

Older adults: Kidney disease or senescent aging? HUGE vs. CKD-EPI scale. The approach to the elderly.

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Abstract

Introduction: The approach to the renal condition of the elderly requires diagnostic tools for this age group, which allow discerning its renal condition between chronicity and senescence. This research aimed to analyze whether the HUGE scale is a companion tool to determine the existence of chronic kidney disease in older adult patients seen in outpatient clinics.

Methods: This observational, analytical and cross-sectional study was carried out in the nephrology outpatient clinic of the Specialty Hospital of the Armed Forces No. 1 in 2015-2018.

Results: We included 285 patients. The prevalence of chronic kidney disease was higher in people older than 75 (60.7%). With the HUGE formula, a lower proportion of chronic kidney disease was established in 37% of men and 60% of women ($P = 0.002$) than in the CKD-EPI formula (83% and 89%, respectively). The specificity achieved by the HUGE formula was higher than the CKD-EPI and MDRD formulas (97% vs. 80% vs. 79%, respectively), having the highest discriminative capacity (NPV 70%). Hyperuricemia and diabetes mellitus are associated with the development of chronic kidney disease.

Conclusions: This research showed that the HUGE formula helps discern those older adults with decreased glomerular filtration due to senescent aging in those with kidney disease. The HUGE formula is recommended as a complementary tool in the approach to chronic kidney disease in older adults.


Keywords:

MESH: Kidney Failure, Chronic; Renal Insufficiency, Chronic; Glomerular Filtration Rate; Aged; Frail Elderly.

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According to the KDIGO criteria, the group of older adults with a glomerular filtration rate of 45 and 59 ml/min/1.73 m² are carriers of chronic kidney disease (CKD). For example, a study carried out among 610 people over 70 years of age showed that half had a glomerular filtration rate of 60 ml/min/1.73 m² and, therefore, would meet the criteria for the diagnosis of CKD, according to the criteria of KDIGO [1].

Contrary to this classification concept, patients with a glomerular filtration rate of 45 to 59 ml/min/1.73 m² do not have a reduced life expectancy compared to patients with CKD G1–2 [2] and even more so. A Swedish study convincingly demonstrated that CKD G3a was not associated with increased relative mortality risk [3].

Renal functional deterioration, related to age, has minimal effect on life expectancy and, by itself, should not exclude older people motivated to donate kidneys, for example. It is established that nephrosclerosis and cortical volume loss are compensated by the hypertrophy of the remaining nephrons, associated with a lower metabolic demand [4], which confers a lower glomerular filtration rate, without these concepts fully explaining the decrease in age-related glomerular filtration rate [5].

Renal senescence is of clinical relevance when treating geriatric patients, as they are more susceptible to acute kidney injury and a more severe initial presentation of truly progressive disease [6]; therefore, fixed glomerular filtration rate thresholds to diagnose CKD are not reasonable since they do not take into account the decrease in glomerular filtration rate with normal aging. Distinguishing between an older adult individual with a "normal for age and gender" low glomerular filtration rate and one with the same glomerular filtration rate resulting from kidney disease is very important because treatment of the former has not been shown to reduce the risks of cardiovascular events or progression to end-stage renal disease. The Álvarez-Gregori et al. group considered the physiological conditioning factors of the senescent process, as well as the comorbidities associated with aging (chronic noncommunicable diseases). They proposed to establish, through biochemical parameters of accessible medication and the sex of the patient, a screening test capable of differentiating CKD from the decrease in the glomerular filtration rate generally associated with the renal aging process. In their analysis, they developed the hematocrit, blood urea, and sex (HUGE) screening formula, which offers a simple, easily accessible, and inexpensive method to differentiate between a glomerular filtration rate < 60 ml/min/1.73 m², typical of the senescent condition of true CKD [7].

HUGE as a screening tool makes it possible to discern that healthy older adults are not mistakenly classified as having

CKD, as well as the identification of the group of patients with renal insufficiency and at risk of progression to renal disease [8, 9]. The objective of the present study was to establish if the renal risk prediction table using the HUGE formula is valid to discriminate the senescent renal condition in the elderly attended in the nephrology outpatient clinic at the Armed Forces Specialty Hospital No. 1 in Quito, Ecuador.

Materials and methods

Study design

The present study is observational, cross-sectional and analytical.

Scenery

The study was carried out in the nephrology outpatient service of the Specialty Hospital of the Armed Forces No. 1 in Quito-Ecuador. The study period was from January 1, 2015, to December 31, 2018. The study ended the data collection phase on March 30, 2019.

Participants

Patients classified as adults older than 65 years of age were included, in whom all the paraclinical information was available (hematocrit, urea, creatinine) and who had calculations of the renal condition established by formulas (CKD-EPI, MDRD, Cockcroft Gault). Patients with incomplete medical records were excluded.

Variables

The independent variable was renal function with the CKD-EPI formula, the Keller formula, the MDRD formula, and the BIS1 formula. The dependent variable was the HUGE formula. The intervening variables were age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, cancer, hypothyroidism, heart failure, benign prostatic hypertrophy, glomerulopathy, urinary tract infection, and the use of NSAIDs.

Data sources/measurements

The variables were taken from the institutional clinical file. The CKD-EPI formula is as follows: glomerular filtration rate = $141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ (if female) $\times 1.159$ (if male). of black race).

where Scr: serum creatinine.

κ : 0.7 if female and 0.9 if male

α : -0.329 if female and -0.411 if male

$\min(\text{Scr}/\kappa, 1)$: whichever is smaller between Scr/κ and 1

$\max(\text{Scr}/\kappa, 1)$: whichever is greater between Scr/κ and 1



The HUGE formula used was the following $=2.505458 - (0.264418 \times \text{hematocrit}) + (0.118100 \times \text{urea}) + (1.383960 \text{ if male})$.

Keller's formula is as follows: Glomerular filtration rate = $(130 - \text{age [in years] mL/min})$.

The MDRD formula is as follows: $eGFR = 175 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$.

Biases

To avoid possible interviewer, information, and memory biases, the data were guarded at all times by the principal investigator with appropriate guidelines and records. Observation and selection bias was avoided by applying the participant selection criteria. Participants were asked to be consistent in their diet: Avoid eating meat and protein the day before the study.

Studio size

The sample was probabilistic from a universe of 1098 patients; the sample calculation was 285 patients, estimating a heterogeneity of 50% (patients diagnosed with chronic kidney disease), with a margin of error of 5 and a confidence level of 95%. To choose the sample, we performed a simple random assignment, complying with the inclusion, exclusion, and elimination criteria.

Quantitative variables

Glomerular filtration rate estimates (Keller, MDRD, CKD-EPI, BIS1, HUGE) are presented as the mean and standard deviation. Mean differences are made between the estimates. The diagnostic performance of the sensitivity, specificity, and positive and negative predictive values of the Keller, MDRD CKD-EPI, and HUGE formulas were analyzed.

Statistical analysis

The analysis of the presence or absence of CKD in patients with the CKD-EPI and the HUGE formula is presented; the significant difference is presented with Chi-square and P value <0.05 as significant. The prevalence of CKD is presented concerning comorbidities; percentages are compared with Chi-square and P value <0.05 . The estimation of the glomerular filtration rate (mean and standard deviation) is presented with the Keller, MDRD, CKD-EPI, BIS1, and HUGE formulas and their mean differences between the formulas. The primary analysis focuses on the HUGE formula compared to the CKD-EPI formula; diagnostic tests are presented for each formula. A secondary analysis compares the presence of comorbidities by clinical stages of CKD-EPI (2 to 5) in the presence or absence of CKD with the HUGE formula.

Results

Participants

A total of 285 patients entered the study. The diagram of the participants is presented in Figure 1.

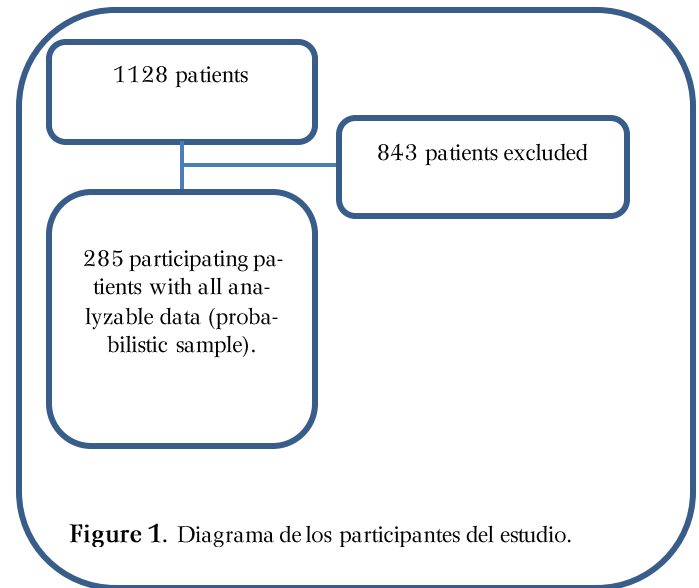


Figure 1. Diagrama de los participantes del estudio.

Characteristics of the study population

There were 285 patients from 65 to 60 years old, 3 cases (1.05%); from 70 to 79 years old, 157 cases (55.09%); from 80 to 89 years old, 110 cases (38.60%); and from 90 to 99 years old, 14 cases (4.91%). and >100 years in 1 case (0.35%). The average age of the group was 75.56 years. Because attention corresponds to military service servers, most patients correspond to the male sex (80%).

Comorbidities

Most of the comorbidities were chronic noncommunicable diseases: essential arterial hypertension, type 2 diabetes mellitus, and cancer (Figure 2). Table 1 shows a higher proportion of chronic kidney disease in patients older than 75 years, with a similar prevalence to patient sex. Using the CKD-EPI formula, it is established that on average, 86.5% of those evaluated have some degree of chronic kidney disease, with a similar prevalence in both sexes. While the HUGE formula shows a lower prevalence of chronic kidney disease, there is a difference because there is greater CKD in women. There were no differences in the prevalence of comorbidities between men and women, except for hyperuricemia, which was more prevalent in women in 20 cases (36.4%) versus 42 cases in men (18.3%) ($P = 0.003$). Table

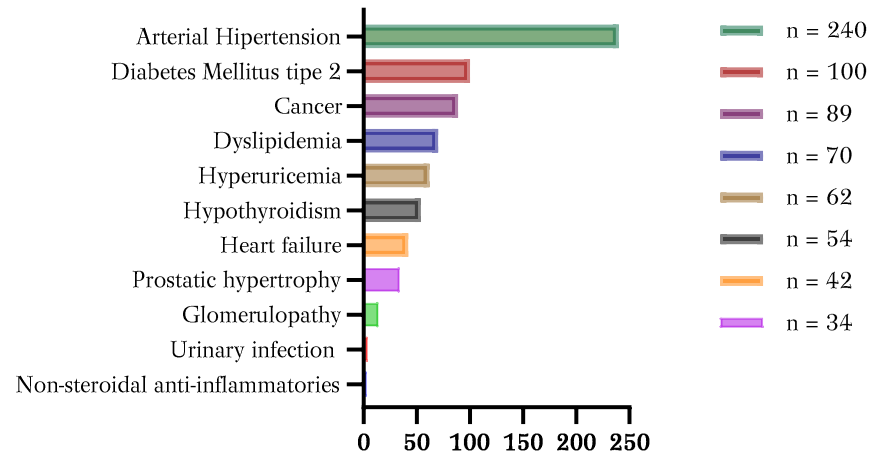


Figure 2. Bar graph of the prevalence of comorbidities.

2 shows statistically significant differences in the hemato-crit value between men and women. The CKD-EPI, BIS1, and MDRD formulas presented a significant difference when compared by sex. The average glomerular filtration rates using the MDRD, CKD-EPI, and BIS1 formulas were 69, 44, 23, and 8 for stages 2, 3, 4, and 5, respectively. The Keller formula, like creatinine or urea, does not show statistical significance in the comparison by sex (Table 1). The values obtained by Keller's formula were inconsistent with the CKD stage.

Table 2 shows the incidence of CKD by the HUGE method compared with the MDRD and CKD-EPI methods. The MDRD

formula has significant differences from the HUGE formula. The diagnostic performance to establish the diagnosis of chronic kidney disease using the Keller formula does not present diagnostic utility (Table 3). The MDRD Formula denotes being inferior to the HUGE formula and yielding higher than the CKD-EPI formula. Comparing the HUGE formula shows greater sensitivity and negative predictive value with the MDRD and CKD-EPI formulas. The formulas used show different performances in the parameters analyzed about their ability to detect chronic kidney disease, with the HUGE formula being the formula with the best diagnostic performance.

Table 1. Characterization of chronic kidney disease concerning sex.

| Variable | Men n=230 | Women n=55 | P |
|----------------------------|---------------|---------------|--------|
| Age under 75 years | 97 (42.2%) | 20 (36.4%) | 0.431 |
| Age over 75 years | 133 (57.8%) | 35 (63.6%) | |
| Presence of CKD (CKD-EPI)* | 193 (83.9%) | 49 (89.1%) | 0.335 |
| Absence of CKD (CKD-EPI) | 37 (16.1%) | 6 (10.9%) | |
| Presence of CKD (HUGE)** | 85 (37.0%) | 33 (60.0%) | 0.002 |
| Absence of CKD (HUGE) | 145 (63.0%) | 22 (40.0%) | |
| Creatinine (mg/dL) | 1.715 ± 1.16 | 1.571 ± 0.8 | 0.390 |
| Urea (mg/dL) | 58.74 ± 28.65 | 66.66 ± 33.62 | 0.076 |
| Hematocrit (%) | 45.58 ± 6.8 | 40.89 ± 7.1 | 0.001* |
| GFR (MDRD)** | 49.33 ± 17.9 | 43.29 ± 22.2 | 0.033* |
| GFR (BIS1)* ** | 43.37 ± 13.0 | 38.98 ± 16.2 | 0.033* |
| GFR (Keller) | 50.57 ± 6.9 | 50.89 ± 7.9 | 0.529 |
| GFR (CKD-PID)*** | 46.88 ± 17.3 | 40.69 ± 21.2 | 0.024* |

MDRD: Modification of Diet in Renal Disease, * BIS1: Berlin Initiative Study, **CKD-EPI: Chronic Kidney Disease, Epidemiology Collaboration, **HUGE (Hematocrit, Urea, Gender), * Pearson Chi-Square

**Table 2.** Average values studied in the population with chronic kidney disease by sex.

| | CKD by HUGE n=118 | Without CKD due to HUGE n=167 | P |
|---------------------------|----------------------|----------------------------------|-------|
| determined CKD by MDRD | 46 (16.1%) | 0 (0%) | 0.001 |
| CKD determined by CKD-EPI | 103 (36.1%) | 139 (48.8%) | 0.346 |

CKD: chronic kidney disease. MDRD: Modification of Diet in Renal Disease. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Table 3. Performance of diagnostic tests.

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-----------------|-----------------|-----------------|--------------|---------|
| HUGE Formula | 97% | 30% | 3% | 70% |
| CKD-EPI formula | 80% | 95% | 60% | 5% |
| MDRD Formula | 79% | 100% | twenty-one % | 0% |
| Keller Formula | 32% | 33% | 68% | 67% |

MDRD: Modification of Diet in Renal Disease. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Discussion

Renal senescence and chronic renal failure are two completely different conditions from a physiological point of view. In chronic kidney disease, there is a failure in the management of erythropoietin, urea, potassium, calcium, phosphorus, and magnesium, and the implications of the therapeutic approach, such as unnecessary medicalization and the request for diagnostic tests that are not needed, can lead to harmful consequences associated with overdiagnosis [10]. In clinical practice, renal senescence is very often confused with some type of chronic kidney disease. Situation expressed particularly as a glomerular filtration rate expressed as a "critical value < 60 ml/min/1.73 m²", which is accompanied by complications associated with manifestations of chronic kidney disease such as anemia, hyperkalemia, hyperphosphatemia, acidosis, hypocalcemia and bone mineral alteration [11].

In patients already diagnosed with chronic kidney disease, the estimation of the glomerular filtration rate by the CKD-EPI or MDRD formula is valid for staging and monitoring progression; however, in patients without a known diagnosis of kidney disease, the use of the glomerular filtration rate for screening becomes controversial in its interpretation, since it does not consider other assessment parameters required to establish the diagnosis, which is why it is considered a discouraged practice.

Similar to previous studies, the HUGE equation has better diagnostic performance in older adults with a glomerular filtration rate <60 ml/min/1.73 m² [7, 8], with a sensitivity of 97.0%, which is higher than that of the original study (92.8%) [7]. The HUGE equation showed adequate performance in older people >75 years of age with a GFR <45 ml/min/1.73 m² [8], corroborating this study.

The HUGE equation does not consider the glomerular filtration rate or the analysis of proteinuria, variables that establish the diagnosis of chronic kidney disease. Therefore, a triple diagnostic strategy was established in this group. It should be noted that the combined strategy of using the HUGE formula with other simple variables, such as the estimated filtration rate, provides better performance in detecting chronic kidney disease in older people. This situation can be extrapolated to the general population.

Other studies consider urinalysis as an additional tool to provide better performance to conventional formulas for estimating glomerular filtration rate and the HUGE screening formula. As shown by Musso et al., the performance of the combined triple screening strategy for CKD (urinalysis, HUGE, and estimated glomerular filtration rate) in the elderly population (65-79 years) had no false-negative cases and few cases. Of false positives [8]. Regardless of its estimation, the glomerular filtration rate alone needs to be supplemented in the elderly to avoid the mistaken exclusion of healthy older adults from receiving surgical or pharmacological treatments that are necessary for the patient but contraindicated in renal failure.

The preceding makes it possible to establish that the HUGE equation has acceptable performance for screening for CKD stages III-V in older adults. Additionally, it has an excellent performance in screening for chronic kidney disease in the general population in combination with estimating glomerular filtration rate, either by CKD-EPI and MDRD or in conjunction with urinalysis.

The present study makes it possible to establish the recommendation not to classify an older adult with an estimated glomerular filtration rate <60 ml/min/1.73 m² as a carrier of chronic kidney disease in the absence of confirmation with complementary tools such as EMO or renal ultrasound or by evaluation of a nephrologist or geriatrician.



This research denotes diagnostic complementarity of the HUGE formula to establish the condition of chronic kidney disease. Conclusion established based on the diagnostic capacity of the CKD-EPI formula, provided that it is standardized for the Ecuadorian elderly population, or failing that, the MDRD formula. This research allows us to establish that the current scheme for classifying chronic kidney disease based on the glomerular filtration rate must be redesigned to be calibrated by age. This trial would better reflect the underlying biology of kidney aging and the risks of mortality and advanced chronic kidney disease.

The impact of oncological diseases denotes a significant commitment to the epidemiological profile of comorbidities associated with aging, although this denotes greater involvement in developing chronic kidney disease.

Given the findings of the study, it is recommended not to exclude from clinical trials older adults erroneously and inconclusively classified as having chronic kidney disease with the sole criterion of an estimated glomerular filtration rate <60 ml/min/1.73 m², since it would deprive us of acquiring experience and therapeutic evidence.

Conclusions

The HUGE formula makes it possible to screen older adults with actual chronic kidney disease for those with a physiological decline in kidney function typical of senescent conditions. However, the formula does not allow establishing the stage of chronic kidney disease in those patients with a chronic condition.

Chronic noncommunicable diseases, mainly diabetes mellitus and hyperuricemia, are associated with impaired renal function in older adults. It should be noted that the generational change associated with lifestyles can influence the commitment and impact of comorbidities on the development of chronic kidney disease.

Abbreviations

MDRD: Modification of Diet in Renal Disease.

BIS1: Berlin Initiative Study.

CKD-EPI: Chronic Kidney Disease, Epidemiology Collaboration.

CKD: Chronic kidney disease.

HUGE: Hematocrit, Urea, Gender.

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Supplementary information

Supplementary materials have not been declared.

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Author contributions

Harold David Álvarez Bolaños: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.

Washington Xavier Osorio Chuquitarco: conceptualization, supervision, validation, visualization, writing: revision and editing.

All authors read and approved the final version of the manuscript.

Financing

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Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable academic request.

Statements

Ethics committee approval and consent to participate

It was not needed.

Consent to publication

This does not apply when images or photographs of the physical examination or radiography/tomography/MRI of patients are not published.

Conflicts of interest

The authors report having no conflicts of interest.

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