Original Article

Factors predictive of long-term mortality in lupus nephritis: A multicenter retrospective study of a Japanese cohort

Kunihiro Ichinose[1], Mineaki Kitamura[2], Shuntaro Sato[3], Keita Fujikawa[4], Yoshiro Horai[5], Naoki Matsuoka[6], Masahiko Tsuboi[6], Fumiaki Nonaka[7], Toshimasa Shimizu[1], Shoichi Fukui[1], Masataka Umeda[1], Tomohiro Koga[1], Shin-ya Kawashiri[1], Naoki Iwamoto[1], Mami Tamai[1], Hideki Nakamura[1], Tomoki Origuchi[8], Tomoya Nishino[2] and Atsushi Kawakami[1]

[1]Department of Immunology and Rheumatology, Unit of Advanced Preventive Medical Sciences, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[2]Department of Nephrology, Nagasaki University Hospital, Nagasaki, Japan

[3]Clinical Research Center, Nagasaki University Hospital, Nagasaki, Japan

[4]Department of Rheumatology, JCHO Isahaya General Hospital, Isahaya, Japan

[5]Department of Rheumatology, Clinical Research Center, NHO Nagasaki Medical Center, Omura, Japan

[6]Nagasaki Medical Hospital of Rheumatology, Nagasaki, Japan

[7]Department of Internal Medicine, Sasebo City General Hospital, Sasebo, Japan

[8]Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Running head: CR at 12 months helps predict mortality in LN

***Corresponding author:** Dr. Kunihiro Ichinose, Department of Immunology and Rheumatology, Unit of Advanced Preventive Medical Sciences, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel: +81-95-819-7262; Fax: +81-95-849-7270. Email: kichinos@nagasaki-u.ac.jp

ABSTRACT

Background: Lupus nephritis (LN) is a major determinant of mortality in systemic lupus erythematosus (SLE). Here we evaluated the association between complete renal response (CR) and mortality in LN.

Methods: We retrospectively analyzed the cases of 172 of 201 patients with LN for whom data on the therapeutic response at 6 and 12 months after induction therapy were available. The patients underwent a renal biopsy at Nagasaki University Hospital and community hospitals in Nagasaki between the years 1990 and 2016. We determined the CR rates at 6 and 12 months after induction therapy induction and evaluated the predictive factors for CR and their relationship with mortality. We performed univariate and multivariable competing risks regression analyses to determine the factors predictive of CR. The patients' survival data were analyzed by the Kaplan-Meier method with a log-rank test.

Results: The median follow-up duration after renal biopsy was 120 months (interquartile range: 60.3–191.8 months). The 5-, 10-, 15- and 20-year survival rates of our cohort were 99.3%, 94.6%, 92.0% and 85.4%, respectively. During follow-up, nine patients (5.2%) died from cardiovascular events, infection, malignancy and other causes. The multivariate analysis revealed that the following factors were predictive of CR. At 6 months: male gender (odds ratio [OR] 0.23, 95% confidence interval [CI] 0.08–0.65, p=0.0028),

proteinuria (g/gCr) (OR 0.83, 95%CI 0.71–0.97, p=0.0098) and index of activity (0–24) (OR 0.84, 95%CI 0.71–0.99, p=0.0382). At 12 months: male gender (OR 0.25, 95%CI 0.09–0.67, p=0.0043) and index of activity (0–24) (OR 0.82, 95%CI 0.69–0.98, p=0.0236). The Kaplan-Meier analysis showed that compared to not achieving CR at 12 months, achieving CR at 12 months was significantly correlated with the survival rate (OR 0.18, 95%CI 0.04-0.92, p=0.0339).

Conclusions: Our results suggest that the survival rate of patients with LN is associated with the achievement of CR at 12 months after induction therapy, and that male gender and a higher index of activity (0–24) are the common predictive factors for failure to achieve CR at 6 and 12 months.

Keywords: complete renal response, lupus nephritis, survival rate, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with a broad spectrum of clinical and immunologic manifestations, among which lupus nephritis (LN) is the most common cause of morbidity and mortality.[1] Indeed, SLE patients with LN have 6–6.8-fold higher standardized mortality rates compared to those without LN (2.4-fold).[2-5] Notably, over the past few decades, the 10-year survival rate of LN has improved dramatically from 46% to 95% among patients in whom disease remission can be achieved.[6] Nonetheless, approximately 5%–20% of patients with LN will progress to end-stage renal disease (ESRD) within 10 years after diagnosis despite receiving aggressive immunosuppressive therapy.[7-9]

Although the causes and prognostic predictors of renal outcomes and mortality in LN have been studied, there is only limited data on LN in Japan. The recommendations for LN management published by the European League Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) propose that a complete renal response (CR) or at least a partial renal response (PR) should be achieved preferably within 6 months and no later than 12 months after the initiation of treatment.[10] Various demographic, clinical and experimental variables have been associated with poor outcomes in LN, including age, gender, ethnicity,

duration of disease, uncontrolled hypertension, anemia, elevation of serum creatinine, reduction of the glomerular filtration rate, and chronic kidney disease.[5,11] However, only a few clinical immunological parameters have been determined to be predictive of achieving CR at 6 and 12 months.

We conducted the present study to evaluate the causes of mortality in biopsy-proven LN patients and to identify the factors predictive of renal outcome and mortality among the LN patients treated at Nagasaki University Hospital and community hospitals in Nagasaki, Japan.

Patients and Methods

We conducted an analysis of the retrospectively collected data of 201 patients with biopsy-proven LN treated between 1990 and 2016 at Nagasaki University Hospital and community hospitals in Nagasaki. To obtain the pathological information of the patients with LN, biopsy specimens were reclassified separately by two expert nephropathologists (M.K and T.T.) based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification,[12,13] regardless of the patients' previous World Health Organization (WHO) or ISN/RPS classification. Patients were excluded if they had advanced comorbidity or other diseases associated with kidney dysfunction, including

diabetic kidney disease or primary kidney disease. Patients with inadequate medical records or follow-up periods <12 months were also excluded from this study. All patients were followed at 1–3-month intervals, from the time of renal biopsy for ≥12 months.

We divided the 201 patients based on whether or not they achieved CR, and we compared the two groups to identify predictors of achieving CR at 6 and 12 months of treatment. The CR group was defined as achieving CR at 6 and 12 months with prednisolone and/or immunosuppressive treatment, and those without CR formed the non-CR group. Some of the patients provided written informed consent for the use of their data, and an opt-out strategy was chosen for the remaining patients. Those who rejected informed consent were excluded. The study was reviewed and approved by the Medical Ethical Committee of Nagasaki University Hospital (approval nos. 12012397 and 17082129).

Data collection

Baseline characteristics were collected at the time of renal biopsy. Demographic data included the patient's age at the onset of SLE, gender, the disease duration of SLE (the time from the diagnosis of SLE until the renal biopsy), comorbidities of Sjögren syndrome (SS)/anti-phospholipid syndrome (APS), and the induction treatment used. We

analyzed the patients' laboratory data, including white blood cell (WBC) count, lymphocyte count, hemoglobin, platelet counts, albumin, proteinuria, urine protein/creatinine ratio (Up/Ucr), urinary N-acetyl-β-D-glucosaminidase (NAG), urinary β2-microglobulin (β2MG), serum β2MG, serum creatinine (Cr), blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR), as well as immunologic parameters including complement 3 (C3), complement 4 (C4), total hemolytic complement (CH50), immunoglobulin (Ig)G, IgA, IgM, anti-nuclear antibodies, anti-double-stranded DNA antibodies (anti-dsDNA), anti-Smith (Sm) antibodies, anti-ribonucleoprotein (RNP) antibodies, anti-Ro/SSA antibodies, and anti-La/SSB antibodies. Histologic features of activity and chronicity scores were determined as described previously.[14]

Treatment and the definition of renal remission

The patients were treated with immunosuppressive agents, depending on the clinical judgment of a rheumatologist and the treatment guidelines/recommendations for LN published by the American College of Rheumatology (ACR) and EULAR/ERA-EDTA.[10,15] Therapies included prednisolone (PSL) with intravenous cyclophosphamide (IVCY; 500–1,000 mg/m^2 body surface area once a month for six months), or PSL with

the first-line immunosuppressive regimen used for the treatment of LN, followed by quarterly intravenous CYC or oral immunosuppressants. PSL was given at the dose of 0.5–1 mg/kg/day, with or without intravenous methylprednisolone (mPSL) pulse therapy (500–1,000 mg/day × 3 days). Plasma exchange (PE) was performed for patients who were resistant to other treatments.

At the discretion of the treating physician, induction therapy was implemented for a period of approximately 6 months. We defined CR at 6 and 12 months as an Up/Ucr ratio <50 mg/mmol (roughly equivalent to proteinuria <0.5 g/24 hr) and a normal or near-normal (within 10% of a normal glomerular filtration rate [GFR] if previously abnormal) GFR. We defined partial renal response (PR) as a ≥50% reduction in proteinuria to subnephrotic levels and a normal or near-normal GFR.

Mortality, causes of death, and occurrence of ESRD

The primary outcome was mortality due to any cause. The secondary outcome was ESRD, defined as dialysis dependence for >3 months. Data were collected until either the patient's final follow-up or until July 30, 2018, whichever occurred later. Risk factors for mortality were determined.

Statistical analyses

A nonparametric Wilcoxon rank sum test was used for inter-group comparisons of multiple variables. Fisher's exact test or chi-squared test was also used to test the possible association between each variable factor and the treatment response. We performed univariate and multivariable competing-risks regression analyses to determine the predictive factors of clinical response. The data on the time to death or the duration of survival after renal biopsy were analyzed using the Kaplan-Meier method with a log-rank test. All of the statistical analyses were performed using JMP® Pro14 software (SAS Institute, Cary, NC). The significance level was set at $p<0.05$.

Results

Baseline characteristics of the studied patients

Among the total 201 cases, we were able to examine the therapeutic responses of 172 patients at 6 and 12 months after initiation of therapy **(Fig. 1)**. The demographic and disease-related features of the 172 patients are shown in **Supplementary Table S1**. Most of the patients were female (84.3%). The median age at onset of LN was 34.0 years (interquartile range [IQR] 26.0–45.8 years), and the disease duration of LN was 22 months (IQR 1.0–119.5 months). The median follow-up duration after renal biopsy was

120 months (IQR 60.3–191.8 months). The renal pathology of 97 (56.4%) patients was classified as ISN/RPS Class III or IV, and 35 (20.3%) patients were ISN/RPS Class V. One hundred-three (59.9%) patients were treated with intravenous mPSL pulse therapy, 40 (23.3%) patients were treated with IVCY, and 59 (34.3%) patients were treated with Tacrolimus (TAC) for induction therapy.

We divided the 172 patients into two groups based on their CR status at 6 months **(Table 1)** and 12 months **(Table 2)** after induction therapy. Seventy-nine patients (45.9%) achieved CR at 6 months, and 101 patients (58.7%) achieved CR at 12 months. Among the disease-related features at baseline, a higher percentage of males (p=0.0106), the amount of proteinuria (p<0.0001), the percentage of ISN/RPS Class III or IV (p=0.0036), a higher index of activity (0-24) (p=0.0002) and chronicity (0–12) (p=0.0034) were significantly related to failure to achieve CR at 6 months. A higher percentage of males (p=0.0183), the amount of proteinuria (p=0.0489), elevated serum BUN (p=0.0027), elevated serum Cr (p=0.0109), the percentage of ISN/RPS Class III or IV (p=0.0420), a higher index of activity (0-24) (p=0.0005) and chronicity (0–12) (p=0.0027), and lower hemoglobin (p=0.0178) were significantly related to failure to achieve CR at 12 months.

Twenty-year survival rates of the cohort

The 5-, 10-, 15- and 20-year survival rates of our cohort were 99.3%, 94.6%, 92.0% and 85.4%, respectively. There were a total of nine deaths (5.2%) with the main causes being cardiovascular disease (n=3, 33.3%), infection (n=1, 11.1%) and malignancy (n=1, 11.1%). Four (44.4%) patients died from other causes; one patient died from a pulmonary hemorrhage, one died of lupus enterocolitis, and the cause of death in the other two patients was not known **(Suppl. Table S2)**. Eight of the nine patients had a disease duration in excess of 5 years.

The patients who died during the observation period were significantly older at the onset of LN (42 vs. 34 yrs old, p=0.0256), had significantly higher serum Cr at the onset of LN (0.9 vs. 0.7 mg/dl, p=0.0237) and had a significantly lower eGFR at the onset of LN (56.4 vs. 78.7 ml/min/1.73 m^2, p=0.0190) compared to the non-fatalities.

Predictors of CR at 6 months and 12 months after induction therapy

The multivariate logistic analysis revealed that male gender (odds ratio [OR] 0.23, 95% confidence interval [CI] 0.08–0.65, p=0.0028), proteinuria (g/gCr) (OR 0.83, 95%CI 0.71–0.97, p=0.0098) and index of activity (0-24) (OR 0.84, 95%CI 0.71–0.99, p=0.0382) were predictive of achieving CR at 6 months after induction therapy **(Table 3)**, and male gender (OR 0.25, 95%CI 0.09–0.67, p=0.0043) and the index of activity (0–24) (OR 0.82,

95%CI 0.69–0.98, p=0.0236) were predictive of achieving CR at 12 months **(Table 4)**.

Analysis of survival rate: CR at 6 months and 12 months

Six patients (3.5%) progressed to ESRD and nine patients (5.2%) died during the observation period. The Kaplan-Meier analysis showed that compared to not achieving CR at 12 months, the achievement of CR at 12 months **(Fig. 2B)** was significantly correlated with the survival rate, whereas no such correlation was shown for the achievement of CR at 6 months **(Fig. 2A)**. The renal survival rate was not correlated with the achievement of CR at 6 or 12 months **(Suppl. Fig. S1)**.

Discussion

LN can result in serious organ damage, and among patients with SLE, the presence or absence of LN is related to mortality.[7,16] Several studies have conducted short- to medium-term follow-ups of survival and renal outcomes in LN. However, few studies have examined the long-term prognosis in LN (i.e., over a follow-up period >10 years).[5,17-24]

To our knowledge, the present study is the first to show an association between the long-term survival rate and therapeutic responses in a cohort of Japanese patients with LN. We found that the 5-, 10-, 15- and 20-year survival rates in our cohort were 99.3%,

94.6%, 92.0% and 85.4%, respectively, which were comparable to the previously reported survival rates.[2,5,19]

The survival rate of our LN patients was significantly correlated with the achievement of CR at 12 months after induction therapy. A previous study found that the survival rate was greater in patients who achieved CR or PR than in those with no remission.[6] Another report showed that patients who achieved CR at 24 months after biopsy were significantly less likely to experience ESRD/mortality compared to patients who were not in remission.[25] However, these studies did not discuss the reasons for the survival rate and therapeutic responses in LN.

A few baseline variables have emerged as risk factors for fatalities. The mortality was markedly increased for older patients in previous studies, and age was one of the baseline predictors of death in a cohort of patients with LN.[5,26] Elevated serum Cr is also reported to be associated with an increased risk of mortality.[26,27] Impairment of renal function with a reduced eGFR at the baseline was reported to be associated with mortality.[28,29] We speculated that if patients with LN who achieved CR are less exposed to immunosuppressive agents (such as cyclophosphamide and high-dose corticosteroid) and also have a less severe inflammatory condition, they might be less vulnerable to organ damage than patients with LN who fail to achieve CR.

In our cohort, cardiovascular complications, malignancy and infection were the leading causes of mortality, and this is similar to other reports.[2,7] Due to advances in immunosuppressive treatment, supportive therapy, socio-economic conditions and earlier diagnoses, the survival of individuals with LN has improved significantly over the past few decades. LN-related causes of death including uncontrolled disease or acute renal failure are now rare. However, infection remains an important cause of mortality, and cardiovascular and malignancy complications with longer patient survival have emerged as important causes of late mortality.[2,3]

In our study, 79 patients (45.9%) achieved CR at 6 months and 101 patients (58.7%) achieved CR at 12 months. These results are similar to those of previous studies, which reported remission rates of 33.0%–50.4% at 6 months and 49.3%–58.0% at 12 months.[30-32] The significance of achieving CR on the long-term prognosis of LN has been described in many studies. We demonstrated that male gender and a higher index of activity (0–24) were the common predictive factors for the failure to achieve CR at 6 and 12 months. It has also been shown that male patients responded less to treatment and had a poorer course.[24,26,33] In the Hopkins Lupus cohort, there was a doubled-odds of renal biopsy, renal insufficiency, and renal failure among males compared to females, with adjustment for age, duration of SLE, ethnicity, and smoking status.[34] In that cohort, male

gender was also associated with a twofold greater risk of death.[35] Wang et al.[33] showed that males with LN had significantly lower remission rates at 6 months after starting treatment, which is similar to our present finding. In our study, there were more male LN patients whose onset was at age ≥50 years (p=0.0310, data not shown). As mentioned above, later onset of LN with older age is linked to poorer renal outcome and mortality. However, according to a recent critical review of the literature,[36] the concept of worse prognoses in males compared to females with LN remains controversial in light of the limited evidence.

A higher index of activity (0–24) is known to be a predictor of poorer renal outcome and mortality.[26,37-39] However, other studies failed to demonstrate a relationship between the index of activity and the course of LN.[40] As a potential alternative marker, other investigations have shown that a combined activity and chronicity index has a strong predictive value in the course of LN.[41]

The limitations of our study deserve some discussion. First, our cohort included a relatively small number of patients with few fatalities treated at a university hospital and community hospitals in a rural area. Second, it is difficult to generalize in regard to previously adopted risk factors for mortality and therapeutic response because different response criteria and various observation periods were used in the past and present

investigations. Third, because we used a long-term follow-up period, the therapeutic regimens of the patients could have differed between our study and the previous ones; in particular, we could not enroll patients who were treated with hydroxychloroquine (HCQ). Because HCQ for SLE patients was approved relatively recently in Japan (in September 2015), the percentage of patients excluded due to HCQ use would have been greater in our study than in the previous investigations. Further observational studies of larger multicenter populations are required to test our findings and to further assess the clinical relevance of mortality and the attainment of CR at 12 months.

In conclusion, we retrospectively analyzed the association between the mortality rate and therapeutic responses with a mean 10-year follow-up in LN. We found that the survival rate was associated with the achievement of CR at 12 months after induction therapy. In addition, male gender and a higher index of activity (0–24) were the common predictive factors for failure to achieve CR at 6 and 12 months. Our results suggest that the attainment of CR at 12 months could predict the survival rate and that male patients and the histological score should be carefully followed for the prediction of renal outcomes and the prevention of renal flares.

Funding

This work was supported by a Grant-in-Aid for Scientific Research (to K.I.; no.

17K09977), the Japan Intractable Diseases Research Foundation, and the Nagao Memorial Foundation.

Conflicts of interest statement

The authors declare no conflict of interest.

Figure Legends

Fig. 1. Patient enrollment flow: 201 patients with lupus nephritis (LN) were enrolled.

Fig. 2. Kaplan-Meier analysis of the cumulative survival rate, according to the achievement of CR at 6 **(**A**)** and 12 **(**B**)** months. The red line indicates the number of patients who had achieved CR, and the blue line indicates the number who had not achieved CR at each time point. The raw numbers of patients analyzed in each subset at each time point are included below the figures; these were patients whose survival was considered to be "at risk."

Suppl. Fig. S1. Kaplan-Meier analysis cumulative renal survival rate, according to achieved CR at 6 **(**A**)** and 12 **(**B**)** months. The red line indicates the number of patients who had achieved CR, and the blue line indicates the number who had not achieved CR at each time point. The raw numbers of patients analyzed in each subset at each time point are included below the figures; these were patients whose renal survival was considered to be "at risk."

.

Table 1. The baseline characteristics of the patients who did or did not achieve complete renal response at 6 months

Baseline variable	Complete renal response				p-value	Baseline variable	Complete renal response				p-value
	Achieved (n=79)		Not achieved (n=93)				Achieved (n=79)		Not Achieved (n=93)		
	Median	IQR	Median	IQR			Median	IQR	Median	IQR	
Age at onset, years	35	27.0–43.0	34	25.5–46.0	0.9046	IgA, mg/dl	276	191–441	264	195–366	0.1397
Gender (%male)	6/79 (7.6)		21/93 (22.6)		0.0106*	IgM, mg/dl	109	70.2–157.9	90	58.6–164.9	0.2864
Disease duration, months	4	1–88	42	2–125	0.1067	CH50, mg/dl	21.8	11.3–31.1	19.8	13.1–30.1	0.8404
Proteinuria, g/gCr	1.0	0.5–2.3	2.6	1.1–4.1	<0.0001*	C3, mg/dl	46	32.4–64.2	48.5	32.1–73.0	0.6465
White blood cell count, /μl	4900	3900–7300	5150	4000–7170	0.7637	C4, mg/dl	7.8	4.3–14.1	9.4	5.5–15.4	0.3296
Lymphocyte count, /μl	818	557–1286	967	572–1521	0.2339	Comorbidities of SS (%)	12/79 (15.2)		10/93 (10.8)		0.4930
Hemoglobin, g/dl	11.3	10.1–12.6	11.1	9.7–12.2	0.3101	Comorbidities of APS (%)	6/79 (7.6)		12/93 (12.9)		0.3215
Platelet counts, x104/μl	20.7	13.3–26.9	21.8	16.4–27.0	0.5154	ISN/RPS III or IV (%)	35/79 (44.3)		62/93 (66.7)		0.0036*
Albumin, g/dl	3.3	2.7–3.9	3.1	2.7–3.7	0.1781	ISN/RPS V (%)	15/79 (19.0)		20/93 (21.5)		0.7083
BUN, mg/dl	14.5	11.0–19.3	17	12.1–22.0	0.0905	Index of activity (0–24)	4	2–7	6	4–8	0.0002*
Cr, mg/dl	0.7	0.6–0.9	0.8	0.6–1.1	0.0557	Index of chronicity (0–12)	2	0–3	2	1–4	0.0034*
eGFR, ml/min/1.73 m^2	79.0	58.1–101.1	77.0	51.3–98.4	0.3117	mPSL pulse (%)	45/79 (57.0)		58/93 (62.4)		0.5332
ANA	640	160–1280	640	160–1280	0.7634	TAC (%)	28/79 (35.4)		31/93 (33.3)		0.8721
Anti-ds-DNA antibodies, U/ml	40.4	12.5–184.9	31.2	7.4–136.0	0.5353	CyA (%)	6/79 (7.6)		14/93 (15.1)		0.1557
Anti-RNP antibodies, U/ml	9.1	2.6–65.2	8.8	4.2–128.8	0.3139	IVCY (%)	18/79 (22.8)		22/93 (23.7)		1

Anti-Sm antibodies, U/ml	5.0	0.9–35.2	8.4	3.2–55.4	0.096	MMF (%)	2/79 (2.5)	7/93 (7.5)	0.1814
IgG, mg/dl	1620	1189–2000	1430	957–2150	0.3949	PE (%)	7/79 (8.9)	8/93 (8.6)	1

P-values were determined by nonparametric Wilcoxon rank sum test and Fisher's exact test. *p<0.05. IQR: interquartile range; WBC: white blood cell; TAC:Tacrolimus

Table 2. The baseline characteristics of the patients who did or did not achieve complete renal response at 12 months

Baseline variable	Complete renal response				p-value	Baseline variable	Complete renal response				p-value
	Achieved (n=101)		Not achieved (n=71)				Achieved (n=101)		Not achieved (n=71)		
	Median	IQR	Median	IQR			Median	IQR	Median	IQR	
Age at onset, years	35	26.5–44.0	34	25.0–48.0	0.8764	IgA, mg/dl	273	197–423	252	195–361	0.2236
Gender (% male)	10/101 (9.9)		17/71 (23.9)		0.0183*	IgM, mg/dl	107	69.5–173.0	91	54.6–142.5	0.1047
Disease duration, months	10	1–115	42	2–123	0.2428	CH50mg/dl	21.8	12.6–31.4	18.9	11.0–29.6	0.2865
Proteinuria, g/gCr	1.4	0.6–3.5	2.6	1.0–3.6	0.0489*	C3mg/dl	47.7	31.6–72.5	46	33.0–60.5	0.6594
White blood cell count, /μl	5550	4100–7810	4700	3800–6600	0.1159	C4mg/dl	8.1	4.7–14.3	9.4	5.8–15.5	0.3811
Lymphocyte count, /μl	857	599–1462	846	532–1339	0.5546	Comorbidities of SS (%)	16/101 (15.8)		6/71 (8.5)		0.1719
Hemoglobin, g/dl	11.4	10.1–12.7	10.5	9.7–12.0	0.0178*	Comorbidities of APS (%)	8/101 (7.9)		10/71 (14.1)		0.2139
Platelet counts, $x10^4$/μl	21.1	16.2–27.3	19	14.9–26.4	0.424	ISN/RPS III or IV (%)	50/101 (49.5)		47/71 (66.2)		0.0420*
Albumin, g/dl	3.2	2.7–3.7	3.1	2.7–3.8	0.3301	ISN/RPS V (%)	20/101 (19.8)		15/71 (21.1)		0.8494
BUN, mg/dl	14	11–19	18	13–26	0.0027*	Index of activity (0–24)	5	2.5–7.0	6	4.0–8.0	0.0005*
Cr, mg/dl	0.7	0.6–0.9	0.8	0.6–1.1	0.0109*	Index of chronicity (0–12)	2	1.0–3.0	3	2.0–4.0	0.0027*
eGFR, ml/min/1.73 m^2	79.5	58.8–104.1	75.1	44.2–96.3	0.1008	mPSL pulse (%)	54/101 (53.5)		49/71 (69.0)		0.0576
ANA	640	160–1280	640	160–1280	0.8073	TAC (%)	34/101 (33.7)		25/71 (35.2)		0.8712
Anti-ds-DNA antibodies, U/ml	39.2	11.6–204.4	31.2	7.2–125.3	0.2844	CyA (%)	10/101 (9.9)		10/71 (14.1)		0.4713

Anti-RNP antibodies, U/ml	15.1	4.7–86.7	6.85	2.4–120.6	0.2857	IVCY (%)	19/101 (18.8)	21/71 (29.6)	0.1419
Anti-Sm antibodies, U/ml	9	1.8–59.7	5.4	1.8–28.1	0.6264	MMF (%)	4/101 (4.0)	5/71 (7.0)	0.4909
IgG, mg/dl	1561	1120–2075	1405	906–2022	0.1876	PE (%)	12/101 (11.9)	3/71 (4.2)	0.1019

P-values were determined by nonparametric Wilcoxon rank sum test and Fisher's exact test. *p<0.05.; TAC:Tacrolimus

Table 3. Multivariate regression model of predictive factors of achieving complete renal response at 6 months

Parameter	OR	95%CI	p-value
Gender (% male)	0.23	0.08–0.65	0.0028*
Proteinuria, g/gCr	0.82	0.70–0.95	0.0098*
ISN/RPS III or IV, %	1.26	0.52–3.04	0.6333
Index of activity (0–24)	0.83	0.70–0.99	0.0382*
Index of chronicity (0–12)	0.88	0.72–1.08	0.2550

*$p<0.05$.

Table 4. Multivariate regression model of predictive factors of achieving complete renal response at 12 months

Parameter	OR	95%CI	p-value
Gender, %male	0.26	0.10–0.70	0.0043*
Proteinuria, g/gCr	1.00	0.88–1.13	0.7211
Hemoglobin, g/dl	1.08	0.90–1.30	0.2988
BUN, mg/dl	0.98	0.92–1.03	0.5259
Cr, mg/dl	1.33	0.45–3.90	0.5316
ISN/RPS III or IV, %	1.43	0.59–3.46	0.5239
Index of activity (0–24)	0.83	0.70–0.98	0.0236*
Index of chronicity (0–12)	0.86	0.71–1.05	0.1567

*p<0.05.

References

1. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011; 365: 2110-21.
2. Yap DY, Tang CS, Ma MK, Lam MF and Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transplant*. 2012; 27: 3248-3254.
3. Lerang K, Gilboe IM, Steinar Thelle D and Gran JT. Mortality and years of potential life loss in systemic lupus erythematosus: a population-based cohort study. *Lupus*. 2014; 23: 1546-1552.
4. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006; 54: 2550-2557.
5. Faurschou M, Dreyer L, Kamper AL, Starklint H and Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. *Arthritis Care Res (Hoboken)*. 2010; 62: 873-880.
6. Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ and Collaborative Study G. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol*. 2008; 3: 46-53.
7. Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford)*. 2016; 55: 252-262.
8. Chen Y, Sun J, Zou K, Yang Y and Liu G. Treatment for lupus nephritis: an overview of systematic reviews and meta-analyses. *Rheumatol Int*. 2017; 37: 1089-1099.
9. Croca SC, Rodrigues T and Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. *Rheumatology (Oxford)*. 2011; 50: 1424-1430.
10. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis*. 2012; 71: 1771-1782.
11. Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis*. 2010; 69: 61-64.
12. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004; 15: 241-250.
13. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int*. 2004; 65: 521-

530.
14. Austin HA, 3rd, Muenz LR, Joyce KM, et al. Prognostic factors in lupus nephritis. Contribution of renal histologic data. *Am J Med*. 1983; 75: 382-391.
15. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012; 64: 797-808.
16. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)*. 2003; 82: 299-308.
17. Donadio JV, Jr., Hart GM, Bergstralh EJ and Holley KE. Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. *Lupus*. 1995; 4: 109-115.
18. Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P and Ponticelli C. The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant*. 2007; 22: 2531-2539.
19. Teh CL, Phui VE, Ling GR, Ngu LS, Wan SA and Tan CH. Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience. *Clin Kidney J*. 2018; 11: 56-61.
20. Bono L, Cameron JS and Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. *QJM*. 1999; 92: 211-218.
21. Mok CC, Wong RW and Lau CS. Lupus nephritis in Southern Chinese patients: clinicopathologic findings and long-term outcome. *Am J Kidney Dis*. 1999; 34: 315-323.
22. Esdaile JM, Abrahamowicz M, MacKenzie T, Hayslett JP and Kashgarian M. The time-dependence of long-term prediction in lupus nephritis. *Arthritis Rheum*. 1994; 37: 359-368.
23. Mok CC, Ying KY, Yim CW, Ng WL and Wong WS. Very long-term outcome of pure lupus membranous nephropathy treated with glucocorticoid and azathioprine. *Lupus*. 2009; 18: 1091-1095.
24. Kono M, Yasuda S, Kato M, et al. Long-term outcome in Japanese patients with lupus nephritis. *Lupus*. 2014; 23: 1124-1132.
25. Davidson JE, Fu Q, Ji B, et al. Renal Remission Status and Longterm Renal Survival in Patients with Lupus Nephritis: A Retrospective Cohort Analysis. *J Rheumatol*. 2018.
26. Moroni G, Vercelloni PG, Quaglini S, et al. Changing patterns in clinical-histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. *Ann Rheum Dis*. 2018; 77: 1318-1325.
27. Momtaz M, Fayed A, Wadie M, et al. Retrospective analysis of nephritis

response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: a university hospital experience. *Lupus*. 2017; 26: 1564-1570.
28. Pamuk ON, Akbay FG, Donmez S, Yilmaz N, Calayir GB and Yavuz S. The clinical manifestations and survival of systemic lupus erythematosus patients in Turkey: report from two centers. *Lupus*. 2013; 22: 1416-1424.
29. Alarcon GS, McGwin G, Jr., Bartolucci AA, et al. Systemic lupus erythematosus in three ethnic groups. IX. Differences in damage accrual. *Arthritis Rheum*. 2001; 44: 2797-2806.
30. So MW, Koo BS, Kim YG, Lee CK and Yoo B. Predictive value of remission status after 6 months induction therapy in patients with proliferative lupus nephritis: a retrospective analysis. *Clin Rheumatol*. 2011; 30: 1399-1405.
31. Korbet SM, Lewis EJ and Collaborative Study G. Complete remission in severe lupus nephritis: assessing the rate of loss in proteinuria. *Nephrol Dial Transplant*. 2012; 27: 2813-2819.
32. Park DJ, Choi SE, Xu H, et al. Chronicity index, especially glomerular sclerosis, is the most powerful predictor of renal response following immunosuppressive treatment in patients with lupus nephritis. *Int J Rheum Dis*. 2018; 21: 458-467.
33. Wang YF, Xu YX, Tan Y, Yu F and Zhao MH. Clinicopathological characteristics and outcomes of male lupus nephritis in China. *Lupus*. 2012; 21: 1472-1481.
34. Tan TC, Fang H, Magder LS and Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. *J Rheumatol*. 2012; 39: 759-769.
35. Kasitanon N, Magder LS and Petri M. Predictors of survival in systemic lupus erythematosus. *Medicine (Baltimore)*. 2006; 85: 147-156.
36. Murphy G and Isenberg D. Effect of gender on clinical presentation in systemic lupus erythematosus. *Rheumatology (Oxford)*. 2013; 52: 2108-2115.
37. Yoo CW, Kim MK and Lee HS. Predictors of renal outcome in diffuse proliferative lupus nephropathy: data from repeat renal biopsy. *Nephrol Dial Transplant*. 2000; 15: 1604-1608.
38. Kammoun K, Jarraya F, Bouhamed L, et al. Poor prognostic factors of lupus nephritis. *Saudi J Kidney Dis Transpl*. 2011; 22: 727-732.
39. Malvar A, Pirruccio P, Alberton V, et al. Histologic versus clinical remission in proliferative lupus nephritis. *Nephrol Dial Transplant*. 2017; 32: 1338-1344.
40. Martins L, Rocha G, Rodrigues A, et al. Lupus nephritis: a retrospective review of 78 cases from a single center. *Clin Nephrol*. 2002; 57: 114-119.
41. Austin HA, 3rd, Muenz LR, Joyce KM, Antonovych TT and Balow JE. Diffuse

proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. *Kidney Int*. 1984; 25: 689-695.

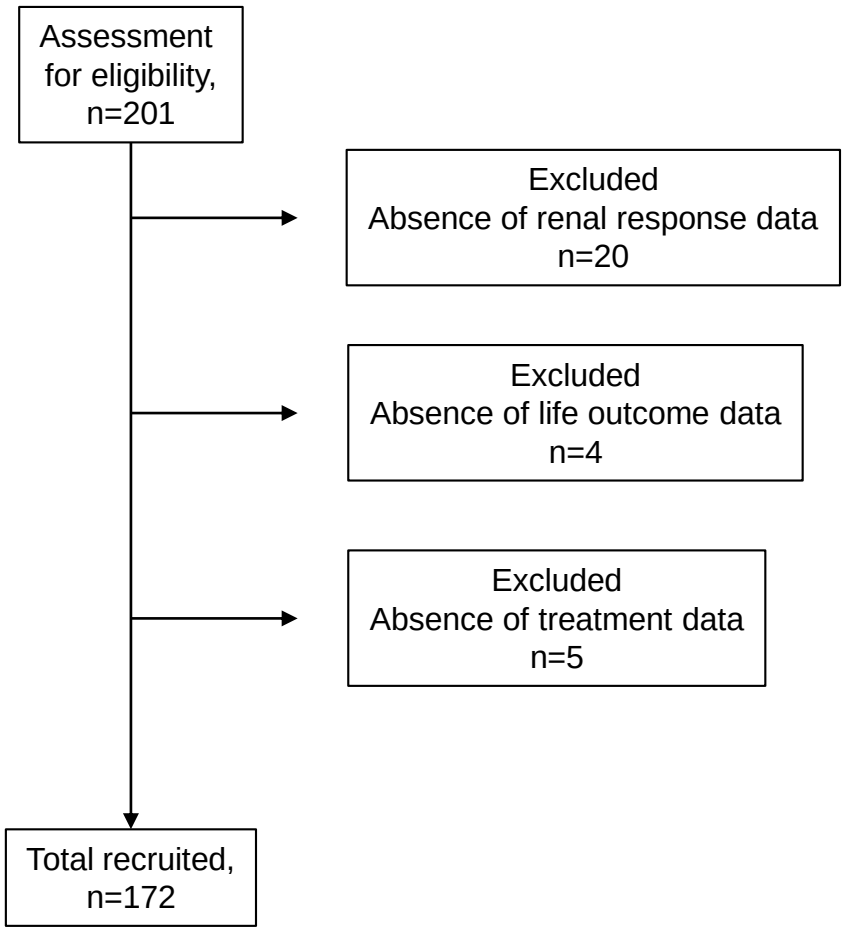

Assessment for eligibility, n=201
Excluded
Absence of renal response data
n=20
Excluded
Absence of life outcome data
n=4
Excluded
Absence of treatment data
n=5
Total recruited, n=172

Fig. 1

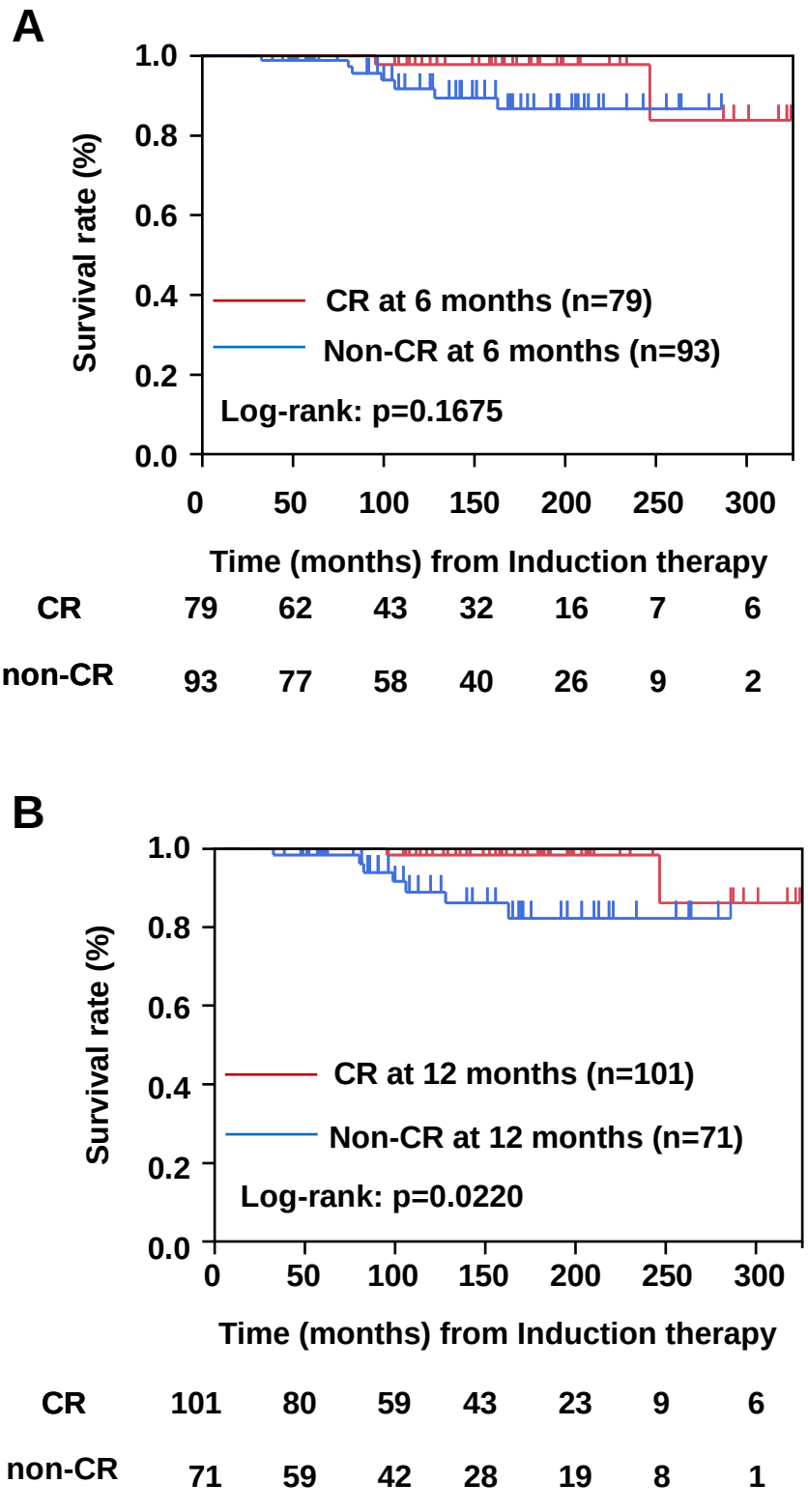

A
1.0
0.8
0.6
0.4
0.2
0.0
Survival rate (%)
CR at 6 months (n=79)
Non-CR at 6 months (n=93)
Log-rank: p=0.1675
0
50
100
150
200
250
300
Time (months) from Induction therapy
CR 79 62 43 32 16 7 6
non-CR 93 77 58 40 26 9 2
B
1.0
0.8
0.6
0.4
0.2
0.0
Survival rate (%)
CR at 12 months (n=101)
Non-CR at 12 months (n=71)
Log-rank: p=0.0220
0
50
100
150
200
250
300
Time (months) from Induction therapy
CR 101 80 59 43 23 9 6
non-CR 71 59 42 28 19 8 1

Fig. 2

Supplementary Table S1. Baseline characteristics of the patients

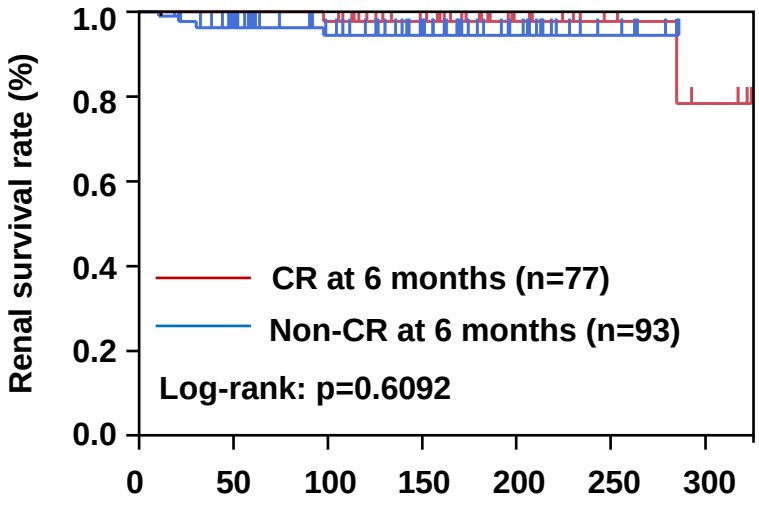
Characteristic	Median	IQR	Characteristic	Median	IQR
Age at onset, years	34.0	(26.0–45.8)	IgA, mg/dl	271	(195–392)
Gender (%female)	145/172 (84.3)		IgM, mg/dl	96.6	(62.3–160.0)
Disease duration, months	22	(1.0–119.5)	CH50, mg/dl	20.9	(12.0–30.9)
Proteinuria, g/gCr or g/24 hr	1.6	(0.8–3.6)	C3, mg/dl	46.9	(32.2–70.8)
White blood cell count, /μl	5020	(3920–7260)	C4, mg/dl	8.9	(5.0–14.8)
Lymphocyte count, /μl	846	(568–1410)	Comorbidities of SS (%)	22/172 (12.8)	
Hemoglobin, g/dl	11.1	(9.8–12.4)	Comorbidities of APS (%)	18/172 (10.5)	
Platelet counts, $x10^4$/ μl	21.1	(15.7–26.9)	ISN/RPS III or IV (%)	97/172 (56.4)	
Albumin, g/dl	3.2	(2.7–3.8)	ISN/RPS V (%)	35/172 (20.3)	
BUN, mg/dl	15	(12–21)	Index of activity (0–24)	5	(3–8)
Cr, mg/dl	0.7	(0.6–1.0)	Index of chronicity (0–12)	2	(1–3)
eGFR, ml/min /1.73 m^2	77.8	(56.4–99.6)	mPSL pulse (%)	103/172 (59.9)	
ANA	640	(160-1280)	TAC (%)	59/172 (34.3)	

Anti-ds-DNA antibodies, U/ml	38	(9.7–153.9)	CyA (%)	20/172 (11.6)
Anti-RNP antibodies, U/ml	9	(3.6-90.2)	IVCY (%)	40/172 (23.3)
Anti-Sm antibodies, U/ml	6.5	(1.8–48.9)	MMF (%)	9/172 (5.2)
IgG, mg/dl	1495	(1046–2050)	PE (%)	15/172(8.7)

Suppl. Table S2. Causes of death

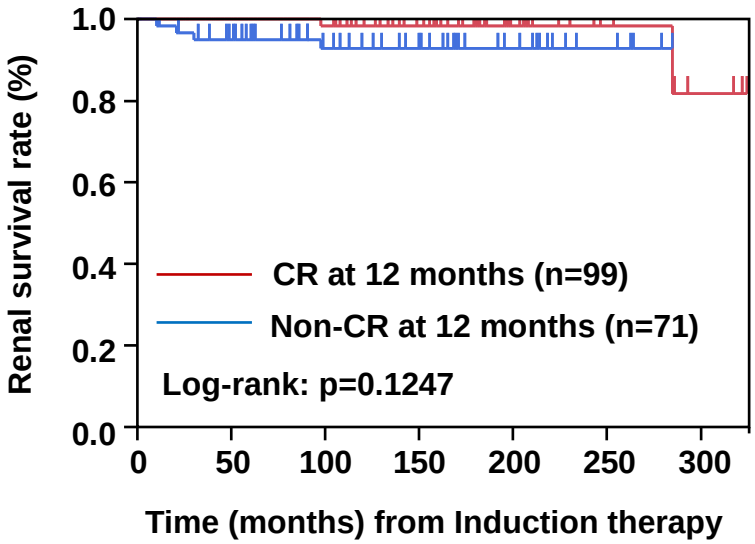
Cause of death	n
Cardiovascular disease	3
Infection	1
Malignancy	1
Others:	
Pulmonary hemorrhage	1
Lupus enterocolitis	1
Unknown	2
Total	9

A



CR	77	58	43	32	13	7	4
non-CR	93	71	55	40	24	7	

B



CR	99	75	58	43	19	8	4
non-CR	71	56	40	29	19	9	

Suppl. Fig. S1