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Development and validation of creatinine-based estimates of the glomerular filtration rate equation from chromium EDTA imaging in the multiracial Malaysian population

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Abstract

Introduction: The glomerular filtration rate (GFR) is a reliable parameter for assessing kidney function. It is estimated from equations such as Cockcroft–Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease- Epidemiology Collaboration (CKD-EPI). However, these equations were derived using Western population demographic data and had different performances when applied to other ethnicities and populations.
Objective: We developed a new equation (NE) based on the ^{51}Cr-EDTA-measured GFR, that can be used explicitly in the Malaysian multiracial population.
Methods: A cross-sectional study was conducted using electronic medical records of patients who underwent 51Cr-EDTA imaging between 2013 and 2021. Ethical approval was obtained.

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Results: A total of 209 patients were recruited, of which 105 patients were randomised to the development cohort and 104 patients to the validation cohort. The NE was developed using the development cohort data, and its performance was subsequently tested in the validation cohort. The result showed that CKD-EPI had the highest precision and accuracy in estimating GFR. CG had the lowest bias, while the NE performed second best. CKD-EPI had the highest correlation to ^{51}Cr-EDTA imaging-measured GFR, followed by the NE.
Conclusion: CKD-EPI demonstrated the best performance among the estimated GFR equations. However, NE showed comparable performance, exhibiting low bias, high precision, and good accuracy.

Keywords: ^{51}Cr EDTA-measured glomerular filtration rate, glomerular filtration rate equations, Malaysia, multiracial population

Introduction

Chronic kidney disease (CKD) is a global health concern, causing significant socioeconomic and healthcare challenges. It is not only a progressive disease, but also a significant risk factor for coronary events and mortality. Fortunately, CKD is treatable and preventable. Early detection of kidney dysfunction and appropriate management can prevent deterioration of kidney function and thus reduce the risk of dialysis.[1] Serum creatinine is commonly used in clinical practice as a marker of kidney function. However, interpretation based on serum creatinine alone is not accurate, as its levels are influenced by factors such as muscle mass, age, and dietary lifestyle.[2]

A more reliable indicator of kidney function is the glomerular filtration rate (GFR). Accurate estimation of GFR is essential in daily clinical practices, where it affects drug dosing, nutrition in critically ill patients, fluid requirement, and staging of kidney disease.[1] GFR can be measured directly using inulin, ^{51}chromium ethylenediamine tetra-acetic acid (^{51}Cr-EDTA), technetium-99m diethylene-triaminepenta-acetic acid (99mTC-DTPA), and iohexol. However, these direct measurement methods are expensive, complex, time-consuming, and not widely available. Therefore, it is essential to have a reliable, convenient, and precise method to estimate GFR in the clinical setting.[3]

Several equations are used to estimate GFR, including Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI),[4] Modification of Diet in Renal Disease (MDRD),[5] and Cockcroft–Gault (CG).[6] However, these equations were derived using Western population demographic data and perform differently when applied to

other ethnicities and populations.[7-9] Countries such as China, Korea, Japan, and Thailand have recognised this issue, and have modified these equations by incorporating ethnic-specific coefficients to enhance accuracy for their populations.[10-13]

There have been a few studies conducted in Malaysia to evaluate the performance of existing estimating GFR equations in the Malaysian population by comparing the calculated GFR with the GFR value measured by ^{51}Cr-EDTA,[3,14.15] and the performance of the equations varied. The study conducted by Ralib *et al.* aimed to develop an estimated GFR (eGFR) equation that tailored to the Malaysian population. However, this study primarily examined patients from East Coast of Malaysia, who were predominantly of Malay ethnicity, thereby lacking representation from other major ethnic groups in Malaysia, such as the Chinese and Indian populations.[9] Therefore, the findings may not be fully generalisable to the broader Malaysian demographic.

Our study aimed to develop a new equation (NE) based on measured GFR obtained from ^{51}Cr-EDTA imaging that can be explicitly used in our population. All equations were evaluated in the validation cohort, comparing the bias, precision, and accuracy.

Methods and materials

This was a cross-sectional study conducted at the University Malaya Medical Centre (UMMC). Ethical approval was obtained from the Medical Research Ethics Committee, UMMC (MREC ID NO:2021105-10644). This study involved the electronic medical records (EMR) of patients who underwent 51Cr-EDTA imaging at the Nuclear Medicine Centre, UMMC. Patients aged 16-year-old and above who underwent ^{51}Cr-EDTA imaging at the Nuclear Medicine Centre, UMMC from the year 2013 to 2021 were included in this study. We excluded patients of races other than Malay, Chinese, and Indian, as well as inadequate or missing data in the EMR.

A name list of patients who underwent ^{51}Cr-EDTA imaging was obtained from the Department of Radiology, and the records of the patients were traced via the EMR. Demographic data and renal function of the patients were collected, including age, gender, height, weight, ethnicity, and urea and creatinine level. In patients with multiple measurements of scans, the latest ^{51}Cr-EDTA imaging result was taken. The renal function test had to be within 3 months from the date of ^{51}Cr-EDTA imaging.

Patients were randomised into a development and validation cohort using a random number generated in Microsoft Excel. The data were then analysed using SPSS 26 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were performed on

demographic data and clinical variables. Parametric data were presented as mean ± SD, whereas skewed data sets were shown in the median (interquartile range). Independent t-test was used to compare 2 parametric variables, and Mann-Whitney U test was used for non-parametric variables. Analysis of categorical variables was done using the Chi-square test. Linear regression was performed to evaluate the relationship between estimated and measured GFR. We considered statistical significance at $P < 0.05$.

A new eGFR equation (NE) was developed using a non-linear regression model and a generalised least squares algorithm in the development cohort. Internal validation was performed in the validation cohort by comparing accuracy, bias, precision, and Pearson correlation between all the formulas (NE, CG, MDRD, and CKR-EPI) and the measured GFR.

The accuracy of equations was denoted as the proportion of eGFR values that lay within 30% and 50% of measured GFR, mean absolute value (MAE), and root mean square error (RMSE) of difference between measured and estimated values. Bland-Altman plot was performed in the validation cohort to test the agreement between estimated and measured GFR by looking at mean bias and precision. Mean bias was defined as the average differences between measured GFR and estimated GFR in the dataset. Precision was defined by the standard deviation of the differences between estimated and measured GFR

Results

A total of 486 qualified patients were identified from the EMR. However, a total of 277 patients were excluded from this study; of these, 149 of them were less than 16 years old, 127 of the patient's data were missing, and 1 of the patients was a foreigner. Thus, a total of 209 patients were successfully recruited into the study (Fig. 1). The included patients were then randomised into 2 cohorts: the developmental cohort (105 patients) and the validation cohort (104 patients).

Table 1 shows the demographic and renal function of the patients in the study. No statistical differences were found in demographic and renal function between the development and the validation groups. The mean of CG (105.03 ml/min) is nearest to the mean measured GFR (107.52 ml/min), followed by the mean of the NE.

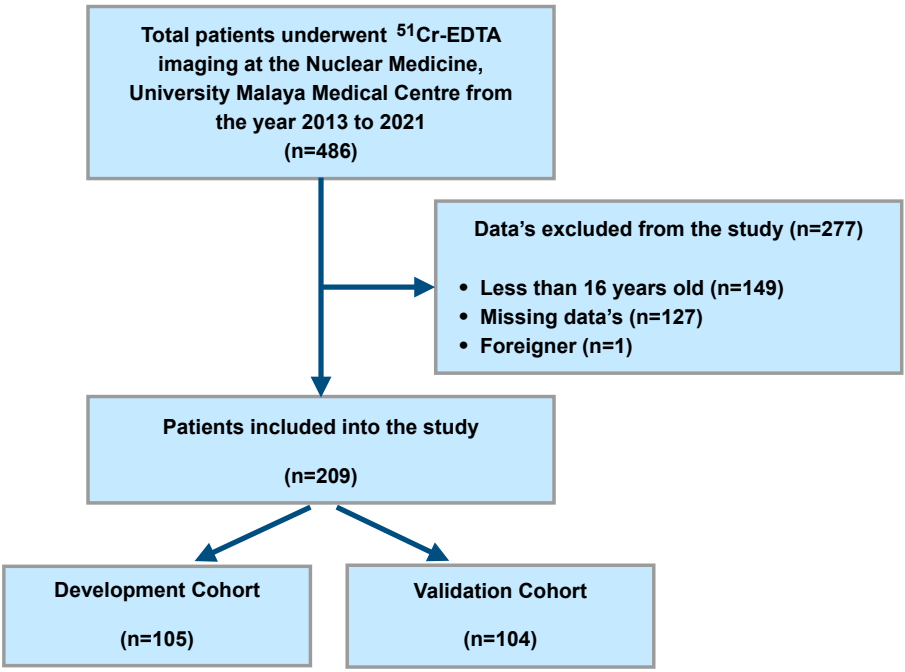


Fig. 1. Process of patient recruitment.

Development of a new equation of eGFR from the development cohort

A total of 105 patients was randomised into the development cohort. We used generalised least square algorithm to the NE (Fig. 2). The GFR was regressed against the patients' serum creatinine in the development cohort. The R^2 value for equation ethnicity 1 (Malay) was 0.525, with an adjusted value of 0.498; for equation ethnicity 2 (Chinese) was 0.305, with an adjusted value of 0.275; and for ethnicity 3 (Indian) was 0.31 with an adjusted value of 0.218 (Fig. 3).

Internal validation from the validation cohort

We validated the newly developed equation in 104 patients in the validation cohort. The mean eGFR value obtained from the NE was 111.04 ml/min, higher than the measured GFR in the validation cohort, which was 107.52 (Table 1). The CKD-EPI equation had estimated the lowest mean of eGFR among all the equations.

Table 1. Demographic and renal function of the patients.

Variables	All patients (*n* = 209)	Development cohort (*n* = 105)	Validation cohort (*n* = 104)	*P* value
Age (years)	49.95 ± 15.26	49.78 ± 15.89	50.10 ± 14.66	0.87
Gender				
Male	88 (42.11)	51 (48.6)	37 (35.58)	0.06
Female	121 (57.89)	54 (51.4)	67 (64.42)	
Weight (kg)	67.81 ± 15.7	68.30 ± 14.65	67.3 ± 16.75	0.65
Height (cm)	160.33 ± 8.90	160.85 ± 8.81	159.80 ± 9	0.4
Body mass index (kg/m2)	26.26 ± 5.10	26.30 ± 4.82	26.22 ± 5.39	0.92
Ethnicity				
Malay	68 (32.54)	38 (36.2)	30 (28.85)	0.4
Chinese	107 (51.20)	49 (46.7)	58 (55.77)	
Indian	34 (16.26)	18 (17.1)	16 (15.38)	
99mTc-DTPA-measured GFR (ml/min)	107.03 ± 38.01	106.54 ± 38.27	107.52 ± 37.92	0.85
Plasma creatinine (µmol/L)	63 (52-84.5)	59 (54-91.5)	60(51.25-80.5)	0.06
Estimated GFR by CG (ml/min)	102.79 ± 43.28	100.56 ± 42.44	105.03 ± 44.21	0.46
Estimated GFR by MDRD (ml/min)	100.6 ± 38.62	98.39 ± 40.35	102.83 ± 36.84	0.41
Estimated GFR by CKD-EPI (ml/min)	93.82 ± 28.71	92.60 ± 28.53	95.05 ± 28.98	0.49
Estimated GFR by NE (ml/min)	108.83 ± 25.42	106.64 ± 25.92	111.04 ± 24.82	0.21

GFR: glomerular filtration rate; CG: Cockcroft–Gault; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; NE: new equation
Qualitative data are expressed as number (%).
Parametric data are expressed as the mean ± SD.
Non-parametric data are expressed as median (interquartile range).

$$GFR = \begin{cases} 28.219(0.9925)^{Age}\left(\frac{S_{Cr}}{15.779}\right)^{-0.5780} & if\ Ethnicity = 1 \\ 34.099(0.9967)^{Age}\left(\frac{S_{Cr}}{26.266}\right)^{-0.3849} & if\ Ethnicity = 2 \\ 54.628(0.9869)^{Age}\left(\frac{S_{Cr}}{976480}\right)^{-0.08464} & if\ Ethnicity = 3 \end{cases}$$

Fig. 2. A new equation was developed to estimate GFR.

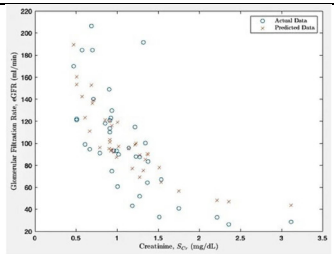
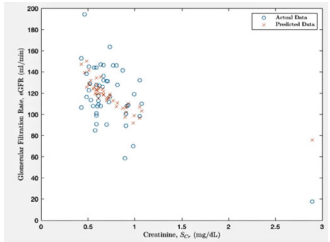
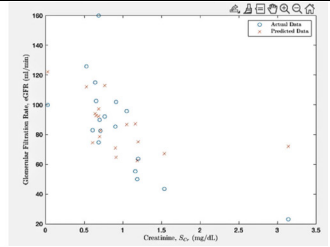
Ethnicity		
1 **MALAY**		Nonlinear regression model: y ~ (b1*((x1/b2)^ - b3)*(b4^x2)) Estimated Coefficients: Estimate SE tStat pValue b1 28.219 7.0676 3.9927 0.00031887 b2 15.779 7.3069 2.1594 0.037756 b3 0.57801 0.15028 3.8461 0.00048603 b4 0.9925 0.0033998 291.93 7.2514e-61 Number of observations: 38, Error degrees of freedom: 35 Root Mean Squared Error: 33.1 R-Squared: 0.525, Adjusted R-Squared 0.498 F-statistic vs. zero model: 131, p-value = 4.24e-19
2 **CHINESE**		Nonlinear regression model: y ~ (b1*((x1/b2)^ - b3)*(b4^x2)) Estimated Coefficients: Estimate SE tStat pValue b1 34.099 11.28 3.023 0.0040826 b2 26.266 5.6389 4.6581 2.7417e-05 b3 0.38493 0.1064 3.6178 0.00073589 b4 0.99674 0.0020279 491.52 3.1545e-87 Number of observations: 49, Error degrees of freedom: 46 Root Mean Squared Error: 24.1 R-Squared: 0.305, Adjusted R-Squared 0.275 F-statistic vs. zero model: 401, p-value = 5.67e-33
3 **INDIAN**		Nonlinear regression model: y ~ (b1*((x1/b2)^ - b3)*(b4^x2)) Estimated Coefficients: Estimate SE tStat pValue b1 54.618 63.926 0.8544 0.40632 b2 9.7648e+05 0.00030283 3.2245e+09 3.1657e-135 b3 0.08464 0.071311 1.1869 0.25372 b4 0.98685 0.0068664 143.72 5.7839e-25 Number of observations: 18, Error degrees of freedom: 15 Root Mean Squared Error: 28.3 R-Squared: 0.31, Adjusted R-Squared 0.218 F-statistic vs. zero model: 57.3, p-value = 1.91e-08

Fig. 3. Linear regression model of GFR and serum creatinine of patients in the development cohort.

Table 2 shows the correlation analysis between eGFR and measured GFR. CKD-EPI had the highest positive correlation ($R = 0.82$), followed by the NE ($R = 0.76$). CKD-EPI also had the highest ability to predict the actual GFR, with an R^2 value of 0.67, followed by the NE with an R^2 value of 0.58.

Table 3 highlights the performance of various eGFR equations in terms of accuracy. Among the equations, the CKD-EPI demonstrated the highest accuracy, achieving 85.58% in P30 and 100% in P50 for estimating GFR, outperforming all other equations. Furthermore, CKD-EPI exhibited both low MAE and low RMSE. Notably, the NE equation recorded the lowest RMSE among all eGFR equations,

Bland-Altman analyses were performed to measure the agreement between all eGFR equations and measured GFR (Fig. 4). CG and NE had the least bias of 2.46 ml/min and 3.52ml/min, respectively. On the other hand, CKD-EPI had the most precision to estimate GFR, with the lowest SD of 22.04 ml/min, followed by NE with an SD value of 25.05 ml/min.

Table 2. Correlation analysis between eGFR and measured GFR

	Equations	***R***	**95% CI**	***R²***	***p***
^{51}Cr-EDTA measured-GFR	CG	0.66	0.52 to 0.71	0.44	< 0.001
	MDRD	0.73	0.60 to 0.86	0.53	< 0.001
	CKD-EPI	0.82	0.70 to 0.93	0.67	< 0.001
	NE	0.76	0.63 to 0.89	0.58	< 0.001

GFR: glomerular filtration rate; CG: Cockcroft–Gault; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; NE: new equation

Table 3. Accuracy of eGFR equations

	P_{30} (%)	**P_{50} (%)**	**MAE (ml/min)**	**RMSE (ml/min)**
CG	72.12	91.35	25.11	34.03
MDRD	81.73	96.15	20.76	27.8
CKD-EPI	85.58	100	18.5	25.24
NE	77.88	84.62	19.37	25.19

CG: Cockcroft–Gault; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; NE: new equation; MAE: mean absolute value; RMSE: root mean square error

Table 4. Bland-Altman analyses between eGFR and measured GFR

Equation	Mean bias ± SD (ml/min)	Differences (IQR)	Percent differences (IQR)
CG	2.49 ± 3.41	-7.08 (-21.22–13.99)	-8.45 (-19.94–12.84)
MDRD	4.69 ± 27.54	-5.2 (20.41–9.94)	-4.4 (-21.51–11.08)
CKD-EPI	12.47 ± 22.04	-9.45 (-24.83–1.56)	-9.6 (-21.49–1.82)
NE	3.52 ± 25.05	3.76 (-10.83–21.73)	3.77 (-8.96–21.09)

IQR: interquartile range; CG: Cockcroft–Gault; CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; NE: new equation
Parametric data are expressed as the mean ± SD.
Non-parametric data are expressed as median (interquartile range).

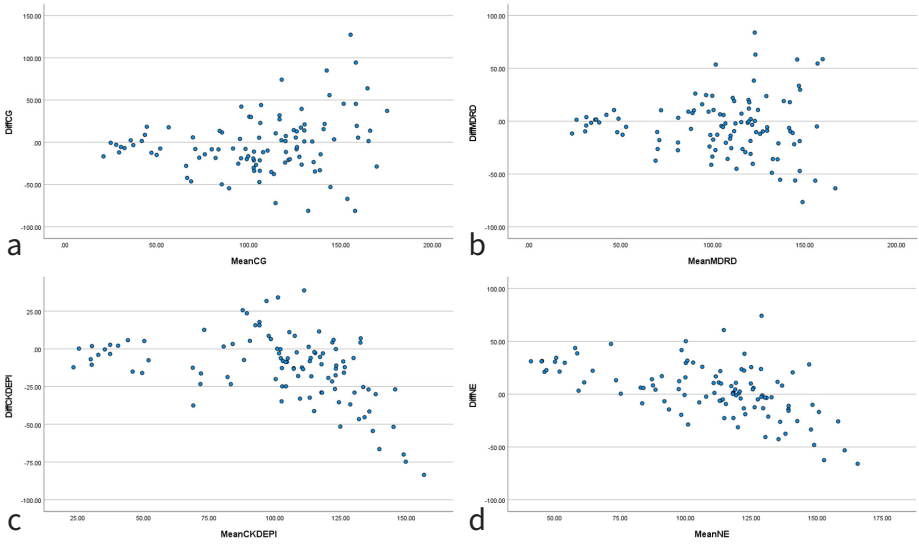


Fig. 4. Bland-Altman plots of eGFRs and measured GFRs for *(a)* CG, *(b)* MDRD, *(c)* CKD-EPI, and *(d)* NE. The dotted line shows the mean of bias, and the bold line shows the 1.96 SD of the mean bias.

Discussion

This study aimed to develop an NE to estimate the GFR for the Malaysian multiracial population, addressing limitations of widely used equations such as CG, MDRD, and CKD-EPI.

Among the formulas, the CKD-EPI demonstrated the strongest performance. showcasing the highest accuracy, with 85.58% of estimates falling within 30% (P30) of the measured GFR and 100% within 50% (P50). It also recorded low MAE and low RMSE, indicating its reliability. The precision of CKD-EPI was good, with a low standard deviation of 22.04 ml/min, reflecting its low variability and consistent performance in estimating GFR. It exhibited the highest positive correlation with the measured GFR (R = 0.82), indicating its ability to produces value closely aligned with the actual GFR values. However, CKD-EPI exhibited the highest mean bias among the formulas, which reflected its tendency to overestimate the GFR value. Overall, CKD-EPI is the most accurate and reliable formula for estimating GFR in the Malaysian multiracial population.

The newly developed NE was able to provide a fairly accurate GFR value with 77.88% in P30 and 84.62% in P50. Notably, it had the lowest RMSE among the equations. The NE had a lower mean bias (3.52 ml/min), meaning its estimates were generally closer to the measured values, and less prone to overestimation of GFR. Despite a slightly higher standard deviation (25.05 ml/min), suggesting more variability, the NE was strongly correlated with the measured GFR (R = 0.76), although slightly lower than that of the CKD-EPI. These results indicate that NE offered comparable performance to existing equations, but it required refinement with larger sample size.

The MDRD had higher P30 and P50 than NE, but it also showed a higher error tendency with MAE 20.76 ml/min and RMSE 27.8 ml/min. It tends to overestimate the GFR more than NE, and showed less consistency as evidenced by the highest standard deviation (27.54 ml/min) among all equations. It had a good correlation with the measured GFR with r value of 0.73, slightly weaker than NE and CKD-EPI. These findings suggested that MDRD estimated GFR fairly well, but less reliably compared to CKD-EPI.

While CG demonstrated high precision in estimating GFR, its accuracy was relatively low compared to other equations. CG had the weakest correlation with the measured GFR, but it had the lowest mean bias (2.49 ml/min), consistent with findings from a previous local study.14 [14] These results indicate that CG has weaker overall performance compared to the other equations.

Our study found that CKD-EPI demonstrated the best overall performance in our sample multiracial population, which is consistent with findings from previous studies.15,16 [15,16] Interestingly, when applied specifically to the Malay population, MDRD appeared to outperform CKD-EPI, as reported in earlier research. This highlights the significance of ethnicity in influencing the performance of GFR equations and the need for a robust equation that explicitly applies to the Malaysian multiracial population.

Limitations

NE was developed using local data, which theoretically should capture the population-specific characteristics. However, the relatively small sample size in the development cohort (105 patients) limited the equation's robustness, potentially affecting its precision and accuracy. Nevertheless, NE performed reasonably well and showed its potential for estimating GFR in the Malaysian multiracial population.

Moreover, this study was conducted at a single centre, and the ethnic distribution of the sampling population was unequal (51.2% were Chinese, 32.54% were Malay, and 16.26% were Indian). This racial distribution did not fully reflect Malaysia's overall demographic composition, where Malays constitute the majority. Therefore, the results from the current study were unlikely to represent Malaysia's general population.

Conclusion

Based on the findings of this study, we concluded that CKD-EPI demonstrated the best performance among the eGFR equations, offering the highest precision and accuracy for estimating GFR in the Malaysia population. However, the newly developed NE showed comparable performance, exhibiting low bias, high precision, and good accuracy.

Future research with large sample size is needed to produce a robust equation that can be explicitly applied to the Malaysian population in order to improve CKD diagnosis and management in Malaysia.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Medical Research Ethics Committee, Universiti Malay Medical Centre (MREC ID NO:2021105-10644).

Competing interests

AMR, SHC and IIS are the members of the Editorial Board of Malaysian Journal of Anaesthesiology; they were not involved in any part of the editorial process prior to article acceptance. The other authors declare that they have no competing interests.

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None to declare.

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None to declare.

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Baxter

In the latest edition of the **Recommendations for Safety Standards and Monitoring during Anaesthesia and Recovery**, the following statement was made:[1]

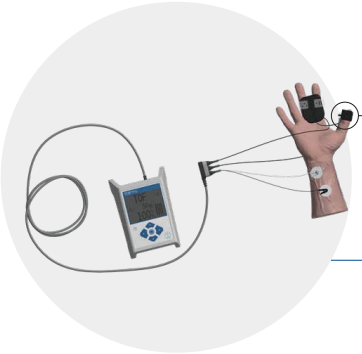
3.7 Neuromuscular function

3.7.1 A peripheral nerve stimulator should be available when muscle relaxants are used to monitor neuromuscular function.

- **Various stimulation modes**
  - TOF, PTC, TC, DBS, Single Twitch
- **Adjustable continuous measurement**

- **3D AMG available to measure muscle movement more precisely**

- **Portable to be used at various locations**



The more distal the acceleration sensor is placed on the thumb, the stronger the acceleration signal.

This effect can be used to adjust the signal strength.

Testimonial

"TOF3D is a standalone device for the measurement of Nueromuscular Transmission (NMT). I have used the device to **rule out residual neuromuscular blockade** for postoperative patients in the PACU. It is **portable** and **reliable**. NMT monitoring device is **essential** in the provision of **safe** and **high-quality** neuromuscular blockade."

Dr Shahridan Mohd Fathil
Consultant Anaesthesiologist
Gleneagles Hospital Johor

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Reference :
1 Recommendations for Safety Standards and Minimal Monitoring Standards during Anaesthesia and Recovery (5th Edition) 2022: College of Anaesthesiologists, Academy of Medicine Malaysia and Malaysian Society of Anaesthesiologists [cited 2023 May 20]. Available from: https://www.msa.net.my/view_file.cfm?fileid=230

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