




The Incidence of Hemolytic and Serologic Transfusion Reactions Among Patients with Hematological Malignancies at Mbarara Regional Referral Hospital and the Uganda Cancer Institute, in Uganda

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Background: Blood transfusions are essential in the supportive care of patients with hematological malignancies but carry a risk of adverse reactions. Data on the incidence of transfusion reactions remain scarce in Uganda. This study evaluated the incidence of hemolytic and serologic transfusion reactions among patients with hematological malignancies at Mbarara Regional Referral Hospital and the Uganda Cancer Institute in Uganda.

Materials and Methods: This prospective cohort study enrolled hospitalized patients aged ≥ 2 years with hematological malignancies and a history of prior red blood cell (RBC) transfusions. Participants received additional transfusions and were monitored for up to 14 days. Blood samples were collected on day 0 (transfusion day), days 7, and 14 to assess hemoglobin (Hb) levels, lactate dehydrogenase (LDH), and perform direct and indirect antiglobulin tests. Participants' medical records were also reviewed for transfusion and pregnancy histories. Repeated Measures-Analysis of Variance was used to compare mean Hb and LDH levels over time points.

Results: Of the 467 participants enrolled (median age: 36.4 years, interquartile range: 27.3–46.9), 382 completed the follow-up period. A progressive increase in mean Hb levels (g/dL) was observed: 6.6 (95% confidence interval [CI]: 6.1–8.9) on day 0, 7.5 (7.3–10.1) on day 7, and 8.9 (8.4–10.6) on day 14. No acute or delayed hemolytic reactions occurred. The incidence of delayed serologic transfusion reactions (DSTRs) was 0.86 in 100 (95% CI: 0.02–1.69), while the overall RBC alloantibody prevalence was 2.4% (95% CI: 0.98–3.74). The identified alloantibodies were directed against antigens in the Rh, Kell, Lewis, and MNS group systems.

Conclusion: Despite a low incidence of DSTRs, a notable prevalence of RBC alloimmunization was observed among patients with hematological malignancies. These findings underscore the need to strengthen pre-transfusion antibody testing to prevent hemolytic complications and improve transfusion outcomes in this population.

Keywords: hematological malignancies, transfusion reactions, Uganda

Background

Hematological malignancies including leukemias, lymphomas, and plasma cell disorders arise from abnormal proliferation of hematopoietic or lymphoid cells and commonly disrupt normal bone marrow function.^{1,2} This derangement results in cytopenias, particularly anemia and thrombocytopenia.³ Cytopenias may occur as a result of the underlying malignancy or from myelosuppressive treatment such as chemotherapy.^{4,5} Consequently, patients with hematological malignancies often experience pancytopenia and require repeated supportive transfusions to prevent related complications.⁶ Among the cytopenias, anemia is particularly common and clinically significant.⁷ In the European Cancer Anemia Survey, a large multinational

study involving cancer centres across 24 European countries, the prevalence of anemia among patients with cancer ranged from 22.7%⁸ to 63%,⁹ and further increased to 89% after the initiation of cancer-related treatments.¹⁰ Among patients with hematological malignancies, the prevalence of anemia also varies by cancer type, ranging from 6% in acute lymphoblastic leukemia to about 55% in chronic lymphoproliferative disorders.¹¹ Although red blood cell (RBC) transfusions remain a standard therapeutic approach for alleviating anemia symptoms, transfusion therapy is not without risks.¹² As patients with hematologic malignancies often require multiple transfusions over the course of their disease and treatment, they experience cumulative exposure to allogeneic donor blood and therefore represent a population at increased risk of being alloimmunized,¹³ defined as the development of antibodies directed against non-self blood group antigens. Noteworthy, alloimmunization is a clinically important complication of chronic transfusion that increases the likelihood of hemolytic and serologic transfusion reactions and limits the availability of compatible donor blood, potentially causing serious morbidity and delays in necessary therapy.¹⁴

Despite the clinical importance of transfusion safety, hemovigilance data remain sparse in resource-limited settings. Available studies from sub-Saharan Africa report substantial variation in the incidence of transfusion reactions. In Namibia, 28 acute reactions were recorded among 1162 transfusion events, yielding an incidence of 3.4 in 100 (11.5 per 1000 units transfused).¹⁵ In Ethiopia, a prospective study documented at least one acute transfusion reaction in 5.7 in 100 of the 384 patients who received transfusions.¹⁶ In contrast, a 12-year retrospective analysis from Zimbabwe documented 308 adverse events among 670,625 component transfusions, corresponding to 0.046 in 100 per component transfused.¹⁷ A survey conducted by the World Health Organization for the African Region across 25 countries found 424 transfusion reactions among 1649,787 transfused patients in 7 countries, an incidence of 0.26 per 1000 transfused patients.¹⁸ In Uganda, three studies have reported on transfusion reactions. One study assessed the clinical transfusion practices at Mbarara Regional Referral Hospital and found that 10 reactions were documented among 1674 transfused patients, yielding an incidence of 0.6 per 100.¹⁹ A second study conducted at Mulago National Referral Hospital reported an incidence of confirmed acute transfusion reactions of 8.9 in 100, over 507 transfusions.²⁰ Finally, in a study conducted among patients with cancer who received platelet transfusions at the Uganda Cancer Institute, acute transfusion reactions occurred during 11 transfusion episodes in eight patients involving 13 platelet units, yielding incidences of 4.0 per 100 (13 of out of a total of 323) units used, and 7.3 per 100 (11 of 151 transfusions) per transfusion event.²¹

Given the high transfusion requirements among patients with hematological malignancies and the potential risk of transfusion reactions, there is an urgent need to assess their incidence, particularly in resource-limited settings where hemovigilance data are scarce. In this prospective cohort study conducted at Mbarara Regional Referral Hospital and the Uganda Cancer Institute, in Uganda, we assessed the incidence of hemolytic and serologic transfusion reactions among patients with hematological malignancies, while also assessing the presence and generation of transfusion-associated RBC alloantibodies in the recipients upon transfusion and 2 weeks after transfusion.

Materials and Methods

Study Design, Site, and Duration

This prospective cohort study was conducted between August 30th, 2024, and January 4th, 2025, at Mbarara Regional Referral Hospital (MRRH) and the Uganda Cancer Institute (UCI)-Mulago, in Uganda. UCI is a tertiary cancer centre in Kampala, while the cancer unit at MRRH is an auxiliary unit of UCI in southwestern Uganda.

MRRH is a tertiary healthcare facility located in Mbarara City, southwestern Uganda, approximately 270 Kilometres from the capital city, Kampala. It's owned by the Ministry of Health, Uganda, and has a bed capacity of about 600. MRRH serves a population of over 6 million people across 13 districts in southwestern Uganda, as well as neighbouring regions of Rwanda, Tanzania, and eastern Democratic Republic of Congo. MRRH provides a wide range of services, including comprehensive cancer screening, diagnosis, and treatment. The cancer unit has two in-patient wards for adults and children, as well it also conducts weekly outpatient clinics, attending to over 500 patients.

The Uganda Cancer Institute (UCI), located in Upper Mulago, Kampala, is a specialized tertiary healthcare facility under the Ministry of Health, Uganda. It's located about 5 Kilometres northeast of Kampala, along Upper Mulago Hill Road. UCI provides comprehensive cancer services, including prevention, diagnosis, treatment, consultation, research, and training. The

facility has expanded to include bone marrow transplantation, further enhancing its specialized care. Recognized as the East African Center of Excellence for Oncology, UCI serves an estimated combined population of over 100 million people across the East African region.

Study Population, Sample Size Estimation, and Recruitment Criteria

Patients with hematological malignancies were enrolled as soon as the request to transfuse was made for that hospitalization. Patients were eligible if they were diagnosed with hematological malignancies, aged ≥ 2 years with prior transfusion history, and received a blood transfusion as part of their clinical care during the study period. Patients received additional transfusions between day 0 and day 14. Non-admitted patients were excluded from the study. Participants received ABO/RhD-compatible and non-leucocyte-depleted blood and red cell concentrates. While routine pre-transfusion testing typically involved a saline crossmatch at room temperature, any indication of suspicious serological incompatibility warranted further investigation using an antihuman globulin crossmatch. In Uganda, blood transfusions are prescribed by physicians in accordance with Ministry of Health guidelines. Blood was indicated for patients with Hb levels below 7g/dL, or 6g/dL for those with sickle cell anemia.²² Any transfusions received in the days before enrollment were documented as part of the transfusion history in the data capture form.

The sample size was calculated using the EPITOOLS calculator for a Cohort study.²³ A previous study in Uganda reported an 8.9% (49 of the 507 transfusion adverse events).²⁰ The sample was based on a power of 80%, a 95% confidence level, and an anticipated 10% loss-to-follow-up. Based on these, a total of 382 patients were recruited and included.

Participants were enrolled using a purposive sampling approach, targeting patients with hematological malignancies who were clinically indicated for blood transfusion during hospitalization. This approach aimed to include participants relevant to the study aims, thereby enabling the validity and interpretability of the study outcomes.

Study Procedures

Patients with a clinical indication of transfusion were approached and requested to consent (for adult participants) or assent (for participants under 18 years).

The study time points were day 0 (transfusion day), days 7 and 14. A permissible window of ± 3 days was allowed for the day 14 time point to provide flexibility and minimize the loss-to-follow-up. At each study visit, venous blood samples were collected following a standard phlebotomy procedure. Approximately 4 millilitres (mL) of blood was drawn into an Ethylene di-amine tetra acetic acid (EDTA) vacutainer, and about 2 mL was collected into a plain (non-anticoagulated) vacutainer for the respective laboratory analyses.

During each transfusion, bedside monitoring was conducted by the facility nurse, who documented any signs and symptoms in accordance with transfusion guidelines.²² Participants' medical charts were reviewed to document demographic information, details of the transfused blood component (whole blood or red cell concentrates), and any documented transfusion-related adverse event, including the date and time of occurrence. Also, clinical signs and symptoms such as fever, malaise, respiratory distress, agitation, chills, rigours, burning sensation at the infusion site, headache, diffuse bleeding, reduced urine output, nausea, vomiting, tachycardia, hypotension, hypertension, altered consciousness, and allergic manifestations were recorded. The overall prognosis following the transfusion was also noted. A facility nurse ascertained if the participants' symptoms met the criteria for a specific transfusion reaction.

Laboratory Analyses

Blood Collection and Processing

The EDTA anticoagulated sample was used to perform a complete blood count (CBC) or Hb estimation at least within less than 30 minutes of sampling. Thereafter, the EDTA sample was aliquoted to obtain 1.5 mL for the direct antihuman globulin test (DAT). The remaining sample was centrifuged to separate the plasma and buffy coat, which were then transferred into a cryogenic vial and freeze-stored at -80°C at the study sites to be used for immunohematological testing. These tests were performed for all the enrolled participants at each of the study time points.

Complete Blood Counts, Hb Estimation, LDH, and DAT Testing

The complete blood count and lactate dehydrogenase (LDH) analyses at UCI were routine tests for clinical care. For the enrolled participants, the study ensured that the test was done at all the time points. The complete blood count was performed using the Sysmex analyzers (*Sysmex Corporation, Kobe, Japan*), and LDH was performed using Cobas c311 (*Roche Diagnostics GmbH, Germany*). The direct antiglobulin test was performed at the Uganda Blood Transfusion Services (UBTS) using Neo Iris (*Immucor, Inc., Germany*).

At MRRH, Hb estimation was conducted by the study team using Hemocue301 (*HemoCue AB, Sweden*), and LDH testing was done using Cobas c111 (*Roche Diagnostics GmbH, Germany*). DAT testing was performed using Echo Lumena™ (*Immucor, Inc., Georgia, United States*). Testing procedures were as per the manufacturers' recommendations and laboratory standard operating procedures.

RBC Alloantibody Screening Protocol

The frozen plasma samples were shipped to the Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. Plasma samples were screened for the presence of RBC alloantibodies by use of a standard 3-cell panel of reagent group O RBCs (ID-DiaCell I-II-III) (Catalogue number: 004310; Bio-Rad Laboratories, DiaMed GmbH, Switzerland). In a three-phase (immediate spin, enhancement with low-ionic-strength saline at 37°C, and antihuman globulin steps), an indirect antiglobulin test (IAT) using the tube agglutination method²⁴ with polyspecific anti-human globulin (AHG) (rabbit anti-IgG and monoclonal anti-C3d) (Catalogue number: 804020; Bio-Rad Laboratories, DiaMed GmbH, Switzerland) was used. Samples that showed agglutination in the screening phase were further used for a more detailed analysis of RBC allo-antibodies using an 11-cell commercial panel of reagent group O RBCs of selected phenotypes (ID-DiaCell 1–11) (Catalogue number: 004114; Bio-Rad Laboratories, DiaMed GmbH, Switzerland). The RBC alloantibody testing protocol was as follows;

During the immediate spin (IS), 2 drops (about 100µL) of plasma were added to a corresponding labelled 10×75 mm glass tube. Then, one drop of 5% reagent RBCs was added to the respective tube and gently mixed. The tubes and their contents were then centrifuged at 200g for 2 minutes, after which the cell button was gently dislodged. Agglutination in the IS phase was checked for cold agglutinating antibodies, which were recorded and interpreted as autoantibodies. In the enhancement phase, 2 drops of low-ionic-strength saline were added to the unagglutinated tubes in the IS phase. These were gently mixed, incubated at 37°C for 30 minutes, and then centrifuged at 200g for 2 minutes. The cell button was gently dislodged, and each tube was checked for warm agglutinating antibodies and recorded. In the AHG phase, the unagglutinated tubes were then washed three times by adding excess 0.9% saline. The tubes were then centrifuged at 200g for 5 minutes; the supernatant was completely decanted and blotted dry. Two drops of polyspecific AHG reagent were added to each tube, gently mixed, and centrifuged at 200g for 2 minutes. The cell button was gently dislodged, and the tubes were checked for agglutination and recorded. Each tube was read and graded 0–4+, corresponding to the amount of red cell agglutinin.²⁵ Tubes that did not show agglutination during the AHG phase were confirmed microscopically, and validated by adding 1 drop of IgG-coated RBCs (Catalogue number: 816030; Bio-Rad Laboratories, DiaMed GmbH, Switzerland). Here, the tubes were gently mixed and centrifuged at 200g for 2 minutes. A positive reaction was considered to validate the result; otherwise, it was repeated. The presence of alloimmunization among participants was deemed only if antibodies to one or more RBC antigens were identified.

If initial alloantibody screening was positive, further alloantibody identification was done by testing the plasma samples with an 11-cell commercial panel of reagent group O RBCs of selected phenotypes (ID-DiaCell 1–11). This was performed following similar or additional steps as described for the alloantibody screening, as required.

Interpretation of Reactions

The specificity of the alloantibodies was established through a systematic interpretation of the reaction patterns on the antigram, panel cell antigen profiles, hetero- and homozygosity of the identification panels, the manufacturers' reported cell panel specificities, exclusion criteria, and the "rule of three" (that is, at least 3 positive reactions with antigen-positive cells and 3 negative reactions with antigen-negative cells), as previously described.²⁶ Interpretation conformed to previous studies and the manufacturer's recommendations.^{27–29}

Delayed serological transfusion reaction (DSTR) occurs as the post-transfusion cases of “new” RBC alloantibodies without causing hemolysis.^{30–32} In this study, participants who were IAT negative on day 0 but developed RBC alloantibodies detected on days 7 and 14 were classified as cases of DSTR.

Quality Control

The testing for the hemoglobin, lactate dehydrogenase, direct and indirect antiglobulin tests incorporated internal quality controls, and the equipment was well-maintained. Quality controls for hemoglobin were performed using Sysmex commercial control materials at three levels (1, 2 and 3), with manufacturer-assigned hemoglobin expected ranges spanning approximately 5.3–6.0g/dL (level 1), 11.4–12.0g/dL (level 2), and 14.3–15.8g/dL (level 3). On the other hand, quality controls for LDH were performed using Lymphocheck commercial controls, with three levels (low, normal and High). Their target means were manufacturer-assigned: approximately 120–160U/L (low control), 200–280U/L (normal control) and 300–600U/L (high control). Quality control runs were validated if results fell within the manufacturer’s specified ranges for each level and specific lots used. UCI and MRRH laboratories are both accredited by the South African Accreditation System (SANAS). Also, they participated in external proficiency schemes by the Randox International Quality Assessment Scheme (RIQAS) and the United Kingdom National External Quality Assessment Service (UKNEQAS), respectively. All laboratory testing followed the manufacturer’s guidelines.²⁷

Statistical Analysis

The data entered in the Epi InfoTM software suite (Atlanta, Georgia) was exported into Microsoft Excel (Microsoft, Redmond, United States). The dataset was systematically cleaned to address errors and inaccuracies, including missing data, duplicate entries, inconsistent units, and erroneous values. This aimed to ensure accuracy and reliability for analysis. The cleaned data were exported into SPSS version 20.0 for statistical analysis. The outcomes included a comparison of pre- and post-transfusion mean Hb levels to evaluate RBC incremental gain. Additionally, we analyzed pre- and post-transfusion LDH levels across time points. We also analyzed the incidence of antibodies detected in participants who received transfusions during the study period. Descriptive statistics, including means, standard deviations, frequencies, and percentages, were used to summarize participants’ characteristics and outcomes. The incidence of hemolytic and serologic transfusion reactions was determined as a cumulative incidence and reported as a proportion of 100. To evaluate changes in Hb and LDH levels over time, analysis of variance was performed. Changes in mean Hb and LDH levels over time (Days 1, 7, and 14) were evaluated using Repeated Measures Analysis of Variance to assess the statistical significance of differences between time points. Patients with missing measurements at any time point were excluded from the analysis using listwise deletion. Prior to analysis, the assumption of Repeated Measure-Analysis of variance was assessed. Sphericity was tested using Mauchly’s test, and when the assumption was violated, the Greenhouse-Geisser correction was considered to adjust the degrees of freedom. In addition to univariate Repeated Measure-Analysis of Variance, multivariate tests, including Pillai’s Trace, Wilks’ Lambda, Hotelling’s Trace, and Roy’s Largest Root tests, were conducted to determine the statistical significance at $p < 0.05$. Where the overall effect of time was significant, post-hoc pairwise comparisons with a Bonferroni adjustment were performed. Effect sizes for repeated measures were reported as partial eta squared.

Ethical Approval

The study was approved by the Mbarara University of Science and Technology Research and Ethics Committee (MUST-2024-1505), the Uganda National Council for Science and Technology (HS4551ES), and the Health Research Ethics Board of Alberta-Cancer Committee (HREBA-CC-25-0052), Alberta, Canada. Written informed consent was obtained from all participants above 18 years. On the other hand, participants under 18 years provided informed written assent, and written informed consent from their parents or legal guardians. The study procedures adhered to the Declaration of Helsinki.

Results

Of the 514 participants approached, 467 provided day 0 samples, and 382 completed the follow-ups of days 7 and 14 (Figure 1).

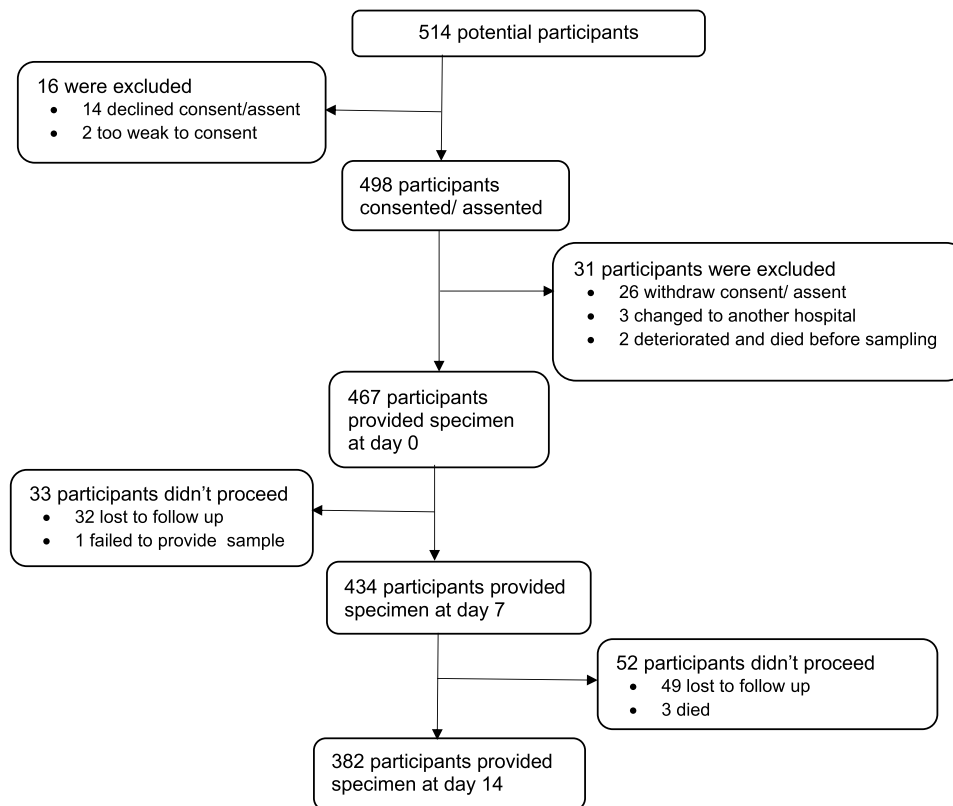


Figure 1 Enrollment and participant follow-up. Shows the status of participants across Day 1, Day 7 and Day 14 and reasons for exclusion.

Characteristics of Participants

At baseline (day 0), 467 patients with hematological malignancies were enrolled, with a median age of 36.4 years (IQR: 27.3–46.9). Of these, 51.2% were males and 43.7% were aged 31–65 years. All participants had previously received at least one blood transfusion; the median number of transfusions was 4 (interquartile range, IQR: 2–13). A total of 382 participants completed the follow-up period (Figure 1), and their median age was 31.7 years (IQR: 26.1–48.6) (Table 1).

Table 1 Characteristics and Clinical Outcomes of the Followed Participants

Variable (n=382)	
Age, years; median (interquartile range, IQR)	31.7 (26.1, 48.6)
Sex, number (%)	
Female	167 (43.7)
Male	215 (56.3)
Age category, years; number (%)	
<5	1 (0.3)
5-12	14 (3.7)
13-19	41 (10.7)
20-30	91 (23.8)
31-65	167 (43.7)
>65	68 (17.8)

(Continued)

Table 1 (Continued).

Variable (n=382)	
Diagnosis	
Leukemia	188 (49.2)
Lymphoma	83 (21.7)
Myeloma	56 (14.7)
Myeloproliferative neoplasms	21 (5.5)
Myelodysplastic syndromes	34 (8.9)
Hemoglobin concentration, g/d; mean (95% Confidence Interval)	
Day 0 (visit 1)	6.6 (6.1, 8.9)
Day 7 (visit 2)	7.5 (7.3, 10.1)
Day 14 (visit 3)	8.9 (8.4, 10.6)
Lactate dehydrogenase levels, u/L; mean (95% Confidence Interval)	
Day 0 (visit 1)	433.5 (376.1, 491.0)
Day 7 (visit 2)	371.2 (330.5, 411.8)
Day 14 (visit 3)	350.9 (307.4, 394.3)
Number of blood units transfused, median (IQR)	4 (2, 13)
Number of blood units transfused; number (%)	
<5	142 (37.2)
5-10	186 (48.7)
>10	54 (14.1)
Specificity of the transfusion unit; number (%)	
Whole blood	167 (43.7)
RBC concentrates	215 (56.3)
Reportable transfusion adverse event; number (%)	
Yes	0
No	382 (100.0)
Clinical outcome; number (%)	
Alive	355 (92.1)
Dead	27 (7.9)

Changes in Hb and LDH Levels Across Time Points

There was a progressive improvement in Hb levels following transfusion across the time points (Figure 2). Relatedly, mean Hb increased, while mean LDH levels decreased over the same period (Table 1). All the Pillai's Trace, Wilks' Lambda, Hotelling's Trace, and Roy's Largest Root tests indicated statistically significant differences in mean Hb and LDH levels over time ($p < 0.001$). Additionally, the Repeated Measures Analysis of Variance confirmed that the changes in mean Hb and LDH across the time points were statistically significant ($p < 0.001$).

Post hoc pairwise comparisons with Bonferroni adjustment confirmed significant increases in Hb between Day 0 versus Day 7 ($p = 0.015$), between Day 7 versus Day 14 ($p = 0.010$), and between Day 0 versus Day 14 ($p < 0.001$). Similarly, LDH decreased significantly between Day 0 versus Day 7 ($p = 0.021$), Day 7 versus Day 14 ($p = 0.034$), and Day 0 versus Day 14 ($p < 0.001$), demonstrating a stepwise and statistically significant rise in Hb levels and reduction in LDH levels during the follow-up period.

Transfusion Reactions and RBC Alloimmunization

No acute or delayed hemolytic transfusion reactions or transfusion-related acute lung injury (TRALI) were observed. However, a total of 11 participants had a positive antibody screen across the three time points: 7 participants at day 0, 1

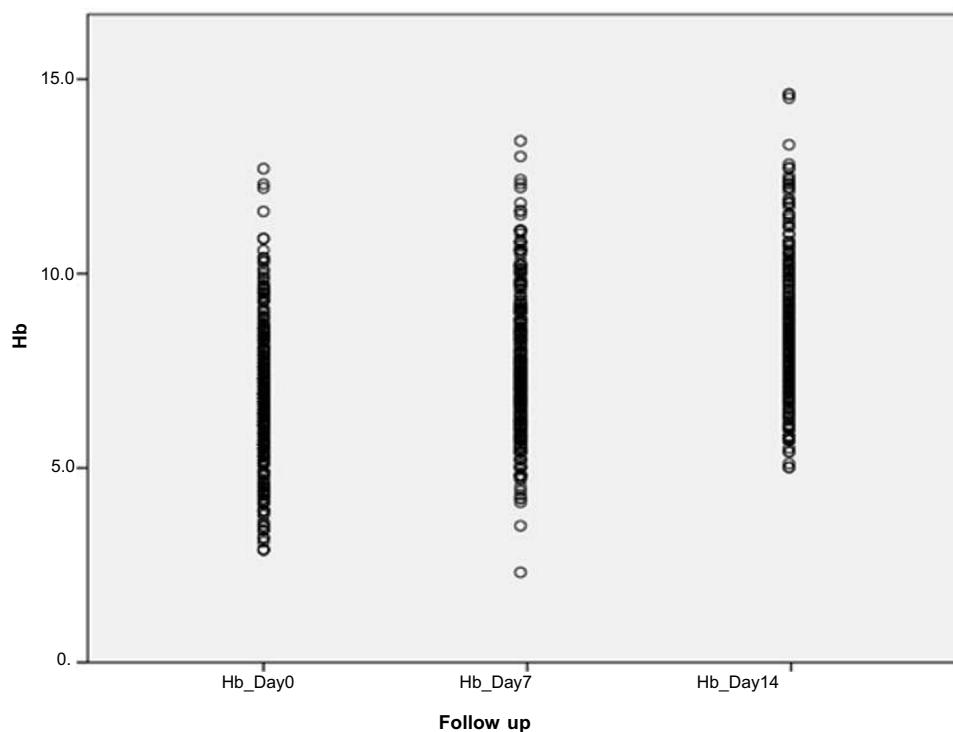


Figure 2 Individual Hb levels across time points. Shows Dot plot of individual Hb levels across Day 1, Day 7 and Day 14 time points.
Note: Marginal means of Hb are measured in grams/deciliters.

participant at day 7, and 3 participants at day 14. The cumulative incidence of DSTRs was 0.86 in 100 persons (4 of 467 patients with hematological malignancies) (95% CI: 0.02–1.69).

Of the seven participants with a positive RBC antibody screen on day 0, one participant with anti-K antibodies tested negative on both days 7 and 14. Conversely, one participant who did not have a positive RBC antibody screen on day 0 tested positive on both days 7 and 14. Additionally, three participants who tested negative for RBC antibody on both days 0 and 7 tested positive at day 14 (Table 2).

Transfusion history revealed participants with DSTRs had been exposed to a high number of blood units, with 75% receiving more than 10 transfusion units. Additionally, 75% (3 out of 4) of the participants with DSTRs had been transfused with whole blood. The demographic and clinical characteristics of participants with DSTRs are given in Table 3.

Table 2 Direct and Indirect Antiglobulin Tests Among Participants

	Day 0 (n=467)		Day 7 (n=434)		Day 14 (n=382)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Direct antiglobulin test						
Negative	436	93.4	405	93.3	351	91.9
Positive	24	5.1	26	6.0	27	7.1
Invalid	7	1.5	3	0.7	4	1.0
Indirect antiglobulin test						
Negative	460	98.5	433	99.8	379	99.2
Positive	7 [†]	1.5	1	0.2	3	0.8

Notes: (i). A total of 11 participants (7 on days 0, 1 on day 7, and 3 on day 14) tested positive for RBC alloantibody. (ii). [†]denotes that of the 7 participants who tested positive for RBC alloantibody at day 0, only one participant with anti-K tested negative on both days 7 and 14. No other participants with RBC alloantibodies at days 0 and 7 tested negative at day 14. Thus, the total number of participants considered as “new cases” of RBC alloimmunization on days 7 and 14 was 4.

Table 3 Characteristics of Participants with DSTRs

Characteristic (N=4)	Number of Participants (%)
Age category	
20-30	1 (25.0)
31-65	2 (50.0)
>65	1 (25.0)
Sex	
Female	2 (50.0)
Male	2 (50.0)
Diagnosis	
Leukemia	2 (50.0)
Lymphoma	1 (25.0)
Myelodysplastic syndromes	1 (25.0)
Number of blood units transfused; number (%)	
<10	1 (25.0)
>10	3 (75.0)
Specificity of the transfusion unit; number (%)	
Whole blood	3 (75.0)
RBC concentrates	1 (25.0)

Table 4 The Specificity of RBC Alloantibodies Among Participants

	Anti-C	Anti-D	Anti-E	Anti-e	Anti-K	Anti-Le ^a	Anti-S
Day 0 (N=7)	3	2	1	0	1	0	0
Day 7 (N=7)	2	1	2	0	0	1	1
Day 14 (N=10)	2	2	2	1	1	1	1
Frequency (%)	7 (29.2)	5 (20.8)	5(20.8)	1 (4.2)	2(8.3)	2 (8.3)	2 (8.3)

Among this cohort of patients, DAT was positive among 24 (5.1%) participants. Although the number of DAT-positives increased across time points, this change was not statistically significant (Cochran's Q, $p>0.05$).

The overall RBC alloantibody prevalence was 2.4% (95% CI: 0.98–3.74). Twenty-four plasma specimens tested positive for RBC alloantibodies. Seven singly RBC alloantibodies against the antigens of the Rh blood group system (C, D, E, e) were identified in 18 samples. Additional RBC alloantibodies were found against the Kell (K) 2; Lewis (Le^a) 2; and MNS (S), 2 blood group systems (Table 4). No additional antibodies were detected in any participant at subsequent time points.

Discussion

This study evaluated the incidence of hemolytic and serologic transfusion reactions among patients with hematological malignancies at Mbarara Regional Referral Hospital and the Uganda Cancer Institute in Uganda.

Following transfusion, an increase in the mean Hb concentration was observed. The incidence of DSTRs was 0.86 in 100, while the prevalence of RBC alloimmunization was 2.4%. The detected RBC alloantibodies were directed against antigens in the Rh, Kell, Lewis, and MNS group systems. No acute or delayed hemolytic reactions or TRALI were reported.

The observed increase in mean Hb concentrations following transfusion is likely multifactorial. First, it reflects the anticipated physiological and clinical benefits of red blood cell transfusion in patients with hematological malignancies. Consistent with previous reports, transfusion was associated with an improvement in the Hb levels of patients.^{33–35}

However, this observation should be interpreted with caution, as anemia in this population is typically multicausal. Concurrent clinical interventions, including antibiotic therapy and supportive care, as well as factors such as cessation of bleeding, improved nutritional status, and recovery from acute illness, may as well influence Hb levels. As this study did not precisely investigate the etiologies of anemia, the relative contribution of transfusion versus other interventions to post-transfusion Hb recovery cannot be definitively established and necessitates further investigations. Nonetheless, the sustained increase in mean Hb levels observed up to day 14 may suggest an overall improvement in the patients' clinical status. These findings may support the potential role of transfusion support as an important component of comprehensive care for patients with hematological malignancies.

Although limited studies have documented the phenomenon of DSTRs, they remain clinically significant and pose a risk to recipients. In this study, the incidence of DSTRs was 0.86 per 100. The observed frequency may be influenced by multiple factors, including the antibody detection threshold of the method as well as the natural waning of alloantibody levels over time.³² This aligns with well-documented evidence that some alloantibodies gradually decline to levels below the threshold of detection.³⁶ For example, in one case, a 47-year-old male participant with a diagnosis of Hodgkin's lymphoma tested positive for anti-K alloantibodies at day 0; however, these antibodies were no longer detectable in plasma specimens collected on days 7 and 14, suggesting a possible waning effect. The reactivity in this case (graded as 1+) may support the likelihood of low titres, and thus the observed decline in detectability across the time points. Additionally, consistent with the literature, certain antibodies, such as those of the Kidd (Jk^a, Jk^b) and Lewis (Le^a) systems, have been seen to appear shortly after transfusion but persist for only a limited duration.³⁶ Furthermore, as reported in a previous study, the detection of RBC alloantibodies within a population is dependent on the specific antigen profile of the screening cells.³⁷ The use of non-ethnically matched screening panels, particularly those derived from non-African donors, may underestimate the true alloimmunization rates in this study. Importantly, while DSTRs are often underreported, they remain clinically significant as the development of RBC alloantibodies increases the risk of subsequent hemolytic transfusion reactions (HTRs).³¹ Moreover, the transient detectability of these antibodies can heighten the risk of inadvertently transfusing antigen-incompatible RBCs during subsequent transfusion episodes.

Our study found antibodies against the Rh, Kell, Lewis, and MNS blood group systems. This is similar to another study in Uganda, in which anti-S, -K, Le^a, -Rh (D, E), and a combination of anti-E plus anti-K were previously reported.³⁸ Moreover, other studies in sub-Saharan Africa also reported anti-E, -D, -K, and anti-C as dominant alloantibodies.³⁹ In addition to the detected alloantibodies, nineteen cases had a very weak serologic positivity grade of less than 1+ (mixed field interpreted as possible dual population due to post-transfusion), and weak reactions interpreted as barely visible tiny clumps or hemolysis often too weak for clear grading on screening,²⁷ and all such samples became non-reactive at subsequent time points. This finding suggested possible low-titre or low-affinity antibodies that may transiently appear and subsequently fall below detection thresholds of standard screening methods. As the study did not genotype these patients, we could not ascertain whether the patients had weak D or partial D variants. This phenomenon underscores the need for sensitive tests and prospective monitoring of multi-transfused patients.

The direct antiglobulin testing showed that 5.1% of participants had pre-existing RBC sensitization at Day 0, and the proportion of DAT-positive patients remained stable over the follow-up period. This finding suggests that transfusion did not significantly alter the *in vivo* RBC sensitization during the study period, consistent with earlier findings of similar DAT positivity rates among multi-transfused patient populations.^{39,40} Conversely, the IAT identified RBC alloantibodies directed against clinically significant antigens, underscoring the risk of alloimmunization despite the absence of overt hemolytic reactions.^{38,41} These findings highlight the need for improved pre-transfusion testing among patients likely to require frequent transfusions.

The absence of acute or delayed hemolytic transfusion reactions in this study contrasts with previous findings. For instance, a previous study at Mbarara Regional Referral Hospital reported an incidence of transfusion reactions at 0.6 per 100.¹⁹ Relatedly, a study conducted at Mulago National Referral Hospital reported the incidence of confirmed acute transfusion reactions at 8.9 in 100 of 507 transfusion episodes.²⁰ Furthermore, a study conducted at Uganda Cancer Institute reported an incidence of 4.0 per 100 (13 of 323 units) per platelet unit or 7.3 per 100 (11 of 151 episodes) per transfusion episode.²¹ Notably, no cases of TRALI were observed in this study, which aligns with findings from a previous report.²¹ The variations in the observed frequency of transfusion-related adverse events are multifaceted and may be attributed to the fact that non-acute HTRs are often clinically

asymptomatic or that symptoms are masked by the underlying severity of cancer.^{42,43} Moreover, delayed transfusion reactions are generally mild, self-limiting, and asymptomatic,⁴⁴ which can result in underestimation of their true incidence. Nevertheless, HTRs remain clinically important due to their association with life-threatening hemolysis, worsening anemia, increased transfusion needs, and, in severe cases, death.^{45,46}

Although overt transfusion reactions were not recorded in this study, the incidence of DSTRs, while subtle, carries important translational significance, as it reflects latent RBC alloimmunization in a population of patients likely to require frequent transfusions. The presence of RBC alloantibodies on day 0 suggests prior RBC alloimmunization, likely resulting from earlier transfusions or other sensitizing events. Studies have demonstrated that many patients develop alloantibodies early in their transfusion course, often after only a few exposures to foreign antigens.^{47,48} Detection of new RBC alloantibodies within 14 days post-transfusion indicates either a memory response to previous sensitization or de novo antibody formation.⁴⁷ Although this study did not explore the phenomenon of memory response to a previous antigen immune response in depth, future research with extended follow-up periods may provide further insights into the kinetics and implications of RBC alloantibody development. Although transfusions are beneficial, 75% of patients with DSTRs received more than 10 units cumulatively, reflecting the persistent risk of transfusion-related sensitization. This finding, consistent with a previous report,⁴⁹ underscores the dual need of optimizing transfusion benefits while maintaining safe pre-transfusion practices to minimize the risk of alloimmunization.

The strength of this study lies in its relatively large sample size of hospitalized participants enrolled from two tertiary healthcare facilities in Uganda, enhancing the generalizability of the findings. Also, efforts were made to minimize the loss to follow-up, including phone call reminders (for the discharged participants) and, in some cases, coordinating return clinic visits with the primary care team when the return dates fell within the study window. Additionally, transfusion adverse events were monitored using routine clinical protocols in conformity with the Ministry of Health, Uganda guidelines.²²

Despite these strengths, there remains a potential for underreporting of transfusion-related adverse events. However, this limitation may have been partially mitigated by the study's active follow-up design, which did not rely solely on routine clinical documentation. In addition, the study population consisted exclusively of patients with a prior history of transfusion, which limits the generalizability of the findings to transfusion-naïve individuals. Prior transfusion may influence the baseline Hb levels, alloimmunization, or the underlying disease severity. Thus, future studies ought to include transfusion-naïve individuals to more accurately delineate the independent effects of transfusion and to enhance the understanding of Hb dynamics across the spectrum of patients with hematological malignancies. More, while transfusion is expected to increase Hb levels, post-transfusion Hb in patients with hematological malignancies is likely multifactorial, as factors unrelated to transfusion, such as cessation of bleed, resolution of infections, or concurrent interventions, may also contribute to Hb increase, confounding the direct attribution of post-transfusion Hb changes to transfusion alone. Notably, LDH was considered as a potential marker of hemolysis; however, LDH is a nonspecific enzyme that may be elevated in a number of clinical contexts, including malignancy, liver disease, severe infection, myocardial infarction and muscle injury, all of which were not investigated in this cohort. The fact that we did not investigate other markers of hemolysis, such as haptoglobin, indirect bilirubin, or reticulocytosis, limits the ability to conclude hemolytic activity. Another limitation is the relatively short follow-up period, which ended on day 14 (± 3). As such, the findings reflect only adverse events occurring within this timeframe. In a previous study,⁵⁰ we observed a higher prevalence of RBC alloantibodies among patients who had received their most recent transfusion at least two weeks prior, suggesting a potential time-dependent development of alloimmunization in this population. These limitations underscore the need for further research with extended follow-up periods to better characterize the full spectrum of transfusion-related complications. The relatively small sample size and limited follow-up mean that the confidence intervals around these estimates are wide, and the findings should be interpreted as indicative rather than definitive. Furthermore, a limitation of this study relates to the inclusion criteria, as participants were not stratified according to their prior transfusion exposure or the duration since the diagnosis of the underlying hematological malignancy. Previous transfusions are known risk factors for transfusion reactions, particularly immunological reactions, since repeated exposure to donor antigens can lead to the development of clinically significant antibodies.⁵¹ In addition, the duration and stage of the malignancy may influence the immune status, treatment exposure, and transfusion requirements, conditions likely to modify the susceptibility to adverse transfusion events.⁴⁷ The absence of detailed information on the participants' cumulative transfusion histories and time since diagnosis, therefore, limited the ability to assess these variables as potential cofounders or effect modifiers in the occurrence of hemolytic transfusion reactions. Also, due to logistical challenges,

we did not investigate autoimmunity in our RBC alloantibody screening. As such, we could not clearly distinguish the positive direct antiglobulin tests due to autoimmunity. Lastly, this study focused exclusively on hemolytic and serologic transfusion reactions and did not assess non-hemolytic transfusion reactions such as febrile non-hemolytic reactions, allergic reactions, or transfusion-associated circulatory overload events.

Conclusion

This study observed an increase in mean Hb levels over time in patients with hematological malignancies who received red cell transfusions. No acute or delayed HTRs or TRALI were reported; however, DSTRs were observed. More, RBC alloantibodies against antigens in the Rh, Kell, Lewis, and MNS group systems were identified. Consistent with previous studies,^{38,52} these findings underscore the importance of strengthening pre-and post-transfusion antibody testing for RBC alloantibodies, particularly among patients requiring frequent transfusions, to prevent hemolytic complications and improve transfusion outcomes.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

May Choi reports consulting fees from AstraZeneca, consulting fees from Biogen, consulting fees from Werfen, consulting fees and Associate Director from MitogenDx, outside the submitted work. The authors declare no other conflicts of interest in this work.

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