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Original Article

Effects of alternative remission criteria on outcome of pediatric proliferative lupus nephritis: a multi-center retrospective study of pediatric proliferative lupus nephritis

Lizhi Chen[1*], Mei Tan[2*], Jun Huang[3,4,5*], Sijia Wen[1], Cheng Cheng[1], Yihao Liu[6], Bin Li[6], Wei Chen[7], Sui Peng[6], Zihua Yu[3,4,5], Yingjie Li[2], Xiaoyun Jiang[1]

[1]Department of Pediatrics, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, P. R. China; [2]Department of Nephrology, Guangzhou Women and Children Medical Center, Guangzhou, P. R. China; [3]Department of Pediatrics, Dongfang Hospital, Fuzhou, P. R. China; [4]Department of Pediatrics, Fuzhou Clinical Medical College, Fujian Medical University, Fuzhou, P. R. China; [5]Department of Pediatrics, Affiliated Dongfang Hospital, Xiamen University, Fuzhou 350025, Fujian, P. R. China; [6]Clinical Trials Unit, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P. R. China; [7]Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, P. R. China. [*]Equal contributors.

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Abstract: Objectives: To observe the induction efficacy of mycophenolate mofetil and cyclophosphamide under different complete remission (CR) criteria in children with proliferative lupus nephritis, and to further explore the factors influencing the judgment of remission. Methods: From 2003 to 2019, children who diagnosed proliferative lupus nephritis underwent induction therapy of MMF or CYC in three hospitals were consecutively collected. Based on this population, we compared CR rates between two groups under six CR criteria selected from related recommendations and clinical trials. Then degrees and impact factors of disagreement among CR rates evaluated by selected criteria would be analyzed by Kappa test and multivariable logistic-regression models. Results: A total of 161 children were included in this study, 27 patients received induction therapy of mycophenolate mofetil (MMF) and 134 patients recieved cyclophosphamide (CYC). Under different CR criteria, CR rates in MMF group fluctuated between 18.5%-74.1% and that in CYC group ranged from 16.4%-73.9%. Moreover, comparison between the two drugs in induction treatment under different criteria showed an opposite trend in efficacy. The results of six criteria were inconsistent, with pair-to-pair *Kappa* values ranging from 0.118 to 0.858. The most important factors leading to disagreement in judgment were urinary protein and urinary red blood cells. Conclusions: The definition of complete response, especially the factors of the urinary protein and urinary red blood cells, significantly impacts the clinical judgment of children with lupus nephritis.

Keywords: Pediatric lupus nephritis, outcome measures, complete response, immunosuppressant

Introduction

As a heterogeneous autoimmune disease with multiple organs involvement, the severity and morbidity of systemic lupus erythematosus (SLE) vary among different races and ages [1]. The incidence of lupus nephritis (LN) is 67%-82% in children, which is significantly higher than that in adults [2, 3]. About 15% of pediatric LN (pLN) patients die between 22 and 27 years of age due to disease damage or treatment complications, it is also significantly higher than adults [4]. Therefore, it's vital to pay more attention to the diagnosis and treatment of pLN.

Whether complete response or remission (CR) is achieved after initial induction treatment is decisive to evaluate the prognosis [5, 6] and guide subsequent maintenance treatment [7-11], especially for the proliferative LN, the most common pathological type with the worst prognosis [2, 12]. With the absence of randomized controlled trials (RCT) on pediatric LN in

the past 20 years [13], guidelines for pediatric LN were mainly based on evidences from RCTs in adult or retrospectivestudies of children [7, 9]. Adult LN guidelines recommended Mycophenolate Mofetil (MMF) and Cyclophosphamide (CYC) as both the first line induction therapy [8, 10, 11]. However, different pediatric guidelines held different opinions on the use of MMF and CYC [7, 9], since that LN in children differs greatly from adults, such as a higher disease activity score, a greater demanding for moderate-to-high dose corticosteroids and a higher incidence of adverse events [2, 3]. Furthermore, responses to MMF and CYC are diverse in patients with LN in different races [14], and there is no study aiming at Asian children with proliferative LN up to now. Also, studies [15-17] have shown that CYC has severer and higher rates of adverse events than MMF, primarily gonadal suppression, bone marrow suppression and severe infection, which could cause great harms to children in a long term. Therefore, it is crucial to balance clinical efficacy and potential harms properly between CYC and MMF in the induction treatments for LN specifically in children.

An important obstacle to this clarity is that current definition of CR standard is still not uniform, and different studies and guidelines set various definitions. Among RCTs of adult proliferative LN [15-17], the reported CR rates ranged from 8.6% to 81.0% for MMF and 5.8% to 76.0% for CYC according to different criteria. Different definitions of CR make it more challenging to explore the efficacy of MMF and CYC in pediatric LN. Up till now, there are only three small-sample studies [18-20] have reported the effectiveness of MMF compared with CYC in proliferative pediatric LN, and the observed CR rates also varied markedly with different definitions of CR.

The purpose of this study was to observe the efficacy of MMF and CYC under different CR definitions based on a retrospective multicenter cohort in Asian children with LN, and to explore the impact factors accounting for the disagreement between the CR standards in efficacy evaluation and to provide evidence for the establishment of an unified and comparable CR standard for future prospective clinical studies of pediatric LN.

Materials and methods

Data collection

This study retrospectively included LN children in the First Affiliated Hospital of Sun Yat-sen University, Guangzhou Women and the 900th Hospital of The Joint Logistic Support Force of The Chinese People's Liberation Army from January 1, 2003, to July 31, 2019. Inclusion criteria included all of the following: 1) Diagnosis of SLE according to the American College of Rheumatology (ACR) criteria in 1997 [21]. 2) Aged ≤18 years old. 3) Kidney biopsy with a histologic diagnosis of LN (International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis [22]) class III or class IV, alone or in combination with class V. 4) 24 hours urine protein >500 mg at initial assessment. Patients with an estimated glomerular filtration rate (eGFR) lower than 30 mL/min/1.73 m^2 or accepting pulse methylprednisolone therapy within two weeks or treated regularly with MMF, CYC or other immunosuppressive agents within six months in other hospitals were excluded.

The study flow chart is shown in **Figure 1**. Clinical and laboratory data including age, gender, duration of disease, clinical manifestations, weight and height, urinalysis, serum levels of complement 3 and 4, serum creatinine (Scr), albumin (ALB), hemoglobin and treatment regimens were collected. This study was approved by the ethics committee of hospitals and the license number of ethics approval was [2019]248, and informed consent was waived.

Treatment protocols

MMF group: Children were treated with oral MMF combined with oral corticosteroids. The initial dose of prednisone was 2 mg/kg/d with a daily maximum of 60 mg, followed by gradual reduction. And the prescription of MMF was 20-30 mg/kg/d with a daily maximum of 2 g, or initial dose was 1 g/d and gradually increased to 2 g/d, both divided into twice a day and administered for six months.

CYC group: Children were treated with intravenous CYC combined with oral corticosteroids. The therapeutic regimens of corticosteroids were the same as MMF group. And the dose of

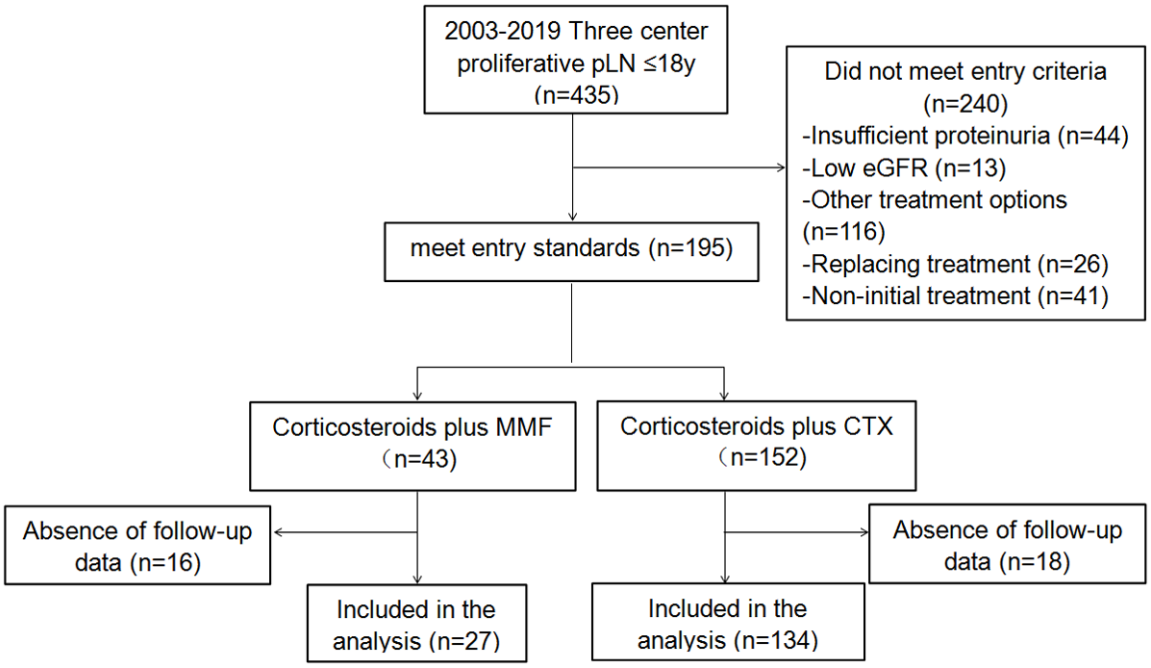

Figure 1. Patient disposition.

CYC was 8-12 mg/kg/d, once every 2 weeks for 2 days in a row, totally for 6-8 times, or 0.5-1 g/m^2, once a month and 6 times in total.

Screening for CR

Firstly, we adopted two definitions of complete response from Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations in 2012 [11] and Chinese Pediatric Society of Chinese Medical Association pediatric lupus nephritis guidelines in 2016 [7]. And then we searched for published LN clinical trials from 1999 to 2019 on PubMed with the search strategy of lupus nephritis treatment [Journal] Filters: Clinical Trial. We included all trials published on journals with an impact factor above 5.0, and those with consistent definitions with guidelines or previous studies were excluded (Supplementary Figure 1).

Finally, four clinical trials including Chan et al. [16], Ginzler et al. [17], Deng et al. [23], and ALMS (the Aspreva Lupus Management Study) trial [15] were included in this study, as well as the CR criteria of the EULAR/ERA-EDTA and the Chinese pLN guidelines (see **Table 1** for the specific definition of CR). In general, these criteria set by four selected trials and guidelines involved four factors, namely urinary protein, renal function, urinary sediment and Serum Albumin (ALB). All criteria defined a threshold for urinary protein quantification, with the minimum of 0.15 g/d as defined by the Chinese pLN guidelines, and the maximum of 0.5 g/d as defined by the EULAR/ERA-EDTA and the ALMS. As for renal function, Ginzler, ALMS and Deng assessed Serum Creatinine (Scr), while those two guidelines used eGFR. All criteria but the EULAR/ERA-EDTA included urinary sediment. However, the Chinese pLN guidelines and Deng merely defined the threshold value of urinary red blood cells (uRBCs), and only Chan's criteria included ALB.

When comparing the differences of CR rate in MMF and CYC groups using CR criteria from the four trials, patients enrolled for this analysis would also meet the inclusion criteria of the corresponding trial (Supplementary Tables 1 and 2). When comparing the consistency between two different CR criteria, we analyzed based on the all patients included.

Statistical analysis

Stata/MP 14.0 (StataCorp LP, College Station, TX) was conducted for analysis. The quantita-

Table 1. Definitions of complete remission in lupus nephritis trials or recommendations

Source of criteria	Factors			
	Urine protein	Renal function	Urinalysis	ALB
EULAR/ERA-EDTA*	<0.5 g/d	Within 10% of normal eGFR	-	-
2016-CLN*	<0.15 g/d	Normal eGFR	uRBCs <5/HP	
Chan	<0.3 g/d	Both Scr and eGFR that were 15% or less above the base-line values	Normal	Normal
Ginzler	Within 10% of normal values	Within 10% of normal values of Scr	Within 10% of normal values	-
ALMS	≤0.5 g/d	Normal Scr	Normal	-
Deng	<0.3 g/d	Within 20% of baseline values of Scr	uRBCs <10/HP	-

*2016-CLN: the guideline for children released by pediatric group, Chinese Medical Association in 2016. EULAR/ERA-EDTA: the recommendation of Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association in 2012.

Table 2. Characteristics of patients at the beginning of induction therapy

Characteristic	MMF (*n*=27)	CYC (*n*=134)	Total (*n*=161)	*P*
Age (year)	12.6±3.9	10.9±3.1	11.2±3.3	0.014
Sex (male/female)	9/18	29/105	38/123	0.217
Duration of SLE (mo)	1.5 (0.6, 4.0)	1.1 (0.6, 2.1)	1.1 (0.6, 2.6)	0.249
Duration of LN (mo)	0.9 (0.5, 3.4)	0.7 (0.4, 1.3)	0.7 (0.4, 1.6)	0.132
Urine protein (g/24 h)	1.9 (1.0, 3.9)	2.5 (1.5, 4.2)	2.4 (1.4, 4.0)	0.306
Scr (μmol/L)	72.0 (52.0, 96.0)	74.0 (52.0, 107.0)	73.0 (52.0, 106.0)	0.955
eGFR (ml/min/1.73 m^2)	110.9 (75.6, 151.1)	97.0 (68.7, 137.9)	100.6 (69.5, 141.0)	0.349
ALB (g/L)	27.8±7.8	24.9±5.9	25.4±6.3	0.030
Serum C3 (g/L)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.022
uRBCS* (*n*, %)				0.728
-	3 (11.1)	7 (5.2)	10 (6.2)	
±	1 (3.7)	10 (7.5)	11 (6.8)	
+	4 (14.8)	27 (20.1)	31 (19.3)	
++	6 (22.2)	36 (26.9)	42 (26.1)	
+++	7 (25.9)	24 (17.9)	31 (19.3)	
++++	6 (22.2)	30 (22.4)	36 (22.4)	
Range of GFR (ml/min/1.73 m^2, *n*, %)				0.507
≥90	17 (63.0)	77 (57.5)	94 (58.4)	
≥60 to <90	8 (29.6)	34 (25.4)	42 (26.1)	
≥30 to <60	2 (7.4)	23 (17.2)	25 (15.5)	
Renal biopsy class (*n*, %)				0.064
III	8 (29.6)	14 (10.4)	22 (13.7)	
IV	17 (63.0)	103 (76.9)	120 (74.5)	
III+V	0 (0.0)	3 (2.2)	3 (1.9)	
IV+V	2 (7.4)	14 (10.4)	16 (9.9)	

*: The number of red blood cells per high-power field corresponding to urinary red blood cell grades: -, 0/HP; ±, 1-5/HP; +, 6-50/HP; ++, 51-100/HP; +++, 101-300/HP; ++++, 301-full field/HP.

tive data conforming to the normal distribution was expressed by means ± standard deviation, and the contrast between groups was evaluated by *t* test. As for the quantitative data not fitting the normal distribution, it was represented by median (*M*) and quartile spacing, and Mann-Whitney U test was applied for comparing. Similarly, the rate (%) and Fisher's exact tests were employed for qualitative data. The agreement means that patients were judged as CR or No remission (NR) under different criteria, expressed as percent concordance and the strength was determined using *Kappa* scores which are considered to be near perfect, substantial, moderate, fair, poor or null when they are 1-0.8, 0.8-0.6, 0.6-0.4, 0.4-0.2, 0.2-0 or ≤0, respectively. And then we set up multivariable logistic-regression models to excavate the relative contribution of various factors to agreement or disagreement between different standards. Tests with *p*-values of <0.05 were considered statistically significant.

Results

Patients

This study included 161 children with LN, whose baseline data was shown in **Table 2**. There were 27 patients in the MMF group, including 9 males (33.3%) and 18 females (66.7%), with an average age of 12.6±3.9 years. And in the 134 patients of the CYC group, males accounted for 21.6% (29/134), while the proportion of females was 78.4% (105/134), with an average age of 10.9±3.1 years. Although the age, ALB and serum C3 of the MMF group were higher than those of the CYC group (*P*<0.05), there was no significant difference in the duration of SLE, duration of LN, Scr, eGFR, 24-hour urinary protein quantification or urinary

Table 3. CR rates at 6 months in MMF group and CYC group on the basis of the corresponding study population

Source of criteria (*n*, %)	MMF	CYC	*P*
EULAR/ERA-EDTA	20/27 (74.1)	99/134 (73.9)	1.000
2016-CLN	5/27 (18.5)	22/134 (16.4)	0.781
Chan	3/14 (21.4)	11/ 98 (11.2)	0.379
Ginzler	5/20 (25.0)	38/146 (26.0)	1.000
ALMS	5/19 (26.3)	29/146 (19.9)	0.548
Deng	5/17 (29.4)	34/ 88 (38.6)	0.588

Table 4. *Kappa* Consistency test of pairwise CR criteria

Kappa	EULAR/ ERA-EDTA	2016-CLN	Chan	Ginzler	ALMS	Deng
Deng	0.427	0.415	0.378	0.587	0.394	
ALMS	0.167	0.796	0.809	0.750		
Ginzler	0.203	0.735	0.723	0.203		
Chan	0.118	0.858				
2016-CLN	0.133					
EULAR/ERA-EDTA						

red blood cells between MMF and CYC groups at baseline ($P>0.05$). The main pathological types of the MMF and CYC groups were class IV making up 63.0% and 76.9%, respectively.

Complete response rates

In this study, six CR criteria were used to evaluate the efficacy of MMF and CYC groups in the corresponding population cluster at 6-month (see **Table 3**). The CR rates of MMF group were superior to that of CYC group under the evaluation of CR criteria in the EULAR/ERA-EDTA, Chinese pLN guidelines, Chan and ALMS; and under the CR criteria of Ginzler and Deng, the CR rates of CYC group were superior to that of MMF group ($P>0.05$). CR rates evaluated by different CR standards varied greatly between groups. For the evaluation of MMF groups, the lowest CR rate was 18.5% as assessed in the Chinese pLN guidelines, and the highest was 74.1% as assessed in the EULAR/ERA-EDTA. Similarly, the lowest CR rate in the CYC group was 11.2% as assessed by Chan, and the highest was 73.9% as assessed by the EULAR/ERA-EDTA. And the results obtained from the all patients were similar to those from specific patients' clusters (Supplementary Table 3).

Baseline data for patients with or without CR under different CR criteria are shown in Supplementary Table 4. eGFR and serum ALB of baseline were higher, and urine protein was lower in CR patients than NR under all CR criteria ($P<0.05$).

Agreement of different criteria

Supplementary Table 5 showed that the CR rates of all patients under different criteria. The highest CR rate is 73.9%, and the lowest is 15.0%. As showed in **Table 4**, the consistency of different CR standards varied greatly. The CR criteria of Chinese pLN guidelines, Chan, Ginzler and ALMS showed high consistency in the assessment (*Kappa:* 0.723-0.858), while the EULAR/ERA-EDTA guidelines had a low degree of compliance with other CR criteria (*Kappa*: 0.118-0.427). Moreover, the criteria of Deng showed moderate consistency with other standards (*Kappa*: 0.378-0.587).

Impact factors of disagreement

In the multivariable logistic-regression analysis, the main factors leading to the inconsistencies between the EULAR/ERA-EDTA or Deng and other standards were urinary protein ($OR_{2016\text{-}CLN\ vs.\ EULAR/ERA\text{-}EDTA}$ =141.49, $OR_{Deng\ vs.\ EULAR/ERA\text{-}EDTA}$ =156.33, $OR_{Chan\ vs.\ EULAR/ERA\text{-}EDTA}$ =11.93, $OR_{Ginzler\ vs.\ EULAR/ERA\text{-}EDTA}$ =125.95, $P<0.01$; $OR_{2016\text{-}CLN\ vs.\ Deng}$ =18.94, $OR_{Ginzler\ vs.\ Deng}$ =7.34, $P<0.05$) and urinary red blood cells ($OR_{2016\text{-}CLN\ vs.\ EULAR/ERA\text{-}EDTA}$ =21.07, $OR_{Deng\ vs.\ EULAR/ERA\text{-}EDTA}$ =37.77, $OR_{Chan\ vs.\ EULAR/ERA\text{-}EDTA}$ =7.48, $OR_{Ginzler\ vs.\ EULAR/ERA\text{-}EDTA}$ =25.04, $OR_{ALMS\ vs.\ EULAR/ERA\text{-}EDTA}$ =25.54, $P<0.001$; $OR_{2016\text{-}CLN\ vs.\ Deng}$ =32.18, $OR_{Chan\ vs.\ Deng}$ =15.29, $OR_{Ginzler\ vs.\ Deng}$ =35.27, $OR_{ALMS\ vs.\ Deng}$ =11.82, $P<0.001$) (**Figure 2**; Supplementary Table 6). There was no significant correlation between the disagreement of evaluation and differences in the definitions of leukocytes of urinary sediment ($P>0.05$). Analysis of the EULAR/ERA-EDTA or Deng compared to other CR criteria showed that differences in renal-function definitions did not increase the risk of inconsistencies ($OR_{EULAR/ERA\text{-}EDTA\ vs.\ Ginzler}$ <1, $OR_{Deng\ vs.\ 2016\text{-}CLN}$ <1, $P<0.05$; Others, $P>0.05$). And according to the comparison between

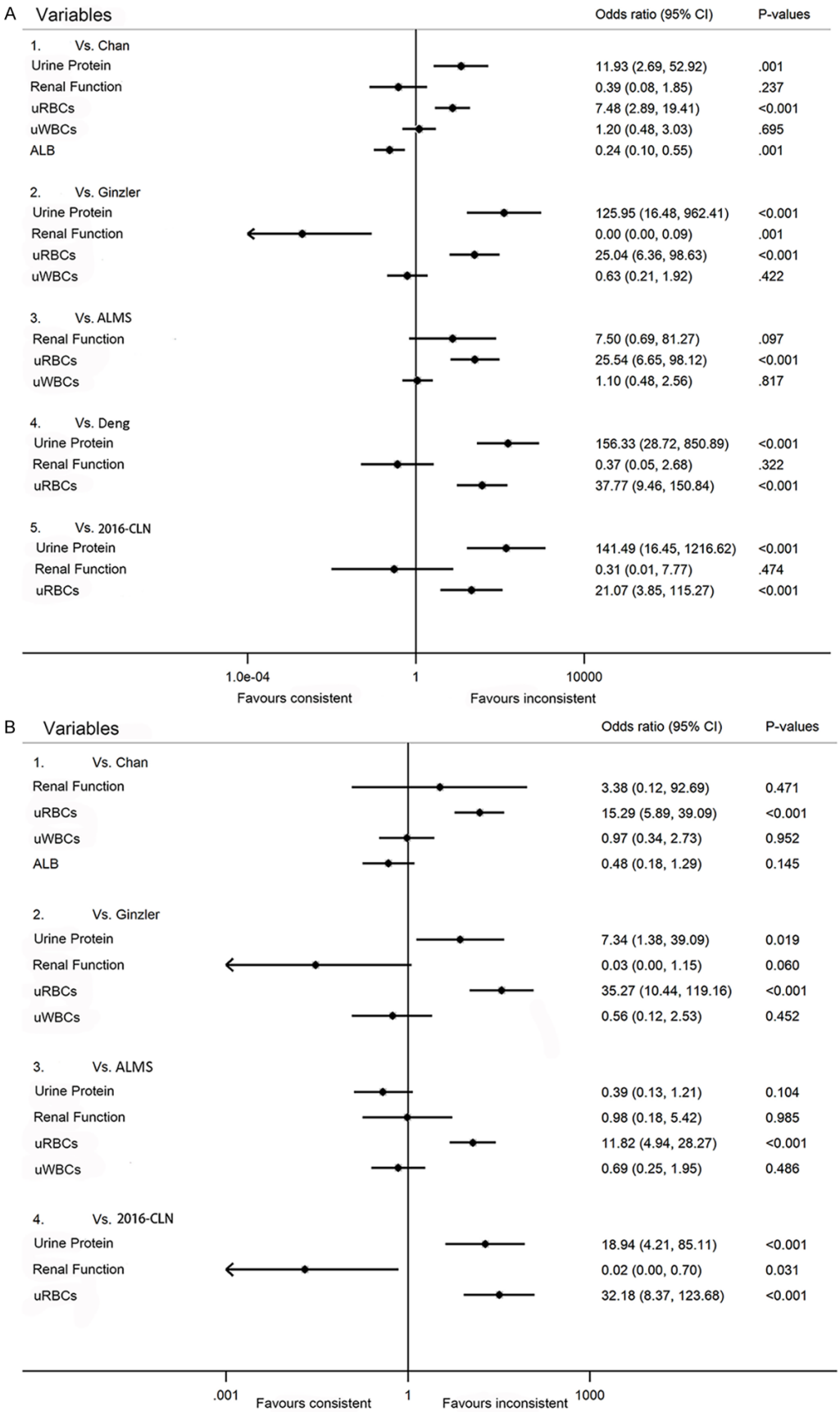

Figure 2. Multivariable logistic-regression models compared with EULAR/ERA-EDTA (A) or Deng trial (B).

Chan and EULAR/ERA-EDTA or Deng, serum albumin also did not increase the risk of disagreement ($OR_{\text{EULAR/ERA-EDTA vs. Chan}}$ <1, P<0.05; $P_{\text{Deng vs. Chan}}$ >0.05).

Discussion

According to our Asian multicenter retrospective pLN cohort study, the CR rates range from 18.5% to 74.1% for MMF and 16.4% to 73.9% for CYC under different standards. Also, consistency on response between any two CR criteria varied widely. Further multivariable logistic regression analysis revealed that the disagreement of responses evaluated by six different CR criteria was mainly caused by two factors, urine protein and urine red blood cells.

CR is widely used in clinical trials, guidelines, and clinical practice as a composite indicator to evaluate the outcome and efficacy in treatments of LN, but its definition has not yet uniformed. A total of 161 patients with proliferative LN were included in this study, which is the largest study to evaluate the efficacy of MMF and CYC in induction therapy of proliferative pLN. On the basis of our study population, we comprehensively compared the six most representative CR standards. Notably, we excluded studies that only used spot UPCR for urinary protein excretion assessment because it was confirmed that spot UPCR could not effectively predict 24-hour UPCR when urine protein beyond the range of 0.5-3.0 g/24 h, the range where most of the patients with LN flares would fall [24]. The 6-month complete response rates of total population in this study varied significantly according to six criteria, ranging from 15.0% as assessed by Chan criteria to 73.9% by the EULAR/ERA-EDTA criteria, which was similar to the adult study [25]. In addition, the CR rates of different treatment groups also fluctuated greatly, among which the rates of MMF group ranged from 18.5% to 74.1%, while the rates of CYC group ranged from 11.2% to 73.9%. Moreover, comparison between the two drugs in induction treatment under different CR standards showed an opposite trend in efficacy.

Based on multiple clinical trials, guidelines [8, 10, 11] for adult LN have recommended both MMF and CYC as the first-line induction treatment. However, a well-accepted recommendation was not reached in pLN guidelines [7, 9]. A retrospective study [20] with 13 LN children reported a CR rate of 66% in MMF group and 0% in CYC group (P>0.05). The other two [18, 19], also limited by small sample sizes, reported that the efficacy of MMF was similar to CYC, which is consistent with our findings. These retrospective studies have small sample sizes and low-evidence quality hence large RCTs for children are of great importance. Compared with adults, lack of evidence from children RCTs would require more careful consideration before initiatiation of trials. Although long-term renal survival and mortality rates remain to be the golden standard for evaluating the treatment efficacy of LN, CR is the most commonly selected surrogate end point in LN clinical trials [26] due to its clinical features of relapsing and long-course. A suitable surrogate endpoint should be clearly defined in order to effectively reflect the patient's disease courses [27-29]. The six CR standards included in this study evaluated four aspects: urinary protein, renal function, urinary sediment and serum albumin, among which urinary protein was included in all standards, with a threshold value ranges from 0.15 g/d to 0.5 g/d. Renal function was assessed by serum creatinine or in combination with eGFR. Urinary sediment including urine red blood cells and urine white blood cells should be normal according to Chan, Ginzler and ALMS criteria, while the 2016-CLN guidelines and Deng only defined the cut-off value of urinary RBCs. Urinary albumin was only included in Chan's criteria. Among these factors, differences in the cut-off values of urinary protein and urinary red blood cell significantly influenced the results of CR evaluation in different criteria. Although the indexes or cut-off values of renal function, serum albumin and urinary leukocyte were obviously different, they did not significantly relate to the differences in rates of complete remission. On the other hand, Chan, Ginzler, ALMS and 2016-CLN guidelines criteria have a high consistency in the assessment of remission. Although setting different cut-off values of other factors, these studies selected the same cut-off value for urinary-red blood cell. Which further indicated that the urinary RBCs may be the most important factor affecting the evaluation of remission. Previous research [30] has reported that 24-hour urinary protein is the best independent predictor of long-term prognosis among all kinds of commonly used renal pa-

rameters, such as serum creatinine and urinary RBCs. The prognosis-predictive capacity of urinary protein combined with urinary RBCs would reduce compared to that of urinary protein alone. Qualified surrogate endpoints should reflect patients' ultimate clinical benefits. Therefore, defining the threshold for urinary protein, the most important prognostic indicator, in a uniform and clear way is crucial in developing CR standards for pLN randomized controlled trials. Since the addition of urinary RBCs reduces the ability to predict prognosis, and different threshold values of urinary red blood cells lead to disagreement of remission rates between different criteria, this factor should be carefully included.

Limitations of this study include the relatively small sample size of MMF group, with only 27 cases. Secondly, the follow-up time of this study was short and was insufficient to evaluate long-term renal survival rate and mortality rate. Hence in the comparison between the efficacy of MMF and CYC, only complete remission was taken into account without a long-term efficacy.

In summary, different CR criteria will impact the efficacy of MMF and CYC in pediatric proliferative lupus nephritis induction therapy. CR rates with different definitions in comparison of MMF and CYC fluctuated markedly and even an opposite trend of efficacy was observed. The urine protein and urine red blood cells significantly related to the differences in rates of complete remission. However, urinary red blood cells could not increase the ability to predict long-term prognosis, therefore it is not recommended to include this parameter in CR evaluation. This study also provides the basis for establishing uniform and comparable complete remission criteria for prospective clinical studies of pediatric lupus nephritis.

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Disclosure of conflict of interest

None.

Address correspondence to: Xiaoyun Jiang, Department of Pediatrics, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, P. R. China. E-mail: jxiaoy@mail.sysu.edu.cn; Yingjie Li, Department of Nephrology, Guangzhou Women and Children Medical Center, Guangzhou, P. R. China. E-mail: liyingjie_2006@163.com; Zihua Yu, Department of Pediatrics, Dongfang Hospital, Fuzhou, P. R. China; Department of Pediatrics, Fuzhou Clinical Medical College, Fujian Medical University, Fuzhou, P. R. China; Department of Pediatrics, Affiliated Dongfang Hospital, Xiamen University, Fuzhou 350025, Fujian, P. R. China. E-mail: zihua_yu@126.com

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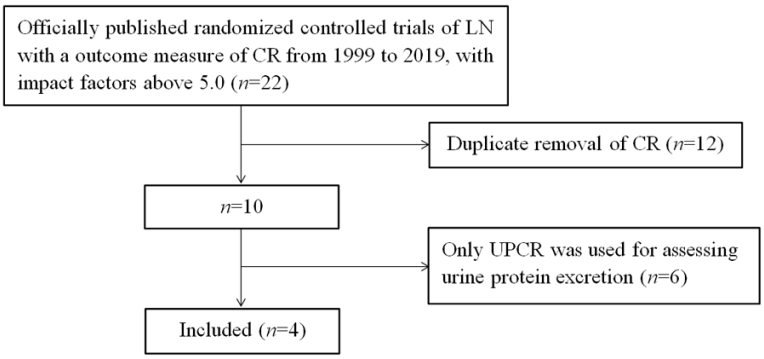

Supplementary Figure 1. Trials screening.

Supplementary Table 1. The screening population according to entry criteria from each trial

Source of criteria	MMF	CYC	Total
EULAR/ERA-EDTA*	27	134	161
2016-CLN*	27	134	161
Chan	14	98	112
Ginzler	20	146	166
ALMS	19	146	165
Deng	17	88	105

*: The EULAR/ERA-EDTA and the Chinese LN guides for children had no entry criteria and therefore remission was assessed against the total population.

Supplementary Table 2. The entry criteria calibrated according to each trial*

	Chan	Ginzler#	ALMS		Deng
Renal biopsy	IV, IV+V	III±V, IV±V	IV	III, III+V, IV+V	III, IV
Renal function	Scr ≤300 μmol/L	Scr <265.2 μmol/L	Scr >115 μmol/L	Scr >115 μmol/L	Scr ≤250 μmol/L
Serum ALB	≤35 g/L	-	-	-	
Urinary protein	≥1 g/d	>0.5 g/d	≥1 g/d	≥2 g/d	≥1 g/d
Urinary sediment	-	uRBCs >5/HP	active	-	active
Others	-	-	-	-	SLEDAI >8 or BILAG A/B. And white cell count ≥2.5×10^9/L

*: The EULAR/ERA-EDTA and the Chinese LN guides for children had no entry criteria and therefore remission was assessed against the total population. #: Patients with class III or V were required to have a serum creatinine level greater than 88.5 μmol/L or proteinuria greater than 2 g/d. Active urinary sediment: any of >5 WBC/HP, >5 RBC/HP. SLEDAI, systemic lupus erythematosus disease activity index. BILAG, the British Isles Lupus Assessment Group score.

Supplementary Table 3. CR rates at 6 months in MMF group and CYC group on the basis of the total population

Source of criteria (n, %)	MMF (N=27)	CYC (N=134)	*P*
EULAR/ERA-EDTA	20 (74.1)	99 (73.9)	1.000
2016-CLN	5 (18.5)	22 (16.4)	0.781
Chan	5 (18.5)	19 (14.2)	0.549
Ginzler	6 (22.2)	32 (23.9)	1.000
ALMS	6 (22.2)	26 (19.4)	0.792
Deng	10 (37.0)	60 (44.8)	0.527

Supplementary Table 4. Characteristics of CR or NR patients at the beginning of induction therapy

		Age of onset (year)	Urine protein (g/24 h)	uRBCs	eGFR (ml/min/1.73 m^2)	ALB (g/L)	Duration of SLE (mo)	Duration of LN (mo)
EULAR/ERA-EDTA	CR	11.2	2.8	*P*>0.05	116.5	26.0	3.2	2.0
	NR	12.5&	4.1&		87.6&	24.0&	3.1	2.6&
2016-CLN	CR	11.7	2.1	*P*<0.05	138.6	28.2	4.1	3.2
	NR	11.5	3.3&		103.0&	24.4&	3.0	2.0
Chan	CR	11.4	2.1	*P*>0.05	141.6	29.3	3.0	3.3
	NR	11.5	3.3&		103.0&	24.7&	3.2	2.0
Ginzler	CR	11.5	2.3	*P*>0.05	132.7	28.6	5.0	2.3
	NR	11.6	3.4&		101.4&	24.4&	2.7	2.1
ALMS	CR	11.6	2.2	*P*>0.05	141.5	28.8	4.3	4.2
	NR	11.5	3.4&		100.6&	24.6&	3.0	1.7
Deng	CR	10.6	2.3	*P*<0.05	121.7	27.6	3.0	2.1
	NR	11.7&	3.8&		99.2&	23.7&	3.2	2.2

&: *P*<0.05.

Supplementary Table 5. The 6-month CR rates of the total population

Source of criteria (n, %)	CR	NCR
EULAR/ERA-EDTA	119 (73.9)	42 (26.1)
2016-CLN	27 (16.8)	134 (83.2)
Chan*	24 (15.0)	136 (85.0)
Ginzler	39 (24.2)	122 (75.8)
ALMS	33 (20.5)	128 (79.5)
Deng	70 (43.5)	91 (56.5)

*: The ALB value was missing from the follow-up data in 1 case and could not be evaluated.

Supplementary Table 6. Odds ratios for disagreement between criteria in multivariable logistic-regression models

(A) Compare with EULAR/ERA-EDTA

	2016-CLN		Deng		Chan		Ginzler		ALMS	
	Variables	Odds ratios	Variables	Odds ratios	Variables	Odds ratios	Variables	Odds ratios	Variables	Odds ratios
Urine protein (g/d)	≥0.5 or <0.15	141.49	≥0.5 or <0.3	156.33	≥0.5 or <0.3	11.93	≥0.5 or ≤0.165	125.95	-	
Renal function	eGFR ≥90 or <81	No sense	(Scr ≤1.2 times baseline values and eGFR ≥81) or (Scr >1.2 times baseline values and eGFR <81)	No sense	Scr ≤1.15 times baseline values and eGFR ≥0.85 times baseline values and eGFR ≥81 or (Scr >1.15 times baseline values or eGFR <0.85 times baseline values) and eGFR <81	No sense	(eGFR ≥81 and Scr ≤1.1 times normal values) or (eGFR <81 and Scr >1.1 times normal values)	<0.01	(eGFR ≥81 and normal Scr) or (eGFR <81 and abnormal Scr)	No sense
uRBCs	-	21.07	<10/HP	37.77	-	7.48	≤5/HP	25.04	-	25.54
uWBCs					-	No sense	≤1.1 times normal values	No sense	-	No sense
ALB (g/L)					≥35	0.24				

(B) Compare with Deng

	2016-CLN		Chan		Ginzler		ALMS	
	Variables	Odds ratios	Variables	Odds ratios	Variables	Odds ratios	Variables	Odds ratios
Urine protein (g/d)	≥0.3 or <0.15	18.94			≥0.3 or ≤0.165	7.34	>0.5 or <0.3	No sense
Renal function	(eGFR ≥90 and Sc ≤1.2 times baseline values) or (eGFR <90)	0.02	(Scr ≤1.15 times baseline values and eGFR ≥0.85 times baseline values) or (Scr >1.2 times baseline values)	No sense	(Scr ≤1.2 times baseline values and greater than 1.1 times normal values) or (Scr >1.2 times baseline values and greater than 1.1 times normal values)	No sense	(eGFR ≥81 and normal Scr) or (eGFR <81 and abnormal Scr)	No sense
uRBCs	- or ≥10/HP	32.18	- or ≥10/HP	15.29	≤5/HP or ≥10/HP	35.27	-	11.82
uWBCs			-	No sense	≤1.1 times normal values	No sense	-	No sense
ALB (g/L)			≥35	No sense				

OR=1: When the defined conditions of variables were met, namely, the remission results of the two CR standards are consistent. The Blank lattice means that factors from the two standards are defined in the same. WBC, White Blood Cell. The unit of eGFR is ml/min/1.73 m^2.