Research Article

Standardizing The Biochemical Tests for Chronic Kidney Disease (CKD): Where Do We Stand? A National Survey of Laboratories Across Pakistan

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Abstract

Introduction: CKD affects 8.6% of the global population, with South Asian countries seeing prevalence rates between 10.6% and 23.3%, including 21.2% in Pakistan. CKD's burden is further exacerbated in South Asia due to rising hypertension and diabetes. Accurate estimation of glomerular filtration rate (GFR) and albuminuria are vital for CKD management. Despite increasing CKD studies, regional testing remains underdeveloped. This survey evaluates CKD testing practices in Pakistan, aiming to propose recommendations for improving uniformity, enhancing surveillance, and advancing CKD care standards.

Methods: A cross-sectional survey was conducted by the Chemical Pathology section at Aga Khan University (AKU) using a validated questionnaire developed by International Federation of Clinical Chemistry (IFCC) which was modified for local context. The survey, distributed via Google Forms to major laboratories across Pakistan, focused on CKD testing methods. Data were analyzed using Excel (Microsoft Corporation, 2018) software.

Results: A total of 13 laboratories participated in the survey. All laboratories measured serum creatinine, while two measured serum cystatin C, eleven measured urinary protein, and ten measured urinary albumin. GFR was estimated using equations in 10 laboratories, with CKD-EPI 2021 (29%), MDRD (22%), and CKD-EPI Pak (14%) being the most commonly used. However, only six laboratories employed pediatric equations for children. Significant variability was

observed in the testing methods for serum creatinine, urinary protein, and urinary albumin.

Conclusion: Our findings emphasize the urgent need to standardize CKD testing in Pakistan. Inconsistencies in estimated GFR reporting, serum creatinine measurement and proteinuria testing highlight the need for harmonized protocols to improve diagnosis, management, and public health outcomes.

Introduction

The Global Burden of Disease Study estimated that there were 697.3 million cases of chronic kidney disease (CKD) worldwide in 2019 [1]. CKD affects approximately 8.6% of the global population, with prevalence rates in South Asian countries ranging from 10.6% to 23.3%, and about 21.2% in Pakistan [2, 3]. Although CKD is a global public health challenge, its impact is especially severe in South Asian populations due to the increasing incidence of risk factors such as hypertension and diabetes [4, 5]. Consequently, complications such as accelerated cardiovascular disease, premature mortality, and kidney failure have a significantly detrimental impact on the national economies of low- and middle- income countries [6, 7].

As CKD often progresses silently, clinicians depend heavily on clinical laboratory results for diagnosing, classifying, treating, and managing patients. The Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines has classified CKD patients into six stages based on the estimated glomerular filtration rate (eGFR), which is derived from the serum concentration of creatinine, as well as three levels of kidney damage based on albuminuria [8, 9]. Thus, measurement of creatinine and albuminuria is central to the management of CKD that help in assessing the severity, risk and prognosis of patients.

Despite a growing number of studies on CKD prevalence and incidence over the past decade, global capacity for CKD testing and monitoring remains significantly less developed compared to that for hypertension, diabetes, and cardiovascular disease [7]. The first step to making progress in improving CKD monitoring activities is to ensure consistent and accurate results across clinical laboratories. Not only would this enable optimal patient care, but also lead to a high level of harmonization in regional CKD testing methodology and measurements. For effective patient care, including accurate diagnosis, referral prioritization, clinical research, and public health prioritization, laboratory results must be comparable across different times, locations, and measurement methods. This necessitates precision and agreement between laboratories, with traceability to accepted reference standards [10].

Thus, we aim to assess the current status of Pakistani clinical laboratories in standardizing CKD testing tools and assays/ equipment. Through this survey, we will evaluate the methods used for calculating eGFR and albuminuria in clinical laboratories across Pakistan. By gathering this data, we can propose recommendations to enhance uniformity in CKD testing practices, strengthen CKD surveillance by ensuring consistent documentation of laboratory abnormalities, and support a national effort to improve the standard of care in CKD management.

Materials and Methods

A cross-sectional survey was conducted by the section of Chemical Pathology, Department of Pathology and Laboratory Medicine, Aga Khan University, Karachi after approval from the institutional ethical review committee (AKU- 2024-9947-28892). A previously validated questionnaire developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee on Kidney Disease – C-KD was used with subsequent modifications according to local context [11].

The survey was designed and circulated via a Google Forms link to the lead Pathologists of 13 major clinical laboratories across Pakistan. The survey consisted of multiple sections, first was informed consent and general information about the laboratory; followed by questions regarding testing methodology for serum creatinine, eGFR creatinine, serum cystatin C, eGFR cystatin C, urinary protein, and urinary albumin.

The survey accepted responses from April-May 2024. 13 pathologists attempted the survey, and all responses were included in the final analysis. The data was analysed using Excel (Microsoft Corporation, 2018) software.

Results

A total of 13 laboratories participated in our survey. The location of these laboratories and their general characteristics are depicted in Figure 1 and Table 1 respectively.

Figure 1: Map of Pakistan showing the cities from which the responses came, along with the frequencies of responses.

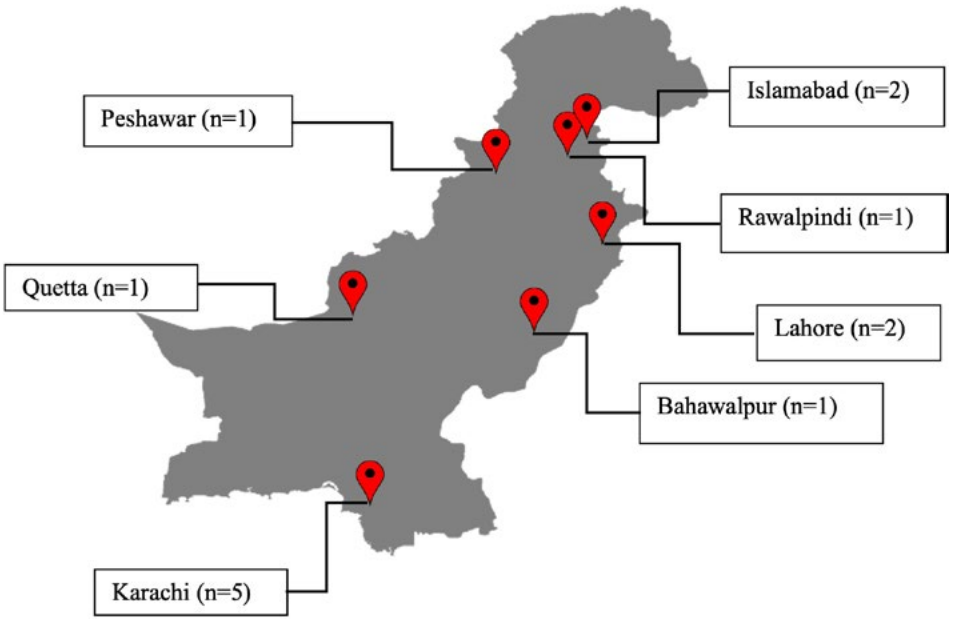


Table 1: General characteristics of laboratories who participated in the survey.

Number of laboratories				
Laboratory processes requests from:				
Specialized physicians, primary care physicians and self-referred or walk in patients	7			
Specialized physicians only	2			
Primary care physicians and self-referred or walk in patients	2			
Self-referred or walk in patients only	1			
CKD testing available at the laboratory:	**Serum creatinine**	**Serum cystatin C**	**Urinary protein**	**Urinary albumin**
Yes	13	2	11	10
No	0	11	2	3
Measurement of eGFR using equations:	**eGFR creatinine**		**eGFR cystatin C**	
Yes	10		2	
No	3		11	
Measurement of eGFR using equations in children:				
Yes	6			
No	7			
Number of serum creatinine requests received in a day:				
<100	1			
100-999	7			
1000-5000	5			
>5000	0			

Number of serum cystatin C requests received in a day:	
<100	2
100-999	0
1000-5000	0
>5000	0
Number of urinary protein requests received in a day:	
<100	6
100-999	5
1000-5000	0
>5000	0
Number of urinary albumin requests received in a day:	
<100	7
100-999	3
1000-5000	0
>5000	0
Turnaround time for serum cystatin C measurement:	
<6 hours	0
6-12 hours	0
12-24 hours	1
24-48 hours	1
Turnaround time for urinary protein measurement:	
<6 hours	4
6-12 hours	3
12-24 hours	4
24-48 hours	0
Turnaround time for urinary albumin measurement:	
<6 hours	4
6-12 hours	3
12-24 hours	2
24-48 hours	1

Only six laboratories provide e GFR based on creatinine for children, with half of them using the original Schwartz equation and the remaining using the modified Schwartz equation.

While the use of serum cystatin C is still limited, two respondents measure serum cystatin C using immunonephelometry and immunoturbidimetry. Equations used for estimating GFR using serum cystatin C are depicted in Figure 3.

The different methods used for measuring serum creatinine (SCr) and equations for estimating GFR using SCr are shown in Figures 2A and 2B.

Figure 2A: Different methods used for measuring serum creatinine.

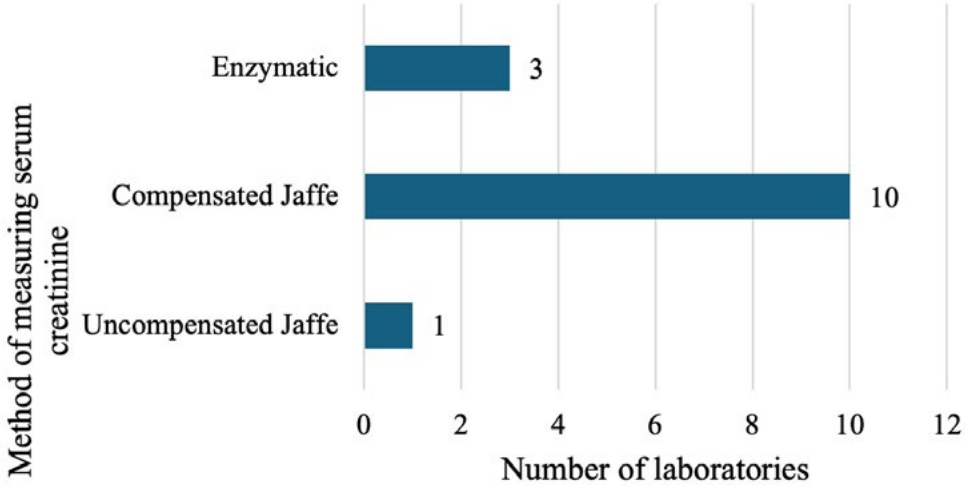


Figure 2B: Variations in the type of eGFR creatinine equations used.

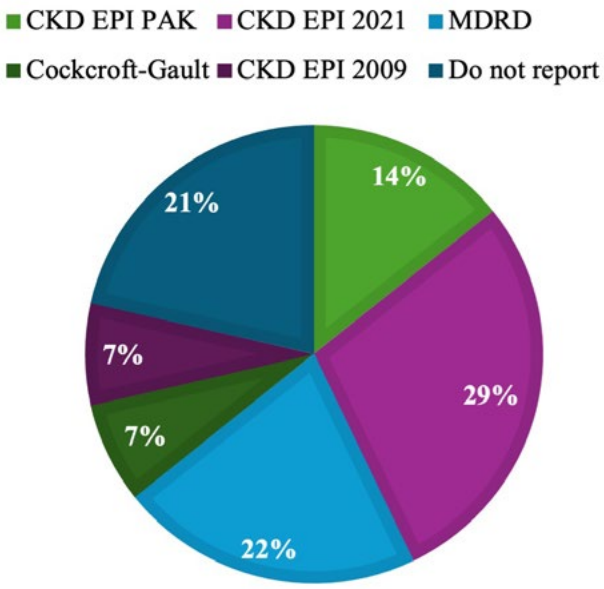
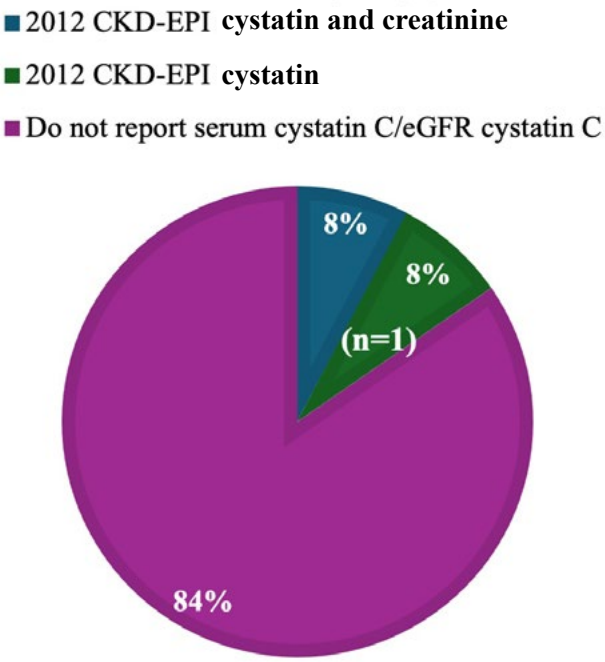


Figure 3: Use of serum cystatin C and eGFR cystatin C.



Regarding the reporting of eGFR creatinine or eGFR cystatin C, almost one-third (n=4) of the laboratories automatically report it with every result of serum creatinine or serum cystatin C while four report it only when requested by the physician.

Regarding the presentation of eGFR results, more than half of the respondents (n=8) report the exact value while just one laboratory only reports the numerical value when it is <60ml/min/1.73m2. Eight laboratories also report eGFR with reference values along with some type of commentary to facilitate clinical interpretation.

	The GFR measurement obtained is always reported, regardless of the value (n)	**The numerical value is only reported when GFR is <60ml/min/1.73m2 (n)**	**Not applicable (n)**
How are the eGFR results presented?	**8**	**1**	**4**

	Yes (n)	**No (n)**	**Not applicable (n)**
Are the eGFR results presented with reference values?	**8**	**1**	**4**
Are eGFR results presented with some type of commentary facilitating clinical interpretation?	**8**	**2**	**3**

The reasons for not reporting eGFR varied with laboratories stating that the formulas used for calculating GFR are not sufficiently validated to warrant their routine use (n=1), the clinical departments have not requested it (n=1), the digital database system of the laboratory does not allow it (n=1).

The methods and urine samples used to measure proteinuria and albuminuria are depicted in Figures 4 and 5, respectively.

Figure 4A: Variations in the type of preferred urine sample to measure urinary protein.

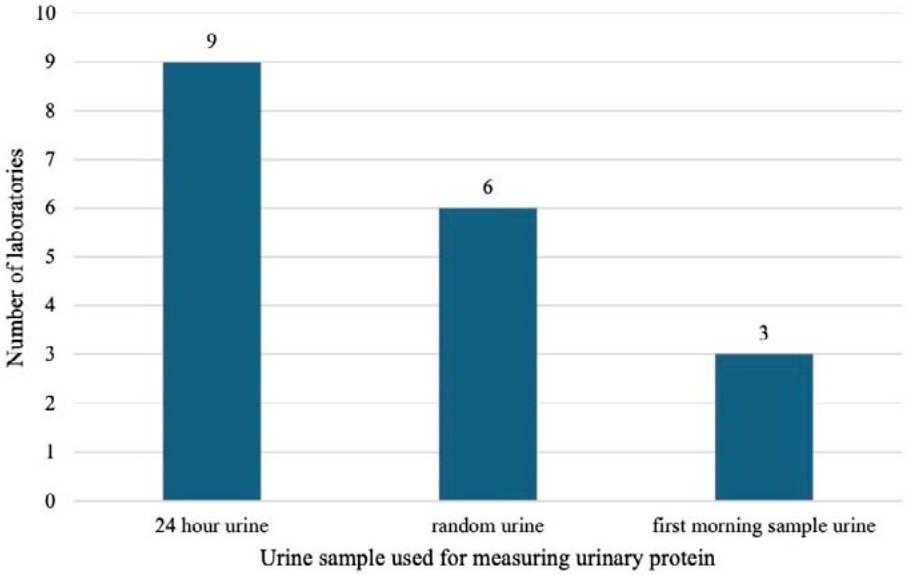


Figure 4B: Methods of urinary protein estimation.

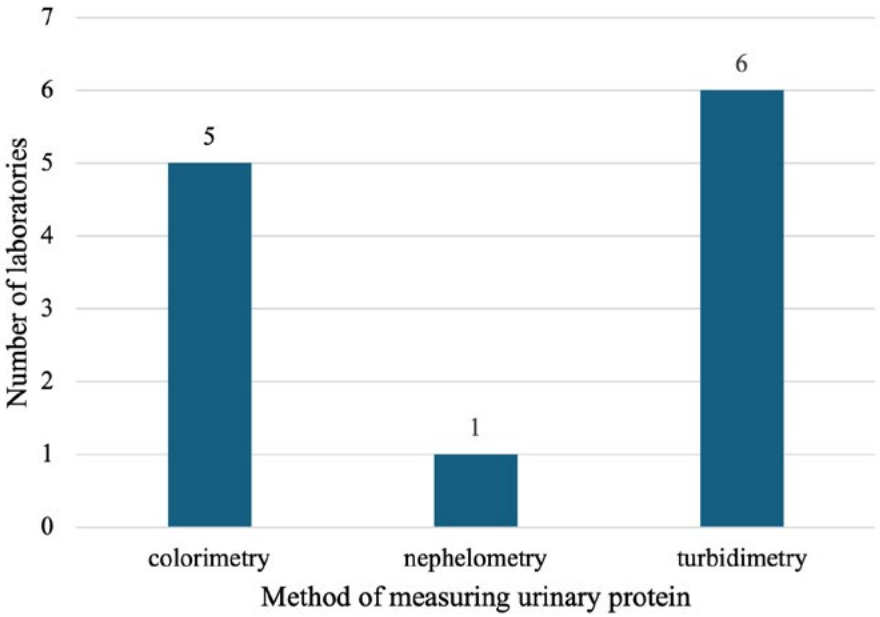


Figure 5A: Preferred urine sample for urinary albumin estimation.

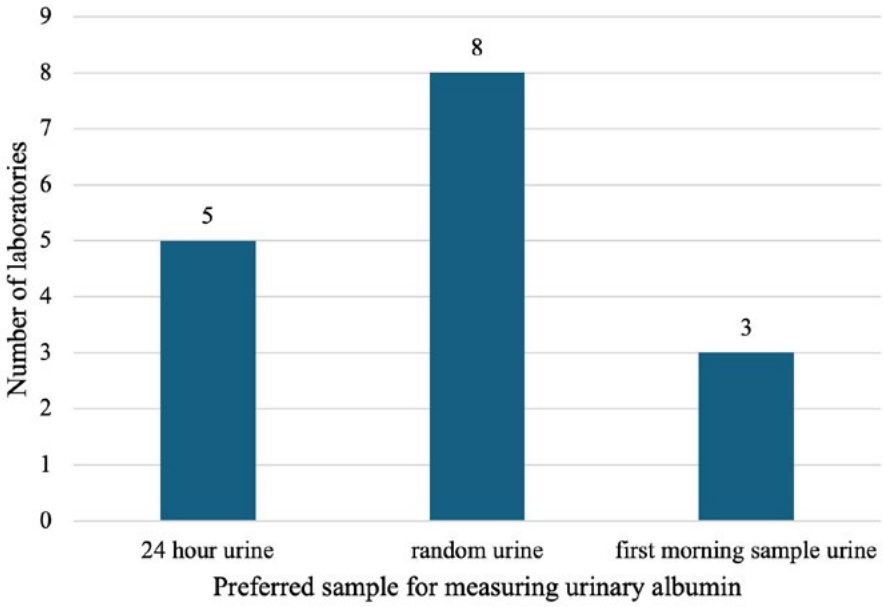
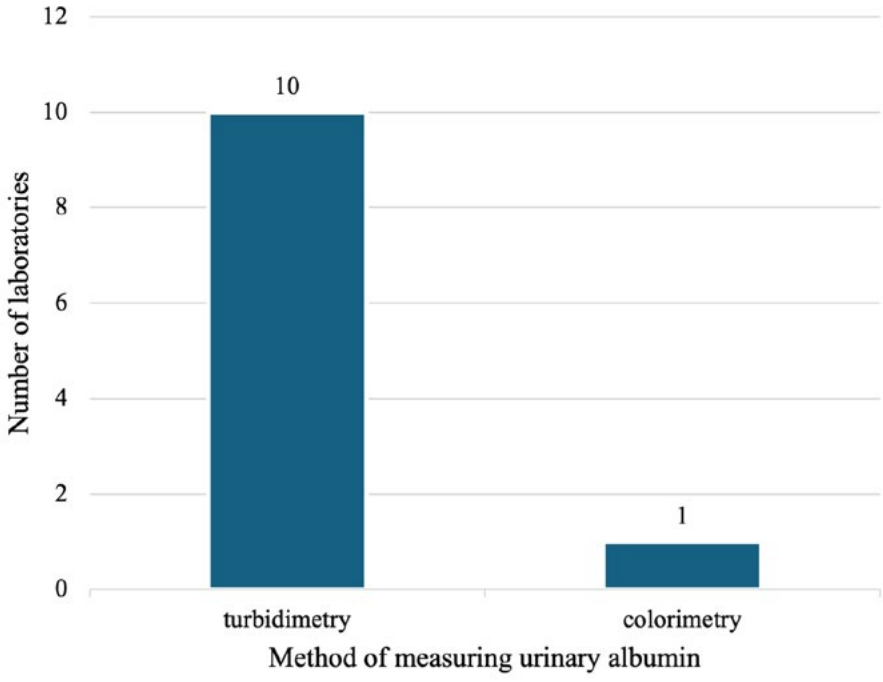


Figure 5B: Methods of urinary albumin estimation.



The analyzers and reference cut-offs used in the measurement of proteinuria and albuminuria are shown in Table 2.

Table 2: Variations in the analyzers and corresponding reagents used in the testing of urinary protein and urinary albumin.

Test	Analyzer	No. of laboratories	Reference Cut-offs
Urinary protein	**Abbott** **Siemens** **Roche**	**3** **2** **6**	**<150mg/dl, <300mg/day, <150mg/day** **<100mg/day, <15mg/dl** **<100mg/day, <300mg/mmol, <150mg/day, <300mg/day**
Urinary albumin	**Abbot** **Siemens** **Roche**	**2** **2** **6**	**<30mg/day, <30mg/g** **30mg/day, >4000 mg/day** **30, <20 mg/L, <30mg/24h** **<30mg/g creatinine, microalbuminuria 30 to 300 mg/g,>300 mg/g macroalbuminuria, <20 mg/L, >34mg/mmol, 30mg/day, >4000 mg/day**

Discussion

Our findings highlight prominent inconsistencies and deviations from recommended guidelines in CKD testing practices across the country. While measuring GFR is the gold standard for assessing kidney function, it is labor-intensive, time-consuming, and expensive, limiting its widespread use. To address these challenges eGFR calculations have been widely adopted, utilizing over 50 predictive equations, primarily based on serum creatinine (SCr) or cystatin C. The National Kidney Disease Education Program (NKDEP) recommends including eGFR with every SCr test, as it provides a more accessible assessment of kidney function and helps identify chronic kidney disease (CKD) without added costs or inconvenience [12, 13]. However, despite nearly 80% of surveyed laboratories estimating GFR using SCr equations, less than half offer reflex reporting of eGFR with every SCr test, indicating a need for improvement.

The majority of surveyed laboratories use the Jaffe technique for SCr measurement due to its low cost. However, variations in SCr measurement methods significantly impact both nephrology research and routine clinical practice. Standardizing SCr measurement, with a preference for the enzymatic method due to its lower variability, is essential for generating more reliable GFR estimates [14, 15].

Cystatin C, an alternative marker for estimating GFR, offers advantages over creatinine due to its reduced influence from muscle mass, diet, and ethnicity. Only 15% of our respondents use cystatin C, which is understandable given its higher costs, assay variability, and incomplete understanding of non-GFR factors affecting its concentration. Consequently, KDIGO and NICE guidelines recommend using cystatin C alongside creatinine primarily for the confirmation of CKD [16, 17].

Various eGFR creatinine equations are being used across Pakistani laboratories, with CKD-EPI 2021 (29%), MDRD (22%), and CKD-EPI Pak (14%) being the most common. Literature suggests that the CKD-EPI Pak equation is more accurate and precise for estimating GFR in the Pakistani population [3], highlighting the need to harmonize its implementation across laboratories in the region. Additionally, less than half of the laboratories are using pediatric equations to estimate GFR in children which warrants immediate attention.

Although most laboratories provide clinical commentary to aid in interpreting GFR results for non-nephrology specialists, many still report exact GFR values. Guidelines recommend expressing GFR values greater than 60 ml/min/1.73m² as “>60 ml/min/1.73m²” due to the limited precision and accuracy of equations at higher values [18]-a practice currently followed by only one Pakistani laboratory.

Interpreting survey results on proteinuria and albuminuria is more challenging, as most participants conducted these tests but reported results in different units, with varying cut-offs even among laboratories using the same analyzers. Methods of measuring proteinuria and albuminuria vary broadly and there is also no consensus on the optimal urine sample type for measuring these markers.

Harmonizing CKD testing is critical, especially given the increasing burden of CKD risk factors like diabetes and hypertension in Pakistan, as well as the rise in CKD of unknown origin (CKDu) in regions close to the equator, including South Asia. Since CKDu often presents with mild or absent proteinuria, simple urinalysis is ineffective for screening, underscoring the need for standardized clinical testing guidelines [19]. Such guidelines can improve clinical practice, care coordination, and drive quality improvement and population health initiatives [20, 21].

Conclusion

In conclusion, our findings underscore the urgent need for standardization and adherence to recommended guidelines in CKD testing practices across Pakistan. Despite the widespread adoption of eGFR calculations, significant gaps remain in

the reflex reporting of eGFR, the standardization of SCr measurement methods, implementation of more accurate equations like CKD-EPI Pak, and utilization of pediatric equations. The inconsistencies in proteinuria and albuminuria testing additionally emphasize the necessity for harmonized practices. Addressing these discrepancies is vital to improving CKD diagnosis and management, particularly in the face of rising CKD risk factors in the region. By standardizing testing protocols, we can enhance clinical practice, improve patient outcomes, and support broader public health efforts.

Conflict of interest statements

The authors declare no conflict of interests.

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None.

Ethical Approval

The study was done in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki, after approval from the institutional ethical review committee (AKU- 2024-9947-28892).

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