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Spot PC ratio estimates of 24hr proteinuria are more unreliable in lupus nephritis than in other forms of chronic glomerular disease

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Spot urine protein/creatinine ratio (PCR) is often used clinically to estimate 24-hour (24-h) proteinuria. However, urine PCR shows considerable hour to hour variability.^{1,2} In lupus nephritis (LN), spot PCR reveals this variability, while longer timed collections conceal it.^{3–5} Spot PCR performs well in cohort studies, where its variability is mitigated by averaging the data.⁶ However spot PCR variability becomes a liability for individual patient management. This work is the first to compare spot PCR variability in LN and chronic kidney disease (CKD).

For LN, we used the published works (N=3, 165 patients) that documented the completeness (creatinine content) of the 24-h urine collections^{3–5} (LN studies A, B, and C respectively). For CKD, we used a standard CKD cohort (REIN Trial, 98 patients) which documented completeness of the collections.⁶ Almost all spot PCRs were from morning collections.

As shown in the calibration plots (Figure 1), in each cohort most [spot PCR/24-h PCR] values fall outside the limits of agreement with 24-h urine PCR for subnephrotic proteinuria (PCR = 3.00), the most common degree of proteinuria. So, spot PCR is an unreliable estimate of 24-h PCR in both LN and CKD. Also, spot PCR is not a reliable screening test,

as it overestimates and underestimates 24-h PCR with about equal frequency, especially in LN.

The degree of unreliability of spot PCR for subnephrotic proteinuria, as reflected by the coefficient of variation (CV) of [spot PCR/24-h PCR], is significantly greater in each of the LN studies (A, B, and C) compared to the CKD study (Table 1). Spot PCR may also be unreliable in nephrotic range proteinuria, but there were too few measures for adequate statistical testing (Table 1).

The reason for the greater PCR variability in LN than CKD is unclear. However, the cohorts have substantial differences, e.g. CKD is mostly older males with lower eGFR; LN is mainly the opposite. However, neither difference in ACE inhibition/ARB use, serum creatinine level, or completeness of urine collection explain the greater PCR variability in the LN patients compared to the CKD patients (data not shown).

KDOQI⁷⁸ and the ACR⁹¹⁰ recommend spot PCR for patient monitoring. This approach may substantially compromise clinical decision making, especially in LN. For example, a BILAG-A renal flare (increase in proteinuria by 1.0g/d, if baseline proteinuria is <1.0g/d), expressed as PCR change, is about 0.6 in an average size person. Figure 1 shows that a PCR change of 0.6 would not be reliably detected by spot PCR.

Conclusion

Spot PCR testing is substantially inaccurate, particularly in LN. The extent to which spot PCR use compromises clinical management requires further study. To avoid the inaccuracy of spot PCR we recommend PCR of intended 24-h urine collections. Often these are large over or under collections. However, that is “OK” if the collection is 50% of a complete collection based on creatinine content. The PCR of such collections provide a reliable estimate of the PCR of the complete 24-h collection (3–5).

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Figure 1.

Relationship between 24-h PCR and the ratio [Spot PCR/24-h PCR] in CKD and LN patients with subnephrotic proteinuria. The dashed lines indicate the expected limits of agreement ($\pm 15\%$) if spot PCR provided the same result as testing an aliquot of the 24-h collection. The data sources are CKD⁶, LN study A³, B⁴, and C⁵.

Table 1

Analysis of the coefficients of variation (CVs) of the ratio of [Spot PCR/24-h PCR] in the subnephrotic and nephrotic cohorts of CKD and LN studies A, B, and C.

			Median ^a	CV (95% CI) ^b	P-value ^c
CKD	24-h PCR	3 (n=69)	1.690	0.336 (0.383, 0.722)	
	24-h PCR > 3	(n=28)	3.815	0.335 (0.185, 0.456)	
All LN	24-h PCR	3 (n=156)	0.925	0.538 (0.459, 0.621)	<0.001
	24-h PCR > 3	(n=38)	4.610	0.394 (0.270, 0.487)	0.202
LN Study A	24-h PCR	3 (n=60)	1.000	0.527 (0.426, 0.637)	<0.001
	24-h PCR	3 (n=26)	4.540	0.327 (0.194, 0.424)	0.545
LN Study B	24-h PCR	3 (n=62)	1.000	0.502 (0.388, 0.607)	0.001
	24-h PCR > 3	(n=7)	3.460	0.485 (0.223, 0.599)	NC ^d
LN Study C	24-h PCR	3 (n=34)	0.425	0.567 (0.377, 0.714)	0.001
	24-h PCR > 3	(n=5)	5.110	0.468 (0.148, .0724)	NC ^d

^a"Median" is the median 24-h PC ratio.

^b"CV" is the coefficient of variation of the ratio: spot PC/24-h PC. The 95% confidence intervals for the CV are percentile-based confidence bounds from 1000 bootstrapped replications of the CV.

^cBased on a z-test of equality of CV for CKD patients compared to the various LN groups for PCRs or > 3.

^dNC, p-value was not calculated because of small sample size