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ORIGINAL RESEARCH

Demographic and epidemiologic characterization of transfusion recipients from four US regions: evidence from the REDS-III recipient database

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BACKGROUND: Blood transfusion is one of the most common medical procedures during hospitalization in the United States. To understand the benefits of transfusion while mitigating potential risks, a multicenter database containing detailed information on transfusion incidence and recipient outcomes would facilitate research.

STUDY DESIGN AND METHODS: The Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) program has developed a comprehensive transfusion recipient database utilizing data from hospital electronic health records at 12 participating hospitals in four geographic regions. Inpatient and outpatient data on transfusion recipients from January 1, 2013 to December 31, 2014 included patient age, sex, ethnicity, primary diagnosis, type of blood product provided, issue location, pretransfusion and post-transfusion hemoglobin (Hgb), and hospital outcomes. Transfusion incidence per encounter was calculated by blood product and various patient characteristics.

RESULTS: During the 2-year study period, 80,362 (12.5%) inpatient encounters involved transfusion. Among inpatients, the most commonly transfused blood products were red blood cells (RBCs; 10.9% of encounters), followed by platelets (3.2%) and plasma (2.9%). Among patients who received transfusions, the median number of RBC units was one, the pretransfusion Hgb level was 7.6 g/dL, and the Hgb increment per unit was 1.4 g/dL. Encounter mortality increased with patient age, the number of units transfused, and the use of platelet or plasma products. The most commonly reported transfusion reaction was febrile nonhemolytic.

CONCLUSION: The database contains comprehensive data regarding transfusion use and patient outcomes. The current report describes an evaluation of the first 2 years of a planned, 4-year, linked blood donor-component-recipient database, which represents a critical new resource for transfusion medicine researchers.

Transfusion of human-derived blood products is essential to life for many clinical conditions, making it one of the most common medical procedures for inpatient hospitalizations in the United States. The study of transfusion practice presents challenges to investigators whose subjects, treatments, and duration of follow-up are often heterogeneous. Access

ABBREVIATIONS: DCC = data coordinating center; ICU(s) = intensive care unit(s); IQR(s) = interquartile range(s); SCANDAT = Scandinavian Donations and Transfusions Database; TM = transfusion medicine.

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to detailed clinical data for large numbers of transfusion recipient populations from geographically diverse health care institutions may allow for a more refined characterization of transfusion medicine (TM) practice and consequent outcomes in the United States.

The use of large databases that extract data from various independent sources is becoming more common in TM, but examples of well-validated, TM-focused databases are few. Key advantages of databases of this type include the ability to conduct observational studies that are sufficiently large to allow both detailed risk assessment and subgroup analyses.[1,2] Databases of this type can also assist clinical trial or observational study design by informing enrollment projections and timelines rather than conducting pilot studies.[2] One of the most successful recent examples is the Scandinavian Donations and Transfusions Database (SCANDAT).[2] In its most current form, SCANDAT contains donation and transfusion data on 3.7 million unique persons with lengthy follow-up derived from linkage to national registries.[2] This database has been used to determine the risk for recipient mortality based on both red blood cell (RBC) storage and donor age,[3,4] to determine the risk for gastric cancer based on ABO blood group,[5] to elucidate the inverse relationship between donor mortality and donation frequency,[6] and to clarify the partial genetic heritability of blood donation tendencies between monozygotic and dizygotic twins.[7] Despite its utility, SCANDAT is limited by a lack of granular clinical data, such as comprehensive laboratory values, medications, vital signs, and issue locations, which reduces its usefulness in some studies.

In the United States, a few large transfusion recipient-focused databases have been created to explore blood-management strategies and specific transfusion-related adverse events or populations: examples include databases from Johns Hopkins, the Mayo Clinic, Kaiser Permanente Northern California, and Medicare.[8-12] However, each of these databases is limited because of either finite inpatient clinical data or limitation to a single institution or region.

To address these limitations, over the past 6 years, the National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-III (REDS-III (see Appendix) has developed and validated a linked, donor-component, transfusion-recipient database.[2] This database combines recipient, blood component, and donor information from four major blood centers and 12 community and academic hospitals in the United States.[13] The REDS-III Transfusion Recipient Database specifically utilizes and combines clinical and laboratory patient data from multiple distinct inpatient and outpatient electronic records for both transfusion recipients and non-recipients and is the subject of this report. A study using a piloted version of this database was able to show both over-utilization and inadequate dosing of plasma transfusions based on a correlation with pretransfusion and post-transfusion coagulation laboratory values.[14]

This report aims to: 1) describe the methods employed in creating this database and ensuring its quality; 2) present broad statistics on transfusion utilization using 2 years of transfusion inpatient and outpatient recipient data gathered from this new national resource; and 3) define the database's breadth and depth of scope, which will be used in future REDS-III analyses.

MATERIALS AND METHODS

Database structure

The infrastructure of the REDS-III Domestic Program was previously described.[13] In brief, four large US blood centers (located in Connecticut, Pennsylvania, Wisconsin, and California) serve as "hubs," with "spokes" comprised of selected hospitals, including a mix of large academic medical centers and smaller community-based hospitals. Institutional review board approval was obtained by each participating entity and the data coordinating center (DCC). Data collected in the REDS-III transfusion recipient database are subject to the NHLBI *Policy for Data Sharing from Clinical Trials and Epidemiological Studies*[15] for eventual release as a public-use data set.

Data were extracted at the hospital level and harmonized at the hub level using a codebook developed by the REDS-III program. Data were reviewed and revised between hub blood centers and hospital partners until the data extracted for the period met program codebook standards. Cleaned data from multiple hospitals were then aggregated at the hub for transmission to the DCC. Data were encrypted with secure FIPS 140-2 encryption schemes and transmitted to the DCC's enhanced security network. Once at the DCC, data were maintained on secure servers hosted by the Research Triangle International enhanced security network.

The transfusion recipient database itself is comprised of 18 relational tables with data from individual inpatient and outpatient encounters, laboratory diagnostics, clinical care interventions, and health outcomes of interest (Fig. 1). Data were extracted on a quarterly basis, and individual patient encounters were extracted into the database only after the patient had been discharged. Each hospital system preserved patient privacy using an "honest broker" system, namely, by transforming medical record numbers or other identifiers into a new numeric string that served as a local primary key, with the linkage retained by the provider. Consequently, individual patients may be tracked within a hospital or, in some cases, a hospital grouping, but not across hubs. Core clinical data were included for all inpatient encounters during the study period, and more detailed clinical data were included for encounters involving a blood transfusion (Fig. S1,

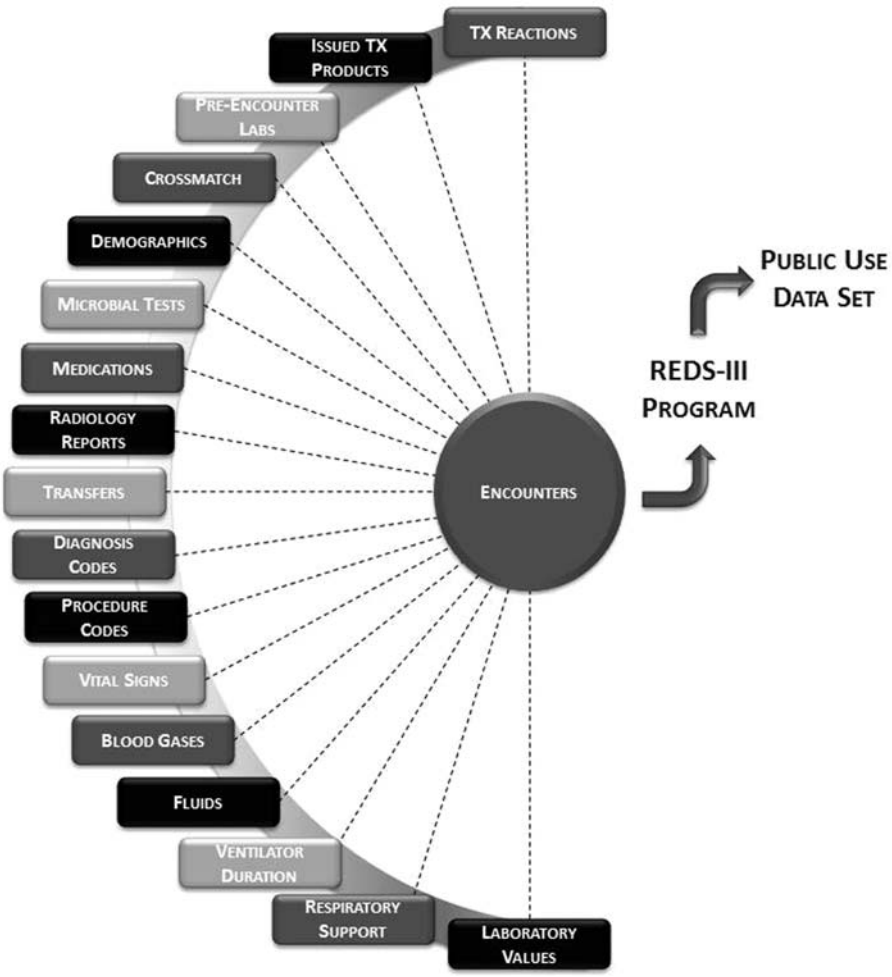

Fig. 1. Relational schematic representation of the REDS-III Recipient Outcomes Database design. Each box represents a table within which reside data elements available for analysis. The completeness of each table depended on patient encounter type and transfusion (TX) history.

available as supporting information in the online version of this paper). Patient-level and encounter-level data consisted of hospital medical records, diagnosis codes, laboratory data, and transfusion service data. Outpatient data were included only from patient encounters with a type-and-screen, type-and-crossmatch, and/or transfusion designation. Outpatients who did not receive a transfusion, type-and-screen, or type-and-crossmatch but were admitted to the hospital and received one of the above tests within 45 days of an outpatient encounter were also included in the data set.

The quality-control process involved a regular review of comprehensive quarterly reports for each of the relational table data files by a central working group consisting of an investigator from each hub and the DCC. Data for each quarter were compared with those from one or more prior quarters for consistency. A quality-control manual was maintained to document identified quality issues and associated resolutions.

Study variables

The current analysis includes data collected from the recipient database over the calendar years 2013 and 2014, although the database will eventually contain linked blood donor, component manufacturing, and transfusion recipient information over a 4-year period from January 1, 2013, through December 31, 2016. Data analysis was conducted with the SAS/STAT software package (version 9.4; SAS System for Windows; SAS Institute, Inc.).

For this study, a hospital encounter was defined as a unique patient medical event with recorded dates and times of admission and discharge. For each inpatient and outpatient hospital encounter, associated demographic variables (sex, age, race/ethnicity), in-hospital location and transfers, primary diagnosis, patient outcome (death or no death), and transfusion information (type of unit, number of units, transfusion adverse reactions, and issue location) were recorded. Patients could have more than one encounter during the study interval. To categorize

patient admitting diagnoses and comorbidities, International Classification of Diseases, Ninth Revision diagnosis codes were converted to Health Care Utilization Project (http://www.ahrq.gov/data/hcup) single-level and multilevel Clinical Classifications Software categories.[8] Transfusion reactions were recorded at each hospital according to passive reporting, namely, reactions were voluntarily reported to the transfusion service by practitioners. These reactions were then evaluated and diagnosed by the attending blood bank physician using standard hemovigilance diagnostic criteria. Transfusion reaction data were captured and entered into the database in a standard format using the National Healthcare Safety Network/Centers for Disease Control and Prevention (NHSN/CDC) Hemovigilance reporting module either through exchanges with NHSN/CDC-participating hospitals, through the AABB Patient Safety Organization via data transfer agreement, or through direct upload of online forms completed by the hospital.[16]

A transfusion episode was defined as all transfused units of a particular type provided within a continuous 4-hour period, as defined by transfusion issue date and time; and a transfusion dose was defined as the number of units provided in one episode (a platelet dose was either one apheresis platelet or a single pool of whole-blood–derived platelets). To evaluate the association between hemoglobin (Hgb) thresholds for issue location and primary diagnosis, the pretransfusion Hgb for each transfusion episode was defined as the most proximate Hgb level within 24 hours of RBC transfusion. The post-transfusion Hgb was defined as the next proximate Hgb value identified after the last RBC unit was given for a transfusion episode within 24 hours of that transfusion. Only transfusions that had both pretransfusion and post-transfusion Hgb levels available were used for analyses involving these variables.

Statistical analysis

Categorical variables were summarized as frequencies with percentages, and continuous variables were summarized as means with standard deviations or medians with interquartile ranges (IQRs), as appropriate. Counts and frequencies were calculated both overall and by subgroup. In a small minority of cases (<3%), encounters could be counted more than once: namely, when an encounter had more than one primary diagnosis listed, transfusions were issued to more than one location per encounter, or more than one transfusion product type was provided per encounter (the encounter would be counted toward the tally of total encounters for each issued product type). Overall and subgroup-specific transfusion incidence was calculated for inpatient encounter variables where applicable and was calculated as the number of encounters with a transfusion divided by the number of encounters overall or per subgroup (whether a transfusion was issued or not) for that recipient variable. Incidence of outpatient transfusions could not be calculated, because not all outpatient encounters were recorded in the database. Encounter inpatient mortality was calculated as the number of encounters that included a patient death divided by the total number of encounters of the same type (i.e., the number of encounters with male patients who received a RBC unit and died divided by all male encounters in which a RBC unit was issued).

RESULTS

Hospital characteristics

This retrospective patient database comprises data from 12 academic and community hospitals, including 5 Level I trauma centers. The hospitals range in size from 177 to 1500 beds and include hospitals on the East Coast (five hospitals), in the Midwest (four hospitals), and on the West Coast (three hospitals). Subspecialty practice was also well represented, with subspecialty surgery, subspecialty intensive care units (ICUs), and neonatology units present in 100%, 83%, and 50% of reporting hospitals, respectively.

Inpatient transfusions

During the 2-year study period, our inpatient cohort included 641,751 total inpatient encounters, of which 80,362 (12.5%) involved a transfusion. Inpatients were most likely to receive a RBC unit (10.9% of inpatient encounters involved a RBC transfusion), followed by platelets (3.2%) and plasma (2.9%) (Table 1). Inpatient transfusion encounters most often consisted of 2 units of RBCs, 2 units of plasma, or one dose of platelets. Encounters involving any transfusion were 4 to 6 days longer (median, 9-11 days; IQR, 5-21 days), depending on the product transfused, than encounters that did not involve a transfusion (median, 4 days; IQR, 3-6 days). Common primary Health Care Utilization Project diagnoses for which blood products were most commonly provided included blood diseases (highest incidence of RBC and platelet use), infectious diseases (highest incidence of plasma use), neoplasms, cardiovascular diseases, gastrointestinal disease, and injury (Table 1). Finally, approximately one-half of all transfused units (n = 517,708) were issued to the general wards (overall, 47.1% of all issued transfusions; RBC use, 52.8%; platelet use, 41.1%; plasma use, 32.1%), followed by the ICU (25.7% overall) and the operating room (19.8% overall; data not shown).

T1

When evaluating transfusion incidence by encounter, no marked differences were observed by sex or race/ethnicity, but black non-Hispanic patients did have a slightly lower incidence of plasma or platelet transfusions, and Hispanic patients had slightly lower incidence of RBC

TABLE 1. Transfusions by patient demographics and clinical characteristics for inpatient and outpatient encounters*

	Inpatient encounters, N = 641,751				Outpatient encounters, N = 106,758			
Demographics	RBC	PLT	PLS	No Txn	RBC	PLT	PLS	No Txn
Total	69,726 (10.9)	20,509 (3.2)	18,573 (2.9)	561,398 (87.5)	25,939	11,629	1,404	71,240
Sex								
Male	33,599 (10.9)	12,190 (3.9)	10,693 (3.5)	268,513 (87.0)	12,562	6,726	721	34,582
Female	36,116 (10.9)	8,316 (2.5)	7,879 (2.4)	292,590 (87.9)	13,377	4,903	683	36,657
Age, y								
Neonate/infant: <1	987 (2.6)	493 (1.3)	548 (1.4)	37,472 (97.0)	131	38	15	137
Child/adolescent: 1-20	2,129 (6.5)	914 (2.8)	510 (1.6)	30,492 (92.7)	1,373	805	45	1,862
21-49	13,150 (7.5)	3,608 (2.1)	3,259 (1.9)	159,967 (91.9)	4,916	2,160	510	18,471
50-69	28,789 (12.8)	9,494 (4.2)	7,780 (3.5)	191,644 (85.3)	10,479	5,597	563	32,696
≥70	24,669 (14.4)	5,999 (3.5)	6,476 (3.8)	141,787 (83.1)	9,041	3,029	265	18,075
Race/ethnicity								
White, non-Hispanic	46,123 (11.6)	14,317 (3.6)	12,608 (3.2)	345,224 (86.5)	17,828	9,238	922	51,151
Black, non-Hispanic	10,358 (10.4)	1,757 (1.8)	1,945 (2.0)	88,188 (88.7)	4,279	631	248	8,380
Hispanic	4,831 (8.9)	1,710 (3.1)	1,326 (2.4)	48,792 (89.9)	1,430	838	64	4,349
Asian	1,659 (12.1)	610 (4.5)	484 (3.5)	11,806 (86.3)	739	373	38	1,067
Other	6,755 (9.0)	2,115 (2.8)	2,212 (2.9)	67,379 (89.5)	1,663	549	132	6,293
Primary diagnosis								
Blood disease	4,795 (55.9)	1,280 (14.9)	238 (2.8)	3,447 (40.2)	8,206	1,913	247	2,435
Circulatory	10,504 (11.1)	4,664 (5.0)	4,240 (4.5)	81,087 (86.1)	671	79	181	2,338
Gastrointestinal	8,633 (15.6)	1,848 (3.3)	3,022 (5.5)	45,495 (82.2)	303	189	88	1,370
Genitourinary	2,463 (9.8)	276 (1.1)	411 (1.6)	22,503 (89.4)	323	39	52	1,287
Infectious	5,594 (19.4)	1,705 (5.9)	1,882 (6.5)	22,482 (77.9)	108	87	22	163
Injury or fracture	11,761 (16.6)	3,307 (4.7)	3,600 (5.1)	56,706 (80.2)	280	119	165	1,158
Musculoskeletal	4,772 (11.1)	530 (1.2)	769 (1.8)	37,780 (88.1)	210	27	11	3,935
Neoplasm	8,835 (19.1)	3,416 (7.4)	1,697 (3.7)	36,204 (78.4)	7,013	5,367	45	8,257
Respiratory	2,716 (6.9)	528 (1.3)	639 (1.6)	36,122 (92.2)	71	34	18	236
Other	11,064 (4.6)	3,360 (1.4)	2,413 (1.0)	226,834 (94.7)	8,790	3,778	581	50,098
No. of units per encounter								
1	18,403 (26.4)	8,667 (42.2)	2,523 (13.6)	N/A	10,038	10,763	186	N/A
2	24,122 (34.6)	4,856 (23.7)	6,160 (33.2)	N/A	13,619	762	414	N/A
3-4	14,574 (20.9)	3,202 (15.6)	4,684 (25.2)	N/A	1,246	78	362	N/A
5-8	7,925 (11.4)	1,985 (9.7)	2,927 (15.8)	N/A	790	20	143	N/A
>8	4,702 (6.7)	1,799 (8.8)	2,281 (12.3)	N/A	246	6	299	N/A
Encounter duration								
Days: Median [IQR]	9 [5-16]	11 [6-21]	10 [6-19]	4 [3-6]	N/A	N/A	N/A	N/A

* Incidence is calculated for inpatients only (in parentheses) and represents the percentage of encounters with a transfusion by demographic variable, or row percentage. The percentage incidence for the number of units transfused uniquely uses the total number of encounters in which a specific blood product was provided as the denominator, rather than the total number of encounters by row category. Encounters in which more than one blood product type was provided were included in the count totals for each product type issued.

RBC = RBCs transfused alone or in combination with other products; PLT = platelets transfused alone or in combination with other products; PLS = plasma transfused alone or in combination with other products; No Txn = no units given; N/A = not applicable.

transfusions (Table 1). Transfusion incidence increased with patient age; and transfusion incidence, when stratified by age, was similar in male and female inpatients (Fig. 2). Among males, most transfusion encounters occurred in the group ages 60 to 69 years (14,131 encounters; mean age, 66 years), and transfusion incidence was highest for those ages 80 to 89 years (21.5%). Similarly, transfusion encounters were most common for females ages 60 to 69 years (12,741 encounters; mean age, 69 years), and transfusion incidence was highest at ages 70 to 79 years (20.6%). Transfusion incidence generally followed a bimodal distribution, with incidence peaks at ages 2 to 5 years and 70 to 89 years.

Table 2 shows the inpatient encounters in which the patient died. The overall inpatient mortality for those who received any transfusion was 6.9%, which was markedly higher than the mortality for those who did not receive a transfusion during their hospital encounters (1.4%). Mortality was notably higher for encounters in which a platelet (12.6%) or a plasma (14.8%) unit was transfused, either alone or in combination with other products, compared with a RBC unit either alone or with other products (6.6%). No marked differences in mortality were observed by sex or race/ethnicity, but mortality was slightly higher among black, non-Hispanic patients when a plasma unit (15.7%) or platelet unit (15.7%) was provided. Mortality increased with age and was highest at the extremes (ages <1 year and >70 years) for each blood product type. Mortality also increased with increasing blood use, with mortality exceeding 20% when more than 8 units of any one product type were transfused and with specific diagnoses

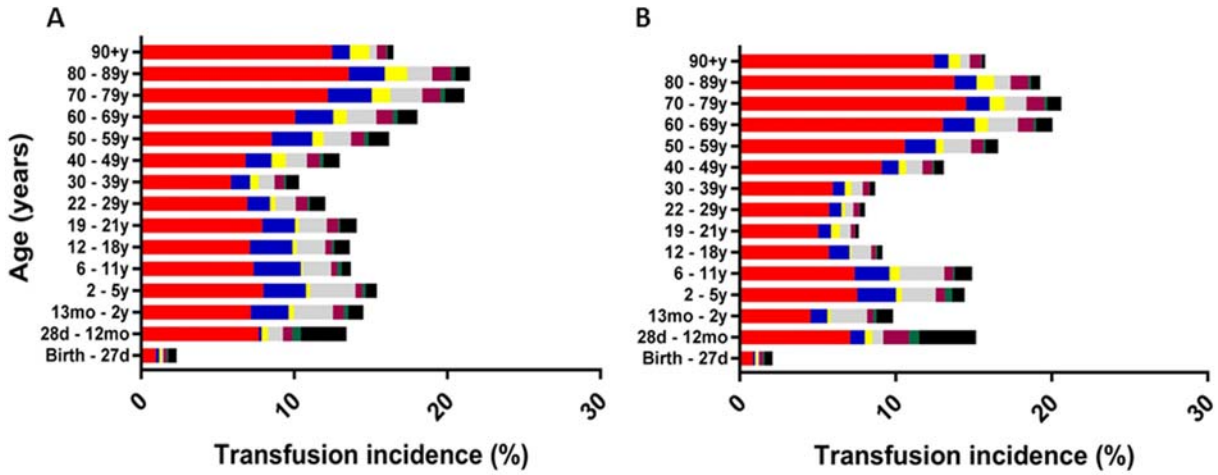

Fig. 2. Inpatient transfusion incidence per encounter (%) by products received, age, and sex (A, male; B, female). Red = RBCs only; blue = platelets only; yellow = plasma only; gray = RBCs and platelets; purple = RBCs and plasma; green = platelets and plasma; black = all products. [Color figure can be viewed at wileyonlinelibrary.com]

(i.e., when infection or respiratory illness was the primary diagnosis).

Outpatient transfusions

During the 2-year study period, 38,972 outpatient transfusion encounters were recorded in the database. The most common outpatient transfusion product was a RBC unit (n = 25,939), followed by platelets (n = 11,629), and plasma (n = 1,404) (Table 1). Compared with inpatient encounters, the overall proportion of outpatient transfusion encounters was similar by sex, age, ethnicity, and the number of units per encounter for each blood product type. Although transfusion incidence could not be calculated, because outpatient encounters were only partially captured in this database, most outpatient encounters involving a transfusion were for blood diseases or neoplasms, diagnoses that also had a high incidence of transfusion for inpatients.

Transfusions by diagnosis and Hgb values

The median pretransfusion and post-transfusion Hgb values as a function of issue location, the number of RBC units used per episode, and primary diagnoses are shown in Figure 3. A median of 1 RBC unit was transfused per transfusion episode for most locations and primary diagnoses considered. The overall median pretransfusion Hgb was 7.6 g/dL (IQR, 7.0-8.2 g/dL), and the median Hgb value ranged between 7.0 and 8.0 g/dL for all clinical diagnoses and issue locations recorded, including specific clinical diagnoses, such as acute coronary syndrome (7.9 g/dL), stroke/intracranial hemorrhage (7.5 g/dL), and acute gastrointestinal bleeding (7.4 g/dL; data not shown). RBC transfusions that were issued to the operating room were associated with higher pretransfusion and post-transfusion Hgb levels than other locations (pretransfusion Hgb: median, 7.9 g/dL; IQR, 7.4-8.4 g/dL; post-transfusion Hgb: median, 9.5 g/dL; IQR, 8.7-10.3 g/dL) but were also associated with a lower adjusted transfusion increment per unit (0.8 g/dL), suggesting that the transfusion occurred in the setting of acute hemorrhage. Outpatient transfusions had pretransfusion and post-transfusion Hgb levels of 7.7 g/dL (IQR, 7.1-8.3 g/dL) and 9.2 g/dL (IQR, 8.5-9.9 g/dL), respectively; however, unlike the operating room, the adjusted Hgb increment was not different from that reported at other locations (1.5 g/dL). Finally, the median pretransfusion Hgb level was slightly higher for circulatory (7.8 g/dL) and musculoskeletal (7.9 g/dL) primary diagnoses than for other diagnoses.

Reported adverse transfusion events

Transfusion reaction events were captured in this database when they were reported to the hospital transfusion service. The most commonly reported transfusion reaction was a febrile nonhemolytic transfusion reaction (n = 742 reported cases; 11.3 events per 1000 patients, 6.4 events per 1000 encounters, and 1.4 events per 1000 transfused units), followed closely by allergic transfusion reactions (n = 573 reported cases; 8.7 events per 1000 patients, 4.9 events per 1000 encounters, and 1.1 events per 1000 transfused units). Together, these two reactions accounted for over 75% of reported events. Severe transfusion reactions reported to blood banks, such as transfusion-related acute lung injury and acute hemolysis, were rare (approximately 1% of all reported transfusion reactions) (Table 3).

TABLE 2. Number of deaths and mortality per inpatient encounter, according to patient demographics and clinical characteristics

	No. of deaths (% mortality)*			
Demographics	RBC	PLT	PLS	No Txn
All encounters	69,726	20,509	18,573	561,398
Total deaths	4,580 (6.6)	2,758 (12.6)	2,758 (14.8)	7,624 (1.4)
Sex				
Male	2,553 (7.6)	1,537 (12.6)	1,581 (14.8)	4,086 (1.5)
Female	2,024 (5.6)	1,052 (12.7)	1,175 (14.9)	3,520 (1.2)
Age, y				
Neonate/infant: <1	121 (12.3)	88 (17.8)	91 (16.6)	188 (0.5)
Child/adolescent: 1-20	72 (3.4)	47 (5.1)	42 (8.2)	56 (0.2)
21-49	649 (4.9)	387 (10.7)	423 (13.0)	577 (0.4)
50-69	1,923 (6.7)	1,171 (12.3)	1,165 (15.0)	2,365 (1.2)
≥70	1,813 (7.3)	897 (15.0)	1,035 (16.0)	4,436 (3.1)
Race/ethnicity				
White, non-Hispanic	2,997 (6.5)	1,713 (12.0)	1,816 (14.4)	5,171 (1.5)
Black, non-Hispanic	575 (5.6)	275 (15.7)	305 (15.7)	834 (0.9)
Hispanic	292 (6.0)	181 (10.6)	173 (13.0)	422 (0.9)
Asian	120 (7.2)	70 (11.5)	65 (13.4)	225 (1.9)
Other	596 (8.8)	352 (16.6)	399 (18.0)	972 (1.4)
Primary diagnosis				
Blood disease	489 (5.5)	283 (8.3)	212 (12.5)	736 (2.0)
Circulatory	890 (8.5)	567 (12.2)	576 (13.6)	2,268(2.8)
Gastrointestinal	492 (5.7)	265 (14.3)	371 (12.3)	330 (0.7)
Genitourinary	92 (3.7)	41 (14.9)	48 (11.7)	205 (0.9)
Injury or fracture	737 (6.3)	484 (14.6)	507 (14.1)	645 (1.1)
Infectious	1,055 (18.9)	529 (31.0)	633 (33.6)	1,404 (6.2)
Musculoskeletal	50 (1.0)	20 (3.8)	24 (3.1)	50 (0.1)
Neoplasm	66 (1.4)	46 (3.6)	20 (8.4)	13 (0.4)
Respiratory	353 (13.0)	132 (25.0)	153 (23.9)	1,082 (3.0)
Other	435 (3.9)	265 (7.9)	258 (10.7)	1,161 (0.5)
No. of units per encounter				
1	863 (4.7)	823 (9.5)	241 (9.6)	N/A
2	956 (4.0)	512 (10.5)	622 (10.1)	N/A
3-4	921 (6.3)	427 (13.3)	654 (14.0)	N/A
5-8	831 (10.5)	389 (19.6)	560 (19.1)	N/A
>8	1,009 (21.5)	440 (24.5)	681 (29.9)	N/A

* Mortality is shown as a percentage (in parentheses) where applicable. The overall inpatient mortality was 6.9% (5545 encounter deaths/80,362 encounters) for patients who received any transfusion and 1.4% (7624 encounter deaths/561,398 encounters) for those who did not receive a transfusion. Encounters with mortality in which more than one blood product type was provided were included in the counts for each product type issued.

RBC = RBCs transfused alone or in combination with other products; PLT = platelets transfused alone or in combination with other products; PLS = plasma transfused alone or in combination with other products; No Txn = no units given; N/A = not applicable.

DISCUSSION

Our findings provide a description of transfusion practice across a multicenter consortium of hospitals over 2 years and demonstrate the feasibility of using a database that combines clinical information from different electronic medical record systems. Using data from 80,362 inpatient transfusion encounters and 38,972 outpatient encounters, we demonstrate that transfusion incidence increases with age and differs minimally by sex and ethnicity. Mortality was higher in those who received a transfusion. The pretransfusion Hgb trigger for a single RBC unit transfusion at most hospital locations and clinical diagnoses was between 7 and 8 g/dL, which is lower than historical transfusion triggers and consistent with the widespread adoption of more restrictive transfusion policies. Overall, as described in the paragraphs below, these data confirm findings reported in previous studies and demonstrate the utility of this database for detailed future analyses of transfusion practice and health outcomes.

The key strength of this study is the reliance on a large-scale, detailed database with complete or near-complete coverage of all inpatients and outpatients who received transfusions at 12 hospitals. This database has also undergone rigorous quality control and is as accurate as possible given its sourcing from disparate electronic medical records. Databases like these are critically important, and similar international databases, such as SCANDAT, PROTON (Profiles of Transfusion Recipients), and SHOT (Serious Hazards of Transfusion), have been used successfully to address several critical questions regarding blood donors and transfusion recipients.[2-7,17-19] However, those databases lack the granular inpatient clinical data contained within the REDS-III clinical database, such as laboratory values, medications,

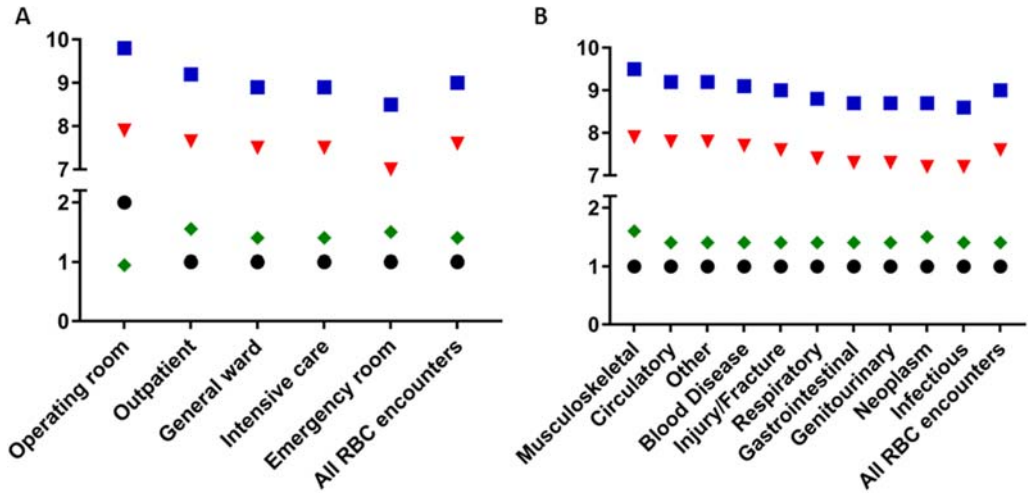

Fig. 3. Inpatient RBC transfusion practice by (A) issue location and (B) primary diagnosis. Median values are shown. Squares = post-transfusion Hgb (g/dL); triangles = pretransfusion Hgb (g/dL); diamonds = Hgb change per RBC dose (g/dL); circles = median number of units per episode.

TABLE 3. Adverse transfusion events reported during 2013 through 2014

Adverse event	Events reported: No. (% of total)	Events per 1000 transfused units, N = 517,708	Events per 1000 transfusion recipients, N = 65,694	Event per 1000 transfusion encounters, N = 116,185
Total	1711	3.3	26.0	14.7
Febrile nonhemolytic transfusion reaction (FNHTR)	742 (43.4)	1.4	11.3	6.4
Allergic reaction, including anaphylaxis	573 (33.5)	1.1	8.7	4.9
Other	86 (5.0)	0.17	1.3	0.74
Transfusion-associated circulatory overload (TACO)	84 (4.9)	0.16	1.3	0.72
Unknown	54 (3.2)	0.1	0.82	0.47
Delayed hemolytic transfusion reaction (DHTR)	47 (2.7)	0.09	0.72	0.40
Delayed serologic transfusion reaction (DSTR)	38 (2.2)	0.07	0.58	0.33
Hypotensive transfusion reaction	36 (2.1)	0.07	0.55	0.31
Transfusion-associated dyspnea (TAD)	33 (1.9)	0.064	0.50	0.28
Transfusion-related acute lung injury (TRALI)	11 (0.64)	0.021	0.17	0.1
Acute hemolytic transfusion reaction (AHTR)	7 (0.41)	0.014	0.11	0.06

vital signs, and issue locations for each transfusion encounter and blood product. Another large database of similar type and granularity is in development in Canada[20]; however, to our knowledge, the REDS-III database is the largest multicenter collection of highly granular medical records for inpatient and outpatient transfusion recipients currently available.

Our initial review of transfusion practice using this database is likely to be representative of transfusion practice across the United States, because it is consistent with the data reported from other large national surveys of transfusion practice, such as the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey Report.[21] Our findings similarly identify the general ward as the most common location for a transfusion and indicate that febrile nonhemolytic transfusion reactions are the most commonly reported adverse transfusion events at a rate of approximately 1:1000 units.[21] The AABB survey, however, does not capture encounter-level data for individual transfusion recipients; therefore, our analysis is more comparable to a study performed using the PROTON database in 2010.[17,18] The PROTON database included 290,043 patients and 2,405,012 blood product transfusions over 20 hospitals. Although our database reflects trends that

are generally similar to those reported by the PROTON database, we observed a greater proportion of single-unit RBC transfusions at both the episode and encounter levels (26.4%), suggesting a possible increasing influence of patient blood management strategies in selected hospitals.[8,9,22] Further comparisons between large databases will have the potential to reveal differences in the profile of blood product users in different countries over different time frames, possibly reflecting differences in patient mix and/or clinical practice.

Several databases capture clinical information on individual transfusion recipients, but few capture complete data from transfusion recipients and non-recipients. Although other studies, such as those using the Kaiser Permanente Northern California database,[8] have also calculated transfusion incidence, our database includes a broader range of tertiary care and trauma centers than the community-based Kaiser network. The REDS-III database allows us to calculate transfusion incidence by sex, age, ethnicity, and clinical diagnosis and to determine the number of transfused products used per inpatient encounter. Nevertheless, it is noteworthy that RBC transfusion incidence was similar between the two databases (11% vs. 13%).[8] We also found that transfusion incidence was similar for sex, increased with age, and was higher for certain primary diagnoses and ethnicities (e.g., blood diseases). The lower platelet and plasma transfusion incidence in black patients, combined with higher mortality among black patients who received these products, was notable and suggests either a possible disparity in how these products are administered or a different mix of indications for platelet or plasma transfusions in that population. Future analyses of the full 4 years of REDS-III data will permit a review of trends in transfusion incidence and a characterization of transfusion practice over time by geographic region, specific patient population, and/or subcategories of hospitals.

Using this database, we were able to quantify inpatient mortality according to patient demographics and type and dose of transfused blood products. We found, as observed in other database studies,[8,22] that mortality was higher for transfusion recipients overall, increased with the number of units provided during the encounter, and increased with patient age. However, these findings likely reflect an indication bias: patients who receive increasing numbers of transfusions for any indication are more ill than patients who do not receive transfusions and thus are more likely to die during an encounter. Our finding that mortality was higher for all demographic variables with the receipt of platelet and plasma products versus RBCs is also likely subject to indication bias, as reported by smaller studies in specific populations, such as patients undergoing aortic valve replacement or cardiac bypass, and by the PROTON study.[18,23-25]

Outpatient transfusion practices are rarely studied, and the REDS-III database provides comprehensive access to clinical data surrounding this patient population. Previous transfusion practice studies on outpatients have focused mainly on those with sickle cell disease, leukemia, or aplastic anemia.[26-28] The REDS-III database revealed that patients with blood diseases and neoplasms represented the largest proportion of outpatient transfusion encounters, with distributions for sex, age, and race/ethnicity being generally similar to those for inpatients. Outpatients most commonly received 1 or 2 units of RBCs with a pretransfusion Hgb between 7 and 8 g/dL. These observations add to the limited literature on this topic and closely mirror the findings from a physician-based survey recently performed for patients with acute leukemia.[27] Future subanalyses using this database will be able to address whether these transfusion practices are consistent across different outpatient primary diagnoses.

Finally, although we were capable of looking at laboratory values related to any type of component using this database, we focused our evaluation on RBC transfusions and Hgb triggers. Recent large clinical trials support the use of a restrictive transfusion strategy and a pretransfusion Hgb of 7 g/dL.[22,29-32] National guidelines have now been published supporting the use of this restrictive strategy,[33] and blood management groups have formed in many hospitals to reduce RBC use by using these evidence-based guidelines.[8,11,22] We found that, with the exception of surgical patients, current RBC transfusion practice generally follows a pretransfusion Hgb trigger between 7 and 8 g/dL and that physicians in these 12 hospitals are generally ordering 1 RBC unit per inpatient transfusion episode. However, we also observed that some patient populations, like those with acute cardiovascular disease, received RBC transfusions at slightly higher pretransfusion Hgb levels. These findings support the conclusion that transfusion practice for RBCs, whether attributable to new guidelines or patient blood management programs, generally follows the current evidence and standards.[22,30-33]

This study has several limitations, mostly related to the source data. First, the database was limited by how each electronic medical record system recorded the clinical variables, and there were some missing, inaccurate, or unavailable clinical data. Data regarding hospital admission location were difficult to interpret because of the way several hospitals recorded intra-hospital transfers, making a calculation of transfusion incidence by admission location (e.g., emergency department, ICU, general ward) impossible. The database also does not capture discharge summaries that would facilitate the evaluation of cause of death, intraoperative fluid use, or transfusion indication(s), which may limit its ability to answer some transfusion-specific questions. Data on post-hospital mortality also were not available or reliable from most source

systems and were not included. Second, although it is very large, the database is based on 12 geographically dispersed but predominantly academic hospitals and is not necessarily representative of all hospital transfusion practice in the United States. In this analysis, we do not report on variability in transfusion practice among hospitals, although such variability could be a focus of future analyses. Finally, while our reported outpatient transfusion data are novel, they are limited by the lack of a reliable denominator for outpatient encounters.

In conclusion, we have described the methods used, preliminary data, and potential utility for the largest, multisite, clinical database for TM in the United States. Despite some inherent weaknesses, this database has the size and granularity necessary to inform many hypothesis-driven research questions for both inpatient and outpatient transfusion recipients. This database will contain recipient data through the end of 2016 and will be linked to donor and component databases over the same time period, greatly expanding the utility of this data set. The substantial effort devoted to creating this database will yield many dividends in improving the ability of TM to address current and future questions of blood utilization, patient safety, and clinical outcomes.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

APPENDIX

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Fig. S1. Data extraction by recipient type (blue = data extracted; orange = data not extracted; inpt = inpatient; outpt = outpatient; T & S = type and screen; T & C = type and cross).