Comorbidities and poor long-term outcomes of lupus nephritis in adult patients in the United States

Isabelle Ayoub,[1] Janice Ma,[2] Konrad Pisarczyk,[2] Richard Leff,[3] Eunmi Park,[3] Li Long[3]

[1]The Ohio State University Wexner Medical Center, Columbus, OH, USA [2]Maple Health Group LLC, New York, New York, USA [3]Kezar Life Sciences, Inc. South San Francisco, California, USA

Background

- Lupus nephritis (LN) is a serious and common complication of systemic lupus erythematosus (SLE) associated with considerable morbidities, including an increased risk of end-stage kidney disease (ESKD).
- For patients with refractory LN, disease outcomes tend to be worse compared to those without refractory disease.[1,2]
- The objective of this literature review was to qualitatively summarize the reported literature on the long-term disease outcomes and comorbidities of LN in adult SLE patients in the United States (US).

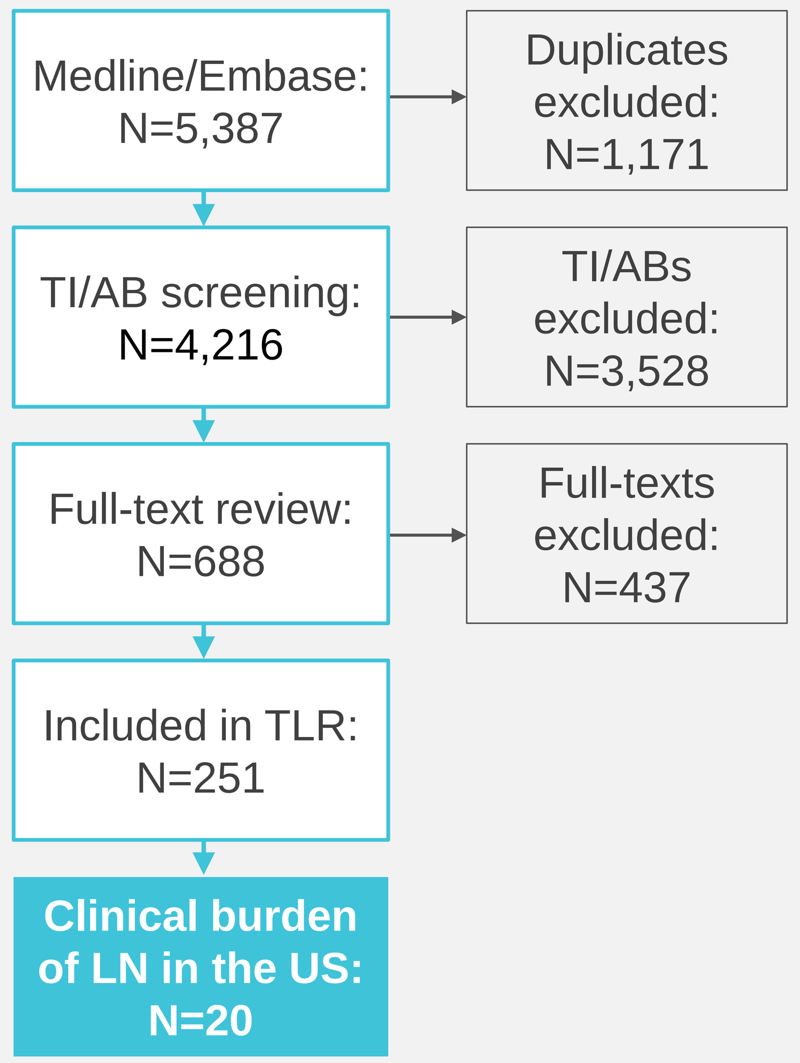
Methods

- A targeted literature review (TLR) was conducted in MEDLINE/Pubmed and Embase to identify studies in adult patients with diagnosed LN.
- A search strategy was developed separately for the two databases to identify relevant peer-reviewed articles published in English between March 2012 and March 2022, and conference abstracts indexed in Embase since 2019.
- All records were screened by a single reviewer according to pre-specified inclusion and exclusion criteria.

Results

- Of 4,216 records identified in the medical databases, 20 non-interventional studies[3-22] reported on the long-term outcomes and burden of comorbidities associated with LN in the US (**Figure 1**).
- The majority of studies were retrospective analyses of longitudinal cohorts or large, nationwide claims and medical databases.

Figure 1. PRISMA diagram



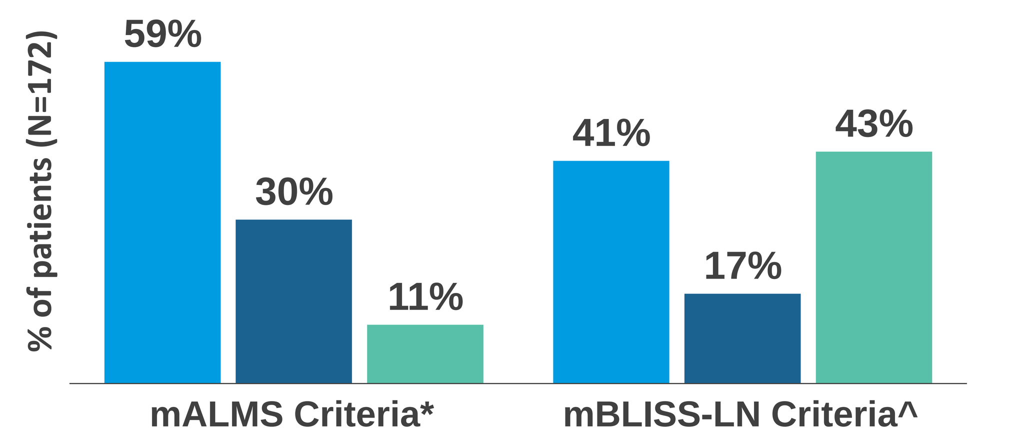
Results (cont'd)

RENAL RESPONSE AND LONG-TERM OUTCOMES OF DISEASE

- At 1 year of follow-up from starting therapy, only 26% of adult patients with LN achieved complete response, defined as reduction in urine protein creatinine ratio (UPCR) to <0.5, normal serum creatinine (sCr) ≤125% of baseline, and <10 mg/day prednisone at time of response assessment.[3,4]
- At 2 years of follow-up, 41 – 59% of adults with LN achieved complete renal remission, defined as return to normal sCr and urine protein ≤0.5 g/day or normal estimated creatinine clearance and UPCR <0.5 (**Figure 2**).[5]
- Patients who did not achieve renal response (CR or PR) at 2 years from starting therapy were more likely to develop ESKD or die compared to those who did achieve renal response according to both mALMS (p=0.004) and mBLISS-LN (p=0.01) response criteria (**Figure 2**).[5]

Figure 2. Only ~50% of adult patients with LN achieved renal remission, and those who did were less likely to die or develop ESKD compared to those who did not achieve remission

RR at 2 years from starting therapy[5]



Risk of 2-year mortality or ESKD after achieving RR at 2 years from starting therapy[5] (HR [95% CI])

mALMS Criteria*	0.23 (0.06, 0.83) *p=0.025*	0.58 (0.17, 1.94) *p=0.373*
mBLISS-LN Criteria^	0.25 (0.08, 0.79) *p=0.018*	0.14 (0.02, 1.09) *p=0.059*

Complete Remission | Partial Remission | No Remission

*mALMS criteria: CR defined as return to normal sCr and urine protein ≤0.5 g/day; PR defined as either a return to normal sCR or urine protein ≤ 0.5 g/day
^mBLISS-LN: CR defined as normal estimated creatinine clearance and UPCR <0.5; PR defined as occurrence of creatinine clearance of ≤10% below the baseline value or within normal range and ≥50% decrease in UPCR to <1.0 (if the baseline ratio were ≤3.0) or <3.0 (if the baseline ratio were >0.3)

COMORBIDITIES

- Adults with LN frequently suffer from hypertension (35 – 78%),[6,7] cachexia (62%),[8] serious infections requiring hospitalization (26%),[9] and mental health disorders (29%).[10]
- Patients with LN were more likely to: experience cardiovascular disease (CVD),[7,11] fractures,[12] and hospitalization due to posterior reversible encephalopathy syndrome (PRES) compared to adults with or without SLE (**Figure 3**).[13]

Figure 3. Patients with LN are more likely to experience multiple comorbidities compared to patients with or without SLE

Comorbidities in LN vs. SLE-only or matched controls without SLE (%)

	LN	SLE-only / Demographically matched non-SLE controls	
CVD[7]	9.9%	4.5%	*p<0.001*
Hypertension[7]	35.2%	18.7%	*p<0.001*
Osteoporosis[7]	9.8%	2.5%	*p<0.001*
Coronary artery disease[11]	15.9%	6.5%	*p = NR*
Cerebrovascular disease[11]	10.5%	4.9%	*p = NR*

LN | SLE-only | Demographically matched non-SLE controls

Comparative risks in LN

Fractures in LN vs SLE-only[12] (HR, 95% CI)	1.58 (1.20, 2.07) *p<0.01*
PRES hospitalization in LN vs SLE-only and other rheumatic diseases* with PRES hospitalizations[13] (OR, 95% CI)	7.53 (4.07, 13.92) *p<0.0001*

*Other rheumatic diseases include ANCA-associated vasculitis, PsA, and systemic sclerosis

Results (cont'd)

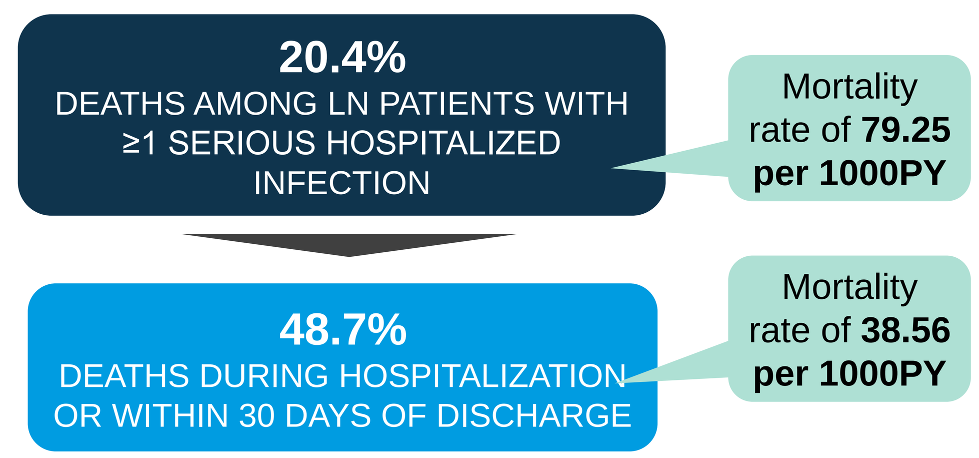
MORTALITY

- In an analysis of Medicaid data, deaths occurred in 20% of patients with LN with serious infections requiring hospitalization, with nearly 50% of deaths occurring during hospitalization or up to 30 days after discharge (**Figure 4**).[9]
- In two analyses of USRDS data, 40% of patients with LN who developed ESKD died during follow-up,[6] and up to 42% of deaths were related to CVD and 14% related to infections (**Figure 4**).[14]

Figure 4. Serious infections are a key cause of death in adults with LN and CVD-related events are a key cause of death in those who developed ESKD

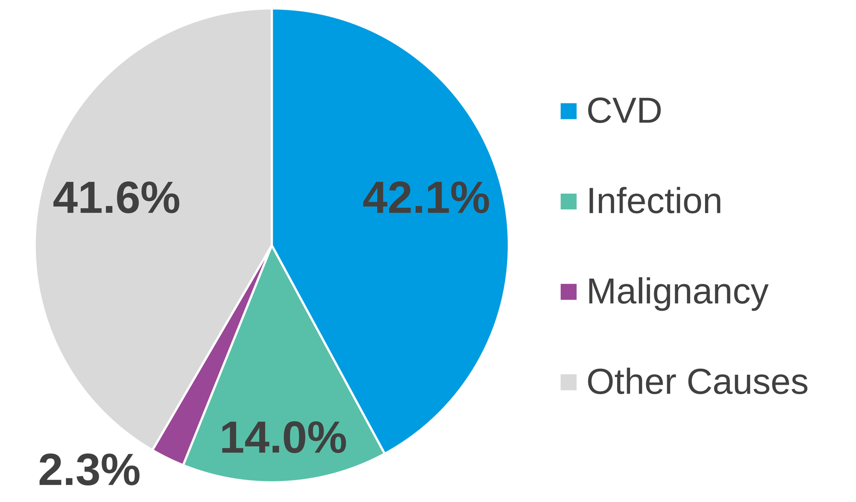
Increased mortality due to serious infections requiring hospitalization[9]

BASED ON A MEDICAID CLAIMS ANALYSIS (2000 – 2006)



Mortality in patients with LN who developed ESKD[14]

BASED ON A USRDS ANALYSIS (1996 – 2011)



Conclusions

- **Uncontrolled LN is associated with poor long-term outcomes, such as ESKD or death, and increased risk of comorbidities such as CVD or infections, compared to SLE alone or non-SLE controls.**
- **Only about half of adult patients with LN achieve complete renal response with existing therapies and may still be hospitalized or die due to CVDs and infections.**
- **Thus, there is a high unmet need for new therapies that can improve disease management and long-term disease outcomes in LN.**

References

1. Yo JH, et al. Open Access Rheumatol. 2019;11:179-188. **2.** Kronbichler A, et al. Autoimmun Rev. 2019;18(5):510-518. **3.** Carlucci P, et al. Arthritis Rheumatol.2020;72(SUPPL 10):3070-3072. **4.** Fava A. et al., Arthritis Rheumatol.2020;72(SUPPL 10):495-497. **5.** Davidson JE, et al., J Rheumatol.2018;45(5):671-677. **6.** O'Shaughnessy M, et al. Transplantation.2017;101(10):2636-2647. **7.** Furst DE, et al., J Med Econ.2013;16(4):500-509. **8.** Stojan G, et al., Arthritis Care Res.2021;73(11):1577-1582. **9.** Feldman CH, et al., Arthritis Rheumatol.2015;67(6):1577-1585. **10.** Petri MA, et al., Ann Rheum Dis.2021;80(SUPPL 1):377-378. **11.** Starzyk K, et al., Value Health.2020;23:S376. **12.** Tedeschi SK, et al., Arthritis Rheumatol.2019;71(7):1141-1146. **13.** Manadan A, et al., J Clin Rheumatol.2021;27(8):e391-e394. **14.** O'Shaughnessy MM, et al., Clin J Am Soc Nephrol.2015;10(7):1170-8. **15.** Gupta S, et al., Arthritis Rheumatol.2021;73(SUPPL 9):1207-1209. **16.** Cintron D, et al., Arthritis Rheumatol.2021;73(SUPPL 9):3399-3400. **17.** Katz P, et al. Qual Life Res.2020;29(12):3251-3261. **18.** Katz P, et al., J Manag Care Spec Pharm.2020;26(3):275-283A. **19.** Rogers JL, et al., Lupus Sci Med.2019;6:A84-A86. **20.** Ilori TO, et al., PLoS ONE.2016;11(6). **21.** Plantinga LC, et al., BMC Nephrology.2015;16(1). **22.** Plantinga LC, et al., Arthritis Rheumatol.2015;67(3):761-772.

Author Disclosures and Acknowledgements

I. Ayoub: Aurinia Pharmaceuticals (advisory fees); **J. Ma**: None; **K. Pisarczyk**: None; **R. Leff**: Kezar Life Sciences, Inc.; **E. Park**: Kezar Life Sciences, Inc.; **L. Long**: Kezar Life Sciences, Inc.

Correspondence to: Eunmi Park, Medical Affairs, Kezar Life Sciences, epark@kezarbio.com

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; CR, complete remission; CVD, cardiovascular disease; ESKD, end-stage kidney disease; HR, hazard ratio; LN, lupus nephritis; NR, not reported; OR, odds ratio; PRES, posterior reversible encephalopathy syndrome; PsA, psoriatic arthritis; RR, renal response; sCr, serum creatinine; SLE, systemic lupus erythematosus; TI/AB, title and abstract; TLR, targeted literature review; UPCR, urine protein creatinine ratio; US, United States of America; USRDS, United States Renal Data System.

Presented at American Society of Nephrology Kidney Week 2022, November 3-6, 2022