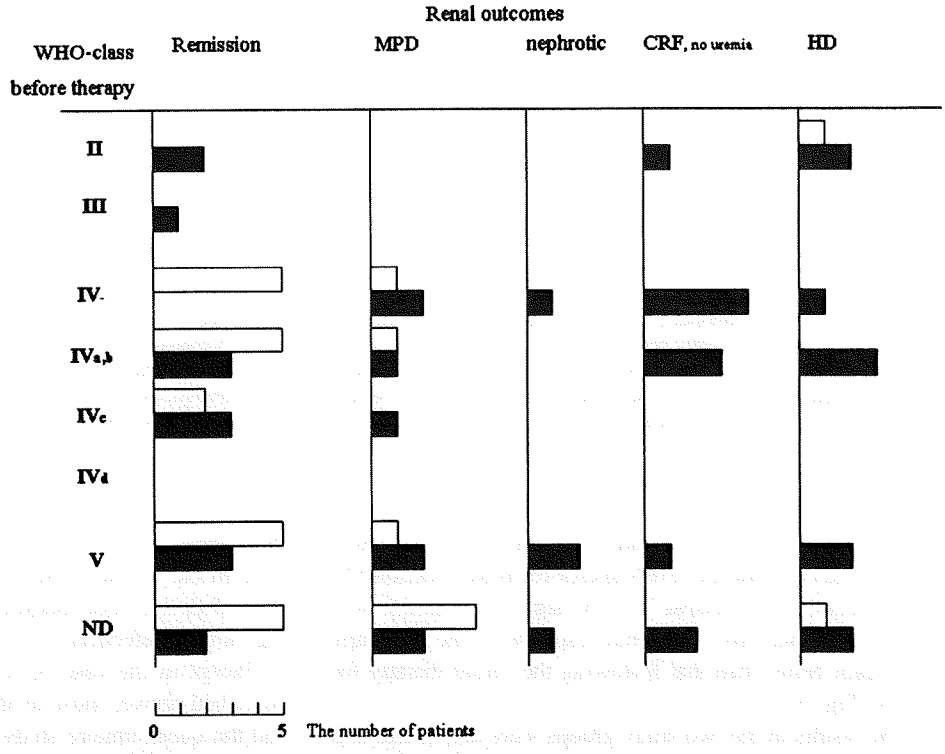


**Fig. 4** Renal outcomes in 31 I-LN patients and 47 D-LN patients in the chart review study in reference to renal pathology at biopsy before initial therapy for LN. Each *bar* denotes the number of patients (*white bar* I-LN, *black bar* D-LN). "IV-" includes diffuse proliferative LN when lacking information regarding activity, necrosis or sclerosis findings. The definition of "V" is given in the text. *ND* not done, *MPD* mild persistent disease, *CRF* chronic renal failure without uremia, *HD* hemodyalysis

*Patients with I-LN* Class IV was common in these patients but rarely associated with the irreversible renal damage at the time of the last observation. Two patients had end-stage renal disease: a patient with RPGN at SLE onset followed by repeated renal relapses, and another patient with class II-LN at SLE onset and suffering from later developed thrombotic thrombocytopenic purpura (TTP) that caused uremia.

*Patients with D-LN* Irreversible renal damage was common in these patients having various renal pathology classes including class IV before initial therapy for the LN. TTP was involved in two patients and directly caused chronic renal failure in at least one of the patients.

*Renal pathology before therapy for relapsed LN (change of the histology)*

The renal pathology at time of the LN relapse was documented in five I-LN patients and nine D-LN patients. These findings are described below in reference to those at first biopsy (in parentheses) and clinical renal outcomes in terms defined in Table 2.

*Patients with I-LN* In four patients, retherapy for relapsed LN of class II (V), IVa (V), IVa (ND) or IVc (V) led to a clinical remission at the last observation. In another patient, LN of class IVc + V (IVa) manifested after self-discontinuation of maintenance therapy, and responded to retherapy and led to mild persistent disease (MPD) that was relapse-free for 16 years by the present time.

*Patients with D-LN* In two patients, each of the retherapies for relapsed LN of class IVc (V) using combined cyclophosphamide improved nephrotic syndrome to MPD. In another three patients, relapsed LN of class IVa (II), IVd (IVb) or IVd (ND) resulted in CRF without uremia despite retherapy. In the remaining four patients, relapsed LN of class IVd (V), IVd (II), IVc (IVa) or Va (V) accompanied by intractable nephrotic syndrome resulted in CRF on hemodialysis despite retherapy.

As described above, class IV with sclerosing lesions was commonly uncovered at the second biopsy in the D-LN patients who resulted in CRF. On the other hand, a transformation of renal histology observed in most of the examined cases of relapsed I-LN showed a small impact on clinical prognosis.

## Discussion

The present chart review study and questionnaire study consistently showed a relatively better prognosis of I-LN patients compared with D-LN patients. Half of the I-LN patients were expected to be relapse-free after the initial therapy (Fig. 2) and most of the relapse-free patients

achieved renal remission throughout the observation period. In the I-LN cases of relapsed LN, most patients responded to retherapy (Fig. 3). Consistent with these findings, more than 70% of the I-LN patients had obtained prolonged renal remission at the last observation (Table 2). In contrast, a poor prognosis of D-LN patients was shown, and irreversible real damage was precipitated in this category of LN. The resulting data (Figs. 2, 3 and Table 2) in the two study groups were surprisingly similar, and strongly suggested the prognostic impact of the difference between the two chronological categories I-LN and D-LN. A pathological transformation towards class IV with sclerosing lesions was found at the second biopsy in most of the examined D-LN cases in the chart review.

Despite a similarity in the patients' demographics between the present two study groups (Table 1), there was a large difference in the ratio of D-LN to I-LN patients: 51/34 (1.5) in the chart review and 34/91 (0.37) in the questionnaire study ($P < 0.00001$). The chart review study in our hospital included all of the deceased patients and numerous numbers of referral patients because of intractable disease, and thus patients with severe forms of SLE may be overrepresented in the chart review study. The result of the higher D-LN/I-LN ratio in the chart review than that in the questionnaire study may be consistent with the putative poorer prognosis of D-LN compared with I-LN.

The present study suggested that D-LN tended to progress in renal damage despite steroid therapy, in contrast to the good therapeutic response of I-LN even having renal pathology class IV. Cyclophosphamide, which has been included recently in a standard regimen for treating LN in our hospital, had not been widely used for the cases in the present study that included only therapies occurring more than 5 years ago. Therapy using steroid and combined cyclophosphamide may improve the prognosis of D-LN patients, and the efficacy of therapy for I-LN and that for D-LN should be estimated separately because of a probable difference in therapeutic response between the two LN categories.

## Conclusions

The time of the initial appearance of renal symptoms in the course of SLE may have a prognostic impact on lupus nephritis.

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## References

1. Chan TM, Li FK, Tang CSOT, Wong RWS, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N Engl J Med. 2000;343:1156–62.
2. Mok CC, Ying KY, Tang S, Leung Y, Lee KW, Ng WL, et al. Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. Arthritis Rheum. 2004;50:2559–68.
3. D'Agati VD, Appael GB. Lipus nephritis: pathology and pathogenesis. In: Wallace DJ, Hahn BH, editors. Dubois' lupus erythematosus. 7th ed. Philadelphia: Lippincott Wiliams & Wikins; 2007. p. 1094–111.
4. Huong DLT, Papo T, Beaufils H, Wechsler B, Bletry O, Baumelou A, et al. Renal involvement in systemic lupus erythematosus. A study of 180 patients from a single center. Medicine. 1999;78:148–66.
5. Austin Ha III, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe histologic nephritis: contributions of clinical and histologic data. Kidney Int. 1994;45:544–50.
6. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15:241–50.
7. Yokoyama H, Wada T, Hara A, Yamahara J, Nakaya I, Kobayashi M, et al. The outcome and a new ISN/RPS 2003 classification of lupus nephritis in Japanese. Kidney Int. 2004;66:2382–8.
8. Schwartz MM, Lan SP, Bernstein J, Hill GS, Holley K, Lewis EJ. Role of pathology indices in the management of severe lupus glomerulonephritis. Lupus nephritis collaborative study group. Kidney Int. 1992;42:743–8.
9. Hill GS, Delahousse M, Nochy D, Balow JE. Predictive power of the second renal biopsy in lupus nephritis: significance of macrophage. Kidney Int. 2001;59:304–16.
10. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–7.
11. Cervera R, Khamashta MA, Font J, Sbastiani GD, Gil A, Lavilla P, 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. 2003;82:299–307.
12. Illei GG, Takada K, Parkin D, Austin HA, Crane M, Yarboro CH, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy. Arthritis Rheum. 2002;46:995–1002.