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► To cite this version:

Mamadou Adama Sow, Julien Magne, Fatouma Toure, Marie-Pierre Teissier, Victor Aboyans. Comparison of four equations for estimation of glomerular filtration rate in predicting cardiovascular events and subclinical vascular disease in patients with type-2 diabetes. *Primary Care Diabetes*, 2022, 10.1016/j.pcd.2021.12.014 . hal-03520523

HAL Id: hal-03520523

<https://unilim.hal.science/hal-03520523>

Submitted on 22 Jul 2024

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Comparison of Four Equations for Estimation of Glomerular Filtration Rate in Predicting Cardiovascular Events and Subclinical Vascular Disease in Patients with Type-2 Diabetes.

Mamadou Adama SOW¹, Julien MAGNE^{1,2}, Fatouma TOURE³, Marie-Pierre TEISSIER^{1,4}, Victor ABOYANS^{1,2}

¹INSERM 1094 & IRD, University of Limoges, 87025, 2, Rue Marcland, Limoges, France. Email: mamadouadama403@gmail.com

²Department of Cardiology, Dupuytren 2 University Hospital, 16, Rue B. Descottes, 87042, Limoges, France

³Department of Nephrology, Dupuytren 2 University Hospital, 16, Rue B. Descottes, 87042, Limoges, France

⁴Department of Endocrinology and Diabetology, Dupuytren 2 University Hospital, 16, Rue B. Descottes, 87042, Limoges, France

Corresponding author:

Pr. Victor Aboyans, MD, PhD, FAHA, FESC

Department of Cardiology

Dupuytren University Hospital

Limoges, France

Phone: +33 555 56310

Email: victor.aboyans@unilim.fr

Abstract

Aims: Chronic kidney disease (CKD), defined by a low glomerular filtration rate (GFR), is a predictor of cardiovascular disease in patients with type-2 diabetes (T2D). We aimed to compare four GFR equations in predicting future cardiovascular events in T2D and the presence of subclinical vascular disease.

Methods: Four equations were used to estimate GFR in asymptomatic T2D patients consulting our centre for cardiovascular assessment. Follow-up was performed to collect cardiovascular events. Cox proportional hazard ratio (HR) was used to build and compare prediction models, and the incremental value of the addition of GFR with any of the 4 formulas was evaluated. The ability to triage patients with and without CVD events according to GFR were assessed by comparing the receiver operator characteristics (ROC) curves with the 4 models.

Results: Among 829 asymptomatic T2D patients, the CKD prevalence was 20.2% for Modification of Diet in Renal Disease (MDRD), 17.3% for Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), 20.7% for Lund-Malmö Revised (LMR) and 21.4% for Full Age Spectrum (FAS). All the estimated GFRs were well correlated from one formula to another, with stronger agreement to define CKD ($GFR < 60 \text{ ml/min/1.73 m}^2$) between MDRD and CKD-EPI, and between LMR and FAS. The 5-year incidence of cardiovascular events was 8% ($n=63$). After adjustment on covariables, CKD was significantly associated with cardiovascular events when defined by MDRD ($HR=2.04$; 1.15-3.60) and CKD-EPI ($HR=1.90$; 1.05-3.41) but missed statistical significance when using LMR ($HR= 1.74$; 0.97-3.14) or FAS ($HR= 1.71$; 0.94-3.14). Only the prediction models including MDRD and CKD-EPI provided a significant incremental information to the predictive model without GFR, but the area under the ROC curves were similar with the 4 models: 0.60 [0.54-0.68] for MDRD, 0.61 [0.49-0.65] for CKD-EPI and 0.62 [0.55-0.69] for LMR and FAS, without any significant difference among formulas.

Conclusion: In asymptomatic T2D patients, MDRD and CKD-EPI may be preferable when more specificity is desired (stronger association between GFR and CVD events), while LMR and FAS appear more sensitive by including a higher number of patients with $GFR < 60 \text{ ml/min/1.73 m}^2$.

Keywords: Glomerular filtration rate; Cardiovascular diseases; Renal disease; Type 2 Diabetes.

INTRODUCTION

Cardiovascular diseases (CVD) is the leading cause of death in people with type 2 diabetes (T2D) ^[1], with significantly higher mortality and morbidity rates than in the non-diabetic population ^[2]. Diabetes is associated with CVD with a relative risk ranging from 1.6 to 2.6 ^[3]. The most frequent CVD associated with diabetes are coronary heart disease, cerebrovascular disease, peripheral artery disease and congestive heart failure ^[3].

Diabetes is also the leading cause of chronic kidney disease (CKD), with a prevalence of 10-40% among patients with T2D ^[4]. Decreased renal function has been shown to be an independent risk factor for CVD ^[5] and patients with diabetes and CKD are at high risk of developing CVD ^[6]. As for illustration, the United Kingdom Prospective Diabetes Study (UKPDS) reported an annual cardiovascular death rate of 0.7% in the absence of any nephropathy, rising to 2%, 3.5% and even 12.1% in the presence of microalbuminuria, proteinuria and renal failure, respectively ^[7]. Hence, glomerular filtration rate (GFR) is a key predictor of cardiovascular prognosis in patients with T2D ^[8].

Among the GFR estimation formulas, those taking into account plasma creatinine (pCr), age, sex and race assess more accurately the GFR than those taking only into account pCr ^[9]. Thus, the most accurate formulas considered nowadays for the calculation of the GFR are the Modification of Diet in Renal Disease formula (MDRD), the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) ^[4], the Lund-Malmö Revised formula (LMR) ^[10] and the Full Age Spectrum formula (FAS) ^[11]. Some of these formulas were used in several studies to predict cardiovascular events ^[12]. However, to our best knowledge, no study has compared the cardiovascular events predictive performances of these 4 formulas estimating GFR in patients with T2D.

Therefore, the aim of this study was to identify the GFR estimation formula predicting better the occurrence of cardiovascular events and the presence of subclinical vascular diseases (SCVD) most effectively in patients with T2D.

MATERIALS AND METHODS

Population study and design

We conducted a longitudinal and retrospective cohort study based on the analysis of data collected from T2D patients who consulted at our University Hospital for cardiovascular check-up. From 01/2007 to 12/2016, a total of 1332 T2D patients in primary prevention were

enrolled with a follow-up of each patient up to 5 years after inclusion. Of these, patients with glomerular hyperfiltration defined by GFR (estimated by MDRD) greater than 135 mL/min/1.73 m² [13,14] were excluded. Finally, 829 patients were included in this study.

GFR equations

We studied four plasma creatinine-based GFR formulas. Plasma creatinine was measured using an enzymatic method with isotopic dilution mass spectrometry (IDMS) standardisation.

For each patient all four GFR equations were used to estimate the renal function:

MDRD (ml/min/1.73 m²) = 186 × (pCr in μmol/l × 0.011)^{-1.154} × (age)^{-0.0203} × (0.742, if woman) × (1.210 if black) [12,15].

CKD-EPI (ml/min/1.73 m²) = 141 × min (pCr in μmol/l /k,1)^a × max (pCr/k,1)^{-1.209} × 0.993^{age} × (1.018 if woman) × (1.159 if black).

k = 0.7 (women) and k = 0.9 (men); a = -0.329 (women) and a = -0.411 (men); *min* indicates the minimum serum creatinine adjusted by k or 1 and *max* indicates the maximum serum creatinine adjusted by k or 1 [12,15].

LMR Study equation (ml/min/1.73 m²) [10,16] = e^{X - 0.0158 × age + 0.438 × ln(age)}

Female and pCr < 150: X = 2.50 + 0.0121 × (150 - pCr)

Female and pCr ≥ 150: X = 2.50 - 0.926 × ln(pCr/150)

Male and pCr < 180: X = 2.56 + 0.00968 × (180 - pCr)

Male and pCr ≥ 180: X = 2.56 - 0.926 × ln(pCr/180)

With pCr in μmol/l.

FAS (ml/min/1.73 m²) [11,17] = 107.3/(pCr/Q), for 2 ≤ age ≤ 40 years;

and FAS (ml/min/1.73 m²) = 107.3/(pCr/Q) × 0.988^(age - 40) for age > 40 years

With pCr in mg/dL, Q = 0.7 mg/dL if women ≥ 20 years and Q = 0.9 mg/dL if men ≥ 20 years.

In all of these GFR equations, the CKD was defined as a GFR < 60 ml/min/1.73 m².

Endpoints

The primary endpoint was a composite of occurrence of at least one of the following cardiovascular events, whichever comes first: cardiovascular death, acute coronary syndrome, coronary revascularization, stroke, hospitalization for lower extremity artery disease.

The secondary endpoint was the presence of SCVD defined as the presence of plaque in at least 2 locations among the 2 femoral arteries bifurcations and 2 carotid arteries bifurcations.

Statistical analysis

Qualitative data were presented as a number (percent, %) and quantitative data as mean \pm standard deviation (if normal distribution) and median [quartile 1 and quartile 3] (if non-normal distribution). Comparisons between 2 groups were made using Student's t-test for continuous variables with a normal distribution, Mann Whitney's U-test for those with a non-normal distribution, and Pearson's χ^2 test for qualitative variables. Spearman's correlation test was used to assess the correlations between the GFR estimation formulas by gender. Kappa's test and Bland-Altman's method were used to assess their agreement.

Variables where p-value was < 0.20 in the univariate analysis were included in the multivariate models. For the prediction of cardiovascular events, a Cox model analysis was first fitted to age and sex (general model) and then included the GFR for each formula (model A: general model + GFR_{MDRD}; B: general model + GFR_{CKD-EPI}; C: general model + GFR_{LMR}; D: general model + GFR_{FAS}). For each formula included in the models, the GFR ≥ 60 ml/min/1.73 m² was used as a reference (no CKD). Comparison of the prediction performance of each formula was made by comparing the χ^2 values derived from the respective models and their association strength was estimated as Hazard ratio (HR) and 95% confidence interval (CI95%). For each formula, a receiver operation characteristic (ROC) curve was constructed, the area under the curve (AUC) with 95% confidence interval (95%CI) was calculated and the AUCs were compared by the DeLong test ^[18]. The association between GFR and SCVD was evaluated by multivariate logistic regression. A general model was also constructed and adjusted for age, sex, hypertension and dyslipidemia. Four additional models were constructed, each including GFR according to one formula (models A to D) as in the Cox analysis described above. The χ^2 of the models were also compared and the Odds-ratio (OR) and 95%CI were carried forward to estimate the risk.

The survival and cardiovascular events occurrence analysis were performed by the Kaplan-Meier method and the curves obtained were compared by the Log Rank test. Follow-up time was defined as the period between the date of the screening visit and the date of last news, for living patients without event, or the date of cardiac event, for living patients who developed event, or the date of death, for deceased patients. The statistical tests were considered significant when the p-value was < 0.05 . All data were entered and stored using Epi-info software and then statistical analyses were performed using SPSS V26 software.

RESULTS

During the study period, 1332 asymptomatic T2D patients without CVD attended for a cardiovascular screening consultation in our centre. Among them, 829 patients with full dataset were analysed in this study. Figure 1 shows the flow chart of patient selection.

Baseline characteristics

The average age of the study population was 60.4 ± 10.6 years and 351 patients (42.3%) were males. Other characteristics are shown in Table 1.

Correlations and agreements between the GFR formulas

The mean GFR was 82.1 ± 26.5 , 81.9 ± 22.1 , 74.6 ± 19.6 and 80.4 ± 25.2 mL/min/1.73 m² using MDRD, CKD-EPI, LMR and FAS estimations, respectively. All formulas showed a strong correlation among each other (Table 2).

The Kappa (κ) agreement coefficient for defining renal failure with GFR < 60 mL/min/1.73 m² was also better ($\kappa = 0.96$ [0.94-0.97]) between LMR and FAS as well as MDRD and CKD-EPI (0.90 [0.87-0.92]) compared to other combinations (Table 2). In Figure 2, Bland-Altman's graphs show that this agreement is better between LMR and FAS as well as CKD-EPI and MDRD, although the latter overestimates the GFR for values greater than 100 ml/min/1.73 m².

Prevalence of CKD according to the four GFR formulas

The prevalence of CKD (GFR < 60 ml/min/1.73 m²) was 20.2%, 17.3%, 20.7% and 21.4% when using respectively the MDRD, CKD-EPI, LMR and FAS formulas. Figure 3 shows the prevalences of CKD stages according to the formulas.

Incidence of cardiovascular events

The incidence of cardiovascular events according to the renal status are shown in Figure 4. The mean time to onset of cardiovascular events was 3.7 ± 1.7 years. There were statistically significant differences of the cardiovascular events occurrence between patients with and without CKD using all formulas ($p < 0.001$).

Prediction of cardiovascular events by GFR estimated according to the formulas

The occurrence of cardiovascular events appeared inversely related to the level of GFR. When GFR level was lower, the probability of these events occurring was higher. The AUCs of the ROC curves were 0.60 [0.54-0.68] for MDRD, 0.61 [0.49-0.65] for CKD-EPI and 0.62 [0.55-

0.69] for LMR and FAS. The AUCs comparison using Delong test shows no significant difference between formulas (Supplement table).

Association between cardiovascular events and GFR according to the formulas

Univariate Cox analysis was performed for all variables known to be associated with the occurrence of cardiovascular events. Only age, sex, and GFR were significant in the multivariate Cox model. The CKD defined by a $GFR \leq 60$ ml/min/1.73 m² according to the formulas of MDRD (HR= 2.04; 1.15-3.60) and CKD-EPI (HR = 1.90; 1.05-3.41) showed a statistically significant association with the occurrence of cardiovascular events. Also, there was no significant difference ($p = 0.99$) between the prediction performance of cardiovascular events by MDRD ($\chi^2=24.5$) and CKD-EPI ($\chi^2=24.6$). The LMR and FAS formulas had borderline but not significant association with the occurrence of cardiovascular events (HR = 1.74; 0.97-3.14 and HR = 1.71; 0.94-3.14 respectively).

Prevalence of subclinical vascular disease

Among the 763 patients, 380 (49.8%) had SCVD. The prevalence of SCVD was significantly higher in patients with CKD when using any of the 4 GFR formulas, as compared to those without. The χ^2 for the prediction performance was approximately comparable between the general model and the other models including GFR formulas.

DISCUSSION

In this study in patients with T2D, we found a significant association between the occurrence of cardiovascular events and CKD defined by a GFR_{MDRD} or a $GFR_{CKD-EPI}$ less than 60 ml/min/1.73 m² in patients with T2D, while only borderline results with LMR and FAS formula. Using the two latter, a slightly higher proportions of patients were classified as with CKD ($GFR < 60$ ml/min/1.73 m²). In addition, there was no statistically significant difference between the predictive performances between MDRD and CKD-EPI formulas. In contrast to the occurrence of cardiovascular events, none of the formula outweighed the others for the SCVD prediction.

Among all formula, the correlation found was strong and the agreements for defining CKD between MDRD and CKD-EPI as well as LMR and FAS were also better than with other comparisons. The same results between MDRD and CKD-EPI were found in earlier studies by Sombolos et al. ^[19] and Korhonen et al. ^[9]. The correlation between MDRD and LMR found in our study was also consistent with that found by Ji et al. ^[20] Li et al. ^[21] found a good

agreement between CKD-EPI and FAS in patients undergoing a coronary artery bypass grafting, which is line with our findings.

In our study we report a 5-year incidence of cardiovascular events of 8%. This is lower than that found in another French study by Sosner et al. ^[22] reporting an incidence of 19.3% over a 65-month follow-up period and in a cohort of patients with type-2 diabetes for more than 2 years, with or without symptoms or history of CVD at baseline. Thus, our low incidence could be explained by the inclusion of asymptomatic patients with type 2 diabetes in primary prevention and as well as the shorter duration of their diabetes.

In our study, the occurrence of cardiovascular events was inversely related to the level of GFR; when the GFR was lower, the probability of occurrence of these events was higher. In the Kaplan Meier analysis, we found a statistically significant differences in cardiovascular events occurrence between patients with and without CKD in all formulas. However, in the multivariate Cox analysis, only the prediction models including MDRD and CKD-EPI had a significantly better performance in predicting cardiovascular events than the general age- and sex-adjusted model, without significant difference between the two models. Zhang et al. ^[23] found no significant difference in the occurrence of cardiovascular events between patients with and without CKD when using the MDRD and CKD-EPI formulas. The two studies' populations differed as they included patients with coronary heart disease independent of diabetes status. Wang et al. ^[24] found that CKD-EPI was a better predictor of heart failure than MDRD. In that study in T2D patients, they chose 75 ml/min/1.73 m² as the threshold for defining a lowered GFR and heart failure alone as the event to be predicted, whereas in our study the GFR threshold was 60 ml/min/1.73 m² and the events to be predicted were multiple.

Despite the good correlation between CKD-EPI and LMR formulas, we found that CKD-EPI was the one that could significantly predict CVD, while GFR calculated with the LMR missed the statistical significance. This could be explained by the fact that the LMR formula provides systematically a lower GFR than the CKD-EPI, and therefore classifies some borderline patients with GFR above 60 ml/min/1.73 m² according to the CKD-EPI in the CKD group. These patients have overall less CV risk than the average of patients with CKD and therefore "weaken" the hazard ratio" between CKD and CV events for the LMR formula, which is not so surprising. It is plausible than with a larger study population, we might have reached significance also for LMR (and even FAS). This means that LMR and FAS are more "sensitive" to capture CKD but less "specific" to predict CV risk in this population, while overall, the predictive ability of classifying patients with- or without future CVD events,

assessed by the AUC, were similar among the 4 formulas. Hence, the choice of the formula may depend on the objective, using either more sensitive (LMR, FAS) or specific (CKD-EPI, MDRD) formulas.

The prevalence of SCVD was significantly higher in patients with CKD versus those without, and the difference was similar when using any of the 4 GFR formulas. This result is in line with several studies and could be explained by the fact that CKD is known to be a risk factor for atherosclerosis^[25].

The addition of each formula to a predictive model explaining the presence of SCVD did not change the overall informational value of the model. To the best of our knowledge, this study is the first to estimate the predictive performance of SCVD using the GFR estimation formulas.

Study limitations

Because the aim of the consultation for our patients was cardiovascular screening in CVD-free and asymptomatic subjects, our findings cannot be extended to other T2D patients populations. However, the prediction of cardiovascular risk is particularly interesting in diabetic patients in primary prevention, and CKD is known to predict these events in T2D.

We excluded almost 20% of the patients in the cohort because of glomerular hyperfiltration. Glomerular hyperfiltration defined by a GFR > 135 ml/min/1.73 m² is usually found in the natural history of type 1 diabetes (10-67%) and T2D (6-73%) in the early stages of nephropathy^[14]. The non-exclusion of these patients could distort the objectives set for this study because a recent meta-analysis by Kanbay et al.^[13] in 2019 with 19 published articles showed that glomerular hyperfiltration is also known to be an independent risk factor for cardiovascular disease. However, the study of the correlation between different formula and the CVD events would have been more difficult because of a “J-shape” relation between GFR at full spectrum and cardiovascular events, as glomerular hyperfiltration is considered as the first stage of diabetic nephropathy.

Finally, information bias is possible in this study because of its retrospective type and requires prospective validation.

CONCLUSION

In our study, the GFR estimated by MDRD and CKD-EPI formula was significantly associated with cardiovascular events, while we found borderline results with the LMR and

FAS formulas which classified more patients under the 60 ml/min/1.73 m² threshold. Bearing in mind that the association between GFR and cardiovascular risk is a continuum, MDRD and CKD-EPI may be preferable when more specificity is desired (stronger association between GFR and CVD events), while LMR and FAS appear more sensitive by including a slightly higher number of patients as with stages 3-5 CKD. As for the prediction of the existence of subclinical CVD, none of the 4 formula was superior to others.

Figures Titles

Figure 1: Flow chart of patient's selection

Figure 2: Bland-Altman's plot showing the agreement between the GFR formulas

Figure 3: Distribution of patients between CKD stages and according to GFR formulas

Figure 4: Kaplan Meier curve describing the occurrence of cardiovascular events according to the presence or absence of CKD.

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Demographical	
Age, years	60.64± 10.6
Male gender, n (%)	351 (42.3)
BMI, Kg/m ²	31.6 [27.6 ; 36.0]
Clinical	
Systolic blood pressure, mmHg	130 [120 ; 140]
Diastolic blood pressure, mmHg	70 [70 ; 80]
Heart rate, beats/min	80 [71 ; 88]
Heart rhythm disorder, n (%)	9 (1.1)
LVH, n (%)	181 (24.6)
ABI*	1.1±0.2
Biological	
Total cholesterol, g/L	1.8 [1.54 ; 2.08]
Triglycerides, g/L	1.4 [1.1 ; 2.1]
HbA1c, %	7.7 [6.6 ; 9.0]
Plasma creatinine, µmol/L	73.0 [64.0 ; 86.0]
Risk factors	
Diabetes duration, years	7.0[3.0 ; 13.0]
Smoking, n (%)	
Non-smokers	348 (44.0)
Old smokers	171 (21.6)
Current smokers	272 (34.4)
Family CV history, n (%)	178 (23.9)
Treated HBP, n (%)	522 (65.7)
Treated dyslipidemia, n (%)	533 (67.5)
Treatments	
Glycose lowering drugs, n (%)	742 (96.0)
Antihypertension drugs, n (%)	565 (73.2)
Lipid lowering drugs, n (%)	532 (68.8)
Antithrombotic drugs, n (%)	234 (30.3)
Glomerular filtration rate	
MDRD, mL/min/1.73m ²	83.5 [66.0 ; 104.4]
LMR, mL/min/1.73m ²	78.4 [65.9 ; 88.2]
CKD-EPI, mL/min/1.73m ²	85.7 [67.0 ; 98.0]
FAS, mL/min/1.73m ²	81.3 [66.1 ; 96.2]

ABI*: Ankle brachial index (the lower of the two sides was considered); BMI: Body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CV: Cardiovascular; FAS: Full age spectrum; HbA1c: Glycated haemoglobin; HBP: High blood pressure; LMR: Revised Lund-Malmö; LVH: Left ventricular hypertrophy; MDRD: Modification of Diet in Renal Disease.

Table 1: Characteristics of the study population

Table 2: Correlation coefficient and kappa (κ) agreement between GFR formulas

Formulas	Correlation		Agreement	
	r	p-Value	κ	95% CI
FAS vs LMR	0.99	< 0.001	0.96	0.94-0.97
CKD-EPI vs FAS	0.99	< 0.001	0.86	0.84-0.88
CKD-EPI vs LMR	0.99	< 0.001	0.89	0.87-0.91
MDRD vs FAS	0.96	< 0.001	0.85	0.82-0.87
MDRD vs LMR	0.95	< 0.001	0.87	0.84-0.89
MDRD vs CKD-EPI	0.96	< 0.001	0.90	0.87-0.92

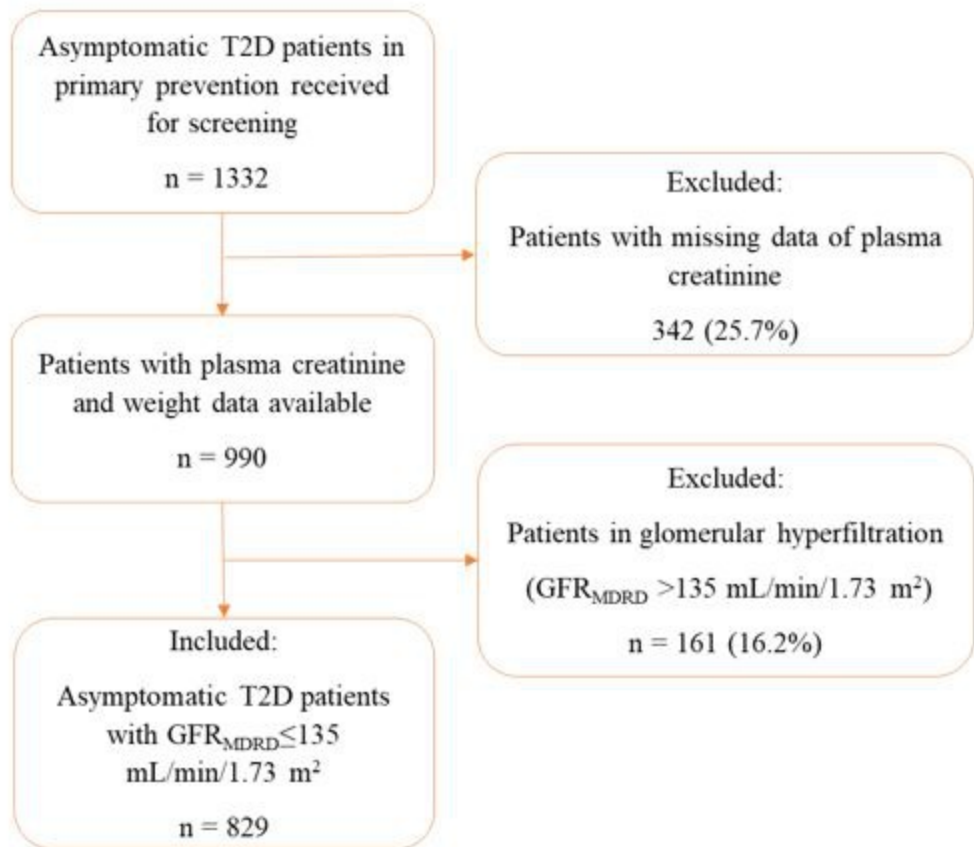
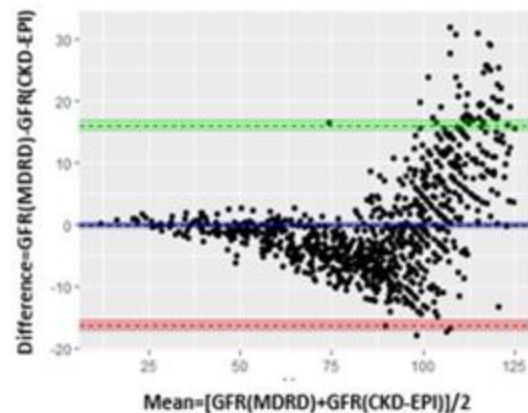
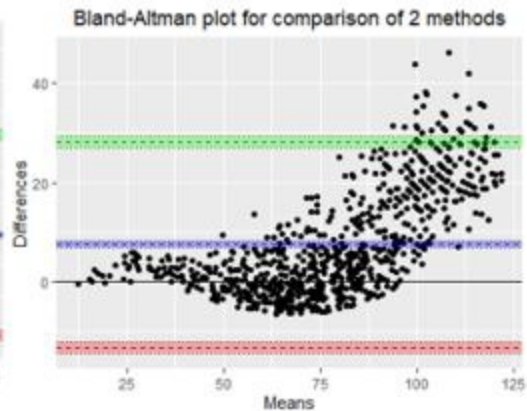
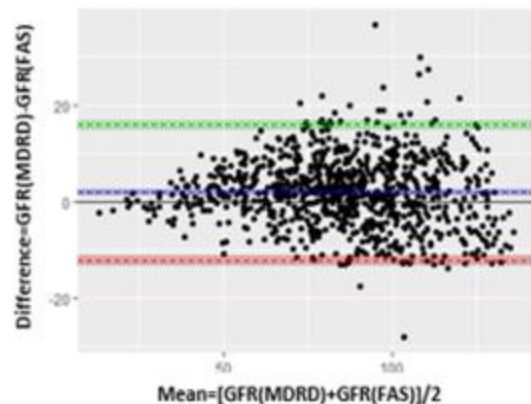
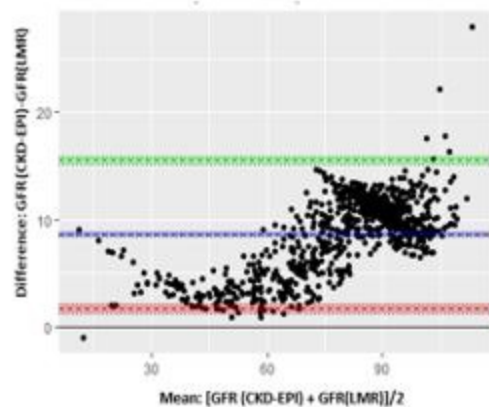
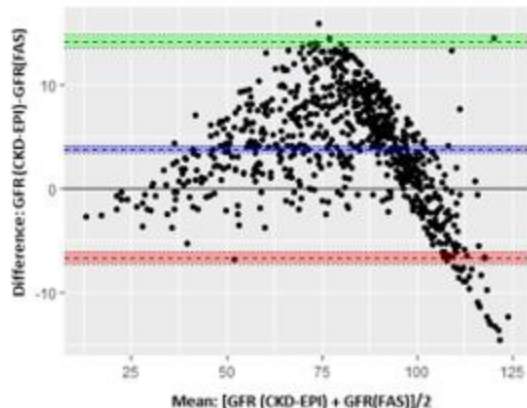
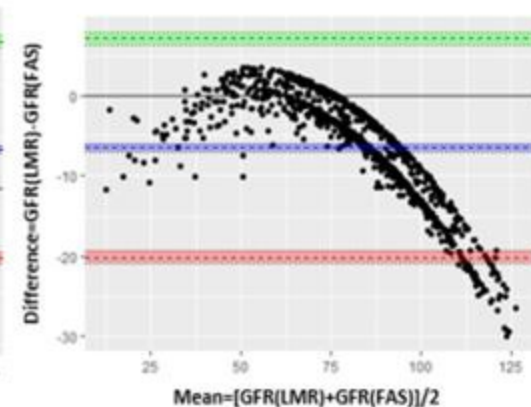


Figure 1

A - MDRD vs CKD-EPI**C - MDRD vs LMR****D - MDRD vs FAS****F - CKD-EPI vs LMR****G - CKD-EPI vs FAS****J - LMR vs FAS****Figure 2**

n = 829

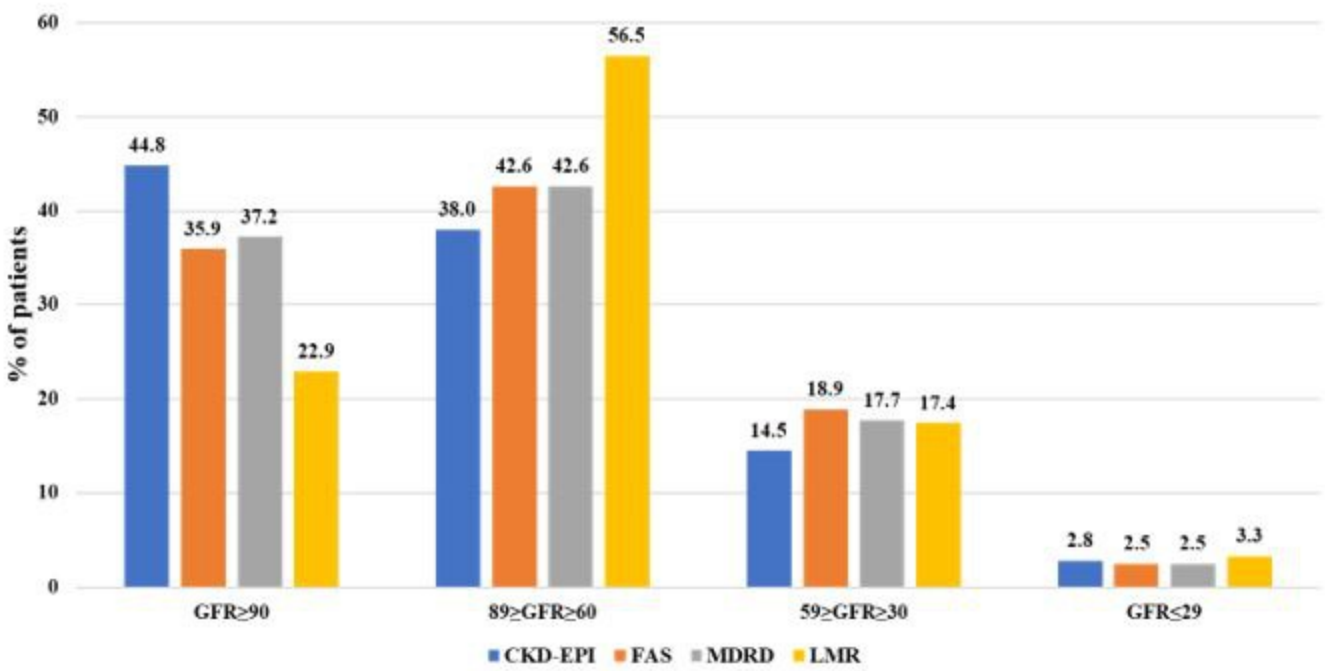


Figure 3

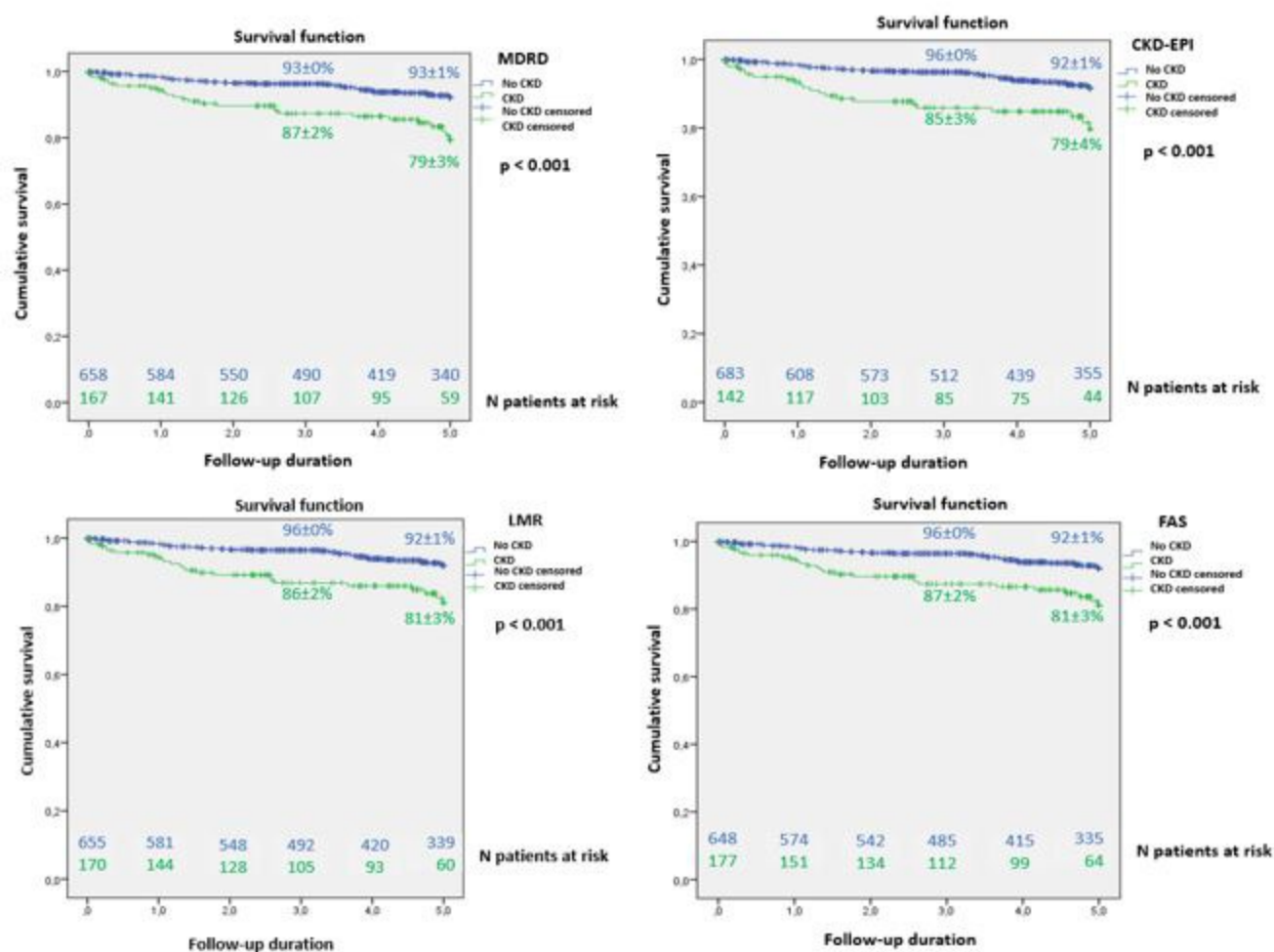


Figure 4