

## ORIGINAL ARTICLE

### A national audit of estimated glomerular filtration rate and proteinuria and the MACB CKD Task Force recommendations

Pavai STHANESHWAR<sup>1</sup>, Leslie Charles LAI<sup>2\*</sup>, Raja Elina RAJA AZZIDIN<sup>3</sup>, Baizurah MOHD. HUSSAIN<sup>4</sup>, Siti Sharina ANAS<sup>5</sup>, Sivasangkari SUPREMANIAM<sup>6</sup>, Low Yoke LEE<sup>7</sup>, Nafisah MOHAMAD NOOR<sup>8</sup>, & Harmiza Bte HARUN<sup>8</sup>

<sup>1</sup>Department of Pathology, Faculty of Medicine, University Malaya; <sup>2</sup>Gleneagles Hospital, Kuala Lumpur; <sup>3</sup>Malaysian Association of Clinical Biochemists; <sup>4</sup>Hospital Ampang; <sup>5</sup>Department of Pathology, Hospital Putrajaya; <sup>6</sup>Pathology Department, Women and Children Hospital, Kuala Lumpur; <sup>7</sup>Pantai Premier Pathology Sdn Bhd, Kuala Lumpur; and <sup>8</sup>Department of Pathology, Hospital Kuala Lumpur.

#### Abstract

**Introduction:** The Malaysian Association of Clinical Biochemists (MACB) established a Task Force for Chronic Kidney Disease. A survey was undertaken by the Task Force on the reporting of estimated glomerular filtration rate (eGFR) and urine albumin by hospital laboratories in Malaysia in both the government and private sectors. **Materials and Methods:** An e-mail invitation to participate in an online survey was sent to hospital laboratories in Malaysia (n=140). Questions regarding methods for measuring creatinine, equations for calculating eGFR, eGFR reporting, the terminology used in reporting urine albumin, types of samples and the cut-off values used for normal albuminuria. **Results:** A total of 42/140 (30%) laboratories answered the questionnaire. The prevalent method used for serum creatinine measurement was the Jaffé method (88.1%) traceable to isotope-dilution mass spectrometry. eGFR was reported along with serum creatinine by 61.9% of laboratories while 33.3% of laboratories report eGFR on request. The formula used for eGFR reporting was mainly MDRD (64.3%) and results were reported as exact numbers even when the eGFR was >60 ml/min/1.73m<sup>2</sup>. The term microalbumin is still used by 83.3% of laboratories. There is a large heterogeneity among the labs regarding the type of sample recommended for measuring urine albumin, reference interval and reporting units. **Conclusion:** It is evident that the laboratory assessment of chronic kidney disease in Malaysia is not standardised. It is essential to provide a national framework for standardised reporting of eGFR and urine albumin. Recommendations developed by the MACB CKD Task Force, if adopted by all laboratories, will lead to a reduction in this variability.

**Keywords:** CKD, eGFR, Urine albumin

#### INTRODUCTION

Chronic kidney disease (CKD) represents a significant public health problem because of its associated socio-economic and health consequences. In 2011, the National Health and Morbidity Survey (NHMS) showed a 9.07% prevalence of CKD in West Malaysia.<sup>1</sup> However, the prevalence of CKD in Malaysia had increased to 15.48% in 2018.<sup>2</sup> CKD is defined as an abnormality of kidney structure or function, present for > 3 months. Glomerular filtration rate (GFR) is accepted as the best overall index of kidney function. The criterion for the diagnosis of

CKD is a GFR value < 60 ml/min/1.73m<sup>2</sup>. A GFR < 60 ml/min/1.73m<sup>2</sup> can be detected by routine laboratory testing. Equations for calculating estimated GFR (eGFR) based on serum creatinine (SCr) are sensitive for detecting measured GFR < 60 ml/min/1.73m<sup>2</sup>.<sup>3</sup> The National Pathology Service of Malaysia implemented reporting of eGFR using the Modification of Diet in Renal Disease (MDRD) formula in the year 2012.<sup>4</sup> Pertaining to urine albumin measurement, urine albumin/creatinine ratio of 2.5 to 30 mg/mmol is microalbuminuria in the male and, in the female when the ratio is 3.5 to 30 mg/mmol. A ratio of >

\*Address for correspondence: Leslie Charles Lai, Gleneagles Hospital, Kuala Lumpur, Malaysia. Tel: 03-42510433 Fax: 03-42520433. E-mail: lesliecharleslai@gmail.com

30 mg/mmol is considered as macroalbuminuria/ overt proteinuria.

The Kidney Disease Improving Global Outcomes (KDIGO) CKD Working Group released the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.<sup>5</sup> The diagnosis and staging of CKD are based on eGFR and albuminuria. The recommended formula for reporting eGFR in this guideline is the Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) equation. The requirement for reporting eGFR by CKD-EPI is the measurement of serum creatinine by using standardised assays traceable to isotope-dilution mass spectrometry (IDMS). Regarding the evaluation of albuminuria, the KDIGO guideline recommends the following measurements for initial testing (in descending order of preference, in all cases an early morning urine sample is preferred): 1) urine albumin-to-creatinine ratio (ACR); 2) urine protein-to-creatinine ratio (PCR); 3) reagent strip urinalysis for total protein with automated reading; 4) reagent strip urinalysis for total protein with manual reading. They recommended that the term microalbuminuria should no longer be used by laboratories.

Following the changes in the recommendations of reporting eGFR and albuminuria by the 2012 KDIGO guideline, it was not certain whether laboratories in Malaysia were following the recommendations of the KDIGO guideline in the measurement of serum creatinine, the laboratory reporting of eGFR and urine albumin. This national audit, therefore, was conducted to determine how eGFR and urine albumin is currently reported by Malaysian laboratories in comparison to current KDIGO guidelines. This background of information would be helpful for developing national recommendations. The Malaysian Association of Clinical Biochemists (MACB) formed a CKD Task Force to provide recommendations for the laboratory reporting of eGFR and urine albumin.

## MATERIALS AND METHODS

National guidelines recommending routine reporting of the eGFR, as well as other standardised clinical and laboratory practices, have been published in a number of countries, including Australia and New Zealand, Croatia, Turkey, and the United Kingdom.<sup>6-9</sup> The MACB CKD Task Force prepared an online survey based on questionnaires used in other countries. An

e-mail invitation to participate in the on-line survey was sent to all Chemical Pathologists and Clinical Biochemists of the Ministry of Health, Ministry of Education and private clinical laboratories in Malaysia (n=140). The online survey was performed using the Google form. A simple questionnaire was designed comprising 11 questions (Table 1) seeking information about current practice in biochemistry laboratories regarding laboratory tests for CKD: creatinine, eGFR and urine albumin. Questions about the methods used, reagent manufacturers for measuring creatinine, equations used for calculating eGFR, as well as reporting of eGFR were included. Regarding urine albumin, information on the types of samples used for measuring, units of measurement, reference interval and the terminology used was sought. Data received were tabulated in Microsoft Excel. Results are presented as absolute numbers and percentages.

## RESULTS

A limitation of this study is the low percentage of laboratories that completed the survey. Only 42 of the 140 laboratories (30%) invited to participate answered the questionnaire. Responses were received from four Ministry of Education hospital laboratories, 25 Ministry of Health laboratories and 13 private laboratories.

### Creatinine

KDIGO 2012 recommended that clinical laboratories should measure serum creatinine using a specific assay with calibration traceable to international standard reference materials and have minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology. Thirty-seven laboratories measured serum creatinine by the Jaffé method (88.1%) and the enzymatic method was used by the remaining laboratories. Forty of the laboratories (95%) that responded, used methods that were traceable to IDMS. In March 2011, Siemens Healthcare Diagnostics issued a technical bulletin that provided a correction factor to enable reporting of IDMS traceable results for the Jaffé methods used with Dimension and Vista analysers.<sup>10</sup> Five of the 37 laboratories (13.5%) used correction factors to report serum creatinine. Only two of these five laboratories used the appropriate correction factor as recommended by the manufacturer.

**TABLE 1: Survey form for eGFR and urine albumin reporting**

1. Which serum creatinine method do you use?
 

Principle of the assay	Enzymatic	Jaffe
Reagent supplier:		
Calibration to IDMS	Yes	No
  
2. Are the serum creatinine results adjusted with any factors to report results?
 

Factor used	Yes	No
If yes, what adjustments had been made?		
  
3. Do you report eGFR in your lab?
 

Reporting eGFR	Yes	No
----------------	-----	----
  
4. If so, which formula are you using to report eGFR?
 

Formula	MDRD	CKD-EPI
If other formula is used, name of the formula.....		
  
5. How do you report eGFR?
 

Upper threshold used	≥ 60 mL/min/1.73 m <sup>2</sup>	≥ 90mL/min/1.73 m <sup>2</sup>
Do you report more than 90mL/min/1.73 m <sup>2</sup> ?	Yes	No
  
6. Which terminology is being used in the laboratory regarding urine albumin?
 

Terminology used:	Microalbumin	Albumin
-------------------	--------------	---------
  
7. What type of sample is recommended by the laboratory?
 

Sample type:	24 hours urine
	Timed urine collection (state the time period.....)
	Random spot sample
	Early morning urine sample
  
8. What is the reporting unit used for spot urine sample?
 

Unit used:	mg/L	g/L	µg/mL	mg/mmol	g/mol
------------	------	-----	-------	---------	-------
  
9. What is the unit used for timed urine sample?
 

Unit used:	mg/L	g/L	mg/day	g/min	g/day
------------	------	-----	--------	-------	-------
  
10. Reference interval used by the laboratory in reporting timed urine sample
 

Reference interval used by the laboratory	.....
Unit used by the laboratory	.....
  
11. Reference interval used by the laboratory for reporting albumin creatinine ratio
 

Reference interval used by the laboratory	.....
Unit used by the laboratory	.....

### Estimated glomerular filtration rate

KDIGO recommended that  $eGFR_{\text{creat}}$  should be reported in addition to the serum creatinine concentration in adults and the equation used should be specified whenever  $eGFR_{\text{creat}}$  is reported. The KDIGO guideline recommended that the 2009 CKD-EPI equation should be used to report  $eGFR_{\text{creat}}$  in adults. An alternative to the creatinine-based GFR estimating equation is acceptable if it has been shown to improve the accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation. Teo *et al.* recommended adopting the CKD-EPI creatinine equation without ethnic adjustment for estimating GFR in multiethnic Asian patients with CKD.<sup>11</sup>

$eGFR$  was reported along with serum creatinine by 26 (61.9%) of the laboratories while 14 (33.3%) of the laboratories reported  $eGFR$  only on request. Two laboratories did not report  $eGFR$  at all. The most commonly used formula for calculating  $eGFR$  was the MDRD equation. Twenty-seven (27) laboratories (64.3%) used the MDRD equation and 15 laboratories used the CKD-EPI equation in calculating  $eGFR$ . Two laboratories used both the MDRD and CKD-EPI equations to calculate  $eGFR$  and reported both values. The survey also enquired about formula other than MDRD and CKD-EPI that was used by the laboratory to calculate  $eGFR$  and one lab responded stating that the Cockcroft-Gault formula was used to calculate  $eGFR$  on request.

The MDRD equation was developed and recommended for  $eGFR$  reporting in adults by the National Kidney Disease Education Program (NKDEP) and by the Department of Health in the UK.<sup>12,13</sup> Because of imprecision at higher GFR, NKDEP recommended that  $eGFR > 60 \text{ mL/min/1.73m}^2$  computed using the MDRD equation should not be reported as a numeric value.<sup>5</sup> The CKD-EPI equation has less bias than the MDRD equation, especially at  $GFR > 60 \text{ mL/min/1.73m}^2$ , a small improvement in precision and a greater accuracy, and can be reported up to values of  $90 \text{ mL/min/1.73 m}^2$ .<sup>5</sup> Values above  $90 \text{ mL/min/1.73 m}^2$  will be reported as  $> 90 \text{ mL/min/1.73 m}^2$ . Thirty-two laboratories (76%) reported results as exact numbers regardless of the  $eGFR$  cut-off values for the MDRD and CKD-EPI equations.

### Urine albumin

KDIGO recommended the following measurements for the initial testing of proteinuria, in descending order of preference on an early morning urine sample:

- 1) urine albumin-to-creatinine ratio (ACR)
- 2) urine protein-to-creatinine ratio (PCR)
- 3) reagent strip urinalysis for total protein with automated reading
- 4) reagent strip urinalysis for total protein with manual reading.

The term albuminuria should be used. Microalbuminuria should no longer be used.

The audit revealed that the preferred terminology for 35 laboratories (83.3%) when reporting urine albumin is still microalbumin. There was a wide disparity regarding the preferred urine specimen type for measurement of urine albumin, ranging from 24 h urine samples, random spot urine samples and first void morning spot urine samples. However, 23 laboratories (54.8%) were receiving random spot urine samples and only 11 laboratories (23.8%) received first morning spot urine samples.

Reporting units and cut-off values:

The recommended units for reporting ACR and Albumin Excretion Rate (AER) are mg/mmol and mg/24 hours, respectively. The KDIGO recommended normal or mild albuminuria reference intervals for ACR and AER are  $< 3.0 \text{ mg/mmol}$  and  $< 30 \text{ mg/24 hours}$ , respectively. Eight laboratories (19%) reported AER and the reporting unit was in mg/L with no appropriate reference intervals. Only 23 laboratories (55%) reported ACR in mg/mmol and 15 of the 23 laboratories (65%) used gender-specific reference intervals for ACR.

### DISCUSSION

Laboratory medicine plays an important role in the diagnosis and management of CKD. As per the KIDGO 2012 guideline, the two simple laboratory tests for screening of CKD are  $eGFR$  and assessment of albuminuria. Survey results about these biomarkers of kidney damage show considerable heterogeneity among the laboratories in Malaysia. Hence, the MACB CKD Task Force prepared recommendations on laboratory reporting of  $eGFR$  and urine albumin based on the KDIGO 2012 and NICE guidelines.<sup>6,14</sup>

Recommendations for laboratory reporting of estimated glomerular filtration rate ( $eGFR$ ):

1. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation shall be used in the calculation of  $eGFR$  and not the Modification of Diet in Renal Disease (MDRD) equation.

2. eGFR values < 90 ml/min/1.73m<sup>2</sup> shall be reported as whole numbers.
  3. eGFR values > 90 ml/min/1.73m<sup>2</sup> shall be reported as > 90 ml/min/1.73m<sup>2</sup>.
  4. eGFR shall be calculated for all creatinine measurements EXCEPT for people < 18 years of age and pregnant women.
  5. Patients shall be advised to abstain from consuming any meat in the 12 hours before a blood test for serum creatinine as a protein meal can raise serum creatinine levels substantially and lead to low eGFR values.
  6. Creatinine measurement shall be traceable to isotope-dilution mass spectrometry (IDMS). A specific method for creatinine measurement (enzymatic method) is preferred. The analytical imprecision of the creatinine assay should be less than 3%, bias less than 4% and the total allowable error of less than 8.9%.<sup>15</sup>
  7. Where a correction factor has been provided by a manufacturer to enable reporting of IDMS-traceable results for the Jaffé methods, this correction factor shall be used to conform to the recommendation that all creatinine procedures have calibration traceable to the IDMS reference measurement procedure.
  8. A correction factor shall be applied in the calculation of eGFR using the CKD-EPI equation for people of African-Caribbean or African family origin (multiply eGFR by 1.159 where creatinine is measured in SI units).
  9. eGFR has to be interpreted with caution in people with extremes of muscle mass or certain illnesses (e.g., bodybuilders, people who have had amputations, muscle wasting disorders, acute myocardial infarction and acute kidney injury).
  10. After the age of 30 years, the glomerular filtration rate (GFR) progressively declines at an average rate of 8 ml/min/1.73m<sup>2</sup> per decade. There is considerable debate regarding the significance of this age-related decline in kidney function, which has been variously attributed to the effects of hypertension, atherosclerosis, or other comorbidities such as cardiovascular disease. Recent evidence suggests that even very elderly patients (> 80 years of age) with modest reductions in eGFR (45–59 ml/min/1.73m<sup>2</sup>) have a higher prevalence of CKD-related complications compared to patients with an eGFR ≥ 60 ml/min/1.73m<sup>2</sup>.
  11. Serum creatinine must be measured within 12 hours of venepuncture as serum creatinine levels increase beyond 12 hours with the kinetic Jaffé method but not with the enzymatic method.
  12. Laboratories using methods for creatinine measurement that are not IDMS-aligned shall not calculate eGFR using the IDMS-aligned CKD-EPI or MDRD equations as the values will be erroneous.
  13. All laboratories that measure creatinine must participate in a national or an international external quality assessment scheme for creatinine.
- Recommendations for laboratory reporting of urine albumin
1. Albuminuria shall replace the term microalbuminuria.
  2. Albumin to Creatinine Ratio (ACR) shall replace Protein to Creatinine Ratio (PCR) in the initial screening for proteinuria for the following reasons:
    - I. ACR has greater sensitivity than PCR for low levels of proteinuria.
    - II. Albumin measurement can be standardised and is more precise at low levels of proteinuria.
    - III. Albumin is the predominant protein in the vast majority of proteinuric kidney diseases.
    - IV. Total protein measurement is non-specific and subject to a range of false positive and false negative problems.
  3. The first void urine in the morning shall be used for the measurement of ACR for the following reasons:
    - I. Large day-to-day variation in urine albumin excretion of up to 40%.
    - II. This variation is less with the first void urine sample in the morning than with a random urine sample.
  4. For quantification and monitoring of large amounts of urine protein, > 70 mg/mmol, PCR may be used as an alternative.
  5. PCR may be measured in hypertensive disorders of pregnancy, as stated in current NICE guidelines on hypertensive disorders of pregnancy, when there is significant proteinuria, i.e., when urine PCR is > 30 mg/mmol or a validated 24-hour urine collection result is > 300 mg protein.
  6. ACR, and not PCR, is recommended for screening people with diabetes.
  7. In the initial detection of proteinuria/albuminuria, if the initial urine ACR is

between 3 and 70 mg/mmol this should be confirmed by measuring ACR on another early morning urine sample within 3 months. If the second urine sample is < 3 mg/mmol then a third early morning urine sample is required to confirm albuminuria (value > 3 mg/mmol) within 6 months of the first urine sample. (Algorithm A is recommended but Algorithm B may be used if financial resources are limited.)

8. If the initial urine ACR is > 70 mg/mmol a repeat urine sample need not be tested.
9. A 24-hour urine albumin excretion rate

may be measured to monitor patients after albuminuria has been confirmed but is not recommended for the initial detection of proteinuria/albuminuria.

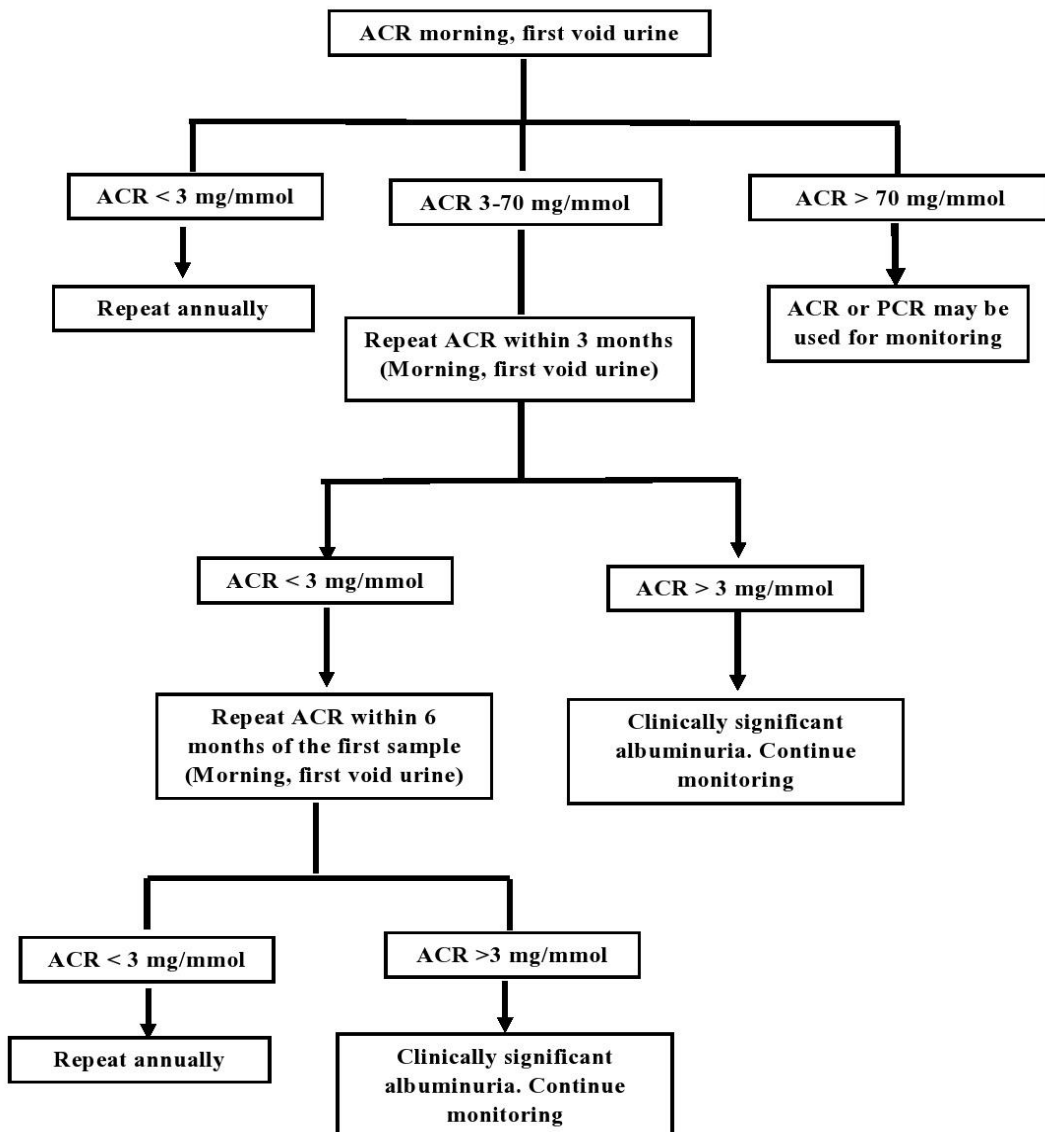
10. A 24-hour urine albumin concentration alone shall not be reported but as part of a report of albumin excretion rate.

**CONCLUSION**

It is evident from the survey results that many laboratories still use the MDRD formula and report exact numbers obtained even for values

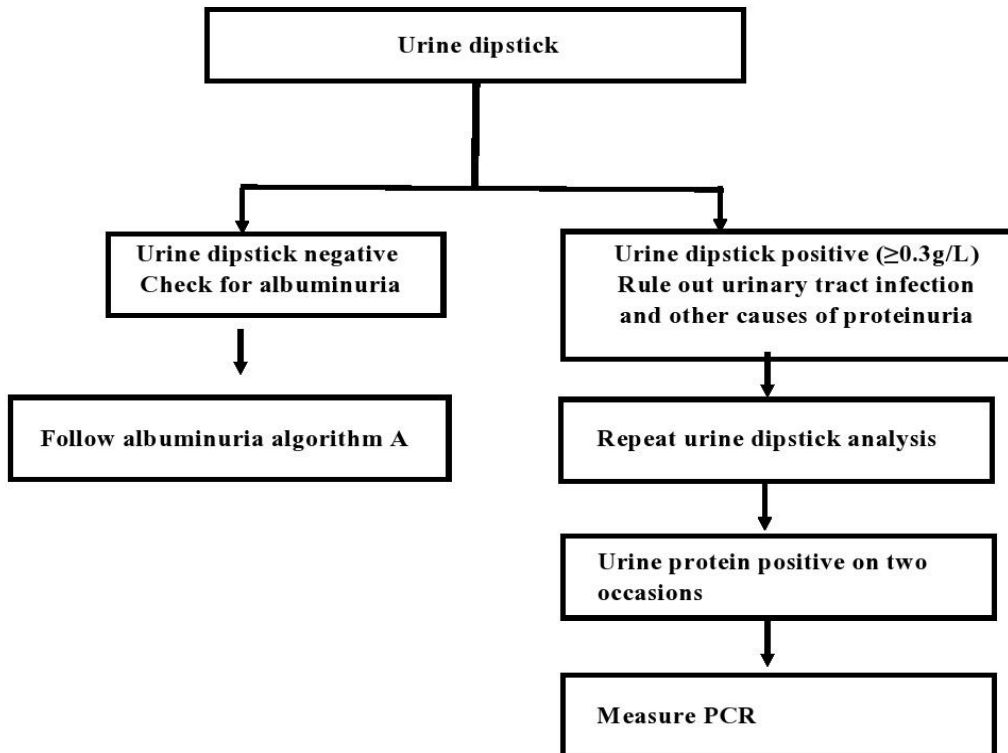
**ALGORITHM A**

**ASSESSMENT OF ALBUMINURIA IN CHRONIC KIDNEY DISEASE (CKD)**



**ALGORITHM B (may be used when financial resources as limited)**

**REAGENT STRIP USED FOR INITIAL SCREENING FOR PROTEINURIA**



> 60 ml/min/1.73m<sup>2</sup> for MDRD or > 90 ml/min/1.73m<sup>2</sup> for CKD-EPI. Reporting an eGFR value with every serum creatinine result is not done routinely. There is large heterogeneity in urine samples recommended, reference intervals and types of units in albuminuria measurement. The challenge is to provide standardised and harmonised information to all possible recipients. Recommendations developed by MACB CKD Task Force, if adopted by all laboratories, will lead to a reduction in this variability.

*Authors' contribution:* Pavai STHANESHWAR is the principal author and developed the questionnaire and analysed the questionnaire used in the survey. All other authors contributed to the writing of this paper and the finalisation of the questionnaire used in the survey. All authors are members of the MACB CKD Task Force, chaired by Leslie C LAI, and contributed to the development of these guidelines.

*Conflict of interest:* The authors declare no conflict of interest.

**REFERENCES**

1. Hooi LS1, Ong LM, Ahmad G, *et al.* A population-based study measuring the prevalence of chronic kidney disease among adults in West Malaysia. *Kidney Int.* 2013; 84: 1034-40.
2. Bavanandam S, Saminathan Tamil Arasu TA, Hooi LS, *et al.* "Is Chronic Kidney Disease on the rise in Malaysia? Findings from a nationwide study" *Int Rep.* 2019; 4: S1-S437.
3. Stevens LA, Coresh J, Greene T, Levey SA. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473-83.
4. Laboratory Investigation Guidelines for Chronic Kidney Disease and utilisation of eGFR in Adults. [www.patologi.gov.my > assets > policy > JD005805Guideline](http://www.patologi.gov.my/assets/policy/JD005805Guideline)
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int.* 2013; 3: 1-150.
6. Jones GR. Laboratory reporting of urine albumin. *Clin Biochem Rev.* 2011; 32: 103-7.
7. Kilpatrick ES, Verrill H; National Clinical Biochemistry Audit Group. A national audit of estimated glomerular filtration rate and proteinuria

- reporting in the UK. *Ann Clin Biochem.* 2011; 48: 558-61.
8. Biljak VR, Honović L, Matica J, Knežević B, Vojak SŠ. Laboratory diagnostics of chronic kidney disease in Croatia: state of the art. *Biochem Med (Zagreb).* 2015; 25: 73-83.
  9. Johnson DW, Jones GR, Mathew TH, *et al.* Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. *Med J Aust.* 2012; 197: 224-5.
  10. Creatinine Standardization Recommendations NIDDK. [Internet]. Available from <https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate/creatinine-standardization/recommendations>.
  11. Teo BW, Koh YY, Toh QC, *et al.* Performance of the CKD-EPI creatinine-cystatin C glomerular filtration rate estimation equations in a multiethnic Asian population. *Singapore Med J.* 2014; 55: 656-9.
  12. Levey AS, Coresh J, Greene T, *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006; 145: 247-54.
  13. Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999; 130: 461-70.
  14. Clinical Guidelines on Chronic kidney disease in adults: assessment and management. Published on 23 July 2014. [nice.org.uk/guidance/cg182](http://nice.org.uk/guidance/cg182).
  15. Biljak VR, Honović L, Matica J, *et al.* The role of laboratory testing in detection and classification of chronic kidney disease: national recommendations. *Biochem Med (Zagreb).* 2017; 27: 153-76.