A Systematic Review of Multiple Linear Regression-Based
Limited Sampling Strategies for Mycophenolic Acid Area Under
the Concentration–Time Curve Estimation

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Abstract

Background and Objective  One approach of therapeutic drug monitoring in the case of mycophenolic acid (MPA) is a limited sampling strategy (LSS), which allows the evaluation of the area under the concentration–time curve (AUC) based on few concentrations. The aim of this systematic review was to review the MPA LSSs and define the most frequent time points for MPA determination in patients with different indications for mycophenolate mofetil (MMF) administration.

Methods  The literature was comprehensively searched in July 2021 using PubMed, Scopus, and Medline databases. Original articles determining multiple linear regression (MLR)-based LSSs for MPA and its free form (fMPA) were included. Studies on enteric-coated mycophenolic sodium, previously established LSS, Bayesian estimator, and different than twice a day dosing were excluded. Data were analyzed separately for (1) adult renal transplant recipients, (2) adults with other than renal transplantation indication, and (3) for pediatric patients.

Results  A total of 27, 17, and 11 studies were found for groups 1, 2, and 3, respectively, and 126 MLR-based LSS formulae (n = 120 for MPA, n = 6 for fMPA) were included in the review. Three time-point equations were the most frequent. Four MPA LSSs: 2.8401 + 5.7435 × C0 + 0.2655 × C0.5 + 1.1546 × C1 + 2.8971 × C4 for adult renal transplant recipients, 1.783 + 1.248 × C1 + 0.888 × C2 + 8.027 × C4 for adults after islet transplantation, 0.10 + 11.15 × C0 + 0.42 × C1 + 2.80 × C2 for adults after heart transplantation, and 8.217 + 3.163 × C0 + 0.994 × C1 + 1.334 × C2 + 4.183 × C4 for pediatric renal transplant recipients, plus one fMPA LSS, 34.2 + 1.12 × C1 + 1.29 × C2 + 2.28 × C4 + 3.95 × C6 for adult liver transplant recipients, seemed to be the most promising and should be validated in independent patient groups before introduction into clinical practice. The LSSs for pediatric patients were few and not fully characterized. There were only a few fMPA LSSs although fMPA is a pharmacologically active form of the drug.

Conclusions  The review includes updated MPA LSSs, e.g., for different MPA formulations (suspension, dispersible tablets), generic form, and intravenous administration for adult and pediatric patients, and emphasizes the need of individual therapeutic approaches according to MMF indication. Five MLR-based MPA LSSs might be implemented into clinical practice after evaluation in independent groups of patients. Further studies are required, e.g., to establish fMPA LSS in pediatric patients.
1 Introduction

Mycophenolate mofetil (MMF) is an immunosuppressive drug, whose active form is mycophenolic acid (MPA). MMF is administered after solid organ transplantation [1] as the prophylaxis against acute rejection, as well as being given in autoimmune diseases [2] and nephrotic syndrome [3, 4], as well as in atopic dermatitis [5]. MPA is highly protein bound (97–99%) with free MPA (fMPA) being pharmacologically active [6]. MPA pharmacokinetics are complex and highly variable, with numerous factors influencing the interindividual variability [2].

Due to the pharmacokinetic variability, therapeutic drug monitoring (TDM) in the case of MPA is recommended in clinical practice [2, 7]. TDM has been shown to be favorable not only in renal transplant recipients [8] but also in patients with lupus nephritis [9] and steroid-dependent nephrotic syndrome [10–12]. The most accurate approach to TDM is the determination of the full pharmacokinetic profile of the drug and calculation of the area under the concentration–time curve from 0 to 12 h (AUC 0–12), as the concentration determined before the next dose (C\textsubscript{trough}) does not reflect the overall exposure to MPA [8]. Determining AUC\textsubscript{0–12} is, however, time-consuming, expensive, and uncomfortable for patients; therefore, different approaches of TDM are being investigated.

One of the possibilities of TDM is establishing a limited sampling strategy (LSS) and predicting AUC\textsubscript{0–12} on the basis of only a few blood samples [8]. LSS may be calculated using a Bayesian approach or multiple linear regression (MLR) analysis, which uses an equation derived from step-wise regression analysis based on concentrations measured at pre-defined times after dosing [7, 13]. Each MLR LSS constitutes an equation: 

\[
\text{AUC} = b + M_{t1} \times C_{t1} + M_{t2} \times C_{t2} + M_{t3} \times C_{t3} + \ldots + M_{tn} \times C_{tn},
\]

where AUC indicates predicted AUC, \(b\) indicates the intercept, \(C_{t1}, C_{t2}, C_{t3}, C_{tn}\) indicate the concentrations obtained at \(t_1, t_2, t_3\) and \(t_n\) time points, respectively, and \(M_{t1}, M_{t2}, M_{t3}\) and \(M_{tn}\) indicate the coefficients associated with each timed concentration [14].

Such strategies have been proposed for MPA in many groups of patients [15–19], with emphasis that each LSS should be applied to the same group of patients for whom it was established [20]. As it does not depend on the pharmacokinetic model of the drug and can be calculated with simple software or manually [14], MLR is easier to use in clinical practice than Bayesian analysis; however, the MLR approach has some limitations. First is the reliance of the equations' accuracy on exact times of blood sample collection [7, 14]. Second is the poor prediction of the exposure to the drug in patients with abnormal pharmacokinetics [14]. And third is its applicability limitation for the dosage regimen and the population from which MLR LSS was derived. The main disadvantage of the Bayesian approach is the requirement of advanced software and highly-qualified staff. However, as this methodology uses the population approach [14], it does not require strict adherence to sampling times and is characterized by better precision and accuracy [7, 14]. The aim of this systematic review was to summarize the MPA LSSs established with MLR for different groups of patients. The summary also aimed at defining the most frequently used sampling points for MPA determination.

2 Methods

2.1 Search Strategy

The literature databases PubMed, Scopus, and Medline were comprehensively searched in July 2021 with the combination of ‘mycophenolic acid’ or ‘mycophenolate mofetil’ and the terms, ‘limited sampling strategy’, ‘limited sampling strategies’, ‘limited sampling’, ‘optimal sampling’, ‘sparse sampling’, and ‘minimal sampling’. Additionally, the reference lists of studies found in the literature were searched to detect articles potentially eligible for inclusion. Only studies published in English were included.
2.2 Study Selection

The flow diagram of article selection is presented in Fig. 1.

2.3 Inclusion Criteria

Original articles determining LSS based on MLR calculations for MPA and fMPA were included. The studies concerned adult and pediatric patients receiving MMF as a prophylaxis after transplantation (solid organ, hematopoietic stem cells) to treat autoimmune diseases or nephrotic syndrome.

2.4 Exclusion Criteria

The articles describing LSS for enteric-coated mycophenolic sodium (EC-MPS) were excluded, as there is an evident difference in MPA pharmacokinetics for these two formulations, MMF and EC-MPS [unpredictable absorption profile, delayed maximum concentration (C\text{max}), and higher pre-dose concentration (C\text{0}) after EC-MPS administration] [2, 21]. Therefore, in our opinion, EC-MPS LSSs should be analyzed separately. Also, the studies using previously established LSS, those with Bayesian estimator, with different than twice a day MMF dosing schedules and reviews were excluded. There are some studies establishing MPA LSSs with a Bayesian estimator, and although this approach has some advantages (e.g., better accuracy and precision, the lack of strict adherence to sampling times, and number of samples [7]), we decided to include only MLR-based MPA LSSs due to the excessive amount of data and the difficulty in analyzing MLR-based LSSs and Bayesian-approach LSSs.

2.5 Data Analysis

The data were analyzed according to the most frequently used time points in three groups of patients treated with MMF: (1) adult renal transplant recipients, (2) adults receiving MMF due to other indication than renal transplantation, and (3) pediatric patients. The most frequently used time points were calculated in relation to the number of LSSs equations in each group, and as the percentage of the sum

Fig. 1. The flow diagram of article selection. *Six records fulfilled more than one exclusion condition. †One study included pediatric patients after renal transplantation as well as with autoimmune diseases.
of all time points used in all LSSs equations in each group of patients. Whenever possible, the predictive performance results of the LSSs (bias, precision, validation group) were included in the review, as was the information whether the validation was internal or external. If the LSS was validated with data which were at the same time used for LSS determination, then the validation was internal. If the data from a separate group of patients (or the patients were divided into two groups) were used for the validation, then the validation was external. The best MPA LSSs were chosen based on the following criteria of the predictive performance: \( r^2 > 0.950 \), bias and precision < 10%.

## 3 Results

### 3.1 Study Identification and Characteristics

The search of the literature returned 55 studies concerning MLR LSSs for MPA and fMPA. In this review, 126 MLR-based LSS formulae were included [16–20, 22–71], among which two studies included both MPA and fMPA LSS [40, 61] and one study concerned only fMPA LSS [51]. There was one study which concerned patients receiving either MMF or EC-MPS as one group and established the MPA was one study which considered patients receiving either MMF or EC-MPS as one group and established the MPA LSSs for them [30]. If the study included several LSSs, those which the authors described as the best or those with the best \( r^2 \) were chosen. Most of the studies concerned adult patients, who were treated with MMF after renal transplantation (\( n = 27 \); Table 1) or due to other indications (\( n = 17 \); Table 2). A total of 11 studies with MLR-based LSSs were found for children (Table 3). The data are presented in the tables in chronological order (the newest first).

Based on all LSSs found in the literature, blood samples for MPA determination were collected before the administration of the next dose and subsequently at 20 min, 0.5 h, 40 min, 1 h, 1.25 h, 1.5 h, 2 h, 3 h, 3.5 h, 4 h, 6 h, 7 h, 8 h, 9 h, 10 h, and 12 h afterwards. These time points were included in LSSs as C20min, C0.5, C40min, C1, C1.25, C1.5, C2, C3, C3.5, C4, C6, C7, C8, C9, C10 and C12, where ‘C’ is the concentration. In the LSS equations, MPA concentration determined before the next MMF dose is named as C0; however, it must be emphasized that, due to administration of MMF every 12 h, this concentration is the pre-dose trough concentration and should be named as \( C_{\text{trough}} \) or \( C_{\text{min}} \). In the MLR-based LSSs, it is more convenient to write C0 instead of \( C_{\text{trough}} \).

For most of the studies, the predictive performance results were found. Bias was expressed as mean or median percentage prediction error; however, in some studies, bias was expressed as mean prediction error (MPE) or mean bias with units of the concentration multiplied by time. Precision was expressed as mean or median absolute percentage prediction error, however, in some studies, precision was expressed as mean absolute error with units of the concentration multiplied by time. Root square mean prediction error (RMSE) was also calculated in some studies as precision. Validation methods, if performed, included the bootstrap method, jackknife method, validation group, or cross-validation. Some LSSs were characterized by the good guess which is the percentage of the predicted AUC (AUC\(_{\text{pred}}\)) within ±15%, ±20%, or ±25% of the calculated AUC (AUC\(_{\text{total}}\)).

### 3.2 The MLR-Based LSSs for Adult Renal Transplant Recipients

As MMF was primarily administered in prophylaxis of acute rejection in solid organ transplantation, most of the studies concerning MLR LSSs included renal transplant recipients [22–48] (Table 1). Three fMPA LSSs were included in the results as the occurrence of \( C_{\text{max}} \) and \( C_{\text{max2}} \) should be the same for MPA and fMPA.

The equations included up to five time points with three time-point LSSs being the most frequent (59%). Of all the time points, those collected within 0–2 h after MMF administration constituted 58% of the total, whereas sampling between 3–5 h and 6–12 h after drug administration constituted 26% and 16%, respectively.

Of 59 MLR equations, the most frequently used time points were C4 and C2, which were included in 32 (54%) and 29 (49%) equations, respectively, and constituted 18% and 16% of the sum of all time points from 59 equations, respectively. The 22 (37%) equations including C0 and C0 constituted 13% of all time points. The most frequently included time point within 6–12 h after MMF administration was C6 (19% of equations). Two LSSs included C12 which is equal to C0 if blood samples are collected in steady-state; however, C12 was not analyzed with C0 when calculating the percentage.

If analyzed according to the calcineurin inhibitor co-administered, among all equations established for MMF and cyclosporine (CsA) treatment (\( n = 28 \)), the most frequent time points in LSSs were C2 (18% of all time points, 54% of the equations), and C4 (17% of all time points, 50% of the equations). For tacrolimus (Tac) co-administration (30 LSSs), the time points most often included were C4 (19% of all time points, 57% of the equations), and C2 (15% of all time points, 47% of the equations). LSSs established by Gaies et al. [25] was not included as the authors did not separately analyze patients receiving CsA and Tac.

With respect to the post-transplant period, the LSSs were divided into two groups: established for patients less than 1 month after transplantation, and longer than 3 months after transplantation. The LSSs established in the early post-transplant period (\( n = 22 \)) most frequently included C2 (25% of all time points, 73% of
Table 1  The characteristics of MLR-based equations found in the literature for predicting MPA AUC\textsubscript{pred} in adult renal transplant recipients treated with MMF

| No. | Equation                                                                 | $r^2$ | CNI co-administered | Bland–Altman analysis | Bias$^a$ | Precision$^b$ | RMSE  | Validation method/type | Additional information | References |
|-----|--------------------------------------------------------------------------|-------|----------------------|------------------------|----------|---------------|--------|------------------------|------------------------|------------|
| 1   | 9.57 × C6 + 27.238                                                      | 0.907 | –                    | –                      | Not different from zero | –       | 7.91               | Jackknife method       | –                      | [22]$^c$   |
| 2   | 14.04 + 10.43 × C8 + 1.58 × C2$^d$                                      | 0.87  | Tac                  | 10% outside 95% CI     | 10.28%   | 12.99%        | –      | Validation group/external | SE of estimation: 8.2 | [23]       |
| 3   | 11.95 + 8.9 × C8 + 1.41 × C2 + 1.48 × C4$^d$                            | 0.91  | Tac                  | 5% outside 95% CI      | 8.64%    | 12.93%        | –      | –                      | SE of estimation: 6.76 | [23]       |
| 4   | 8.36 + 7.49 × C8 + 1.34 × C2 + 1.66 × C4 + 0.76 × C1$^d$                | 0.948 | Tac                  | 5% outside 95% CI      | 5.26%    | 8.35%         | –      | –                      | SE of estimation: 5.34 | [23]       |
| 5   | 3.542 + 3.332 × C0.5 + 1.117 × C1.5 + 3.946 × C4$^d$                    | 0.90$^e$ | Tac                  | 5% outside 95% CI      | 1.67%    | 8.90%         | 12.20% | –                      | –                      | [24]       |
| 6   | 8.149 + 1.442 × C2 + 1.056 × C4 + 7.133 × C6$^f$                       | 0.88$^e$ | Tac                  | 5% outside 95% CI      | −0.2%    | 9.20%         | 13.20% | –                      | –                      | [24]       |
| 7   | 0.414 + 1.210 × C0.5 + 2.256 × C1.5 + 4.134 × C4$^f$                   | 0.85  | CsA/Tac              | 1.65%                  | –        | 5.81%         | –      | Validation group/external | –                      | [25]       |
| 8   | 7.4 + 2.3 × C0 + 1.2 × C1 + 2.3 × C3 + 4.4 × C6                         | 0.85  | Tac                  | –                      | –        | 5.5           | –      | Leave-one-out cross-validation/internal | < 31 postoperative day | [26]       |
| 9   | 10.6 + 1.1 × C1 + 1.1 × C2 + 2.0 × C4 + 3.9 × C6                       | 0.86  | Tac                  | –                      | –        | 5.5           | –      | –                      | ≥ 31 of postoperative day | [26]       |
| 10  | 3.8 + 3.5 × C0 + 1.2 × C1 + 1.9 × C3 + 5.4 × C6                        | 0.92  | Tac                  | –                      | –        | 3.9           | –      | –                      | –                      | [26]       |
| 11  | 4.272 + 4.074 × C6 + 1.896 × C2 + 4.680 × C10 + 0.859 × C0.5            | 0.918 | Tac                  | 5.17% outside 95% CI   | −0.20%   | 8.70%         | 14.20% | –                      | –                      | [27]       |
| 12  | 7.951 + 4.040 × C6 + 1.893 × C2 + 4.542 × C10                           | 0.863 | Tac                  | 6.9% outside 95% CI    | −0.30%   | 12.20%        | 17.30% | –                      | –                      | [27]       |
| 13  | 17.3 + 4.4 × C0 + 1.1 × C1 + 2.9 × C4                                  | 0.86  | Tac                  | –                      | –        | 14.51%        | 16.04% | –                      | –                      | [28]       |
| 14  | 14.9 + 1.3 × C1 + 3 × C4 + 3.7 × C6                                   | 0.87  | Tac                  | –                      | –        | 14.38%        | 14.86% | –                      | More accurate in patients with two MPA peaks | [28]       |
| 15  | 20.30 + 5.80 × C0 + 3.06 × C4                                          | 0.91  | Tac                  | –                      | –        | –             | –      | SD of residual error: 11.2 μg·h/mL; pre-Tx period | –                      | [29]       |
| 16  | 23.37 + 4.21 × C0 + 3.60 × C4                                          | 0.48  | Tac                  | –                      | –        | –             | –      | SD of residual error: 11.1 μg·h/mL; 1 month post-Tx | –                      | [29]       |
| 17  | 22.93 + 4.63 × C0 + 5.60 × C6                                          | 0.6   | Tac                  | –                      | –        | –             | –      | SD of residual error: 12.8 μg·h/mL; 3 months post-Tx | –                      | [29]       |
| No. | Equation | $r^2$ | CNI co-administered | Bland–Altman analysis | Bias$^a$ | Precision$^b$ | RMSE | Validation | References |
|-----|----------|------|---------------------|----------------------|--------|--------------|------|------------|------------|
| 18  | $16.5 + 4.9 \times C1.5 + 6.7 \times C3.5^b$ | 0.82/0.66$^i$; 0.71$^j$ | Tac | – | – | 14%/17%$^k$; 13%$^l$ | 9%/24%$^m$; 17%$^n$ | Bootstrap/external | – | [30] |
| 19  | $0.81 + 1.07 \times C0.5 + 2.20 \times C2 + 3.48 \times C4$ | 0.79$^c$ | Tac | – | – | 0.20% | 13.60% | 3.60% | Jackknife/internal | – | [31] |
| 20  | $9.328 + 1.311 \times C1 + 1.455 \times C2 + 2.901 \times C4$ | 0.838 | Tac | – | – | 3.80% | 14.90% | – | Jackknife/internal | – | [32] |
| 21  | $-0.5754 + 1.0664 \times C0.5 + 1.4692 \times C1.5 + 4.7313 \times C3^g$ | 0.901 | Tac | – | – | 1.74% | 11.79% | – | Jackknife/internal | – | [33] |
| 22  | $0.3546 + 0.9297 \times C0.5 + 1.2872 \times C1.5 + 3.6416 \times C3 + 2.9424 \times C4^g$ | 0.901 | Tac | – | – | 2.60% | 9.39% | – | – | – | [33] |
| 23  | $-0.2677 + 3.0326 \times C0 + 0.7353 \times C0.5 + 0.5545 \times C1 + 0.7171 \times C1.5 + 3.6757 \times C3^g$ | 0.939 | Tac | Minimal bias | 0.67% | 7.73% | – | – | – | [33] |
| 24  | $8.64 + 5.13 \times C0 + 0.62 \times C0.66 + 2.84 \times C2$ | 0.79 | CsA/Sir | – | – | 0.90% | – | 14% | Validation group/external | – | [34] |
| 25  | $8.32 + 0.904 \times C1.5 + 1.955 \times C4 + 10.206 \times C10$ | 0.965 | CsA | – | – | MPE: 0.71 mg·h/L | – | 5.41 mg·h/L | – | Jackknife/internal | – | [35] |
| 26  | $11.629 + 1.286 \times C1.5 + 14.418 \times C4$ | 0.919 | CsA | – | – | MPE: 0.34 mg·h/L | – | 6.38 mg·h/L | – | – | – | [35] |
| 27  | $15.547 + 14.46 \times C10$ | 0.882 | CsA | – | – | MPE: 0.17 mg·h/L | – | 8.06 mg·h/L | – | – | – | [35] |
| 28  | $10.43 + 1.47 \times C0 + 1.06 \times C0.66 + 1.65 \times C2$ | 0.862 | CsA | – | – | – | 4.1 | Dataset-splitting method similar to a bootstrap/external | 83% (±20%)$^o$ | [36] |
| 29  | $3.13 + 2.44 \times C0 + 1.31 \times C1.25 + 6.12 \times C4$ | 0.828 | CsA | – | – | – | 4.6 | – | 81% (±20%)$^o$ | [36] |
| 30  | $7.77 + 1.99 \times C0 + 1.05 \times C0.66 + 3.88 \times C3$ | 0.809 | CsA | – | – | – | 4.9 | – | 83% (±20%)$^o$ | [36] |
| 31  | $8.31 + 5.91 \times C0 + 0.79 \times C0.66 + 0.822 + 5.86 \times C4$ | 0.822 | Sir | – | – | – | 10 | – | 78% (±20%)$^o$ | [36] |
| 32  | $7.05 + 5.57 \times C0 + 1.24 \times C1.25 + 5.66 \times C4$ | 0.818 | Sir | – | – | – | 10.1 | – | 70% (±20%)$^o$ | [36] |
| 33  | $10.19 + 7.15 \times C0 + 0.80 \times C0.66 + 2.05 \times C2$ | 0.774 | Sir | – | – | – | 11.3 | – | 69% (±20%)$^o$ | [36] |
| 34  | $15.94 + 1.77 \times C2 + 2.34 \times C4 + 4.76 \times C9$ | 0.877 | Tac | – | – | 2.90% | 10.90% | 14.80% | Validation group/external | – | [37] |
| 35  | $20.38 + 0.26 \times C0 + 2.06 \times C2 + 3.82 \times C4$ | 0.693 | Tac | – | – | 2.90% | 17.10% | 21.50% | – | – | [37] |
Table 1 (continued)

| No. | Equation                                                                 | $r^2$ | CNI co-administered | Bland–Altman analysis | Bias | Precision | RMSE | Validation method/type | Additional information | References |
|-----|---------------------------------------------------------------------------|-------|----------------------|------------------------|------|-----------|------|------------------------|------------------------|------------|
| 36  | $4.24 + 2.05 \times C2 + 8.51 \times C7 + 2.29 \times C12$              | 0.94  | Tac                  | No value beyond ±2 SD  | 1.15 ± 3.08 | –         | –    | –                      | –                      | [38]       |
| 37  | $14.81 + 0.80 \times C0.5 + 1.56 \times C2 + 4.80 \times C4$            | 0.70  | CsA                  | Mean error: 10.1 mg·h/L| 1.3 ± 12.8% | 10.2 ± 7.6% | –    | Validation group/external | 76% (±15%)m | [39]       |
| 38  | $11.29 + 0.51 \times C0.5 + 2.13 \times C2 + 8.15 \times C8$            | 0.88  | CsA                  | Mean error: 6.9 mg·h/L | –0.6 ± 8.6% | 6.9 ± 5.0%  | –    | –                      | 92% (±15%)m | [39]       |
| 39  | $10.403 + 0.841 \times C2 + 1.105 \times C3 + 0.447 \times C4$         | 0.901 | CsA                  | Good agreement; a few values beyond 95% CI; average bias of < 1% | 0.56 ± 28.21% | 11.22 ± 0.94% | –    | Jackknife/internal | –                      | [40]       |
| 40  | $3.504 + 1.098 \times C1 + 0.670 \times C2 + 5.659 \times C4$          | 0.937 | CsA                  | Good agreement; a few values beyond 95% CI; average bias of < 1% | 1.48 ± 11.76% | 14.70 ± 0.58% | –    | –                      | –                      | [40]       |
| 41  | $178.167 + 0.954 \times C2 + 4.001 \times C4$                          | 0.975 | CsA                  | Mean error: 10.1 mg·h/L | 0.34 ± 3.56% | 12.67 ± 0.72% | –    | –                      | LSS for fMPA | [40]       |
| 42  | $180.543 + 0.956 \times C2 − 0.223 \times C3 + 4.342 \times C4$        | 0.975 | CsA                  | Mean error: 10.1 mg·h/L | 2.38 ± 7.18% | 14.35 ± 0.60% | –    | –                      | LSS for fMPA | [40]       |
| 43  | $136.826 + 0.76 \times C1 + 0.84 \times C2 + 3.914 \times C4$          | 0.982 | CsA                  | Mean error: 10.1 mg·h/L | 3.04 ± 3.56% | 12.67 ± 0.72% | –    | –                      | LSS for fMPA | [40]       |
| 44  | $3.0410 + 9.8588 \times C0 + 0.5963 \times C0.5 + 2.5612 \times C3$    | 0.893 | CsA                  | Mean error: 10.1 mg·h/L | – 3.85 | –         | –    | –                      | –                      | [41]       |
| 45  | $2.8401 + 5.7435 \times C0 + 0.2655 \times C0.5 + 1.1546 \times C1 + 2.8971 \times C4$ | 0.956 | CsA                  | Mean error: 10.1 mg·h/L | – 2.45 | –         | –    | –                      | –                      | [41]       |
| 46  | $12.61 + 0.37 \times C0.5 + 0.49 \times C1 + 3.22 \times C4 + 8.17 \times C10$ | 0.92  | CsA                  | Mean error: 10.1 mg·h/L | – 2.45 | –         | –    | –                      | –                      | [42]       |
| 47  | $7.182 + 4.607 \times C0 + 0.998 \times C0.67 + 2.149 \times C2$       | 0.73  | CsA                  | Mean bias: 0.0 mg·h/L (−1.5/0.2)l | 19.3 mg·h/L (6.9/8.1)l | Validation-nondiabetics; usefulness-diabetics/external | 62%/62%l; (±25%)m | [43]       |
| 48  | $15.3 + 7.06 \times C4 + 6.77 \times C8 − 3.76 \times C12$             | 0.97  | Tac                  | –                      | –         | –         | –    | –                      | –                      | [44]       |
| 49  | $−0.247 + 11.73 \times C6 + 2.92 \times C2$                            | 0.99  | CsA                  | –                      | –         | –         | –    | –                      | –                      | [44]       |
Table 1 (continued)

| No. | Equation                                      | $r^2$ | CNI co-administered | Bland–Altman analysis | Bias$^a$ | Precision$^b$ | RMSE | Validation method/type | Additional information | References |
|-----|-----------------------------------------------|-------|----------------------|------------------------|----------|-----------------|------|------------------------|------------------------|------------|
| 50  | $3.48 + 0.58 \times C_{20min} + 0.97$ $\times C_1 + 6.64 \times C_3$ | 0.946 | CsA                  | –                      | –        | –               | 13.6%| Jackknife/internal     | –                      | [45]       |
| 51  | $4.38 + 2.14 \times C_1 + 7.19 \times C_9$ | 0.906 | CsA                  | –                      | –        | –               | 13.8%| –                      | –                      | [45]       |
| 52  | $4.42 + 1.74 \times C_1 + 2.99 \times C_4$ $+ 5.43 \times C_9$ | 0.944 | CsA                  | –                      | –        | –               | 11.3%| –                      | –                      | [45]       |
| 53  | $10.2 + 0.72 \times C_{20min} + 8.65$ $\times C_3$ | 0.903 | CsA                  | –                      | –        | –               | 17.9%| –                      | –                      | [45]       |
| 54  | $7.75 + 6.49 \times C_0 + 0.76$ $\times C_{0.5} + 2.43 \times C_2$ | 0.862 | Tac                  | Prediction error: $6.1 \pm 19.0\%$ | –        | –               | –    | Validation group (cross-validation)/external | 82% ($\pm 15\%$)$^m$ | [46]       |
| 55  | $15.93 + 0.73 \times C_{1.25} + 0.8$ $\times C_2 + 7.32 \times C_{10}$ | 0.861 | CsA                  | Good agreement         | –        | –               | –    | –                      | –                      | [47]       |
| 56  | $15.19 + 6.92 \times C_0 + 1.08$ $\times C_1 + 0.72 \times C_2$ | 0.756 | CsA                  | –                      | –        | –               | –    | –                      | –                      | [47]       |
| 57  | $10.72 + 0.94 \times C_{1.25} + 0.84 \times C_2 + 1.46 \times C_4 + 6.5 \times C_{10}$ | 0.901 | CsA                  | Good agreement         | –        | –               | –    | –                      | –                      | [47]       |
| 58  | $6.02 + 5.61 \times C_0 + 1.28 \times C_1$ $+ 0.9 \times C_2 + 2.54 \times C_4$ | 0.89  | CsA                  | Good agreement         | –        | –               | –    | –                      | –                      | [47]       |
| 59  | $9.02 + 3.77 \times C_0 + 1.33 \times C_1$ $+ 1.68 \times C_3 + 2.96 \times C_{6}$ | 0.841 | CsA                  | –                      | –        | –               | –    | –                      | –                      | [48]       |

$^a$Mean or median percentage prediction error

$^b$Mean or median absolute percentage prediction error

$^c$Only abstract available

$^d$Dispersible tablet

$^e$Adjusted $r^2$

$^f$Capsule

$^g$Generic MMF

$^h$Most of the pharmacokinetic data simulated based on the literature data; C3.5 calculated as the arithmetic mean of C3 and C4

$^i$Simulated data/observed data from MMF- and EC-MPS-treated patients

$^j$Only for data from MMF-treated patients

$^k$Mean relative prediction error

$^l$Patients with diabetes/patients without diabetes

$^m$Good guess (number of AUC$_{pred}$ within $\pm 15\%$ or $\pm 20\%$ or $\pm 25\%$ of AUC$_{read}$)

$AUC_{pred}$ predicted area under the concentration-time (0–12 h) curve, $CI$ confidence interval, $CNI$ calcineurin inhibitor, CsA cyclosporine, fMPA free mycophenolic acid, MLR multiple linear regression, MMF mycophenolate mofetil, MPA mycophenolic acid, MPE mean prediction error, RMSE root mean square prediction error, SD standard deviation, SE standard error, Sir sirolimus, Tac tacrolimus, Tx transplantation, Cx concentration at x h
| No. | MMF indication                          | Equation                                                                 | $r^2$ | CNI co-administered | Bland–Altman analysis | Bias$^a$            | Precision$^b$   | RSME | Validation method          | Additional information | References |
|-----|----------------------------------------|--------------------------------------------------------------------------|-------|---------------------|-----------------------|---------------------|------------------|------|---------------------------|------------------------|------------|
| 1   | Heart transplantation                   | 8.424 + 0.781 × C0.5 + 1.263 × C2 + 1.660 × C4 + 3.022 × C6            | 0.844 | Tac                 | One case exceed 95% confidence interval | 2.09 ± 14.05%      | 11.17 ± 8.52%   | –    | Bootstrap (internal)/validation group (external) | 87%d [70]             |           |
| 2   | Hematopoietic cell transplantation      | 1.2039 × AUC$_{1-4}$ + 8.9727$^c$                                       | 0.65  | CsA                 | –                     | –                   | –                | –    | Validation group/external | 92.31% [49]            |           |
| 3   | Lung transplantation                    | 4.04 + 1.64 × C1 + 3.08 × C4 + 5.17 × C6                                | 0.74  | Tac                 | –                     | 2.00%               | 11.16%           | –    | Validation group/external | 77.27%d [50]           |           |
| 4   | Anti-neutrophil cytoplasmic antibody-associated vasculitis | 8.5 + 0.77 × C0.5 + 4.0 × C2 + 1.7 × C4                                 | 0.928 | –                   | –                     | –                   | –                | –    | –                         | –                      | [71]       |
| 5   | Liver transplantation                   | 34.2 + 1.12 × C1 + 1.29 × C2 + 2.28 × C4 + 3.95 × C6                  | 0.976 | Tac                 | Mean error 9.02 mg·h/L| 2.33 ± 13.0%        | 9.74 ± 8.81%    | –    | Bootstrap/ internal        | 74.5%d [51], LSS for fMPA |           |
| 6   | Islet transplantation                   | 1.783 + 1.248 × C1 + 0.888 × C2 + 8.027 × C4                          | 0.98  | Tac                 | –                     | –                   | 3.09%            | 9.53%          | –                          | Jackknife/ internal    | 75%d [20]  |
| 7   |                                      | 2.778 + 1.413 × C1 + 0.963 × C3 + 7.511 × C4                          | 0.973 | Tac                 | –                     | –                   | 3.22%            | 11.02%         | –                          | –                      | 81.25%d [20] |
| 8   |                                      | 1.448 + 1.239 × C1 + 0.271 × C1.5 + 9.108 × C4                       | 0.96  | Tac                 | –                     | –                   | 1.90%            | 11.46%         | –                          | –                      | 75%d [20]  |
| 9   |                                      | 1.410 – 0.259 × C0 + 1.443 × C1 + 9.622 × C4                          | 0.957 | Tac                 | –                     | –                   | 2.68%            | 11.53%         | –                          | –                      | 75%d [20]  |
| 10  |                                      | 1.547 + 1.417 × C1 + 9.448 × C4                                       | 0.957 | Tac                 | –                     | –                   | 2.46%            | 11.14%         | –                          | –                      | 75%d [20]  |
| 11  | Heart transplantation                   | 9.693 + 0.626 × C0.5 + 0.606 × C1 + 2.197 × C2                       | 0.841 | CsA                 | Good agreement        | 3.2 ± 16.73%       | –                | –    | Validation group/external | 70%d [52]             |           |
| 12  | Autoimmune disease (antineutrophil cytoplasmic antibody-associated systemic vasculitis; systemic lupus erythematosus) | 38.3 + 11.7 × C0                                                      | 0.48  | –/CsA$^d$           | –                     | 3.4%              | 26.8%           | –    | Validation group/external | –                      | [53]       |
| 13  | Autoimmune disease (antineutrophil cytoplasmic antibody-associated systemic vasculitis; systemic lupus erythematosus) | 30.8 + 10.1 × C0 + 0.7 × C0.67                                      | 0.53  | –/CsA$^d$           | –                     | 4.8%              | 25.1%           | –    | Validation group/ internal | –                      | [53]       |
| 14  | Autoimmune disease (antineutrophil cytoplasmic antibody-associated systemic vasculitis; systemic lupus erythematosus) | 17.5 + 7.1 × C0 + 1.0 × C1 + 2.6 × C3                                | 0.61  | –/CsA$^d$           | –                     | 0.8%              | 22.6%           | –    | –                          | –                      | [53]       |
| 15  | Autoimmune disease (antineutrophil cytoplasmic antibody-associated systemic vasculitis; systemic lupus erythematosus) | 12.3 + 4.7 × C0 + 1.2 × C1 + 2.7 × C3 + 1.8 × C6                    | 1.7   | –/CsA$^d$           | –                     | 20.4%             | 17.3%           | –    | –                          | –                      | [53]       |
| No. | MMF indication       | Equation                                                                 | \( r^2 \) | CNI co-administered | Bland–Altman analysis | Bias\(^a\) | Precision\(^b\) | RSME | Validation method | Additional information                  | References |
|-----|---------------------|--------------------------------------------------------------------------|-----------|---------------------|------------------------|------------|----------------|------|------------------|-------------------------------------------|-----------|
| 16  | Liver transplantation | 4.46 + 0.81 \times C1 + 1.78 \times C2 + 2.51 \times C4 + 4.94 \times C8 | 0.95      | Tac                 | The best agreement; mean error 9.02 mg·h/L | 0.27 ± 1.79% | 8.83 ± 1.24% | –    | Bootstrap/inter- | 83.3\(^d\)                      | [54]      |
| 17  |                     | 5.92 + 1.10 \times C1 + 1.01 \times C2 + 1.77 \times C4 + 4.80 \times C6 | 0.927     | Tac                 | –                      | 0.36 ± 1.86% | 9.71 ± 1.21% | –    | –                | 83.3\(^d\)                      | [54]      |
| 18  |                     | 9.37 + 2.18 \times C2 + 2.10 \times C4 + 4.71 \times C8                | 0.901     | Tac                 | –                      | 0.81 ± 2.70% | 12.64 ± 11.97% | –    | –                | 75\(^d\)                        | [54]      |
| 19  |                     | 10.56 + 1.55 \times C1.5 + 6.44 \times C6                               | 0.859     | Tac                 | –                      | 1.78 ± 2.64% | 14.41 ± 1.61% | –    | –                | 58.3\(^d\)                      | [54]      |
| 20  | Heart transplantation | 1.25 \times C1 + 5.29 \times C4 + 2.90 \times C8 + 3.61 \times C10     | 0.95      | Tac                 | –                      | MPE: − 0.007 ± 0.123 | –       | –              | Crossvalidation/ internal | 79\(^d\) | [55]      |
| 21  |                     | 3.37 \times C0 + 0.97 \times C0.5 + 1.20 \times C1 + 2.70 \times C2     | 0.87      | Tac                 | –                      | MPE: − 0.006 ± 0.189 | –       | –              | –                            | 46\(^d\) | [55]      |
| 22  |                     | 1.53 \times C1 + 5.51 \times C4 + 4.62 \times C8                        | 0.91      | Tac                 | –                      | MPE: − 0.017 ± 0.180 | –       | –              | –                            | 68\(^d\) | [55]      |
| 23  |                     | 1.09 \times C0.5 + 1.19 \times C1 + 3.60 \times C2                      | 0.84      | Tac                 | –                      | MPE: − 0.017 ± 0.208 | –       | –              | –                            | 50\(^d\) | [55]      |
| 24  |                     | 1.65 \times C0.5 + 4.74 \times C2                                       | 0.75      | Tac                 | –                      | MPE: − 0.032 ± 0.253 | –       | –              | –                            | 36\(^d\) | [55]      |
| 25  | Heart transplantation | 0.10 + 11.15 \times C0 + 0.42 \times C1 + 2.80 \times C2               | 0.96      | CsA                | –                      | 0.15 ± 7.85% | –                | –    | –                | 100\(^d\)                      | [56]      |
| 26  |                     | −0.51 + 11.47 \times C0 + 3.24 \times C2                                | 0.94      | CsA                | −                      | 0.495 ± 10.35% | –      | –              | –                            | 90.9\(^d\) | [56]      |
| 27  | Liver transplantation | 6.03 + 0.89 \times C1 + 1.94 \times C2 + 2.24 \times C6 + 4.64 \times C8 | 0.911     | Tac                 | Good agreement        | 1.18 ± 11.84% | –               | –    | Validation group/ external | 90.3\(^d\) | [57]      |
| 28  | Liver transplantation | 5.503 + 0.919 \times C1 + 1.871 \times C2 + 3.176 \times C6 + 3.664 \times C8 | 0.921     | Tac                 | Good agreement; mean error ± 9.89 mg·h/mL | 1.24 ± 11.19% | 8.24 ± 7.61% | –    | –                | 88\(^d\)                        | [58]      |
| 29  |                     | 10.229 + 0.925 \times C1 + 1.750 \times C2 + 4.586 \times C6            | 0.855     | Tac                 | −                      | 2.42 ± 15.73% | 11.47 ± 10.95% | –    | –                | 70.8\(^d\)                      | [58]      |
| 30  |                     | 17.930 + 1.992 \times C2 + 4.136 \times C6                             | 0.751     | Tac                 | −                      | 4.33 ± 21.74% | 16.35 ± 14.84% | –    | –                | 62.5\(^d\)                      | [58]      |
| No. | MMF indication | Equation | \( r^2 \) | CNI co-administered | Bias\(^a\) | Precision\(^b\) | RSME | Validation method | Additional information | References |
|-----|----------------|----------|----------|---------------------|----------|----------------|------|-------------------|-----------------------|-----------|
| 31  | Lung transplantation | 1.14 + 0.241 × logC0 + 0.406 × logC2 | 0.828 | CsA/Tac | – | – 5.82\% | – | 5.97\(^b\) | Validation group/external | 89\(^a\); LSS for logAUC | [59] |
| 32  | | 1.09 + 0.202 × logC0 + 0.411 × logC1.5 | 0.791 | CsA/Tac | – | – 5.71\% | – | 6.94\(^b\) | 89\(^a\); LSS for logAUC | [59] |
| 33  | | 1.000 + 0.153 × logC0 + 0.327 × logC0.6 + 0.354 × logC2 | 0.873 | CsA/Tac | – | – 3.70\% | – | 5.81\(^b\) | 89\(^a\); LSS for logAUC | [59] |
| 34  | | 1.024 + 0.192 × logC0 + 0.213 × logC1 + 0.355 × logC2 | 0.827 | CsA/Tac | – | – 6.88\% | – | 6.88\(^b\) | 100\(^a\); LSS for logAUC | [59] |
| 35  | | 1.154 + 0.253 × logC0 − 0.070 × logC1.5 + 0.460 × logC2 | 0.8 | CsA/Tac | – | – 5.90\% | – | 6.03\(^b\) | 100\(^a\); LSS for logAUC | [59] |
| 36  | Liver transplantation | 8.144 + 2.880 × C3 | 0.575 | CsA/Tac | – | 12.6\% | – | – | – | – | [60] |
| 37  | Hematopoietic cell transplantation | 4.43 + 2.76 × C0 + 0.51 × C1 + 1.97 × C2 + 4.27 × C6 | 0.85 | CsA | – | 0.8 μg·h/mL/7.1 ± 16.6\%\(^c\) | MAE: 2.3 μg·h/mL | – | Validation group/external | Oral | [61] |
| 38  | | 63.92 + 2.01 × C0 + 0.67 × C1 + 2.05 × C2 + 4.26 × C6 | 0.9 | CsA | – | 21.7 ng·h/mL/10.4 ± 17.0\%\(^d\) | MAE: 39.0 ng·h/mL | – | Oral; LSS for fMPA | – | [61] |
| 39  | | −0.49 + 1.58 × C2 + 0.41 × C4 + 13.88 × C6 | > 0.99 | CsA | – | 1.7 μg·h/mL/7.6 ± 17.5\%\(^d\) | MAE: 2.3 μg·h/mL | – | Intravenous | – | [61] |
| 40  | | 7.99 + 1.40 × C2 + 2.47 × C4 + 9.54 × C6 | > 0.99 | CsA | – | 0.3 μg·h/mL/1.1 ± 13.1\%\(^d\) | MAE: 22.7 ng·h/mL | – | Intravenous; LSS for fMPA | – | [61] |
| 41  | Heart transplantation | 5.568 + 0.902 × C1.25 + 2.022 × C2 + 4.594 × C6 | 0.926 | CsA | Good agreement | – | – | – | – | – | [62] |
| 42  | | 3.800 + 1.015 × C1.25 + 1.819 × C2 + 1.566 × C4 + 3.479 × C6 | 0.948 | CsA | – | – | – | – | – | – | [62] |

\( AUC_{\text{pred}} \) predicted area under the concentration-time (0–12 h) curve, \( CNI \) calcineurin inhibitor, \( CsA \) cyclosporine, \( fMPA \) free mycophenolic acid, \( MAE \) mean absolute error, \( MLR \) multiple linear regression, \( MMF \) mycophenolate mofetil, \( MPA \) mycophenolic acid, \( MPE \) mean prediction error, \( RMSE \) root mean square prediction error, \( Tac \) tacrolimus, \( Cx \) concentration at \( x \) h

\(^a\)Mean or median percentage prediction error
\(^b\)Mean or median absolute percentage prediction error
\(^c\)Dispersible tablets
\(^d\)Good guess (number of \( AUC_{\text{pred}} \) within ±15\% of \( AUC_{\text{total}} \))
\(^e\)Sampling time 1, 2 and 4 for \( AUC_{1-4} \)
\(^f\)Predictive accuracy
\(^g\)Only 3 patients (8\%) received CsA
\(^h\)Precision
\(^\circ\)Bias/mean prediction error %
Table 3  The characteristics of MLR-based equations found in the literature for predicting MPA AUC_{pred} in children treated with MMF

| No. | MMF indication          | Equation                                                                 | \( r^2 \) | CNI co-administered | Bland–Altman analysis | Bias\(^{d} \) | Precision\(^{b} \) | Validation method | Additional information | References |
|-----|-------------------------|--------------------------------------------------------------------------|----------|---------------------|------------------------|-------------|----------------|-------------------|-----------------------|------------|
| 1   | Nephrotic syndrome      | 1.62 + 2.22 × C0 + 1.27 × C1 + 2.32 × C3 + 1.32 × C4 + 3.07 × C6         | 0.9477   | –                   | –                      | – 0.39%     | 2.87%          | Validation group/external | 94\(^{c} \) | [19]       |
| 2   | Nephrotic syndrome      | 7.10 + 1.21 × C1 + 3.75 × C3 + 3.08 × C6                                | 0.8388   | –                   | –                      | – 2.69%     | 12.92%         | Bootstrap          | 92\(^{c} \) | [19]       |
| 3   | Nephrotic syndrome      | 8.7 + 4.63 × C0 + 1.90 × C1 + 1.52 × C2                                  | 0.9      | –                   | –                      | 3.88 ± 3.72%| –              | Validation group/external | –          | [63]       |
| 4   | Nephrotic syndrome      | 6.9 + 3.69 × C0 + 1.84 × C1 + 1.09 × C2 + 2.32 × C4                      | 0.92     | –                   | –                      | 2.71 ± 3.13%| –              | –                 | –                     | [63]       |
| 5   | Nephrotic syndrome      | 6.27 + 0.93 × C1 + 5.36 × C4 + 6.56 × C8                                | 0.96     | –                   | –                      | 1.12 ± 3.36%| –              | –                 | –                     | [63]       |
| 6   | Idiopathic nephrotic syndrome | 21.971 + 2.6059 × C2                                                | 0.6405   | CsA                 | –                      | –           | –              | –                 | –                     | [64]       |
| 7   | Systemic lupus erythematosus | 12.82 + 4.86 × C0 + 0.66 × C1 + 0.15 × C1.5 + 0.95 × C2 + 2.25 × C3     | 0.88     | –                   | –                      | 1.96%       | 11.28%         | Bootstrap/external | –                     | [18]       |
| 8   | Renal transplantation   | 13.81 + 0.68 × C1 + 1.08 × C2 + 2.21 × C3 + 4.62 × C0                   | 0.87     | –                   | –                      | 1.92%       | 11.24%         | –                 | –                     | [18]       |
| 9   | Renal transplantation   | 18.6 + 4.3 × C0 + 0.54 × C0.5 + 2.15 × C2\(^{a} \)                      | 0.72     | CsA                 | Mean difference 0.14 mg·h/L; prediction variation ±24.4 mg·h/L | –           | –              | Validation group/external | –         | [65]       |
| 10  | Renal transplantation   | 10.6 + 3.18 × C0 + 1.39 × C0.5 + 2.08 × C2\(^{a} \)                      | 0.67     | CsA                 | Mean difference – 1.26 mg·h/L; prediction variation ±26.9 mg·h/L | –           | –              | –                 | –                     | [65]       |
| 11  | Renal transplantation   | 9.55 + 4.50 × C0 + 0.88 × C0.5 + 2.67 × C2                             | 0.77     | CsA                 | –                      | 6.48 ± 2.53%| –              | –                 | –                     | [65]       |
| 12  | Renal transplantation   | 9.87 + 0.90 × C1 + 1.73 × C2 + 6.86 × C8                               | 0.91     | CsA                 | –                      | 3.56 ± 1.54%| –              | –                 | –                     | [65]       |
| 13  | Renal transplantation   | 8.217 + 3.163 × C0 + 0.994 × C1 + 1.334 × C2 + 4.183 × C4              | 0.9456   | Tac                 | Good agreement (better than 3 points LSS) | –           | –              | –                 | –                     | [16]       |
| 14  | Renal transplantation   | 10.01391 + 3.94791 × C0 + 3.24253 × C0.5 + 1.0108 × C2                 | 0.8996   | Tac                 | Good agreement; mean error of 2.9% | –           | –              | –                 | –                     | [16]       |
| No. | MMF indication               | Equation                                                                 | $r^2$ | CNI co-administered analysis | Bias\(^a\) | Precision\(^b\) | Validation method | Additional information | References |
|-----|-----------------------------|--------------------------------------------------------------------------|-------|-------------------------------|------------|----------------|---------------------|------------------------|------------|
| 15  | Renal transplantation       | $12.62 + 7.78 \times C0 + 0.90 \times C1 + 1.30 \times C2$             | 0.75  | CsA/Tac                       | Prediction variation of ±12.2 μg·h/mL | –          | –                  | –                   | – [17]     |
| 16  |                             | $13.73 + 9.024 \times C0 + 1.779 \times C2$                            | 0.67  | CsA/Tac                       | Prediction deviation of ±14 μg·h/mL | –          | –                  | –                   | – [17]     |
| 17  |                             | $15.1 + 9.68 \times C0 + 1.28 \times C1$                                | 0.67  | CsA/Tac                       | Prediction deviation of ±14 μg·h/mL | –          | –                  | –                   | – [17]     |
| 18  | Renal transplantation       | $7.73 + 0.94 \times C1 + 2.55 \times C2 + 5.48 \times C6$             | 0.845 | CsA/Tac/~                     | Mean deviation 0.0 ± 10.6 mg·h/mL | –          | –                  | –                   | – [66]     |
| 19  |                             | $8.22 + 3.16 \times C0 + 0.99 \times C1 + 1.33 \times C2 + 4.18 \times C4$ | 0.867 | CsA/Tac/~                     | Mean deviation 0.0 ± 9.8 mg·h/mL | –          | –                  | –                   | – [66]     |
| 20  | Renal transplantation and autoimmune diseases | $10.75 + 0.98 \times C1 + 2.38 \times C2 + 4.86 \times C6$         | 0.87  | CsA/Tac                       | Good agreement, mean error ± 9.5 μg·h/mL | –          | –                  | –                   | – [67]     |
| 21  |                             | $15.79 + 2.05 \times C0 + 0.95 \times C0.5 + 3.73 \times C2$          | 0.74  | CsA/Tac                       | –          | –                  | –                   | – [67]     |
| 22  |                             | $14.57 + 1.62 \times C0 + 1.5 \times C1 + 5.15 \times C6$             | 0.76  | CsA/Tac                       | –          | –                  | –                   | – [67]     |
| 23  | Renal transplantation       | $12.9 + 5.99 \times C0 + 0.528 \times C40min + 2.4 \times C2$        | 0.7396 | –                             | –          | –                  | –                   | – [68]     |
| 24  | Renal transplantation       | $5.2 + 7.1 \times C0 + 1.0 \times C1.25 + 5.4 \times C6$             | 0.88  | CsA                           | –          | –                  | –                   | – [69]     |
| 25  | Renal transplantation       | $9.13 + 5.7 \times C0 + 1.1 \times C40min + 2.1 \times C2$           | 0.74  | CsA                           | –          | –                  | –                   | – [69]     |

\(AUC_{pred}\) predicted area under the concentration-time (0–12 h) curve, CNI calcineurin inhibitor, CsA cyclosporine, MLR multiple linear regression, MMF mycophenolate mofetil, MPA mycophenolic acid, Tac tacrolimus, \(C_x\) concentration at \(x\) h

\(^a\)Mean or median percentage prediction error

\(^b\)Mean or median absolute percentage prediction error

\(^c\)Good guess (number of \(AUC_{pred}\) within ±15% of \(AUC_{total}\))

\(^d\)Given as imprecision

\(^e\)For MPA concentrations determined with HPLC

\(^f\)For MPA concentrations determined with EMIT
the applied to patients receiving either CsA or Tac; however, advantages of being validated in a validation group and 

\[ C_0.5 + 2.256 \times C_{1.5} + 4.134 \times C_4 \] [25], which had the 

equations were: MPA AUC pred = 2.8401 + 5.7435 \times C_0 

bias and precision was MPA AUC pred = 0.414 + 1.210 \times 

C_{1.5} + 4.134 \times C_4 \] [25], which had the 

\[ C_0 \] C_{1.5} + 4.134 \times C_4 \] [25], which had the 

\[ C_0 + 1.1546 \times C_1 + 2.8971 \times C_4 \] if CsA 

\[ C_6 + 2.92 \times C_2 \] [44]; however, the bias and 

was C6 (36% of equations). The latter equation had 

the advantage of being validate in an external group of 

patients. The LSSs which was characterized by very good 

bias and precision was MPA AUC pred = 0.414 + 1.210 \times 

C_{0.5} + 2.256 \times C_{1.5} + 4.134 \times C_4 \] [25], which had the 

advantages of being validated in a validation group and 

to patients receiving either CsA or Tac; however, 

\[ r^2 < 0.5 \] [29]. Interestingly, the LSS with the same time 

points (C0 and C4), established in the same study but 

before transplantation, was characterized by much better 

\[ r^2 (0.91) \] [29]. The value of \[ r^2 \] above 0.98 was obtained 

for three LSSs, among which one included five time 

points [33], one included two time points [44], and one 

concerned fMPA [40]. The bias was within the range of 

\[ 3.80 \] to 10.28%. MPA LSS in one study was characterized 

by mean bias equal 0 mg h/L [41]. In other study, 

bias of one LSS was expressed as MPE and equal to 0.00 

[43]. The precision defined as mean or median absolute 

percentage prediction error or RMSE ranged from 6.9 to 

17.10% and 3.60 to 24%, respectively. Some studies 
calculated the good guess. The best results amounted to 92% 

[39], 83% [36], and 62% [43] for good guesses of AUC pred 

within \[ \pm 15\% \], \[ \pm 20\% \], or \[ \pm 25\% \] of AUC total, respectively. 

Based on the results of the predictive performance, the most 

promising MPA LSSs for renal transplant recipients were: MPA AUC pred = 2.8401 + 5.7435 \times C_0 + 0.2655 \times C_{0.5} + 1.1546 \times C_1 + 2.8971 \times C_4 

if CsA was co-administered [41] and MPA AUC pred = 8.36 + 7.49 \times C_8 + 1.34 \times C_2 + 1.66 \times C_4 + 0.76 \times C_1 

if Tac was co-administered [23]. The latter equation had 

the advantage of being validate in an external group of 

patients. The LSSs which was characterized by very good 

bias and precision was MPA AUC pred = 0.414 + 1.210 \times 

C_{0.5} + 2.256 \times C_{1.5} + 4.134 \times C_4 \] [25], which had the 

advantages of being validated in a validation group and 

applied to patients receiving either CsA or Tac; however, 

the \( r^2 \) was < 0.950. High \( r^2 \) was observed for the following 

equations: AUC pred = 8.32 + 0.904 \times C_{1.5} + 1.955 \times C_4 + 10.206 \times C_{10} [35], AUC pred = 15.3 + 7.06 \times C_4 + 6.77 \times C_8 – 3.76 \times C_{12}, and AUC pred = -0.247 + 11.73 \times C_6 + 2.92 \times C_2 [44]; however, the bias and 

precision were given in AUC units [35] or not given at all [44], so it is therefore difficult to compare these results 

with those expressed as percentages. For CsA co-treated 

patients, fMPA LSSs were characterized by high \( r^2 \) (> 0.950); however, precision was > 10% for all three 

equations and the validation was internal [40].

### 3.3 The MLR-Based LSSs for Adult Patients Treated with MMF with Different Indication than Renal Transplantation

Among other MMF indications in adults than rejection prophylaxis after renal transplantation, studies aiming at 
establishing LSS for liver transplant recipients \((n = 5)\) [51, 54, 57, 58, 60], heart transplant recipients \((n = 5)\) [52, 55, 56, 62, 70], lung transplant recipients \((n = 2)\) [50, 59], and hematopoietic stem cell transplant recipients \((n = 2)\) [49, 61] were found. There were single studies including patients after islet transplantation [20], patients with autoimmune diseases (antineutrophil cytoplasmic antibody-associated systemic vasculitis and systemic lupus erythematosus) [53] and patients with anti-neutrophil cytoplasmic antibody-associated vasculitis [71] (Table 2). In one study, separate LSSs were established after oral and intravenous MMF administration for both total and fMPA [61]. One LSS consisted of AUC \(_{1-4}\) instead of particular time points [49].

The equations included up to four time points with three 
time-point LSSs being the most frequent (48%). Of all time 

points, those collected within 0–2 h after MMF administration 

constituted 64% of the sum of all time points, whereas 
sampling between 3–5 h and 6–12 h after drug administration 

constituted 18% and 19%, respectively. Of 42 MLR equations, the most frequently used time 

points were C2 and C1. C2 was included in 28 (67%) equations and constituted 22% of the sum of all time points from 42 
equations, while C1 was included in 24 (57%) equations and constituted 19% of all the time points from 42 
equations. The number of 15 (36%) equations including C0 and 
C1 constituted 12% of all time points. The most frequently 
included time point within 6–12 h after MMF administration 
was C6 (36% of equations).

For other indications than renal transplantation, most 

MPA LSSs \((n = 21)\) were established when Tac 

was co-administered. For these LSSs, the most frequent 
time points were C1 (24% of all time points, 76% of the 
equations), C2, and C4 (19% of all time points, 62% of the 
equations). Interestingly, for MMF and Tac co-
administration, C0 was used in only two LSSs (10%). For 

CsA co-administration (10 LSSs), the time points most 
often included were C2 (31% of all time points, 100% of the 
equations), C6 (19% of all time points, 60% of the 
equations), and C1 (16% of all time points, 50% of the 
equations). C0 was used in four LSSs (40%) and constituted 
13% of all time points. Four LSSs established for patients 
among whom only 8% received CsA [53] were 
not included in this analysis. Additionally, there were six 
LSSs established for the group of patients treated with 
two agents, either MMF and CsA or MMF and Tac [59, 60]. 

Five of them included logarithmic concentrations and 
sampling up to 2 h after drug administration [59]. 

Adis
sixth LSS which was established for patients receiving concomitantly with MMF CsA or Tac included only one time point, and its $r^2$ was low (0.575) [60].

For LSSs established for patients treated with MMF less than 1 month, the most frequently included time points were C2 (27% of all time points, 87% of the equations) and C6 (23% of all time points, 73% of the equations). LSSs established for patients treated with MMF longer than 3 months most frequently consisted of C2 (24% of all time points, 69% of the equations), and C0 (22% of all time points, 62% of the equations).

The $r^2$ value of 0.98 was reached for four LSSs [20, 51, 61]. The bias was within −1.1% to 20.4%. No LSS was characterized by bias equal to 0. The closest to zero bias was 0.15% [56] and −0.006 expressed as MPE [55]. The precision defined as mean or median absolute percentage prediction error or RMSE ranged from 8.24 to 16.35% and 5.81 to 26.8%, respectively. The best results of AUC pred within ±15% of AUC total amounted to 100% [56, 59].

Based on the results of the predictive performance, the most promising MPA LSS were: AUC pred = 1.783 + 1.248 × C1 + 0.888 × C2 + 8.027 × C4 [20] established for patients after islet transplantation and AUC pred = 4.46 + 0.81 × C1 + 1.78 × C2 + 2.51 × C4 + 4.94 × C8 for liver transplant recipients [54]. Both equations were established for patients co-treated with Tac. For CsA co-treated patients after heart transplantation, the best LSS was AUC pred = 0.10 + 11.15 × C0 + 0.42 × C1 + 2.80 × C2; however, precision was not shown [56]. The LSSs for Tac co-treated liver transplant recipients were characterized by very good bias and precision (AUC pred = 5.92 + 1.10 × C1 + 1.01 × C2 + 1.77 × C4 + 4.80 × C6 [54] and AUC pred = 5.503 + 0.919 × C1 + 1.871 × C2 + 3.176 × C6 + 3.664 × C8 [58]); however, $r^2$ was <0.950 in both cases. High $r^2$ was observed for externally validated LSS for CsA co-treated patients after hematopoietic stem cell transplantation (AUC pred = −0.49 + 1.58 × C2 + 0.41 × C4 + 13.88 × C6 [61]); however, the bias and precision were given in AUC units. The best LSS for fMPA, characterized by high $r^2$ and good bias and precision, was AUC pred = 34.2 + 1.12 × C1 + 1.29 × C2 + 2.28 × C4 + 3.95 × C6, and was established for liver transplant recipients [51]. All five LSSs with log-transformed concentrations, established for lung transplant recipients, were characterized by good bias and precision; however, $r^2$ was <0.90 for all of them [59]. Another fMPA LSS, which was characterized by high $r^2$ (AUCpred = 7.99 + 1.40 × C2 + 2.47 × C4 + 9.54 × C6), was established for intravenous MMF administration and validated externally; however, the results of bias and precision were expressed in ng·h/mL [61].

### 3.4 The MLR-Based LSS for Pediatric Patients Treated with MMF

A total of 25 LSSs established for pediatric patients were included. These LSSs were found in 11 studies [16–19, 63–69]. Most of these concerned children after renal transplantation [16, 17, 65, 66, 68, 69]. There were three studies concerning nephrotic syndrome [19, 63, 64], one concerning systemic lupus erythematosus [18], and one which included both children after renal transplantation and with autoimmune diseases [67].

The equations included up to five time points. Three time-point LSSs were the most frequent (64%). Of all the time points, those collected within 0–2 h after MMF administration constituted 78% of all the time points, whereas sampling between 3–5 h and 6–12 h after drug administration constituted 11% and 10%, respectively.

Of 25 MLR equations, the most frequently used time points were C0 and C2. Each of these concentrations was included in 19 (76%) equations and constituted 24% of the sum of all time points from 25 equations. The most frequently included time point within 6–12 h after MMF administration was C6 (24% of equations). Among 14 LSSs established for children after renal transplantation, the most frequently included time points were the same as for all the pediatric studies. C0 and C2 were included in 12 LSSs (86%) and each constituted 29% of the sum of all time points from 14 equations.

Pediatric patients for whom MPA LSSs were established received concomitantly CsA (seven LSSs), Tac (two LSSs) or either CsA or Tac, but were analyzed together (eight LSSs). For eight LSSs, solely MMF was administered. The most frequently included time points only for LSSs established for children co-administered with CsA were analyzed. For these LSSs, the most frequent time points were C2 (32% of all time points, 88% of the equations), C0 (26% of all time points, 71% of the equations), and C0.5 (16% of all time points, 43% of the equations).

The best $r^2$ was for three time points LSSs (C1, C4, C8) and was established for children with nephrotic syndrome. The best LSSs for renal transplant recipients ($r^2$ = 0.91) also included three time points (C1, C2, C8). None of the equations reached $r^2$ above 0.98. Only four studies included the bias (−2.69% to 6.48% with −0.39% being the closest to zero) and precision (2.87–12.92%). In one study [19], the results of a good guess were shown (the percentage of AUC pred within ±15% of AUC total).

The best LSSs were AUC pred = 6.27 + 0.93 × C0 + 5.36 × C4 + 6.56 × C8 [63], and AUC pred = 1.62 + 2.22 × C0 + 1.27 × C1 + 2.32 × C3 + 1.32 × C4 + 3.07 × C6 [19], both for children with nephrotic syndrome treated solely with MMF. For pediatric renal transplant recipients co-treated with Tac, the best LSS was AUC pred = 8.217
Several studies excluded patients that did not fully supervise the contribution of concomitant trace proteinuria during the day of blood collection [19], or other limitations concerned the pharmacokinetics, such as MPA LSS overprediction of AUC by 30% [61], low frequency of the sample collection at time intervals [19, 50], and the exclusion from the dataset of profiles with either extraordinarily high MPA C₀ or delayed absorption (t_max > 2 h) [36]. In one study, the lack of control patients was emphasized [64]. Other limitations included the limited universality of the LSS method [26, 48, 52].

4 Discussion

Estimating LSS is the approach of TDM applied for many drugs, e.g., MPA, levofoxacin, etoposide, moxifloxacin, ganciclovir, Tac, and CsA [72–78] in many diseases. Due to numerous factors influencing MPA pharmacokinetics, it is extremely difficult to establish a universal MPA LSS which might be applied in all MMF-treated patients. In our opinion, the review of MPA LSSs may be useful, as summaries of MLR LSSs for MPA which included the years up to 2009 [14] and up to 2013 [7] were found, and, therefore, this study contains the actual literature review. Moreover, some studies in which the LSS developed for one population was used to predict MPA exposure in another population [15, 79, 80] were found in the literature. The authors [15] observed that the application of LSS established for lung transplant recipients to predict MPA AUC in patients after heart transplant yielded satisfactory prediction results (bias and precision within ±15%); however, they concluded that the LSSs seem to be center-specific. Moreover, in Gellermann et al.’s study [81], the authors applied the LSSs established for children after renal transplantation and adult heart transplant recipients to evaluate AUC in children with nephrotic syndrome. In Katsuno et al.’s study [9], the LSS established for renal transplant recipients was used to predict AUC in patients with lupus nephritis. Additionally, Tong et al. [80] applied the LSS established with the HPLC method to evaluate AUC for patients for whom EMIT was used for MPA determination, while Neuberger et al. [79] applied MPA LSS established after EC-MPS administration in MMF-treated patients.

This review has included LSSs for total MPA generated with MLR mostly after oral MMF administration; however, there was one study [61] which included MPA LSS developed after separate oral and intravenous administration. Three studies established LSSs for fMPA [40, 51, 61]. There were also a few LSSs which included particular formulations, such as suspension [65], dispersible tablets [23, 24, 70], or a generic form of the drug [25, 33].

Most of the studies established LSSs with the intercept included, except those established by Kaczmarek et al. [55].
Table 4  Additional information on MLR-based equations found in the literature for predicting MPA AUC<sub>pred</sub> for patients treated with MMF

| Additional data                                                                 | References |
|---------------------------------------------------------------------------------|------------|
| Demographic data, age, years                                                     |            |
| 0–5                                                                              |            |
| 6–11                                                                             | [17, 19, 63–65] |
| ≥ 12                                                                             | [16, 18, 66–68] |
| 18–29                                                                            | [35]       |
| 30–49                                                                            | [23–29, 31, 32, 36–40, 42–45, 48–52, 56–59, 70] |
| ≥ 50                                                                             | [20, 34, 41, 53–55, 60, 62, 71] |
| Drugs co-administered                                                            |            |
| CsA                                                                              | [34, 41, 45, 49, 53]<sup>a</sup>, [61, 64, 66, 67] |
| CsA, corticosteroids                                                             | [17, 25, 35, 36, 39, 40, 42–45, 47, 48, 52, 56, 59, 60, 62, 64, 65, 69] |
| Tac                                                                              | [16, 20, 29, 32, 46, 55, 57, 66, 67] |
| Tac, corticosteroids                                                             | [17, 23–28, 30, 31, 33, 37, 38, 44, 50, 51, 54, 58–60, 70] |
| Steroids                                                                         | [19, 53, 71] |
| Sirolimus, daclizumab, corticosteroids                                           | [34, 36] |
| None                                                                             | [18, 63, 66, 67] |
| No information                                                                   | [22]<sup>b</sup>, [68]<sup>b</sup> |
| Analytical method                                                                |            |
| HPLC                                                                             | [18–20, 22, 25, 32–44, 46–49, 51, 52, 55–59, 61, 62, 65, 68, 69] |
| UPLC-UV                                                                          | [23]       |
| UPLC with photodiode array detection                                             | [30]       |
| LC-MS/MS                                                                         | [31, 70]   |
| LC/ESI-MS/MS                                                                     | [50]       |
| EMIT                                                                             | [16, 17, 24, 27–29, 45, 53, 54, 60, 63, 65–67, 71] |
| PETINIA technique                                                                | [26, 64]   |
| Post-transplant time or the duration of MMF treatment                             |            |
| Pre-transplantation                                                               | [29]       |
| Within 7 days                                                                     | [20, 23, 24, 27, 31, 36, 48, 49, 51, 60, 61, 63] |
| Within 7 days and 1 month                                                         | [16, 30, 35, 37, 39, 40, 43, 46–48, 54, 57, 58, 60, 65, 66]<sup>c</sup>, [67]<sup>c</sup>, [68–70]<sup>f</sup>, [71]<sup>f</sup> |
| 1–3 months                                                                        | [16, 20, 29, 36, 41, 42, 44, 46, 52, 53, 62] |
| 3 months                                                                          | [18, 46, 47] |
| ≥ 3 months                                                                        | [16, 31, 32] |
| < 6 months                                                                        | [25]       |
| 3–6 months                                                                        | [33, 36, 44, 65, 68, 69] |
| 6–12 months                                                                       | [25, 44, 45, 47, 52, 56, 65] |
| < 1 year                                                                          | [19, 20, 26, 28, 34, 52] |
| > 1 year                                                                          | [17, 19, 20, 25, 26, 28, 44, 45, 50, 52, 55, 59, 64, 65] |
| Stable post-transplant period, stable trough concentrations                      | [22]<sup>f</sup>, [38] |

AUC$_{\text{pred}}$ Predicted area under the concentration-time (0–12 h) curve. CsA cyclosporine, EMIT enzyme multiplied immunoassay technique, HPLC high-performance liquid chromatography, LC/ESI-MS/MS liquid chromatography positive ion electrospray ionization tandem mass spectrometry, LC-MS/MS liquid chromatography–tandem mass spectrometry, MLR multiple linear regression, MMF mycophenolate mofetil, MPA mycophenolic acid, PETINIA homogeneous particle-enhanced turbidimetric inhibition immunoassay technique, Tac tacrolimus, UPLC-UV ultra-performance liquid chromatography with ultraviolet detection

<sup>a</sup>Only 3 patients (8%) received CsA

<sup>b</sup>All information provided are based on the article abstract

<sup>c</sup>Median 21 days after transplantation

<sup>d</sup>At least 7 days, the upper time limit was not defined

<sup>e</sup>At least 2 weeks, the upper time limit was not defined

△ Adis
According to these authors [55], the equation without an intercept distributes relative prediction errors fairly evenly throughout the measuring range, whereas non-homogeneous models tend to yield larger relative prediction errors for lower values. However, the approach of not including the intercept was not found in other studies.

Among all MPA LSSs included in this review, the most often used time points were 2 h after MMF administration, that is near MPA $t_{\text{max}}$ [1], and 6 h after MMF administration. Surprisingly, in adult renal transplant recipients, the most often used time point was C4, which is between $t_{\text{max}}$ and $t_{\text{max}2}$ [82]. C0 was the most frequently included only in LSSs for pediatric patients. As MPA undergoes enterohepatic recirculation [2], it seems reasonable that, to describe MPA exposition accurately, the LSS should contain sampling over 6 h after MMF administration. Time points within 6–12 h after drug administration constituted less than 20% of all time points in each analyzed group. For adult transplant recipients, sampling within 3–5 h after MMF administration constituted a quarter of all time points.

Particular attention must be paid to the kind of calcineurin inhibitor co-administered. According to the literature, Tac does not influence MPA clearance [4]; however, in the case of CsA, MPA concentrations are lower if MMF and CsA are administered concomitantly [1]. CsA inhibits MPA enterohepatic recirculation [2] which causes the decrease in MPA exposition, and, therefore, in the case of CsA co-administration, the blood sampling does not require including time points around the second MPA maximum concentration ($C_{\text{max2}}$) [7]. Comparing LSSs between patients treated concomitantly with CsA or Tac, the time points beyond 6 h were more frequently included in LSS when Tac was co-administered. For adult renal transplant recipients, the most frequently used time points were C2 and C4, and C4 and C2 if treated with MMF and CsA or MMF and Tac, respectively. When the indication for MMF treatment was different for renal transplantation, the most frequently used time points were C2, C1, and C6 and C1, C2, and C4 if CsA and Tac were co-administered, respectively. For pediatric patients, only a subgroup treated with MMF and CsA was evaluated as Tac co-treatment referred to only two LSSs. For MMF and CsA administration, in MPA LSSs, the most frequently included time points were C2, C0, and C0.5.

Constantly improving renal function after transplantation affects MPA pharmacokinetics [1]; therefore, some differences in time points included in LSSs which were established for patients treated with MMF less than 1 month after renal transplantation and longer than 3 months after renal transplantation were expected. Surprisingly, the most frequently used time points were within 4 h after drug administration irrespective of the post-transplant period (C2 and C4 and C1 and C3, for less than 1 month and longer than 3 months post-transplant, respectively). In MPA LSSs developed for patients with other than renal transplantation indication for MMF treatment, different sets of time points were used more frequently. These time points were C2 and C6 versus C2 and C0 for patients treated with MMF less than 1 month and longer than 3 months, respectively. For pediatric patients, the comparison of the results in relation to duration of MMF treatment were impossible to be found, as in most studies MPA LSSs were developed for children in the early as well as in stable post-transplant period or treated with MMF less than 1 month and longer than 3 months.

Some LSSs were used in numerous studies or applied in clinical practice to estimate MPA AUC and improve MPA TDM. Van Hest et al. [43] checked the utility of MPA LSS established for patients without diabetes in patients with diabetes and showed LSS suitability in the latter group. The LSS developed by Weber et al. [65] was applied to calculate MPA $AUC_{0-12}$ and to obtain the optimal MMF dose in children after allogeneic hematopoietic cell transplantation [83]. The authors [83] proved that pharmacological monitoring of MPA $AUC_{0-12}$ allowed a reduction in the incidence of acute and chronic graft-versus-host disease in patients who were undergoing prophylactic treatment with Tac and MMF. The MPA $AUC_{0-12}$ was calculated using the LSS developed by Yamaguchi et al. [29] to evaluate the effects of UDP-glucuronosyltransferases polymorphisms on the pharmacokinetics of MMF in Chinese renal transplant recipients [84]. MPA $AUC_{0-12}$ estimated based on the LSS from the Musumba et al. study [30] was used to check the influence of omeprazole on MMF pharmacokinetics in kidney transplant recipients [85]. Poulin et al. [32] used LSS to perform population pharmacokinetic analysis of Tac and MMF concomitant administration in adult kidney recipients [86] as well as to determine associations between the absolute neutrophil count, MPA exposure, and the polymorphisms in metabolism or transporter genes responsible for MPA disposition [87]. The LSS of Miura et al. [37] was applied in renal transplant recipients to check the utility of plasma level monitoring of MPA and to correlate it with clinical outcomes [88]. The LSS developed for autoimmune disease [53] was used to investigate MPA exposure in patients with systemic sclerosis treated with MMF [89].

We found a few LSSs with satisfactory bias and precision; however, the usefulness of some of them is limited by the inclusion of time points beyond 4 h after MMF administration. Some of the LSSs were characterized by good bias and precision, but the $r^2$ was $<0.90$. Nevertheless, several MLR-based LSSs might help in establishing MPA $AUC_{\text{total}}$ for efficient TDM. With respect to the MMF indications, the following LSSs seems to be the most promising:

$$\text{MPA } AUC_{\text{pred}} = 2.8401 + 5.7435 \times C_0 + 0.2655 \times C_{0.5} + 1.1546 \times C_1 + 2.8971 \times C_4 \text{ for adult renal transplant recipients co-treated with CsA [41];}$$

$\Delta$ Adis
MLR–based LSSs for MPA AUC Estimation

MPA AUC\textsubscript{pred} = 1.783 + 1.248 \times C1 + 0.888 \times C2 + 8.027 \times C4 for adult patients after islet transplantation co-treated with Tac [20];
MPA AUC\textsubscript{pred} = 0.10 + 11.15 \times C0 + 0.42 \times C1 + 2.80 \times C2 for adult patients after heart transplantation co-treated with CsA [56];
fMPA AUC\textsubscript{pred} = 34.2 + 1.12 \times C1 + 1.29 \times C2 + 2.28 \times C4 + 3.95 \times C6 for adult liver transplant recipients [51];
MPA AUC\textsubscript{pred} = 8.217 + 3.163 \times C0 + 0.994 \times C1 + 1.334 \times C2 + 4.183 \times C4 for pediatric renal transplant recipients co-treated with Tac [16].

These LSSs require further evaluation in independent groups of patients before introducing them into clinical practice. The above LSS for fMPA might be difficult to implement as it included one time point 6 h after MMF administration. For MMF indications other than those listed above, we did not find any LSS which would fulfill the criteria of \( r^2 > 0.95 \) and precision and bias < 10%. The usefulness of other LSSs with satisfactory results of predictive performance is limited by the inclusion of time points more than 4 h after drug administration. MPA LSSs established in pediatric populations were less numerous and rarely included the bias and precision. Moreover, we did not find any fMPA LSS established in a pediatric population. Those found for adult renal transplant recipients were not characterized by sufficient bias and precision, although, for these patients, fMPA monitoring should be of particular interest as it reflects the pharmacologically active form of the drug.

The limitation of our study is the lack of EMBASE search. Another limitation is that several articles did not fully characterize patient groups or did not show the results of predictive performance.

5 Conclusions

We found five MLR-based MPA LSSs which might be considered as useful in clinical practice; however, they require further evaluation in independent groups of patients. The LSSs for pediatric patients were less numerous and not fully characterized. There were only a few fMPA LSSs, although fMPA is a pharmacologically active form of the drug. For adult patients, MPA LSSs most frequently included C2 and C4, while, for pediatric patients, C0 and C2 were the most often used. The fact that the time points of MPA concentrations most frequently included in LSSs were different for adult renal transplant recipients, adults after other than renal transplantation, and in children treated with MMF, emphasizes the need of individual therapeutic approaches for each group of MMF-treated patients. Whereas the methodology of developing MPA LSS is rather a simple method enabling TDM, establishing the most accurate MPA LSSs require numerous factors to be considered, such as the drugs co-administered with MMF (particularly calcineurin inhibitors), the time elapsed from the transplantation or the duration of treatment with MMF, and the indication for MMF treatment. LSS is a useful tool in MPA therapeutic monitoring; however, if sampling beyond few hours after MMF administration is required, optimizing drug dosage by the LSS approach appears to be less convenient.

Declarations

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