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Systematic Review

Can Single Nucleotide Polymorphisms Be Used to Predict Post-Transplant Infection after Kidney Transplant? A Systematic Review

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ABSTRACT

Background: Post-transplant infections are a major cause of morbidity and graft dysfunction in kidney recipients. Genetic polymorphisms involved in immune responses may influence susceptibility to these infections.

Objective: This systematic review aimed to investigate the relationship between genetic polymorphisms and the risk of bacterial, fungal, and viral infections after kidney transplantation.

Methods: The databases PubMed (Medline), ProQuest, Scopus, and Web of Science were systematically searched from 1990 to 2022 for English studies examining associations between SNPs and post-transplant infections in kidney recipients. Studies with genotype frequencies for infected and non-infected groups were included. Data were extracted on study characteristics, SNPs investigated, infection types, and associations between SNPs and infection risk.

Results: In total, 3,189 studies were identified during the primary search, and 3,172 studies were excluded by duplicate, title/abstract, and screening. Finally, 17 articles were included in the systematic review. Among 17 eligible studies, 31 genes and 55 SNPs were extracted. Of these 55 SNPs, only 6 SNPs included rs1878672 (*IL-10*), rs1800896 (*IL-10*), rs16944 (*IL-1β*), rs2430561I (*IFN-γ*), rs733618 (*CTLA4*), and rs1800629 (*TNF-α*) were evaluated in more than one study, and the rest of the SNPs were assessed only in one study. Of these 6 SNPs, rs16944 (*IL-1β*), rs2430561 (*IFN-γ*), and rs1800471 (*TGF-β*) had significant association with post-renal transplant infection. However, the results were contradictory across studies.

Conclusion: Current evidence suggests certain SNPs may influence susceptibility to post-transplant infections, but findings are inconsistent. Larger, well-designed studies investigating the relationships between genetic factors and specific infection types are needed to understand the role of SNPs better and to guide personalized management strategies for transplant recipients.

KEYWORDS: Single nucleotide polymorphisms; Kidney, Renal function; Transplantation; Infection

INTRODUCTION

The kidney transplant process has undergone many changes since the first transplant. Significant advances in surgical techniques and induction and maintenance immunosuppressive regimens have improved allograft outcomes. However, infections are one of the main complications after kidney transplantation [1]. Solid organ transplant (SOT) recipients are at increased risk of a variety of infections compared to non-transplant recipients due to the persistent effect of immunosuppressive therapies [2].

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Single nucleotide polymorphisms (SNPs) are changes that occur in one nucleotide of a gene and lead to the creation of different alleles. The presence of SNPs in coding genes can alter protein production, potentially increasing or decreasing susceptibility to certain infections. SNPs in genes regulating immune responses can increase the risk of post-transplant infection [3]. Identification of SNPs helps in diagnosing people at risk of developing various infections after kidney transplantation, defining pathophysiological mechanisms, and identifying new targets for drug therapy [4].

In the present study, we aim to investigate the relationship between genetic polymorphisms and susceptibility to bacterial, fungal, and viral infections after kidney transplantation. Therefore, we performed a systematic review to comprehensively evaluate the existing literature for possible associations between genetic SNPs and different types of infections after kidney transplantation.

MATERIALS AND METHODS

Literature Search

The protocol for the present systematic review was registered in the international Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022342342. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [5], we conducted a systematic search from 1 January 1990 to 19 June 2022.

Eligibility Criteria

The following PICO elements were applied in the systematic review: (1) Population: renal transplant patients; (2) Intervention: single nucleotide polymorphisms; (3) Comparators: wild-type allele with no polymorphism; and (4) Outcome: post-transplant infection.

The inclusion criteria included (a) the original study should examine the association between SNP and infections in patients after kidney transplantation; (b) available genotype frequencies in the presence and absence of post-transplant infection; (c) should have data available for calculating risk ratios (RRs), 95% confidence intervals (CIs) and associated p-value ($p < 0.05$); and (d) study type: cohort or case-control studies.

Studies were excluded if: (a) did not involve renal transplant; (b) they did not report allelic or genetic frequencies in infection and non-infection group (unavailability of detailed data), or when available combined with SNPs in other genes and other organ transplant that preventing proper data extraction; (c) included duplicated or overlapping data; (d) were qualitative studies, in vitro experiments, case series without a comparison group, reviews, comments, conference or poster abstracts, duplicated data, book chapters, letters or animal studies; (e) Non-English studies. (f) Did not have access to full-text articles after 3 times sending three emails were sent to the corresponding author.

Search Strategy and Screening

A systematic search was performed using the four electronic databases including PubMed (Medline), ProQuest, Scopus and Web of Science and the following combination of mesh terms: (genome OR single nucleotide polymorphism OR SNP OR mutation OR variant) AND (infection OR "infectious complication") AND ("organ transplantation" OR "organ transplant" OR "kidney transplantation" OR "Renal Transplantation" OR Kidney Grafting). References cited in the retrieved articles were also hand-screened to avoid missing other publications. The references of the articles were screened to avoid missing other publications. Two authors independently searched the databases according to PRISMA guidelines. Articles were selected by title and abstract by two authors using the inclusion–exclusion criteria, and full articles were reviewed by the three authors.

Data Extraction

Two authors independently reviewed and extracted data for each retrieved article using a standard process. Discrepancies regarding study eligibility or data extraction were resolved under the supervision of a third author.

Table 1: Characteristics of studies included in the systematic review.

Study author (year)	Country	Study type	Total sample size	Sex	Age
Rodrigo et al. (2007)	Spain	Case-Control	255	Male and Female	41.7 ± 14.6
Hoffmann et al. (2009)	France	Case-Control	253	NA	NA
Ramírez et al. (2009)	Spain	Case-Control	119	Male and Female	NA
Cattaneo et al. (2009)	Italy	Cohort	147	Male and Female	43.1 ± 1.2
Pazik et al. (2011)	Poland	Case-Control	171	Male and Female	40.1 ± 12.2
Wan et al. (2013)	China	Case-Control	96	Male and Female	39.3 ± 10.2
Karimi et al. (2013)	Iran	Case-Control	100	Male and Female	34.6 ±14.2
Guo et al. (2013)	China	Case-Control	304	Male and Female	43.7 ± 12.0
Wu et al. (2013)	China	Case-Control	142	Male and Female	38.0 ± 11.0
Vu et al. (2014)	Spain	Cohort	247	Male and Female	47.7 ± 11.2
Alkharsah et al. (2014)	Saudi Arabia	Cohort	152	Male and Female	47.4 ± 14.2
Fernández-Ruiz et al. (2015)	Spain	Cohort	315	Male and Female	53.7 ± 11.8
Niknam et al. (2016)	Iran	Case-Control	172	Male and Female	38.3 ± 14.3
Guberina et al. (2017)	Germany	Cohort	178	Male and Female	41.9 ± 15.9
Rohn et al. (2018)	Germany	Cohort	181	Male and Female	41.9 ± 15.8
Pérez-Flores et al. (2019)	Spain	Cohort	498	Male and Female	52.2 ± 13.2
Zununi Vahed et al. (2021)	Iran	Case-Control	115	Male and Female	41.6 ± 4.5

For all studies, the extracted information included: first author; year of publication; country; study design (cohort or case-control); number of patients genotyped; number of patients studied (with or without post-transplant infection); and allelic frequency in each group—the outcome of interest comprised associations between SNP and infection after kidney transplantation. RR or OR were ex tracted from the primary studies; if these data were not reported, the raw data were used to calculate the RR/OR (supplementary file S1).

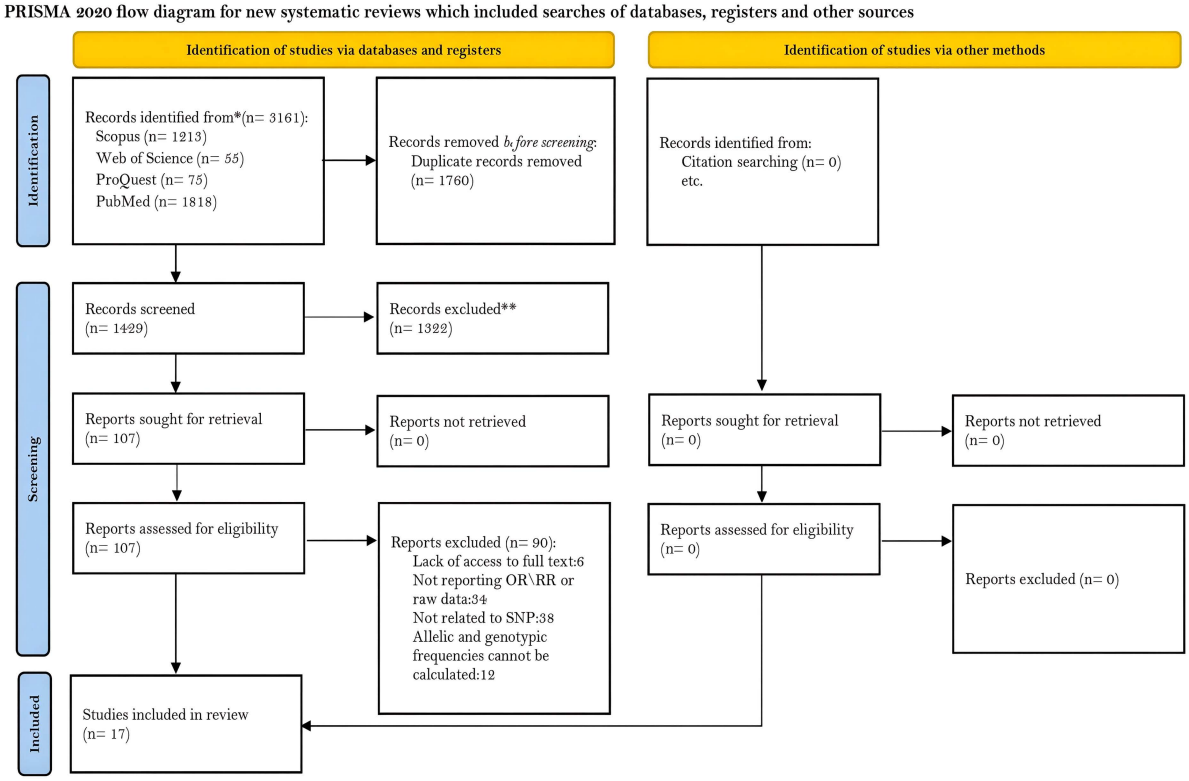
Risk of Bias Assessment and Certainty of Evidence

The included articles were assessed based on their study designs, using an appropriate risk-of-bias assessment tool by two reviewers. Cohort and case-control studies were assessed using the National Heart, Lung, and Blood Institute (NHLBI) (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools), which consists of 14 and 13 questions for cohort and case-control design, respectively. The questions evaluate the research question, sample characteristics, and inclusion and exclusion criteria for the case and control groups. Based on identified weaknesses or fatal flaws, each study was assigned an overall quality rating of good, fair, or poor.

Our level of evidence has been assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework, which evaluates the overall quality of evidence based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

The flow diagram of the study selection process according to the PRISMA is shown in Fig. 1. In total, 3161 studies were identified during the primary search. Subsequently, duplicated studies were omitted (N= 1760), and other studies were excluded based on their title or abstract (N= 1322) or full-text (N= 90) during screening. Finally, 17 articles were included in the systematic review [6-22]. The included studies were published from 2006 to 2021, and 10 were case-control studies; the rest were cohort studies. Ten studies were per



Source: Page MJ, *et al*. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Figure 1: PRISMA flow diagram

formed in the European population, and seven in the Asian population. The characteristics of studies included in the systematic review were presented in Table 1.

Of these, 17 articles, 31 genes, and 55 SNPs were extracted and evaluated. Of these 31 genes, only 7 genes included *IL-10*, *IL-1β*, *IFN-γ*, *IL-4*, *CTLA4*, *TGF-β*, and *TNF-α* were evaluated in more than one study, and the rest of the genes were assessed only in one study.

Three studies explored the association between the *IL-10* gene and post-transplant infection, and three SNPs were assessed as being related to infection: rs1800872 [11, 12], rs1878672 [6], and rs1800896 [11]. But these studies found no significant association between these SNPs and infection risk (P-values> 0.05).

The relationship between *IL-1β* was investigated in three studies, and only one SNP was observed, namely, rs16944 [10, 12, 13]. Of these three studies, only one showed a significant association between SNP rs16944 and infection risk and reported that rs16944 increases the risk of infection in renal transplant patients (RR: 1.6, 95% CI: 1.1,2.4, P-value: 0.007) [10].

In our systematic review, two articles evaluated the association between *IFN-γ* and post-transplant infection in renal transplant recipients, and both examined rs2430561 [8, 11]. Both of these demonstrated a significant association between SNP rs2430561 and CMV infection, and results showed that this SNP increases the CMV infection risk after renal transplantation (RR: 1.92, 95%CI: 1.18-3.11, P-value: 0.007) (RR: 0.24, 95%CI: 0.06-0.92, P-value: 0.037) [8, 11].

Table 2: Infection type and distribution of genotype and allele in included studies.

Study author (year)	Infection Type	Gene symbol	SNP ID	Genotype			Mutant Genotype (Dominant)	OR/RR (95%CI)	P-value
Rodrigo et al. (2007)	NA	*IL-1β*	rs16944	TT	CT	CC	C	1.68 (1.15-2.46)	0.007*
		IL-12	rs3212227	CC	CA	AA	C	1.89 (1.22-2.93)	0.004*
		TGF-β	rs1800469	TT	CT	CC	C	1.24 (0.87-1.76)	0.200
			rs1800471	CC	CG	GG	G	0.48 (0.24-0.92)	0.020*
		TNF-α	rs1800629	GG	GA	AA	A	1.58 (0.93-2.68)	0.080
		IL-4	rs2243248	TT	TG	GG	G	0.80 (0.42-1.51)	0.500
Hoffmann et al. (2009)	CMV	*IL-12β*	rs3212227	AA	AC	CC	C	1.77 (1.07-2.92)	0.027*
Ramírez et al. (2009)	HCV	*HFE*	rs1800562	GG	GA	AA	A	0.33 (0.03-3.25)	0.600
			rs1799945	CC	CG	GG	G	0.97 (0.50-1.78)	0.900
Cattaneo et al. (2009)	CMV	*ABCB1*	rs1128503	CC	CT	TT	T	2.22 (1.16-4.23)	0.010*
			rs2032582	GG	GT	TT	T	3.31 (1.56-7.01)	0.001*
			rs1045642	CC	CT	TT	T	2.42 (1.18-4.96)	0.010*
Pazik et al. (2011)	NA	*IMPDH2*	rs11706052	TT	TC	CC	C	0.73 (0.2-2.64)	0.630
Wan et al. (2013)	Bacterial and Fungal	*TNF-β*	rs909253	AA	AG	GG	G	5.36 (1.47-19.58)	0.006*
		IL-10	rs1800872	AA	AC	CC	C	0.83 (0.44-1.59)	0.500
		IL-1β	rs16944	TT	CT	CC	C	0.97 (0.53-1.77)	0.900
Karimi et al. (2013)	HCV	*IL-6*	rs1800795	GG	GC	CC	C	1.20 (0.35-4.18)	0.700
		TGF-β	rs1800470	CC	CT	TT	T	1.68 (0.52-5.42)	0.300
		IL4	rs2243250	CC	CT	TT	T	1.58 (0.45-5.52)	0.400
		IFN-γ	rs2430561	TT	TA	AA	A	0.24 (0.06-0.92)	0.037*
	HBV	*IL-6*	rs1800795	GG	GC	CC	C	1.51 (0.35-6.46)	0.700
		TGF-β	rs1800470	CC	CT	TT	T	1.32 (0.41-4.19)	0.600
		IL4	rs2243250	CC	CT	TT	T	1.60 (0.46-5.52)	0.500
		IFN-γ	rs2430561	TT	TA	AA	A	1.53 (0.51-4.56)	0.400
Guo et al. (2013)	Viral	*CTLA4*	rs733618	TT	CT	CC	C	1.08 (0.68-1.07)	0.730
			rs4553808	AA	AG	GG	G	0.70 (0.40-1.17)	0.170
			rs5742909	CC	CT	TT	T	0.82 (0.40-1.42)	0.490
			rs231775	AA	AG	GG	G	1.03 (0.65-1.63)	0.880
			rs3087243	GG	GA	AA	A	1.59 (0.79-3.20)	0.180
	Bacterial	*CTLA4*	rs733618	TT	CT	CC	C	0.93 (0.62-1.39)	0.730
			rs4553808	AA	AG	GG	G	0.93 (0.57-1.51)	0.770
			rs5742909	CC	CT	TT	T	0.91 (0.54-1.52)	0.720
			rs231775	AA	AG	GG	G	0.91 (0.60-1.37)	0.660
			rs3087243	GG	GA	AA	A	1.12 (0.63-1.99)	0.680
Wu et al. (2013)	Bacterial	*TNF-β*	rs909253	AA	AG	GG	G	1.35 (0.84-2.17)	0.210
		IL-1β	rs16944	TT	TC	CC	C	1.34 (0.84-2.16)	0.210
Vu et al. (2014)	CMV	*IFN-γ*	rs2430561	TT	TA	AA	A	1.92 (1.18-3.11)	0.007*
		TNF-α	rs1800629	GG	GA	AA	A	0.95 (0.48-1.86)	0.800
		IL-10	rs1800896	AA	AG	GG	G	1.39 (0.85-2.28)	0.120
			rs1800872	AA	AC	CC	C	1.24 (0.80-1.92)	0.300

Table 2: Continued.

Study author (year)	Infection Type	Gene symbol	SNP ID	Genotype			Mutant Genotype (Dominant)	OR/RR (95%CI)	P-value
Alkharsah et al. (2014)	Kaposi's sarcoma herpesvirus	*VEGF*	rs1570360	AA	AG	GG	G	0.86 (0.52-1.63)	0.730
			rs13207351	AA	AG	GG	G	1.43 (0.86-2.51)	0.200
			rs59260042	CC	CA	AA	A	4.80 (1.42-17.12)	0.005*
			rs2010963	CC	CG	GG	G	1.27 (0.50-1.41)	0.430
Fernández-Ruiz et al. (2015)	CMV	*IL-10*	rs1878672	GG	GC	CC	C	1.01 (0.75-1.31)	0.910
		CCR5	rs1800023	AA	AG	GG	G	1.20 (0.85-1.62)	0.250
		TLR2	rs5743708	GG	GA	AA	A	0.16 (0.05-0.57)	0.001*
		DC-SIGN	rs735240	GG	GA	AA	A	0.82 (0.62-1.12)	0.540
		TLR9	rs5743836	TT	TC	CC	C	1.27 (0.81-1.95)	0.280
		MCP1	rs13900	CC	CT	TT	T	0.79 (0.52-1.15)	0.250
		IL-28β	rs12979860	CC	CT	TT	T	0.72 (0.55-1.02)	0.150
Niknam et al. (2016)	CMV	*CTLA4-1661*	rs4553808	AA	AG	GG	G	0.59 (0.27-1.29)	0.100
		CTLA4-1722	rs733618	TT	TC	CC	C	0.63 (0.16-2.84)	0.700
		CTLA4-318	rs5742909	CC	CT	TT	T	1.08 (0.4-2.4)	0.800
		CTLA4-49	rs231775	AA	AG	GG	G	0.77 (0.4-1.4)	0.400
		PDCD1.3	rs11568821	GG	GA	AA	A	0.75 (0.4-1.7)	0.400
		PDCD1.9	rs2227982	CC	CT	TT	T	0.64 (0.3-2.5)	0.200
		CD28 +17	rs3116496	TT	TC	CC	C	1.18 (0.68-2.10)	0.500
Guberina et al. (2017)	CMV	*HLA-G*	rs1063320	CC	CG	GG	G	2.01 (1.02-3.94)	0.040*
Rohn et al. (2018)	CMV	*Mica129*	rs1051792	AA	AG	GG	G	0.80 (0.40-1.50)	0.480
		Mica	rs2596538	AA	AG	GG	G	0.60 (0.30-1.30)	0.200
		NKG2D	rs1049174	CC	CG	GG	G	0.70 (0.40-1.60)	0.600
Pérez-Flores et al. (2019)	—	*IL-18 -607C/A*	rs1946518	AA	AC	CC	C	1.68 (1.01-2.77)	0.043*
		IL-18 -137G/C	rs187238	GG	GC	CC	C	2.36 (0.96-5.75)	0.059
Zununi Vahed et al. (2021)	Viral	*ApaI*	rs7975232	GG	GT	TT	T	0.74 (0.43-1.30)	0.300
		FokI	rs2228570	TT	TG	GG	G	2.03 (1.06-2.89)	0.030*
		BsmI	rs1544410	GG	GT	TT	T	1.12 (0.61-2.07)	0.700
		VDBP	rs7040	TT	TG	GG	G	0.4 (0.24-0.67)	0.006*

Among the investigated genes, the association of the *CTLA4* gene with post-transplant infection has been examined, and four SNPs were evaluated, namely rs733618 [7, 9], rs4553808 [9], rs5742909 [9], and rs231775 [9]. None of these studies found a significant association between these SNPs and post-transplant infection (P-values> 0.05).

The association of the *TGF-β* gene with post-transplant infection was examined, and three SNPs were identified in these studies: rs1800470 [8], rs1800469 [10], and rs1800471 [10]. Only one significant association between an SNP and infection was found, with SNP rs1800471, and results showed that this SNP decreased post-transplant infection (RR: 0.4, CI95%: 0.2-0.9; P-value: 0.02) [10].

Table 3: Risk of bias assessment of Case-Control studies.

Study author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Overall
Rodrigo et al. (2007)	YES	NO	NO	YES	NO	NO	NR	CD	YES	YES	NR	yes	POOR
Hoffmann et al. (2009)	YES	YES	NO	YES	NO	NO	NR	CD	YES	YES	NR	YES	POOR
Ramírez et al. (2009)	YES	NO	NO	YES	NO	YES	NR	CD	YES	YES	NR	YES	FAIR
Pazik et al. (2011)	YES	YES	NO	YES	NO	NO	NR	CD	YES	YES	NR	NO	POOR
Wan et al. (2013)	YES	YES	NO	YES	NO	YES	NR	CD	YES	YES	NR	YES	FAIR
Karimi et al. (2013)	YES	YES	NO	YES	NO	YES	NR	CD	YES	YES	NR	NO	POOR
Guo et al. (2013)	YES	YES	NO	YES	YES	NO	NR	CD	YES	YES	NR	NO	POOR
Wu et al. (2013)	YES	YES	NO	YES	YES	YES	NR	CD	YES	YES	NR	NO	POOR
Niknam et al. (2016)	YES	YES	NO	YES	YES	YES	NR	CD	YES	YES	NR	NO	POOR
Zununi Vahed et al. (2021)	YES	YES	NO	NO	YES	YES	NR	CD	YES	YES	NR	NO	POOR

CD: cannot determine, NR: not reported

Regarding *TNF-α*, two studies were conducted, both evaluating a single SNP, rs1800629. Both studies found no significant association between this SNP and post-transplant infection [10, 11].

The rest of genes were evaluated only in one study that some of them found significant association between SNP and post-transplant infection included *IL-12* rs3212227 (RR: 1.8, CI95%: 1.22-2.93; P-value: 0.004) [10], *ABCB1* rs1128503 (RR: 2.2, CI95%: 1.16-4.23; P-value: 0.01), *ABCB1* rs2032582 (RR: 3.31, CI95%: 1.56-7.01; P-value: 0.001), and *ABCB1* rs1045642 (RR: 2.42, CI95%: 1.18-4.96; P-value: 0.01) [16], *TNF-β* rs909253 (RR: 5.3, CI95%: 1.47-19.5; P-value: 0.006) [12], *VEGF* rs59260042 (RR: 4.8, CI95%: 1.4-17.1; P-value: 0.005) [22], *HLA-G* rs1063320 (RR: 2.01, CI95%: 1.028-3.94; P-value: 0.04) [20], *IL-18* 607 rs1946518 (RR: 1.68, CI95%: 1.01-2.77; P-value: 0.04) [21], *FOKI* rs2228570 (RR: 2.03, CI95%: 1.06-2.89; P-value: 0.03) [19], *VDBP* rs7040 (RR: 0.4, CI95%: 0.24-0.67; P-value: 0.0006) [19], *IL-6* rs1800795 (RR: 1.51, CI95%: 0.35-6.46; P-value: 0.7), and *IL-6* (RR: 1.20, CI95%: 0.35-4.18; P-value: 0.7). The infection type and distribution of genotype and allele in included studies were presented in Table 2.

Risk of Bias Assessment

We evaluated the methodological quality of included studies using the National Heart, Lung, and Blood Institute (NHLBI) risk-of-bias assessment tools, applying the appropriate checklist according to study design (cohort or case–control). In the case–control studies, six clearly defined their case and control groups, while one selected its control sample from a population different from that of the cases. Four studies adjusted potential confounders in their analysis. Concurrent recruitment of control groups and random selection of eligible cases and/or controls were not reported in any of the case–control studies. Overall, two case–control studies were rated as having fair quality, whereas all others were rated as poor due to insufficient reporting on items identified as fatal flaws. Among the cohort studies, adjustment for potential confounding variables was not reported in two studies, both of which

Table 4: Risk of bias assessment of cohort studies.

Study author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall
Cattaneo et al. (2009)	YES	YES	YES	YES	NO	YES	YES	NR	YES	NO	YES	NR	YES	YES	FAIR
Vu et al. (2014)	YES	YES	YES	YES	NO	yES	YES	NR	YES	NO	YES	NR	YES	YES	FAIR
Alkharsah et al. (2014)	YES	YES	YES	YES	NO	YES	YES	NR	YES	NO	YES	NR	YES	NO	POOR
Fernández-Ruiz et al. (2015)	YES	YES	YES	YES	NO	YES	YES	NR	YES	NO	YES	NR	YES	YES	FAIR
Guberina et al. (2017)	YES	YES	YES	YES	NO	YES	YES	NR	YES	YES	YES	NR	YES	NO	POOR
Rohn et al. (2018)	YES	YES	YES	YES	NO	YES	YES	NR	YES	NO	YES	NR	YES	YES	FAIR
Pérez-Flores et al. (2019)	YES	YES	YES	YES	NO	YES	YES	NR	YES	NO	YES	NR	YES	YES	FAIR

NR: not reported

were rated as having poor overall quality. The remaining studies reported adjustment of potential confounders. Blinding of outcome assessors to exposure status of study groups, exposure measurement levels, and sample size justification was not reported in any of the included studies. Overall, of the seven cohort studies, two were rated as poor, while the remaining studies were rated as fair due to incomplete reporting on several quality items. Table 3 and Table 4.

Certainty of Evidence

We conducted a qualitative assessment of the certainty of evidence using the GRADE approach. The certainty was downgraded due to the risk of bias and inconsistent reporting of results across the included studies. Since no large effect, dose–response relationship, or strong biological plausibility was identified, the overall certainty of evidence was not upgraded. Based on these considerations, the overall GRADE rating for our review was very low.

DISCUSSION

Solid organ transplantation is a lifesaving procedure for people with chronic and end-stage diseases, and it can improve the quality of life for the recipient. However, transplant-related complications may occur, increasing the risk of infection, graft rejection, and subsequent patient morbidity and mortality. Risk factors such as age, immunosuppression, and genetic makeup can further complicate the onset and progression of infection. This review evaluated seventeen studies to determine the impact of SNPs on infection after kidney transplantation. The results of this systematic review show that genetic SNPs are associated with higher [rs16944 (*IL-1β*), rs2430561 (*IFN-γ*)] or lower [rs1800471 (*TGF-β*)] infection risk in kidney transplant patients, whereas the results were contradictory across studies.

Three studies examined the relationship between the *IL-10* gene and post-transplant infection, and our systematic review identified three SNPs-rs1800872 [11, 12], rs1878672 [6] and rs1800896 [11]-that were evaluated in studies as being associated with infection. SNP rs1800872 is located at position chr1:206773062 and conferred a nucleotide substitution from A to C [23]. Vu *et al.* examined the association between the C allele at SNP rs1800872 and CMV infection in the Spanish population; however, they found no evidence of a meaningful correlation [11]. Additionally, Wan *et al.* assessed the relationship between the C allele and infection in the Chinese population and discovered no connection between this allele and fungal or bacteri-

al infection [12]. At position chr1:206770368, the other SNP, rs1878672, caused a nucleotide alteration from G to C [24]. A study involving a cohort of Spanish patients evaluated post-transplant CMV infection. After 315 patients underwent kidney transplantation, the C allele at SNP rs1800872 was not associated with CMV infection, according to the results [6]. The final SNP, rs1800896, located at chr1:206773552, changed the nucleotide from A to G [25].

Vu *et al.* examined the relevance of the G allele in CMV infection following renal transplantation in the Spanish population, but they found no association between the G allele and CMV infection in renal transplant recipients [11]. Therefore, no meaningful correlation was found in the current systematic review between *IL-10* SNPs and post-transplant infection.

The relationship between *IL-1β* was investigated in three studies, and only one SNP was evaluated, namely, rs16944. SNP rs16944 is located at position chr2:112837290 and conferred a nucleotide substitution from T to C [23]. Of the three investigations, only Rodrigo et al. found that the C allele of SNP rs16944 was associated with a higher likelihood (approximately 60%) of post-renal transplant infection in the Spanish population [10].

The impact of this SNP on infection risk in the Chinese population was examined in two other studies; however, neither found a statistically significant association between the C allele and infection [12, 13]. A class of cytokines known as interferons is generated in reaction to an infection or other inflammatory stimuli. These cytokines influence immune cell function and have strong antiviral properties. The association between SNPs in the *IFN-γ* gene and infection in kidney transplant recipients was investigated by analyzing *IFN-γ* levels. Two studies were conducted to assess the relationship between *IFN-γ* and post-transplant infection in recipients of renal transplants in the current systematic review, and each examined only one SNP, rs2430561 [8, 11].

The effects of SNP rs2430561 on post-transplant infection in renal transplant recipients were investigated in a case-control study conducted in Spain involving 247 patients. The results showed that recipients with the AA or AT genotype had a higher CMV infection rate than those with the TT genotype, and that the SNP allele was associated with infection [11]. Karimi *et al.* [8] did not identify any significant association between *IFN-γ* and infection in renal transplant recipients in the Iranian population. According to Santiago *et al.* there was no discernible association between the A allele of SNP rs2430561 and CMV infection in the Spanish population, as reported by Karimi's study [26].

In our systematic review, we examined the association between infection risk and SNPs in cytokine genes, such as *TGF-β* and *TNF-α*. Regarding *TNF-α*, rs1800629, a single SNP, was evaluated. Positioned at chr6:31575254, SNP rs1800629 caused a nucleotide change from G to A [27]. The impact of the A allele of SNP rs1800629 on CMV infection in patients undergoing kidney transplantation was examined in a case-control study conducted in the Spanish population. The study's findings did not reveal a statistically significant correlation between the A allele and CMV infection [11]. Furthermore, no significant correlation was found between the A allele and post-transplant infection in another case-control study with a Spanish population [10]. Therefore, our systematic review's findings indicated that no substantial link between SNPs has yet been discovered by research.

Our systematic review revealed no significant correlation between post-transplant infection and SNPs of *CTLA4* and *TNF-α* [7, 9-11]. However, a noteworthy correlation was identified between post-transplant infection and *TGF-β* gene SNP rs1800471. According to research by Rodrigo et al., the G allele of SNP rs1800471 reduced the risk of post-renal transplant infection [10], but no significant correlation was found between post-renal transplant infection and the other SNPs of the *TGF-β* gene [8].

Because of the diversity in data reporting and the limited number of studies investigating each specific SNP, we were unable to pool the extracted data to perform a meta-analysis. Most of the included studies had a risk of bias, which reduced the overall quality and certainty of our findings. Furthermore, some studies were excluded due to incomplete or inappropriate data reporting and the inability to access their full texts, which might have affected the strength of our conclusions. Therefore, further well-designed studies focusing on individual SNPs are needed to clarify their association with post–kidney transplant infections. Such research could provide valuable insights for predicting post-transplant complications and ultimately improve outcomes in kidney transplant recipients.

In conclusion, this systematic review suggests that certain single-nucleotide polymorphisms (SNPs) may influence susceptibility to post-transplant infections in kidney transplant recipients. Specifically, rs16944 (*IL-1β*) and rs2430561 (*IFN-γ*) appeared to increase the risk of infection, whereas rs1800471 (*TGF-β*) showed a potential protective effect. However, findings were inconsistent across studies, and the overall certainty of evidence was very low. Further well-designed, multicenter studies are needed to clarify these associations and guide the development of individualized strategies to improve post-transplant outcomes.

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