

Prevalence and Risk Factors of Donor-Specific Anti-HLA Antibodies in Haploidentical Allograft Candidates: A 9698-Patient Cohort Study

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Article

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Abstract

Donor-specific anti-HLA antibodies (DSA) are associated with hematopoietic stem cell transplantation graft failure and other adverse outcomes. The distribution and risk factors for DSA in large, clinically heterogeneous haploidentical-allograft candidate populations remain unclear, which we analyzed in 9,698 consecutive candidates enrolled between July 2015 and December 2025. Multivariate binary logistic regression to identify DSA risk factors and subgroup analyses stratified by age, underlying disease, pregnancy, and sex were conducted. In this cohort, 9.6% of patients (931/9,698) were DSA positive; on multivariate analysis, women with prior pregnancy, transfusion, and longer disease duration were independently associated with DSA positivity ($P < 0.001$). Compared with children, adults and older adults had a significantly increased likelihood of DSA positivity ($P = 0.001$). Analysis of underlying diseases, with AML as the reference, showed ALL and other diseases conferred lower risk ($P < 0.001$ and $P = 0.015$, respectively), whereas MDS and AA conferred higher risks ($P = 0.007$ and $P = 0.001$, respectively). Risk factors differed across subgroups stratified by age, underlying disease, and prior pregnancy, red blood cell transfusion was consistently a common significant risk factor. DSA sensitization was strongly associated with pregnancy, transfusion exposure, disease duration, age, and underlying diseases; risk factor-adapted DSA monitoring and donor selection for haploidentical transplant candidates is warranted.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective curative treatment for patients with hematological or non-hematological malignancies^{1–3}. Donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA) are transplant candidate markers that help specifically recognize the mismatched HLA antigens of the prospective donor^{3,4}. They constitute a major barrier to successful engraftment and are associated with graft failure, poor graft function, and prolonged isolated thrombocytopenia, all of which lead to inferior survival in patients who undergo HLA-mismatched allografting, such as haploidentical-HSCT, unrelated donor transplantation, and cord blood transplantation^{5–8}.

The prevalence of DSA ranges from 3.5% to 27.3% in haploidentical, HLA-mismatched unrelated, and HLA-mismatched cord blood HSCT candidates^{3, 5–11}. However, none of these studies were large enough to investigate the prevalence and risk factors for DSA in patient subgroups³. Pregnancy and transfusion are the most consistent risk factors for anti-HLA antibody positivity across multiple mean fluorescence intensity (MFI) thresholds^{12,13}. As the prevalence and risk factors for DSA were not evaluated in a previous study¹³; we expanded the cohort from 3,805¹³ to 9,698 consecutive haploidentical allograft candidates and aimed to: (i) estimate the overall and subgroup-specific prevalence of DSA, and (ii) identify independent risk factors for DSA in the overall cohort and across age, pregnancy, and disease strata. The large sample size and detailed subgroup analyses enabled the characterization of the

heterogeneous risk profiles that smaller cohorts could not capture, and thus provide a solid basis for DSA monitoring and donor selection.

SUBJECTS AND METHODS

Patients

This single-center cohort included 9,698 consecutive patients with hematological diseases who were evaluated as candidates for haploidentical allogeneic HSCT at Peking University People's Hospital between July 2015 and December 2025. Patients were excluded if they had previously undergone solid organ or hematopoietic transplantation; had fever or clinical evidence of active infection within 40 days before enrollment; or had received an intervention known to substantially alter anti-HLA antibody responses within 40 days before testing, which was consistent with a prior protocol¹³.

The clinical data collected at the time of antibody testing included age, sex, diagnosis, history of pregnancy, number of RBC transfusions, number of platelet transfusions, and disease duration. Age groups were defined as children, adults, and older patients (1–18, 19–59, and ≥ 60 years, respectively). Underlying diseases were categorized as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), aplastic anemia (AA), and other hematological diseases. Other hematologic diseases mainly include lymphomas (including Hodgkin and non-Hodgkin lymphoma), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and myeloproliferative neoplasms (MPN).

The study was conducted in accordance with the principles underlying the Declaration of Helsinki and was approved by the Ethics Committee of Peking University People's Hospital. Written informed consent was obtained from patients or their legal guardians.

DSA detection

Serum samples were collected in the month before the initiation of the haploidentical HSCT-conditioning regimen. Classes I and II anti-HLA immunoglobulin G antibodies were screened using the LABScreen Mixed assay (One Lambda, Canoga Park, CA, USA), and antibody specificities were resolved using the LABScreen Single Antigen bead assay, according to the manufacturer's instructions and a previously published protocol^{12, 13}. The MFI values were normalized to those of the negative controls.

A DSA is defined as an anti-HLA antibody whose specificity corresponds to a mismatched HLA antigen expressed by an intended haploidentical donor. DSA positivity was defined as a normalized MFI ≥ 500 ^{12, 13}. For patients with multiple candidate donors, the donor selected for DSA was used.

Definitions and evaluation:

Quantitative variables were dichotomized using receiver operating characteristic (ROC) curve-derived thresholds. The overall and subgroup analyses used cut-offs of ≥ 1 versus < 1 RBC transfusions, ≥ 1 versus < 1 platelet transfusions, and disease duration ≥ 5 versus < 5 months.

Statistical Analysis

Patient characteristics are summarized using counts and percentages. DSA prevalence was calculated for the total cohort and for sex with pregnancy-, age-, and disease-defined subgroups, with 95% confidence intervals (CIs) estimated using the Wilson method. Group differences in crude prevalence were evaluated using the chi-square or Fisher's exact test, as appropriate. Multivariable binary logistic regression was used to identify the independent factors associated with DSA positivity. The variables included age group, diagnosis, pregnancy, RBC transfusion, platelet transfusion, and disease duration according to the supplied models. The results are reported as aORs with 95% CIs. Two-sided *P*-values < 0.05 were considered statistically significant. Analyses were performed using [SPSS v22.0].

RESULTS

Patient characteristics and DSA prevalence

Among the 9,698 haploidentical allograft candidate participants, 5,408 were males (55.8%), 1,329 never-pregnant females (13.7%), and 2,961 females with prior pregnancy (30.5%). There were 2,137 children (22.0%), 6,890 adults (71.0%), and 671 older patients (6.9%). AML was the most common diagnosis ($n = 3,729$; 38.4%), followed by ALL ($n = 2,489$; 25.7%), MDS ($n = 1,348$; 13.9%), other hematologic diseases ($n = 1,172$; 12.1%), and AA ($n = 960$; 9.9%) Class I DSA had a median (range) MFI of 5726.28 (502.53–26679.83), and that of class II was 3879.69 (508.37–24074.24) for patients with positive DSA defined according to an MFI cutoff of ≥ 500 (Table 1).

Table 1
Patient characteristics

All patients	9698
Gender, n(%)	
Male	5408(55.8)
Female without Pregnancy	1329(13.7)
Female with Pregnancy	2961(30.5)
Diagnosis, n(%)	
AML	3729(38.4)
ALL	2489(25.7)
MDS	1348(13.9)
AA	960(9.9)
Others	1172(12.1)
Age, n(%)	
Children	2137(22.0)
Adults	6890(71.0)
Elderly	671(6.9)
Number of RBC transfusions, median (range)	1(0-320)
Number of PLT transfusions, median (range)	1(0-324)
Disease duration, months, median (range)	5(1-498)
DSA	
Class I only (+), n (%)	239(2.5)
Class II only (+), n (%)	157(1.6)
Class I and II positive, n (%)	535(5.5)
Class I or II positive, n (%)	931(9.6)
Median MFI (range)	
Class I (+)	5726.28(502.53-26679.83)
characteristics	
Abbreviations: AA, aplastic anemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; DSA, donor-specific anti-HLA antibodies; MDS, myelodysplastic syndromes; MFI, mean fluorescence intensity; PLT, platelet; RBC, red blood cell.	

All patients	9698
Class II (+)	3879.69(508.37-24074.24)
characteristics	
Abbreviations: AA, aplastic anemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; DSA, donor-specific anti-HLA antibodies; MDS, myelodysplastic syndromes; MFI, mean fluorescence intensity; PLT, platelet; RBC, red blood cell.	

Overall, 931 patients (9.6%) were DSA-positive. Of these, the majority had class I DSA (83.1%, n = 774) whereas 74.3% (n = 692) had class II DSA. Concurrent positivity for both class I and class II was observed in 57.5% (n = 535) of DSA-positive patients (Fig. 1A). The prevalence of DSAs differed significantly according to sex, pregnancy, age, and diagnosis ($P < 0.001$), and was higher in pregnant women than males (18.9% vs. 5.2%, $P < 0.001$). Adult and older patients had similar prevalence estimates (11.2% and 11.0%, respectively), both of which were substantially higher than those observed in children (4.0%; $P < 0.001$). The prevalence of DSA was the highest in AA (15.0%) and MDS (14.8%), intermediate in AML (10.0%), and lower in ALL (6.0%) and other diseases (5.0%) (Fig. 1B–D). The subgroup characteristics are presented in Supplementary Tables 1–3.

Independent risk factors in the overall cohort

In the multivariate model, prior pregnancy was strongly associated with DSA positivity (aOR, 3.922; 95% CI, 3.335–4.612; $P < 0.001$). RBC transfusion (aOR, 3.502; 95% CI, 2.824–4.342; $P < 0.001$), platelet transfusion (aOR, 1.987; 95% CI, 1.633–2.416; $P < 0.001$), and longer disease duration (aOR, 1.492; 95% CI, 1.285–1.732; $P < 0.001$) were independently associated with DSA.

Age was independently associated with DSA positivity ($P < 0.001$). Compared to children, both adults (aOR, 1.810; 95% CI, 1.379–2.376; $P < 0.001$) and older patients (aOR, 1.894; 95% CI, 1.301–2.758; $P = 0.001$) had significantly higher adjusted risks of DSA. Using AML as the reference, patients with ALL (aOR, 0.677; 95% CI, 0.551–0.832; $P < 0.001$) and those with other hematologic diseases (aOR, 0.690; 95% CI, 0.512–0.930; $P = 0.015$) had a lower risk of DSA, whereas patients with MDS (aOR, 1.311; 95% CI, 1.077–1.596; $P = 0.007$) and AA (aOR, 1.495; 95% CI, 1.189–1.879; $P = 0.001$) had a higher risk (Table 2).

Table 2
Multivariate analysis of risk factors for donor-specific anti-HLA antibodies in 9,698 haploidentical candidates (MFI $\geq$ 500)

Gender	P	aOR	95% CI
Male		1	
Female without pregnancy	0.078	1.275	0.973–1.670
Female with pregnancy	< 0.001	3.922	3.335–4.612
Age	< 0.001		
Children		1	
Adults	< 0.001	1.810	1.379–2.376
Elderly	0.001	1.894	1.301–2.758
Diagnosis	< 0.001		
AML		1	
ALL	< 0.001	0.677	0.551–0.832
MDS	0.007	1.311	1.077–1.596
AA	0.001	1.495	1.189–1.879
Others	0.015	0.690	0.512–0.930
RBC transfusion	< 0.001	3.502	2.824–4.342
PLT transfusion	< 0.001	1.987	1.633–2.416
Disease duration	< 0.001	1.492	1.285–1.732
Abbreviation: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; aOR, adjusted odds ratio; MDS, myelodysplastic syndrome; MFI, mean fluorescence intensity; PLT, platelet; RBC, red blood cell			

Independent risk factors identified across various subgroups

In pediatric patients, RBC transfusion (aOR, 2.741; $P = 0.004$) and platelet transfusion (aOR, 2.627; $P = 0.002$) were independent risk factors for DSA positivity. Among the diagnostic categories, only MDS showed a borderline significantly increased risk compared with AML (aOR, 2.182; $P = 0.050$), whereas ALL (aOR, 0.586; $P = 0.111$), AA (aOR, 1.374; $P = 0.269$), and other diseases (aOR, 1.490; $P = 0.402$) did not reach significance.

In adults, diagnosis remained significantly associated with DSA (global $P < 0.001$). Compared with AML, ALL (aOR, 0.733; $P = 0.007$) and other diseases (aOR, 0.655; $P = 0.013$) conferred a lower risk, whereas MDS (aOR, 1.464; $P < 0.001$) and AA (aOR, 1.619; $P < 0.001$) conferred a higher risk. Females with prior pregnancy (aOR, 4.106), RBC transfusion (aOR, 3.636), platelet transfusion (aOR, 1.906), and longer disease duration (aOR, 1.484) were all significant risks ($P < 0.001$) whereas non-pregnant women were not (aOR, 1.228; $P = 0.251$).

Among older patients, diagnosis showed a significant association (global $P = 0.002$). Compared to AML, MDS was associated with a lower risk (aOR, 0.417; $P = 0.013$), whereas AA was associated with a higher risk (aOR, 3.719; $P = 0.023$). ALL (aOR, 0.392; $P = 0.063$) and other diseases (aOR, 0.581; $P = 0.252$) were not significant. RBC transfusion (aOR, 3.036; $P = 0.001$), platelet transfusion (aOR, 2.011; $P = 0.034$), and longer disease duration (aOR, 2.318; $P = 0.003$) were identified as independent risk factors.

Adults (aOR, 2.044; $P = 0.003$) and older patients (aOR, 3.102; $P < 0.001$) had a higher risk of AML than children. Females with prior pregnancy (aOR, 2.904), RBC transfusion (aOR, 3.007), platelet transfusion (aOR, 2.482), and longer disease duration (aOR, 1.669) were all significant risks ($P < 0.001$) whereas non-pregnant female status was not (aOR, 1.377; $P = 0.167$).

In ALL, female with prior pregnancy had the largest effect (aOR, 8.122; $P < 0.001$), followed by RBC transfusion (aOR, 4.324; $P < 0.001$), platelet transfusion (aOR, 2.234; $P = 0.001$), and longer disease duration (aOR, 2.216; $P < 0.001$); however, being female without a prior pregnancy was not a significant risk factor (aOR, 1.421; $P = 0.278$). In MDS, the principal independent risk factors were female sex with pregnancy (aOR, 3.405; $P < 0.001$) and RBC transfusion (aOR, 5.858; $P < 0.001$), whereas age (adults: aOR, 1.485, $P = 0.318$; older adults: aOR, 0.673, $P = 0.424$) and female without pregnancy (aOR, 1.460; $P = 0.282$) were not significant risk factors.

In AA, adults (aOR, 1.806; $P = 0.025$) and older patients (aOR, 4.424; $P = 0.015$) were at a higher risk than children. Pregnancy (aOR, 4.263) and RBC transfusion (aOR, 6.038) were strongly associated ($P < 0.001$) whereas female without prior pregnancy was not (aOR, 0.945; $P = 0.833$). For other hematological diseases, pregnancy (aOR, 7.414; $P < 0.001$), RBC transfusion (aOR, 1.987; $P = 0.044$), platelet transfusion (aOR, 3.459; $P = 0.001$), and longer disease duration (aOR, 2.505; $P = 0.003$) were all independently associated.

In males, adults (aOR, 1.711; $P = 0.003$) and older patients (aOR, 2.736; $P < 0.001$) had higher DSA risks than the children; compared with AML, ALL (aOR, 0.415; $P < 0.001$) and other diseases (aOR, 0.379; $P = 0.001$) were associated with lower risk, whereas MDS (aOR, 1.163; $P = 0.356$) and AA (aOR, 1.296; $P = 0.191$) were not significant; RBC transfusion (aOR, 2.456), platelet transfusion (aOR, 2.064), and longer disease duration (aOR, 1.835) remained independent risk factors (all $P < 0.001$).

In females without prior pregnancy, RBC transfusion (aOR, 3.954) and platelet transfusion (aOR, 3.262) remained significant (both $P = 0.002$). In females with prior pregnancy, MDS (aOR, 1.359; $P = 0.023$) and AA (aOR, 2.090; $P < 0.001$) were associated with a higher risk than AML; RBC transfusion (aOR, 4.151),

platelet transfusion (aOR, 1.815), and longer disease duration (aOR, 1.457) remained significant ($P < 0.001$; Supplementary Tables 4 and 5).

DISCUSSION

This study demonstrated that the prevalence of DSA was 9.6%, which is consistent with previous literature^{3, 5–11}. In the total patient group, the risk factors for developing DSA included pregnancy, prior receipt of cellular blood product transfusions, disease duration, and age. In contrast to previous studies^{12, 13}; moreover, we found a correlation between the underlying diseases. Subgroup analysis according to pregnancy, age, and underlying diseases confirmed the association between pregnancy and prior receipt of cellular blood product transfusions, especially RBC transfusion, and the incidence of DSA across different subsets. Overall, our study provides new information on the risk factors for the prevalence of DSA, which may be helpful for donor selection in haploidentical settings.

We confirmed the effects of older age on the prevalence of DSA in the total patient group and in the subgroups of female patients, male patients, and those with AML, MDS, or AA. This could be related to higher non-self-antigen exposure among older recipients and age-dependent maturation of the B-cell receptor repertoire from naïve to antigen-experienced clones¹⁴. Younger age was associated with lower alloimmunization with blood cell antigens¹⁵. The significantly lower DSA prevalence in children (4.0%) versus adults/older individuals may be explained by¹⁶: (1) fetal exposure to non-inherited maternal HLA antigens that induce B-cell unresponsiveness, (2) maternal microchimeric cells sustaining NIMA-specific tolerance via FOXP3⁺ regulatory T cells^{17, 18}, and (3) intensive chemotherapy in young patients suppressing transfusion-related alloimmunization. Holohan et al. found that only 13% of intensively treated patients with cancer developed persistent HLA antibodies compared to 88% of aplastic anemia patients¹⁹. Together with previous reports^{13, 20} by other researchers and us¹³, age is a risk factor for both anti-HLA antibody and DSA.

We found that underlying diseases were risk factors for DSA prevalence in haploidentical candidates. Patients with ALL have a lower prevalence of DSA than those with AML, which may be related to the use of glucocorticoids, cyclophosphamide, anti-CD20 antibodies, or blinatumomab during pre-transplantation therapy^{10, 20}. Fewer cellular blood transfusions and younger age may contribute to the lower DSA prevalence observed in other disease groups than in patients with AML¹³. The elevated DSA prevalence in MDS and AA reflects not only transfusion dependence, but also immunologic dysregulation^{21–24}; for example, patients with MDS exhibit T-cell dysregulation, such as expanded but functionally impaired Tregs^{25, 26}. These aberrations, compounded by prolonged transfusion, collectively contribute to higher DSA risk in patients with MDS and AA.

Another risk factor for higher DSA prevalence was longer disease duration, which was found not only in the total patient group, but also in subgroups of female, male, adult, or older patients, as well as in subsets with AML, ALL, or other diseases. Several reasons may explain this. First, a longer disease

duration was correlated with more cumulative transfusions, increasing HLA exposure²⁴. Second, as discussed above, patients with MDS and AA with prolonged courses experience sustained chronic inflammation^{25, 26} which may progressively disrupt their tolerance to alloantigens. Third, longer duration allows more frequent infections as “danger signals” that enhance antigen presentation and antibody production²⁷. In summary, our results suggest that longer disease duration is a novel risk factor for DSA in haploidentical candidates.

This study has some limitations. First, this was a retrospective, single-center study; therefore, a multicenter prospective study is warranted to confirm our findings. Second, our results were obtained from haploidentical candidates, which should be investigated in HLA-mismatched unrelated and cord blood candidates. Third, although we identified key risk factors, detailed data on complement-binding capacity (C1q) or temporal kinetics were lacking, which might further refine risk stratification. Fourth, we did not collect detailed information on chemotherapy regimens, infectious episodes, or genetic mutations that could influence alloimmunization, thus limiting causal inference.

In conclusion, this large single-center cohort study confirmed that pregnancy, cellular blood product transfusions, and older age were independently associated with DSA positivity, with substantial heterogeneity across the different clinical subgroups. We have added new evidence suggesting that underlying diseases and longer disease duration are risk factors for DSA. These findings provide robust evidence for DSA monitoring and haploidentical donor selection.

Declarations

Conflict of interest:

The authors confirm that there are no conflicts of interest.

Conflict of Interest

The authors declare no conflict of interests.

Author Contributions

NM and JZ contributed to the data collection, data analysis, and manuscript preparation. XZ, LX, XZ, YW, XM, YS, XZ, YC, XH, and YC contributed to data collection. YC contributed to the research design and preparation of the manuscript and reviewed it.

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Figures

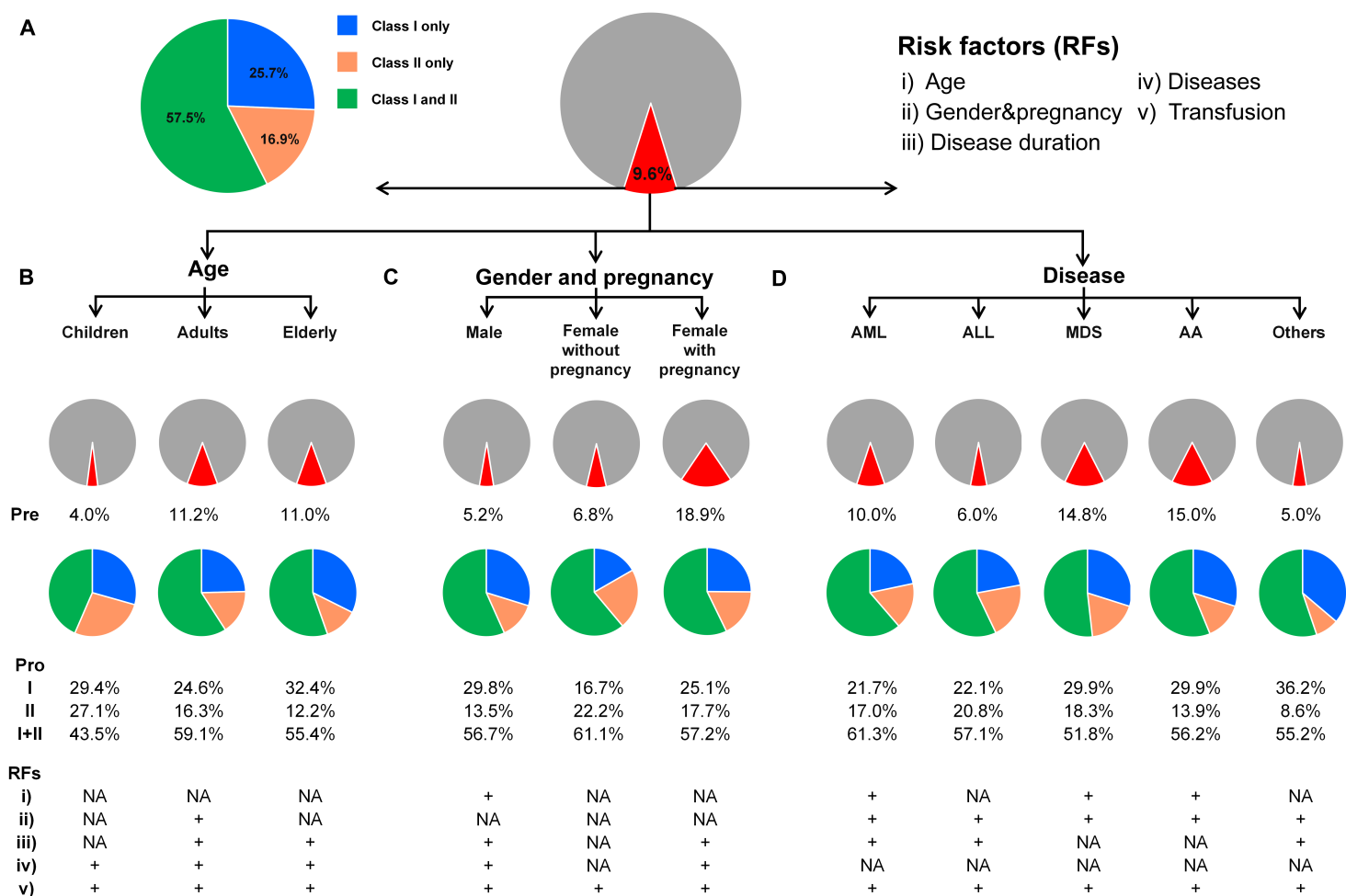


Figure 1

Prevalence and risk factors for donor specific anti-HLA antibodies (DSA).

(A) In the overall study population, the prevalence of DSA positivity was 9.6%. Among DSA-positive patients, classes I and II antibodies represented the highest proportion (57.5%), followed by class I only (25.7%) and class II only (16.9%). Identified risk factors for DSA included age, gender and pregnancy, disease duration, underlying disease, and blood transfusion history. (B-D) Prevalence, risk factors, and antibody class distribution of DSA across subgroups stratified by age (B), gender and pregnancy (C), and underlying disease (D), as indicated in the corresponding panels.

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; NA, not available; Pre, prevalence; Pro, proportion; RFs, risk factors.

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