ISSN: 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

# Association of *IMPDH1* and *IMPDH2* gene polymorphisms with efficacy and toxicity of mycophenolic acid treatment in renal transplant patients: a narrative review

**Dimo Pratama[1]*, Zullies Ikawati[2], Adam Hermawan[3]**

[1]Master in Clinical Pharmacy Program, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia, [3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia

https://doi.org/10.22146/ijpther.20875

Submitted: 18-04-2025
Accepted : 23-06-2025

***Keywords***:
*IMPDH1*;
*IMPDH2*;
mycophenolate;
single nucleotide polymorphism (SNP);
renal transplant recipients

## ABSTRACT

Immunosuppressive regimen treatment in renal transplant recipients is necessary to prevent acute rejection from the body's immune system. Mycophenolic acid (MPA), commonly prescribed for renal transplant recipients, exists in two formulations: mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS). Both drugs act by inhibiting inosine-5'-monophosphate dehydrogenase (IMPDH), an enzyme that is responsible for the guanosine nucleotide synthesis pathway of T and B lymphocytes. IMPDH exists in two isoforms, IMPDH1 and IMPDH2, encoded by *IMPDH1* and *IMPDH2* gene, respectively. Polymorphisms in these genes may alter the enzyme activity, potentially influencing MPA pharmacodynamics and leading to variations in therapeutic responses among renal transplant patients taking MPA. A systematic literature search was performed using Scopus, PubMed, and Web of Science with the Boolean search strategy: "IMPDH AND Polymorphism* AND Mycophenol* AND ((Renal OR Kidney) Transplant* OR Graft*)". The articles yielded from this literature search were screened, resulting in 15 articles that were included in this review. Some studies reported the association between the *IMPDH1* or *IMPDH2* polymorphism and acute rejection, while others found no significant correlation. Regarding toxicity, leukopenia was linked to *IMPDH1* SNPs (rs2278293, rs2278294), although the results were inconsistent. Most of the studies found no significant association between *IMPDH2* SNPs and leukopenia incidence.

## ABSTRAK

Pemberian regimen imunosupresan pada pasien penerima transplantasi ginjal diperlukan untuk mencegah terjadinya rejeksi akut oleh sistem imun tubuh. Mycophenolic acid (MPA) umum diresepkan pada pasien penerima transplantasi ginjal yang tersedia dalam 2 jenis formulasi, yaitu mikofenolat mofetil (*MMF*) dan sodium mikofenolat salut enterik (*EC-MPS*). Kedua obat tersebut bekerja dengan menghambat inosine-5'-monophosphate dehydrogenase (IMPDH), yaitu suatu enzim yang berperan dalam jalur sintesis nukleotida guanosin pada limfosit T dan B. IMPDH terdiri dari dua isoform, yaitu IMPDH1 dan IMPDH2 yang masing-masing dikode oleh gen *IMPDH1* dan *IMPDH2*. Adanya polimorfisme pada kedua gen ini dapat mempengaruhi aktivitas enzim yang berpotensi mempengaruhi farmakodinamik MPA sehingga menyebabkan bervariasinya respons terapi antarpasien penerima transplantasi ginjal yang menggunakan MPA. Penelusuran literatur secara sistematis dilakukan pada *database* Scopus, Pubmed, dan Web of Science dengan memanfaatkan *Boolean operator*: "IMPDH AND Polymorphism* AND Mycophenol* AND ((Renal OR Kidney) Transplant* OR Graft*)". Artikel-artikel yang dihasilkan dari penelusuran tersebut diskrining hingga mendapatkan 15 artikel yang ditinjau. Beberapa studi melaporkan adanya hubungan antara polimorfisme gen *IMPDH1* atau *IMPDH2* dan rejeksi akut, tetapi studi lainnya menyatakan tidak menemukan korelasi yang signifikan. Dalam hal toksisitas, leukopenia dihubungkan dengan SNP *IMPDH1* (rs2278293, rs2278294), meskipun hasil ini tidak konsisten. Sebagian besar studi menunjukkan tidak ada hubungan yang signifikan antara SNPs *IMPDH2* dengan kejadian leukopenia.

*corresponding author: dimopratama@mail.ugm.ac.id

## INTRODUCTION

Renal transplantation is the preferred treatment for patients with end-stage renal disease.[1] However, rejection episodes remain a significant challenge due to immune system responses against the grafted organ. Therefore, immunosuppressive therapy is essential to prevent acute rejection and prolong graft survival. Immunosuppressant therapy for renal transplant recipients is categorized into induction and maintenance regimens.[2] As outlined in the KDIGO Guidelines, the maintenance immunosuppressive regimen for renal transplant recipents consisting of a calcineurin inhibitor (cyclosporine or tacrolimus) and an antiproliferative agent (azathioprine or mycophenolate), with or without corticosteroids.[3] Despite advances in immunosuppressive therapy, rejection remains a major concern in renal transplantation.[4] Acute rejection is one of the most common complications occurring within one year after renal transplantation and an important risk factor causing chronic rejection, kidney graft failure, and one of the main factors affecting the survival of renal transplant recipients.[5]

Among the available antiproliferative immunosuppressants, mycophenolic acid is still regarded as the standard agent in immunosuppressive regimen across transplant centers and is also recommended by KDIGO Guidelines as the first line antiproliferative therapy.[3,6] The immunosuppressant activity exerts by inhibiting the inosine-5'-monophosphate dehydrogenase (IMPDH), a key enzyme in the de novo guanosine nucleotide synthesis pathway, suppressing T and B lymphocyte proliferation.[7] Currently, two types of MPA formulation exist, mycophenolate mofetil (MMF) an ester prodrug, and enteric-coated mycophenolate sodium (EC-MPS).[8] Both formulations are therapeutically equivalent and have similar safety profiles.[9] MPA may cause several dose-dependent gastrointestinal side effects, including diarrhea (45%), abdominal pain (23%), and nausea and vomiting (16%).[10,11] In post-renal transplantation patients, hematological complications such as leukopenia, anemia, and thrombocytopenia are common side effects of mycophenolic drugs.[12]

Despite its benefits, MPA treatment shows interindividual variability in efficacy and toxicity. This variability may be attributed to genetic variation in a gene encoding enzymes that are responsible for drug metabolism or target proteins. Variation in DNA nucleotide sequence occurs at a frequency of at least 1%, called polymorphisms.[13] Single nucleotide polymorphism (SNP) is the most common polymorphism type found in human DNA, approximately once every 300 nucleotide base pairs.[14,15] A genetic variant is considered a SNP if substitution of a single nucleotide base occurs in ≥ 1% of the population. Variability of therapeutic response among individuals as the impact of the difference in genetic profile is studied in a field called pharmacogenetics.

IMPDH is an enzyme that acts as a mycophenolic acid target that exists in two isoforms, IMPDH type I (IMPDH1) expressed constitutively in all tissues and IMPDH type II (IMPDH2) expressed by T and B lymphocytes after activation [16]. Both of the enzymes are encoded by *IMPDH1* and *IMPDH2*, respectively. Polymorphisms in *IMPDH1* and *IMPDH2* can modify IMPDH enzyme activity, potentially affecting MPA's immunosuppressive effects. Several identified SNP variants of both of the enzymes can generate variability either in clinical outcome or adverse effect of MPA therapy among renal transplant recipients. This review explores the impact of *IMPDH1* and *IMPDH2* gene polymorphisms on MPA efficacy and toxicity in renal transplant recipients, emphasizing their implications for personalized medicine. In transplant patients, personalized medicine can be applied to the prescribing of immunosuppressive regimens based on each individual's genetic profile which may influence the pharmacokinetics and pharmacodynamics of one or more

drugs within the immunosuppressive regimen.

Polymorphism in the *IMPDH1* and *IMPDH2* genes have been considered as potential factors in individualizing mycophenolate therapy, particularly by identifying the SNP status of the both genes in individual patients. This pharmacogenetic approach may help optimize therapeutic outcomes and enhance the predictability of potential toxicities. Patients carrying the variant alleles of *IMPDH2* (TC or CC genotypes) have been shown to exhibit lower sensitivity to the inhibitory activity of MPA on the IMPDH2 enzyme compared to those with the wild-type genotype.[17] In addition, two SNPs of *IMPDH1*, rs2228075 dan rs2278294, have been associated with a delayed onset of leukopenia and individuals with homozygous G allele (GG) demonstrated a higher protective effect against leukopenia than those with GA or AA genotypes.[18]

Several review studies have investigated gene polymorphisms that altering either pharmacokinetics or pharmacodynamics of mycophenolate. However, these reviews have not specifically focused on pharmacogenetics studies of *IMPDH1* and *IMPDH2*, the genes encoding the enzyme targeted by MPA. In addition, many of the published reviews did not emphasize clinical use of mycophenolate treatment in renal transplant recipients. This present review aims to explore studies investigating polymorphisms of genes encoding IMPDH enzyme which play a critical role in determining the pharmacodynamic response to MPA and may ultimately influence both its efficacy and toxicity. A previous review by Cheng *et al.* also addressed the association between polymorphism of gene encoding IMPDH and MPA response. However, the evaluation of clinical outcomes was largely limited to allograft rejection which as a measure of efficacy. In contrast, this review provides a broader perspective by also addressing MPA-related toxicity. Therefore, this study seeks to offer a more comprehensive overview of the relationship between *IMPDH1* and *IMPDH2* gene polymorphisms and clinical outcomes in renal transplant patients treated with mycophenolate.

## METHODS

A comprehensive literature search for this narrative review was conducted using Scopus, PubMed, and Web of Science to identify relevant studies. The articles were included in this review if they met the following criteria: 1). Clinical studies involving renal transplant recipients investigating the association of *IMPDH1* and/or *IMPDH2* gene polymorphism with MPA efficacy and toxicity, 2). Published in English, 3). Full-text availability.

Exclusion criteria: 1). Non-original articles (e.g., reviews, editorials), 2). Studies not involving renal transplant recipients, 3). Studies lacking genetic analysis of IMPDH polymorphism

Search terms included “IMPDH”, “Polymorphism”, “Mycophenolate”, and “Kidney or Renal Transplant/Graft”, combined with Boolean operators. Duplicate records and non-original studies were removed during screening process. The selection process followed PRISMA guidelines, ensuring systematic article selection and eligibility assessment. The flowchart of the literature search and screening is shown in FIGURE 1.

## RESULTS

The database search yielded 103 articles: 28 from Scopus, 24 from PubMed, and 51 from Web of Science. After removing duplicates and non-original studies, 32 studies were assessed for eligibility. Of these, 17 studies were excluded based on study population and relevance to the review focus, resulting in 15 studies were included in this review as presented in TABLE 1 and TABLE 2. These tables summarize association studies of *IMPDH* gene polymorphism with the efficacy and toxicity of mycophenolic acid, respectively.

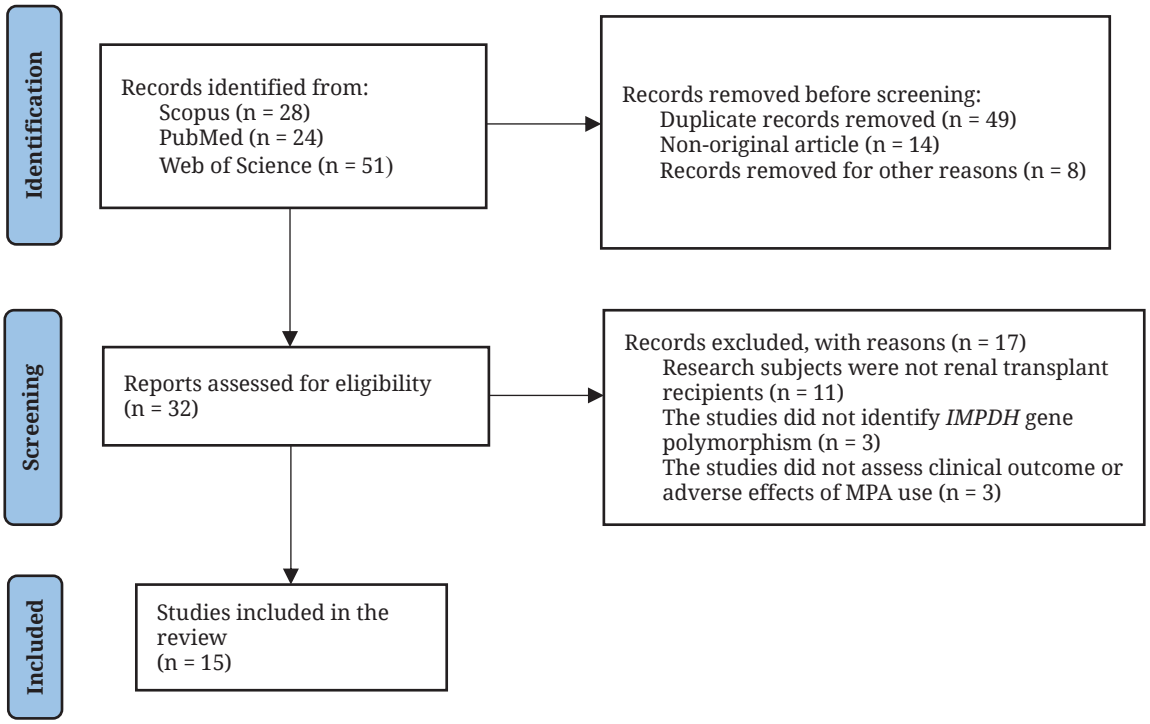


FIGURE 1. Flow diagram of the literature search and screening process

TABLE 1. Association Studies of *IMPDH1* and *IMPDH2* SNPs With Mycophenolic Acid Efficacy

| Reference | *IMPDH* SNPs of Interest | Study Design | Number of Subjects and Site of Study | Immunosuppressive Regimen | Result |
|---|---|---|---|---|---|
| Penezić *et al.*[19] | *IMPDH2 3757T>C* (rs11706052) | Observational study (prospective) | 254- Croatia | MPA (as EC-MPS or as MMF) + CNI (cyclosporin or tacrolimus + Prednisone | Polymorphisms of the *IMPDH2* gene did not influence renal graft function within one year post transplantation |
| Winnicki *et al.*[20] | *IMPDH2* rs11706052 | Prospective (Cohort Study) | 277 - Austria | Mycophenolate Sodium | No correlation was identified between the rs11706052 SNP status and graft rejection |
| Abderahmene *et al.*[17] | *IMPDH1-125G>A* (*rs2278293*); *IMPDH1-106G>A* (*rs2278294*); *IMPDH2-3757T>C* (*rs11706052*) | Retrospective | 245 - Tunisia | MMF + Cyclosporine/ Tacrolimus | Individuals carrying at least one variant allele of *IMPDH2-3757T>C* (rs11706052) experienced a markedly higher incidence of rejection episodes compared to noncarriers |
| Cilião *et al.*[21] | *IMPDH2* (rs11706052) | Retrospective (Case-Control) | 145 - Brazil | MMF + corticosteroid ± calcineurin inhibitor or mTOR inhibitor | The presence of at least one C allele (T/C and C/C) in the SNP rs11706052 (*IMPDH2*) conferred a 4.2-fold enhancement in protection against rejection |

TABLE 1. Cont.

| Reference | SNPs of Interest | Study Design | Number of Subjects and Site of Study | Immunosuppressive Regimen | Result |
|---|---|---|---|---|---|
| Shah *et al.*[22] | *IMPDH1* (rs2278293, rs2278294); *IMPDH2* (rs11706052) | Prospective Study | 1040 - UK | Dual immunosuppressive regimens: calcineurin inhibitor (cyclosporine or tacrolimus) and MMF | The study doesn't prove that IMPDH variants are associated with renal allograft rejection and graft survival |
| Pazik *et al.*[16] | (*IMPDH2*) rs11706052 | Prospective Study | 177 - Poland | MMF + glucocorticoids + calcineurin inhibitor) ± antithymocyte globulin (ATG) | There was an association between the 3757C allele (rs11706052) and higher lymphocyte counts. Nonetheless, there is no substantial distinction between patients carrying the C and T allele regarding the risk of acute rejection episodes |
| Gensburger *et al.*[23] | *IMPDH1* (rs2278293, rs2278294 ), *IMPDH2* (rs4974081, rs11706052, 787C>T) | Prospective Study | 456 - France | MMF-Cyclosporine or MMF-Tacrolimus | A notable correlation was identified between the *IMPDH1* SNP (rs2278294) and a reduce risk of BPAR occurrence<br>No correlation exists between the *IMPDH2* SNP and BPAR episodes |
| Kagaya *et al.*[24] | *IMPDH1* (rs2278293, rs2278294) | Prospective study | 82 - Japan | Tacrolimus + MMF (1.0, 1.5, or 2.0 g/day in equally divided doses every 12 hours) | A notable disparity in the prevalence of subclinical acute rejection was seen among the SNP *IMPDH1* rs2278293 genotypes (A/A, A/G, and G/G); patients carrying the A/A genotype have a relatively low risk of subclinical acute rejection episodes |
| Grinyó *et al.*[25] | *IMPDH1* (rs2228075)<br>*IMPDH2* (rs11706052) | Randomized Clinical Trial | 237 - Spain | daclizumab induction, MMF (2 g/hari), corticosteroid, and low-dose cyclosporine | Patients with one or two C alleles of *IMPDH2* SNP (rs11706052) are more predisposed for experiencing biopsy-proven acute rejection (BPAR) at 3 months compared to patients with TT homozygous carriers; the polymorphism in intron 7 of *IMPDH2* (rs11706052) correlates with a 3-fold increase in the likelihood of experiencing BPAR at 12 months |
| Wang *et al.*[26] | *IMPDH1* (rs2288553, rs11770116, rs2288548, rs2288549, rs4731448, rs2278293, rs2278294, rs2228075, 898G>A, rs2288550, 1552G>A) | Retrospective study | 191 - USA | Tacrolimus + MMF + prednison-based immunosuppressant | Two *IMPDH1* SNPs (rs2278293 and rs2278294) shown a strong correlation with the occurence of BPAR within the first year following transplantation |

TABLE 2. Association Studies of *IMPDH1* and *IMPDH2* SNPs With Mycophenolic Acid Toxicity

| Reference | *IMPDH* SNPs of Interest | Study Design | Number of Subjects and Site of Study | Immunosuppressive Regimen | Result |
|---|---|---|---|---|---|
| Thishya *et al.*[27] | *IMPDH1* rs2278294, *IMPDH2* c.787C>T (rs121434586, Lue263Phe) | Prospective study | 255 - India | Triple immunosuppressant regimen (tacrolimus + mycophenolate + steroid) | rs2278294 SNP is not significantly linked with adverse events in renal transplant patients receiving mycophenolate treatment |
| Pazik *et al.*[28] | *IMPDH1* (rs2278294, rs2278293); *IMPDH2* (rs11706052) | Observational longitudinal research | 190 - Poland | MMF + prednisone + Cyclosporine A/ tacrolimus | The G allele of rs2278294 genotype was substantially correlated with slower increase in BMI gain; no association was found between BMI change and either rs11706052 or rs2278293 |
| Varnell *et al.*[18] | *IMPDH1* (rs2228075, rs2278293, rs2278294); *IMPDH2* (rs11706052, rs4974081) | Multicenter retrospective research | 284 - USA | Mycophenolate mofetil (MMF) | Two SNPs of *IMPDH1* (rs2228075, rs2278294) demonstrated prolongation of time to onset of leukopenia and specifically, individuals carrying homozygote G allele have more protective effects against developing leukopenia than GA or AA genotypes |
| Woillard *et al.*[29] | *IMPDH2* IVS7 + 10 T>C (rs11706052); *IMPDH1* C>T (rs2278923); IMPDH1 C>T (rs2278924) | Randomized parallel group trial | 189 - France | Cyclosporine A + EC-MPS ± steroid (methylprednisolone) | There is no association of *IMPDH1* SNP (rs2278923, rs2278924) and *IMPDH2* SNP (rs11706052) with the incidence of leukopenia and anemia |
| Pazik *et al.*[16] | (*IMPDH2*) rs11706052 | Prospective Study | 177 - Poland | MMF + glucocorticoids + calcineurin inhibitor) ± antithymocyte globulin (ATG) | There was an association between the 3757C allele (rs11706052) and higher lymphocyte counts as well as a reduced incidence of lymphopenia. Nonetheless, there is no substantial distinction between patients carrying the C and T allele regarding the occurence of severe infections, gastrointestinal side effects, or neutropenia |

TABLE 2. Cont.

| Reference | *IMPDH* SNPs of Interest | Study Design | Number of Subjects and Site of Study | Immunosuppressive Regimen | Result |
|---|---|---|---|---|---|
| Michelon *et al.*[30] | *IMPDH1* (-106G>A, rs2278294; 125G>A, rs2278293) | Retrospective study | 218 - France | MPA + CsA ± Steroid<br>MPA + TCL ± Steroid<br>MPA + mTOR inhibitor ± Steroid<br>MPA + Steroid | No significant association was found between the *IMPDH1* gene SNPs (106G>A, rs2278294; 125G>A, rs2278293) and the adverse effects induced by MPA and BPAR |
| Gensburger *et al.*[23] | *IMPDH1* (rs2278293, rs2278294 ), *IMPDH2* (rs4974081, rs11706052, 787C>T) | Prospective Study | 456 - France | MMF-Cyclosporine or MMF-Tacrolimus | A notable correlation was identified between the *IMPDH1* SNP (rs2278294) and an increased risk of leukopenia within one year post-transplantation<br>No correlation exists between the *IMPDH2* SNP and these clinical outcomes: CMV infection, other infections, leukopenia |

**The Genotype Frequency of *IMPDH1* and *IMPDH2* SNPs**

There are two isoforms of the IMPDH enzyme, IMPDH type I and IMPDH type II, encoded by *IMPDH1* and *IMPDH2* genes, respectively. Both of the genes are located in two different chromosomes, chromosome 7 locus 7q31.3 and chromosome 3 locus 3p21.2, respectively.[31,32] The most frequently investigated *IMPDH1* SNPs are *IMPDH1-125G>A* (rs2278293) and *IMPDH1-106G>A* (rs2278294). In terms of *IMPDH2*, the SNP most frequently evaluated is *IMPDH2-3757T>C* (rs11706052). From the pharmacogenetic studies included in this review, which involved subjects from various ethnicities or races, the distribution of genotype frequency is summarized in TABLE 2. There are some genotyping methods applied in each study, including PCR-RFLP, DNA sequencing, and TaqMan assay. Some studies determined the Hardy-Weinberg equilibrium status, while the rest of the studies did not show statistical data analysis to determine Hardy-Weinberg Equilibrium (HWE) status. A population in HWE state exhibits no significant deviation between the observed and expected genotype frequencies (based on HWE equation). Furthermore, statistical analysis of HWE deviation is often performed to detect potential genotyping errors, such as excess heterozygote. In *IMPDH1-125G>A* SNP, the frequency of GG genotype is 27.5 – 51%, GA 39.6 – 51.3%, AA 9.4 – 25.5%. The distribution of genotype frequency in *IMPDH1-106G>A* are GG 27.5 – 50.5%, GA 39.8 – 51.3%, dan AA 9.7 – 21.2%. The distribution of genotype frequency in *IMPDH2 - 3757T>C* is TT 73.9 – 87.3%, TC 11.8 – 22.9%, CC 0 – 3.3%.

TABLE 3. The Genotype Distributions of *IMPDH1* and *IMPDH2* SNPs from Several Studies

| Study Reference | Ethnicity/Race | SNP Genotyping Method | Prevalence of Genotype (%) | | | Hardy-Weinberg Equilibrium Status* |
|---|---|---|---|---|---|---|
| | | | rs2278293 (*IMPDH1-125G>A*) | rs2278294 (*IMPDH1-106G>A*) | rs11706052 (*IMPDH2 – 3757T>C*) | |
| Penezić *et al.*[19] | Slavic (Central-Eastern European) | TaqMan assay | - | - | TT: 79.5<br>TC: 19.7<br>CC: 0.8 | N/A |
| Winnicki *et al.*[20] | Austrian | DNA sequencing | - | - | TT: 79.8<br>TC: 18.8<br>CC: 1.44 | N/A |
| Abderahmene *et al.*[17] | Tunisian | PCR-RFLP | GG: 51<br>GA: 39.6<br>AA: 9.4 | GG: 44.1<br>GA: 42.9<br>AA: 13.1 | TT: 73.9<br>TC: 22.9<br>CC: 3.3 | Yes |
| Cilião *et al.*[21] | Brazilian | TaqMan assay | GG: 31.7<br>GA: 42.8<br>AA: 25.5 | - | TT: 79.3<br>TC: 19.3<br>CC: 1.4 | N/A |
| Pazik *et al.*[28] | Caucasian | PCR-RFLP | GG: 30.8<br>GA: 48.1<br>AA: 21.1 | GG: 50.5<br>GA: 39.8<br>AA: 9.7 | TT: 84.6<br>TC: 15.4<br>CC: 0 | N/A |
| Woillard *et al*[29] | French | TaqMan assay | GG: 27.5<br>GA: 51.3<br>AA: 21.2 | GG: 27.5<br>GA: 51.3<br>AA: 21.2 | TT: 79.9<br>TC: 19<br>CC: 1 | Yes |
| Shah *et al.*[22] | White ethnicity from Europe and North America | TaqMan assay | GG: 33.9<br>GA: 45.9<br>AA: 20.2 | GG: 42.8<br>GA: 44.8<br>AA: 12.4 | TT: 78.9<br>TC: 19.4<br>CC: 1.7 | Yes |
| Pazik *et al.*[16] | Polish | PCR-RFLP | - | - | TT: 84.7<br>TC: 15.3<br>CC: 0 | Yes |
| Gensburger *et al.*[23] | Multiracial | TaqMan assay | GG: 28.9<br>GA: 51.1<br>AA: 20 | GG: 28.9<br>GA: 51.1<br>AA: 20 | TT: 82.1<br>TC: 17.4<br>CC: 0.4 | Yes |
| Kagaya *et al.*[24] | Japanese | DNA sequencing and PCR-RFLP | GG: 33<br>GA: 46.3<br>AA: 20.7 | GG: 30.5<br>GA: 48.8<br>AA: 20.7 | - | Yes |
| Grinyó *et al.*[25] | Caucasian | DNA sequencing | - | - | TT: 87.3<br>TC: 11.8<br>CC: 0.9 | Yes |

*Determined based on statistical analysis of deviation from HWE. "Yes" denotes that the genotype distribution in the study population was consistent with HWE principle ($p > 0.05$). "N/A" denotes that the HWE analysis was not reported

### *IMPDH1* Polymorphisms

A study involving 255 renal transplant recipients concluded that the rs2278294 SNP was not significantly associated with adverse events in patients treated with MPA.[27] In line with this study, another study involving a larger sample size with a randomized parallel group trial study design found no association between either rs2278923 or rs2278924 SNP and leukopenia, anemia, and diarrhea.[29] Likewise, a retrospective study of 218 multiracial patients reported no significant correlation between *IMPDH1* SNPs (rs2278923 and rs2278924) and MPA-induced adverse effects including diarrhea, leukopenia, anemia, infection, and other adverse effects.[30]

Leukopenia is a well-recognized toxicity associated with mycophenolate use following transplantation. A study

involving a multiracial population found that individuals carrying the rs2278294 SNP have an increased risk of developing leukopenia during the first year following transplantation.[23] In contrast, the retrospective study that also involving multiracial patients demonstrated the G allele of the rs2278294 SNP and the G allele of the rs2228075 were experiencing a delayed onset time of leukopenia incidence, and further analysis showed the individuals carrying the homozygous G allele (GG) had a 90-day longer onset time of leukopenia incident than individuals carrying the GA or AA genotype.[18] Another finding related to leukopenia incidence showed that the study group carrying the variant alleles of rs2278293 and treated by the MMF + Cyclosporine regimen had a lower leukopenia incidence.[17] In addition to the previously mentioned adverse effects, another potential risk associated with MPA use is malnutrition, which may be evaluated through changes in body mass index (BMI). In the observational prospective longitudinal study until 5 years post-transplantation involving 190 Caucasian renal transplant patients, it was concluded that allele G of rs2278294 SNP was associated with a slower increase in BMI.[28]

In addition to its adverse effects, *IMPDH1* gene polymorphisms may also influence MPA efficacy in renal transplant patients, particularly in relation to acute rejection incidence. A retrospective study published in 2008 investigated the association between *IMPDH1* polymorphisms and biopsy-proven acute rejection (BPAR), reporting significant association between the rs2278293 and rs2278294 SNPs and BPAR incidence within the first year after transplantation.[26] Another retrospective study involving a smaller Japanese cohort found a significant difference in subclinical acute rejection incidence among AA, AG, and GG genotypes of the rs2278293 SNP but not the rs227829 SNP.[24] In patients carrying the *IMPDH1* rs2278293 AA genotype, subclinical acute rejection episodes tend to be lower.[24] Supporting these findings, a larger prospective study involving a multiracial cohort identified a significant association between the rs2278294 SNP and a reduced risk of BPAR incidence.[23] In contrast, the retrospective study involving 218 multiracial patients found no significant association between the rs2278293 and rs2278294 SNPs and BPAR incidence.[30]

### *IMPDH2* Polymorphisms

A prospective study involving 456 multiracial individuals investigated the association of *IMPDH2* SNP with BPAR incidence, CMV infection, other infections, and leukopenia, finding no significant association.[23] Similarly, a prospective study of 177 Polish kidney transplant patients reported no significant difference between patients carriers of the C and T alleles in acute rejection episodes, serious infection incidence, GI adverse effects, or neutropenia.[16] In line with these findings, another prospective study involving individuals of European and North American descent found no association between *IMPDH* polymorphism and renal allograft rejection or graft survival.[22] Likewise, a study of 189 French renal transplant patients reported no association between IMPDH SNPs and BPAR, leukopenia, anemia, or diarrhea.[29] Additionally, an investigation of *IMPDH2* SNPs (rs11706052, rs4974081) found no correlation with MMF-induced leukopenia or the onset time of leukopenia in adult and pediatric patients.[18] In contrast to the rs2278294 *IMPDH1* SNP, the rs11706052 *IMPDH2* SNP was not associated with BMI changes.[28]

A randomized clinical trial (RCT) study involving 237 Caucasian renal transplant patients identified the rs11706052 SNP as one of four polymorphisms significantly associated with BPAR incidence. In this study, individuals carrying 1 or 2 C alleles (TC or CC) were three times more

likely to experience BPAR within three months post-transplantation compared to those with the homozygous T allele (TT) at 12 months.[25] Consistent with these findings, another study reported that the patients with at least one variant allele of rs11706052 SNP had a higher risk of rejection episodes than those with the wild-type allele.[17]

A retrospective study of 145 Brazilian renal transplant recipients reported contradictory findings. The TC and CC genotypes of the rs11706052 SNP provided a 15.6-fold increase in protection against rejection, while multivariate regression analysis indicated that carrying at least one C allele (TC or CC) was associated with a 4.4-fold greater protection.[21] A trend test in another study suggested a potential relationship between rs11706052 SNP status and the renal graft rejection risk; however, the sample size in the overall analysis was too small to be considered statistically significant.[20] Additionally, a study on transplanted kidney function found that rs11706052 SNP had no impact on kidney function after 1 year of tranplantation.[19]

## DISCUSSION

The pharmacogenetics studies of *IMPDH1* and *IMPDH2* genes included in this review were published from 2008 to 2024 and involved renal transplant patients from various regions: Europe (9 countries), Asia (2 countries), Africa (1 country), North America (2 countries), and South America (1 country). Most of the studies employed observational designs, either prospective or retrospective studies with only one study utilizing a randomized controlled trial (RCT) design. The study with the largest sample size (1040 patients) was conducted in the UK using prospective study design in 2012. Overall, the populations involved in the *IMPDH1* and *IMPDH2* polymorphism studies were predominantly European descent, originating from Europe and North America.

Inosine-5'-monophosphate dehydrogenase (IMPDH), the target of MPA, plays a key role in the de novo synthesis pathway of guanosine nucleotides needed for lymphocyte proliferation.[16] Genetic variations in *IMPDH1* and *IMPDH2* can influence the proliferation of T and B lymphocytes and may ultimately alter MPA's therapeutic responses. Based on the studies reviewed, studies on *IMPDH1-125G>A* (rs2278293), *IMPDH1-106G>A* (rs2278294), and *IMPDH2-3757T>C* (rs11706052) SNP are the most frequently investigated and recently published SNPs in gene-encoded IMPDH. This prevalence suggests their potential role in significantly affecting MPA efficacy or toxicity in renal transplant recipients. Thus, this review focuses on these SNPs. Additionally, the studies frequently investigate the relationship between *IMPDH1* polymorphisms and MPA-induce adverse effects, including leukopenia, anemia, diarrhea, and infection, though some studies also investigate their association with biopsy-proven acute rejection (BPAR) incidence.

This review includes 15 studies investigating the association of IMPDH gene polymorphisms with the clinical outcomes or adverse effects of mycophenolate use in renal transplant recipients. The clinical outcomes assessed in the studies include acute rejection incidence, graft survival, or renal graft function. In terms of adverse effects, some of the conditions evaluated included leukopenia, neutropenia, anemia, increased BMI, gastrointestinal side effects (e.g., diarrhea), CMV infection, and other infections. Studies on *IMPDH2* gene polymorphism found no significant relationship with the adverse effects of MPA. On the other hand, research on *IMPDH1* polymorphisms yielded inconsistent findings. *IMPDH1* SNPs (rs2278923 and rs2278924) were frequently linked to leukopenia, a common adverse effect of MPA therapy, but the findings varied across studies.

An RCT conducted in the 1990s

identified leukopenia as a relatively common adverse event of MMF use.[33] In a clinical study involving renal transplant patients, the incidence of leukopenia was 19% with a 2 g dose and 38% with a 3 g dose over the course of one year.[34] Leukopenia increases susceptibility to various infections, thereby necessitating reduction or cessation of immunosuppressant dosing, which in turn raises the risk of allograft rejection. The exact mechanism of mycophenolate-induce leukopenia remains unclear.[35] Studies evaluating *IMPDH1* SNPs rs2278923 and rs2278924 have yielded inconsistent findings regarding their association with mycophenolate-related leukopenia. However, these SNPs profiles may have potential as predictive markers for leukopenia risk due to mycophenolate toxicity, warranting further investigation. Therefore, SNP profiling may inform alternative strategies for optimizing mycophenolate dosing regimens.

The primary goal of immunosuppressant treatment in renal transplant recipients is to prevent biopsy-proven acute rejection (BPAR), which is a common complication occuring in post-transplantation. BPAR incidence serves as the main parameter for evaluating the efficacy of immunosuppressant regimens in renal transplant recipients.[36] Several studies have investigated the association of either *IMPDH1* or *IMPDH2* SNPs with BPAR incidence. The study on *IMPDH1* (rs2278923, rs2278924) and *IMPDH2* (rs11706052) SNPs has demonstrated potential association with BPAR risk. In contrast, a recent study by Penezic *et al.*, involving 254 renal transplant recipients in Croatia, found no significant effect of *IMPDH2* polymorphism on graft function within the first year post-transplantation. Similarly, research by Winnicki *et al.* reported no association between the rs11706052 variant and graft rejection. This discrepancies may be attributed to differencies in co-treatment besides MPA or to variations in baseline clinical characteristics among study populations.

The mechanism underlying the association between *IMPDH1* polymorphism and acute rejection is still unclear. Nevertheless, the probable explanation is related to the other SNPs that enable controlling the expression of *IMPDH1* mRNA, enzyme activity, and eventually altering leukocyte proliferation.[26] Regarding the mechanism of action, MMF tends to more effectively inhibits IMPDH2, which is specifically expressed in activated T and B lymphocytes rather than IMPDH1 which is constitutively expressed in various tissues to maintain basal levels of guanine nucleotides.[7,37,38]

Inconsistencies in findings across existing studies may be atributted to variations in the ethnic backgrounds of study populations which can lead to genetic variabilty that influences the therapeutic response to mycophenolate. In addition, differences in sample size may also affect the results of association analysis conducted. Further research is needed to clarify these inconsistencies. Large-scale, multi-ethnic studies with standarized methodologies are required to establish definitive associations. Integrating pharmacogenetic testing into clinical practice may optimize MPA therapy by minimizing toxicity and enhancing efficacy.

## CONCLUSION

This review highlights the potential impact of *IMPDH1* and *IMPDH2* gene polymorphisms on MPA efficacy and toxicity in renal transplant recipients. In terms of efficacy, biopsy-proven acute rejection (BPAR) is the primary parameter used to evaluate immunosuppressant response, while leukopenia serves as a key indicator of mycophenolate-related toxicity. Although *IMPDH1* SNPs rs2278923 and rs2278924 have been reported to be significantly associated with BPAR incidence, this finding varied across studies. Similarly, the *IMPDH2* SNP rs11706052 has shown inconsistent associations with BPAR. Regarding

toxicity, *IMPDH1* SNPs rs2278923 and rs2278924 have been linked to leukopenia in some studies, while the rest of studies have found no association. Most of the studies showed no relationship between *IMPDH2* SNPs and leukopenia. Given these inconsistencies, profiling *IMPDH1* and *IMPDH2* SNPs in renal transplant recipients may be a valuable approach for predicting both efficacy and toxicity of mycophenolate-based immunosuppressive therapy, contributing to a more personalized treatment strategy. Further pharmacogenetic investigations should prioritize multi-center and multi-ethnic prospective studies utilizing standarized clinical and genetic endpoints to validate and extend the findings across diverse populations.

## ACKNOWLEDGEMENT

The author thank the LPDP (Lembaga Pengelola Dana Pendidikan) scholarship for supporting my master's study and my colleagues for their motivation in preparing this review.

## REFERENCES

1. Szumilas K, Wilk A, Wiśniewski P, Gimpel A, Dziedziejko V, Kipp M, et al. Current status regarding immunosuppressive treatment in patients after renal transplantation. Int J Mol Sci 2023; 24(12):10301. https://doi.org/10.3390/ijms241210301
2. National Institute for Health and Care Excellence. immunosuppressive therapy for kidney transplant in adults [Internet]. 2017 [cited 2025 Mar 26]. https://www.nice.org.uk/guidance/ta481
3. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; Suppl 3:S1-155. https://doi.org/10.1111/j.1600-6143.2009.02834.x
4. Alasfar S, Kodali L, Schinstock CA. Current therapies in kidney transplant rejection. J Clin Med. 2023 Jul 27;12(15):4927. https://doi.org/10.3390/jcm12154927
5. Cheng L, Yao P, Weng B, Yang M, Wang Q. Meta-analysis of the associations of IMPDH and UGT1A9 polymorphisms with rejection in kidney transplant recipients taking mycophenolic acid. Eur J Clin Pharmacol. 2022 Aug;78(8):1227-38. https://doi.org/10.1007/s00228-022-03311-4
6. Khan MA, Hanna A, Sridhara S, Chaudhari H, Me HM, Attieh RM, et al. Maintenance immunosuppression in kidney transplantation: a review of the current status and future directions. J Clin Med 2025; 14(6):1821. https://doi.org/10.3390/jcm14061821
7. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology 2000; 47(2-3):85-118. https://doi.org/10.1016/S0162-3109(00)00188-0
8. Na Takuathung M, Sakuludomkan W, Koonrungsesomboon N. The impact of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of mycophenolic acid: systematic review and meta-analysis. Clin Pharmacokinet 2021; 60(10):1291-302. https://doi.org/10.1007/s40262-021-01037-7
9. Salvadori M, Holzer H, De Mattos A, Sollinger H, Arns W, Oppenheimer F, et al. Enteric-Coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. Am J Transplant. 2004 Feb;4(2):231-6. https://doi.org/10.1046/j.1600-6143.2003.00337.x
10. Dudley C, Pohanka E, Riad H, Dedochova J, Wijngaard P, Sutter C, *et al*. Mycophenolate mofetil substitution for cyclosporine a in

renal transplant recipients with chronic progressive allograft dysfunction: the "creeping creatinine" study. Transplantation. 2005; 79(4):466-75. https://doi.org/10.1097/01.TP.0000151632.21551.00
11. Omair MA, Alahmadi A, Johnson SR. Safety and effectiveness of mycophenolate in systemic sclerosis. A systematic review. PLoS One 201; 10(5):e0124205. https://doi.org/10.1371/journal.pone.0124205
12. Baradaran H, Hashem Zadeh A, Dashti-Khavidaki S, Laki B. Management of drug-induced neutropenia, thrombocytopenia, and anaemia after solid organ transplantation: A comprehensive review. J Clin Pharm Ther 2022; 47(12):1895-912. https://doi.org/10.1111/jcpt.13775
13. Bertino JS, Kashuba ADM, Ma JD, Fuhr U, DeVane CL. Pharmacogenomics: An Introduction and Clinical Perspective. McGraw-Hill; 2013.
14. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy a pathophysiologic approach. 10th Edition. McGraw-Hill; 2017.
15. Zdanowicz MM. Concepts in pharmacogenomics: fundamentals and therapeutic applications in personalized medicine. ASHP Publications; 2017. https://doi.org/10.37573/9781585285174
16. Pazik J, Ołdak M, Podgórska M, Lewandowski Z, Sitarek E, Płoski R, et al. Lymphocyte counts in kidney allograft recipients are associated with IMPDH2 3757T>C gene polymorphism. Transplant Proc 2011; 43(8):2943-5. https://doi.org/10.1016/j.transproceed.2011.08.037
17. Abderahmene A, Ellouz A, Amor D, Ajmi M, Khalij Y, Hamdouni H, et al. The pharmacogenetics of mycophenolate mofetil in Tunisian renal transplant patients. Per Med 2022; 19(5):383-93. https://doi.org/10.2217/pme-2021-0092
18. Varnell CD, Fukuda T, Kirby CL, Martin LJ, Warshaw BL, Patel HP, *et al*. Mycophenolate mofetil-related leukopenia in children and young adults following kidney transplantation: Influence of genes and drugs. Pediatr Transplant 2017; 21(7). https://doi.org/10.1111/petr.13033
19. Penezić L, Nađ-Škegro S, Hadžavdić A, Ganoci L, Kaštelan Ž, Trkulja V, et al. Inosine monophosphate dehydrogenase type 2 polymorphism IMPDH2 3757T>C (rs11706052) and 12-month evolution of the graft function in renal transplant recipients on mycophenolate-based immunosuppression. Pharmacogenomics J 2024; 24(3):15. https://doi.org/10.1038/s41397-024-00335-0
20. Winnicki W, Fichtenbaum A, Mitulovič G, Herkner H, Regele F, Baier M, et al. Individualization of mycophenolic acid therapy through pharmacogenetic, pharmacokinetic and pharmacodynamic testing. Biomedicines 2022; 10(11):2882. https://doi.org/10.3390/biomedicines10112882
21. Cilião HL, Camargo-Godoy RBO, Souza MF, Zanuto A, Delfino VDA, Cólus IMS. Polymorphisms in IMPDH2, UGT2B7, and CES2 genes influence the risk of graft rejection in kidney transplant recipients taking mycophenolate mofetil. Mutat Res Genet Toxicol Environ Mutagen 2018; 836(Pt B):97-102. https://doi.org/10.1016/j.mrgentox.2018.06.008
22. Shah S, Harwood SM, Döhler B, Opelz G, Yaqoob MM. Inosine monophosphate dehydrogenase polymorphisms and renal allograft outcome. Transplantation 2012; 94(5):486-91. https://doi.org/10.1097/TP.0b013e31825b7654
23. Gensburger O, Van Schaik RH, Picard

N, Le Meur Y, Rousseau A, Woillard JB, *et al*. Polymorphisms in type I and II inosine monophosphate dehydrogenase genes and association with clinical outcome in patients on mycophenolate mofetil. Pharmacogenet Genomics 2010; 20(9):537-43. https://doi.org/10.1097/FPC.0b013e32833d8cf5

24. Kagaya H, Miura M, Saito M, Habuchi T, Satoh S. Correlation of IMPDH1 gene polymorphisms with subclinical acute rejection and mycophenolic acid exposure parameters on day 28 after renal transplantation. Basic Clin Pharmacol Toxicol 2010; 107(2):631-6. https://doi.org/10.1111/j.1742-7843.2010.00542.x
25. Grinyó J, Vanrenterghem Y, Nashan B, Vincenti F, Ekberg H, Lindpaintner K, *et al*. Association of four DNA polymorphisms with acute rejection after kidney transplantation. Transpl Int 2008; 21(9):879-91. https://doi.org/10.1111/j.1432-2277.2008.00679.x
26. Wang J, Yang J, Zeevi A, Webber S, Girnita D, Selby R, et al. IMPDH1 gene polymorphisms and association with acute rejection in renal transplant patients. Clin Pharmacol Ther 2008; 83(5):711-7. https://doi.org/10.1038/sj.clpt.6100347
27. Thishya K, Sreenu B, Raju SB, Kutala VK. Impact of pharmacogenetic determinants of tacrolimus and mycophenolate on adverse events in renal transplant patients. Curr Drug Metab 2021; 22(5):342-52. https://doi.org/10.2174/1389200222666210114123349
28. Pazik J, Lewandowski Z, Nowacka Cieciura E, Ołdak M, Podgórska M, Sadowska A, et al. Malnutrition risk in kidney recipients treated with mycophenolate mofetil is associated with IMPDH1 rs2278294 polymorphism. Transplant Proc 2018; 50(6):1794-7. https://doi.org/10.1016/j.transproceed.2018.02.125
29. Woillard JB, Picard N, Thierry A, Touchard G, Marquet P; DOMINOS study group. Associations between polymorphisms in target, metabolism, or transport proteins of mycophenolate sodium and therapeutic or adverse effects in kidney transplant patients. Pharmacogenet Genomics 2014; 24(5):256-62. https://doi.org/10.1097/FPC.0000000000000045
30. Michelon H, König J, Durrbach A, Quteineh L, Verstuyft C, Furlan V, *et al*. SLCO1B1 genetic polymorphism influences mycophenolic acid tolerance in renal transplant recipients. Pharmacogenomics 2010; 11(12):1703-13. https://doi.org/10.2217/pgs.10.132
31. Sombogaard F. Pharmacodynamic monitoring of inosine monophosphate dehydrogenase activity: a basis for optimized and individualized mycophenolate mofetil therapy. [Utrecht]: Erasmus University Rotterdam; 2010.
32. Zimmermann AG, Spychala J, Mitchell BS. Characterization of the human inosine-5'-monophosphate dehydrogenase type II gene. J Biol Chem 1995; 270(12):6808-14. https://doi.org/10.1074/jbc.270.12.6808
33. Hartmann EL, Gatesman M, Roskopf-Somerville J, Stratta R, Farney A, Sundberg A. Management of leukopenia in kidney and pancreas transplant recipients. Clin Transplant 2008; 22(6):822-8. https://doi.org/10.1111/j.1399-0012.2008.00893.x
34. Von Vietinghoff S, Ouyang H, Ley K. Mycophenolic acid suppresses granulopoiesis by inhibition of interleukin-17 production. Kidney Int 2010; 78(1):79-88. https://doi.org/10.1038/ki.2010.84
35. Jacobson PA, Schladt D, Oetting WS, Leduc R, Guan W, Matas AJ, et al. Genetic determinants of mycophenolate related anemia

and leukopenia following transplantation. Transplantation 2011; 91(3):309. https://doi.org/10.1097/TP.0b013e318200e971
36. Cooper JE. Evaluation and Treatment of Acute Rejection in Kidney Allografts. Clin J Am Soc Nephrol 2020; 15(3):430-8. https://doi.org/10.2215/CJN.11991019
37. Subedi A, Magder LS, Petri M. Effect of mycophenolate mofetil on the white blood cell count and the frequency of infection in systemic lupus erythematosus. Rheumatol Int 2015; 35(10):1687-92. https://doi.org/10.1007/s00296-015-3265-6
38. Ni S, Zhang T, Zhou C, Long M, Hou X, You L, et al. Coordinated formation of IMPDH2 cytoophidium in mouse oocytes and granulosa cells. Front Cell Dev Biol. 2021 May 28;9. https://doi.org/10.3389/fcell.2021.690536