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The HUGE formula (hematocrit, urea, gender) for screening for chronic kidney disease in elderly patients: a study of diagnostic accuracy

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Abstract Chronically reduced glomerular filtration rate (GFR) in old people does not always mean that they suffer from chronic kidney disease (CKD) since their GFR can just be reduced by aging. The HUGE equation has been recently described and validated in Spain for screening CKD without taking into account the patient's GFR value. This equation is based on patient's hematocrit, plasma urea levels and gender. The present study documented that the HUGE equation had and acceptable performance for screening CKD in elderly Argentine patients.

Keywords Elderly · HUGE equation · Chronic kidney disease

Introduction

It is already known that a chronically reduced glomerular filtration rate (GFR) in an old individual does not always mean that he/she suffers from chronic kidney disease (CKD) since this glomerular filtration reduction could be secondary to aging [1]. Conversely, a CKD patient may have no GFR reduction as it happens in those individuals who have an altered urinalysis (proteinuria and/or hematuria) or an abnormal renal image with a normal GFR value, as is the case of Stage I—CKD [2].

Because of the above exposed reasons, Alvarez-Gregori et al. originally described and validated in Spain a new equation (HUGE) which can detect the presence of CKD (or its absence) not taking into account the patient's GFR value. This equation offers a straightforward, readily available and inexpensive method for screening CKD, which is based on the patient's hematocrit, plasma urea levels and gender [3]. In this sense, the HUGE equation has been found to be more accurate than the GFR equations (MDRD, CKD-EPI, BIS1) for differentiating CKD in those individuals with an estimated GFR < 60 ml/min/1.73 m^2, a clinical setting where their low GFR could just be attributed to aging [1, 3].

In order to evaluate the external validity of the HUGE equation, we evaluated its performance in a group of elderly Argentine patients.

Materials and methods

This was a retrospective study to assess the operational characteristics of the HUGE equation for diagnosing CKD (diagnostic accuracy) in an ambulatory population of elderly patients (≥65 years old). From 2200 individuals who had been referred to our Nephrology Division at the Hospital Italiano de Buenos Aires (Argentina) since 2013, from January 1, 2013, December 31, 2013, 371 individuals who had the inclusion criteria were gathered for the study.

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The inclusion criteria were: to have information regarding the patient's age, gender, serum and urine urea, creatinine, sodium, potassium, estimated GFR (MDRD, CKD-EPI, BIS1), serum hematocrit, hemoglobin, glucose, calcium, phosphorus, parathyroid hormone, urinalysis and renal ultrasound. All these determinations should have been carried out during the period of the study.

After that, all the recruited patients were classified as having or not CKD after their evaluation by two independent nephrologists who based their diagnoses on the patient's medical record, blood and urine laboratories, as well as renal images, but were blind to the HUGE equation result and were not allowed to calculate it. This categorization in normal aging kidney (NAK) or CKD was based on a coincident double-blind nephrological evaluation which was considered to be the gold standard for diagnosing the presence or absence of chronic nephropathy (see clinical diagnosis criteria in "Appendix")[4].

Therefore, the HUGE equation was obtained from each volunteer, and HUGE was calculated applying the following equation [3]:

$$\begin{aligned}\text{HUGE} &= 2.505458 - [0.264418 \times \text{hematocrit}] \\ &\quad + \left[0.118100 \times \text{serum urea(mg/dl)}\right] \\ &\quad + [1.383960 \text{ if male}]\end{aligned}$$

$$\text{HUGE} < 0 = \text{normal renal function}$$

$$\text{HUGE} \geq 0 = \text{chronic kidney disease.}$$

Assuming sensitivity and specificity to be approximately 90%, we calculated a total of 135 individuals with NAK and 135 with CKD to estimate those operative characteristics with a 5% of semi-amplitude confidence interval. With an estimated CKD prevalence of 65% in our referred population, we calculated a total sample of 385. Sensitivity and specificity of the HUGE equation were evaluated to diagnose CKD using as gold standard the diagnosis based on clinical criteria (coincidence in the diagnosis made by two nephrologists who were blind to this study). Additionally, the causes of false positive and negative HUGE values were analyzed. Finally, correlation between MDRD-estimated GFR (CKD stages) and the HUGE value was obtained (Spearman coefficient) [5].

The present study was approved by the institutional review board, and all participants provided written informed consent at the time of registration for their assistance in our hospital.

Results

Data from 371 elderly patients were evaluated by two independent nephrologists (gold standard) who determined that 113 individuals had normal aging kidney (NAK) while 258 suffered from CKD.

Regarding age and gender, the CKD group was significantly older that NAK group: 81 ± 0.7 years old (NAK) versus 83 ± 0.5 years old (CKD), $p = 0.003$ (Table 1), while male gender represented 74 and 50% of the studied population in NAK and CKD groups, respectively (Table 1).

The concordance in the estimation of GFR through BIS1, CKD-EPI and MDRD equations was evaluated through the methodology proposed by Bland and Altman. Although their results were not fully concordant, the means of differences between the estimated GFR of the three possible pairs of comparisons (BIS1 vs. MDRD; BIS1 vs. CKD-EPI and MDRD vs. CKD-EPI) did not exceed 3.6 ml/min (CI 1.86–4.36).

Additionally, despite the sort of estimating GFR equation used for performing nephrological evaluation of these patients (gold standard), there was no significant change in their diagnosis (NAK or CKD) in this studied group (Table 1).

Regarding the GFR equations (MDRD, CKD-EPI, BIS1) and HUGE, estimated GFR was significantly higher in NAK group compared to CKD group: $p = <0.001$ (Table 1); while HUGE value was significantly lower in NAK group than in CKD group: −1.5 ± 0.2 (NAK) versus 5.2 ± 0.4 (CKD), $p = <0.001$.

From 258 CKD patients, 215 were detected by the HUGE equation (HUGE ≥ 0), which means that HUGE as an instrument for screening CKD had a sensitivity of 83.3%, IC 78.2–87.7% (43 false negative). Besides, from 113 healthy individuals, 93 were considered as free of renal disease by HUGE equation (HUGE < 0), which means that

Table 1 Comparison between chronic kidney disease (CKD) and normal aging kidney (NAK) elderly individuals: age, gender, MDRD and HUGE equations

	NAK ($n = 113$) Mean ± SD	CKD ($n = 258$) Mean ± SD	p	Normal values
Age (years)	81 ± 0.7	83 ± 0.5	0.003	–
Gender (male)	84 (74%)	128 (50%)	<0.001	–
MDRD (ml/min/1.73 m^2)	50.2 ± 0.6	36.9 ± 0.8	<0.001	50 ± 5*
CKD-EPI (ml/min/1.73 m^2)	60.5 ± 16	36.1 ± 17	<0.001	50 ± 5*
BIS1 (ml/min/1.73 m^2)	53.8 ± 13	36.0 ± 14	<0.001	50 ± 5*
HUGE	−1.5 ± 0.2	5.2 ± 0.4	<0.001	<0

* Normal glomerular filtration rate expected by age (oldest old individuals)

Table 2 HUGE equation sensitivity and specificity

	Reference test (comprehensive evaluation by two nephrologists)		
	Positive	Negative	
Index test (HUGE equation)			
Positive	TP: 215	FP: 20	
Negative	FN: 43	TN: 93	
	ToP: 258	ToN: 113	Total 371
	Sensitivity = 215/258 = 0.83 (IC 78.2–87.7%)	Specificity = 93/113 = 0.82 (CI 95% 0.74–0.89)	

TP true positive, *FP* false positive, *TN* true negative, *FN* false negative, *ToP* total positives, *ToN* total negatives

Table 3 Correlation between chronic kidney disease (CKD) stages and HUGE value

	HUGE Median (range)	Studied people *n* (%)
NAK	−1.65 (−3.2/−0.6)	113 (30)
CKD Stage II GFR: 89–60 ml/min	−3.2 (−5.6/−2.6)	8 (2)
CKD Stage IIIa GFR: 59–45 ml/min	2.2 (0.4/5.0)	77 (21)
CKD Stage IIIb GFR: 44–30 ml/min	3.9 (1.9/7.3)	104 (28)
CKD Stage IV GFR: 29–15 ml/min	5.1 (2.9/9.9)	50 (14)
CKD Stage V GFR < 15 ml/min	6.4 (3.7–13.1)	19 (5)

NAK normal aging kidney, *GFR* glomerular filtration rate

HUGE had a specificity of 82.3%, IC 74.0–88.9% (20 false positive) (Table 2).

The performance of the HUGE equation to classify healthy renal people as NAK was very good since it detected 83.9% of them. Regarding people suffering from CKD, the HUGE equation incorrectly classified as NAK 25% of patients with Stage IIIa CKD, 10.9% of Stage IIIb, 7.4% of Stage IV and 5% of Stage V.

A significant an inverse correlation between GFR level (based on MDRD) and HUGE value was documented in CKD patients: Spearman correlation: 0.68, $p = <0.001$ (Table 3).

Finally, no significant difference in the HUGE equation sensitivity and specificity between old (age ≥ 65 years) and very old patients (age ≥ 80 years) was documented, $p =$ NS.

Discussion

The HUGE equation was originally described in Spanish population, and its relevance as an instrument for screening CKD in people with GFR < 60 ml/min/1.73 m^2 was documented [3, 6, 7, 8]. Because of that, we decided to evaluate HUGE performance in people who characteristically have low GFR (elderly) and also to check its performance in a non-Spanish population (external validity).

For this purpose, we decided to evaluate the performance of the HUGE equation in elderly Argentine patients, finding that HUGE had a good external validity since it showed an acceptable sensitivity (83.3) and specificity (82.3) for screening CKD in elderly Argentine patients. Even though the HUGE equation showed a better performance in the Spanish study where it was originally described (sensitivity: 92.8%, and specificity: 93.2%), it should be taken into account that the equations performance is usually better in the population where they are originally described [3, 5].

False positive ($n = 20$) and false negative ($n = 43$) cases were analyzed in order to understand why the HUGE equation failed in these cases:

The main causes of false positive diagnosis (in order of frequency) were:

- low hematocrit and high serum urea levels secondary to acute renal failure.
- severe anemia of non-renal origin.

The main causes of false negative (in order of frequency) were:

- slightly low or normal hematocrit and serum urea values (mild CKD: Stages I–II).
- very high hematocrit (polycythemia).
- very low serum urea (malnutrition).

Consequently, it seems that to exclude acute renal failure, malnourished, polycythemic, non-renal anemic patients could improve HUGE equation performance.

Additionally, a significant correlation was documented between the HUGE numerical value and the severity of GFR reduction (stages) in CKD patients. Thus, it seems that HUGE can determine the presence of CKD and also to provide an idea regarding its severity (Table 3).

Another interesting finding of this study was that HUGE equation was not able to detect early stages of CKD (e.g., Stage II) (Table 3). This phenomenon could be explained because the diagnosis of kidney disease in the early stages of CKD are based on ultrasound or urinary abnormalities, which are precisely not variables taken into account by the HUGE equation.

It is worth pointing out that since we studied an elderly group, even those who had no renal disease presented a reduced GFR secondary to aging. In this context, 113 individuals (30%) would have been incorrectly considered CKD patients if a MDRD < 60 ml/min/1.73 m^2 criteria for nephropathy diagnosis would have been applied. Thus, it seems that HUGE equation is a much more reliable tool for performing screening of CKD compared to MDRD equation in elderly population (Table 3).

Conclusion

Our study documented that the HUGE equation had and acceptable performance for screening CKD in elderly Argentine patients.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all the participants included in the study.

Appendix [4]

CKD diagnosis: to have at least an abnormal value in one of the following parameters: GFR, urinalysis and renal ultrasound.

- Reduced GFR: a GFR value lower than the expected one secondary to aging: expected GFR = 130 − age (ml/min/1.73 m^2).
- Abnormal urinalysis: presence of renal (dysmorphic) hematuria (>3 red blood cells) and/or proteinuria (>0.2 g/day).
- Abnormal renal ultrasound: presence of at least one of the following alterations in renal parenchyma: reduced size, asymmetry, increased parenchyma echogenicity, many cysts and altered cortex–medulla proportion.

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