Review

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Review on adherence of the literature to official recommendations on albuminuria harmonization and standardization

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Abstract: Albuminuria standardization is a key issue to produce reliable and equivalent results between laboratories. We investigated whether official recommendations on albuminuria harmonization are followed in the literature. The PubMed database was searched from June 1 to September 26, 2021. The search terms included urine albumin, UACR, and albuminuria. A total of 159 articles were considered eligible; 50.9 % reported the type of urine collection. Specifically, 58.1 % collected a random spot urine specimen, 21 % collected a first morning void, and 6.2 % collected a 24-h specimen. Overall, 15 % of articles reported data on sample shipping, storage, and centrifugation and 13.3 % mentioned the preanalytical phase without any data on albuminuria. The method for albuminuria was properly described in 31.4 % of articles; of these, 54.9 % used immunological methods, and 8.9 % contained errors or missing data. Most articles (76.7 %) expressed test results as albuminuria-to-creatininuria ratio. Different decision levels were utilized in 130 articles; of these, 36 % used a decision level of ≤30 mg/g creatininuria and 23.7 % used three decision levels (≤30, 30–300, and ≥300 mg/g). The failure to follow guidelines on albuminuria harmonization was mainly found in the preanalytical phase. The poor awareness of the importance of preanalytical steps on test result may be a possible explanation.

Keywords: albuminuria; analytical methods; creatininuria; harmonization; pre-analytical phase; standardization

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Introduction

The diagnostic and prognostic value of albuminuria in clinical practice was recognized a century ago [1]. Over time, the importance of albuminuria has dramatically increased and its role as a biomarker of endothelial dysfunction and microvascular disease has been extensively elucidated. Albuminuria is strategic for the early recognition and management of diabetic nephropathy and the classification of chronic kidney disease (CKD) in combination with estimated glomerular filtration rate (eGFR). The magnitude of albuminuria is an independent prognostic factor for CKD outcomes, hypertension, cardiovascular disease (CVD), cardiovascular mortality, and all-cause mortality [2–4]. Recently, albuminuria has been added to serum creatinine and urine output to assessing the stage severity of acute kidney disease (AKD) [5, 6]. Accordingly, albuminuria test results should be reliable and standardized in order to produce equivalent results between different laboratories and different methods [7]. In 2008, the former National Kidney Disease Education Program Laboratory Working Group (NKDEP LWG) together with the International Federation of Clinical Chemistry and Laboratory Medicine Working Group for Standardization of Albumin in Urine (IFCC WG-SAU) launched a project for standardization, including a roadmap for albuminuria traceability, and published key recommendations [8, 9], namely: (a) laboratories should report the urine albumin-to-creatinine ratio (uACR) along with albuminuria concentration; (b) the preferred urine collection is the first-morning void specimen. Spot urine specimens could be used for the initial evaluation of kidney disease but results ≥30 mg/g should be confirmed in a subsequent first-morning void urine specimen; (c) results obtained

by semiquantitative methods should be confirmed by quantitative immunoassays; and (d) clinical decision levels for albuminuria should be set at <30 mg/g creatininuria (uACR normal to mildly increased), 30–300 mg/g creatininuria (uACR moderately increased), and >300 mg/g creatininuria (uACR severely increased). The aim of this review was to investigate the extent to which official recommendations and guidelines for albuminuria standardization and harmonization have been followed in clinical studies involving the measurement of albuminuria.

Materials and methods

Search strategy

This study was designed in September 2021. Studies were identified by searching the PubMed electronic database (https://pubmed.ncbi.nlm.nih.gov/; last access April 15, 2023). We used the following medical subject headings (MeSH) and keywords: urine albumin, UACR, albuminuria and 2021. The query was ("URINE ALBUMIN" OR "ALBUMINURIA" [Title/Abstract]) AND ("UACR" OR [Title/Abstract]) ("2021/06/01" [Date – Create]: "2021/09/26" [Date – Create]). The search was limited to articles that were written in English, that included only human beings, and that were published between 2021/06/01 and 2021/09/26.

Eligibility assessment and data abstraction were performed independently in an unblinded standardized manner by two reviewers (A.C. and M.M.); disagreements between the reviewers were resolved by consensus. Eligibility criteria included any clinical study (e.g., cross-sectional, prospective longitudinal, case-control, randomized double-blind placebo-controlled trial, multicenter observational, community-based cohort, retrospective population-based cohort) or case report using albuminuria as a surrogate endpoint for various diseases (e.g., CKD, hypertension, CVD, diabetes), or for discriminating patient cohorts or assessing the risk of CKD, CVD, diabetic nephropathy, cancer, and other non-communicable disease. Exclusion criteria included abstracts published in conference proceedings, book chapters, letters to the editor, guidelines, position papers, systematic reviews, meta-analyses, *in vitro* studies, studies using animal models, and full-text articles written in languages other than English.

Analysis of data

Based on recommendations for albuminuria standardization and harmonization [8, 9], we analyzed whether and how each article described the most relevant steps of the total testing process. First, we evaluated the type of urine collection, and the specimen shipping, storage, and centrifugation. Second, we evaluated whether and how each article reported data on: (a) albuminuria and creatininuria analytical methods, (b) test results expression, (c) units of measurement, and (d) decision levels. Errors, missing data, and incomplete data were also recorded and analyzed.

Results

Literature sorting was conducted following the PRISMA flow diagram [10], as reported in Figure 1. The search resulted in 278 articles; two articles were excluded because of the unavailability of the full text linked to the respective digital object identifier (DOI). The remaining 276 articles were examined on the basis of title, abstract, and key words; 41 studies using animal models, 38 systematic reviews or meta-analyses, 10 *in vitro* studies, 9 book chapters, and 6 consensus statements or personal views were excluded. Next, the full-text of the remaining 172 articles was evaluated; five non-English articles and three articles containing no results on albuminuria were excluded. After a final review of the remaining 164 articles, we excluded one article reporting epidemiological data on albuminuria in diabetic patients, two articles reporting results on proteinuria but not albuminuria, and two articles reporting no result for albuminuria, even though albuminuria was included in their list of key words. Ultimately, 159 articles, each of them identified with a univocal identification number (B_XXX) were considered eligible for our study (Supplementary Table 1); 73 involved diabetic patient cohorts, eight of them with co-morbidities or other concomitant diseases (e.g., CKD); 34 involved patients with kidney disease (17 with CKD, 7 with AKI, and 10 with other diseases), 27 involved patient cohorts with one or more risk factors for CKD, CVD, liver disease, and other non-communicable diseases; seven involved patients with hypertension; five involved patients with infectious diseases; and the remaining 13 involved patients with various other diseases. Of the articles, 23.9 % reported data extracted from electronic health records (EHRs).

The majority of the articles included in this study (61 %) termed the loss of albumin with the urine either "urine albumin" or "albuminuria," and 39 % went on to use the term "microalbuminuria." No article reported any data on preanalytical variables potentially influencing albuminuria excretion, such as physical activity, posture, or fever [11, 12]. Approximately half of the studies (50.9 %) indicated the type of urine collection; among them, 58.1 % collected a random spot urine specimen (48.2 % during the daytime and 9.9 % specifically in the morning) and 21 % a first morning void urine specimen (Table 1). Overall, 24 articles (15 %) reported data on the sample shipping, storage, and centrifugation, whereas 71.7 % did not; the remaining 13.3 % mentioned the preanalytical phase without providing any data on albuminuria (Supplementary Figure 1). Of the 24

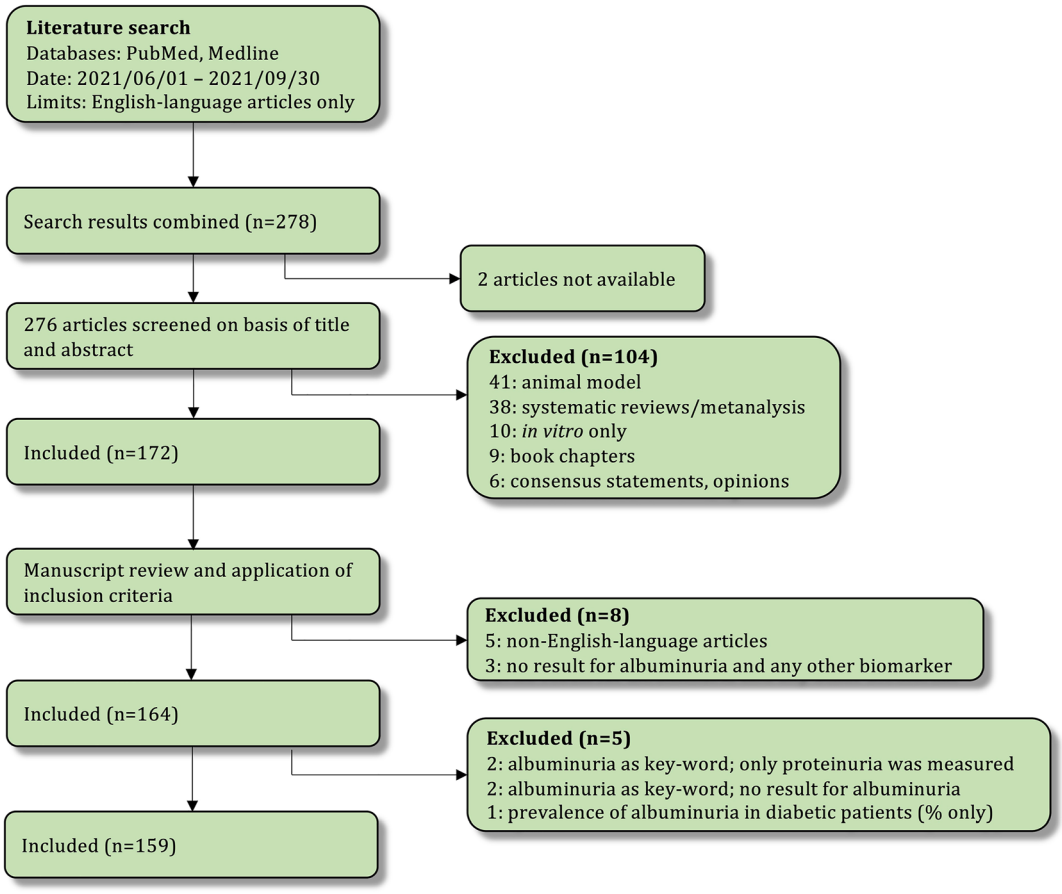

Figure 1: Inclusion of articles in the review according to the PRISMA flow diagram.

Table 1: Type of urine sample used for measuring albuminuria in 159 clinical studies.

Urine specimen collection	n	%
Reported	81	50.9
Not reported	78	49.1
Data on 81 types of urine specimen collection		
Random spot	39	48.2
First morning	17	21.0
Undefined in the morning	8	9.9
Mix (dual specimen collection)	8	9.9
24-h	5	6.2
Others (overnight, 2nd morning void, mid-stream spot, after oral water load	4	4.8

articles that did, seven reported conditions for sample shipping, 12 for sample storage, and six for sample centrifugation (Table 2). However, most data were incomplete; specifically, five articles described sample shipping and storage but not centrifugation, four storage and centrifugation but not shipping, two just sample shipping, three just sample storage, and two just sample centrifugation. Further data on urine sample storage are given in Supplementary Table 2; out of 159, 12 articles (7.5 %) mentioned sample storage conditions with details, six (3.8 %) measured albuminuria in fresh specimens immediately or within a day of sample arrival at the laboratory, and three (1.9 %) mentioned sample storage without specify any condition or detail. One article (B_066) extrapolated data on preanalytical steps from the literature (0.7 %). Finally, thirteen articles (8.2 %) reported details of preanalytical steps taken for other blood and stool biomarkers but not for albuminuria, and five additional articles (3.1 %) only for the biomarkers they evaluated in the study but not for albuminuria.

Analytical methods for albuminuria and creatininuria were mentioned in 64 and 55 studies, respectively (Figure 2). However, 38 articles contained errors, missing data, or false information on the analytical methods they used (21.9 % for albuminuria and 43.6 % for creatininuria), leaving 50 articles that precisely reported the analytical method for albuminuria and only 31 for creatininuria (Table 3). Among the 50 studies indicating the method for albuminuria, 29.7 % used immunoturbidimetry, 23.5 % immunonephelometry, and

Table 2: Data on pre-analytical steps for urine albumin testing reported in 24 out of 159 studies.

	Shipping, n (%)	Storage, n (%)	Centrifugation, n (%)
Not mentioned	12 (50 %)	3 (12.5 %)	14 (58.3 %)
Mentioned without any data	2 (8.3 %)	3 (12.5 %)	4 (16.7 %)
Available data	7 (29.2 %)	12 (50 %)	6 (25 %)
Other	3[a] (12.5 %)	6[b] (25 %)	–
Total	24	24	24

[a]Immediately analyzed after sample collection. [b]Analysis performed on fresh urine sample.

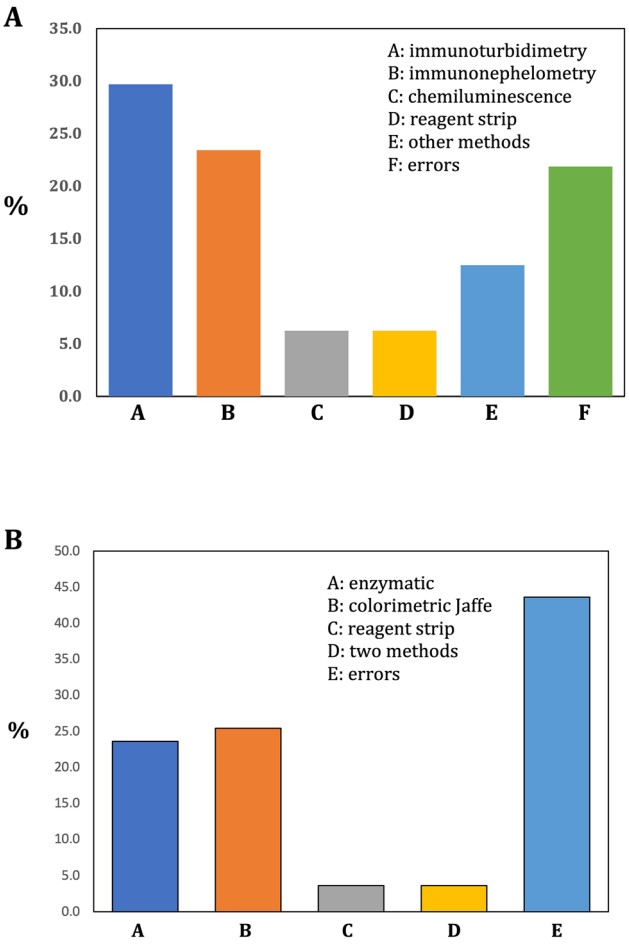

Figure 2: Analytical methods for albuminuria reported in 64 and 55 out of 159 articles for albuminuria (A) and creatininuria (B), respectively.

6.2 % reagent strips (Figure 2A). Meanwhile, approximately half of the studies measured creatininuria using colorimetric or enzymatic methods (25.5 and 23.6 %, respectively), and 5.5 % used reagent strips (Figure 2B). The most frequent error recognized in studies mentioning analytical methods was to name the analytical platform used without specifying

Table 3: Indication of the analytical method utilized in 159 clinical studies for the measurement of albuminuria and creatininuria.

Analytical methods	Albuminuria, n (%)	Creatininuria, n (%)
Not reported	95 (59.7 %)	104 (65.4 %)[a]
Properly reported	50 (31.4 %)	31 (19.5 %)
Reported with errors or missing data	14 (8.9 %)	24 (15.1 %)

[a]Including 6 papers reporting albuminuria as AER.

the type of assay (50 % for albuminuria and 37.5 % for creatininuria), and the second was to indicate they had used a unique immunoassay for uACR (28.5 %). Notably, 20.8 % claimed to use a traceable method for creatininuria (Table 4). Approximately two thirds of the studies (76.7 %) reported the albuminuria result as uACR and the vast majority of these (96.7 %) used mg/g or mg/mmol as the unit of measurement (Table 5). Thirteen articles reported the albuminuria excretion rate (AER) and 16 used both uACR and AER (with one article combining uACR and reagent strips); one of these was also included in the group of articles containing errors in reporting the unit of measurement (Supplementary Table 3). Albuminuria clinical decision levels were utilized in 130 articles; 114 (71.6 %) used a single (e.g., <30 mg/g) or multiple (e.g., 30–300 mg/ and >300 mg/g) clinical decision levels, and 16 (10.1 %) used more than one approach to the single or multiple decision levels (Table 6). In particular, 36 % of 114 articles used a clinical decision level of ≤30 mg/g, 23.7 % used three decision levels (≤30, 30–300, and ≥300 mg/g), and 5.3 % used gender-related

Table 4: Errors and missing data in the description of analytical methods for albuminuria and creatininuria in 159 selected clinical studies involving the measurement of albuminuria.

Type of error	%
Albuminuria (n=14)	
Method described by reporting the name of the analytical platform only	50.0
Method for uACR described as immunoturbidimetry or immunonephelometry	28.5
Albuminuria measured by picric acid	14.4
Undefined method for albuminuria (immunoassay)	7.1
Creatininuria (n=24)[a]	
Analytical method reported as name of analytical platform only	37.5
Analytical method reported as traceable	20.8
Analytical method reported as single immunoassay for uACR	20.8
Unclear (ambiguous) description of the analytical method	12.5
Analytical method reported as immunoassay	8.3

uACR, urine Albumin-to-Creatinine Rate. [a]Out of 24 studies containing mistakes in reporting the method for creatininuria, 1 was also included in another group (studies using two methods).

Table 5: Albuminuria test result expression in 159 clinical studies.

Albuminuria expression	n[a]	%[a]
uACR		
Overall	122	76.7
mg/g	101	63.5
mg/mmol	17	10.7
g/g	4	2.5
AER		
Overall	13	8.2
mg/24 h	7	4.4
mg/L	2	1.3
g/L	1	0.6
µg/min	1	0.6
Dipstick 1+, 2+	2	1.3
uACR and AER	16	10.1
Errors	4	2.5
Not reported	4	2.5

[a]Data referred to 159 articles. uACR, urine albumin-to-creatinine rate; AER, albumin excretion rate.

Table 6: Utilization of clinical decision values for albuminuria in 159 clinical studies.

Albuminuria clinical decision values	n	%
Single or multiple decision value	114	71.6
More than one single or multiple decision value[a]	16	10.1
Not utilized (albuminuria as continuous variable)	4	2.5
Not reported	22	13.9
Errors	3	1.9

[a]For details, see Supplementary Table 5.

clinical decision levels (Supplementary Table 4). Finally, 14 % used many single or multiple clinical decision levels (Supplementary Table 5). Furthermore, in 22 articles (13.8 %), the measurement of proteinuria was added to that of albuminuria; some of them used proteinuria and albuminuria interchangeably, either for enrolling patients in their study or as the endpoint, whereas others considered proteinuria and albuminuria as synonyms.

Discussion

Although restricted to a limited time interval, our study sheds light on the adherence of the literature to official guidelines and recommendations for albuminuria standardization. Since the urine sample type impacts the albuminuria results, the lack of data on urine collection, recognized in approximately half of the articles (49.1 %), limits results' interpretation and strength. The majority of articles reporting the type of urine collection used random spot specimens; only 21 % used the first morning void urine specimen, and 9.9 % indicated the collection of a spot urine sample during the morning but without any further detail (Table 1). This omission is not trivial; the urinary excretion rate of proteins, including albumin, may significantly differ in samples collected with the second void in the morning compared to random spot samples collected in the course of the morning [13]. These discrepancies may considerably affect the accuracy of the prediction of CKD progression and stage. Briefly, the highest albumin excretion rate occurs during the day because of orthostatism and the high GFR; conversely, the lowest albumin excretion rate occurs during the night and early in the morning [14]. Thus, albuminuria is higher in random spot urine samples compared to first morning void samples; robust data, obtained from a large cohort of patients and by collecting paired samples, demonstrated that near 30 mg/g (3 mg/mmol) random urine samples yielded about 50 % higher values than first morning void urine samples [15]. First morning void urine samples also have lower uACR variability than random samples when considered between 30 and 300 mg/g, but not below 30 mg/g [16]. The utilization of clinical decision values based on urine sample type remains to be elucidated [17]. Overall, the first morning void correlates more closely with the 24-h urine collection than random spot specimens do when collected during the day [18]. The current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on CKD [19] recommend the first morning void, and it is unclear whether this recommendation was or was not followed by studies reporting urine collection as "random spot specimens". Our survey suggests a low degree of urine sampling standardization for albuminuria in clinical trials and longitudinal studies; consequently, results cannot be considered harmonized and comparable to each other.

The high rate of articles failing to report any data on sample shipping, centrifugation, and storage (71.7 %) may be due to the assumption these steps are trivial for albuminuria, a hypothesis supported by the recognition of 18 articles reporting detailed information on shipping, centrifugation, and storage for other blood and/or fecal biomarkers but not for albuminuria. It is otherwise hard to explain why the authors of these articles ignored the impact of the preanalytical phase on the results' reliability, meaning it seems reasonable to assume they were unaware of the importance of standardizing the preanalytical phase. Further confirmation comes from the 24 articles that detailed the sample shipping, centrifugation, and storage in that none of them reported complete data (Table 2).

Among 12 articles reporting data on sample storage, only one study (B_042) stored urine samples at −20 °C, whereas

all the remaining articles stored urine samples at −80 °C. Freezing the urine sample at −20 °C, over a period from two weeks to three years, causes the loss of measurable albumin and is not recommended [20]. Urine sample storage at −20 °C yields an average decline in albuminuria concentration of 0.27 % per day of storage, due to the molecular degradation [21]. Urine storage conditions may impact results depending on the analytical method for albuminuria; for example, when albuminuria was measured by immunonephelometry but not by high performance liquid chromatography (HPLC), sample storage at −20 °C resulted in 21 %, 28 %, and 34 % albuminuria decrease (mean value) after four, eight, and twelve months, respectively [22]. Further data showed that the urine storage at −20 °C led to a 36.9 % loss in albuminuria levels along with a 34.3 % in uACR levels measured by an enzyme linked immunosorbent assay (ELISA) [23]. Regrettably, no article included in our review reported the length of sample storage and/or the utilization of preservatives (e.g., boric acid, pepstatin). Finally, three articles (B_031, B_054, B_140) described urine sample storage by using general statements, without providing any detail of specific conditions, such as length or temperature (Supplementary Table 2).

Only a minority of articles properly indicated the analytical methods for albuminuria (31.4 %) and creatininuria (19.5 %); all others described the analytical methods with errors or incomplete information. The lack of information on analytical methods for albuminuria and creatininuria, together with the relative high number of studies containing errors, may be due to various factors, including poor communication between clinicians and lab teams, false perception of equivalence between analytical methods and platforms or between different assays, and the description of materials and methods by non-specialists in laboratory medicine.

Examples of relevant errors were the mention of: (a) a unique method for uACR (28.5 %), (b) an undefined “immunoassay” as the method used for measuring uACR (20.8 %), (c) a picric acid-based method for albuminuria (14.4 %), and (d) a traceable method for creatininuria (20.8 %). The latter deserves elucidation. The expression “creatininuria measured by a traceable method” could be interpreted either as a result of incomplete/incorrect information or the practice of calibrating the urine creatinine assay with the serum-based reference material SRM 967 [24]. Regrettably, the measurement of creatininuria by a reference system based on a primary standard calibrator for serum creatinine does not make traceable the analytical method for creatininuria, because of differences between serum and urine matrices. In 2013, the National Institute of Standards Technology (NIST), in collaboration with the former NKDEP LWG, developed a certified reference material consisting of creatinine in frozen human urine (SRM 3667), but this has not yet been used by *in vitro* diagnostic (IVD) manufacturers. In 2018, the NIST developed the recombinant human albumin certified primary reference material SRM 2925 for a mass spectrometry-based reference measurement procedure but not for immunoassays [20]. Currently, the NIST, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases Laboratory Working Group (NIDDKD LWG) of the National Institute of Health (NIH), is testing a new certified reference material (SRM 3666) consisting of albumin and creatinine in frozen human urine that is intended to be commutable with clinical samples. However, a reference measurement system linking routine clinical albuminuria measurements to higher-order standards via an unbroken chain of metrological traceability is not yet available. Thus, creatininuria and albuminuria are not yet traceable [25].

The majority of articles met the recommendation to report albuminuria results as uACR in untimed urine samples, with 118 articles (74.2 %) using mg/g or mg/mmol as the unit of measurement (Table 5). Notably, we found few minor errors across articles, and any we found were mainly due to mistyping rather than failures of logic (Supplementary Table 3). This may be considered to denote satisfactory adherence to the guidelines for albuminuria standardization; unfortunately, no article reported whether uACR results were associated with those referred to the albuminuria concentration (e.g., mg/L). Most articles indicated the decision level(s) for albuminuria (Table 6); more than half of them used either uACR ≤30 mg/g or uACR <30, 30–300, and >300 mg/g as decision limits (Supplementary Table 4). It is unclear why some articles used more than one approach to the single or multiple decision levels, though the approaches were poorly comparable (Supplementary Table 5). Beyond that, we noted that a small number of articles (B_038, B_049, B_050, B_114, B_118) considered albuminuria as a continuous variable, even below 30 mg/g, a choice largely supported by the fact that the risk of adverse events (e.g., CKD, CVD, mortality) is a continuous function of the albuminuria level [26].

Our review is affected by several limitations. First, the literature search was conducted using only the PubMed electronic database. However, the PubMed library covers more than 35 million citations for biomedical literature from MEDLINE, life science journals, and online books. Thus, the 159 articles may be considered qualitatively and quantitatively adequate to represent the current adherence of clinical studies to official recommendations on albuminuria harmonization and standardization. Another limitation is the short time period (June–September 2021) used to search

for articles, though this limitation is partially counterbalanced by the high heterogeneity of scientific journals resulting from our PubMed search, namely 159 articles from 117 different journals (Supplementary Table 1). The number of articles included in our analysis and their heterogeneity contribute to supporting the robustness of our results.

Conclusions

Our study sheds light on the state of the art since the early publication of recommendations for albuminuria harmonization [8]. The term "microalbuminuria" is still popular among clinicians, though all official guidelines recommend to discourage its utilization. Moreover, failure to adhere to guidelines on albuminuria standardization is predominant in the preanalytical phase, as evidenced by the lack of information on urine specimen collection in 49.1 % of the articles, and by the very small fraction of articles that reported the conditions for sample storage (7.5 %). It seems reasonable to assume that this failure originates from a poor awareness of the impact of preanalytical steps on test results. Currently, the lack of a traceable method is a critical issue preventing standardization of the analytical phase, since fixed clinical decision levels cannot be applied uniformly for various diseases and conditions until equivalent results can be produced between different methods. Recommendations for standardizing the postanalytical phase have achieved the best compliance, with the majority of articles now reporting the albuminuria-to-creatininuria ratio using mg/g or mmol/mol as the unit of measurement. Harmonization of the unit of the measurement is a crucial issue to compare results across the literature [27]. A negligible fraction of articles reported the albuminuria concentration in milligrams per liter, g/L, or micrograms per minute (overall, 2.5 %), demonstrating a good adherence to recommendations.

Recent publications based on a large clinical database tested the diagnostic accuracy of equations for converting urine protein-to-creatinine ratio (PCR) and dipstick protein to ACR in CKD screening and staging [28–30]. Although they found a consistent relationship between PCR and ACR, the utilization of equations can be restricted in certain retrospective clinical or research applications where only PCR is available. The lack of standardization of proteinuria assays, the excretion of various proteins in variable amounts (e.g., Tamm-Horsfall protein, transferrin, Bence Jones protein), and the type of kidney injury may originate proteinuria results that cannot be reliably extrapolated to albumin results [31]. Indeed, the relationship between PCR and ACR is nonlinear and at lower levels of PCR the correlation between the two tests is weak [32].

Future educational initiatives on the importance of standardizing the preanalytical phase, paired with the introduction of albuminuria traceability, are strongly desirable for improving albuminuria harmonization.

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