Kidney Medicine

Correlation Between 24-Hour Urine Protein and Random Urine Protein-Creatinine Ratio in Amyloid Light-Chain Amyloidosis

Lisa Mendelson, Vaishali Sanchorawala, Lawreen Connors, Tracy Joshi, Gheorghe Doros, Alexander Pogrebinsky, and Andrea Havasi

Rationale & Objective: Test the feasibility of replacing 24-hour urine collection with a single voided urinary protein-creatinine ratio (UPCR) in patients with amyloid light-chain (AL) amyloidosis.

Study Design: Retrospective study examining the correlation between a 24-hour urine measurement and UPCR at various proteinuria levels using a linear regression analysis with Pearson's correlation coefficient (r). We assessed how using these 2 different measurements would alter the diagnosis, staging, and kidney response assessment in patients with AL amyloidosis.

Setting & Participants: We included 265 patients with systemic AL amyloidosis who visited the Amyloidosis Center at Boston University between July 2018-January 2020 and had proteinuria measurement by both methods on the same day.

Tests Compared: 24-hour urine collection for protein versus UPCR.

Results: The correlation between 24-hour urine and UPCR was moderate in patients with proteinuria levels of 500-3,000 mg/day and >3,000 mg/day, with r values of 0.57 and 0.62, respectively. Replacing the 24-hour urine collection with UPCR changed kidney staging in 10% of the patients: 77% were reclassified to a worse kidney stage and 23% to a more favorable stage. The majority of changes (85%) in kidney staging occurred in the >3,000 mg/day cohort. There were 35 patients whose kidney response was assessed by concomitant 24-hour urine collection and UPCR with visits at least 6 months apart. Of these patients, 20% had discordance between the 24-hour urine collection and UPCR that changed their definition of organ response.

Limitations: Given the rarity of AL amyloidosis, our sample size is small and from a single referral center.

Conclusions: Although the 24-hour urine collection is cumbersome, we continue to recommend it in patients with AL amyloidosis because replacing the 24-hour urine collection with UPCR would change kidney staging and organ response in 10%-20% of patients. In addition, the correlation between the 2 modalities was moderate at best in patients with nephrotic-range proteinuria.

Visual Abstract included

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Amyloidosis is a disease characterized by insoluble extracellular protein deposition in various organs. In systemic amyloid light-chain (AL) amyloidosis, the underlying amyloidogenic proteins are immunoglobulin light chains that misfold and aggregate, leading to fibril formation, deposition, and organ dysfunction.[1] Kidney involvement affects approximately 80% of AL amyloidosis cases, often presenting with proteinuria and nephrotic syndrome.[2] Proteinuria is a sign of organ damage and reflects what is happening in the kidney at the ultrastructural level. Quantification of proteinuria is imperative for determining kidney involvement and staging at presentation.[3] It is also used in the assessment of organ responses to therapies and the risk of progression to dialysis.[2,3] Currently, 24-hour urine collection is regarded as the gold standard for proteinuria assessment. However, this process is time consuming and cumbersome for patients and laboratories and can be complicated by individual variabilities in collection, leading to under- or overcollection.[4] Recently, there has been a movement towards replacing the 24-hour urine collection with a spot urinary protein-creatinine ratio (UPCR) or urinary albumin-creatinine ratio, to decrease inconvenience to the patients.[5]

In various other kidney diseases, there are a plethora of studies that have demonstrated a relatively strong correlation between 24-hour urine collection and UPCR.[6-8] However, in many forms of kidney diseases a difference of 10%-30% between these modalities would not be considered significant and would not change management.[9] In AL amyloidosis, a difference of this magnitude can affect disease staging at diagnosis and organ response assessment after antiplasma cell therapies. Prior data have suggested the correlation between these 2 measurements decreases with higher levels of proteinuria.[9-11] Two of the previous studies investigated the use of the urinary albumin-creatinine ratio instead of 24-hour urine in patients with AL amyloidosis; however, at some institutions the urinary albumin-creatinine ratio cannot be used to quantify albuminuria >2,000 mg/g—the limit placed by the manufacturer of some assays—and UPCR has to be ordered instead at higher proteinuria levels.[5,6] Given that many patients with AL amyloidosis have a wide range of proteinuria, often in the nephrotic range, this study examined the correlation between 24-hour urine testing and UPCR at various proteinuria levels in patients with AL amyloidosis. We also assessed how using these different

PLAIN-LANGUAGE SUMMARY

In amyloid light-chain amyloidosis, quantification of proteinuria is used for the diagnosis of amyloid deposition, assessment of the severity of the involvement (kidney staging), and organ response to therapies. Our patients often complain that the 24-hour urine collection is cumbersome to do. Our study compares the gold-standard 24-hour urine collection to a less cumbersome but less precise test: a spot urine protein-creatinine measurement. Every patient who visited our center over an 18-month period did both tests. We discovered that the correlation between the 2 tests is only moderate. We conclude that use of the 24-hour urine proteinuria measurement should be continued in the majority of patients with amyloid light-chain amyloidosis.

measurements would alter the staging, prognostication, and kidney response.

METHODS

This retrospective study includes 265 patients with systemic AL amyloidosis who visited the Amyloidosis Center at Boston University Medical Center between July 1, 2018-January 1, 2020. Data collected from the prospectively maintained Amyloidosis Center database, along with electronic medical records, were used. All patients had histologic evidence of AL amyloidosis. The Institutional Review Board of Boston University Medical Center approved the study (H-22838). All patients provided written consent for research under the approval of the Institutional Review Board and in accordance with the Declaration of Helsinki (ClinicalTrials.gov Identifier: NCT00898235). Patients with proteinuria measurements from both 24-hour urine collection and UPCR on the same day were included. Those with localized AL amyloidosis and myeloma-associated AL amyloidosis were excluded from the analysis. Patients with significant Bence Jones proteinuria or end-stage kidney disease were not included in this analysis. Spot urines were collected in the morning but were not necessarily the first void. All patients had their kidney function checked on the same day as the urine tests. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.[1,2] At our institution, urinary protein, microalbuminuria, and urinary creatinine are measured via the Abbott Alinity Analyzer photometric assay. The adequacy of the collection was assessed by 24-hour urine creatinine excretion. Kidney staging was defined as: stage 1, eGFR ≥ 50 ml/min/1.73 m^2 and ≤5 g/24h proteinuria; stage 2, eGFR < 50 ml/min/1.73 m^2 or >5 g/24h proteinuria; and stage 3, eGFR < 50 ml/min/1.73 m^2 and >5 g/24h proteinuria.[3] Kidney response was classified as a ≥30% decrease in proteinuria or proteinuria below 0.5 grams in 24 hours without kidney progression. Kidney progression was defined as a ≥25% decrease in eGFR.[3] Patient groups were divided into 3 cohorts based on their proteinuria measured by 24-hour urine collection (mg/day): <500 mg/day (n = 126), 500-3,000 mg/day (n = 53) and >3,000 mg/day (n = 86).

Data are expressed as numbers, medians with ranges, or median with 25^{th}-75^{th} percentiles. The correlation between 24-hour urine protein measurement and UPCR was investigated using a linear regression analysis with Pearson's correlation coefficient (r).

RESULTS

Correlation Between 24-Hour Urine Collection and UPCR

A total of 265 patients with systemic AL amyloidosis underwent testing with a 24-hour urine output collection and UPCR on the same day. The patient characteristics are summarized in Table 1. The median proteinuria measurement was 598 mg/day (range, 25-22,888 mg/day), with a median serum creatinine measurement of 1.2 mg/dL (range, 0.5-10.1 mg/dL) and a median eGFR of 55.4 mL/min/1.73 m^2 (range, 4.05-125.92 mL/min/1.73 m^2). To assess the correlation at various levels of proteinuria, the patients were divided into 3 cohorts based on their 24-hour urine proteinuria: <500 mg/day, 500-3,000 mg/day, and >3,000 mg/day. In the <500 mg/day cohort (n = 126), the median proteinuria measurement was 87.5 mg (range, 0-475 mg), with a median creatinine measurement of 1.1 mg/dL (range, 0.65-3.42 mg/dL) and a median eGFR of 59.9 ml/min/1.73 m^2 (range, 18.65-113.7 ml/min/1.73 m^2). In the 500-3,000 mg/day cohort (n = 56) the median proteinuria measurement was 1,202 mg/day (range, 515-2,941 mg/dL) with a median creatinine measurement of 1.42 mg/dL (range, 0.71-10.15 mg/dL) and a median eGFR of 50.31 ml/min/1.73 m^2 (range, 4.77-109.4 ml/min/1.73 m^2). The third cohort, which had >3,000 mg/day proteinuria (n = 86), had a median proteinuria measurement of 6,148 mg/day (range, 3,036-22,888 mg/dL) with a median creatinine measurement of 1.34 mg/dL (range, 0.55-9.95 mg/dL) and a median eGFR of 48.55 ml/min/1.73 m^2 (range, 4.05-129.42 ml/min/1.73 m^2). Pearson correlation coefficients estimating the relationships between 24-hour urine collection and UPCR are shown in Fig 1A-C. The correlation was found to be moderate in the 500-3,000 mg/day cohort, with a Pearson correlation coefficient of 0.57 (Fig 1B). A similar result was found in the >3,000 mg/day group (correlation coefficient of 0.62; Fig 1C).

Figure 2 depicts the corresponding 24-hour proteinuria and UPCR numbers in each individual patient. While most of the patients in the <500 mg/day group had no clinically

Table 1. Baseline Patient Characteristics

Characteristic	Overall (n = 265)	<500 mg Proteinuria (n = 126)	500-3,000 mg Proteinuria (n = 53)	>3,000 mg Proteinuria (n = 86)
Male, n (%)	144 (54)	67 (53)	35 (66)	42 (48)
Median age (25^{th}-75^{th} percentile)	66 (58-71)	67 (59-72)	63 (57-69)	65 (58-70)
Median BMI, kg/m^2 (25^{th}-75^{th} percentile)	26.9 (24.2-29.7)	26.9 (23.2-29.3)	26.9 (24.3-30.6)	26.9 (24.2-30.1)
Median creatinine, mg/dl (25^{th}-75^{th} percentile)	1.22 (0.84-1.87)	1.11 (0.84-1.59)	1.42 (0.99-2.65)	1.33 (0.86-2.59)
Median eGFR, ml/min/1.73 m^2 (25^{th}-75^{th} percentile)	55.4 (33.5-82.4)	59.9 (40.2-82.3)	50.3 (23.0-75.0)	48.5 (23.3-87.3)
Median 24-hour proteinuria, mg/d (25^{th}-75^{th} percentile)	598 (95-3,813)	87.5 (0-165)	1,202 (774-1,719)	6,148 (3,844-9,399)
Median UPCR (25^{th}-75^{th} percentile)	0.71 (0.10-4.4)	0.1 (0.09-0.1)	0.9 (0.6-1.8)	7.2 (4.3-10.7)
Kidney stage 1	119 (44.9%)	76 (60.3%)	27 (50.9%)	16 (18.6%)
Kidney stage 2	123 (46.4%)	50 (39.7%)	26 (49.1%)	47 (54.7%)
Kidney stage 3	23 (8.7%)	0	0	23 (26.7%)
Organ involvement				
Heart	103 (38.8%)	56 (44.4%)	21 (39.6%)	26 (30.3%)
Kidney	185 (69.8%)	61 (48.4%)	42 (79.3%)	82 (95.4%)
PN/AN	31 (11.7%)	18 (14.2%)	3 (5.7%)	10 (11.6%)
Liver	12 (4.5%)	7 (5.5%)	2 (3.8%)	3 (3.5%)
GI	31 (11.7%)	23 (18.2%)	11.3 (20.7%)	2 (2.3%)
Pulmonary	7 (2.6%)	5 (3.9%)	1 (1.9%)	1 (1.2%)
Soft tissue	45 (16.9%)	28 (22.2%)	7 (13.2%)	10 (11.6%)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; PN/AN, peripheral neuropathy/autonomic neuropathy; UPCR, urinary protein-creatinine ratio.

meaningful difference between the 2 measurements, the other groups had a number of patients with a significant decrease or increase in the level of proteinuria. In the 500-3,000 mg/day group, 45% of the patients had lower proteinuria levels when measured with UPCR, with a mean decrease of 23% and a median decrease of 19% (range, 0.9%-91%). In this group, 55% of the patients had higher proteinuria, with a mean increase of 93% and median increase of 42% (range, 5%-439%). In the >3,000 mg/day group, 44% of the patients had a lower proteinuria measurement by UPCR (mean, 26%; median, 26%; range, 0.4%-62%) and 56% had a higher measurement (mean, 68%; median, 52%; range, 4%-251%; Fig 2).

Evaluating Kidney Staging in AL Amyloidosis Using UPCR in Lieu of 24-Hour Urine Collection

We tested whether using UPCR in lieu of 24-hour urine collection would affect the staging of kidney amyloidosis, a

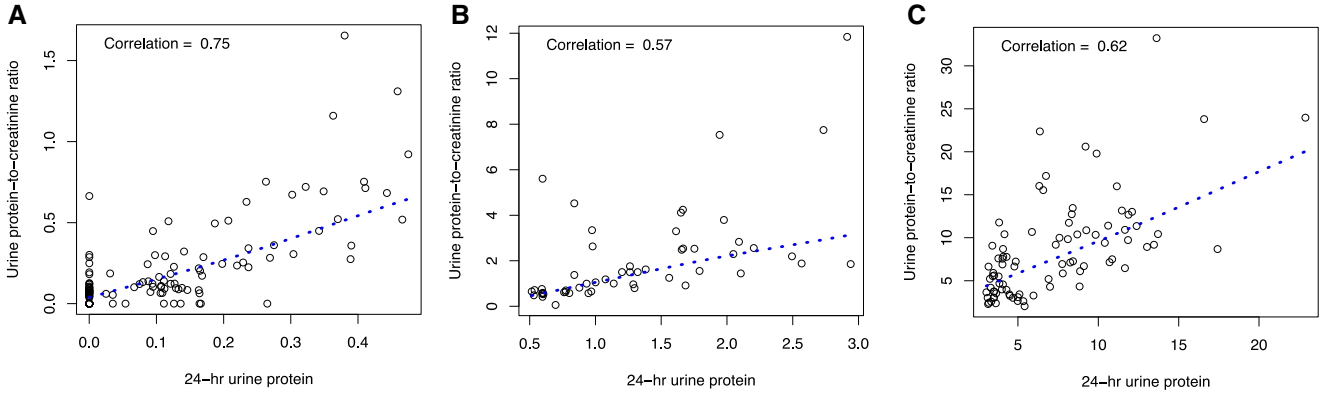

Figure 1. Correlation between 24-hour urine (g/day) and UPCR in patients with (A) <0.5 g/day (n = 126), (B) 0.5-3 g/day (n = 53), (C) >3 g/day (n = 86) of proteinuria (correlation: Pearson coefficient).

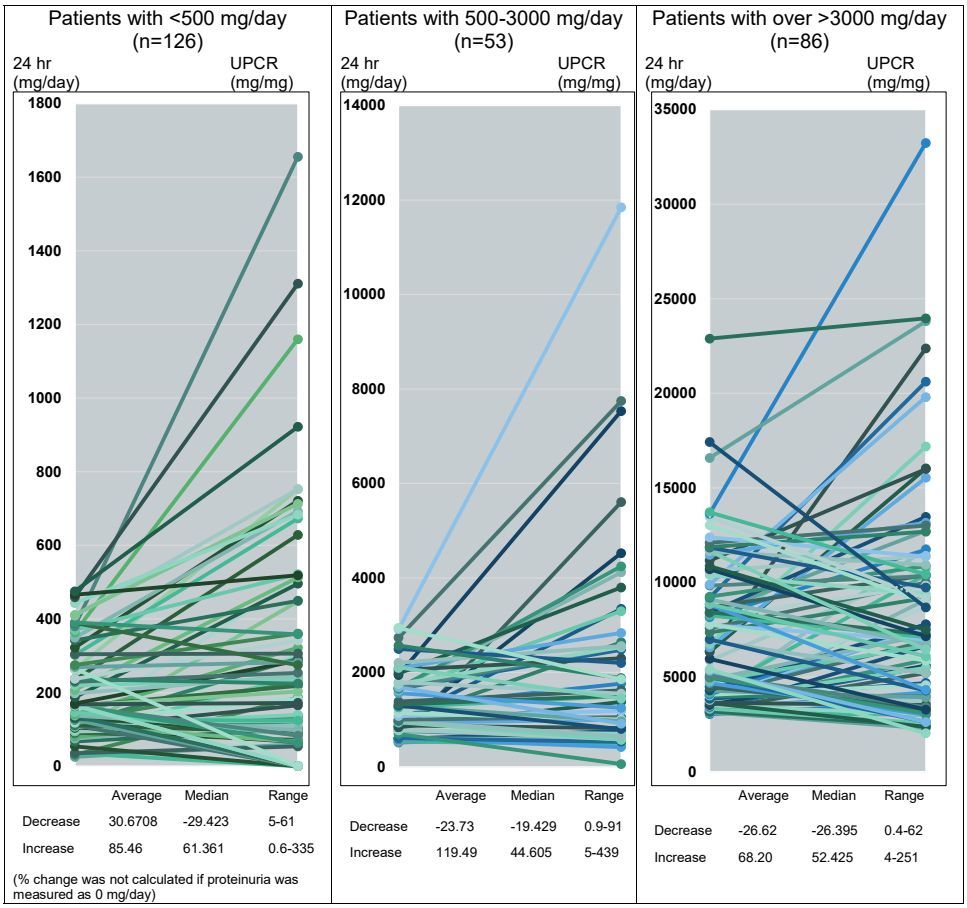

Figure 2. The amount of proteinuria measured by 24-hour urine protein and UPCR in each patient. Every line represents 1 individual patient. Abbreviation: UPCR, urinary protein-creatinine ratio.

validated prognostic factor currently in clinical use.[3] In the overall cohort, replacing the 24-hour urine collection with UPCR changed kidney staging in 27 out of 265 patients (10%; Table 2). Twenty-one patients were reclassified as having a higher kidney staging, while 6 were moved to a more favorable, lower stage. A total of 6 patients were reclassified to stage 2 from stage 1; 15 were reclassified to stage 3 from stage 2; 4 were reclassified to stage 1 from stage 2; and 2 were reclassified to stage 2 from stage 3 (Table 2). We analyzed how many patients were reclassified in 3 subgroups based on their baseline level of proteinuria: patients with <500 mg, 500-3,000 mg, and >3,000 mg of proteinuria from 24-hour urine collection (Table 2). The agreement in terms of kidney staging between the 2 proteinuria measurements was 100% in the <500 mg group, with 76 patients (60.3%) in stage 1 and 50 (39.7%) in stage 2. In the 500 to 3,000 mg/day cohort (n = 53), replacing the 24-hour urine collection with UPCR changed kidney staging in 4 patients, all of whom were reclassified from stage 2 to 3. In the >3,000 mg/day cohort (n = 86), 17 patients were upgraded: 6 from stage 1 to 2 and 11 from stage 2 to 3. In this cohort, downgrading occurred in 6 patients: 4 changed from stage 2 to 1 and 2 from stage 3 to 2 (Table 2).

Evaluating Kidney Response Using UPCR in Lieu of 24-Hour Urine Collection

A total of 35 patients completed a kidney response assessment. These patients had both UPCR and 24-hour urine studies checked at baseline and at a follow-up visit at least 6 months apart. The current definition of kidney response includes a 30% decrease in proteinuria.[3] Of these patients, 7 (20%) had discordance between UPCR and 24-hour urine collection results that changed their definition of organ response at the 6- or 12-month follow-up. Five of the 7 patients (14%) were classified as having a kidney response by UPCR but did not reach this threshold by 24-hour urine collection. All of these patients had levels of proteinuria >1 gm/day.

DISCUSSION

We show that the correlation between 24-hour urine collection and UPCR is only moderate in patients with proteinuria <500 mg/day. In our cohort, using UPCR in lieu of 24-hour urine collection changed the kidney staging assessed at diagnosis in 10% of the follow-up patients and the kidney response in 20%. It is crucial to assess proteinuria accurately in the management of AL

Table 2. Difference in Kidney Staging by UPCR Versus 24-Hour Urine Collection

Patients With <500 mg/day Proteinuria						Patients With 500-3,000 mg/day of Proteinuria				Patients With >3,000 mg/day of Proteinuria			
24-hour Urine	UPCR					UPCR				UPCR			
	Stage	1	2	3	Total	1	2	3	Total	1	2	3	Total
	1	76	50	0	126	27	0	0	27	10	6	0	16
	2	50	0	0	50	0	22	4	26	4	32	11	47
	3	0	0	0	0	0	0	0	4	0	2	21	23
	Total	126	50	0	126	27	22	4	53	14	40	32	86
	% pts changed staging				n 0 (0%)				n 4 (7.5%)				n 23 (26%)
Kappa	(95%CI)				1 (1-1)				0.85 (0.73-0.98)				0.56 (0.41-0.71)

Note: Kidney staging in AL amyloidosis is defined as: stage 1, eGFR ≥50 ml/min/1.75 m^2 and ≤5 g/24h of proteinuria; stage 2, eGFR <50 ml/min/1.75 m^2 or >5 g/24h of proteinuria; and stage 3, eGFR <50 ml/min/1.75 m^2 and >5 g/24h of proteinuria.[3]
Abbreviation: CI, Confidence interval; UPCR, urinary protein-creatinine ratio.

amyloidosis. Proteinuria, along with measurement of eGFR, is a powerful predictor of kidney outcomes.[13] Moreover, therapeutic success and kidney response in AL amyloidosis is determined by the magnitude and direction of the change in proteinuria.[2,3,10] Due to these reasons, accurate measurement of proteinuria is critical, and our study aimed to determine whether 24-hour urine collection can be replaced by a UPCR to monitor proteinuria. Both modalities have advantages and disadvantages. The 24-hour urine collection is cumbersome and prone to over- or undercollection by human error. Also, the interpreting physician must determine whether it is accurately timed (ie, full 24-hour urine collection), based on the specimen's total 24-hour creatinine content, a subtlety than can be lost by nonnephrology clinicians.[4,9] In comparison, although UPCR is simple to execute, it is less accurate because it is a "snapshot" in time that changes based on the time of day, activity level, and dietary intake. Even individuals in a controlled environment, on strict bedrest, and on diet restrictions can have substantial cyclic variation in the spot urine collection results during the same day or during a 72-hour period.[13,14] Additionally, creatinine production can decrease over time with muscle wasting, amputation, or a prolonged decrease in physical activity or increase over time with increased muscle mass, increased activity, muscle damage, and creatine supplementation, further increasing spot variability in UPCR values. Overall, 24-hour hour urine output testing helps level out some of these variations.[13,14]

Few previous studies have examined the clinical impacts of replacing 24-hour urine collection with UPCR in patients with AL amyloidosis. In other proteinuric kidney diseases, studies showed variable results in terms of the correlation between the 2 modalities, and that variability increased at higher proteinuria levels.[9,10,15] We found only a modest correlation in our cohort at clinically significant proteinuria levels. Pearson's correlation coefficients were 0.57 and 0.62 in the 500-3,000 mg/day and >3,000 mg/day groups, respectively. In our study, the correlation was better at low levels of proteinuria (<500 mg/day), but at that level better correlation does not translate into clinical significance.

Importantly, in our study, kidney staging was impacted in 10% of the patients when 24-hour urine collection was replaced with UPCR. This could lead to incorrect risk assessments in terms of kidney outcomes using the currently available prediction models.[3] A high level of disagreement between UPCR and 24-hour urine collection led to reclassification of the kidney response in 20% of the patients. This change in the kidney response classification would certainly have therapeutic significance.

Precise measurement of proteinuria is not only important in everyday clinical practice: past and current clinical investigations in the field of AL amyloidosis also require a 24-hour urine collection to measure proteinuria. These studies and trials include, for example, the development of prediction models to assess the risk of end-stage kidney disease and the development of kidney response criteria for various clinical studies of new therapeutic regimens.[2,3] Before clinical trials can rely on UPCR to assess outcomes, its use has to be validated in large cohorts, which has not been done to date.

There are some inherent limitations to our study. First, this is an observational study and we did not control for certain variables that may alter proteinuria. Although patients were educated on how to correctly do the 24-hour urine collection, we did not control for recent exercise, dietary changes, or comorbid conditions that may affect collection. Due to the rarity of AL amyloidosis, our sample size is small. In addition, we had a limited number of patients with follow-up data to assess whether the response criteria would be impacted by replacing the 24-hour urine collection with UPCR. Lastly, the patients were treated at a single institution that serves as an international referral center for AL amyloidosis.

Although UPCR clearly has a role in screening for proteinuria, we favor continuing to use 24-hour urine collection in the evaluation of patients with AL amyloidosis for the reasons discussed above. We also note that diagnosis of a plasma cell dyscrasia and monitoring of hematologic responses in AL amyloidosis depend on the

identification and quantification of monoclonal protein in the urine and serum by immunofixation electrophoresis.[16-18] Although monoclonal immunoglobulin may be identified on spot urine by immunofixation, 24-hour urine collection is needed to quantify the monoclonal spike. Thus, patients with AL amyloidosis will not likely be spared the burdensome experience of a 24-hour urine collection.

In summary, although 24-hour urine collection is cumbersome, we continue to recommend it in patients with AL amyloidosis and kidney involvement. This population often has nephrotic-range proteinuria, and we demonstrate that the correlation between 24-hour urine and spot urine measurements is weaker in this group. Replacing 24-hour urine collection with UPCR changes the diagnosis of kidney involvement, kidney staging, and determining organ response in some patients. Using UPCR for diagnosis, staging, and determining kidney response would require validation in larger studies involving patients with AL amyloidosis.

ARTICLE INFORMATION

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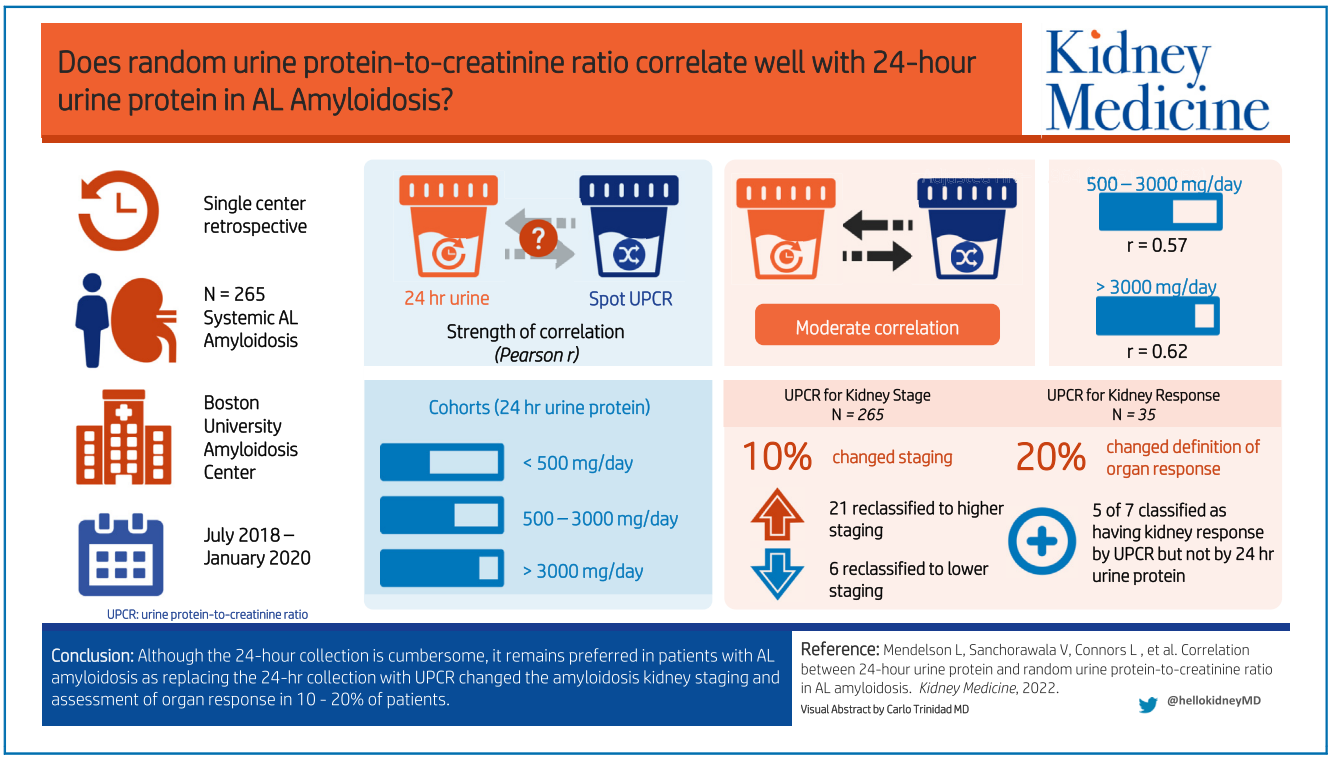
Does random urine protein-to-creatinine ratio correlate well with 24-hour urine protein in AL Amyloidosis?
Kidney Medicine
Single center retrospective
N = 265 Systemic AL Amyloidosis
Boston University Amyloidosis Center
July 2018 – January 2020
UPCR: urine protein-to-creatinine ratio
24 hr urine
Spot UPCR
Strength of correlation (Pearson r)
Moderate correlation
500 – 3000 mg/day
r = 0.57
> 3000 mg/day
r = 0.62
Cohorts (24 hr urine protein)
< 500 mg/day
500 – 3000 mg/day
> 3000 mg/day
UPCR for Kidney Stage N = 265
10% changed staging
21 reclassified to higher staging
6 reclassified to lower staging
UPCR for Kidney Response N = 35
20% changed definition of organ response
5 of 7 classified as having kidney response by UPCR but not by 24 hr urine protein
Conclusion: Although the 24-hour collection is cumbersome, it remains preferred in patients with AL amyloidosis as replacing the 24-hr collection with UPCR changed the amyloidosis kidney staging and assessment of organ response in 10 - 20% of patients.
Reference: Mendelson L, Sanchorawala V, Connors L , et al. Correlation between 24-hour urine protein and random urine protein-to-creatinine ratio in AL amyloidosis. Kidney Medicine, 2022.
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