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Review article

Immunosuppression of HLA identical living-donor kidney transplant recipients: A systematic review

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ABSTRACT

Background: Kidney transplant (KT) recipients of HLA identical siblings (HLAid) have lower immunological risk, but there are no specific recommendations for immunosuppression. Our aim was to analyze evidence about results from HLAid living-donor recipients under different immunosuppression in the current era of immunological risk assessment.

Methods: Systematic review of studies describing associations between outcomes of HLAid living-donor KT recipients according to their immunological risk and applied immunosuppression.

Results: From 1351 studies, 16 (5636 KT recipients) were included in the analysis. All studies were retrospective, ten comparing immunosuppression strategies, and six immunological risk strata. Of those ten, six studies were published in 1990 or earlier and only three included tacrolimus. The evidence is poor, and the inclusion of calcineurin inhibitors does not demonstrate better results. Furthermore, only few studies describe different immunosuppression regimens according to the patient immunological risk and, in general, they do not include the assessment with new solid phase assays.

Conclusions: There are no studies analyzing the association of outcomes of HLAid KT recipients with current immunological risk tools. In the absence of evidence, no decision or proposal of immunosuppression adapted to modern immunological risk assessment can be made currently by the Descartes Working Group.

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1. Introduction

Already from the first successful kidney transplant (KT) that was performed between two male twins [1], results have been consistently better among those KT recipients with higher vs. lower human leukocyte antigen (HLA) matching [2–4]. The best evidence is represented by KT recipients from HLA identical (HLAid) donors, who consistently have lower rejection rates and greater graft survival compared to other KT patients [5–7].

KT recipients from an HLAid donor are considered to have lower immunological risk, and, in accordance, they have been prescribed less potent immunosuppression regimens [8,9]. However, there are no universally accepted recommendations or guidelines on the management of immunosuppression in these recipients, and physicians usually act according to local protocols or even personal clinical viewpoints. Furthermore, studies describing immunosuppressive regimens among HLAid KT recipients are mostly several decades old [10–14], and apparently, no exploration of the optimal immunosuppression in these recipients in the modern era of immunosuppressant protocols has been done so far.

It can be hypothesized that some of those categorized as HLAid KT recipients in old studies were not actually HLAid if they would be evaluated with more recent molecular HLA typing. Also, immunological risk has moved to be based on HLA antibody detection with solid phase assays rather than with the older serological techniques [15–17]. In this setting, recipients qualified as having low immunological risk in 1980 would be different from those with low immunological risk in 2023. Besides, recently discovered non-HLA antigens and antibodies might be responsible for the unexplained variation in observed immune-modulated outcomes among recipients of HLAid KT [18–21].

The purpose of this study was to analyze associations between outcomes of HLAid living-donor (siblings) KT recipients and immunosuppression in the current era of immunological risk assessment. As outcomes, we addressed rejection rate, patient survival and graft survival; we mainly focused on the following mediators: a) the type and intensity of immunosuppression received; b) the immunological risk; and c) whether the immunosuppression received was adapted to the presumed immunological risk.

2. Methods

Relevant studies were obtained from a systematic literature search. The literature search included MEDLINE (within the OVID system) and Cochrane Central Register of Controlled Trials (CENTRAL) to March 2021, as well as clinicaltrial.gov (Supplemental Table 1). The protocol of this systematic review is published in PROSPERO register (#CRD42023444381). We have followed the PRISMA Guidelines to report this systematic review [22].

We included studies according to the following criteria: all randomized clinical trials or observational studies including patients older than 18 years receiving a kidney from a living- donor (sibling but not identical twins), who have 0 mismatches and which report data on the outcomes of interest that was based on perceived immunological risk or different immunosuppressive regimens. We excluded reviews, case reports, experimental studies, and articles we could not find from all reasonable sources (very old articles). We also included handpicked studies from reference lists of included papers and studies from proceedings or abstracts. The titles and abstracts were screened independently by four reviewers (MJPS, DR, DM, and MC) who discarded studies based on in and exclusion criteria. Discrepancies were cleared by JP. The same reviewers assessed retrieved abstracts, and, if applicable, the full text of these studies was read to determine which studies satisfy the inclusion and exclusion criteria. Data extraction was carried out by NM and checked by MJPS for each of the review sections. Relevant data such as patient survival, graft survival and acute rejection rate, and data on immunological risk and immunosuppressive regimen were extracted and tabulated.

A relative odds analysis summarizing the true effect of the different variables on the outcomes has been done when data could be obtained from the reports.

For dichotomous outcomes (mortality, graft failure, and acute rejection), results were expressed as odds ratios with 95% confidence intervals. As none of the analyses resulted in any significant differences, forest plot figures are shown in the Supplemental material.

Heterogeneity was examined firstly by visual inspection of forest plots. Secondly, we assessed statistical heterogeneity, by using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [23]. Risk of bias was assessed independently by two authors using the ROBINS-I tool [24].

3. Results

We retrieved 1158 reports, of which 1142 were discarded due to: wrong population [$n = 949$], wrong intervention [$n = 87$], not available in English [$n = 61$], ongoing trials [$n = 42$] or duplicates [$n = 3$], (Fig. 1). For the meta-analysis, and according to the prespecified protocol, data were grouped according to different immunosuppressive strategies (azathioprine + prednisone vs. azathioprine alone ($n = 2$ reports), azathioprine vs. calcineurin inhibitor (CNI) ($n = 4$), azathioprine or mycophenolate mofetil (MMF) vs. azathioprine or MMF + CNI ($n = 4$). Only three studies included tacrolimus in the immunosuppressive regimen. Six additional studies were considered for the tables but not included in the forest plot analysis since results were not disaggregated according to the immunosuppression received. The 16 studies finally considered for the analysis comprised: studies comparing outcomes according to different immunosuppression strategies: azathioprine +/− steroids ($n = 2$), azathioprine +/− steroids vs. therapies including CNI ($n = 8$) (Fig. S1), or studies comparing outcomes according to the immunological risk ($n = 6$): low (non-transfused, patients without acute rejection, PRA <5%, no pregnancy, first transplant) vs. high (transfused, with acute rejection, PRA > 5, pregnancy, retransplant).

The first study comparing results among different immunosuppression schemes concerning LD HLAid KT recipients was performed in 1987. Flechner et al. [10] found better graft survival with cyclosporine A (CsA) compared with azathioprine (3y 96 vs. 88%). Several subsequent studies confirmed the benefit of CNI over a regimen with only antimetabolites with regards to graft survival [3,13,14,25,26], patient survival [12–14], as well as acute rejection rates [13,26]. The most recent study, Verghese et al. [8] also reported a patient survival benefit with tacrolimus over azathioprine (5y 95 vs. 89%). Table 1.

Only three studies reported results based on different immunosuppression protocols according to the recipients' immunological risk. In 1989, Hodge et al. considered transfused patients with low immunological risk, and they received azathioprine as immunosuppression treatment. The risk of rejection was much higher compared to non-transfused recipients who received CsA (50 vs. 0%) [27]. De Mattos et al. adapted the immunosuppression schema according to different sensitization events, and CsA was administered in 10 "high immunological risk recipients", compared to 98 recipients who received azathioprine. The authors found poorer results (10y graft survival 33% among those with ≥2 acute rejection episodes vs. 86% if no rejection) among those recipients who were sensitized (except for transfusions, which were considered protective for acute rejection) [28]. More recently, Keitel et al. analyzed their results in first KT recipients (who received azathioprine) vs retransplant recipients (who received CsA). The CsA group showed lower rates of acute rejection (14.7 vs. 39.4%) and higher graft survival (5y 94 vs. 78%) [29].

Regardless of immunosuppression, HLAid KT recipients with higher immunological risk have been reported to have worse graft [9,18,30–32] and patient survival [18].

Heterogenicity between studies comparing AZA vs CNI was low in all of the outcomes studied. However, a high heterogenicity was detected

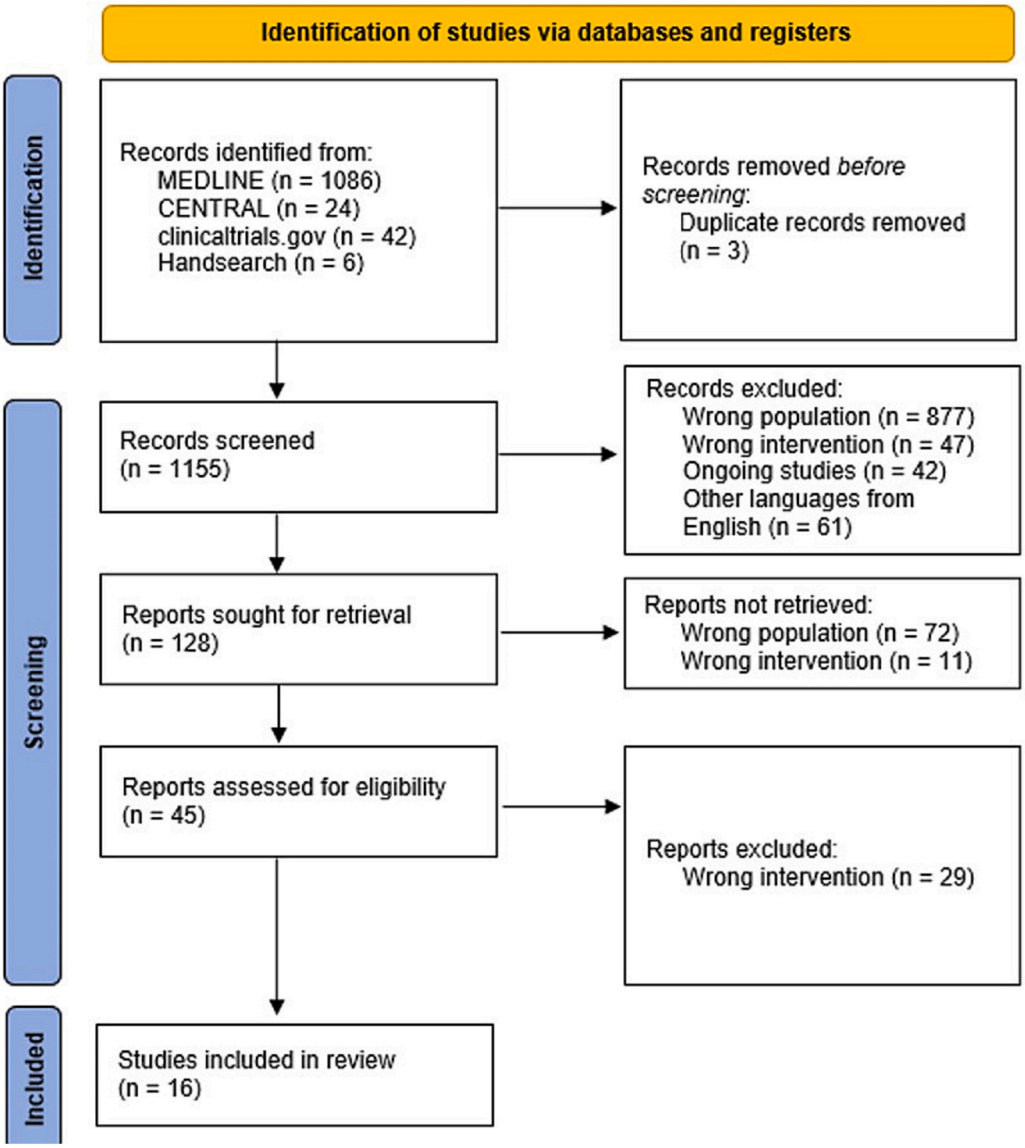

Fig. 1. PRISMA flow diagram.

between studies that compared AZA/MMF vs AZA/MMF + CNI, especially in the outcome of graft loss. Reasons for increased heterogenicity might be differences in the selection of the population to receive each immunosuppressive regimen, e.g. all people receiving a second or third graft were treated with CNI in Keitel et al. [29] Due to the low number of studies, we could not perform a subgroup analysis.

The overall risk of bias in the studies included in the systematic review is moderate or serious (Fig. 2).

Therefore, we resume that in HLAid KT: 1) CNI seem to add a benefit with regards to acute rejection rates and survival over azathioprine-based immunosuppression regimens, although evidence from the literature is not strong enough to confirm these data; and 2) recipients with higher immunological risk have worse outcomes after KT.

4. Discussion

4.1. What has changed in the last 10 years regarding immunological risk assessment

The assessment of immunological risk has markedly changed during the past 30 years and the impact on HLAid LD KT recipients should not be different. In 1986, Norman et al. described lower rates of acute rejection and better graft survival among those HLAid KT recipients who had received transfusions vs. those who had not prior to transplantation [30]. The authors claimed a beneficial effect of pretransplant third-party blood transfusion on allograft rejection. Later, Opelz et al. described how outcomes differed between HLAid KT recipients depending on their PRA level, calculated by complement-dependent lymphocytotoxicity [18]. Recipients with higher PRA had poorer patient and graft results. Other reports have accounted for inferior results among recipients with acute rejection vs. rejection-free recipients, which could be a surrogate of the patient immunological risk background [9,31]. In addition, recipients with previous sensitization events have also shown worse results after HLAid KT[32].

Two major issues arise in the era of new immunological risk assessment tools. First, these studies do not provide enough-quality evidence or knowhow regarding the actual immunological risk (and, therefore, the most suitable immunosuppression to use) of HLAid KT recipients with previous sensitization events (transfusions, pregnancies, previous transplants) and/or patients who display high levels of anti-HLA Abs (obviously non-donor specific, as the donor is HLA identical). The revolution of molecular HLA typing and solid phase assays techniques

Table 1
Studies of HLA identical KT recipients reporting outcomes based on immunosuppression used or patient's immunological risk.

Author Journal, year	Type of study	Number of HLA id-KTR recipients	Mean Follow-up	Pre-KT Standard immunological risk work-up	Criteria for risk assessment	Induction IS	Maintenance IS	AR (%)	Graft survival (%)	Patient survival (%)
Studies of HLAid KT recipients: immunosuppression and outcomes (not reporting if immunological risk influenced immunosuppression regimen)										
Norman DJ Transplantation, 1986&	Prospective cohort with historical controls	Transfused preKT: 15 Non-transfused preKT: 18 Total: 33	30 months.	Test: not specified Immunological risk: Transfused preKT (n = 15); Non-transfused preKT (n = 18)	–	None	AZA + PRED Transfused preKT: high PRED (n = 4), low PRED load (n = 8), low PRED no load (n = 3). Non-transfused preKT: high PRED (n = 2), low PRED load (n = 11), low PRED no load (n = 5)	Transfused preKT: 16% Non-transfused preKT: 61%	Transfused preKT: 3y 89% Non-transfused preKT: 3y 75%	Not specified
Flechner SM Transplantation Proceedings, 1987#	Retrospective cohort	48	4.5 years	Not specified	–	None	AZA + PRED (since 1979): 20 CsA + PRED (since 1981): 28	Not specified	AZA + PRED: 3y 88%, 4.5y 76% CsA + PRED: 3y 96%, 4.5y 96%	AZA + PRED: 4.5y 95% CsA + PRED: 4.5y 96%
Stratta RJ Transplantation, 1988#	Prospective cohort with historical controls	Steroid withdrawal: 12 Control: 12 Total: 24	Steroid withdrawal: 9,1 months Control: 12 months	Test: CDC PRA Immunological risk: not specified	–	None	Steroid withdrawal POD 12: CsA + PRED Control: PRED + AZA	Steroid withdrawal: 41.7% Control: 41.7%	9.1mo steroid withdrawal: 100% 12mo control: 100%	9.1mo steroid withdrawal: 100% 12mo control: 100%
MacDonald AS Transplantation Proceedings, 1989#	Retrospective cohort	48	1–6.5 years	Not specified	–	None	AZA + PRED: 15 CsA + PRED: 21 CsA monotherapy: 12	Not specified	AZA + PRED: 1y 100% 3y 86% CsA + PRED: 1y 100%, 3y 100% CsA monotherapy: 1y 100%, 3y 94%	AZA + PRED: 1y 100%, 3y 93% CsA + PRED: 1y 100%, 3y 100% CsA monotherapy: 1y 100%, 3y 100%
Sumrani M Am J Kidney Dis, 1990#	Retrospective cohort	AZA + PRED (1972–83): 72 CsA + PRED (1983–89): 34 Total: 106	AZA + PRED: 5 years CsA + PRED: 2.9 years	Test: CDC* XM and MLC Immunological risk: negative XM and MLC	–	None	AZA + PRED (1972–83) CsA + PRED (1983–89)	AZA + PRED: 2.8% CsA + PRED: 0%	AZA + PRED: 1y 85% CsA + PRED: 1y 97%	AZA + PRED: 1y 91%, 5y 82% CsA + PRED: 1y 100%, 5y 96%
Van Buren D Transpl Proceedings, 1994#	Cohort	88	5 years	Not specified	–	ATG	AZA + PRED (1980–92): 53 AZA + PRED+CsA (1986–92): 35	Not specified	At 1 and 5 years: AZA + PDN: 96%, 77% AZA + PDN + CsA: 100%, 90%	At 1 and 5 years: AZA + PDN: 100%, 94% AZA + PDN + CsA: 100, 91%
D'Alessandro AM Annals of surgery, 1995**#	Retrospective cohort	PreCsA era: 49 CsA era: 108 Total: 157	1966–1994	Test: CDC XM and CDC PRA Immunological risk: PRA <40% or > 40% and negative XM *n of patients in each group not specified	–	None	preCsA era (1966–86): AZA + PRED CsA era (1986–94): AZA + PRED + CsA	Not specified	preCsA era: 8y 79.6% CsA era: 8y 91.7%	Not specified

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Table 1 (*continued*)

Author Journal, year	Type of study	Number of HLA id-KTR recipients	Mean Follow-up	Pre-KT Standard immunological risk work-up	Criteria for risk assessment	Induction IS	Maintenance IS	AR (%)	Graft survival (%)	Patient survival (%)
MacDonald AS Transpl Proceedings, 1997**#	Retrospective cohort	90	5–10 years	Not specified	–	None	AZA: 18 CsA: 72	Not specified	AZA: 12y 50% CsA: 12y 84%	AZA: 12y 88% CsA: 12y 95%
Al-Kerithy M Transpl Proceedings, 2001**&	Retrospective cohort	Group 1 (without AR): 121 Group 2 (with AR): 20 Total: 141	15 years	Test: CDC* PRA Definition: Group 1 (w/o AR): PRA 0% ($n = 81$), 1–50% ($n = 30$), >50 ($n = 10$). Group 2 (with AR): PRA 0% ($n = 17$), 1–50% ($n = 2$), >50% (n = 1)	–	Not specified	Group1: 7% AZA / 93% CsA Group 2: 25% AZA / 75% CsA	14,2%	Group 1: 1y 100%, 10y 87%, 15y 80% Group 2: 1y 95%, 10y 72%, 15y 24%.	Group 1: Global survival 92% Group 2: Global survival 80%
Peddi VR Transplantation Proceedings, 2001#	Retrospective cohort	28	9 years	Not specified	–	None	AZA + PRED (prior 1990): 15 AZA + PRED+CsA (1990–96): 13	AZA + PRED: 47% AZA + PRED+CsA: 0%	AZA + PRED: 10y 69% AZA + PRED+CsA: 10y 70%	Not specified
Opelz G Lancet, 2005**&	Retrospective cohort	No PRA: 3001 1–50% PRA: 803 >50% PRA: 244 Total: 4048	10 years	Test: CDC-PRA Definition: PRA 0% ($n = 3001$), 1–50% ($n = 803$), >50% ($n = 244$)	–	None	CsA: 2712 (67%) TAC: 122 (3%) IS without CNI: 1214 (30%)	Not specified	0% PRA: 10y 82.5% 1–50% PRA: 10y 75.3% >50% PRA: 10y 63.1%	No PRA: 10y 86.2% 1–50% PRA: 10y 81.7% >50% PRA: 10y 81.9%
Verghese P Nephrology Dialysis Transplantation, 2014#	Retrospective cohort	Era 1 (up to 1984): 114 Era 2a (1984–99): 262 Era 2b (1999–2011): 77	Era 1: 20 years Era 2a: 20 years Era 2b: 5 years	Test: CDC* peak PRA Definition: Era1: peak PRA 0% ($n = 79$), 1–50% ($n = 23$), 51–100% ($n = 12$) Era2a: peak PRA 0% ($n = 199$), 1–50% ($n = 42$), 51–100% ($n = 21$) Era 2b: peak PRA 0% ($n = 59$), 1–50% ($n = 14$), 51–100% (n = 4)	–	Era 1: ALG Era 2a: ATG Era 2b: ATG	Era 1: AZA + PRED ($n = 114$) Era 2a: TAC + PRED+MMF ($n = 262$) Era 2b: TAC + MMF ($n = 77$)	Era 1: 0% Era 2a: 1.1% Era 2b: 0%	At 1, 5, 10, 20, 30 years: •Era 1: 98%, 96%, 86%, 76%, 74%. •Era 2a: 99%, 93%, 88%, 73%, N/A. •Era 2b: 100%, 94%, N/A, N/A, N/A.	At 1, 5, 10, 20 years: Era 1: 96%, 89%, 82%, 60% Era 2a: 98%, 95%, 84%, 65% Era 2b: 96%, 93%, N/A, N/A.
Ossman R Transplantation, 2020**&	Retrospective cohort	AR group: 21 Non-AR group: 142 Total: 163	10 years	Test: PRA, ELISA or Luminex class I/II Immunological risk: not specified	–	19,6% Polyclonal 38% Anti IL2 Receptor 31.3% Solumedrol 11.1% no induction	Steroids (64.4%) TAC (46.6%) CsA (25.1%) Antimetabolite (88%) CNI withdrawal: AR group (n = 9), non-AR group ($n = 11$)	12.9%	10y 77% AR group 10y 85.4% non-AR group	1y 100% AR group 1y 99.93% non-AR group
Studies of HLAid KT recipients: immunosuppression and outcomes (considering immunological risk for immunosuppression regimen)										
Hodge EE Journal of Urology, 1989&	Non-randomized trial	CsA group: 16 AZA group: 18 Total: 34	CsA group: 18 ± 1.7 months AZA group: 89 ± 7 months	Test: CDC* XM and CDC* PRA Immunological risk: peak PRA ≥ 60% ($n = 0$), mean peak PRA = 9.9%, mean current PRA = 8.6%	Transfused preKT	None	Non-transfused preKT: CsA + PRED Transfused preKT: AZA + PRED	CsA/non-transfused group: 0% AZA/ transfused group: 50%	CsA/non-transfused group: 1y 100% AZA/ transfused group: 1y 89%	CsA/non transfused group: 1y 100% AZA/transfused group: 1y 94%

(*continued on next page*)

Table 1 (*continued*)

Author Journal, year	Type of study	Number of HLA id-KTR recipients	Mean Follow-up	Pre-KT Standard immunological risk work-up	Criteria for risk assessment	Induction IS	Maintenance IS	AR (%)	Graft survival (%)	Patient survival (%)
de Mattos AM Clinical Transpl, 1999**&	Retrospective cohort	108	130.9 ± 58.2 months	Test: CDC* peak PRA Immunological risk: 1st KT, peak PRA <2% (*n* = 83), 2–10% (n = 11), 11–50% (*n* = 10), >50% (n = 4)	Non-transfused preKT or multiple rejections	None	AZA + PRED (*n* = 98) CsA + PRED (n = 10): multiple rejections in dual therapy (n = 2), intolerance to AZA (n = 5), none transfused preKT (n = 3)	Total: 46% Peak PRA < 2% (n = 83): 44% Peak PRA ≥ 2% (*n* = 25): 52% Non-transfused preKT (n = 23): 61.9% Transfused preKT (*n* = 84): 43.3% No pregnancy preKT (n = 14): 57.1% Pregnancy preKT (*n* = 38): 47.8%	Total: 5y 88%, 10y 76% No AR (*n* = 58): 10y 86% Single AR (n = 38): 10y 71% ≥2 AR (n = 12): 10y 33% Peak PRA < 2% (n = 83): 10y 76% Peak PRA ≥ 2% (n = 25): 10y 75% Non-transfused preKT (n = 23): 10y 63% Transfused preKT (n = 84): 10y 78% No pregnancy preKT (n = 14): 10y 86% Pregnancy preKT (n = 38): 10y 76%	Total: 5y 92%, 10y 82%
Keitel E Transplantation Proceedings, 2003#	Retrospective cohort	67	0.5–5 years	Not specified	Retransplant	None	No retransplants depends on era AZA + PRED (before April 1995): 33 AZA + PRED+CsA (1995–2000): 34 Retransplants: AZA + PRED+CsA	AZA + PRED: 39.4% AZA + PRED+CsA: 14.7%	AZA + PRED: 5y 78% AZA + PRED+CsA: 5y 94%	Not specified

CDC, complement dependent cytotoxicity; HLA, human leukocyte antigen; iHLA, identical HLA; KT, kidney transplantation; MLC, mixed lymphocyte culture; MLR, mixed lymphocyte reaction; PRA, panel reactive antibodies; XM, crossmatch; ALG, antilymphocyte globulin; ATG, antithymocyte globulin; AZA, azathioprine; CNI, calcineurin inhibitors; CsA, cyclosporine; EVR, everolimus; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; KT, kidney transplantation; MMF, mycophenolate mofetil; mo, months PRED, prednisone; TAC, tacrolimus; y, years.

* If test was not specified, CDC was assumed as the technique.

** Studies not included in the meta-analysis; #, studies comparing outcomes according to different immunosuppression strategies; &, studies comparing outcomes according to different immunological risk.

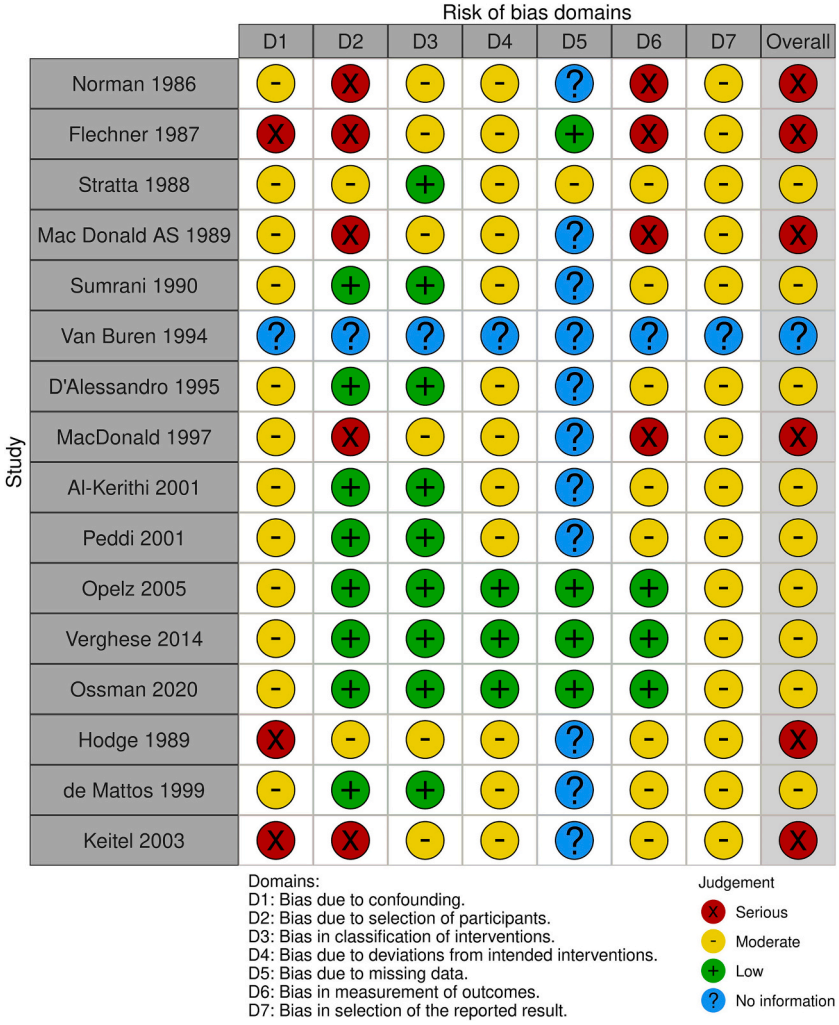

Fig. 2. Risk of bias of the included studies.

[15–17] have built a completely different scenario where all that we allegedly knew about HLAid KT recipients and their outcomes should be questioned. Secondly, new actors with a potentially critical role in HLAid KT immunity have arrived in the past few years. In 2005, Opelz et al. pointed for the first time at non-HLA immunity as relevant for long-term graft survival among LD HLAid KT recipients [18]. The authors claimed that lymphocytotoxic antibodies expressed as patients' PRA were a surrogate of non-HLA immunity, meaning that non-HLA antibodies could have triggered the antigen-antibody reaction. However, the study considered HLAid based on A, B and DR loci matches and typing was performed by serology. Therefore, we could speculate if the impact of high PRA observed in some recipients was the result of non-HLA immunity, or, on the contrary, the accuracy of the techniques at that moment could have missed essential HLA antibodies responsible for the antigen-antibody reaction. It has been shown that donor-recipient pairs matched at A, B, and DR have a >80% probability of being mismatched at DP loci [32]. Nevertheless, in the past few years, well-described non-HLA or minor antigens have been reported as relevant in graft loss and rejection among KT recipients [19–21], so they most likely contributed to the lower outcomes of HLA sensitized patients, with HLA sensitization being here a surrogate marker for the presence of non-HLA donor-specific Abs.

4.2. What we are supposed to change given what we already know and changes in the immunological risk assessment

So far, we established that the outcomes are better: 1) in lower immunological risk recipients; 2) if CNI is used in place of azathioprine in case of high immunological risk (despite the lack of strong evidence in the literature). More recently, due to the spread of HLA molecular typing and solid phase assays to detect HLA antibodies as well as the potential role of non-HLA immunity, it seems natural to investigate the best immunosuppression strategy to be administered to these recipients, adapted to an up-to-date immunological risk assessment. However, research has not evolved that far in this setting. The most important fact to highlight now is the lack of evidence regarding immunosuppression strategies among LD HLAid KT recipients in the modern era.

Table 1 summarizes the studies comparing different immunosuppression strategies over the last 25 years. From a total of 16 studies included in this review, 10 described outcomes of HLAid KT recipients with different immunosuppression protocols [3,8,10–14,25,26,29]; and 6 reported outcomes according to different immunological risk [9,18,27,28,30,31]. Moreover, only one study included new solid phase assay techniques for immunological risk assessment, but this information was not used in the study to adapt immunosuppression [9].

Therefore, immunosuppression practices in HLAid KT recipients are based on local protocols and clinical experience, as there is no evidence to support how, when and in which recipients, immunosuppression should be tapered or withdrawn. Induction therapy was usually not used in old studies, while the most recent ones have reported both anti-lymphocyte therapies [8,9,14] and anti-IL2 monoclonal antibody use [9]. Steroid withdrawal is described in two studies: one from 1989 showing similar results between recipients who withdrew steroids and those who kept them as part of their immunosuppression protocol [11], and a more recent one where outcomes were also similar compared with a retrospective cohort [8]. In terms of CNI withdrawal, only one study reported a higher risk of rejection among those recipients who withdrew CNI[9].

Immunosuppression policies among LD HLAid KT recipients have not changed following the advances in immunological risk assessment.

5. Conclusion: Immunological risk and immunosuppression stratification

Few studies have reported outcomes based on different immunosuppression strategies and/or different patient's immunological risk, and no studies have analyzed the impact on relevant outcomes using current immunological assessment techniques. Considering the previous findings and the lack of evidence, we are unable to provide a consensus opinion regarding immunosuppression stratification in HLAid KT recipients.

However, we should be able to establish the immunological risk of our patients as much detailed as possible. Despite scientific evidence is mostly non-existing, two different aspects may be considered before establishing immunological risk (and, in accordance, immunosuppression strategy) in an HLAid KT candidate:

- How are we going to define HLA identity?
- What is the HLA sensitization degree of my candidate?

HLAid should be defined by molecular HLA typing and include 11 identical loci (HLA-A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPA1 y DPB1). Then, a detailed immunological history (including all the potential sensitization events) should be registered, and a solid phase assay (including single antigen bead test) should be performed. Different categories of immunological risk may arise from these studies.

The sensitization degree may be estimated with calculated PRA (cPRA). Usually, cPRA below 50% is considered low-medium sensitization, and > 50% hypersensitization. However, cPRA >50% could be related to HLA antibodies against very common antigens, such as anti-A2 plus anti-A3 or anti-A11. This may occur in a recipient who does not have any DSA- like HLAid-, even below the lowest threshold, or in a patient in whom we have ruled out DSA after full high resolution HLA typing of the donor with multiple sera.

Although there are two available kits directed towards detection of antibodies against non-HLA antigens (www.immucor.com, Life code non-HLA and One Lambda www.onelambda.com), they have not demonstrated consistent influence on graft outcomes, are not yet widely used in the clinical practice and there are no data about risk stratification according to these potential findings.

Once the immunological risk of a HLAid KT recipient is established, immunosuppression may vary according to each center, although usually lower than non-HLAid recipients. We urgently need studies performed on HLAid recipients in the current era of both immunological risk assessment and immunosuppression.

Author's contributions

MC and JP conceptualized the study. NM did the literature search. MJPS, DR, DM, and MC performed the literature review. NM extracted and pooled the data. MJPS, NM, MC, and JP wrote the manuscript. All the authors gave their insight and contributed to the manuscript development.

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Declaration of Competing Interest

The results presented in this paper have not been published previously in whole or part. The authors of this study declare no conflict of interest.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2023.100787.

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