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Impact of *MBL2* gene polymorphisms on the risk of infection in solid organ transplant recipients: A systematic review and meta-analysis

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Mannose-binding lectin (MBL) is a soluble pattern recognition molecule involved in complement activation. Single nucleotide polymorphisms (SNPs) in the *MBL2* gene have been associated with susceptibility to infection, although data in solid organ transplant recipients remains inconclusive. This meta-analysis was primarily aimed at investigating the association between posttransplant bacterial and fungal infection and variant alleles of *MBL2* gene SNPs in the promoter/5' untranslated region and exon 1. Cytomegalovirus (CMV) infection and/or disease were considered secondary outcomes. PubMed, EMBASE, and Web of Knowledge were searched for relevant articles up to August 2018. Eleven studies (comprising 1858 patients) were included, with liver transplant (LT) recipients accounting for 80.4% of the pooled population. As compared to high-MBL expression haplotypes (YA/YA, YA/XA), any MBL-deficient haplotype was associated with an increased risk of posttransplant bacterial and fungal infections (risk ratio [RR]: 1.30; $P = .04$). Low/null-MBL expression haplotypes (XA/O, O/O) also increased the risk of primary outcome (RR: 1.51; $P = .008$) and CMV events (RR: 1.50; $P = .006$). No effect was observed for individual promoter SNPs. In conclusion, MBL-deficient haplotypes are associated with a significant, albeit moderate, increase in the risk of posttransplant infection, with this association being mainly restricted to LT recipients.

KEYWORDS
clinical research/practice, complication: infectious, genetics, immune deficiency, infection and infectious agents, infectious disease, meta-analysis

1 | INTRODUCTION

Long-term immunosuppression administered to solid organ transplant (SOT) recipients is associated with an increased risk of infectious complications. Current immunosuppressive drugs are mostly aimed at suppressing T cell–mediated adaptive immunity, potentially giving innate immunity a crucial role in protecting against pathogens in the transplant setting.[1,2]

Mannose-binding lectin (MBL) is a soluble pattern recognition molecule critically involved, along with ficolins, in complement activation through the lectin pathway.[3] This C-type lectin is mainly synthesized in the liver, although extrahepatic sources also exist. By binding to N-acetyl-glucosamine and D-mannose residues on microbial surfaces, MBL activates MBL-associated serine proteases, which cleave complement factors C4 and C2 and induce the formation of

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HIV, human immunodeficiency virus; KT, kidney transplantation; LT, liver transplant; LuT, lung transplant; MBL, mannose-binding lectin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROSPERO, Prospective Register of Systematic Reviews; RR, risk ratio; SNP, single nucleotide polymorphism; SOT, solid organ transplantation; UTR5, untranslated region.

C3 and C5 convertase complexes.[4] Subsequent processes of opsonophagocytosis, release of chemoattractant mediators (such as C5a), and assembly of the membrane attack complex lead to bacterial killing and inflammation. Therefore, MBL serves as an important effector of the innate response.[3-5]

The functions mediated by MBL are directly correlated with the serum concentrations of the biologically active protein form, for which large inter-individual variations have been observed.[6,7] The gene *MBL2*, mapped in chromosome 10q11.2-q21, encodes for human MBL.[8] It is well established that functional MBL levels are critically determined by various polymorphisms in the promoter and coding regions of this gene, with up to 1000-fold variation across different genotypes.[9,10] Three common single nucleotide polymorphisms (SNPs) in exon 1 induce the replacement of certain amino acids in the collagen domain of the protein, leading to the synthesis of dysfunctional variant forms with low serum levels and reduced biological activity due to impaired oligomerization. These SNPs are located at codons 52 (Arg → Cys substitution [rs5030737]), 54 (Gly → Asp substitution [rs1800450]) and 57 (Gly → Glu substitution [rs1800451]), with variant alleles termed "D," "B," and "C," respectively. For clarity purposes, the variant alleles are usually grouped together as allele "O," whereas the presence of wild-type alleles in each of these SNPs is denoted as allele "A." Three further SNPs have been identified in the promoter/5′ untranslated region (UTR) of the gene, at positions −550 C>G (rs11003125 [also known as "H/L" variant, where "L" is the wild-type allele]), −221 G>C (rs7096206 ["X/Y" variant, where "Y" is the wild-type allele]), and +4 C>T (rs7095891 ["P/Q" variant, where "P" is the wild-type allele]).[11,12]

The presence of low or deficient serum MBL levels has been associated with an increased risk of infectious complications after SOT, particularly for cytomegalovirus (CMV) infection,[13-15] although discrepant results can be also found.[16,17] In view of the major role played by genetic determinants, the potential impact of variant alleles or haplotypes of SNPs located in the *MBL2* gene has also been investigated, with most[2,18,19] but not all studies[20] reporting an association with the occurrence of posttransplant infection.

Over recent years, a number of meta-analyses have explored the effect of *MBL2* gene polymorphisms on the risk of different infectious outcomes in the general population.[21-26] Nevertheless, such methodology has not been yet applied to the SOT population. The aim of this study was to ascertain whether polymorphisms in promoter/UTR region and exon 1 of the *MBL2* gene are associated with an increased risk of infection after SOT.

2 | MATERIALS AND METHODS

2.1 | Inclusion and exclusion criteria

The protocol of the present systematic review and meta-analysis was registered in the international Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42018099684), and the study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[27] We included all published case-control or cohort studies that fulfilled the following criteria: (a) the study should explore the association between *MBL2* gene polymorphisms and posttransplant infections; (b) should be restricted to SOT recipients; (c) should have available genotype distributions among patients with or without infections for calculating risk ratios (RRs) and 95% confidence intervals (CIs); and (d) should follow statistically acceptable data collection and analysis methodology. Studies were excluded if: (a) they did not report genotype frequencies; (b) included duplicated or overlapping data; or (c) were case series without a comparison group, reviews, comments, or animal studies. In case of partially overlapping publications, the study with the highest number of individuals was included in the analysis.

2.2 | Search strategy

A systematic search was performed using the databases PubMed (Medline), EMBASE, and Web of Knowledge and the following combination of search terms: ("mannose-binding lectin" OR *MBL2* OR *MBL* OR "mannose-binding protein" OR *MBP*) AND (gene OR polymorphism OR SNP OR mutation OR variant) AND (infection OR "infectious complication") AND ("organ transplantation" OR "organ transplant" OR "kidney transplantation" OR "liver transplantation" OR "heart transplantation" OR "lung transplantation" OR "pancreas transplantation" OR "small bowel transplantation"). We searched the electronic databases from inception to August 15, 2018 and included publications published in English, French, or Spanish. The references of all the resulting articles were reviewed to avoid missing other relevant publications. In addition, the references cited in review articles were manually screened for potential related studies.

2.3 | Data extraction

Two investigators (M.F.R. and E.G.) independently reviewed and extracted data by duplicate using a standard process for each retrieved article. The following information was collected: first author; year of publication; study design (case-control or cohort); SOT population; analyzed outcomes; number of patients genotyped; number of patients with or without posttransplant infection; and frequency of the *MBL2* genotypes in each of these groups. The risk of bias within individual studies was evaluated through the Newcastle-Ottawa Quality Assessment Scale, which uses a star-rating system (from 0 to 9) to assess the quality of nonrandomized studies.[28] Studies scoring ≥5 stars were considered to be of moderate to high quality. Authors of original studies were contacted if additional information was required. Discrepancies regarding study eligibility, data extraction, or quality assessment were resolved by consensus.

The primary study outcome was the association between posttransplant bacterial and fungal infections and the presence of variant alleles in the promoter/UTR region (H/L [rs11003125], X/Y [rs7096206], P/Q [rs7095891]) and exon 1 (collectively A/O [rs5030737, rs1800450, rs1800451]) of the *MBL2* gene. The

occurrence of any posttransplant CMV event (asymptomatic infection and/or disease) was considered as a secondary outcome.

2.4 | Statistical analysis

Pooled RRs with the corresponding 95% CIs were used as the summary effect measure. Both dominant and recessive genetic models were evaluated for each single SNP. The heterogeneity assumption was evaluated by the chi-square-based Cochran's Q test (which was considered significant at $P < .05$) and quantified with the I^2 statistic (with values <25%, 25% to 75%, and >75% interpreted as representing low, moderate, and high levels of heterogeneity, respectively). Random-effects model with the Mantel-Haenszel method was used for pooling results from primary studies in the presence of significant heterogeneity; otherwise, a fixed-effects model was applied. We conducted a set of subgroup analyses stratifying the pooled results by type of SOT (liver versus non-liver transplantation). Publication bias was assessed by visual inspection of funnel plots and quantified by the Egger's linear regression test. Statistical analysis and figures were performed with Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and meta package of R software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Characteristics of included studies

Preliminary computerized searches resulted in 138 articles. Four further articles were manually identified from reference lists. After removing of duplicate studies and detailed evaluation of titles and abstracts, 45 articles were fully assessed for eligibility.[1,2,5,13,14,18-20,29-55] Eleven studies[18-20,48-55] (Table 1) fulfilled the inclusion and exclusion criteria and were finally included in the present study (PRISMA flow chart shown in Figure 1). Two further studies[33,35] had to be excluded due to the lack of relevant data despite repeated attempts to contact corresponding authors to obtain additional details. Three of the meta-analyzed studies came from the same institution but comprised consecutive nonoverlapping cohorts.[18,19,48] Two studies were performed in essentially the same cohort of patients,[52,53] but analyzed different outcomes and were analyzed separately.

These 11 studies comprised a total of 1858 SOT recipients: 1494 (80.4%) liver transplant (LT) recipients, 317 (17.1%) kidney or kidney-pancreas (KT), recipients and 47 (2.5%) lung transplant (LuT) recipients. Although only one study detailed the ethnicity of the genotyped participants,[55] most patients (87.9% [1634/1858]) came from studies performed in countries with predominant Caucasian populations.[18-20,48-53] All but two studies[51,55] assessed the impact of polymorphisms in both the promoter and exon 1 regions of the *MBL2* gene (Table 1). Given the instrumental role played by the liver in the synthesis of MBL, donor genotype was investigated in all the studies involving LT, either exclusively[20,48,55] or in parallel to the recipient genotype.[19,49,50,52,53]

Methodological quality assessment according to the Newcastle-Ottawa Scale showed that all the studies scored 5 or more stars, suggesting a moderate to high quality (Table 2).

All the 11 included studies provided data on the incidence of posttransplant infection according to recipient (for KT and LuT) or donor (for LT) haplotypes of the *MBL2* gene. Nevertheless, variations were observed in the criteria used to group genotypes according to the predicted MBL production, with some of them comparing sufficient versus (any) deficient haplotypes and others stratifying across high-, intermediate- or low/null-expressing haplotypes (Table 3).

Seven studies[48-52,54,55] (comprising 797 patients) reported separate data on the incidence of posttransplant infection according to genotypic distributions of SNPs located in the promoter/UTR region and/or exon 1 of the *MBL2* gene (Table 4).

Out of the five studies in which LT recipient *MBL2* genotyping (in addition to liver donor) was performed, only two (with largely overlapping populations but different outcomes)[52,53] provided separate data for the occurrence of posttransplant infection according to recipient genotypes (Table 5).

3.2 | Association between MBL-deficient haplotypes and posttransplant bacterial and fungal infections

Seven studies[18-20,40,49,50,54] (comprising 1093 patients) reported enough data for the pooled analysis of high- versus intermediate- or low/null-MBL expression haplotypes (YA/YA, YA/XA vs. XA/XA, YA/O, XA/O, O/O). The presence of *MBL2* haplotypes other than YA/YA or YA/XA was associated with an increased risk of posttransplant bacterial and fungal infections (random-effect RR: 1.30; 95% CI: 1.01–1.66; $P = .04$; moderate heterogeneity [$Chi^2 = 12.21$; $P = .06$; $I^2 = 51\%$]) (Figure 2A).

Five studies[18,20,49,50,52] (comprising 987 patients) provided data for the analysis of high- or intermediate- versus low/null-MBL expression haplotypes (YA/YA, YA/XA, XA/XA, YA/O vs. XA/O, O/O). Low/null-expression haplotypes were associated with an increased risk of posttransplant bacterial and fungal infections (random-effect RR: 1.51; 95% CI: 1.11–2.05; $P = .008$; moderate heterogeneity [$Chi^2 = 7.18$; $P = .13$; $I^2 = 44\%$]) (Figure 2B).

To further characterize these associations, we investigated pairwise comparisons across high- (YA/YA, YA/XA), intermediate- (XA/XA, YA/O) and low/null-MBL expression haplotypes (XA/O, O/O). Three studies[18,49,50] (comprising 387 patients) reported enough data for this subanalysis. As compared to high-MBL expression haplotypes, intermediate-MBL expression haplotypes were associated with a near significant increase in the risk of posttransplant infection (random-effects RR: 1.80; 95% CI: 0.99–3.24; $P = .05$; moderate heterogeneity [$Chi^2 = 4.40$; $P = 0.11$; $I^2 = 55\%$]). On the other hand, no significant association was found for the comparison between intermediate- and low/null-MBL expression haplotypes (fixed-effects RR: 1.01; 95% CI: 0.65–1.56; $P = .97$; no heterogeneity [$Chi^2 = 1.66$; $P = .44$; $I^2 = 0\%$]).

TABLE 1 Characteristics of included studies

Author, year [reference]	Study design	Type of SOT	Sample	Country/ethnicity	*MBL2* gene polymorphisms (position of SNPs analyzed)	Outcomes	Length of posttransplant follow-up
Bouwman, 2005[49]	Cohort study	Liver	49	The Netherlands/NR	Promoter region (−550 and −221); exon 1 (codons 52, 54, and 57)	Bacterial infection (BSI, IAI, pneumonia)[a]	One year[g]
Cervera, 2007[18]	Cohort study	Kidney, kidney-pancreas	236	Spain/NR	Promoter region (−221); exon 1 (codons 52, 54, and 57)	Bacterial infection (BSI, pneumonia, deep SSI, cUTI)[a] CMV infection or disease	Median of 1571 (high-), 1338 (intermediate-) and 1561 days (low/null *MBL2* haplotypes)
Cervera, 2009[48]	Cohort study	Liver	95	Spain/NR	Promoter region (−550, −221 and +4); exon 1 (codons 52, 54, and 57)	Bacterial infection (BSI, pneumonia, deep SSI, cUTI)[a] or proven/probable IFI[b] Septic shock	NR
Worthley, 2009[50]	Cohort study	Liver	102	Australia/NR	Promoter region (−550 and −221); exon 1 (codons 52, 54, and 57)	Clinically significant infection (BSI, IAI, pneumonia, CMV end-organ disease, IFI)[c]	Median of 4 years (range, 0-8.1 years)
Kerschner, 2009[51]	Cohort study	Lung	47	Austria/NR	Exon 1 (codons 52, 54, and 57)	CMV infection requiring preemptive therapy[d]	At least 1 year[g]
de Rooij, 2010[52]	Cohort study	Liver	310	The Netherlands/NR	Promoter region (−550 and −221); exon 1 (codons 52, 54, and 57)	Bacterial infection (BSI, IAI, pneumonia)	At least 7 days[g]
de Rooij, 2011[53]	Cohort study	Liver	295	The Netherlands/NR	Promoter region (−550 and −221); exon 1 (codons 52, 54, and 57)	CMV infection[e] or disease	At least 7 days[g]
Curvelo, 2011[20]	Cohort study	Liver	290	The Netherlands/NR	Promoter region (−221); exon 1 (codons 52, 54, and 57)	Bacterial infection (BSI, IAI, pneumonia)[a]	Three months[g]
Wan, 2013[54]	Case-control	Kidney	81	China/NR	Promoter region (−550, −221 and +4); exon 1 (codons 52, 54, and 57)	BSI	One year[g]
Zhong, 2016[55]	Cohort study	Liver	113	China/Han	Promoter region (−550)	Bacterial infection (BSI, IAI, pneumonia, deep SSI, cUTI)[a]	NR
Lombardo-Quezada, 2018[19]	Cohort study	Liver	240	Spain/NR	Promoter region (−550, −221 and +4); exon 1 (codons 52, 54, and 57)	Bacterial infection (BSI, IAI, pneumonia, SSI, cUTI, SSSI, other)[f]Septic shock Proven/probable IFI[b] CMV infection[d] or disease Other viral infection	Mean ± SD of 339 ± 79 days

BSI, bloodstream infection; CMV, cytomegalovirus; cUTI, complicated (i.e., febrile) urinary tract infection; IAI, intraabdominal infection; IFI, invasive fungal infection; NR, not reported; SD, standard deviation; SNP, single-nucleotide polymorphism; SOT, solid organ transplantation; SSI, surgical site infection; SSSI, skin, and soft tissues infection.

[a]Only microbiologically documented infections requiring hospital admission.

[b]According to EORTC/MSG criteria.

[c]Only microbiologically documented infections (except for episodes of pneumonia, in which the presence of typical clinical and radiographic features was sufficient for diagnosis even in the absence of an identified causative agent).

[d]Plasma CMV DNA load >10^3 copies/mL.

[e]p65 antigenemia ≥1 cell per 50 000 leukocytes or plasma CMV DNA load ≥0.90 $\log^{10}$ copies/mL.

[f]Microbiologically documented infections or episodes without microbiological isolation that resolved with antimicrobial therapy.

[g]No detailed data on the length of follow-up was available (i.e., only generic statements on the "minimum follow-up" or "point prevalence rate" were provided).

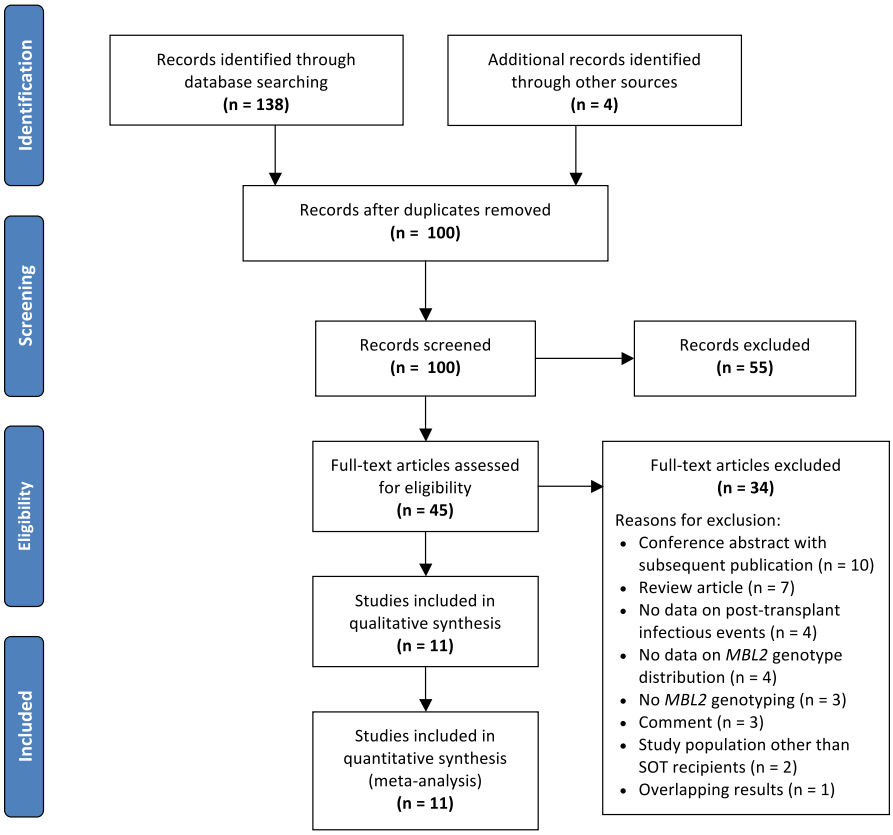


FIGURE 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow chart for literature search and study selection in the present meta-analysis. SOT, solid organ transplantation [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Association between individual exon 1 polymorphisms and posttransplant bacterial and fungal infections

Next, the impact of variant alleles of individual SNPs located in the exon 1 coding region (rs5030737, rs1800450, rs1800451) was analyzed. Five studies[48-50,52,54] (comprising 637 patients) contained sufficient data for the pooled analysis of wild-type versus any variant allele genotype in a dominant genetic model (A/A vs. A/O, O/O). No significant association was detected (random-effects RR: 1.46; 95% CI: 0.83–2.57; $P = .19$; high heterogeneity [$Chi^2 = 16.63$; $P = .002$; $I^2 = 76\%$]) (Figure 3A).

Three studies[49,50,52] (comprising 461 patients) reported sufficient data for the recessive genetic model analysis (A/A, A/O vs. O/O). In this case, the presence of the variant allele homozygous genotype (OO) was associated with an increased risk of posttransplant infection (fixed-effects RR: 1.72; 95% CI: 1.10–2.68; $P = .02$; low heterogeneity [$Chi^2 = 2.56$; $P = .28$; $I^2 = 22\%$]) (Figure 3B).

3.4 | Association between individual promoter polymorphisms and posttransplant bacterial and fungal infections

Next, we assessed the association between individual SNPs within the promoter/UTR region of the *MBL2* gene and the occurrence of posttransplant infection.

Three[49,52,55] and five studies[48,49,52,54,55] (comprising 472 and 647 patients) provided data for the pooled analysis of wild-type versus mutant alleles of the rs11003125 (C>G) SNP at position −550 in dominant (L/L vs. H/L, H/H) and recessive genetic models (L/L, L/H vs. H/H), respectively. No significant association with the occurrence of posttransplant bacterial and fungal infections was observed in any of these analyses (Figures 4A,B).

Two[49,52] and four studies[48,49,52,54] (comprising 359 and 535 patients) provided data for the comparison of wild-type versus mutant alleles of the rs7096206 (G>C) SNP at position −221 in dominant (Y/Y vs. Y/X, X/X) and recessive genetic models (Y/Y, Y/X vs. X/X), respectively. Again, no significant association with the primary study outcome was detected (Figures 5A,B).

Only two studies detailed data on the allele distribution of the rs7095891 (C>T) SNP at position +4 (P/Q variant).[48,54] Both studies used disparate criteria for grouping genotypes according to the observed occurrence of posttransplant infection (Table 4), thus preventing either dominant or recessive model analyses.

3.5 | Association between MBL2 gene polymorphisms and CMV events

Next, we investigated the association between MBL-sufficient and deficient haplotypes of the *MBL2* gene or variant alleles of individual exon 1 SNPs and the posttransplant occurrence of CMV events (asymptomatic infection and/or disease).

TABLE 2 Quality assessment according to the Newcastle-Ottawa Scale for the included studies

	Selection				Comparability	Outcome		
Cohort studies	Representativeness of exposed cohort	Ascertainment of exposure	Selection of non-exposed cohort	Evidence that the outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Adequate length of follow-up	Adequacy of follow-up
Bouwman, 2005[49]	*	*	*	*		*	*	
Cervera, 2007[18]	*	*	*	*	**	*	*	*
Cervera, 2009[48]	*	*	*	*	**	*		
Worthley, 2009[50]	*	*	*	*	**	*	*	
Kerschner, 2009[51]	*	*	*	*		*	*	
de Rooij, 2010[52]	*	*	*	*	**	*		
de Rooij, 2011[53]	*	*	*	*	**	*		
Curvelo, 2011[20]	*	*	*	*		*		
Zhong, 2016[55]	*	*	*	*	**	*		
Lombardo-Quezada, 2018[19]	*	*	*	*	**	*	*	

	Selection				Comparability	Exposure		
Case-control studies	Representativeness of cases	Adequacy of case definition	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Rate of non-response
Wan, 2013[54]	*	*	*	*	*	*	*	*

TABLE 3 Cumulative incidence rates of posttransplant infection according to the presence of MBL-sufficient or deficient haplotypes (donor genotype was considered for studies on liver transplant recipients)

Author, year [reference]	High YA/YA, YA/XA	Intermediate XA/XA, YA/O	Low/null XA/O, O/O	Sufficient YA/YA, YA/XA	(Any) deficient XA/XA, YA/O, XA/O, O/O
Bacterial and fungal infections [n (%)]					
Bouwman, 2005[49]	3/25 (12.0%)	4/12 (33.3%)	7/12 (58.3%)	3/25 (12.0%)	11/24 (45.8%)
Cervera, 2007[18]	32/124 (25.8%)	23/75 (30.7%)	10/37 (27.0%)	32/124 (25.8%)	33/112 (29.5%)
Cervera, 2009[48]	—	—	—	21/53 (39.6%)	15/42 (35.7%)
Worthley, 2009[50]	12/58 (20.7%)	18/35 (51.4%)	4/9 (44.4%)	12/58 (20.7%)	22/44 (50.0%)
de Rooij, 2010[52]	69/257 (26.8%)		26/53 (49.1%)	—	—
Curvelo, 2011[20]	88/243 (36.2%)		22/47 (46.8%)	59/159 (37.1%)	51/131 (38.9%)
Wan, 2013[54]	—	—	—	11/54 (20.4%)	6/27 (22.2%)
Lombardo-Quezada, 2018[19]	—	—	—	61/127 (48.0%)	74/113 (65.5%)
CMV event (asymptomatic infection or disease) [n (%)]					
Cervera, 2007[18a]	5/124 (4.0%)	4/75 (5.3%)	4/37 (10.8%)	5/124 (4.0%)	8/112 (7.1%)
Worthley, 2009[50b]	5/58 (8.6%)	2/35 (5.7%)	1/9 (11.1%)	5/58 (8.6%)	3/44 (6.8%)
de Rooij, 2011[53c]	93/245 (37.9%)		27/50 (54.0%)	—	—
Lombardo-Quezada, 2018[19b]	—	—	—	9/127 (7.1%)	5/113 (4.4%)

CMV, cytomegalovirus; SNP, single nucleotide polymorphism.
[a]CMV viral syndrome or end-organ disease.
[b]CMV end-organ disease.
[c]CMV infection or disease.

Three studies[18,19,50] (comprising 578 patients) reported data for the analysis of high- versus intermediate- or low/null-MBL expression haplotypes (YA/YA, YA/XA vs. XA/XA, YA/O, XA/O, O/O), with no significant association observed (fixed-effect RR: 0.98; 95% CI: 0.51–1.86; $P = .94$); no heterogeneity [$Chi^2 = 1.92$; $P = .38$; $I^2 = 0\%$]). Three studies[18,50,53] (comprising 633 patients) provided data for the comparison of high- or intermediate- versus low/null-MBL expression haplotypes (YA/YA, YA/XA, XA/XA, YA/O vs. XA/O, O/O). In this case, there was a significant association with the occurrence of CMV events (fixed-effect RR: 1.50; 95% CI: 1.12–2.01; $P = .006$); no heterogeneity [$Chi^2 = 0.78$; $P = .68$; $I^2 = 0\%$]) (Figure S1 in Supporting Material).

Two studies[50,51] (comprising 149 patients) contained sufficient data for the pooled analysis of wild-type versus variant allele genotypes in exon 1 SNPs. A significant association was observed for

TABLE 4 Cumulative incidence rates of posttransplant infection according to genotypic distributions of different SNPs in the *MBL2* gene (donor genotype was considered for studies on liver transplant recipients)

Author, year [reference]	Exon 1 (codons 52 [rs5030737], 54 [rs1800450] and 57 [rs1800451]) A/A	 A/O	 O/O	Promoter region (−550 [rs11003125]) H/H	 H/L	 L/L
Bacterial and fungal infections [n (%)]						
Bouwman, 2005[49]	3/25 (12.0%)	7/18 (38.9%)	4/6 (66.7%)	1/3 (33.3%)	5/26 (19.2%)	8/20 (40.0%)
Cervera, 2009[48]	28/58 (48.3%)	12/37 (32.4%)		4/11 (36.4%)	36/83 (43.4%)	
Worthley, 2009[50]	12/62 (19.4%)	21/36 (58.3%)	1/4 (25.0%)	—	—	—
de Rooij, 2010[52]	49/182 (26.9%)	39/114 (34.2%)	7/14 (50.0%)	9/39 (23.1%)	51/148 (34.5%)	35/123 (28.5%)
Wan, 2013[54]	12/56 (21.4%)	5/25 (20.0%)		3/18 (16.7%)	14/63 (22.2%)	
Zhong, 2016[55]	—	—	—	34/62 (54.8%)	7/37 (18.9%)	3/14 (21.4%)
CMV event (asymptomatic infection or disease) [n (%)]						
Worthley, 2009[50a]	5/62 (8.1%)	2/36 (5.6%)	1/4 (25.0%)	—	—	—
Kerschner, 2009[51b]	13/24 (54.2%)	5/22 (22.7%)	1/1 (100.0%)	—	—	—

CMV, cytomegalovirus; SNP, single nucleotide polymorphism.
[a]CMV end-organ disease.
[b]CMV infection requiring preemptive therapy.

the recessive (A/A, A/O vs. O/O) (fixed-effects RR: 2.33; 95% CI: 1.01–5.38; $P = .05$; no heterogeneity [$Chi^2 = 0.39$; $P = .53$; $I^2 = 0\%$]) but not for the dominant genetic model (A/A vs. A/O, O/O) (fixed-effects RR: 0.59; 95% CI: 0.30–1.16; $P = .12$; no heterogeneity [$Chi^2 = 0.68$; $P = .41$; $I^2 = 0\%$]) (Figure S2).

3.6 | Subgroup analyses

Finally, we performed an a priori subgroup analysis stratified by the type of SOT. Since most of the included studies (72.7% [8/11]) only comprised LT recipients, subgroup estimates were mainly restricted to this population. Reported associations remained essentially unchanged when pooled RRs were exclusively based on studies comprising LT recipients. The only analysis performed in a nonliver transplant population (KT recipients [317 patients]) compared high- versus intermediate- or low/null-MBL expression haplotypes and revealed no significant association with the occurrence of posttransplant bacterial and fungal infections (Table S1).

3.7 | Publication bias

The visual inspection of funnel plots showed no obvious asymmetry (Figures S3 and S4 [only plots for exon 1 SNPs and MBL-deficient haplotypes are depicted]). In addition, the Egger's test revealed no statistical evidence of publication bias (Table S2).

4 | DISCUSSION

Genetic susceptibility to infection among SOT recipients appears to be driven by a number of allelic variants in genes orchestrating innate and adaptive immune responses,[2] whose clinical impact may be at least partially unmasked by the effect of posttransplant immunosuppression. In the present meta-analysis comprising 11 studies and more than 1800 SOT recipients we observed that, as compared to high-MBL expression haplotypes (YA/YA or YA/XA), the risk of posttransplant bacterial and fungal infections significantly increases by 30% in the presence of any MBL-deficient haplotype. This difference was more evident, reaching a 51% risk increase, when the comparison was focused on haplotypes known to be associated with low/null serum MBL levels (XA/O or O/O). The carriers of these haplotypes were also found to face an increased risk of CMV events. The pooled analysis of individual SNPs only revealed the impact on study outcomes of exon 1 polymorphisms in the recessive, but not the dominant, model (A/A or A/O vs. O/O). On the other hand, the presence of variant alleles in SNPs located in the promoter region showed no association with the development of posttransplant infection.

Due to the long-term inhibition of the T cell–mediated (and, partially, B cell-mediated) immunity exerted by immunosuppressive regimens, it is assumed that the innate immunity may play an important role in SOT recipients, proportionally more relevant than in immunocompetent individuals. It should be noted, however, that the significant RRs for posttransplant bacterial and fungal infections ranged from 1.10 to 1.72, which translates, at most, into a moderate impact on the host's susceptibility. The existence of a network of redundant mechanisms and both soluble and membrane-bound receptors involved in the recognition of pathogen-associated molecular patterns may contribute to partially dilute the detrimental effect attributable to impaired MBL production.[56,57] Interestingly, the absolute values of these RRs were in line with those estimated in the general population for the development of sepsis among carriers of variant alleles of exon 1 SNPs.[24,25]

In order to assess the plausibility of a codominant model, we performed pairwise comparisons between different *MBL2* haplotypes grouped according to the expected translation in terms of functional

Promoter region (−221 [rs7096206])			Promoter region (+4 [rs7095891])		
X/X	X/Y	Y/Y	P/P	P/Q	Q/Q
0/0 (0.0%)	4/14 (28.6%)	10/35 (28.6%)	–	–	–
3/5 (60.0%)	37/90 (41.1%)		38/91 (41.8%)		2/4 (50.0%)
–	–	–	–	–	–
3/18 (16.7%)	37/110 (33.6%)	55/182 (30.2%)	–	–	–
1/2 (50.0)	16/79 (20.3%)		10/62 (16.1%)	7/19 (36.8%)	
–	–	–	–	–	–
–	–	–	–	–	–
–	–	–	–	–	–

TABLE 5 Cumulative incidence rates of posttransplant infection according to recipient haplotypes or genotype combinations in studies on liver transplant recipients

Author, year [reference]	Sufficient A/A	Deficient A/O, O/O	Sufficient YA/YA, YA/XA	Intermediate XA/XA, YA/O	Low/null XA/O, O/O	Sufficient YA/YA, YA/XA	Deficient XA/XA, YA/O, XA/O, O/O
Bacterial and fungal infections [n (%)]							
de Rooij, 2010[52]	64/190 (33.7%)	31/120 (25.8%)	81/263 (30.8%)		14/47 (29.8%)	–	–
CMV event (asymptomatic infection or disease) [n (%)]							
de Rooij, 2011[53]	–	–	107/251 (42.6%)		13/44 (29.5%)	–	–

CMV, cytomegalovirus.

MBL serum levels. A borderline significant association with the risk of posttransplant infection (RR: 1.80; 95% CI: 0.99–3.24) was observed for carriers of XA/XA or YA/O haplotypes (intermediate production) compared to wild-type (YA/YA or YA/XA) haplotypes. On the contrary, the comparison between intermediate- and low/null-expression haplotypes showed no evident association. However, as only three studies[18,49,50] could be pooled for this subanalysis, insufficient statistical power cannot be excluded. These results would imply that even relatively minor decreases in the production of functional MBL protein might have a measurable impact on the occurrence of bacterial or fungal infections after SOT.

Polymorphisms in the promoter region of the *MBL2* gene at positions −550 (H/L) and −221 (X/Y) have been shown to affect the transcription level of MBL.[11,12,58] Nevertheless, there was no suggestion of an effect on the incidence of posttransplant infection either in the recessive or dominant modeling. This apparent lack of impact for promoter SNPs is concordant with other meta-analyses focused on the risk of sepsis,[25] tuberculosis,[22] or progression/chronicity of hepatitis B virus infection[59] in nontransplant populations.

Most of the included studies did not provide detailed microbiological or clinical data for the episodes of posttransplant infection. Lombardo-Quezada et al. found that recipients of MBL-deficient livers had higher incidence of bacterial pneumonia and infections due to *Pseudomonas aeruginosa*.[19] *MBL2* polymorphisms have been also shown to predispose to *P. aeruginosa* airway colonization in patients with cystic fibrosis.[60] In addition, MBL-deficient livers conferred an increased risk of posttransplant septic shock in two of the studies.[19,48] The impact of the MBL pathway on the severity of infection may be related to its modulating role in the production of

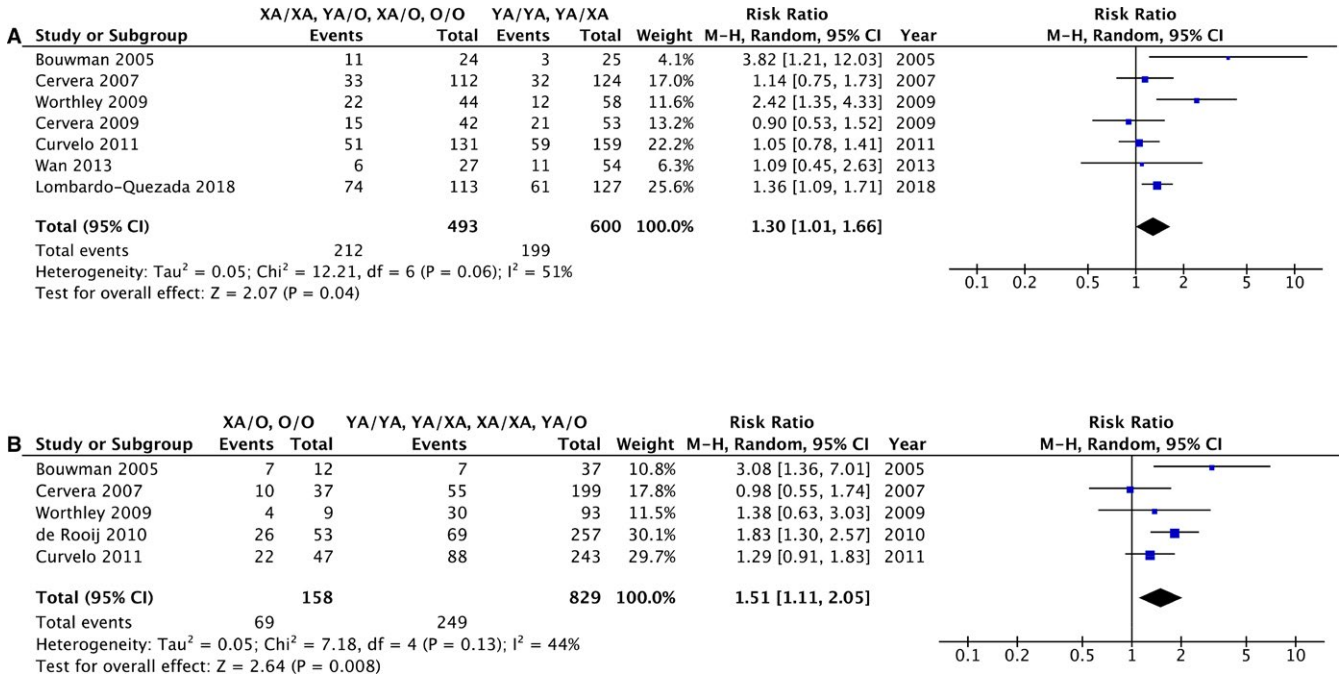
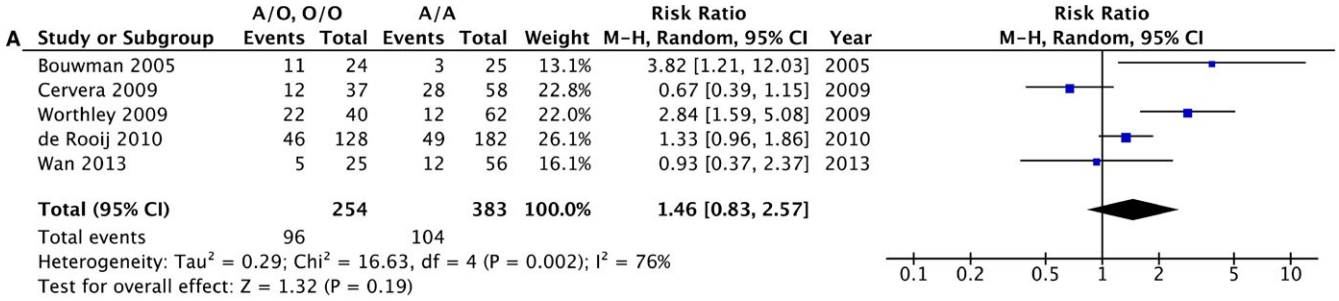


FIGURE 2 Forest plots of risk ratios for posttransplant bacterial and fungal infections (primary study outcome) associated with the presence of MBL-deficient haplotypes of the *MBL2* gene: (A) high-MBL expression (YA/YA, YA/XA) vs intermediate- or low/null-MBL expression haplotypes (XA/XA, YA/O, XA/O, O/O); (B) high- or intermediate-MBL expression (YA/YA, YA/XA, XA/XA, YA/O) vs low/null-MBL expression haplotypes (XA/O, O/O). CI, confidence interval; M-H, Mantel-Haenszel method [Color figure can be viewed at wileyonlinelibrary.com]



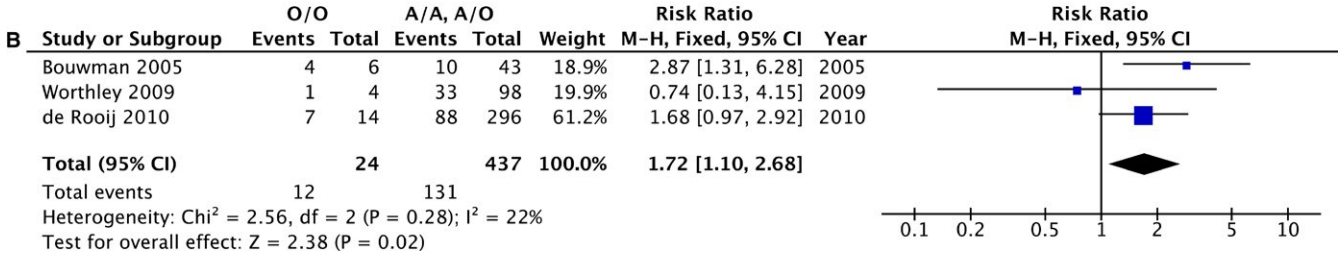
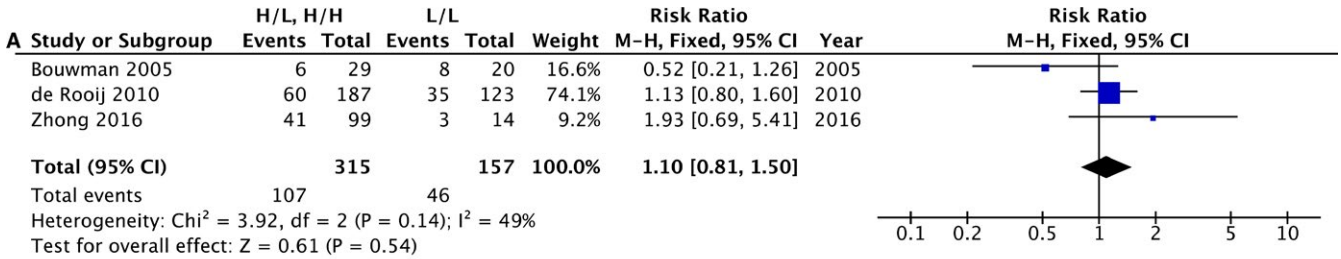


FIGURE 3 Forest plots of risk ratios for posttransplant bacterial and fungal infections (primary study outcome) associated with SNPs (rs5030737, rs1800450, rs1800451) located in the exon 1 coding region of the *MBL2* gene: (A) dominant genetic model (A/A vs. A/O, O/O); (B) recessive genetic model (A/A, A/O vs. O/O). CI, confidence interval; M-H, Mantel-Haenszel method; SNP, single-nucleotide polymorphism [Color figure can be viewed at wileyonlinelibrary.com]



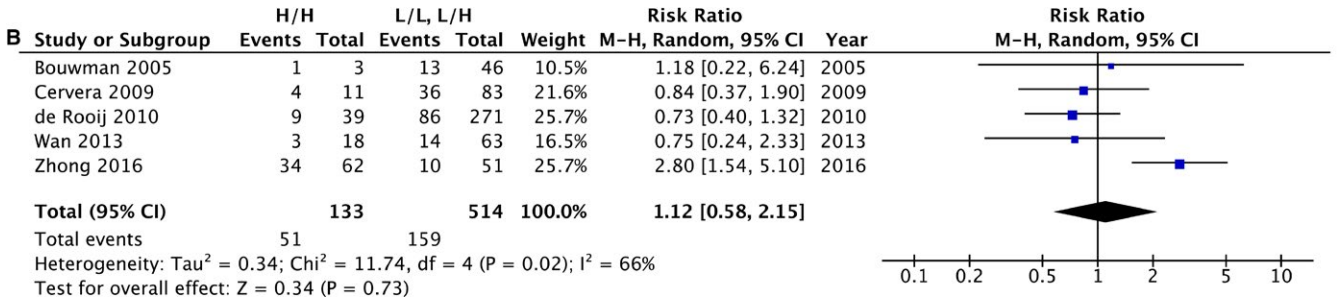


FIGURE 4 Forest plots of risk ratios for posttransplant bacterial and fungal infections (primary study outcome) associated with the rs11003125 (C>G) SNP at position −550 in the promoter region of the *MBL2* gene: (A) dominant genetic model (L/L vs. H/L, H/H); (B) recessive genetic model (L/L, L/H vs. H/H). CI, confidence interval; M-H, Mantel-Haenszel method; SNP, single-nucleotide polymorphism [Color figure can be viewed at wileyonlinelibrary.com]

proinflammatory mediators (such as interleukin-6 or C5a) in response to bacterial pathogens.[61] A case-control study reported that variant allele at position +4 (P/Q) in the UTR influenced the susceptibility to bacteremia after KT.[54] Mannans are mannose-based polysaccharides that serve as major components of the fungal cell and are recognized by MBL.[62] Therefore, it may be expected that the risk of invasive fungal infection would be increased in MBL-deficient SOT recipients. Unfortunately, most of the included studies only focused on bacterial

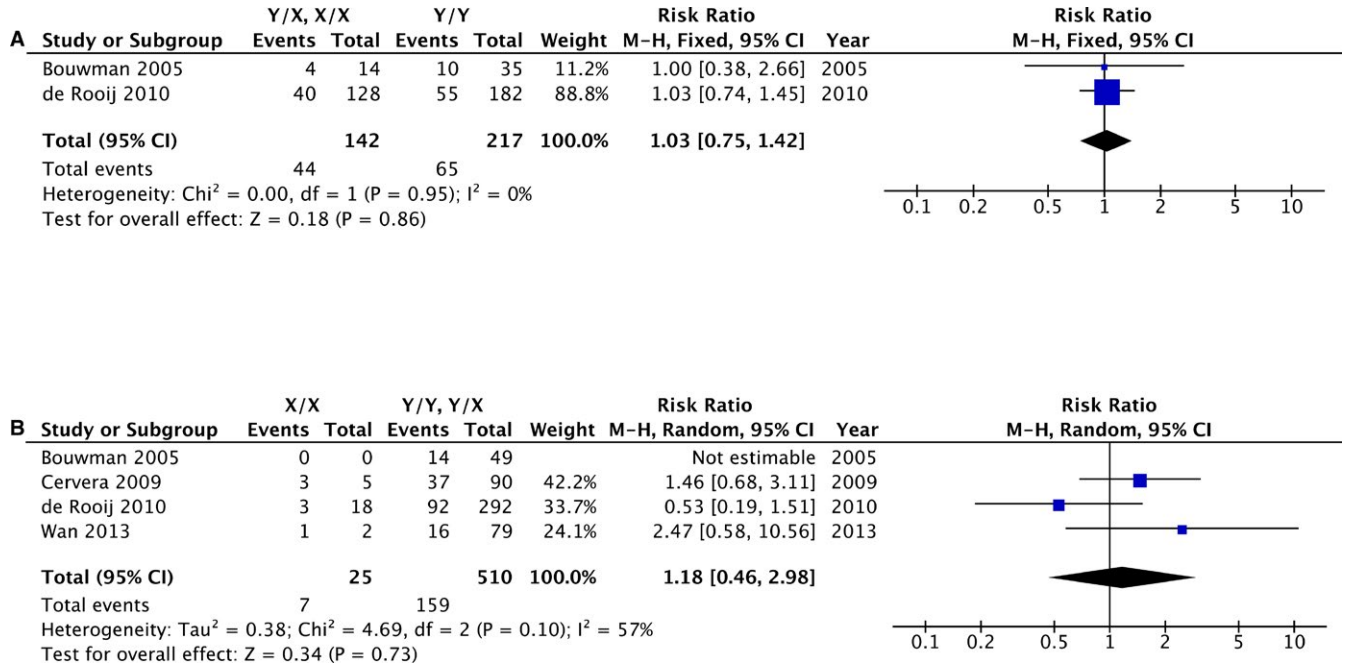


FIGURE 5 Forest plots of risk ratios for posttransplant bacterial and fungal infections (primary study outcome) associated with the rs7096206 (G>C) SNP at position −221 in the promoter region of the *MBL2* gene: (A) dominant genetic model (Y/Y vs. Y/X, X/X); (B) recessive genetic model (Y/Y, Y/X vs. X/X). CI, confidence interval; M-H, Mantel-Haenszel method; SNP, single-nucleotide polymorphism [Color figure can be viewed at wileyonlinelibrary.com]

episodes or did not contain separate rates for bacterial and fungal infections. For these reasons, we were not able to distinguish the occurrence of fungal infection as an individual outcome. Of note, the low number of episodes observed in the few studies detailing such data[18,19] may have contributed to underestimating the real effect of *MBL2* polymorphisms on the risk of invasive fungal infection, emphasizing the need of further research focused on this specific outcome.

We considered the occurrence of CMV infection or disease as a priori secondary outcome. Indeed, it has been shown that polymorphisms in genes involved in the orchestration of innate immune responses may influence the susceptibility to posttransplant CMV infection.[63] Glycoproteins of the viral envelope that play key roles in the process of CMV entry into host cells are also potential targets for MBL binding. However, the extent to which MBL deficiency may increase the risk of CMV infection remains controversial, with studies reporting a lack of association for human immunodeficiency virus patients[64] or perinatal CMV infection.[65] A first small study involving high-risk KT recipients found that low serum MBL levels were more common among patients that developed CMV events compared to those who remained free from infection.[13] It has been also suggested that the wild-type AA genotype in exon 1 might confer a higher risk of tissue-invasive CMV disease, a seemingly contradictory result.[40] Here, on the basis of three studies[18,50,53] including more than 600 patients, we found that the presence of haplotypes leading to low/null MBL expression (XA/O or O/O) was associated with a 50% increase in the risk of developing a CMV event as compared to high- or intermediate-MBL expression haplotypes, whereas no association was observed when XA/XA or YA/XA were used as the reference category. Accordingly, variant alleles in SNPs located in exon 1 only showed significant association in the recessive genetic model. These findings would suggest that, in contrast to bacterial or fungal infections, only a major decline in MBL production exerts a clinically meaningful impact on the risk of CMV infection. Nevertheless, caution is needed when interpreting this secondary analysis, since the number of patients included was low, both asymptomatic infection and clinical disease were jointly considered due to the lack of individualized data, and the potential confounding of relevant variables (such as donor/recipient serostatus, frequency of monitoring for CMV viremia or use of antiviral prophylaxis) could not be accounted for.

Since the MBL protein is mainly (but not exclusively) synthetized in the liver,[4] most of the included studies comprising LT recipients were restricted to the impact of donor genotypes. Only two studies based on partially overlapping cohorts[52,53] reported specific rates for posttransplant bacterial and CMV infection according to recipient genotypes, therefore preventing a pooled analysis. Of note, both studies suggest that the relative contribution of recipient polymorphisms in the *MBL2* gene following LT should be considered negligible. In fact, the risk of bacterial infection was almost doubled among carriers of high- or intermediate-MBL expression haplotypes who received a MBL-deficient (XA/O or O/O) liver compared to other combinations, demonstrating that the genetic background of the recipient is outweighed by that of the donor.[52] In view of these findings, genotyping efforts should be focused on liver graft donors rather than recipients as the major determinant of MBL-related susceptibility to infection.

Given the relatively low sample sizes (particularly for minor allele populations) and single-center designs of most

existing studies, the meta-analytic approach offers a valid tool for analyzing the association between *MBL2* polymorphisms and posttransplant infection, as previously shown for nonimmunocompromised individuals.[21-26] Nevertheless, limitations must be acknowledged. Due to the lack of consistency in criteria applied for grouping *MBL2* genotypes, comparisons had to be restricted to subgroups of studies, with significant heterogeneity detected for some of them. Most studies did not separately report incidence rates according to causative agents or clinical syndromes. Therefore, our meta-analysis somewhat lacks detailed clinical data to provide specific estimates for bacterial and fungal infections, or to distinguish between asymptomatic CMV infection and clinically evident disease. In addition, meaningful differences in incidence rates were observed across certain studies,[48,49,54] suggesting the existence of disparate diagnostic criteria and follow-up periods, which would have contributed in turn to the significant heterogeneity detected. The subgroup analysis for nonliver transplant recipients only included two studies[18,54] and did not reveal any statistical association. Therefore, our findings mostly apply to the LT population. In this sense, we were not able to meta-analyze the contribution of recipient *MBL2* genotypes or haplotypes, as noted above. Finally, it remains unclear whether *MBL2* genotyping offers practical advantages over a more dynamic strategy based on the monitoring of serum levels of the functionally active MBL protein. It could be hypothesized that the latter approach would reflect the combined effect of both *MBL2* gene SNPs and liver graft function throughout the posttransplant period.

In conclusion, this comprehensive meta-analysis indicates that the presence of any MBL-deficient haplotype has a significant association with the susceptibility to bacterial and fungal infections after SOT in comparison with high-expression haplotypes (YA/YA or YA/XA) in the *MBL2* gene. Low/null-MBL expression haplotypes (XA/O or O/O) also confer an increased risk for CMV infection or disease. Due to the scarcity of studies dealing with other transplant populations, such findings mostly apply to LT recipients. Therefore, current evidence indicates that *MBL2* gene polymorphisms and the lectin pathway of complement activation play a meaningful contribution to the defense against pathogens after SOT. The implications for patient management remain to be determined.

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DISCLOSURE

The authors have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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REFERENCES

1. Razonable RR. Innate immune genetic profile to predict infection risk and outcome after liver transplant. *Hepatology*. 2010;52:814-817.
2. Sanclemente G, Moreno A, Navasa M, Lozano F, Cervera C. Genetic variants of innate immune receptors and infections after liver transplantation. *World J Gastroenterol*. 2014;20:11116-11130.
3. Garred P, Genster N, Pilely K, et al. A journey through the lectin pathway of complement-MBL and beyond. *Immunol Rev*. 2016;274:74-97.
4. Dobo J, Pal G, Cervenak L, Gal P. The emerging roles of mannose-binding lectin-associated serine proteases (MASPs) in the lectin pathway of complement and beyond. *Immunol Rev*. 2016;274:98-111.
5. Ibernon M, Moreso F, Seron D. Innate immunity in renal transplantation: the role of mannose-binding lectin. *Transplant Rev (Orlando)*. 2014;28:21-25.
6. Bouwman LH, Roep BO, Roos A. Mannose-binding lectin: clinical implications for infection, transplantation, and autoimmunity. *Hum Immunol*. 2006;67:247-256.
7. Holdaway J, Deacock S, Williams P, Karim Y. Mannose-binding lectin deficiency and predisposition to recurrent infection in adults. *J Clin Pathol*. 2016;69:731-736.
8. Naito H, Ikeda A, Hasegawa K, et al. Characterization of human serum mannan-binding protein promoter. *J Biochem*. 1999;126:1004-1012.
9. Crosdale DJ, Ollier WE, Thomson W, et al. Mannose binding lectin (MBL) genotype distributions with relation to serum levels in UK Caucasoids. *Eur J Immunogenet*. 2000;27:111-117.
10. Turner MW, Hamvas RM. Mannose-binding lectin: structure, function, genetics and disease associations. *Rev Immunogenet*. 2000;2:305-322.
11. Madsen HO, Garred P, Thiel S, et al. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. *J Immunol*. 1995;155:3013-3020.
12. Steffensen R, Thiel S, Varming K, Jersild C, Jensenius JC. Detection of structural gene mutations and promoter polymorphisms in the mannan-binding lectin (MBL) gene by polymerase chain reaction with sequence-specific primers. *J Immunol Methods*. 2000;241:33-42.
13. Manuel O, Pascual M, Trendelenburg M, Meylan PR. Association between mannose-binding lectin deficiency and cytomegalovirus infection after kidney transplantation. *Transplantation*. 2007;83:359-362.
14. Carroll KE, Dean MM, Heatley SL, et al. High levels of mannose-binding lectin are associated with poor outcomes after lung transplantation. *Transplantation*. 2011;91:1044-1049.
15. Kwakkel-van Erp JM, Paantjens AW, van Kessel DA, et al. Mannose-binding lectin deficiency linked to cytomegalovirus (CMV) reactivation and survival in lung transplantation. *Clin Exp Immunol*. 2011;165:410-416.
16. Sagedal S, Thiel S, Hansen TK, Mollnes TE, Rollag H, Hartmann A. Impact of the complement lectin pathway on cytomegalovirus disease early after kidney transplantation. *Nephrol Dial Transplant*. 2008;23:4054-4060.
17. Liman P, Babel N, Schachtner T, et al. Mannose-binding lectin deficiency is not associated with increased risk for polyomavirus nephropathy. *Transpl Immunol*. 2012;26:123-127.

18. Cervera C, Lozano F, Saval N, et al. The influence of innate immunity gene receptors polymorphisms in renal transplant infections. *Transplantation*. 2007;83:1493-1500.
19. Lombardo-Quezada J, Sanclemente G, Colmenero J, et al. Mannose-binding lectin-deficient donors increase the risk of bacterial infection and bacterial infection-related mortality after liver transplantation. *Am J Transplant*. 2018;18:197-206.
20. Curvelo LA, de Mare-Bredemeijer E, de Canck I, et al. Does the donor mannose-binding lectin genotype really predict the risk of bacterial infections after liver transplantation? *Hepatology*. 2011;53:1786-1787.
21. Denholm JT, McBryde ES, Eisen DP. Mannose-binding lectin and susceptibility to tuberculosis: a meta-analysis. *Clin Exp Immunol*. 2010;162:84-90.
22. Areeshi MY, Mandal RK, Akhter N, et al. A meta-analysis of *MBL2* polymorphisms and tuberculosis risk. *Sci Rep*. 2016;6:35728.
23. Atan O, Kucukcelebi A, Atik T, Ozkinay F. Mannose binding lectin codon 54 polymorphism and susceptibility to recurrent respiratory tract infections in children: a meta-analysis. *Int J Pediatr Otorhinolaryngol*. 2016;81:41-45.
24. Luo J, Xu F, Lu GJ, Lin HC, Feng ZC. Low mannose-binding lectin (MBL) levels and MBL genetic polymorphisms associated with the risk of neonatal sepsis: an updated meta-analysis. *Early Hum Dev*. 2014;90:557-564.
25. Zhang AQ, Yue CL, Pan W, et al. Mannose-binding lectin polymorphisms and the risk of sepsis: evidence from a meta-analysis. *Epidemiol Infect*. 2014;142:2195-2206.
26. Nedovic B, Posteraro B, Leoncini E, et al. Mannose-binding lectin codon 54 gene polymorphism and vulvovaginal candidiasis: a systematic review and meta-analysis. *Biomed Res Int*. 2014;2014:738298.
27. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.
28. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa: Ottawa Health Research Institute; 1999.
29. Berger SP, Roos A, Mallat MJ, et al. Low pretransplantation mannose-binding lectin levels predict superior patient and graft survival after simultaneous pancreas-kidney transplantation. *J Am Soc Nephrol*. 2007;18:2416-2422.
30. Bohlouli A, Ebrahimzadeh ME, Kafil HS, Asgharzadeh M. Evaluation mannose-binding lectin gene and promoter polymorphism in renal transplant recipients. *J Pak Med Assoc*. 2008;58:294-298.
31. Munster JM, van der Bij W, Breukink MB, et al. Association between donor MBL promoter haplotype and graft survival and the development of BOS after lung transplantation. *Transplantation*. 2008;86:1857-1863.
32. Golshayan D, Wojtowicz A, Bibert S, et al. Polymorphisms in the lectin pathway of complement activation influence the incidence of acute rejection and graft outcome after kidney transplantation. *Kidney Int*. 2016;89:927-938.
33. Van Den Broek MA, Olde Damink SWM, Adamzik M, et al. Gene polymorphisms and the risk of clinically significant infections and in-hospital mortality in living donor liver transplant recipients. *HPB*. 2010;12:56.
34. Pyndiah N, Kralidis G, Wójtowicz A, et al. Does mannose-binding lectin plasma level predict the incidence of cytomegalovirus disease in solid-organ transplant recipients? *Am J Transplant*. 2013;13:212.
35. Carbone J, Arraya M, Lozano F, Palomo J, Sarmiento E. Mannose-binding lectin serum levels and pre-tranplant genotypes for personalized anti-CMV prophylaxis in heart recipients. *J Heart Lung Transplant*. 2015;34:S125.
36. Verschuren JJ, Roos A, Schaapherder AF, et al. Infectious complications after simultaneous pancreas-kidney transplantation: a role for the lectin pathway of complement activation. *Transplantation*. 2008;85:75-80.
37. de Mare-Bredemeijer EL, Mancham S, Utomo WK, et al. Genetic polymorphisms in innate immunity receptors do not predict the risk of bacterial and fungal infections and acute rejection after liver transplantation. *Transpl Infect Dis*. 2013;15:120-133.
38. Lambourne J, Agranoff D, Herbrecht R, et al. Association of mannose-binding lectin deficiency with acute invasive aspergillosis in immunocompromised patients. *Clin Infect Dis*. 2009;49:1486-1491.
39. Ou XT, Wu JQ, Zhu LP, et al. Genotypes coding for mannose-binding lectin deficiency correlated with cryptococcal meningitis in HIV-uninfected Chinese patients. *J Infect Dis*. 2011;203:1686-1691.
40. Cervera C, Lozano F, Linares L, et al. Influence of mannose-binding lectin gene polymorphisms on the invasiveness of cytomegalovirus disease after solid organ transplantation. *Transplant Proc*. 2009;41:2259-2261.
41. Degn SE, Jensenius JC, Bjerre M. The lectin pathway and its implications in coagulation, infections and auto-immunity. *Curr Opin Organ Transplant*. 2011;16:21-27.
42. Gunesacar R, Tastemir D, Yildirim A, Eryilmaz N. Structure, function, molecular genetics, disease asociations and therapeutic potential of mannose binding lectin: review. *Türkiye Klinikleri Tıp Bilimleri Dergisi*. 2011;31:1250-1261.
43. van Hoek B, de Rooij BJ, Verspaget HW. Risk factors for infection after liver transplantation. *Best Pract Res Clin Gastroenterol*. 2012;26:61-72.
44. Huang YF, Chen H, Wang X, Fan TY. Cytomegalovirus infection after liver transplantation: its effects on rejection and graft. *Chin J Tissue Eng Res*. 2014;18:4423-4428.
45. Ruttens D, Vandermeulen E, Verleden SE, et al. Role of genetics in lung transplant complications. *Ann Med*. 2015;47:106-115.
46. Kalil AC. Can serum mannose-binding lectin levels aid with the diagnosis of invasive aspergillosis? *Clin Infect Dis*. 2009;49:1492-1495.
47. Perkins JD. Predicting posttransplantation infection risk with gene polymorphisms. *Liver Transpl*. 2006;12:488-489.
48. Cervera C, Balderramo D, Suarez B, et al. Donor mannose-binding lectin gene polymorphisms influence the outcome of liver transplantation. *Liver Transpl*. 2009;15:1217-1224.
49. Bouwman LH, Roos A, Terpstra OT, et al. Mannose binding lectin gene polymorphisms confer a major risk for severe infections after liver transplantation. *Gastroenterology*. 2005;129:408-414.
50. Worthley DL, Johnson DF, Eisen DP, et al. Donor mannose-binding lectin deficiency increases the likelihood of clinically significant infection after liver transplantation. *Clin Infect Dis*. 2009;48:410-417.
51. Kerschner H, Jaksch P, Karigl G, Popow-Kraupp T, Klepetko W, Puchhammer-Stockl E. Cytomegalovirus DNA load patterns developing after lung transplantation are significantly correlated with long-term patient survival. *Transplantation*. 2009;87:1720-1726.
52. de Rooij BJ, van Hoek B, ten Hove WR, et al. Lectin complement pathway gene profile of donor and recipient determine the risk of bacterial infections after orthotopic liver transplantation. *Hepatology*. 2010;52:1100-1110.
53. de Rooij BJ, van der Beek MT, van Hoek B, et al. Mannose-binding lectin and ficolin-2 gene polymorphisms predispose to cytomegalovirus (re)infection after orthotopic liver transplantation. *J Hepatol*. 2011;55:800-807.
54. Wan QQ, Ye QF, Zhou JD. Mannose-binding lectin 2 and ficolin-2 gene polymorphisms influence the susceptibility to bloodstream infections in kidney transplant recipients. *Transplant Proc*. 2013;45:3289-3292.

55. Zhong L, Li H, Li Z, et al. C7 genotype of the donor may predict early bacterial infection after liver transplantation. *Sci Rep*. 2016;6:24121.
56. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. *Science*. 2010;327:291-295.
57. Fischer A, Rausell A. What do primary immunodeficiencies tell us about the essentiality/redundancy of immune responses? *Semin Immunol*. 2018;36:13-16.
58. Minchinton RM, Dean MM, Clark TR, Heatley S, Mullighan CG. Analysis of the relationship between mannose-binding lectin (MBL) genotype, MBL levels and function in an Australian blood donor population. *Scand J Immunol*. 2002;56:630-641.
59. Xu HD, Zhao MF, Wan TH, Song GZ, He JL, Chen Z. Association between Mannose-binding lectin gene polymorphisms and hepatitis B virus infection: a meta-analysis. *PLoS ONE*. 2013;8:e75371.
60. Haerynck F, Van Steen K, Cattaert T, et al. Polymorphisms in the lectin pathway genes as a possible cause of early chronic *Pseudomonas aeruginosa* colonization in cystic fibrosis patients. *Hum Immunol*. 2012;73:1175-1183.
61. Jack DL, Read RC, Tenner AJ, Frosch M, Turner MW, Klein NJ. Mannose-binding lectin regulates the inflammatory response of human professional phagocytes to *Neisseria meningitidis* serogroup B. *J Infect Dis*. 2001;184:1152-1162.
62. Camargo JF, Husain S. Immune correlates of protection in human invasive aspergillosis. *Clin Infect Dis*. 2014;59:569-577.
63. Fernández-Ruiz M, Corrales I, Arias M, et al. Association between individual and combined SNPs in genes related to innate immunity and incidence of CMV infection in seropositive kidney transplant recipients. *Am J Transplant*. 2015;15:1323-1335.
64. Egli A, Schafer J, Osthoff M, et al. Low levels of mannan-binding lectin or ficolins are not associated with an increased risk of cytomegalovirus disease in HIV-infected patients. *PLoS ONE*. 2013;8:e51983.
65. Szala A, Paradowska E, Nowakowska D, et al. Mannan-binding lectin-2 (MBL2) gene polymorphisms in prenatal and perinatal cytomegalovirus infections. *Mol Immunol*. 2011;48:2203-2206.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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