Research Article

Renal Function Assessment Gap in Clinical Practice: An Awkward Truth

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Abstract

Introduction: An accurate assessment of renal function is needed in the majority of clinical settings. Unfortunately, the most used estimated glomerular filtration rate (eGFR) formulas are affected by significant errors in comparison to gold standards methods of measured GFR (mGFR). ***Objective:*** The objective of the study is to determine the extent of the error of eGFR formulas compared to the mGFR in different specific clinical settings. ***Methods:*** A total retrospectively consecutive cohort of 1,320 patients (pts) enrolled in 2 different European Hospitals (Center 1: 470 pts; Center 2: 850 pts) was collected in order to compare the most common eGFR formulas used by physicians with the most widespread mGFR methods in daily clinical practice (Iohexol Plasma Clearance -Center 1 [mGFR-iox] and Renal Scintigraphy -Center 2 [mGFR-scnt]). The study cohort was composed by urological, oncological, and nephrological pts. The agreement between eGFR and mGFR was evaluated using bias (as median of difference), precision (as interquartile range of difference) accuracy (as P_{30}), and total deviation index. ***Results:*** The most accurate eGFR formula in the comparison with gold standard method (Iohexol plasma clearance) in Center 1 was represented by s-creatinine and cystatin C combined Chronic Kidney Disease-Epidemiology Collaboration-cr-cy, even though the P_{30} is re-

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duced (84%) under the threshold of 60 mL/min/1.73 m^2. Similar results were found in Center 2, with a wider discrepancy between mGFR-scnt and eGFR formulas due to the minor accuracy of the nuclear tool in respect to the mGFR-iox. **Conclusions:** The loss of accuracy observed for the formulas at lower values of GFR suggests the mandatory use of gold standards methods as Iohexol Plasma Clearance to assess the correct status of renal function for critical cases. The center 2 showed lower levels of agreement between mGFR and eGFR suggesting that the errors are partially accounted for the Renal Scintigraphy technique too. In particular, we suggest the use of mGFR-iox in oncological urological and nephrological pts with an eGFR lower than 60 mL/min/1.73 m^2.

Introduction

Glomerular filtration rate (GFR) can be assessed by 2 different categories of methods, the estimated ones and the measured ones. The former group aims to indirectly estimate GFR (eGFR) using formulas based on endogenous markers such as creatinine and/or cystatin-C. The latter one intends to measure straight the GFR (mGFR) by means of the pharmacokinetic analysis of exogenous substances, such as inulin, radio-labeled markers (^{51}Cr-EDTA, ^{99m}Tc-DTPA), or nonlabeled contrast media (iohexol, iothalamate) [1, 2].

Indirect methods are fast, user-friendly, and cost-effective while direct ones deserve time, skills, and a specific equipment [3, 4].

Several papers in literature have already demonstrated that GFR calculated by formulas shows an average error in reflecting the *real* GFR of about ±30% in patients (pts) affected by type 2 diabetes, chronic kidney diseases, autosomal polycystic kidney diseases, and in renal transplantation [5]. Surprisingly, there is a scarce evidence on the error of eGFR in pts with urological and oncological diseases, even though an accurate assessment of renal function is of paramount importance in that specific clinical setting [6].

As a matter of fact, in renal cancer pts, preoperative kidney function represents one of the major factors affecting relevant decision making like selecting conservative versus radical surgery [7]. Similarly, the dosage of several oncological nephrotoxic therapies is based on eGFR or creatinine clearance and not on mGFR in several metastatic urological malignancies [8]. Moreover, the most prominent clinical trials of the new anticoagulants agents are still based on Cockroft Gault formula [9].

Finally, a precise evaluation of GFR is crucial in the evaluation of possible living kidney donors and in kidney recipients after transplantation [5, 10].

In this study, we analyzed the agreement between mGFR and eGFR in the evaluation of renal function in 2 different Centers with different clinical settings, with a particular focus on the oncological and urological pts.

Materials and Methods

Population Study

This is a cross-sectional retrospective study involving 2 different hospitals: Hospital Universitario de Canarias (Tenerife-Spain; Center 1) and San Raffaele Hospital (Milano-Italy; Center 2). These 2 centers perform mGFR on a routine basis to pts with diverse clinical conditions. Inclusion criteria were (a) prostate, bladder, kidney, and testis urological cancer, (b) nonurological cancer with urological involvement (e.g., hydronephrosis) for whom is necessary to estimate the renal function to use the correct dose of immunotherapy treatment

Table 1. Clinical characteristics of the study cohorts

Center 1	
Number	470
Age, years, median (IQR)	57 (48–78)
Gender, male, n (%)	305 (65)
Nephrological disease, n (%)	252 (54)
Kidney donor, n (%)	86 (18)
Kidney transplant, n (%)	252 (20)
mGFR, mL/min/1.73 m^2, mean, (SD)	47.9 (27.8)
Serum creatinine, mg/dL, mean, (SD)	1.92 (1.25)
Serum cystatin C, g/dL, mean, (SD)	1.91 (0.98)
Center 2	
Number	850
Age, years, median (IQR)	61 (45–72)
Gender, male, n (%)	498 (59)
Nephrological disease, n (%)	124 (15)
Urological functional disease, n (%)	396 (47)
Oncological, n (%)	282 (33)
Kidney donor, n (%)	48 (5)
mGFR, mL/min/1.73 m^2, mean, (SD)	75.7 (32.8)
Serum creatinine, mg/dL, mean, (SD)	1.22 (0.67)

IQR, interquartile range; mGFR, measured glomerular filtration rate.

(breast, colorectal, lung, uterus, ovary, and others), (c) benign urological diseases (pelvi-ureteric junction obstruction, stones, ureteral stenosis, hydronephrosis, endometriosis, and neurological bladder), (d) living kidney donors, (e) renal transplanted pts, and (f) pts with nephrological diseases with different grades of chronic kidney disease according the KDIGO guidelines. Exclusion criteria include (a) age <18 years, (b) genetic diseases such as Von Hippel Lindau and acquired autosomal polycystic kidney disease hereditary. The clinical and pathological features of pts are resumed in Table 1.

Measured Glomerular Filtration Rate
Renal function was measured with the following methods:

Plasma clearance of iohexol (mGFR-iox; *Center 1 – n = 470*). In the morning of examination, 5 mL of iohexol (Omnipaque 300, GE-Healthcare) was injected intravenously during 2 min [11]. Afterward, venous or capillary blood was obtained by finger prick at 120, 180, 240, 300, 360, 420, and 480 min for pts with eGFR ≤40 mL/min/1.73 m^2; or at 120, 150, 180, 210, and 240 min for those with eGFR >40 mL/min/1.73 m^2. Iohexol was measured in plasma or dried blood spot (DBS) as previously shown [12]. Both methods using plasma or DBS showed excellent agreement and can be considered interchangeable [12]. Iohexol levels were measured by HPLC, as previously described. For the DBS analysis, a fixed volume of capillary blood (10 µL) was taken by a capillary pipette and deposited on filter paper [12]. Finally, a circle of filter paper containing the whole drop of blood was punched out for analysis [12]. Plasma iohexol clearance was calculated according to a one-compartment model and then corrected by the formula proposed by Bröchner-Mortensen [11].

Renal scintigraphy using Tc 99m-DTPA (mGFR-scnt; *Center 2 – n = 850*). Renal scans were performed according to published guidelines [13], and all subjects were instructed to drink at least 500 mL of water in the 30 min before examination. After i.v. injection on Tc 99m-DTPA (111–185 MBq), a kidney posterior view was obtained for 30 min in supine position using a gamma camera (Infinia, General Electric Healthcare) equipped with a LEHR collimator and a

dedicated computer to store all images. Each renal scan was processed using Gates method to analyze the mGFR-scnt, taking into consideration height, weight, and body surface to compute mGFR-scnt, expressed as $mL/min/1.73/m^2$ of body surface.

Estimated GFR by Formulas

Simultaneously to the measurement of GFR, serum creatinine alone (Center 2) or together with cystatin-C (Center 1) were collected to calculate commonly used equations creatinine-based: Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI-cr) [14], Modification of Diet in Renal Disease (MDRD) [15], Full Age Spectrum (FAS) [16], Mayo Clinic Quadratic (MCQ) [17], cystatin-C based: Le Bricon [18], Rule [19] and CKD-EPI-cy [20], and creatinine-cystatin-C based: CKD-EPI-cr-cy [20]. Formulas equations are reported in online supplementary Table 1 (see www.karger.com/doi/10.1159/000504649 for all online suppl. material).

The agreement between formulas and mGFR was evaluated with values adjusted for body surface area.

Biochemistry

Creatinine was measured by Jaffè IDMS-traceable creatinine (cobas c711 module, Roche Diagnostics; Center 1) or Kinetic Picrate (COBAS C 800) IMDS standardized (Center 2) and cystatin-C levels by immunonephelometry (the BN II System, Siemens Healthcare Diagnostics), calibrated with ERM-DA471/IFCC (Center 2).

Statistical Analysis

The performance of eGFR in reflecting mGFR was assessed by statistics of agreement evaluating 3 parameters usually used for these comparisons [21]: bias, precision, and overall accuracy. Bias is expressed as the median of the percent difference mGFR-eGFR and should indicate if the eGFR harbors systematic errors among the population. Precision is expressed as interquartile range (IQR) of the difference mGFR-eGFR and represents the variability of the difference among the average difference. The overall accuracy is evaluated using the P_{30} parameters which indicate the percent of estimates within 30% of mGFR. The agreement was also evaluated using percentage total deviation index (TDI) as metric [22]: the TDI calculates a percentage value such that the 95% of the percentages differences between measurements and estimations will be lower than this. Finally, the percentage of pts whose eGFR differs from the mGFR for >5, 10, 15, and 20 $mL/min/1.73$ m^2 was evaluated in the cases with mGFR ≤60 $mL/min/1.73$ m^2. The analysis was performed using R-Studio environment for R version 3.6.0.

Results

The 2 cohorts of pts were treated separately.

Center 1

In the Center 1, GFR was measured using Iohexol Plasma Clearance. The comparisons between the mGFR-iox and the 8 considered formulas showed that some of the estimated methods are biased for the comparisons in our cohort. In particular, CKD-EPI-cr, MCQ, FAS, and Le Bricon tend to overestimate the GFR with a median of, respectively, 6, 25, 12, and 25%; Rule equation tends to underestimate with a median of 12%. MDRD, CKD-EPI-cy, and CKD-EPI-cr-cy seem to be the unbiased methods in our cohort with a median difference of 0, 2 (underestimation), and 0%. Evaluating the precision of the formulas, all the IQRs are included between 11 and 14 $mL/min/1.73$ m^2, except for the MCQ with 32 $mL/min/1.73$ m^2. The P_{30}

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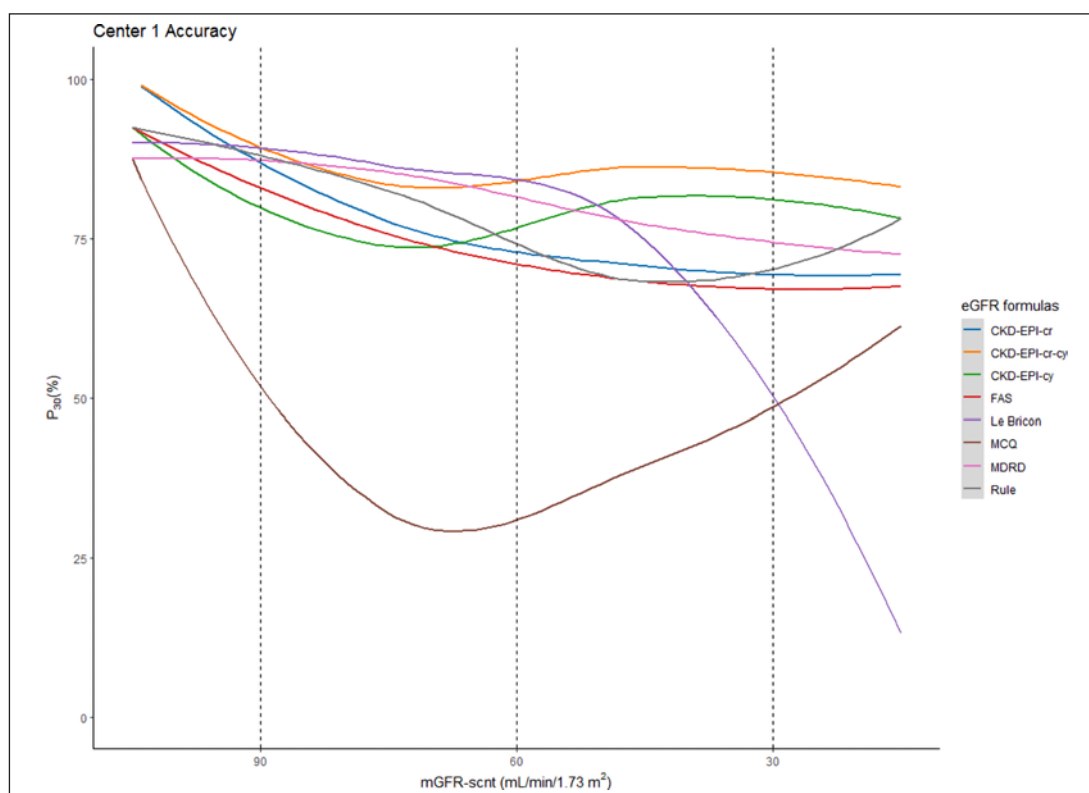
Fig. 1. Accuracy trend of EGFR formulas compared different MGFR intervals in center 1. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic.

Table 2. Accuracy, bias and precision for eGFR formula compared to mGFR-iox in center 1

Formula	$P_{30, \%}$	$Bias_{, \%}$	IQR, mL/min/ 1.73 m^2	$TDI_{, \%}$
CKD-EPI-cr	74	−6	14	70.6
MDRD	78	0	12	65.3
MCQ	49	−25	32	117
FAS	72	−12	14	74.1
Rule	77	13	11	51.8
CKD-EPI-cy	80	2	12	50.9
Le Bricon	58	−25	11	99.5
CKD-EPI-cr-cy	85	0	11	43.9

IQR, interquartile range; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic; TDI, total deviation index.

showed the accuracy for all the formulas: in this cohort, the CKD-EPI-cr-cy resulted in the most accurate with a value of 85%, whereas the MCQ and Le Bricon resulted in the less accurated with, respectively, 49 and 58%. All the other formulas were included between 72 and 80%. The TDI calculation reported similar results confirming the highest agreement for CKD-EPI-cr-cy (43.9%) and low agreement for MCQ (117%) and Le Bricon (99.5%; Table 2).

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Table 3. Accuracy P30 for formulas versus mGFR-iox in cohort 1 stratified by CKD stages

CKD stage	P_{30}, %							
	CKD-EPI-cr	MDRD	MCQ	FAS	CKD-EPI-cy	rule	lebricon	CKD-EPI-cr-cy
I	100	88	88	93	93	93	90	100
II	78	85	32	76	74	83	86	83
III	71	77	40	68	81	68	75	86
IV	69	73	61	68	78	78	13	83

mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic.

Table 4. Percentages of patients with mGFR-iox lower than 60 mL/min/1.73 m^2 whom eGFR differs from mGFR-iox at different thresholds in center 1

	Differences up to 5 mL/min/1.73 $m^{2, \%}$	Differences from 5 to 20 mL/min/1.73 $m^{2, \%}$	Differences over 20 mL/min/1.73 $m^{2, \%}$
CKD-EPI-cr	50	41	9
MDRD	56	37	7
MCQ	39	33	28
FAS	55	34	11
Rule	49	47	4
CKD-EPI-cy	54	44	2
Le Bricon	21	74	5
CKD-EPI-cr-cy	59	38	3

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic.

The P_{30} was also evaluated at different range of GFR, observing an overall high accuracy for high values of GFR (higher than 90 mL/min/1.73 m^2) with the CKD-EPI-cr and CKD-EPI-cr-cy scoring a 100% and the others between 88 and 93%. For lower values of GFR, a common loss of accuracy was observed with the Le Bricon formulas showing a value of 13% at GFR under 30 mL/min/1.73 m^2 (Fig. 1).

The accuracy of the eGFR formulas was evaluated for each stage of CKD according to mGFR-iox (Table 3), observing a decay of P_{30} at lower stages.

Considering the pts with mGFR-iox lower than 60 mL/min/1.73 m^2, we calculated the percentages of pts who had an estimated value that differed from measurement by <5 mL/min /1.73 m^2, between 5 mL/min/1.73 m^2 and 20 mL/min/1.73 m^2 and over 20 mL/min/1.73 m^2 for all the formulas (Table 4).

In particular, we observed that the eGFR, calculated with the most common formulas based on serum creatinine and/or serum cystatin C, demonstrated in the 52% of pts a discrepancy higher than 5 mL/min1.73 m^2 in comparison to the gold standard.

Accuracy analysis based on age tertiles is presented in online supplementary Table 2 for both cohorts

Center 2

Different results were obtained from the Center 2 cohort where renal scintigraphy was adopted to measure the GFR. In this case only, the 4 creatinine-based formulas were used, and

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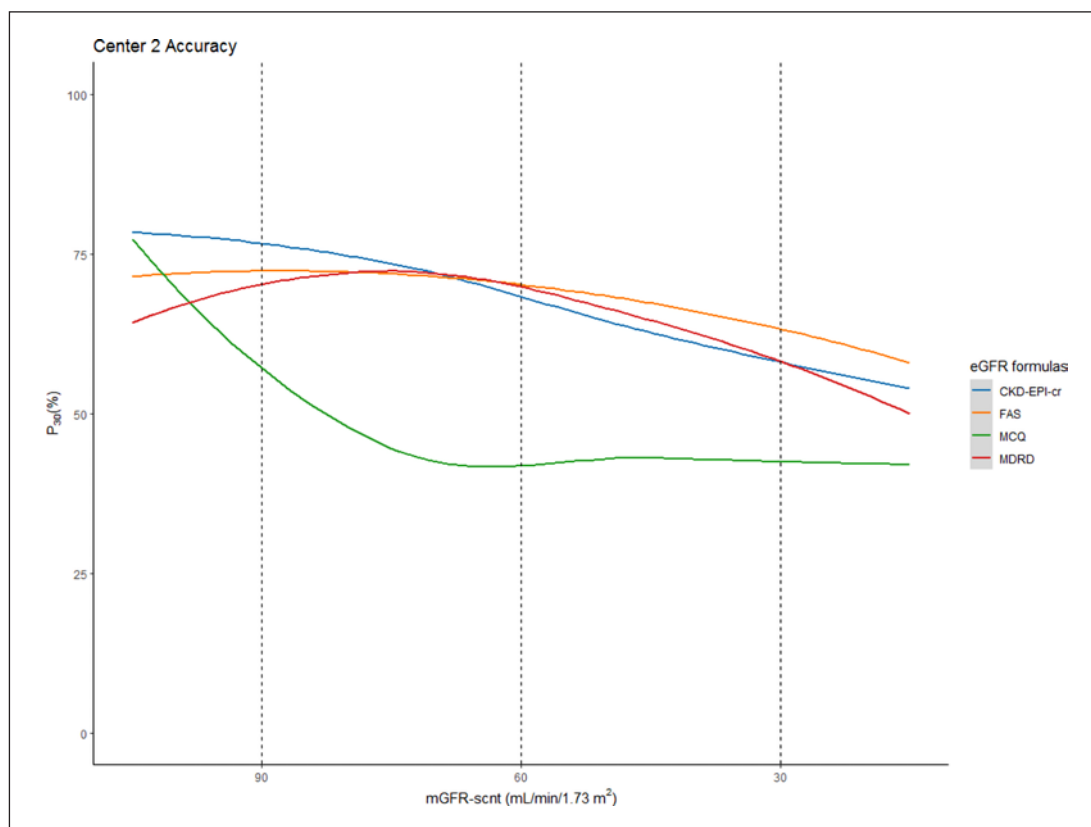
Fig. 2. Accuracy trend of EGFR formulas compared to different MGFR intervals in center 2. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic.

we observed that the formulas tend to over/underestimate the mGFR-scnt value as follows: CKD-EPI-cr, MDRD, and FAS median underestimation of 6, 10, and 7% while MCQ overestimation of 16%. The IQR resulted higher for Center 2 with values between 25 and 35 mL/min/1.73 m². The overall accuracy resulted lower observing 71% for CKD-EPI-cr, 66% for MDRD, 70% for FAS, and 55% for MCQ (higher than Center 1). The TDI remained in line with Center 1 confirming the low agreement for MCQ formula (97.6%; Table 5).

As for Center 1, the accuracy at different ranges showed a loss of accuracy at lower values of GFR (Fig. 2) and lower CKD stages (Table 6).

Considering the pts with mGFR-scnt lower than 60 mL/min/1.73 m², we observed that also in this cohort, for MCQ the percentages of pts with a difference of 20 mL/min/1.73 m² or higher is the biggest among all formulas with a value of 39% against the mean 15% of the others. For differences lower than 5 mL/min/1.73 m², the mean was 24.5%, while between 5 and 20 mL/min/1.73 m² was 54.5% with all the percentages being comparable between formulas (Table 7).

Discussion

Intro

In daily clinical practice, the use of an "ideal" marker of renal damage uncorrelated to serum creatinine such as inulin, iothalamate, diethylene, triamine penta-acetic acid, or iohexol

Table 5. Accuracy, bias, and precision for eGFR formula compared to mGFR-scnt in center 2

Formula	$P_{30, \%}$	Bias$_{, \%}$	IQR, mL/min/ 1.73 m^2	TDI$_{, \%}$
CKD-EPI-cr	71	6	26	65.9
MDRD	66	10	29	68.7
MCQ	55	–16	35	97.6
FAS	70	7	25	67.9

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic; IQR, interquartile range; TDI, total deviation index.

Table 6. Accuracy P30 for formulas versus mGFR-scnt in cohort 2 stratified by CKD stages

CKD stage	$P_{30, }$ %			
	CKD-EPI-cr	MDRD	MCQ	FAS
I	78	64	77	71
II	73	72	45	72
III	63	65	43	67
IV	54	50	42	58

CKD, chronic kidney disease; mGFR, measured glomerular filtration rate; CKD-EPI, CKD-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic.

Table 7. Percentages of patients with mGFR-scnt lower than 60 mL/min/1.73 m^2 whom eGFR differs from mGFR-scnt at different thresholds in center 2

|	Differences up to 5 mL/min/1.73 m$^{2, \%}$	Differences from 5 to 20 mL/min/1.73 m$^{2, \%}$	Differences over 20 mL/min/1.73 m$^{2, \%}$
CKD-EPI-cr	24	58	18
MDRD	30	58	12
MCQ	16	45	39
FAS	28	57	15

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; MCQ, Mayo Clinic Quadratic.

is often discouraged because expensive and time consuming [4]. For these reasons, different types of formulas for estimating GFR have been proposed, driving nowadays clinical decisions in many hospitals and laboratories [15].

Center 1

The Center 1 is a nephrological department where most of the pts suffered from nephrological diseases or end-stage renal diseases treated with kidney transplant. In general, the P_{30} for all the equations evaluated averaged 72% ranging from 50 to 85%. This means that 50 to 85% of the estimations had an error up to 30% from mGFR-iox. Importantly, this error was
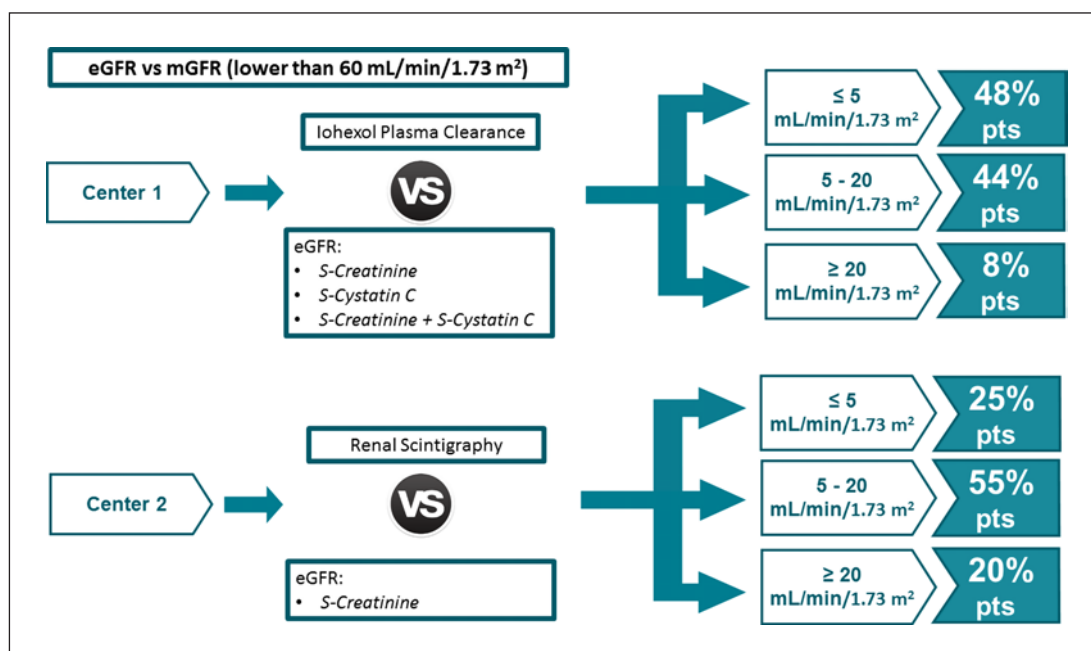
Fig. 3. Mean difference at different thresholds for pts with MGFR lower than 60 mL/min/1.73 m². eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

larger than 30% in a nonneglectable number of cases: 50 or 40% for the Le Bricon and MCQ equations. Thus, large variability between eGFR and mGFR-iox is frequent and severe. The agreement, expressed as TDI, confirmed this situation, showing that, to obtain the 95% of the estimates, a boundary is needed of at least 44% in the best-case scenario (CKD-EPI-cr-cy).

It is important to notice that a systematic error (bias) occurs for 5 of the 8 formulas considered, while CKD-EPI-cr-cy, MDRD, and CKD-EPI-cy turned out to have a negligible bias.

The comparisons between the eGFR formulas and mGFR-iox show that there is a loss of accuracy at lower values of GFR (≤ 60 mL/min/1.73 m²) where the metrics P_{30} for all the formulas is lower than 85%. In particular, a not negligible percentage of patient with mGFR-iox lower than 60 mL/min/1.73 m², tends to be wrongly over or underestimated with a discrepancy >20 mL/min/1.73 m² (especially the MCQ formulas).

Surely the MCQ and Le Bricon formulas turned out to be the less effective for the GFR estimation with low accuracy (49 and 58%) and the presence of a remarkable bias.

Center 2

The Center 2 is a urological/oncological department where the use of Renal Scintigraphy is mostly used to decide the best surgical/clinical approach as daily routine. As a matter of fact, even though iohexol technique represents the most accurate method to define the "real renal function," renal scintigraphy with TC 99 m-DTPA or MAG3 remains the most popular functional exam which urologists and oncologists prescribe to pts in clinical practice, thanks to the ability to determinate the separate function of kidneys. Our observations confirm the lower efficacy of the Renal Scintigraphy in the correct determination of GFR, showing a divergent scenario with the results obtained in Center 1. In fact, while the accuracy of the eGFR on mGFR-iox is about 71%, in the Center 2, mGFR-scnt decreases down to 65%. Moreover, a systematic difference seems to be present for all the formulas referring to mGFR-scnt and also the midspread of the difference is double than Center 1.

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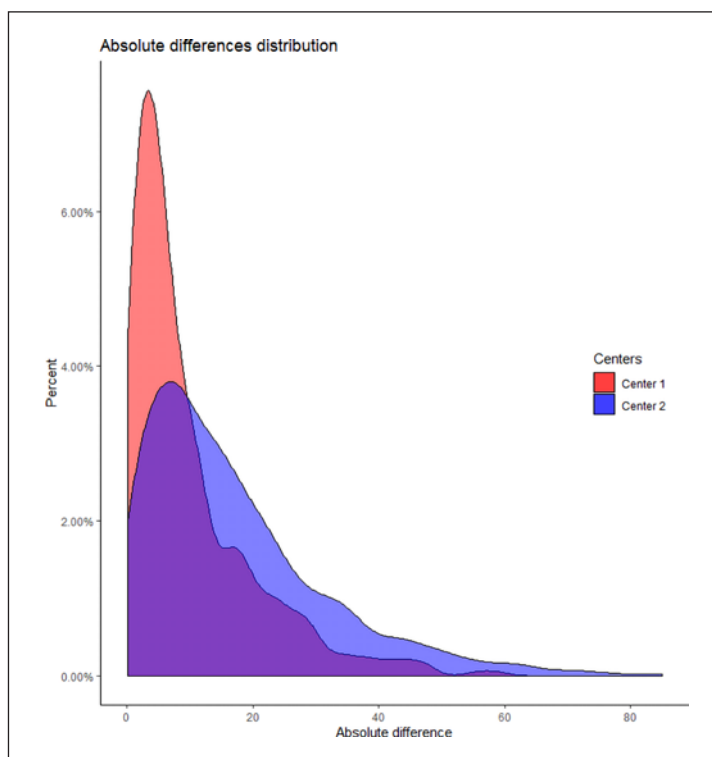
Fig. 4. Distribution of the absolute differences between MGFR and EGFR in the 2 centers.

Overall Considerations

The analysis of our work has obviously elucidated 2 different but cumbersome points; the low reliability of eGFR formulas in comparison to the gold standard mGFR-iox method and the evident disagreement between eGFR and renal scintigraphy.

First (as shown in Fig. 3), the eGFR formulas in comparison to gold standard mGFR-iox appear less accurate to define renal function under 60 mL/min/1.73 m^2, with >50% of pts who are over or underestimated by >5 mL/min/1.73 m^2. Regarding the differences of iohexol renal measurement and renal scintigraphy in respect to eGFR, our work clearly demonstrates that the distribution of the absolute differences between mGFR and eGFR varies among the 2 techniques, with a well-spreaded trend in Center 2 and a narrower one in Center 1 (Fig. 4, 5). Nevertheless, renal scintigraphy remains the unique available technique able to define the separate renal function GFR, a key factor in the surgical management of kidney cancer or transplantation. For this argument, even though lower accuracy in comparison to iohexol plasma clearance, renal scintigraphy remains a valuable tool in clinical field. The 3 methods considered in this study, eGFR mGFR-iox, and mGFR-scnt, and their features (respectively, ease of use, accuracy, and assessment of separate renal GFR) must be considered when approaching a patient during its therapeutic pathway (Fig. 6).

Clinical Implications

In this study, we considered 3 type of medical field in which assessment of GFR plays a key role: urological, oncological, and nephrological.

Regarding urological pts, the determination of the real renal function remains one of the cornerstones in daily clinical management. For instance, preoperative GFR is one of the most important variables which are considered during surgical planning (radical vs. partial
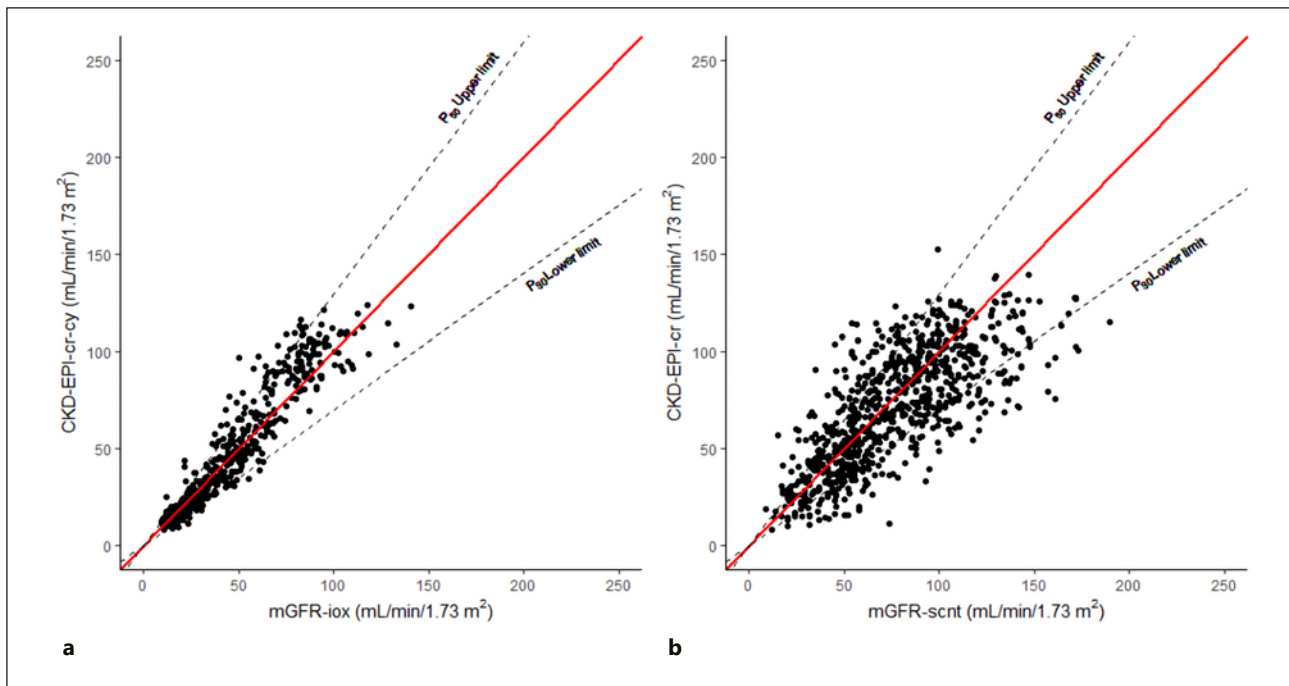
Fig. 5. Scatterplot of EGFR versus MGFR: (**A**) CKD-EPI-CR-CY versus MGFR-IOX; (**B**) CKD-EPI-CR versus MG-FR-SCNT. Red lines represent identity and black dotted lines represent P_{30} boundaries. mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration.
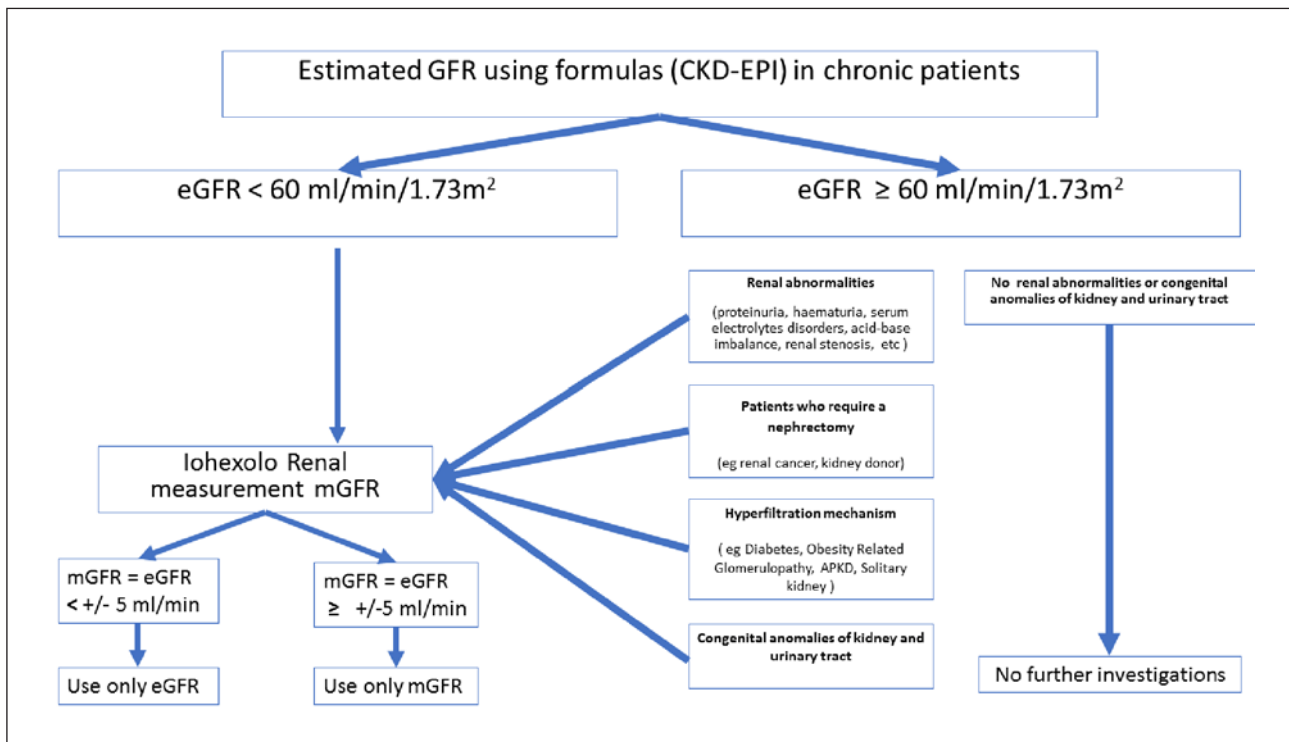
Fig. 6. Summarize of the decisional algorthm between MGFR and EGFR for chronic pts. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration.

nephrectomy) in kidney cancer pts [23]. Similarly, in kidney stones and pyelouretheral junction stenosis, split renal function evaluation is of paramount importance to decide if and how to operate [24]. For those and other aspects related both to research and clinical practice, GFR determination harbors a pivotal role for urologists.

Regarding oncological pts, the use of a reliable method to evaluate renal function is crucial since the prevalence of renal dysfunction (CKD and acute kidney injury) raised up in the last decade up to 50% as reported in some series [25]. The IRMA I and II studies, which included 5,000 adult cancer pts each, showed a rate of GFR lower than 90 mL/min/1.73 m^2, respectively, in 52.9 and 50.2% of cases and a proportion of 12 and 11.8% of CKD stages III and IV [26]. In the IRMA-2 study, pts with a GFR lower than 60 mL/min/1.73 m^2 had a lower mean survival compared to pts with better renal function (16.4 vs. 25.0 months for GFR superior to 60 mL/min/1.73 m^2) in a population of cancer pts nonselected for type and stage of the tumor [27]. Furthermore, in CKD pts stage IIIa-b and IV, dose adjustment for chemotherapy is required to avoid nephrotoxicity and side effects that lead to treatment discontinuation and interruptions. An impaired renal function may affect the indication of neoadjuvant or adjuvant treatment in urothelial cancers, as well. Indeed, pts with a GFR <60 mL/min/1.73 m^2 are generally excluded from pre and/or postoperative treatments due to high risks of toxicity [28, 29]. Many formulas to calculate the GFR have been developed and tested over the years in pts to determine the most effective and safest dose of chemotherapy as carboplatin or cisplatin, but none of these fully addressed the problems of complex pharmacokinetics and changing renal function [30].

Regarding nephrological pts, a reliable determination of renal function is crucial in many clinical situations, including the clinical evaluation of pts with renal insufficiency, the stage in CKD groups, the risk for disease progression, the indication for dialysis therapy, the screening living donors and the dose adjustment of toxic drugs, and so on [31]. Formulas are algorithms based on creatinine and or cystatin-c, age, and sex. However, both creatinine and cystatine-c are not perfect markers of renal function [5, 32]. Creatinine levels depend on muscle mass and protein intake and the levels of cystatin-c can be increased in obesity, subclinical inflammation and diabetes, independently of the level of renal function. This may explain, at least in part, the underestimation of renal function.

Conclusion

Direct measurement of GFR using a gold standard technique must be considered in selected pts before clinical decision. Assuming that performing mGFR for routine practice or in epidemiological studies could be not always feasible, the current findings emphasize the absolute need to determine an mGFR with gold standard method at least for those pts at eGFR lower than 60 mL/min/1.73 m^2 who deserve surgical operations, anticoagulant therapies, nephrotoxic drugs, oncological medical therapies (included experimental protocols), and radiological contrast medium agents injections.

Despite the inaccuracy of eGFR formulas in comparison to gold standard methods is a well-known argument for nephrologists, this message needs to be spread in other clinical fields where the use eGFR prevails unchallenged.

Limitation of the Study

This study is characterized by some limitations due to the nature of the retrospective model design. In particular, the data available for the pts do not include comorbidities such as blood hypertension, diabetes, and obesity which could influence the renal health status. The second limitation is that in Center 2 no actual gold standard method is used to determine

GFR making inappropriate to speculate on eGFR efficacy. The consequence of this limitation is the lack of a cohort where both mGFR techniques where used making impossible to merge the 2 cohorts.

Statement of Ethics

The study was conducted in accordance the World Medical Association Declaration of Helsinki. All pts had signed an informed consent agreeing to deliver their own anonymous information for future studies. The study was approved by local Ethical Committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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