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Verification on the use of the Inoue method for precisely determining glomerular filtration rate in Philippine pediatrics

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Abstract. The objective of this study is to validate the Inoue method so that it would be the preferential choice in determining glomerular filtration rate (GFR) in Philippine pediatrics. The study consisted of 36 patients ranging from ages 2 months to 19 years old. The subjects used were those who were previously subjected to in-vitro method. The scintigrams of the invitro method was obtained and processed for split percentage uptake and for parameters needed to obtain Inoue GFR. The result of this paper correlates the Inoue GFR and In-vitro method ($r = 0.926$). Thus, Inoue method is a viable, simple, and practical technique in determining GFR in pediatric patients.

1. Introduction
Kidney disease causes more mortalities annually than cancers of the breast and prostate, it is currently the ninth most common cause of mortality in the United States and Asians are among the races which are at an increased risk for kidney disease [1]. Chronic Kidney Disease (CKD) is the principal cause of sickness and mortality in children worldwide [2]. Renal cancer among one of them is one of the most common causes of renal dysfunction for pediatric patients, along with nephritides and infections [3]. In alleviating these ailments, it is essential to have an efficient, safe, and practical diagnostic method due to the nature of the disease and the fragility of pediatric patients [4]. Such that, earlier diagnosis and suitable treatment will prevent further progression of renal disease and mortality [1].

Currently, the ninth leading cause of death in the Philippines is due to kidney failure, killing one Filipino hourly. Approximately 120 Filipinos per million populations suffer from failure of the kidneys, increasing the need for kidney transplants and dialysis [5].

Glomerular Filtration Rate (GFR) is the parameter used to determine renal function and to assess any problems in the renal system [6]. It is mainly determined by blood sampling, but urinalysis and imaging testing have gain distinction since 2009 [2].

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There have been four prominent methods used in determining GFR, each employing either the use of endogenous or exogenous markers. These methods are: creatinine clearance, inulin clearance, in-vitro method and the camera-based method. Creatinine clearance being the method primarily used for hospital diagnosis [7]. In spite of this, this method is not the ideal indicator for estimating GFR [8].

Until recently, exogenous radioisotope markers have been used in nuclear medicine for determining GFR measurements. One such marker, Inulin, bears the distinction of an ideal marker [8]. The inulin clearance was traditionally considered the gold standard for measuring GFR, but it is expensive, cumbersome and is only typically used for research rather than in clinical diagnostic purposes [8, 9]. The radiopharmaceutical 99mTc-DTPA has been found to have similar, if not equal qualities as of Inulin; qualities such as volume distribution, transit time, and plasma clearance which are the reasons why Inulin is considered an ideal marker [10]. Currently, the plasma disappearance method, or simply the In-vitro method, uses such a marker and has been recognized as the valid gold standard for nuclear GFR by the Pediatric Committee of the European Association of Nuclear Medicine [3]. Bloodletting in two to three separate occasions is necessary in the evaluation of nuclear GFR through the use of this method. This could be very traumatic, most especially for pediatric patients [11, 12].

Camera based methods, such as the Gates method and the Inoue method, combine the use of 99mTc-DTPA and a gamma camera to assess renal function, which may alleviate the dilemma of children foregoing bloodletting, and the ensuing trauma [11]. This has also been found to be a precise method for the evaluation of GFR independently of inulin and creatinine clearance, which are the methods primarily used for measuring GFR [9]. The forerunner for this camera-based method is typically that of the Gates’ method, but inaccuracies have been found in measuring GFR in pediatric patients. Inaccuracies which have been resolved by Yusuke Inoue’s camera-based method [11].

In differentiating the two camera-based methods, patient positioning, renal depth imaging tool and equations vary in acquiring renal depth and the process in acquiring the gamma counts from the scintigrams make them unique from one another. In acquiring renal depth, the Gates’ Method makes use of the formulas by Tonnesen et al. paired with an ultrasound while the patient is in a seated position and as for the Inoue Method, formulas by Raynaud et al. for pediatric patients and Taylor et al. for adult patients using a CT scan in a supine-positioned patient [11]. CT scan use anatomical markers for reference and yields better measurements and renal depth estimation. The Region of Interests (ROI) is vital to image processing of the scintigram and before the ROI’s are to be contoured it is important to distinguish the time the ROIs should be drawn, the shape of the kidney ROI, and the shape of the kidney background ROI. The Gates’ method makes use of the renal scan from 5 minutes onwards, a time where the tracer has reached the renal pelvis, the non-functional part of the kidneys [11]. The C-shape for Gates’ Method is drawn in order to compensate for the renal pelvis. It is notable that the C-shape omits a certain part of the functional part of the kidney this potentially underestimated GFR. The Inoue Method however, makes use of the 2.0-2.5 minute duration which is a functional phase where the radioisotope has not reached the renal pelvis. This time difference is mainly done to remove the ROI’s compensatory C-shape by the Gate’s method making the ROI shape fit a more natural contour of a bean since the 99mTc-DTPA has not yet reach the non-functional region of the kidneys.

The ROI shape to account for background correction is also different for both methods, asemilunar contour for Gates and perirenal contour for Inoue. A perirenal background correction shape provides a better correction for attenuated gamma rays that where inadvertently collected [11].

The objective of this study is to validate the Inoue method that it would be the preferential choice in determining GFR in Philippine paediatrics.

2. Materials and methodology
The measurement of In-vitro GFR was conducted by the Nuclear Medicine department of St. Luke’s Medical Center, Quezon City, accordingly any form of patient interaction and handling of nuclear materials such as 99mTc-DTPA will not be of concern. Any form of consent is not necessary, since the consent form of St. Luke’s Medical Center, Quezon City applies to any protocols that the patient will
performing. The figurative data gathered from these procedures are considered to be that of the hospitals property, thus the data could possibly be used for research or statistical purposes. Furthermore, amongst the data gathered names and any form of labelling that will single out or put at risk the patient’s identity will not be included in any way or form.

In this study, thirty six (36) pediatric patients subjected to in-vitro GFR determination from 2011 to 2012 were used in the study. Patient’s scintigrams and general information (age, weight and height) were collected and analyzed. The subject’s ages range from 2 months to 19 years of age with a mean age of 7.65 ± 6.98. Subjects have varying degrees of renal function in a 4.5 month data gathering period. Patient numbers 3, 6, 26 and 29 were excluded in the statistical determination. Since, Patient 3 and 6 have incomplete parameters necessary for the calculation of the Inoue GFR; missing left kidney and missing injection site, respectively. Moreover, patient 26 and 29 are missing their In-vitro GFR measurements, thus plotting them would be impractical. Data obtained will be used to determine if the measured results for in-vitro method will also hold true for the Inoue equation for estimation of GFR.

Retrospective in-vitro GFR measurements and respective general information such as age, weight and height was collected to be used in renal depth estimation and correlation. The scintigrams of the pre-injection syringe, post-injection syringe, injection site (1 min), injection site background (1 min), and kidneys was retrieved to be able to process the images for gamma ($\gamma$-) counts.

The eNTEGRA Workstation, a software which interprets the electrical signals from the gammacamera to digital scintigrams, was used to process the images into viable forms of data. Areas of the scintigrams mentioned above are measured for their $\gamma$-counts, either by whole area counting or selective area (ROI) counting. Whole area counting is done for the pre-injection syringe and post-injected syringe, thus the need to draw ROIs is not necessary. Then, the $\gamma$-counts were recorded to be used for the equations to estimate Inoue GFR. As for, selective area counting the scintigrams of the injection site and kidneys were used employing the parameters of Inoue. After adjusting for adequate intensity and contrast to properly distinguish the borders of the kidneys, the ROIs are drawn manually in contour to the borders of the kidneys. The shape of the kidney ROI (bean shape) and kidney background ROI (perirenal) using the compound image from 2.0-2.5 min are followed as indicated in the Inoue Method.[11] With the necessary shaping done, $\gamma$-counts and area of each kidney ROI are recorded and will be used to estimate GFR.

The retrospective data from previously gathered procedures of $^{99m}$Tc-DTPA via in-vitro method for nuclear GFR measurement of pediatric patients was used as the reference values to correlate with the Inoue method and to validate the hypothesis that percent uptakes of the kidney are proportional to In-vitro GFR measurements. This study will implement the parameters and equations proposed by Yusuke Inoue [11]. Linear regression and t-test were used to determine the statistical significance of the two values correlation to each other. The r-values should approximate to +1 in order to substantiate a strong correlation and the p-value should reject the null hypothesis, thus should be greater than 0.05.

3. Results and discussion
The pre-estimated in-vitro GFR measurements were used as the reference value to estimate the relation of the calculated $^{99m}$Tc-DTPA % uptakes of the kidneys. If proven to have adequate correlation, it can be assumed that the total % uptakes of the kidneys correspond to the gamma counts measured in the blood samples extracted from the in-vitro method.

The correlation of the measured total percent uptake and in-vitro GFR was plotted on a scatter plot and determined of its relation to each other. The r-value calculated is 0.916, indicating a strong correlation between total percent uptakes and In-vitro GFR (fig. 1). Thus, estimation of GFR with the use of scintigrams can be done with adequate precision.

Since the results in Figure 1 agree with hypothesis that % uptakes are proportional to the gamma counts taken from the blood samples from the in-vitro GFR method, the method and general equations of Inoue can be applied to this study. The Inoue GFR was calculated for each patient and was correlated using linear regression analysis with that of the reference method, in-vitro GFR. It was found that there is a strong correlation between the two GFR values having an r-value of 0.926 (fig. 2).
Furthermore, using t-test we assume that the null hypothesis (Ho) has no significant difference between the In-vitro method and the Inoue method. The p-value calculated is 0.9037, which is a large value for p (>0.05), which means that there is not enough evidence to reject the null hypothesis. In conclusion, there is no statistical difference between the In-vitro method and the Inoue method.

4. Conclusion
This study confirmed the hypothesis that total percent uptakes of the kidneys taken from the scintigrams are proportional to that of normalized In-vitro GFR with an r-value of 0.916, such that we can assume that GFR can be determined with the use of only the scintigrams via renal percent uptake, thus removing the need to withdraw blood. Estimation of GFR via camera based method in children has been validated due to the strong correlation (r = 0.926) and a large p-value (p = 0.9037) of the statistically calculated Inoue GFR with the reference value (In-vitro GFR). The strong correlation yields a precise value of the clinical gold standard. It is highly encouraged to use the camera based method by Inoue for pediatric patients, given its benefits from other GFR acquisition methods. The
Inoue method has a relatively quick processing time which is void of laboratory processing, has a less traumatic procedure where it is void of bloodletting, and is not subjected to deviation based on patients with lesser body surface area (BSA). This paper ascertains that the Inoue method is a viable method that satisfies the gold standard and is a reliable diagnostic tool in determining GFR in pediatric patients.

References