Comparison of clinical features and outcomes between patients with early and delayed lupus nephritis

Sung Soo Ahn¹, Juyoung Yoo¹, Seung Min Jung¹, Jason Jungsik Song¹,², Yong-Beom Park¹,² and Sang-Won Lee¹,²*

Abstract

Background: Lupus nephritis is associated with increased risk of end-stage renal disease (ESRD) and all-cause mortality. We evaluated the clinical features and outcomes of patients with early and delayed lupus nephritis.

Methods: The medical records of 171 patients who met the 1997 revised classification criteria for systemic lupus erythematosus (SLE) with pathologic confirmation of lupus nephritis were reviewed. Early lupus nephritis was defined when lupus nephritis was histopathologically confirmed as the first clinical manifestation of SLE, whereas delayed lupus nephritis was defined as lupus nephritis that was identified after the diagnosis of SLE. Clinical and laboratory data, as well as kidney histopathology and medication usage were investigated. Kaplan-Meier and Cox-proportional hazard analysis was performed to compare the outcomes of early and delayed lupus nephritis and evaluate factors associated with ESRD and all-cause mortality.

Results: Patients with early lupus nephritis had higher disease activity (median non-renal SLE disease activity index-2000, 6.0 vs. 4.0; \( p < 0.001 \)) and more frequent skin rash, oral ulcer and serositis; however, the proportion of patients with higher renal chronicity index was greater in the delayed lupus nephritis group (\( p = 0.007 \)). Nevertheless, no difference was found regarding ESRD and all-cause mortality between the groups. In Cox-proportional hazard analysis, C-reactive protein level, creatinine level and chronicity index were factors associated with ESRD, while age and haemoglobin level were associated with all-cause mortality.

Conclusions: In conclusion, clinical outcomes of early and delayed lupus nephritis are not significantly different. Rigorous adherence to current treatment recommendations is essential for the treatment of lupus nephritis.

Keywords: Lupus nephritis, Early, Delayed, Prognosis, Predictor

Background

Systemic lupus erythematosus (SLE) is an idiopathic inflammatory disease characterized by multiple organ injury as a result of autoantibody formation [1]. Lupus nephritis is one of the most serious systemic complication of SLE that affects up to 60–70% of patients with SLE during their lifetime [2]. Lupus nephritis is classified into 6 different subtypes based on the pathologic findings, with class III and class IV (proliferative) lupus nephritis being the most aggressive form [3]. The treatment of proliferative lupus nephritis consists of induction therapy, followed by maintenance therapy to achieve remission [4]. However, the prognosis of patients with lupus nephritis remains unfavourable even when aggressive treatment strategies are implemented, mainly...
because of a significantly increased risk of end-stage renal disease (ESRD) and all-cause mortality [5]. Accordingly, the treatment guidelines for SLE recommend prudent monitoring of patients for the development of lupus nephritis [6]. In general, lupus nephritis primarily occurs at the time of or within the first year of SLE diagnosis [7]. On the contrary, the frequency of lupus nephritis occurrence gradually decreases with time; the onset of lupus nephritis is reported to be uncommon after 5 years from SLE diagnosis [8].

Most patients with SLE are treated based on the organ involved, and immunosuppressive agents, such as glucocorticoids and hydroxychloroquine, are the most widely used drugs for the management of SLE [9]. A considerable number of patients who had been diagnosed with SLE before lupus nephritis (delayed lupus nephritis), may have been exposed to glucocorticoids and/or immunosuppressive drugs, while most patients diagnosed with lupus nephritis as the first complication of SLE (early lupus nephritis) may be glucocorticoid and/or immunosuppressive drug-naïve. Therefore, it is theoretically assumed that the clinical features at the time of kidney biopsy and the prognosis may differ between early and delayed lupus nephritis proportionally to the interval between the diagnosis of SLE and lupus nephritis; however, the data from the literature regarding this subject are scarce [10]. Therefore, the objectives of this study were 1) to compare the clinical features of early and delayed lupus nephritis at the time of kidney biopsy and its prognosis and 2) to investigate factors associated with ESRD and all-cause mortality during the follow-up period.

Methods

Patient selection

The records of patients diagnosed with lupus nephritis by kidney biopsy between January 2006 and July 2018 were retrospectively reviewed. The following patients were included: i) patients with histological findings compatible with 2003 International Society of Nephrology/ Renal Pathology Society (ISN/RPS) classification criteria for lupus nephritis [3]; ii) patients who met the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE [11, 12]; iii) patients who were not diagnosed with lupus nephritis prior to pathological confirmation. In case of patients with repeated histopathological results, the first result was used in this study. Finally, 171 patients with lupus nephritis were included in this study. This study was approved by the Institutional Review Board of Severance Hospital, and the need for written informed consent was waived, as this was a retrospective study (4–2018-1083).

Evaluation of clinical and laboratory data and medications

All clinical and laboratory data were assessed at the time of kidney biopsy. Kidney biopsy was performed in the patients when the amount of proteinuria was greater than 1 g per 24 h (either in 24 h urine or spot urine protein/creatinine (P/Cr) ratio) in the absence of alternative causes. The demographic data included age, sex and disease duration after the diagnosis of SLE. The SLE specific variables included non-renal SLE disease activity index-2000 (SLEDAI-2 K), complement (C)3, C4, anti-dsDNA and spot urine P/Cr ratio [13]. Laboratory data collected were white blood cell count, platelet count, lymphocyte count, hemoglobin level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine level and albumin level. Investigated clinical manifestations comprised the components of 1997 ACR classification criteria, including skin rash, photosensitivity, oral ulcer, arthritis, serositis and neurologic, hematologic and immunologic disorder [11]. The number of patients with hypertension, diabetes mellitus and dyslipidaemia prior to the diagnosis of lupus nephritis was counted based on international classification of diseases-10 and Korean drug utilization review (DUR) system. For kidney histopathology data, lupus nephritis class was determined according to the 2003 ISN/RPS criteria, and the activity and chronicity index were calculated based on the scoring system from the National Institutes of Health [3, 14]. Medications that were used prior and after the diagnosis of lupus nephritis were defined as those for achieving or maintaining the remission of SLE and were searched by using the Korean DUR system. In addition, the adverse effects of glucocorticoid and immunosuppressive agents and the cumulative dosage of glucocorticoid was calculated by using the Hospital’s electronic medical record system.

Definition of early and delayed lupus nephritis and clinical outcomes

In this study, early lupus nephritis was defined when lupus nephritis was histopathologically confirmed as the first clinical manifestation of SLE, whereas delayed lupus nephritis was defined as lupus nephritis that was identified after the diagnosis of SLE. In addition, ESRD was defined as an impairment of renal function that required dialysis, while all-cause mortality as death for any reason during the follow-up. The follow-up duration was determined as the gap-time from the diagnosis of lupus nephritis to the last visit for the survived patients, to death for the deceased patients, and to the initiation of dialysis for the patients with ESRD. Composite outcome was defined as either the presence of ESRD and/or all-cause mortality.
Statistical analysis
All statistical analyses were performed using MedCalc statistical software version 18.11.3 (MedCalc Software, Ostend, Belgium). Continuous and categorical variables were represented as median (interquartile ranges) and frequencies (percentages). Comparison of continuous variables was performed by Mann-Whitney U test and categorical variables were compared using chi-square, chi-square for trend, or the Fisher’s exact test as appropriate. Kaplan-Meier analysis with the log-rank test was used to compare the clinical outcomes of early and delayed lupus nephritis. Multivariate Cox-proportional hazard analysis using statistically significant variables in univariate analysis was used to evaluate factors associated with ESRD and all-cause mortality. In all analysis, a two-tailed p < 0.05 was considered statistically significant.

Results
Comparison of patient characteristics
The baseline characteristics of patients are shown in Table 1. The median age was 36.0 years, 153 (89.5%) patients were women and the median follow-up duration was 57.1 months. As we divided our patients into early and delayed lupus nephritis, 106 (62.0%) and 65 (38.0%) patients were classified as having early and delayed lupus nephritis. The median disease duration of delayed lupus nephritis group was 52.6 months, and there was no difference in the follow-up duration between the groups after the diagnosis of lupus nephritis was established. Patients with early nephritis had higher non-renal SLEDAI-2 K and ESR, but lower anti-dsDNA, WBC count and albumin levels compared to those with delayed lupus nephritis. Regarding clinical manifestations, patients with early lupus nephritis had a higher incidence of skin rash, oral ulcer and serositis compared to those with delayed lupus nephritis. In kidney histopathology data, no difference was found in lupus nephritis classes and activity index, but the proportion of patients with higher chronicity index was significantly greater in the delayed lupus nephritis group (p = 0.007). Glucocorticoids were the most frequently selected immunosuppressive agents that were used in the delayed lupus nephritis group prior to the diagnosis of lupus nephritis, followed by hydroxychloroquine and azathioprine (Table 2). Medications that were used after the diagnosis of lupus nephritis were not significantly different between the groups, except for cyclophosphamide that was more frequently used in patients with early lupus nephritis than in those with delayed lupus nephritis (39.6% vs. 23.1%, p = 0.026, Table 3). When we investigated the adverse effects of glucocorticoid and immunosuppressive agents, systemic effects were the most common, followed by infections in both early and delayed lupus nephritis group. There was no significant difference in adverse effects between the groups, only except that myalgia was more common in patients with early lupus nephritis (Supplementary Table 1).

Comparison of clinical outcomes in patients with early and delayed lupus nephritis
Kaplan-Meier analysis was carried out to compare the clinical outcomes in patients with early and delayed lupus nephritis. No differences in renal and overall survival rates were found between the groups (log-rank test p = 0.720 and p = 0.526, Fig. 1a–b). Moreover, the composite outcome free rate was also comparable between early and delayed lupus nephritis (log-rank test p = 0.335, Fig. 1c).

Predictive factors of the development of ESRD in lupus nephritis
Among included variables, age, hemoglobin, CRP and creatinine levels and chronicity index revealed by renal biopsy were associated with the development of ESRD in univariate Cox-proportional hazard analysis. Multivariate analysis revealed that CRP level (odds ratio [OR] 1.021, 95% confidence interval [CI] 1.006–1.037, p = 0.007), creatinine level (OR 2.233, 95% CI 1.539–3.239, p < 0.001) and chronicity index (OR 1.475, 95% CI 1.042–2.090, p = 0.029) were predictive factors of ESRD (Table 4).

Predictive factors associated with all-cause mortality in lupus nephritis
The univariate Cox-proportional hazard analysis showed that age and hemoglobin and CRP levels were predictive of all-cause mortality. However, in multivariate analysis, only age (OR 1.065, 95% CI 1.018–1.114, p = 0.006) and hemoglobin level (OR 0.656, 95% CI 0.448–0.959, p = 0.030) were factors that were independently associated with all-cause mortality during the follow-up (Table 5).

Discussion
The results of this study showed that lupus nephritis affected more than 60% of patients at the time of SLE diagnosis; however, a substantial number of patients developed lupus nephritis after SLE was diagnosed. In this study, the median disease duration of SLE in the delayed lupus nephritis group was < 5 years, which is consistent with data of previous studies [8]. Regarding the clinical characteristics, when lupus nephritis developed early in the course of SLE, affected patients were more likely to have higher disease activity and prominent multiple organ involvement. This finding could be related to the fact that almost every patient with delayed lupus nephritis was being currently or previously treated with immunosuppressive agents. Therefore, it is more likely for
patients with early lupus nephritis to demonstrate higher disease activity and systemic inflammation compared to those with delayed lupus nephritis. However, during the follow-up period, no difference was found in the clinical outcomes of the patients, probably due to the similar effect of administered treatment in these patients. Therefore, the observations from the current study provide useful information regarding the management of patients with lupus nephritis.

An important finding of our study was that the prognosis of patients with early and delayed lupus nephritis was not significantly different. This fact might be

### Table 1 Baseline characteristics of patients with early and delayed lupus nephritis

| Variables                  | Total (n = 171) | Patients with early lupus nephritis (n = 106) | Patients with delayed lupus nephritis (n = 65) | p-value |
|----------------------------|----------------|-----------------------------------------------|-----------------------------------------------|---------|
| **Demographic data**       |                |                                               |                                               |         |
| Age, years                 | 36.0 (26.3–46.0) | 36.0 (25.0–48.0)                              | 36.0 (29.0–44.0)                              | 0.903   |
| Female sex, n (%)          | 153 (89.5)      | 91 (85.8)                                     | 62 (95.4)                                    | 0.070   |
| Disease duration, months   | n/a            | n/a                                           | 52.6 (22.0–118.8)                             | < 0.001 |
| Follow-up duration, months | 57.1 (17.5–90.8)| 40.9 (14.2–91.3)                              | 67.6 (27.0–88.9)                              | 0.119   |
| **SLE specific variables** |                |                                               |                                               |         |
| Non-renal SLEDAI-2 K       | 5.0 (4.0–7.0)   | 6.0 (5.0–8.0)                                 | 4.0 (4.0–6.0)                                 | < 0.001 |
| Complement 3, mg/dL        | 42.7 (28.7–66.4)| 40.3 (26.2–67.3)                              | 46.4 (34.9–64.5)                              | 0.129   |
| Low complement 3, n (%)    | 154 (90.1)      | 95 (89.6)                                     | 59 (90.8)                                    | 0.808   |
| Complement 4, mg/dL        | 5.6 (3.0–12.5)  | 5.3 (3.0–12.5)                                | 6.2 (3.5–12.3)                               | 0.623   |
| Low complement 4, n (%)    | 114 (66.7)      | 73 (68.9)                                     | 41 (63.1)                                    | 0.437   |
| Anti-dsDNA (IU/mL)         | 218.4 (32.3–379.0)| 160.0 (10.0–379.0)                         | 300.0 (143.3–379.0)                          | 0.009   |
| Elevated anti-dsDNA, n (%)| 141 (82.5)      | 83 (78.3)                                     | 58 (89.2)                                    | 0.069   |
| Spot urine P/Cr ratio      | 2.9 (1.5–6.0)   | 3.4 (1.5–6.5)                                 | 2.3 (1.5–4.2)                                | 0.123   |
| **Laboratory data**        |                |                                               |                                               |         |
| WBC count (/μL)            | 4400.0 (3147.5–6145.0)| 3925.0 (3030.5630.0)| 4950.0 (3947.5–6727.5) | 0.018   |
| Platelet count (× 1000/μL) | 203.0 (136.3–247.8)| 200.0 (113.0–240.0)| 213.0 (152.8–253.3) | 0.126   |
| Hemoglobin (g/dL)          | 10.4 (9.1–11.7) | 10.2 (8.9–11.5)                               | 10.9 (9.5–11.9)                              | 0.189   |
| Lymphocyte count (/μL)     | 8600 (580.0–1227.5)| 8400 (550.0–1250.0)| 9000.0 (610.0–1222.5) | 0.999   |
| ESR (mm/hr)                | 53.0 (28.5–76.0) | 57.0 (35.0–84.0)                              | 41.0 (24.8–68.8)                             | 0.013   |
| CRP (mg/L)                 | 2.5 (1.0–8.9)   | 3.0 (1.0–9.6)                                 | 1.9 (1.0–4.9)                                | 0.074   |
| Cr (mg/dL)                 | 0.8 (0.6–1.1)   | 0.8 (0.6–1.1)                                 | 0.8 (0.6–1.0)                                | 0.434   |
| Albumin (g/dL)             | 2.9 (2.2–3.4)   | 2.6 (2.1–3.3)                                 | 3.2 (2.6–3.4)                                | 0.002   |
| **Clinical manifestations** |                |                                               |                                               |         |
| Skin rash                  | 53 (31.0)       | 41 (38.7)                                     | 12 (18.5)                                    | 0.006   |
| Photosensitivity           | 13 (7.6)        | 10 (9.4)                                      | 3 (4.6)                                      | 0.374   |
| Oral ulcer                 | 21 (12.3)       | 19 (17.9)                                     | 2 (3.1)                                      | 0.004   |
| Arthritis                  | 10 (5.8)        | 8 (7.5)                                       | 2 (3.1)                                      | 0.322   |
| Serositis                  | 41 (24.0)       | 35 (33.0)                                     | 6 (9.2)                                      | < 0.001 |
| Neurologic disorder        | 2 (1.2)         | 1 (0.9)                                       | 1 (1.5)                                      | 0.726   |
| Hematologic disorder       | 152 (88.9)      | 95 (89.6)                                     | 57 (87.7)                                    | 0.698   |
| Immunologic disorder       | 159 (93.0)      | 100 (94.3)                                    | 59 (90.8)                                    | 0.376   |
| **Comorbidities**          |                |                                               |                                               |         |
| Hypertension               | 33 (19.3)       | 11 (10.4)                                     | 22 (33.8)                                    | < 0.001 |
| Diabetes mellitus          | 4 (2.3)         | 3 (2.8)                                       | 1 (1.5)                                      | 0.999   |
| Dyslipidemia               | 2 (1.2)         | 2 (1.9)                                       | 0 (0.0)                                      | 0.526   |

Values are expressed as median (interquartile range) or n (%). n/a not applicable, SLEDAI-2 K systemic lupus erythematosus disease activity index-2000, P/Cr protein/creatinine, WBC white blood cell, ESR erythrocyte sedimentation rate, CRP C-reactive protein, Cr creatinine.
### Table 2: Comparison of baseline kidney histopathology data and prior immunosuppressive treatment

| Variables                  | Total (n = 171) | Patients with early lupus nephritis (n = 106) | Patients with delayed lupus nephritis (n = 65) | p-value |
|----------------------------|-----------------|---------------------------------------------|-----------------------------------------------|---------|
| **Kidney histopathology data** |                 |                                             |                                               |         |
| **Lupus nephritis class**   |                 |                                             |                                               |         |
| Class I                    | 3 (1.8)         | 0 (0.0)                                     | 3 (4.6)                                       | 0.053   |
| Class II<sup>a</sup>        | 7 (4.1)         | 4 (3.8)                                     | 3 (4.6)                                       | 0.999   |
| Class III<sup>a</sup>       | 57 (33.3)       | 35 (33.0)                                   | 22 (33.8)                                     | 0.801   |
| Class IV<sup>a</sup>        | 84 (49.1)       | 53 (50.0)                                   | 31 (47.7)                                     | 0.770   |
| Class VI                   | 0 (0.0)         | 0 (0.0)                                     | 0 (0.0)                                       | 0.999   |
| **Activity/Chronicity**     |                 |                                             |                                               |         |
| Activity index             | 7.0 (2.0–11.8)  | 7.0 (2.0–11.0)                              | 8.0 (3.0–12.0)                                | 0.323   |
| Chronicity index, n (%)    |                 |                                             |                                               |         |
| 0–1                       | 104 (60.8)      | 71 (67.0)                                   | 33 (50.8)                                     | 0.007   |
| 2–3                       | 51 (29.8)       | 30 (28.3)                                   | 21 (32.3)                                     |         |
| 4–5                       | 13 (7.6)        | 4 (3.8)                                     | 9 (13.8)                                      |         |
| 6                         | 3 (1.8)         | 1 (0.9)                                     | 2 (3.1)                                       |         |
| **Prior immunosuppressive agent use** |           |                                             |                                               |         |
| Glucocorticoids            | 64 (37.4)       | 0 (0.0)                                     | 64 (98.5)                                     | < 0.001 |
| Cyclophosphamide           | 1 (0.6)         | 0 (0.0)                                     | 1 (1.5)                                       | 0.380   |
| Mycophenolate mofetil      | 2 (1.2)         | 0 (0.0)                                     | 2 (3.1)                                       | 0.143   |
| Tacrolimus                 | 1 (0.6)         | 0 (0.0)                                     | 1 (1.5)                                       | 0.380   |
| Cyclosporine               | 2 (1.2)         | 0 (0.0)                                     | 2 (3.1)                                       | 0.143   |
| Azathioprine               | 10 (5.8)        | 0 (0.0)                                     | 10 (15.4)                                     | < 0.001 |
| Methotrexate               | 3 (1.8)         | 0 (0.0)                                     | 3 (4.6)                                       | 0.053   |
| Hydroxychloroquine         | 44 (25.7)       | 0 (0.0)                                     | 44 (67.7)                                     | < 0.001 |

Values are expressed as median (interquartile range) or n (%)
<sup>a</sup>Mixed lupus nephritis cases were counted for each respective class

### Table 3: Drugs administered during the follow-up

| Variables                  | Total (n = 171) | Patients with early lupus nephritis (n = 106) | Patients with delayed lupus nephritis (n = 65) | p-value |
|----------------------------|-----------------|---------------------------------------------|-----------------------------------------------|---------|
| **Immunosuppressive agents** |                 |                                             |                                               |         |
| Glucocorticoids            | 171 (100.0)     | 106 (100.0)                                 | 65 (100.0)                                    | 0.999   |
| Cumulative glucocorticoid dosage (mg)<sup>a</sup> | 11,315.0 (5195.3–18,697.5) | 10,889.6 (5145.0–17,306.3) | 14,370.0 (5472.5–20,703.8) | 0.181 |
| Cyclophosphamide           | 57 (33.3)       | 42 (39.6)                                   | 15 (23.1)                                     | 0.026   |
| Mycophenolate mofetil      | 133 (77.8)      | 83 (78.3)                                   | 50 (76.9)                                     | 0.834   |
| Tacrolimus                 | 37 (21.6)       | 24 (22.6)                                   | 13 (20.0)                                     | 0.685   |
| Cyclosporine               | 8 (4.7)         | 6 (5.7)                                     | 2 (3.1)                                       | 0.711   |
| Azathioprine               | 24 (14.0)       | 13 (12.3)                                   | 11 (16.9)                                     | 0.396   |
| Hydroxychloroquine         | 98 (57.3)       | 55 (51.9)                                   | 43 (66.2)                                     | 0.051   |

Values are expressed as median (interquartile range) or n (%)
<sup>a</sup>Cumulative glucocorticoid dosage was calculated in prednisolone equivalent dosage
explained by several reasons. First, because current ACR guidelines recommend kidney biopsy for patients with SLE to assess the possibility of lupus nephritis when proteinuria exceeds 1 g [4], the timely intervention to diagnose lupus nephritis and manage inflammation might have hampered the development of irreversible organ damage and in affecting patient mortality. Thus, our findings further emphasize that strict adherence to the current practice guidelines is essential for the proper management of SLE. Second, only a few patients with delayed lupus nephritis were previously treated with cyclophosphamide and mycophenolate mofetil, which is the most commonly used immunosuppressive agent to induce remission in lupus nephritis [15]. Therefore, while almost every patient with delayed lupus nephritis were on immunosuppression, the prior treatment might not have been sufficient to prevent the development of lupus nephritis and influence the treatment response of management.

**Table 4** Univariate and multivariate Cox-proportional hazard analysis of variables associated with end-stage renal disease

| Variable                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | Odds ratio (95% CI) | p-value               | Odds ratio (95% CI) | p-value               |
| Age, years                | 1.046 (1.007–1.086) | 0.021                 |                      |                      |
| Female sex                | 1.648 (0.215–12.638) | 0.631                 |                      |                      |
| SLEDAI-2 K                | 0.915 (0.791–1.057) | 0.227                 |                      |                      |
| Complement 3, mg/dL       | 0.989 (0.967–1.011) | 0.327                 |                      |                      |
| Complement 4, mg/dL       | 0.971 (0.897–1.051) | 0.470                 |                      |                      |
| Anti-dsDNA (IU/mL)        | 0.998 (0.995–1.001) | 0.183                 |                      |                      |
| Spot urine P/Cr ratio     | 1.001 (0.863–1.159) | 0.995                 |                      |                      |
| WBC count (×1000/μL)      | 1.000 (0.999–1.000) | 0.900                 |                      |                      |
| Platelet count (×1000/μL) | 0.995 (0.989–1.002) | 0.139                 |                      |                      |
| Hemoglobin (g/dL)         | 0.601 (0.455–0.795) | < 0.001               |                      |                      |
| Lymphocyte count (µ/L)    | 0.999 (0.998–1.000) | 0.099                 |                      |                      |
| ESR (mm/hr)               | 1.006 (0.990–1.022) | 0.493                 |                      |                      |
| CRP (mg/L)                | 1.015 (1.002–1.028) | 0.028                 | 1.021 (1.006–1.037)  | 0.007                 |
| Cr (mg/dL)                | 2.445 (1.801–3.317) | < 0.001               | 2.233 (1.539–3.239)  | < 0.001               |
| Albumin (g/dL)            | 0.620 (0.306–1.259) | 0.186                 |                      |                      |
| Activity index            | 1.058 (0.959–1.167) | 0.261                 |                      |                      |
| Chronicity index          | 1.581 (1.199–2.083) | 0.001                 | 1.475 (1.042–2.090)  | 0.029                 |
| Early lupus nephritis     | 0.830 (0.295–2.337) | 0.725                 |                      |                      |
| Delayed lupus nephritis   | 1.204 (0.428–3.388) | 0.725                 |                      |                      |

SLEDAI-2 K: systemic lupus erythematosus disease activity index-2000, P/Cr: protein/creatinine, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Cr: creatinine
induction and maintenance therapies. Conversely, although patients with early lupus nephritis exhibited higher disease activity, and thus, were more likely to be treated with cyclophosphamide, the application of aggressive treatment with cyclophosphamide might have resulted in similar clinical outcomes in early and delayed lupus nephritis.

Notably, a recent publication by Ugolini-Lopes and colleagues have evaluated the clinical outcomes in patients with early-onset and late-onset lupus nephritis and found a similar prognosis in both groups [10]. In their study, early-onset lupus nephritis was defined as lupus nephritis occurring in the first 5 years of SLE diagnosis and late-onset lupus nephritis as that occurring after 5 years of disease diagnosis. Similar findings were also found regarding the clinical outcomes in this study, and the renal and overall survival rate of early and delayed lupus nephritis was not significantly different in Kaplan-Meier curve analysis. Although different definitions were adopted for early and delayed lupus nephritis, the present study has several advantages compared to the study by Ugolini-Lopes et al. in terms of a larger number of patients with Asian ethnicity, evaluated factors associated with ESRD and all-cause mortality and detailed data regarding immunosuppressive agents used before and after the diagnosis of lupus nephritis.

Even though the advances of lupus nephritis treatment have led to a lower occurrence of ESRD in the recent decades [16], ESRD still remains to be one of the most morbid condition in lupus nephritis [17]. In multivariate Cox-proportional hazard analysis, higher creatinine and CRP levels along with higher chronicity index at baseline were found to be predictive factors for ESRD. Consistently, poor renal function at initial presentation and higher chronicity index were shown to be predictors of ESRD progression in patients with lupus nephritis [18].

An interesting finding of this study was that even though patients with delayed lupus nephritis had a greater proportion of patients with higher chronicity index, the renal outcome was not significantly different compared to those of patients with early lupus nephritis. This could be related to the fact that the difference in the

| Table 5 | Univariate and multivariate Cox-proportional hazard analysis of variables associated with all-cause mortality |
|---------|----------------------------------------------------------------------------------------------------------|
|         | Univariate analysis | Multivariate analysis |
|         | Odds ratio 95% CI    | p-value | Odds ratio 95% CI    | p-value |
| Age, years | 1.066 1.019–1.115 | 0.006 | 1.065 1.018–1.114 | 0.006 |
| Female sex | 1.117 1.014–1.851 | 0.017 | 0.927 0.782–1.099 | 0.382 |
| SLEDAI-2 K | 0.990 0.963–1.017 | 0.443 | 0.924 0.814–1.048 | 0.220 |
| Complement 3, mg/dL | 0.998 0.995–1.002 | 0.314 | 0.998 0.995–1.002 | 0.314 |
| Complement 4, mg/dL | 0.682 0.458–1.017 | 0.060 | 1.000 0.999–1.000 | 0.445 |
| Anti-dsDNA (IU/mL) | 1.000 0.999–1.000 | 0.445 | 1.000 0.993–1.007 | 0.996 |
| Spot urine P/Cr ratio | 0.653 0.467–0.913 | 0.013 | 0.656 0.448–0.959 | 0.030 |
| WBC count (μL) | 0.999 0.998–1.001 | 0.361 | 1.010 0.991–1.029 | 0.323 |
| Platelet count (×1000/μL) | 1.479 0.889–2.461 | 0.132 | 1.017 1.001–1.033 | 0.034 |
| Hemoglobin (g/dL) | 0.927 0.399–2.152 | 0.860 | 0.927 0.399–2.152 | 0.860 |
| Lymphocyte count (μL) | 1.004 0.892–1.129 | 0.954 | 1.004 0.892–1.129 | 0.954 |
| ESR (mm/hr) | 1.233 0.861–1.766 | 0.252 | 1.233 0.861–1.766 | 0.252 |
| Chronicity index | 0.671 0.194–2.319 | 0.529 | 0.671 0.194–2.319 | 0.529 |
| Early lupus nephritis | 1.490 0.431–5.148 | 0.529 | 1.490 0.431–5.148 | 0.529 |
| Hypertension | 2.965 0.834–10.539 | 0.093 | 2.965 0.834–10.539 | 0.093 |
| Diabetes mellitus* | 1.000 n/a | 0.653 0.467–0.913 | 0.013 | 1.000 n/a | 0.656 0.448–0.959 | 0.030 |
| Dyslipidemia* | 1.000 n/a | 0.653 0.467–0.913 | 0.013 | 1.000 n/a | 0.656 0.448–0.959 | 0.030 |

SLEDAI-2 K systemic lupus erythematosus disease activity index-2000, P/Cr protein/creatinine, WBC white blood cell, ESR erythrocyte sedimentation rate, CRP C-reactive protein, Cr creatinine, n/a not applicable

*The odds ratio was not calculable because no death occurred in patients with diabetes mellitus and dyslipidaemia
chronicity index between the groups was not large enough to reach statistical significance. Therefore, this finding should be verified in future studies.

It has been reported that lupus nephritis is associated with significantly higher mortality in SLE [19]. When we evaluated factors associated with higher mortality, age was associated with increased risk of mortality, while higher hemoglobin level was associated with lower risk of mortality independently of traditional risk factors, such as of hypertension, diabetes mellitus and dyslipidaemia [20–22]. Old age is closely linked to increased risk of mortality in the general population [23]. However, the association with mortality in lupus nephritis is controversial. A previous study has demonstrated that age was a predictor of death in patients with lupus nephritis [24], while in a recent publication by Teh et al. age was not associated with the risk of mortality [25]. These discrepant results between the studies may be related to the different ethnic groups included and the selection of variables for the analysis. On the other hand, anemia was also reported to be an independent factor related to mortality in patients with chronic inflammatory diseases and malignancies [26–28]. Although the direct association between anemia and higher mortality in lupus nephritis is unclear, it could be indirectly associated with higher inflammation in lupus nephritis based on the fact that hemoglobin level could decrease in association with inflammatory burden or as a consequence of impaired renal function [29, 30]. Overall, it could be suggested that age and hemoglobin level should be taken into account when predicting mortality among patients with lupus nephritis.

The main strengths of the present study were the large number of included patients with Asian ethnicity and pathologically confirmed lupus nephritis for the evaluation of outcomes. However, it also has several inherent limitations. First, patient data and adverse effects of glucocorticoids and immunosuppressive agents were investigated retrospectively by reviewing the medical records. Second, the follow-up period of the included patients was relatively short. Third, we were not able to precisely assess the effect of used immunosuppressive agents on the patient prognosis. Fourth, the application of 1997 revised ACR classification criteria, which possess lower sensitivity as compared to the 2012 SLE International Collaborating Clinics criteria and the 2019 European League Against Rheumatism/ACR criteria, could have resulted in selection or classification bias. Additional investigations are necessary to comparatively assess clinical outcomes of early and delayed lupus nephritis.

Conclusions
In conclusion, the distinct clinical features of early lupus nephritis are higher disease activity and more frequent multiple organ involvement. However, long-term clinical outcomes of early and delayed lupus nephritis appear to be similar. Rigorous adherence to current treatment recommendations is important in providing optimal treatment for patients with lupus nephritis.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12882-020-01915-5.

Additional file 1: Supplementary Table 1. Comparison of adverse effects of glucocorticoids and immunosuppressive agents between patients with early and delayed lupus nephritis.

Abbreviations
ACR: American College of Rheumatology; C: Complement; CI: Confidence interval; CRP: C-reactive protein; DUR: Drug utilization review; ESRD: End-stage renal disease; ISN/RPS: International Society of Nephrology/Renal Pathology Society; OR: Odds ratio; P/Cre: Protein/creatinine; SLE: Systemic lupus erythematosus; SLEDAI-2 K: SLE disease activity index-2000

Acknowledgements
Not applicable.

Authors’ contributions
SSA designed the report and wrote the paper; JY and SMJ participated in data acquisition and interpretation; JJS and YBP drafted and revised the manuscript; SWL designed the concept and approved the final paper. All authors have taken care to ensure the integrity of this work, and the final manuscript has been seen and approved by all authors.

Funding
This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1A1A3B07045950) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (HI14C1324). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Severance Hospital, and the need for written informed consent was waived, as this was a retrospective study (4–2018-1083).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 20 June 2019 Accepted: 28 June 2020
Published online: 07 July 2020

References
1. Rahaman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929–39.
2. Davidson A. What is damaging the kidney in lupus nephritis? Nat Rev Rheumatol. 2016;12(3):143–53.
3. Markowitz GS, D’Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. Kidney Int. 2007;71(6):491–5.
4. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, Karpouzas GA, Merrill JT, Wallace DJ, Yazdany J, et al. American College of
Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64(6):797–808.

5. Norby GE, Mjøen G, Bjornklett R, Vikse BE, Holdaas H, Svarstad E, Aasarod K. Outcome in biopsy-proven lupus nephritis: evaluation of biopsies from the Norwegian kidney biopsy registry. Lupus. 2017;26(8):881–5.

6. Wilhelmus S, Bajema IM, Bertiasis GK, Boumpas DT, Gordon C, Lightstone L, Tser V, Jayne DR. Lupus nephritis management guidelines compared. Nephrol Dial Transplant. 2016;31(6):904–13.

7. Seligman VA, Lund RF, Olson JL, Li H, Criswell LA. Demographic differences in the development of lupus nephritis: a retrospective analysis. Arn J Med. 2002;112(9):726–9.

8. Alexandre AR, Carreira PL, Isenberg DA. Very delayed lupus nephritis: a report of three cases and literature review. Lupus Sci Med. 2018;5(1):e000241.

9. Gordon C, Amissah-Arthur MB, Gayed M, Brown S, Bruce IN, D'Cruz D, 'Empson B, Griffiths B, Jayne D, Khamashta M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 2018;57(1):e1–e45.

10. Ugolini-Lopes MR, Santos LPS, Stagnaro C, Seguro LPC, Mosca M, Bonfa E. Late-onset biopsy-proven lupus nephritis without other associated autoimmune diseases: severity and long-term outcome. Lupus. 2019;28(1):123–8.

11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

12. Kim SK, Choe JY, Lee SS. Self-reported physical activity is associated with lupus nephritis in systemic lupus erythematosus: data from KORean lupus network (KORNET) registry. Yonsei Med J. 2018;59(7):857–64.

13. Gladman DD, D'Cruz D, Furst DE, Glassock R, Hunder GG, Jayne D, Khamashta MA, et al. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288–91.

14. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. Kidney Int. 1994;45(2):544–50.

15. Yu F, Haas M, Glassock R, Zhao MH. Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. Nat Rev Nephrol. 2017;13(8):483–95.

16. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971–2015: A systematic review and Bayesian meta-analysis. Arthritis Rheumatol (Hoboken). 2016;68(6):1432–41.

17. Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther. 2012;14(Suppl 4):S4.

18. Contreras G, Pardo V, Cely C, Borja E, Hurtado A, De La Cuesta C, Iqbal K, Lenz O, Asif A, Nahar N, et al. Factors associated with poor outcomes in patients with lupus nephritis. Lupus. 2005;14(11):890–5.

19. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transpl. 2012;27(8):824–54.

20. Zhou D, Xi B, Zhao M, Wang L, Veenanki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III linked mortality study. Sci Rep. 2018;8(1):9418.

21. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. New Engl J Med. 2011;364(9):829–41.

22. Murray CJ, Feigin VL, Forouzanfar MH, Krishnamurthi R, Lim SS, Louvaris Z, Parag J, Scrimgeour AR, Wang H, White RA, et al. Global, regional, and national burden of disease from stroke, 1990–2010. The Global Burden of Disease Study 2010. Lancet. 2012;380(9858):241–87.

23. Ahn C, Hwang Y, Park SK. Predictors of all-cause mortality among 514,866 participants from the Korean National Health Screening Cohort. PLoS One. 2017;12(9):e0185458.

24. Fauschou M, Dreyer L, Kanstrup IL, Taskinen M, Jacobsen S. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res. 2010;62(6):873–80.

25. Teh CL, Phui VE, Ling GR, Ngu LS, Wan SA, Tan CH. Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience. Clin Kidney J. 2018;11(1):56–61.

26. Dixit M, Plawsky L, Diederich M. Anemia in cancer. Ann Oncol. 2010;21(Suppl 7):v167–72.

27. Madu AJ, Ughazor MO. Anaemia of chronic disease: an in-depth review. Med Princ Pract. 2017;26(1):1–9.

28. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133(1):40–50.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.