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Correlation of Kidney Volume on CT-Scan with Kidney Function Tests in Patients with Normal Kidneys at Haji Adam Malik Hospital Medan in 2020-2021

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ABSTRACT

Introduction: Kidneys have filtration and excretion functions; the glomerular filtration rate (GFR) is considered the best indicator of kidney function and may indicate abnormalities. Kidney volume can be an early indicator of kidney disorders before there is a decrease in kidney function. Changes in kidney volume may indicate structural and functional changes that indicate a disorder or disease progression. Radiological examination such as a CT-Scan has an important role in measuring the size and kidney volume and assessing kidney morphological changes for the diagnosis and staging of kidney disease as well as planning therapy. Objective: This study aims to find a correlation between the estimated kidney volume with the ellipsoid method through CT scanning and estimated kidney function by glomerular filtration rate in patients with normal kidneys.
Method: An analytical study used a case-series design; all subjects were patients who had normal CT-Scan results and normal kidney function at the Haji Adam Malik Hospital in Medan in 2020–2021. Used the consecutive sampling technique and had 90 total samples.
Results: There is a moderately positive correlation (r = 0,410-0,499) between volume and kidney function. A moderately negative correlation (r = -0,196 to -0,282) between kidney volume and age. A moderately positive correlation (r = 0,456-0,548) between kidney volume and body weight. There is a moderately negative correlation (r = -0.495) between renal function and age. A moderately positive correlation (r = 0,567) between renal function and body weight.
Conclusion: there is a correlation between kidney volume and kidney function, the correlation between kidney volume and body weight, the correlation between kidney function and body weight.

Keywords CT-Scan, Glomerular filtration rate, Renal function, Renal volume

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INTRODUCTION

The human genitourinary system consists of a pair of kidneys, a pair of ureters, urinary vesicles, and also the urethra. The kidneys include retroperitoneal organs located in the posterior abdominal wall. The kidneys are located on each side of the columna vertebra at thoracal height 12 to lumbar height 3. The superior polus of the kidney is usually oriented slightly posteriorly and medially relative to its inferior polus. The right kidney is usually located more inferiorly than the left kidney due to the pressing effect of the liver. The shape of the kidney is ovoid, bean-shaped with convex areas laterally and concavity areas medially, weighing between 150-200 grams in males and 120-135 grams in females. The kidney is about 10-12 cm long, 5-7 cm wide with a thickness of about 3-5 cm [1-2].

The right kidney is located posteriorly from the ascending colon, the pars II duodenum in the medial, and the hepar in the superior, separated by the hepatorenal recess (Morison's pouch). The left kidney is posterior to the descending colon, the renal hilum is lateral to the cauda pancreas, its superomedial aspect is adjacent to the greater gastric curvature, and the sinistra polus is adjacent to the splenic and is connected to the splenic ligament [4-5].

In the posterior part of the kidney, the diaphragm is in the superior third with costa 12 passing through the superior polus of the kidney. Usually the kidneys are located in the medial aspect of the psoas muscle and the lateral aspect of the quadratus lumborum muscle. Each kidney is lined by two layers of capsule and surronded by perirenal fat, Gerota fascia, Zuckerkandl fascia, and pararenal fat. The proximal ureter generally passes through the psoas muscle as it travels to the pelvic cavity. The renal hilum is found in the medial part, the renal artery enters, renal pelvis and the renal vein exits the renal sinus. The renal vein is more anterior than the renal artery. The renal artery is more anterior than the renal pelvis. The union of 2-3 minor calixes forms a major calix. The union of 2-3 major calyx forms the renal pelvis. At the end of the minor calyx is the renal papilla, which is the apex of the renal pyramid. The pyramid and the surrounding cortical tissue constitute one renal lobe [4-6].

The kidneys consist of the cortex and medulla. The renal cortex consists of the renal corpusculum, convoluted tubules, rectus tubules, collectivus tubules, and blood vessels. The medulla section consists of the rectus and collectivus tubules, which extend into the cortex. The medulla also contains the vasa recta, capillary vessels that play a role in the exchange system counter current. The renal pyramid is a cone-shaped structure formed by the collecting tubules in the medulla, the pyramidal base oriented towards the cortex and the pyramidal apex towards the hilum. At the apex of the pyramis there is a papilla that extends towards the minor calyx that drains its products through the ductus collectivus at its end, the cribrosa area. The ductus collectivus and the group of nephrons around it are called lobules [2].

The kidneys have several functions, including the filtration function, where the kidneys filter about 200 liters of fluid per day. Then there is the excretory function; the kidneys excrete urine containing toxins and various metabolic waste products, remove excess ions, and maintain a balance of various essential substances in the body. Then the kidneys also function in regulating plasma osmolarity by modulating the amount of water, solutes, and electrolytes in the blood. In addition, the kidneys also function in maintaining acid-base balance, producing renin for blood pressure regulation, erythropoietin to stimulate erythrocyte production, and converting vitamin D into active substances [1–2].

Glomerular filtration rate (GFR) is the amount of filtrate that forms throughout the renal corpuscle in both kidneys every minute. GFR represents the flow of plasma from the glomerulus into Bowman's capsule over a specific period of time, and is the primary measurement for assessing kidney function and indicating abnormal kidney conditions [7].

In a healthy person, the volume and length of the kidneys increase until the fourth and fifth decades of life, then followed by a progressive decrease in males, while the volume of the kidneys decreases gradually throughout the life of the female. The cortical volume will decrease at the end of life, this reflects an increase in sclerosis and atubular glomeruli. In previous studies it was found that the things associated with decreased kidney volume were female sex, increased age, higher body mass index, higher blood pressure, lower concentrations of sodium, bicarbonate and hemoglobin, with increased nitrogenous waste and urinary ACR [3].

Glomerular filtration regulation mechanisms regulate the flow of blood into and out of the glomerulus, and alter the glomerular capillary surfaces available for filtration. As blood flow into the capillaries increases, GFR increases, and coordinated control of the diameter of afferent and efferent arterioles regulates glomerular blood flow. There are three mechanisms that control GFR: renal autoregulation, neural regulation, and hormonal regulation [7].

Until recently, GFR was considered the best indicator of kidney function. Measurement of GFR can be carried out with the use of endogenous or exogenous substances. Such an exogenous substance as inulin is not produced in the human body. Inulin clearance is gold standard GFR examination. The average normal value of inulin clearance in adults is 127 mL / min/1.73 m2 in males and 118 mL / min/1.73 m2 on women. Urea, creatinine, cystatin C, beta trace protein (BTP), beta-2 microglobulin, and tryptophan glycoconjugate are endogenous substances that are often used to determine GFR. However, the most commonly used substances are urea and creatinine due to their availability [8].

In normal kidneys without volume depletion, urea clearance is approximately 50% of creatinine clearance, but in conditions of volume depletion, the clearance can be 10% of creatinine clearance. About 40% of the filtered urea is reabsorbed in the proximal tubule. The collecting duct reabsorbs urea along the concentration gradient so that urea is raised in concentration. Most urea is reabsorbed from the medulla and re-enters the tubule at the descending thin limb, which represents recycled intrarenal urea [9].

Radiological examinations such as ultrasound, CT-Scan, and MRI have an important role in assessing the morphological changes of the kidney for diagnosis, staging kidney disease as well as therapy planning [10]. CT-Scan is more commonly used because it can measure kidney size and kidney volume more accurately for preoperative assessment of renal anatomy and can be linked to kidney function. Measurement by ellipsoid examination method is easier and suggested for estimation of kidney volume [11].

Renal volume is one of the useful parameters for the evaluation of renal function. Some studies report a correlation between GFR as measured by the formula Cockroft-Gault and kidney volume as measured by CT-Scan. Shin et al. it examined 113 healthy subjects and reported a total renal volume significantly correlated with GFR (r = 0.43) [12]. Large study using ellipsoid method for kidney volume estimation using CT-Scan for the patient make a progostic normogram for post-operative renal insufficiency. The normogram was found to be predictive of the likelihood of renal failure in 7 years, but did not specifically determine the accuracy of the ellipsoid method for the estimation of renal volume [13]. Another study also reported the accuracy of CT-Scan with contrast to estimate kidney function in 38 potential kidney donors by ellipsoid midification method using nuclear renography as the gold standard. The author states that the measurements taken by radiological, ellipsoid method can eliminate the need for nuclear renography in many patients due to high accuracy (r = 0.84) and shorter time to post-processing [11]. Based on the above background, researchers are interested to find a correlation between kidney volume estimated by ellipsoid method through CT-Scan and kidney function estimated by glomerular filtration rate, in patients with normal kidneys at Haji Adam Malik Hospital Medan in 2020-2021.

METHOD

This research is based on a series of experimental experiments (case series). This study was conducted at The Haji Adam Malik Hospital Medan and has gained Ethical Clearance from The Ethics Committee of the Faculty of Medicine USU. The population of this study was patients who had performed abdominal CT-Scan examinations in 2020 to 2021 and the CT-Scan results were stored in the database. The subjects of the study were a portion of the population that met the following inclusion and exclusion criteria. Inclusion criteria were patients aged 17-60 years who had performed abdominal CT-Scan examination and the result was a normal kidney characterized by normal kidney function and normal kidney volume, and patients with creatinine / GFR medical record data within normal limits. The normal limit of creatinine is 0,8-1,2 mg/dL. Exclusion criteria are patients who have kidneys with primary and secondary anatomical / morphological abnormalities (size, mass, hydronephrosis, cysts, stones, abscesses, depressed / pushed and others) that result in changes in kidney size / volume, creatinine or GFR beyond normal limits, patients with CT-scan results can not / difficult to evaluate (artifacts, massive movements of patients) and patients with incomplete, missing or inaccessible medical record data. The sample size was calculated by numerical comparative analytical research formula against two unpaired groups with a total sample of 90 people. Sampling techniques will be performed non-probability sampling namely with the technique consecutive sampling where samples are taken sequentially according to inclusion and exclusion criteria until the minimum size is met.

RESULT

Sample of this study amounted to 90 people, with patients aged 18-30 years amounted to 10 people (11.1%), patients aged 31-40 years amounted to 21 people (23.3%), patients aged 41-50 years amounted to 32 people (35.6%) and patients aged 51-60 years amounted to 27 people (30%). The number of male patients amounted to 44 people (48.9%) and female patients amounted to 46 people (51.1%).

Table 1. Demographic data of participants.

Demographic Data	n	%
Age		
18-30	10	11.1
31-40	21	23.3
41-50	32	35.6
51-60	27	30
Gender		
Males	44	48.9
Females	46	51.1

In addition, the analysis was also conducted to determine the uniformity between the two readers (R1 = researcher; R2 = comparator) CT-Scan results using the Kappa test.

Table 2. Result of CT-Scan reading uniformity analysis of kidney volume.

Variables	Mean	SD	Median	Min	Max	Kappa	P-value
Right Kidney R1	167.92	46.48	163.2	83.57	335.48	0.787[a]	<0.001[a]
Right Kidney R2	167.99	46.37	164.12	83.57	335.48		
Left Kidney R1	175.45	46.61	174.07	87.98	323.81	0.809[a]	<0.001[a]
Left Kidney R2	175.48	46.57	174.07	87.98	323.81		
Total Kidney R1	343.37	88.93	337.95	186.24	632.92	0.642[a]	<0.001[a]
Total Kidney R2	343.46	88.76	337.15	184.31	629.32		

[a]Kappa Test

Based on the table above, the analysis using the Kappa test is known that the uniformity or consistency of the right kidney volume reading between two readers is considered significant ($P < 0.001$) with a good degree of uniformity or consistency ($P = 0.787$), it is also known that the uniformity or consistency of the left kidney volume reading between two readers is the degree of uniformity or consistency was very good ($P = 0.809$), and the last known result of uniformity or consistency of the total volume of both kidneys between the two readers was assessed as significant ($P < 0.001$) with the degree uniformity or consistency is good ($P = 0.642$).

Table 3. Participants' clinical, laboratory and CT-Scan findings.

Variables	Mean	SD	Median	Min	Max	P-value
Age	44.34	10.04	46	18	60	0.010[b]
Body weight	63.04	14.74	60	43	95	0.001[b]
Creatinine	0.66	0.21	0.62	0.34	1.80	<0.001[b]
GFR	123.68	39.11	118.37	40.29	227.90	0.200[b]
Right Kidney Volume	167.92	46.82	163.20	83.57	335.48	0.005[b]
Left Kidney Volume	175.45	46.61	174.07	87.98	323.81	0.027[b]
Volume Total	343.37	88.93	337.95	186.24	632.92	0.016[b]

[b]Kolmogorov-Smirnov Normality Test

Table 3 shows that the average ± standard deviation and median (min-max) on the age data are 44.34 ± 10.04 and 46 (18-60). The known average ± standard deviation and median (min-max) on the weight data are 63.04 ± 14.74 and 60 (43-95). Average ± standard deviation and median (min-max) on creatinine data are 0.66 ± 0.21 and 0.62 (0.34–1.80). Average ± standard deviation and median (min-max) on GFR data are 123.68 ± 39.11 and 118.37 (40.29–227.90). The average ± standard deviation and median (min-max) on the right kidney volume data are 167.92 ± 46.82 and 163.20 (83.57-335.48). Average ± standard deviation and median (min-max) on the left kidney volume data are 175.45 + 46.61 and 174.07 (87.98-323.81). The known average + standard deviation and median (min-max) on the total kidney volume data are 343.37 + 88.93 and 337.95 (186.24-632.92). In addition, it is also known that the results of the normality test show that only the data on the glomerular filtration rate (GFR) are normally distributed (P-value > 0.05), while the other data are not normally distributed (P < 0.05).

Table 4. Correlation of kidney function with kidney volume.

Kidney Volume		Mean	SD	r	P-value
Kidney Function	Right Kidney	167.92	46.82	0.499[c]	<0.001[c]
	Left Kidney	175.45	46.61	0.410[c]	<0.001[c]
	Kidney Total	343.37	88.93	0.479[c]	<0.001[c]

[c]Spearman Test

In the correlation analysis of kidney function with kidney volume using the Spearman test, it is known that there is a significant correlation between kidney function and right kidney volume (P < 0.001) with a moderately positive correlation degree (r = 0.499), that there is a significant correlation between kidney function and left kidney volume (P < 0.001) with a moderately positive correlation degree (r = 0.410) and that there is a significant correlation between kidney function and the total volume of both kidneys (P < 0.001) with a moderately positive correlation (r = 0.479).

Table 5. Correlation of age with kidney volume.

Kidney Volume		Mean	SD	r	P-value
Age	Right Kidney	167.92	46.82	-0.282[c]	<0.001[c]
	Left Kidney	175.45	46.61	-0.196[c]	<0.001[c]
	Kidney Total	343.37	88.93	-0.250[c]	<0.001[c]

[c]Spearman Test

In the analysis of age correlation with kidney volume using the Spearman test, there was a significant moderate correlation between age and right kidney volume (P < 0.001) with a weak negative correlation degree (r = -0.282), there was a significant moderate correlation between age and left kidney volume (P < 0.001) with a weak negative correlation degree (r = -0.196), and there was a significant moderate correlation between age and total volume of both kidneys (P < 0.001) with a weak negative correlation degree (r = -0.250).

Table 6. Correlation of body weight with kidney volume.

Kidney Volume		Mean	SD	r	P-value
Body Weight	Right Kidney	167.92	46.82	0.548[c]	<0.001[c]
	Left Kidney	175.45	46.61	0.456[c]	<0.001[c]
	Kidney Total	343.37	88.93	0.540[c]	<0.001[c]

[c]Spearman Test

A correlation analysis of body weight with kidney volume using the Spearman test found that there was a significant moderate correlation between age and right kidney volume (P < 0.001) with a moderately positive correlation degree (r = 0.548), there was a significant moderate correlation between age and left kidney volume (P < 0.001) with a moderately positive correlation degree (r = 0.456), and there was a significant moderate correlation between age and the total volume of both kidneys (P < 0.001) with a moderately positive correlation degree (r = 0.540)

Table 7. Correlation of kidney function with age.

	Mean	SD	r	P-value
Kidney Function	123.68	39.11	-0.495[c]	<0.001[cc]
Age	44.34	10.04		

[c]Spearman Test

In renal function correlation analysis using the Spearman test, there is a significant correlation between renal function and age (P < 0.001) with a moderately negative correlation degree (r = -0.495).

Table 8. Correlation of kidney function with body weight.

	Mean	SD	r	P-value
Kidney Function	123.68	39.11	0.567^{c}	$<0.001^{cc}$
Body Weight	63.04	14.74		

[c]Spearman Test

In the correlation analysis of renal function with body weight using the Spearman test, there is a significant correlation between renal function and body weight (P < 0.001) with a moderately positive correlation degree (r = 0.567).

DISCUSSION

This study aims to analyze whether the radiological findings of renal imaging can predict kidney function, so that a clinician can take advantage of the results of the examination. Some characteristics such as age and weight are suspected to affect kidney function, which in this study is represented by creatinine measurement and GFR estimation. The majority of subjects aged 41-50 years, with a relatively equal sex ratio, (male : female, 0.9 : 1), with an average body weight of 63.04 ± 14.74 kilograms.

Interpretation of the results of radiological assessment readings performed by two examiners showed no significant difference (P = 0.787) which indicates that there is uniformity between the results of the examination. The results of the examination of the kidney volume obtained is 167.92 ± 46.82 cm3 (right kidney) and 175.45 ± 46.61 cm3 (left kidney) with a total volume of 343.37 ± 88.93 cm3. Examination of renal function also showed normal mean results of creatinine examination (0.66 ± 0.21 mg/dL) and GFR (123.68 ± 39.11 mg/dL).

Based on the results of the Spearman test to analyze the correlation between kidney function and volume, statistically significant results (P < 0.05) were found with correlative coefficients that were diverse but quite similar between the right kidney (0.499), left kidney (0.410), and total kidney volume (0.479). Thus, there was a relatively stronger correlation between the right kidney and increased kidney function in this study. The results obtained in this study almost resemble the values obtained in research by Piras et al., in 2020, which mentions the existence of a positive correlation between kidney volume and GFR values of 0.32 and 0.35 in the general population and the population aged > 70 years old. It is also similar with Gong et al., researchers who analyzed 539 healthy adult individuals to determine the correlation between kidney volume and function and reported a significant relationship between the two variables, with a correlation coefficient of 0.615 (P < 0.05) for the total population [15]. However, this is not in line with Jovanovic's research et al., there is no significant correlation between kidney volume and its physiological function in the healthy population, except for creatinine clearance parameters (creatine clearance or CCr) over 24 hours with a moderately positive coefficient value (r = 0.44). Meanwhile, the study also mentioned that the correlation between kidney volume and function is only clinically meaningful when used to estimate the examination in patients with chronic renal failure (CKD). Furthermore, Jovanovic et al. also conducted additional analysis of the length, width, and thickness of the kidneys, which showed a moderately positive correlation to body mass index (BMI), age, and weight [14].

The results of the analysis between kidney volume and age in this study found a statistically significant negative correlation. With a correlation coefficient of -0.282 (right kidney), -0.196 (left kidney), and -0.250 (kidney total), it is concluded that the higher or the older a person is, the lower the volume in the individual group. This is in line with Gong's research et al. who concluded the relationship statistically had a higher correlative aspect in the male population compared to the female. The study also investigated whether there was a relationship between age and mean kidney volume in both gender, with the result that there was a decrease in kidney volume from the ages of less than 20 years old and more than 71 years old. A significant difference was also found in males (214.3 ± 35.8 mL) compared to females (182.8 ± 40.1 mL) with a P value < 0.05 at the age of 71 years. The higher the correlation coefficient of the right kidney, the change in the volume of the right kidney is thought to be more sensitive to age changes compared to the left kidney regardless of the sex of an individual considering that this study did not conduct a specific analysis of the influence of gender as did Gong et al. report [15]. This study is also similar with Wang et al. in his study of 1,334 individuals using CT-scan states that there is a progressive decrease in kidney volume with age, but specifically can be observed more in the population aged 50 years with an average decrease in volume of 22 cm3 [17]. Other studies by Roseman et al., has also been concluded a decrease in kidney volume ± 16 cm3/decades of an individual's lifetime although the majority of such macrostructural changes occur at > 60 years old [16]. This three studies also indirectly confirm the findings of this study in the form of a negative correlation between age and kidney volume in the healthy adult population.

In this study, body weight is also known to have a statistically significant correlative aspect with the findings of kidney volume based on CT-Scan examination, with a correlation coefficient of 0.548 (right kidney), 0.456 (left kidney), and 0.540 (both kidney). The statistical findings are related to the previous variable (age), making the volume of the right kidney one of the dependent variables that is more influenced by body weight than the left kidney. Okur et al., in their study of the healthy adult Turkish population using ultrasonography, reported a statistically strong linear relationship between kidney volume and body weight [18]. Despite this, the study contradicts a study by Amirkhanlou of 320 healthy adult individuals from Iran (mean age 48.03 ± 14.86 years old) that mentioned no meaningful correlation between BMI and kidney volume measured using ultrasound [19].

Further analysis of the relationship between renal function and age showed a statistically significant moderate negative correlation with a coefficient value of -0.495. The findings were supported by Eriksen et al. in a meta-analysis that investigates changes in GFR values in cohort studies that included healthy (935 people) and unhealthy (3274 patients) European populations. Reportedly, there was a decrease in GFR values of at least -0.72 mL / min per 1.73 m2 in males and -0.92 mL / min per 1.73 m2 in females for each year of life lived. The decrease in GFR values was also known to be significantly higher in the unhealthy group (-1.03 mL / min per 1.73 m2 in males and -1.22 mL / min per 1.73 m2 in females). Thus, Eriksen et al. concluded the existence of a negative linear relationship between GFR values with older age, which is currently suspected to be due to a decrease in the number of nephrons in old age based on biopsy results as has been reported by Denic et al. in 2017 [20-21]. The rate of decline in GFR values is known to occur starting from the third decade of life, with an average reduction of up to 1 mL/min / m2 based on research by Waas et al [22]. Therefore, all three studies are related to the statistical findings reported in this study which states the older an individual is, the higher the rate of GFR decline that occurs.

Renal function of patients included in this study was also affected by body weight with significant moderate correlative significance ($r = 0.567$; $P < 0.05$). Basically, this statement can mean that the higher the body weight of an individual, the higher the estimated kidney function (GFR and creatinine). Although basically the use of the word "function" here does not necessarily mean the kidneys in high-weight populations are better, it can mean the high physiological burden that occurs on the kidneys. On the other hand, studies by Li et al. a group of healthy adults in China cited variations in the relationship between body mass index and eGFR values. Patients with BMI overweight (23.0-26.9 kg/m2) reported a higher eGFR decrease of 0.33 mL / min per m2 compared with normal BMI Group (19.0-22.9 kg/m2) [23]. other studies by Dada et al. mention the higher the BMI value, the lower the eGFR value obtained so that obesity or overweight it can be considered as one of the most significant risk factors for CKD considering that the physiological and metabolic load received by the kidneys is much greater compared to the normal BMI Group [24]. however, the findings of this study are not consistent with other studies because the comparison was made to the correlation between BMI and kidney function.

LIMITATIONS OF RESEARCH

One of the main limitations of this study is the variable body weight. Body weight basically can not always be used as a marker of anthropological characteristics of the patient, because of the influence of height, so as to make BMI as a more meaningful variable. This study also did not stratify the age group or weight so that the final conclusion that can be drawn from each analysis is whether the change of the value of the independent variable will affect the value of the dependent variable positively or negatively. Therefore, although basically the findings of this study are more "predictive" aspects of a variable such as whether an increase in the value of A will affect the value of B linearly or inversely; which makes the meaning of “significant” in this study only aims to confirm the findings and will be correlated with the clinical aspects findings.

CONCLUSION

Kidney volume is one of the useful parameters for the evaluation of kidney function. Some characteristics such as gender, age and weight are thought to affect kidney function. From this study it can be concluded that there is a correlation between kidney volume and kidney function, the correlation between kidney volume and body weight, the correlation between kidney function and body weight, in addition there is also a negative correlation between kidney volume and age, as well as a negative correlation between kidney function and age in patients with normal kidney in Haji Adam Malik Hospital Medan year 2020-2021. Researchers suggest to do research with a larger number of study subjects and more detailed research parameters (such as the use of BMI to represent a person's nutritional status) in order to obtain reliable results to correlate radiological findings and clinical aspects-characteristics.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and H. Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

None.

AUTHORS’ CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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