The Epidemiology of Multiple Blood Component Transfusion

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the M.Sc. degree in Epidemiology

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Table of Contents

Synopsis

Multicomponent transfusion, or the transfusion of two or more different blood products, has been poorly studied to date, as most of the existing literature has focused on the use of individual blood products. This is of concern as multicomponent transfusion recipients likely differ with respect to characteristics and health outcomes from patients transfused with only one type of blood component (e.g. greater illness severity). Consequently, available data on individual blood product use and outcomes may not be applicable to multicomponent transfused patients. This thesis project identified and synthesized existing literature on the epidemiology of multicomponent transfusion in hospital inpatients, as well as the characteristics and outcomes of its recipients. Based on 37 observational studies, we found that the prevalence of multicomponent transfusion varied greatly by patient population, transfusion timeframe, and type of multicomponent transfusion being studied. The most common types of multicomponent transfusion across the 37 studies were co-transfusions of red blood cells (RBCs) and platelets, and co-transfusions of RBCs and plasma. Multicomponent transfusion was found to be associated with several negative health outcomes, however this was based on low quality evidence due to lack of control for confounding by indication. Our systematic review on multicomponent transfusion identified several knowledge gaps, including the need for studies focusing on patients with hematological malignancies, and studies identifying patient characteristics predictive of multicomponent transfusion. To address areas of knowledge deficiency, and to characterize multicomponent transfusion locally at our own center, we designed and conducted a retrospective cohort study of adult, transfused hospital inpatients. Based on 55,719 transfused inpatient admissions at the Ottawa

Hospital between 2007 and 2017, we calculated the overall prevalence of multicomponent transfusion to be 25.1% (95% CI: 24.7%, 25.5%). Similar to the findings of our systematic review, the prevalence varied greatly by patient type, transfusion timeframe, and type of multicomponent transfusion. In particular, in hematology patients, the prevalence of multicomponent transfusion was 51%. Other patient groups frequently receiving multicomponent transfusions at our institution were cardiac surgery, critical care, cardiology, vascular surgery, trauma, surgery, and internal medicine patients. Using multivariable regression analysis, we found that patient sex, age, and type were predictive of multicomponent transfusion requirement. Additionally, controlling for illness severity and burden, multicomponent transfusion was associated with increased odds of in-hospital mortality, institutional discharge compared to discharge home, and greater length of hospital stay compared to patients transfused with only RBCs. Given our findings that multicomponent transfusion recipients make up a large proportion of transfused hospital patients, and that they have poorer outcomes, it is of importance to continue characterizing these patients – and not only focus on patients receiving a single type of blood component – and to evaluate and monitor the appropriateness of multicomponent transfusion. Additionally, as transfusion practice and guidelines are known to vary from region to region, it is important to study multicomponent transfusion locally, as generalizing results from other studies and centers may not be appropriate. Obtaining robust information on multicomponent transfusion – including prevalence, predictors, and potential health consequences – can aid clinicians in their decision-making for patient blood management, potentially minimizing unnecessary patient exposure to blood

products, and maximizing the use of transfusion alternatives and blood conservation methods.

Acknowledgements

First, to my thesis supervisor, Dr. Dean Fergusson, thank you for giving me the opportunity of working on this project and for your guidance and mentorship throughout the past 2 years. Your expertise in epidemiology and transfusion medicine research is unparalleled and inspiring; to learn from you is truly to learn from the best.

To my TAC committee, Dr. Elianna Saidenberg and Dr. Alan Tinmouth, I am indebted to you for your invaluable clinical and methodological guidance. Your clinical lens into transfusion medicine gave this research context and applicability, without which this work would not have been possible. I am truly thankful for your time and input.

I would also like to thank everyone else who has helped me during the course of this thesis. Dr. Malia Murphy, thank you for your help with obtaining research ethics approval. To Simonne Khair and Emily Dermer, thank you for taking the time out of your busy medical student schedules to help me with article screening and data abstraction, and for doing a thorough and excellent job as second reviewers. I am very grateful to Ms. Jo Ann Colas and Mr. Pedram Noghani for their help with navigating and obtaining data from the Transfusion Data Mart and the Ottawa Hospital Data Warehouse. I would also like to thank Dr. Tim Ramsay for his knowledgeable guidance on statistical matters.

Finally, I would thank my parents and my sister for their constant support and motivation. And to my partner Jesse, I am so very grateful for your unwavering love and support.

Funding

This thesis received funding from an Ontario Graduate Scholarship award, the University of Ottawa Excellence Scholarship, and a stipend from the University of Ottawa/Ottawa Hospital Research Institute Centre for Transfusion Research, which was funded by a Canadian Blood Services Infrastructure Grant.

Figures Index

Chapter 2

Chapter 3

Chapter 4

Tables Index

Chapter 2

Chapter 3

Chapter 4

Chapter 1: Thesis Introduction and Overview

Problem

Studies characterizing transfusion recipients and utilization of blood products are important as they identify trends in transfusion practice, describe the characteristics of transfused patients, and monitor post-transfusion health outcomes. However, such studies generally either focus on a single blood component type (e.g. only describe red blood cell (RBC) usage and recipients), or they analyze different blood components separately (e.g. RBC recipients separate from platelet (PLT) transfusion recipients, separate from plasma (FP) recipients, etc.) [1-16]. However, by doing so, patients who are transfused with more than one type of blood product during a transfusion episode (multicomponent transfused patients) are overlooked or are inadequately captured, creating evidence and knowledge gaps regarding the epidemiology of multicomponent transfusion and its health outcomes.

It would be incorrect to assume that multicomponent transfused patients have the same characteristics and health outcomes as individuals transfused with only one type of blood product. Logically, the necessity of transfusing a patient with two or more different types of blood components, as compared to only one type, indicates greater illness severity or acuity, or a very different clinical indication for transfusion. There may also exist other differences in patient characteristics and health outcomes between multicomponent transfused individuals and those transfused with only one type of blood product. Thus, existing studies on transfusion recipients examining different blood products separately are insufficient to inform multicomponent transfusion practices, and studies looking specifically at multicomponent transfusion recipients are needed in order to better

characterize this patient population and to determine how they compare to recipients of only one blood product type.

Purpose and Rationale

The purpose of this thesis is to investigate the phenomenon of multicomponent blood transfusion with respect to its prevalence, trends over time, and to characterize the hospital patients who are commonly multicomponent transfused. Such information can be used to resolve the current knowledge gap on the epidemiology of multicomponent transfusion and its recipients. There is also a need to gain a more thorough knowledge of multicomponent transfusion practice in various patient populations in order to assess its appropriateness. This in turn can help identify patient groups – if any exist – where multicomponent transfusion practice can be improved and where more blood conservation techniques or transfusion alternatives can be applied. Finally, as transfusion practice is known to vary by region and even by hospital, it is of importance to investigate multicomponent transfusion locally at our own institution – The Ottawa Hospital – as generalizing results from other studies and centres may be inappropriate and inaccurate.

Objectives

Given lack of knowledge on multicomponent transfusion, the objectives of this thesis are as follows:

(1) To determine and synthesize what is already known on the epidemiology of multicomponent transfusion; specifically, to determine its incidence and

prevalence, and to characterize the hospital patient groups receiving multicomponent transfusion.

(2) To describe the epidemiology of multicomponent transfusion at the Ottawa Hospital between 2007 and 2017; in particular, looking at multicomponent transfusion prevalence, trends in time, and the patient groups being multicomponent transfused.

(3) To determine patient characteristics and outcomes associated with multicomponent transfusion, and to compare these with those of patients transfused with only RBCs (RBCs were chosen as the comparator as they are the most commonly transfused individual blood product type).

Overview of Thesis and Manuscripts

This thesis is based on two separate studies, which together address the three thesis objectives presented above. The first study, presented in Chapter 2, is a systematic review that fulfills the first objective of synthesizing the existing literature on multicomponent transfusion. The second study is a retrospective cohort spanning 11 years of inpatient admissions at the Ottawa Hospital, from 2007 to 2017, and is presented in Chapters 3 and 4. Chapter 3 describes the formation of the retrospective study cohort in detail, while Chapter 4 presents the study itself. This first part of the retrospective cohort study is descriptive in nature and addresses objective #2, while the second part of the study is analytical and addresses objective #3 through the use of regression analyses. An overall synthesis and discussion of findings from both studies is presented in Chapter 5.

Chapter 2: The epidemiology of multicomponent blood transfusion: A systematic review (*Manuscript 1*)

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Author Contributions

Dr. Fergusson (thesis supervisor), Dr. Tinmouth (TAC member) and Dr. Saidenberg (TAC member) were involved in the conception and design of the study, as well as critically revising the manuscript. Dr. Fergusson also provided guidance with data analysis. Ms. Simonne Khair and Ms. Emily Dermer were second reviewers and participated in article selection and data abstraction.

Publication Information

As of January 31, 2019, this study has been accepted for publication in *Transfusion Medicine*. See Appendix A at the end of the thesis for the letter of acceptance. Due to copyright agreements, the submitted version of the manuscript (not the accepted version) is presented here.

Additional Information

All tables, figures, and appendices relating to the study are found at the end of the manuscript. A PRISMA checklist for this study can be found in Appendix B at the end of the thesis.

ABSTRACT

Objectives: We performed a systematic review to describe the prevalence of multicomponent blood transfusion, and as a secondary objective, to determine patient characteristics and outcomes associated with multicomponent transfusion.

Background: There is a lack of literature on the epidemiology of multicomponent transfusion, as most studies concentrate on a single blood product and its utilization. Patient care and blood management can be optimized by better understanding the patients that receive multicomponent transfusions.

Methods: The databases Medline, EMBASE, and the Cochrane Library of Systematic Reviews were searched. Observational cohort and cross-sectional studies of hospital patients reporting on multicomponent transfusion prevalence, or on patient characteristics and outcomes associated with multicomponent transfusion, were included. A descriptive synthesis of studies was performed.

Results: A total of 37 eligible studies were included. It was found that multicomponent transfusion prevalence varied greatly by patient population and by the combination of blood products given in the multicomponent transfusion. Multicomponent transfused patients included burn, cardiac surgery, liver surgery and transplant, cancer, infectious diseases, trauma, and ICU patients. Five studies found associations between multicomponent transfusion and adverse health outcomes; however, these findings are likely confounded by indication. The overall quality of evidence was low, given a fair-to-poor individual study quality, inconsistent multicomponent transfusion prevalence estimates, and confounding by indication.

Conclusion: Further research is needed to better understand the epidemiology of multicomponent transfusion, including studies on multicomponent transfusion in hematologic cancer patients, and studies looking for patient characteristics that can better predict multicomponent transfusion need.

Keywords: systematic review, blood transfusion, epidemiology, prevalence, red blood cells, platelets, plasma, cryoprecipitate

INTRODUCTION

Red blood cell (RBC) transfusion is the most frequent medical procedure performed in hospitalized patients, with over 100 million units collected and administered worldwide each year (Pfuntner *et al.* 2013, World Health Organization 2017). The primary reasons for RBC transfusion are low hemoglobin levels and/or symptomatic anemia (Carson *et al.* 2016). Patients may also be transfused other blood components, including platelets (PLTs), frozen plasma (FP), and cryoprecipitate during their hospital stay. Platelet transfusions are indicated in patients with disorders of platelet number or function, as prophylaxis or treatment for bleeding (Kaufman *et al.* 2015). Plasma transfusions are primarily given for restoration of plasma coagulation factors, either prophylactically or to treat bleeding (Roback *et al.* 2010). Cryoprecipitate, prepared from plasma, is primarily administered as a source of fibrinogen replacement to prevent or treat bleeding in patients with acquired or congenital fibrinogen deficiency (Clarke 2013).

Hospital utilization of blood components, as well as the characteristics and outcomes of transfused patients, have been well-studied. However, previous studies typically report on blood utilization and patient outcomes separately for each unique blood component type, or only report findings for one type of product (e.g. only RBCs) (Wells *et al.* 2009, Borkent-Raven *et al.* 2010, Shehata *et al.* 2014, Barr *et al.* 2010). While it is useful to know individual blood component use, there are a number of reasons why it is also valuable to characterize patients who are co-transfused with several different types of blood products within a transfusion episode (multicomponent transfused patients). First, due to their need for multiple blood components, multicomponent transfusion recipients are heavy consumers of blood products in the hospital. Secondly, these patients have

different characteristics compared to those receiving transfusions of only one blood component; often, multicomponent transfused patients are more complex or more acutely ill. As such, studies that have previously described characteristics of transfused patients by single blood components do not represent the multicomponent transfused patient, and are not generalizable to this patient group. In order to make evidence-based transfusion decisions in multicomponent transfused patients, knowledge of their clinical and demographic features is required. Additionally, multicomponent transfused recipients may have different health outcomes due to co-transfusions of various blood components, as opposed to only one component. As the risk of transfusion reactions, particularly non-infectious ones, varies by blood component (Callum *et al.* 2017, MacDonald *et al.* 2012, Pandey & Vyas 2013), multicomponent transfused patients may have a different risk profile for transfusion reactions compared to recipients of single blood components, and studies looking specifically at co-transfusion of blood products are needed to characterize this risk.

Currently, the large majority of the literature addressing transfusions of multiple blood components is in the field of trauma, with studies aiming to determine the best ratio of RBCs to PLTs to FP for bleeding management in trauma patients. Such studies, however, do not describe the characteristics and outcomes of multicomponent transfusion recipients outside of trauma management. As such, there is a lack of literature on the epidemiology of multicomponent transfusion and of multicomponent transfused patients.

Characterizing multicomponent transfusion recipients and trends across patient groups is of importance from both a clinical and a system level perspective. From a clinical point

of view, investigating multicomponent transfusion use in the hospital can help improve patient blood management. By evaluating the appropriateness of multicomponent transfusions in various patient groups, some unnecessary patient exposure to the risks of transfusion could be avoided (Goodnough & Shander 2012). This is of particular importance for multicomponent transfusion recipients, as they are at greater risk of adverse outcomes related to transfusion. Furthermore, with the current focus of existing transfusion literature on individual blood components, investigating multicomponent transfusion and its risks and benefits can help increase physician awareness on this topic and enable better decision-making and patient care with respect to transfusion therapy. At the system level, an understanding of the distribution of blood products in the hospital can help optimize the allocation of blood products across hospital departments.

Given the evidence and knowledge gaps on transfusions of multiple blood components, the purpose of this systematic review was to synthesize current literature on the epidemiology of multicomponent transfusion in adult and pediatric hospital patients. The primary objective was to determine the incidence and prevalence of multicomponent transfusion, and to characterize which patient groups receive multicomponent transfusions. The secondary objective was to determine patient characteristics and health outcomes associated with multicomponent transfusion.

METHODS

This systematic review was performed in accordance with the PRISMA statement and guidelines (Moher *et al.* 2009). The protocol for this systematic review is registered on PROSPERO (CRD42017080060).

Inclusion Criteria

Prospective and retrospective cohorts and cross-sectional studies investigating hospital patients of any age exposed to multicomponent transfusions were eligible. Multicomponent transfusion was defined as a transfusion of two or more different blood components (RBCs, PLTs, FP, cryoprecipitate and/or whole blood) during a transfusion episode. Transfusion episode timeframes were classified as peri-operative transfusions (intra-operative and within 48h of surgery), transfusions within 24h of hospital admission, same-day transfusions, or transfusions throughout an index hospital admission. Studies where the exposure focused on transfusions of one blood component, but where co-transfusion of other blood products was reported were eligible. Eligible comparator groups included no comparator, non-transfused patients, or patients transfused with only one blood component. The primary outcome of interest was the incidence or prevalence of multicomponent transfusion. Studies reporting on the incidence or prevalence of multicomponent transfusion for only a subgroup of their study population were eligible. Multicomponent transfusion incidence was defined as the number of first or "new" multicomponent transfusion occurrences divided by the total number of patients at risk over a specified period of time, and multicomponent transfusion prevalence was defined as the total number of multicomponent transfusion occurrences divided by the total number of patients over a given time interval. The secondary outcome was any patient characteristic or health outcome associated with multicomponent transfusion, along with a measure of strength of association (relative risk, odds ratio, hazard ratio, risk difference, etc.). Studies reporting at least one of our *a*

priori outcomes of interest were included. Post-hoc, another secondary outcome was assessed: the amount of units transfused (mean or median) for each blood component in a multicomponent transfusion. This outcome was added in order to quantify the consumption of blood products in multicomponent transfusions. Full-text, peer-reviewed studies in any language meeting the above criteria were accepted. Conference abstracts without a corresponding full-text publication were also accepted, if enough information was present in the abstract to determine its eligibility. Abstracts were included because from the authors' knowledge of the field, many relevant studies are disseminated only as conference abstracts; as such, failing to include these studies would not capture all the available evidence on the topic of multicomponent transfusion.

Exclusion Criteria

Duplicate publications, case reports and case series were excluded. Case-control studies and clinical trials were not included, because these study designs cannot provide a population-level estimate of prevalence or incidence of multicomponent transfusion.

Search Strategy

A comprehensive search strategy was developed with the guidance of an information specialist. The databases Medline (Ovid), EMBASE (Ovid), and the Cochrane Database of Systematic Reviews were searched without limits from inception until August 2017 using combinations of relevant keywords and Medical Subject Headings. Database searching was supplemented by manual screening of reference lists of identified studies and relevant systematic reviews. Citations were stored and managed using EndNote (Clarivate Analytics, New York, USA).

Study Selection and Data Abstraction

All aspects of study selection and data abstraction were performed independently and in duplicate by three reviewers. Disagreements were settled through discussion, and when necessary another study author was consulted. Titles and abstracts of citations retrieved by the database search were screened based on the eligibility criteria, and relevant articles were read in full-text. Ineligible studies were excluded with reasons documented. Eligible studies were abstracted using a standardized, piloted form.

Risk of Bias Assessment

Risk of bias was assessed at the study level for each eligible study by three reviewers independently and in duplicate. The National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to evaluate study quality, and studies were rated as having a high, fair, or poor quality (National Heart, Blood, and Lung Institute 2017).

Overall Quality of Evidence and Meta-Biases Assessment

The overall quality of the evidence was assessed using GRADE methodology, and was rated as high, moderate, low, or very low (Balshem *et al.* 2011). Meta-biases that could affect the quality of evidence, including publication bias, language bias, and duplicate publication bias, were assessed and minimized.

Data Analysis

A descriptive synthesis of study characteristics and outcomes of interest was performed. For the primary outcome, multicomponent transfusion incidence and prevalence were

analyzed according to various factors that may influence them, including patient population (medical condition or reason for hospitalization), type of multicomponent transfusion administered, timing of transfusion, and date of study publication (as multicomponent transfusion frequency may change over time, given changes in transfusion practice and guidelines), among other factors. Meta-analysis for the primary outcome was not possible due to the presence of significant heterogeneity of study characteristics, including varying patient populations and types of multicomponent transfusions administered. Meta-analysis for the secondary outcome was not possible due to different patient outcomes and types of multicomponent transfusion reported. Meta-analysis for the post-hoc secondary outcome was not feasible due to insufficient data from our included studies for meta-analysis.

RESULTS

Literature Search Results

A total of 3,157 citations were retrieved from the systematic search (figure 1). Following duplicate removal, 2,423 articles were screened based on title and abstract. One hundred and seventy-five relevant studies were then reviewed in full-text. Of these, 138 were excluded with reasons documented (figure 1), and 37 eligible studies were included. A reference list of the included studies is shown in Appendix A.

Summary of Study Characteristics

Twenty-nine (78%) of the included studies were full-text publications, while 8 (22%) were conference abstracts. Study designs included 26 retrospective cohorts (70%), 8 prospective cohorts (22%), and 3 cross-sectional surveys (8%). Publication date ranged

from 1987 to 2017, with the majority of studies (81%) published in 2010 or later. Studies were conducted in a wide variety of regions, with 15 in North America, one in South America, 11 in Europe, 9 in Asia, and one in Africa. Twenty-one studies (57%) were conducted at a single hospital, while 16 studies (43%) were multi-center. A diverse range of patient populations were investigated, including burn patients (two studies), cardiac surgery patients (eight studies), cancer patients (one study), ICU patients (two studies), infectious disease patients (one study), liver transplant or surgery patients (four studies), trauma patients (five studies), transfused hospital patients (seven studies), massively transfused patients (five studies), and any hospital patients (two studies). Twenty-five studies (67%) included adult patients, four studies (11%) investigated pediatric patients, and eight studies (22%) included patients of all ages. Study sample size ranged from 26 to 748,509 participants. Table 1 presents further information on general study characteristics.

Incidence and Prevalence of Multicomponent Transfusion

Thirty-four studies (92%) reported multicomponent transfusion prevalence, and none (0%) reported incidence (table 2). Multicomponent transfusion prevalence varied greatly across studies, depending on the patient population, specific types of multicomponent transfusion, the timing of transfusion, date of study publication, as well as other factors.

Multicomponent Transfusion Prevalence by Timing of Transfusion, Patient Population, and Type of Multicomponent Transfusion

Multicomponent transfusion prevalence according to the timing of transfusion, patient type, and type of multicomponent transfusion is provided in table 2.

Multicomponent transfusion within 24h of hospital admission was investigated by three studies on massively transfused patients, including trauma, obstetric hemorrhage and surgical patients (table 2). Overall, the prevalence of multicomponent transfusion within one day of hospital admission in this patient group ranged from 4.4% to 80.6%, depending on the blood product combination transfused. Co-transfusions of RBCs and FP were most frequent, with prevalence ranging from 23.1% to 80.6%.

One study looked at same-day multicomponent transfusions in pediatric intensive care patients (DeSimone *et al.* 2016). The investigators found that the prevalence of co-transfusions of cryoprecipitate with another blood component ranged from 45.5% to 61.4%, with the most common combination being FP and cryoprecipitate (table 2). Eight studies investigated peri-operative multicomponent transfusion in either cardiac or liver surgery, including intra-operative co-transfusions and those within 48h of surgery (table 2). In cardiac surgery (five studies), the prevalence of peri-operative multicomponent transfusion was 2.2% to 12.9%, depending on the type of co-transfusion. The most prevalent blood product combination was RBCs with PLTs and FP (table 2). The prevalence of peri-operative multicomponent transfusion in transfused liver surgery patients (three studies) was 14.3% to 42.9%. Co-transfusions of PLTs with FP, and co-transfusions of RBCs with PLTs and FP were common in this patient population (table 2).

Twenty-two studies investigated multicomponent at any time during the index hospital admission (table 2). The prevalence of multicomponent transfusion in transfused hospital patients was 0.4% to 77.3%, with variation by type of co-transfusion and patient

population. RBCs and PLT, and RBCs with FP, were the most frequently administered combinations during the course of the hospital stay. In massively transfused patients, multicomponent transfusion prevalence ranged from 23.5% to 99%, with the most common co-transfusion being RBCs with FP. For trauma patients specifically, multicomponent transfusion prevalence ranged from 0.1% to 48.6% for all trauma patients, and from 0.1% to 70.9% for transfused trauma patients. Co-transfusions of RBCs with FP were also most common in trauma patients. Multicomponent transfusion occurred in 9.9% to 44.9% of all burn patients and approximately 28.6% of those transfused. We identified single studies that assessed multicomponent transfusion prevalence in Ewing sarcoma cancer patients, dengue hemorrhagic fever patients, and neonatal intensive care patients, with prevalence varying by patient population and co-transfusion type (table 2).

Figure 2 presents the prevalence estimates for each type of co-transfusion by patient population. The most common types of multicomponent transfusion were RBCs with PLTs, and RBCs with FP (figure 2, table 2). Specific patient groups receiving RBC and PLT co-transfusions were massively transfused trauma, surgical, and obstetric patients, cardiac surgery patients, and Ewing sarcoma patients. Patient populations transfused with RBCs and FP were similar to those receiving RBC and PLT co-transfusions (figure 2).

Multicomponent Transfusion Prevalence by Date of Study Publication

Two studies were published in the 1980s, two in the 1990s, four between 2000 and 2010, and 29 from 2011 to 2017. The prevalence of multicomponent transfusion depended less on the date or decade of study publication, and more on the patient population and type of

multicomponent transfusion administered (table 2). For instance, the prevalence of multicomponent transfusion in studies published between 2011 and 2017 ranged from 0% to 99%, but prevalence estimates were narrower and more similar when looking at studies within one patient population and one type of multicomponent transfusion (table 2). Of our included studies, Sovic *et al.* (2014) investigated the change in multicomponent transfusion over time at their hospital and found that prevalence estimates fluctuated slightly over an 11-year period, but without any distinct increasing or decreasing trend over time. Brouwers *et al.* (2017) also examined multicomponent transfusion prevalence over time and found that prevalence estimates remained stable during their four-year study period.

Other Factors Influencing Multicomponent Transfusion Prevalence

Several studies found that multicomponent transfusion prevalence was also affected by other factors. Karafin *et al.* (2017) showed that multicomponent transfusion prevalence was generally similar between males and females, but that prevalence estimates varied greatly by age. Multicomponent transfusion prevalence peaked in children (one month to 20 years) and in older adults (>50 years), was low for adults (early 20s to 50 years), and was lowest in neonates (birth to one month) (Karafin *et al.* 2017). Brouwers and colleagues (2017) examined the change in multicomponent transfusion prevalence between different types of cardiac surgery, as well as between four hospitals. They found some variation in multicomponent transfusion prevalence between cardiac surgery types, and reported that center differences in prevalence estimates existed. Finally, Yang *et al*. (2017) investigated the change in multicomponent transfusion prevalence in massively transfused patients according to the amount of RBCs transfused. They found that patients

transfused with more RBC units were increasingly more likely to be co-transfused with platelets, plasma, and/or cryoprecipitate.

Association of Multicomponent Transfusion with Patient Characteristics and Health Outcomes

Five studies (14%) reported on associations between multicomponent transfusion and patient health outcomes (table 3). None of the studies reported crude measures of association; only adjusted measures were given, and variables controlled for differed by study and were not reported in three of the studies (table 3). In cardiac surgery patients, multicomponent transfusion was associated with a statistically significant increased odds of developing profound vasoplegia (Alfirevic *et al.* 2011), postoperative thromboembolic events (Miyata 2010, Ghazi *et al.* 2015), and postoperative stroke (Mikkola *et al.* 2012) (table 3). Large volume co-transfusions of RBCs and plasma were found to be associated with significantly increased odds of developing acute lung injury following liver transplant (Zhao *et al.* 2013) (table 3). No study reported on patient characteristics associated with multicomponent transfusion.

Blood Product Consumption in Multicomponent Transfusions

Two studies (5%), both in liver surgery, provided information on the amount of blood units administered in multicomponent transfusions (Kobayashi *et al.* 1999, Kobayashi *et al.* 1997). Blood consumption was high in multicomponent transfused liver surgery patients, with patients receiving on average over 65 units of blood in total, with the exact amount varying by type of co-transfusion (table 2). The remaining studies (n=35, 95%)

did not report on the quantity of blood units transfused, or did not provide information specifically for multicomponent transfusions.

Risk of Bias Assessment

Study quality was fair for 30 (81%) studies and poor for seven (19%) studies (table 1). For the primary outcome of multicomponent transfusion prevalence, study quality was fair for most studies (88%). For the secondary outcome, study quality was poor for all five studies. Studies were rated as having a poor internal validity (high risk of bias) due to significant confounding by indication and residual confounding. Studies that were rated as having a fair study quality were those without major biases and confounding, however, some of these studies had unclear validity of exposure and outcome data from retrospective use of secondary data, and others had incorrect or unclear handling of missing data, which can introduce bias.

Overall Quality of Evidence and Meta-Biases

The overall quality of evidence synthesized by this systematic review was evaluated for each outcome using GRADE methodology (Appendix B). The quality of evidence was low for the primary outcome due to inconsistency of multicomponent transfusion prevalence estimates across studies. Quality of evidence was not downgraded for data coming from observational studies as opposed to clinical trials, as observational studies can provide more generalizable prevalence estimates compared to clinical trials. For the secondary outcome, the overall quality of evidence was low due to poor internal validity of studies stemming from confounding by indication and significant residual confounding. For the post-hoc secondary outcome, quality of evidence was very low due

to indirectness of information, since both studies that reported on this outcome investigated only liver surgery patients, however multicomponent transfusion blood consumption is of interest in many other patient populations, and cannot be generalized from liver surgery patients.

Biases at the systematic review level were minimized and avoided where possible. Language bias was reduced by including studies written in any language. Duplicate publication bias was minimized by thorough article screening that was performed in duplicate. Publication bias could not be assessed due to insufficient data for funnel plot analysis.

DISCUSSION

Our research showed that there is significant variation in multicomponent transfusion between and within patient populations. Additionally, we found little reported evidence on the amount of blood consumed by multicomponent transfusion recipients. Knowledge of multicomponent transfusion utilization, trends, and recipients is needed to help improve patient care and patient blood management at both the local hospital level and the blood supplier level. Physician awareness of the risks and benefits of multicomponent transfusion can help optimize transfusion decision-making, leading to more appropriate transfusion practice, use of additional hemostatic therapies such as antifibrinolytics, and, potentially, the avoidance of unnecessary transfusions. Likewise, quantifying multicomponent transfusion use in the hospital can help optimize the allocation and use of this limited resource, avoid wastage, and plan for future consumption.

Patient populations shown to receive multicomponent transfusions included burn patients, cardiac surgery patients, cancer patients, intensive care patients, dengue hemorrhagic fever patients, liver transplant and surgery patients, and massively transfused patients, including obstetrics, surgery, and trauma patients. Multicomponent transfusion occurred in both adult and pediatric patient populations. Based on low quality evidence, the prevalence of multicomponent transfusion was highest in intensive care and trauma patients. Surprisingly, only one study reported on multicomponent transfusion specifically in cancer patients (Cesari *et al.* 2016), despite this patient population being a high consumer of blood transfusions (Karafin *et al.* 2017, Bosch *et al.* 2011, Wells *et al.* 2009). In particular, hematologic-oncology patients with hypoproliferative cytopenias are routinely transfused with multiple types of blood components (RBCs and platelets), however we found a lack of studies assessing multicomponent transfusion in this patient population. While there is strong evidence for the use of prophylactic platelet transfusions in these patients, there is little research regarding the use of sequential multi-component transfusion therapy (Kaufman *et al.* 2015). While it is very possible that multicomponent transfusion is beneficial for these patients, the best possible practices for delivering such therapy are not known. Local quality assurance studies in this population may help better characterize the nature of multicomponent transfusion in these patients and inform future prospective studies of multicomponent transfusion in patients with hypoproliferative bone marrow disorders.

Multicomponent transfusion prevalence varied not only across patient populations, but also by the type of multicomponent transfusion administered. Although most frequent combinations of blood products varied among patient populations, co-transfusions of

RBCs with plasma, and RBCs with platelets were generally most common. Multicomponent transfusions with cryoprecipitate were infrequent in most patient populations, being most commonly administered in massively transfused patients. However, it should be noted that the use of cryoprecipitate may have been under-estimated in studies if fibrinogen concentrate was administered instead of cryoprecipitate (Winearls *et al.* 2017, Forminsky *et al.* 2016). Based on limited data from two studies, multicomponent transfusion prevalence estimates did not vary greatly over time within patient populations, however, more data is needed prior to drawing conclusions regarding trends over time. Given the numerous changes in transfusion practice and guidelines that have occurred over the years, particularly a growing emphasis on minimizing patient exposure to blood transfusions and providing early plasma transfusions to trauma patients, it would not be surprising to see corresponding changes in multicomponent transfusion prevalence over time (Carson et al. 2012, Canadian Society for Transfusion Medicine 2014). Individual studies also suggested that other factors may influence the prevalence of multicomponent transfusion; however, these findings need to be corroborated by further studies.

Based on low quality evidence, multicomponent transfusions were found to be associated with several adverse outcomes, including profound vasoplegia, postoperative thromboembolic events and postoperative stroke in cardiac surgery patients, and acute lung injury in liver transplant patients. However, these associations are likely confounded by indication – wherein sicker patients are more likely to be transfused and multicomponent transfused, and sicker patients are also at a greater risk of developing adverse events. Consequently, illness severity may be the true cause of patient adverse

outcomes, instead of multicomponent transfusion. Observational studies are unable to fully disentangle true effects from confounding by indication, even with covariate adjustment in multivariable regression models. As such, associations reported by these studies may be entirely spurious and should be interpreted with great caution. Analytical methods such as instrumental variable analysis can be used to remove confounding by indication, however these methods are challenging and complex (Greenland 2000). At the very least, studies should adjust for illness severity and acuity in multivariable regression models, along with other relevant confounders, to attempt to reduce confounding by indication. Only one of the five studies in this systematic review reporting on associations between multicomponent transfusion and patient outcomes controlled for illness severity (Mikkola *et al.* 2012). Future studies in this area should consider adding a measure of illness severity to regression models, and should acknowledge the issue of confounding by indication when interpreting results.

While no studies formally examined associations between patient characteristics and multicomponent transfusion (e.g. through multivariable regression analysis), the study by Karafin and colleagues (2017) did suggest an association between patient age and multicomponent transfusion requirement based on descriptive analyses. This finding is of interest given that older adult patients account for a significant proportion of patients treated for oncologic and cardiovascular diseases, as well as other conditions that we found to be common indications for multicomponent transfusion (Christensen *et al.* 2009, Giannoudis *et al.* 2009, Mistry *et al.* 2011). As many countries have growing populations of older adults, further investigation of the association between age and multicomponent

transfusion requirement may enable hospitals and blood suppliers to better predict future blood product needs (Martel & Hagey 2017).

Going forward, studies describing the epidemiology of transfusion must analyze data from a multicomponent transfusion perspective, and should provide data on the utilization of blood products accounting for multicomponent transfusion, such as mean or total units. Otherwise, by overlooking multicomponent transfusion and the patients who receive it, we do not obtain the full picture of the epidemiology of blood transfusion. At the local (hospital) level, multicomponent transfusion prevalence and appropriateness should be assessed for each multicomponent transfused hospital patient population as part of quality control initiatives. Such analyses can also help with blood product inventory management in hospitals. Multicomponent transfusion use should also be assessed at the regional or national level to help blood supplying agencies plan blood product collection and distribution.

Our systematic review has several limitations. Firstly, multicomponent transfusion prevalence estimates from single-center studies may have a limited generalizability to other hospitals, regions and countries, as transfusion practice may change from location to location due to practitioner-related and organizational-level factors. Even prevalence estimates from multi-center studies may not be fully representative of multicomponent transfusion occurrence at the regional or national level; this would depend on the choice of hospitals for each study and how representative they are of all hospitals in the region of interest. Another factor limiting the generalizability of our results is that the availability of individual blood products may vary by country, which can impact

multicomponent transfusion prevalence rates. Secondly, there is a lack of prospective studies on the topic of multicomponent transfusion; most existing studies were retrospective, and were therefore limited by the disadvantages of their design. Finally, although we investigated different types and combinations of multicomponent transfusions, we did not analyze variations in individual blood components (e.g. leukoreduced versus non-leukoreduced products, whole blood versus apheresis platelets, etc.). However, such information was infrequently provided in our included studies.

CONCLUSION

Our systematic review identified multicomponent transfused groups in the hospital and found that multicomponent transfusion prevalence varied greatly by patient population and by type of multicomponent transfusion administered. Several studies found associations between multicomponent transfusion and adverse patient outcomes in cardiac surgery and liver transplant patients, but these results were likely confounded by indication, which should be better controlled for in future studies either by design or analysis. We identified several knowledge gaps, including the need for further studies on multicomponent transfusion in hematologic cancer patients, as well as studies identifying patient characteristics that are predictive of multicomponent transfusion.

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TABLES

Table 1. Summary of included studies (n=37) and risk of bias assessment, by study design and year of publication (most recent to oldest).

Study	Country	Publication Type	Study Design	Number of sites	Patient Population	Patient Age	Sample Size	Study Quality
Cesari (2016)	Italy	Full text	Prospective cohort	1	Ewing sarcoma patients	Adult	31	Fair
Stanworth (2016)	UK	Full text	Prospective cohort	22	Massively transfused trauma patients	Adult	442	Fair
Javadzadeh Shahshahani (2014)	Iran	Full text	Prospective cohort	3	Transfused hospital patients	All ages	814	Fair
Alfirevic (2011)	USA	Full text	Prospective cohort	1	Cardiac surgery patients	Adult	25,960	Poor
Miyata (2010)	Japan	Abstract	Prospective cohort	11	Cardiovascular surgery patients	Adult	1,429	Poor
Dunne (2008)	USA	Full text	Prospective cohort	1	Patients with severe military combat injuries	Adult	26	Fair
Kobayashi (1999)	Japan	Full text	Prospective cohort	1	Transfused liver surgery patients	Adult	55	Fair
Luban (1987)	USA	Full text	Prospective cohort	2	Transfused infants	Pediatric	100	Fair
Brouwers (2017)	Netherlands	Full text	Retrospective cohort	4	Cardiac surgery patients	Adult	11,150	Fair
Green (2017)	UK	Abstract	Retrospective cohort	2	Massively transfused patients	Adult	701	Fair
Karafin (2017)	USA	Full text	Retrospective cohort	12	Hospital patients	All ages	748,509	Fair
Yang (2017)	China	Full text	Retrospective cohort	20	Massively transfused patients	Adult	1,048	Fair

DeSimone (2016)	USA	Full text	Retrospective cohort	1	PICU patients transfused with cryoprecipitate	Pediatric	44	Fair
Green (2016)	UK	Full text	Retrospective cohort	Multi-center (number of sites not specified)	Massively transfused pregnant women	Adult	181	Fair
Koljonen (2016)	Finland	Full text	Retrospective cohort	1	Burn patients	Adult	558	Fair
Roubinian (2016)	USA	Abstract	Retrospective cohort	21	Hospital patients transfused with platelets	Adult	13,276	Fair
Ghazi (2015)	USA	Full text	Retrospective cohort	1	Cardiac surgery patients	Adult	1,070	Poor
Kaur (2015)	India	Full text	Retrospective cohort	1	Neonates in the NICU	Pediatric	815	Fair
Pitman (2015)	Nambia	Full text	Retrospective cohort	Multi-center (number of sites not specified)	Transfused hospital patients	All ages	39,313	Fair
Triulzi (2015)	USA	Full text	Retrospective cohort	10	Hospital patients transfused with plasma	Adult	9,269	Fair
Xi (2015)	China	Full text	Retrospective cohort	1	Trauma patients	All ages	1,766	Fair
Fujimoto (2014)	Brazil	Full text	Retrospective cohort	2	Patients with dengue hemorrhagic fever	All ages	193	Poor
Livingston (2014)	Canada	Full text	Retrospective cohort	1	Trauma patients	Pediatric	435	Fair
Sovic (2014)	Croatia	Full text	Retrospective cohort	1	Hospital patients	All ages	NR	Fair

Subramanian (2014)	USA	Full text	Retrospective cohort	1	Liver transplant patients	Adult	280	Fair
Lu (2013)	USA	Full text	Retrospective cohort	1	Burn patients	Adult	89	Fair
Zhao (2013)	China	Abstract	Retrospective cohort	1	Liver transplant patients	Adult	1,335	Poor
Mikkola (2012)	Finland	Full text	Retrospective cohort	3	Cardiac surgery patients	Adult	2,226	Poor
Pavenski (2012)	Canada	Abstract	Retrospective cohort	1	Cardiac surgery patients	Adult	579	Fair
Teitel (2011)	Canada	Abstract	Retrospective cohort	1	Cardiac surgery patients	Adult	293	Fair
Sreeram (2005)	USA	Full text	Retrospective cohort	1	Cardiac surgery patients	Adult	6,721	Fair
Como (2004)	USA	Full text	Retrospective cohort	1	Trauma patients	Adult	5,645	Fair
Kobayashi (1997)	Japan	Full text	Retrospective cohort	1	Transfused liver surgery patients	Adult	53	Fair
Takano (1989)	Japan	Full text	Retrospective cohort	1	Transfused hospital patients	All ages	2,596	Fair
Bosch (2011)	Spain	Full text	Cross-sectional survey	107	Transfused hospital patients	All ages	8,019	Fair
Jones (2011)	UK	Abstract	Cross-sectional survey	Multi-center (number of sites not specified)	Massively transfused hospital patients	Adult	277	Poor
Pottle (2011)	UK	Abstract	Cross-sectional survey	1	Massively transfused emergency department patients	Adult	77	Fair

Abbreviations: NR, not reported; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.

Table 2. Prevalence and amount of multicomponent transfusion by timing of transfusion, patient type, and year of publication (most recent to oldest).

Transfusion Timing	Patient Type	Study	Year	Type(s) of MT Administered	Number of Units (Mean)	MT Prevalence (All study participants)		MT Prevalence (Transfused participants)	
						Sample Size	Prevalence	Sample Size	Prevalence
Transfusions within 24h of hospital admission	**Massively transfused hospital patients**[a]	Yang	2017	RBC+PLT RBC+FP RBC+cryo	NR	1,048	4.4-13.7%[b] 72.4-80.6%[b] 16.4-24.2%[b]	1,048	4.4-13.7%[b] 72.4-80.6%[b] 16.4-24.2%[b]
	Trauma patients	Stanworth	2016	RBC+PLT RBC+FP RBC+cryo	NR	442	44.6% 74.7% 27.6%	442	44.6% 74.7% 27.6%
		Livingston	2014	RBC+PLT RBC+FP RBC+PLT+FP RBC+PLT+FP+cryo	NR	435	NR	13[c]	15.4% 23.1% 7.7% 38.5%
Same day transfusions	**ICU patients**[d]	DeSimone	2016	RBC+cryo PLT+cryo FP+cryo	NR	44	45.5% 59.1% 61.4%	44	45.5% 59.1% 61.4%

Peri-operative transfusions (intra-operative and up to 48h after surgery)	**Cardiac surgery patients**	Ghazi	2015	Of RBC, PLT, FP, and cryo: Any 2 blood products Any 3 blood products All 4 blood products Specific combinations: RBC+PLT RBC+FP RBC+PLT+FP RBC+PLT+FP+cryo	NR	1,070	7.6% 6.8% 3.9% 3.8% 2.2% 6.6% 3.9%	506	16.0% 14.4% 8.3% 8.1% 4.7% 13.2% 8.3%
		Mikkola	2012	Of RBC, PLT and FP: Any 2 blood products All 3 blood products	NR	2,226	12.9% 12.3%	1,243	23.1% 22.0%
		Pavenski	2012	RBC+cryo	NR	579	4.8%	278	10.1%
		Teitel	2011	RBC+cryo PLT+cryo	NR	239	3.8% 3.4%	147	7.5% 6.8%
		Sreerarm	2005	RBC+PLT RBC+FP RBC+PLT+FP	NR	6,721	2.7% 4.9% 5.1%	2,657	6.9% 12.3% 13.0%
	Liver transplant or surgery patients	Subramanian	2014	RBC+PLT+FP	NR	280	25.7%	192	37.5%
		Kobayashi	1999	RBC+FP PLT+FP RBC+PLT+FP	10 U, 66 U 50 U, 27 U 6 U, 80 U, 58 U	55	NR	7[e]	14.3% 28.6% 14.3%
		Kobayashi	1997	RBC+FP PLT+FP RBC+PLT+FP	4 U, 65 U 40 U, 28 U 8 U, 20 U, 58 U	53	NR	7[f]	14.3% 14.3% 42.9%

Transfusions throughout an index hospital admission	**Any hospital patients**	Karafin	2017	RBC+PLT RBC+FP PLT+FP RBC+PLT+FP	NR	641,751	0-3.0%[g] 0.2-2.7%[g] 0-0.7%[g] 0.3-3.7%[g]	NR	NR
		Sovic	2014	RBC+PLT+FP	NR	NR	14.6%	NR	NR
	Transfused hospital patients	Roubinian	2016	RBC+PLT PLT+FP	NR	13,276	72.7% 36.8%	13,276	72.7% 36.8%
		Javadzadeh Shahshahani	2015	RBC+PLT RBC+FP	NR	814	19.3% 19.0%	814	19.3% 19.0%
		Pitman[h]	2015	RBC+PLT RBC+FP PLT+FP RBC+PLT+FP	NR	39,313	2.2% 5.0% 0.4% 0.6%	39,313	2.2% 5.0% 0.4% 0.6%
		Triuzli	2015	Any MT with FP RBC+FP PLT+FP FP+cryo	NR	9,269	77.3% 71.3% 42.4% 12.4%	9,269	77.3% 71.3% 42.4% 12.4%
		Bosch	2011	RBC+PLT RBC+FP PLT+FP RBC+PLT+FP	NR	8,019	5.7% 4.0% 0.4% 2.1%	8,019	5.7% 4.0% 0.4% 2.1%
		Takano	1989	Any MT of RBC, PLT, and/or FP	NR	2,596	34.4%	2,596	34.4%
		Luban	1987	RBC+PLT or RBC+FP	NR	100	37.0%	100	37.0%
	Massively transfused hospital	Green	2017	RBC+PLT RBC+FP RBC+cryo	NR	701	80% 91% 62%	701	80% 91% 62%

	patients[a]	Green	2016	RBC+PLT RBC+FP RBC+cryo	NR	181	77% 99% 61%	181	77% 99% 61%
		Jones	2011	RBC+PLT RBC+FP RBC+cryo	NR	277	52.0% 79.1% 23.5%	277	52.0% 79.1% 23.5%
		Pottle	2011	RBC+FP	NR	77	47.0%	77	47.0%
	Burn patients	Koljonen	2016	RBC+PLT+FP	NR	558	9.9%	192	28.6%
		Lu	2013	RBC+FP	NR	89	44.9%	NR	NR
	Cardiac surgery patients	Brouwers	2017	RBC+PLT RBC+FP PLT+FP RBC+PLT+FP	NR	11,150	NR	6,344	8-22%[i] 2-10%[i] 1.5-13%[i] 16.8-55%[i]
	Cancer patients	Cesari	2016	RBC+PLT	NR	31	16.1%	15	33.3%
	ICU patients[d]	Kaur	2015	2 or more types of blood components	NR	815	12.3%	280	35.7%
	Infectious disease patients	Fujimoto	2014	PLT+FP	NR	193	11.4%	62	35.5%
	Trauma patients	Xi	2015	RBC+PLT RBC+FP PLT+FP RBC+PLT+FP RBC+PLT+WB and/or cryo RBC+FP+WB and/or cryo PLT+FP+WB and/or cryo	NR	1,766	0.1% 48.6% 0.2% 2.2% 3.2% 3.3% 3.0%	1,211	0.1% 70.9% 0.2% 3.1% 4.6% 4.9% 4.4%
		Dunne	2008	RBC+PLT RBC+PLT+FWB	NR	26	23.1% 19.2%	22	27.3% 22.7%

		Como	2004	RBC+PLT RBC+FP RBC+cryo	NR	5,645	2.7% 5.3% 0.1%	501	30.1% 60.1% 0.8%

Abbreviations: MT, multicomponent transfusion; RBC, red blood cells; PLT, platelets; FP, plasma; cryo, cryoprecipitate; WB, whole blood; FWB, fresh whole blood; ICU, intensive care unit; NR, not reported; U, units of blood product.

[a] Massively transfused hospital patients consist of many patient types including surgical, trauma, and obstetric hemorrhage, among others.

[b] Prevalence estimates vary according to the number of RBC units transfused.

[c] Multicomponent transfusion prevalence was reported only for a subgroup of participants (n=13) who were massively transfused.

[d] ICU patients include those from neonatal and pediatric ICUs.

[e] All participants (n=55) were transfused, but multicomponent transfusion prevalence was reported only for a subgroup of patients (n=7) who acquired TT hepatitis virus post-transfusion.

[f] All participants (n=53) were transfused, but multicomponent transfusion prevalence was reported only for a subgroup of patients (n=7) who acquired hepatitis G virus post-transfusion.

[g] Prevalence estimates vary according to age group and patient sex; ranges include prevalence values for all ages and both sexes.

[h] The unit of analysis for this study was transfusion requests, not patients.

[i] Prevalence estimates vary according to specific type of cardiac surgery and by hospital; ranges include prevalence values from all cardiac surgeries and all 4 participating hospitals.

Table 3. Association of multicomponent transfusion with patient outcomes.

Study	Patient Population	Type(s) of MT	Outcome	Crude OR (95% CI)	Adjusted OR (95% CI)	Variables Adjusted For
Alfirevic (2011)	Cardiac surgery	RBC+PLT RBC+FP RBC+PLT+FP	Profound vasoplegia[a]	NR	1.22 (1.14, 1.31) 1.20 (1.13, 1.29) 1.07 (1.04, 1.09)	NR
Ghazi (2015)	Cardiac surgery	RBC+FP	Postoperative DVT	NR	1.87 (1.11, 3.22)	RBC transfusion, age, ventilator time, re-intubation
Mikkola (2012)	Cardiac surgery	RBC+PLT+FP	Postoperative stroke	NR	A) 1.73 (1.35, 2.21) B) 4.21 (2.05, 8.64) C) 4.83 (2.37, 2.21) D) 9.50 (1.95, 46.27)	A) Pre-operative Hb and postoperative blood loss B) EUROclass score and postoperative blood loss C) Adjusted using a propensity score with the following variables: age, pre-operative Hb, pre-operative exposure to clopidogrel, chronic use of warfarin, previous cardiac surgery, recent MI, emergency operation, critical operative status, diabetes status, and intra-operative use of tranexamic acid D) Matching using the same propensity score as above (n = 210 matched pairs)
Miyata (2010)	Cardiovascular surgery	RBC (>10 units) + PLT (1 or more units)	Postoperative thromboembolic events	NR	2.6 (1.4, 5.1)	NR
Zhao (2013)	Liver transplant	RBC+FP > 35 units	Acute lung injury following transplant	NR	2.80 ($p<0.05$)	NR

Abbreviations: MT, multicomponent transfusion; OR, odds ratio; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; DVT, deep vein thrombosis; Hb, hemoglobin; MI, myocardial infarction; NR, not reported;
[a] Profound vasoplegia was defined by the study authors as patients requiring use of vasopressin, with or without concomitant use of norepinephrine, on the day of operation and postoperative day 1.

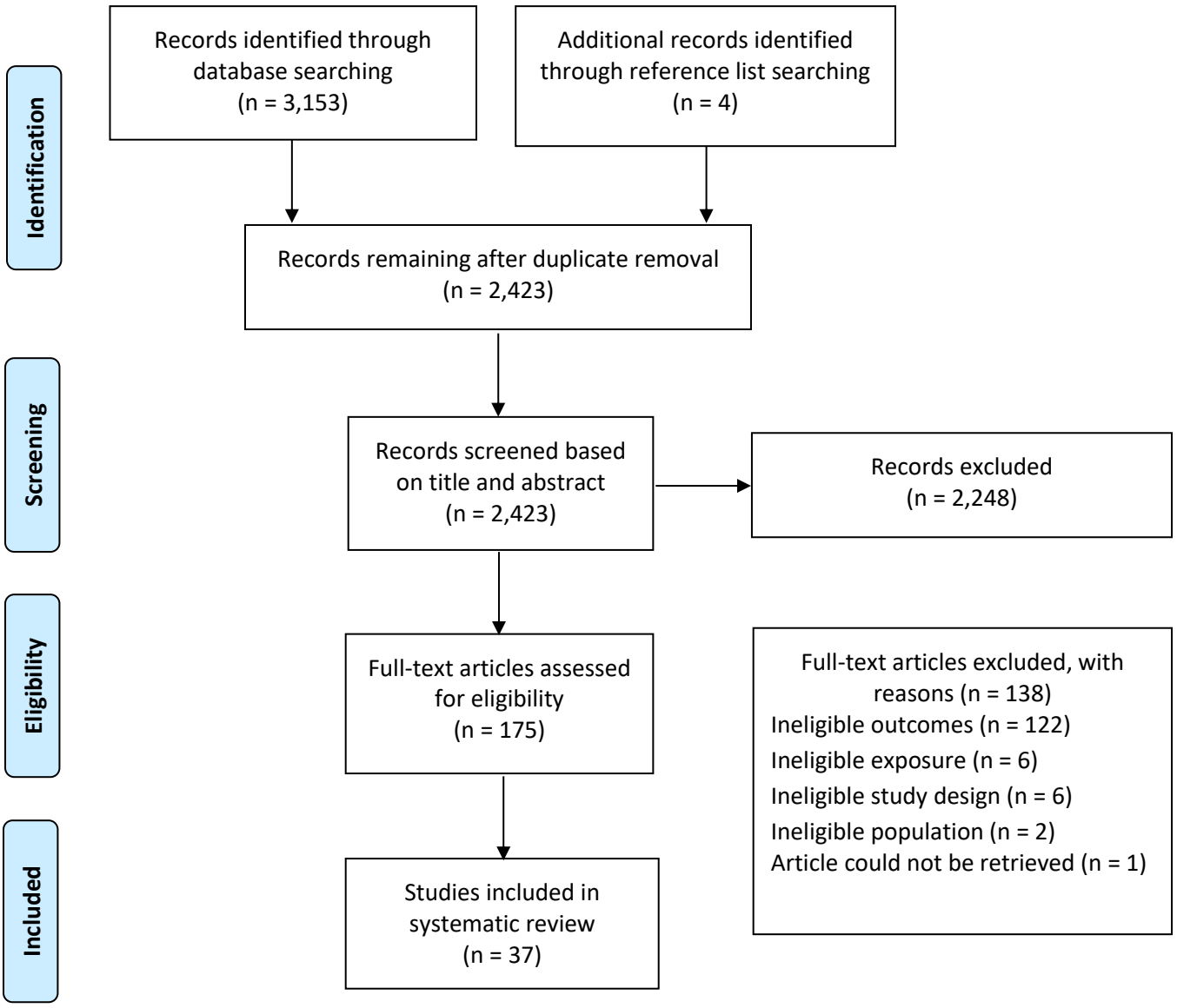

Figure 1. PRISMA flowchart of study selection process.

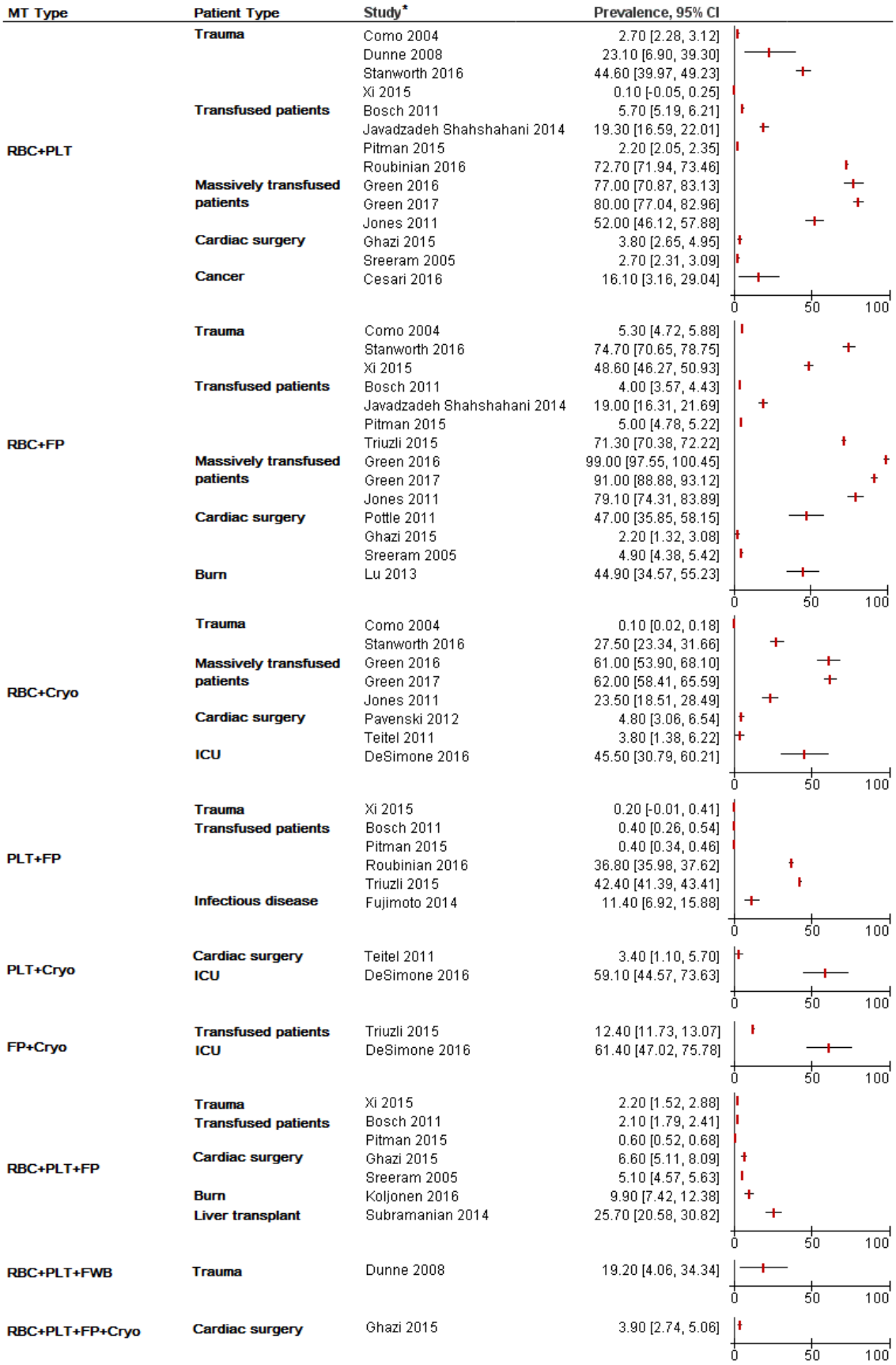
MT Type
Patient Type
Study*
Prevalence, 95% CI
RBC+PLT
Trauma
Como 2004 2.70 [2.28, 3.12]
Dunne 2008 23.10 [6.90, 39.30]
Stanworth 2016 44.60 [39.97, 49.23]
Xi 2015 0.10 [-0.05, 0.25]
Transfused patients
Bosch 2011 5.70 [5.19, 6.21]
Javadzadeh Shahshahani 2014 19.30 [16.59, 22.01]
Pitman 2015 2.20 [2.05, 2.35]
Roubinian 2016 72.70 [71.94, 73.46]
Massively transfused patients
Green 2016 77.00 [70.87, 83.13]
Green 2017 80.00 [77.04, 82.96]
Jones 2011 52.00 [46.12, 57.88]
Cardiac surgery
Ghazi 2015 3.80 [2.65, 4.95]
Sreeram 2005 2.70 [2.31, 3.09]
Cancer
Cesari 2016 16.10 [3.16, 29.04]
0
50
100
RBC+FP
Trauma
Como 2004 5.30 [4.72, 5.88]
Stanworth 2016 74.70 [70.65, 78.75]
Xi 2015 48.60 [46.27, 50.93]
Transfused patients
Bosch 2011 4.00 [3.57, 4.43]
Javadzadeh Shahshahani 2014 19.00 [16.31, 21.69]
Pitman 2015 5.00 [4.78, 5.22]
Triuzli 2015 71.30 [70.38, 72.22]
Massively transfused patients
Green 2016 99.00 [97.55, 100.45]
Green 2017 91.00 [88.88, 93.12]
Jones 2011 79.10 [74.31, 83.89]
Cardiac surgery
Pottle 2011 47.00 [35.85, 58.15]
Ghazi 2015 2.20 [1.32, 3.08]
Sreeram 2005 4.90 [4.38, 5.42]
Burn
Lu 2013 44.90 [34.57, 55.23]
0
50
100
RBC+Cryo
Trauma
Como 2004 0.10 [0.02, 0.18]
Stanworth 2016 27.50 [23.34, 31.66]
Massively transfused patients
Green 2016 61.00 [53.90, 68.10]
Green 2017 62.00 [58.41, 65.59]
Jones 2011 23.50 [18.51, 28.49]
Cardiac surgery
Pavenski 2012 4.80 [3.06, 6.54]
Teitel 2011 3.80 [1.38, 6.22]
ICU
DeSimone 2016 45.50 [30.79, 60.21]
0
50
100
PLT+FP
Trauma
Xi 2015 0.20 [-0.01, 0.41]
Transfused patients
Bosch 2011 0.40 [0.26, 0.54]
Pitman 2015 0.40 [0.34, 0.46]
Roubinian 2016 36.80 [35.98, 37.62]
Triuzli 2015 42.40 [41.39, 43.41]
Infectious disease
Fujimoto 2014 11.40 [6.92, 15.88]
0
50
100
PLT+Cryo
Cardiac surgery
Teitel 2011 3.40 [1.10, 5.70]
ICU
DeSimone 2016 59.10 [44.57, 73.63]
0
50
100
FP+Cryo
Transfused patients
Triuzli 2015 12.40 [11.73, 13.07]
ICU
DeSimone 2016 61.40 [47.02, 75.78]
0
50
100
RBC+PLT+FP
Trauma
Xi 2015 2.20 [1.52, 2.88]
Transfused patients
Bosch 2011 2.10 [1.79, 2.41]
Pitman 2015 0.60 [0.52, 0.68]
Cardiac surgery
Ghazi 2015 6.60 [5.11, 8.09]
Sreeram 2005 5.10 [4.57, 5.63]
Burn
Koljonen 2016 9.90 [7.42, 12.38]
Liver transplant
Subramanian 2014 25.70 [20.58, 30.82]
0
50
100
RBC+PLT+FWB
Trauma
Dunne 2008 19.20 [4.06, 34.34]
0
50
100
RBC+PLT+FP+Cryo
Cardiac surgery
Ghazi 2015 3.90 [2.74, 5.06]
0
50
100

Figure 2. Multicomponent transfusion prevalence estimates (%) and 95% confidence intervals by type of multicomponent transfusion and by patient type. Abbreviations: MT, multicomponent transfusion; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; cryo, cryoprecipitate; FWB, fresh whole blood; ICU, intensive care unit.
*Studies where the specific type of multicomponent transfusion was not specified (n=4), where prevalence ranges were reported instead of prevalence estimates (n=3), where the sample size was not provided leading to inestimable 95% confidence intervals (n=1), and where prevalence was not reported or was only reported for a subgroup of the study population (n=6) were not included in this figure; see table 2 for prevalence estimates for studies not shown in this figure.

Appendix A – Reference List of Studies Included in This Systematic Review

Alfirevic, A., Xu, M., Johnston, D., Figueroa, P., Koch, C.G. (2011) Transfusion increases the risk for vasoplegia after cardiac operations. *Annals of Thoracic Surgery*, 92, 812-819.

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DeSimone, R.A., Nellis, M.E., Goel, R., Haas, T., Vasovic, L., Cushing, M.M. (2016) Cryoprecipitate indications and patterns of use in the pediatric intensive care unit: inappropriate transfusions and lack of standardization. *Transfusion*, 56, 1960-1964.

Dunne, J.R., Lee, T.H., Burns, C., Cardo, L.J., Curry, K., Busch, M.P. (2008) Transfusion-associated microchimerism in combat casualties. *Journal of Trauma*, 64, S92-S97.

Fujimoto, D.E., Koifman, S. (2014) Clinical and laboratory characteristics of patients with dengue hemorrhagic fever manifestations and their transfusion profile. *Revista Brasileira Hematologia e Hemoterapia*, 6, 115-120.

Ghazi, .L, Schwann, T.A., Engoren, M.C., Habib, R.H. (2015) Role of blood transfusion product type and amount in deep vein thrombosis after cardiac surgery. *Thrombosis Research*, 136(6), 1204-1210.

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Jones, A., Birchall, J., Webb, M., MacRate, E., Thompson, P., Cooke, S., Roberts, P. (2011) Massive transfusion: The incidence, cause, blood product use and survival in the south west region. *Transfusion Medicine*, 21, 42.

Karafin, M.S., Bruhn, R., Westlake, M., Sullivan, M.T., Bialkowski, W., Edgren, G., Roubinian, N.H., Hauser, R.G., Kor, D.J., Fleischmann, D., Gottschall, J.L., Murphy, E.L., Triuzli, D.J.

(2017) Demographic and epidemiologic characterization of transfusion recipients from four US regions: evidence from the REDS-III recipient database. *Transfusion*, 57, 2903-2913.

Kaur, A., Dhir, S.K., Kaur, G., Gupta, M., Batta, M. (2015) Blood component therapy in neonates in a neonatal intensive care unit of northern India. *Clinical Epidemiology and Global Health*, 3, S38-S42.

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Miyata, S. (2010) Risk factors for thromboembolic events in patients undergoing cardiovascular surgery: The analyses of a multicenter prospective cohort study. *Vox Sanguinis*, 99, 47.

Pavenski, K., Lam, K., Rockman, R., Teitel, J., Mazer, D. (2012) Cryoprecipitate transfusion in on-pump cardiac surgery. *Haemophilia*, 18, 35.

Pitman, J.P., Wilkinson, R., Liu, Y., von Finkenstein, B., Smit Sibinga, C.T., Lowrance, D.W., Marfin, A.A., Postma, M.J., Mataranyika, M., Basavaraju, S.V. (2015) Blood component use in a sub-Saharan African country: results of a 4-year evaluation of diagnoses associated with transfusion orders in Namibia. *Transfusion Medicine Reviews*, 29, 45-51.

Pottle, J., Staves, J., Murphy, M., Harris, M., Stanworth, S., Curry, N. (2011) Audit of the transfusion management of major blood loss in the emergency department of a UK teaching hospital. *British Journal of Haematology*, 153, 10-11.

Roubinian, N., Escobar, G., Gardner, M., Triuzli, D.J., Hendrickson, J.E., Gottschall, J., Murphy, E. (2016) Epidemology of platelet transfusion in hospitalized patients: Data from an integrated health care delivery system. *Transfusion*, 56, 168A-169A.

Sovic, D., Dodig, J., Banovic, M., Jularic, A. (2014) Transfusion treatment at Sestre Milosrdnice University Hospital Center during a twelve-year period. *Acta Clinica Croatica*, 53, 342-347.

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Triuzli, D., Gottschall, J., Murphy, E., Wu, Y., Ness, P., Kor, D., Roubinian, N., Fleischmann, D., Chowdhury, D., Brambilla, D. (2015) A multicenter study of plasma use in the United States. *Transfusion*, 55, 1313-1319.

Xi, C.Y., Yu, Y., Chen, L.F., Zhu, L.G., Lu, Y., Wang, S.F., Wang, D.Q. (2015) Investigation and analysis of blood transfusion in 1 766 hospitalized trauma patients. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*, 23, 228:233.

Yang, J.C., Wang, Q.S., Dang, Q.L., Sun, Y., Xu, C.X., Jin, Z.K., Ma, T., Liu, J. (2017) Investigation of the status quo of massive blood transfusion in China and a synopsis of the proposed guidelines for massive blood transfusion. *Medicine*, 96, e7690.

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Appendix B – GRADE Assessment for Overall Quality of Evidence

Table B1. GRADE evidence profile for the primary and secondary outcomes.

Outcome	Quality Assessment				
	Types of Studies	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**
Primary Outcome: Multicomponent transfusion prevalence	6 prospective cohorts 24 retrospective cohorts 3 cross-sectional	Not serious	Serious[a]	Not serious	Not serious
Secondary Outcome: Association between multicomponent transfusion and patient outcomes	2 prospective cohorts 3 retrospective cohorts	Serious[b]	Not serious	Not serious	Not serious
Post-Hoc Secondary Outcome: Blood Product Consumption in Multicomponent Transfusions	1 prospective cohort 1 retrospective cohort	Not serious	Some inconsistency[c]	Serious[d]	Not serious

[a] There was inconsistency in multicomponent transfusion prevalence estimates across studies.
[b] Studies had a high risk of bias due to confounding by indication and significant residual confounding.
[c] There was some inconsistency in mean number of blood units reported for some types of multicomponent transfusion (see table 2).
[d] Both studies reporting on this outcome were studies of liver surgery patients; however, there are many other patient populations for which this outcome is of interest, and blood consumption of liver surgery patients cannot be generalized to other patient groups.

Chapter 3: Building a multicomponent transfusion cohort from the Ottawa Hospital Data Warehouse and Transfusion Data Mart

3.1 Preface

Study 1 of this thesis, presented above in Chapter 2, addressed the first thesis objective of synthesizing existing evidence on multicomponent transfusion, its epidemiology, and its recipients. The second and third thesis objectives involved studying multicomponent transfusion locally, at the Ottawa Hospital (Study 2). For this purpose, it was necessary to create a cohort of multicomponent transfused patients at the Ottawa Hospital, as well as a comparator (unexposed) cohort. This chapter will give an introduction to the data sources used to create the study population of interest, and will describe the process of creating the multicomponent transfused cohort and the comparator cohort.

3.2 Introduction to the Ottawa Hospital Data Warehouse and Transfusion Data Mart

The Ottawa Hospital is an academic, three-campus, 1200 bed, tertiary care institution. The Ottawa Hospital Data Warehouse (OHDW) is a repository of routinely collected patient and admission related data from all campuses of the Ottawa Hospital since 1996. It contains information on patient demographics, diagnoses, procedures, transfers across hospital units, laboratory services, pharmacy prescriptions, and physician providers, amongst other data. The OHDW includes inpatients, outpatients, surgical and medical daycare patients, and emergency department patients. The OHDW is widely used for both internal quality assurance and research purposes, and variables have been created to facilitate research using the OHDW, other than those routinely collected during a hospital admission. For instance, there are algorithms in place to calculate variables that are useful for risk adjustment in regression analysis, such as the Charlson Comorbidity Index score and the Hospital-patient One-year Mortality Risk (HOMR) score.

The Transfusion Data Mart (TDM) was created in 2016 as a subsection of the OHDW in order to provide detailed information on transfused hospital patients. The TDM stores data on all blood products for every transfused patient at the Ottawa Hospital, as well as patient demographics, admission characteristics, laboratory tests, diagnoses, procedures, acute care unit stays, and transfers within hospital for transfusion recipients. The earliest transfusion data available in the TDM is from the end of 2006. All data relating to patients and physician providers in the TDM is anonymized and de-identified. Patients, providers, and hospital admissions all have unique numerical identifiers. These unique identifiers allow for privacy of data, as well as for the deterministic linkage of tables within the TDM (e.g. linkage of patient demographic data to patient transfusion data).

3.3 Architecture of the Transfusion Data Mart

The layout of the TDM is shown in figure 1 below. The TDM consists of 8 data tables, coming from 5 different hospital data sources and systems. The data tables used for Study 2 of this thesis were the Transfusion and Encounters tables (see section 3.5 for more detail). The Transfusion table provides data on each blood product transfused, the volume transfused, and the date and time of transfusion. This table is flat on blood product (i.e. one row per ordered blood product). The Encounters table lists all hospital patients who received a minimum of 1 transfusion – of any blood component (e.g. RBCs, PLTs, etc.), or plasma product derivative (e.g. clotting factors, immunoglobulins, etc.) – during their hospital stay. This table provides information on patient demographics (e.g. age, sex), hospital admission characteristics (e.g. start and end date of admission, admitting physician division, etc.), and some general patient outcomes (e.g. in-hospital mortality, transfer to an acute unit, discharge location, etc.). This table is structured so that one row represents one hospital admission.

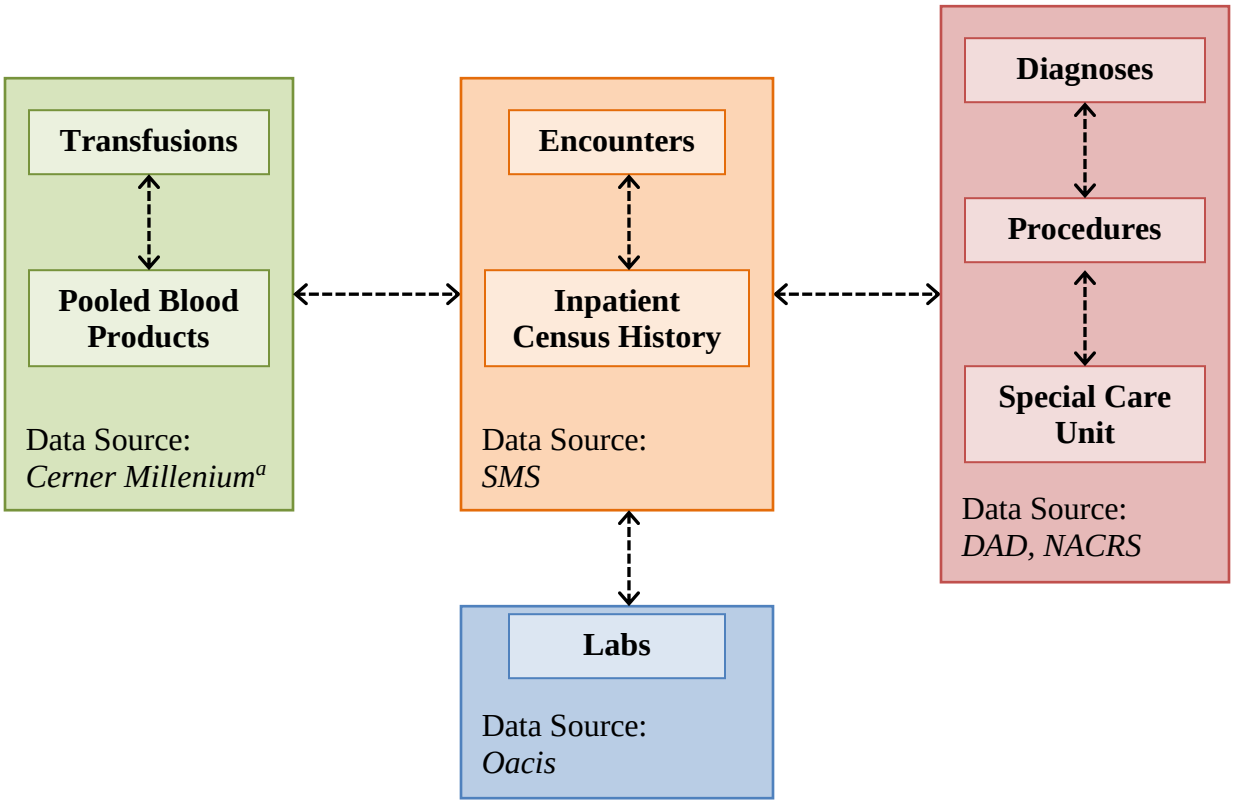

Figure 1. Architecture of the Transfusion Data Mart. Dotted arrows represent the possibility of deterministically linking tables based on unique identifiers. Abbreviations: SMS, Short Messaging System; DAD, Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System.
[a]Cerner Millenium is the transfusion medicine laboratory information system.

3.4 Variables of Interest

This section will provide a detailed description of all the variables from the OHDW and the TDM that were used in Study 2. Table 1 below lists all relevant variables from these two data sources and describes each variable with respect to structure (e.g. levels of the variable) and any changes made to the variable for analysis (e.g. re-categorizing variable levels, dichotomizing continuous variables, etc.). Important variables that were not present in the OHDW or the TDM but that were created for the purpose of Study 2 are also presented in table 1.

Table 1. Variables used in Study 2.

Type of Variable	Variable Name	Description	Changes Made to Variable
Patient Baseline Characteristics	Sex	Patient sex.	None.
	Age	Patient age in years at time of admission (continuous variable).	For one regression analysis in Study 2 (effect of age on the odds of multicomponent transfusion), age was categorized into 10 year intervals due to non-linearity issues in the model: 18-25 years 26-35 years 36-45 years 46-55 years 56-65 years 66-75 years 76-85 years >85 years For all other descriptive and inferential analyses in Study 2, the original (continuous) age variable was used.
Admission Characteristics	Admission date and time	Time and date of hospital admission.	None.
	Discharge date and time	Time and date of hospital discharge.	None.
	Admitting physician division	The hospital division of the admitting physician. See Appendix C for a list of hospital divisions. This variable was used to classify patients into patient types for Study 2 (e.g. surgery patient, internal medicine patient, etc.). We chose to base patient type on this variable instead of other available options (e.g. most responsible physician division, discharge service) because this variable had the least missing data.	Admitting physician hospital divisions were re-grouped to obtain more succinct and informative categories, which were used to define patient type in Study 2. See Appendix C for further detail on the re-classification of this variable.

	Encounter type	Type of hospital admission (inpatient, outpatient, emergency department, medical daycare, surgical daycare).	For Study 2, our population of interest was hospital inpatients; all other admission types were not used in analysis.
Risk Adjustment Variables	Charlson Comorbidity Index Score	The Charlson score was calculated using a validated algorithm by the OHDW analyst team, based on ICD 10 codes. This variable was used a measure of illness burden in Study 2.	None.
	HOMR score	The HOMR score gives the probability of death at 1 year after hospital admission, and is meant as a risk adjustment variable. In Study 2, this variable was used as a measure of illness severity for risk adjustment purposes. It was calculated by the OHDW analyst team using an algorithm based on the following variables: sex, number of emergency department visits, home oxygen, diagnostic risk score, ICU admission, admission by ambulance, urgent readmission, admitting service, age × Charlson Comorbidity score interaction, and living status × admission by ambulance interaction. For more information on the HOMR score and its validation, see references 17 and 18 at the end of the thesis.	None.
Transfusion-Related Variables	Blood product type	Type and name of blood product transfused. For a list of all possible blood products, see Appendix C.	The following blood products were eligible for Study 2: RBCs, PLTs, plasma, cryoprecipitate, and fibrinogen concentrate. There were multiple names or variations for each blood component, so these were re-grouped to obtain one category for RBCs, PLTs, plasma, cryoprecipitate, and fibrinogen concentrate (see Appendix C for more detail).
	Transfusion date and time	Date and time of transfusion.	None.
	Type of	Type of transfusion: allogeneic, autologous, or directed.	For Study 2, we only examined allogeneic

	transfusion		transfusions; autologous and directed transfusions (n=11) were excluded.
	Multicomponent transfusion indicator variable	Not present in OHDW or TDM; created for Study 2. Indicator variable for multicomponent transfusion (1 = yes, 0 = no).	None.
Outcome Variables	In-hospital mortality	Indicator variable for in-hospital mortality (D = died in-hospital, A = alive at discharge).	None.
	Exit code	Discharge location for patients: 01 → Transferred to acute care unit 02 → Transferred to long term care 03 → Transferred to other location 04 → Discharged with support services 05 → Discharged home 06 → Signed out 07 → Patient died in-hospital 08 → Cadaveric donor 09 → Stillbirth	The discharge location variable was dichotomized into institutional discharge (codes 01, 02, 03), and discharge home (codes 04, 05, 06). In Study 2, we evaluated discharge location only for patients alive at time of discharge, so code 07 was excluded from analysis. Codes 08 and 09 did not occur in the dataset for Study 2.
	Length of stay	Length of hospitalization in days, calculated using the admission datetime and discharge datetime variables.	For one regression analysis in Study 2 (effect of multicomponent transfusion on length of stay), the length of stay variable was log base e transformed due to its highly skewed nature (see Chapter 4 for more detail). For all remaining analyses, the variable was used in its original form.
Unique Data Warehouse Identifiers	Encounter identifier	Unique data warehouse identifier for each hospital admission. This variable was used to deterministically merge data tables in the TDM.	None.
	Patient identifier	Unique data warehouse identifier for each hospital patient. This variable was used to deterministically merge data tables in the TDM.	None.

Status Code Variables	Blood product status code	The status of the transfusion record at the moment when the data was extracted (Y = active, N = inactive). This variable was used to ensure that all transfusions were active and had not been cancelled or returned to the blood bank. Inactive transfusions were excluded from analysis in Study 2.	None.
	Valid encounter status codes	Three status codes that verify the status of a hospital admission: dteEncStsCd → encounter status code dteEncOacisStsCd → encounter Oacis status code dteEncAppointmentSts → Encounter appointment status These variables were used to verify that all encounters were valid (e.g. not cancelled, etc.); invalid encounters were excluded from analysis in Study 2.	None.

Abbreviations: FP, plasma; HOMR, Hospital-patient One-year Mortality Risk; ICD, International Classification of Disease; ICU, intensive care unit; OHDW, Ottawa Hospital Data Warehouse; PLTs, platelets; RBCs, red blood cells; TDM, Transfusion Data Mart.

Missing Data in Variables of Interest

All of the variables used in Study 2 had complete data, except for the ones discussed below. Admitting physician division, which was the variable used to determine patient type, was missing in a small proportion of hospital admissions (<<1%). For each missing entry of this variable, admitting physician division was determined by looking at the following variables: most responsible physician division, hospital discharge service, case mix group, and admitting diagnoses. The information from these variables was used to assign the most appropriate admitting physician division. The discharge location variable was missing in 1% of the study population. Given the small amount of missing data, complete case analysis was performed for this variable instead of multiple imputation techniques as any bias resulting from complete case analysis – if any – would be very small and unlikely to affect findings. Finally, the HOMR score could not be calculated for admissions prior to April 2008 (10% of admissions), as some of the variables necessary for its determination (i.e. the variables used by the algorithm to calculate HOMR score) were not collected in the OHDW before April 2008. All analyses involving the HOMR variable were performed for admissions after April 2008 to ensure data completeness. Chapter 4 provides additional information on the handling of missing data in Study 2.

3.5 Creating a Multicomponent Transfused Cohort

To address the second and third objectives of this thesis (Study 2), it was necessary to create a cohort of patients who received one or more multicomponent transfusions during their hospital stay (see Chapter 4 for more detail on Study 2). Additionally, a comparison cohort of non-multicomponent transfused patients – patients who were transfused with only 1 type of blood component during their hospital stay (e.g. only RBCs) – was needed. The paragraphs that follow will describe in more detail the study population of interest for Study 2, and will explain the formation of the two study cohorts, using data from the TDM and the OHDW.

Study Population

The patient population of interest for Study 2 was adult (≥18 years), transfused hospital inpatients. Other patient types (e.g. outpatients, emergency room patients, etc.) were not included as they have distinct transfusion patterns and indications, and should be studied separately from inpatients. The blood components of interest were RBCs, PLTs, FP, cryoprecipitate, and fibrinogen concentrate. Fibrinogen concentrate was included, although it is not a blood component but a blood product derivative manufactured from plasma, as it is increasingly being used as a substitute for cryoprecipitate [19]. Given that cryoprecipitate and fibrinogen concentrate are transfused for the same indications (replacement of fibrinogen), transfusions of these 2 blood products were analyzed together and were collectively termed 'fibrinogen replacement' (FR). Autologous transfusions (wherein blood is collected from an individual patient and is later re-transfused to that same patient) were not included, as these are distinct from the more common allogeneic transfusions (wherein blood is collected from donors and is transfused to patients) and should be studied separately.

Creation of Study Cohorts

Given the above eligibility criteria, we pulled data on all adult, transfused inpatient admissions at the Ottawa Hospital between 2007 and 2017 from the Encounters table in the TDM. The resulting dataset had one row for each admission. We verified that all admissions were valid (e.g. not cancelled, etc.) through the use of status code variables. Next, all eligible transfusions (RBCs, PLTs, FP, and FR), including date and time of transfusion, were pulled from the Transfusion table of the TDM. This dataset had one row per transfusion, and was flattened on a unique admission identifier to obtain a dataset with one row per admission. We verified that all transfusion events were valid (latest status, not returned to blood bank or cancelled, etc.) using

appropriate status code variables. The admissions dataset was inner joined with the flattened transfusions dataset using a unique admission identifier, such that transfusion data was obtained for all adult transfused inpatients, but transfusion data for ineligible patients was discarded. To verify that the merging of these two datasets was done correctly, unique patient identifiers from both original tables were compared for each admission for any mismatches – none were found, indicating accurate deterministic linkage. Next, dichotomous indicator variables were created for multicomponent transfusion (yes/no) and for all possible types of multicomponent transfusion (e.g. RBC+PLT, RBC+PLT+FP, etc.). These indicator variables created a multicomponent transfused cohort (exposed cohort) and a non-multicomponent transfused cohort (unexposed cohort). From the non-multicomponent transfused cohort we created another comparison cohort of patients transfused with only RBCs (as this was the most commonly transfused single type of blood component), by deleting admissions that were transfused with only PLTs, only FP, and only FR, leaving only RBC transfusions.

Finally, several variables that were needed for analysis in Study 2 were unavailable in the TDM, but were present in the OHDW (Charlson score and HOMR score). These two variables were requested and obtained from the OHDW for our study population, and were merged with the existing dataset using unique admission and patient identifiers. The resulting dataset was the complete study population for Study 2 of the thesis (see Chapter 4 for more detail on Study 2).

Chapter 4: Trends and outcomes in multicomponent blood transfusion: An 11-year cohort study of a large multi-site academic center (*Manuscript 2*)

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Author Contributions

Dr. Fergusson (thesis supervisor), Dr. Tinmouth (TAC member) and Dr. Saidenberg (TAC member) were involved in the conception and design the study, as well as critically revising the manuscript. Dr. Fergusson also provided guidance with data analysis.

Publication Information

As of February 18, 2019, this study has been accepted for publication in *Transfusion*. See Appendix D at the end of the thesis for the letter of acceptance. Due to copyright agreements, the submitted version of the manuscript (not the accepted version) is presented here.

Additional Information

All tables, figures, and appendices relating to the study are found at the end of the manuscript. The STROBE checklist and ethics approval for this study can be found in Appendices E and F, respectively, at the end of the thesis.

ABSTRACT

Background: Little is known about patients who are transfused with two or more different blood components (multicomponent transfusions). However, these patients are of importance, as they are large consumers of blood products, and likely have different characteristics and health outcomes than non-transfused patients and patients transfused with only one blood component type. The purpose of this study was to determine the prevalence of multicomponent transfusion at our center and characterize patient groups that are frequently multicomponent transfused. As a secondary objective, we examined patient characteristics and health outcomes associated with multicomponent transfusion.

Methods: We conducted a retrospective cohort study of transfused adult inpatients at the 3 campuses of the Ottawa Hospital between 2007 and 2017. Transfusions of interest were those involving red blood cells (RBCs), platelets, plasma, cryoprecipitate and/or fibrinogen concentrate. Descriptive analyses were done to characterize the study population and determine multicomponent transfusion prevalence. Multivariable regression analysis was performed to determine patient characteristics (sex, age, patient type) and outcomes (in-hospital mortality, discharge location, length of stay) associated with multicomponent transfusion. As RBCs are the most common blood product transfused, multicomponent transfusion patients were compared to those receiving only RBCs in regression analyses.

Results: Of 55,719 adult transfused inpatient admissions, 25.1% received a multicomponent transfusion, while 74.9% were transfused with only 1 type of blood product, of which 90% received only RBCs. Multicomponent transfusion prevalence was highest in hematology, cardiac surgery, critical care, cardiology, vascular surgery, and trauma patients. Patient sex, age, and type were predictive of multicomponent transfusion. Multivariable regression analysis showed

that compared to RBC only transfusion, multicomponent transfusion was associated with a 3.51 time increase in odds of in-hospital mortality (95% CI: 3.28, 3.75), greater odds of institutional discharge as opposed to discharge home (OR=1.22, 95% CI: 1.15, 1.30), and a 1.58 time increase in length of hospital stay (95% CI: 1.55, 1.62).

Discussion: Currently, the majority of studies on blood component utilization overlook multicomponent transfusion patients. Multicomponent transfused patients make up a large proportion of the transfused population and have poorer outcomes. As such, it is of importance to continue characterizing multicomponent transfusion recipients and their outcomes, and to evaluate and monitor transfusion appropriateness in this patient population in order to develop a body of literature that can be used to inform best practices in this population.

Keywords: blood transfusion, red blood cells, platelets, plasma, cryoprecipitate, fibrinogen concentrate, retrospective cohort, epidemiology, prevalence

BACKGROUND

Blood transfusion is the most common procedure performed in hospital, occurring in a wide variety of patient populations and hospital departments [1,2]. Patients may receive transfusions of a single blood component (e.g. only red blood cells), or they may be transfused with several different blood products within a transfusion episode or within a hospitalization (multicomponent transfusion). Existing literature on blood product utilization and epidemiology has largely focused on describing individual blood product usage, consequently ignoring patients who receive multicomponent transfusions [3-18]. Multicomponent transfusion recipients differ from patients transfused with only one type of blood product as they likely have higher illness acuity, or a very different medical condition, which would necessitate the transfusion of several different blood components as opposed to only one type. Co-transfusions of different blood components, as compared to only one component, may also be associated with different post-transfusion health outcomes for patients, since the risk of transfusion reactions varies by blood component and may increase with the number of units transfused. Given the differences between multicomponent transfusion recipients and those receiving transfusions of only one blood component, it is of importance to characterize not only the epidemiology of single blood component transfusion, but also that of multicomponent transfusion. Information on multicomponent transfusion – including prevalence, predictors, and potential health consequences – can aid clinicians in their decision-making for patient blood management, potentially increasing appropriate transfusion practice, minimizing unnecessary patient exposure to blood products, and maximizing the use of transfusion alternatives and blood conservation methods.

Some studies have previously reported on multicomponent transfusion and recipients [2,19-54]. However, multicomponent transfusion was not the primary focus or objective in any of these studies, and consequently little information or detail was provided on co-transfusion of blood products. Of note, almost a quarter of these studies were published only as conference abstracts, presenting very limited data. Furthermore, given the variability of transfusion practice and guidelines across regions and centers, there is a need to characterize multicomponent transfusion and recipients locally. While several of the mentioned studies were conducted in Canada, none have evaluated multicomponent transfusion at our large academic center.

The present study aimed to describe the epidemiology of multicomponent transfusion at three campuses of a large academic hospital in Ottawa, Canada over an 11-year period. We determined the prevalence of multicomponent transfusion at our center between 2007 and 2017, and characterized the patient groups that receive blood product co-transfusions. As a secondary objective, we examined patient characteristics and health outcomes associated with multicomponent transfusion.

METHODS

The STROBE guidelines were followed throughout the conduct and reporting of this study [55]. This study was approved by the Ottawa Health Science Network Research Ethics Board.

We conducted a retrospective cohort using the Ottawa Hospital Data Warehouse (OHDW). The Ottawa Hospital is an academic, three-campus, 1,200 bed institution. It is the largest tertiary-care referral center for adults in a region of over 1.2 million residents. The OHDW is a data repository containing clinical and demographic information on patients admitted to the three campuses of the Ottawa Hospital from 2006/2007 onwards. The Transfusion Data Mart (TDM)

is a subsection of the OHDW containing data on patients who were transfused during their hospital stay. This study utilized data from the TDM, and queried necessary variables not available in the TDM from the OHDW. Patient and hospital admission data were deterministically linked with transfusion data using unique admission and patient identifiers. The unit of analysis was hospital admissions. All patient information was anonymized and de-identified.

All adult (≥18 years) inpatients admitted and discharged from any of the three campuses of the Ottawa Hospital between January 1, 2007, and December 31, 2017, who received a minimum of one blood component transfusion during their hospital stay were included in the study cohort. Eligible transfused blood products were red blood cells (RBCs), platelets (PLTs), plasma (FP), and cryoprecipitate or fibrinogen concentrate (collectively termed 'fibrinogen replacement', FR). All admissions for a given patient between 2007 and 2017 were included. Exclusion criteria were non-inpatients (outpatients, medical daycare, emergency room patients, etc.), pediatric patients, transfusions of blood product derivatives (clotting factors, immunoglobulins, albumin, etc.), and autologous or directed transfusions.

The exposure was multicomponent transfusion, which was defined as a transfusion of two or more different blood components during a transfusion episode. Three definitions of 'transfusion episode' were used to capture various time frames during which different patient groups may receive multicomponent transfusions. Multicomponent transfusion episode was defined as (i) any point during the index admission (overall multicomponent transfusion), (ii) within 4h of the first transfusion of the index admission (≤4h multicomponent transfusion), and (iii) within 24h of the first transfusion of the index admission (≤24h multicomponent transfusion). Multicomponent transfusions were classified into types based on the combination of blood components being co-

transfused (e.g. RBC+PLT, PLT+FP, RBC+PLT+FP, etc.). Data on all blood component transfusions for every admission was obtained from the TDM. Admissions with multicomponent transfusion were compared to admissions with transfusions of only RBCs. RBCs was chosen as the comparator cohort as it is the most frequently transfused blood component.

To identify the patient groups that receive multicomponent transfusions, patients were classified into types by admitting physician division. Trauma patients were identified using the following separate, comprehensive algorithm: admissions with (a) an abstracted diagnosis code for trauma, or (b) admission to trauma nursing unit, or (c) use of trauma services during admission. Using admitting physician division and the trauma algorithm, patient type was categorized as follows: cardiac surgery, vascular surgery, orthopedic surgery, other surgery, cardiology, internal medicine (other than cardiology), trauma, critical care, hematology, oncology, obstetrics and gynecology, geriatrics, otolaryngology, ophthalmology, family practice, physical medicine and rehabilitation, and mental health and psychiatry.

The primary outcome was multicomponent transfusion prevalence among transfused inpatients, which was calculated overall for the study period, for each year of the study period, for each patient type, and for each multicomponent transfusion timeframe (≤4h, ≤24h). Our secondary outcomes were patient characteristics and outcomes associated with multicomponent transfusion. The patient characteristics of interest were sex, age, and patient type (as defined by admitting physician division). The patient outcomes of interest were length of hospital stay (days), in-hospital mortality, and discharge location for patients alive at discharge. Discharge location was dichotomized into institutional discharge (transferred to an acute care unit, long term care facility, etc.) or discharge home (patient discharged home, or signed out, with or without support services).

Data was also collected on available patient-level risk-adjustment variables, including the Charlson Comorbidity Index score, and the Hospital-patient One-year Mortality Risk (HOMR) score. The Charlson index is a validated measure of disease or comorbidity burden [56]. The HOMR score, developed for use as a risk-adjustment variable, predicts the risk of any cause mortality at 1 year after hospital admission based on a variety of baseline patient demographic, illness burden and acuity, and hospitalization level factors [57]. The HOMR score has been validated both internally and in several external cohorts, with excellent calibration and discrimination (c-statistic>0.89) [57,58]. The HOMR score probability ranges from 0 to 1, with higher numbers indicating greater probability of 1-year any cause mortality.

Complete data was available for all study variables, with the exception of discharge location, which was missing in 1% of admissions. Given the very small proportion of missing data, complete case analysis was performed rather than using imputation methods. Additionally, the HOMR score was only available in our database from April 2008 onwards, and was consequently unavailable for admissions prior to that date (n=5830 admissions, 10% of the study cohort). Analyses involving this variable (i.e. all multivariable regression analysis) were performed for hospital admissions between April 2008 and December 31st, 2017 to ensure complete data.

Statistical Analysis

Descriptive analysis was performed to characterize the study population. Comparisons between study groups were done using Chi-square tests, T-tests, or median tests for categorical, continuous, or skewed continuous data, respectively. Multicomponent transfusion prevalence

was calculated using the following formula: number of admissions with multicomponent transfusion / total number of transfused adult inpatient admissions between 2007 and 2017.

Multivariable logistic regression was performed to determine associations between patient characteristics (sex, age, patient type) and the odds of multicomponent transfusion. Age was categorized into 10-year intervals for this analysis due to non-linearity. The age category with the lowest odds of multicomponent transfusion (>85 years) was used as the reference group.

Multivariable logistic regression was performed to determine the association between multicomponent transfusion and the outcomes of in-hospital mortality and discharge location. Finally, the outcome of length of stay (LOS) was analyzed using three approaches: (1) multivariable linear regression, (2) multivariable linear regression with a $\log_e$ transformation of LOS (due to the highly skewed distribution of LOS), and (3) multivariable Cox regression looking at time to hospital discharge, censoring in-hospital deaths. Due to the issue of competing risks between LOS (hospital discharge) and in-hospital mortality, linear regression models for LOS were done separately for patients alive and dead at hospital discharge. Competing risks was accounted for in the Cox models by using the Fine and Gray approach [59].

All multivariable regression models were adjusted for sex, age, patient type, illness burden and severity (Charlson and HOMR scores), and year of hospital admission. Clustering at the level of the patient (since a given patient may have had multiple hospital admissions during the study period and thus been included multiple times in our cohort) was accounted for in all regression analyses by using a marginal regression model with an exchangeable correlation matrix. For each analysis, separate regression models were run for (a) overall multicomponent transfusion, (b) different multicomponent transfusion timeframes (≤4h, ≤24h), and (c) the four most frequent

types of multicomponent transfusion. All regression analyses were done using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and the significance level was set at $p<0.05$.

RESULTS

Study Population

Figure 1 shows a flowchart of the study population selection process, and tables 1-3 show the baseline characteristics of the study cohort for overall, ≤4h, and ≤24h multicomponent transfusion. Between 2007 and 2017, there were a total of 56,340 transfused adult inpatient admissions, of which 55,719 (99%) had complete data and were included in this study. Of these, 13,985 admissions (25.1%) received multicomponent transfusions, whereas 41,734 did not (74.9%). Of the admissions without multicomponent transfusion, 89.8% were administered only RBCs, while 4.5% received only PLTs, 5.6% were transfused only plasma, and 0.2% received only fibrinogen replacement (table 1). Admissions with multicomponent transfusion were more likely to be male; younger; hematology, cardiac surgery, cardiology or critical care patients; and less likely to have a Charlson Comorbidity Index score of zero compared to admissions without multicomponent transfusion ($p<0.0001$) (table 1).

Multicomponent Transfusion Prevalence

In our study population, the overall prevalence of multicomponent transfusion among all transfused inpatients between 2007 and 2017 was 25.1% (95% CI: 24.7%, 25.5%). Meanwhile, the prevalence of ≤4h and ≤24h multicomponent transfusion was 7.7% (95% CI: 7.4%, 7.9%) and 16.2% (95% CI: 15.9%, 16.5%), respectively, over the course of the study period.

The most frequent types of multicomponent transfusion were co-transfusions of RBC+PLT, RBC+FP, RBC+PLT+FP, and RBC+PLT+FP+FR, with prevalence rates of 8.8%, 7.0%, 4.1%, and 3.12%, respectively, in the entire study population, and prevalence rates of 35.2%, 27.8%, 16.5%, and 12.4%, respectively, in the multicomponent transfused cohort (table 1). Other co-transfusions of blood products were uncommon, accounting for less than 10% of all multicomponent transfusions (table 1).

Prevalence Over Time

Between 2007 and 2017, the overall prevalence of multicomponent transfusion remained largely stable, fluctuating slightly between 22.5% and 27.5% (figure 2a). The prevalence of ≤4h and ≤24h multicomponent transfusion was also stable over this time period (figure 2a). However, when examining change in prevalence over time for specific types of multicomponent transfusion, we found some variation in prevalence over the study period. Specifically, the prevalence of both RBC+PLT and RBC+PLT+FP+FR co-transfusions increased from 2007 to 2017, while the prevalence of RBC+FP and RBC+PLT+FP co-transfusions decreased (figure 2b).

Prevalence Across Inpatient Populations

Multicomponent transfusion, when assessed over the entire hospital stay, was most prevalent in hematology patients (50.7%), followed by cardiac surgery patients (45.2%), critical care patients (39.8%), cardiology patients (33.0%), and vascular surgery patients (23.4%) (figure 3a). Meanwhile, ≤24h multicomponent transfusion was most prevalent in cardiac surgery patients (41.2%), followed by cardiology (27.7%) and critical care patients (26.6%). ≤4h multicomponent

transfusion was most prevalent in critical care patients (17.7%), cardiac surgery patients (13.1%), and vascular surgery patients (12.2%).

Multicomponent transfusion prevalence across inpatient populations varied by the specific combination of blood products co-transfused. Figure 3b shows prevalence estimates for the four most common types of multicomponent transfusion in frequently co-transfused patient populations. Multicomponent transfusions of RBC+PLTs were most common in hematology patients, being administered to 43.5% of this patient group. Co-transfusions of RBC+FP were most prevalent in critical care patients (15.3% of patients) and in surgery patients (not including cardiac, orthopedic, and vascular surgery) (11.2% of patients). Multicomponent transfusions of RBC+PLT+FP were most commonly administered to cardiac surgery, cardiology, and critical care patients, with prevalence rates of 12.5%, 9.2%, and 8.8%, respectively. Co-transfusions of RBC+PLT+FP+FR were most prevalent in cardiac surgery and cardiology patients, being administered in 10.2% and 8.8% of these patient groups, respectively.

Patient Characteristics Associated with Multicomponent Transfusion

With respect to patient sex, we found that being male significantly increased the odds of overall multicomponent transfusion by 1.54 times compared to female patients (95% CIs: 1.46, 1.61). The finding that males were more likely than females to receive multicomponent transfusions as opposed to transfusions of only RBCs was consistent across specific multicomponent transfusion types and timeframes (figures 4,5).

Patient age was strongly associated with the need for multicomponent transfusion. The odds of multicomponent transfusion, overall and for specific types, were generally highest in patients between the ages of 26 and 45, and then the odds decreased as age increased (figures 4,5).

Patients over the age of 85 had the lowest odds of receiving multicomponent transfusion compared to all other age groups.

Patient type also strongly influenced the odds of multicomponent transfusion. The effect of individual patient types on multicomponent transfusion requirement typically varied across different multicomponent transfusion types and timeframes (figures 4,5). Being a cardiac surgery, cardiology, critical care, or trauma patient significantly increased the odds of receiving a multicomponent transfusion, as compared to a transfusion of only RBCs, for all multicomponent transfusion timeframes and types (figures 4,5). Hematology patients were overall found to have 8 times the odds of being multicomponent transfused than transfused with only RBCs (adjusted odds ratio (aOR) = 8.07, 95% CIs: 6.91, 9.42), but this effect varied by type of multicomponent transfusion. Hematology patients had 29 times the odds of receiving co-transfusions of RBC+PLT than RBC only transfusions (aOR=29.32, 95% CIs: 21.35, 40.26), but were 70% less likely to receive RBC+FP co-transfusions (aOR=0.30, 95% CIs: 0.20, 0.44). Being an internal medicine patient slightly increased the odds of overall MT, and the odds of RBC+FP and RBC+PLT+FP co-transfusions, but did not significantly affect the odds of being transfused with RBC+PLT or with RBC+PLT+FP+FR, as compared to only RBCs only (figures 4,5). Oncology patients were overall less likely to be multicomponent transfused (aOR = 0.77, 95% CIs: 0.65, 0.92), but had 2.4 times the odds of receiving RBC+PLT co-transfusions than RBCs only (95% CI: 1.71, 3.36). Orthopedic surgery patients had increased odds of being ≤4h and ≤24h multicomponent transfused (figure 4). Being a vascular surgery or other surgery (other than cardiac, orthopedic, and vascular) patient increased the odds of overall, ≤4h, and ≤24h multicomponent transfusion, as compared to RBCs only (figures 4).

Outcomes Associated with Multicomponent Transfusion

In-Hospital Mortality

In-hospital mortality occurred in a total of 5,363 adult, transfused inpatient admissions (11.6%) over the course of the study period. Multivariable regression analysis, adjusting for patient characteristics and illness burden and severity, showed than multicomponent transfusion recipients had 3.5 times the odds of in-hospital mortality (aOR=3.51, 95% CIs: 3.28, 3.75) compared to patients transfused with only RBCs. This finding of increased odds of in-hospital mortality was also observed for ≤4h and ≤24h multicomponent transfusion recipients, as well as for common types of multicomponent transfusion (table 4).

Discharge Location

Among patients alive at hospital discharge (n=40,921), 72.5% were discharged home, while 27.5% were discharged to an institution (transferred to an acute care unit, long term care facility, etc.). The effect of multicomponent transfusion on discharge location (institutional discharge versus discharged home) was evaluated with multivariable logistic regression. We found that overall multicomponent transfusion, as compared to RBC only transfusion, increased the odds of institutional discharge by 22% (aOR=1.22, 95% CIs: 1.15, 1.30). When looking at multicomponent transfusion timeframe, ≤4h multicomponent transfusion was associated with a 13% increase in the odds of institutional discharge compared to RBC only transfusion (aOR=1.14, 95% CIs: 1.03, 1.25), whereas ≤24h multicomponent transfusion had a slight but non-significant effect on discharge location (aOR=1.07, 95% CIs: 1.00, 1.15). Compared to RBC only transfusion, the odds of institutional discharge were significantly increased for patients receiving co-transfusions of RBC+FP, RBC+PLT+FP, and RBC+PLT+FP+FR, but not for those receiving RBC+PLT co-transfusions (table 5).

Length of Stay

The mean (SD) and median (IQR) LOS in our study population were 20.3 days (28.0) and 12.1 days (6.0, 24.0), respectively. The association between multicomponent transfusion and hospital LOS was examined using three different methods (Appendix A). Firstly, multivariable linear regression was performed, separately for patients alive and dead at discharge due to the issue of competing risks between LOS and in-hospital mortality (table A1). For patients alive at discharge, we found that overall multicomponent transfusion increased hospital LOS by 8.9 days (95% CIs: 8.17, 9.61), compared to transfusion of RBCs alone. An increase in LOS was also observed when examining different timeframes and types of multicomponent transfusion (table A1). Co-transfusion of RBC+PLT+FP+FR as compared to RBCs increased LOS by 16.7 days (95% CIs: 14.46, 18.91). In patients who passed away in-hospital, overall multicomponent transfusion either decreased LOS or had no significant effect on LOS (table A1).

The above analysis was repeated with a $\log_e$ transformation of LOS, given its highly skewed distribution. Distributions of the original and log transformed LOS variables can be found in Appendix B. Table A2 shows the results of the $\log_e$ transformed LOS analysis, with parameter estimates exponentiated to the power of e for ease of interpretation. For patients alive at hospital discharge, overall multicomponent transfusion increased LOS by 1.6 times (95% CIs: 1.55, 1.62), compared to transfusion of RBCs alone. Different multicomponent transfusion types and timeframes were also associated with an increased LOS (table A2). For patients that died in-hospital, multicomponent transfusion either decreased LOS or had no significant effect on LOS, depending on the type and timeframe of multicomponent transfusion (table A2).

Finally, to account for competing risks between LOS and in-hospital mortality using a more rigorous method, we performed Cox regression using the Fine and Gray approach [59], using

hospital discharge (LOS) as the outcome and censoring in-hospital deaths. This analysis showed that overall multicomponent transfusion recipients were 41% less likely to be discharged (aHR=0.59, 95% CIs: 0.57, 0.60), compared to RBC only recipients. This finding held when analyzing by different multicomponent transfusion types and timeframes (table A3).

We performed a sensitivity to examine the effect of excluding patients with an extreme LOS, which we defined as greater than 200 days, from regression analysis. There were 165 encounters in the analytic dataset having LOS greater than 200 days; the median LOS among these was 253 days (IQR: 221, 308). These encounters were primarily trauma (28%), internal medicine (27%), and surgery (12%) patients, and had a higher prevalence of multicomponent transfusion compared to the rest of the study population (36% versus 25%). In-hospital mortality occurred in 28% of these encounters, while in those who survived, the majority (80%) were discharged to an institution (e.g. long-term care), as opposed to being discharged home. Removing LOS outliers from regression models did not alter effect estimates, and did not significantly reduce the number of influential observations or improve model fit. As such, LOS outliers were kept in regression analyses.

DISCUSSION

Patients transfused with several different types of blood components are largely overlooked by studies on the epidemiology of blood products, as these studies typically focus on single blood product transfusion. Consequently, there is a paucity of literature describing multicomponent transfusion recipients and their health outcomes. In our study, we analyzed an 11-year cohort of transfused adult patients to provide a description of the inpatient groups that receive multicomponent transfusions and to determine trends in multicomponent transfusion prevalence over time. We also compared multicomponent transfusion recipients to patients receiving only

RBC transfusions – the most common single blood component type transfusion – with respect to patient characteristics and health outcomes.

The overall prevalence of multicomponent transfusion in our study population between 2007 and 2017 was high, with over one-quarter of transfused adult inpatients receiving two or more different blood products during their hospital admission. The high prevalence of multicomponent transfusion highlights the importance of studying multicomponent transfused patients and their outcomes. Several previous studies have examined multicomponent transfusion prevalence in a general adult population of transfused hospital patients, and have reported prevalence rates that range from 0.4% to 77.3% [20,30,49,51]. The variability in prevalence rates may stem from regional and center differences in transfusion practice, from differences in patient type distribution across hospitals (e.g. one center may receive fewer trauma or surgery patients than another), and from different types of multicomponent transfusion being investigated (some types are much more prevalent than others).

When looking at trends in multicomponent transfusion over time, we found that the overall prevalence of multicomponent transfusion remained stable between 2007 and 2017. This finding is supported by two previous studies, both of which reported that multicomponent transfusion prevalence did not change much over time in their study populations [21,45]. This is surprising, given the changes that have occurred in transfusion practice and guidelines over the past decades, including a shift towards minimizing patient exposure to transfusions, and changing ratios of blood components for trauma patients [60-63]. However, when looking at specific types of multicomponent transfusion, we observed changes in prevalence over time: RBC+PLT and RBC+PLT+FP+FR co-transfusion prevalence rates increased from 2007 to 2017, whereas those of RBC+FP and RBC+PLT+FP co-transfusions decreased. These trends may be in part explained

by a previous study conducted at our center than found an increase in the number of admission transfused with RBC and PLT, and a decrease in the proportion of admissions receiving FP between 2006 and 2012 [5]. Additionally, the introduction of prothrombin complex concentrate – a concentrate of several blood clotting factors, distributed in Canada since 2008 – has decreased the use of FP to reverse anticoagulant effects in bleeding patients. Furthermore, changing proportions of patient types admitted to our hospital over the course of the study period may help explain the observed trends in multicomponent transfusion prevalence. In our study population, there was a 3% decrease in the proportion of internal medicine admissions since 2013, a 3% increase in the proportion of hematology admissions since 2014, and a gradual 2.5% increase in the proportion of trauma admissions since 2007. We found that internal medicine admissions were associated with both RBC+FP and RBC+PLT+FP co-transfusions, which may explain the observed decrease in prevalence of these two multicomponent transfusion types over time. Meanwhile, trauma and hematology admissions were associated with the need for both RBC+PLT and RBC+PLT+FP+FR co-transfusions, which may have resulted in the observed increase in prevalence of these multicomponent transfusion types.

We also characterized the inpatient groups that commonly receive multicomponent transfusions in the hospital. These included (from highest to lowest multicomponent transfusion prevalence) hematology, cardiac surgery, critical care, cardiology, vascular surgery, trauma, surgery, and internal medicine patients. Multicomponent transfusion prevalence varied not only by patient type but also by the combination of blood products being transfused; we found that co-transfusions of RBC+PLT were most common at our center, followed by RBC+FP, RBC+PLT+FP, and RBC+PLT+FP+FR co-transfusions.

To extend our descriptive analysis, we performed an exploratory inferential analysis to determine patient characteristics and outcomes associated with multicomponent transfusion. We found that patient sex, age and type all predicted multicomponent transfusion requirement. Males and patients aged 26-45 had the highest odds of receiving a multicomponent transfusion. With respect to health outcomes, multivariable regression analysis controlling for a variety of factors including illness burden and severity showed that multicomponent transfusion increased the odds of in-hospital mortality, the odds of institutional discharge (as opposed to discharge home), and greatly prolonged hospital length of stay, as compared to patients receiving only RBC transfusions. Worsened outcomes for multicomponent transfusion recipients pose implications at the hospital and healthcare system level, given the costs associated with longer hospital stays and long-term care institutions, as well as the lack of beds. Although residual confounding, including confounding by indication, may be a possible explanation for these results, it is also possible that other reasons exist for the poorer outcomes observed for multicomponent transfusion recipients compared to those receiving only RBC transfusions. For instance, receiving several different types of blood products may increase one's risk of transfusion-related adverse events, which in turn may lead to worse outcomes including mortality or prolonged hospitalization. Going forward, it would be of interest to examine the role of transfusion-related adverse events as mediators in the association between multicomponent transfusion and outcomes such as mortality and hospital length of stay.

Several other studies have looked at outcomes of multicomponent transfusion in specific patient populations. It has been reported that in cardiac surgery patients, multicomponent transfusion is associated with increased odds of profound vasoplegia, postoperative stroke, and postoperative thromboembolic events, and in liver transplant patients, it has been associated with greater odds of acute lung injury [19,27,39,40,54]. Our study is the first to report on outcomes of in-hospital

mortality, LOS, and discharge location, and for a general hospital population as opposed to a particular patient group. Another strength of our study is that we controlled for both illness severity and burden using validated measures to attempt to minimize confounding by indication, whereas only one of the previous studies adjusted for illness severity and none adjusted for illness burden.

To better understand and describe the nature of multicomponent transfusion, we used 3 different timeframes and definitions of co-transfusion: ≤4h, ≤24h, and overall (at any point in the hospital admission) multicomponent transfusion. We found that certain multicomponent transfusion timeframes were more relevant for certain patient types than for others. For instance, cardiac surgery was more strongly associated with ≤24h multicomponent transfusion than with overall or ≤4h co-transfusion. Similarly, trauma and critical care were both more strongly predictive of ≤4h multicomponent transfusion than of ≤24h or overall multicomponent transfusion. As such, by using different timeframes and definitions of multicomponent transfusion, we were able to more accurately capture multicomponent transfusion in various patient populations.

Our study findings give rise to several questions, which could be directions for future research on multicomponent transfusion. Firstly, regarding patient characteristics, it would be of interest to determine the reasons behind the observed increased odds of multicomponent transfusion for males compared to females, and for the age differences in the odds of multicomponent transfusion. Secondly, there is the question of how multicomponent transfusion recipients who died in-hospital differ from those who survived.

When blood product utilization is studied individually (e.g. RBC recipients separate from PLT recipients, separate from FP recipients, etc.), multicomponent transfused patients are consequently incorrectly captured or are overlooked. Given our findings that (a) multicomponent

transfused recipients make up a large portion of transfused hospital patients, (b) multicomponent recipients have different characteristics and outcomes compared to patients transfused with only one blood product type, and that (c) the outcomes of multicomponent transfusion recipients are often poorer, it is important to explicitly characterize patients receiving multicomponent transfusions, to monitor the appropriateness of transfusion in these individuals, and to employ blood conservation techniques and blood alternatives where appropriate. Future studies looking to describe transfusion recipients or the utilization of blood components should not only describe individual blood component use, but also the phenomenon of multicomponent transfusion. In this way, all transfusion recipients will be accurately captured and described.

Our study has limitations. Firstly, despite our large sample size and data from three campuses of our institution, this was a single institution study, which limits the generalizability of our results. Secondly, this was a retrospective study using already collected health administrative data, and as such we were somewhat limited by the quality of data, availability of variables, and missing data. For instance, while we wished to investigate the association between multicomponent transfusions and transfusion reactions, we were unable to do so due to poor quality data and frequent underreporting of transfusion reactions. Ideally, prospectively collected data would be needed to study this association. A third limitation is that we treated multicomponent transfusion as a single dichotomous variable, and not as a time-dependent effect. Consequently, there is the possibility of immortal time bias, since for patients who eventually received a multicomponent transfusion during their admission, follow-up time between the initial transfusion of the admission and subsequent transfusion of a different component was not classified as 'unexposed'.

CONCLUSION

In our 11-year retrospective cohort study of transfused adult hospital inpatients, we found that over 25% of admissions received one or more multicomponent transfusions, while the remaining admissions received only one type of blood product (mostly RBCs). Inpatient groups that were frequently co-transfused were hematology, cardiac surgery, critical care, cardiology, vascular surgery, trauma, surgery, and internal medicine patients. RBC+PLT and RBC+FP co-transfusions were most common. Patient characteristics such as sex, age, and patient type were predictive of multicomponent transfusion. Finally, multivariable regression analysis found multicomponent transfusion to be associated with greater odds of in-hospital mortality, institutional discharge as opposed to discharge home, and increased length of hospital stay. Given the large proportion of transfused admissions with multicomponent transfusion, and the poorer health outcomes associated with multicomponent transfusion, it is of importance to continue studying multicomponent transfused individuals and their outcomes, and to monitor transfusion appropriateness in these patients.

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TABLES

Table 1. Characteristics of multicomponent transfused adult inpatient admissions, compared to admissions without multicomponent transfusion and those with only red blood cell transfusions.

Characteristic	MT[a] (n = 13,985)	No MT[b] (n = 41,734)	No MT: RBCs Only (n = 37,471)	MT vs No MT P-value[c]	MT vs RBC Only P-value[c]
Age (years), mean (SD)	62.3 (16.1)	66.3 (17.2)	66.6 (17.2)	<0.0001	<0.0001
Sex, n (%)					
Male	8,389 (60.0)	20,031 (48.0)	17,228 (46.0)	<0.0001	<0.0001
Female	5,596 (40.0)	21,703 (52.0)	20,243 (54.0)		
Patient Type, n (%)					
Hematology	3,340 (23.9)	3,249 (7.8)	2,537 (6.8)	<0.0001	<0.0001
Cardiac surgery	2,070 (14.8)	2,513 (6.0)	2,079 (5.6)		
Internal medicine[d]	1,606 (11.5)	8,202 (19.7)	7,375 (19.7)		
Cardiology	1,536 (11.0)	3,124 (7.5)	2,848 (7.6)		
Trauma	1,464 (10.5)	5,916 (14.2)	5,545 (14.8)		
Surgery[e]	1,410 (10.1)	6,405 (15.4)	5,583 (14.9)		
Critical Care	896 (6.4)	1,356 (3.3)	1,058 (2.8)		
Vascular surgery	606 (4.3)	1,983 (4.8)	1,825 (4.9)		
Oncology	555 (4.0)	4,785 (11.5)	4,577 (12.2)		
Orthopedic surgery	224 (1.6)	1,921 (4.6)	1,884 (5.0)		
Obstetrics & gynecology	191 (1.4)	1,443 (3.5)	1,378 (3.7)		
Family Practice	68 (0.5)	651 (1.6)	610 (1.6)		
Geriatrics	17 (0.1)	154 (0.4)	151 (0.4)		
Physical medicine & rehabilitation	1 (0.01)	8 (0.02)	7 (0.02)		
Ophthalmology	1 (0.01)	7 (0.02)	4 (0.01)		
Mental health & psychiatry	0 (0)	11 (0.03)	10 (0.03)		
Types of blood products administered, n (%)					
RBC	13,409 (95.9)	37,471 (89.8)	37,471 (100)	<0.0001	<0.0001
PLT	9,764 (69.8)	1,866 (4.5)	0 (0)	<0.0001	<0.0001
FP	8,647 (61.8)	2,318 (5.6)	0 (0)	<0.0001	<0.0001
FR	2,502 (17.9)	79 (0.2)	0 (0)	<0.0001	<0.0001
Types of MT administered, n (%)					
RBC+PLT	4,925 (35.2)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FP	3,888 (27.8)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FR	97 (0.7)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FP	363 (2.6)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FR	52 (0.4)	0 (0)	0 (0)	<0.0001	<0.0001
FP+FR	46 (0.3)	0 (0)	0 (0)	<0.0001	<0.0001

RBC+PLT+FP	2,307 (16.5)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+PLT+FR	264 (1.9)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FP+FR	190 (1.4)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FP+FR	115 (0.8)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+PLT+FP+FR	1,738 (12.4)	0 (0)	0 (0)	<0.0001	<0.0001
Charlson comorbidity index score, n (%)					
0	2,830 (20.2)	11,638 (27.9)	10,476 (28.0)		
1-2	6,416 (45.9)	14,864 (35.6)	13,051 (34.8)	<0.0001	<0.0001
3-4	2,944 (21.1)	7,538 (18.1)	6,844 (18.3)		
5+	1,795 (12.8)	7,694 (18.4)	7,100 (19.0)		
HOMR 1-year mortality probability[f], median (IQR)	0.23 (0.08, 0.54)	0.26 (0.07, 0.64)	0.26 (0.07, 0.65)	<0.0001	<0.0001

Abbreviations: MT, multicomponent transfusion; n, number; %, percent; RBCs, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate); HOMR, Hospital-patient One-year Mortality Risk score.

[a] Any type of multicomponent transfusion at any point in the index admission.

[b] Admissions with transfusions of any one type of blood component, but not multicomponent transfusions.

[c] P-value from Chi-square test, T-test, or median test for categorical, continuous, or skewed continuous data, respectively.

[d] Internal medicine other than cardiology.

[e] Surgeries other than cardiac, vascular, orthopedic, and obstetric/gynecologic surgeries.

[f] The HOMR score was unavailable for admissions prior to April 2008, data shown are based on a total sample size of n=49,889.

Table 2. Characteristics of adult inpatient admissions with multicomponent transfusion within 4h of the first transfusion of the admission, compared to admissions without immediate multicomponent transfusion and those with only red blood cell transfusions.

Characteristics	≤4h MT (n=4,271)	≤4h No MT[a] (n=51,448)	≤4h No MT: RBCs Only (n=43,501)	MT vs No MT P-value[b]	MT vs RBC Only P-value[b]
Age (years), mean (SD)	61.7 (17.0)	65.6 (17.0)	66.2 (17.0)	<0.0001	<0.0001
Sex, n (%)					
Male	2,605 (61.0)	25,815 (50.2)	20,844 (47.9)	<0.0001	<0.0001
Female	1,666 (39.0)	25,633 (49.8)	22,657 (52.1)		
Patient Type, n (%)					
Trauma	715 (16.7)	6,786 (13.2)	6,134 (14.1)		
Cardiac surgery	601 (14.1)	3,982 (7.7)	3,391 (7.8)		
Internal medicine[c]	433 (10.1)	9,381 (18.2)	8,017 (18.4)		
Surgery[d]	545 (12.8)	7,149 (13.9)	5,945 (13.7)		
Hematology	454 (10.6)	6,135 (11.9)	3,883 (8.9)		
Cardiology	433 (10.1)	4,227 (8.2)	3,793 (8.7)		
Critical Care	397 (9.3)	1,855 (3.6)	1,245 (2.9)		
Vascular surgery	315 (7.4)	2,274 (4.4)	2,030 (4.7)		
Obstetrics & gynecology	143 (3.4)	1,491 (2.9)	1,411 (3.2)	<0.0001	<0.0001
Orthopedic surgery	121 (2.8)	2,024 (3.9)	1,959 (4.5)		
Oncology	100 (2.3)	5,240 (10.2)	4,859 (11.2)		
Family Practice	12 (0.3)	707 (1.4)	647 (1.5)		
Geriatrics	2 (0.1)	169 (0.3)	164 (0.4)		
Physical medicine & rehabilitation	0 (0)	9 (0.02)	8 (0.02)		
Mental health & psychiatry	0 (0)	11 (0.02)	10 (0.02)		
Ophthalmology	0 (0)	8 (0.02)	5 (0.01)		
Types of blood products administered, n (%)					
RBC	3,518 (82.4)	43,501 (84.6)	43,501 (100)	0.0002	<0.0001
PLT	2,336 (54.7)	4,036 (7.8)	0 (0)	<0.0001	<0.0001
FP	3,277 (76.7)	3,737 (7.3)	0 (0)	<0.0001	<0.0001
FR	746 (17.5)	174 (0.3)	0 (0)	<0.0001	<0.0001
Types of MT administered, n (%)					
RBC+PLT	864 (20.2)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FP	1,742 (40.8)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FR	31 (0.7)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FP	454 (10.6)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FR	82 (1.9)	0 (0)	0 (0)	<0.0001	<0.0001
FP+FR	74 (1.7)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+PLT+FP	465 (10.9)	0 (0)	0 (0)	<0.0001	<0.0001

RBC+PLT+FR	17 (0.4)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FP+FR	88 (2.1)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FP+FR	143 (3.4)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+PLT+FP+FR	311 (7.3)	0 (0)	0 (0)	<0.0001	<0.0001
Charlson comorbidity index score, n (%)					
0	1,186 (27.8)	13,282 (25.8)	11,510 (26.5)		
1-2	1,773 (41.5)	19,507 (37.9)	15,855 (36.5)	<0.0001	<0.0001
3-4	813 (19.0)	9,669 (18.8)	8,222 (18.9)		
5+	499 (11.7)	8,990 (17.5)	7,914 (18.2)		
HOMR 1-year mortality probability[e], median (IQR)	0.19 (0.06, 0.50)	0.26 (0.08, 0.63)	0.25 (0.07, 0.63)	<0.0001	<0.0001

Abbreviations: MT, multicomponent transfusion; n, number; %, percent; RBCs, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate); HOMR, Hospital-patient One-year Mortality Risk score.

[a] Admissions with transfusions of any one type of blood component within 4h, but not multicomponent transfusions.

[b] P-value from Chi-square test, T-test, or median test for categorical, continuous, or skewed continuous data, respectively.

[c] Internal medicine other than cardiology.

[d] Surgeries other than cardiac, vascular, orthopedic, and obstetric/gynecologic surgeries.

[e] The HOMR score was unavailable for admissions prior to April 2008, data shown are based on a total sample size of n=49,889.

Table 3. Characteristics of adult inpatient admissions with multicomponent transfusion within 24h of the first transfusion of the admission, compared to admissions without 24h multicomponent transfusion and those with only red blood cell transfusions.

Characteristics	≤24h MT (n=9,019)	≤24h No MT[a] (n=46,700)	≤24h No MT: RBCs Only (n=40,056)	MT vs No MT P-value[b]	MT vs RBCs Only P-value[b]
Age (years), mean (SD)	63.5 (16.0)	65.6 (17.2)	66.2 (17.2)	<0.0001	<0.0001
Sex, n (%)					
Male	5,557 (61.6)	22,863 (49.0)	18,639 (46.5)	<0.0001	<0.0001
Female	3,462 (38.4)	23,837 (51.0)	21,417 (53.5)		
Patient Type, n (%)					
Cardiac surgery	1,886 (20.9)	2,697 (5.8)	2,165 (5.4)		
Cardiology	1,242 (13.8)	3,418 (7.3)	3,044 (7.6)		
Hematology	1,182 (13.1)	5,407 (11.6)	3,549 (8.9)		
Trauma	1,119 (12.4)	6,382 (13.7)	5,855 (14.6)		
Internal medicine[c]	942 (10.4)	8,872 (19.0)	7,759 (19.4)		
Surgery[d]	938 (10.4)	6,756 (14.5)	5,719 (14.3)		
Critical Care	599 (6.6)	1,653 (3.5)	1,170 (2.9)		
Vascular surgery	483 (5.4)	2,106 (4.5)	1,896 (4.7)		
Oncology	246 (2.7)	5,094 (10.9)	4,776 (11.9)	<0.0001	<0.0001
Orthopedic surgery	175 (1.9)	1,970 (4.2)	1,914 (4.8)		
Obstetrics & gynecology	170 (1.9)	1,464 (3.1)	1,391 (3.5)		
Family Practice	30 (0.3)	689 (1.5)	636 (1.6)		
Geriatrics	7 (0.1)	164 (0.4)	159 (0.4)		
Physical medicine & rehabilitation	0 (0)	9 (0.02)	8 (0.02)		
Mental health & psychiatry	0 (0)	11 (0.02)	10 (0.02)		
Ophthalmology	0 (0)	8 (0.02)	5 (0.01)		
Types of blood products administered, n (%)					
RBC	8,247 (91.4)	40,056 (85.9)	40,056 (100)	<0.0001	<0.0001
PLT	5,973 (66.2)	3,405 (7.3)	0 (0)	<0.0001	<0.0001
FP	6,424 (71.2)	3,096 (6.6)	0 (0)	<0.0001	<0.0001
FR	1,944 (21.6)	143 (0.3)	0 (0)	<0.0001	<0.0001
Types of MT administered, n (%)					
RBC+PLT	2,322 (25.8)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FP	2,741 (30.4)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FR	84 (0.9)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FP	452 (5.0)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FR	83 (0.9)	0 (0)	0 (0)	<0.0001	<0.0001
FP+FR	70 (0.8)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+PLT+FP	1,560 (17.3)	0 (0)	0 (0)	<0.0001	<0.0001

RBC+PLT+FR	106 (1.2)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+FP+FR	151 (1.7)	0 (0)	0 (0)	<0.0001	<0.0001
PLT+FP+FR	167 (1.9)	0 (0)	0 (0)	<0.0001	<0.0001
RBC+PLT+FP+FR	1,283 (14.2)	0 (0)	0 (0)	<0.0001	<0.0001
Charlson comorbidity index score, n (%)					
0	2,115 (23.5)	12,353 (26.5)	10,811 (27.0)		
1-2	3,926 (43.5)	17,354 (37.2)	14,280 (35.7)	<0.0001	<0.0001
3-4	1,920 (21.3)	8,562 (18.2)	7,414 (18.5)		
5+	1,058 (11.7)	8,431 (18.1)	7,551 (18.9)		
HOMR 1-year mortality probability[e], median (IQR)	0.18 (0.06, 0.48)	0.26 (0.08, 0.64)	0.27 (0.08, 0.65)	<0.0001	<0.0001

Abbreviations: MT, multicomponent transfusion; n, number; %, percent; RBCs, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate); HOMR, Hospital-patient One-year Mortality Risk score.

[a] Admissions with transfusions of any one type of blood component within 24h, but not multicomponent transfusions.

[b] P-value from Chi-square test, T-test, or median test for categorical, continuous, or skewed continuous data, respectively.

[c] Internal medicine other than cardiology.

[d] Surgeries other than cardiac, vascular, orthopedic, and obstetric/gynecologic surgeries.

[e] The HOMR score was unavailable for admissions prior to April 2008, data shown are based on a total sample size of n=49,889.

Table 4. Association between multicomponent transfusion (MT), as compared to transfusion of only red blood cells, and the odds of in-hospital mortality, for various MT types and timeframes.

MT Type	Crude OR (95% CIs)	aOR (95% CIs)
Overall MT	2.75 (2.60, 2.92)	3.51 (3.28, 3.75)
MT ≤24h	2.35 (2.20, 2.51)	2.94 (2.72, 3.17)
MT ≤4h	2.80 (2.58, 3.04)	3.14 (2.87, 3.45)
RBC+PLT	1.69 (1.54, 1.85)	2.18 (1.94, 2.44)
RBC+FP	3.09 (2.82, 3.38)	3.16 (2.85, 3.50)
RBC+PLT+FP	3.68 (3.30, 4.10)	4.76 (4.19, 5.41)
RBC+PLT+FP+FR	4.31 (3.84, 4.83)	6.99 (6.09, 8.04)

Abbreviations: MT, multicomponent transfusion; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

Note: Each MT type was modeled in a separate logistic regression model. Regression models were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type. Correlation of data at the patient level (due to patients with multiple hospital admissions during the study period) was accounted for by using marginal regression models.

Table 5. Association between multicomponent transfusion (MT), as compared to transfusion of only red blood cells, and the odds of institutional discharge versus discharge home for patients alive at hospital discharge (n=40,921), for various MT types and timeframes.

MT Type	Crude OR (95% CIs)	aOR (95% CIs)
Overall MT	0.86 (0.82, 0.91)	1.22 (1.15, 1.30)
MT ≤24h	0.84 (0.79, 0.89)	1.07 (1.00, 1.15)
MT ≤4h	1.03 (0.95, 1.11)	1.14 (1.03, 1.25)
RBC+PLT	0.51 (0.47, 0.55)	0.95 (0.85, 1.07)
RBC+FP	1.22 (1.12, 1.33)	1.23 (1.12, 1.36)
RBC+PLT+FP	1.00 (0.89, 1.12)	1.27 (1.11, 1.45)
RBC+PLT+FP+FR	1.29 (1.14, 1.46)	1.91 (1.64, 2.22)

Abbreviations: MT, multicomponent transfusion; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

Note: Each MT type was modeled in a separate logistic regression model. Regression models were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type. Correlation of data at the patient level (due to patients with multiple hospital admissions during the study period) was accounted for by using marginal regression models.

FIGURES

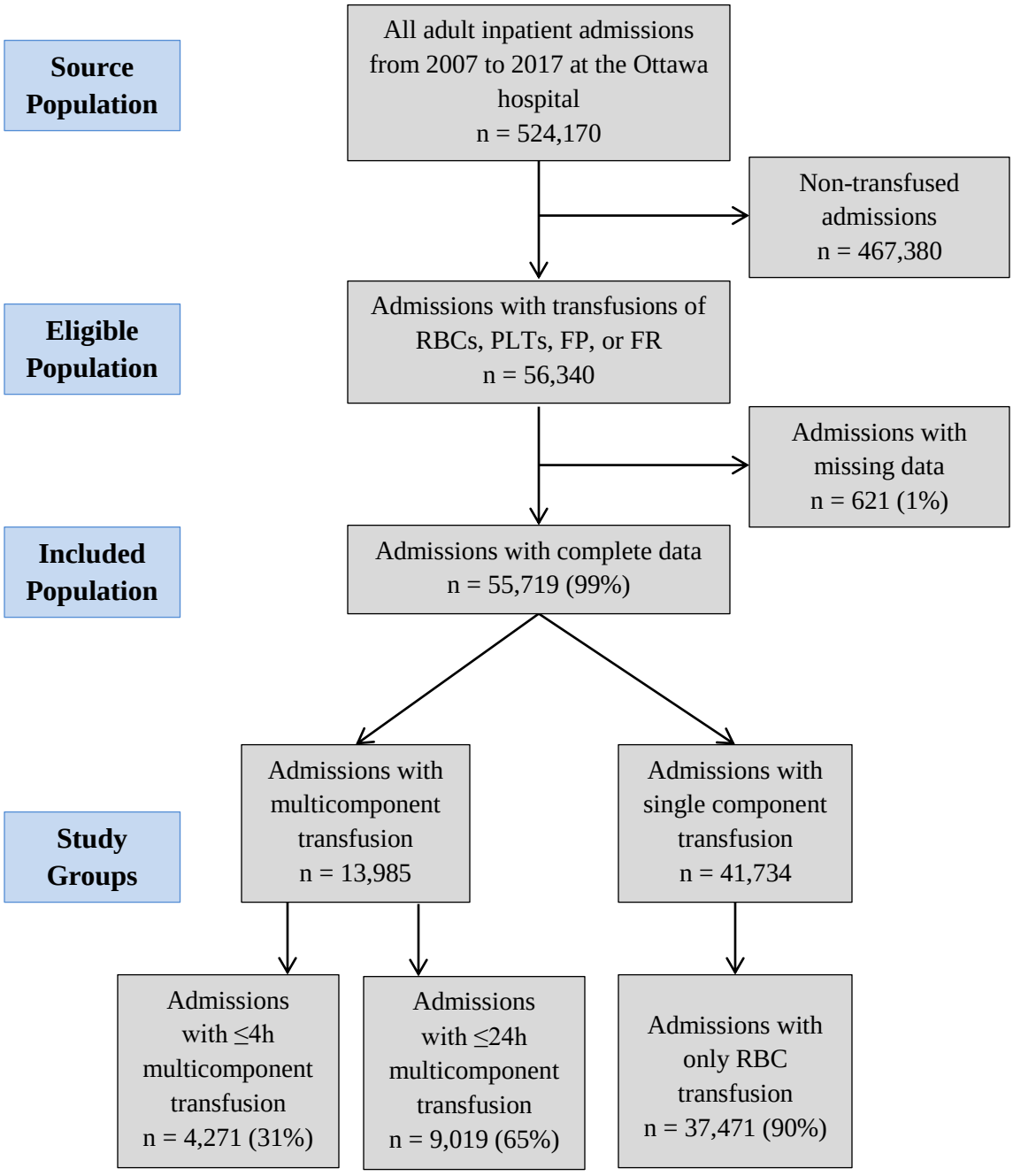

Figure 1. Study population selection process.

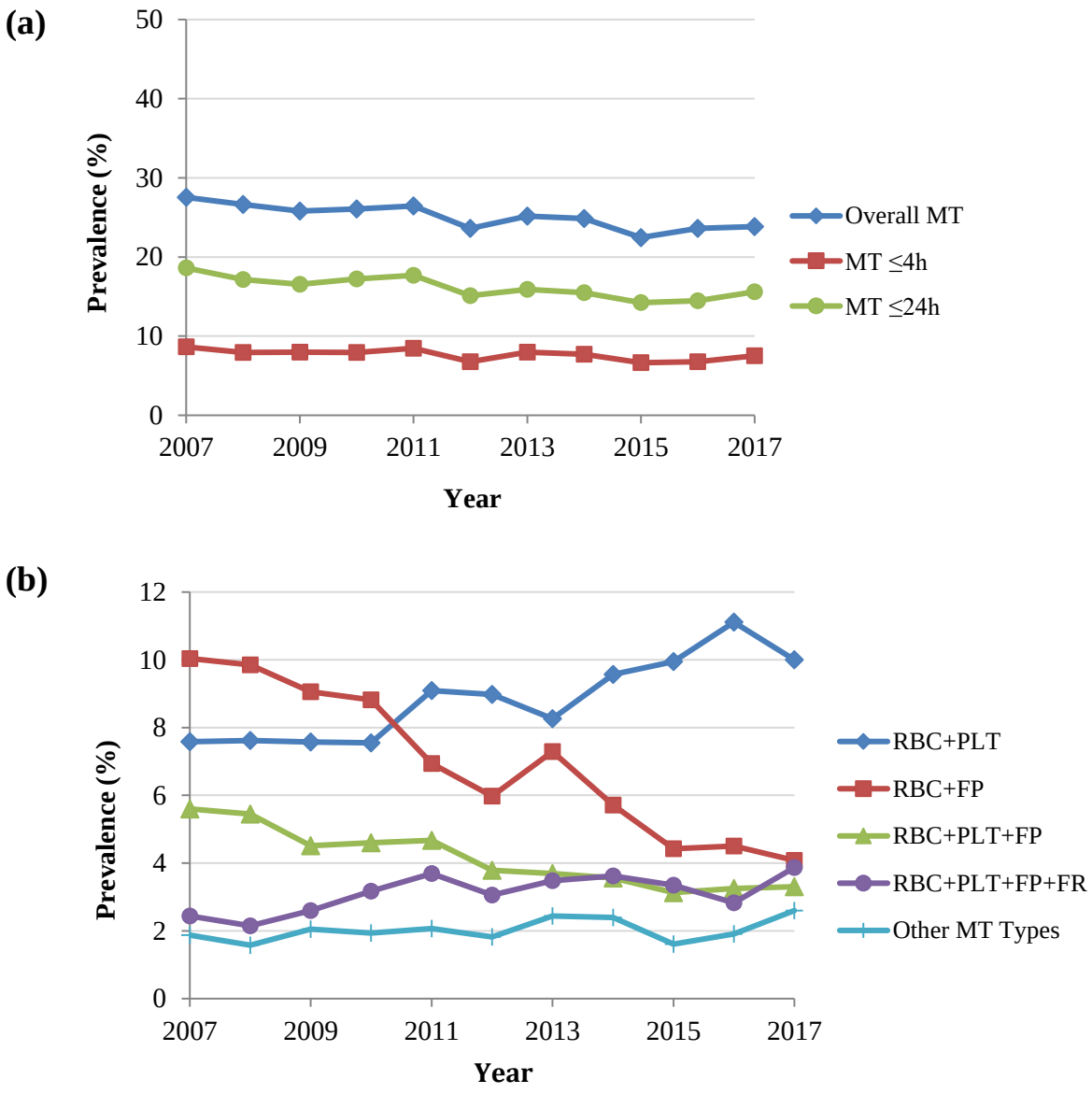

Figure 2. Prevalence of multicomponent transfusion (MT) over the course of the study period (2007-2017), by (a) timeframe (overall, ≤4h, ≤24h) and (b) type of multicomponent transfusion. Abbreviations: RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

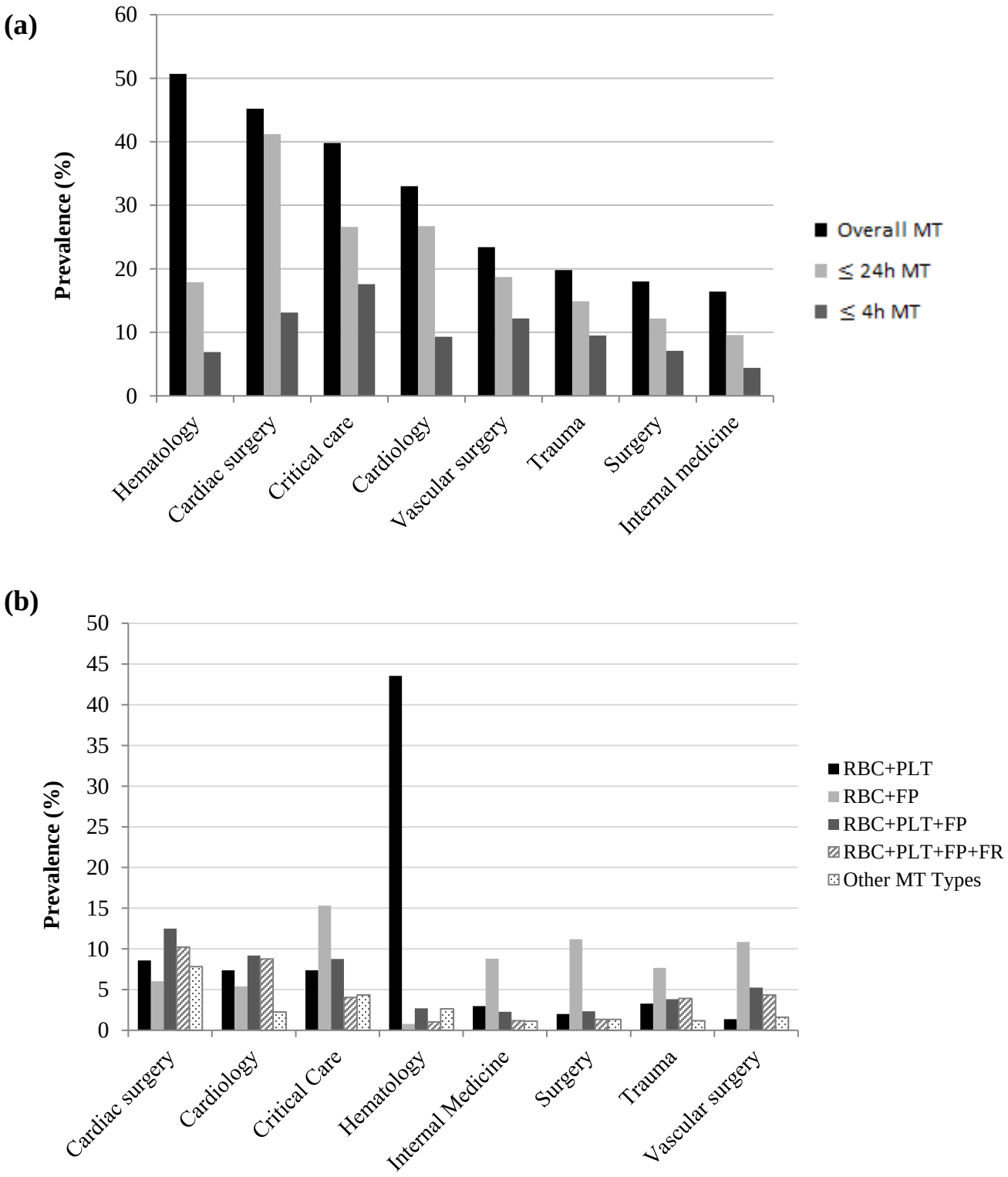

Figure 3. Multicomponent transfusion (MT) prevalence (%) in commonly co-transfused patient populations, by (a) timeframe (overall, ≤4h, ≤24h) and (b) type of multicomponent transfusion. Abbreviations: RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

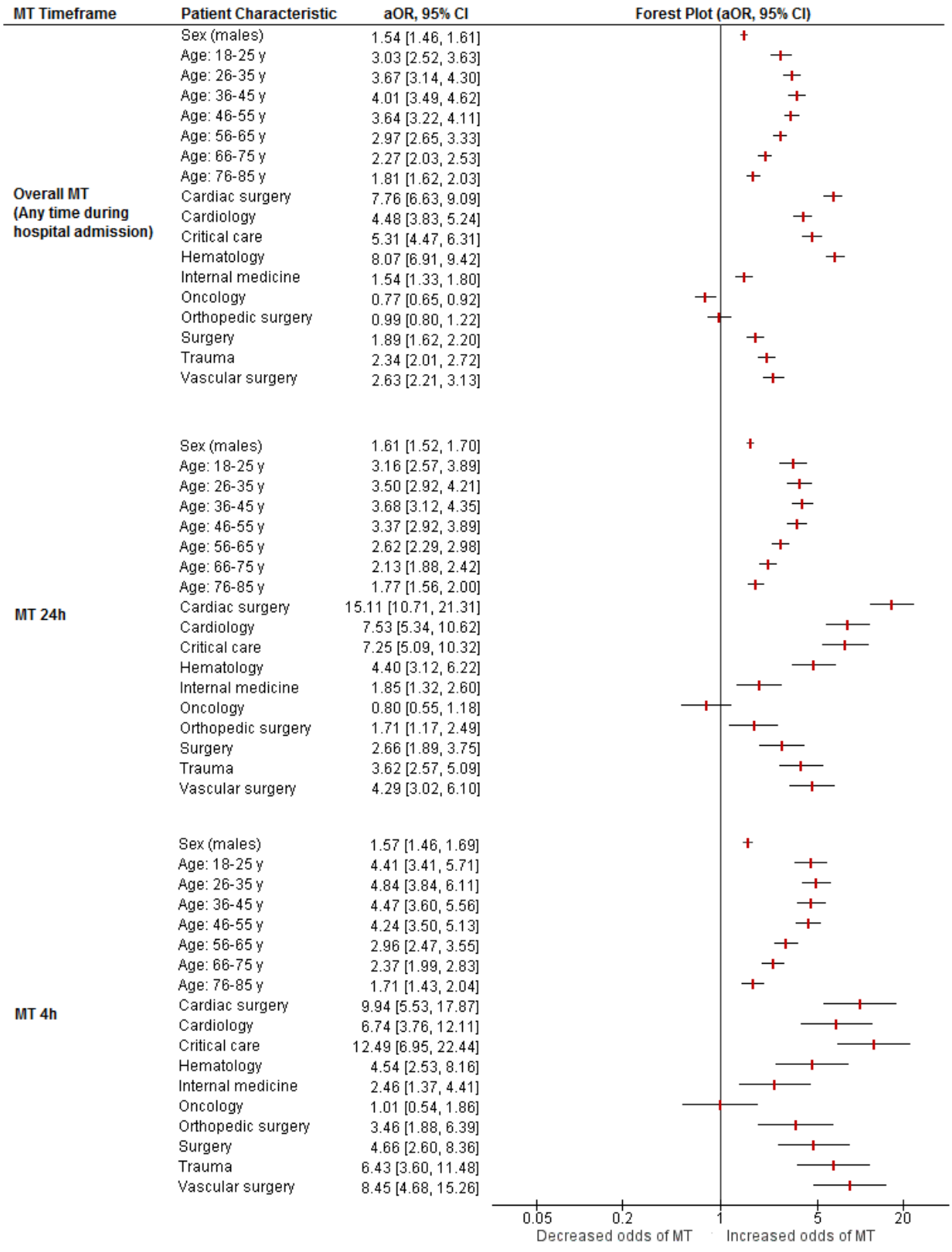
MT Timeframe
Patient Characteristic
aOR, 95% CI
Forest Plot (aOR, 95% CI)
Overall MT (Any time during hospital admission)
Sex (males) 1.54 [1.46, 1.61]
Age: 18-25 y 3.03 [2.52, 3.63]
Age: 26-35 y 3.67 [3.14, 4.30]
Age: 36-45 y 4.01 [3.49, 4.62]
Age: 46-55 y 3.64 [3.22, 4.11]
Age: 56-65 y 2.97 [2.65, 3.33]
Age: 66-75 y 2.27 [2.03, 2.53]
Age: 76-85 y 1.81 [1.62, 2.03]
Cardiac surgery 7.76 [6.63, 9.09]
Cardiology 4.48 [3.83, 5.24]
Critical care 5.31 [4.47, 6.31]
Hematology 8.07 [6.91, 9.42]
Internal medicine 1.54 [1.33, 1.80]
Oncology 0.77 [0.65, 0.92]
Orthopedic surgery 0.99 [0.80, 1.22]
Surgery 1.89 [1.62, 2.20]
Trauma 2.34 [2.01, 2.72]
Vascular surgery 2.63 [2.21, 3.13]
MT 24h
Sex (males) 1.61 [1.52, 1.70]
Age: 18-25 y 3.16 [2.57, 3.89]
Age: 26-35 y 3.50 [2.92, 4.21]
Age: 36-45 y 3.68 [3.12, 4.35]
Age: 46-55 y 3.37 [2.92, 3.89]
Age: 56-65 y 2.62 [2.29, 2.98]
Age: 66-75 y 2.13 [1.88, 2.42]
Age: 76-85 y 1.77 [1.56, 2.00]
Cardiac surgery 15.11 [10.71, 21.31]
Cardiology 7.53 [5.34, 10.62]
Critical care 7.25 [5.09, 10.32]
Hematology 4.40 [3.12, 6.22]
Internal medicine 1.85 [1.32, 2.60]
Oncology 0.80 [0.55, 1.18]
Orthopedic surgery 1.71 [1.17, 2.49]
Surgery 2.66 [1.89, 3.75]
Trauma 3.62 [2.57, 5.09]
Vascular surgery 4.29 [3.02, 6.10]
MT 4h
Sex (males) 1.57 [1.46, 1.69]
Age: 18-25 y 4.41 [3.41, 5.71]
Age: 26-35 y 4.84 [3.84, 6.11]
Age: 36-45 y 4.47 [3.60, 5.56]
Age: 46-55 y 4.24 [3.50, 5.13]
Age: 56-65 y 2.96 [2.47, 3.55]
Age: 66-75 y 2.37 [1.99, 2.83]
Age: 76-85 y 1.71 [1.43, 2.04]
Cardiac surgery 9.94 [5.53, 17.87]
Cardiology 6.74 [3.76, 12.11]
Critical care 12.49 [6.95, 22.44]
Hematology 4.54 [2.53, 8.16]
Internal medicine 2.46 [1.37, 4.41]
Oncology 1.01 [0.54, 1.86]
Orthopedic surgery 3.46 [1.88, 6.39]
Surgery 4.66 [2.60, 8.36]
Trauma 6.43 [3.60, 11.48]
Vascular surgery 8.45 [4.68, 15.26]
0.05
0.2
1
5
20
Decreased odds of MT
Increased odds of MT

Figure 4. Forest plots of the adjusted odds and 95% confidence intervals (CIs) of multicomponent transfusion (MT) for various patient characteristics, by timeframe of MT (overall, ≤24h, ≤4h). Odds ratios were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type.

MT Type	Patient Characteristic	aOR, 95% CI
RBC+PLT	Sex (males)	1.47 [1.35, 1.59]
	Age: 18-25 y	2.16 [1.57, 2.97]
	Age: 26-35 y	2.45 [1.83, 3.28]
	Age: 36-45 y	3.25 [2.50, 4.22]
	Age: 46-55 y	2.89 [2.27, 3.68]
	Age: 56-65 y	2.54 [2.02, 3.19]
	Age: 66-75 y	1.89 [1.51, 2.37]
	Age: 76-85 y	1.56 [1.25, 1.95]
	Cardiac surgery	6.15 [4.41, 8.59]
	Cardiology	4.10 [2.94, 5.72]
	Critical care	5.41 [3.82, 7.67]
	Hematology	29.31 [21.35, 40.25]
	Internal medicine	1.35 [0.97, 1.88]
	Oncology	2.40 [1.71, 3.36]
	Orthopedic surgery	0.69 [0.42, 1.14]
	Surgery	1.01 [0.72, 1.43]
	Trauma	1.90 [1.37, 2.64]
	Vascular surgery	0.64 [0.40, 1.01]
RBC+FP	Sex (males)	1.35 [1.25, 1.46]
	Age: 18-25 y	2.60 [1.95, 3.46]
	Age: 26-35 y	2.90 [2.27, 3.71]
	Age: 36-45 y	2.63 [2.11, 3.29]
	Age: 46-55 y	2.58 [2.15, 3.11]
	Age: 56-65 y	2.23 [1.89, 2.63]
	Age: 66-75 y	1.89 [1.61, 2.22]
	Age: 76-85 y	1.58 [1.35, 1.85]
	Cardiac surgery	2.88 [2.22, 3.73]
	Cardiology	1.76 [1.36, 2.28]
	Critical care	4.26 [3.29, 5.52]
	Hematology	0.30 [0.20, 0.44]
	Internal medicine	1.85 [1.48, 2.33]
	Oncology	0.42 [0.31, 0.56]
	Orthopedic surgery	1.30 [0.97, 1.73]
	Surgery	2.76 [2.20, 3.47]
	Trauma	2.10 [1.67, 2.65]
	Vascular surgery	2.86 [2.20, 3.70]
RBC+PLT+FP	Sex (males)	1.73 [1.56, 1.92]
	Age: 18-25 y	4.50 [2.96, 6.86]
	Age: 26-35 y	4.70 [3.19, 6.93]
	Age: 36-45 y	5.62 [3.99, 7.92]
	Age: 46-55 y	5.90 [4.40, 7.90]
	Age: 56-65 y	3.90 [2.95, 5.16]
	Age: 66-75 y	3.19 [2.43, 4.19]
	Age: 76-85 y	2.47 [1.88, 3.24]
	Cardiac surgery	17.78 [11.64, 27.14]
	Cardiology	10.17 [6.69, 15.47]
	Critical care	9.84 [6.37, 15.21]
	Hematology	3.37 [2.18, 5.20]
	Internal medicine	1.74 [1.14, 2.67]
	Oncology	0.46 [0.27, 0.77]
	Orthopedic surgery	1.23 [0.72, 2.13]
	Surgery	2.00 [1.30, 3.07]
	Trauma	4.00 [2.63, 6.09]
	Vascular surgery	4.86 [3.11, 7.61]
RBC+PLT+FP+FR	Sex (males)	1.73 [1.54, 1.93]
	Age: 18-25 y	7.21 [4.40, 11.83]
	Age: 26-35 y	13.62 [8.88, 20.87]
	Age: 36-45 y	13.42 [8.93, 20.16]
	Age: 46-55 y	9.34 [6.37, 13.71]
	Age: 56-65 y	6.70 [4.62, 9.71]
	Age: 66-75 y	4.41 [3.05, 6.38]
	Age: 76-85 y	3.44 [2.38, 4.97]
	Cardiac surgery	13.07 [9.35, 18.27]
	Cardiology	9.31 [6.67, 12.99]
	Critical care	4.51 [3.06, 6.64]
	Hematology	1.29 [0.86, 1.93]
	Internal medicine	0.88 [0.61, 1.27]
	Oncology	0.14 [0.07, 0.28]
	Orthopedic surgery	0.70 [0.41, 1.20]
	Surgery	0.98 [0.67, 1.42]
	Trauma	3.44 [2.48, 4.78]
	Vascular surgery	3.63 [2.49, 5.28]

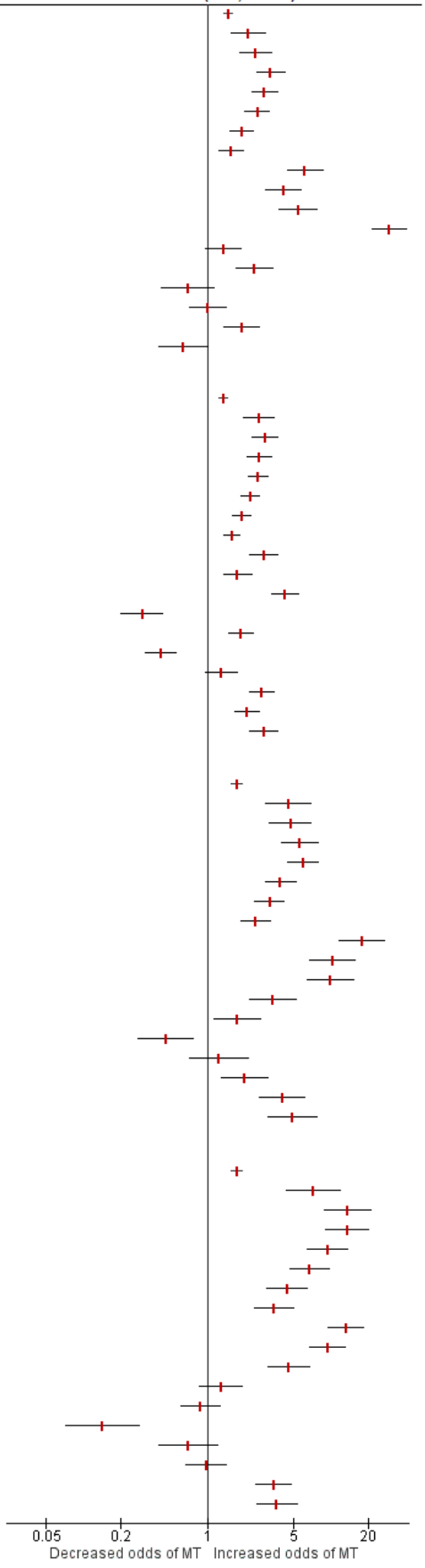

Figure 5. Forest plots of the adjusted odds and 95% confidence intervals (CIs) of multicomponent transfusion (MT) for various patient characteristics for common types of MT. Odds ratios were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type.

Appendix A - Length of Stay Analyses

Table A1. Effect of multicomponent transfusion (MT), as compared to transfusion of only red blood cells, on length of hospital stay (days), for patients alive and dead at hospital discharge for various MT types. Linear regression parameter estimates and 95% confidence intervals are shown.

	Alive at Discharge		Dead at Discharge	
MT Type	**Crude Parameter Estimate (95% CIs)**	**Adjusted Parameter Estimate (95% CIs)**	**Crude Parameter Estimate (95% CIs)**	**Adjusted Parameter Estimate (95% CIs)**
Overall MT	8.91 (8.24, 9.57)	8.86 (8.17, 9.61)	-0.51 (-2.60, 1.57)	-1.34 (-3.78, 1.09)
MT ≤24h	3.97 (3.26, 4.69)	3.13 (2.39, 3.88)	-10.10 (-12.10, -8.11)	-11.08 (-13.59, -8.58)
MT ≤4h	3.64 (2.58, 4.70)	2.48 (1.43, 3.53)	-12.98 (-15.13, -10.84)	-13.28 (-16.05, -10.52)
RBC+PLT	6.41 (5.62, 7.20)	7.96 (7.06, 8.86)	0.24 (-2.57, 3.06)	-0.25 (-3.86, 3.37)
RBC+FP	9.56 (8.16, 10.95)	7.74 (6.37, 9.12)	-0.19 (-3.38, 3.00)	-1.29 (-4.74, 2.15)
RBC+PLT+FP	10.65 (9.16, 12.15)	9.14 (7.61, 10.68)	5.40 (0.82, 9.97)	3.77 (-1.30, 8.85)
RBC+PLT+FP+FR	17.95 (15.72, 20.19)	16.69 (14.46, 18.91)	-3.39 (-6.52, -0.25)	-4.87 (-9.10, -0.63)

Abbreviations: MT, multicomponent transfusion; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

Note: Each MT type was modeled in a separate linear regression model. Regression models were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type. Correlation of data at the patient level (due to patients with multiple hospital admissions during the study period) was accounted for by using marginal regression models.

Table A2. Effect of multicomponent transfusion (MT), as compared to transfusion of only red blood cells, on length of hospital stay (days), for patients alive and dead at hospital discharge for various MT types. Length of stay was $\log_e$ transformed due to its skewed distribution. Due to the transformation, linear regression parameter estimates and 95% confidence intervals (95% CIs) are shown exponentiated to the power of e.

	Alive at Discharge		Dead at Discharge	
MT Type	**Crude Parameter Estimate (95% CIs)**	**Adjusted Parameter Estimate (95% CIs)**	**Crude Parameter Estimate (95% CIs)**	**Adjusted Parameter Estimate (95% CIs)**
Overall MT	1.66 (1.63, 1.70)	1.58 (1.55, 1.62)	0.81 (0.76, 0.87)	0.86 (0.80, 0.93)
MT ≤24h	1.32 (1.28, 1.35)	1.20 (1.16, 1.23)	0.46 (0.43, 0.50)	0.51 (0.47, 0.56)
MT ≤4h	1.21 (1.16, 1.25)	1.13 (1.09, 1.17)	0.32 (0.29, 0.35)	0.39 (0.35, 0.44)
RBC+PLT	1.63 (1.58, 1.69)	1.70 (1.63, 1.76)	1.17 (1.06, 1.30)	1.13 (1.01, 1.26)
RBC+FP	1.57 (1.50, 1.63)	1.44 (1.39, 1.50)	0.74 (0.66, 0.82)	0.78 (0.69, 0.88)
RBC+PLT+FP	1.83 (1.74, 1.91)	1.54 (1.47, 1.62)	1.00 (0.89, 1.13)	1.05 (0.92, 1.20)
RBC+PLT+FP+FR	2.22 (2.10, 2.34)	1.88 (1.78, 1.99)	0.65 (0.57, 0.74)	0.74 (0.63, 0.87)

Abbreviations: MT, multicomponent transfusion; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

Note: Each MT type was modeled in a separate linear regression model. Regression models were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type. Correlation of data at the patient level (due to patients with multiple hospital admissions during the study period) was accounted for by using marginal regression models.

Table A3. Association between multicomponent transfusion (MT), as compared to transfusion of only red blood cells, and length of hospital stay (time to discharge), modeled by the Fine and Gray competing risks Cox regression model, censoring in-hospital deaths.

MT Type	Crude HR (95% CIs)[a]	aHR (95% CIs)[a]
Overall MT	0.62 (0.61, 0.63)	0.59 (0.57, 0.60)
MT ≤24h	0.80 (0.78, 0.82)	0.81 (0.79, 0.83)
MT ≤4h	0.82 (0.80, 0.85)	0.83 (0.80, 0.87)
RBC+PLT	0.70 (0.68, 0.72)	0.57 (0.55, 0.60)
RBC+FP	0.62 (0.60, 0.64)	0.65 (0.63, 0.68)
RBC+PLT+FP	0.54 (0.52, 0.57)	0.55 (0.52, 0.58)
RBC+PLT+FP+FR	0.49 (0.47, 0.51)	0.48 (0.46, 0.51)

Abbreviations: MT, multicomponent transfusion; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; RBC, red blood cells; PLT, platelets; FP, plasma; FR, fibrinogen replacement (cryoprecipitate or fibrinogen concentrate).

Note: Each MT type was modeled in a separate Gray and Fine cox regression model. Regression models were adjusted for illness severity and burden (HOMR score, Charlson score), time (year of hospital admission), sex, age, and patient type. Correlation of data at the patient level (due to patients with multiple hospital admissions during the study period) was accounted for by using marginal regression models.

[a] Hazard ratios below 1 indicate that patients are less likely to be discharged (longer length of hospital stay).

Appendix B - Distribution of Original and Transformed Length of Stay Variable

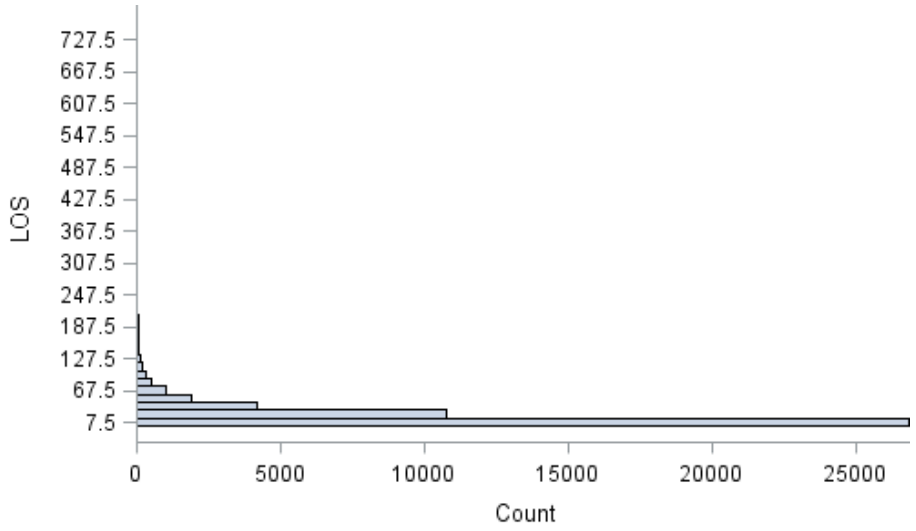

Figure B1. Frequency distribution of the untransformed length of stay (LOS) variable, in days.

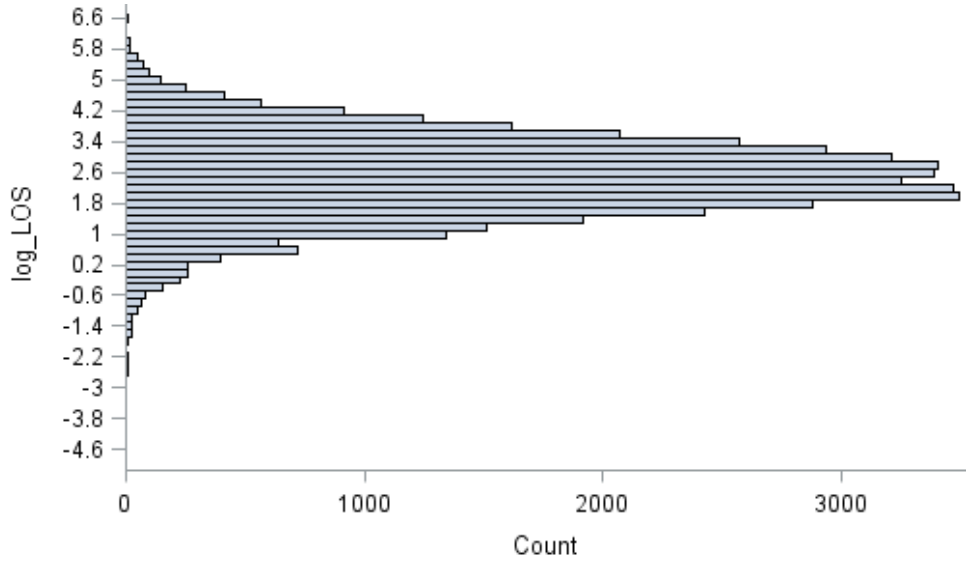

Figure B2. Frequency distribution of $\log_e$ transformed length of stay (log_LOS) variable. LOS was transformed due to its highly skewed distribution, which caused issues with linearity in regression analyses.

Chapter 5: Discussion

5.1 Summary and Discussion of Findings

This thesis consisted of the following three objectives: (1) to synthesize the existing literature on multicomponent transfusion in hospital inpatients; (2) to describe the epidemiology of multicomponent transfusion and its recipients at our own institution, the Ottawa Hospital; and (3) to determine patient characteristics and outcomes that are associated with multicomponent transfusion, and to compare these to those of patients receiving transfusions of only one blood product type, such as RBCs, which is the most common blood product transfused. The following paragraphs summarize how each objective was addressed and will synthesize and discuss our findings.

The first objective was evaluated by a systematic review of the literature, which to our knowledge was the first systematic review conducted on multicomponent transfusion. While we found 37 studies that reported on multicomponent transfusion in some capacity, multicomponent transfusion was not the main focus of any of these studies, and consequently there was often little detail or fragmented information provided on the co-transfusion of blood products. Furthermore, our systematic review found great variability in the prevalence of multicomponent transfusion across studies, which could have been the result of different types of multicomponent transfusion or different patient types being investigated, or simply differences due to regional variation in transfusion practice and guidelines. As a result, it was difficult to paint a complete picture of multicomponent transfusion in the hospital, and challenging to compare results from different studies due to the heterogeneity in study characteristics and reported results. It was also evident that

although some research had already been done on the topic of multicomponent transfusion, there were some remaining gaps and areas for further investigation. For instance, we did not find any studies looking at multicomponent transfusion in patients with hematological malignancies, although from both clinical practice and literature not specifically focused on multicomponent transfusion we know that these individuals are frequently co-transfused with RBCs and PLTs [20,21]. Finally, we found a need for better quality research looking at outcomes of multicomponent transfusion recipients. Several studies had identified outcomes associated with multicomponent transfusion, but with poor or no control for illness severity and burden, resulting in a high risk of confounding by indication, which limits the validity of these findings.

To fill in the knowledge and evidence gaps identified by our systematic review we designed and conducted a retrospective cohort study of multicomponent transfusion at the Ottawa Hospital. This study addressed the second and third objectives of this thesis.

Overall, the descriptive results of our retrospective cohort fell within the realm of the findings from our systematic review. We found that the prevalence of multicomponent transfusion in adult hospital inpatients at the Ottawa Hospital was 25% between 2007 and 2017, which was within the range of prevalence rates reported by studies of adult transfused inpatients in our systematic review (prevalence range=0.4% to 77.3%). In our retrospective study, prevalence was found to vary by the specific type of multicomponent transfusion, by patient type, and by transfusion timeframe, which also corresponds with the findings from our systematic review. Both our retrospective study and the systematic

review showed that the most frequent types of multicomponent transfusion were RBC+PLT and RBC+FP co-transfusions.

One of the knowledge gaps identified by our systematic review was multicomponent transfusion in patients with hematologic cancers. In the retrospective study, we evaluated blood product co-transfusion in hematology patients and found that over 50% received one or more multicomponent transfusions during their hospital stay, of which almost 90% were RBC+PLT co-transfusions. Given the high prevalence of RBC+PLT co-transfusion in hematology patients, it is important to monitor multicomponent transfusion appropriateness and safety, including relevant post-transfusion health outcomes and reactions, in this patient population.

In the inferential analyses portion of the retrospective study we investigated patient characteristics and outcomes associated with multicomponent transfusion. We found that patient baseline attributes such as sex, age, and patient type were predictive of the need for multicomponent transfusion. Specifically, males, adults aged 26 to 45, and hematology, cardiac surgery, critical care, and cardiology patients had the greatest odds of being multicomponent transfused. Such information can be of use to clinicians for individual patient risk assessment for multicomponent transfusion. To our knowledge, ours is the first study to determine patient characteristics associated with multicomponent transfusion using multivariable regression analysis and controlling for a variety of relevant confounders. A previous study by Karafin and colleagues had performed a descriptive analysis of multicomponent transfusion by patient age and sex, and they found that age, but not sex, influenced multicomponent transfusion need [22].

Meanwhile, our results showed that both age and sex have an effect on multicomponent transfusion requirement. This discrepancy may be explained by the fact that the study by Karafin et al. did not adjust for confounders, being largely descriptive in nature.

We also evaluated the effect of multicomponent transfusion on patient outcomes (in-hospital mortality, length of hospital stay, and discharge location for patients alive at discharge). As confounding by indication is a concern in these associations – since sicker patients are more likely to receive a multicomponent transfusion and are also more likely of having poorer outcomes – we included both a measure of illness burden and illness severity in our regression models, along with other relevant confounders and patient baseline characteristics. By doing so, we addressed one of the weaknesses in the existing literature on outcomes following multicomponent transfusion, as previous studies were highly susceptible to confounding by indication due to lack of adjustment for illness severity. From our regression analyses, we found that compared to patients receiving only RBCs, multicomponent transfusion significantly increased the odds of in-hospital mortality, the odds of institutional discharge as opposed to discharge home, and length of hospital stay. Previous studies have looked at different outcomes following multicomponent transfusion in cardiac surgery and liver transplant patients, but not in a general transfused patient population spanning various patient types [23-27]. It would be of interest to see if our findings could be reproduced in other studies and centers.

An important factor to consider is the generalizability of the findings from our retrospective study. Given the known variability in transfusion practice across hospitals and regions, as well as the consideration that our study was conducted at a single center,

it is evident that our findings may not be readily generalizable to other centers and regions. However, our study does have several factors that strengthen its external validity, including a large sample size and the use of data from all three campuses of our hospital representing a broad spectrum of patient types. To further explore the extent of generalizability, we can compare our study population of adult transfused patients to that from several large, well-known, high quality transfusion databases, namely the REDS and SCANDAT databases.

The REDS database is an American initiative consisting of transfusion data for blood donors and transfusion recipients from 12 academic and community hospitals spread across the United States [22]. Currently, there is published data from the REDS database on 80,353 transfused inpatient encounters for the years 2013 and 2014 [22]. Our own cohort of adult transfused inpatients, which spanned 2007 to 2017, was similar to the REDS transfused inpatient population with respect to sex and age distributions, although it should be noted that the REDS database included not only adults, but also pediatric and neonatal patients. Comparing patient types between REDS and our own data was challenging due to different methods of categorizing patients (primary diagnosis versus admitting physician division). In terms of blood products transfused, in the REDS database, 87%, 26%, and 23% of inpatients received RBCs, PLTs, and FP, respectively. In our data, 91%, 21%, and 20% of adult inpatients were administered RBCs, PLTs, and FP, respectively, showing a good degree of consistency with REDS data. With regards to patient outcomes, inpatient mortality was almost twice as high in our study population than in the REDS database (12.2% versus 6.9%), and median length of stay was on average several days longer in our data compared to REDS (12 days versus ~10 days).

Overall, despite some similarity in patient baseline characteristics and transfusion utilization between our cohort and that of REDS, there were nevertheless some crucial differences, particularly regarding patient outcomes. Our cohort had poorer outcomes compared to REDS, suggesting that our patient population may in general be more severely or acutely ill.

Another well-established transfusion database is SCANDAT, which consists of information on all blood donors and recipients in both Sweden and Denmark, with data from as early on as the 1960s [28]. A publication using SCANDAT data from 1983 to 2002 described transfused patients, adult and pediatric, during this timeframe (n=1,118,261 patients, not specified whether inpatients, outpatients, or a mix of both), and can be used for comparison with our own data [29]. More females were transfused than males in the SCANDAT database, which was the opposite of what was observed in our data and in REDS, and the bulk of SCANDAT transfusions were administered in patients aged 65-80, which is an older age group than in our cohort and in REDS. Of all transfusions in SCANDAT, 72% were RBCs, 7% were PLTs, 19% were FP, and 2% were other blood products, which differs from the transfusion distribution in our study population (see paragraph above). Overall, the SCANDAT database was dissimilar to ours; our patient population had more in common with patients in the REDS database than with those in SCANDAT. This may be due to several factors. Firstly there may be greater variability in transfusion practice and guidelines between Canada (our study) and Europe (SCANDAT), than Canada and the United States (REDS). Secondly, the SCANDAT database covered a different (earlier) time period than both our database and REDS, which can be a factor as transfusion practice has evolved over time. Thirdly, there

are likely important differences in the health status of North Americans (our study and REDS) and citizens of northern Europe (SCANDAT) due to differing lifestyles (diet, exercise, environment, etc.).

Overall, comparing our study population to that of other large, transfusion databases highlighted concerns regarding generalizability of results across studies and regions. This emphasizes the importance of conducting transfusion studies, including those on multicomponent transfusion, locally, as generalizing results from one center to another may be challenging and at times inaccurate.

Apart from generalizability, there are other limitations to this thesis; these are discussed in detail in Chapters 2 and 4, and will be briefly summarized here. Study 1 (systematic review) was somewhat limited by the overall low quality of evidence, and by the lack of rigorous prospective studies available on the topic of interest. Limitations of Study 2 (retrospective cohort) included issues with missing data and availability of data stemming from the use of retrospectively collected data, and analyzing multicomponent transfusion as a dichotomous variable instead of a time-dependent effect.

5.2 Future Directions

While this thesis provided a thorough characterization of multicomponent transfusion trends, recipients, and outcomes, there are areas remaining to be investigated on this topic.

First, this thesis focused on inpatients, however, other patient types (outpatients, emergency department patients, etc.) are also transfused – and potentially

multicomponent transfused – and require further investigation. In our systematic review, although we found 37 studies reporting on multicomponent transfusion in inpatients, we came across only one study, published only as a conference abstract, looking at outpatients [30]. Evidently, multicomponent transfusion outside of hospital inpatients is poorly studied to date and is an area of interest for future studies.

A second direction for further research is multicomponent transfusion in neonatal and pediatric populations. In our systematic review we identified two studies on neonates and two studies on pediatric patients [31-34]. Most of these studies focused on multicomponent transfusion in trauma or intensive care settings; none looked at multicomponent transfusion in neonatal or pediatric patients in other relevant settings, such as childhood cancers. In our retrospective study, we were unable to investigate pediatric patients, as data was available only for adults in the OHDW and the TDM. As a next step, it would be of interest to obtain transfusion data from the Ottawa Hospital neonatal intensive care units, as well as data from the children's hospital adjacent to the Ottawa Hospital, and perform a similar analysis on multicomponent transfusion using this data, thereby enabling the comparison of blood product co-transfusion between adult, pediatric, and neonatal patients.

A third direction for future studies is investigating the appropriateness of multicomponent transfusion. Many studies exist on the appropriateness of transfusion of individual blood product (e.g. RBCs, PLTs, FP, etc.), however, to our knowledge there are none to date looking specifically at the appropriateness of co-transfusions of different blood components. It is important to monitor transfusion appropriateness in multicomponent

transfused patients, given our finding that these patients make up a quarter of all transfused hospital patients, and also particularly important in patient populations having a high prevalence of multicomponent transfusion, such as hematology patients. Laboratory parameters (hemoglobin values, platelet counts, etc.), along with data on the number of units of each blood product transfused, can be used to judge multicomponent transfusion appropriateness based on existing transfusion guidelines. There are important implications of such studies for patient care; for instance, increased physician awareness of multicomponent transfusion appropriateness at the institution level may promote better transfusion practice, including greater adherence to recommended guidelines, and increased use of transfusion alternatives and blood conservation techniques.

Finally, Study 2 of this thesis highlighted an important question requiring further investigation. Our finding that, after adjustment for patient baseline characteristics and illness severity, multicomponent transfused patients had a 3.5 times increase in the odds of in-hospital mortality compared to patients transfused with only RBCs, merits further inquiry. In particular, it would be of interest to investigate any differences between multicomponent recipients who died in-hospital and those who survived.

5.3 Conclusion

A synthesis of existing studies on the epidemiology of multicomponent transfusion in hospital inpatients showed great variation in multicomponent transfusion prevalence from study to study, highlighting the concern of generalizability from one center to another, and indicating the need for studies to be conducted locally. To address this need, we conducted an 11-year retrospective cohort of multicomponent transfusion in transfused

adult inpatients at our institution, the Ottawa Hospital. We found that the overall prevalence of multicomponent transfusion in our patient population was 25%, although this varied by specific patient groups, and by types and timeframes of multicomponent transfusion. Patient types that were frequently multicomponent transfused included hematology (51%), cardiac surgery (45%), critical care (40%), and cardiology (33%) patients. Multivariable regression analysis showed that patient baseline attributes such as sex, age, and patient type were predictive of multicomponent transfusion requirement. Finally, we found that compared to transfusion of only RBCs, multicomponent transfusion was associated with a 3.5 times increased odds of in-hospital mortality, a slight increase in the odds of institutional discharge as opposed to discharge home, and a prolonged hospital stay. Given the observed poorer outcomes for multicomponent transfusion recipients, and the high prevalence of multicomponent transfusion at our institution, it is important to monitor the appropriateness of multicomponent transfusion to ensure optimal transfusion practice and to avoid unnecessary patient exposure to blood products.

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Appendix A – Confirmation of Acceptance for Study 1

The manuscript for Study 1 of the thesis was accepted for publication by the journal *Transfusion Medicine* on January 31, 2019. Below is an email from the journal confirming the acceptance.

Transfusion Medicine - Manuscript TME-2018-0091.R1
6 messages

Thu, Jan 31, 2019 at 4:15 AM

31-Jan-2019

Dear Ms Iris Perelman,

Re: The epidemiology of multicomponent blood transfusion: A systematic review (ms no. TME-2018-0091.R1)

I am pleased to confirm that we have decided to accept your paper for publication in Transfusion Medicine.

Your article cannot be published until you have signed the appropriate license agreement. Within the next few days you will receive an email from Wiley's Author Services system which will ask you to log in and will present you with the appropriate licence for completion.

Your paper will now be passed to the production department and proofs will follow in due course. Please be aware that production times can vary depending on the number of manuscripts being processed.

As part of the Journal's continued commitment to its authors, the Editorial Office and Publisher wish to keep you informed about what will happen next, below you will find important information regarding journal publication and services for authors, you may wish to save it for future reference.

Yours sincerely

Dr Lise Estcourt

On behalf of
Dr David Roberts
Editor-in-Chief, Transfusion Medicine

Appendix B – PRISMA Checklist for Study 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	4
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	10-11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	11
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable,	11-12

		included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12-13
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 and pages 11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	13-14, and Tables 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	18-19
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group	Tables 1-3

		(b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	19-20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24-25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	All funding is listed on page vi of thesis

***PRISMA checklist from**:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix C – Re-Classification of Variables for Study 2

Preface

Two variables from the TDM required complex re-classification in preparation for analysis in Study 2. This appendix provides a detailed explanation of how each variable was re-grouped.

Admitting Physician Division Variable

The original admitting physician division variable, as found in the TDM, consisted of 44 physician divisions. For Study 2, we re-grouped these divisions into 16 relevant groups that would be used to classify patient types (e.g. critical care patient, surgery patient, etc.). Figure C1 shows the original admitting physician divisions. Table C1 shows the new patient type variable that was created by re-classifying the admitting physician division variable. Re-classification was done in one of 2 ways:

(1) Physician divisions that were subcategories of a larger medical division were grouped together (e.g. general surgery, thoracic surgery, neurosurgery, plastic surgery, urogynecalogic surgery, and pelvic surgery were all grouped together as 'Surgery');

(2) In instances where it was not possible to group an entire division with another division, admissions were re-classified on an individual basis to the most appropriate division based on information from a combination of other variables (case mix group, admitting diagnoses, principal diagnosis, discharge service, etc.). For example, patients admitted under the physician division of 'Palliative Care' were re-classified on an individual basis to either 'Oncology', 'Critical Care',

'Surgery', etc., as appropriate, by looking at their diagnoses, case mix groups, and discharge services.

Some related admitting physician divisions were not combined, as they represented important and relevant patient groups in regards to multicomponent transfusion utilization, and were therefore kept separate for analysis. For example, the division of 'Cardiac Surgery' was not combined with the rest of the 'Surgery' division, as cardiac surgery patients are frequently multicomponent transfused, and more often than other types of surgery patients, and it is thus of interest to investigate this patient group distinctly from other surgery types.

Trauma patients present an important patient group with regards to multicomponent transfusion. However, there was no category for trauma patients specifically in the admitting physician division variable; trauma patients were dispersed among other divisions, such as critical care, surgery, etc. In order to identify trauma patients as separate group, the following validated algorithm was used:

(1) Admissions with an abstracted diagnosis code for trauma, or

(2) Admission to trauma nursing unit, or

(3) Use of trauma services during admission.

1. Anatomical Pathology
2. Anesthesiology
3. Cardiac Anesthesiology
4. Cardiac Surgery
5. Cardiology
6. Critical Care
7. Dental Surgery
8. Dermatology
9. Emergency
10. Endocrine and Metabolism
11. Eye Institute
12. Family Practice
13. Gastroenterology
14. General Medicine
15. General Obstetrics and Gynecology
16. General Psychiatry
17. General Surgery
18. Geriatrics
19. Gynecologic Oncology
20. Hematology
21. Hematopathology and Transfusion
22. Infectious Diseases
23. Maternal Fetal Medicine
24. Maternal and Newborn Care
25. Medical Oncology
26. Mental Health
27. Midwifery
28. Nephrology
29. Neurology
30. Neurosurgery
31. Nuclear Medicine
32. Orthopedic Surgery
33. Otolaryngology
34. Palliative Care
35. Physical Medicine and Rehabilitation
36. Plastic Surgery
37. Radiation Oncology
38. Reproductive Medicine
39. Respirology
40. Riverside Eye Care Center
41. Thoracic Surgery
42. Urogynecology & Pelvic Surgery
43. Urology
44. Vascular Surgery

Figure C1. Original admitting physician divisions in alphabetical order.

Table C1. New classification of admitting physician division (new patient type variable).

New Categories for Patient Type Variable	Old Categories From Admitting Physician Division Variable That Make Up New Patient Type Category
Cardiac Surgery	Cardiac Surgery, Cardiac Anesthesiology, Anesthesiology (individual basis, as appropriate)
Cardiology	Cardiology, Anesthesiology (individual basis, as appropriate)
Critical Care	Critical Care, Emergency, Infectious Diseases (individual basis, as appropriate), Palliative Care (individual basis, as appropriate), Anesthesiology (individual basis, as appropriate)
Family Practice	Family Practice
Geriatrics	Geriatrics
Hematology	Hematology, Hematopathology and Transfusion Medicine
Internal Medicine	General Medicine, Endocrinology and Metabolism, Gastroenterology, Nephrology, Neurology, Respirology, Nuclear Medicine (individual basis, as appropriate), Dermatology, Anatomical Pathology (individual basis, as appropriate), Infectious Diseases (individual basis, as appropriate), Anesthesiology (individual basis, as appropriate)
Mental Health and Psychiatry	Mental Health, General Psychiatry
Obstetrics and Gynecology	General Obstetrics and Gynecology, Midwifery, Maternal Fetal Medicine, Maternal and Newborn Care, Reproductive Medicine, Anesthesiology (individual basis, as appropriate)
Oncology	Medical Oncology, Radiation Oncology, Gynecologic Oncology, Palliative Care (individual basis, as appropriate)
Ophthalmology	Riverside Eye Center, Eye Institute
Orthopedic Surgery	Orthopedic Surgery, Anesthesiology (individual basis, as appropriate)
Physical Medicine and Rehabilitation	Physical Medicine and Rehabilitation
Surgery (other than cardiac, orthopedic, and vascular)	General Surgery, Dental Surgery, Plastic Surgery, Neurosurgery, Urogynecalogic and Pelvic Surgery, Thoracic Surgery, Urology, Otolaryngology, Palliative Care (individual basis, as appropriate), Anesthesiology (individual basis, as appropriate)
Vascular Surgery	Vascular Surgery, Anesthesiology (individual basis, as appropriate)

Blood Product Type Variable

The variable that specified the type of blood product being transfused was also re-classified for analysis in Study 2. First, all blood products that were not of interest for Study 2 (all blood product derivatives, including clotting factors, immunoglobulins, albumin, etc.) were excluded. The remaining blood products were RBCs, PLTs, plasma, cryoprecipitate, and fibrinogen concentrate. However, there were multiple variations in the TDM for each of these blood products. Table C2 below shows how these were re-grouped in order to obtain 5 categories for the blood product type variable, one for each blood product of interest.

Table C2. Re-classification of the blood product type variable.

New Blood Product Type Category	Blood Product Name Variations Making Up Each Category
Red Blood Cells	'QUAD RED CELLS', 'QUAD RED CELLS WASH', 'RBC AS-3 LR (HQ)', 'RBC SAGM IRR LR Reduced', 'RBC SAGM IRR LR Split', 'RBC SAGM IRR LR Split Washed', 'RBC SAGM IRR LR WASH', 'RBC SAGM IRR LR Washed', 'RBC SAGM LR Split', 'RBC SAGM LR WASH', 'RBC SAGM LR Washed', 'RED CELLS', 'RED CELLS DEGLYCEROL', 'RED CELL PLASMA POOL', 'RED CELLS WASHED', 'Reconstituted Red Blood Cells', 'Red Blood Cell Deglycerized Leukoreduced', 'Red Blood Cell SAGM Irradiated Leukoreduced', 'Red Blood Cell SAGM Leukoreduced'
Platelets	'Apheresis Platelets Irradiated - 2', 'Apheresis Platelets Irradiated - 2 Reduced', 'Apheresis Platelets Irradiated Leukored - 2 Split Reduced', 'Apheresis Platelets Irradiated Leukoreduced', 'Apheresis Platelets Irradiated Leukoreduced (HQ)', 'Apheresis Platelets Irradiated Leukoreduced (HQ) Reduced', 'Apheresis Platelets Irradiated Leukoreduced - 2', 'Apheresis Platelets Irradiated Leukoreduced - 2 (HQ)', 'Apheresis Platelets Irradiated Leukoreduced - 2 Reduced', 'Apheresis Platelets Irradiated Leukoreduced - 2 Split', 'Apheresis Platelets Irradiated Leukoreduced Reduced', 'Apheresis Platelets Irradiated Leukoreduced Split', 'Apheresis Platelets Irradiated Leukoreduced Split Reduced', 'Apheresis Platelets Leukoreduced', 'Apheresis Platelets Leukoreduced (HQ)', 'Apheresis Platelets Leukoreduced - 2', 'Apheresis Platelets Leukoreduced - 2 (HQ)',

	'Apheresis Platelets Leukoreduced - 2 Reduced', 'Apheresis Platelets Leukoreduced Reduced', 'Mirasol Platelets', 'Mirasol Platelets IRR', 'MIRASOL PLATELETS', 'PLATELET APHERESIS', 'PLATELET APHERESIS R', 'PLATELETS', 'PLATELETS BUFFY COAT', 'PLATELETS POOLED', 'PLATELETS REDUCED', 'PLT BUFFY COAT RED.', 'POOLED PLT CPD IRR LR (HQ)', 'POOLED PLT CPD IRR LR Split', 'POOLED PLT CPD LR (HQ)', 'Pooled Platelets CPD Irradiated Leukoreduced', 'Pooled Platelets CPD Leukoreduced'
Plasma	'Apheresis Fresh Frozen Plasma ACD Thawed', 'Apheresis Fresh Frozen Plasma Thawed', 'CRYOSUP PLASMA THAW', 'FFP APHE.LOWVOL THAW', 'FFP APHERESIS', 'FFP APHERESIS LOWVOL', 'FFP APHERESIS THAWED', 'FFP THAWED', 'FROZEN PLASMA', 'FROZEN PLASMA THAWED', 'Frozen Plasma CPD Divided Thawed', 'Frozen Plasma CPD Thawed', 'QUAD FFP', 'QUAD FFP THAWED', 'SD PLASMA THAWED', 'SD Plasma Thawed'
Cryoprecipitate	'CRYO PPT POOLED', 'CRYO PPT THAWED', 'Cryoprecipitate CPD Thawed', 'Cryoprecipitate Pool', 'Cryoprecipitate Pool 10 Units', 'Cryoprecipitate Pool 5 Units'
Fibrinogen Concentrate	'FIBRINOGEN CONC', 'Octafibrin Fibrinogen Pool', 'RECONST FIBRINOGEN', 'RECONST RIASTAP FIBR', 'RiaSTAP Fibrinogen 1 g', 'RiaSTAP Fibrinogen Pool'

Appendix D – Confirmation of Acceptance for Study 2

The manuscript for Study 2 of the thesis was accepted for publication by the journal *Transfusion* on February 18, 2019. Below is an email from the journal confirming the acceptance.

Transfusion - Decision on Manuscript ID Trans-2018-0821.R1
3 messages

Mon, Feb 18, 2019 at 12:50 PM

18-Feb-2019
Trans-2018-0821.R1Trends and outcomes in multicomponent blood transfusion: An 11-year cohort study of a large multi-site academic center

Dear Ms. Perelman:

Thank you for sending the revised version of your manuscript entitled, Trends and outcomes in multicomponent blood transfusion: An 11-year cohort study of a large multi-site academic center.

I am pleased to inform you that it has been accepted for publication in Transfusion.

The journal's current production schedule should result in publication of the article within the next six to eight months. Please note that minor editorial changes may be made in accepted material to ensure consistency of style with the journal.

Transfusion now publishes articles online approximately four months before print publication in its Early View section (see: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1537-2995/earlyview). Articles appearing in Early View are in final form (copyedited, typeset, and corrected by the author), and though they have not yet been assigned to an issue, can still be cited using the DOI number posted with the article. Note that your article can only be included in Early View if your corrected page proofs are returned promptly after receipt.

Thank you for your fine contribution. On behalf of the Editors of Transfusion, we look forward to your continued contributions to the Journal.

Sincerely,
Dr. Beth Shaz
Associate Editor, Transfusion

Appendix E – STROBE Checklist for Study 2

Item	Item No	Recommendation	Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	65
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	65-66
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	67-68
Objectives	3	State specific objectives, including any prespecified hypotheses	68
Methods			
Study design	4	Present key elements of study design early in the paper	68
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	68-71
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	68-69
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	69-71
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	68-71
Bias	9	Describe any efforts to address potential sources of bias	70-71
Study size	10	Explain how the study size was arrived at	N/A (all available hospital admissions were used)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	69-71
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	71-72
		(*b*) Describe any methods used to examine subgroups and interactions	72
		(*c*) Explain how missing data were addressed	71

		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1-3
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-3
		(c) Summarise follow-up time (eg, average and total amount)	N/A (follow-up was length of hospital stay for all patients)
Outcome data	15*	Report numbers of outcome events or summary measures over time	73-75, 76-77
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 4-5, figures 4-5, and pages 75-78
		(*b*) Report category boundaries when continuous variables were categorized	Figures 4-5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 4-5, figures 4-5, and pages 73-78
Discussion			
Key results	18	Summarise key results with reference to study objectives	79-81
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	82-83
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	79-81
Generalisability	21	Discuss the generalisability (external validity) of the	82

		study results	
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	All funding is listed on page vi of thesis

STROBE checklist from: von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335:806.

Appendix F – Ethics Approval for Study 2

Study 2 of this thesis, the retrospective cohort study using the TDM and the OHDW, was one of several transfusion related studies submitted for REB approval under the protocol entitled "Assessment of Blood Product Utilization and Appropriateness at the Ottawa Hospital using the TOH Data Warehouse" (Ottawa Health Science Network REB reference number: 20160767-01H). This proposal was submitted to the REB by the University of Ottawa Center for Transfusion Research, with the principal investigator being the head of the research centre, Dr. Alan Tinmouth (TAC member). The proposal, including my study, received REB approval from 2016 to 2017, and was later renewed by the REB until October 2018. The documents below show the initial REB approval, followed by the renewed approval. In the document showing initial REB approval, my name is listed under the section "Additional Staffing".

Initial REB Approval

Ethics Project Summary for 20160767-01H

Project Overview

Protocol ID: 20160767-01H
Ethics Status: APPROVED
Received: 9/28/2016

Project Title (Summary)
Assessment of Blood Product Utilization and Appropriateness at the Ottawa Hospital using the TOH Data Warehouse

Project Title (Description)
Assessment of Blood Product Utilization and Appropriateness at the Ottawa Hospital using the TOH Data Warehouse

Investigators

Principal Investigator (at this site)
Dr. Alan Tinmouth, MD

Co-Investigators
Dr. Michael Chasse, Transfusion Research Fellow

Dr. Dean Fergusson,

Dr. Alan Forster, Senior Scientist

Dr. Antonio Giulivi, Division Head

Dr. Guy Hebert, Chief, Emergency Medicine

Dr. Kumanan Wilson, Clinical Scholar

Dr. Jason Woodfine, Medical Resident

Study Details

Type of Study
Clinical/Human Research Study
Cohort
Database Research
Longitudinal
Observational Research
Program Evaluation

This Centre
Anticipated Start Date - 10/1/2016
Anticipated Duration - 5 Year(s)

No. patients to be Rec. - 60000

Type of Drug Study

Hazards to Patients

Multicentre Trial
P.I. Name -
Telephone - ext.
Number of centres participating -
Total number of patients to be rec - 0

Impact of Research on Hospital
Database Warehouse

Additional Staffing
Malia Murphy
Iris Perelman
Irwin Schweitzer

Contacts
Primary Contact: Alan Tinmouth
Alternate Contact: Phone: ext.

Discrepancies

Notes
Health Canada regulated = No U.S. involvement = No All future annual renewals required Full Board review = No Review fee = No Copy PI, Irwin Schweitzer and Malia Murphy on docs - Jason Woodfine added as co-I as per Protocol Amendment Report of December 14, 2016- km

Ethics Fees
Has review fee been requested? - No
Has review fee been invoiced? - No
Other funding info -

Renewed REB Approval

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

uOttawa

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa
Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
http://www.ohri.ca/ohsn-reb

November 01, 2017

Dr. Alan Tinmouth
Ottawa Hospital - General Campus
Clinical Epidemiology Program
Centre for Practice Changing Research
501 Smyth Road, Room L2265
Ottawa, ON K1H 8L6

Dear Dr. Tinmouth:

RE: Protocol# - 20160767-01H **Assessment of Blood Product Utilization and Appropriateness at the Ottawa Hospital using the TOH Data Warehouse**

Renewal Expiry Date - October 02, 2018

Thank you for the Annual Renewal Report dated September 25, 2017. I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the Protocol without the OHSN-REB's review and approval.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the REB office.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

TB/ab