

Is ABO-Compatible but Non-Identical Intestinal Transplant Comparable to ABO-Identical Transplant? An Analysis of the UNOS Registry

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Abstract

ABO-compatible intestinal transplants have been more frequently performed in the US in recent years (from 4% to 16%). However, they have not been clearly shown to have comparable short- and long-term graft outcome compared to ABO-identical transplants.

The US national registry database was analyzed to show the current status of ABO-compatible intestinal transplantation and to determine its effect on acute rejection and long-term graft survival.

Blood type A, B, and AB patients received 11%, 26%, and 62% of ABO-compatible intestinal transplants, respectively. ABO-compatible transplant recipients experienced a higher rate of acute rejection than ABO-identical patients (77% vs. 64%, $p < 0.0001$). In addition, they had a significantly lower 10-year graft survival rate than ABO-identical transplant recipients (27% vs. 35%, $p = 0.020$). Acute rejection was the cause of graft failure in 42% of ABO-compatible and 25% of ABO-identical patients who lost intestinal transplants ($p = 0.041$).

Since ABO-compatible transplants were associated with high rates of acute rejection and graft failure, intense induction/maintenance immunosuppressive therapies are recommended for ABO-compatible transplant recipients. In addition, packed red blood cells of donor type and plasma of recipient type, if needed, should be considered as a safer transfusion strategy for ABO-compatible transplant patients to avoid intensification of allograft injury by GVH immunity.

Keywords: Small bowel transplantation; ABO compatibility; Rejection; Graft survival

Abbreviations

GVH: Graft-Versus-Host

Introduction

ABO-compatible but non-identical transplants have been performed in all organ types for decades. It is controversial whether ABO-compatible transplants have comparable outcomes compared to identical transplants. Some studies have shown ABO-compatible and identical transplants have similar graft

survival in the heart [1,2], lung [3,4], and liver [5] transplants. However, careful investigation of these studies demonstrates that ABO-compatible transplants have lower graft survival than identical transplants in some of these studies, though the differences do not reach statistical significance. Koukoutisis [6] and Bjoro [7] reported that ABO-compatible liver transplant recipients actually have significantly lower graft and patient survival than ABO-identical transplant patients.

Compared to other organ transplantation, intestinal transplantation remains the least frequently performed transplantation. There are more than 40 US centers performing intestinal transplants and case numbers in recent years were only around 100 per year in the US, with most centers performing fewer than 10 transplants per year [8]. With limited intestinal transplant cases, it is very difficult or it may take a long time for a single center to provide convincing evidence to show whether ABO-compatible and identical transplants have comparable graft outcome, especially long-term outcome. Our recent analysis demonstrated that during 1990-2013, 9.7% of US intestinal recipients received transplants from ABO-compatible donors. More importantly, we found there was a very significant increasing trend of ABO-compatible intestinal transplants in recent years (from 4% to 16%). These findings make it urgent to know whether it is safe to perform ABO-compatible intestinal transplantation and what we should do to minimize the potential risk if the ABO-compatible transplant is associated with graft failure. By analyzing US national registry data, we show the current status of ABO-compatible intestinal transplantation in the US and its detrimental effects on short- and long-term intestinal allograft outcomes. We also discuss the potential mechanisms of graft-versus-host reaction-induced graft injury and corresponding strategies.

Materials and Methods

Study population

Between 1/1/1990 and 6/27/2013, a total of 2,287 US intestinal transplants were reported to the Organ Procurement

and Transplantation Network and were included in this study. Among them, 2,061 (90.3%) patients received ABO-identical transplants and 222 patients (9.7%) received ABO-compatible transplants. Four patients who received ABO incompatible intestinal transplants were excluded from this study. Patient demographics of ABO-compatible and ABO-identical transplant recipients are summarized in Table 1.

Statistical Analysis

All statistical analyses were performed using STATA version

Table 1: Patient demographics.

Variables	ABO identical	ABO compatible	p-value
Case No.	2061	222	
patient gender (female)	47.99%	51.35%	0.3400
donor gender (female)	40.27%	40.09%	0.9580
patient age	20.02 ± 0.46	19.15 ± 1.40	0.5506
donor age	11.58 ± 0.29	9.8 ± 0.77	0.0530
patient race (white/nonwhite)	70.31%	60.36%	0.0000
donor race (white)	63.03%	55.41%	0.5980
HLA mismatches	4.64 ± 0.03	4.61 ± 0.08	0.6874
A locus			0.0980
No mismatch	6.46%	10.53%	
1 mismatch	42.32%	38.95%	
2 mismatches	51.22%	50.53%	
B locus			0.5360
No mismatch	2.01%	1.05%	
1 mismatch	26.10%	24.21%	
2 mismatches	71.89%	74.74%	
DR locus			0.8100
No mismatch	5.25%	6.2%	
1 mismatch	40.33%	40.53%	
2 mismatches	54.43%	53.16%	
patient CMV IgG+	35.19%	34.27%	0.0090
patient CMV IgM+	3.23%	2.16%	0.4900
donor anti CMV serology+	45.51%	44.55%	0.0730
patient HBV surface antigen +%	1.58%	2.48%	0.0020
patient HCV serostatus +%	1.52%	0.94%	0.0000
Patient EBV serostatus (+ %)	55.87%	57.63%	0.6555
Donor anti-EBV IgG (+ %)	73.88%	78.99%	0.2320
Donor anti-EBV IgM (+ %)	2.24%	0.92%	0.3650
Donor cause of death (head trauma %)	58.14%	56.40%	0.6250
patient weight (kg)	39.23 ± 0.66	35.99 ± 1.89	0.1231
Donor type (deceased donor %)	98.59%	95.05%	0.0000
Total ischemic time (hr)	7.91 ± 0.06	7.62 ± 0.25	0.1419

primary tx %	90.64%	90.54%	0.9630
Multiorgan tx			0.1370
Intestine only	38.38%	45.05%	
multivisceral tx with liver	54.63%	49.55%	
multivisceral tx without liver	6.00%	5.41%	
Patient primary diagnosis			0.3010
Short gut syndrome	75.77%	81.25%	
functional bowel problem	17.44%	13.94%	
retransplant	5.46%	3.37%	
others	1.32%	1.44%	
patient on life support at tx	14.58%	15.98%	0.5820
Patient liver dysfunction at tx (+ %)	61.68%	74.42%	0.0190
Induction therapy recipient (%)	68.27%	60.81%	0.0240
No. of maintenance of immunosuppression	2.06 ± 0.84	2.18 ± 0.88	0.0000
0	4.37%	6.76%	
1	15.82%	7.66%	
2	53.13%	49%	
3	23.48%	33.78%	
4	2.91%	2.70%	
5	0.29%	0%	

13 (StataCorp LP, College Station, TX) with all available updates as of January 2015. The difference in the distribution of categorical variables between groups was investigated using the chi-square test. Unpaired-test or one-way analysis of variance was used for numerical variables. Graft survival rates of transplant recipients were estimated using Kaplan-Meier methods, with significance determined by log-rank test.

To determine whether ABO-compatible but non-identical transplantation is an independent risk factor associated with acute rejection, univariate logistic regression analysis were used to screen all potential risk factors, and multivariate logistic regression analysis were used to calculate odds ratios for the associations between acute rejection occurrence and ABO-compatible transplantation while adjusting for other risk factors of acute rejection. Variables in the final multivariate logistic regression model included ABO-compatible transplants (0 = identical, 1 = compatible), patient and donor race (0 = white, 1 = non-white), patient age, total ischemic time (hours), multi-organ transplantation (0 = intestine alone, 1 = multivisceral transplantation with liver, 2 = multivisceral transplantation without liver), induction immunosuppression (0 = No, 1 = Yes), and number of maintenance of immunosuppression. ABO-compatible transplantation had an odds ratio of 1.85 with a p-value of 0.001.

To establish multivariate Cox models, the registry data were first explored using univariate analyses to screen for potential predictors of graft loss. The log-rank test was used for categorical variables, whereas univariate Cox proportional hazard

regression was used for continuous variables. The variable with a p-value of less than or equal to 0.2 was included as a potential predictor of graft failure in a stepwise Cox model. The limit for stepwise backward and forward elimination was $p < 0.1$. The variables with more than 10% missing observations were excluded from multivariate Cox analysis (Table 2). The final Cox model included donor and recipient compatibility of ABO blood group (compatible), recipient age, non-white donor, donor cause of death (non-head trauma), regraft, number of maintenance immunosuppressants, induction immunosuppression, transplant year (Table 3). In the final multivariate Cox analyses, data were reported as a hazard ratio (relative risk of graft failure) with a 95% confidence interval. Two-sided p-value less than 0.05 were considered significant.

Results

ABO-compatible transplant recipients include blood group

Table 2: Univariate analysis of potential risk factors for intestinal graft failure.

Variables	Hazard ratio	p-value	Observation number	Missing observation %
donor anti-EBV IgM +	1.5593	0.1660	874	61.72%
patient HCV serostatus +	1.4568	0.1150	1437	37.06%
patient HBV surface antigen +	1.4476	0.1030	1508	33.95%
regraft	1.3565	0.0010	2301	No
ABO compatible transplant	1.2439	0.0200	2283	No
donor race (non-white)	1.2372	0.0000	2303	No
patient CMV IgG+	1.1914	0.0120	1659	27.33%
induction therapy recipient	1.1531	0.0210	2303	No
donor cause of death (non head trauma)	1.1413	0.0220	2255	1.23%
donor age	1.0087	0.0000	2300	No
patient age	1.0045	0.0010	2302	No
patient weight (kg)	1.0029	0.0030	2187	4.20%
transplant year	0.9692	0.0000	2302	No
multiorgan tx	0.8942	0.0190	2303	No
No. of maintenance of immunosuppression	0.8919	0.0010	2303	No
patient liver dysfunction at tx	0.8906	0.1160	1202	47.35%
total ischemic time (hr)	1.0161	0.2150	2023	11.39%
donor anti CMV serology+	1.0690	0.2440	2241	1.84%
patient on life support at tx	1.0952	0.2610	2280	0.13%
donor anti-EBV IgG +	1.1472	0.2690	928	59.35%

patient EBV serostatus +	0.9319	0.2870	1782	21.94%
donot type (living donor)	1.2285	0.3090	2302	No
HLA mismatches	1.0139	0.6120	2037	10.78%
DR locus mismatch	1.0196	0.6970	2037	10.78%
A locus mismatch	1.0188	0.6990	2050	10.21%
patient CMV IgM+	1.0638	0.7700	1542	32.46%
patient primary diagnosis (FBP)	1.0173	0.8270	1902	16.69%
B locus mismatch	1.0108	0.8610	2050	10.21%
patient race (non-white)	1.0079	0.8990	2303	No
patient gender (female)	0.9952	0.9310	2303	No
donor gender (female)	0.9956	0.9390	2302	No

Table 3: Independent predictors of intestinal graft failure.

Variables	Hazard ratio	p
ABO compatible transplantation	1.417	0.000
recipient age	1.006	0.000
nonwhite donor	1.314	0.000
non-head trauma donor	1.138	0.026
regraft	1.427	0.000
No. of maintenance immunosuppressants	0.871	0.000
induction immunosuppression	1.139	0.049
transplant year	0.959	0.000

A and B patients who received transplants from O donors and blood group AB patients who received transplants from A, B, or O donors. Figure 1A shows the annual trend of ABO-compatible intestinal transplantation in the US from Jan 1990 to Jun 20013. Linear regression analysis suggests a significant trend of an increase in the annual number of ABO-compatible transplants ($r^2 = 0.32, p = 0.004$). This increasing trend is more obvious in recent years (from 4% in 2003 to 16% in 2013). Among all ABO-compatible transplant recipients, 11% of blood group A and 26% of blood group B recipients received transplants from ABO group O donors, while 62% of group AB recipients received transplants from compatible donors of A, B, or O blood types (Figure 1B).

A significantly higher percentage of ABO-compatible intestinal transplant recipients experienced acute rejection than ABO-identical transplant recipients (Table 4, 77% vs. 64%, $p < 0.0001$). This comparison is based on the data collected before discharge since the reporting rates of acute rejection at 6 months and 1-year post-transplant were low (47-63%). The association between occurrence of acute rejection and ABO-compatible transplantation was further verified in univariate and multivariate logistic regression analyses (see Materials and Methods for a detailed description). There is no difference between groups in the total number of rejection episodes each patient experienced ($p = 0.7777$).

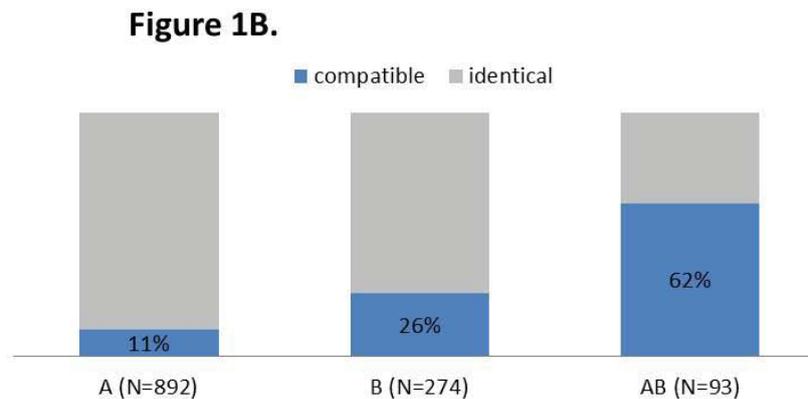
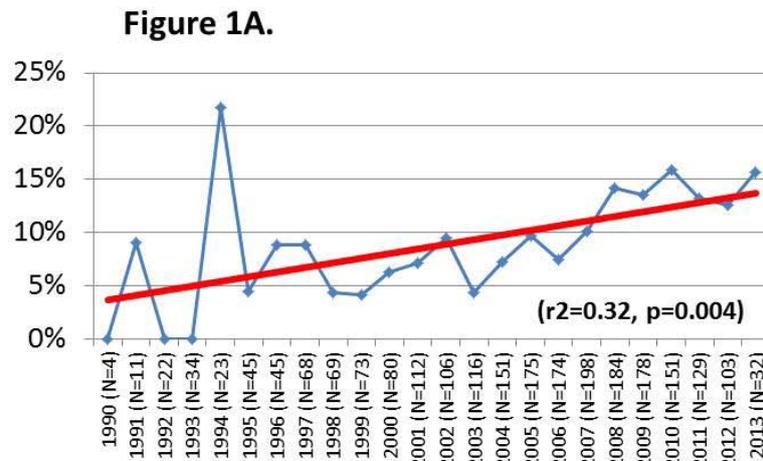


Figure 1: 1A: Increasing trend of ABO-compatible intestinal transplantation in the US; 1B) Percentages of ABO-compatible intestinal transplants by patient blood type

Table 4: Comparison of early rejection episode between groups.

Rejection before discharge	Identical (N = 2061)	Compatible (N = 222)	p value
Acute rejection			0.0000
No	742 (36.00%)	51(22.97%)	
Yes	1319 (64.00%)	171(77.03%)	
Acute rejection episodes			0.7777
1	297 (22.52%)	42(24.56%)	
2	21 (1.59%)	2(1.17%)	
3	1001 (75.89%)	127 (74.27%)	

ABO-compatible transplant recipients had a significantly lower 10-year graft survival rate than ABO-identical transplant recipients (Figure 2A). A more significant graft survival difference was observed in the intestine-alone transplantation which occurred within the 1st year post-transplant (Figure 2B). Transplantation of intestine with liver seemed to reduce the significance of the graft survival difference between ABO-

compatible and identical transplants (Figure 2C). As described in the materials and methods section, after adjustment of all influencing variables, multivariate Cox analysis confirmed the association between ABO-compatible transplantation and graft failure, with a hazard ratio of 1.42 ($p < 0.001$).

A total of 1,150 ABO-identical and 129 ABO-compatible

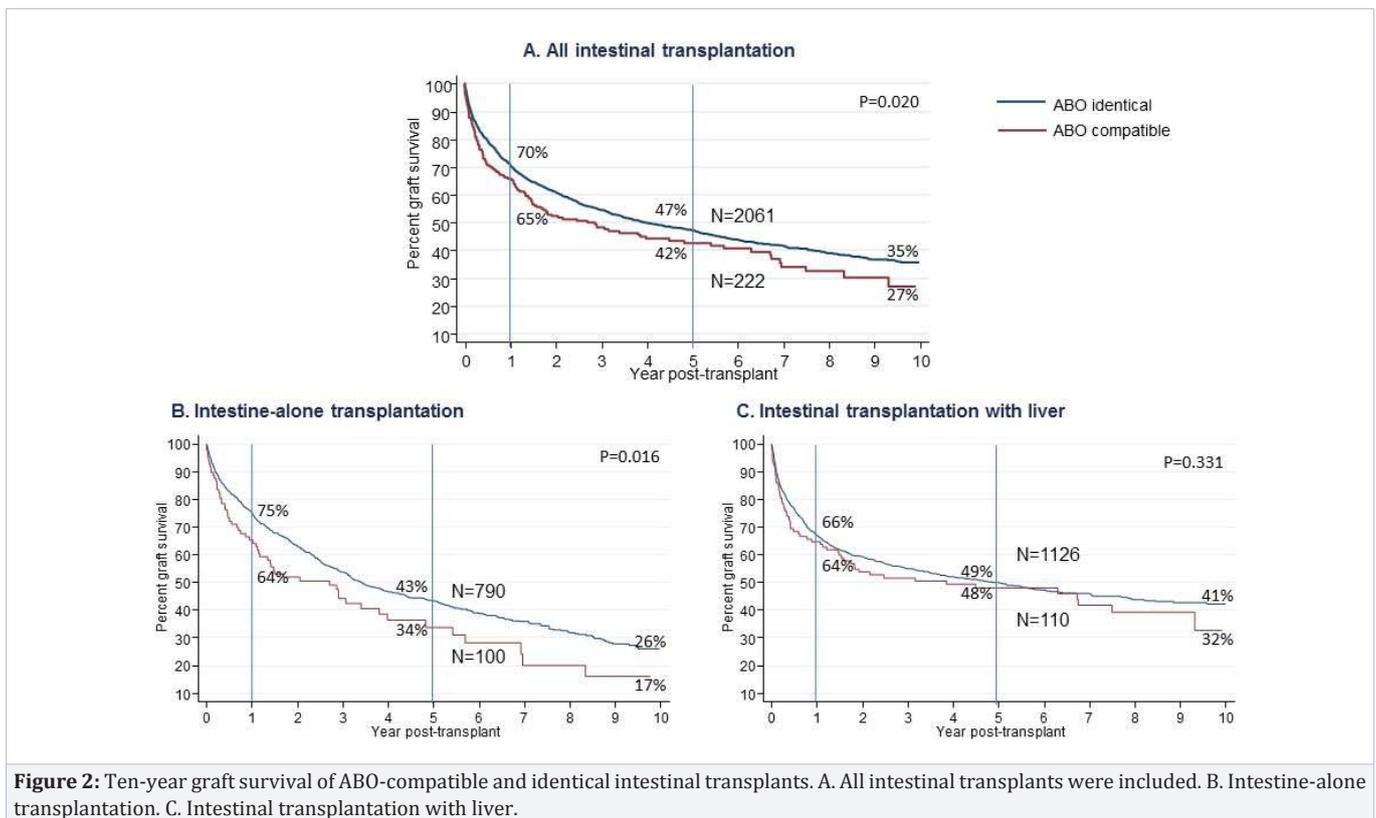


Figure 2: Ten-year graft survival of ABO-compatible and identical intestinal transplants. A. All intestinal transplants were included. B. Intestine-alone transplantation. C. Intestinal transplantation with liver.

transplant recipients lost allografts post-transplant. Causes of graft failure were reported to the registry for 525 (45.65%) ABO-identical and 63 (48.84%) compatible transplant recipients. Figure 3 shows that immunological causes (acute and chronic rejection) accounted for 52.5% and 54.0% of graft loss in ABO-identical and compatible transplantation, respectively. Interestingly, acute rejection alone accounted for 41% of all graft loss in ABO-compatible transplant recipients, which was significantly higher than that in ABO-identical transplant patients (25%, $p = 0.041$).

Discussion

In this study, very surprisingly, we found ABO-compatible intestinal transplant recipients had a significantly higher chance of experiencing acute rejection than ABO-identical transplant recipients. More importantly, these patients also had a significantly lower rate of long-term graft survival. Analysis of the causes of graft failure indicates that acute rejection accounted for 41% of graft loss in ABO-compatible transplantation, which is significantly higher than that in ABO-identical transplantation (25%).

The major concern for ABO-compatible but non-identical transplantation is the potential risk of GVH antibodies against mismatched recipient ABO antigens. GVH antibodies might be obtained from plasma transfusions of donor type or from passive transfer of donor-derived antibodies [9-11]. It has also been proven that GVH antibodies can be produced by viable graft-derived lymphocytes from lymphoid tissues of transplants [10-13]. Bakr, et al. [14] reported that in ABO-compatible kidney transplantation, GVH antibodies causes hemolysis at the frequency

of 60%. Possibly due to the fact that kidney transplant contains fewer GVH antibodies and GVH antibody-producing cells, GVH antibody-induced hemolytic anemia was mild and does not cause serious consequences in kidney transplantation. In liver transplantation, with presumably more GVH antibodies or GVH antibody-producing cells, Koukoutis [6] and Bjoro [7] reported that ABO-compatible transplant recipients have significantly lower graft and patient survival compared to ABO-identical transplant patients. The intestine possesses the largest mass of lymphoid tissue of any solid organ in the human body [15]. Not surprisingly, therefore, intestinal transplantation is reported to have a higher rate of GVH disease (GVHD, 5.6%-9.1%) [16-18] than a transplant of any other organ type, including liver (1-2%) [19,20]. Since GVHD in transplant recipients is associated with a very high mortality rate (up to 85%) [18] and intestinal transplant recipients have a high rate of GVHD, this may explain why ABO-compatible transplants have a lower graft survival than identical transplants.

Graft loss and patient death in intestinal transplant recipients with GVHD have been reported to be associated with the infection since GVH reactions may damage host lymphoid tissues and produce profound immunosuppression [18,21]. However, in this study, the percentage of graft loss due to infection is only slightly higher incompatible transplants than identical transplants (14.3% vs. 10.7%), while graft loss resulting from acute rejection is much higher incompatible transplants than in identical transplants (41.3% vs. 25.3%). These data imply that there might be a potential association between GVH reactions and acute rejection.

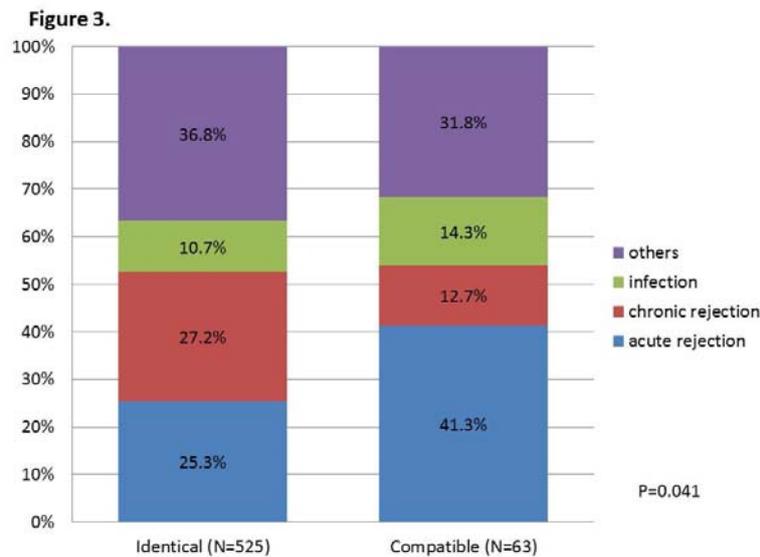


Figure 3: Causes of graft failure in ABO identical and compatible transplant recipients.

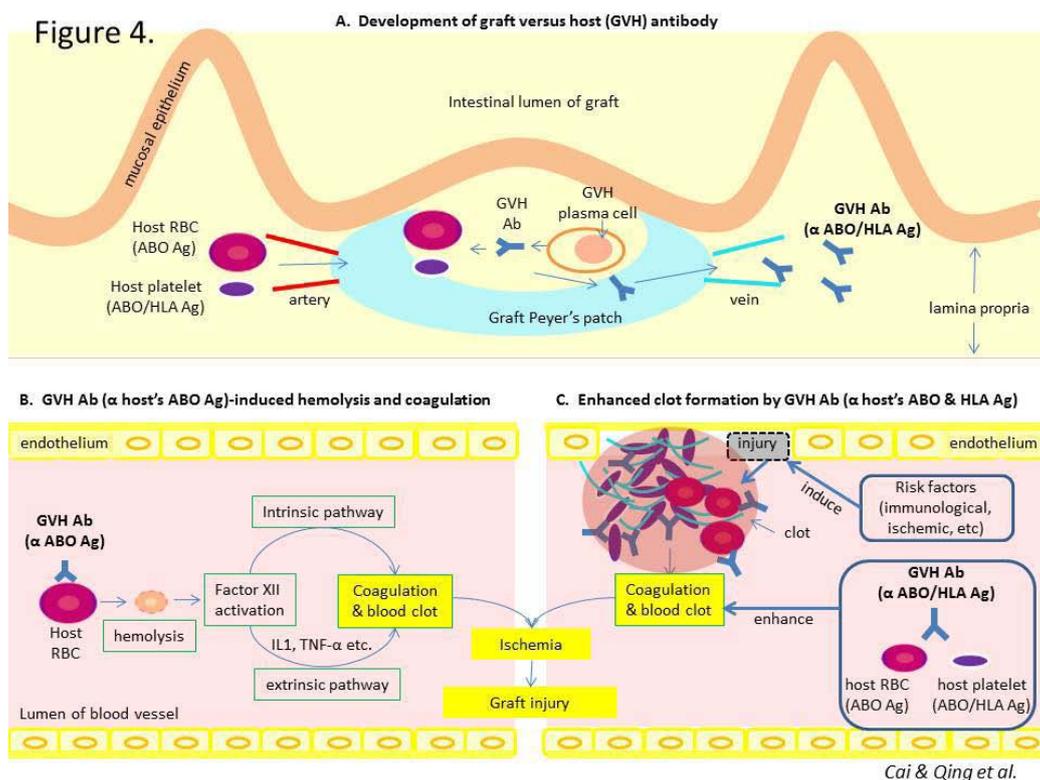


Figure 4: Development of graft versus host (GVH) antibody and its roles in allograft injury. A) Development of GVH antibody. Peyer's patch is used as a representative intestinal lymphoid tissue. In ABO-compatible but unmatched transplantation, host RBC, platelet, and other cells with mismatched host's alloantigens (ABO, HLA etc.) on the surface may trigger GVH antibody responses in intestinal lymphoid tissues. **B) GVH antibody-induced hemolysis and coagulation.** GVH antibodies against host RBC surface antigens bind and lyse host RBC-hemolysis, which activate coagulation and blood clot formation via both intrinsic and extrinsic pathways. Blood clot formation results in allograft ischemia and consequent tissue injury and dysfunction. **C) Enhanced clot formation by GVH antibodies.** Primary endothelium injury of intestinal transplant might be induced by various risk factors which include patient's immune reaction against graft's antigens or by allograft ischemia and reperfusion. Endothelia injury activates coagulation and clot formation. GVH antibodies against both platelets and RBCs, the major components of a blood clot, further enhance the formation of the clot and deteriorate the ischemic injury of the allograft.

In the diagnosis of allograft rejection in intestinal transplants, lymphoid activation is commonly found in the Peyer's patch (a closely aggregated nodule of lymphoid tissue in the wall of the small intestine) of the allograft [22]. However, activated lymphocytes in the graft Peyer's patch may be of either recipient or donor origin. Activated lymphocytes of recipient origin demonstrate an active host versus graft immunity; while if activated lymphocytes are of donor origin, GVH immune responses are indicated. Interestingly, in a rat small bowel transplant rejection model, donor lymphocytes became more activated than recipient lymphocytes in the graft mesenteric lymph node and Peyer's patches. The presence of more activated GVH immune responses suggests that GVH immunity may contribute to graft damage [23]. Unfortunately, from this registry database analysis, we could not determine whether the allograft rejection and consequent graft loss in the ABO-compatible transplant group are associated with GVH disease since information on patients' GVH disease and biopsy reports of cases of rejection is not available in the registry data.

We propose that in ABO-compatible intestinal transplantation, GVH immune reactions against mismatched host blood type antigens may participate in the pathogenesis of transplant rejection through two potential mechanisms. Certainly, other mismatched host alloantigens, such as Human Leukocyte Antigens (HLA), may also trigger GVH immune responses.

The first potential mechanism of GVH immunity participating in allograft rejection involves intravascular hemolysis, which results from GVH immune responses against mismatched recipient blood type antigens. When an allograft from a blood type O donor is transplanted to a blood type A recipient (host), immune cells (e.g. GVH plasma cells) from the graft will mount immune responses (e.g. GVH antibodies) against surface antigens of host blood cells [ABO antigens on Red Blood Cells (RBCs) and platelets, and HLA antigens on platelets, etc.] (Figure 4A). These GVH antibodies produced by graft lymphoid tissues against host RBCs will cause intravascular hemolysis in ABO-compatible transplant recipients (Figure 4B). Coagulation activity of hemolysis has been discovered and confirmed for decades [24-28]. The clinical consequence of coagulation depends on the severity of intravascular hemolysis. It has been reported that acute massive intravascular hemolysis may sometimes cause Disseminated Intravascular Coagulation (DIC), the most severe form of coagulation [27,28]. In ABO-compatible intestinal transplantation, the amount of anti-host RBC antibodies produced from GVH reactions might not be high enough to rapidly cause systemic symptoms like DIC as reported in transfusion reactions [29] and in a large dose IVIG treatment [28]. However, the effects of these GVH antibodies on induction of immune hemolysis, activation of platelet aggregation/coagulation, and formation of blood clots will certainly be harmful to the function of the allograft. The clinical manifestations of this GVH antibody-induced hemolysis and consequent coagulation/clot formation may perfectly mimic allograft rejection caused by the host versus graft immunological reactions. However, it is still possible to distinguish the tissue injuries resulting from these two different causes since GVH antibody-induced hemolysis and consequent clot formation will affect not only the allograft itself, but also the

patient's native tissues, while inflammatory changes of allograft rejection are only seen within the intestinal graft itself.

The second potential mechanism of GVH immunity participating in allograft rejection involves the enhanced platelet aggregation, coagulation, and clot formation in the vasculature of the intestinal allograft (Figure 4C). Primary endothelial injury of intestinal transplant may be initiated by a patient's immune reaction against the graft antigens or by allograft ischemia and reperfusion. Endothelial injury activates the coagulation cascade in which the recipient's platelet is the major player in forming a blood clot. The consequences of blood clot formation in the vasculature include ischemia and even infarction of graft tissues supplied by clotted vessels. The secondary tissue damage following primary endothelial injury will further deteriorate the allograft function, which finally results in graft failure [30]. In ABO-compatible intestinal transplantation (e.g. O donor to A recipient) with a large quantity of lymphoid tissue, the transplant may contain enough of the recipient's antigen-specific immune cells that will mount GVH immune responses against mismatched recipient's antigens. These antigens include not only ABO blood type antigens, but also HLA antigens, which are all expressed on the surface of platelets [18-21]. Either GVH HLA- or ABO-specific antibodies will bind to platelets or other blood cells of recipient origin at the site of activation of coagulation, which further enhances the formation of blood clots and results in graft failure.

Since this is a database analysis, findings and conclusions drawn from this study might be limited by the availability and integrity of variables of the database. Major limitations of this study include: 1) a high rate of missing observations for some variables; and 2) hypothesized mechanisms to be proven. Some variables show potential association with graft failure in univariate Cox analysis, such as donor Epstein-Barr virus sera status, patient hepatitis C virus sera status, patient hepatitis B virus surface antigens, patient cytomegalovirus immunoglobulin antibodies, patient liver dysfunction at transplantation, etc. However, there are 27-62% of patients with no information about these potential failure predictors. Therefore, they have to be excluded from multivariate Cox analysis to avoid selection bias. Exclusion of key variables from the analysis may affect the accuracy of the analysis. Even though we proposed potential mechanisms regarding how GVH reactions are involved in allograft injuries, there was no direct evidence from registry data to support these hypotheses. Further investigations are required to prove these hypotheses.

In conclusion, ABO-compatible intestinal transplants were associated with a higher rate of acute rejection and a lower rate of long-term graft survival as compared to ABO-identical transplants. We need to seriously reconsider the strategies to deal with ABO-compatible transplants. First, it is reasonable to avoid ABO-compatible transplantation when an identical donor is available. Certainly, this must be balanced against the potential risk of waiting for an ABO-identical donor in the face of imminent death from liver failure. In addition, the patient's sensitization to HLA antigens needs to be considered, especially

when donor specific antibodies are preexisting. Second, when ABO-compatible transplant is the only choice, the recipient deserves a more intense induction or maintenance immunosuppression to minimize the potential risk of GVH immune reactions. Third, monitoring patients for GVH immune reactions (GVH ABO or HLA antibodies, effector T-cells, et al), especially within the 1st year post-transplant, may help to identify patients under risk of acute rejection and graft failure who need to be treated accordingly. Last, when RBC transfusion is needed for an ABO-compatible transplant recipient with detectable GVH antibodies, donor-type packed RBCs are recommended and should be washed to remove anti-recipient antibodies. In contrast, plasma should be of recipient's ABO type. Since a recipient type RBC transfusion will increase the target cells of GVH antibodies and a donor type plasma transfusion will increase the effectors-GVH antibodies, both will further intensify the GVH reaction-induced graft injury.

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