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Title of Study or Project:	*Factors Associated with Large Volume Transfusion Ratios During Postpartum Hemorrhage*
Primary Institution:	Brigham and Women's Hospital
Primary Author:	Michael J. Furdyna, MD
Co-Authors:	Kara G. Fields, MS; John J. Kowalczyk, MD; Shubhangi Singh, MBBS; Sharon C. Reale, MD
Statistician(s):	Kara Fields
Type of Study:	Retrospective Observational
Data Source(s):	MPOG Database
IRB Number/Status:	IRB approval has been obtained for this limited dataset (2024P001448) [X] NOTE: IRB *must* specify that dataset is a *limited dataset* (i.e., not de-identified) [X] PI (Sharon Reale) is listed on the site IRB
Hypotheses / Aims:	Our primary aim is to estimate the association of patient, case/delivery, management, and institution factors with large volume transfusion ratios during postpartum hemorrhages that occur during anesthetic care. Large volume transfusions will be defined as ≥4 units of packed red blood cells. Our primary outcome will be the use of balanced, or approximately 1:1, fresh frozen plasma to packed red blood cell ratios (binary outcome). Additionally, sensitivity analyses will assess transfusion ratio as (1) an ordinal outcome, (2) a continuous outcome, (3) blood transfused as a low/high binary value, and (4) the interaction of blood volume and institutional delivery volume. Our secondary aim A is to describe the proportion of large volume transfusions that have balanced, or approximately 1:1, platelet to packed red blood cell ratios (binary outcome). Our secondary aim B is to estimate the association of FFP:pRBC transfusion ratios with maternal outcomes including mortality, length of stay, incidence of intraoperative intubation, and incidence of postoperative mechanical ventilation, TRALI, TACO, acute kidney injury, venous thromboembolism, and pulmonary embolism.
Number of Patients/Participants:	Inclusion criteria are all women aged 15-50 undergoing delivery (vaginal or cesarean) at all MPOG sites between 2016 and 2023 (>740,000 cases) who received at least four units of packed red blood cells (>1,000 cases). We will identify deliveries using the 'Obstetric Anesthesia' phenotype and query these cases.
Power Analysis:	Based on a preliminary review of the eligible cohort blinded to the exposure and secondary outcome variables of interest, approximately 1,000 deliveries (across approximately 50 institutions) received ≥4 units of packed red blood cells, and an

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	estimated 40% of these transfusions used a 1:1 ratio. A report from a prior study of massive transfusion activations in non-trauma patients (25% obstetric cases) which observed 24.1% of transfusions with an approximate 1:1 ratio.[1] With a total of approximately 240-400 deliveries with a 1:1 transfusion ratio, the association of a maximum of 12-20 patient, case/delivery, management and institution factors with the use of a 1:1 transfusion ratio (i.e., 20 events per factor) can be estimated to minimize bias in estimated regression coefficients.[2]
Proposed statistical tests/analyses:	The percentage of deliveries with a balanced FFP:pRBC transfusion ratio will be presented as a point estimate with 95% confidence interval. Primary Aim The association of patient, case/delivery, management and institution factors with use of a balanced FFP:pRBC transfusion ratio will be estimated using mixed effects binary logistic, Poisson, or negative binomial regression (depending upon the incidence of the balanced transfusion ratio and the satisfaction of the respective model assumptions) with institution ID included as a random effect. Number of pRBCs will be included as a continuous model covariate as an approximate measure of hemorrhage severity. The ratio of cryoprecipitate to pRBCs will be included as a continuous model covariate as a measure of fibrinogen repletion. Sensitivity analyses will include: (1) analysis of transfusion ratio as an ordinal outcome using mixed effects ordinal logistic regression, (2) analysis of transfusion ratio as a continuous outcome using mixed effects linear regression, (3) analysis of number of pRBCs as a binary (i.e., 4-8 versus >8) covariate, and (4) inclusion of an interaction term between number of pRBCs and annual institutional delivery volume to assess whether the association between annual institutional delivery volume and use of a balanced FFP:pRBC transfusion ratio varies by number of pRBCs. Secondary Aim A The analysis plan for the balanced PLT:pRBC transfusion ratio outcome is identical to the plan for the balanced FFP:pRBC outcome in the Primary Aim. Secondary Aim B The association of a balanced FFP:pRBC transfusion ratio with binary maternal outcomes will be estimated using multivariable logistic regression. Institution ID will be included as a random effect using mixed models where possible, however convergence may not be achieved for some rare outcomes for which it is likely that multiple institutions will have 0 outcome events. Mixed effects linear regression will be used to estimate the association between transfusion ratios and length of stay, with Institution ID included as a random effect. Sensitivity analyses will include: (1) analysis of FFP:pRBC transfusion ratio as an ordinal exposure variable, (2) analysis of FFP:pRBC transfusion ratio as a continuous exposure variable, (3) analysis of number of pRBCs as a binary (i.e., 4-8 versus >8) covariate, and (4) if/when the sample size allows, inclusion of a interaction term between number of pRBCs and FFP:pRBC ratio to assess whether the association between FFP:pRBC ratio and maternal outcomes varies by number of pRBCs.

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Resources (Brief summary of resources for data collection, personnel, financial):	BWH Anesthesiology, Perioperative and Pain Medicine (BWH Anesthesia) departmental funding will support the efforts of staff, including investigators and statisticians outlined above (Furdyna, Kowalczyk, Reale, Fields).

Introduction

Obstetric hemorrhage is a leading cause of global maternal morbidity and mortality and remains challenging to manage even in high-resource settings. Data from the United States, Canada, and other high-resource countries demonstrate an increasing rate of severe postpartum hemorrhage requiring blood transfusion, likely driven by increasing rates of cesarean deliveries, placental abnormalities, and increasing maternal comorbidities and complexity.[3,4] With this increase in severe hemorrhage and transfusions, there has been a concurrent rise in obstetric 'massive' transfusions.[5,6] Commonly used criteria in the literature include administration of greater than 8-10 units of packed red blood cells (pRBCs), administration of 4 or more units in an hour, or presence of hemorrhagic shock; while there is growing evidence that transfusions of this scale are increasing, there is limited consensus on what should constitute a 'massive' transfusion or major hemorrhage, and associated interventions, in this setting.[5,7–9]

Currently, there is a lack of agreement, and quality evidence, on how to best balance blood product administration in obstetric transfusions of this scale. Most institutional obstetric 'massive transfusion' protocols are based on a 1:1:1 transfusion model to balance pRBCs, fresh frozen plasma (FFP), and platelets (PLTs), respectively, with scheduled additions of cryoprecipitate.[10] However, this ratio is derived from the trauma literature, whereas the majority of obstetric hemorrhage stems from mechanisms unique to delivery (such as uterine atony, placenta accreta spectrum, hysterotomy extensions, and abruption).[8] Additionally, peripartum coagulation and hemostasis differ significantly from that of the non-pregnant population, with a more pronounced role of fibrinogen in hemorrhage progression.[7,8,11–14] While some societal guidelines have shifted to reflect a ratio that favors pRBCS over FFP, weight-based dosing of FFP, or point of care guided transfusion practices, there is still significant variability in guidance and clinical practice.[15,16]

The primary aim of this retrospective, observational study is to describe FFP:pRBC transfusion ratios in anesthetic cases with 'large volume' obstetric hemorrhage, defined as cases requiring 4 or more pRBCS, as well as estimate the association of patient, case/delivery, management (e.g., laboratory testing), and institution factors with the use of a 'balanced' transfusion ratio. The secondary aims include similarly describing PLT: pRBC ratios and estimating the association between the above factors and a 'balanced' ratio. Additionally, the secondary aims will include estimating the association between transfusion ratios and maternal outcomes including mortality, length of stay, intensive care admission, and other transfusion-related complications such as postoperative mechanical ventilation, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and acute kidney injury. The results of this study, in addition to describing current practices, may offer insight both into appropriate transfusion ratios as well as when an obstetric hemorrhage should be treated as 'massive' and might benefit from a standardized protocol.

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Methods

Study Design

This is a multicenter, retrospective, observational study using the Multicenter Perioperative Outcomes Group (MPOG) database. Founded in 2008, MPOG is a research consortium with a shared database of anesthetic records from over 70 hospitals. Quality control is performed at each institution to ensure data adequacy and facilitate consistency across hospital and electronic health records (EHR) systems. Institutional Review Board has been obtained for this limited dataset (Protocol Number 2024P001448). This study is in accordance with the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) extension of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study protocol is being submitted to an MPOG peer review committee prior to accessing data.

Study Population

The study population will include all women aged 15-50 who underwent vaginal or cesarean delivery between January 1, 2016 and December 31, 2023 at any participating MPOG site. Only data that meets inclusion criteria for the MPOG ‘Intraoperative Research Standard’ and that has in-hospital mortality data will be included. The study population of peripartum patients will be initially identified using the ‘Obstetric Anesthesia Type’ MPOG phenotype; cases with a “No” value will be excluded. Cases from institutions with less than 20 obstetric cases per year will be excluded as well in order to mitigate potential issues with data quality, unless they are determined to account for >5% of the initial study population; if so, data from these institutions will undergo manual review prior to inclusion. For included patients, all additional anesthetic records within 48 hours will be accessed in order to capture instances of postpartum operative interventions for hemorrhage.

From this population, we will assemble a cohort of patients who received a large-volume transfusion, defined as ≥4 units of packed red blood cells, in the immediate peripartum period while under anesthetic care. Cases with an Obstetric Anesthesia Type other than “No” who received ≥4 packed red blood cells, as measured by the ‘Blood Product Total – pRBCs’ MPOG phenotype, will be included in the study population.

Cases which received whole blood as all or part of their transfusion will be excluded from analyses. If more than 10% of patients at a given institution in a given year that are transfused receive whole blood, data for that institution-year will be excluded to reduce potential confounding.

Additionally, patients who have a second anesthetic record within 24 hours of the end of the obstetric anesthetic record will have their blood product totals combined in order to capture situations where postpartum hemorrhage resuscitation is split across two records (e.g., vaginal delivery followed by dilation and curettage). Combined records that have ≥4 packed red blood cells will be included but will undergo manual review of case time, procedure text, and surgical diagnosis in order to determine whether the anesthetic record represents an intervention for hemorrhage or an unrelated procedure (e.g., postpartum salpingectomy), in which case it will be excluded.

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Cases with an Obstetric Anesthesia Type of "No" that received ≥4 packed red blood cells will undergo manual review of case time, procedure text, and surgical diagnosis in order to determine whether the anesthetic record represents an atypical delivery record and/or management of postpartum hemorrhage.

Cases of HELLP with concern for severe quantitative or qualitative thrombocytopenia (initial platelet count < 50), or cases of DIC (initial fibrinogen < 100) will be excluded, as these represent transfusions in the setting of severely dysregulated coagulation. Additionally, cases where the first blood product is either cryoprecipitate or platelets will either be excluded or undergo manual review, depending on case volume.

Data source

Data for this study will be extracted from the MPOG database.

Primary outcome

The primary aim of this study is to estimate the association of patient, case/delivery, management and institution factors with large volume transfusion ratios during postpartum hemorrhages that occur during anesthetic care. The primary outcome is use of 1:1 or 'balanced' transfusion ratios in obstetric cases requiring large-volume transfusions. For each case we will obtain the total of each blood product using the relevant MPOG phenotype and dichotomize them into 'balanced' or 'non-balanced'. For FFP:pRBC ratios we will consider <0.75 to represent 'non-balanced' ratios, and a range of 0.75 to 1.34 to represent a 1:1 or 'balanced' ratio. This range for 'balanced' ratios is intended to capture attempted adherence to a 1:1 ratio while accounting for situations such as incomplete blood product documentation or completion of transfusion prior to administration of the final unit of FFP. Cases in which the FFP:pRBC is >1.34 will be not be included in either group, but may treated as a third group for descriptive purposes and will be included in the ordinal sensitivity analysis (see below).

As platelets are typically administered in pools of 5 to 6 units and commonly not administered until the 5^{th} or 6^{th} unit of pRBCs, we will not consider ratios of platelet transfusions except for cases that meet or exceed this number of pRBCs. We will dichotomize consider patients to be 'non-balanced' if the ratio of (PLT x 6):pRBC is <0.75, and 'balanced' if the ratio is 0.75 to 1.34.

Four sensitivity analyses will assess transfusion ratio as (1) an ordinal outcome, (2) a continuous outcome, (3) blood transfused as a low/high (4-8 pRBCs *vs* 8+ pRBCs) binary value, and (4) the interaction of blood volume and institutional delivery volume.

Secondary outcome(s), if applicable

The secondary aim of this study is to estimate the association of transfusion ratios with maternal outcomes. These secondary study outcomes include mortality, length of stay, intubation during anesthetic record (for vaginal deliveries), conversion to general anesthesia (for cesarean deliveries), and frequency of postoperative mechanical ventilation, acute kidney injury, TRALI, and TACO.

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Exposure Variables and Covariates

Primary Aim

Factors/exposures that will be examined as possible sources of variation in FFP:pRBC transfusion ratios include patient factors such as body mass index (BMI, <30 [reference], 30 to <35, 35 to <40, ≥40), American Society of Anesthesiologists (ASA) Physical Status (I or II [reference], III, IV); case/delivery factors including number of pRBCs transfused (as a measure of hemorrhage severity), cryoprecipitate:pRBC ratio (as a measure of fibrinogen repletion), initial type of anesthetic (neuraxial vs general anesthesia), labor to cesarean status, relevant comorbidities (including placental abruption, placenta accreta spectrum, and trauma); management factors including use of ‘standard’ intraoperative laboratory testing (i.e., hemoglobin, PTT, INR, platelets, fibrinogen), availability of viscoelastic testing (TEG and ROTEM); and institution factors including academic (medical school affiliation) vs community status and annual delivery volume (as in our cohort).

Secondary Aim

A. Platelet to Packed Red Blood Cell Ratio

The factors/exposures that will be examined as possible sources in PLT:pRBC transfusion ratios are the same as in the primary aim.

B. Transfusion Ratio and Outcomes

The association of FFP:pRBC transfusion ratio (the exposure) with clinical outcomes will be estimated with adjustment for the following covariates: patient factors including age (<35 [reference], 35-40, ≥40), BMI (as above), ASA Physical Status (as above); case/delivery factors including number of pRBCs transfused (as a measure of hemorrhage severity), cryoprecipitate:pRBC ratio (as a measure of fibrinogen repletion) method of delivery (vaginal [reference], labor to cesarean, planned cesarean), use of general anesthesia (in cesarean deliveries), clinically relevant comorbidities (see Appendix); and institution factors including academic (medical school affiliation) vs community status and annual delivery volume (as in our cohort).

Statistical analysis

Primary Aim

The percentage of deliveries with a balanced FFP:pRBC transfusion ratio will be presented as a point estimate with 95% confidence interval.

The association of patient, case/delivery, management and institution factors (as listed in the Exposure Variables and Covariates Section) with use of a balanced FFP:pRBC transfusion ratio will be estimated using mixed effects binary logistic, Poisson, or negative binomial regression. Poisson or negative

binomial regression will only be used if their respective model assumptions are satisfied and the incidence of a balanced transfusion ratio is ≥10%.[17]

Secondary Aim

A. Platelet to Packed Red Blood Cell Ratio

The analysis plan for the balanced PLT:pRBC transfusion ratio outcome is identical to the plan for the balanced FFP:pRBC outcome in the Primary Aim.

B. Transfusion Ratio and Outcomes

The association of a balanced FFP:pRBC transfusion ratio with binary maternal outcomes will be estimated using multivariable logistic regression, with adjustment for covariates listed in the Exposure Variables and Covariates section. Institution ID will be included as a random effect using mixed models where possible, however convergence may not be achieved for some rare outcomes for which it is likely that multiple institutions will have 0 outcome events. Mixed effects linear regression will be used to estimate the association between transfusion ratios and length of stay, with fixed effects included as listed in the Exposure Variables and Covariates section and Institution ID included as a random effect.

The above statistical analyses, as well as any modifications to the planned tests, will be done under the guidance of a statistician. SAS (SAS Institute, Cary, NC), R (R Foundation for Statistical Computing, Vienna, Austria), and STATA(StataCorp, College Station, TX) software will be used for all statistical analyses.

Pre-specified Sensitivity / Subgroup / Secondary outcome analyses (optional)

Sensitivity analyses for the Primary Aim and Secondary Aim A will include:

(1) Analysis of transfusion ratio as an ordinal outcome using mixed effects ordinal logistic regression
(2) Analysis of transfusion ratio as a continuous outcome (log-transformed if this stabilizes variance and improves normality of model residuals) using mixed effects linear regression
(3) Analysis of number of pRBCs as a binary covariate (4-8 versus >8)
(4) Inclusion of an interaction term between number of pRBCs and annual institutional delivery volume to assess whether the association between annual institutional delivery volume and use of a balanced transfusion ratio varies by number of pRBCs.

Sensitivity analyses for Secondary Aim B will include:

(1) Analysis of FFP:pRBC transfusion ratio as an ordinal exposure variable
(2) Analysis of FFP:pRBC transfusion ratio as a continuous exposure variable
(3) Analysis of number of pRBCs as a binary (i.e., 4-8 versus >8) covariate
(4) If sample size allows, inclusion of a interaction term between number of pRBCs and FFP:pRBC ratio to assess whether the association between FFP:pRBC ratio and maternal outcomes varies by number of pRBCs

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Power analysis

Based on a preliminary review of the eligible cohort blinded to the exposure and secondary outcome variables of interest, approximately 1,000 deliveries (across approximately 50 institutions) received ≥4 units of packed red blood cells, and an estimated 40% of these transfusions used a 1:1 ratio . A report from a prior study of massive transfusion activations in non-trauma patients (25% obstetric cases) which observed 24.1% of transfusions with an approximate 1:1 ratio.[1] With a total of approximately 240-400 deliveries with a 1:1 transfusion ratio, the association of a maximum of 12-20 patient, case/delivery, management and institution factors with the use of a 1:1 transfusion ratio (i.e., 20 events per factor) can be estimated to minimize bias in estimated regression coefficients.[2]

Handling of missing or invalid data

Erroneous or out of range values will be removed and treated as missing data. We will account for missing data using multiple imputation by chained equations (fully conditional specification). The imputation model will include all covariates and outcomes assessed in the analytic models as well as auxiliary variables. Estimates obtained from analyzing each imputed dataset will be combined using Rubin's rules to obtain final pooled estimates.

Major Threats to Inference & Mitigation Strategies

Information Bias: Inter-Institution
There are multiple threats to interference that may affect this study, most of which relate to the accuracy and quality of data pertaining to blood product and factor concentrate administration. The principal threat is information bias, as there may be systematic differences in documentation across different institutions, different electronic health records (EHR) systems, over time, or due to other factors. Primarily, we anticipate that this may introduce systematic biases resulting from the way administration of blood products outside of the operating room as well as administration of factor concentrates are handled between institutions. Additionally, institutions may differ in how they document immediate 'take-back' cases (i.e., one anesthetic record versus two), which may result in the same blood products in the same time frame failing to meet the threshold of 4 units in one record.

We will attempt to mitigate these threats in several ways. We will exclude institutions that contribute less than 20 obstetric cases per year, as these institutions may have less optimal obstetric data quality. If case volume allows, we will group cases by institution. Additionally, by incorporating blood product totals from immediately subsequent anesthetic records we expect to not only increase our sensitivity for large volume transfusions but also mitigate the issue of one hemorrhage split across anesthetic records.

Additionally, for our cohort we will query the dataset for free-text notations pertaining to parameters that we suspect may be documented differently between institutions, including (based on prior MPOG experience) factor concentrates and viscoelastic testing. In addition to querying for their respective MPOG concepts, we will query our cohort for free-text notations containing words related to factor

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concentrates (e.g., “concentrate”, Novo-Seven, Fibryga) and viscoelastic testing (e.g., “viscoelastic”, “TEG”, “ROTEM”). If it is feasible with the number of positive cases, we will then manually review these cases to determine whether these medications were given or laboratory tests were run.

Information Bias: Intra-Institution

A different form of information bias may exist in the differing documentation between types of obstetric anesthesia (e.g., labor epidural or planned cesarean delivery) and patient location during anesthetic care, even intra-institution. Based on our experience with MPOG data, medication (including blood products) administration documentation tends to be more accurate during cases that take place in the operating room. If blood products administered in labor rooms are systematically underreported, then our blood product threshold will underestimate the proportion of vaginal deliveries requiring large volume transfusion. Additionally, if there are situations where part of a resuscitation takes place in a labor room with limited documentation and is followed by a well-documented case in an operating room, the apparent transfusion ratio will be systemically biased to not reflect the initial blood products (typically pRBCs). By considering ranges of 0.75 to 1.5 to represent an attempted 1:1 ratio, we expect partially mitigate this (e.g., 4 FFP to 4 pRBC, where one pRBC isn’t reported, would result in a ratio of 4:3 or 1.33). Our approach to platelet ratios offers a similar margin of error. If in the course of our analysis it becomes apparent that there are significant limitations to data quality outside of the operating room, then we may restrict some or all analyses to cesarean deliveries.

Generalizability

Although MPOG is the largest dataset of its kind, it is predominantly composed of large, academic hospitals. Therefore, both the obstetric patients in this cohort, as well as the resources used to care for them (including blood products) may not be representative of obstetric hemorrhage management in the broader population. If sample size allows, we will perform subgroup analyses by academic status or hospital delivery volume, and will discuss these limitations.

Other Confounders

While we intend to control for patient and delivery characteristics, there will likely be some confounding factors that cannot be controlled for, including institution-specific factors. To mitigate these, we will use mixed effects models, including treating MPOG institution as a random effect.

Preliminary Data

Data Direct Query 7.17.2024

Filter Type	Filter Description	Case Count	Institution Count
Population	Starting Population: Outcome Research Standard - Mortality	23,087,049	75
Demographics	Age: 15-50	7,963,280	75
Cases	Procedure Date: 01/01/2016-12/31/2023	6,273,498	73
Procedures	Procedure Type: Obstetric Anesthesia Type	901,258	69

*Data from MPOG Maternal Cardiac Arrest Project (Query ~11.2023)**

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Filter Type	Filter Description	Patient Count	Case Count	Institution Count
Population	Obstetric Anesthesia Type != “No” + All Records within 7 Days	699541	805607	60
Transfusion Filter	Received 1 or more pRBCs	7105	7379	59
Transfusion Filter	**Received 4 or more pRBCs**	**1067**	**1102**	**53**
Transfusion Filter	Received 8 or more pRBCs	287	290	42

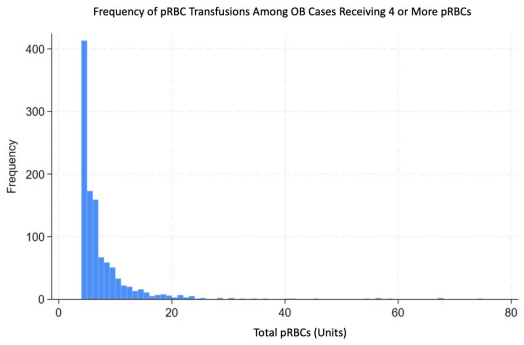
*Note: Cases from 2015 included in this estimate.

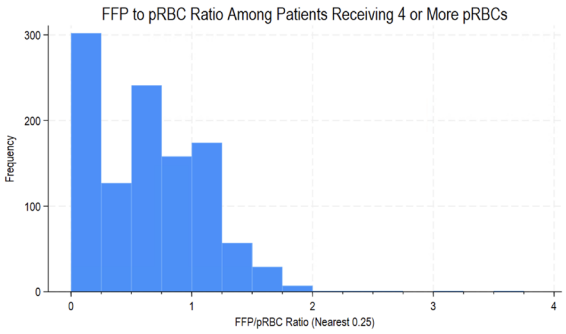
*Transfusion Ratios Among Obstetric Patients (Based on Cardiac Arrest Project)**

Filter Type	Filter Description	Case Count
Population	**4 or more pRBCs (see above**	**1102**
FFP/pRBC Ratio	FFP/pRBC Ratio <0.75	670
FFP/pRBC Ratio	0.75 >= FFP/pRBC Ratio <=1.5	408
PLT/pRBC Ratio**	PLT/pRBC Ratio <0.75	590
PLT/pRBC Ratio**	0.75 >= PLT/pRBC Ratio <=1.5	491

*Note: Cases from 2015 included in this estimate.

**Note: Each MPOG ‘unit’ of PLT multiplied by six





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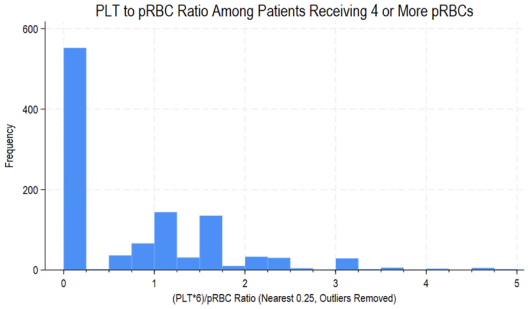

*Preliminary Institutional Data (Based on our Institution’s Data from the Cardiac Arrest Project)**

Data for approximately 35,000 anesthetic cases from our institution, accounting for 34,676 delivery hospitalizations, were obtained from a prior MPOG proposal with a similar initial cohort.

Delivery hospitalizations with an anesthetic record (either delivery or subsequent) that received 4 or more pRBCs were classified as large volume transfusions. Due to limitations of the dataset, blood products were not pooled across anesthetic cases within 48 hours, as they would be with this proposal.

44 delivery hospitalizations had cases meeting criteria for LVT. 3 cases had an FFP:pRBC ratio > 1.5 and were excluded.

	Delivery Hospitalizations (N= 34676)			**Large Volume Transfusion (N = 41)**	
Factor	**Large Volume Transfusion?**			**Balanced Transfusion?**	
Age	No	Yes		No	Yes
< 35	22655 (99.9%)	19 (.1%)		4 (22.2%)	14 (77.8%)
35-39	9709 (99.8%)	17 (.2%)		6 (40%)	9 (60%)
>= 40	2268 (99.6%)	8 (.4%)		2 (25%)	6 (75%)
BMI					
< 30	17528 (99.9%)	19 (0.1%)		7 (36.8%)	12 (63.2%)
30- <35	9503 (99.9%)	14 (0.1%)		3 (21.4%)	11 (78.6%)
35- <40	4131 (99.9%)	5 (0.1%)		1 (20%)	4 (80%)

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>= 40	2657 (99.9%)	2 (0.1%)		1 (50%	1 (50%)
ASA					
I, II	29964 (99.9%)	24 (0.1%)		9 (37.5%)	15 (62.5%)
III	4612 (99.7%)	16 (0.3%)		3 (18.8%)	13 (81.3%)
IV	53 (98.1%)	1 (1.9%)		0 (0%)	1 (100%)
Emergent Status					
No	34211 (99.9%)	39 (0.1%)		12 (30.8%)	27 (69.2%)
Yes	421 (99.5%)	2 (0.5%)		0 (0.0%)	2 (100.0%)
Race					
Black, non-Hispanic	3998 (99.8%)	10 (0.2%)		4 (40.0%)	6 (60.0%)
White, non-Hispanic	20113 (99.9%)	16 (0.1%)		4 (25.0%)	12 (75.0%)
Other	5234 (99.9%)	6 (0.1%)		1 (20.0%)	4 (80.0%)
Unknown	5287 (99.8%)	9 (0.2%)		3 (33.3%)	6 (66.7%)
Obstetric Anesthesia Type					
Labor Epidural	22543 (>99.95%)	5 (<0.05%)		3 (60.0%)	2 (40.0%)
Conversion to Cesarean (or C-Hyst)	4117 (99.7%)	13 (0.3%)		3 (23.1%)	10 (76.9%)
(Planned) Cesarean	7893 (99.1%)	7 (0.1%)		2 (28.6%)	5 (71.4%)
(Planned) Cesarean, (Planned/Unplanned) Hysterectomy	79 (83.2%)	16 (16.8%)		4 (25.0%)	12 (75.0%)
General Anesthesia					
No	321 (96.1%)	13 (3.9%)		9 (32.1%)	19 (67.9%)
Yes	34311 (99.9%)	28 (0.1%)		3 (23.1%)	10 (76.9%)

COMORBIDITIES	**Large Volume Transfusion?**				**Balanced Transfusion?**		
Preterm Delivery	No	Yes	Frequency in Background Population		No	Yes	Frequency in LVT Population
No	32817 (99.9%)	37 (0.1%)			10 (27.0%)	27 (73.0%)	
Yes	1815 (99.8%)	4 (0.2%)	1819 (5.2%)		2 (50.0%)	2 (50.0%)	4 (9.8%)
Multiple Gestation							
No	33535 (99.9%)	38 (0.1%)			12 (31.6%)	26 (68.4%)	

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Yes	1097 (99.7%)	3 (0.3%)	1100 (3.2%)		0 (0.0%)	3 (100.0%)	3 (7.3%)
Preeclampsia							
No	32056 (99.9%)	35 (0.1%)			11 (31.4%)	24 (68.6%)	
Yes	2576 (99.8%)	6 (0.2%)	2582 (7.4%)		1 (16.7%)	5 (83.3%)	6 (14.6%)
Chorioamnionitis							
No	30571 (99.9%)	31 (99.9%)			9 (29.0%)	22 (71.0%)	
Yes	4061 (99.8%)	10 (0.2%)	4071 (11.7%)		3 (30.0%)	7 (70.0%)	10 (24.4%)
Placental Abruption							
No	33800 (99.9%)	35 (0.1%)			9 (25.7%)	26 (74.3%)	
Yes	832 (99.3%)	6 (0.7%)	838 (2.4%)		3 (50.0%)	3 (50.0%)	6 (14.6%)
Placenta Previa							
No	33448 (99.9%)	22 (0.1%)			9 (40.9%)	13 (59.1%)	
Yes	1184 (98.4%)	19 (1.6%)	1203 (3.5%)		3 (15.8%)	16 (84.2%)	19 (46.3%)
Placenta Accreta Spectrum							
No	34310 (99.9%)	23 (0.1%)			10 (43.5%)	13 (56.5%)	
Yes	322 (94.7%)	18 (5.3%)	340 (1.0%)		2 (11.1%)	16 (88.9%)	18 (43.9%)
Diabetes							
No	34194 (99.9%)	40 (0.1%)			12 (30.0%)	28 (70.0%)	
Yes	438 (99.8%)	1 (0.2%)	439 (1.3%)		0 (0.0%)	1 (100.0%)	1 (2.4%)
OUTCOMES/COMPLICATIONS	**Large Volume Transfusion?**				**Balanced Transfusion?**		
Death	No	Yes	Frequency in Background Population		No	Yes	Frequency in LVT Population
No	34631 (99.9%)	41 (0.1%)			12 (29.3%)	29 (70.7%)	
Yes	1 (100.0%)	0 (0.0%)	1 (<0.05%)		0	0	0 (0.0%)
Thromboembolism							
No	34588 (99.9%)	41 (0.1%)			12 (29.3%)	29 (70.7%)	
Yes	44 (100.0%)	0 (0.0%)	44 (0.1%)		0	0	0 (0.0%)
ARDS							
No	34598 (99.9%)	31 (0.1%)			8 (25.8%)	23 (74.2%)	
Yes	34 (77.3%)	10 (22.7%)	44 (0.1%)		4 (40.0%)	6 (60.0%)	10 (24.4%)
Acute Renal Failure							
No	34340 (99.9%)	34 (0.1%)			10 (29.4%)	24 (70.6%)	
Yes	292 (97.7%)	7 (2.3%)	299 (0.9%)		2 (28.6%)	5 (71.4%)	7 (17.1%)
Stillbirth							
No	34363 (99.9%)	39 (0.1%)			12 (30.8%)	27 (69.2%)	
Yes	269 (99.3%)	2 (0.7%)	271 (0.8%)		0 (0.0%)	2 (100.0%)	2 (4.9%)

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Acute Heart Failure w/ Pulmonary Edema							
No	34578 (99.9%)	39 (0.1%)			11 (28.2%)	28 (71.8%)	
Yes	54 (96.4%)	2 (3.6%)	56 (0.2%)		1 (50.0%)	1 (50.0%)	2 (4.9%)
Mean Post-Delivery Length of Stay (SD)							
Labor Epidural	2.41 (.77)	3.4 (.89)			3 (0)	4 (1.41)	
Conversion to Cesarean (or C-Hyst)	4.46 (1.06)	6.3 (2.19)			7 (2.65)	6.11 (2.15)	
(Planned) Cesarean	3.77 (1.10)	6.57 (5.00)			8.5 (4.95)	5.8 (5.35)	
(Planned) Cesarean, (Planned/Unplanned) Hysterectomy	4.05 (.85)	4.88 (1.09)			5.75 (1.71)	4.58 (.67)	

*Note: Cases from 2015 included in this estimate.

Areas for discussion

This project has several limitations, primarily related to issues of data quality. MPOG relies on data being accurately reported by individual institutions, and in our experience certain parameters tend to be accurately and consistently reported, such as most intraoperative medications, whereas other parameters tend to have more missing data and variability between institutions, such as factor concentrates or medications administered outside of the operating room. Consequently, our data may vary in quality between institutions, and cases that take place across multiple settings (e.g., labor epidural to Cesarean delivery) may likewise have variable quality. We have discussed these limitations, as well as the steps we are taking to mitigate them, in the ‘Threats’ section above. We welcome any input on additional steps that we can take to mitigate these issues.

Additionally, while this study will represent one of the largest studies of transfusions in obstetric hemorrhage to have data this granular, it is still expected to have less than 1,500 observations. Therefore, we may be inadequately powered to investigate practice variations beyond ~2 levels, detect certain outcomes, or control for particular comorbidities in our analyses.

We also wish to discuss our approach of classifying transfusions as ‘large volume’ and our inclusion criteria. We selected this term instead of ‘massive’, as well as our threshold of 4 or more pRBCs, in order to be inclusive of competing definitions of ‘massive.’ Additionally, based on our own experience we believe that 4 pRBCs is frequently a trigger to begin administering FFP, whereas smaller transfusion volumes are more likely to be limited to pRBCs. However, we welcome discussion as to whether our threshold should be more inclusive. Finally, as the more commonly used definitions of ‘massive’ transfusion have cutoffs of 8-10 pRBCs, we intend to follow this project with a second publication that focuses on this subgroup in greater detail.

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APPENDIX A – Criteria for Case Selection

Below are the criteria that will be used to initially flag patients. Please see attached query specification template for full list of variables needed.

Initial Criteria for Identifying Obstetric Patients

Phenotype Name / Concept ID	Notes
Starting Population: Outcome Research Standard - Mortality	Must meet intraoperative research standard with mortality data available, except blood pressure measurement not required
Case Start	Cases from 1/1/2016 to 12/31/2023
Obstetric Anesthesia Type	Any value other than 0 (“No”)
Case Duration	Duration is not NULL, and is >= 1 minute
Institution	Institution ID

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APPENDIX B – Clinically Relevant Comorbidities

Clinically relevant comorbidities will be defined by the following ICD10 codes:

Comorbidity	ICD10 Codes
Preterm Delivery	ICD10: O60.1x
Multiple Gestation	ICD10: O30.x
Presence of Pre-Eclampsia or Eclampsia	ICD10: O11.x, O14.x, O15.x, or MPOG Phenotype
Chorioamnionitis	ICD10: O41.1x
Placental Abruption	ICD10: O45.x
Placenta Previa	ICD10: O44.x
Placenta Accreta Spectrum	ICD10: O43.2x
Diabetes Mellitus	ICD10: E08.x, E09.x, E10.x, E11.x, E13.x

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APPENDIX C – Outcome Diagnoses

Clinically relevant comorbidities will be defined by the following ICD10 codes:

Comorbidity	ICD10 Codes
Postoperative Mechanical Ventilation	5A1935Z, 5A1945Z, 5A1955Z
Transfusion-Related Acute Lung Injury	ICD10: J95.84
Transfusion-Associated Circulatory Overload	ICD10: O11.x, O14.x, O15.x
Acute Respiratory Distress Syndrome / Acute Respiratory Failure	J80, J95.22, J95.821, J95.822, J96.00, J96.01, J96.02, J96.20, J96.21, J96.22, J96.90, J96.91, J96.92, R09.2
Acute Kidney Injury	ICD10: O41.1x or MPOG phenotype
Acute Renal Failure	N17.0, N17.1, N17.2, N17.8, N17.9, N99.0, O90.4, O90.49
Deep Venous Thrombosis	ICD10: I82.4*, I82.4Y9, I82.4Z*, I82.6*
Pulmonary Embolism	ICD10: I26.9*

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Reporting Guidelines Checklist

Please review the EQUATOR Network, determine the appropriate guidelines for reporting your proposal, use the checklist associated with those guidelines. Common examples include:

- Routinely collected EHR data (MPOG data) - RECORD extension of STROBE guidelines
- Clinical prediction or diagnostic models - TRIPOD guidelines
- Quality Improvement Studies - SQUIRE guidelines

For convenience, the most common checklist for MPOG studies – the RECORD extension of the STROBE guidelines – is listed below, but please replace with the appropriate checklist if needed.

	Item No.	STROBE items	Page #	RECORD items	Page #
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	3		
Objectives	3	State specific objectives, including any prespecified hypotheses	3		
Methods					
Study Design	4	Present key elements of study design early in the paper	3		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	3-4	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the	3-4

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		Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	4-6; Appendix C	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	3-4; Appendix A; Appendix B
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6; Appendix C		
Bias	9	Describe any efforts to address potential sources of bias	6-8; Appendix C		
Study size	10	Explain how the study size was arrived at	**N/A, descriptive**		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	5-6		
Data access and cleaning methods				RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	3
Linkage				RECORD 12.3: State whether the study included person-level, institutional-level, or	N/A

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				other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	***N/A for PCRC***	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	***N/A for PCRC***
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	***N/A for PCRC***		***N/A for PCRC***
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	***N/A for PCRC***		***N/A for PCRC***
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	***N/A for PCRC***		***N/A for PCRC***
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	***N/A for PCRC***		***N/A for PCRC***
Discussion					
Key results	18	Summarize key results with reference to study objectives	***N/A for PCRC***		***N/A for PCRC***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6-9	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	6-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity	***N/A for***		***N/A for***

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		of analyses, results from similar studies, and other relevant evidence	***PCRC***		***PCRC***
Generalisability	21	Discuss the generalisability (external validity) of the study results	***N/A for PCRC***		***N/A for PCRC***
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Departmental Funding		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	N/A