pulmonary complications. Risk factors in recipients (e.g., smoking status)[3] and in transfused blood products (e.g., antibodies, bioreactive substances, older red blood cells (RBCs) storage age)[4] have been noted, and only recently have been described in general populations of transfused patients. Availability of large administrative and electronic healthcare databases is providing new opportunities to examine serious but rare transfusion associated adverse events such as TRALI. [1, 3, 5, 6]

Ultimately, development of a surveillance system to monitor adverse events following transfusion of blood and blood products/components could inform FDA regulatory actions and impact physicians' ability to assess and potentially mitigate risks for individual patients.

B. HOSPITAL CORPORATION OF AMERICA

Hospital Corporation of America (HCA) is a leading provider of inpatient services, operating in 20 states and the United Kingdom. HCA is comprised of locally managed facilities, and currently includes more than 165 hospitals and 115 freestanding surgery centers. Nearly 5 percent of all inpatient care delivered in the United States is provided by HCA facilities; this currently includes approximately 26 million patient

encounters per year.[7] As a large network of acute inpatient hospitals as well as other facilities, HCA provides a unique new set of data to the Sentinel distributed data network.

HCA became a full Sentinel Data Partner in January 2016, and has transformed available data into the Sentinel Common Data Model (SCDM).[8] Status as a full Sentinel data partner signifies that the Sentinel Operations Center (SOC) has approved the HCA's Sentinel database as SCDM-compliant, quality-checked and queryable. This database currently includes approximately 2 million inpatient encounters per year, as well as emergency room and outpatient visits to HCA facilities. HCA's data transformation includes two new Sentinel tables (current structure of these tables is included in **Appendix A)**, which capture inpatient pharmacy and inpatient transfusion data.

C. INPATIENT RED BLOOD CELL, PLATELETS AND PLASMA ADMINISTRATION

More than 90% of blood transfusions in the United States are performed in inpatient settings.[9] The 2015 National Blood Collection and Utilization Survey includes estimates for the amount of blood collected and transfused in the United States per year.[10] This survey estimates 11,349,000 whole blood (WB) and red blood cell (RBC) units were transfused at acute care hospitals in the United States in 2015. Estimates of platelets transfused totaled 1,983,000 units. An estimated 2,727,000 units of plasma were also transfused. Thus, in 2015 the most commonly transfused blood component pertaining to this protocol was RBCs, followed by plasma, and platelets. These numbers provide some context for what may be expected in terms of blood components transfused per year in Sentinel inpatient EMR data.

D. TRANSFUSION-RELATED ACUTE INJURY (TRALI)

TRALI is a leading cause of transfusion related fatalities in the United States.[2] Broadly, TRALI is defined as the onset of respiratory distress during or within 6 hours of blood transfusion.[11] TRALI is relatively rare, and the estimated U.S. incidence of TRALI has varied widely across studies.[12-14] This variation may be partially attributed to the lack of population-based TRALI studies and focus on specific hospitals or centers, but studies in critically ill patients have noted higher TRALI incidence rates.[12] However, a recent population-based study examining TRALI occurrence in elderly Medicare beneficiaries estimated an overall rate of 22.5 per 100,000 transfused inpatient stays.[1] TRALI has been associated with almost all blood components including transfusions of RBCs, fresh frozen plasma (FFP), platelets, as well as cryoprecipitate and granulocytes.[15-17]It has also been reported rarely after intravenous immunoglobulin treatment.[18, 19]

TRALI is a syndrome for which no specific clinical test is available and diagnosis is based on clinical, laboratory and radiological findings.[5, 11] The Centers for Disease Control and Prevention National Healthcare Safety Network [20] has defined TRALI as new onset of acute lung injury (ALI) occurring during or within 6 hours of blood transfusion (**Table 1**). The term 'Possible TRALI' is used when there is a temporal relationship to an alternative ALI risk factor (**Table 2**). Additionally, the literature suggests that some patients may meet the TRALI definition, but have symptoms beginning outside of the six-hour post-transfusion window, and thus a delayed TRALI definition has been suggested to capture such patients.[21, 22]

Table 1. Transfusion-Related Acute Lung Injury (TRALI) definitions

Definition	Clinical Description
Definitive TRALI[20, 23, 24]	A. No evidence of acute lung injury (ALI) prior to transfusion AND B. ALI onset during or within 6 hours of transfusion AND C. Hypoxemia defined by any of these methods: a. PaO2 / FiO2 ≤300 mm Hg b. Oxygen saturation is < 90% on room air c. Other clinical evidence AND D. Radiographic evidence of bilateral infiltrates AND E. No evidence of left atrial hypertension (i.e. circulatory overload) AND F. No temporal relationship to an alternative risk factor for ALI during or within 6 hours of completion of transfusion
Possible TRALI[20, 23, 24]	Same as above EXCEPT there is a temporal relationship to a specific ALI risk factor (Table 2)
Delayed TRALI definition, defined in critically ill patients	
Delayed TRALI[21, 22]	Same as for possible TRALI except allows for symptom onset within 6 to 72 hours of blood transfusion

Table 2. Alternate risk factors for Acute Lung Injury (ALI)

Direct Lung Injury	Indirect lung injury
Aspiration	Severe sepsis
Pneumonia	Shock
Toxic inhalation	Multiple trauma
Lung contusion	Burn injury
Near drowning	Acute pancreatitis
	Cardiopulmonary bypass
	Drug overdose

TRALI is believed to be caused by immune mediated mechanisms that lead to neutrophil activation, damage to endothelial cells, and pulmonary edema.[25] A two-hit hypothesis[11, 21] has been suggested for TRALI, with the first hit associated with patient risk factors that result in primed neutrophils adhering to the patient's pulmonary endothelium. The second hit may be antibody-mediated or non-antibody mediated but relates to blood transfusion mediators activating endothelial cells and pulmonary neutrophils causing capillary leakage and thus pulmonary edema.

According to the two hit model, risk factors for TRALI are both patient and transfusion dependent.[25] Blood products containing plasma have been commonly associated with TRALI, and HLA antibodies in blood products containing plasma from multiparous female donors specifically have been implicated.[26] Blood product age (i.e., longer storage) may play a role.[27] Numerous patient risk factors have been implicated, and include sepsis, cardiac surgery, trauma, and other ALI risk factors.[11] Higher incidence of TRALI has also been reported in patients with alcohol use disorder, patients who smoke cigarettes, and in patients with end stage liver disease.[12, 22] ICU patients have also been reported to have a higher incidence of TRALI, presumably due to underlying co-morbidities.[22, 28]

IV. OBJECTIVES

A. PRIMARY OBJECTIVES

1. To describe identification of potential TRALI cases, risk factors for TRALI, and relevant transfusion exposures in HCA's Sentinel database
2. To describe incidence rates of TRALI subsequent to plasma, platelet, packed red blood cell administration using HCA's Sentinel database
3. To determine through medical chart review the performance of an ICD-9-CM code based algorithm for identifying TRALI
4. To determine through medical chart review the positive predictive value of reported transfused product exposure in identified TRALI cases

B. EXPLORATORY OBJECTIVES

1. To explore the potential for comparing blood component specific TRALI incidence rates
2. To explore the ability to identify specific categories of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated)
3. To explore methods for reducing any relevant missing transfusion information in HCA's Sentinel database
4. To describe the distribution of possible patient risk factors, such as age, sex, and relevant comorbidities, among cases of TRALI
5. To describe the distribution of possible transfusion risk factors, such as volume of transfusion and component processing (e.g., leukoreduction, irradiation) among cases of TRALI
6. To identify which HCA data elements are included in the Sentinel Common Data Model (SCDM) that are useful/relevant for studying TRALI, and to identify additional inpatient data elements that may be useful but are not included in the SCDM

V. METHODS

A. STUDY POPULATION AND DATA SOURCES

This assessment included HCA hospitals systematically contributing inpatient transfusion data to the Sentinel Distributed Database (SDD). The population consisted of all individuals hospitalized September 30, 2013 through September 30, 2015 with evidence of a transfusion. This time-period was selected because prior to September 2013 many HCA hospitals were not systematically providing transfusion data to Sentinel. Within this period, individuals were included in the analyses if they were identified as potential-TRALI cases (defined below) in the HCA Sentinel database or b) had evidence of a transfusion of a relevant blood component/product (defined below). This project confirmed TRALI and transfusion information for potential-TRALI cases through medical chart review. Exploratory analyses focused on the feasibility of examining patient and TRALI associated transfusion risk factors, as well as identification of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated). We used information derived from electronic data and medical chart review to inform these explorations.

B. STUDY DESIGN AND OVERVIEW OF ANALYSIS PLAN

To address the primary and exploratory objectives, we utilized a retrospective cohort study design to examine TRALI occurrence among patients transfused in a hospital inpatient setting September 2013 through September 2015. Within this cohort, capture of potential-TRALI cases, risk factors for TRALI, and relevant transfusion exposures were described. We calculated rates of TRALI occurrence subsequent to plasma, platelet, red blood cell administration. Medical chart reviews were conducted to confirm the outcome (TRALI) and the transfusion exposure, and the positive predictive value of each electronic algorithm was evaluated. We also validated mechanical ventilation in potential TRALI cases. The gold standard was medical chart confirmed outcomes and transfusion exposures.

Exploratory analyses were included as feasibility analyses. However, we explored the potential to compare blood component specific TRALI rates, examine TRALI patient and TRALI associated transfusion risk factors, and identify specific categories of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated). Finally, we described data elements included in the SCDM that are useful/relevant for studying TRALI. We also identified inpatient data elements that could be useful but have not been included and assessed the feasibility of adding these elements based on their availability and accuracy.

Table 3. Overview of analysis methods

Method	Analysis	Data used
Descriptive analysis examining capture of potential TRALI cases, risk factors for TRALI, and relevant transfusion exposures	Primary	Transfusions: Sentinel Data Outcome: Sentinel Data
Descriptive analyses, examining potential to compare blood component specific TRALI unadjusted rates	Exploratory	Transfusions: Sentinel Data Outcome: Sentinel Data
Descriptive analyses, examining: • **ability to identify specific categories of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated)** • **methods for reducing any relevant missing transfusion information in the Sentinel database** • **distribution of possible patient risk factors, such as age, sex, and relevant comorbidities, among cases of TRALI** • **distribution of possible transfusion risk factors, such as volume of transfusion, indication, pregnancy history, component processing (e.g., leukoreduction, irradiation) among cases of TRALI** • **transfusion stays with TRALI vs without TRALI, comparing demographic characteristics (age, gender, race), length of stay, mechanical ventilation (identified with ICD-9-CM procedure codes) and inpatient mortality**	Exploratory	Transfusions: Sentinel Data Outcome: Sentinel Data
Descriptive analysis, calculating unadjusted rates of TRALI in identified cohort	Primary	Transfusions: Sentinel Data Outcome: Sentinel Data
Validation of TRALI outcome, in identified TRALI cases	Primary	Transfusions: Sentinel Data Outcome: Sentinel Data and Chart Review
Validation of transfusion exposure in identified TRALI cases	Primary	Transfusions: Sentinel Data Outcome: Sentinel Data and Chart Review

Method	Analysis	Data used
Descriptive analysis identifying which data elements are included in the SCDM that are useful/relevant for studying TRALI, and which inpatient data elements could be useful but have not been included, and to assess the feasibility and need for adding these elements based on their availability, accuracy, and usefulness for blood and other biological products	Exploratory	Transfusions: Sentinel Data Outcome: Sentinel Data

C. EXPOSURES OF INTEREST

Primary objectives of this protocol include comparing electronic Sentinel inpatient transfusion data to information in medical charts, and thus required the electronic identification of blood component type (i.e., plasma, platelets, and packed RBCs) in electronic data.

Two coding systems are in use to identify transfusions within the HCA Sentinel inpatient transfusion table, the International Standard for Blood and Transplant-128 coding system (ISBT-128) and Codabar systems. These systems allow for identification of blood component type and may allow for identification of processing method (e.g., leukocyte-reduced, irradiated). ISBT-128 and Codabar systems include >4,500 codes and > 1,500 codes, respectively. Historically there has been use of both Codabar and ISBT-128 product codes to identify transfusions. Although both systems are still in use, there has been an increased uptake in use of ISBT-128 codes and a decrease in use of Codabar codes over time within the HCA Sentinel database. For example, by mid-2015 less than 1% of transfusions were coded with a Codabar code.

A database of ISBT-128 product codes is updated monthly by the International Council for Commonality in Blood Banking Automation, Inc. (ICCBBA). Codabar codes are no longer updated. Endorsed by the AABB (Advancing Transfusion and Cellular Therapies Worldwide), ICCBBA is an international non-governmental organization (NGO) in official relations with the World Health Organization (WHO) that manages, develops, and licenses ISBT 128, the international information standard for the terminology, coding and labeling of medical products of human origin.[29] To address the primary objectives, we utilized these coding systems and the Sentinel inpatient transfusion table to identify transfusions within the HCA Sentinel database. We also used these systems to identify blood components, and to explore the potential electronic identification of component processing (e.g., leukoreduction, irradiation).

In order to identify blood component categories (i.e., RBCs, plasma, or platelets), and explore processing methods, we used the National Healthcare Safety Network's (NHSN) variable and categories of Prod_CDC[30], in combination with ISBT and Codabar code systems. Categories included in the NHSN system are listed in **Appendix A**. Essentially, each ISBT-128 or Codabar code received a NHSN label to allow for collapsing of granular codes into relevant categories. The latest version of the NHSN's data dictionary[30] and the ICCBBA database[31] available at the time of program development was used to accomplish this task.

D. OUTCOME DEFINITION

Potential cases of TRALI were identified with the codes and electronic criteria included in **Appendix B**. As TRALI is likely under-diagnosed, this protocol focused not only on the TRALI-specific ICD-9-CM code (Criterion A: 518.7), but also on specific respiratory failure codes (Criterion B: 518.81, acute respiratory

failure; Criterion C: 518.82, Other pulmonary insufficiency, not elsewhere classified) in combination with an ICD-9-CM code for a transfusion reaction (ICD-9-CM codes: 999.80, 999.89, E934.7. Hereafter, these criteria are referred to as potential-TRALI$_A$, potential-TRALI$_B$, potential-TRALI$_C$, or potential-TRALI$_{A,B,C}$. TRALI criteria only include ICD-9-CM codes, as the time-period of interest for this protocol-based assessment precedes the transition to ICD-10-CM coding in the United States. All other inpatient stays occurring during the study period without diagnosis codes meeting TRALI criteria were labeled non-TRALI inpatient stays.

Electronic criteria and diagnosis codes were used to identity TRALI cases in the HCA Sentinel inpatient EMR database and were used to calculate incident rates of TRALI subsequent to plasma, platelet, and packed red blood cell administration. Stratifications were made by TRALI criterion, as feasible. These TRALI criteria were also used to identify TRALI cases in HCA's Sentinel database for chart review. Medical charts were obtained for relevant cases, reviewed, and adjudicated by clinical experts. This chart information was the gold standard for primary validation objectives.

E. TRALI AND TRANSFUSION EXPOSURE VALIDATION

1. Overview of chart review process

Medical records of all cases of inpatient diagnosis of TRALI were reviewed, regardless of transfusion status or timing relative to transfusion. As per protocol, the maximum number of cases to be reviewed was 200. If the number of available cases exceeded 200, a pre-specified sampling scheme based on the diagnosis criteria was to be used to ensure the highest-priority cases were reviewed. Charts were selected based on the following criteria:

a. All charts meeting TRALI$_A$, identified in the time-period of interest, were reviewed

b. Charts meeting TRALI$_B$ or TRALI$_C$, identified during the time-period of interest, were randomly selected for review, until a total of 200 charts was reached

The workgroup collaborated with content experts to develop the chart adjudication form and to ensure all necessary information was collected from the medical records. This form is included in **Appendix C.** To identify the cases and obtain the medical charts, the SOC developed programs to run on uniform-format patient-level files at the Data Partner. These programs identified encounters which met TRALI criteria, produced a report of the number and characteristics (e.g., age and sex) of the cases, and included information on clinical setting and diagnosis. A report including a list of potential TRALI encounters was provided to the Data Partner, who then located patient names and medical record numbers for these encounters so that charts could be located. These charts were requested, retrieved, and made available to adjudicators who then adjudicated each case to verify the transfusion exposure and the TRALI diagnosis.

All medical charts were reviewed by at least one clinician certified in both pulmonary care and critical care, or certified in internal medicine and currently working in an intensive care unit and were familiar with transfusions and vents. Medical records of all cases with an inpatient TRALI diagnosis code were requested, regardless of transfusion status in the database, or timing of events relative to transfusion.

The validation piece of this study was conducted in two phases. In the pilot phase, an adjudication form was developed by the TRALI workgroup and tested for the review of 20 potential TRALI cases. At least two adjudicators reviewed each of the 20 potential TRALI cases. Study investigators did not interact with adjudicators during the chart adjudication period. Clinicians were blinded to results beyond their own adjudication review and were blind to assignment of the second adjudicator. Two clinicians

independently reviewed two rounds of 10 charts (total n=20), blinded to the other's decision. The adjudication form was revised according to clinician feedback, to ensure classification rules and instructions were clear (see **Appendix C** for adjudication form). After double adjudication of each case was complete, two SOC staff reviewed completed adjudication forms, identified discrepancies, followed up with adjudicators as needed for clarifications, assigned cases to a third adjudicator (as appropriate), entered adjudication form into the study database, and followed up with adjudicators to ensure forms were completed appropriately. Charts were provided to the adjudicator by data partner staff, and Sentinel staff or study investigators had no access to the medical charts themselves.

For a small number of clinically complex cases (see Section D2 for details), some discrepancies between reviewers persisted during the pilot phase. After the pilot was completed and the adjudication form was finalized, adjudicators proceeded to a single adjudication phase for the remainder of cases but were given the option of requesting a second opinion. In such instances, cases were provided to an adjudicator certified in both pulmonary and critical care, for a final case decision.

Hospital care setting at the time of TRALI diagnosis (e.g., inpatient, institutional, outpatient, or emergency department), admission type (e.g., emergency, urgent, elective), and hospital unit (e.g., coronary care unit, intensive care unit, trauma unit), was either confirmed (encounter type is in the SCDM) or recorded (hospital unit and admission type are not in the SCDM). Transfusion information in identified patients with TRALI was reviewed by the adjudicators to correctly identify the transfusion exposure. For patients with a prior transfusion identified in the HCA Sentinel database, the transfusion record prior to and closest to the TRALI event was sought, to confirm or correct transfusion date and timing, number of transfused units, volume of transfusion, type of blood component transfused, and blood component processing (e.g., leukocyte reduced, irradiated). Hospital care setting at the time of transfusion exposure was confirmed.

Information about indications for blood transfusion and history of prior events was collected for analysis in the exploratory objectives. Use of mechanical ventilation before and after TRALI was confirmed. For patients without a prior transfusion recorded in the HCA Sentinel database, if the case was ultimately classified as TRALI, then medical records were reviewed to attempt to confirm or correct the absence of a transfusion exposure prior to TRALI onset.

2. Adjudication criteria for study endpoints

Clinicians utilized the National Healthcare Safety Network (NHSN) Manual: Biovigilance Component definition of TRALI (summarized in **Table 1** of this protocol) to diagnose TRALI.[20] Delayed TRALI was diagnosed in the same manner, but allowed for symptom onset between 6 and 72 hours of the transfusion. While all analyses included in this protocol are descriptive, primary analyses were based on definitive TRALI, and secondary analyses included possible TRALI and delayed TRALI.

Positive predictive value was determined for each electronic TRALI criterion as compared to definitive TRALI confirmed by clinical adjudicators. PPVs were calculated for TRALI electronic criteria as compared to definitive, possible, and delayed TRALI as confirmed by clinical adjudicators.

Adjudicators recorded information about the transfusion of interest for all potential TRALI cases. In instances where there was no evidence of ALI, adjudicators recorded information about the first observed transfusion in the medical chart. The PPV was determined for the transfusion exposure as identified in HCA Sentinel data, as compared to confirmed transfusion exposure obtained by clinical adjudicators during chart review.

F. STATISTICAL ANALYSIS

1. Descriptive analyses using electronic data

Univariate and bivariate descriptive analyses were carried out prior to calculating rates of TRALI, with the purpose of characterizing the transfusion and TRALI data in the HCA Sentinel database. These included frequency distributions of TRALI cases meeting each TRALI electronic criterion, and frequency distributions of relevant transfusion variables including any relevant missing information. We used Codabar and ISBT-128 codes, along with the NHSN system to identify plasma, platelets and packed RBCs. The number of potential TRALI inpatient transfusion stays were identified, and frequencies of specific blood component exposures among inpatient transfusions stays are presented.

In potential TRALI and non-TRALI inpatient stays we examined the frequency of certain blood component exposures. Blood components of interest include RBCs, plasma, platelets, or other (e.g., cryoprecipitate). As risk of TRALI may differ by various transfusion related factors, we conducted a series of transfusion and specific blood component analyses to better understand Sentinel electronic inpatient transfusion data. The first focused on examining proportions of potential-TRALI $_{A,B,C}$ and non-TRALI stays with exposures to any RBCs, plasma, platelets, or other (e.g., cryoprecipitate) during their hospitalization. The second examined mutually exclusive blood component categories (e.g., only exposed to RBCs), and the third examined median numbers of transfused units during inpatient stays. Finally, to understand potential for missing information, we included analyses of units that could not be attributed to a specific blood component, (i.e., 'unknown' defined as a blank or unrecognized blood code included in the Sentinel inpatient transfusion table during a relevant inpatient stay). Descriptive analyses were also conducted to examine TRALI case demographics (age at admission, sex, race) and hospitalization characteristics (length of stay, discharge disposition).

Exploratory analyses examining patient risk factors for TRALI (e.g., smoking status, alcohol abuse, direct lung injury, indirect lung injury, diabetes, end stage liver disease, liver transplant, post inflammatory pulmonary fibrosis), as well as TRALI associated transfusion risk factors (number of units, blood component transfused), were also conducted using Sentinel electronic data (See **Appendix D** for condition code lists).

To explore whether electronic identification of component processing (e.g., leukoreduction, irradiation) was possible within the HCA Sentinel database, we identified relevant codes in Codabar and ISBT-128 systems (as described in **Section V.C**). We also examined the ability to identify apheresis-derived and whole-blood-derived products. Frequency of these specific categories of blood component exposures in the database were calculated, in both potential TRALI and non-TRALI cases.

2. Calculation of unadjusted TRALI occurrence rates, and rate ratios, with electronic data

Unadjusted rates of TRALI occurrence among transfused inpatient stays during the study time-period were calculated, along with exact 95% confidence intervals. Any transfusion was defined as exposure to plasma, platelets, or packed RBCs as defined in the HCA Sentinel database. Potential-TRALI was defined using ICD-9-CM based codes in the HCA Sentinel database, and the primary analysis focused on $TRALI_A$, all other inpatient stays with transfusions occurring during the study period without diagnosis codes meeting $TRALI_B$ or $TRALI_C$ were labeled non-TRALI inpatient stays for these analyses. A secondary analysis focused on $TRALI_{A,B,C,}$ and all other inpatient stays with transfusions occurring during the study

period were labeled as non-TRALI inpatient stays for these analyses. Unadjusted potential TRALI rates (per 100,000 inpatient transfusion stays) were stratified by year, blood component groups (i.e., plasma, platelets, and RBCs), age, sex, race, discharge disposition, and quantified units.

In exploratory analyses, we calculated unadjusted rates of TRALI occurrence (OR) after any exposure to the following: only 1 blood component type (i.e., RBCs-only, plasma-only, and platelets-only); multiple blood component types (i.e., plasma and platelets, RBCs and platelets, plasma and RBCs, plasma and RBCs and platelets); non-specific blood components (units with missing information). Given small numbers, it was not feasible to stratify number of units by children versus adults. We also calculated unadjusted rate ratios (RR) and exact 95% confidence intervals (95% CI) for the following variables: year (reference=2013), sex (reference=male), age (reference=age category 20-34 years), race (reference=white), mechanical ventilation during the inpatient stay (reference =no), discharge disposition (reference =discharged alive), blood component groups (reference =RBCs only), and quantified units during the inpatient stay (reference =1 unit). For categorical variables, corresponding chi-square tests were also computed and Fishers exact tests were utilized for small cell counts (<10). Wilcoxon rank sum tests were used for continuous variables

3. Quantification of algorithm Positive Predictive Value with electronic data and medical charts

a. TRALI outcome

We examined the positive predictive value (PPV) of electronic TRALI criteria ($TRALI_{A,B,C}$) and diagnosis codes through chart review. In PPV calculations, we counted definitive, possible, and delayed TRALI as confirmed cases, but also stratified results by specific clinical case definition. Exact binomial 95% confidence intervals were calculated for all PPV estimates in this report to quantify their precision. Charts were adjudicated according to the workgroup approved TRALI clinical case definitions. We quantified the PPV value for each electronic TRALI criterion, as compared to chart review. PPVs were also calculated for each electronic TRALI criterion as compared to definitive, possible, and delayed TRALI as confirmed by clinical adjudicators. We stratified results by age and gender where feasible. Additional exploratory analyses included: stratification of PPV results by whether electronic transfusion data were available, and examination of PPV for TRALI in relation to 'present on admission' or 'principal discharge diagnosis' flags in the Sentinel electronic data. Finally, in exploratory analyses, we examined the effect of excluding from analysis, encounters in which adjudicators were 'unable to determine' the TRALI outcome.

b. Transfusion exposure

Medical chart review was conducted to validate transfusion exposure details for all identified potential TRALI cases without regard to whether a prior transfusion record existed in the electronic data. Adjudicators were provided with the medical chart of the entire hospitalization for each potential TRALI case. Blood bank information often was not available on the standard EMR platform at many hospitals, but if this information was available it was also provided to adjudicators for review. Adjudicators abstracted and adjudicated every potential TRALI case and verified the specific transfusion of interest (i.e., associated with ALI). If no ALI event could be located in the patient chart, adjudicators abstracted information about the first available transfusion in the medical record. We compared the information gathered about the transfusion of interest from charts to transfusion information in the Sentinel electronic database. To make this comparison, we located transfusions by blood components on the same date(s) [+- 1 day] of the transfusion (s) of interest in Sentinel electronic data, and attempted to match them to transfusion of interest abstracted by adjudicators. The +- 1 day time frame was chosen to

accommodate transfusions that spanned days (i.e., crossed midnight). The PPV of electronic Sentinel transfusion data, as compared to medical chart review, was then examined. To further understand discrepancies between Sentinel transfusion data and data abstracted from medical charts, we reviewed and described instances in which the transfusions of interest located by adjudicators in medical charts could not be found in Sentinel data.

During chart review, adjudicators also collected information about blood components, as well and specific categories of blood components including: any available blood processing (irradiated, leukocyte-reduced, apheresis-derived) or pathogen-reduction methods, whether or not a blood product was whole blood derived, and whether it was product derived from a single donor or pooled. Adjudicators also recorded volume transfused and unit age (days) when available. We described the availability of these data in patient charts, and compared PPVs of blood processing method captured in the Sentinel electronic data to information abstracted by the adjudicators from charts where feasible.

c. Mechanical ventilation

Medical chart review was conducted to validate mechanical ventilation in all identified potential TRALI cases. Mechanical ventilation was defined using procedure codes (see **Appendix E**). We examined the positive predictive value of mechanical ventilation as defined in electronic transfusion data as compared to medical chart review.

4. Exploring methods for reducing missing transfusion information in electronic data

During this project, we focused on two aspects of potential missing transfusion information: 1) Transfusion information that was not available in Sentinel electronic data, but could be collected within patient charts (e.g., volume of transfusion, or transfusion information that was missing from the database entirely) and 2) Information that was entered into the Sentinel database, but could not be identified (e.g., units transfused that did not have a recognizable label code that could be used to identify blood component, or label was missing entirely).

To explore what transfusion information was missing in the data but available in medical charts, we asked adjudicators to record the following: volume transfused, age of unit (days), and transfusion environment. We described the availability of this information in medical charts. We also asked adjudicators to record transfusions of interest in all potential TRALI cases and examined potential reasons for lack of transfusion information in the Sentinel electronic data. This information is described qualitatively under Section VI.D. 4., Transfusion exposure.

To explore methods for reducing missing information in variables included in the HCA Sentinel database, we first examined the ISBT-128 database for frequency of updates and numbers of labeled codes. We found that the ISBT-128 database and method of classification is generally updated monthly, and any newly introduced blood codes beyond 2013 would have been incorrectly classified as 'missing' if the NHSN Codabar system was utilized alone. Thus, during this project we focused on utilizing the latest ISBT-128 database (version 7.4) in combination with the NHSN system, to label the processing method for valid ISBT-128 codes not included in the NHSN ProdCDC labeling system. In other words, we used the NHSN system to identify blood categories/ processing methods included in HCA's blood codes along with the ISBT-128 system to create up to date code lists for ISBT-128 codes. This approach reduces mislabeling of newly introduced ISBT-128 codes as 'missing'. We also examined unprocessed Sentinel electronic data for potential TRALI cases, to see if any missing transfusion data patterns were observed and described them qualitatively.

5. Identifying electronic data elements are that are useful/relevant for studying TRALI

After all analyses above were conducted and reviewed by the workgroup, a qualitative summary was prepared, identifying data elements that are useful/relevant for studying TRALI, as well as highlighting potentials for future data expansion.

VI. RESULTS

A. DESCRIPTIVE ANALYSES

1. Frequency of potential TRALI inpatient stays in electronic data

We identified 208 potential TRALI inpatient stays among 3,945,217 inpatient stays at 169 hospitals in the HCA Sentinel database [**$TRALI_A$** =118 (57%), **$TRALI_B$** only=85 (41%), **$TRALI_C$** only=5 (2%)] (**Table 4-6**). A transfusion was recorded in electronic data during 92% of these stays (n=192**, Table 7**).
There were 62 inpatient stays that met **$TRALI_A$**, as well as **$TRALI_B$** and/or **$TRALI_C$**; a transfusion was recorded in electronic data during 95% of these stays (**Table 4**).

Table 4. Number of inpatient stays meeting Transfusion-Related Acute Lung Injury (TRALI) criteria, stratified by capture of transfusion data in the Sentinel database (September 2013-September 2015)

Algorithms for identifying potential-TRALI	Met potential-TRALI Criterion N (%)	Transfusion captured N (%)
$TRALI_A$ only: TRALI, ICD-9-CM code in any position (518.7)	56 (27%)*	50 (89%)
$TRALI_A$ and $TRALI_B$ and/or $TRALI_C$:See below for Criterion details	62 (30%)	59 (95%)
$TRALI_B$ only: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7)	85 (41%)	80 (94%)
$TRALI_C$ only: Other pulmonary insufficiency (518.82), WITH IICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7)	5 (2%)	3(60%)
$TRALI_{A,B,C}$ listed above	208	192 (92%)

**During the study time-period, one patient had two inpatient stays that met TRALI criterion A, and is included twice in this table.*

2. Descriptive analyses- All inpatient stays included in electronic data

Among all inpatient stays during the study time-period (September 2013-September 2015), 208 potential-$TRALI_{A,B,C}$ inpatient stays were identified among 3,945,217 inpatient stays (with and without transfusions) in 169 hospitals [Calendar Year 2013= 27/479,792 (0.006%), 2014=108/1,965,939 (0.005%), 2015=73/1,499,486 (0.005%)]. Review of the demographic characteristics, ALI risk factors, and hospital features associated with potential-$TRALI_{A,B,C}$ and non-TRALI inpatient stays showed that the populations were dissimilar. Specifically, patients with potential-$TRALI_{A,B,C}$ inpatient stays were older on admission (median age: 63 vs. 54 years), had longer lengths of stay (LOS) (median LOS: 10 vs. 3 days), and were discharged as expired more frequently (21% vs. 2%) than non-TRALI patients (**Table 5**).

In general, more risk factors for ALI were observed in potential-$TRALI_{A,B,C}$ stays than were observed in non-TRALI stays. The following direct lung injury ALI risk factors were significantly higher in potential TRALI vs. non-TRALI inpatient stays: Aspiration (10% vs. 2%), pneumonia (32% vs. 7%), and lung contusion (1% vs. 0.1%). Similarly, the following indirect lung injury ALI risk factors were significantly higher in potential TRALI vs non-TRALI inpatient stays: Sepsis (27% vs. 5%), severe sepsis (12% vs. 1%), shock (24% vs. 2%), cardiogenic shock (6% vs. 0.3%), septic shock (12% vs. 1%), and cardiopulmonary bypass (5% vs. 0.7%). The following patient related factors that were significantly higher in potential TRALI vs non-TRALI inpatient stays: Alcohol use disorder (10% vs. 5%), smoking cigarettes (38% vs. 25%), end stage liver disease (ESLD) (3% vs. 0.4%), liver transplant surgery (0.5% vs. 0.1%), diabetes (30% vs.

22%), and post-inflammatory pulmonary fibrosis (4% vs. 0.6%). Mechanical ventilation was also more common during potential TRALI inpatient stays (58% vs 4%) [**Table 5,** see **Appendix D** for condition code lists].

Table 5. Baseline characteristics associated with potential Transfusion-Related Acute Lung Injury (TRALI) and non-TRALI inpatient stays identified in the Sentinel Distributed Database, September 2013-September 2015: ***All inpatient encounters (with and without transfusions)***

	Any potential-TRALI$_{A,B,C}$[†], N=208	Any potential - TRALI$_{A,B,C}$[†], %	No TRALI, N=3,945,009	No TRALI, %	p-value
Hospitalization Characteristics					
Discharge Disposition: Discharged Alive	165	79.33%	3,870,858	98.10%	<.0001
Discharge Disposition: Expired	43	20.67%	74,151	1.88%	<.0001
Discharge Disposition: Unknown	0	0.00%	0	0.00%	-
Length of Stay, median (min, max, standard deviation)	10	(1,87, SD 13.34)	3	(1, 628, SD 6.39)	<.0001
Patient Demographics					
Age in years, median (min, max, standard deviation)	63	(0*, 97, SD 21.71)	54	(0*, 65, SD 27.56)	<.0001
Age Group: 0-19	11	5.29%	638,061	16.20%	<.0001
Age Group: 20-34	21	10.10%	630,564	16.00%	0.0205
Age Group: 35-49	32	15.38%	507,051	12.90%	0.2753
Age Group: 50-64	46	22.12%	771,516	19.60%	0.3522
Age Group: 65-79	60	28.85%	848,678	21.50%	0.0101
Age Group: 80+	38	18.27%	549,122	13.90%	0.0699
Sex: Female	111	53.37%	2,293,737	58.10%	0.1625
Sex: Male	97	46.63%	1,650,782	41.80%	0.1614
Sex: Ambiguous	0	0.00%	0	0.00%	-
Sex: Unknown	0	0.00%	490	0.01%	1.0000
Race: White	149	71.63%	2,786,758	70.60%	0.7528
Race: Black/African American	27	12.98%	589,165	14.90%	0.4292
Race: Other	<10	0.00%	5,050	0.12%	NS[‡]
Race: Unknown	31	14.90%	564,036	14.30%	0.8027
Patient Related Conditions					
Mechanical Ventilation	120	57.69%	170,075	4.31%	<.0001
Direct Lung Injury: Aspiration	20	9.62%	61,088	1.55%	<.0001
Direct Lung Injury: Pneumonia	67	32.21%	268,171	6.80%	<.0001
Direct Lung Injury: Toxic Inhalation	0	0.00%	12	<0.00%	1.0000

	Any potential-TRALI$_{A,B,C}$†, N=208	Any potential - TRALI$_{A,B,C}$†, %	No TRALI, N=3,945,009	No TRALI, %	p-value
Direct Lung Injury: Lung Contusion	3	1.44%	4,577	0.12%	<.0001
Direct Lung Injury: Near Drowning	0	0.00%	440	0.01%	0.8789
Indirect Lung Injury: Sepsis	56	26.92%	208,126	5.28%	<.0001
Indirect Lung Injury: Severe Sepsis	25	12.02%	48,997	1.24%	<.0001
Indirect Lung Injury: Shock	50	24.04%	73,560	1.86%	<.0001
Indirect Lung Injury: Cardiogenic Shock	12	5.77%	13,002	0.33%	<.0001
Indirect Lung Injury: Septic Shock	25	12.02%	48,970	1.24%	<.0001
Indirect Lung Injury: Multiple Trauma	18	8.65%	234,207	5.94%	0.0973
Indirect Lung Injury: Burn Injury	0	0.00%	22	<0.00%	1.0000
Indirect Lung Injury: Acute Pancreatitis	6	2.88%	54,042	1.37%	0.0682
Indirect Lung Injury: Cardiopulmonary Bypass	10	4.81%	27,544	0.70%	<.0001
Patient related: Drug Overdose	1	0.48%	46,637	1.18%	0.5270
Patient related: Alcohol use disorder	21	10.10%	215,623	5.47%	0.0033
Patient related: Smoking cigarettes [Diagnosis, Procedure codes and NDCs]	80	38.46%	969,214	24.60%	<.0001
Patient related: Smoking cigarettes [NDCs only]	15	7.21%	221,339	5.61%	0.3157
Patient related: End stage liver disease	6	2.88%	15,015	0.38%	<.0001
Patient related: Liver Transplant surgery	1	0.48%	4,652	0.12%	0.2177
Patient related: Diabetes	63	30.29%	883,129	22.40%	0.0063
Patient related: Post inflammatory pulmonary fibrosis	8	3.85%	24,576	0.62%	<.0001

**Represents infants/children under 1 year of age*

†TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.

TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).

TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

TRALI$_C$: Other pulmonary insufficiency (518.82), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).
‡NS= not statistically significant at the p≤0.05; exact value not included due to small sample size.

3. Descriptive analyses-Transfused inpatient stays included in electronic data

We conducted two analyses focused on transfused inpatient stays, the first focused on all transfused inpatient stays, the other focused on transfused inpatient stays with exposure to RBCs, platelets or plasma.

a. Transfused inpatient population (all transfusions)

During the study period, 1,287,763 units of blood products were transfused to 285,774 patients during 353,749 inpatient transfusion stays. We identified 192 potential-TRALI$_{A,B,C}$ and 353,557 non-TRALI transfused inpatient stays in 153 hospitals included in the HCA Sentinel database [Calendar Year 2013= 26/47,554 (0.06%), 2014= 97/ 181,319 (0.05%), 2015= 69/124,876 (0.06%)]. There were 191 potential-TRALI$_{A,B,C}$ and 285,583 non-TRALI patients associated with these inpatient stays.

When TRALI was defined with potential-TRALI$_{A,B,C}$ criteria, there were 0.75 potential TRALI cases per 5,000 units of blood products (0.15 cases per 1,000 units; 1.49 cases per 10,000 units), and 0.42 cases per 5,000 units when TRALI was defined only by the potential-TRALI$_A$ criterion (0.08 cases per 1,000 units; 0.85 cases per 10,000 units).

Conditioning on presence of a transfusion in electronic data was intended to create more similar populations. As compared to inpatient stays without TRALI diagnosis codes, patients with potential TRALI diagnoses during transfused inpatient stays were significantly younger on admission (median age: 63 vs 67 years), had longer LOS (median LOS: 11 vs. 6 days), were discharged expired more frequently (22% vs. 7%) (**Table 6**).

As in analyses examining all inpatient stays, we observed more ALI risk factors in potential TRALI $_{A,B,C}$ vs non-TRALI transfused inpatient stays. However, when analyses were restricted to the transfused inpatient stays, the following proportions were no longer statistically significant in potential TRALI $_{A,B,C}$ vs non-TRALI transfused inpatient stays: cardiopulmonary bypass (5% vs. 5%), drug overdose (0.5% vs. 0.5%), ESLD (3% vs. 2%), liver transplant surgery (0.5% vs. 0.4%), or diabetes (29% vs. 33%).

Other potential risk factors, that were significantly higher in potential-TRALI $_{A,B,C}$ inpatient stays, remained significantly higher in analyses focused on transfused inpatient stays, but effects were often attenuated. Specifically, the following direct lung injury ALI risk factors were significantly higher in potential-TRALI $_{A,B,C}$ vs. non-TRALI transfused inpatient stays: aspiration (9% vs. 4%), pneumonia (32% vs. 14%), and lung contusion (2% vs. 0.4%). Similarly, the following indirect lung injury ALI risk factors were significantly higher in potential-TRALI $_{A,B,C}$ vs. non-TRALI transfused inpatient stays: sepsis (28% vs. 15%), severe sepsis (13% vs. 6%), shock (26% vs. 9%), cardiogenic shock (6% vs. 1%), and septic shock (13% vs. 6%). While proportions of potential-TRALI $_{A,B,C}$ and non TRALI stays with acute pancreatitis were similar in analyses focused on inpatient stays and transfused inpatient stays (3% vs 1%), statistical significance was only observed in analyses restricted to transfused inpatient stays (inpatient stays only p=0.07; transfused inpatient stays p=0.03). Patient related factors that were significantly higher in potential-TRALI $_{A,B,C}$ vs non-TRALI transfused inpatient stays included the following: alcohol use disorder (10% vs. 7%), smoking cigarettes (38% vs. 28%), and post-inflammatory pulmonary fibrosis (4% vs. 0.8%). Mechanical ventilation was also more common in potential TRALI transfused inpatient stays (58% vs 15%) [**Table 6,** See **Appendix D** for condition code lists].

The majority of patients associated with both potential-TRALI$_{A,B,C}$ or non-TRALI inpatient stays were exposed to RBCs (89% vs 86%, p=0.318). Significantly higher proportions of potential-TRALI$_{A,B,C}$ patients with transfused inpatient stays were exposed to platelets or plasma during their stays: any plasma (34% vs 14%, p<0.0001) and any platelet (38% vs 14%, p<0.0001). Nine percent of potential-TRALI$_{A,B,C}$ and 8% of non-TRALI transfused inpatient stays included at least one administered unit which could not be attributed to a blood component (i.e., blood component 'any unknown'). However, when analyses were restricted to stays in which all administered units received during the encounter were unable to mapped to a blood component, proportions reduced to 3% of potential-TRALI$_{A,B,C}$ and 5% of non-TRALI transfused inpatient stays [**Table 6**]. These 'unknown' units were examined in more detail in exploratory analyses (**see Section C, Exploratory Analyses**).

When we examined mutually exclusive component exposure categories, the following proportions were observed in potential-TRALI $_{A,B,C}$ vs non-TRALI transfused inpatient stays: RBCs only (45% vs 72%, p<0.0001) plasma only (4% vs 5%, p=0.53), platelets only (3% vs 3%, p=0.59), platelets and plasma only (1% vs 1%,p= 0.28), RBCs and plasma only (9% vs 5%, p=0.02), RBCs and platelets only (13% vs 6%, p=<0.0001), RBCs and plasma and platelets only (9% vs 3%, p<0.0001), other (defined as another combination, which might include cryoprecipitate) (14% vs 2%, p<0.0001) [**Table 6**]. We observed more administered units during potential-TRALI$_{A,B,C}$ inpatient stays (median 5 units, range 1-226 units) than during non-TRALI inpatient stays (median 2 units, range 1-660 units). When number of units transfused were examined, potential-TRALI$_{A,B,C}$ vs non-TRALI inpatient stays were as follows: 1 unit (10% vs. 24%), 2-4 units (38% vs. 59%), 5-9 units (21% vs. 12%), 10+ units (31% vs 6%) [**Table 6**].

Table 6. Baseline characteristics associated with potential Transfusion-Related Acute Lung Injury (TRALI) and non-TRALI inpatient stays identified in the Sentinel Distributed Database, September 2013-September 2015: Limited to *Encounters with a Transfusion (transfused inpatient stays)*

	Any potential TRALI $_{A,B,C}$ ‡, N=192	Any potential TRALI $_{A,B,C}$ ‡, %	No TRALI, N=353,557	No TRALI, %	p-value
Hospitalization Characteristics					
Discharge Disposition: Discharged Alive	150	78.13%	330,580	93.50%	<.0001
Discharge Disposition: Expired	42	21.88%	22,977	6.50%	<.0001
Discharge Disposition: Unknown	0	0.00%	0	0.00%	-
Length of Stay, median (min, max, standard deviation)	11	(1,87, SD 13.57)	6	(1,442, SD 13)	<.0001
Patient Demographics					
Age in years, median (min, max, standard deviation)	63	(1, 97, SD 21.89)	67	(0*,165, SD 20.93)	0.0151
Age Group: 0-19	10	5.21%	13,535	3.83%	0.3190
Age Group: 20-34	21	10.94%	28,435	8.04%	0.1403
Age Group: 35-49	29	15.10%	38,143	10.80%	0.0540
Age Group: 50-64	44	22.92%	80,906	22.90%	0.9913
Age Group: 65-79	53	27.60%	114,837	32.50%	0.1492
Age Group: 80+	35	18.23%	77,701	22.00%	0.2099

	Any potential TRALI $_{A,B,C}$ ‡, N=192	Any potential TRALI $_{A,B,C}$ ‡, %	No TRALI, N=353,557	No TRALI, %	p-value
Sex: Female	103	53.65%	199,337	56.40%	0.4449
Sex: Male	89	46.35%	154,203	43.60%	0.4441
Sex: Ambiguous	0	0.00%	0	0.00%	-
Sex: Unknown	0	0.00%	17	<0.00%	1.0000
Race: White	139	72.40%	253,361	71.70%	0.8212
Race: Black/African American	25	13.02%	60,621	17.10%	0.1295
Race: Other	<10	0.00%	457	0.13%	NS
Race: Unknown	27	14.06%	39,118	11.10%	0.1855
Patient Related Conditions					
Mechanical Ventilation	113	58.85%	53,233	15.03%	<.0001
Direct Lung Injury: Aspiration	18	9.38%	14,043	3.97%	0.0001
Direct Lung Injury: Pneumonia	62	32.29%	47,600	13.50%	<.0001
Direct Lung Injury: Toxic Inhalation	0	0.00%	3	<0.00%	0.9678
Direct Lung Injury: Lung Contusion	3	1.56%	1,249	0.35%	0.0048
Direct Lung Injury: Near Drowning	0	0.00%	34	0.01%	1.0000
Indirect Lung Injury: Sepsis	53	27.60%	54,408	15.40%	<.0001
Indirect Lung Injury: Severe Sepsis	25	13.02%	20,977	5.93%	<.0001
Indirect Lung Injury: Shock	50	26.04%	32,291	9.13%	<.0001
Indirect Lung Injury: Cardiogenic Shock	12	6.25%	4,762	1.35%	<.0001
Indirect Lung Injury: Septic Shock	25	13.02%	20,975	5.93%	<.0001
Indirect Lung Injury: Multiple Trauma	18	9.38%	40,053	11.30%	0.3932
Indirect Lung Injury: Burn Injury	0	0.00%	8	<0.00%	1.000
Indirect Lung Injury: Acute Pancreatitis	6	3.13%	4,762	1.35%	0.0327
Indirect Lung Injury: Cardiopulmonary Bypass	10	5.21%	15,969	4.52%	0.6445
Patient related: Drug Overdose	1	0.52%	1,721	0.49%	0.9459
Patient related: Alcohol use disorder	21	10.94%	25,054	7.09%	0.0376

	Any potential TRALI $_{A,B,C}$ ‡, N=192	Any potential TRALI $_{A,B,C}$ ‡, %	No TRALI, N=353,557	No TRALI, %	p-value
Patient related: Smoking cigarettes [Diagnosis, Procedure codes and NDCs]	76	39.58%	97,912	27.70%	0.0002
Patient related: Smoking cigarettes [NDCs only]	15	7.81%	16,096	4.55%	0.0303
Patient related: End stage liver disease	6	3.13%	6,063	1.71%	0.1325
Patient related: Liver Transplant surgery	1	0.52%	1,535	0.43%	0.8551
Patient related: Diabetes	56	29.17%	114,735	32.50%	0.3311
Patient related: Post inflammatory pulmonary fibrosis	7	3.65%	3,139	0.89%	0.0018
Blood Components, Any Exposure					
Blood Components Group: Any RBC Exposure	171	89.06%	306,202	86.61%	0.3177
Blood Components Group: Any Plasma Exposure	65	33.85%	50,610	14.31%	<.0001
Blood Components Group: Any Platelet Exposure	72	37.50%	48,047	13.59%	<.0001
Blood Components Group: Any Unknown Blood Component Exposure †	17	8.85%	29,292	8.28%	0.7748
Blood Components, Mutually Exclusive Groups					
Blood Components Group: RBCs only	87	45.31%	253,132	71.60%	<.0001
Blood Components Group: Plasma only	7	3.65%	16,216	4.59%	0.5333
Blood Components Group: Platelets only	5	2.60%	11,632	3.29%	0.5943
Blood Components Group: Platelets and Plasma only	2	1.04%	1,930	0.55%	0.2822
Blood Components Group: RBCs and Plasma only	17	8.85%	18,036	5.10%	0.0182
Blood Components Group: RBCs and Platelets only	25	13.02%	20,044	5.67%	<.0001
Blood Components Group: RBCs and Plasma and Platelets only	17	8.85%	9,207	2.60%	<.0001
Blood Components Group: Other only	27	14.06%	7,030	1.99%	<.0001

	Any potential TRALI $_{A,B,C}$ ‡, N=192	Any potential TRALI $_{A,B,C}$ ‡, %	No TRALI, N=353,557	No TRALI, %	p-value
Blood Components Group: Unknown only	5	2.60%	16,335	4.87%	0.1833
Transfused Units					
# transfused units during encounter, median (min, max, standard deviation)	5	(1,226, SD 25.95)	2	(1,660, SD 7.12)	<.0001
Transfused Units: 1	20	10.42%	82,973	23.50%	<.0001
Transfused Units: 2-4	72	37.50%	208,560	59.00%	<.0001
Transfused Units: 5-9	40	20.83%	42,259	12.00%	<.0001
Transfused Units: 10+	60	31.25%	19,765	5.59%	<.0001
Total Units Transfused	2,477		1,285,286		

**Represents infants/children under 1 year of age*

†Represents the number of inpatient stays with at least one transfused unit that could not be attributed to a blood component (i.e., 'unknown' is defined as a blank or unrecognized blood code included within inpatient transfusion data)

‡TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.

TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).

TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

TRALI$_C$: Other pulmonary insufficiency (518.82), WITH IICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

b. Transfused inpatient population restricted to RBCs, plasma, or platelets

To further explore Sentinel transfusion data, we conducted analyses restricted to transfused inpatient stays that were labeled with specific exposure to RBCs, platelets, or plasma in the HCA Sentinel database. This population restriction removed 3% of potential-TRALI$_{A,B,C}$ (n=6) and 5% (n=16,743) of non-TRALI transfused inpatient stays from the analysis. Excluded stays included stays in which all blood components could not be mapped (i.e., all blood units administered during the stay were 'unknown', due to blank, missing blood codes, or blood codes could not be mapped to a component) and others exposed only to cryoprecipitate.

During the study period, 1,258,036 units of blood products were transfused to 271,156 patients during 337,000 inpatient transfusion stays with any exposure to RBCs, platelets, or plasma. We identified 186 potential-TRALI$_{A,B,C}$ and 336,814 non-TRALI transfused inpatient stays in the HCA Sentinel database with this restriction [Calendar Year 2013=26/45,369 (0.06%), 2014=92/173,100 (0.05%), 2015=68/118,531 (0.06%)]. There were 185 TRALI and 285,583 non-TRALI patients associated with transfused inpatient stays identified with any transfusion of RBCs, platelets of plasma in the HCA Sentinel database **[Appendix F, and Table 7**].

General patterns remained similar between analyses focused on populations with transfused inpatient stays (all transfusions) and analyses focused on diagnoses during transfused inpatient stays with RBCs, plasma or platelet exposure remained significantly younger on admission (median: 62 vs 67 years), had longer LOS (median LOS: 11 vs. 6 days). Patients with potential-TRALI $_{A,B,C}$ codes during their inpatient stay were discharged expired more frequently (22% vs. 7%) [**Table 7**].

We reviewed analyses focused on transfused inpatient stays (all transfusions), and transfused inpatient stays with exposure to RBCs, platelets and plasma for similarities. In both analyses, similar proportions of potential-TRALI $_{A,B,C}$ and non-TRALI stays were identified for the following variables: cardiopulmonary bypass (5% vs. 5%), drug overdose (0.5% vs. 0.5%), ESLD (3% vs. 2%), liver transplant surgery (0.5% vs. 0.4%), or diabetes (29% vs. 33%). None of these analyses crossed the threshold for statistical significance.

Restricting the analyses from transfused inpatient stays to transfused inpatient stays with RBCs, platelets, plasma, potential ALI risk factors that were significantly higher in potential TRALI transfused inpatient stays (all transfusions), remained significantly higher in analyses focused on transfused inpatient stays with RBC, platelet or plasma exposure. The following direct lung injury TRALI risk factors were significantly higher in potential-TRALI $_{A,B,C}$ vs. non-TRALI transfused inpatient stays with RBC, plasma, or platelet exposure: aspiration (9% vs. 4%), pneumonia (33% vs. 14%), and lung contusion (2% vs. 0.4%). The following indirect lung injury TRALI risk factors were significantly higher in potential-TRALI$_{A,B,C}$ vs. non-TRALI transfused inpatient stays: Sepsis (28% vs. 16%), severe sepsis (13% vs. 6%), shock (26% vs. 9%), cardiogenic shock (7% vs. 1%), septic shock (13% vs. 6%), and acute pancreatitis (3% vs. 1%). Patient related factors with significantly higher proportions in potential-TRALI $_{A,B,C}$ vs non-TRALI transfused inpatient stays with RBCs, plasma, or platelet exposure included the following: Alcohol use disorder (11% vs. 7%), smoking cigarettes (39% vs. 28%), and post-inflammatory pulmonary fibrosis (4% vs. 0.9%). Mechanical ventilation was also more common in potential-TRALI $_{A,B,C}$ transfused inpatient stays with exposure to RBCs, platelets and plasma (60% vs 16%) [**Table 7** See **Appendix D** for condition code lists].

When we examined transfusion related TRALI risk factors in the transfused inpatient population with RBCs, platelets and plasma exposure, results resembled other analyses, but proportions often increased slightly (i.e., denominators were reduced by the RBCs, platelets or plasma exposure restriction). For example, the frequency of any RBCs, any platelets, or any plasma exposure were identical in all transfused inpatient analyses, but smaller denominators in the transfused inpatient population increased proportions exposed. The majority of both potential-TRALI $_{A,B,C}$ and non-TRALI inpatient stays were exposed to RBCs (92% vs 91%, p=0.63). Significantly higher proportions of potential-TRALI $_{A,B,C}$ patients were exposed to platelets or plasma during their stays: any plasma (35% vs 15%, p<0.0001) and any platelets (39% vs 14%, p<0.0001). Proportions of inpatient stays with 'any' RBCs, platelets, or plasma exposure as well as an administered unit that could not be attributed to a blood component were similar in both groups (6% vs 4%, p=0.06) **[Table 7**].

When we examined mutually exclusive component exposure categories, the following proportions were observed in potential-TRALI $_{A,B,C}$ vs non-TRALI transfused inpatient stays with exposure to RBCs, platelets, or plasma: RBCs only (47% vs 75%, p<0.0001) plasma only (4% vs 5%, p=0.50), platelets only (3% vs 3%, p=0.56), platelets and plasma only (1% vs 1%,p= 0.28), RBCs and plasma only (9% vs 5%, p=0.02), RBCs and platelets only (13% vs 6%, p=<0.0001), RBCs and plasma and platelets only (9% vs 3%, p<0.0001), other (defined as another combination, which might include cryoprecipitate) (14% vs 2%, p<0.0001) [**Table 7**].

Median number of units administered during transfused inpatient stays were identical in analyses focused on transfused inpatient stays with exposure to RBCs, platelets or plasma. Similar trends were observed in potential-TRALI$_{A,B,C}$ vs non-TRALI inpatient stays when number of units was categorized into categories: 1 unit (10% vs. 22%), 2-4 units (35% vs. 60%), 5-9 units (21% vs. 12%), 10+ units (32% vs 6%) [**Table 7**].

Table 7. Baseline characteristics associated with potential Transfusion-Related Acute Lung Injury (TRALI)$_{A,B,C}$ and non-TRALI inpatient stays identified in the Sentinel Distributed Database, September 2013-September 2015: Limited to *Encounters with RBCs, plasma or platelets*

	Any potential TRALI $_{A,B,C}$, N=186	Any potential TRALI $_{A,B,C}$, %	No TRALI, N=336, 814	No TRALI, %	p-value
Hospitalization Characteristics					
Discharge Disposition: Discharged Alive	145	77.96%	314,308	93.30%	<.0001
Discharge Disposition: Expired	41	22.04%	22,506	6.68%	<.0001
Discharge Disposition: Unknown	0	0.00%	0	0.00%	-
Length of Stay, median (min, max, standard deviation)	11	(1,87, SD 13.76)	6	(1,442, SD 13.07)	<.0001
Patient Demographics					
Age in years, median (min, max, standard deviation)	62	(0*,97, SD 22.01)	67	(0*,165, SD 20.44)	0.0008
Age Group: 0-19	10	5.38%	12,432	3.69%	0.2230
Age Group: 20-34	21	11.29%	21,983	6.53%	0.0086
Age Group: 35-49	29	15.59%	35,940	10.70%	0.0298
Age Group: 50-64	44	23.66%	78,809	23.40%	0.9339
Age Group: 65-79	50	26.88%	112,003	33.30%	0.0652
Age Group: 80+	32	17.20%	75,647	22.50%	0.0860
Sex: Female	102	54.84%	186,651	55.40%	0.8740
Sex: Male	84	45.16%	150,147	44.60%	0.8730
Sex: Ambiguous	0	0.00%	0	0.00%	-
Sex: Unknown	0	0.00%	16	<0.00%	1.0000
Race: White	133	70.97%	240,585	71.40%	0.9818
Race: Black/African American	25	13.44%	58,815	17.50%	0.1487
Race: Other	<10	0.00%	441	0.13%	NS
Race: Unknown	27	14.52%	36,973	11.00%	0.1227
Patient Related Conditions					
Mechanical Ventilation	111	59.68%	52,059	15.50%	<.0001
Direct Lung Injury: Aspiration	17	9.14%	13,818	4.10%	0.0005
Direct Lung Injury: Pneumonia	62	33.33%	46,668	13.90%	<.0001
Direct Lung Injury: Toxic Inhalation	0	0.00%	3	<0.00%	0.9675

	Any potential TRALI $_{A,B,C}$, N=186	Any potential TRALI $_{A,B,C}$, %	No TRALI, N=336, 814	No TRALI, %	p-value
Direct Lung Injury: Lung Contusion	3	1.61%	1,239	0.37%	0.0321
Direct Lung Injury: Near Drowning	0	0.00%	32	0.01%	1.0000
Indirect Lung Injury: Sepsis	52	27.96%	53,353	15.80%	<.0001
Indirect Lung Injury: Severe Sepsis	24	12.90%	20,567	6.11%	0.0001
Indirect Lung Injury: Shock	49	26.34%	31,629	9.39%	<.0001
Indirect Lung Injury: Cardiogenic Shock	12	6.45%	4,666	1.39%	<.0001
Indirect Lung Injury: Septic Shock	24	12.90%	20,565	6.11%	0.0001
Indirect Lung Injury: Multiple Trauma	17	9.14%	39,136	11.60%	0.2914
Indirect Lung Injury: Burn Injury	0	0.00%	8	<0.00%	0.9470
Indirect Lung Injury: Acute Pancreatitis	6	3.23%	4,669	1.39%	0.0320
Indirect Lung Injury: Cardiopulmonary Bypass	10	5.38%	15,708	4.66%	0.6450
Patient related: Drug Overdose	1	0.54%	1,668	0.50%	0.9344
Patient related: Alcohol use disorder	21	11.29%	24,419	7.25%	0.0337
Patient related: Smoking cigarettes [Diagnosis, Procedure codes and NDCs]	73	39.25%	95,373	28.30%	0.0009
Patient related: Smoking cigarettes [NDCs only]	15	8.06%	15,787	4.69%	0.0294
Patient related: End stage liver disease	6	3.23%	5,894	1.75%	0.1475
Patient related: Liver Transplant surgery	1	0.54%	1,435	0.43%	0.8153
Patient related: Diabetes	54	29.03%	112,068	33.30%	0.2198
Patient related: Post inflammatory pulmonary fibrosis	7	3.76%	3,060	0.91%	0.0017

	Any potential TRALI $_{A,B,C}$, N=186	Any potential TRALI $_{A,B,C}$, %	No TRALI, N=336, 814	No TRALI, %	p-value
Blood Component, Any Exposure					
Blood Components Group: Any RBC Exposure	171	91.94%	306,202	90.91%	0.6271
Blood Components Group: Any Plasma Exposure	65	34.95%	50,610	15.03%	<.0001
Blood Components Group: Any Platelet Exposures	72	38.71%	48,047	14.27%	<.0001
Blood Components Group: Any Unknown Blood Component Exposure †	12	6.45%	12,927	3.84%	0.0637
Blood Component, Mutually Exclusive Groups					
Blood Components Group: RBCs only	87	46.77%	253,132	75.15%	<.0001
Blood Components Group: Plasma only	7	3.76%	16,216	4.81%	0.5032
Blood Components Group: Platelets only	5	2.69%	11,632	3.45%	0.5676
Blood Components Group: Platelets and Plasma only	2	1.08%	1,930	0.57%	0.2887
Blood Components Group: RBCs and Plasma only	17	9.14%	18,036	5.35%	0.0219
Blood Components Group: RBCs and Platelets only	25	13.44%	20,044	5.95%	<.0001
Blood Components Group: RBCs and Plasma and Platelets only	17	9.14%	9,207	2.73%	<.0001
Blood Components Group: Other transfusion combination only	26	13.98%	6,617	1.96%	<.0001
Transfused Units					
Transfused Units of RBCs, plasma, or platelets: median [min, max, standard deviation (SD)]	5	(1,226, SD 26.31)	2	(1,660, SD 7.27)	<.0001

	Any potential TRALI $_{A,B,C}$, N=186	Any potential TRALI $_{A,B,C}$, %	No TRALI, N=336, 814	No TRALI, %	p-value
Transfused Units: 1	19	10.22%	72,616	21.60%	0.0002
Transfused Units: 2-4	68	35.48%	202,850	60.20%	<.0001
Transfused Units: 5-9	39	20.97%	41,728	12.40%	<.0001
Transfused Units: 10+	60	32.26%	19,620	5.83%	<.0001
Total Units RBCs, plasma, or platelets transfused	2,458	-	1,255,578	-	

**Represents infants/children under 1 year of age*

†Represents examined the number of inpatient stays with at least 1 transfused unit that could not be attributed to a blood component (i.e., 'unknown' is defined as a blank or unrecognized blood code included within inpatient transfusion data)

‡TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.

TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).

TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

TRALI$_C$: Other pulmonary insufficiency (518.82), WITH IICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

4. Additional exploratory descriptive analyses conducted using electronic data

In these descriptive analyses, some ALI risk factors, such as smoking cigarettes or alcohol use disorder, were included as feasibility items, as under capture of information for these risk factors was possible (See **Appendix D** for condition code lists). Smoking cigarettes was captured in Sentinel data (potential TRALI=38% vs. non-TRALI=25%) [**Table 5**], and use of NDC codes included in the Sentinel inpatient pharmacy table may have increased this population of identified cigarette smokers (7% of potential TRALI and 6% of non-TRALI stays were exposed to smoking cessation medications during their stay) [**Table 5**]. Inpatient stays with alcohol use disorder were also captured with procedure and diagnosis codes (potential TRALI=10% vs. non-TRALI=7%), but drug overdose may have been under captured with diagnosis and procedure codes (potential TRALI=0.5% vs. non-TRALI=1%) [**Table 5**].

Other potentially useful analyses included explorations of the following Sentinel variables: race, sex, age, and discharge disposition. Age was well captured during inpatient stays, but distribution of age ranges indicated certain outliers which may be due to data entry errors [**Table 5-Table 7**]. Approximately 85% of inpatient stays included some race information [**Table 5-Table 7**], however, there may be misclassification given the small proportions of inpatient stays with race information in Asian, Native Hawaiian/Pacific Islander, American Indian or Alaska Native categories. The SCDM does not currently support selection of multiple race categories, which may explain the likely under-capture of race information in some categories. The SCDM variables of hospital discharge disposition and sex were well populated, as all inpatient stays were labeled with discharge disposition information and just a small number of inpatient stays were missing information on sex [**Table 5-Table 7**].

B. UNADJUSTED OCCURANCE RATES AND RATE RATIOS IN ELECTRONIC DATA

1. Unadjusted occurrence rates of potential-TRALI$_A$

Unadjusted occurrence rates (OR) of TRALI per 100,000 inpatient stays are displayed in **Table 8** (potential-TRALI $_A$)). The OR of **potential-TRALI$_A$** per 100,000 transfused inpatient stays was 30.8 per 100,000 transfused inpatient stays (95% CI: 25.0-36.6). TRALI occurrence was highest among patients who died [OR per 100,000=117.4 (95% CI: 73.1-161.6)] or who were mechanically ventilated during their inpatient stay [OR per 100,000=123.8 (95% CI: 94.0-153.7)].

Unadjusted occurrence rates were similar in all study years [Year 2013=33.7 (95% CI: 17.2-50.1), 2014=28.1(95% CI: 20.4-35.9), 2015=33.6 (95% CI: 23.5-43.8)]. Other demographic stratifications showed the largest OR in males [males=31.1 (95% CI: 22.3-39.9); females=30.6 (95% CI: 22.9-38.3)]. When examining OR for age categories, the largest OR was observed in the 20-34 year age category, and smaller ORs were observed in the 65+ year age categories [Age 0-19= 44.3 (95% CI: 8.9-79.8); Age 20-34=45.7 (95% CI: 20.9-70.5); Age 35-49=44.5 (95% CI: 23.4-65.7); Age 50-64=35.8 (95% CI: 22.8-48.9); Age 65-79=23.5 (95% CI: 14.6-32.4); Age 80+=21.9 (95% CI: 11.5-32.3)]. The OR per 100, 000 was 29.6 (95% CI: 22.9-36.3) for Whites, 31.3 (95% CI: 17.2-45.4) for Black or African Americans, and 35.8 (95% CI: 17.2-54.5) for inpatient stays where race information was unknown. Other categories of the SCDM race variable were not well populated, and thus rates may not be stable.

While it was not possible to distinguish whether or not units were administered before or after TRALI occurrence in analyses focused only on electronic data, rates increased as number of units recorded during an inpatient stay increased, and patients with >9 units of blood during their hospital stay had the highest ORs [OR per 100,000 inpatient stays=191.9 (95% CI: 130.9-252.9)]. Unadjusted OR per 100,000 (95% CI) were highest for inpatient stays with multiple blood component exposures: Platelets and Plasma only: OR=103.5 (95% CI: 34.0-247.0), RBCs and Plasma only: OR=49.9 (95% CI: 17.3-82.5), RBCs and Platelets only: OR=74.8 (95% CI: 36.9-112.6), RBCs and Plasma and Platelets only: OR=130.2 (95% CI: 56.5-203.8), Other Transfusion Combination: OR=241.2 (95% CI: 126.6-355.9). In contrast, inpatient stays with just one type of blood component exposure had generally lower ORs: RBCs only=18.6 (95% CI: 13.3-23.9), Platelets only=25.8 (95% CI: 3.4-55.0), Plasma only: OR=12.3 (95% CI: 4.8-29.4).

2. Exploratory analyses, comparative

Salient findings include significantly higher RRs of TRALI for the following conditions: patients who died during the hospitalization as compared to those discharged alive [RR=4.7 (95% CI: 3.1-7.3)], and patients mechanically ventilated as compared to those who were not ventilated during their stay [RR=8.7 (95% CI: 5.9-12.7)].

When compared to RBCs-only stays, the unadjusted rate comparisons show significantly increased TRALI risk with RBCs and Plasma only: RR=2.7 (95% CI: 1.3-5.5), RBCs and Platelets only: RR=4.0 (95% CI: 2.3-7.2), RBCs and Plasma and Platelets only: RR=7.0 (95% CI 3.7-13.2), as well as the Other transfusion combination category: RR=13.0 (95% CI: 7.5-22.6). While it was not possible to distinguish whether units were administered before or after TRALI occurrence in analyses focused only on electronic data, higher rates of TRALI were observed in patients that received greater than 1 unit of blood during their inpatient stay. TRALI rates increased as number of units increased, with patients exposed to 5 or more units having significantly higher rates of TRALI than those exposed to one unit [RR 2-4 units=2.3 (95% CI: 1.0-5.1); RR 5-9 units= 6.7 (95% CI: 2.9-15.6); RR >9 units=22.8 (95% CI: 10.2-51.0)].

As compared to patients ages 20 to 34 years, significantly lower rates of TRALI were observed in patients that were over 65 years of age on admission [RR 65-79 years=0.51 (95% CI: 0.27-1.00); RR 80+years=0.48 (95% CI: 0.23-0.99)].

3. Sensitivity analysis

ORs of potential-TRALI $_{A,B,C}$ per 100,000 inpatient stays are displayed in Table 9. Rates were generally higher than those included in the primary rates analysis focused on potential-TRALI$_A$, mainly as more potential-TRALI inpatient stays were identified by the broader criteria (n=192) than were defined when restricting analyses to potential-TRALI (n=109).

Similar to primary analyses examining all potential-TRALI$_{A,B,C}$ transfused inpatient stays, the OR of TRALI per 100,000 transfused inpatient stays was highest among patients who expired [OR per 100,000=182.5 (95% CI: 127.3-237.6)] or who were mechanically ventilated during their inpatient stay [OR per 100,000=211.8 (95% CI: 172.8-250.9)]. While it was not possible to distinguish whether or not units were administered before or after TRALI occurrence in analyses focused only on electronic data, ORs increased as number of units recorded during an inpatient stay increased, and patients with >9 units of blood during their hospital stay had the highest OR observed in this study [OR per 100,000=302.7 (95% CI: 226.1-379.2)].

As in the primary analysis examining all potential-TRALI$_{A,B,C}$ transfused inpatient stays, unadjusted ORs were similar in all study years [Year 2013: OR=54.7 (95% CI: 33.7-75.7), 2014: OR=53.5 (95% CI: 42.9-64.1), 2015: OR=55.3 (95% CI: 42.2-68.3)]. Other demographic stratifications showed the largest rates in males [males: OR=57.7 (95% CI: 45.7-69.7); females: OR=51.6 (95% CI: 51.7-61.6)]. When examining TRALI occurrence in each age category, the largest rate was observed in the 35-49 year age category [Age 0-19: OR= 73.8 (95% CI: 28.1-119.6); Age 20-34: OR=73.8 (95% CI: 42-105.4); Age 35-49: OR=76.0, (95% CI: 48.3-103.6); Age 50-64: OR=54.4 (95% CI: 38.3-70.4); Age 65-79: OR=46.1 (95% CI: 33.7-58.6); Age 80+: OR=45.0 (95% CI: 30.1-59.9)]. The OR per 100,000 was 54.8 (95% CI: 45.7-63.9) for Whites, 41.2(95% CI: 25.1-57.4) for Black or African Americans, and 69.0 (95% CI: 43.0-95.0) for inpatient stays where race information was unknown. Other categories of the SCDM race variable were not well populated, and thus rates may not be stable.

Significantly higher ratios of potential-TRALI$_{A,B,C}$ were observed for the following conditions: patients who died as compared to those discharged alive [RR=4.0 (95% CI: 2.9-5.7)], and patients mechanically

ventilated as compared to those who were not ventilated during their stay [RR=8.4 (95% CI: 6.3-11.2)]. Higher rates of TRALI were observed in patients that received greater than 1 unit of blood during their inpatient stay. While it was not possible to distinguish whether or not units were administered before or after TRALI occurrence in analyses focused only on electronic data, TRALI rates increased as number of units increased, with patients exposed to 5 or more units having significantly higher rates of TRALI than those exposed to one unit [RR 2-4 units=1.4 (95% CI: 0.87-2.4), RR 5-9 units= 3.9 (95% CI: 2.3-6.7), RR >9 units=12.6 (95% CI: 7.6-20.8)]. Similarly, significantly higher rates of TRALI were observed in patients who were exposed to multiple blood components, as compared to those only exposed to RBCs [RBCs and Plasma only: RR =2.7 (95% CI: 1.6-4.6); RBCs and Platelets only: RR= 3.6 (95% CI: 2.3-5.7); RBCs and Plasma and Platelets only: RR=5.4 (95%CI: 3.2-9.0), Other transfusion combination: RR=11.1 (95% CI: 7.2-17.1)].

Table 8. Comparison of unadjusted potential-Transfusion-Related Acute Lung Injury (TRALI)$_A$ rates by year, blood components, demographic characteristics, and transfused units among inpatient transfusion stays in the Sentinel database, September 2013- September 2015: *TRALI inpatients stays meeting Criterion A)*

	Inpatient encounters with transfusions †	Potential TRALI$_A$* inpatient encounters with transfusions	Potential TRALI$_A$* rate per 100,000 inpatient transfusion stays (95%, Confidence Interval)	Unadjusted rate ratio (95% Confidence Interval)	p-value
Hospitalization Characteristics					
Calendar: 2013	47,544	16	33.7 (17.2-50.1)	Reference	-
Calendar: 2014	181,273	51	28.1 (20.4-35.9)	0.84 (0.48-1.47)	0.531
Calendar: 2015	124,849	42	33.6 (23.5-43.8)	1.00 (0.56-1.78)	0.999
Disposition: Discharged Alive	330,662	82	24.8 (19.4-30.2)	Reference	-
Disposition: Expired	23,004	27	117.4 (73.1-161.6)	4.73 (3.06-7.31)	<.0001
Disposition: Unknown	-	-	-	-	-
Patient Demographics					
Age: 0-19	13,541	6	44.3 (8.9-79.8)	0.97 (0.37-2.55)	0.950
Age: 20-34	28,448	13	45.7 (20.9-70.5)	Reference	-
Age: 35-49	38,160	17	44.5 (23.4-65.7)	0.98 (0.47-2.01)	0.945
Age: 50-64	80,935	29	35.831 (22.8-48.9)	0.78 (0.41-1.51)	0.465
Age: 65-79	114,864	27	23.5 (14.6-32.4)	0.51 (0.27-1.00)	0.045
Age: 80+	77,718	17	21.9 (11.5-32.3)	0.48 (0.23-0.99)	0.041
Age: Unknown	-	-	-	-	-
Sex: Female	199,398	61	30.6 (22.9-38.3)	0.98 (0.67-1.43)	0.930
Sex: Male	154,251	48	31.1 (22.3-39.9)	Reference	--
Sex: Ambiguous	-	-	-	-	-
Sex: Unknown	17	0	0	0	-
Race: White‡	253,436	75	29.6 (22.9-36.3)	Reference	
Race: Black/African American‡	60,640	19	31.3 (17.2-45.4)	0.94 (0.57-1.56)	0.824
Race: Unknown‡	39,132	14	35.8 (17.2-54.5)	0.83 (0.47-1.46)	0.514

	Inpatient encounters with transfusions †	Potential $TRALI_A$* inpatient encounters with transfusions	Potential $TRALI_A$* rate per 100,000 inpatient transfusion stays (95%, Confidence Interval)	Unadjusted rate ratio (95% Confidence Interval)	p-value
Mechanical Ventilation					
Mechanical Ventilation: No	300,367	43	14.3 (10.0-18.6)	Reference	-
Mechanical Ventilation: Yes	53,299	66	123.8 (94.0-153.7)	8.65 (5.89-12.70)	<.0001
Blood Component, Mutually Exclusive Groups					
Blood Component: RBCs Only	253,179	47	18.6 (13.3-23.9)	Reference	-
Blood Component: Platelets Only	11,635	3	25.8 (3.4-55.0)	1.39 (0.43-4.46)	0.623
Blood Component: Plasma Only	16,218	2	12.3 (4.8-29.4)	0.66 (0.16-2.74)	0.569
Blood Component: Platelets and Plasma Only	1,932	2	103.5 (34.0-247.0)	5.58 (1.36-22.94)	0.053
Blood Component: RBCs and Plasma Only	18,045	9	49.9 (17.3-82.5)	2.69 (1.32-5.48)	0.011
Blood Component: RBCs and Platelets Only	20,059	15	74.8 (36.9-112.6)	4.03 (2.25-7.20)	<.0001
Blood Component: RBCs and Plasma and Platelets Only	9,219	12	130.2 (56.5-203.8)	7.01 (3.72-13.21)	<.0001
Blood Component: Other transfusion combination	7,047	17	241.2 (126.6-355.9)	13.00 (7.47-22.62)	<.0001
Blood Component: Unknown/can't be mapped	16,332	2	12.5 (4.7-29.2)	0.66 (0.16-2.72)	0.769
Transfused Units					
Transfused Unit: 1 unit	82,980	7	8.4 (2.2-14.7)	Reference	-
Transfused Unit: 2-4 units	208,600	40	19.2 (13.2-25.1)	2.27 (1.02-5.07)	0.039
Transfused Unit: 5-9 units	42,283	24	56.8 (34.1-79.5)	6.73 (2.90-15.62)	<.0001
Transfused Unit: >9	19,803	38	191.9 (130.9-252.9)	22.75 (10.16-50.95)	<.0001

**$TRALI_A$: TRALI, ICD-9-CM code in any position (518.7). See Table 4.*

† *Inpatient encounters with transfusions excluded encounters meeting $TRALI_B$ and/or $TRALI_C$*

‡Other race categories are not reported due to small sample sizes for some demographic cells and to desire to prevent the ability to derive from other reported cells.

Table 9. Comparison of unadjusted potential Transfusion-Related Acute Lung Injury (TRALI)$_{A,B,-C}$ rates (OR) by year, blood components, demographic characteristics, and transfused units among inpatient transfusion stays in the Sentinel database, September 2013- September 2015: *All potential TRALI encounters (all criteria)*

	Inpatient encounters with transfusions †	Potential TRALI$_{A,B,C}$* inpatient encounters with transfusions	Potential TRALI$_{A,B,C}$* OR rate per 100,000 inpatient transfusion stays (95%, Confidence Interval)	Unadjusted rate ratio (95% Confidence Interval)	p-value
Hospitalization Characteristics					
Calendar: 2013	47,554	26	54.7 (33.7-75.7)	Reference	-
Calendar: 2014	181,319	97	53.5 (42.9-64.1)	0.98 (0.64-1.51)	0.921
Calendar: 2015	124,876	69	55.3 (42.2-68.3)	1.01 (0.64-1.59)	0.963
Disposition: Discharged Alive	330,730	150	45.4 (38.1-52.6)	Reference	-
Disposition: Expired	23,019	42	182.5 (127.3-237.6)	4.02 (2.86-5.66)	<.0001
Disposition: Unknown	-	-	-	-	-
Patient Demographics					
Age: 0-19	13,545	10	73.8 (28.1-119.6)	1.00 (0.47-2.12)	0.999
Age: 20-34	28,456	21	73.8 (42.2-105.4)	R	R
Age: 35-49	38,172	29	76.0 (48.3-103.6)	1.03 (0.59-1.81)	0.919
Age: 50-64	80,950	44	54.4 (38.3-70.4)	0.74 (0.44-1.24)	0.247
Age: 65-79	114,890	53	46.1 (33.7-58.6)	0.63 (0.38-1.04)	0.066
Age: 80+	77,736	35	45.0 (30.1-59.9)	0.61 (0.36-1.05)	0.071
Age: Unknown	-	-	-	-	-
Sex: Female	199,440	103	51.6 (41.7-61.6)	0.90 (0.67-1.19)	0.445
Sex: Male	154,292	89	57.7 (45.7-69.7)	Reference	-
Sex: Ambiguous	-	-	-	-	-
Sex: Unknown	17	0	-	-	-
Race: White ǂ	253,500	139	54.8	Reference	-

	Inpatient encounters with transfusions †	Potential $TRALI_{A,B,C}$* inpatient encounters with transfusions	Potential $TRALI_{A,B,C}$* OR rate per 100,000 inpatient transfusion stays (95%, Confidence Interval)	Unadjusted rate ratio (95% Confidence Interval)	p-value
			(45.7-63.9)		
Race: Black/African American≠	60,646	25	41.2 (25.1-57.4)	0.75 (0.49-1.15)	0.188
Race: Unknown≠	39,145	27	69.0 (43.0-95.0)	1.26 (0.83-1.90)	0.274
Mechanical Ventilation					
Mechanical Ventilation: No	300,400	79	26.3 (20.5-32.1)	Reference	-
Mechanical Ventilation: Yes	53,346	113	211.8 (172.8-250.9)	8.37 (6.26-11.20)	<.0001
Blood Component, Mutually Exclusive Groups					
Blood Component: RBCs Only	253,219	87	34.4 (27.1-41.6)	Reference	--
Blood Component: Platelet Only	11,637	5	43.0 (5.3-80.6)	1.25 (0.51-3.08)	0.626
Blood Component: Plasma Only	16,223	7	43.1 (11.2-75.1)	1.26 (0.58-2.71)	0.561
Blood Component: Platelets and Plasma Only	1,932	2	103.5 (40.0-247.0)	3.01 (0.74-12.23)	0.146
Blood Component: RBCs and Plasma Only	18,053	17	94.2 (49.4-138.9)	2.74 (1.63-4.61)	<.0001
Blood Component: RBCs and Platelets Only	20,069	25	124.6 (75.7-173.4)	3.63 (2.33-5.66)	<.0001
Blood Component: RBCs and Plasma and Platelets Only	9,224	17	184.3 (96.7-271.9)	5.36 (3.19-09.02)	<.0001
Blood Component: Other transfusion combination	7,057	27	382.6 (238.3-526.9)	11.14 (7.24-17.14)	<.0001
Blood Component: Unknown/can't be mapped	16,335	5	30.6 (3.8-57.4)	0.89 (0.36-2.19)	0.802
Transfused Units					
Transfused Unit: 1 unit	82,993	20	24.1 (13.5-34.7)	Reference	-
Transfused Unit: 2-4 units	208,632	72	34.5 (26.5-42.5)	1.43 (0.87-2.35)	0.153
Transfused Unit: 5-9 units	42,299	40	94.6 (65.3-123.9)	3.92 (2.30-6.71)	<.0001

	Inpatient encounters with transfusions †	Potential $TRALI_{A,B,C}$* inpatient encounters with transfusions	Potential $TRALI_{A,B,C}$* OR rate per 100,000 inpatient transfusion stays (95%, Confidence Interval)	Unadjusted rate ratio (95% Confidence Interval)	p-value
Transfused Unit: >9	19,825	60	302.7 (226.1-379.2)	12.56 (7.57-20.83)	<.0001

**$TRALI_{A,B,C}$: $TRALI_A$, $TRALI_B$, and $TRALI_C$ as listed below. See Table 4.*

$TRALI_A$: TRALI, ICD-9-CM code in any position (518.7).

$TRALI_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

$TRALI_C$: Other pulmonary insufficiency (518.82), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

† Included all inpatient encounters with transfusions.

‡Other race categories are not reported due to small sample sizes for some demographic cells and to desire to prevent the ability to derive from other reported cells.

C. EXPLORING THE ABILITY TO IDENTIFY SPECIFIC CATEGORIES OF BLOOD COMPONENTS, INCLUDING COMPONENT TYPE AND PROCESSING METHOD IN ELECTRONIC DATA

Table 10 explores whether or not electronic identification of component processing (e.g., leukoreduction, irradiation) was possible within the HCA Sentinel database, using relevant codes in Codabar and ISBT-128 coding systems (as described in Methods, Section C). We also examined the ability to identify apheresis-derived and whole-blood-derived products. An additional analysis intending to understand the magnitude of ISBT-128 code use (as opposed to Codabar) within the database is located in the Appendix **[Appendix F, Table 5].** This analysis found the majority of blood exposures were labeled with ISBT-128 codes, but to ensure comprehensive data descriptions we focused on use of both ISBT-128 and Codabar codes to describe exposures in the below summary.

When the analyses were restricted to the transfused inpatient population, we identified 192 potential-TRALI$_{A,B,C}$ and 353,557 non-TRALI transfused inpatient stays in the HCA Sentinel database.

1. Platelets

When the number of transfused inpatient stays with any platelet exposure was examined, 38% of potential-TRALI $_{A,B,C}$ and 14% of non-TRALI stays were identified with platelet exposures. While it was not possible to distinguish whether or not units were administered before or after TRALI occurrence in analyses focused only on electronic data, potential TRALI inpatient stays had a higher median number of administered platelet units than did non-TRALI inpatient stays [potential-TRALI$_{A,B,C}$ median 2 (range 1-9) vs non-TRALI median 1 (range 1-21)]. Most inpatient stays with platelet exposures had apheresis derived platelets exposures (potential-TRALI $_{A,B,C}$ 100% vs non-TRALI 98%), and fewer encounters had whole blood derived platelet exposures (potential-TRALI $_{A,B,C}$ 4% vs non-TRALI 6%). In addition, most inpatient stays with platelet exposures in both groups were labeled as exposed to leukocyte reduced apheresis derived platelets (97% in both groups). Fewer inpatient stays with irradiated platelet exposures were identified (potential-TRALI $_{A,B,C}$ 29% vs non-TRALI 32%).

2. RBCs

The majority of both potential-TRALI$_{A,B,C}$ and non-TRALI transfused inpatient stays were exposed to RBCs (potential-TRALI $_{A,B,C}$ 89% vs non-TRALI 87%). The median number of administered RBC units was 2 units in both groups stays [TRALI median 2 (range 1-14) vs non-TRALI median 2 (range 1-42)]. Most inpatient stays with RBC exposures had whole blood derived RBC exposures (potential-TRALI$_{A,B,C}$ 96% vs non-TRALI 88%), but a substantial number of inpatient stays also had apheresis derived RBC exposures (potential-TRALI$_{A,B,C}$ 51% vs non-TRALI 41%) or more specifically leukocyte-reduced apheresis RBCs (potential-TRALI$_{A,B,C}$ 50% vs non-TRALI 40%). Fewer inpatient stays with irradiated RBC exposures were identified (potential-TRALI$_{A,B,C}$ 18% vs non-TRALI 10%), and the majority appeared to be exposed to irradiated leukocyte-reduced RBCs (potential-TRALI$_{A,B,C}$ 18% vs non-TRALI 9%) specifically. Irradiated apheresis RBC exposures appear to be less common than other RBC exposures examined (potential-TRALI$_{A,B,C}$ 8% vs non-TRALI 4%).

3. Plasma

When the number of transfused inpatient stays with any plasma exposure was examined, 34% of potential-TRALI$_{A,B,C}$ and 14% of non-TRALI stays were identified with plasma exposures. While it was not possible to distinguish whether or not units were administered before or after TRALI occurrence in analyses focused only on electronic data, potential TRALI inpatient stays had a higher median number of administered plasma units during their hospitalization than did non-TRALI inpatient stays [potential-

TRALI$_{A,B,C}$ median 2 (range 1-7) vs non-TRALI median 1(range 1-33)]. Most inpatient stays with plasma exposures had whole blood derived plasma exposures (potential-TRALI$_{A,B,C}$ 91% vs non-TRALI 89%), but a substantial number had apheresis-derived plasma exposures (potential-TRALI$_{A,B,C}$ 37% vs non-TRALI 33%). Irradiated (potential-TRALI$_{A,B,C}$ 3% vs non-TRALI 3%) or leukocyte reduced plasma (potential-TRALI$_{A,B,C}$ 2% vs non-TRALI 1%) exposures were not commonly identified.

4. Cryoprecipitate

When the number of transfused inpatient stays with any cryoprecipitate exposure was examined, 14% of potential-TRALI$_{A,B,C}$ and 2% on non-TRALI stays were identified with cryoprecipitate exposures. The median number of administered cryoprecipitate units was 1 unit in both groups stays [potential-TRALI$_{A,B,C}$ median 1 (range 1-3) vs non-TRALI median 1 (range 1-8)].

5. Transfused inpatient stays with missing component information

We examined three types of potentially missing information. First, we examined the number of transfused inpatient stays with no ISBT-128 or Codabar codes available for blood component identification and found 2% of potential-TRALI$_{A,B,C}$ and 3% of non-TRALI stays without any ISBT-128 or Codabar codes. Second, we examined the number of transfused inpatient stays in which all ISBT-128 or Codabar codes provided during an encounter could not be mapped to a component (unrecognized or invalid codes). One percent of potential-TRALI$_{A,B,C}$ transfused inpatient stays and 2% of non-TRALI transfused inpatient stays were identified with these potentially invalid or unrecognized codes for all recorded transfusions in the database. Finally, we examined number of transfused inpatient stays in which any ISBT-128 or Codabar codes provided during an encounter could not be mapped to a component (unrecognized or invalid codes). This proportion was high, at 3% of potential-TRALI$_{A,B,C}$ and 1% of non-TRALI cases. These analyses indicate that there are a small proportion (<3%) of inpatient stays within the HCA Sentinel database for which blood components cannot be determined due to unrecognized coding (i.e., codes were either invalid or could not be identified using current methods). It is possible that local hospital coding may exist in such instances, or that additional standardization of transfusion codes included in the database may be useful.

Table 10. Description of blood products and components identified with ISBT-128 and Codabar codes in potential-Transfusion-Related Acute Lung Injury (TRALI)$_{A,B,C}$ and non-TRALI inpatient stays in the Sentinel database, September 2013- September 2015

Blood product/component	**Inpatient** *stays with evidence of transfusion and potential TRALI$_{A,B,C}$* (n=**192** inpatient stays)*	**Inpatient** *stays without TRALI and evidence of transfusion (n=**353,557**)*
Any Platelets	72 (38%)	48,047 (14%)
Platelet units per inpatient stay, median (min, max, Standard Deviation)	2 (1,9, SD 1.7)	1 (1,21, SD 1.27)
Apheresis platelets	72 (100%)	46,873 (98%)
Leukocyte-reduced platelets	70 (97%)	47,555 (99%)
Irradiated platelets	21 (29%)	15,271 (32%)
Whole blood-derived platelets	3 (4%)	2,675 (6%)
Leukocyte-reduced apheresis platelets	70 (97%)	46,377 (97%)
Irradiated apheresis platelets	21 (29%)	15,014 (31%)
Irradiated leukocyte-reduced	19 (26%)	15,086 (31%)
Irradiated leukocyte-reduced apheresis platelets	19 (26%)	14,832 (31%)
Any Red Blood Cells (RBCs)	171 (89%)	306,202 (87%)
RBC units per inpatient stay, median (min, max, Standard Deviation)	2 (1, 14, SD 2.5)	2 (1, 42, SD 1.43)
Irradiated RBCs	30 (18%)	29,701 (10%)
Leukocyte-reduced RBCs	164 (96%)	293,168 (96%)
Apheresis-derived RBCs	87 (51%)	124,729 (41%)
Whole blood-derived RBCs	161 (96%)	268,809 (88%)
Irradiated apheresis RBCs	14 (8%)	11,381 (4%)
Leukocyte-reduced apheresis RBCs	86 (50%)	121,622 (40%)
Irradiated leukocyte-reduced RBCs	30 (18%)	28,747 (9%)
Irradiated leukocyte-reduced apheresis RBCs	14 (8%)	11,109 (4%)
Any Plasma	65 (34%)	50,610 (14%)
Plasma units per inpatient stay, median (min, max, ST)	2 (1,7, SD 1.24)	1 (1,33, SD 1.25)
Irradiated plasma	2 (3%)	1,526 (3%)
Leukocyte-reduced plasma	1 (2%)	301 (1%)
Apheresis-derived plasma	24 (37%)	16,716 (33%)
Whole blood-derived plasma	59 (91%)	45,216 (89%)
Irradiated apheresis plasma	1 (2%)	611 1%)
Leukocyte-reduced apheresis plasma	0	182 (0%)
Irradiated leukocyte-reduced plasma	0	16 (0%)
Irradiated leukocyte-reduced apheresis plasma	0	5 (0%)
Cryoprecipitate	27 (14%)	6,927 (2%)
Cryoprecipitate, units per inpatient stay, median (min, max, Standard Deviation)	1 (1,3, SD 0.7)	1 (1,8, SD 0.46)

Blood product/component	**Inpatient** *stays with evidence of transfusion and potential TRALI$_{A,B,C}$* (n=**192** inpatient stays)*	**Inpatient** *stays without TRALI and evidence of transfusion (n=**353,557**)*
Number of inpatient stays with transfusions with NO ISBT or Codabar codes	5 (3%)	12,302 (3%)
Number of inpatient stays with transfusions with all ISBT or Codabar codes that could not be mapped	1 (1%)	5,309 (2%)
Number of inpatient stays with transfusions with any (not all) ISBT or Codabar codes that could not be mapped	6 (3%)	4,563 (1%)

**TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.*

TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).

TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

TRALI$_C$: Other pulmonary insufficiency (518.82), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

D. QUANTIFICATION OF ALGORITHM POSITIVE PREDICTIVE VALUE WITH ELECTRONIC DATA AND MEDICAL CHARTS

We identified 208 potential TRALI inpatient stays (n=207 patients), and charts were requested for all identified encounters. Of the identified 208 potential TRALI inpatient stays, 195 (94%) charts were retrieved and provided for adjudicator review. Adjudicators confirmed the TRALI endpoint, transfusion exposure, and mechanical ventilation.

1. Eligible samples for positive predictive value (PPV) calculations for TRALI based on inpatient diagnoses recorded in the administrative data

We report on the PPVs separately for each of the three TRALI criterion (**Appendix F**, **Table 4**). Demographic and hospitalization characteristics for these patients are provided in Table 11. Demographic and hospitalization characteristics for patients meeting clinical definitions for definitive, possible, or delayed TRALI are included in **Appendix F, Table 4**. PPVs were calculated by dividing the number of confirmed cases by the number of potential TRALI$_{A,B,C}$ cases with available medical charts). In our PPV calculations, we counted definitive, delayed, and possible TRALI as confirmed cases. Exact binomial 95% CIs were calculated for the PPV estimates to quantify their precision.

Table 11. Description of potential Transfusion-Related Acute Lung Injury (TRALI) $_{A, B,C}$ patient demographics

	Inpatient stays *with potential TRALI$_{A,B,C}$* as defined with inpatient diagnosis codes (n=195) No. inpatient stays (%)*
Race	
White	146 (75%)
Black/African American	20 (10%)
Other/Unknown	29 (15%)
Ethnicity	
Hispanic	31 (16%)
Not Hispanic	125 (64%)
Unknown	39 (20%)
Sex	
Female	106 (54%)
Male	89 (46%)
Unknown	-
Age (years) at encounter admission or visit	
0-19	10 (5%)
20-34	19(10%)
35-49	27(14%)
50-64	45 (23%)
65-79	57 (29%)
80+	37 (19%)
Year of encounter admission	
2013	26 (13%)
2014	98 (50%)
2015	71 (36%)
Discharge Disposition	
Discharged Alive	154 (79%)
Expired	41 (21%)
Unknown	-

**TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.*

TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).

TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

TRALI$_C$: Other pulmonary insufficiency (518.82), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

2. Adjudication pilot

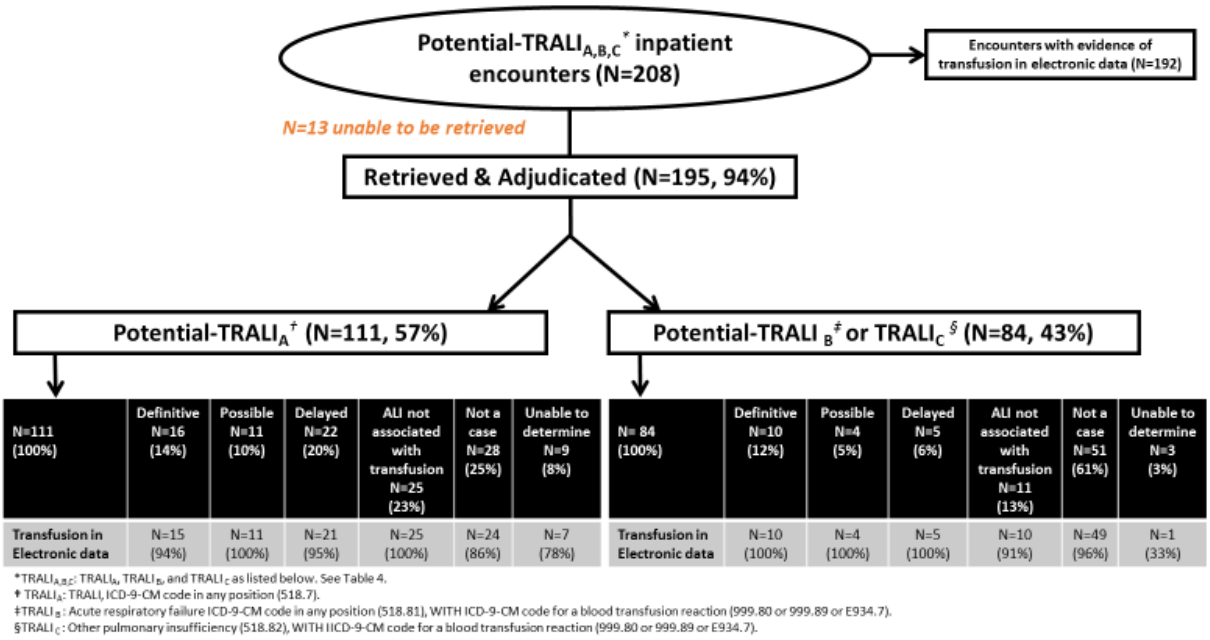
Twenty potential-TRALI$_{A,B,C}$ cases were reviewed during a pilot phase, all pilot cases were reviewed by at least two adjudicators. Adjudicators independently reached the same TRALI case decision for 14 of 20 (70%) charts included in the adjudication pilot. Of the 6 charts with discrepant TRALI case decisions, 4 had minor discrepancies (i.e., not a TRALI case vs unable to determine), and 2 had major discrepancies (i.e., TRALI case vs unable to determine). Minor discrepancies were associated with missing chart information (e.g., illegible notes, or minimal available transfusion information for patients transferred from a non-HCA hospital, etc.) and differences in understanding of when to select 'not a TRALI case', 'ALI not associated with a transfusion', and 'unable to determine' on the adjudication form. When definitions were clarified all minor discrepancies were easily resolved and consensus was achieved. Adjudicators recommended defining 'Not a case of TRALI' and 'Unable to determine' more clearly, and the adjudication form was revised. Two major discrepancies were due to case complexity. In one instance, one adjudicator did not feel there was enough available chart information to completely rule out TACO and thus listed 'unable to determine' while the other was confident that there was enough information to rule out TACO and the case met all TRALI criteria. In the second discrepant case, the blood transfusion of interest was administered at another hospital prior to the patient's transferred to a HCA hospital. Both adjudicators stated there was missing medical chart information, and stated that it was a judgement call. The two cases with major discrepancies were provided to a third adjudicator for a final decision, and neither case was determined to meet clinical criteria for TRALI. After this process was complete, there were 7 TRALI cases meeting clinical definitions for definitive, possible, or delayed TRALI (35%) in the pilot.

To address these instances going forward within the scope of the project, adjudicators made two recommendations. First, they recommended clarifying the adjudication form as described above. Second, adjudicators recommended implementing a second opinion option, which could be requested when a case was particularly complex. Both recommendations were implemented for the remainder of the study (see **Appendix C** for adjudication form). During the remainder of the study, adjudicators requested the second opinion option in 17 instances. In 12 instances (71%), there was overall agreement between adjudicators on TRALI case status (i.e., met one of the clinical TRALI case definitions, or was not a case of TRALI), and in 5 (29%) instances the second adjudicator revised the case decision. Seven (41%) of these 17 potential-TRALI cases met clinical definitions for definitive, possible, or delayed TRALI (5 from the group of 12 cases with agreement, 2 from the group of 5 with incomplete agreement).

3. TRALI endpoint

Disposition of all TRALI inpatient stays ascertained in the Sentinel Distributed Database (SDD) is summarized in **Figure 1**. Of 195 potential-TRALI$_{A,B,C}$ inpatient encounters with available charts, 68 (35%) were confirmed as TRALI, [26 (38%) definitive TRALI, 15 (22%) possible TRALI, 27 (40%) delayed TRALI], 79 (41%) were not cases of TRALI, 36 were determined to be acute lung injury (ALI) not associated with a transfusion, and 12 (6%) were adjudicated as unable to determine (e.g., complex cases, chart lacking critical information often to due hospital transfers, or incompleteness or ambiguity). For the one patient with two potential TRALI inpatient encounters, neither event was confirmed as TRALI. Instead, both events were determined to be ALI not associated with a transfusion.

Figure 1. Disposition of all potential Transfusion-Related Acute Lung Injury (TRALI) inpatient stays ascertained in the Sentinel Distributed Database (SDD)



N=111 (100%)	Definitive N=16 (14%)	Possible N=11 (10%)	Delayed N=22 (20%)	ALI not associated with transfusion N=25 (23%)	Not a case N=28 (25%)	Unable to determine N=9 (8%)
Transfusion in Electronic data	N=15 (94%)	N=11 (100%)	N=21 (95%)	N=25 (100%)	N=24 (86%)	N=7 (78%)

N= 84 (100%)	Definitive N=10 (12%)	Possible N=4 (5%)	Delayed N=5 (6%)	ALI not associated with transfusion N=11 (13%)	Not a case N=51 (61%)	Unable to determine N=3 (3%)
Transfusion in Electronic data	N=10 (100%)	N=4 (100%)	N=5 (100%)	N=10 (91%)	N=49 (96%)	N=1 (33%)

*TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.
† TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).
‡TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).
§TRALI$_C$: Other pulmonary insufficiency (518.82), WITH IICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).

Approximately 17% (n=22) of potential-TRALI $_{A,B,C}$ cases that were ultimately not confirmed as definitive, possible, or delayed TRALI cases by adjudicators (n=127), had transfusion reactions that were suspected to be either cases of Transfusion Related Circulatory Overload (TACO) (n=15, 12%) or Transfusion Related Anaphylaxis (TRA) (n=7, 5%). Other potential diagnoses noted by adjudicators included non-transfusion related circulatory overload or pulmonary edema (n=32, 25%), and ALI not associated with a transfusion (n=21, 17%).

To compare to the literature, we calculated crude OR of TRALI utilizing only cases meeting clinical definitions for definitive, possible, or delayed TRALI with medical charts (n=68), and found a crude TRALI OR of 0.02% per transfused patient, and 0.26 TRALI cases per 5,000 units of blood products (0.05 cases per 1,000 units; 0.53 cases per 10,000 units). There were 19.2 cases meeting clinical definitions for definitive, possible, or delayed TRALI per 100,000 inpatient transfusion stays (95% CI: 14.7 - 23.8). When we restricted our analyses to only definitive TRALI cases (n=26), the TRALI OR was 0.001% per transfused patient, and 0.10 TRALI cases per 5,000 units of blood products (0.02 cases per 1,000 units; 0.20 cases per 10,000 units). There were 7.3 cases meeting the clinical definition for definitive TRALI per 100,000 inpatient transfusion stays (95% CI: 4.5 - 10.2).

Positive predictive values (PPVs) of the electronic code based TRALI algorithm are included in **Table 12**. The PPVs for all inpatient TRALI diagnoses recorded in the Sentinel electronic data (TRALI Criterion A, B, or C) were 35% overall (68/195, 95% CI: 28-42). The PPV for TRALI$_A$ was 44% (49/111, 95% CI: 35-54) and TRALI$_B$ was 24% (19/79, 95% CI: 15-33) [**Table 12**]. There were no TRALI cases meeting clinical definitions for definitive, possible, or delayed clinical definitions identified by TRALI$_C$ (0/5).

PPVs were calculated separately for definitive, possible, and delayed TRALI clinical case definitions. The overall PPV, when the electronic algorithm including all TRALI criteria was compared to definitive TRALI, was 13% (26/195, 95% CI: 9-19%). PPV results for the electronic algorithm as compared to possible or delayed TRALI were similar to definitive TRALI comparisons [Possible: PPV=8% (15/195, 95% CI: 4-12%)

and Delayed: PPV=14% (27/195, 95% CI: 9-20%)]. PPVs of <20% were also observed when each electronic TRALI criteria was compared to confirmed definitive, possible, and delayed TRALI [**Table 13**].

Table 12. Positive predictive values (PPVs) associated with inpatient diagnosis codes for Transfusion-Related Acute Lung Injury (TRALI)

PPVs associated with inpatient diagnosis codes for TRALI, compared to chart review (N =195)	
Stratifications	**% (95% Confidence Interval)**
Potential-TRALI$_{A,B,C}$[a]	35% (68/195, 95% CI: 28-42%)
By TRALI Criterion recorded in electronic data	
Potential-TRALI$_{A}$[b]	44% (49/111, 95% CI: 35-54%)
Potential-TRALI$_{B}$ [c]	24% (19/79, 95% CI: 15-33%)
Potential-TRALI $_{C}$[d]	- (0/5)
Potential-TRALI$_{B\ or\ C}$[e]	23% (19/84, 95% CI: 14-33%)
By sex in electronic data	
Female	41% (43/106, 95% CI: 31-51%)
Male	28% (25/89, 95% 19-37%)
By age category in electronic data	
0-19 years	10% (1/9, 95% CI, 0.3-43%)
20-34 years	32% (6/19, 95% CI: 13-57%)
35-49 years	35% (9/27, 95% CI: 17-54%)
50-64 years	38% (17/45, 95% CI: 24-52%)
65-79 years	39% (22/57, 95% CI: 26-52%)
80+ years	35% (13/37, 95% CI: 20-53%)
By whether any blood transfusion was recorded in electronic data	
Transfusion recorded in electronic data	36% (66/182, 95% CI: 29-44%)
No transfusion recorded in electronic data	15% (2/13, 95% CI: 2-45%)
By whether a potential-TRALI$_{A}$ **diagnosis code and 'Principal diagnosis code' flag was included in electronic data**	
Potential-TRALI$_{A}$[b] diagnosis code with a 'Principal diagnosis' flag recorded in electronic data	44% (4/9, 95% CI: 14-79%).
By whether a potential-TRALI$_{A}$ **diagnosis code and 'Present on admission' flag was included in electronic data**	
Potential TRALI$_{A}$[b] diagnosis code with a 'Present on admission' flag recorded in electronic data	36% (19/53, 95% CI: 23-50%).

[a] *TRALI$_{A,B,C}$: TRALIA, TRALI$_{B}$, and TRALI$_{C}$ as listed below. See Table 4.*

[b] *TRALI$_{A}$: TRALI, ICD-9-CM code in any position (518.7). See Table 4.*

[c] *TRALI$_{B}$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7). See Table 4.*

[d] *TRALI$_{C}$: Other pulmonary insufficiency (518.82), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7). See Table 4.*

[e] *TRALI$_{B\ or\ C}$: TRALI$_{B}$, or TRALI$_{C}$ as listed above. See Table 4.*

Table 13. Positive predictive values (PPVs) associated with inpatient diagnosis codes for Transfusion-Related Acute Lung Injury (TRALI$_{A,B,C}$*) as compared to definitive, possible, delayed clinical case definitions attained from medical chart review

PPVs associated with inpatient diagnosis codes for TRALI, compared to chart review (N =195)	
Stratifications	**% (95% Confidence Interval)**
Potential-TRALI$_{A,B,C}$* compared to definitive TRALI	13% (26/195, 95% CI: 9-19%)
Potential-TRALI$_{A,B,C}$* compared to possible TRALI	8% (15/195, 95% CI: 4-12%)
Potential-TRALI$_{A,B,C}$* compared to delayed TRALI	14% (27/195, 95% CI: 9-20%)
Potential-TRALI$_A$† compared to definitive TRALI	14% (16/111, 95% CI:9-22%)
Potential TRALI$_A$† compared to possible TRALI	10% (11/111, 95% CI: 5 17%)
Potential TRALI$_A$† compared to delayed TRALI	20% (22/111, 95% CI: 13-28%)
Potential TRALI$_B$‡ compared to definitive TRALI	13%, (10/79, 95% CI: 6-22%)
Potential TRALI$_B$‡ compared to possible TRALI	5% (4/79, 95% CI: 1-12%)
Potential TRALI$_B$‡ compared to delayed TRALI	6% (5/79, 95% CI, 2-14%

**TRALI$_{A,B,C}$: TRALI$_A$, TRALI$_B$, and TRALI$_C$ as listed below. See Table 4.*
†TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7). See Table 4.
‡TRALI$_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7). See Table 4.
TRALI$_C$: Other pulmonary insufficiency (518.82), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7). See Table 4.

In exploratory analyses, we examined the PPV for the specific TRALI code (potential TRALI$_A$) when it was coded as 'Principal' or 'Present on admission' in the Sentinel database, as compared to all chart confirmed TRALI cases (i.e., cases meeting clinical definitions for definitive, possible, or delayed TRALI). The PPV for the specific TRALI code in principal position was 44% (4/9, 95% CI: 14-79%). The PPV for a TRALI code flagged as 'present on admission' was 36% (19/53, 95% CI: 23-50%). As we were interested in learning if recording of blood transfusion in Sentinel data would modify the PPV for TRALI, we stratified PPVs by this information. PPVs for TRALI diagnosis codes were higher in encounters for which electronic transfusion records were available (transfusion recorded, PPV=36%, 95% CI: 29-44%; transfusion not recorded PPV=15%, 95% CI: 2-45%), but PPVs remained similar to those observed in primary analyses. When stratifying PPVs by sex and age category, the PPV of the TRALI electronic algorithm was highest in females (females: PPV=41%, 95% CI: 31-51%, males: PPV=28%, 95% CI: 19-37%) and in 65 to 79-year age category (65-79 years: PPV=39%, 95% CI: 26-52%) **[Table 12].**

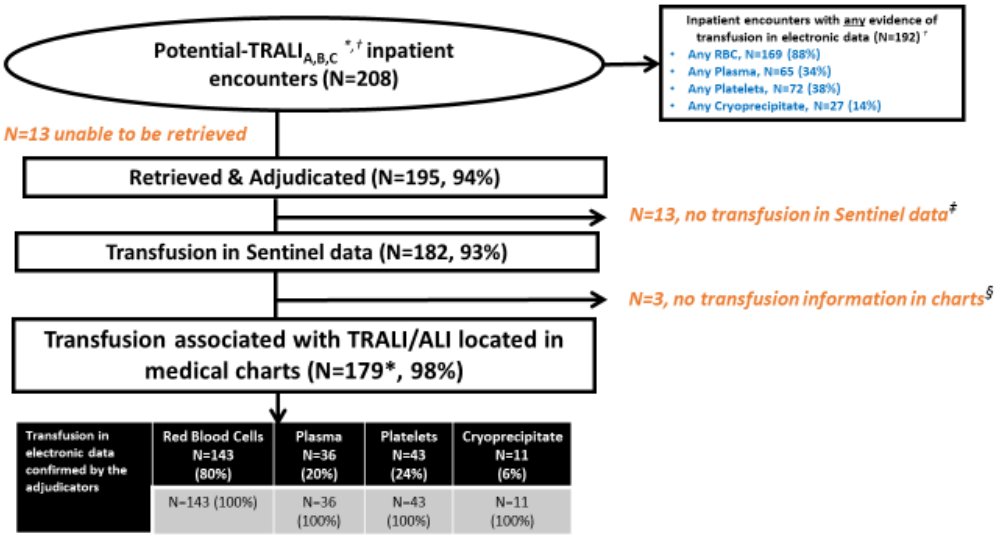
Also in exploratory analyses, we focused on the PPV of TRALI diagnosis codes, we examined the effect of excluding from analysis encounters in which adjudicators were 'unable to determine' the TRALI outcome (n=12 encounters, **Appendix F, Table 5**). PPVs for TRALI increased moderately but were consistent with primary analysis results in **Table 12** and remained below 50% for all stratifications.

4. Transfusion exposure

Of 208 potential-TRALI$_{A,B,C}$ inpatient stays identified in electronic data, 192 (92%) had a relevant blood transfusion exposure in the HCA Sentinel database, 81% (n=169) had any RBC exposure, 35% (n=72) had any platelet exposures, 31% (n=65) had any plasma exposure, and 13% (n=27) had a cryoprecipitate exposure during their inpatient stay. Rather than abstracting all transfusions occurring during the entire hospitalization, adjudicators focused on extracting information about the blood transfusion(s) associated with TRALI or ALI. Thus, there was often a greater number of blood transfusion recorded in the Sentinel inpatient transfusion data than abstracted by adjudicators (i.e., some patients had lengthy stays with multiple transfusions, many were not associated with ALI).

Of the 208 potential-TRALI$_{A,B,C}$ inpatient stays, 195 (94%) had an available medical chart (see section 6, Chart retrieval process for more details), and 182 of these (93%) had a relevant transfusion exposure included in HCA Sentinel electronic data **[Figure 2].** Of the 13 records labeled as not having a transfusion in the HCA Sentinel electronic database, adjudicators located reasons for lack of transfusion information in 10 patient records. The majority (n=9/10) had evidence of transfusion administration prior to hospitalization (i.e., transfusion of interest occurred in another hospital, emergency department, or outpatient setting, hospital transfer often noted), and Intravenous Immunoglobulin (IVIg) was the exposure of interest in one instance (n=1/10).

Figure 2. Disposition of all potential Transfusion-Related Acute Lung Injury (TRALI) inpatient stays and transfusion information ascertained in the Sentinel Distributed Database (SDD) and medical charts



*TRALI$_{A,B,C}$: TRALI$_A$, TRALI $_B$, and TRALI $_C$ as listed below. See Table 4.
TRALI$_A$: TRALI, ICD-9-CM code in any position (518.7).
TRALI $_B$: Acute respiratory failure ICD-9-CM code in any position (518.81), WITH ICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).
TRALI $_C$: Other pulmonary insufficiency (518.82), WITH IICD-9-CM code for a blood transfusion reaction (999.80 or 999.89 or E934.7).
† Please note, multiple components were often administered during a transfusion interest
‡Of 13 with missing transfusion information in Sentinel data- 9 received transfusions at another facility, ED, or outpatient setting, 1 had IVIg administration in charts, and 3 no transfusion information that could be obtained from charts
§ Transfusion of interest occurred in a different facility (i.e., transferred from another hospital, or ED)

Adjudicators located a transfusion of interest (transfusion closest to the ALI event of interest) within medical charts for 179 (98%) of 182 potential-TRALI$_{A,B,C}$ inpatient stays with transfusion information available in Sentinel electronic data **[Figure 2**]. In all three instances where adjudicators did not identify a transfusion of interest in medical charts, patients had received their transfusion of interest in another facility, and were labeled as hospital transfers (i.e., incomplete information existed because transfusion of interest was administered at a different facility).

The PPV for any relevant transfusion exposure in the HCA Sentinel database as compared to medical charts was 98.4**% [Table 14].** The following component exposures were confirmed by adjudicators in potential TRALI cases: RBCs 143 (79%), platelets 43 (24%), plasma 36 (20%), and cryoprecipitate 10 (6%). Perfect concordance was observed between blood components as identified in the HCA Sentinel database as compared to transfusions of interest located by adjudicators in medical charts (PPVs=100%).

Concordance of dates and times of transfusion administrations between medical chart information and Sentinel data was generally observed [Median date difference 0 (SD: 0.21, Min: -1, Max 1); Median start time difference in minutes, 0 minutes (SD: 199, Min: -1451, Max: 1706]; Median time difference in hours, 0 hours (SD: 3.3, Min: -24, Max: 28]. When transfusion times did not match, some patterns were observed. For example, when dates crossed midnight there may have been date discrepancies in the

chart (i.e., patient admitted 23:00, transfusion started 1 am, but date recorded was admission date). Also, in instances where multiple units were given during a transfusion, discrepancies may have been introduced when adjudicators were not able locate every start and end time for every administered unit.

At least one processing method or specific blood component type was located by adjudicators for transfusions occurring during 96 (54%) encounters with relevant blood transfusion exposure in the Sentinel database. Please see **Table 14** for specific sample sizes and PPVs for processing methods by blood component type.

Overall, blood transfusions and component were well captured in electronic transfusion data, and we observed high concordance between component information in electronic transfusion data and medical charts. Processing and collection information was typically available in electronic transfusion data. However, lack of consistent access to blood bank portions of the EMR during the adjudication process restricted the ability to examine concordance of this information in medical charts and electronic transfusion data. When comparing Sentinel electronic information on processing methods or specific blood type to the limited amount of information gathered by adjudicators, PPVs were below 61% [**Table 14**]. When adjudicators were able to locate processing methods or collection information in a small sample of medical charts, there was perfect concordance with Sentinel electronic data [**Table 14**].

Table 14. Positive predictive values (PPVs) for blood transfusions captured in electronic data amongst potential Transfusion-Related Acute Lung Injury (TRALI) inpatient stays

	PPVs for factors associated with blood transfusion (N = 182, with transfusion recorded in the Sentinel database) % (n/N; 95% Confidence Interval)
Any transfusion	98.4% (179/182; 95.3%, 99.7%)
Blood component	
Red blood cells any	100% (143/143; 97.5%, 100%)
Platelets any	100% (43/43; 91.8%, 100%)
Plasma any	97.3% (36/37; 85.8%, 99.9%)
Cryoprecipitate any	90.9% (10/11; 58.7%, 99.8%)
Blood processing or collection method	
Red blood cells	
Apheresis-derived	60% (23/39; 42.1%, 74.4%)
Leukocyte-reduced	46.9% (61/130; 38.1%, 55.9%)
Irradiated	41.7% (5/12; 15.2%, 72.3%)
Whole blood derived	8.6% (10/117, 4.1%, 15.2%)
Platelets	
Apheresis-derived	41% (16/39; 25.6%, 57.9%)
Leukocyte-reduced	39.5% (15/38, 24%, 56.6%)
Irradiated	60% (6/10; 26.2%, 87.8%)
Whole blood derived	-
Plasma	
Apheresis-derived	40% (4/11; 12.2%, 73.8%)
Leukocyte-reduced	-
Irradiated	-
Whole blood derived	3.7% (1/27; 0.09%, 18.9%)

	PPVs for factors associated with blood transfusion (N = 182, with transfusion recorded in the Sentinel database) % (n/N; 95% Confidence Interval)
Restricting only to blood processing or collection method confirmed by the adjudicators	
Red blood cells	
Apheresis-derived	100% (23/23; 85.2%, 100%)
Leukocyte-reduced	100% (61/61; 94.1%, 100%)
Irradiated	100% (5/5; 47.8%, 100%)
Whole blood derived	100% (10/10, 69.2%, 100%)
Platelets	
Apheresis-derived	100% (16/16; 79.4%, 100%)
Leukocyte-reduced	100% (15/15, 78.2%, 100%)
Irradiated	100% (6/6; 54.1%, 100%)
Whole blood derived	-
Plasma	
Apheresis-derived	100% (4/4; 39.8%, 100%)
Leukocyte-reduced	-
Irradiated	-
Whole blood derived	100% (1/1; 2.5%, 100%)
Concordance of transfusion dates and time administered	
Transfusion date match*	Median 0 (SD: 0.21, Min: -1, Max 1)
Transfusion time match*	Median 0 minutes (SD 199, Min -1451, Max 1706 Median 0 hours (SD 3.3, Min -24, Max 28)

**In three instances, dates and times gathered by adjudicators may have been discrepant as transfusion events crossed days (e.g., transfusion began before midnight and ended the next day).*

While units that had been leukocyte-reduced, apheresis-derived, or irradiated were sometimes labeled available in medical charts, other elements had limited to no availability. The following information was generally not available within patient charts: Pathogen-reduction methods (N=2) whether or not a blood product was whole blood derived (N=11), blood product age (days) (N=0), and whether it was product derived from a single donor or pooled (N=13). Information about volume transfused was often available in charts, 25 listed information about halted transfusions. Of note, although blood product age itself was not noted in charts, notes about expiration dates existed by unit on some medical chart transfusion records.

5. Mechanical ventilation

All potential-TRALI$_{A,B,C}$ inpatient stays with retrievable charts were reviewed to confirm mechanical ventilation before and after the potential TRALI event. Of the 195 charts reviewed, 112 (57%) also had a code for mechanical ventilation in Sentinel inpatient data (See **Appendix E** for mechanical ventilation codes). Adjudicators found evidence of mechanical ventilation in 95 (PPV: 85%, 95% CI: 77-91) of these encounters (**Table 15**). Reasons cited for not being able to locate specific mechanical ventilation in charts included extremely long inpatient stays with lengthy charts or hospital transfer (i.e., limited information about mechanical ventilation). We reviewed the 17 cases in which mechanical ventilation was not confirmed by adjudicators. Adjudicators noted 4 (24%)of these patients were placed on Bilevel Positive Airway Pressure (BiPAP) during their inpatient stay, 1 (5%) was transferred from another hospital and placed on a non-rebreather oxygen mask, 3 (18%) were hospital transfers. No pertinent

mechanical ventilation information related to the potential ALI event could be located for 9 (53%) inpatient stays.

Table 15. Positive predictive value (PPV) associated with inpatient procedure codes for mechanical ventilation amongst potential Transfusion-Related Acute Lung Injury (TRALI) inpatient stays

	PPVs associated with inpatient procedure codes for mechanical ventilation* compared to chart review
Any mechanical ventilation†	85% (95/112, 95% Confidence Interval: 77%-91%)

**Codes used to define mechanical ventilation in the HCA Sentinel database are included in Appendix D.*

†Adjudicators recorded mechanical ventilation in medical records when observed. However, for lengthy charts adjudicators focused on ALI events of interest and did necessarily try to locate mechanical ventilation which occurred at other time points.

During chart review, adjudicators also collected information about whether mechanical ventilation occurred before or after ALI. Of the 95 patients with evidence of mechanical ventilation in both Sentinel electronic data and chart data, 48 (51%) were ventilated after the ALI event of interest, 22 (23%) prior to the ALI event of interest, and adjudicators were unable to determine the specific timing in relation to the ALI event in 25 (26%) patients.

6. Additional information derived from medical charts

Appendix F Table 4 includes additional patient demographics and other relevant clinical information in chart confirmed TRALI cases. Pertinent findings include information discharge disposition [Expired at discharge: Definitive TRALI=12%(n=3), Possible TRALI=13%(n=2), Delayed TRALI=30% (n=8)] and severity of the TRALI reaction [Severe (PaO2/FiO2 <100): Definitive TRALI=27%(n=7), Possible TRALI=30%(n=3), Delayed TRALI=44%(n=12)]. Pneumonia was the most common temporally associated ALI risk factor in both possible TRALI (40%, n=6) and delayed TRALI cases (22%, n=6). Many confirmed TRALI patients were cared for in an intensive care unit at the time of initial ALI/TRALI diagnosis (Definitive TRALI=19% (n=5), Possible TRALI 40% (n=6), Delayed TRALI 37%(n=10), but other levels of care were also located (**Appendix F Table 4**).

7. Chart review process

This project was the first to employ medical record review at a Sentinel inpatient EMR based data partner. Charts were unavailable for 13 (6%) potential TRALI inpatient stays. Of the 13 charts that could not be retrieved, ten (77%) were located in hospitals which utilized an EMR system that could not retrieve charts on a standard platform. The other three charts were unavailable for the following reasons: key laboratory and nursing information could not be retrieved on the chart platform [n=1], issues with mapping from data warehouse to correct chart (i.e., medical chart could not be located) [n=1], issues with reviewing the chart on the platform before access expired [n=1]. In prior Sentinel assessments that included chart validation of outcome in other Sentinel data partners, charts have been unobtainable for 20-32% of potential cases.

E. ADDITIONAL EXPLORATORY ANALYSES, SUMMARIZING INFORMATION IN ELECTRONIC DATA AND MEDICAL CHARTS

1. Exploring methods for reducing missing transfusion information

During this project, we focused on two aspects of potential missing transfusion information: A) Transfusion information that was not available in the Sentinel electronic data, but could be collected within patient charts (e.g., volume of transfusion, or transfusion information that was missing from the Sentinel database entirely) and B) Information that was entered into the Sentinel database, but could not be identified (e.g., units transfused that did not have a recognizable code that could be used to identify blood component, or code was missing entirely). We describe these items qualitatively.

a. Transfusion information not available in the Sentinel electronic data, but could be collected within patient charts

With medical charts, adjudicators attempted to collect blood transfusion information that is not consistently included in Sentinel inpatient electronic data, such as volume of transfusion and blood product age. Lack of consistent access to blood bank records limited the sample sizes available to examine the following: Pathogen-reduction methods (N=2) whether a blood product was whole blood derived (N=11), blood product age (N=0), and whether the product was derived from a single donor or pooled (N=13). Information about volume transfused was often located by abstractors and in 25 instances information was listed about halted transfusions. Of note, although blood product age itself was not located by adjudicators, notes about expiration dates existed by unit on some medical chart transfusion records and would also likely exist in blood bank records.

b. Transfusion information that was entered into the Sentinel database, but could not be identified

Use of blood product coding systems to reduce missing information: Sentinel inpatient transfusion data includes two types of blood product codes - Codabar and ISBT-128 codes - to identify blood products. Codabar is an older blood product coding system, no longer in wide use in the United States. In this project, we explored and combined two methods for classifying both Codabar and ISBT-128 blood codes into relevant categories by way of reducing missing information, and conclusions are below.

ProdCDC: This is a labeling variable that the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network provides to Codabar codes and to a selected list of ISBT-128 codes so they can be categorized into blood components/products. This assignment was made to 1,536 Codabar and 4,654 ISBT-128 codes. We used ProdCDC labels in combination with an ISBT-128 database as described below.

ISBT-128: This coding system is managed by the International Council for Commonality in Blood Banking Automation (ICCBBA https://www.iccbba.org/). With an update made on April 18, 2017, a total of 9,069 ISBT-128 blood codes was available. Given the fact that ICCBAA manages the ISBT-128 system, and updates it frequently, this ISBT-128 database is the most comprehensive. After review of both ProdCDC and ISBT systems, future work should utilize the updated ISBT-128 database to develop comprehensive code lists and thereby reduce missing information, when the blood codes in electronic databases also uses ISBT. ProdCDC labels can selectively be used in combination with the ISBT-128 database, and are particularly useful for labeling Codabar blood codes.

Use of other information in Sentinel inpatient transfusion data to reduce missing information: In this TRALI project, two major items were noted that may reduce missing transfusion information in the future. First, it was noted that at times blood codes were generally standardized within the Sentinel

database, but on occasion were not entered into the database in a standard format. For example, a code such as E0424 may have been entered in the database as e0424 (note the lower-case "e"). Assuming validation work with HCA confirms that a remedy for this type of issue is to force all codes to upper-case format, distributed programs could be designed to standardize such information during routine Sentinel queries, as such data entry inconsistencies could contribute to missing information. Second, occasionally an entry may be included in Sentinel transfusion data, but blood codes may be entirely missing. This means blood component information and other transfusion details may not available for such blood transfusions currently. However, in the SCDM inpatient transfusion table (**Appendix A**), a variable named 'Orig_TransProd' might be able to be explored to reduce missing information in the future. This variable is available within the Data Partner's database and is labeled as the Data Partner blood product name but has not yet been examined. Any values included in this field are likely to be non-standardized, but possible that use of this variable in instances in which ISBT-128 and Codabar blood product codes are missing, may increase transfusion information available for future analyses, and could be explored.

2. Identifying data elements that are useful/relevant for studying TRALI

During this TRALI focused project, it became apparent that lack of some timing information in the current Sentinel Common Data Model (SCDM, v 6.0.2) also limited the types of transfusion related safety assessments that could be completed with just the electronic Sentinel distributed database (SDD). Specifically, the SCDM does not include procedure or diagnosis date and time variables, limiting the ability to identify specific ALI dates and times and their association with transfusion exposures. Thus, most analyses examining TRALI or other transfusion related outcomes with just electronic data would suffer from temporality concerns without chart review information. The workgroup recommends investigating the availability of procedure and diagnosis dates and times at Sentinel data partners, and if available expanding the SCDM and populating the SDD with this information in the future.

VII. DISCUSSION

A. KEY FINDINGS

Using all electronic diagnosis codes for TRALI, we identified 208 potential-TRALI $_{A,B,C}$ inpatient stays among 3,945,217 inpatient stays in 169 hospitals the HCA Sentinel database [Criterion A=118 (57%), B only=85 (41%), C only=5 (2%)]. A transfusion was recorded in 92% of these stays (n=192 TRALI, 353,557 non-TRALI transfused inpatient stays).

1. TRALI occurrence rates in electronic data

Primary analyses were restricted to transfused inpatient stays in hospitals capturing electronic transfusion data during the September 2013 through September 2015 (n=153 hospitals). During the study period 1,287,763 units of blood products were transfused to 285,774 patients during 353,749 inpatient stays with a transfusion. When examining the TRALI specific diagnosis code (TRALI Criterion A: ICD-9-CM 518.7), an overall OR of 30.8 (95% CI: 25.0-36.6) per 100,000 inpatient transfusion stays was observed. This translates to 0.42 TRALI cases per 5,000 units of administered blood products (0.08 cases per 1,000 units; 0.85 cases per 10,000 units).

Potential TRALI$_A$ ORs were highest among patients who expired [rate per 100,000 inpatient transfusion stays: 117.4 (95% CI: 73.1-161.6) or who were mechanically ventilated during their inpatient stay [rate per 100,000 inpatient transfusion stays: 123.8 (95% CI: 94.0-153.7)]. While it was not possible to distinguish whether or not units were administered before or after TRALI occurrence in analyses focused

only on electronic data, rates increased as number of transfused units recorded during an inpatient stay increased, and patients receiving >9 units of blood during their hospital stay had the highest OR [(OR per 100,000=191.9 (95% CI: 130.9-252.9)]. Unadjusted ORs per 100,000 inpatient transfusion stays were similar in all study years [Year 2013=33.7 (95% CI: 17.2-50.1), 2014=28.1 (95% CI: 20.4-35.9), 2015=33.6 (95% CI: 23.5-43.8)]. When examining ORs of TRALI in specific age categories, the highest OR was observed in the 20-34 year age category, and lower rates were observed in the 65+ year age categories [Age 0-19: OR= 44.3 (95% CI: 8.9-79.8); Age 20-34: OR=45.7 (95% CI: 20.9-70.5); Age 35-49: OR=44.5 (95% CI: 23.4-65.7); Age 50-64: OR=35.8 (95% CI: 22.8-48.9); Age 65-79: OR=23.5 (95% CI: 14.6-32.4); Age 80+: OR=21.9(95% CI: 11.5-32.3)].

In comparative analyses, significantly higher rates of TRALI (defined with TRALI Criterion A: ICD-9-CM 518.7) were observed for the following conditions: patients who expired as compared to those discharged alive [RR=4.7 (95% CI: 3.1-7.3)], and patients mechanically ventilated as compared to those who were not ventilated during their stay [RR=8.7 (95% CI: 5.9-12.7)]. While it was not possible to distinguish whether units were administered before or after TRALI occurrence in analyses focused only on electronic data, higher rates of TRALI were observed in patients that received greater than 1 unit of blood during their inpatient stay. TRALI rates increased as number of units increased, with patients exposed to 5 or more units having significantly higher rates of TRALI than those exposed to one unit [(2-4 units: RR=2.3 (95% CI: 1.0-5.1), 5-9 units: RR=6.7 (95% CI: 2.9-15.6), >9 units: RR=22.8 (95% CI: 10.2-51.0)]. Similarly, significantly higher rates of TRALI were observed in patients who were exposed to multiple blood components, as compared to those only exposed to RBCs [RBCs and plasma only: RR=2.7 (95% CI: 1.3-5.5); RBCs and Platelets only: RR=4.0 (95% CI: 2.3-7.2); RBCs and plasma and Platelets only: RR=7.0 (95% CI: 3.7-13.2); RR Other transfusion combination: RR=13.0 (95% CI: 7.5-22.6)]. As compared to patients ages 20 to 34 years, significantly lower rates of TRALI were observed in patients that were over 65 years of age on admission [65-79 years: RR=0.51 (95% CI: 0.27-1.00), 80+years: RR=0.48 (95% CI: 0.23-0.99)].

2. Validation of TRALI outcome in electronic data with medical charts

Of 195 potential-$TRALI_{A,B,C}$ inpatient encounters with available charts 68 (35%) met TRALI clinical definitions, [26 (38%) definitive TRALI, 15 (22%) possible TRALI, 27 (40%) delayed TRALI], 79 (41%) were not cases of TRALI, 36 were determined to be acute lung injury (ALI) not associated with a transfusion, and 12 (6%) were adjudicated as unable to determine (e.g., complex cases, chart lacking critical information often to due hospital transfers, or incompleteness or ambiguity). Approximately 17% (n=22) of potential-$TRALI_{A,B,C}$ cases that were ultimately classified as 'not a case of TRALI' by adjudicators had transfusion reactions were suspected to be either cases of TACO (n=15, 12%) or TRA (n=7, 5%). Other potential diagnoses noted by adjudicators included non-transfusion related circulatory overload or pulmonary edema (n=32, 25%), and ALI not associated with a transfusion (n=21, 17%). Given that the HCA Sentinel database captures all diagnoses captured during an inpatient stay, rather than only billable diagnoses, it is possible that some potential TRALI inpatient stays were coded with TRALI diagnosis codes when TRALI was recorded as a differential diagnosis. This has implications for future work, as consideration of differential diagnoses may be key when designing electronic algorithms for use in Sentinel EMR inpatient data.

The positive predictive value of the TRALI electronic algorithm (potential-$TRALI_{A,B,C}$ criteria) as compared to medical charts was poor (<50%) for all analyses conducted. The PPV for all inpatient TRALI diagnoses recorded in the Sentinel electronic data (potential-$TRALI_{A,B,C}$) was 35% overall (95% CI: 28-42%). The PPV for potential-$TRALI_A$ was 44% (95% CI: 35-54%) and potential-$TRALI_B$ was 24% (95% CI: 15-33%). There were no confirmed TRALI cases identified by potential-$TRALI_C$ (0/5). Stratification of results by age group,

sex, presence or absence of transfusion information in electronic data, TRALI as a principal discharge diagnosis, TRALI flagged as present on admission did not generally increase PPVs.

To compare to the literature, we calculated a crude OR of TRALI utilizing only cases meeting clinical definitions for definite, possible or delayed TRALI, and found a crude TRALI OR of 0.02% per transfused patient, and 0.26 TRALI cases per 5,000 units of blood products (0.05 cases per 1,000 units; 0.53 cases per 10,000 units). There were 19.2 TRALI cases meeting clinical definitions for definite, possible or delayed TRALI (n=68) per 100,000 inpatient transfusion stays (95% CI: 14.7-23.8). When we restricted our analyses to only definitive TRALI cases (n=26), the TRALI OR was 0.001% per transfused patient, and 0.10 TRALI cases per 5,000 units of blood products (0.02 cases per 1,000 units; 0.20 cases per 10,000 units). There were 7.3 cases meeting the clinical definition for definitive TRALI per 100,000 inpatient transfusion stays (95% CI: 4.5-10.2).

3. Validation of transfusion exposures in electronic data with medical charts

We observed high concordance between blood transfusion exposures captured in Sentinel data and transfusion information gathered from medical charts by adjudicators. The PPV for any relevant transfusion exposure in the HCA Sentinel database as compared to any transfusion in medical charts was 98.4%. There was nearly perfect concordance between administered blood components administered in the Sentinel electronic database and medical chart information [RBCs any, PPV=100% (143/143; 97.5%-100%; n=143); platelets any, PPV=100% (91.8%-100%; n=43); plasma any, PPV=97.3% (85.8%-99.9%; n=36/37); cryoprecipitate any, PPV=90.9% (58.7%-99.8%; n=10/11)]. Concordance of transfusion dates and times between medical chart information and Sentinel data was generally observed.

Of the 195 potential TRALI inpatient stays with available charts, 13 records were labeled as not having a transfusion in Sentinel electronic data. Adjudicators located reasons for lack of transfusion information in 10 of 13 patient records. The majority (n=9/10) had evidence of transfusion administration prior to hospitalization (i.e., transfusion of interest occurred in another hospital, emergency department, or outpatient setting, hospital transfer often noted), and Intravenous Immunoglobulin (IVIg) was the exposure of interest in one instance (n=1/10).

4. Exploratory analyses with electronic data and medical charts

Overall, specific blood processing method or component type was captured well in the Sentinel electronic data. When comparing Sentinel electronic information on processing methods or specific blood type to information gathered by adjudicators from medical charts, PPVs were below 61% mainly because little or no blood processing method detail was available in the medical charts available to adjudicators (i.e., blood bank information was not always available to adjudicators because it is a separate module in many EMR systems). However, when processing method or specific component type was documented in charts, there was perfect concordance with the Sentinel electronic data, but sample sizes were limited.

In addition, lack of consistent access to blood bank records limited the sample sizes available to examine the following: Pathogen-reduction methods (N=2) whether or not a blood product was whole blood derived (N=11), blood product age (N=0), and whether the product was derived from a single donor or pooled (N=13). Information about volume transfused was often located by abstractors and in 25 instances information was listed about halted transfusions. Of note, although blood product age itself was not located by adjudicators, notes about expiration dates existed by unit on some medical chart transfusion records and would also likely exist in blood bank records.

Finally, some data-related recommendations were highlighted by the workgroup as part of this project. First, the workgroup recommends investigating the availability of procedure and diagnosis dates and times in Sentinel partners databases, as lack of procedure or diagnosis timing information in the current database limited analyses utilizing just electronic data. If diagnosis and procedure timing information is available, the workgroup recommends expanding the SCDM and populating the SDD with this information in the future. Second, further exploration of data elements included in the current inpatient transfusion table might be useful in understanding if it is possible to reduce any missing blood component information. Specifically, to reduce any missing information in the future, a variable named 'Orig_TransProd' which includes additional details about blood product names within the data partner may be able to be explored. In addition, the workgroup noted that some added standardization on blood codes within the Sentinel database may also be valuable in reducing missing and should also be explored.

B. COMPARISON WITH RESULTS FROM PRIOR STUDIES

TRALI incidence rates have varied considerably in the literature. Given limitations in Sentinel data, we estimated TRALI occurrence in a defined population, and could only approximate incidence rates. However, the observed TRALI rates in this study were generally lower than those in some previous studies which often focused on specific hospitals or centers and did not use diagnosis codes to define TRALI.[12-14] We found a crude potential-TRALI occurrence rate (OR) range of 0.02%-0.04% per transfused patient depending on how TRALI was defined (ICD-9-CM codes or with medical charts), but the ability to follow patients beyond their initial hospital stay was limited. Previous estimates of the incidence of TRALI have ranged from 0.04 to 8.0% per transfused patient.[13, 32-36] When we defined TRALI with just the TRALI-specific ICD-9-CM code (potential-$TRALI_A$), there were 0.42 TRALI cases per 5,000 units of blood products (0.08 cases per 1,000 units; 0.85 cases per 10,000 units).

This Sentinel study focused on inpatient stays captured in large electronic databases and may be more comparable to a recent population-based study that utilized large electronic databases to examine TRALI occurrence in elderly Medicare beneficiaries, and estimated an overall OR of 22.5 per 100,000 transfused inpatient stays.[1] While the overall unadjusted OR of potential-$TRALI_A$ in Sentinel inpatient electronic EMR data was 30.8 per 100,000 transfused inpatient stays (95% CI, 25.0- 36.6), rates we found in the over 65 population included in this study were quite similar to the Menis et al. study [Age 65-79 OR=23.5 per 100,000 transfused inpatient stays (95% CI: 14.6-32.4); Age 80+ OR=21.9 per 100,000 transfused inpatient stays (95% CI: 11.5-32.3)]. The Menis study also reported increased potential-$TRALI_A$ ORs with plasma or platelet transfusions, and in females. In our study, increased TRALI risk was not observed in females as compared to males, and we observed very few potential TRALI cases with just platelets (n=2) or plasma exposure (n=3). The general pattern we observed in crude analyses was increased risk of TRALI with a higher number of transfused units, and exposure to multiple blood components. All plasma-containing blood products have been implicated in TRALI,[15, 16] including IVIg [18, 19] and cryoprecipitate[37]. There were no TRALI cases meeting definitive, possible, or delayed clinical definitions with only cryoprecipitate exposure. However, there were 10 cases that met clinical definitions for TRALI that had cryoprecipitate and other component exposures.

The overall mortality rate in TRALI cases meeting definitive, possible, or delayed TRALI case definitions in this study was 19%. However, when mortality was stratified by TRALI case definition, we found delayed TRALI cases had a higher crude mortality rate (definitive TRALI=12%, possible TRALI=13%, delayed TRALI=30%). This observation could be due to confounding, random variation, or small sample sizes. However a general pattern of higher mortality in critically ill patients with and without delayed TRALI has been observed previously.[21, 22] In addition, studies in critically ill patients have generally noted higher

TRALI incidence rates,[12] but unfortunately flags for critical care environments do not exist in the Sentinel common data model, and thus could not be directly examined in our study. However, when we examined medical chart data, we found 33% of confirmed TRALI cases were in an ICU environment at the time of ALI/TRALI diagnosis.

To our knowledge, this is one of the few TRALI studies thus far which has utilized a large electronic database in combination with medical record review to validate ICD-9-CM codes for TRALI. The PPV of potential-TRALI$_A$) was 44% (n=49 cases meeting definitive, possible, or delayed), which was poor but slightly higher than the PPV of 35% found in a recent population study conducted within a large administrative database.[3] As TRALI is likely under-diagnosed, we focused not only potential-TRALI$_A$ [TRALI specific ICD-9-CM code (ICD-9-CM, 518.7)], but also on specific respiratory failure codes in combination with an ICD-9-CM code for a transfusion reaction. This approach yielded an additional 19 confirmed TRALI cases, but the gains in sensitivity compromised specificity, with the overall performance of TRALI$_{A,B,C}$ outcome falling from 44% to 35%.

Other hospital based studies examining TRALI have generally been prospective, been conducted in specific populations, or had the benefit of laboratory information.[36 38 13] Our study did not have access to electronic hospital laboratory information, but did benefit from electronic transfusion data derived from blood bank information which included transfusion timing, as well as the number and type of units (component, processing method, etc.) administered.

C. STRENGTHS

The ability to examine TRALI in a database that included 169 hospitals (n=153 providing electronic transfusion information during the study time period) in the United States and review all available medical records with potential TRALI codes during a 2-year period was a strength of this study.

The rate of retrievable medical records was larger than expected based on prior Sentinel product assessments (94% of potential TRALI charts retrieved, compared to 68-80% of potential cases in prior Sentinel assessments that included chart validation of outcomes). We postulate this could be due the Sentinel inpatient data partner type and structure.

Availability of electronic transfusion information was also a strength. Validation of this transfusion information in this electronic database with the medical records of potential-TRALI$_{A,B,C}$ cases showed excellent concordance between information included in medical charts and electronic transfusion information. The confirmation of exposure, outcome, and the timing of each with medical charts was quite important to the validity of study results.

Other strengths were that the large inpatient database utilized by the study, which provided large numbers of encounters with inpatient stays with transfusions necessary for examination of rates of TRALI. The underlying denominator data allowed for the estimation of rate ratios. Most administrative databases lack information about transfusion timing and other important transfusion information (e.g., units, processing method etc.). Thus, utilization of the Sentinel inpatient transfusion data was also a strength, given its detailed account of transfused units, transfusion start and end times, processing method, and other important transfusion information.

D. LIMITATIONS

While there were strengths to this study, there were also limitations. While it would have been ideal to implement double or triple adjudication for all potential-TRALI $_{A,B,C}$ cases, this was beyond the scope of this project. However, we included a pilot phase in which medical charts associated with 20 potential-

TRALI $_{A,B,C}$ cases were reviewed up to three times by separate adjudicators to ensure classification rules were clear. Beyond the pilot phase, we also implemented a 'second opinion' option which could be requested when a potential-TRALI case was particularly complex. This option was able to be implemented within the scope of the project and was employed for the remainder of the study.

While we identified 208 potential TRALI cases, there were only 68 cases meeting definitive, possible, or delayed TRALI clinical definitions in this study, which limited the types of analyses that could be conducted. It is also possible that some misclassification of the outcome may have occurred, as potential TRALI cases might not have been identified in our study if a transfusion reaction was not recognized and coded by physicians. We attempted to mitigate this limitation by focusing not only on the TRALI specific ICD-9-CM code (ICD-9-CM, 518.7), but also on specific respiratory failure codes described above in combination with an ICD-9-CM code for a transfusion reaction. However, this mitigation strategy would not have captured cases in which no ALI or transfusion diagnosis codes were coded during the relevant inpatient stay.

Some hospitals in the HCA system were on an EMR system that did not support chart retrieval. These hospitals are included in denominators for electronic aims, but were not included in the chart review and thus total sample size available for some aspects of this study was reduced from 208 to 195 potential TRALI stays, for some aspects of this study. As this project focused on exploration of blood transfusion data, some limitations with regards to these data were also uncovered. For example, we learned that there are some administered units in the current Sentinel inpatient transfusion table that could not be mapped to blood components. However, we described some alternative mapping and additional explorations that could be conducted in the future to increase the number of units that cannot be mapped to blood components.

This study only included ICD-9-CM codes, as the time-period of interest for this protocol-based assessment preceded the transition to ICD-10-CM coding in the United States. It is possible that rates or exposure patterns may have changed in recent years. Further, while we validated transfusion information in potential-TRALI$_{ABC}$ cases during the chart review process, it was not possible to distinguish whether units were administered before or after TRALI occurrence in analyses focused only on electronic data, and thus any conclusions that can be drawn from these analyses are limited.

E. APPLICATIONS TO SENTINEL

There were several practical lessons learned from this study which could be applied broadly to Sentinel activities, including lessons concerning identifying transfusion exposures in Sentinel inpatient data, event timing, validation of the TRALI outcome, and the potential utility of developing Sentinel tools for similar analyses.

1. Transfusion exposures in Sentinel inpatient data

Blood transfusions and component information were well captured in electronic transfusion data, and we observed high concordance between component information in electronic transfusion data and medical charts. Processing and collection information was typically available in electronic transfusion data. However, lack of consistent access to blood bank portions of the EMR during the adjudication process restricted the ability to examine concordance of this information in medical charts and electronic transfusion data. When adjudicators were able to locate processing and collection methods in small sample of medical charts, they were concordant with processing and collection methods observed in electronic data.

Transfusion dates and times recorded in electronic data were found to be generally concordant with those in medical charts. This bodes well for any future studies utilizing these electronic transfusion data.

2. Event timing in Sentinel inpatient data

The following variables can be used to identify event or exposure timing in the HCA Sentinel database: hospital admission and discharge dates, transfusion start and end dates, transfusion start and end times, medication administration start date, and medication administration time. Procedure and diagnosis dates or times are not currently available within the HCA Sentinel database. However, this information may be available in operational data, and data expansion efforts focusing on these timing elements would make these data more useful for future pharmacoepidemiology studies, and would help establish temporality between exposure and outcomes.

3. Validation of TRALI outcome

The positive predictive value of the TRALI electronic algorithm as compared to medical charts was poor (<50%) for all analyses conducted. This was not unexpected, as TRALI is rare and difficult to diagnosis clinically. There were no cases meeting definitive, possible or delayed TRALI clinical definitions identified by $TRALI_C$ [Other pulmonary insufficiency ICD-9-CM in any position (518.82), WITH a code for a blood transfusion reaction (999.80 or 999.89 or E934.7)], and thus it may be prudent to exclude this criterion in any future studies utilizing these data. In contrast, a substantial number of confirmed TRALI cases (n=15, 22%) were identified with $TRALI_B$ [Acute respiratory failure ICD-9-CM code in any position (518.81), WITH code for a blood transfusion reaction (999.80 or 999.89 or E934.7)]. Thus, if algorithm sensitivity is a priority, we would recommend utilization of $TRALI_B$ to identify potential TRALI cases, but studies implementing this approach would require confirming diagnoses with medical records given the low PPVs we observed for TRALI diagnosis codes.

4. Sentinel inpatient tool

It would be possible to build a routine analytic tool to conduct many of the electronic analyses included in this study. If similar transfusion associated questions are common, it may be useful to consider the development of a tool which could automate at least some of the analyses conducted with ad hoc code in this study. However, given the low PPV of the TRALI outcome in this study, it is possible that chart review may be needed often if future studies of similar transfusion associated outcomes were to be implemented.

5. Other areas for future work

Further exploration of data elements included in the current inpatient transfusion table might be useful in understanding if it is possible to reduce any missing blood component information. Specifically, a variable named 'Orig_TransProd' which includes additional details about blood product names within each hospital, may have potential for reducing missing information. Thus, exploration of this and other data elements may be useful. In addition, the workgroup noted that some added standardization on blood codes within the Sentinel inpatient database may also be valuable in reducing missing and could also be explored.

F. CONCLUSIONS

This data exploration study established the feasibility of utilizing electronic Sentinel inpatient EMR data from 169 US hospitals to capture exposure to blood component type and processing method (e.g.,

leukocyte-reduced, irradiated), as well as transfusion dates and times. Capture of potential TRALI cases and potential patient and TRALI associated transfusion risk factors was also feasible. However, during medical record review of potential-TRALI cases we found the PPV of the TRALI electronic algorithm was poor in all analyses conducted (<50%). Review of medical records associated with 195 potential TRALI cases identified with diagnosis codes for TRALI or ALI and a transfusion reaction in electronic data, yielded 68 TRALI cases meeting clinical definitions for definitive, possible, or delayed TRALI. Complexity of the diagnosis and the considerable number of codes available in Sentinel inpatient EMR databases may explain the observed low PPV of the electronic TRALI algorithm. In addition, diagnosis codes used to identify potential TRALI cases may have represented differential diagnoses that were coded. While the PPV of diagnosis codes for ALI and a transfusion reaction was <50%, use of these codes yielded cases meeting clinical definitions for definitive, possible, or delayed TRALI (19 of 68 cases), and may be considered in future studies where sensitivity may be desired. In contrast, blood component information in electronic transfusion data corresponded well with medical charts (PPV>98%). Processing and collection information was typically available in electronic transfusion data and corresponded to information collected by adjudicators, but lack of consistent access to blood bank portions of the EMR across hospitals limited sample sizes for this analysis and also conclusions that can be drawn. Identified areas for data improvement and expansion include strategies for understanding and reducing missing data in Sentinel inpatient transfusion data, and understanding the potential for expanding the Sentinel electronic database to include procedure and diagnosis dates and times.

This study focused on calculating potential-TRALI occurrence rates with inpatient electronic data, and found lower TRALI occurrence rates than have been previously reported in the literature, but also found some correspondence with a recent study which examined TRALI as defined with diagnosis codes in the Medicare population.[1] Given the low PPV of the TRALI algorithm, further investigation of results within validated TRALI cases in future work is warranted. Specifically, future work should focus on describing ORs, transfusion exposures, as well as patient and TRALI associated transfusion risk factors within validated TRALI cases.

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IX. REFERENCES

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