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Can we identify who gets benefit or harm from mycophenolate mofetil in systemic lupus erythematosus? A systematic review

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ABSTRACT

Objectives: We aimed to summarize the evidence examining factors that predict differential response to mycophenolate mofetil (MMF) in systemic lupus erythematosus (SLE).
Methods: Systematic searches of randomized clinical trials (RCT) to identify predictors of the effects of MMF (moderators), and cohort studies to explore prognostic factors associated with MMF outcomes (response, relapse, or adverse events) were performed. Two reviewers independently assessed the methodological quality of RCTs using the Cochrane Collaboration risk of bias tool and cohort studies using the QUality In Prognosis Studies tool. The quality of subgroup analysis, providing evidence for moderation, was evaluated. The Grading of Recommendations Assessment, Development, and Evaluation working group approach summarized the quality of evidence (QoE), considering the risk of bias, imprecision, inconsistency, indirectness, and publication bias.
Results: From 26 studies (13 from 7 RCTs and 13 cohort studies) we found low QoE evidence for Black/Hispanic race/ethnicity predicting better renal responses to MMF in lupus nephritis (LN) from one RCT. There was low QoE evidence from cohort studies that a higher baseline creatinine and membranous features on renal biopsy were associated with poorer responses in LN. There was very low QoE for other moderators or prognostic factors associated with MMF treatment outcomes. QoE from RCTs was affected by exploratory or insufficient evidence from subgroup analysis and in both study types high risk of bias, indirectness and imprecision also affected QoE.
Conclusions: In SLE, evidence for predictors of response to MMF is limited and none can be recommended for use in routine clinical practice. Specific studies of predictors measured at baseline and during treatment are needed with *a priori* hypotheses based on preliminary evidence to date and with sufficient power to determine which factors can be employed in clinical decision making.

Introduction

Personalized medicine is one of the emerging strategic plans of clinicians, academics, and policy makers to improve treatment outcomes in different conditions. The ability to identify subgroups of patients prior to treatment that are most likely to experience benefit (or least likely to experience harm) could allow treatments to be personalized, reduce health care costs, and accelerate the development of new therapeutics [1].

Personalized medicine is particularly relevant in SLE; in spite of current standard of care, 20–70% of patients with lupus nephritis (LN) fail to achieve remission [2] and 10–15% of patients still progress to end-stage renal disease within 10 years [3]. The current mainstay of management of LN and moderate–severe non-renal SLE is hydroxychloroquine, corticosteroids, and non-specific immunosuppressive drugs in the majority of patients [4]. As such, identification of those subgroups of patients with

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increased, or decreased, likelihood of success to different treatments would be of value to help physicians choose the "best treatment" for each patient, and to improve treatment outcomes [1].

Recent guidelines suggested that mycophenolate mofetil (MMF) can be considered a therapeutic option in patients with LN [5–7]. Randomized controlled trials (RCTs) show that MMF efficacy is similar to intravenous cyclophosphamide (IVC) in the induction phase, and superior to azathioprine in the maintenance [8–10]. There is also evidence suggesting that black and Hispanic patients are more likely to achieve a renal response with MMF than with IVC induction [8,11]. However, guidelines have not included MMF as a therapeutic option for the management of non-renal lupus activity including neuropsychiatric manifestations [12].

A wide range of factors may potentially predict the effects of treatment on outcomes such as response, remission, or relapse in SLE patients, including genetic [13], sociodemographic [11], clinical [14,15], histopathological [16], and drug-related factors [15,17]. However, predictors (moderators) of the effects of MMF remain poorly understood. In recent years, the importance of moderators in testing the effectiveness of clinical interventions in RCTs has become increasingly apparent [18]. Effect moderators represent variables, for example, patient characteristics, measured at baseline that interact with treatment to change outcome for specific subgroups in RCTs. These specify for whom and under what conditions treatment is most effective, and can improve power in subsequent trials by better selection of target groups for stratification. Cohort studies may also provide exploratory evidence of predictors of treatment outcomes [19], in two different ways: (1) all participants are treated with MMF, but in this case it will not be quite clear if the factor predicts response to MMF, or would predict response regardless of treatment (i.e., it might "just" be a prognostic factor) and (2) response to MMF is compared to another type of treatment (as in a non-randomised trial). Such studies may provide evidence for moderation (similar subgroup analyses may be conducted as in trials), but of course, there is a risk of confounding by indication, as there is no randomization.

To date some RCTs and cohort studies in SLE have evaluated potential predictors of treatment response to MMF. The identification of potential moderators can, however, suffer seriously from limitations such as the lack of an *a priori*, evidence-/theoretical-based hypothesis, and the use of unreliable or invalid measures of moderators [20]. In this regard, an assessment of the risk of bias and validity of studies is required to provide an adequate understanding of the strength of the evidence for predictors of response to MMF. To the best of our knowledge, no systematic review has aimed to address this question.

The objectives of this systematic review, therefore, were as follows: (1) to identify predictors of differential response to MMF treatment for SLE (effect moderators) in RCTs and (2) to identify prognostic factors that are associated with clinical outcomes following MMF treatment for SLE (outcome predictors) in observational cohorts.

Methods

Literature search

We searched MEDLINE via Ovid (1946 to October 2015), EMBASE via Ovid (1974 to October 2015), The Cochrane Central Register of Randomized Controlled Trials (CENTRAL-The Cochrane Library) via Ovid (to October 2015) and Web of Science (to October 2015). Additional hand-searches were carried out on the references of selected studies. The search strategies used for Ovid MEDLINE® and applied to other databases in the literature are available in Table 1 (Supplementary File A). Only articles published in English, Spanish, and Italian were considered for inclusion. We identified studies where the drug used was mycophenolic acid or mycophenolate mofetil.

Selection criteria

The articles were selected by two independent reviewers: (C.M.P.) and (C.P.), who judged irrelevance of articles based on their title and abstract. The inclusion criteria were as follows: (1) RCTs and quasi-randomized studies in all different phases that compared MMF versus control in SLE patients. RCTs were used to identify those articles that included analysis of effect moderation, for example, subgroup analysis. (2) Prospective or retrospective cohort studies, which included a standardised assessment prior to treatment and reported associations with MMF outcomes following treatment. Observational studies were used to identify baseline factors or those measured during the MMF treatments that were associated with outcome (response, relapse/flare, and adverse events). Treatment outcomes were defined as a significantly increased response/remission or relapse/flares rates (according the criteria defined by each study author) or a greater decrease of disease activity measured using any validated index (Supplementary File A, Table 2). We also included adverse events to retain a balance between the desirable and undesirable effects of an intervention [21].

We excluded review articles, opinion papers, letters to the editor, case reports, case series, or conference abstracts. Studies reporting predictors of outcomes using MMF in as part of a combination therapy, except for hydroxychloroquine (HCQ) or corticosteroids were also excluded.

Study screening

References and abstracts identified by the search were imported into Reference Manager (RefMan) Version 12 and duplicates were removed. Titles and abstracts were screened to remove editorials, commentaries, and letters. The full text of each remaining article was then tested against the inclusion and exclusion criteria by two reviewers (C.M.P. and C.P.). The literature review team also made every effort to identify multiple publications from a single trial. Reason(s) for ineligibility were documented for all studies excluded in the second phase of screening, using prepiloted form. Disagreements were resolved through discussion or by a third reviewer (I.N.B. or B.P.) if necessary.

Data extraction

Study details for RCTs: author identification, year of publication, setting, number of patients included, intervention, and control treatment including dose and administration details, study duration, possible moderators or mediators, and relevant outcomes. Study details for cohort studies: study design, setting, study duration, number of patients included, age and gender of participants, risk factors, relevant outcomes, and adjustment for confounders. Data extraction was done independently by two reviewers. When available, subgroup effects or associations of prognosis factors with MMF treatment outcome were extracted from each published report. When there was insufficient information regarding estimates of associations or treatment effects in original reports, where possible these were estimated using methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [22].

Methodological quality assessment

Risk of bias in RCTs

We assessed study quality according to the PRISMA guidelines [23]. For RCTs, the overall study quality was assessed using the Cochrane Collaboration's risk of bias tool using the following domains: sequence generation, allocation concealment, blinding performance, incomplete outcome data, selective outcome reporting, and other sources of bias [24]. The purpose of the quality appraisal was to describe the QoE, relevant studies not to include or excluded based on quality. Each domain was rated as adequate, inadequate or unclear risk of bias. Where a study had multiple publications, risk of bias assessment was conducted on the article containing the main study findings. Two reviewers (C.M.P. and C.P.) independently rated the methodological quality of the selected studies. The two reviewers discussed disagreement about whether a criterion was met, and resolved by consensus.

Quality of subgroup analyses

Due to the lack of an established standard for assessing the quality of studies with subgroup (moderation) analyses we used the following criteria, based on guidance from the Cochrane handbook and a consensus study of international experts [20].

(1) Was the subgroup analysis specified *a priori*?
(2) Was the selection of subgroup factors for analysis theory/evidence driven?
(3) Were subgroup factors measured prior to randomization?
(4) Was measurement of subgroup factors measured by adequate (reliable and valid) measurements, appropriate for the target population?
(5) Does the analysis contain an explicit test of the interaction between moderator and treatment?

We classified studies complying with all five criteria as providing confirmatory evidence, the presence of the final three was considered to provide exploratory evidence of moderation. Two or less criteria were classified as providing insufficient evidence [20].

We applied the criteria by Pincus et al. for inclusion of any trial in a meta-analysis of moderators, that is, baseline factors should be measured prior to randomization. Adequate quality of measurement of baseline factors [20].

Risk of bias in cohort studies

Cohort studies were assessed using the QUality In Prognosis Studies (QUIPS) tool [25]. This includes six major headings each addressing a possible bias that could occur in a prognostic study (study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and analysis). The tool was applied to each article in the review (using guidelines published by the developers of the tool) and each heading was rated as "Low," "Moderate," or "High" risk of bias.

Studies were judged to be of low overall risk of bias if all or most of the domains were judged as low risk, and studies in which all or most of the domains were judged as high risk were considered to be of high overall risk of bias. Studies with a moderate risk of bias were those with all or most of the domains being judged as moderate risk of bias [25]. Differences between reviewers were discussed and a decision made by agreement.

Data synthesis

Due to the expected heterogeneity of selected studies, we performed a qualitative best evidence synthesis of evidence for potential predictors from RCTs and cohort studies, taking into account the strength of the association and the methodological quality of the studies. We identified six PICO (Population, Intervention, Comparator, and Outcome) questions [21] for RCTs and six PICO questions for cohort studies to examine population features likely to influence the effect of MMF and to assess the QoE for each PICO question using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) [26,27]. The PICO comparison (C) category was not applicable and dropped for cohort studies (Supplementary File A, Table 3). We used GRADE approach to structure the evidence synthesis and to assess the strength of evidence for each potential predictor/prognostic factor.

Two reviewers (C.M.P. and C.P.) judged how the GRADE factors—phase of investigation, study limitations (Cochrane Collaboration's risk of bias tool; subgroup analyses; QUIPS), inconsistency, indirectness, imprecision, publication bias, and moderate or large effect size—impacted the overall QoE (Supplementary File A, Tables 4 and 5). The level of evidence was rated as high, moderate, low, or very low according to the GRADE approach [28]. We used Review Manager (RevMan) and GRADE profiler (GRADEpro) software to summarize the data on interventions and to produce the GRADE profile, respectively.

Potential predictors were grouped into the following six categories: sociodemographic (e.g., age and gender) biological (e.g., genetic), laboratory parameters measured at baseline or during the treatment (e.g., renal function, autoantibodies, and complement), histopathological (e.g., LN classification) or drug-related characteristics (e.g., concomitant HCQ use and pharmacokinetics).

Results

Summary of studies selected

Our search yielded 319 articles (Fig. 1) of which 26 (seven RCTs with six subgroups analyses and 13 cohort studies) were included in the analysis. A full list of excluded studies and the reason for exclusion are available (Supplementary File A, Table 6).

Study characteristics

We included analyses from seven RCTs (Table 1) [8,9,29–33] including secondary articles with post hoc subgroup analysis and 13 cohort studies (Table 2) [34–46]. Three RCTs presented more than one subgroup analysis, including seven separate subgroup analyses from the Aspreva Lupus Management (ALMS) Trial [9,11,14,47–50]. Each subgroup was analyzed separately presenting analysis of each moderator separately [8,9].

Five studies included participants aged 12–18 years [8,9,31,38,43]. The follow-up duration varied across studies; ranging between 6 months (24 weeks) and 36 months for RCTs and 6–60 months for cohort studies. All RCTs and subgroup analyses included patients with active LN. Only three cohort studies took into account extra-renal lupus as opposed active LN alone [40–42,45]. No RCTs or cohort studies were identified that described the effect of pharmacogenetics polymorphisms on outcomes in SLE patients with MMF (PICO 4).

Methodological quality of studies and evidence

Risk of bias of RCTs

The method of randomization was explicit (low risk) in four RCTs. Allocation concealment was adequate (low risk) in five trials. Two trials were described as double blinded (participant or outcome assessment) and rated as low risk [9,32]; however, in one study only researchers conducting assessments were masked (Fig. 2) [8]. Seven trials included an intention to treat (ITT) analysis and only one did not carry out an ITT analysis [32]. All trials had no

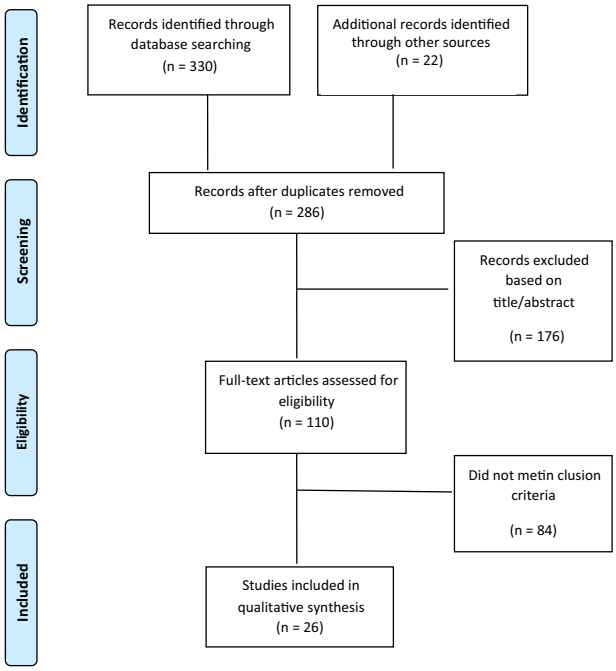

Fig. 1. Study flow diagram detailing the literature search.

evidence of selective outcome reporting and dropout rate analyses were adequately presented (low risk). One study declared independent or academic funding bodies [30]. Four declared sponsorship by a pharmaceutical industry company, or included an author who declared pharmaceutical company affiliation and three did not disclose study funding sources (Fig. 3).

Quality of subgroup (moderation) analysis

None of the subgroup studies provided confirmatory evidence; three studies provided exploratory evidence for race and severe LN when MMF was compared to IVC for induction; two for race and severe LN when MMF was compared to IVC for induction therapy in LN [11,49] and one more for race when MMF was compared to azathioprine for maintenance therapy [9]; and four studies provided insufficient data to judge quality of subgroup analyses for age, change in laboratory parameters at 8 weeks and membranous LN (MLN) when MMF was compared to IVC for induction therapy in LN [14,47,50] and when MMF was compared to tacrolimus [30] (Table 3).

Risk of bias of cohort studies

The overall methodological quality of five studies was scored as "moderate," eight studies scored "low," and no study was judged as "high" quality (Supplementary File A, Table 7). In almost all studies, measurement of prognostic factors and outcomes were performed in a similar, valid, and reliable way for all participants, that is, "low" to "moderate" risk of bias. Due to lack of reporting on key characteristics of the source population ('study participation') and of participants loss to follow-up ("study attrition"), bias could not be ruled out. We were, therefore, compelled to classify studies as "low" ($n = 1$), "moderate" ($n = 7$) and "high" risk ($n = 5$) of selection bias. The statistical analysis, model-building process or completeness of reporting were judged to be inadequate in all studies, resulting in "moderate" to "high" risks of bias. The majority of the studies reviewed only presented results from univariable analysis on the prognostic factor(s) studied [34,35,37,38,40–42,44]. The GRADE qualitative synthesis of evidence for factors analyzed in cohort studies is shown in Table 4.

Summary of QoE

All RCTs that initially were considered as high QoE were downgraded to low or very low because most included post hoc subgroup analyses (exploratory or insufficient evidence) without interaction tests and serious to very serious risk for imprecision due to low sample sizes (Supplementary File B and Table 4).

The QoE of the cohort studies was initially rated as moderate. These were downgraded due to very serious limitations concerning for example, description of sampling frame and recruitment, sample size, multiple uncontrolled confounding factors, and inadequate description of dropouts. Inconsistency could not be assessed, except for one prognostic factor, because only a single study within the existing body of literature investigated specific factors (Table 4). Almost all cohort studies were also downgraded for lack of precision due to inadequate sample size and incompleteness in reporting of results. The QoE was downgraded for publication bias if a very small number of studies assessed the prognostic factor of interest and only reported positive associations. The grading could not be uprated for effect size in most of included studies due to an absence of moderate to large effect sizes (in terms of subgroup effects or associations with outcome), or lack of investigating a dose effect.

Synthesis of evidence

Sociodemographic factors

Age and gender (PICOs 1 and 7). Two RCTs [8,9] evaluated age using a post hoc analysis without any interaction test (Table 3) [47] and did not show age to be a moderator of MMF responses or adverse (Supplementary File B, PICO 1). Only one low QoE cohort study
($n = 70$) found a significant association between younger age and the time to renal flare at 24 months (Tables 4 and 5) [35].

No RCTs evaluated/reported the influence of gender on MMF treatment response in SLE. Two cohort studies (low QoE, $n = 146$) [35,43] showed that gender was not associated with complete renal response at 6 months nor the rate of renal relapse at a median follow-up of 24 months following treatment with MMF (Table 5).

Race/ethnicity (PICO 2 and 7). Two RCTs, comparing MMF with synthetic therapies [8,9], showed insufficient or only exploratory evidence of subgroup effects based on race/ethnicity. One subgroup analysis (Table 3) found that MMF and IVC response rates for induction (24 weeks) in LN were similar for Asians and Whites, but differed in the combined 'Other' and Black group [11] (Supplementary File B, PICO 2). Exploratory evidence from subgroup analysis and serious imprecision resulted in the QoE to be rated as "low." Similar findings using MMF therapy were not described in other RCTs having longer period of follow up and with different outcomes (treatment failure and adverse events) [9].

No cohort studies reported any association of race/ethnicity with MMF outcomes in SLE.

Laboratory parameters

Baseline renal function measures (PICO 3 and 9). In one RCT, treatment with MMF vs. IVC in patients with LN did not show a difference in renal response, development of end-stage renal disease, or the incidence of serious adverse events including infections at 24 weeks [49] using poor renal function (eGFR < 30 mL/min/1.73 m^2) as a moderator. This study had a high risk of bias as it used post hoc subgroup analyses with very serious imprecision.

Table 1
Characteristic of RCTs

Study ID	PICO	Setting	Population	No. of patients	Intervention	Follow-up	Predictor	Outcomes
Dall'Era et al. 2011 (ALMS) [8,14]	6	International	LN III, IV, V	370	MMF 3 g/day vs. IVC 0.5–1 g/m^2/m	24 w	Reduction in proteinuria Reduction in anti-dsDNA Normalization of C3 and C4	Renal response
Dooley et al. (ALMS) [9]	2	International	LN III, IV, V	227	MMF 2 g per day vs. azathioprine 2 mg/kg/day	36 m	Race	Treatment failure Mortality
Ginzler et al. 2010 (ALMS) [8,48]	5	International	LN III, IV, V	370	3 g/day vs. IVC 0.5–1 g/m^2/m	24 w	Active LN	Extra-renal manifestation response
Isenberg et al. 2010 (ALMS) [8,11]	2	International	LN III, IV, V	370	MMF 3 g/day vs. IVC 0.5–1 g/m^2/m	24 w	Race	Renal Response Infectious adverse events Serious adverse events Mortality
Mok et al. [30]	4	China	LN III, IV, V	28	MMF 3 g/day vs. Tacrolimus 0.06–0.1 mg/kg/day	6 m	Pure MLN	Complete renal response
Radhakrishnan et al. 2010 (US and ALMS) [8,29,50]	4	International	LN V	87	MMF 3 g/day/day vs. IVC 0.5–1 g/m^2/m	24 w	Nephrotic syndrome	Change in urine protein and SCr Renal response Severe infections
Sundel et al. 2012 (ALMS) [8,9,47]	1	International	LN III, IV, V	24	MMF 3 g/day vs. IVC 0.5–1 g/m^2/m MMF 2 g/d vs. azathioprine 2 mg/kg/d	24 w 36 m	Age	Renal response Treatment failure Infectious adverse events Serious adverse events End-stage disease and Mortality
Tang et al. [31]$^{\$}$	3	China	Crescent LN	44	MMF 0.75–1 g twice daily vs. IVC 0.5–0.75 g/m^2/m	12 m	Crescent LN	Cumulative remission % change active and chronic lesions
Walsh et al. 2013 (ALMS) [8,49]	3	International	LN III, IV, V	32	MMF 3 g/day vs. IVC 0.5–1 g/m^2/m	24 w	Poor kidney function	Renal responseEnd-stage renal disease Infection
Wang et al. [33]$^{\$}$	6	China	NINV LN	20	MMF 0.75 or 1 g twice daily vs. IVC 0.5–0.75 g/m^2/m	6 m	Non-inflammatory necrotizing vasculopathy LN	Complete response Partial response Adverse events
Yap et al. [32]*	4	China	LN V	16	MMF 0.75–1 g twice daily (starting dose) vs. Tacrolimus 0.1–0.15 mg/kg per day	12 m	Pure MLN	Complete response Infections

#, $, and * multiple papers on partially the same cohort.
Studies are listed in alphabetical order; ALMS, Aspreva Lupus Multicenter Study; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; m, monthly; IVC, intravenous cyclophosphamide; LN, lupus nephritis; MMF, mycophenolate mofetil; NINV LN, Non-inflammatory necrotizing vasculopathy lupus nephritis; PICO, Population, Intervention, Comparator, Outcome (number of PICO question); RCT, randomized clinical trial; w, weeks.

Two publications with very low QoE (high risk of bias and imprecision) from one retrospective cohort [43,44] indicated that low eGFR was an independent prognostic factor for complete renal response but not rate of renal relapse, end-stage disease or adverse events (gastrointestinal and infections). Similarly, baseline serum creatinine was an independent negative prognostic factor for remission at 24 weeks in patients LN on MMF according to one (low QoE) prospective cohort [39], but was not associated with an increased rate of any adverse event [42]. Moreover, baseline proteinuria was not associated with the rate of renal relapse at 12 months [44].

Laboratory parameters over time (PICO 6 and 12). In one RCT, normalization of C3/C4 (or both) and reduction in proteinuria by $>25\%$ were associated with renal response in LN patients with MMF therapy (Supplementary File B, PICO 6). However, these factors were also found to be predictive in patients who received IVC [14], indicating that they were not predictors of differential treatment response (moderators), but were prognostic factors regardless of type of treatment received. Reduction in anti–double-stranded DNA (anti-dsDNA) by week 8 did not predict renal response in the same study (to either drug).

A very low QoE prospective cohort showed that persistently elevated anti-dsDNA titers after complete renal response (CRR) was associated with reduced time to renal flare; however, persistent hypocomplementaemia was not [35] (Table 5). Improvement in serum albumin levels was found to be associated with the time to CRR in the same cohort [35] and proteinuria at 6 months had a significantly negative impact on IgG level but supported by very low QoE [46] (Table 5).

Histopathological factors (PICO 4 and 10)

Three post hoc subgroup analyses from 2 RCTs [8,29,30] (very low QoE), two reported in one publication [50] and one specific RCT for MLN [32] did not find significant differences in response rates, percent change urine protein, serum creatinine or severe infections between MMF therapy and comparator treatments (tacrolimus and IVC) in patients with MLN and nephrotic-range proteinuria (Supplementary file B, PICO 4).

Two RCTs (very low QoE) did not show difference in renal response or side effects between MMF and IVC at 6 months in patients having either crescentic LN or non-inflammatory necrotizing vasculopathy NL [31,33]. In a group of nine patients with crescentic LN who had renal re-biopsy, it was found that the active

Table 2
Characteristics of studies on prognostic factors

Study ID	Setting	PICO	Design	No. of patients	Dose MMF	Follow-up	Predictor	Outcomes	Adjustment for confounders
Alexander et al. [34]	India	11	Prospective cohort	34	1.5 g/day at entry[a]	12 m	MPA AUC	Renal response Adverse events	Not indicated
Cortes-Hernandez et al. [35]	Spain	7 9 10 12	Prospective cohort	70	1 g two times a day	24 m[b]	Age, improvement serum albumin levels Persistent anti-dsDNA Persistent Hypocomplementaemia Histopathological classification MPA trough plasma concentrations	Renal response Renal relapse Treatment failure	Not indicated
Kasitanon et al. [36]¥	USA	11	Retrospective cohort	29	2120.7 mg/day[b]	12 m	Concomitant HCQ use	Complete renal remission in MLN	Presence of anti-dsDNA antibody
Kasitanon et al. [37]¥	USA	10	Retrospective cohort	29	2000 mg/day (starting dose)	12 m	Mixed MLN	Complete renal remission	Not indicated
Laskari et al. [38]	Greece	11	Retrospective cohort	44	2 (1.2–3) g/day[a]	30 m[a]	Duration of MMF	Relapse Side effects	No
Lu et al. [39]	China	9 10	Prospective cohort	213	MMF initiated at 1.0 g/day in patients with less than 50 kg; 1.5 g/day: 50–70 kg and 2.0 g/day: over 70 kg	24 w	Baseline serum creatinine Pathological classification	Renal remission	Not indicated
Mino et al. [40]	Japan	11	Prospective cohort	34	Started on 500 mg/day MMF, and its dose was increased by 500 mg/day a week up to 2500 mg/day	13 m[a]	Plasma concentration of MPA or MPAG	Changes in disease markers	Not indicated
Nannini et al. [41]	USA	11	Retrospective cohort	29	1328 mg/day[b]	14.8 m[b]	Concomitant HCQ use	Disease flares	Not indicated
Riskalla et al. [42]	USA	9 11	Retrospective cohort	54	125–3000 mg/day	12.4 m[b]	Baseline serum creatinine MMF dose	Side effects	Not indicated
Rivera et al. [43]£	Spain	7 9 10	Retrospective cohort	90	2 g/day[a]	36 m[a]	Gender, Poor renal function Histopathological classification	Complete response Infectious	Age, gender, eGFR, LN class and proteinuria
Rivera et al. [44]£	Spain	9	Retrospective cohort	56	1 g/day[a]	24 m (3–108)[a]	Gender, Proteinuria Poor renal function Histopathological classification	End-stage disease Mortality	Gender, baseline eGFR, proteinuria and LN class
Tselios et al. [45]	Canada	9	Retrospective cohort	177	No renal group: 1350 mg/day[b] renal group: 1687.5 mg/day[b]	12 m	Renal involvement	Extra-renal manifestation improvement	Not indicated
Yap et al. [46]*	China	11 and 12	Retrospective cohort	46	1.8 ± 0.3 g/day at 6 m and 1.2 ± 0.4 g/day at 12 m[b]	12 m	Proteinuria Serum creatinine, Anti-dsDNA and C3, white cell count lymphocyte count at 6 m MMF dose	Circulating IgG level	Proteinuria, serum creatinine, anti-dsDNA, C3, white cell count and lymphocyte count at 6 m; MMF dose/body weight

¥, £, and * multiple papers on partially the same cohort.
Studies are listed in alphabetical order; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; m, months; LN, lupus nephritis; MLN, membranous lupus nephritis; MMF, mycophenolate mofetil; MPA AUC, mycophenolic acid area under the curve; MPAG, mycophenolic acid glucuronide; PICO, Population, Intervention, Comparator, Outcome (number of PICO question); w, weeks.

[a] Median.
[b] Mean.

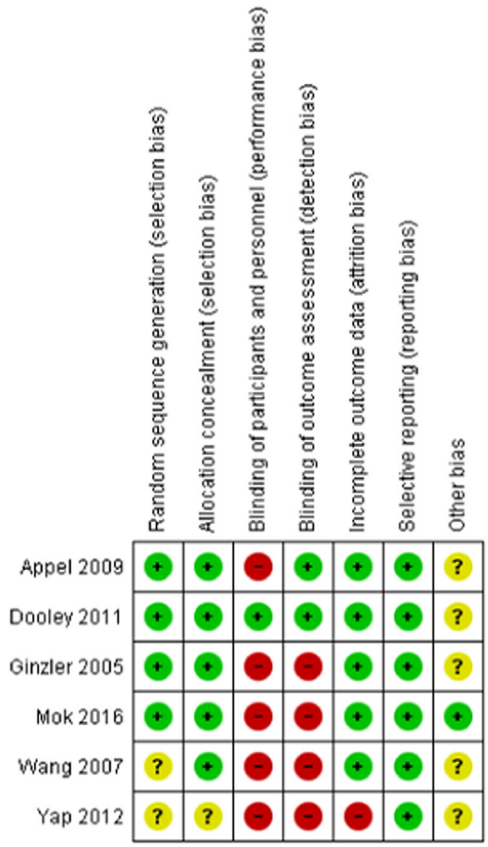

Fig. 2. Risk of bias summary.

lesions were significantly decreased, while chronic lesions were increased in both MMF and IVC groups [31].

The prognostic value of histopathological LN class in renal response was also investigated in four cohort studies (very low to low QoE). One cohort study ($n = 213$) indicated that concomitant membranous features on biopsy was an independent prognostic factor for non-remission at 24 weeks on MMF (Table 5) [39]. Three studies ($n = 180$, very low QoE) (6–24 months follow up) did not demonstrate significant associations between histological LN class and renal response [35,37,43]. Similarly, LN class was not significantly associated with the rate of relapse in one small cohort ($n = 56$) [44].

Drug-related factors (PICO 11)

No RCTs evaluated this variable. Concomitant use of HCQ with MMF was significantly associated with renal response when adjusted for the presence of anti-dsDNA in MLN at 12 months (very low QoE) ($n = 29$) [36] but this association was not confirmed for overall disease flare in one study ($n = 29$) with a

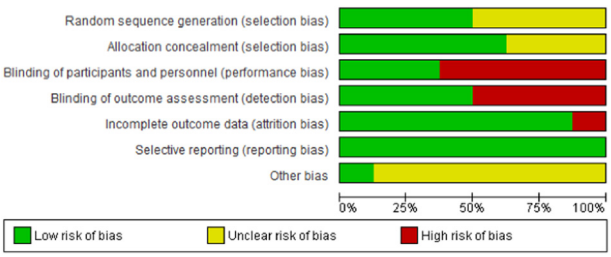

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all RTC included studies.

mean time period of follow-up after starting MMF of 14.8 months [41] (Tables 4 and 5).

The impact of length of use and dose of MMF treatment on outcome was examined in three cohorts (very low QoE) (Tables 4 and 5). Duration of MMF treatment ≤ 18 months was associated with relapse at long-term (median 30 months) but not associated with side effects in one study [38]. MMF dose was not associated with side effects including reduced IgG levels at 6 and 12 months in two studies ($n = 98$) [42,46].

One very low QoE study found that mycophenolic acid area under the curve (MPA AUC ≥ 30 mg h L^{-1} was associated with renal response but not associated with side effects (infections) at 12 months [34]. MPA and MPA glucuronide (MPAG) levels in the interquartile ranges of 0.94–2.96 and 18.6–53.7 μg/mL, respectively improved clinical laboratory markers (serum creatinine, complement fractions, and immunoglobulins) in one study (very low QoE) [40].

Other factors (PICO 5)

Only one RCT ($n = 370$, moderate to very low QoE) did not find any influence of organ/system involvement on response to MMF vs. IVC using either the BILAG (British Isles Lupus Assessment Group) or SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index) [48] (Supplementary File B, PICO 5).

One retrospective cohort study ($n = 177$ of very low QoE) also noted that MMF had similar outcomes in refractory extra-renal manifestations at 6 and 12 months in patients with or without renal involvement [45].

Discussion

Our systematic review summarizes the evidence on possible predictors (moderators) of the effect of MMF treatment for SLE in RCTs, and factors predicting for outcomes of MMF therapy in SLE patients in cohorts studies. For the first objective, we identified only potential moderation by sociodemographic (race/ethnicity) of the effect of MMF therapy on renal response in patients with active LN [11]. Black/Hispanic population with LN were more likely to have a renal response at 24 weeks to MMF vs. IVC in induction therapy. This result was, however, found in only one post hoc subgroup analysis from an RCT with serious imprecision, resulting in low overall quality of evidence. Race/ethnicity was studied as a potential moderator in one additional RCT comparing MMF therapy vs. azathioprine therapy [9], but a moderating effect was not found.

We found no evidence for other potential effect moderators for response or adverse events; thus current data do not allow us to recommend targeting interventions with MMF at these particular groups.

Limitations in these RCTS included the lack of "*a priori*" hypotheses regarding potential moderators, insufficient statistical power, and absence of interaction tests. Our review also highlights the importance of clarifying drug-specific effects from generic predictors of treatment response. Therefore, while it was demonstrated that an early normalization of complement and reduction in proteinuria independently predict renal response to therapy at 6 months [14], those findings were not exclusive for MMF but also were seen in the control group (IVC), indicating they are likely to be generic prognostic factors for treatment outcome in SLE and do not indicate a specific action of one particular drug in SLE.

In observational cohorts, the qualitative synthesis according to the GRADE approach resulted in "low" quality evidence for baseline serum creatinine and histological LN classification for renal

Table 3
Methodological quality of subgroup analysis

Quality appraisal for subgroup studies	Was the analysis *a priori*?	Was selection of factors for analysis theory/evidence driven	Were subgroups measured prior to randomization?	Adequate quality of measurement of baseline factors?	Contains an explicit test of the interaction between subgroup and treatment (e.g., regression)?	Strength of evidence
Dooley et al. (ALMS) [9][a]	Yes	Yes	N/A	Unclear	Yes	Exploratory
DallEra et al. (ALMS) [14][a]	No	No	Yes	Yes	No	Insufficient
Isenberg et al. (ALMS) [11][a]	No	No	N/A	Unclear	Yes	Exploratory
Mok et al. [30]	No	No	Yes	Yes	No	Insufficient
Radhakrishnan et al. (US and ALMS [50][a]	No	No	Yes	Yes	No	Insufficient
Sundel et al. (ALMS) [47][a]	No	No	Yes	Yes	No	Insufficient
Walsh et al. (ALMS) [49][a]	No	No	Yes	Yes	Yes	Exploratory

Confirmatory evidence: The study fulfils all of the quality assessment criteria for moderator studies (*a priori* analysis, factors evidence driven, moderators measured prior to randomization, adequate measurement of baseline factors and explicit test of the interaction between moderator and treatment).
Exploratory evidence: Fulfilling the last three quality assessment criteria.
Insufficient evidence: The study did not carry out an explicit test of interaction or measurement of the subgroups was reported to take place post randomization. ALMS, Aspreva Lupus Multicenter Study.

[a] Multiple papers partially the same cohort.

response as predictors of MMF treatment outcome, due the limited sample sizes and inconsistency of study findings. Very low QoE was noted for a range of other prognostic factors in cohort studies. Such factors, while not being sufficiently robust for routine clinical decisions making, do nevertheless raise potential hypotheses for evaluation when planning future studies of predictors of MMF responses.

SLE is recognized to be a heterogeneous condition and this heterogeneity complicates the development of prognostic models. In addition there has been limited success in drug development such that only a small number of positive RCTs of synthetic or biologic therapies have been reported. It is therefore not surprising that there is a limited number of studies examining prognostic factors for individual drugs nor that most work in this field to date has been post hoc, secondary analyses. For the same reasons work to better define subsets or "strata" of patients most likely to respond to a particular agent is urgently needed. For many drugs such as MMF, response rates may only be 40–60% meaning that a significant proportion are destined not to respond or to develop AEs. Such periods awaiting a response may contribute to new damage, excess steroid exposure and may also affect patient confidence in any future therapy offered. As such SLE is a condition where stratified or precision medicine has potential to deliver better long-term outcomes through more efficient selection of patients for new treatments as well as lower overall steroid exposure.

Our review mainly focused on clinical factors and factors routinely available to physicians caring for SLE patients. More detailed knowledge about the genetic and molecular mechanisms is also required to allow us to develop more accurate prediction models. In this context, the identification of polymorphic enzymes involved in MMF metabolism may be of relevance. Uridine diphosphate glucuronosyltransferase (UGT-1A9), inosine monophosphate dehydrogenase (IMPDH-1), cytochrome P450 (CYP-2C8), and ATP-binding cassette multidrug resistance transporter (ABC-C2) have implications for efficacy and toxicity in kidney transplant patients on MMF therapy [51–55]. We identified only one cross-sectional study with 19 LN, which did not meet the selection criteria, showing that clinical and demographic parameters were 2–4 times more important in MPA disposition than genotypes (UGT1A7, UGT2B7, and ABCB1/MDR1 single nucleotide polymorphisms) and explained 30–40% of the pharmacokinetic parameters [56]. Clearly more detailed phenotyping of patients as well as a better understanding at a molecular level of the pharmacodynamics of MMF in SLE may identify novel approaches to predicting MMF treatment responses.

Strength and limitations

We reported our findings as recommended by the PRISMA statement [23] and employed not only the Cochrane Collaboration risk of bias tool but also a tool to assess the quality of subgroup analyses in RCTs and the QUIPS tool for the appraisal of quality of prognostic factor studies. We judged the QoE based on the recommendations from the GRADE working group. We believe that the GRADE framework applied to prognostic factor research was valuable for assessing and transparently reporting the QoE of the possible prognostic factors. To the best of our knowledge, this is the first time GRADE has been used in the evaluation of prognostic studies in SLE.

Limitations regarding the interpretation of the results from this study should be taken into consideration. The high variability in prognostic factors and outcomes evaluated as well as in statistical measures and data reported made it impossible to conduct a meta-analysis of study results. It is possible that we have missed studies that are not indexed for these databases, but by checking references of included studies, we presume that no relevant articles were missed. A total of 24 of the 28 included studies in our review referred to patients with LN. The high number of studies concerning patients with LN may affect the external validity of the results to patients with extra-renal manifestation. Future studies assessing prognostic factors for extra-renal manifestations in SLE patients on MMF therapy are needed. Similarly, most studies included in this systematic review were in adult populations. Another common limitation in systematic reviews is the risk of selective reporting of primary study results. Our review included cohort studies on prognostic factors. Such studies harbor a high risk that non-significant findings are not reported or only included in the first (unadjusted) part of the analysis. Any non-reporting of non-significant results increase the risk that the findings in the synthesis were overestimated. No attempt was made to contact study authors to obtain individual patient-level data and carry out a meta-analysis based on such individual patient data.

Implications for clinical practice and for future research

From clinical practice point of view, no high-quality evidence was provided for any of the potential moderators or prognostic factors; therefore, no definite clinical conclusion can be made about how to identify SLE patients most likely to respond to MMF therapy. This study is, however, of value in that it identifies factors that should be included in any future study of predictors of response to MMF and also it underscores the need to separate

Table 4
Adapted GRADE table for narrative systematic reviews of prognostic studies

			GRADE factors															
			Univariate analysis			Multivariate Analysis												
Possible predictors	*N* studies	*N* cohorts	+	0	−	+	0	−	Phase	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate-large effect size	Exposure-response gradient	Overall quality	Outcomes
Gender [43]	1	1	0	1	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Renal response
Gender [44]	1	1	0	1	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Renal relapse or flare
Younger age at study [35]	1	1	1	0	0				1	×	✓	✓	×	×	✓	×	+	Renal Relapse or flare
Baseline eGFR [43]	1	1	0	0	1	0	0	1	1	×	✓	✓	×	×	×	×	+	Renal response
Baseline eGFR [44]	1	1	0	1	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Relapse or flare
Baseline eGFR [43]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	End-stage disease
Baseline eGFR [43]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Side effects
Baseline serum creatinine [39]	1	1	0	0	1	0	0	1	1	×	✓	✓	✓	×	×	×	++	Renal response
Baseline serum creatinine [42]	1	1	0	0	1	0	0	1	1	×	✓	✓	×	×	×	×	+	Side effects
Baseline proteinuria [44]	1	1	0	1	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Renal relapse or flare
Improvement serum albumin levels [35]	1	1	1	0	0				1	×	✓	✓	×	×	×	×	+	Renal response
Persistent anti-dsDNA titers [35]	1	1	1	0	0				1	×	✓	✓	×	×	×	×	+	Renal relapse or flare
Persistent hypocomplementaemia [35]	1	1	0	1	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Renal relapse or flare
Biologic factors at 6 m [46]	1	1	1	0	0	1	0	0	1	×	✓	✓	×	×	×	×	+	Side effects
Active LN [45]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Extra-renal improvement
LN class [35,37,39,43]	4	4	0	3	1	0	1	1	1	×	×	✓	×	✓	✓	×	++	Renal response
LN class [44]	1	1	0	1	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Renal relapse or flare
Concomitant HCQ use [36]	1	1	1	0	0	1	0	0	1	×	✓	✓	×	×	×	×	+	Renal response
Concomitant HCQ use [41]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Overall relapse or flare
Duration of MMF [38]	1	1	1	0	0				1	×	✓	✓	×	×	×	×	+	Renal relapse or flare
MPA AUC [34]	1	1	1	0	0				1	×	✓	✓	×	×	×	×	+	Renal response
MPA AUC [34]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Side effects
Plasma concentration of MPA [40]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Changes in disease markers
Plasma concentration of MPAG [40]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Changes in disease markers
MPA trough plasma concentration [34]	1	1	0	1	0				1	×	✓	✓	×	×	×	×	+	Side effects
MMF dose [42,46]	2	2	0	2	0	0	1	0	1	×	✓	✓	×	×	×	×	+	Side effects

Phase, phase of investigation: phase 1 explanatory study, identifying associations; phase 2 explanatory study, testing independent associations; phase 3 explanatory study, understanding prognostic pathways.
For uni- and multivariate analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; and −, number of significant effects with a negative value.
For GRADE factors: ✓, no serious limitations; ×, serious limitations (or not present for moderate/large effect size, dose effect); unclear, unable to rate item based on available information. For overall quality of evidence: +, very low; ++, low; +++, moderate; ++++, high.
Abbreviations: eGFR, estimated glomerular filtration rate; GRADE, grading of recommendations assessment, development and evaluation; HCQ, hydroxychloroquine; MPA AUC, mycophenolic acid area under the curve.

Table 5
Prognostic factors related to outcome measures

Prognostic factor	No. of participants	Statistical analysis	Strength of association	Quality score	Level of evidence Considered judgement
Outcome: overall response or remission or improvement					
Histopathological factors					
Active LN	1 [45] (177)	Logistic regression	Patient with musculoskeletal manifestation and renal involvement had higher risk to have improvement compared to those with non-renal involvement (RR = 1.3571; 95% CI: 1.03–1.77; $P = 0.025$). For other non-renal manifestations (skin, hematological, CNS, and serositis) were not significant.	"Very low" evidence	There is "very low" evidence that renal involvement is not associated with non-renal manifestations improvement.
Outcome: Overall relapse or flares					
Drug-related factors					
Concomitant HCQ use	1 [41] ($n = 29$)	Person year methods	Not significant.	"Very low" evidence	There is "very low" evidence that concomitant HCQ use is not associated with disease flares.
Outcome: Renal response or remission					
Socio-demographic factors					
Gender	1 [43] ($n = 90$)	Logistic regression (Cox proportional hazards)	Not significant.	"Very low" evidence	There is "very low" evidence that gender is not associated with complete renal response.
Biochemical factors					
Baseline eGFR	1 [43] ($n = 90$)	Logistic regression (Cox proportional hazards)	eGFR was an independent risk factor (HR = 2.3; 95% CI: 1.2–4.4; $P = 0.007$).	"Very low" evidence	There is "very low" evidence that eGFR at baseline is associated with complete renal response.
Baseline serum creatinine	1 [39] ($n = 213$)	Logistic regression (Cox proportional hazards	Baseline serum creatinine was independent risk factors for not remission (OR = 1.007; 95% CI: 1.002–1.011, $P = 0.001$).	"Low" evidence	There is "low" evidence that baseline serum creatinine is associated with renal remission.
Improvement serum albumin levels	1 [35] ($n = 70$)	Cox regression analysis	Time to CR was associated with improvement in serum albumin levels (HR = 1.12; 95% CI: 1.03–1.22; $P = 0.011$).	"Very low" evidence	There is "very low" evidence that improvement serum albumin is associated with complete renal response.
Histopathological factors					
LN class	1[39] ($n = 213$)[a] 3 [35,37,43] ($n = 180$)[b]	x^2 for categorical or Fisher's exact test [37] z test for differences in proportions when comparing two groups [35] [39,43]Logistic regression (Cox proportional hazards)	Not significant [35,37,43]. Pathological classification (concomitant membranous features on biopsy) is independent risk factor for not remission (OR = 2.967; 95% CI: 1.479–6.332; $P = 0.001$) [39].	"Low" evidence	There is "low" evidence that histopathological classification of LN is associated with renal remission.
Drug-related factors					
Concomitant HCQ use	1 [36] ($n = 29$)	Cox proportional hazards model	There is an association between concomitant HCQ use and complete renal remission ($P = 0.026$).	"Very low" evidence	There is "very low" evidence that concomitant HCQ use is associated with a complete renal remission in MLN.

MPA AUC	1 [34] ($n = 34$)	Logistic regression analyses	Patients with MPA AUC ≥ 30 mg h L^{-1} at entry had a greater chance of achieving renal response at 1 year ($P = 0.057$).	"Very low" evidence	There is "very low" evidence that a MPA AUC ≥ 30 mg h L^{-1} is associated with renal response.
Outcome: renal relapse or flare					
Socio-demographic factors					
Age at study inclusion	1 [35] ($n = 70$)	Cox regression models	Younger patients HR = 0.36; 95% CI: 0.14–0.90, $P = 0.029$.	"Very low" evidence	There is "low" evidence that to be a younger patient is associated with the time to renal flare.
Gender	1 [44] ($n = 56$)	Logistic regression (Cox proportional hazards)	Not significant.	"Very low" evidence	There is "very low" evidence that gender is not associated with the rate of renal relapse.
Biochemical factors					
Baseline eGFR	1 [44] ($n = 56$)	Logistic regression (Cox proportional hazards)	Not significant.	"Very low" evidence	There is "very low" evidence that eGFR is not associated with the rate of renal relapse.
Proteinuria	1 [44] ($n = 56$)	Logistic regression (Cox proportional hazards)	Not significant.	"Very low" evidence	There is "very low" evidence that proteinuria is not associated with the rate of renal relapse.
Persistent anti-dsDNA titers	1 [35] ($n = 70$)	Cox regression models	HR = 1.001; 95% CI: 1.001–1.003; $P = 0.005$.	"Very low" evidence	There is "very low" evidence that persistent anti-dsDNA titers are associated with the time to renal flare.
Persistent hypocomplementaemia	1 [35] ($n = 70$)	Cox regression models	Not significant.	"Very low" evidence	There is "very low" evidence that persistent hypocomplementaemia is not associated with the time to renal flare.
Histopathological factors					
Histopathological classification	1 [44] ($n = 56$)	Logistic regression (Cox proportional hazards)	Not significant.	"Very low" evidence	There is "very low" evidence that histopathological classification is not associated with the rate of renal relapse.
Drug-related factors					
Duration of MMF $\leq$ 18 months after remission	1 [38] ($n = 44$)	Cox regression models	Univariate analysis HR = 6.85; 95% CI: 2.21–21.22; $P = 0.001$.	"Very low" evidence	There is "very low" evidence that duration of MMF $\leq$ 18 months is associated with relapse.
Outcome: end-stage renal disease					
Clinical characteristics					
Baseline eGFR	1 [44] ($n = 70$)	Unpaired *t*-test or Mann–Whitney test	Not significant.	"Very low" evidence	There is "very low" evidence that baseline eGFR is not associated with end-stage renal disease.
Outcome: change in disease markers					
Drug-related factors					
Plasma concentration of MPA	1 [40] ($n = 31$)	Spearman's rank correlation test	The ratio of the last follow-up IgA level to that at the start of MMF correlated significantly ($\rho = -0.52$, $P = 0.02$). Other markers did not correlate significantly.	"Very low" evidence	There is "very low" evidence that plasma concentration of MPA baseline is associated with changes of disease markers.

Table 5 (*continued*)

Prognostic factor	No. of participants	Statistical analysis	Strength of association	Quality score	Level of evidence Considered judgement
Plasma concentration of MPAG	1[40] ($n = 31$)	Spearman's rank correlation test	The ratios of the last follow-up C4, IgG, and serum concentration of albumin levels to that at the start of MMF also correlated significantly ($\rho = 0.41$, $P = 0.03$; $\rho = -0.46$, $P = 0.03$; and $\rho = 0.43$, $P = 0.02$). Serum creatinine correlated significantly ($\rho = 0.58$, $P < 0.01$).		There is "very low" evidence that plasma concentration of MPAG baseline is associated with changes of disease markers.
Outcome: side effects					
Clinical characteristics					
Baseline serum creatinine	1 [42] ($n = 54$)	Logistic regression	Not significant.	"Very low" evidence	There is 'very low' evidence that baseline serum creatinine is not associated with side effects.
Baseline eGFR	1 [43] ($n = 90$)	Unpaired *t*-test or Mann–Whitney test	Not significant.	"Very low" evidence	There is 'very low' evidence that baseline eGFR is not associated with side effects (gastrointestinal and infections).
Biologic factors within the first 6 months of treatment	1 [46] ($n = 46$)	Multiple linear regression (adjusting for class of LN and use of pulse CTS, RASI, and HCQ)	Proteinuria at 6 m had a significantly negative impact on IgG level ($\beta = -1.409$, $P = 0.028$). Other biologic factors (serum creatinine, anti-dsDNA, C3, white cells count and lymphocyte count) not significant.	"Very low" evidence	There is "very low" evidence that proteinuria at 6 m is associated with side effects (reduced IgG levels).
Duration of MMF	1 [38] ($n = 44$)	Binary logistic regression	Not significant.	"Very low" evidence	There is "very low" evidence that duration of therapy is not associated with side effects.
MPA AUC	1 [34] ($n = 34$)	Logistic regression analyses	Not significant.	"Very low" evidence	There is "very low" evidence that MPA AUC is not associated with side effects (infections).
MPA trough plasma concentrations	1 [34] ($n = 34$)	Logistic regression analyses	Not significant.	"Very low" evidence	There is "very low" evidence that MPA trough plasma concentrations are not associated with side effects (infections).
MMF dose	2 [42,46] ($n = 98$)	Multiple linear regression (adjusting for class of LN and use of pulse CTS, RASI, and HCQ) [42] Linear regression [46]	Not significant.	"Very low" evidence	There is "very low" evidence that MMF dose is not associated with side effects.

Abbreviations: CI, confidence interval; CR, complete response; CTS, corticosteroids; eGFR, estimated glomerular filtration rate; GRADE, grading of recommendations assessment, development and evaluation; HCQ, hydroxychloroquine; HR, hazard ratio; m, months; MMF, mycophenolate mofetil; MNL, membranous lupus nephritis; MPA AUC, mycophenolic acid area under the curve; MPAG, mycophenolic acid glucuronide; RASI, renin-angiotensin system inhibitor.

[a] Significant association reported number of studies (participants).

[b] Not significant association reported number of studies (participants).

out generic predictors of better outcomes in SLE from those factors that are drug specific.

Future studies on prognostic factors in SLE patients on MMF therapy should be conducted as large, prospective, registered, and protocol-based prognostic factor studies with sufficient study populations and transparent reporting of all factors studied. Next, the effectiveness of stratified MMF therapy targeting specific SLE patient subgroups based on their prognostic profiles should be tested in RCTs.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2017.01.009.

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