^{99m}Tc-MAG$_3$ diuresis renography in differentiating renal obstruction: Using statistical parameters as new quantifiable indices

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ABSTRACT

Objective: The aim of this study was to research, develop and assess the feasibility of using basic statistical parameters derived from renogram, "mean count value (MeanCV) and "median count value (MedianCV)", as novel indices in the diagnosis of renal obstruction through diuresis renography.

Subjects and Methods: First, we re-digitalized and normalized 132 renograms from 74 patients in order to derive the MeanCV and MedianCV. To improve the performance of the parameters, we extrapolated renograms by a two-compartmental modeling. After that, the cutoff points for diagnosis using each modified parameter were set and the sensitivity and specificity were calculated in order to determine the best variants of MeanCV and MedianCV that could differentiate renal obstruction status into 3 distinct classes – i) unobstructed, ii) slightly obstructed, and iii) heavily obstructed.

Results: The modified MeanCV and MedianCV derived from extended renograms predicted the severity of the renal obstruction. The most appropriate variants of MeanCV and MedianCV were found to be the $MeanCV_{50}$ and the $MedianCV_{60}$. The cutoff points of $MeanCV_{50}$ in separating unobstructed and obstructed classes as well as slightly and heavily obstructed classes were 0.50 and 0.72, respectively. The cutoff points of $MedianCV_{60}$ in separating unobstructed and obstructed classes as well as slightly and heavily obstructed classes were 0.35 and 0.69, respectively. Notably, $MeanCV_{50}$ and $MedianCV_{60}$ were not significantly influenced by either age or gender.

Conclusions: The $MeanCV_{50}$ and the $MedianCV_{60}$ derived from a renogram could be incorporated with other quantifiable parameters to form a system that could provide a highly accurate diagnosis of renal obstructions.

1. Introduction

Developing a quantitative method for the diagnosis of renal obstruction has been a major challenge in the past two decades. Currently, the most objective and accurate quantifiable parameter used in determining renal obstructions is the fluid pressure measured by the Whitaker test [1,2]. However, this an invasive test and may cause renal damage [3–5]. The non-invasive approach regularly used in medical practice to detect renal obstructions is the renography [6–8]. Renography is a renal imaging technique in which a radioisotope is injected into the human circulatory system and then filtered by the kidneys. This technique produces dynamic images of a kidney, which is useful for tracking its functionality. Several studies have been performed to improve and standardize the renography technique [9–11].

The use of renography for the evaluation of renal obstructions was first studied by O'Reilly et al. during the 1970s [4]. Their study showed the feasibility of using renography as a rapid non-invasive assessment of renal obstructions. Conventionally, the diagnosis of renal obstructions using renography is based on a visual interpretation of renograms [12,13]. This method of interpretation is highly subjective and dependent on the readers' experience [14]. On the other hand, studies have been carried out for decades to determine more accurate quantitative indices in differentiating renal obstructions. However, none of these studies was accepted clinically due to their drawbacks [15]. Variability methods in deriving the parameters led to discordant interpretations [16]. Furthermore, existing parameters cannot determine the severity

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of renal obstructions. They can only predict obvious cases of consistent increasing or decreasing renograms, which could be achieved by a simple visual inspection [17].

Here, we report new quantitative indices derived from renograms that can produce an objective and accurate evaluation of the renal obstruction status, *i.e.* to be able to differentiate if the kidney is "un-obstructed", "slightly obstructed" or "heavily obstructed". Slightly obstructed refers to the condition where there is a resistance to the fluid flow due to partial obstructions in the kidney, while heavily obstructed is the complete obstruction, which may lead to a rapid loss of renal function if left untreated. In this study, we provide the feasibility of using statistical parameters, mean count value (MeanCV) and median count value (MedianCV), as indicators of renal obstructions. They are simple parameters yet never be reported or explored in any existing literature. Further, we demonstrate an improved ability of the parameters in differentiating the severity of obstruction through the application of a two-compartmental analysis. The reference values of the best variants of MeanCV and MedianCV in a normal and diseased population are also presented. In addition, the effects of age and gender on the parameters are assessed in the study.

2. Methods

2.1. Patients and data acquisition

The use of renograms in this study was approved by the Institutional Review Board (CIRB Ref: 2014/808/C) and the anonymized data were analyzed. We obtained renography data from 74 patients with suspected renal obstructions from the Department of Nuclear Medicine and Molecular Imaging, Singapore General Hospital, Singapore. The renography was carried out based on the F + 10 protocol. Patients were hydrated and positioned supine with a gamma camera placed under the table. The radioisotope used was 5 mCi (or 185 MBq) of ^{99m}Tc-MAG$_3$. Data acquisition started immediately after radioisotope injection. Ten minutes after the administration of the tracer, the furosemide was injected based on the body weight at 0.5 mg/kg to a maximum of 40 mg. Serial 1-min images (64x64 matrix) were acquired for a total imaging of 25–30 min from the start of the imaging. Time-activity curves were generated for the whole kidney as the region of interest. In the subsequent analysis, we standardized all renogram samples by using only the first 25 min of the renograms as this was the minimum duration of the scanning.

2.2. Data processing

First, we re-digitalized the time-activity curves into MATLAB R2017b (The Mathworks Inc., Natick, Massachusetts, USA). Because of this re-digitalization, the time intervals between successive digitalized data points were not identical. In order to calculate the statistics of the data, we performed a linear interpolation to tabulate the renal counts from an initial time $t = 0$ min to $t = 25$ min with a step size of 1 s. After that, we normalized the digitalized renogram by the peak count value. The result was then used to derive the MeanCV and the MedianCV.

Next, we modified the means to derive the MeanCV and the MedianCV in order to improve their performances in separating different diagnosis classes. Instead of deriving the parameters from a standard imaging duration-renogram (25 min), variants of the MeanCV

and the MedianCV were derived from extended renograms. To obtain renograms with a duration longer than that of the standard procedure, we applied the two-compartmental analysis to find the best-fit curves to model the renogram. The curve fitting process was performed in MATLAB R2017b.

2.3. Clinical evaluation

Renograms from both right and left kidneys of 74 patients (148 renograms) were acquired. After screening by certified nuclear medicine experts, 16 renograms were excluded from further processing as they were deemed to be nonfunctional kidneys. Certified nuclear medicine doctors provided the clinical diagnosis of the renograms based on patient information, history, renogram (including existing quantifiable parameters: half time $T_{1/2}$, time to peak T_{max}, ratio of the renal counts at 20 min to peak count $R_{20/max}$, peak count and differential renal function), and other diagnostic outcomes. These experts classified the renograms into three classes – i) unobstructed, ii) slightly obstructed and iii) heavily obstructed. Out of 132 renograms, the experts evaluated 90 of them as unobstructed kidneys, 17 of them as slightly obstructed kidneys and 25 of them as heavily obstructed kidneys.

2.4. Compartmental analysis

The compartmental analysis is a method used to describe the kinetic behavior of a substance and to predict its concentration change rate. This study implemented a compartmental analysis developed using a two-compartmental model to depict the fluid transfer phenomena in a renography [18]. In a diuretic renography, the tracers are injected into a body and flow through a circulatory system to reach kidneys. To model this system, two compartments were used to represent the body (the circulatory system) and the kidney as illustrated in Fig. 1.

The governing equations of the tracer flow rate in the circulatory system and the kidney were shown in equations (1) and (2), respectively.

$$\frac{dG_1}{dt} = -FC_1 + I(t) \tag{1}$$

$$\frac{dG_2}{dt} = FC_1 - C_2 U(t) \tag{2}$$

where, $G_1 = C_1 V_1$ and $G_2 = C_2 V_2$ represented the renal counts. G was the amount of tracers (count), V was the volume of a compartment (m³), I was the tracer input function [counts/s], F was the filtrate flow rate from renal parenchyma to renal pelvis [m³/s], U was the urine outflow rate from kidney [m³/s] and C was the concentration of the tracer in a compartment (count/m³). After formulation of the flow rate equations, the concentration of tracer in a kidney could be derived in the form of a second-order differential equation as shown in equation (3). Equation (3) was obtained through the combination and differentiation of equations (1) and (2).

$$\frac{V_2 d^2 C_2}{dt^2} = \left(\frac{F}{V_1}\right)I - \frac{dC_2}{dt}\left(\frac{FV_2}{V_1} + U\right) - \left(\frac{FU}{V_1}\right)C_2 \tag{3}$$

There were 3 solutions to the model, *i.e.* under-damped, critically damped and over-damped systems. The best system to fit a renogram was an over-damped system, which was a more realistic model to depict fluid flow in a human kidney and was proved to be the best solution to
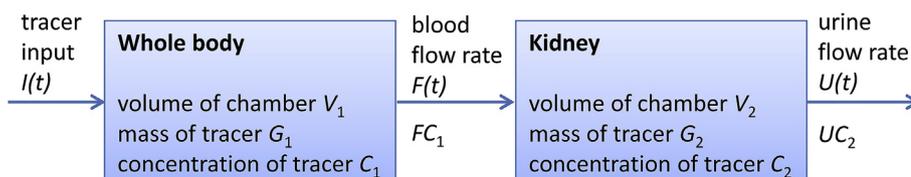

tracer input I(t) | **Whole body** volume of chamber V_1 mass of tracer G_1 concentration of tracer C_1 | blood flow rate F(t) FC_1 | **Kidney** volume of chamber V_2 mass of tracer G_2 concentration of tracer C_2 | urine flow rate U(t) UC_2

Fig. 1. Separation of tracer flow into two control volumes to depict the fluid transport in renography.

fit a renogram with the least error [18]. We obtained the best curve to fit the renogram sample through curve fitting using the mathematical solution of an over-damped system, which represented the renal counts as a function of time as shown in equation (4).

$$G_2(t) = a e^{-bt} \sinh ct \qquad (4)$$

where,

$$a = \frac{2FV_2}{FV_2 - UV_1}$$

$$b = \frac{1}{2}\left(\frac{F}{V_1} + \frac{U}{V_2}\right)$$

$$c = \frac{1}{2}\left(\frac{F}{V_1} - \frac{U}{V_2}\right)$$

U/V_2 was the normalized urine flow rate with respect to the chamber volume. This final solution was used as an input to the MATLAB R2017b to run the curve fitting function.

2.5. Statistical analysis

We carried out unpaired t-tests to assess the viability of the MeanCV and the MedianCV to classify samples into three classes. A probability of less than 0.05 of an unpaired t-test was considered to have a significant effect in differentiating the classes (between unobstructed and obstructed classes as well as between slightly and heavily obstructed classes). To limit the familywise error rate due to the multiple comparisons, we applied Holm-Bonferroni correction in evaluating the results of the t-tests. Another statistical tool that we used was the goodness of fit to determine the best curve that matched with the renogram and was assessed using the R-squared (R^2) method [19,20].

2.6. Existing quantitative parameters

Several quantifiable indices derived from renograms have previously been proposed as objective means of diagnosis. The time to peak T_{max} and half time $T_{1/2}$ have been used as indicators of renal obstructions since the early development of renography. T_{max} is the amount of time required to reach the peak of counts in a renogram [21]. $T_{1/2}$ is the time taken for the renal counts to drop to half of its peak count [22]. Besides, the normalized residual activity at 20 min NORA$_{20}$ and the ratio of the renal counts at 20 min to the peak count $R_{20/max}$ [23,24] are the parameters that gained popularity in recent years. NORA$_{20}$ is the ratio of the renal counts at 20 min to the renal counts at 2 min [25]. In addition, in our previous study, a flow rate parameter, U/V_2, was proposed as a potential indicator of renal obstruction [18]. The values of these 5 existing parameters were derived from the renogram samples and used to evaluate the performance of the newly proposed parameters of this study.

3. Results

3.1. Derived statistical parameters: basic MeanCV and MedianCV

We first evaluated the feasibility of using basic MeanCV and MedianCV (or MeanCV$_{25}$ and MedianCV$_{25}$), which were calculated from the original 25 min F + 10 renograms, as the indicators of renal obstructions. The calculated values of both parameters were laid out as scatter plots and marked according to their diagnosis as depicted in Fig. 2. As demonstrated in the plots, the basic MeanCV and MedianCV could successfully separate the samples into unobstructed and obstructed classes. The scatter plots clearly indicated the potentiality of using these parameters as indices in differentiating renal obstruction. However, in determining the severity of obstruction, neither of the parameters could differentiate the slightly and heavily obstructed classes.

3.2. Compartmental modeling for extrapolation of renograms

To improve the accuracy of the MeanCV and the MedianCV in predicting the severity of renal obstructions, renograms were extended to a total duration of 100 min using the two-compartmental analysis. Variants of the MeanCV and the MedianCV were calculated for various durations of renograms starting from 10 min to 100 min with a step size of 10 min. After obtaining all the variants of MeanCV and MedianCV, results were plotted as scatter plots (Fig. 3a and b). As shown in Fig. 3a, the MeanCV$_{10}$ that was derived from 10 min renograms could not separate different classes of renal obstruction. The three classes started to be differentiated and clustered into three separate regions as the duration increased beyond 10 min. These plots signified that the MeanCV could be an effective indicator of renal obstruction when it was derived from a longer duration renogram. Similarly, the MedianCV calculated from longer duration renograms performed better in separating the samples into different classes of renal obstruction (Fig. 3b). In addition, MedianCV values were close to 0 in unobstructed kidneys and 1 in heavily obstructed kidneys, while the MeanCV showed variations of values in both unobstructed and heavily obstructed kidneys.

3.3. Evaluation of the performance of MeanCV and MedianCV derived from different durations of renograms

We next evaluated the ability of the extended MeanCV and MedianCV derived from different durations of renograms in differentiating the severity of obstructions using unpaired t-tests. The t-test was carried out in two stages - (1) the first stage was to check if the index could separate unobstructed and obstructed classes and (2) the second stage was to further split the obstructed classes into slightly and heavily obstructed classes. The results of the unpaired t-tests on variants of MeanCV and MedianCV are tabulated in Table 1.

Table 1 showed that the MeanCV was able to differentiate unobstructed and obstructed classes significantly when it was derived from the renograms with duration of 20 min and longer. It could differentiate slightly and heavily obstructed classes significantly when MeanCV was derived from the renograms with duration of 30 min and longer. For the variants of MedianCV, the results showed that renograms with duration of 10 min or longer were able to derive MedianCV that could separate unobstructed and obstructed classes significantly and renograms with duration of 30 min or longer was able to be used in deriving MedianCV that could further separate the samples into slightly and heavily obstructed classes.

3.4. Selection of the best variants

In addition to taking the p-values into the consideration in choosing the best variants of MeanCV and MedianCV as indicators of renal obstruction, the sensitivity and specificity of each parameter in differentiating the severity of renal obstruction were also evaluated. The cutoff point of each parameter was derived by finding the intercept point between the distributions of 2 classes. Then using the cutoff points, the sensitivity and specificity of diagnosis were computed as tabulated in Table 1.

The sensitivity and specificity of MeanCV in differentiating unobstructed and obstructed classes increased initially as the duration of renogram was extended. Then it stayed in a steady-state where there were only slight changes in the performance of parameters as we continued to increase the duration of renogram. This steady-state started around MeanCV$_{40}$. This condition occurred most likely due to the infinitesimal changes in the extrapolated data points as the renogram was extended. A similar trend was observed in the sensitivity and specificity of MeanCV in differentiating slightly and heavily obstructed classes. The performance of the parameter ceased to improve after MeanCV$_{50}$.
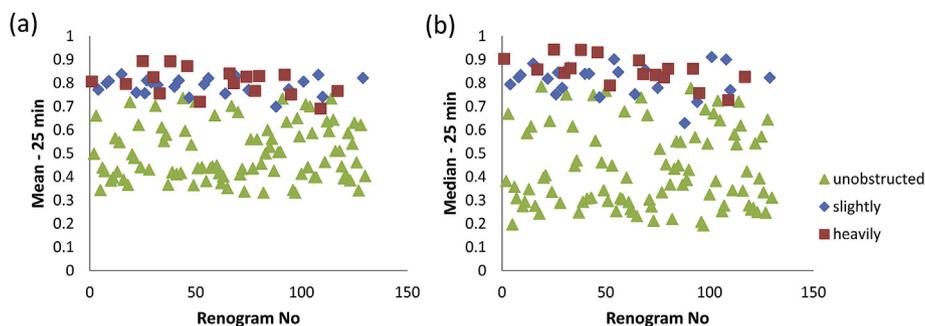
Fig. 2. The scatter plots of MeanCV25 (a) and MedianCV25 (b) derived from renograms. The color and shape of points represent their clinical diagnosis; *i.e.* green triangles represent unobstructed kidneys, blue diamonds represent slightly obstructed kidneys, and red squares represent heavily obstructed kidneys.
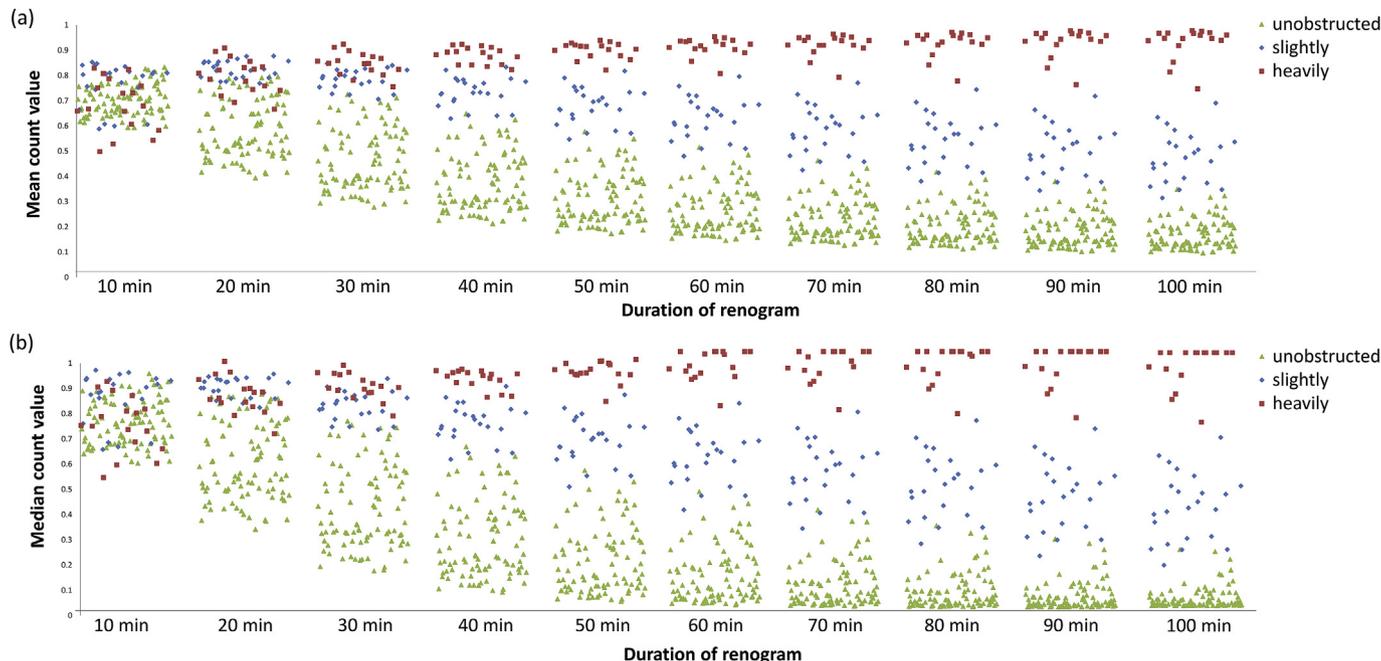

Fig. 3. The scatter plots of extended MeanCVs (a) and MedianCVs (b). These variants of MeanCV and MedianCV were derived from 132 renograms for 10 different durations; *i.e.* starting from 10 to 100 min. These extended parameters were obtained from curve fitting of renogram using two-compartmental modeling.

Table 1
Cutoff points, sensitivity, and specificity of the variants of MeanCV and MedianCV.

Parameter	Unobstructed vs obstructed				Slightly vs heavily obstructed			
	p-value	Cutoff point	sensitivity	specificity	p-value	Cutoff point	sensitivity	specificity
MeanCV$_{10}$	5.89E-02	NA	NA	NA	5.48E-02	NA	NA	NA
MeanCV$_{20}$	4.62E-22[a]	0.7	0.93	0.79	3.27E-01	NA	NA	NA
MeanCV$_{30}$	6.13E-36[a]	0.67	0.98	0.96	1.36E-04[a]	0.78	0.8	0.76
MeanCV$_{40}$	1.29E-43[a]	0.58	1.00	0.98	4.65E-08[a]	0.76	0.8	0.88
MeanCV$_{50}$	3.51E-46[a]	0.5	1.00	0.98	6.58E-09[a]	0.72	0.84	0.94
MeanCV$_{60}$	1.10E-45[a]	0.43	1.00	0.97	3.89E-09[a]	0.69	0.8	0.94
MeanCV$_{70}$	8.72E-44[a]	0.38	1.00	0.97	3.58E-09[a]	0.66	0.8	0.94
MeanCV$_{80}$	1.99E-41[a]	0.34	1.00	0.97	3.95E-09[a]	0.64	0.76	0.94
MeanCV$_{90}$	4.76E-39[a]	0.31	1.00	0.97	4.76E-09[a]	0.6	0.76	0.94
MeanCV$_{100}$	7.94E-37[a]	0.28	1.00	0.93	5.99E-09[a]	0.57	0.76	0.94
MedianCV$_{10}$	3.99E-03[a]	0.83	0.55	0.73	1.33E-02	NA	NA	NA
MedianCV$_{20}$	2.21E-22[a]	0.74	0.97	0.83	3.84E-01	NA	NA	NA
MedianCV$_{30}$	1.52E-33[a]	0.67	0.98	0.91	1.95E-04[a]	0.81	0.8	0.71
MedianCV$_{40}$	7.97E-42[a]	0.56	0.98	0.97	8.16E-08[a]	0.77	0.8	0.88
MedianCV$_{50}$	2.04E-46[a]	0.44	1.00	0.96	8.50E-09[a]	0.73	0.84	0.94
MedianCV$_{60}$	7.44E-47[a]	0.35	1.00	0.97	5.43E-09[a]	0.69	0.8	0.94
MedianCV$_{70}$	2.27E-45[a]	0.28	1.00	0.97	3.65E-09[a]	0.65	0.8	0.94
MedianCV$_{80}$	1.39E-42[a]	0.22	1.00	0.97	3.27E-09[a]	0.61	0.8	0.94
MedianCV$_{90}$	1.73E-39[a]	0.18	1.00	0.97	3.32E-09[a]	0.57	0.8	0.94
MedianCV$_{100}$	1.75E-36[a]	0.14	1.00	0.96	3.63E-09[a]	0.54	0.8	0.94

[a] There is a significant difference of the parameter in differentiating 2 classes based on Holm-Bonferroni method.

Table 2

Statistics of MeanCV$_{50}$ and MedianCV$_{60}$ in unobstructed and obstructed kidneys.

Renal status	No of renogram	Mean	Standard deviation	Min	5th Percentile	95th Percentile	Max
MeanCV$_{50}$							
Unobstructed	90	0.29	0.10	0.16	0.18	0.48	0.56
Obstructed	42	0.74	0.13	0.51	0.55	0.90	0.92
MedianCV$_{60}$							
Unobstructed	90	0.12	0.10	0.01	0.02	0.33	0.45
Obstructed	42	0.73	0.20	0.38	0.44	1.00	1.00

Note: Extremely significant differences were found in both MeanCV50 and Median CV60 between unobstructed and obstructed kidneys ($p < 0.0001$).

Based on these observations, we recommended 50 min as the duration of renogram used to derive the MeanCV.

A similar observation was found in the trend of sensitivity and specificity of MedianCV as the duration of renogram was increased. In differentiating unobstructed and obstructed classes, the performance of the parameters did not increase after MedianCV$_{60}$. The performance of parameters in differentiating slightly and heavily obstructed classes reached steady state after MedianCV$_{50}$. Based on these observations, we recommended 60 min as the duration of renogram used to derive the MedianCV.

3.5. Ranges of MeanCV$_{50}$ and MedianCV$_{60}$ for diagnosis

The statistics of the proposed parameters were computed (Table 2). The means of MeanCV$_{50}$ were 0.29 ± 0.10 for unobstructed kidneys and 0.74 ± 0.13 for obstructed kidneys. An unpaired *t*-test showed an extremely significant difference between the unobstructed and obstructed classes in terms of the means of MeanCV$_{50}$. On the other hand, the means of MedianCV$_{60}$ were found to be 0.12 ± 0.10 in unobstructed kidneys and 0.73 ± 0.20 in obstructed kidneys. An unpaired *t*-test showed an extremely significant difference between the 2 classes in terms of the means of MedianCV$_{60}$.

The confusion matrix obtained by applying the cutoff points of MeanCV$_{50}$ and MedianCV$_{60}$ in providing the diagnosis of renogram samples is tabulated in Table 3. The MeanCV$_{50}$ successfully diagnosed the presence of an obstruction in all obstructed kidneys (42/42) while it was able to determine 98% (88/90) of unobstructed kidneys. In determining the severity of obstruction, this parameter correctly classified 94% (16/17) of slightly obstructed class and 84% (21/25) of heavily obstructed class. The MedianCV$_{60}$ were also 100% (42/42) accurate in diagnosing the presence of an obstruction and had an accuracy of 97% (87/90) in determining unobstructed kidneys. For the further classification of obstructed class into slightly and heavily obstructed, this parameter correctly determined 94% (16/17) of slightly obstructed classes and 80% (20/25) of heavily obstructed classes.

3.6. Effect of age and gender on MeanCV$_{50}$ and MedianCV$_{60}$

Next, the effects of age and gender on MeanCV$_{50}$ and MedianCV$_{60}$ were investigated. The means of MeanCV$_{50}$ were 0.29 ± 0.09 and 0.30 ± 0.12 in unobstructed kidneys of men and women gender groups, respectively and 0.75 ± 0.13 and 0.75 ± 0.12 in obstructed kidneys of

men and women groups, respectively (Fig. 4a(i)). No significant difference was found in MeanCV$_{50}$ between men and women in both unobstructed ($p = 0.70$) and obstructed classes ($p = 0.95$). For different age groups, the means of MeanCV$_{50}$ were 0.29 ± 0.10 and 0.31 ± 0.09 in unobstructed kidneys of the younger population (<42 years old) and older population (≥ 42 years old), respectively and 0.76 ± 0.13 and 0.74 ± 0.13 in obstructed kidneys of the younger and older populations, respectively (Fig. 4a(ii)). There was no significant difference between the younger and older populations in the unobstructed ($p = 0.33$) and obstructed classes ($p = 0.77$).

The means of MedianCV$_{60}$ were 0.12 ± 0.09 and 0.14 ± 0.13 in unobstructed kidneys of men and women gender groups, respectively and 0.74 ± 0.22 and 0.73 ± 0.20 in obstructed kidneys of men and women groups, respectively (Fig. 4b(i)). No significant difference was found in MedianCV$_{60}$ between men and women in both unobstructed ($p = 0.75$) and obstructed classes ($p = 0.15$). For different age groups, the means of MedianCV$_{60}$ were 0.11 ± 0.11 and 0.14 ± 0.10 in unobstructed kidneys of the younger and older populations, respectively and 0.75 ± 0.21 and 0.73 ± 0.20 in obstructed kidney of the younger and older populations, respectively (Fig. 4b(ii)). There was no significant difference between the younger and older populations in the unobstructed ($p = 0.34$) and obstructed classes ($p = 0.81$).

3.7. Comparison of the performance of the proposed parameters and existing quantifiable parameters

Lastly, we compared the ability of proposed MeanCV$_{50}$ and MedianCV$_{60}$ in differentiating renal obstruction status with five parameters found in the literature, which were $T_{1/2}$, T_{max}, NORA$_{20}$, $R_{20/max}$, and U/V_2 as tabulated in Table 4.

4. Discussion

Diuresis renography has become an imaging technique performed regularly to determine the functionality of kidneys for the past decades. Unfortunately, until today, there is still no agreement on the gold standard in the quantification of renogram. Here, we proposed the MeanCV and MedianCV as new parameters for the diagnosis of renal obstruction through renography.

In the first part of the study, the basic MeanCV and MedianCV, which were derived from 25 min-renograms, were proved to be potential indicators of renal obstruction. However, both parameters were

Table 3

Confusion matrix obtained from applying the proposed cutoff points of MeanCV$_{50}$ and MedianCV$_{60}$.

Confusion Matrix		Prediction					
		MeanCV$_{50}$			MedianCV$_{60}$		
		Unobstructed	Slightly obstructed	Heavily obstructed	Unobstructed	Slightly obstructed	Heavily obstructed
Clinical interpretation	Unobstructed	88	2	0	87	3	0
	Slightly obstructed	0	16	1	0	16	1
	Heavily obstructed	0	4	21	0	5	20

(a) MeanCV

(i) Gender Group

(ii) Age Group

(b) MedianCV

(i) Gender Group
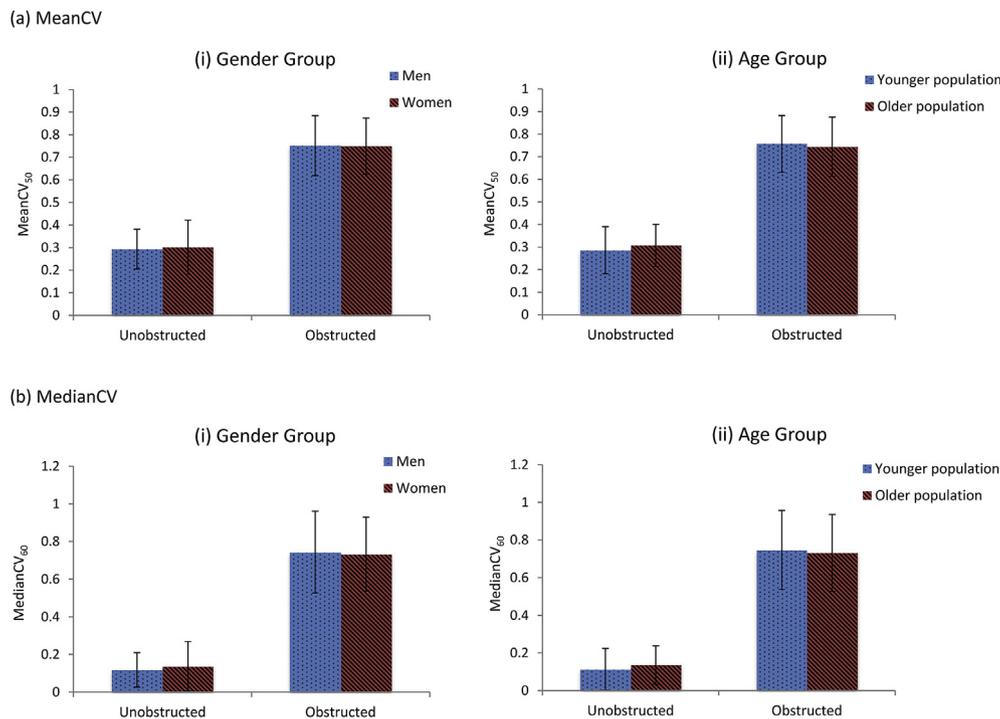
(ii) Age Group

Fig. 4. The distribution of MeanCV$_{50}$ and MedianCV$_{60}$ in different gender and age groups. The younger population refers to the patients younger than 42 years old and the older population refers to the patients older than or equal to 42 years old.

Table 4
Comparison of newly proposed parameters MeanCV$_{50}$, and MedianCV$_{60}$ and the existing parameters in the literature $T_{1/2}$, T_{max}, NORA$_{20}$, $R_{20/max}$, and U/V_2

Parameter	p-value (U vs O)	Rank	Parameter	p-value (S vs H)	Rank
MedianCV$_{60}$	7.44×10^{-47}	1	MedianCV$_{60}$	5.44×10^{-9}	1
MeanCV$_{50}$	3.50×10^{-46}	2	MeanCV$_{50}$	6.58×10^{-9}	2
U/V_2	7.31×10^{-32}	3	U/V_2	7.72×10^{-8}	3
$R_{20/max}$	2.58×10^{-28}	4	T_{max}	3.22×10^{-5}	4
NORA$_{20}$	1.41×10^{-25}	5	$R_{20/max}$	2.17×10^{-2}	5
$T_{1/2}$	4.47×10^{-11}	6	NORA$_{20}$	5.78×10^{-2}	6
T_{max}	1.76×10^{-7}	7	$T_{1/2}$	1.50×10^{-1}	7

Note: U: unobstructed, O: obstructed, S: slightly obstructed, and H: heavily obstructed.

unable to provide information about the severity of obstruction; the slightly and heavily obstruction classes could not be separated. When the duration of imaging was extended beyond the standard duration of renography (beyond 25–30 min), the value of MeanCV and MedianCV were shown to be able to differentiate the severity level of renal obstruction. However, practically, performing diuresis renography clinically with a duration longer than 30 min is not recommended due to the physical discomfort in patients who have to maintain the same body posture for a long imaging duration. One of the feasible solutions to obtain a longer duration renogram is to model the behavior of a renography and predict the curve's trend beyond 30 min. This can be done by applying the two-compartmental model to find the best-fit curve of a renogram and using this curve to estimate the value of the parameters. In a previous study, compartmental analysis has been found to be useful in predicting the flow behavior of the radioisotopes in renography [18].

As the renogram date was extended, majority of MeanCV values were clustered close to the value of 0 and 1 while the values of MedianCV were more distributed between 0 and 1. This could be because the extrapolated data points kept going up and reached a plateau at the value of 1 in the renogram of an obstructed kidney, which caused the MedianCV to have a value close to 1. On the contrary, the extended

renogram of unobstructed kidney fell downwards to a value close to 0. This could be because tracers were excreted out of the kidneys, and hence, the MedianCV became closer to 0. The value of MeanCV, on the other hand, was derived as the average value of the data points, which took into account the initial uptake phase of a renogram. Consequently, the values of MeanCV had a more distributed pattern between the values 0 and 1. Based on these observations, the MedianCV could provide a more accurate diagnosis of renal obstruction with a high level of confidence as compared to MeanCV. However, as a tradeoff, the MedianCV could not indicate the severity level of obstruction as their values were clustered closely at both extreme ends, hence, the MeanCV might be a better parameter to provide an insight on the relative severity of renal obstruction.

Among the variants of MeanCV and MedianCV derived from extended duration renograms, MeanCV$_{50}$ and MedianCV$_{60}$ were selected as the newly proposed parameters for the diagnosis of renal obstruction. The proposed parameters are put in comparison with 5 existing parameters in the literature: i) T_{max} [26] and ii) $T_{1/2}$ [22], which are being used as indicators of renal obstruction since the early development of renography, iii) NORA$_{20}$ [25] and iv) $R_{20/max}$ [27], which gained popularity as indicators of obstruction in recent years and v) U/V_2 [18], which is a physical fluid flow parameter and has recently been proposed for use in clinics. These parameters were derived by applying the methods described in the literature on the same datasets that were used to derive the MeanCV$_{50}$ and the MedianCV$_{60}$, and then the performances of all the parameters were compared. As showed in Table 4, all 7 parameters could be used to separate unobstructed and obstructed classes with extremely significant differences according to their p-values with Holm-Bonferroni correction. However, NORA$_{20}$ and T_{max} were not able to separate the slightly obstructed and heavily obstructed classes. Both MeanCV$_{50}$ and MedianCV$_{60}$ were found to perform better than existing quantitative parameters of a renogram.

Despite the good performance of the parameters, there are some limitations of the study. First, the sample size used in this study is small. This is because renography is not performed tremendously in the hospitals, which is a frequent obstacle in most renography studies. Next,

there is no true independent gold standard in using "Clinical Evaluation" with old parameters such as half-emptying and time to peak (T_{max}), and thus having some AI algorithms to better predict the prolonged acquisition data should be explored. There is also an imbalance in the number of healthy and diseased samples. Out of a total of 132 renograms used in the current study, 90 were unobstructed and 42 were obstructed kidneys (17 were slightly obstructed and 25 were heavily obstructed). This imbalance of data may lead to a bias towards the majority class and produce a lower accuracy in predicting the minority class. Future studies with larger sample size are required to verify and further improve the findings of this work.

There are several distinctive protocols regarding the timing of furosemide administration. For example, in the United States, the commonly used protocol is F + 20 where the furosemide is injected 20 min after radioisotopes injection. The renogram samples of the current study is based on the F + 10 protocol, which is accepted in many centers, particularly in Asia because of the shorter imaging time that meets the need of heavier patient load typically seen in Asian centers. Besides, the application of F + 10 can reduce bladder filling and avoid disruption during the procedure due to voiding [28]. In the future study, the proposed MeanCV$_{50}$ and MedianCV$_{60}$ can be tested on F + 20 or other protocols, and the reference values can be adjusted based on the chosen protocol.

The proposed parameters, *i.e.* MeanCV$_{50}$ and MedianCV$_{60}$, can potentially form a sophisticated system for the diagnosis of renal obstructions by incorporating them together with other parameters obtained from renograms, such as the key parameters proposed by Bao et al. [29] using machine learning algorithms. Several studies have proposed the use of combined parameters, for instance, the use of a computer system incorporating a number of quantitative parameters and setting up logical sequences for the diagnosis of renal obstruction, such as RENEX [30,31] and iRENEX [32]. The inclusion of MeanCV$_{50}$ and MedianCV$_{60}$ into the system may further improve the accuracy of diagnosis.

5. Conclusions

The current study demonstrates the use of statistical parameters for the diagnosis of renal obstructions. By applying two-compartmental modeling to extrapolate the duration of the renograms in combination with the MeanCV and the MedianCV derived from extended renograms effectively classify the renal status as unobstructed, slightly obstructed and heavily obstructed. Based on the severity levels of renal obstruction, the medical doctor will be able to suggest more personalized and appropriate follow-up plans.

Authors' contributions

S, E.Y.K.N. and C.E.D.N. developed the two-compartmental model. S, X.S.Y. and N.K.V. implemented the model and analyzed data. S wrote the manuscript with critical input from E.Y.K.N and N.K.V. All authors read and approved the final manuscript.

Agreements

All authors approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This article does not contain any studies with human participants directly or animals performed by any of the authors. This study solely processed the renograms and the use of renograms was approved by the

Institutional Review Board (CIRB Ref: 2014/808/C). The data were analyzed anonymously.

Statement of conflict of interest

The authors of the paper "^{99m}Tc-MAG$_3$ diuresis renography in differentiating renal obstruction: Using statistical parameters as new quantifiable indices" hereby declare that there are no conflicts of interest.

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