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Transfusion requirements and alloimmunization to red blood cell antigens in orthotopic liver transplantation

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Abstract

Background and Objectives: Orthotopic liver transplantation (OLT) has been associated with high blood transfusion requirements. We evaluated the transfusion needs and frequency of alloimmunization to RBC antigens among OLT recipients pre- and post-transplantation.

Materials and Methods: We reviewed the medical records of patients who underwent a first OLT between January 2007 and June 2017. Transfusions given only during the perioperative period, defined by 1 week before OLT until 2 weeks following OLT, were included in this study. Records were reviewed in June 2019 for updated antibody testing results.

Results: A total of 970 patients underwent OLT during the study period. The median age of patients was 57 years; 608(62.7%) were male. During the perioperative period, transfused patients received an average of 10.7 (±10.7) RBC units, 15.6 (±16.2) thawed plasma units and 4.1 (±4.3) platelet units. At the time of OLT, a total of 101 clinically significant RBC alloantibodies were documented in 58(5.98%) patients. Fifty-three of these antibodies were directed against Rh blood group antigens. Twenty-two (37.9%) patients had more than one alloantibody. Patients with alloimmunization before OLT ($N = 58$) received perioperatively comparable number of RBCs to non-alloimmunized patients (10.5 ± 10.6 vs. 9.6 ± 10.7; $p = 0.52$). There was no significant difference in perioperative or intraoperative RBC transfusion between patients with one alloantibody and those with multiple alloantibodies. Only 16 patients (16/737; 2.17%) developed new alloantibodies at a median of 61 days after OLT. The overall alloimmunization rate was 9.8% (72/737), and female patients were more likely to be alloimmunized.

Conclusion: Blood transfusion requirements in OLT remain high. However, the rate of RBC alloimmunization was not higher than the general patient population.

KEYWORDS
alloimmunization, orthotopic liver transplantation, RBC, transfusion

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INTRODUCTION

Orthotopic liver transplantation (OLT) has advanced throughout the years and has become the standard of care for end-stage liver disease [1]. It has significantly improved the outcome and survival rate of patients with acute liver failure [2]. With the improvement of surgical techniques, implementing preoperative optimization, use of antifibrinolytic medications and better transfusion management, OLT has witnessed a significant decrease in transfusion requirements [3, 4]. In addition, accumulating evidence in the medical literature indicates that high transfusion requirements on any blood component are associated with adverse events, prolonged hospital stays and poor postoperative outcomes [5–9]. However, OLT is still associated with major blood loss and consequently high blood transfusion requirements [10], which can extend postoperatively due to bleeding complications and abnormal haemostasis [11].

Immunohaematologic complications can result from a blood transfusion and can complicate patient management [12]. Due to multiple blood transfusions, liver transplant patients can get alloimmunized to red blood cell (RBC) antigens. RBC alloimmunization can cause adverse events resulting in acute or delayed haemolytic transfusion reactions and can result in difficulty locating compatible blood [13]. With the institution of patient blood management in most institutions and with the evidence supporting restrictive haemoglobin thresholds, there has been a decline in transfused RBC units [14]. However, blood transfusion remains the most common procedure performed during a patient's hospitalization with more than 11 million RBC units transfused annually in the United States [15]. Studies have reported an alloimmunization incidence of 6%–23% in OLT [16, 17], which is higher than the 1%–5% of the general patient population [18–20].

With a very active liver transplant programme at our institution, we aimed, through the current study, to determine the transfusion needs in OLT during an 11-year period. In addition, we wanted to evaluate the frequency of alloimmunization and its specificity to RBC antigens among liver transplantation recipients.

MATERIALS AND METHODS

This study was performed at Henry Ford Hospital, an 877-bed tertiary academic medical centre located in Detroit, Michigan. The study was approved by our institutional review board and was carried out in accordance with the Helsinki declaration. Informed consent was waived due to the study design. Patients were identified through the Liver Transplant database. Electronic medical records and blood bank files of 970 consecutive patients who underwent a first OLT over an 11-year period (January 2007 through June 2017) were reviewed. Patients undergoing combined liver and other organ transplants were included in the analysis. Patients who had a second OLT were excluded. Transfusions given only during the perioperative period were included in this database. The perioperative period was defined as the period spanning 1 week before OLT until 2 weeks following OLT.

The following variables were collected for each patient: gender; age; race; diagnosis; recipient ABO blood group and Rh type; antibody screening (indirect antiglobulin test [IAT]) and antibody specificity; transfusion requirements (number of units of RBCs, thawed plasma, platelets and cryoprecipitate) during the perioperative period and alloimmunization at any time after OLT with antibody specificity. Records were reviewed in June 2019 for updated antibody testing results.

Antibody screening (IAT) was performed using solid-phase technology on a fully automated analyser Galileo Neo (GALILEO: Immucor Inc., Norcross, GA) using a two-cell screen. Positive samples were investigated for antibody identification with a 14-cell panel. Advanced immunohaematologic investigations would include manual methods, such as adsorption and elution, whenever required. All tests were performed according to manufacturers' instructions.

During the study period, the blood bank utilized leukoreduced blood products, pooled platelet concentrates (available until 2015) or apheresis platelets, fresh frozen plasma (FFP) or plasma frozen within 24 h (PF24) and cryoprecipitate (each unit was a pool of five units). For OLT, the blood bank would start issuing irradiated RBCs and platelets on the day of the transplant.

Immunosuppressive regimen

Per our protocol, induction immunosuppression included rabbit antithymocyte globulin at a dose of 0.5–1.0 mg/kg on postoperative days 1, 3 and 5 or basiliximab at 20 mg on postoperative days 0 and 4. The maintenance immunosuppression regimen consisted of tacrolimus, mycophenolate mofetil and steroids. Tacrolimus was started within 5 days after transplantation. The target trough levels of tacrolimus were 8–12 ng/ml during the first 3 months, 6–10 ng/ml between months 3 and 12 and 5–8 ng/ml after 12 months. Mycophenolate mofetil was administered 500 mg every 12 h and was withdrawn by 1 year. Steroids were tapered off by 3 months.

Anaesthetic and surgical procedures

Prior to liver transplant surgery, patients were always evaluated by the anaesthesia and surgery teams. All patients received general anaesthesia with endotracheal intubation, standard American Society of Anaesthesiologists intraoperative monitoring, central venous and invasive arterial blood pressure monitoring, pulmonary artery pressure monitoring and transesophageal echocardiography assessment of cardiac function. For patients who required intraoperative continuous veno-venous haemofiltration, dialysis access was obtained. Optimally balanced anaesthesia with inhaled agents, opioids and muscle relaxants was provided by the liver transplant anaesthesiologist. Donor's livers were flushed with histidine-tryptophan-ketoglutarate solution. Surgical techniques were used as described previously [21]. Blood product transfusion was managed based on the clinical judgement of the anaesthesiologist utilizing intraoperative monitoring parameters, cell salvage, antifibrinolytics and coagulation testing results.

Transfusion management

The liver transplant coordinator notified the blood bank of a potential liver transplant as soon as a donor was identified. The blood bank records of recipients were reviewed for previous alloimmunization to RBC antigens. A recipient sample was sent for antibody screening (IAT). If the previous and current antibody screening were negative, 20 ABO-compatible RBC units were reserved for the recipient. If clinically significant alloantibodies to RBC antigens were identified by history or on the current antibody screening, 30 antigen-negative serologically cross-matched RBC units were reserved. The blood bank would keep an additional 10–15 antigen-negative uncross-matched RBC units for patients with more than one alloantibody; during massive bleeding, we would use the uncross-matched units and reserve the compatible units for the end of surgery. Blood would be stocked in the blood bank 24 h in advance of the day of the transplant. Thawed plasma units were kept in the blood bank inventory at all times (6–10 Group A units, 4 Group B, 2 Group O and 2 Group AB units). Additional plasma units would be thawed as needed. Platelet units were provided as needed, and cryoprecipitate units were thawed upon request. Blood products were ordered by the anaesthesiologist.

The criteria for transfusion were the available AABB criteria at the time for the pre- and post-operative transfusion. During transplant surgery, transfusion was dictated by the intraoperative needs as reflected by haemodynamic instability, intraoperative course, blood loss, oozing from the surgical field or other surgical complications, which may extend the duration of the procedure. In addition, laboratory values, mostly haemoglobin, platelet count international normalized ratio (INR) and fibrinogen level, were used to support the transfusion needs. Thromboelastography was not available during the study period.

Statistical analysis

Descriptive statistics were presented for variables. Results were expressed as mean ± SD or median plus range for continuous variables, and as numbers with percentages for categorical variables. The Mann–Whitney *U*-test for continuous variables was used to compare the groups when applicable. Pearson's Chi-square test or Fisher's exact test was used to compare categorical variables. Results were considered significant at $p < 0.05$ using two-sided tests. SPSS version 17.0 software was used for the statistical analysis of data.

RESULTS

A total of 970 patients underwent OLT from January 2007 to June 2017. The median age of patients was 57 years (range: 16.6–74.6 years); 608 (62.7%) were male. Most of the patients were Caucasian ($N = 815$;

TABLE 1 Blood component usage in patients undergoing orthotopic liver transplantation ($N = 970$)

Blood component	Number of transfused patients (%)	Mean (units)	SD	Median (units)	Minimum	Maximum
Perioperative						
RBC	874 (90.1)	10.7	10.7	7	1	101
FFP/PF24	877 (90.4)	15.6	16.2	11	1	128
Platelets	559 (57.6)	4.1	4.3	3	1	32
Cryo[a]	584 (60.2)	3.6	3.6	2	1	32
Preoperative						
pRBC	134 (13.8)	3.6	5.1	2	1	55
FFP/PF24	151 (15.6)	8.7	8.8	6	1	54
Platelets	71 (7.3)	2.0	1.8	1	1	11
Cryo[a]	40 (4.1)	2.8	3.3	2	1	17
Intraoperative						
pRBC	782 (80.6)	5.9	6.5	4	1	57
FFP/PF24	831 (85.7)	10.2	8.9	8	1	82
Platelets	422 (43.5)	2.0	1.4	2	1	10
Cryo[a]	490 (50.5)	2.7	2.2	2	1	17
Postoperative						
pRBC	729 (75.2)	5.8	6.6	4	1	88
FFP/PF24	508 (52.4)	7.6	12.4	4	1	117
Platelets	385 (39.7)	3.4	4.0	2	1	31
Cryo[a]	249 (25.7)	2.5	3.2	2	1	31

Abbreviations: Cryo, cryoprecipitate; FFP, fresh frozen plasma; PF24, plasma frozen within 24 h; RBC, red blood cells; SD, standard deviation.
[a]Each cryo unit represents a pool of five units.

TABLE 2 Alloantibodies to RBC antigens identified serologically or by history prior to orthotopic liver transplantation

Antibody specificity	Number of patients (total $N = 58$)	Blood group system/antibody	No. of patients with alloantibodies (total $N = 101$)
E	11	Rh	
Jk^a	6	Anti-E	26
D	5	Anti-D	13
M	4	Anti-C	10
C	3	Anti-c	4
c	1	Kell	
E, K	4	Anti-K	16
K	3	Kidd	
Le^a	2	Anti-Jk^a	11
E, Jk^a	2	Anti-Jk^b	3
C, E, K	1	Duffy	
E, c, K	1	Anti-Fy^a	5
S	1	MNS	
E, c	1	Anti-M	4
E, Fy^a	1	Anti-S	4
E, Fy^a, Jk^b	1	Lewis	
E, K, Jk^b	1	Anti-Le^a	4
D, C, S	1	Colton	
D, C, Le^a	1	Anti-Co^b	1
D, Fy^a	1		
D, K	1		
C, D, E, K, Fy^a, Jk^a, Le^a	1		
C, D, K, Jk^a	1		
C, D, K	1		
C, D, K, S, Co^b	1		
E, c, Fy^a, Jk^b	1		
E, K, S, Jk^a	1		

84%). Sixty-eight patients had a simultaneous liver-kidney transplant and eight patients had multivisceral transplant.

During the perioperative period, transfused patients received an average of 10.7 (±10.7) RBC units, 15.6 (±16.2) thawed plasma units, 4.1 (±4.3) platelet units and 3.6 (±3.6) cryoprecipitate units. Table 1 summarizes the perioperative blood component usage in OLT.

At the time of OLT, a total of 101 clinically significant RBC alloantibodies were documented in 58 (5.98%) patients through positive antibody screening and/or history of alloimmunization to RBC antigens. The patients included 21 males and 37 females, with a median age of 56 years (range: 20–70 years). Forty-nine (84.5%) of these patients were Caucasian. These antibodies were formed against a range of antigens as listed in Table 2. Fifty-three (53%) of these antibodies were directed against the Rh blood group antigens; the next common antibodies were against the Kell (16 antibodies), Kidd (14 antibodies), MNS (8 antibodies) and Duffy (5 antibodies) blood group antigens. Twenty-two (37.9%) patients had more than one alloantibody. Of these, 10 had two antibodies, 7 had three, 3 had four, 1 had five and 1 had seven antibodies (Table 2). One patient had warm autoantibodies, and another had cold autoantibodies on antibody screens at the time of liver transplantation. In addition, six patients had a positive antibody screen with non-specific findings.

Patients with history of RBC alloimmunization before OLT ($N = 58$) received perioperatively comparable number of RBCs to non-alloimmunized patients (10.5 ± 10.6 vs. 9.6 ± 10.7; $p = 0.518$); 54 (93.1%) of the alloimmunized patients received perioperative RBC transfusions. There was no significant difference in perioperative or intraoperative RBC transfusion between patients with one alloantibody and those with multiple alloantibodies (9.6 ± 7.9 units vs. 12.2 ± 13.8 units perioperatively; $p = 0.36$ and 4.6 ± 5.3 units vs. 5.6 ± 7.8 units intraoperative; $p = 0.67$, respectively).

Serological follow-up with antibody screen was available for 737 (76%) patients with a median follow-up of 23 (interquartile range [IQR], 14–260) days following OLT; 696/737 (94.4%) patients received perioperative RBC transfusion. The average number of antibody screening

TABLE 3 Characteristics and immunohaematologic findings of patients who had alloimmunization after liver transplantation

Pts	Age (yrs)	Gender	Race	No. of transfused RBC units periop	Interval (OLT - last ab screen before Allo)	Post-OLT new ab specificity	DAT at Allo	Interval (OLT – Allo)
1	56.3	F	C	27	15.3 months	Anti-E	NP	15.6 months
2	53.6	M	A	10	NP	Anti-E	Negative	3.5 months
3	59.9	M	C	10	13 days	Anti-E	Negative	81 days
4	58.9	M	A	17	NP	Anti-E	NP	8 days
5	43.0	M	C	12	4 days	Anti-D*	Positive (IgG)	14 days
6	37.4	F	C	8	NP	Anti-D*	Positive (IgG)	3 days
7†	55.0	F	C	19	58 days	Anti-c	NP	67 days
8	57.8	M	C	6	10 days	Anti-K	NP	28 days
9	62.5	F	C	5	NP	Anti-K	NP	21.5 months
10	69.0	F	C	20	NP	Anti-K	NP	3.7 months
11	59.9	M	A	6	NP	Anti-K	NP	55 days
12	52.6	F	C	11	4.7 months	Anti-Kp^a	NP	7.3 months
13	38.7	F	C	5	NP	Anti-Kp^a	Positive (IgG)	15 days
14	62.0	F	C	7	NP	Anti-Jk^b	Positive (IgG)	22 days
15	41.4	F	A	6	7.2 months	Anti-Jk^b	NP	20.4 months
16†	22.2	F	A	6	NP	Anti-C, Fy^a, K	Positive (IgG, C3)	15 days

Abbreviations: A, African American; Ab, antibody; Allo, alloimmunization; C, Caucasian; DAT, direct antiglobulin test; F, female; M, male; NP, not performed; OLT, orthotopic liver transplantation; Pts, patients; yrs, years.

*Passenger lymphocyte syndrome.

†Patients 7 and 16 had anti-E + Jka and anti-E, respectively, before OLT.

post-OLT was 1.49. Only 16 patients (16/737; 2.17%) developed new alloantibodies after OLT: anti-E (four patients), anti-K (four patients), anti-K and anti-C and anti- Fy^a (1), anti-Jk^b (2), anti-Kp^a (2), anti-D (2) and anti-c (1). These patients included 6 males and 10 females, with a median age of 55.6 years (range: 22.2–69 years). Identification of alloantibodies was at a median of 61 (IQR, 15–191.5) days after OLT. Table 3 summarizes the characteristics and immunohaematologic findings of these patients. The overall RBC alloimmunization rate in our cohort was 9.8% (72/737). Female patients were more likely to be alloimmunized compared to males (45/362 [12.4%] females and 27/608 [4.4%] males; $p < 0.001$). We had a significantly higher number of African American patients transfused perioperatively compared to Caucasian patients (149/155, 96.1% vs. 725/815, 89%; $p = 0.006$). However, there was no significant difference in overall alloimmunization between African American patients and Caucasian patients (13/155, 8.4% vs. 59/815, 7.2%; $p = 0.62$).

Two D-positive patients receiving OLT from D-negative donors developed anti-D antibodies with positive direct antiglobulin test (DAT) due to passenger lymphocyte syndrome. The first patient was a 37-year-old female with primary sclerosing cholangitis who developed anti-D antibodies 3 days following OLT. She did not have evidence of haemolysis, was managed with immunosuppressive therapy and her DAT was negative 43 days after OLT. The second patient was a 43-year-old male with liver cirrhosis secondary to hepatitis C who developed anti-D antibodies 14 days following OLT. He did not show evidence of increased haemolysis. We did not have a close follow-up on his DAT.

Twenty-four D-negative patients were transfused with D-positive RBC units (median 8.5 units; range: 1–90 units) perioperatively. None of the patients with available serological follow-up ($N = 19$) developed a positive antibody screen after a median serological follow-up of 41.9 months (range: 17 days–127.7 months).

DISCUSSION

We reviewed the medical records of OLT patients to determine their perioperative transfusion requirements and the overall rate of alloimmunization to RBC antigens. During the perioperative period, transfused patients received an average of 10.7 (±10.7) RBC units, 15.6 (±16.2) thawed plasma units, 4.1 (±4.3) platelet units and 3.6 (±3.6) cryoprecipitate units. A total of 101 clinically significant RBC alloantibodies were documented in 58(5.98%) patients at the time of OLT. Only 16 patients (16/737; 2.17%) developed new alloantibodies after OLT. The overall alloimmunization rate was 9.8% (72/737), and female patients were more likely to be alloimmunized.

More than 90% of our OLT patients required RBC and plasma transfusions perioperatively, with an average of 10.7 and 15.6 units, respectively. Most of the blood products were transfused intraoperatively – RBCs and FFPs were transfused in almost 81% and 86% of patients, respectively. Our experience with the transfusion requirements of blood products, especially intraoperative transfusions, is consistent with the published literature on OLT [22, 23]. Still, higher

transfusion requirements have been reported by others [7]. Although the AABB transfusion guidelines are widely used [24, 25], transfusion practices remain variable among transplant centres.

The results of our study showed that more plasma has been transfused than RBCs, which is consistent with some studies [7, 26]. In fact, there is emerging literature that a higher plasma to packed RBC transfusion ratio during liver transplantation is associated with a decreased need for RBC transfusions. In a retrospective study by Pagano and colleagues, 188 patients were evaluated for the volume ratio of transfused plasma (PL Vol) to RBC (RBC Vol). A low PL Vol/RBC Vol was associated with excess RBC transfusion with significant findings using logistic regression [26].

Several studies reported on RBC alloimmunization before and, some of them, after OLT [12, 16, 17, 27–29]. Alloimmunization frequency ranged from 4% to 23% pre-OLT and from 1% to 7.5% post-OLT. Patients having multiple antibodies accounted for up to 45% of alloimmunized patients. The results of the current study are comparable to previous findings: we documented pre-OLT and post-OLT alloimmunization in 6% and 2% of patients, respectively; 38% of alloimmunized patients had multiple antibodies. The profile of antibody specificity, most commonly against the Rh and Kell blood group systems, is consistent with the reported literature [16, 17]. We identified two patients with passenger lymphocyte syndrome due to anti-D antibodies. We cannot tell with certainty if these were the only two cases in our cohort as most passenger lymphocyte syndrome cases are subclinical, and even now, there is no standardized consensus on screening for passenger lymphocyte syndrome in transplant patients [30].

In the current study, patients with RBC alloimmunization before OLT received a comparable number of RBCs perioperatively to non-alloimmunized patients. Our findings did not concur with others' findings [28, 29]. Solves and colleagues [28] reviewed 654 OLT patients from Spain, 27 of whom were alloimmunized before OLT. The investigators found that patients who suffered "any immunohaematologic incident" including those who were alloimmunized received more RBCs during hospital admission. The authors did not give a discussion about their results. In another study [29], only 192 Chinese recipients of liver transplants were surveyed with 17 (8.8%) patients having RBC alloantibodies. The authors found that the presence of RBC alloantibodies was associated with increased blood requirements; however, they acknowledged that the numbers of cases and events were small and that their perioperative variables were highly heterogeneous, and thus cautioned the readers that conclusions were to be verified. The findings of these two studies did not seem to be based on biologic basis, and definitive conclusions in regard to alloimmunization and increased blood requirements need to be investigated in large prospective studies.

We did not find a statistically significant difference in RBC transfusion requirements in patients with single versus multiple antibodies. Contrary to our findings, Shariatmadar and colleagues noted that patients with multiple antibodies required more RBCs compared to those with a single antibody; however, this statistical significance was only applicable when patients required 40 units of RBCs. The cause of this increase in blood utilization was not clear to the authors [16].

The majority of our patients (68%) were alloimmunized to the Rh and Kell blood group antigens at the time of liver transplantation. The question remains whether phenotypically matched blood for Rh and Kell would have a potential benefit in preventing alloimmunization in liver transplant candidates. A definitive answer to this question cannot be provided based on our study. However, we can argue based on our findings that phenotypically matched RBCs might not be of great benefit in this patient population. First, the rate of alloimmunization in our cohort at the time of liver transplantation (5.98%) was not greater than the general patient population, and the rate of new alloimmunization post-liver transplant was even lower at 2.17%. This makes it not worth the efforts needed to find phenotypically matched RBCs during the pre-transplant period. Second, although our study did not specifically assess the challenges in finding compatible blood for alloimmunized patients, we generally did not face difficulties in securing blood during the perioperative period. Based on these observations, we believe providing phenotypically matched RBCs for Rh and Kell blood group antigens might be demanding and not of great benefit in liver transplant candidates. The risks of alloimmunization to RBC antigens need to be evaluated in large prospective studies.

This study has several strengths including the large number of patients undergoing OLT over a long period of institution experience. One of the limitations of this study is its nature and being dependent on medical record documentation. The possibility of data recording bias cannot be excluded. Some parameters that would affect alloimmunization were not collected and these include pregnancy history of female patients, transfusion history before 7 days prior to OLT and transfusion requirements after 14 days after OLT. Another limitation relates to the lack of systematical time course for antibody screening as reflected in the relatively short median antibody screen follow-up time of 23 days; thus, new alloantibodies might have been missed. The lack of a protocol for detecting delayed serologic/haemolytic transfusion reactions is another limitation.

In conclusion, despite blood management, blood transfusion requirements in OLT remain high during the perioperative period. However, the rate of alloimmunization to RBC antigens was not higher than the general patient population. More importantly, RBC alloimmunization in this patient population did not increase RBC utilization. Implementing a patient blood management programme is needed to address preoperative anaemia optimization, minimizing blood loss, implementation of restrictive transfusion thresholds and other principles to minimize blood transfusion and improve outcome. There is also a need to evaluate the appropriateness of blood transfusions in OLT, a process that might not be easy to apply especially in the intraoperative setting.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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