chart form also allowed us to alter the default therapy fluid rates depending on the projected number of days of supply when clinically safe to do so.

CONCLUSION

The unprecedented surge of nephrology inpatients during the COVID-19 pandemic in New York City required us to develop novel census- and supply-tracking and forecasting tools. These tools allowed us to stay informed about the availability of resources and our supply chain to ensure that patients in need of RRT had access to this form of life support. Our tools allowed for an organized, data-driven divisional response and facilitated the planning necessary for rapid reorganization of nephrology services within our institution. While these tools still rely on manual entry rather than an automatic feed from an electronic health record, it required minimal entry time for any given provider as each service was responsible for updating the census for their own service. These tools are complex enough to deal with the challenges of a large program such as ours, but they are also easily adaptable for smaller nephrology programs and we have made these tools available for general use given their adaptability and potential to benefit consultative services at other institutions.

These tools are be available through Academic Commons at Columbia University: Census Tracking Tracker and Dashboard, https://doi.org/10.7916/d8-kja6-k736; CRRT Sharing Protocol Tracker and Dashboard, https://doi.org/10.7916/d8-8619-gn42.

DISCLOSURE

All the authors declared no competing interests.

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Creatinine Fluctuation in Patients With Lupus Nephritis: Considerations for Clinical Trial Endpoints

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Lupus nephritis (LN) is a common manifestation of systemic lupus erythematosus (SLE) and a major driver of morbidity and mortality. Proliferative forms of LN are typically managed with immunosuppressive therapy, with the aim of attenuating renal inflammation and preserving kidney function.[1] Unfortunately, despite several clinical trials of LN conducted over the past 30 to 40 years, none has translated into new Food and Drug Administration (FDA)–approved therapies. Multiple issues in clinical trial design likely contributed to these negative outcomes, such as confounding background medications (especially high-dose glucocorticoids), trial duration, and the choice of trial endpoints. Most trials incorporated composite endpoints to define clinical response based on proteinuria and kidney function. Kidney function was generally assessed as a change in estimated glomerular filtration rate or serum creatinine (sCr) as compared to the patients' values at trial entry.[2] Thresholds were then chosen to define the extent of the clinical response (complete, partial, or no response). However, evidence supporting these thresholds is not robust. For example, most studies used a proteinuria cutoff of <0.3 to 0.5 g/d to describe complete response; however, a *post hoc* analysis of 2 large LN trials demonstrated that proteinuria levels of <0.7 to 0.8 g/d after 1 year of treatment predicted favorable long-term kidney outcomes, suggesting that a less stringent proteinuria cutoff may be reasonable. Similarly, an sCr value <15% above baseline has often been required for complete response in LN trials.[S1–S5] However, day-to-day variations in sCr measurements are routinely observed in clinical practice in patients with and without chronic kidney disease, even when measured within a 24-hour period.[3] To determine a threshold of kidney function that accounts for expected day-to-day variations, we investigated the fluctuation of sCr in a cohort of patients with LN who were complete renal responders.

Individual data from 574 patients participating in 3 clinical trials and several real-world observational cohorts were reviewed.[2] After excluding 283 patients because they did not have at least 3 sCr measurements after having achieved a complete renal response (defined as proteinuria ≤0.5 g/d), data from 291 patients were analyzed. Patients were classified as upward fluctuators and nonfluctuators based on having at least 1 sCr measurement >115% of baseline or no sCr measurement >115% of baseline, respectively (Table 1). There were no differences between the 2 groups based on race/ethnicity, sex, biopsy histopathologic class, proteinuria levels, or induction immunosuppressive regimen. The upward fluctuators had a lower baseline creatinine (0.70 vs. 0.86, $P < 0.0001$) and were younger (28.5 vs. 33, $P = 0.006$) than the nonfluctuators. The median number of sCr measurements per patient was slightly higher in the upward fluctuator group (8 vs. 7, $P = 0.02$), and the upward fluctuators had a numerically longer follow-up (Table 2). In the fluctuator group, 33%, 20%, and 12% of each patient's sCr measurements were 15%, 20%, and 25% above their baseline sCr, respectively (Table 3).

Table 1. Patient and disease characteristics

Characteristic	Upward fluctuator	Nonfluctuator	*P* value
Total	84 (28.9)	207 (71.1)	
Ethnicity			0.19
Caucasian	44 (52.4)	104 (50.2)	
Asian	21 (25.0)	71 (34.3)	
African descent	9 (10.7)	20 (9.7)	
Other	10 (11.9)	12 (5.8)	
Sex			0.14
Female	79 (94.0)	181 (87.4)	
Male	5 (6.0)	26 (12.6)	
Age	28.5 (22–37)	33 (25–41)	**0.01**
Lupus nephritis class			0.79
Proliferative	61 (76.3)	160 (79.6)	
Pure membranous	10 (12.5)	22 (10.9)	
Mixed	9 (11.3)	19 (9.5)	
Baseline C	0.7 (0.6–0.8)	0.86 (0.8–1.01)	**<0.001**
Baseline proteinuria	0.3 (0.18–0.40)	0.3 (0.17–0.4)	0.37
Induction regimen[a]			0.42
AZA	2 (2.9)	3 (1.9)	
MMF	32 (47.1)	62 (39.0)	
CYC	34 (50.0)	94 (59.1)	

AZA, azathioprine; Cr, creatinine; CYC, cyclophosphamide; MMF, mycophenolate mofetil.
Data are n (%) or median (interquartile range).
By convention, P values that are less than 0.05 are considered statistically significant and bolded.
[a]MAINTAIN Nephritis Trial (Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis) data not included.

Table 2. Sample breakdown in each group

Measurement characteristics	Upward fluctuator	Nonfluctuator	*P* value
Total no. of sCr measurements	741	1598	
No. of sCr measurements per patient, median (IQR)	8 (5–11.25)	7 (4.5–10)	**0.022**
Mo of response, median (IQR)	29.75 (18.5–37.5)	24.1 (16.5–36)	0.054

IQR, interquartile range; sCr, serum creatinine.
By convention, *P* value that is less than 0.05 is considered statistically significant and is bolded.

Table 3. Serum creatinine fluctuates widely in the upward fluctuator group

sCr Measurement characteristics	Total, n	Per patient, median (IQR)	% of Patient's no. of follow-up samples, median (IQR)
Total no. of sCr measurements	741	8 (5–11.25)	—
sCr measurements >115% of baseline	224	2 (1–4)	33.3% (17.8–50.0)
sCr measurements >120% of baseline	142	1 (1–2)	20.0% (10.8–33.3)
sCr measurements >125% of baseline	109	1 (0–2)	11.8% (0.0–27.0)

IQR, interquartile range; sCr, serum creatinine.

The variables age, follow-up time, sex, number of sCr measurements, and baseline sCr were evaluated in a multivariable logistic regression model. Future fluctuation of sCr was significantly associated with the number of sCr measurements made (odds ratio, 1.09; 95% confidence interval, 1.01–1.16 for each additional measurement), and a lower baseline sCr (odds ratio, 0.02; 95% confidence interval, 0.00–0.05 for each 1-mg/dl increase in baseline sCr).

To assess whether upward fluctuators developed a persistent change in sCr over time, suggestive of a progressive decline or improvement in kidney function, each individual's serial sCr values were plotted and analyzed with simple linear regression (Figure 1) and analyzed with simple linear regression. Only 7 of the 84 upward fluctuators had a positive β with an unadjusted P value < 0.05, suggesting that the vast majority of patients did not have a progressive increase or decrease in serum creatinine. The median β of those 7 patients was 0.087 (interquartile range, 0.06–0.13), translating into an increase in serum creatinine of 0.087 mg/dl for every year of follow-up.

A complete renal response is often the endpoint in clinical trials of new therapeutics for LN. Although there is no consensus as to what constitutes a complete renal response, based on recent trials, patients whose final sCr is 10% to 30% higher than their baseline sCr are not considered complete responders.[2] Using a large cohort of prospectively followed LN patients who achieved and maintained a complete clinical renal response, we found considerable variability in sCr over time. About 30% of patients had episodic increases in sCr of ≥15% without clinical consequences, and over 10% of patients had episodic increases in SCr of more than 25%. These natural and clinically inconsequential fluctuations of sCr could result in patients being labeled as partial responders or nonresponders, potentially affecting the outcome of a trial. This is especially important, because many trials measure sCr only once at the conclusion of the trial.

The likelihood of having sCr fluctuations ≥15% increased in patients with low baseline sCr values. This is an important issue in LN, in which most patients are young women who often have low sCr levels normally. In such patients, small changes in sCr translate into higher percent changes and could be misinterpreted as a decline in kidney function.

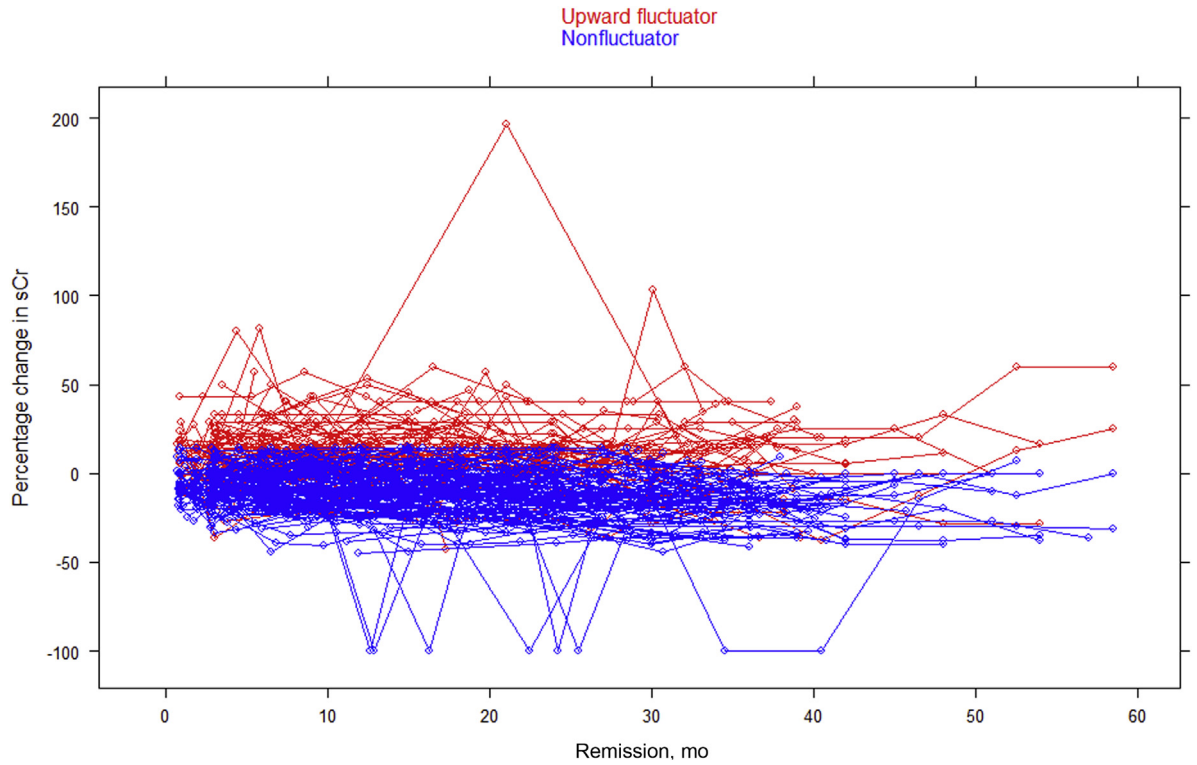

Figure 1. Percentage change in creatinine over time. sCr, serum creatinine.

Intraindividual variability of sCr in healthy patients can be due to biological variability and technical variability of the assay used to measure sCr. In healthy individuals, the biological variability of sCr is about 4.5%.[4,5] Biological variability may be higher in a kidney that has suffered prior injury, such as flares of LN. The analytic variability of the Jaffe method, a commonly used technique for measuring sCr, is 5.5%.[4] Between biological and analytical variability, the smallest change between 2 sCr measurements in an individual that warrants clinical concern is 19%.[6] Commonly used medications, such sulfamethoxazole/trimethoprim, angiotensin-converting enzyme inhibitors, and angiotensin blockers, can also cause fluctuations in sCr. We cannot exclude that a change in medications affected the measurements seen in our patients.

In summary, variability in sCr measurements is commonly observed in clinical practice and does not necessarily indicate a decline or improvement in kidney function. In a cohort of lupus patients who have had at least 1 episode of LN, a large proportion of patients who otherwise appear to have achieved a stable complete renal response based on proteinuria criteria have sCr fluctuations of 15% or more, suggesting that a 15% cutoff to define the success of a trial may be overly conservative. To define complete renal response, we recommend that a 25% cutoff for the upper limit of change in sCr might be more appropriate. Furthermore, a single measurement of sCr at the end of a trial cannot be put into an appropriate context, and sCr should be measured on at least 2 occasions.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

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Acute Kidney Injury Following Paracentesis Among Inpatients With Cirrhosis

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