

## Donor – recipient selection using epitope mismatches in kidney transplantation

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### ABSTRACT

**Aim.** To evaluate the potential option of selecting donor – recipient pairs by using the number of epitope mismatches.

**Materials and methods.** An observational cohort study was carried out, which included 824 adult recipients of ABO compatible deceased donor kidneys. The end point was a transplant loss. If a recipient with a functioning graft died, the observation was censored. The number of epitope mismatches (EpMM) was calculated using open source information on the population frequency of haplotypes and the repertoire of epitopes with confirmed immunogenicity. All possible combinations of the donor and recipient genotypes were compiled, and the probability of each combination was calculated. After that, the number of donor epitopes absent in the recipient was calculated for each combination with a non-zero probability, whereupon the weighted mean EpMM was calculated, where the weight coefficient was the normalized probability of occurrence of each combination.

**Results.** All of the donor – recipient pairs had HLA-mismatches (HLA MM): 1.9% of recipients had 1 HLA MM, 6.7% had 2 HLA MM, 29.9% had 3 HLA MM, 38.5% had 4 HLA MM, 18.1% had 5 HLA MM, and 4.9% had 6 HLA MM. The HLA MM impacted graft survival was determined: log-rank test  $p < 0.0001$ , Breslow test  $p < 0.0001$ . The median values and the interquartile ranges of EpMM were 6 [4; 7], 12 [7.74; 17.25], 18 [14; 22], 24 [20; 30], 30.5 [25; 37] and 36 [26.5; 44.5] for the cases of 1, 2, 3, 4, 5 and 6 HLA MMs, respectively. An increase in HLA MM resulted in a higher risk of developing donor-specific anti-HLA antibodies (DSA). Hazard ratio (HR) = 1.21 [95% confidence interval (CI): 0.7; 1.9], 1.71 [95% CI: 1.22; 2.36], 2.04 [95% CI: 1.42; 2.73], 2.25 [95% CI: 1.63; 2.96], 2.59 [95% CI: 2.03; 3.29] for 2, 3, 4, 5, and 6 HLA MM, respectively, versus HLA MM = 1. An increase in EpMM also resulted in a higher risk of developing DSA. HR = 1.66 [95% CI: 1.09; 2.47], 2.1 [95% CI: 1.46; 2.91], 2.41 [95% CI: 1.86; 3.03], 2.61 [95% CI: 2.12; 3.12], 2.77 [95% CI: 2.26; 3.33] for 10–19, 20–29, 30–39, 40–49 and >50 EpMM, respectively, versus EpMM < 10. An increase in HLA MM was associated with an increased risk of transplant loss. HR = 1.24 [95% CI 0.7; 2.15], 1.48 [95% CI 0.86; 2.33], 1.88 [95% CI 1.32; 2.52], 2.41 [95% CI 2; 2.93], 2.98 [95% CI 2.59; 3.46] at 2, 3, 4, 5, and 6 HLA MM, respectively, versus HLA MM = 1. An increase in EpMM also was associated with an increased risk of transplant loss. HR = 1.71 [95% CI 1.1; 2.49], 2.11 [95% CI 1.59; 2.68], 2.4 [95% CI 1.96; 2.86], 2.59 [95% CI 2.17; 3.04], 2.71 [95% CI 2.31; 3.15] at 10–19, 20–29, 30–39, 40–49 and >50 EpMM, respectively, versus EpMM < 10. In order to demonstrate the effectiveness of EpMM accounting, we analyzed graft survival among the patients with 4 HLA MM. With the number of EpMM in the range from 10 to 24 and from 25 to 43 the difference in survival rates was statistically significant, but only at the late stages of the post-transplant period: log-rank test  $p = 0.0067$ , Breslow test  $p = 0.0982$ . The median survival for EpMM 10–24 was 10.33 [95% CI 9.05; 11.61] years, for EpMM 25–43 – 8.67 [95% CI 7.68; 9.66] years, HR 1.537 [95% CI 1.114; 2.12]. At the same time, it was not the median of survival that increased, but the proportion of patients with a functioning graft: at 10–24 EpMM after 15 years, 18.28% [95% CI 8.2; 31.67] grafts functioned, while at 25–43 EpMM only 4.75% [95% CI 0.94; 13.64] functioned.

**Conclusion.** In the routine practice of a transplantation center with a short waiting list of its own, it might be possible to improve the kidney transplant survival as a result of considering epitope mismatches, thus reducing the risk of developing donor-specific anti-HLA antibodies and ensuring a higher graft survival rate. This method can be used for additional ranking of transplantation candidates depending on the number of epitope mismatches within the fixed number of HLA-mismatches and thus select the optimal one. Besides, it is theoretically possible to use this method as an alternative to the traditional donor/recipient histocompatibility evaluation. Additional research is required.

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**Key words:** kidney transplantation, HLA, epitope, eplet, tissue compatibility, recipient selection, donor-specific antibodies, anti-HLA antibodies.

**Conflict of interest.** The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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**Conformity with the principles of ethics.** The study was approved by the local Ethics Committee at Moscow Regional Research and Clinical Institute (Protocol No. 9 of 12.10.2017).

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## Селекция пары «донор – реципиент» с учетом эпитопных несоответствий при трансплантации почки

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### РЕЗЮМЕ

**Цель.** Оценить потенциал селекции пары «донор – реципиент» с учетом количества эпитопных несоответствий.

**Материалы и методы.** Проведено обсервационное ретроспективное когортное исследование, в которое включено 824 совершеннолетних реципиента трупной почки, совместимых по группе крови. Конечной точкой считали утрату трансплантата. В случае смерти реципиента с функционирующим трансплантатом наблюдение подвергали цензурированию. Подсчет количества эпитопных несоответствий (ЕрММ) проводили с использованием информации из общедоступных ресурсов о популяционной частоте гаплотипов и репертуаре эпитопов с подтвержденной иммуногенностью. Составлялись все возможные сочетания генотипов донора и реципиента, подчитывали вероятность каждого сочетания. Затем для каждого сочетания с ненулевой вероятностью определяли количество эпитопов донора, отсутствующих у реципиента. После этого вычисляли взвешенное среднее ЕрММ, где весовым коэффициентом была нормированная вероятность появления каждого сочетания.

**Результаты.** Все пары «донор – реципиент» имели HLA несовместимости (HLA MM): 1,9% – 1 HLA MM, 6,7% – 2 HLA MM, 29,9% – 3 HLA MM, 38,5% – 4 HLA MM, 18,1% – 5 HLA MM, 4,9% – 6 HLA MM. Различия в HLA MM влияли на выживаемость трансплантатов: log-rank test  $p < 0,0001$ , Breslow test  $p < 0,0001$ . Медиана ( $Me$ ) и интерквартильный размах [ $Q_1$ ;  $Q_3$ ] ЕрММ составили 6 [4; 7], 12 [7,74; 17,25], 18 [14; 22], 24 [20; 30], 30,5 [25; 37] и 36 [26,5; 44,5] для 1, 2, 3, 4, 5 и 6 HLA MM соответственно. Увеличение HLA MM было связано с ростом риска появления донор-специфических анти-HLA антител (ДСА). Отношение рисков (HR) = 1,21 [95%-й доверительный интервал (95%-й ДИ) 0,7; 1,9], 1,71 [95%-й ДИ 1,22; 2,36], 2,04 [95%-й ДИ 1,42; 2,73], 2,25 [95%-й ДИ 1,63; 2,96], 2,59 [95%-й ДИ 2,03; 3,29] при 2, 3, 4, 5 и 6 HLA MM соответственно по отношению к HLA MM = 1. Увеличение ЕрММ также было связано с ростом риска появления ДСА. HR = 1,66 [95%-й ДИ 1,09; 2,47], 2,1 [95%-й ДИ 1,46; 2,91], 2,41 [95%-й ДИ 1,86; 3,03], 2,61 [95%-й ДИ 2,12; 3,12], 2,77 [95%-й ДИ 2,26; 3,33] при 10–19, 20–29, 30–39, 40–49 и >50 ЕрММ соответственно по отношению к ЕрММ < 10. Увеличение HLA MM было связано с ростом риска утраты трансплантата. HR = 1,24 [95%-й ДИ 0,7; 2,15], 1,48 [95%-й ДИ 0,86; 2,33], 1,88 [95%-й ДИ 1,32; 2,52], 2,41 [95%-й ДИ 2; 2,93], 2,98 [95%-й ДИ 2,59; 3,46] при 2, 3, 4, 5 и 6 HLA MM соответственно по отношению к HLA MM = 1. Для демонстрации эффективности учета ЕрММ мы проанализировали выживаемость трансплантатов у пациентов с HLA MM = 4. Выживаемость при 10–24 и 25–43 ЕрММ различалась статистически значимо, но только на поздних этапах посттрансплантационного периода: log-rank test  $p = 0,0067$ , Breslow test  $p = 0,0982$ . Медиана выживаемости для ЕрММ 10–24 составила 10,33 [95%-й ДИ 9,05; 11,61] лет, для ЕрММ 22–43 – 8,67 [95%-й ДИ 7,68; 9,66] лет, HR = 1,537 [95%-й

ДИ 1,114; 2,12]. При этом главным образом увеличивалась не медиана выживаемости, а доля больных с функционирующим трансплантатом: при 10–24 ЕрММ через 15 лет 18,28% [95%-й ДИ 8,2; 31,67] трансплантатов функционировало, тогда как при 25–43 ЕрММ – только 4,75% [95%-й ДИ 0,94; 13,64].

**Заключение.** В рутинной практике трансплантационного центра с небольшим, обособленным листом ожидания учет эпитопных несоответствий может улучшить результаты трансплантации почки: снизить риск появления донор-специфичных анти-HLA антител и повысить выживаемость трансплантатов. Применение этого метода позволяет дополнительно ранжировать кандидатов на трансплантацию в зависимости от количества эпитопных несовпадений в рамках фиксированного количества HLA несовпадений и выбрать оптимального. Вместе с тем существует теоретическая возможность использования этого метода в качестве альтернативы традиционной оценке тканевой совместимости донора и реципиента. Необходимы дополнительные исследования.

**Ключевые слова:** трансплантация почки, HLA, эпитоп, эплет, тканевая совместимость, выбор реципиента, донор-специфичные антитела, анти-HLA антитела.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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## INTRODUCTION

Over the history of clinical transplantology, the histocompatibility between the donor and the recipient has always been one of the key factors on which kidney allograft survival depended. As is known that the smaller the number of HLA-mismatches (HLA-MM), the better the survival rate of the graft. This has been proven both in the case of deceased donor kidney transplantation [1] and in the case of living donor kidney transplantation [2].

Despite the fact that the effect of this factor gradually decreases over the years, it still remains important in the current era of immunosuppression therapy.

Each HLA-antigen comprises a unique repertoire of epitopes. At that, some of them are totally unique and peculiar only to the specific allelic variant of a molecule (private epitopes), and some can be common for several HLA-molecules (public epitopes) [3].

Existence of public epitopes determines the possibility of selecting the donor/recipient pair based on this information.

The aim of the study was to evaluate the potential option of selecting donor/recipient pairs using the number of epitope mismatches.

## MATERIALS AND METHODS

*Study design and patients.* An observational retrospective cohort study was conducted which included 824 adult recipients. All of the patients underwent transplantation of a deceased donor kidney compatible by ABO blood group. The end point was a transplant loss. If a recipient with a functioning graft died, the observation was censored.

In all cases, HLA-typing was performed (HLA A, B and DR loci). Before 2003, the serological HLA-typing was used (the split antigen level), while later, low resolution HLA-genotyping by means of SSO or SSP methods (allelic group level) was utilized. The cross-match test (complement dependent lymphocytotoxic test) was negative in all cases. The anti-HLA antibody screenings were performed using multiplex technology on Luminex platform with LIFECODES Lifescreen Deluxe (Immucor) reagents, while identification of antibodies were done with the sets of LIFECODES LSA.

Patient data are presented in Table 1.

Table 1

Patient data	
Parameter	Value
Recipient sex M/F, %	58/42
Age of recipients, years, <i>Me</i> [ $Q_1$ ; $Q_3$ ]	43 (27; 50)
Time on dialysis before transplantation, months, <i>Me</i> [ $Q_1$ ; $Q_3$ ]	34 (14; 42)
Repeated transplantation, %	9
Preexisting antibodies (PRA* $\geq 10\%$ )	12.8
Age of donors, years, <i>Me</i> [ $Q_1$ ; $Q_3$ ]	38.1 (31.2; 51.8)
Brain death donor/asystolic donor, %	46/54
Preservation time, h, <i>Me</i> [ $Q_1$ ; $Q_3$ ]	8.4 (6; 14)
Follow up observation period, years, <i>Me</i> [ $Q_1$ ; $Q_3$ ]	8.1 (4.8; 10.4)

\* panel-reactive antibody

## RESULTS

The recipients demonstrated different levels of compatibility with the donor kidney (Fig. 1).

At that, HLA-incompatibility remains an important parameter that determines long term graft survival (Fig. 2).

Generally, differences in HLA-A locus compatibility significantly affected graft survival: log-rank test  $p = 0.0005$ , Breslow test  $p = 0.0049$ . The median survival for the 0, 1 and 2 HLA-A MM were 9.5 [95% CI 8.77; 10.23], 8.42 [95% CI 8; 8.87] and 8.33 [95% CI: 7.71; 8.96] years, respectively. Pair-wise comparisons: 0–1 HLA-A MM – log-rank  $p = 0.0092$ ,

Breslow  $p = 0.0107$ , HR 1.32 [95% CI 1.079; 1.615]; 1–2 HLA-A MM – log-rank  $p = 0.2157$ , Breslow  $p = 0.3156$ , HR 1.114 [95% CI 0.936; 1.326]; 0–2 HLA-A MM log-rank  $p = 0.0003$ , Breslow  $p = 0.0012$ , HR 1.485 [95% CI 1.204; 1.831].

Differences in HLA-B locus compatibility significantly affected graft survival: log-rank test  $p = 0.0034$ , Breslow test  $p = 0.0008$ . The median survival for the 0, 1 and 2 HLA-B MM were 9.99 [95% CI 8.38; 11.6], 8.67 [95% CI 8.1; 9.26] and 8.25 [95% CI 7.81; 8.69] years, respectively. Pair-wise comparisons: 0–1 HLA-B MM – log-rank  $p = 0.0656$ , Breslow  $p = 0.0632$ , HR 1.353 [95% CI 0.997; 1.836]; 1–2 HLA-B MM – log-rank  $p = 0.0424$ , Breslow  $p = 0.1363$ , HR 1.19 [95% CI 1.009; 1.404]; 0–2 HLA-B MM log-rank  $p = 0.0031$ , Breslow  $p = 0.0076$ , HR 1.582 [95% CI 1.213; 2.062].

Differences in HLA-DRB1 locus compatibility significantly affected graft survival: log-rank test  $p < 0.0001$ , Breslow test  $p < 0.0001$ . The median survival for the 0, 1 and 2 HLA-DR1 MM were 10.08 [95% CI 9.15; 11.02], 9 [95% CI 8.47; 9.53] and 8.25 [95% CI 7.58; 8.92] years, respectively. Pair-wise comparison: 0–1 HLA-DR1 MM – log-rank  $p = 0.0021$ , Breslow  $p = 0.0152$ , HR 1.472 [95% CI 1.166; 1.858]; 1–2 HLA-DR1 MM – log-rank  $p = 0.0038$ , Breslow  $p = 0.0146$ , HR 1.283 [95% CI 1.084; 1.52]; 0–2 HLA-DR1 MM log-rank  $p < 0.0001$ , Breslow  $p < 0.0001$ , HR 1.888 [95% CI 1.532; 2.237].

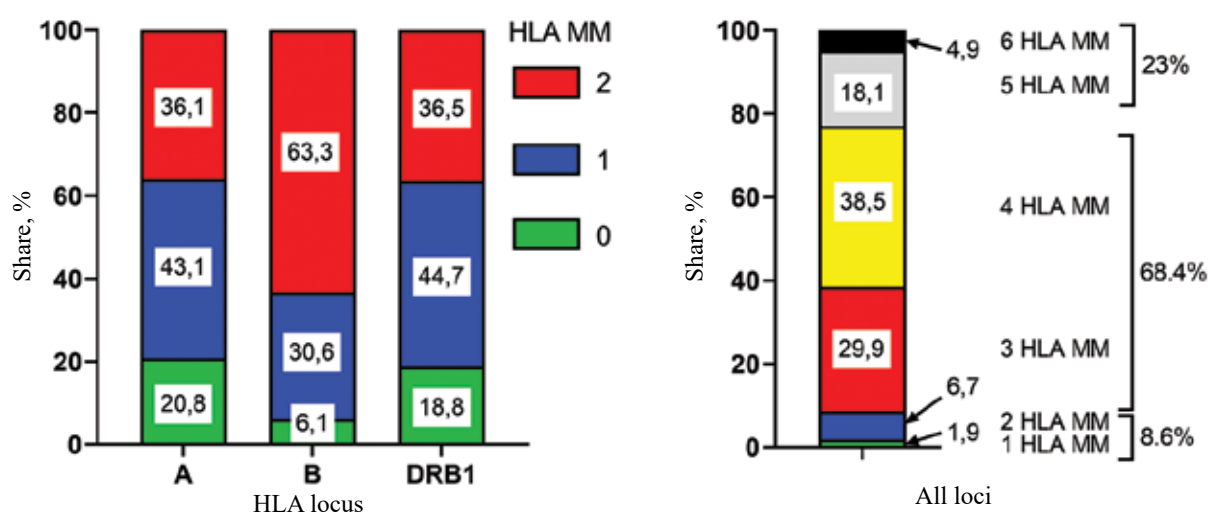


Fig. 1. HLA incompatibility distribution: HLA MM – the number of donor antigens absent in the recipient

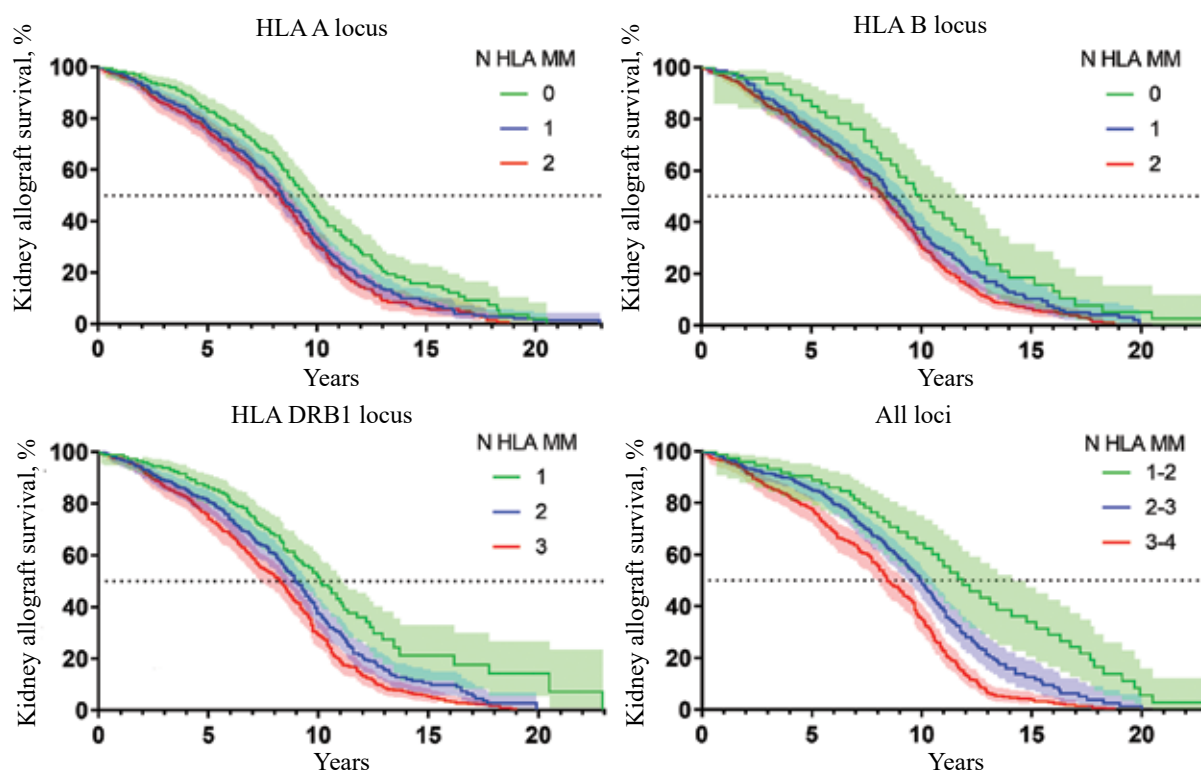


Fig. 2. Death-censored graft survival. The graphs depict the results of assessment of differences according to the log-rank criterion for three curves

Altogether, the differences in compatibility across all loci significantly affected graft survival: log-rank test  $p < 0.0001$ , Breslow test  $p < 0.0001$ . The median survival for 1-2 HLA MM, 3-4 HLA-MM and 5-6 HLA-MM were 11.85 [95% CI 9.93; 13.78], 10 [95% CI 9.4; 10.6] and 8.42 [95% CI 7.82; 9.02] years, respectively. Pair-wise comparisons: 1-2 HLA MM and 3-4 HLA MM – log-rank  $p = 0.001$ , Breslow  $p = 0.041$ , HR 1.617 [95% CI 1.233; 2.121]; 3-4 HLA MM and 5-6 HLA MM – log-rank  $p < 0.0001$ , Breslow  $p < 0.0001$ , HR 1.531 [95% CI 1.286; 1.824]; 1-2 HLA MM and 5-6 HLA MM log-rank  $p < 0.0001$ , Breslow  $p < 0.0001$ , HR 2.365 [95% CI 1.863; 3.002].

We calculated the average number of epitope mismatches for each HLA-MM quantity (Fig. 3).

An increase in numbers of HLA-mismatches and epitope mismatches significantly heightens the risk of anti-donor anti-HLA antibodies development and of graft loss (Fig. 4).

In order to demonstrate that it is possible to apply the method of donor/recipient pair selection based on epitope mismatches in practice, we analyzed graft survival in case of 4 HLA-mismatches (the most

common variant at our center) (Fig. 5). The patients were divided into two groups: the ones with EpMM less or equaling the median (the average number) and the ones with higher values.

The difference in graft survival rates for the 10-24 EpMM and 25-43 EpMM was statistically significant, but only at late stages of the post-transplant period: log-rank test  $p = 0.0067$ , Breslow test  $p = 0.0982$ . The median survival for the 10-24 EpMM was 10.33 [95% CI 9.05; 11.61] years, for the 25-43 EpMM – 8.67 [95% CI 7.68; 9.66] years, HR 1.537 [95% CI 1.114; 2.12].

## DISCUSSION

At present (data date: August 2019), the modern HLA nomenclature includes 28 serologically identifiable antigens of HLA A locus, 62 antigens of HLA B locus, 24 antigens of HLA DRB1 locus [7]. Considering the enormous amount of potential combinations, it becomes evident that in order to select the optimal recipient, the waiting list must be comprised of thousands of transplant candidates. Unified waiting lists of this kind exist in Europe (Eurotransplant) and in the USA (United Network for Organ Sharing).

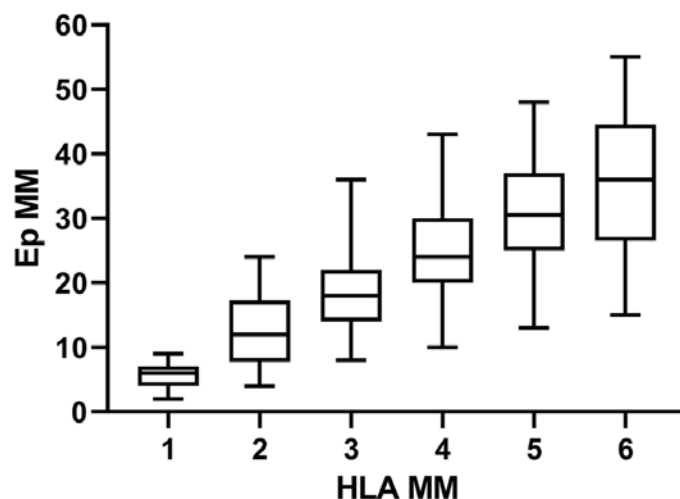


Fig. 3. Concordance between HLA MM and the estimated number of EpMM: the graph shows the median, interquartile range, minimum and maximum values, HLA MM – the number of donor antigens absent in the recipient, EpMM – the number of donor epitopes absent in the recipient.

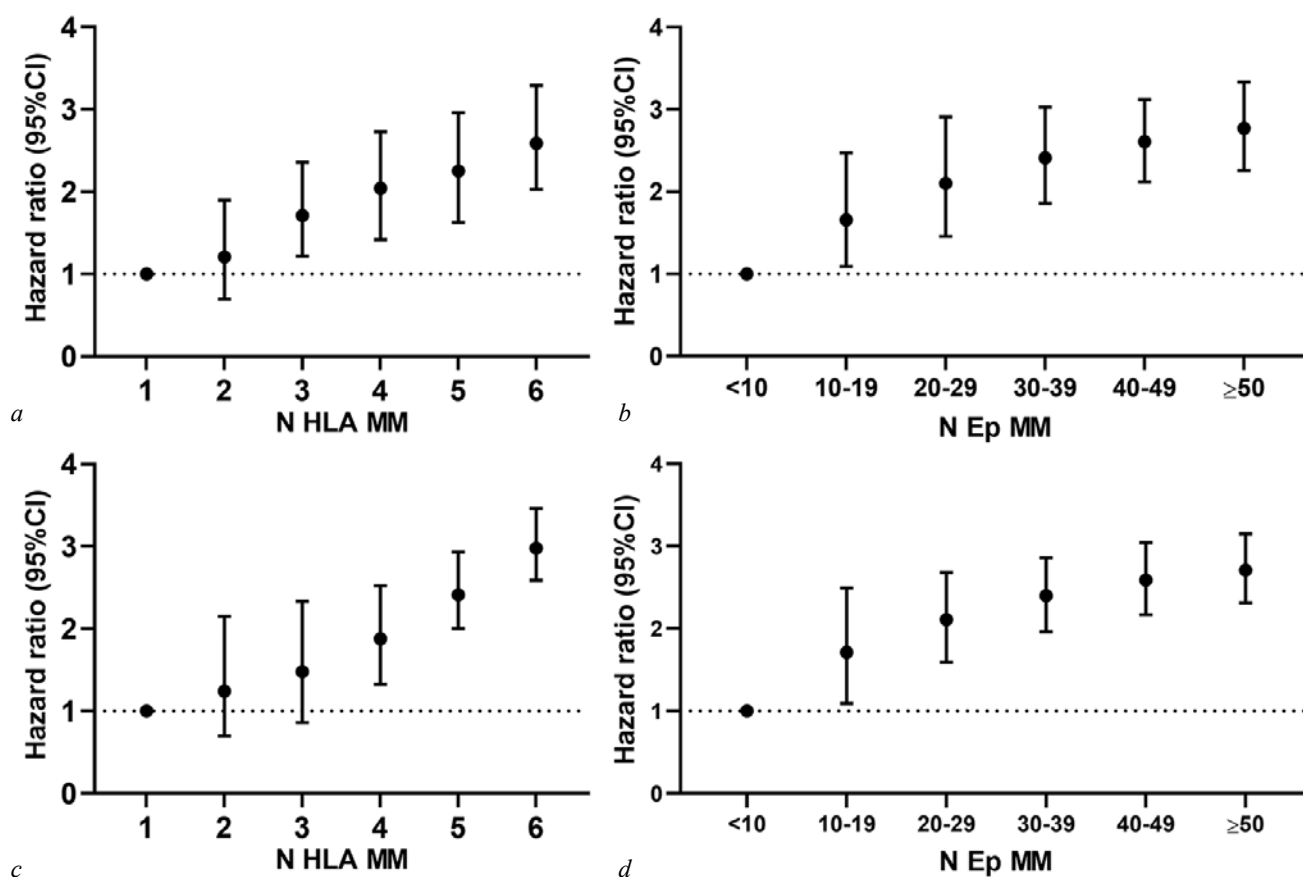


Fig. 4. The relationship between the risk of *de novo* donor-specific antibody development and HLA MM (a), EpMM (b), the relationship between the risk of graft loss and HLA MM (c), EpMM (d)



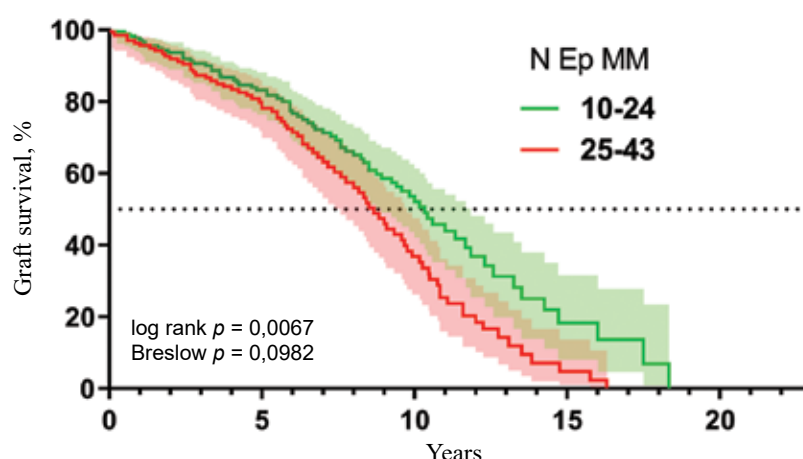


Figure 5. Death-censored graft survival in patients with 4 HLA mismatches: EpMM – the number of donor epitopes absent in the recipient, the median of EpMM in patients with HLA MM = 4 was 24

In Russia, each transplantation center keeps a waiting list of its own, which substantially hinders selection of the optimal recipient in terms of histocompatibility. Most of the recipients (68.4% according to the data of our center) receive a graft carrying 3 to 4 mismatched antigens, as waiting for a better match would mean substantially longer waiting times. As we have shown before [8], extended waiting for transplantation while on dialysis worsens the comorbid background, which, in turn, reduces transplantation probability and leads to a higher risk of death.

At the same time, the question of relative significance of such factors as the comorbid background and histocompatibility at various stages of waiting remains unresolved. At that, the importance of histocompatibility remains high. As we have demonstrated, the lower the number of HLA-mismatches, the better the graft survival rate, and this dependence is statistically significant.

However, it is remarkable that even with the total number of mismatches in terms of three loci considered, the median survival increases, though moderately (11.85 [95%CI 9.93; 13.78] years in case of 1–2 mismatches and 8.42 [95%CI 7.82; 9.02] years in case of 5–6 mismatches). Clinical interpretations of this fact can differ. On the one hand, it may be regarded as a confirmation of immunosuppression effectiveness, thus, histocompatibility becomes less significant. On the other hand, it indicates its insufficient effectiveness at the late stages of the post-transplantation period. Good histocompatibility generally leads to a substantial increase in the number of pa-

tients with a functioning graft in the late period rather than to the extension of the mean time of the graft functioning (median survival). Thus, in 15 years 33.8% [95% CI 20.6; 47.41] of patients with 1 or 2 HLA MM had their graft still functioning. In cases of 3 or 4 mismatches the graft remained functioning with 12.8% [95% CI 7.76; 19.2] of patients, and in cases of 5 or 6 mismatches with 3.6% [95% CI 1.84; 6.21] of patients only.

Most recipients get grafts with 4 HLA-mismatches (with consideration to HLA-A, HLA-B and HLA-DRB1 loci only). At that, each of them is deemed a totally equal candidate for the transplant in terms of histocompatibility. We believe it would be a promising possibility to be able to additionally rank candidates within the fixed HLA value taking into account EpMM. The expediency of application of such an approach to selecting the donor/recipient pair remains one of the main questions.

A major cause of graft loss at later periods is antibody-mediated rejection, which accounts for approximately 50% of cases [9]. At that, it is already known that an increase in HLA-mismatches leads to a higher risk of occurrence of *de novo* DSA [10]. We have convincing evidence to support this fact (Fig. 4a). An increase in HLA MM and an increase in EpMM both significantly heightened the risk of *de novo* DSA occurrence. At that, the rate of risk increase was somewhat different: the risk increase in line with the increase of HLA MMs is linear ( $r^2 = 0.9873$ ). At the same time, the relation between the risk and EpMM is described quite well by the logarithmic approximation ( $r^2 = 0.9991$ ). In

other words, an increase in the number of HLA MMs proportionally increases the “antigen load” and the risk of antibodies occurrence, while to EpMM this risk seems to relate in a more complex manner. We did not notice a significant increase in risk with two HLA MM compared with one HLA MM. In view of that, pursuance of accounting epitope mismatches within the fixed amount of HLA MMs (in addition to the traditional approach to selecting the donor/recipient pair) seems to be promising when it comes to the reduction of the “antigen load”. When the number of EpMM increases from  $> 10$  to the range of 10 to 19, the risk of DSAs gets substantially higher. It is an important aspect in the context of this research, for, as is shown in Figure 3, the EpMM quantity of 10 to 19 can correspond both to 2 and to 6 HLA MMs. This, in its turn, defines whether it is potentially possible to select donor/recipient pairs using epitope mismatches not in addition, but as an alternative to the traditional approach. In order to evaluate the validity of this hypothesis, additional research is required.

Four and more HLA MMs entailed a substantial risk of losing the graft function. Considering this fact, one is to admit that most of our recipients initially have an unfavorable “immunological profile” due to poor histocompatibility of donors and recipients. Considering the current state of affairs in transplantology assistance, one can presume that this will be applicable to the vast majority of transplantology centers in Russia.

The form of relation between the risk of graft loss and HLA-MMs can be well described using the exponential approximation ( $r^2 = 0.9978$ ). At that, if the number of EpMM exceeds 10, it substantially increases the risk of the graft loss; this relation is also well described by means of logarithmic approximation ( $r^2 = 0.9976$ ). At the same time, the benefits of its use in selection of donor/recipient pairs become evident only after a long-term follow-up: we have noticed substantial differences over a long-term period only. Even though it leads only to a moderate increase in the median survival (from 8.67 to 10.33 years Fig. 5), it makes it possible to increase substantially the share of recipients who have the graft still functioning in the long-term period: with 10 to 24 EpMM 18.28% [95 CI 8.2%; 31.67] of grafts were still functioning 15 years later, while only 4.75% with 25 to 43 EpMM [95 CI 0.94; 13.64].

**Research limitations.** Firstly, the study was retrospective. Secondly, the study was based on a large amount of clinical material collected over a long period of time (around 30 years). In our analysis we did not consider factors such as immunosuppressive therapy. At the same time, it is evident that the immunosuppression approaches have substantially evolved over this period of time [1, 2]. Thirdly, knowledge of antigenicity and immunogenicity consistently grows; we used the base [10] that was up-to-date in August 2019. It is entirely possible that the results might differ if we repeat our calculations using a more recent and updated base.

## CONCLUSION

Summarizing all of the above, we come to a conclusion that in a routine practice of a transplantation center with a short individual waiting list, consideration of epitope mismatches will make it possible to improve kidney transplantation results, reducing the risk of developing donor specific anti-HLA antibodies and increasing graft survival. Using this method, it will be possible to perform additional ranking of transplant candidates, depending on the number of epitope mismatches within the fixed number of HLA-mismatches, and thus select the optimal one. Besides, theoretically it might be possible to use this method as an alternative to the traditional evaluation of histocompatibility between the donor and the recipient. Additional research is required.

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