

Determining the relevance of HLA/KIR matching/mismatching on kidney and liver transplantation rejection: A meta-analysis

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Abstract. Batuan B, Cajayon CJ, Castro BA, Austria ML, Co DN, Ebreo SK, Clemente B, Tiongco RE. 2021. Determining the relevance of HLA/KIR matching/mismatching on kidney and liver transplantation rejection: A meta-analysis. Nusantara Bioscience 13: 211-218. The kidney and liver are solid organs commonly transplanted nowadays. However, there are cases wherein graft rejection occurs due to foreign Human Leukocyte Antigen (HLA) proteins. Furthermore, the function of Natural Killer (NK) cells and their receptors in solid organ transplantation is not yet fully elucidated. This study aims to determine the relevance of matching HLA/Killer cell Immunoglobulin-like Receptors (KIR) with kidney and liver transplantation outcomes. First, articles were screened according to the inclusion and exclusion criteria provided, which garnered eight definitive studies. Next, data were tabulated using a standardized extraction form. A meta-analysis was conducted to formulate conclusions regarding the significance of HLA/KIR matching and mismatching in kidney and liver transplantations. Fixed- and random-effects models were utilized to compute and establish 95% CI and pooled ORs wherein a p-value of less than 0.05 is considered significant. A combined Chi-square-based Q test and I² statistics were used to identify heterogeneity, which was resolved with a funnel plot. In this meta-analysis, only the HLA-Bw4/KIR3DL1 combination was found significant to lower the risk of allograft rejection (OR=0.73; PA=0.009; PH=0.42). Other combinations include HLA-C1 and KIR2DL2/3, HLA-C1 and KIR2DS2/3, HLA-C2 and KIR2DL1/DS2, and HLA-Bw4/KIR3DS1 were found to be insignificant; hence, these do not influence the allograft rejections. In conclusion, the role of HLA/KIR combinations on solid organ transplantation rejection is only significant in HLA-Bw4/KIR3DL1 interaction, which correlates with decreased odds of allograft rejection. Factors including KIR allele variations, insufficient data and journals related to the topic, and unestablished association of HLA/KIR in other organ transplantations affected the results of this meta-analysis; thus, these are recommended to be considered in future studies.

Keywords: Graft rejection, HLA, KIR, HLA/KIR matching, kidney, liver, natural killer cells, solid organ transplantation

Abbreviations: HLA: Human Leukocyte Antigen, HSCT: Hematopoietic Stem Cell Transplantation, KIR: Killer-cell Immunoglobulin-like Receptors, MHC: Major Histocompatibility Complex, NK: Natural Killer, UCBT: Umbilical Cord Blood Transplantation

INTRODUCTION

The kidney and liver are two of the most significant organs transplanted (Upadhyay 2019; Eteng et al. 2020). In many cases of organ transplantation, the recipient's adaptive immune response to the grafted tissues is a substantial impediment to the transplant's effectiveness. Allograft rejection occurs when the alloantigen on the tissue graft differs from the recipient's (Janeway et al. 2001). Organ transplantation is highly dependent on Major Histocompatibility Complex (MHC), also known as Human Leukocyte Antigen (HLA). The recognition of foreign HLA by the recipient's CD4 and CD8 T cells is believed to cause graft rejection. The interaction between HLA molecules and T cells determines which cells are considered "self" particles and which cells are regarded as "foreign" particles (García et al. 2012). Thus, having an HLA antigen match between the donor and recipient has been shown to improve the outcome of graft transplantation.

Killer cell Immunoglobulin-like Receptors (KIR) play a crucial role in Natural Killer (NK) cell activation, development, and control. They are transmembrane glycoproteins found at the cell surface of NK cells. KIRs fall under the classification of inhibitory receptors and have MHC class I ligands. They are varied, polymorphic, and responsible for the immune system's ability to trigger various immunological responses against infections (Khakoo and Jamil, 2011). The KIR genes found in a person can be categorized into group A and B haplotypes, each with four framework genes. Group A has a more inhibitory function, while group B has a more activating function for the NK cell. 15 unique KIR genes have been identified (KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3 and two pseudogenes, KIR2DP1 and KIR3DP1) (Middleton and Gonzales 2010). Inhibitory receptors KIR2DL2 and KIR2DL3 and activating receptors KIR2DS2 and KIR2DS3 are specific toward HLA-

C1 KIR ligands. Furthermore, inhibitory receptor KIR2DL1 and activating receptor KIR2DS1 are specific toward HLA-C2 KIR ligands. Inhibitory receptor KIR3DL1 and activating receptor KIR3DS1 are specific for HLA-Bw4 KIR ligand (Littera et al. 2017).

Research regarding the effect of the KIR receptors in recipients and HLA ligands in donor grafts in determining the success rate of organ transplantation has been inconclusive. Some key studies, including those from Kreijveld et al. (2007), Kunert et al. (2007), and Lee et al. (2017), did not find a correlation between HLA-KIR matching and allograft rejection. However, some studies such as La Manna et al. (2013), Legaz et al. (2013), Alam et al. (2015), Jafari et al. (2017), and Littera et al. (2017) were able to find some correlation between HLA/KIR matching and allograft rejection. This meta-analysis intends to investigate the impact of HLA/KIR matching on organ transplantation success rates, particularly in kidney and liver transplantation, to clarify conflicting studies regarding this study and to provide scientific evidence to address conflicting results regarding the effect of HLA/KIR matching on the success rate of organ transplantation. However, this study is limited only to the following KIRs: KIR2DL2, KIR2DL3, KIR2DS2, KIR2DS3, KIR2DL1, KIR2DS1, and KIR3DS1. The findings of this study could provide scientific data that can resolve conflicting findings of whether HLA/KIR was matching influences organ transplantation success rates. With the results of this meta-analysis, HLA/KIR matching may be first considered when conducting kidney and liver transplants.

MATERIALS AND METHODS

Search strategy

The researchers gathered 59 eligible research publications through Google Scholar, PubMed, and Scopus databases. The keywords used as a search strategy were "HLA/KIR match," "liver transplant/ation," "renal transplant/ation," "killer-immunoglobulin receptor," "matching," "mismatching," and "rejection." Publications were narrowed down to eight after screening using the inclusion and exclusion criteria (Figure 1).

Inclusion criteria

The primary criteria for the study's inclusion are: (i) it should be written in English and (ii) it should be classified as a study involving liver and kidney transplant patients. Then, the studies should conduct cohort or controlled trial studies with HLA-KIR matching involved and have more than 10 patients involved in the examination.

Exclusion criteria

In the preliminary screening, 27 journals were excluded upon reviewing the titles and abstracts. In addition, these studies also have abstract-only viewable and inaccessible content. Then, 19 journals were excluded in the further screening for studies conducted using study designs other than cohort or controlled trials. In addition, articles with no data on the number of rejectors and non-rejectors after transplantation and HLA and KIR matching were not included.

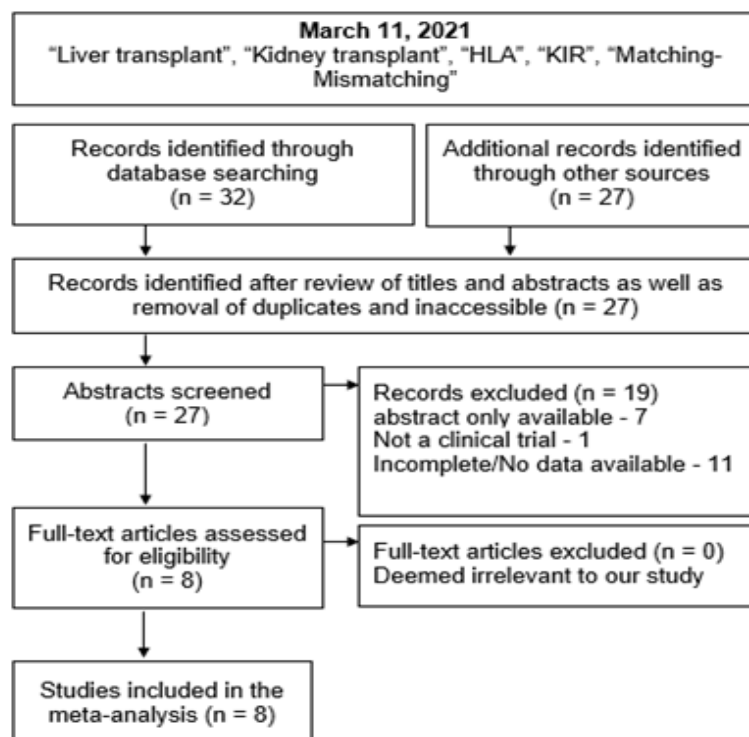


Figure 1. The research design for screening the HLA-KIR journals used in the meta-analysis

Meta-analysis protocol

The methods used in the investigation were adapted from a study by Pabalan et al. (2014), using a standardized data extraction form, and the essential data from the publications were tallied. The HLA/KIR matching and mismatching effect on the success or failure of kidney and liver transplants were established by pooling the odds ratio (OR) and computing the 95% confidence interval (CI). The fixed- or the random-effects models were utilized to calculate the 95% CI and pooled ORs. The OR, p-value of overall effect (PA), and p-value of heterogeneity (PH) were used to interpret the HLA/KIR match and mismatch data with kidney and liver transplantation outcomes. Through the combination of Chi-square based Q test and I² statistics, the studies' heterogeneity was identified if present or not (PH<0.10). Heterogeneity was resolved through a funnel plot.

RESULTS AND DISCUSSION

A total of 59 scholarly articles related to the topic were searched through Google Scholar, PubMed, and other sources using the indicated keywords. After keen scrutiny, only eight research articles met the inclusion criteria set for this meta-analysis and are summarized in Table 1. The

studies included were published as early as 2007 by Kreijveld et al. (2007) and Kunert et al. (2007), while the latest was published in 2017 by Jafari et al. (2017) and Littera et al. (2017). Most of the studies were done in western countries (Kreijveld et al. 2007; Kunert et al. 2007; La Manna et al. 2013; Legaz et al. 2013; Littera et al. 2017) and only three were conducted in Asian countries (Alam et al. 2015; Jafari et al. 2017; Lee et al. 2017). Two of the eight studies delved into liver transplantation rejection (Legaz et al. 2013; Lee et al. 2017). Furthermore, La Manna et al. (2013) and Littera et al. (2017) focused on chronic types of rejection, while the others involved acute graft rejection. Overall, 1,580 participants were included in this meta-analysis, wherein 533 were rejectors, and the remaining 1,047 had successful graft transplantation.

A fixed model was used to analyze the relevance of most HLA/KIR matches and mismatch with kidney and liver transplant success since data shows homogeneity (PH > 0.10), as shown in Table 2. After analysis of the HLA/KIR match and mismatch with kidney and liver graft rejection, the overall results indicate that a match in the HLA-Bw4 and KIR3DL1 type is associated with significantly decreased odds of rejection in kidney and liver transplantation (OR=0.73, PA=0.009).

Table 1. Summary of journals used in the meta-analysis

Authors	Year	Country	Organ	Type of rejection (acute/chronic)	Total no. of participants	Research design	Rejector	Non-rejector
Alam et al.	2015	India	Kidney	Acute	277	Case-control	75	202
Hyeyoung Lee et al.	2016	Korea	Liver	Acute	182	Cohort	53	129
Jafari et al.	2017	Iran	Kidney	Acute	126	Case-control	65	61
Kreijvald et al.	2007	Netherlands	Kidney	Acute	69	Case-control	24	45
Kunert et al.	2007	Germany	Kidney	Acute	224	Case-control	105	119
La Manna et al.	2013	Italy	Kidney	Chronic	126	Case-control	59	67
Legaz et al.	2013	Spain	Liver	Acute	402	Cohort	110	292
Littera et al.	2017	Italy	Kidney	Chronic	174	Case-control	42	132

Table 2. The overall analysis of the HLA/KIR match and mismatching with kidney and liver graft rejection

HLA Type	KIR Type	N	COMPARISONS			
			OR (95% CI)	PA	PH	AM
HLA-C1	KIR2DL2	8	0.81 (0.58, 1.14)	0.23	0.11	F
	KIR2DL3	8	0.87 (0.49, 1.57)	0.65	0.005*	R
	KIR2DS2	5	1.19 (0.48, 1.78)	0.41	0.92	F
	KIR2DS3	3	1.19 (0.79, 1.78)	0.41	0.92	F
HLA-C2	KIR2DL1	8	0.84 (0.64, 1.09)	0.19	0.51	F
	KIR2DS1	7	1.24 (0.83, 1.86)	0.29	0.34	F
HLA-Bw4	KIR3DL1	8	0.73 (0.57, 0.92)	0.009*	0.42	F
	KIR3DS1	3	1.14 (0.67, 1.92)	0.64	0.59	F

Note: N: Number of journals, OR: Odds Ratio, PA: p-value of overall effect, PH: p-value of heterogeneity, AM: Analysis Model, F: Fixed Model, R: Random Model

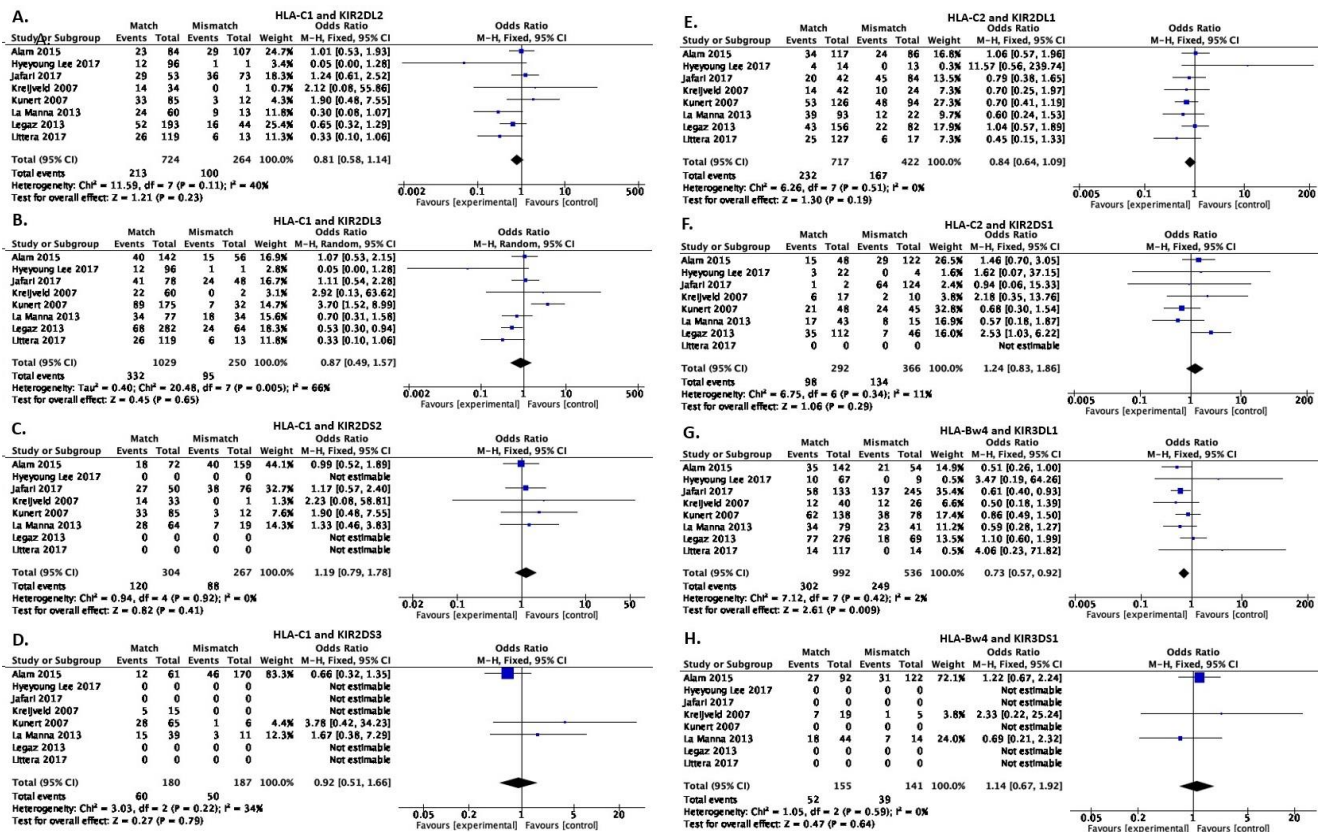


Figure 2. Results of forest plot analysis of eight HLA/KIR combinations showing rejection count, odds ratio, heterogeneity, and overall effect. A. HLA-C1/KIR2DL2; B. HLA-C1/KIR2DL3; C. HLA-C1/KIR2DS2; D. HLA-C1/KIR2DS3; E. HLA-C2/KIR2DL1; F. HLA-C2/KIR2DS1; G. HLA-Bw4/KIR3DL1; H. HLA-Bw4/KIR3DS1

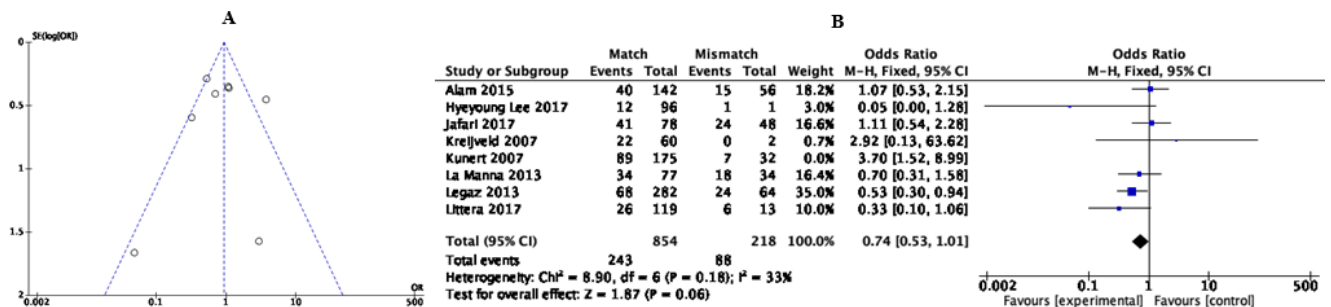


Figure 3. A. Funnel plot depicting the outlier causing heterogeneity in the data; B. Results of post-outlier analysis of HLA-C1 and KIR2DL3 showing rejection count, odds ratio, heterogeneity, and the overall effect

After statistical analyses, HLA/KIR combinations including HLA-C1/KIR2DL2 (OR=0.81, $p=0.23$), HLA-C1/KIR2DL3 (OR=0.87, $p=0.65$), HLA-C1/KIR2DS2 (OR=1.19, $p=0.41$), HLA-C1/KIR2DS3 (OR=0.92, $p=0.79$), HLA-C2/KIR2DL1 (OR=0.84, $p=0.19$), HLA-C2/KIR2DS1 (OR=1.24, $p=0.29$), and HLA-Bw4/KIR3DS1 (OR=1.14, $p=0.64$) showed no significant associations (Figure 2). This result means that matching these HLAs and KIRs does not affect the outcome of allograft transplantation. On the other hand, matching HLA-Bw4/KIR3DL1 showed an odds ratio of 0.73 ($p=0.009$), as shown in Figure 2G. This finding indicates

that correct matching of HLA-B2w4/KIR3DL1 would significantly decrease the odds of rejection of kidneys and liver transplants. Moreover, after thoroughly examining the data, the matching of HLA-C1/KIR2DL3 presented significant heterogeneity ($PH=0.005$). With this, a funnel plot analysis (Figure 3) was performed and showed that the data of Kunert et al. (2007) presented as an outlier. The forest plot analysis was re-run after removing the outlier. The result revealed that the combination is still insignificant (OR=0.74, $p=0.06$) in determining the success of allograft transplantation, as seen in Figure 4.

Discussion

The HLA molecules interact with KIRs so that HLA molecules act as ligands, and KIRs on the NK cell surface act as receptors (Brochot et al. 2016). The degree of contact between KIRs and HLA molecules controls whether activating or inhibitory signals are transmitted, which determines NK cell function (Tuttolomondo et al. 2019). Several types of research have reported on NK cell KIRs, and HLA/KIR combinations in solid organ transplantation, particularly the kidney and liver, but data is scarce and contradictory (Bishara et al. 2005; Tran et al. 2013; Jafari et al. 2017; Lee et al. 2017).

Some studies showing conflicting results point out that the HLA/KIR interaction varies based on the genes of individuals, resulting in significant genetic variety (Khakoo and Jamil 2011). The presence of ligands in recipients that matched the donor's inhibitory KIRs was correlated to better post-transplant outcomes and a lower probability of graft rejection (Zhao et al. 2015). Several studies found a link between HLA/KIR matching and allograft rejection in their investigations (La Manna et al. 2013; Legaz et al. 2013; Alam et al. 2015; Jafari et al. 2017; Littera et al. 2017). That is in contrast to the studies conducted that HLA/KIR mismatching had no significant influence on allograft rejection (Kreijveld et al. 2007; Kunert et al. 2007; Tran et al. 2013; Lee et al. 2017). These varying results led to this meta-analysis to help determine the influence of HLA/KIR match and mismatch on the kidney and liver transplantation outcome.

The role of HLA/KIR matching in Hematopoietic Stem Cell Transplantation (HSCT) has been observed as significant in different studies, which stated that donor selection based on KIR genotypes and HLA allotypes could influence the outcome of the HSCT (Gaafar et al. 2018; Mansouri et al. 2020). It has been established that NK cells reject allografts, as seen in hematopoietic stem cell transplantation (Bishara et al. 2005). T and NK cells of the recipient are considered the primary effector's cells that mediate rejection after allogeneic hematopoietic cell transplantation (Mattsson et al. 2008). Studies have proven that using allogeneic NK cells in the adoptive immunotherapy for HSCT recipients is a relatively safe procedure (Miller et al. 2005; Knorr et al. 2014; Locatelli et al. 2014). With regards to Umbilical Cord Blood Transplantation (UCBT) for acute leukemia, lower incidence of relapse and improved leukemia-free survival in patients who received UCBT from KIR-ligand incompatible donors (specifically HLA-A, HLA-B, and HLA-C) as compared to the KIR-ligand compatible donors with the same HLA groups (Willemze et al. 2009). If the study were to produce the same results in a more extensive series of patients, KIR-ligand incompatibility in the graft-versus-host direction might even be considered a criterion for cord blood donor choice.

The role of NK cells and their receptors in solid-organ transplantations has not been fully defined despite its relevant function, which is the immediate intrusion of an NK cell into the transplanted organ before T lymphocytes (Bishara et al. 2005). The KIR-ligand mismatch could result in a negligible pathogenic impact in solid organ

transplantation. An exception in this little impact was when NK cell effector functions are triggered through interaction with activating KIRs, usually seen when there is a failure to recognize HLA-I alleles on the allograft by KIRs (Moesta and Parham 2012).

Association between HLA-C1 and KIR2DL2/3

This inhibitory receptor, KIR2DL2, has a lysine at position 44. Together with KIR2DL3, they are classified as mediators of HLA-C1 recognition (Moesta and Parham 2012). On the other hand, KIR2DL3 has the amino acid lysine at position 44. It was observed to have less avidity to HLA-C1 allotypes than KIR2DL2 (Moradi et al. 2021). Furthermore, a protective association was observed when receptors KIR2DL2 and KIR2DL3 exhibited a combinatorial effect with their compatible ligand HLA-C1 (Alam et al. 2015). However, the findings of this study showed that combinations of KIR2DL2 and KIR2DL3 with their ligand HLA-C1 are insignificant in determining the fate of kidney and liver grafts within the recipient. This result is in congruence with the findings of Hilton et al. (2012). One possible reason is the cross-reactivity of KIR2DL2/3 to non-canonical HLA-C2 allotypes (Sim et al. 2017). Furthermore, interfaces vary among the patients, affecting the binding strength and possible selectivity of KIR ligands. Hence, possibly rendering it with little to no significance (Hilton et al. 2012).

Association between HLA-C1 and KIR2DS2/3

The KIR2DS2 is considered the "short-tailed, activating counterpart" of KIR2DL2/3. That is because its extracellular immunoglobulin-like domains are distinctly homologous compared to their inhibitory partners. However, tyrosine 45 in KIR2DS2 inhibits it from recognizing HLA-C (Moesta and Parham 2012). On the other hand, the KIR2DS3 is polymorphic and has multiple alleles that encode at least three distinct receptor proteins (VandenBussche et al. 2009). Therefore, both KIR2DS2 and KIR2DS3 are classified as activating KIRs.

A study showed an elevated NK cytotoxicity after allograft was performed in patients with more activating KIR genes specific to HLA-C1 (Vampa et al. 2003). Additionally, a protective effect is produced by activating KIR on acute allograft rejection (Nowak et al. 2010). In contrast, this study showed that the association of HLA-C1 to KIR2DS2/3 in allograft rejection is insignificant and therefore does not affect the organ transplant. The result of this meta-analysis is supported by different studies claiming that activating KIRs has no impact on acute graft rejection (Kunert et al. 2007; Tran et al. 2013).

Association between HLA-C2 and KIR2DL1/DS1

KIR2DL1 has a monomeric integral membrane having two immunoglobulin domains and a long cytoplasmic tail. It functions in inhibiting NK cell activity, which prevents cell lysis. The inhibitory form lies in the extended intracellular portion of KIR2DL1, which contains two characteristic Immunoreceptor Tyrosine-Based Inhibition Motif, which functions in the transduction of inhibitory signals (Bari et al. 2009). On the other hand, KIR2DS1 has

two extracellular Ig domains and a short cytoplasmic tail. The transmembrane domain has a charged lysine residue, while the short cytoplasmic domain has no Immunoreceptor Tyrosine-Based Inhibition Motifs. Due to the presence of a short tail, KIR2DS1 functions in NK cells, triggering or activating NK cell-mediated toxicity (Chewning et al. 2007).

The effect of HLA-C2/KIR2DL1 and KIR2DS1 interaction is still controversial as literature provides contradicting findings (Tran et al. 2013; Lee et al. 2017). However, the presence of HLA-C2 is correlated with more excellent protection from chronic rejection because the interaction of HLA-C2/KIR2DL1 demonstrated a stronger inhibitory signal to NK cells than HLA-C1–KIR2DL2/3 binding (Hanvesakul et al. 2008). Furthermore, the results from a study exhibited that the binding of HLA-C2 and KIR2DL1/DS1 can influence alloreactivity in the transplantation (Lee et al. 2017). On the contrary, studies have stated that HLA-C2 and KIR2DL1/DS1 did not significantly affect solid organ graft survival (Moroso et al. 2011; Tran et al. 2013). Herein, the findings in this study substantially adjoin the claim by showing that the presence of HLA-C2/KIR2DL1 and KIR2DS1 do not influence solid organ transplantation outcomes.

Association between HLA-Bw4 and KIR3DL1

KIR3DL1, an inhibitory receptor, is coded by several alleles in the KIR3DL1/S1 gene. KIR3DL1 can be used as a control in binding to MHC-I peptide complex and MHC-I OC due to its characteristic of being able to bind to MHC-I peptide complex containing Bw4 epitope precisely and not binding to MHC-I peptide complex containing Bw6 epitope (Burian et al. 2016).

The decreased number of the inhibitory receptor KIR3DL1 affects signal transduction on both activating and inhibiting receptors and unsuccessful inhibition of activating signals, which leads to increased cytotoxic function of NK cells. Also, HLA-Bw4**A* and KIR3DL1 association was observed to be lower in number in Acute Kidney Allograft Rejection than function. Their findings indicate that the presence of HLA-Bw4/KIR3DL1 improves the result of kidney grafts in the long term (Jafari et al. 2017). These results are similar to our findings that a correct combination of HLA-Bw4 and KIR3DL1 is correlated with decreased risk of kidney and liver allograft rejection. Another study also had results aligned with our findings. They studied specific alleles of KIR3DL1, namely KIR3DL1*00402/ and KIR3DL1*0010101/HLA-Bw4, and found that they have a significant effect on decreased kidney allograft rejection (Prakash et al. 2017). In addition, patients with chronic rejection have been observed to have a reduced presence of the HLA-Bw4/KIR3DL1 combination rather than patients with stable graft function (Littera et al. 2017). The protective effects of HLA-Bw4/KIR3DL1 were also demonstrated in a study, showing the highest rate of kidney allograft survival (~11 years) (Alam et al. 2015).

Association between HLA-Bw4 and KIR3DS1

KIR3DS1 is the activating counterpart receptor of KIR3DL1. KIR3DS1 triggers the NK cell cytotoxicity and

synthesizes interferon- γ (Carr et al. 2007). The inherited low expression of KIR3DS1 ligand does not allow recognition of HLA-Bw4 in a physiological context. Recognition can only occur, moreover, in instances such as malignancy and viral infections where NK cells are activated (Moya-Quiles et al. 2003). This study revealed that matching between HLA-Bw4 and KIR3DS1 is insignificant in determining the fate of kidney and liver transplants. However, contrary to the findings of this meta-analysis, a study showed that combinations of the HLA ligand and KIR receptor are significant when associated with kidney allograft rejection, particularly the KIR3DS1*01301 haplotype (Prakash et al. 2017).

Several studies have claimed HLA/KIR compatibility contributes to positive results, implying that when activation of KIR gene differences is lower and matched, there is a decreased risk of acute allograft rejection (La Manna et al. 2013; Legaz et al. 2013). The results of this meta-analysis, however, contradicted the claim. The research involved in this study which has been subjected to analysis demonstrated that HLA/KIR match and mismatch for HLA-C1 and KIR1DL2/3 and KIR1DS2/3; HLA-C2 and KIR2DL1/DS1; and HLA-Bw4 and KIR3DS1, do not provide a significant impact on the risk of kidney and liver transplantation rejection while HLA-Bw4 and KIR3DL1 interaction could cause a decreased risk of rejection. In line with this, several researchers have shown similar findings demonstrating that HLA/KIR matching does not influence the risks of kidney and liver transplantations (Moya-Quiles et al. 2003; Bishara et al. 2005; Tran et al. 2005; Moroso et al. 2011; Tran et al. 2013). Furthermore, there is no clear association between the predicted alloreactivity of NK cells and allograft survival (Van Der Touw and Bromberg, 2010).

Moreover, no established evidence directly addresses the varying results. However, probable explanations can be found in published articles. The variation of mRNA expression in different KIR genes could be why different studies have conflicting results, as they do not consider mRNA expression. Different mRNA expressions of KIR genes could have varying effects on kidney graft survival, investigating the mRNA expression of rejection and non-rejection cases (Prakash et al. 2017). Their findings include that HLA-Bw4/KIR3DL1*0010101 expressions are decreased in rejection cases, but HLA/KIR3DL1*00401 and HLA/KIR3DL1*00402 expressions are increased. Moreover, genetic diversity may impact the relevance of KIR ligands' action in kidney and liver organ donation, as HLA/KIR interaction varies depending on the genes of individuals (Khakoo and Jamil, 2011). In addition, HLA/KIR combinations may be affected by cross-reactivity, such as the interaction of KIR2DL3 with HLA allotypes other than HLA-C1 (Sim et al. 2017). Ethnic differences may play a role in the clinical effects of KIR ligand matching (Lee et al. 2017). This study found that Koreans have a lower frequency of the HLA-2 allele when compared with Caucasian individuals, where it is more predominant. Moreover, when KIR gene frequency was analyzed, it was found that Koreans have significantly lower the frequency of KIR2DL2, KIR2DL5, KIR2DS2,

and KIR2DS3 while having a higher frequency of KIR2DL3 when also compared with Caucasian individuals. These ethnic differences in HLA frequency and KIR genotypes could yield different results between the connection of HLA/KIR matching and its relevance in kidney or liver allograft rejection.

In conclusion, this meta-analysis was conducted to shed light on the contradictory findings of different studies on the effect of KIR and HLA matching on solid organ transplantation, particularly kidney and liver transplants. The results of this analysis conclude that the HLA/KIR, specifically HLA-C1/KIR2DL2, HLA-C1/KIR2DL2, HLA-C1/KIR2DS3, HLA-C2/KIR2DL1, HLA-Bw4/KIR3DL1, HLA-C1/KIR2DS2, and HLA-C2/KIR2DS1 match and mismatch mainly had no significant impact on the success rate of kidney and liver transplantation. However, the correlation between HLA-Bw4 and KIR3DL1 significantly impacted the decreased risk of allograft transplantation rejection, which can be used to improve prognosis. Furthermore, inhibitory KIRs may result in a higher allograft survival rate, whereas activating KIRs may result in transplant rejection. Lastly, the genetic variation of the KIR ligands might also influence the relevance of its function in kidney and liver organ transplantation. Cross-reactivity, such as the interaction of KIR2DL3 to HLA allotypes aside from HLA-C1 and weakened expression of the KIR-ligand such as KIR3DS1, could influence the combinations of HLA/KIR and its corresponding transplantation outcomes. Ethnic variations, moreover, could also play a role in the clinical impact of KIR-ligand matching.

For future studies, it is recommended to include more data from studies involving HLA/KIR matching in kidney/liver graft rejection to form a larger sample size and generate better results. Additionally, the number of research articles for kidney and liver transplantation should be much more to provide better findings for both kidney and liver transplantation. A standardized criterion for included studies could also benefit future studies. Future studies should also consider the variation of mRNA expression of KIR genes. There are still other KIRs not often studied; hence, future researchers might opt to delve into their matching with specific HLA. Testing for other organs, such as the heart or lungs, to better determine the effect of HLA/KIR matching could also improve the scope of the study. Producing similar research regarding different transplantable organs can help standardize the results of the impact of HLA/KIR matching on allograft rejection.

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