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IMPACT OF MHC MISMATCHES ON THE DEVELOPMENT OF EARLY POSTTRANSPLANT ACUTE HEART REJECTION

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Objective: to analyze the impact of MHC mismatches, considering recipient nationality and age, on the development of rejection crisis. **Material and methods.** A retrospective study was conducted, including 264 recipients and their 264 matched donors. HLA typing was performed by serological and molecular genetic (SSP) methods. Mismatches in the following MHC class I and II genes were assessed: HLA-A, HLA-B, HLA-DRB1, HLA-DQB1. Recipient age and nationality were also considered in the analysis. **Results.** MHC Class I mismatches (HLA-A, HLA-B) did not significantly impact the occurrence of acute rejection crises. MHC Class II mismatches (HLA-DRB1, HLA-DQB1) significantly increased the risk of acute rejection ($\chi^2 = 6.790$; df = 1; p = 0.009), with an odds ratio (OR) of 5.69 (95% CI: 1.32–24.50). Recipient age had a significant effect on acute rejection ($\chi^2 = 8.200$; df = 1; p = 0.004). Recipients under 45 years experienced rejection in 34.8% of cases, 18.9% more than those aged 45 and older, with an OR of 2.30 (95% CI: 1.29–4.10). Donor-recipient nationality mismatch significantly influenced acute rejection ($\chi^2 = 4.660$; df = 1; p = 0.031), with an OR of 2.00 (95% CI: 1.06–3.79). The analysis, considering all three above-mentioned factors, confirmed that MHC mismatches significantly influence the development of acute graft rejection in Belarusian recipients under 45 years old ($\chi^2 = 4.068$; df = 1; p = 0.044) and in recipients of other nationalities (Russians, Israelis, Georgians, Armenians, Uzbeks, Kazakhs, Azerbaijanis, Ukrainians) under 45 years old ($\chi^2 = 4.342$; df = 1; p = 0.037). Among Belarusian recipients, no cases of rejection were observed with 0–1 MHC mismatches, while rejection occurred in 35.4% of cases with 2–4 mismatches (OR 9.44, CI 0.51–173.61). Similarly, in recipients of other nationalities, acute rejection did not develop with 0–1 mismatches, but occurred in 50.0% of cases with 2–4 mismatches (OR 11.00, CI 0.56–217.69). **Conclusion.** It has been reliably established that MHC class II mismatches, donor-recipient nationality differences, and recipient age under 45 years significantly increase the risk of acute rejection crisis in the postoperative period.

Keywords: heart transplantation, HLA typing, HLA mismatch, graft rejection.

INTRODUCTION

In organ transplantation, the recipient's immune system can recognize the donor organ as foreign due to differences in antigens, leading to a rejection response. This response can manifest as immediate-type hypersensitivity or delayed-type hypersensitivity. While optimal antigen matching between donor and recipient is the goal, in clinical practice, solid organ transplants are often carried out despite varying degrees of antigenic mismatch [1, 2].

As a result, antigen mismatches – regardless of the immune response pathway – increase the risk of transplant rejection. In the case of heart transplants, this rejection leads to graft dysfunction and progression of secondary heart failure (HF) [3].

Currently, there are no clear clinical signs that reliably indicate the onset of graft rejection. One diagnostic method capable of identifying structural changes in the myocardium is magnetic resonance imaging. However, the current gold standard in clinical practice remains endomyocardial biopsy. Despite its diagnostic accuracy, this technique is invasive and carries risks of serious complications, including hemopericardium, cardiac tamponade, pneumothorax, and infections. In some cases, these complications may result in fatal outcomes. These significant limitations underscore the urgent need for further research and the development of non-invasive approaches to improve the diagnosis and prediction of allograft rejection [2–5].

One of the key targets for modern non-invasive methods in predicting graft rejection is the assessment of human leukocyte antigens (HLA). These molecules are referred to as HLA because they were initially identified through antigenic differences observed in human white blood cells [4, 5]. HLAs are categorized into two main groups: major histocompatibility complex (MHC) an-

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tigens and minor histocompatibility antigens (miHAs). miHAs, which are encoded by histocompatibility genes (HCG), play a relatively limited role in the immune response leading to transplant rejection. In contrast, antigens encoded by MHC loci are responsible for eliciting the most significant allograft rejection response [6].

MHC genes are indeed located on the short arm (6p) of chromosome 6. Their primary role is to present antigenic peptides on the surface of cells, allowing T-lymphocytes to identify and target cells that are either infected or have undergone changes [4, 7].

MHC structure:

1. MHC Class I molecules (HLA-A, HLA-B, and HLA-C) are expressed on the surface of all nucleated cells. Their primary role is to present endogenously derived antigens (e.g., viral or intracellular pathogenic peptides) to cytotoxic T-lymphocytes ($CD8^+$ T cells), thereby mediating a targeted cellular immune response against infected or abnormal cells.
2. MHC Class II molecules (HLA-DM, HLA-DO, HLA-DP, HLA-DQ, and HLA-DR) are expressed primarily on professional antigen-presenting cells, including dendritic cells, macrophages, and B lymphocytes. These molecules present exogenous antigens (e.g., bacterial proteins or environmental peptides) to helper T-lymphocytes ($CD4^+$ T cells), triggering humoral immune response and promoting activation of other immune effector cells.
3. MHC Class III encompasses a diverse group of molecules involved in broader aspects of immune regulation, such as components of the complement cascade and certain pro-inflammatory cytokines, including tumor necrosis factor (TNF) family members. Although Class III molecules in graft rejection is less significant, they play important functions in the regulation of inflammation and cellular immune activity [3, 4, 8, 9].

Structure of the HLA class I molecule:

– α-chain (heavy chain): encoded by HLA genes, has a molecular mass of 44–47 kDa.
– β2-microglobulin: a non-HLA encoded subunit with a molecular mass of 12 kDa.
– the α-chain consists of three domains: α1 and α2 form the peptide-binding groove, while the α3 domain is a highly conserved immunoglobulin-like structure that interacts with $CD8^+$ T-lymphocytes.
– It binds peptides that are 8–10 amino acids in length.
– Peptide anchoring is achieved through a network of hydrogen bonds between α-chain residues and the carboxyl terminus of the peptide.
– The groove accounts for the high polymorphism of HLA class I molecules, leading to variations in electrostatic charge, hydrophobicity, and shape, all of which influence peptide binding affinity [10–14].

Structure of the HLA class II molecule:

– α-chain: molecular mass of 32–34 kDa.
– β-chain: molecular mass of 29–32 kDa.
– Both chains are encoded by HLA genes and consist of two domains each.
– α2 and β2 domains: are highly conserved immunoglobulin-like structures that interact with $CD4^+$ T-lymphocytes.
– α1 and β1 domains: come together to form the peptide-binding groove.
– Unlike HLA class I, this groove is open at both ends, enabling the binding of longer peptides – typically 12–24 amino acids, though sometimes even longer.
– Peptides bind in an extended conformation, exposing about one-third of their surface area for interaction with T-cell receptors (TCRs).
– The terminus of the peptides are not rigidly anchored within the groove and may protrude beyond its boundaries [12, 15].

Class I and class II HLA molecules play a central role in T cell–mediated adaptive immune responses. During maturation in the thymus, T lymphocytes develop tolerance to self-HLA molecules, a process crucial for distinguishing self from non-self, even when peptides are bound within the HLA binding groove.

The antigen recognition process involves four key steps: peptide generation or uptake, typical for antigen-presenting cells; peptide processing and HLA binding to HLA molecules; transport to the cell surface; the final step is analysis, direct interaction with (TCRs). In this case, there is a dual recognition of the antigen and the HLA molecule. As mentioned above, a mismatch in HLA molecules disrupts this recognition process and is the primary trigger for T cell activation, involving both immunoregulatory $CD4^+$ T cells and cytotoxic $CD8^+$ T cells [3, 16].

The effector functions of $CD8^+$ and $CD4^+$ T-lymphocytes are different, as $CD8^+$ T-cells exhibit a cytotoxic activity, enabling them to directly destroy cells presenting foreign peptides in the context of HLA class I molecules. These target cells may include virus-infected cells, tumor cells, or allogeneic donor cells that express mismatched or foreign HLA molecules.

$CD4^+$ T-lymphocytes act as central regulators of immune function and are often referred to as “helper” cells. Their effector functions are diverse and depend on their subtype, with three major subsets playing critical roles: Th1 cells that secrete interferon gamma (IFN-γ), which promotes activation and proliferation of $CD8^+$ cytotoxic T cells and enhances macrophage activity; Th2 cells which produce interleukins IL-4 and those that produce IL-5, supporting B-lymphocyte proliferation and synthesis of IgG antibodies. The type of allograft rejection – T-cell-mediated rejection (mediated by $CD8^+$ T

cells) or antibody-mediated rejection (mediated by B cells and antibodies) – depends on both the pathway of alloantigen recognition and the duration of exposure to the donor tissue [3, 16].

Acute rejection (AR) of a donor organ is most commonly driven by cellular immune response. However, antibody-mediated rejection (AMR), can also play a pivotal role in graft failure.

Antibodies targeting histocompatibility antigens (HLA molecules) may be present prior to transplantation or develop postoperatively. Based on their antigen specificity, these antibodies are generally classified into two main categories: donor-specific antibodies (DSA) – these are directed specifically against the donor's HLA antigens; non-donor-specific antibodies (non-DSA) – they may arise from prior blood transfusions or pregnancies.

Two other anti-HLA antibodies merit special attention: natural anti-HLA antibodies, which may be present innately and infection-induced anti-HLA antibodies, which can be triggered by diseases.

Having outlined the mechanisms of action associated with HLA molecules and their critical role in the recognition and destruction of donor cells (as foreign to the recipient), it is important to highlight the two primary methods currently used to predict AR risk: HLA typing and the crossmatch test. HLA typing enables the identification of mismatches between donor and recipient HLA alleles, and its predictive value has been well-documented in the transplantation of solid organs such as the kidney, liver, and lungs [17–20]. The crossmatch test assesses the recipient's immunologic risk by detecting the presence of pre-formed antibodies against donor-specific antigens. However, these methods are not universally applicable and require further research and refinement, including integration with other methods [21].

Another significant risk factor in transplantation is the age of the recipient. Studies have shown that younger recipients are at higher risk of death from AR, cardiac allograft vasculopathy, and graft failure [22, 23].

Race can also be a contributing factor. HLA haplotypes are strongly associated with racial and ethnic background, adding complexity to achieving optimal donor–recipient matching. On average, HLA polymorphism is highest among African American populations and lowest among Caucasians, with Asian, Caucasian, and Hispanic groups exhibiting intermediate variability. This genetic diversity is reflected in clinical outcomes, as recipients of African American, Hispanic, Asian, and Caucasian descent show varying levels of predisposition to AR episodes [24].

Considering these demographic and immunogenetic factors enables the identification of patients at increased risk of rejection. This, in turn, supports the development of personalized monitoring strategies, optimization of immunosuppressive therapy targets post-transplant, and ultimately reducing transplant-related morbidity and mortality.

Objective: to investigate the impact of mismatches in MHC antigens (HLA), while accounting for recipient age and ethnicity, on the likelihood of developing AR. In addition, to evaluate the potential of HLA typing as a predictive tool for immunologic risk assessment during donor–recipient selection.

MATERIAL AND METHODS OF RESEARCH

A retrospective analysis was conducted using inpatient medical records and protocols of heart transplants performed from 2009 to 2023 at the Republican Scientific and Practical Center "Cardiology" ("Cardiology Center"). All patients included in the study underwent orthotopic heart transplantation, either via the classical biatrial technique or the bicaval technique.

HLA typing was performed for a total of 1,054 samples, comprising 527 recipient–donor pairs. Typing was conducted using both serological and molecular genetic methods (sequence-specific primers, SSP). Peripheral venous blood samples were collected from recipients by clinical personnel at Cardiology Center" and from donors at the respective institutions where the donor heart was procured.

The primary antigens selected for evaluation were those most commonly implicated in transplant immunogenicity, including MHC class I antigens (HLA-A, HLA-B) and MHC class II antigens (HLA-DRB1, HLA-DQB1). Typing for HLA-DQA1 was not conducted during the study period, as this antigen was not included in the standard transplantation protocol at our center. HLA-C and HLA-DRB3 were also excluded from analysis, based on literature suggesting limited relevance to transplant outcomes [25].

The following recipients were excluded from the study:

1) Individuals with incomplete HLA typing for HLA-A, HLA-B, HLA-DRB1, or HLA-DQB1;
2) Patients under 18 years of age;
3) Cases involving heart retransplantation;
4) Patients who underwent combined heart–lung transplantation;
5) Recipients who developed an AR crisis verified by endomyocardial biopsy within 7 days after reduction of immunosuppressive therapy due to an infectious complication;
6) Recipients for whom AR diagnosis was inconclusive due to critical clinical condition and subsequent in-hospital mortality.

The final analysis included 264 recipients and 264 matched donors. To ensure adequate sample sizes

for statistical analysis of key parameters, the study population was stratified as follows:

1) By overall mismatch level for each MHC class: subgroups were formed based on the number of mismatches – 0–1 and 2–4.
2) By mismatch in class II antigens (DRB1 and DQB1): subgroups were divided into those with 0 mismatches and those with 1–2 mismatches.
3) By recipient age: the cohort was divided into two subgroups – recipients <45 years of age and those ≥45.
4) By nationality: recipients were grouped into those of Belarusian nationality and those of other nationalities (Russian, Jewish, Georgian, Armenian, Uzbek, Kazakh, Azerbaijani, and Ukrainian).
5) By clinical outcome: two outcome categories were defined – recipients who experienced an AR crisis and those who did not.

Statistical data processing was done using the JAMOVI software package. The chi-square test (χ^2) was used to assess the statistical significance of differences between the groups studied. The odds ratio (OR) with a 95% confidence interval (CI) was calculated to evaluate the strength of associations.

RESULTS

Of the 264 recipients included in the final analysis, 207 (78.4%) were of Belarusian nationality, while 57 (21.6%) represented other nationalities.

Analysis revealed that for MHC class I, a mismatch of 0–1 with the donor was observed in only 5 recipients (1.9%), while 259 recipients (98.1%) had 2–4 mismatches.

For MHC class II, 33 recipients (12.5%) had 0–1 mismatches, whereas 231 recipients (87.5%) had 2–4 mismatches.

Regarding specific HLA class II antigens, 0 mismatches for HLA-DRB1 were found in 14 recipients (5.3%), and for HLA-DQB1, in 39 recipients (14.8%).

The remaining recipients – 250 (94.7%) for DRB1 and 225 (85.2%) for DQB1 – had 1–2 mismatches with their donors.

In the group of recipients of Belarusian nationality, there were 178 men (86.0%) and 29 women (14.0%). Median age of male recipients was 54.00 years (95% CI: 52.20–55.80), while median age of female recipients was 50.00 years (95% CI: 40.90–59.10).

Among recipients of other ethnicities, 50 were male (87.7%) and 7 female (12.3%). The median age of males in this group was 40.00 years (95% CI: 34.00–46.00), and for females, 49.00 years (95% CI: 31.60–66.40).

AR were documented in 64 out of 264 recipients (24.2%). Median age of patients who experienced AR was 47.00 years (95% CI: 41.20–52.80), compared to 53.50 years (95% CI: 52.10–54.90) among those who did not.

An analysis of the association between MHC class mismatches and AR incidence yielded the following results: mismatches in MHC class I did not significantly influence the occurrence of AR episodes ($\chi^2 = 0.0499$; df = 1; p = 0.823). In contrast, MHC class II mismatches were found to have a statistically significant impact, increasing the likelihood of AR ($\chi^2 = 6.790$; df = 1; p = 0.009). AR incidence rose from 6.1% in patients with 0–1 mismatches to 26.8% in those with 2–4 mismatches. The odds ratio (OR) for AR in the presence of MHC class II mismatches was 5.69 (95% CI: 1.32–24.50) (Figs. 1, 2).

An analysis of individual MHC class II antigens and their association with AR revealed that mismatches in HLA-DRB1 ($\chi^2 = 2.350$; df = 1; p = 0.125) and HLA-

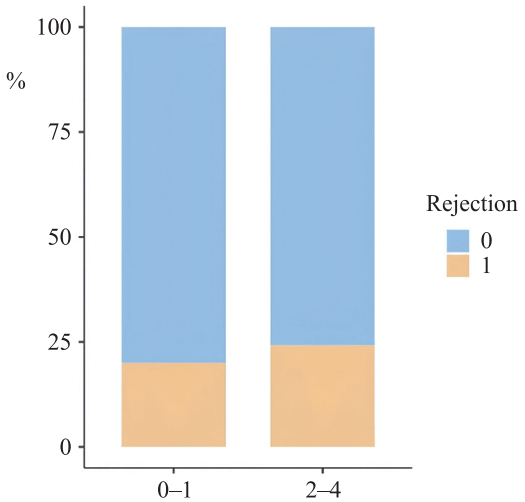

Fig. 1. Distribution of outcomes depending on the number of MHC class I mismatches

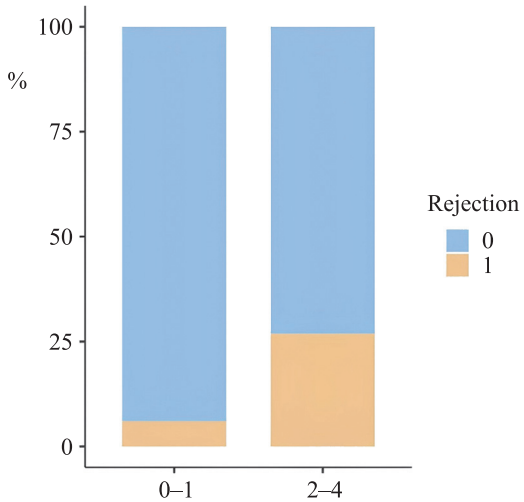

Fig. 2. Distribution of outcomes depending on the number of MHC class II mismatches

DQB1 (χ^2 = 3.250; df = 1; p = 0.071) did not reach statistical significance. However, graphical analysis demonstrated a clear trend toward increased rejection rates with the presence of mismatches: from 7.14% to 25.23% for HLA-DRB1 and from 12.81% to 25.22% for HLA-DQB1, respectively (Figs. 3 and 4).

An analysis of the influence of recipient nationality on the incidence of AR revealed a statistically significant difference (χ^2 = 4.660; df = 1; p = 0.031). Specifically, heart transplant from a Belarusian donor to a recipient of other nationality (Russian, Jewish, Georgian, Armenian, Uzbek, Kazakh, Azerbaijani, and Ukrainian) was associated with a 2.00-fold increased risk of developing an AR (95% CI: 1.06–3.79). The corresponding increase in incidence rose from 21.3% to 35.1% (Fig. 5).

When analyzing age as a risk factor for AR, it was found that recipients under 45 years of age experienced rejection in 34.8% of cases, which is 18.9% higher compared to recipients aged 45 and above. This difference was statistically significant (χ^2 = 8.200; df = 1; p = 0.004), with an OR of 2.30 (95% CI: 1.29–4.10) (Fig. 6).

When analyzing the combined effect of MHC class II mismatches and recipient age, a statistically significant association was observed in the subgroup of recipients under 45 years of age (χ^2 = 8.690; df = 1; p = 0.004). In this group, AR incidence was 0% with 0–1 mismatches, compared to 40.8% with 2–4 mismatches, yielding an OR of 18.69 (95% CI: 1.07–326.1). In contrast, no significant association between MHC class II mismatches and rejection was found in recipients aged 45 and older (Fig. 7).

When evaluating the combined influence of MHC class II antigen mismatches and recipient nationality, it was found that mismatches did not significantly affect AR incidence among Belarusian recipients (χ^2 = 3.560; df = 1; p = 0.059). Similarly, no statistically significant

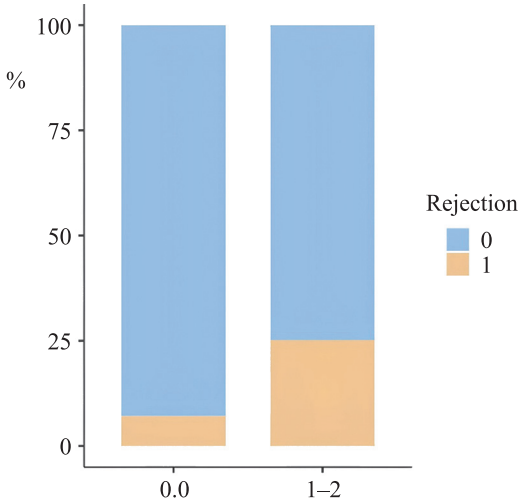

Fig. 3. Distribution of outcomes depending on HLA-DRB1 antigen mismatches

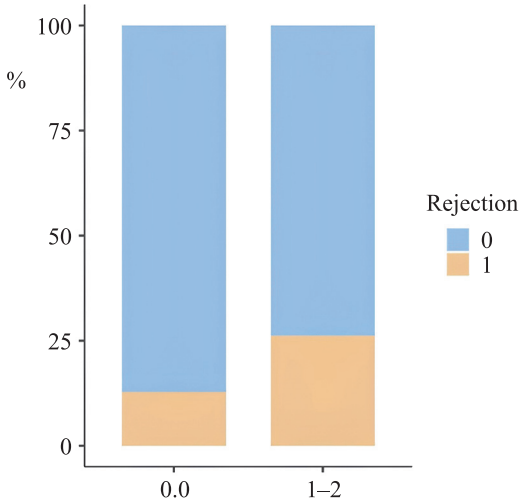

Fig. 4. Distribution of outcomes depending on HLA-DQB1 antigen mismatches

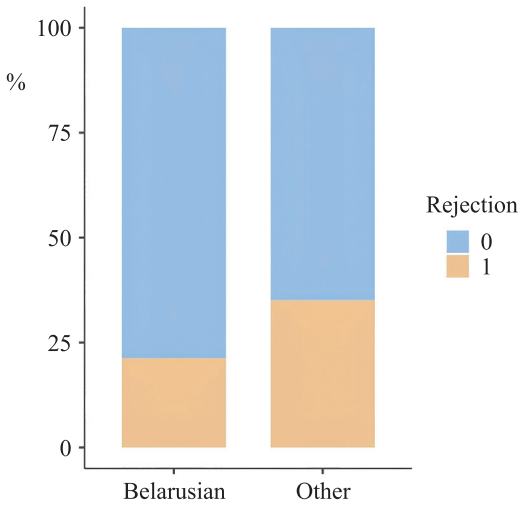

Fig. 5. Distribution of outcomes by nationality

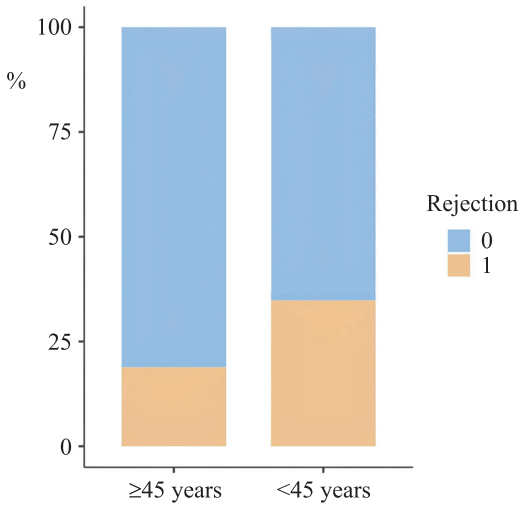

Fig. 6. Distribution of outcomes by age

difference was observed in the subgroup of recipients of other nationalities (χ^2 = 3.620; df = 1; p = 0.057). However, graphical analysis revealed a notable trend: in recipients of non-Belarusian nationality, the incidence of rejection increased from 0% to 39.2% in the presence of 2–4 mismatches, whereas among Belarusian recipients, the increase was from 7.4% to 23.3% (Fig. 8).

An analysis incorporating all three factors – MHC class II mismatches, recipient age, and nationality – revealed that mismatches significantly influenced the incidence of acute graft rejection in recipients under 45 years of age, both among those of Belarusian nationality (χ^2 = 4.068; df = 1; p = 0.044) and of other nationalities (χ^2 = 4.342; df = 1; p = 0.037). In Belarusian recipients under 45 years old, no cases of acute rejection were observed in the 0–1 mismatch subgroup, while the rejection rate increased to 35.4% with 2–4 mismatches (OR = 9.44; 95% CI: 0.51–173.61). Similarly, in recipients of other nationalities under 45, no rejection occurred with 0–1 mismatches, while the incidence reached 50.0% in the 2–4 mismatch group (OR = 11.00; 95% CI: 0.56–217.69) (Fig. 9).

When analyzing HLA-DRB1 antigen mismatches across all subgroups, no statistically significant associations with AR were observed. However, analysis of the HLA-DQB1 antigen revealed a significant association between mismatches and development of AR in the subgroup of recipients of other nationalities (χ^2 = 4.342; df = 1; p = 0.037), with an OR of 11.00 (95% CI: 0.56–217.69) (Figs. 10 and 11).

DISCUSSION

The results of our study demonstrate that recipients with a higher number of MHC class II mismatches (specifically HLA-DQB1 and HLA-DRB1), particularly in the range of 2–4 mismatches, are at an increased risk of

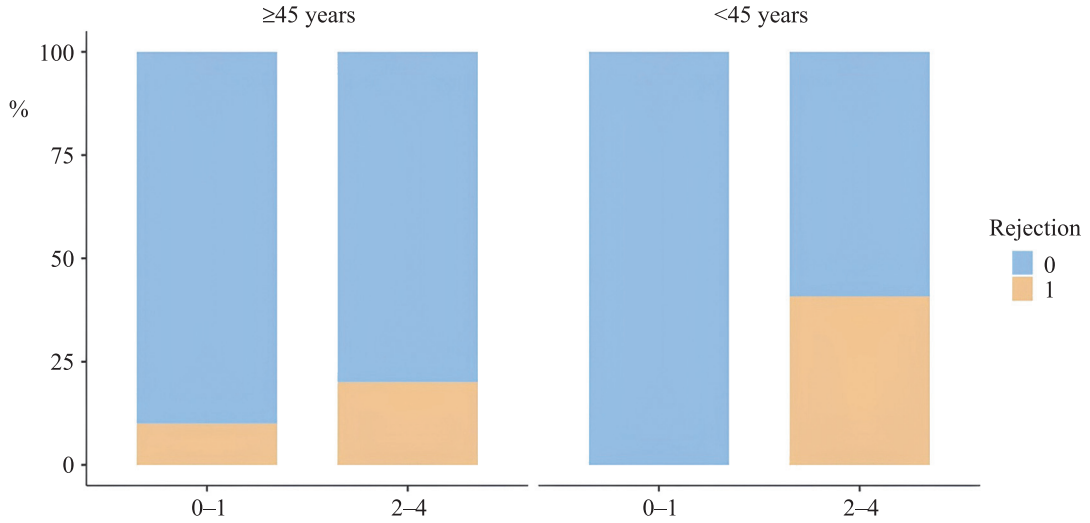

Fig. 7. Distribution of outcomes by MHC class II antigen mismatches and age

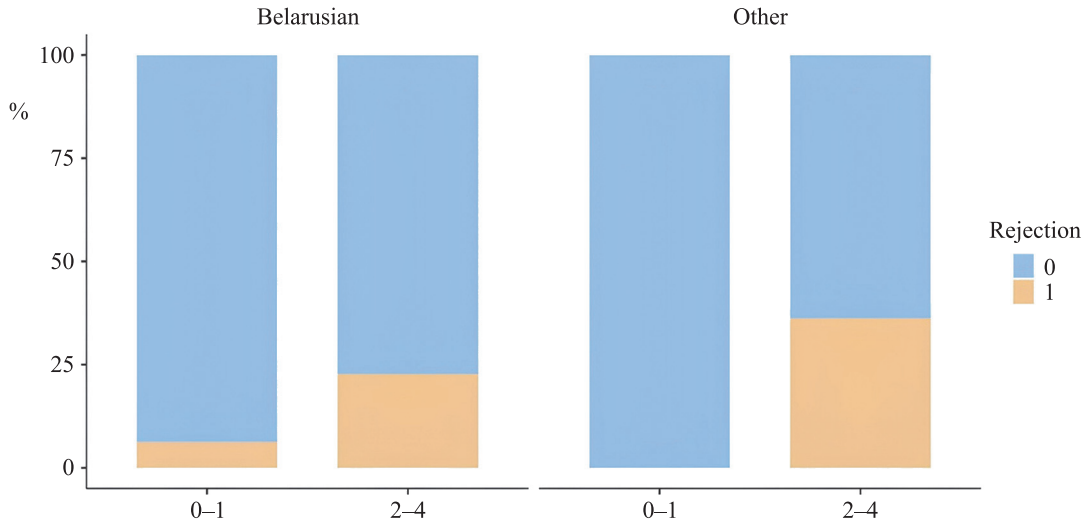

Fig. 8. Distribution of outcomes by MHC class II antigen mismatches and nationality

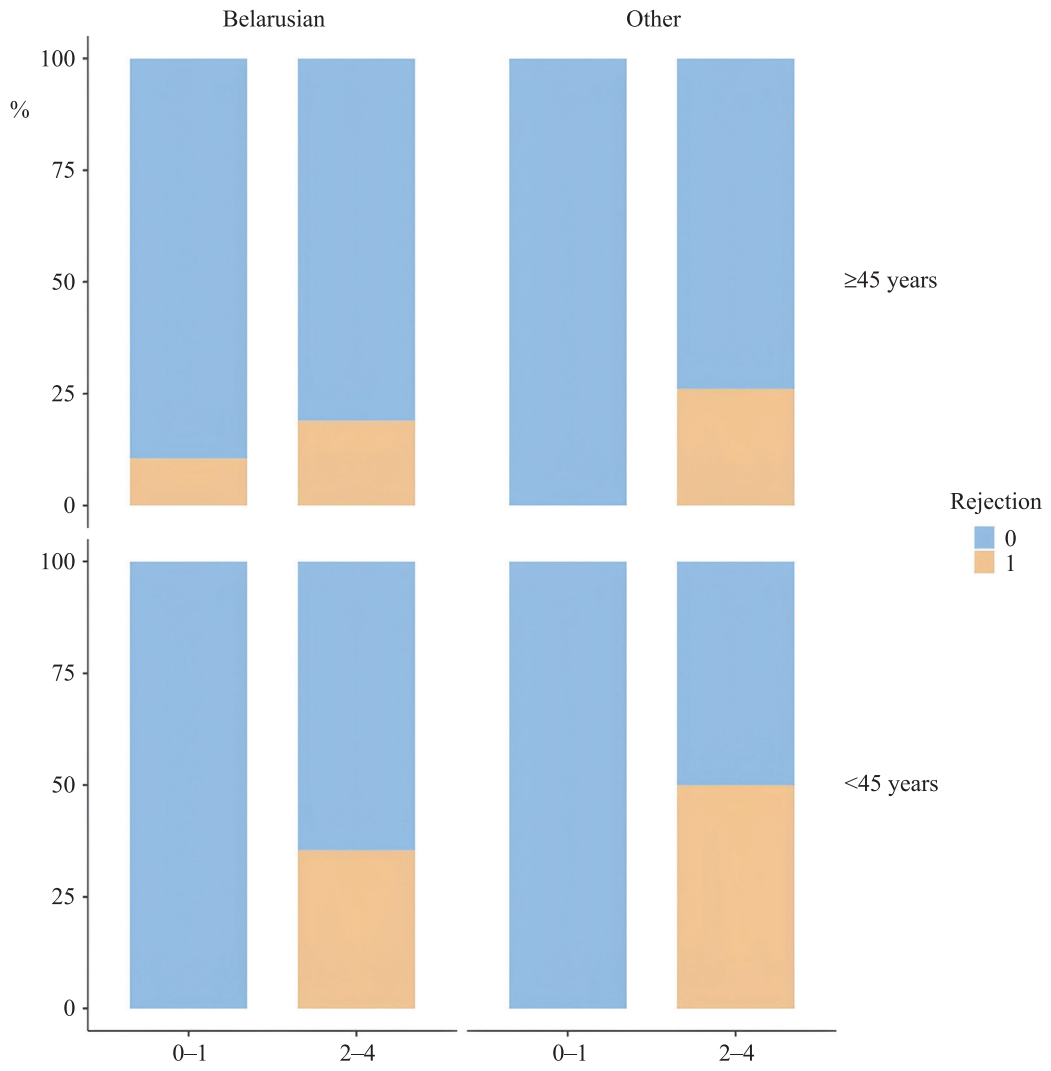

Fig. 9. Distribution of outcomes by MHC class II antigen mismatches, age and nationality

developing an AR in the postoperative period. In contrast, the role of MHC class I mismatches (HLA-A, HLA-B) in the onset of AR could not be conclusively confirmed.

Our findings are consistent with those reported by Johan Nilsson et al. in a 2019 publication in the Journal of the American Heart Association. That study showed that a high number of mismatches in HLA-A, HLA-B, and HLA-DR significantly reduced graft survival ($P < 0.001$). Conversely, the number of HLA-A/B/C mismatches was not associated with graft loss ($P = 0.584$), unlike mismatches in HLA-DR/DQ ($P = 0.025$). Specifically, recipients with more than four mismatched HLA-A/B/C alleles had an unadjusted OR for graft loss of 1.08 (95% CI: 0.99–1.19; $P = 0.099$), while those with four mismatched HLA-DR/DQ alleles had an OR of 1.13 (95% CI: 1.03–1.23; $P = 0.009$) [26].

A retrospective study conducted by Nitta et al. found that the number of HLA-DR mismatches was significantly associated with AR ($p = 0.029$). In their univariate analysis, having two HLA-DR mismatches was identified as the only independent risk factor for the development of AR episodes ($p = 0.017$). While our findings do not align with those of Nitta et al., this discrepancy may be attributed to the smaller sample size in our study, where the number of recipients with 0 HLA-DRB1 mismatches was limited. This issue warrants further investigation.

Regarding the HLA-DQB1 antigen, there is a lack of major studies investigating its impact on adult recipients. However, in 2024, Wright et al. published a study examining HLA-DQB1 mismatches in pediatric transplantation. Their results showed that recurrence-free survival at 5 years was higher in children with 0 DQB1 mismatches (68%) compared to those with 1 (62%) or 2 (63%) mismatches ($p = 0.08$ for both comparisons). Interestingly, rejection was most frequently observed in children with darker skin tones. In our study, recipients under 18 years of age were excluded due to specific study parameters, making direct comparison with the pediatric study less valid. Nevertheless, the findings by Wright et al., along with the limited adult-focused stu-

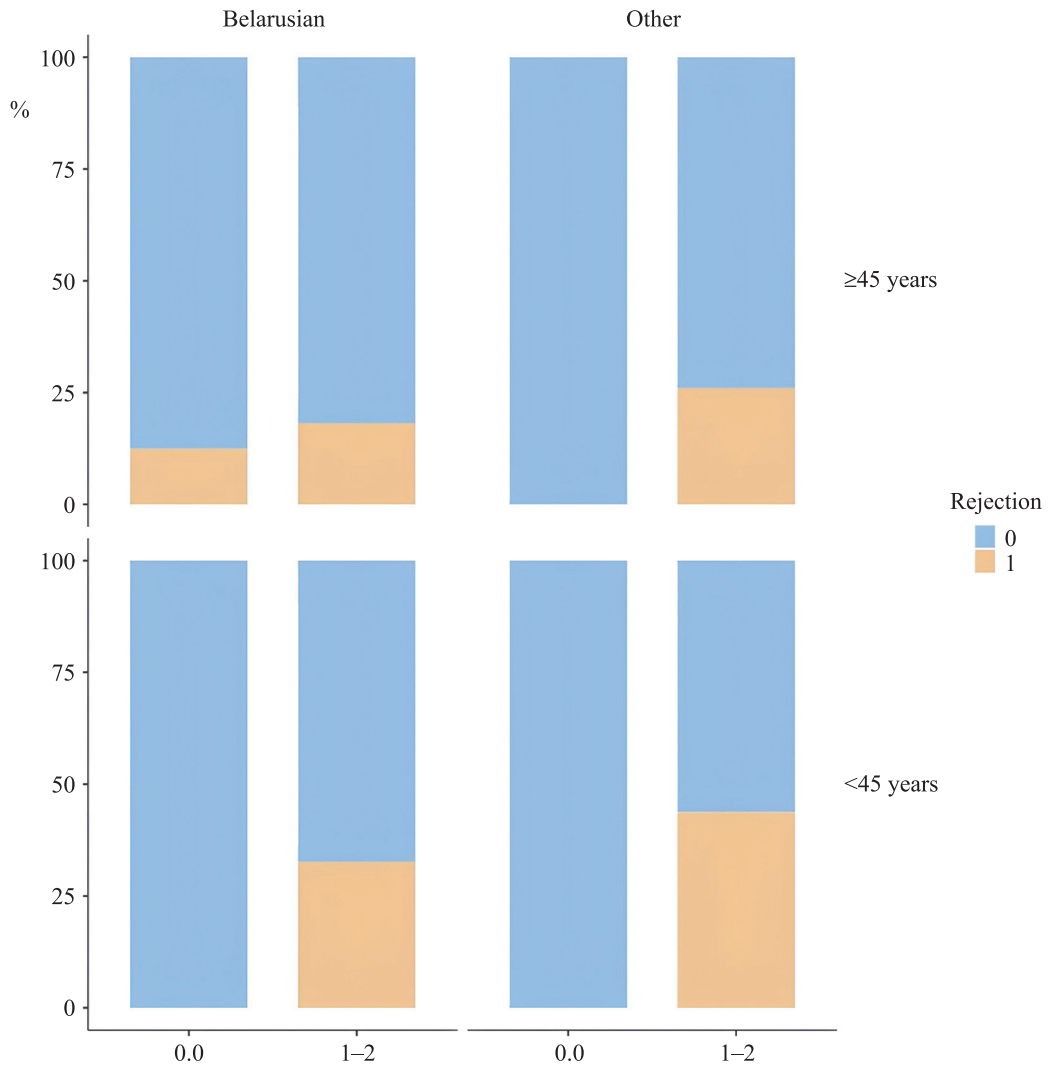

Fig. 10. Distribution of outcomes by HLA-DRB1 mismatches, age and nationality

dies, highlight the need for further investigation into the role of this antigen.

In our study, recipient age (<45 years) and nationality were identified as additional independent risk factors for heart transplant, each significantly increasing the odds of developing an AR – 2.00-fold (CI 95% 1.06 to 3.79) for nationality and 2.30-fold (CI 95% 1.29 to 4.10) for age. These findings are consistent with results from several international studies and systematic reviews [22–24].

When analyzing the combined influence of risk factors, with MHC class II mismatches as the primary factor and recipient age and nationality as secondary factors, we were able to reliably identify the groups at the highest risk for AR. Notably, when considering the combination of HLA-DQB1 mismatches, age, and nationality, a significant effect was observed in recipients of other nationalities under 45 years old. This highlights the importance of further research into the roles of both HLA-DRB1 and HLA-DQB1 antigens in predicting AR risk.

CONCLUSION

1) It was reliably established that MHC class II mismatches, donor-recipient nationality differences, and younger recipient age (<45 years) are all significant risk factors for AR following transplantation.
2) Two groups were identified as most at risk for AR: recipients of Belarusian nationality under 45 years old, and recipients of other nationalities younger than 45 years old. In the presence of 0–1 MHC class II incompatibility, the rejection rate was 0% in both groups. However, with 2–4 mismatches, the rejection rate increased to 35.40% for Belarusian recipients and 50.00% for recipients of other nationalities.
3) The HLA-DQB1 antigen was found to contribute most to the development of AR in non-Belarusian recipients.

The authors declare no conflict of interest.

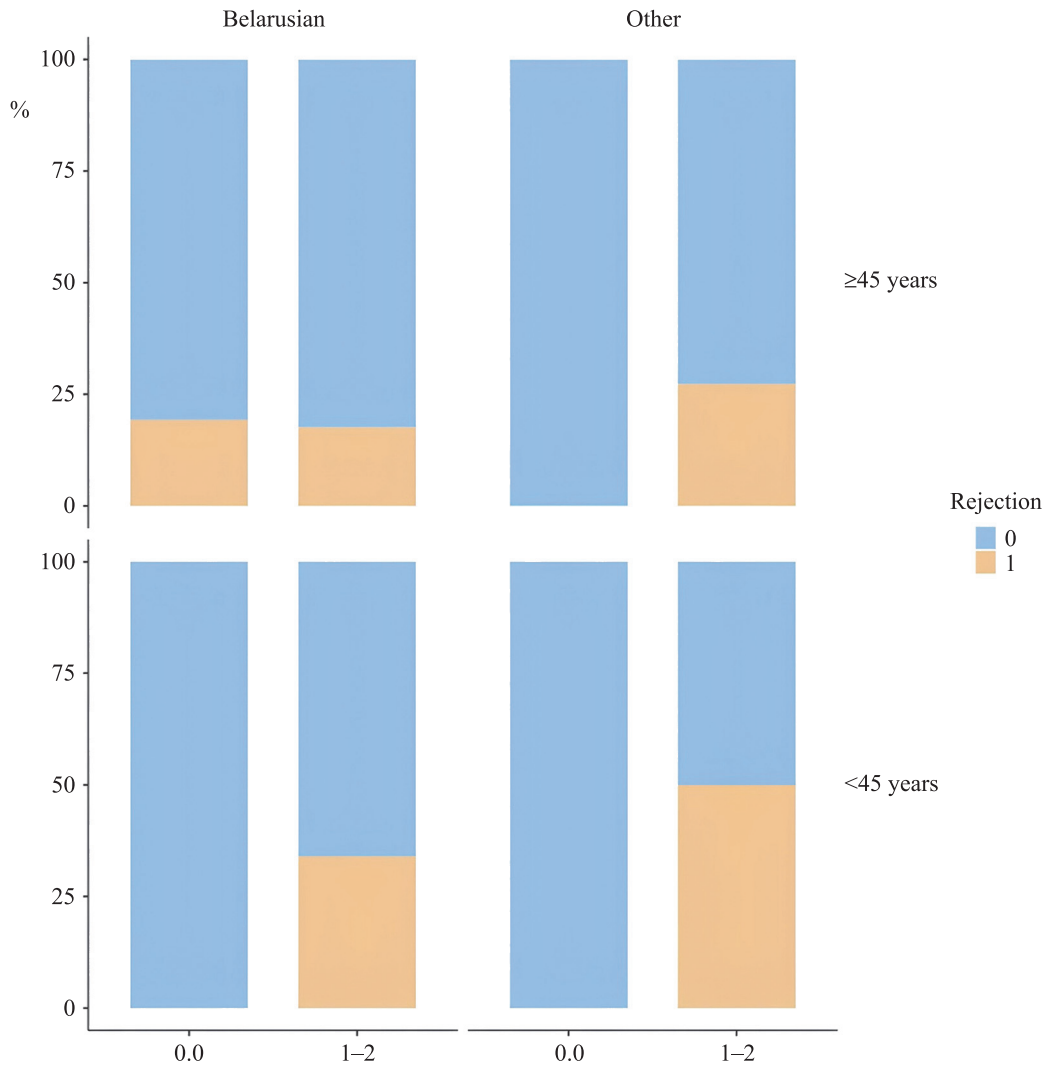

Fig. 11. Distribution of outcomes by HLA-DQB1 mismatches, age and nationality

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