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Transfusion practices among children admitted to a South African PICU following cardiac surgery

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Background. Blood products may be required in patients undergoing cardiac surgery; however, there is a paucity of data on blood transfusion guidelines in the perioperative and postoperative cardiac surgery period.
Objectives. To describe the prevalence of blood product transfusion, factors associated with transfusion and outcomes in patients who received blood products following cardiac surgery.
Methods. This was a prospective, single-centre observational study that consecutively recruited 126 children aged <18 years admitted to the paediatric intensive care unit (PICU) following cardiac surgery between July 2017 and January 2018. Demographic, intraoperative and postoperative blood product transfusion data were extracted from patient records, entered into a standardised case record form and analysed using Statistica version 13 (StatSoft Inc, USA). Statistical significance was set at $p<0.05$.
Results. Of the recruited children, 53% received blood products, with 30.9% receiving cryoprecipitate, 22.2% receiving packed red blood cells, 18.3% receiving albumin, 15.9% receiving fresh frozen plasma and 15.1% receiving platelet concentrates. Factors associated with the use of blood products included previous cardiac surgery, younger age, lower weight and prolonged coagulation parameters ($p<0.05$). Receiving blood products was associated with worse outcomes: a standardised mortality ratio of 3.1 v. 0 ($p<0.0001$), median (IQR) PICU length of stay of 5 (3 - 11) v. 2 (2 - 5) days ($p<0.0001$), and duration of mechanical ventilation of 47 (22 - 132) v. 20 (6 - 27) hours ($p<0.0001$).
Conclusion. There is a high prevalence of blood product use in children in the PICU following cardiac surgery, and this is associated with worse outcomes.

Keywords. Blood products, cardiac surgery, transfusion practices.

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Contribution of the study
This is the first South African study to describe the use of all major blood product types, not only red blood cells, and their indications in children following paediatric cardiac surgery. It demonstrates a markedly different transfusion pattern from that reported in North American PICUs, with cryoprecipitate, rather than red blood cells, being the most frequently used product. Blood product use was common and was independently associated with worse outcomes, including longer PICU stays, prolonged ventilation and higher standardised mortality. These findings highlight the need for locally developed, evidence-based transfusion protocols to support blood product stewardship, particularly in resource-constrained settings that depend on voluntary blood donation.

Blood products are frequently administered to patients undergoing cardiac surgery. However, there is a paucity of data on blood transfusion guidelines during the perioperative and postoperative cardiac surgery period, owing to the non-inferiority in mortality and morbidity associated with conservative compared with liberal transfusion strategies.[1-3]

The factors that predispose patients undergoing cardiac surgery to bleeding include patient- and procedure-related factors. Patient-related factors may be either modifiable or non-modifiable. Modifiable factors include preoperative use of anticoagulants, antiplatelet or antithrombotic therapy, preoperative anaemia, baseline platelet count, and fibrinogen level. Non-modifiable factors include age, race, sex, genetic factors related to coagulopathy, and cardiac function prior to surgery. Procedure-related factors include the type and urgency of the operation, the complexity of the procedure, temperature management, use of cell recovery methods, cardiopulmonary bypass duration, the skill of the surgeon performing the operation and improper heparin reversal.[4]

The primary objectives of this observational study were to describe the use of blood products and their indications during the 72-hour period following cardiac surgery in a cohort of patients at the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa (SA). The secondary objectives were to describe the paediatric intensive care unit (PICU) mortality, PICU length of stay (LOS), duration of ventilation and the factors associated with postoperative blood product use.

Materials and methods

Study site

This study was conducted in the PICU of the RCWMCH, SA, which is a 22-bed multidisciplinary unit serving the Western Cape Province. It is a closed PICU with ~1 300 admissions per year, catering for both medical and surgical specialties. Postoperative cardiac surgery admissions account for ~300 patients annually.

Study population

All children aged <18 years admitted to the PICU following cardiac surgery from 13 July 2017 to 13 January 2018 were prospectively and consecutively recruited. Children admitted to the PICU with medical or surgical conditions other than those undergoing cardiac surgery were excluded. In this study, children were defined as patients younger than 18 years.

Data collection and management

The study was undertaken after obtaining approval from the Department of Paediatrics and Child Health Research Committee and the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (ref. no. HREC 437/2017), and adhered to the 2013 Declaration of Helsinki. The requirement for informed consent was waived owing to the low-risk, observational study design. Patients who met the study eligibility criteria were consecutively enrolled during the 6-month study period (July 2017 to January 2018).

Data were prospectively extracted from blood bank records, intraoperative charts and patient folders, including PICU observation charts. Blood products included red blood cells, fresh frozen plasma (FFP), platelet concentrate, cryoprecipitate and human albumin. Information on the type and characteristics of the blood products administered was obtained from blood bank records and treatment charts (for prescribed human albumin). Chest drain losses were used as a surrogate marker for active bleeding, with losses ≥4 mL/kg/hr (a locally agreed unit policy definition) considered significant. Previous blood transfusion was defined as blood product administration within 14 days preceding the current cardiac surgery. Hypotensive episodes were defined as systolic or mean blood pressure falling below the acceptable lower limit, determined by age and congenital cardiac lesion, as per locally agreed practice set by the intensivists at the RCWMCH PICU.

Intraoperative charts provided the following information: preoperative cardiac diagnosis, surgical procedure performed, type and characteristics of blood products administered intraoperatively, haemoglobin levels pre- and postoperatively, details of cardiopulmonary bypass, and the use of pharmacotherapy (tranexamic acid, vitamin K and activated factor VII) to prevent bleeding. Demographic data (age, sex, weight and dates of PICU admission and discharge) were obtained from patient folders. In addition, data on haemoglobin levels, oxygen saturation, hypotensive episodes, clotting profile, chest drain losses, duration of mechanical ventilation, LOS and mortality (including Paediatric Index of Mortality (PIM 3) scores)[5] in the PICU, as well as previous cardiac surgery, previous blood transfusions and previous ICU admissions, were obtained from patient folders and PICU observation charts.

Details of blood products used in the PICU, indications for administration, and volume (mL/kg) of each blood product prescribed during the first 72 hours following cardiac surgery were recorded. Daily data collection captured chest drain losses (mL/kg/hr) during the first 72 hours following cardiac surgery. Outcomes recorded included PICU LOS, total duration of ventilation and mortality.

All extracted data obtained were entered into standardised case record forms and subsequently transferred to an Excel spreadsheet (Microsoft, USA).

Standard unit practice

The standard practice in the RCWMCH PICU for patients undergoing elective or emergency cardiac surgery includes baseline blood investigations, namely a full blood count, full coagulation screen, renal and liver biochemistry, blood grouping and crossmatch, and C-reactive protein measurement. Thromboelastograms are not routinely performed as part of the preoperative work-up, as a full coagulation profile is done.

The blood bank routinely prepares blood products (packed red blood cells, FFP and platelet concentrate) for all patients scheduled for cardiac surgery. Cryoprecipitate is prepared on an as-needed basis at the doctor's request for patients with excessive perioperative and/or postoperative bleeding.

It is routine practice in this unit to perform 6-hourly arterial blood gases, full blood counts, clotting profiles and renal biochemistry as part of postoperative cardiac surgery monitoring, as it guides the clinical team in the meticulous intensive care management of the postoperative patient. Blood sampling is performed by the nurse assigned to the patient via the indwelling arterial line or central venous catheter.

The locally agreed unit practice for transfusion of blood products includes the following: red blood cells (haemoglobin <7 g/dL or postoperative drain losses >2 mL/kg/hr); FFP (postoperative drain losses >2 mL/kg/hr with an international normalised ratio (INR) >2 and prolonged prothrombin time/activated partial thromboplastin time (PT/APTT) >2 times the control); platelet concentrate (postoperative drain losses >2 mL/kg/hr with a platelet count <100 10^9/L); and cryoprecipitate (postoperative drain losses >2 mL/kg/hr with a fibrinogen level <1 g/L). In the event of excessive postoperative bleeding (defined as drain losses >4 mL/kg/hr, as per locally agreed unit policy), patients receive a combination of red blood cells, FFP and platelet concentrate in a fixed ratio of 1:1:1.

Statistical analysis

Normality tests were used to determine the distribution of the data. Continuous variables were summarised as medians and interquartile ranges (IQR), and categorical variables were summarised as *n* (%). Inferential statistics were conducted to assess outcomes associated with postoperative blood product use (duration of ventilation, PICU LOS and mortality) and factors associated with postoperative blood product use, using the Mann-Whitney *U*-test and χ^2 test, as appropriate. Continuous variables were compared using Spearman's rank-order correlation coefficient (ρ).

Variables found to be significantly associated with blood product use were entered into stepwise binary logistic regression models, together with potential confounders such as age, sex and admission risk-of-mortality scores, to determine independent predictive factors for postoperative blood product use following cardiac surgery (including preoperative anaemia, age, surgical complexity and cardiopulmonary bypass duration).

A significance level of $p<0.05$ was used. Statistical analyses were conducted using Statistica version 13 (StatSoft Inc, USA).

Results

A total of 131 patients met the study eligibility criteria; however, five had missing monitoring and/or laboratory data and were excluded. The final analysis therefore included 126 patients admitted to the PICU following cardiac surgery, and their characteristics are summarised in Table 1. Of the study cohort, 22 patients (17.5%) had undergone previous cardiac surgery, of whom 15.1% had undergone open-heart surgery. The following cardiac lesions comprised almost two-thirds of the enrolled study cohort: atrioventricular septal defect (*n*=17; 13.5%), tetralogy of Fallot (*n*=12; 9.5%), single-ventricle lesions (*n*=12; 9.5%), ventricular septal defect (*n*=11; 8.7%), mitral regurgitation (*n*=7; 5.6%), aortic stenosis (*n*=6; 4.8%), total anomalous pulmonary venous connection (*n*=6; 4.8%), patent ductus arteriosus (*n*=6; 4.8%) and atrial septal defect (*n*=5; 3.9%).

Intraoperative pharmacotherapy to limit bleeding was used in 69 patients (54.8%) admitted to the PICU: 68 patients received tranexamic acid and one patient received both tranexamic acid and activated factor VII. Six patients (4.8%) received additional pharmacotherapy to limit bleeding in the PICU, including vitamin K (*n*=2; 33.3%), tranexamic acid (*n*=2; 33.3%) and activated factor VII (*n*=2; 33.3%).

Additional blood products were administered intraoperatively to 68 patients (53.9%) (over and above priming of the bypass circuit); 50% of these patients received packed red blood cells as a single blood product, and 25% received packed red blood cells with platelets and cryoprecipitate. The PICU LOS was longer in patients who received intraoperative transfusions than in those who did not (5 (2 - 11) v. 3 (2 - 5) days; p=0.002).

Table 2 shows the different blood products and median volumes used following cardiac surgery. A total of 67 patients (53.2%) received blood products in the PICU following cardiac surgery. Cryoprecipitate was the most frequently used blood product (30.9%), followed by packed red blood cells (22.2%), albumin (18.3%), FFP (15.9%) and platelet concentrate (15.1%). Furthermore, 41 patients (32.5%) received blood products both intraoperatively (over and above priming of the bypass circuit) and in the PICU.

Table 1. Baseline characteristics of the study group

Variable	Total (*N*)	Median	IQR
Weight (kilograms)	126	7.6	4.1 - 16.0
Age (months)	126	14.3	3.8 - 66.4
Haemoglobin at PICU admission (g/dL)	126	12.7	11.1 - 14.2
PTT at PICU admission (seconds)	117	32.0	25.6 - 42.7
Fibrinogen at PICU admission (g/L)	118	1.4	1.1 - 1.9
Platelet count at PICU admission (10^9/L)	126	197.5	127.0 - 253.0
Ventilation duration (hours)	112	23.6	17.5 - 90.5
PICU duration (days)	126	3.5	2.0 - 7.0
Risk of mortality (PIM 3)	126	0.01	0.01 - 0.02

Variable	*n* (%)
Female	58 (46.0)
Preoperative cardiac diagnosis	
1 lesion	83 (65.9)
2 lesions	31 (24.6)
≥3 lesions	12 (9.5)
Prior cardiac surgery	22 (17.5)
Previous transfusion	4 (3.2)
Cardiac surgical procedure	
1 lesion repair	85 (67.5)
2 lesion repairs	32 (25.4)
≥3 lesion repairs	9 (7.1)
Blood product use intraoperatively	68 (53.9)
Repeat cardiopulmonary bypass in theatre	14 (11.1)
Pharmacotherapy to prevent bleeding postoperatively	69 (54.8)
Pharmacotherapy to prevent bleeding in PICU	6 (4.8)

IQR = interquartile range; PICU = paediatric intensive care unit; PTT = partial thromboplastin time; PIM 3 = Paediatric Index of Mortality 3.

Table 3 describes the most common indications for the use of different blood products following cardiac surgery. Other indications included resuscitation in the presence of generalised oozing, oozing from the sternal wound and central line insertion site (packed red blood cells, FFP and cryoprecipitate), partial exchange transfusion (FFP) and elevated INR (cryoprecipitate).

Table 4 displays the outcome variables associated with postoperative blood product use. The PICU LOS and duration of mechanical ventilation were longer in patients who received blood products following cardiac surgery than in those who did not (p<0.0001 for both). In addition, there was a significant difference in standardised mortality ratio between the transfused and non-transfused groups (p<0.0001).

Table 5 describes the univariate analysis of factors associated with postoperative blood product use in children. Children who received blood products after cardiac surgery were younger, weighed less, had undergone previous cardiac surgery and had worse clotting parameters than those who did not receive blood products (p<0.005). Postoperative pharmacotherapy use was similar in the transfused and non-transfused groups and was not

Table 2. Blood products used in children following cardiac surgery in the PICU

Blood product	*N*=126 *n* (%)	Volume transfused (mL/kg) Median (IQR)
Cryoprecipitate	39 (30.9)	1.9 (1.6 - 3.0)
Packed red blood cells	28 (22.2)	16.1 (14.2 - 20.1)
Albumin	23 (18.3)	10.1 (5.2 - 22.2)
Fresh frozen plasma	20 (15.9)	12.1 (10.1 - 17.6)
Platelet concentrate	19 (15.1)	14.2 (10.0 - 20.2)

PICU = paediatric intensive care unit; IQR = interquartile range.

Table 3. Indications for blood product use in children following cardiac surgery

Blood product	Indications for use
Cryoprecipitate	Bleeding (67%). Median (IQR) chest drain loss threshold 4.5 (2.3 - 5.9) mL/kg/hr.
	Low fibrinogen level (64%). Median (IQR) fibrinogen level threshold 0.9 (0.7 - 1.1) g/L.
	Hypotensive episodes (23%).
	Consultant orders (10%).
Packed red blood cells	Low haemoglobin level (86%). Median (IQR) haemoglobin threshold 7.9 (7.3 - 8.7) g/dL.
	Hypotensive episodes (32%).
	Bleeding (25%). Median (IQR) chest drain loss threshold 8.5 (5.9 - 18.0) mL/kg/hr.
	Consultant orders (25%).
Albumin	Hypotensive episodes (95%).
	Consultant orders (4%).
Fresh frozen plasma	Bleeding (70%). Median (IQR) chest drain loss threshold 5.6 (2.3 - 7.0) mL/kg/hr.
	PTT level (45%); ≥2 times the control (35%).
	Hypotensive episodes (35%).
	Consultant orders (25%).
Platelet concentrate	Thrombocytopenia (84%). Median (IQR) platelet count threshold 67 (46.5 - 93.5) 10^9/L.
	Bleeding (63%). Median (IQR) chest drain loss threshold 5.9 (4.3 - 10.0) mL/kg/hr.
	Hypotensive episodes (42%).
	Consultant orders (10%).

IQR = interquartile range; PTT = partial thromboplastin time.

Table 4. Outcome variables associated with postoperative blood product use

Variable	PICU transfusion (*n*=67)	No PICU transfusion (*n*=59)	*p*-value*
Death, *n* (%)	4 (5.9)	0 (0.0)	0.2
Risk of mortality†	0.015 (0.010 - 0.034)	0.012 (0.009 - 0.017)	0.10
Standardised mortality ratio	3.1	0	<0.0001
PICU duration (days)†	5.0 (3.0 - 11.0)	2.0 (2.0 - 5.0)	<0.0001
Ventilation duration (hours)†	47.0 (21.8 - 131.5)	19.9 (6.0 - 26.5)	<0.0001

PICU = paediatric intensive care unit.
*p-value derived using χ^2 test.
†Continuous data are presented as median (interquartile range).

Table 5. Factors associated with postoperative blood product use

Variable	PICU transfusion (*n*=67)	No PICU transfusion (*n*=59)	*p*-value*
Previous cardiac surgery, *n* (%)	15 (22.4)	7 (11.9)	0.03
Age (months)†	6.4 (2.2 - 43.0)	31.6 (6.4 - 82.1)	0.003
Weight (kilograms)†	4.8 (3.5 - 13.0)	11.4 (5.6 - 18.2)	0.001
Pharmacotherapy use postoperatively, *n* (%)	37 (55.2)	32 (54.2)	0.9
ACT after bypass/surgery (seconds)†	150.5 (131.0 - 174.5)	133.0 (120.0 - 148.0)	0.002
Haemoglobin level at PICU admission (g/dL)†	13.1 (11.3 - 14.8)	12.4 (10.6 - 13.5)	0.06
PTT level at PICU admission (seconds)†	39.0 (29.0 - 50.9)	27.6 (24.5 - 36.0)	<0.0001
Fibrinogen level at PICU admission (g/L)†	1.3 (0.9 - 1.9)	1.5 (1.3 - 1.9)	0.05
Platelet count at PICU admission (10^9/L)†	161.0 (102.0 - 226.0)	224.0 (160.0 - 269.0)	0.0006

PICU = paediatric intensive care unit; ACT = activated clotting time; PTT = partial thromboplastin time.
*p-value derived using χ^2 test.
†Continuous data are presented as median (interquartile range).

associated with differences in postoperative blood product use (p=0.9). However, on multiple regression analysis, no independent predictors of postoperative blood product use were identified.

Discussion

This prospective observational study demonstrated an overall blood product usage prevalence of 53.2% in children following cardiac surgery. This finding is similar to that of a study by Salvin *et al.*,[6] in which 52% of patients received blood transfusions during their ICU stay following cardiac surgery. Studies investigating blood product transfusion in children have largely focused on the general PICU population and have primarily described the indications for and outcomes associated with red blood cell transfusions,[7,8] whereas this study examined all the different blood products used in a postoperative cardiac surgery cohort.

Cryoprecipitate was the most frequently used blood product in this study (31%), demonstrating a difference in transfusion practices compared with studies conducted in North America, where red blood cells are reported to be the most frequently used blood product among critically ill children and those undergoing paediatric cardiac surgery.[9-11] The main indications for cryoprecipitate use in this study were active bleeding and a low fibrinogen level, which adheres to the current guidelines for cryoprecipitate use. Local practice in this unit is to transfuse cryoprecipitate in patients with active bleeding and fibrinogen levels <1 g/L, owing to the high costs associated with its preparation and its limited availability, as cryoprecipitate is prepared on an as-needed basis.[12]

Packed red blood cell transfusions were administered to 22% of the patients who received blood products in this study, with a low haemoglobin level being the main indication (86%). This may be attributed to a combination of ongoing bleeding following cardiac surgery and low postoperative haemoglobin levels. By contrast, data from 30 North American PICUs showed a significantly higher rate of red blood cell transfusion (79%); however, the proportion of transfusions indicated for low haemoglobin levels was lower (17%) than that observed in this study.[13]

In this study, albumin was mainly used for perceived hypotensive episodes. Acceptable minimum systolic or mean blood pressure levels for individual patients were defined by the attending intensivist, and values falling below these thresholds were managed as hypotensive episodes. Although there is limited literature on the use of albumin for fluid resuscitation in paediatric cardiac surgery, unit policy is to alternate Ringer's lactate and 4.5% albumin boluses for children who are clinically assessed as hypovolaemic. The practice of administering albumin boluses for volume resuscitation in our unit was adopted from the 2016 Surviving Sepsis Guidelines, which recommend the use of albumin in addition to crystalloids for volume resuscitation when larger volumes of crystalloids would otherwise be required.[14]

Haemorrhage was the main indication for the use of FFP in this study (70% of patients), followed by deranged PT/APTT (45% of patients). The British Committee for Standards in Haematology (BCSH) recommends the use of FFP in bleeding patients; however, it should be used cautiously to avoid volume overload, with monitoring of the clinical response.[12] The indications for the use of platelet concentrate in this study were also consistent with current BCSH recommendations for significant bleeding and a platelet count <100 10^9/L following cardiopulmonary bypass surgery.[12,15]

An increased PICU LOS, duration of ventilation and standardised mortality ratio were observed among children who received blood products in the PICU compared with those who did not. In addition, children who received blood products intraoperatively had a significantly longer PICU LOS than those who did not. These findings are similar to those of Salvin *et al.*,[6] who demonstrated significantly increased PICU LOS and duration of ventilation among children transfused following cardiac surgery compared with those who were not transfused.

One possible explanation is that patients who received blood products developed increased morbidity (increased PICU LOS, duration of ventilation and mortality) owing to the 'two-hit hypothesis' described by Despotis *et al.*,[16] possibly as a consequence of transfusion-related acute

lung injury (TRALI), which is often associated with significant volumes of blood products transfused. However, TRALI was not specifically investigated in this study. The 'two-hit hypothesis' refers to a primary precipitating event – the 'first hit'– such as a systemic inflammatory response syndrome resulting from surgery or the underlying illness, followed by a 'second hit' from transfusion of blood products. This introduces biological response modifiers, such as human leucocyte antigen and white cell antibodies, as well as neutrophil-activating mediators present in transfused blood products.[16]

The storage lesion has also been well described as a significant contributor to transfusion-related morbidity owing to the physiological changes that red blood cells undergo during refrigerated storage.[17] Our blood bank issues pre-storage leucocyte-reduced blood for all infants as a policy; however, older children receive leucodepleted blood products only if specifically requested by the prescribing clinician. The age of the blood products used may therefore have contributed negatively to morbidity in this study population.[18]

The factors associated with blood product use identified on univariate analysis in this study were previous cardiac surgery, younger age, lower weight and prolonged coagulation parameters. However, multivariate logistic analysis did not identify any independent risk factors for blood product use. Previous cardiac surgery and prolonged coagulation parameters likely placed these children at higher risk of bleeding owing to adhesions resulting from prolonged re-exploration and ineffective haemostasis, respectively, thereby increasing the need for blood product transfusion.

A strength of this study is its prospective design, which reduces the risk of information bias, as well as the reasonably large sample size included. However, intraoperative factors were often poorly documented, making it difficult to obtain information retrospectively after PICU admission. Another limitation is its single-centre study design, which limits generalisability to other populations and different contexts.

In addition, several potential confounding variables that may have influenced the poor outcomes associated with blood product use were not measured, including organ dysfunction scores, Paediatric Logistic Organ Dysfunction (PELOD) scores, and the storage duration of blood products. Measures of surgical complexity were also not assessed, such as the Risk Adjustment for Congenital Heart Surgery (RACHS-1) score, which influences outcomes following congenital heart surgery; inclusion of such measures is recommended for future studies. Causality between blood product use and morbidity cannot be established on the basis of this study.

While our unit does not have institutional protocols for blood product use in paediatric cardiac surgery, local transfusion practices in postoperative cardiac surgery patients are guided by evidence from published guidelines. The team of intensivists recognises the need for stewardship of blood product use, as SA relies on voluntary, non-remunerated blood donation as a source of blood products, which are required across both surgical and medical specialties in children and adults. Consequently, the intensivists in our unit employ restrictive transfusion strategies in postoperative cardiac surgery patients.

Conclusion

The results of this study demonstrated a high prevalence of blood product use (mainly cryoprecipitate) in children admitted to a SA PICU following cardiac surgery. Postoperative blood product use was associated with significantly increased morbidity and standardised mortality ratio. Larger multicentre studies are recommended to further explore the relationship between intraoperative factors and the use of blood products following cardiac surgery, and to inform the development of evidence-based protocols for the use of blood products in paediatric cardiac surgery.

Data availability statement. Selected de-identified data are available on request for meta-analytical purposes.

Declaration. None.

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Author contributions. All authors were involved in study conceptualisation; KF collected the data and was lead author of the paper drafts; BM conducted data analysis; all authors critically revised manuscript drafts.

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