How histopathological diagnosis interacts with kidney ultrasound parameters to predict glomerular filtration rate

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Abstract

Background

eGFR evaluation is a pivotal staging step in patients with chronic kidney disease (CKD), and renal ultrasound plays an important role in diagnosis, prognosis and progression of CKD. The role of the interaction between histopathological diagnosis and ultrasound parameters in the eGFR determination has not been fully investigated yet.

Methods

The study examined the results of native kidney biopsies performed in 48 Italian centers between 2012 and 2020. The primary goal was if and how the histopathological diagnosis influences the relationship between eGFR and ultrasound parameters.

Results

After exclusion of children, patients with acute kidney injury and patients without measure of kidney length or parenchymal thickness, 2795 patients have been selected for analysis. The median values were 52 years for patient age, 11 cm for bipolar kidney diameter, 16 mm for parenchymal thickness, 2.5 g/day for proteinuria and 70 ml/min/1.73 m^2 for eGFR. The bipolar kidney diameter and the parenchymal thickness predict eGFR values (R square 0.064). Diabetes and proteinuria were associated with a consistent reduction of eGFR, improving the adjusted R square up to 0.100. Addition of histopathological diagnosis in the model increased the adjusted R square to 0.216. There is a significant interaction between histopathological diagnosis and longitudinal kidney diameter (P 0.006).

Conclusions

Renal bipolar length and parenchymal thickness are directly related with eGFR. The magnitude of proteinuria and histopathological kidney diagnosis increased the prediction of eGFR. The association between the kidney length and the level of eGFR depends on the nature of the kidney disease.

INTRODUCTION

Renal Ultrasound (US) plays an important role in the diagnosis and progression of chronic kidney disease (CKD). The evaluation of CKD is classified based on the glomerular filtration rate (GFR) estimate, urinary abnormalities, and ultrasound structural kidney abnormalities. When CKD is suspected or diagnosed, longitudinal kidney diameter, parenchymal thickness and echogenicity grading are the first measures to be gathered, through renal US, as first imaging tool. CKD can be associated with different values of longitudinal kidney diameters. It increases in polycystic kidney disease, in myeloma cast nephropathy, in amyloidosis, and in the beginning of the diabetic Kimmestiel-Wilson nephropathy. Contrarily, it decreases in many other nephropathies, such as chronic glomerulonephritis, nephroangiosclerosis and chronic ischemic nephropathy.

The estimate of GFR (eGFR) in place of its measure ¯ is a pivotal step in the CKD staging and can be performed by using various approaches, like the Cockroft-Gault and the Modification of Diet in Renal Disease (MDRD) study equation . In the clinical practice context, the Cockroft-Gault equation has been progressively abandoned, partially because it requires the knowledge of the patient weight, often unavailable at the laboratory level and, in addition, it overestimates the true GFR at high values of body mass index . On the other side, the first MDRD eGFR equation has been improved to take into account three subsequent needs: a standardized measurement of creatinine , a simplified equation (four variables in place of the first six) [9], and a higher accuracy at GFR values higher than 60 ml/min/1.73 m^2 [6]. In 2012 , 2014 and 2021 , other equations developed in different populations were published, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations have been used more frequently for general clinical purpose. The 2021 CKD-EPI equation offered the opportunity to take out the race information from the eGFR estimation [12]. Unfortunately, this race-free equation may result in substantial change in eGFR estimation, in CKD reclassification, in kidney and cardiovascular prognosis , , , and in substantial error in comparison with the measured GFR, also among kidney transplant recipients .

Future research should focus on the lack of a more precise eGFR equations at the individual level, and the risk of a misleading indexing of glomerular filtration rate for body surface area in obese patients.

The aim of this study, instead, is to define the relationship between the kidney diameters measured in vivo with ultrasound and the estimated GFR according to the CKD-EPI 2009 Eq. 6, taking into account the contributive predictive role of the histopathological diagnosis available with native kidney biopsy.

MATERIALS AND METHODS

Patient selection

The invited Italian study centers and the patients enrolled in this study are described in detail in our previous work . Briefly, as this was an observational study, the enrollment criteria were not questioned. Consequently, all of the consecutive patients undergoing a native kidney biopsy during the active recruitment period were considered eligible and there were no a priori exclusion criteria. In relation with the aim of this study, secondary exclusion criteria were pediatric patients (age at kidney biopsy less than 18 years), unstable patients for acute kidney injury (AKI) or AKI in patients on chronic kidney disease (CKD), unavailability of eGFR or its estimated value higher than 200 ml/min, unavailability of kidney length or of parenchymal thickness of biopsied kidney.

Data collection was centralized and made use of an ad hoc web-based database linked to the Italian Renal Biopsy Registry (http://www.irrb.net/).

All of the patients gave their written informed consent; the study protocol was approved by the Ethics Committee of Bari University and implemented in accordance with the principles of the Declaration of Helsinki. It was not appropriate to involve patients or the public in the design, or conduct, or reporting, or

dissemination plans of our research. This independent study without any sponsorship was registered with ClinicalTrials.gov (No. NCT04948593).

Outcomes

The primary goal of this study was to define the relation between the renal length and parenchymal thickness measured with ultrasounds and estimated GFR (eGFR), taking into account the predictive contribution role of the histopathological diagnosis made by native kidney biopsy.

Variables

Relevant patient-related covariates and factors prospectively recorded included age, gender, diabetes, the clinical presentation of their renal disease, the presence of renal failure, the estimated glomerular filtration rate (eGFR) according to CKD-EPI equations ([9]), the bipolar longitudinal diameter and the parenchymal thickness of the biopsied kidney, the magnitude of proteinuria and the histopathologic kidney diagnosis.

Ultrasound parameters were measured in the biopsied kidney, thus more frequently on the left side (95% of patients), on the midaxillary line with the patient in lateral decubitus. Parenchymal thickness was measured and reported where it was minimum in value, avoiding Bertin's columns.

The type and the severity of diabetic nephropathy according to the criteria of Mazzucco G et al and of the renal pathology system were also considered.

Statistical analysis

For descriptive purposes, quantitative variables were analysed using their median values and the 10th and 90th percentiles, as indexes of central tendency and variability, respectively. Categorical variables were analysed as absolute numbers and percentages.

For inferential purposes, multivariate analysis of variance was performed, using the estimated glomerular filtration rate (eGFR) as dependent variable, according to CKD-EPI Eq. (9) expressed in ml/min/ 1.73 m^2. To investigate the role of the various predictors, a step-by-step approach was used starting from the main predictors, such as the kidney bipolar diameter and parenchymal thickness. According to the suggestion of Lucisano G at al , we have considered also the predictive role of the kidney length indexed for body height compared with the kidney length alone. The next step was adding the histopathologic kidney diagnosis, to test its role as main predictor variable, and its interaction with the US biopsied kidney length. Finally, we added in the model the predictive role of the type and severity of diabetic nephropathy. The amount of explained variance, through the adjusted R square, was used as goodness of fit. The partial Eta square of each predictor was used to test the relative net impact of each one compared to the others.

All the analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 23.0).

RESULTS

This study involved 48 Italian centers (see Appendix 1) and 5312 patients, enrolled from the 3rd of January 2012 to the 4th of August 2020. After exclusion of children (333 patients, 6%), the patients with acute kidney injury (AKI) or AKI on CKD (1390 patients, 26%) and patients without measure of kidney length or parenchymal thickness (894 patients, 17%), the final sample of 2795 patients (53%) was selected for analysis from the pool of 5312 biopsied patients (Fig. 1). Thus 2795 patients, with one kidney biopsy for each patient, constituted the study group for this report. The main characteristics of the analysed patients were shown in Table 1. The median values were 52 years for patient age, 11 cm for bipolar kidney diameter, 16 mm for parenchymal thickness, 2.5 g/day for proteinuria and 70 ml/min/1.73 m^2 for eGFR. Male were prevalent (60.5%), with a clinical diagnosis of diabetes status in 14.9% of the cases. Urinary abnormalities (49.2%) and nephrotic syndrome (39.4%) were the more common clinical presentations of studied patients.

The three more frequent diagnoses were IgA Nephropathy (IgAN), Membranous Nephropathy (MN) and Focal and Segmental GlomeruloSclerosis (FSGS) (Table 2).

Multivariate analysis

The Table 3, Panel A shows how the ultrasound kidney parameters, such as the bipolar kidney diameter and the parenchymal thickness, predict eGFR values. As expected, the B coefficients of both ultrasound parameters were positive, indicating a direct association with the eGFR values. The adjusted model R square value is 0.064, showing that the ultrasound parameters, together with the gender variable, explain only 6.4% of the eGFR variability. This percentage is not improved by using kidney length and parenchymal thickness indexed for body height in place of the kidney length alone (data not shown).

Adding other two predictors easily available before and without kidney biopsy, such as the clinical diabetes status and proteinuria values (Table 3, Panel B), the adjusted model R square value increased from 0.064 to 0.100, with the persistent major contribution of the bipolar kidney diameter (Eta square of 0.048). Interestingly, male gender, diabetes status and proteinuria were associated with a significant and a consistent reduction of eGFR value (see B coefficients in Panel B of Table 3).

The histopathological diagnosis added a lot of information on the eGFR/ultrasound parameters relationship (Table 4, Panel A). Indeed, the adjusted model R square value increased consistently from 0.100 to 0.216, with the major predictive contribution made now by the histopathological diagnosis ($P < 0.001$, Eta square of 0.022). Moreover, as expected, there was a significant interaction of histopathological diagnosis with longitudinal kidney diameter ($P = 0.006$, Eta square of 0.017) suggesting that the association of kidney length with the level of eGFR was dependent on the nature of kidney disease. The histopathological diagnosis, at the time of kidney biopsy, influenced also the distribution of mean eGFR values (Fig. 2): some histopathological diagnoses were associated with a nearly normal eGFR value, as in case of normal kidney, of minimal chance disease (MCD) or of hereditary glomerulopathies. On the other side, small vessel vasculitis and myeloma cast nephropathy were more frequently associated with low eGFR values.

Finally, the global prediction model can be little ameliorated, from 0.216 to 0.219, with the addition of renal pathology score, according to the pathologic classification of diabetic nephropathy [20] (Table 4, Panel B): as expected, a high value of renal pathology score was associated with a decrease of eGFR (Fig. 3).

DISCUSSION

The main findings of this study are i) that is confirmed a direct relationship between eGFR and kidney mass estimated with the kidney bipolar length and the parenchymal thickness, ii) that diabetes status and proteinuria levels can ameliorate the eGFR estimation, and finally iii) that the histopathological diagnosis gives a relevant additional contribution to the eGFR estimation.

Regarding the first finding, renal length and parenchymal thickness are clinically relevant parameters, often used for making clinical decisions . In our study, both renal length and parenchymal thickness were associated directly with eGFR, with a major contribution of renal length (Eta square 0.037) compared with the parenchymal thickness (Eta square 0.006). As renal function loss occurs during the course of CKD, the measurement of kidney bipolar length using ultrasound can become a very useful tool. Several studies have demonstrated the relationship between kidney size and eGFR in kidney donors , in renal transplant patients and in older patients . Since it is well-known that progressive loss of nephrons is associated with a reduction of kidney mass , correlations were performed between renal function in the elderlies and renal US parameters . Apart from some specific kidney diseases such as polycystic kidney , longitudinal renal diameter is considered a pivotal marker of CKD, since it progressively declines together with GFR, thus with a direct relationship. Accordingly, polycystic kidney disease was absent in our sample, and also patients with acute kidney injury or acute kidney injury on chronic kidney disease, other confounding factors on the kidney diameter/eGFR relationship, were excluded from our analysis. Moreover, in most of the patients with acute kidney injury, renal US imaging shows normal or larger renal diameters . For this reason, in our study, also patients with acute kidney injury were excluded.

In course of CKD, it is well known that there is a progressive loss of renal mass and a reduction of kidney length associated with a decline of GFR [4]. With age, this evolution pattern happens also in healthy subjects, in a less impressive manner, and can manifest differently in men and women . Anyways, the relationship eGFR/kidney diameter length remained very weak in our study (adjusted R square value of 0.064) and this can be due to at least two limiting factors: the diameter length was measured only on one kidney, the biopsied one, and the lack of longitudinal observations. In fact, no information was collected on the contralateral kidney diameter. Regarding the latter limiting factor, the cross-sectional design of the study did not permit to take into account the progressive aging kidney atrophy, and the related kidney compensatory hypertrophy common in the CKD course ¯. Kidney atrophy and subsequent opposite compensatory hypertrophy act in opposite directions on kidney length, with the final result of a reduced correlation between the kidney length and the eGFR.

The second relevant finding of our study was related to other two parameters easily available before biopsy that can be used to improve eGFR prediction: the clinical diabetes status and highest levels of proteinuria, that were associated with a significant and a consistent reduction of eGFR value, indeed the adjusted model R square value increased from 0.064 to 0.100. If the reduction of eGFR in diabetic patients at a late stage is an expected finding, the association of high proteinuria levels with a reduction of eGFR is a novel and interesting one. Thus, proteinuria has many predictor roles, not only in various types of glomerulonephritis and in Kidney Disease Screening Programs , but also in CKD staging, influencing directly the value of eGFR.

The third main finding of our study derived from the histopathological diagnosis of the biopsied kidney. In our study the predictor role of histopathological diagnosis on the eGFR estimation was confirmed. Indeed, including this variable in the multivariate analysis, the adjusted R square value increased consistently from 0.100 to 0.216. Moreover, there is a significant interaction of histopathological diagnosis with longitudinal kidney diameter (P = 0.006) suggesting that the association of kidney length with the level of eGFR is dependent on the nature of kidney disease.

CONCLUSIONS

As expected, renal bipolar length and cortical thickness are related directly with eGFR. Magnitude of proteinuria and histopathological kidney diagnosis increased considerably the prediction of eGFR. The association of kidney length with the level of eGFR is dependent on the nature of kidney disease.

Declarations

Informed consent

Informed consent was obtained from all the enrolled patients or their parents/legal guardians.

Contributors

Simeone Andrulli and Antonietta Gigante designed the study and wrote the first draft of the paper. Simeone Andrulli analysed the data. Umberto Venere and Domenico Roselli participated in data collection. Umberto Venere, Domenico Roselli, Giovanni Valsecchi and Simeone Andrulli participated in data quality control. Giovanni Andrulli provided the linguistic revision of the manuscript. All of the authors assisted in the preparation of the final manuscript.

Data availability

Data may be shared upon reasonable request to the corresponding author.

Funding

This was an independent study without any direct sponsorship, and so there was no financial conditioning that may have affected the analyses.

Conflicts of interest

The authors declare that they have no conflict of interest.

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

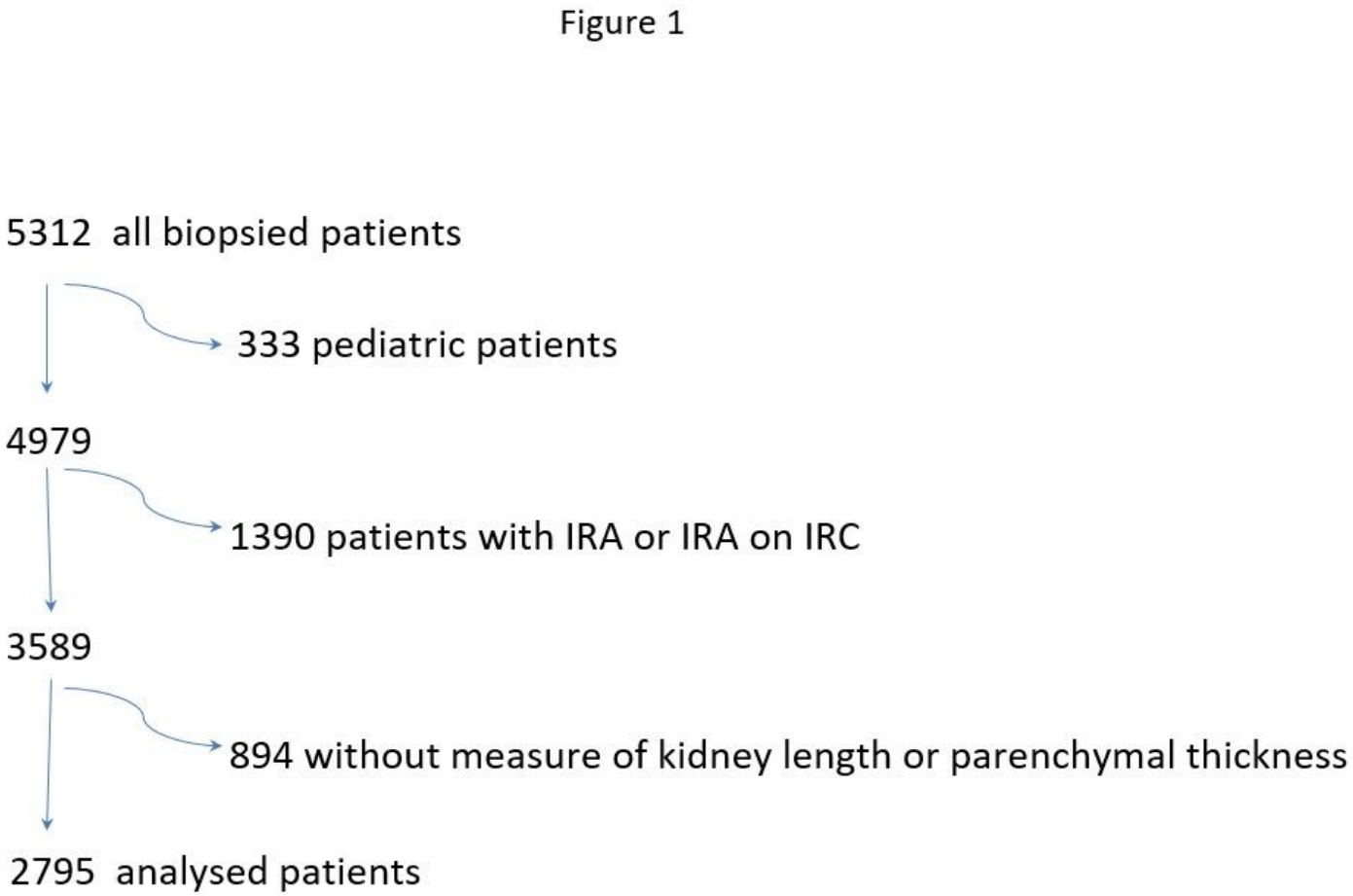

Figure 1

Selection of study sample. The final analysed sample of 2795 patients was selected from a pool of 5312 biopsied patients, after exclusion of children, patients with acute kidney injury (AKI) or AKI on chronic kidney disease (CKD) and patients without measure of kidney length or parenchymal thickness.

Figure 2

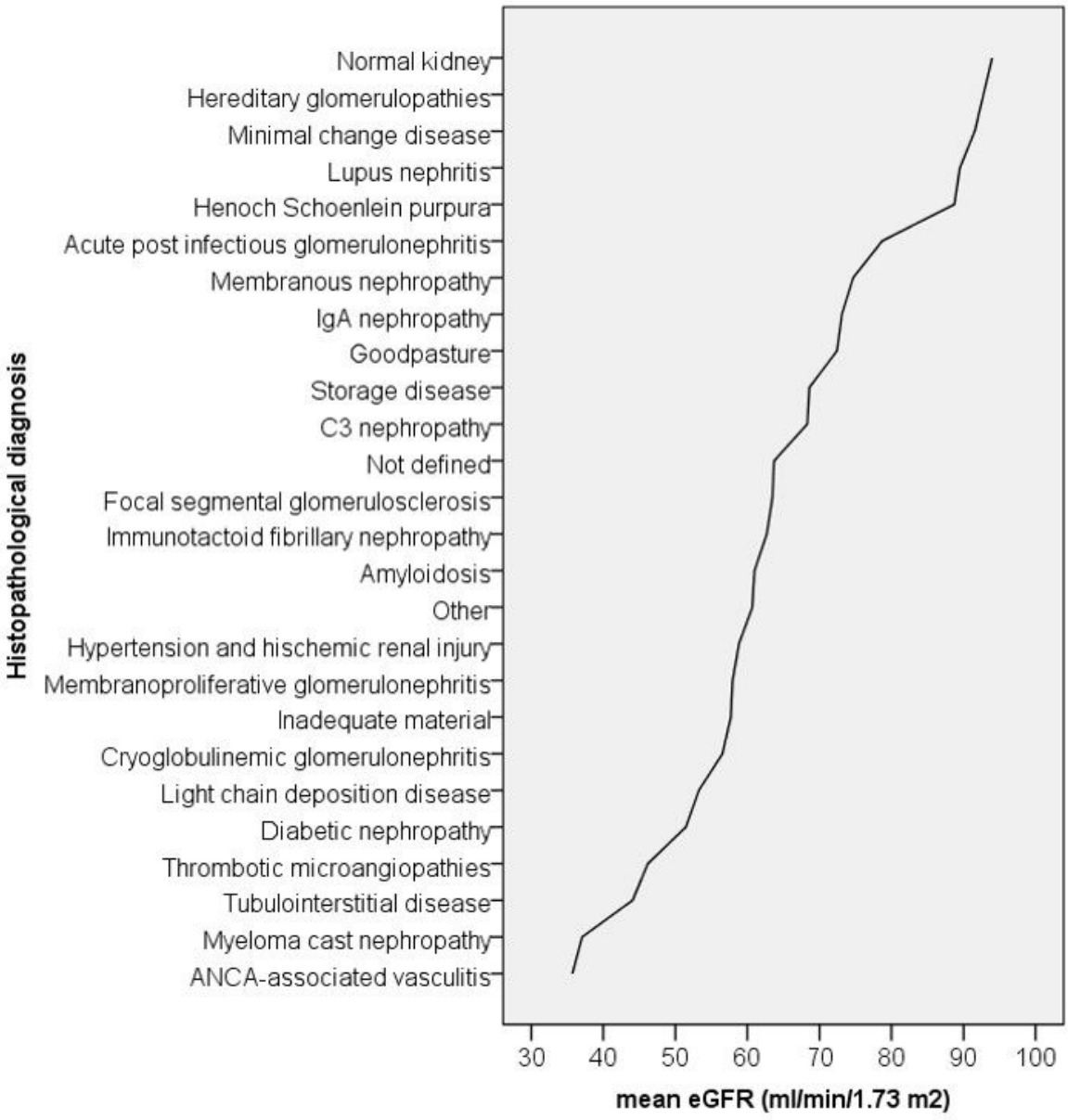

Figure 2

Distribution of mean eGFR values by the histopathological diagnosis, at the time of kidney biopsy. Some histopathological diagnoses were associated with a near normal eGFR value, as in cases of normal kidney, minimal chance disease (MCD) or hereditary glomerulopathies. On the other side, other diseases, as small vessel vasculitis and myeloma cast nephropathy were more frequently associated with low eGFR values.

Figure 3

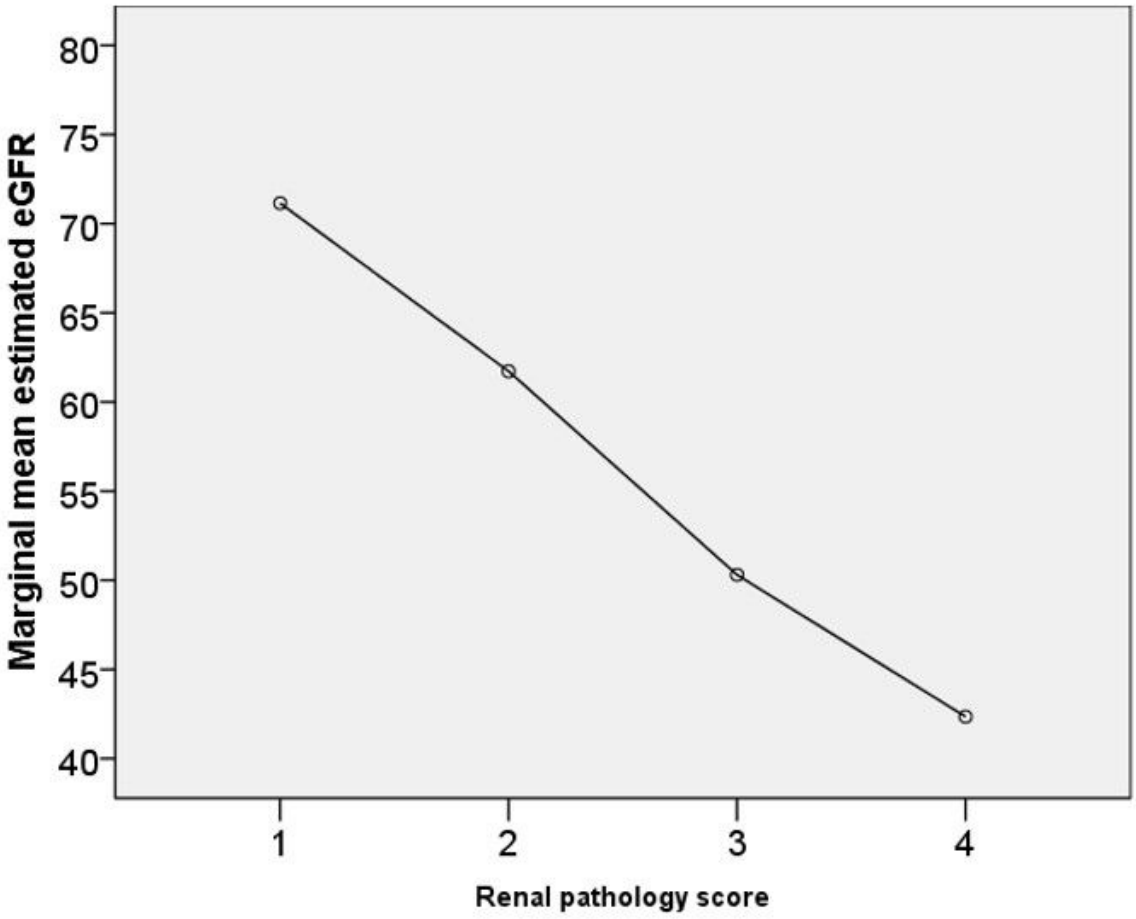

Figure 3

Inverse relationship between renal pathology score and mean eGFR.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 5MDRDTables.docx
- 4Appendix.docx