Indexing Glomerular Filtration Rate to Body Surface Area: Clinical Consequences

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Background: Kidney function is mostly expressed in terms of glomerular filtration rate (GFR). A common feature is the expression as ml/min per 1.73 m², which represents the adjustment of the individual kidney function to a standard body surface area (BSA) to allow comparison between individuals. We investigated the impact of indexing GFR to BSA in cancer patients, as this BSA indexation might affect the reported individual kidney function. **Methods:** Cross-sectional study of 895 adults who had their kidney function measured with ⁵¹chromium ethylene diamine tetraacetic acid. Mean values of BSA-indexed GFR vs. mean absolute GFR were analyzed with a *t*-test for

paired data. Bland–Altman plot was used to analyze agreement between the indexed and absolute GFR values. **Results and Conclusion:** BSA-GFR in patients with a BSA <1.60 m² overestimated GFR with a bias of 10.08 ml/min (11.46%) and underestimated GFR in those with a BSA >2 m² with a bias up to –20.76 ml/min (–23.59%). BSA is not a good normalization index (NI) in patients with extreme body sizes. Therefore, until a better NI is found, we recommend clinicians to use the absolute GFR to calculate individual drug chemotherapy dosage as well as express individual kidney function. *J. Clin. Lab. Anal.* 28:83–90, 2014. © 2013

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Key words: kidney function tests; drug dosage calculations; body weights and measures; radioisotope diagnostic techniques; indexed glomerular filtration rate

INTRODUCTION

Over the last years, there has been an ongoing debate whether body surface area (BSA) should be used as a normalization index (NI) of glomerular filtration rate (GFR). The choice of a reference value set at 1.73 m², as proposed by McIntosh and colleagues (1) in 1928, is also questionable. Indeed, this value was calculated from the Du Bois formula using weight and height of women and men aged 25 years in 1927. The choice of BSA for indexing GFR by McIntosh is based on the following assertion: BSA was “the nearest available parallel to the mass of functioning kidney tissue.” Many authors have now demonstrated that this can pose clinical problems (2–4).

There are other equations to calculate BSA such as Boyd (1935), Gehan and George (1970), Haycock (1978), Mosteller (1987), Livingstone (2001) etc. Most scientists will prefer to use Gehan and George or Haycock formula because they are based on a larger population (401 and 81, respectively), but their superiority over Du Bois and Du Bois has not yet been proven (5).

Moreover, the figure of standard BSA 1.73 m² is no longer applicable. Hense et al. reported a mean BSA of 1.97 m² for men and 1.72 m² for women (6), and Hoy et al. (7) reported a mean BSA of 2.22 m² in a general Caucasian population, with the implications this increasing BSA might have, such as underestimation of GFR. The other problem is that Du Bois formula is based on just nine observations, and underestimates BSA in obese patients by 5% and overestimates BSA by up to 8% in infants (8).

There are many other estimation formulae to calculate BSA, but none of them has been validated in a Caucasian adult population; they have been validated only in Asians (9) and neonates (10). This uncertainty related to

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TABLE 1. Patients Characteristics

	All	Women	Men	P-value
Patients (n)	895	478	417	
Mean age $\pm$ SD (years)	62 $\pm$ 11	62 $\pm$ 10	61 $\pm$ 12	NS
Mean GFR (ml/min) $\pm$ SD	88 $\pm$ 27	81 $\pm$ 22	95 $\pm$ 30	<0.0001
Mean GFR (ml/min per 1.73 m ²) $\pm$ SD (Du Bois)	85 $\pm$ 22	84 $\pm$ 21	84 $\pm$ 24	NS
Mean difference (BSA-indexed – absolute) GFR $\pm$ SD	–3.46 $\pm$ 11	2.29 $\pm$ 8	–10.06 $\pm$ 10	<0.0001
Mean BSA (m ²) $\pm$ SD (Du Bois)	1.79 $\pm$ 0.21	1.68 $\pm$ 0.16	1.92 $\pm$ 0.17	<0.0001
Mean BSA (m ²) $\pm$ SD (Gehan)	1.81 $\pm$ 0.22	1.70 $\pm$ 0.18	1.93 $\pm$ 0.20	<0.0001
Mean weight (kg) $\pm$ SD	70 $\pm$ 15	63 $\pm$ 13	76 $\pm$ 14	<0.0001
Mean height (cm) $\pm$ SD	169 $\pm$ 9	163 $\pm$ 6	174 $\pm$ 7	<0.0001
Mean BMI (kg/m ²) $\pm$ SD	24 $\pm$ 4	24 $\pm$ 5	24 $\pm$ 4	NS
Pearson correlation coefficient GFR-BSA	0.52	0.39	0.51	<0.05

GFR, glomerular filtration rate; SD, standard deviation; BMI, body mass index; BSA, body surface area; NS, not significant.

its accuracy estimates raises the question of the validity of parameters expressed as a BSA index value.

Despite that, the impact of BSA indexation on GFR values is scarce in the normal size population with a standard BSA of around 1.73 m², but several studies have shown that the mean differences between absolute and BSA-indexed GFR are larger in patients with extreme body sizes (4, 11). This observation can have an impact in drug dosing (12), assessment of potential kidney donors (3), and longitudinal follow-up studies of GFR. Indeed, indexation will result in an unacceptable underestimation of GFR in obese patients as well as an overestimation of GFR in malnourished patients (13–15).

Besides, a good NI of GFR has to accomplish with the following statistical requirements: NI has to be highly correlated to GFR; after normalization, there is no residual correlation between GFR and NI; and correlation has to be robust and present in all subgroups (16).

The aim of this study was to investigate whether there are clinically significant differences between indexed BSA and absolute GFR values in 895 adults, some with extreme body sizes, as well as to investigate the accuracy of BSA as a normalization factor.

MATERIALS AND METHODS

A retrospective single center cross-sectional study of 895 adults was approved by the Danish Data Protection Agency (j.nr 2007–41–1006) and conducted in agreement with the principles of the Declaration of Helsinki.

Data Collection

Data were collected from patients referred to the local department of nuclear and clinical physiology over an 8-year period in order to have GFR measured

with ⁵¹chromium ethylene diamine tetraacetic acid (⁵¹Cr-EDTA) before they started treatment with chemotherapy. A total of 1,070 investigations were performed in 895 patients. Only the first investigation was used in the analysis.

Patient characteristics (Table 1)

Fifty-three percent of the patients were female and forty-six percent were male, average age was 62 years. GFR range: 8–216 ml/min. Weight and height range: 35–141 kg and 142–204 cm. BSA and body mass index (BMI) was 1.23–2.58 m² and 15–48.7 kg·m^{–2}, respectively. Despite this large variation in BSA range, the mean BSA for the whole group was 1.79 $\pm$ 0.21 m², which is quite close to the figure of 1.73 m². As expected, BSA was higher for men than for women, which reflects a higher weight and height. No differences were observed in mean BMI but absolute GFR was higher in men.

BSA was calculated from the Du Bois formula despite its limitations, as this formula was used in the Modification in Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae:

$$\text{BSA (m}^2\text{)} = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}.$$

For comparison, BSA was also calculated with Gehan and George formula:

$$\text{BSA (m}^2\text{)} = 0.0235 \times \text{height (cm)}^{0.422} \times \text{weight (kg)}^{0.514}.$$

The same trend was found with regard to BSA whenever Gehan and George formula was used. We looked at absolute values and indexed values; therefore, we used this formula to convert one to another.

Conversion of BSA-indexed GFR values to absolute GFR values

$$\text{Absolute GFR} = (\text{Indexed GFR} \times \text{Patients BSA}) / 1.73 \text{ m}^2 = \text{ml/min}$$

Measured GFR

GFR was determined from the total (renal and extrarenal) ^{51}Cr -EDTA plasma clearance by a simplified single-injection technique with one single-plasma sample (17, 18).

In patients whom GFR was anticipated to be less than 30 ml/min, a slope intercept with four samples technique was performed (19) and if GFR was anticipated to be less than 15 ml/min, a sample was taken at $t = 24$ h as recommended by Groth (20).

Statistics

Data were analyzed with Statistica 99 version by StatSoft Inc. All GFR measurements follow a normal distribution (Kolmogorov–Smirnov test).

Bias, precision, and accuracy of indexed GFR

Bias in this type of analysis is referred to the difference between the average of measurements made on the same patient and its true value, which in this case is assumed to be the measured GFR by ^{51}Cr -EDTA.

Bias: mean difference between BSA-GFR (measured GFR in ml/min per 1.73 m^2) and absolute GFR (measured GFR in ml/min) based on ^{51}Cr -EDTA. In the tables, this value is expressed as Δ (mean delta). Precision was expressed as the SD of the bias. Large width equals low precision. Bias was also expressed as percentage of the difference between BSA-indexed and absolute GFR values (ABS-GFR). Accuracy was defined as the percentage of patients who had an indexed kidney function within 10 and 30% of the absolute GFR. Analysis of bias between absolute and BSA-indexed GFR values was performed with a paired Student's t -test and differences of $P < 0.05$ were considered as significant. Analysis of differences in GFR by gender was performed with an unpaired data Student's t -test, and again differences of $P < 0.05$ were considered significant. The results were expressed as delta (Δ) and standard deviation.

Correlation analysis

We performed a correlation analysis with Pearson correlation coefficient of indexed and absolute GFR values stratified by BSA as well as by gender. It measures the de-

gree of association between both variables. $P < 0.05$ was considered significant.

Agreement analysis

A Bland–Altman plot was chosen to analyze agreement by analyzing the spread of the difference scores. A larger variability indicates large errors. The range considered is two standard deviations above and below the mean of the difference scores, which is equivalent to 95% limits of agreement. A spread equally distributed as well as closely related at both sides of the centerline representing the zero difference is considered as a sign of perfect agreement.

RESULTS

Bias, Precision, and Accuracy of BSA-Indexed GFR (Tables 2 and 3)

There was an overestimation of measured GFR by the BSA-indexed GFR method, demonstrated by a statistically significant bias in patients with $\text{BSA} < 1.60$ of 10.08 ± 4.66 ml/min (11.46%, Table 2).

One could argue that the explanation is that there were fewer men with a $\text{BSA} < 1.60$ (15 vs. 153) but while looking at GFR values stratified by level of BSA (Table 3), there were actually no differences between women and men with regards to measured GFR, expressed as ml/min in the group with $\text{BSA} < 1.60 \text{ m}^2$, but there were statistically significant differences between them when GFR was expressed as ml/min per 1.73 m^2 .

BSA-GFR in the group of patients with $\text{BSA} > 2 \text{ m}^2$ underestimated GFR by -20.76 ± 9.16 ml/min (–23.59%), but in this case this difference could not be explained alone by BSA indexation, as the small number of women in this group might have played a role. The same analysis of bias expressed as a percentage showed an overestimation in the group of patients with a $\text{BSA} < 1.60 \text{ m}^2$, more pronounced in women (11.75 vs. 8.45%) and an underestimation with $\text{BSA} \geq 2$, more pronounced in men (–24.45 vs. –17.64%, Table 2).

There were also statistically and clinically significant differences in absolute GFR values with increasing BSA between genders, with a bias of 20.52 ± 7.45 ml/min in the subgroup with $\text{BSA} \geq 2 \text{ m}^2$ (Table 3).

Correlation Analysis or Analysis of BSA as a NI of GFR (Table 4)

BSA had a significant correlation of 0.52 with measured ABS-GFR (ml/min), but the correlation line does not pass through the 0 point, and the intercept is significantly different from 0: $\text{BSA} = 1.4381 + 0.004 \times \text{ABS-GFR}$.

TABLE 2. Bias, Precision, and Accuracy of BSA-GFR-Indexed Values

	<i>N</i>	Mean GFR (ml/min)	Mean GFR (ml/min per 1.73 m ²)	<i>P</i> -value	Mean BSA	Mean BMI	Δ	$\Delta\%$	SD	P30	P10
All	895	87.99 $\pm$ 27.20	84.53 $\pm$ 22.30	<0.001	1.79 $\pm$ 0.21	24.15 $\pm$ 4.38	-3.46	-3.94%	11.2	99.1%	59.55%
BSA <1.60	168	68.85 $\pm$ 18.21	78.93 $\pm$ 20.64	<0.0001	1.51 $\pm$ 0.07	20.07 $\pm$ 2.70	10.08	11.46%	4.66	97.02%	25.59%
BSA 1.60–1.79	314	83.48 $\pm$ 21.53	84.97 $\pm$ 21.90	<0.001	1.70 $\pm$ 0.05	23.06 $\pm$ 3.03	1.48	1.69%	3.00	100%	100%
BSA 1.80–1.99	262	92.07 $\pm$ 24.96	83.95 $\pm$ 22.27	<0.0001	1.89 $\pm$ 0.05	25.26 $\pm$ 3.32	-8.11	9.22%	3.81	100%	67.17%
BSA $\geq$ 2	151	111.57 $\pm$ 30.75	90.81 $\pm$ 23.46	<0.0001	2.11 $\pm$ 0.10	29.03 $\pm$ 4.53	-20.76	-23.59%	9.16	98.01%	0.0%
	<i>N</i>	Mean GFR (ml/min)	Mean GFR (ml/min per 1.73 m ²)	<i>P</i> -value	Mean BSA	Mean BMI	Δ	$\Delta\%$	SD	P30	P10
Women	478	81.41 $\pm$ 22.35	83.70 $\pm$ 21.11	<0.001	1.68 $\pm$ 0.16	23.65 $\pm$ 4.56	2.29	2.6%	7.98	98.95%	67.57%
BSA <1.60	153	69.66 $\pm$ 18.32	80 $\pm$ 20.71	<0.0001	1.50 $\pm$ 0.07	20.19 $\pm$ 2.69	10.34	11.75%	4.71	96.73%	23.52%
BSA 1.60–1.79	225	84.18 $\pm$ 20.96	86.02 $\pm$ 21.31	<0.001	1.69 $\pm$ 0.05	23.70 $\pm$ 2.99	1.84	2.09%	2.95	100%	100%
BSA 1.80–1.99	81	93.06 $\pm$ 22.95	85.55 $\pm$ 20.60	<0.0001	1.91 $\pm$ 0.08	27.57 $\pm$ 3.70	-7.5	-8.53%	3.62	100%	76.54%
BSA $\geq$ 2	19	93.63 $\pm$ 23.43	78.10 $\pm$ 20.50	<0.001	2.08 $\pm$ 0.06	34.05 $\pm$ 5.72	-15.52	-17.64%	3.67	100%	0.0%
	<i>N</i>	Mean GFR (ml/min)	Mean GFR (ml/min per 1.73 m ²)	<i>P</i> -value	Mean BSA	Mean BMI	Δ	$\Delta\%$	SD	P30	P10
Men	417	95.53 $\pm$ 30.18	85.47 $\pm$ 23.60	<0.0001	1.92 $\pm$ 0.18	24.73 $\pm$ 4.09	-10.06	11.43%	10.72	99.28%	50.35%
BSA <1.60	15	60.6 $\pm$ 15.22	68.04 $\pm$ 16.93	<0.0001	1.54 $\pm$ 0.06	18.81 $\pm$ 2.52	7.43	8.45%	3.22	100%	46.66%
BSA 1.60–1.79	89	81.71 $\pm$ 22.94	82.30 $\pm$ 23.26	NS	1.72 $\pm$ 0.05	21.44 $\pm$ 2.51	0.59	0.67%	2.94	100%	100%
BSA 1.80–1.99	181	91.63 $\pm$ 25.86	83.24 $\pm$ 23.00	<0.0001	1.90 $\pm$ 0.05	24.23 $\pm$ 2.54	-8.38	-9.53%	3.87	100%	54.14%
BSA $\geq$ 2	132	114.16 $\pm$ 30.89	92.64 $\pm$ 23.36	<0.0001	2.12 $\pm$ 0.11	28.30 $\pm$ 3.84	-21.51	-24.45%	9.47	97.72%	0.0%

GFR, glomerular filtration rate; BSA, body surface area; BMI, body mass index; Δ , bias; NS, not significant; P30, percentage of values within 30% of absolute GFR; P10, percentage of values within 10% of absolute GFR.

Differences between absolute and BSA-indexed GFR values by BSA strata as well as gender.

There was also a residual correlation between BSA-GFR (ml/min per 1.73 m²) and BSA in the whole group. When correlation was stratified by BSA, the results were not consistent in all subgroups and there was also residual correlation, which suggests that BSA is not a good NI (Table 4).

Agreement Analysis or Bland–Altman Plot

The analysis of agreement between the absolute and the BSA-GFR values showed a biased pattern, resulting in a negative difference of the measurement more pronounced with increasing GFR above 125 ml/min. Bias was -3.46 ml/min (-4.2 to -2.73 95% CI). The 95% limits of agreement were -25.87 and 18.94 ml/min. The same results are also presented as a percentage of error, with values of bias -3.93% (-4.77 to -3.10% 95% CI) and 95% limits of agreement -29.4 and 21.53% (Fig. 1). Similar results were found whenever BSA was calculated with Gehan and George formula (Fig. 2). Range of potential difference was from -80.93 to 30.78% with BSA-GFR.

SUMMARY OF RESULTS

- BSA is not highly correlated to GFR.
- After normalization, there was still residual correlation between GFR and BSA.
- Correlation was not robust in all subgroups.
- There were clinically significant differences between indexed BSA-GFR and absolute GFR values in the group of patients with BSA $\geq$ 2 and <1.60.

DISCUSSION

To our knowledge, this is the first large clinical study using ⁵¹Cr-EDTA as a reference method for measuring GFR, which demonstrates clinical differences between indexed and absolute GFR values in cancer patients, some with extreme body sizes. Dooley et al. had previously shown that BSA calculated by ideal weight correlates poorly with GFR measured with Tc-99m diethylene triamine penta acetic acid, (21), as correlation was as low as $r = 0.22$. We are able to demonstrate similar results with real body weight.

TABLE 3. Differences in GFR Between Genders With Absolute and Indexed Values

Absolute GFR values	Women		Men		P-value	Δ	SD
	N	Mean GFR (ml/min)	N	Mean GFR (ml/min)			
All	478	81.41 $\pm$ 22.35	417	95.53 $\pm$ 30.18	<0.001	14.11	7.82
BSA <1.60	153	69.66 $\pm$ 18.32	15	60.6 $\pm$ 15.22	NS	-9.06	3.11
BSA 1.60–1.79	225	84.18 $\pm$ 20.96	89	81.71 $\pm$ 22.94	NS	-2.48	1.98
BSA 1.80–1.99	81	93.06 $\pm$ 22.95	181	91.63 $\pm$ 25.86	NS	-1.44	2.91
BSA $\geq$ 2	19	93.63 $\pm$ 23.43	132	114.16 $\pm$ 30.89	<0.05	20.52	7.45
BSA-indexed GFR values	Mean GFR (ml/min per 1.73 m ²)		Mean GFR (ml/min per 1.73 m ²)		P-value	Δ	SD
	N		N				
All	478	83.70 $\pm$ 21.11	417	85.47 $\pm$ 23.60	NS	1.77	2.49
BSA <1.60	153	80 $\pm$ 20.71	15	68.04 $\pm$ 16.93	<0.05	-11.96	3.78
BSA 1.60–1.79	225	86.02 $\pm$ 21.31	89	82.30 $\pm$ 23.26	NS	-3.72	1.95
BSA 1.80–1.99	81	85.55 $\pm$ 20.60	181	83.24 $\pm$ 23.00	NS	-2.31	2.4
BSA $\geq$ 2	19	78.10 $\pm$ 20.50	132	92.64 $\pm$ 23.36	<0.05	14.54	2.86

GFR, glomerular filtration rate; BSA, body surface area; NS, not significant; Δ , mean of the difference; SD, standard deviation. Effect of gender and BSA normalization in GFR values.

The differences between the absolute and the BSA-indexed GFR values in patients with extreme body sizes are clinically important if the GFR values are used to calculate individual drug dosage or to establish whether the patient's level of kidney function allows treatment with cisplatin or carboplatin.

As shown by Schmieder et al., weight gain can lead to a “fall” in renal plasma flow (RPF) if adjusted values in ml/min per 1.73 m² are used, despite the fact that unadjusted values remain unchanged. The opposite is also true as a weight loss will “increase” RPF when in reality the absolute values might fall slightly reducing the cardiovascular risk, probably by reducing hyperfiltration (22).

By indexing GFR to BSA, the effect of body weight is removed, which accounts for 96% of the variance in this group of patients. This is the reason why BSA-

indexed GFR values might fail to identify changes in GFR due to weight gain or loss, if creatinine levels remain unchanged.

We also believe that our study has raised a question regarding the actual paradigm between BSA and GFR, as GFR in this study is not proportional to BSA; and when GFR is adjusted for BSA, there are differences in GFR between men and women regardless of the use of Du Bois or Gehan and George formula. In men GFR increases with increasing BSA, which is not the case in women.

Heaf (2) and others have demonstrated that BSA-indexed GFR is lower than absolute GFR, as BSA has increased over the past few years to a figure of about 1.92 m². As long as one wishes to continue indexing, the solution is not to increase the “standard” BSA, as

TABLE 4. Comparison of Correlation Between BSA and GFR as Absolute and Indexed Values

BSA correlation to GFR and GFR (ml/min per 1.73 m ²), R values								
BSA groups	All			Men			Women	
	N	GFR (ml/min)	GFR (ml/min per 1.73 m ²)	N	GFR (ml/min)	GFR (ml/min per 1.73 m ²)	N	GFR (ml/min per 1.73 m ²)
All	895	0.52***	0.15***	417	0.51***	0.21***	478	0.39***
<1.6	168	0.18 NS	-0.06 NS	15	-0.02 NS	-0.19 NS	153	0.16*
1.60–1.79	314	0.04 NS	-0.08 NS	89	-0.06 NS	-0.18 NS	225	0.1 NS
1.80–1.99	262	0.26***	0.15**	181	0.25***	0.15*	81	0.33**
>2.0	151	0.42***	0.23**	132	0.45***	0.25**	19	-0.29 NS

*P < 0.05; **P < 0.01; ***P < 0.001.

NS, not significant; GFR, glomerular filtration rate; BSA, Body surface area; BMI, body mass index; mean height in centimeters.

Correlation of BSA with GFRs, as well as residual correlation between BSA-indexed GFR and BSA, stratified by levels of BSA as well as by gender.

**GFR ml/min versus BSA indexed GFR
ml/min per 1.73 m² (Du Bois)**

— Mean Bias

----- Limits of 95% agreement

Percentage error -3,93572

MEAN + 2 STD 21,53385

MEAN - 2 STD -29,4053

Limits of 95% agreement

Limits of 95% agreement

Analysis of agreement between body surface area indexed and absolute glomerular filtration rate values, showing a tendency to underestimation of glomerular filtration rate more pronounced with values over 125 ml/min as well as relatively wide confidence intervals.

Fig. 1. Bland–Altman plot absolute GFR vs. BSA-indexed GFR percentage error (Du Bois BSA formula).

this is a changing parameter and would require periodic adjustments, but to look for a more appropriate NI such as height, total body water (TBW), or extracellular volume (ECV).

A study of 1,627 individuals by Eriksen et al. has looked at this issue, suggesting that TBW was superior to BSA as a GFR NI (23). They observed almost identical values across gender and BMI categories using a standard

**GFR ml/min versus BSA indexed GFR
ml/min per 1.73 m² (Gehan)**

— Mean Bias

----- Limits of 95% agreement

Percent error -4,70705

MEAN + 2 STD 22,0684 Limits of 95% agreement

MEAN - 2 STD -31,4825 Limits of 95% agreement

Analysis of agreement between body surface area indexed and absolute glomerular filtration rate values, showing a tendency to underestimation of glomerular filtration rate more pronounced with values over 125 ml/min as well as relatively wide confidence intervals.

Fig. 2. Bland–Altman plot absolute GFR vs. BSA-indexed GFR percentage error (Gehan BSA formula).

TBW of 40 l but not with BSA. One of the limitations in this study is that it relies on estimates rather than direct measurements.

Another option is to abandon indexing renal function (24) as proposed a long time ago by Turner et al. and to use a linear regression method instead.

The lack of measured ECV does not allow us to study other potential indexations such as ECV-indexed GFR and TBW-indexed GFR.

Ideally, this study should be repeated in a healthy population as cancer patients can suffer substantial weight loss that might affect GFR measuring results. Another problem with this study is that no information regarding protein intake or pain around the time when GFR was measured has been collected, and this can lead to large changes in measured GFR in a short period of time, caused by different mechanisms. None of the patients suffered with carcinoid or growth hormone tumors, which also can lead to changes in GFR. A smaller sample from this group of patients showed that the vast majority of patients had lung cancer (77.3%) or ovarian cancer (15.1%) (18).

Some might argue regarding the choice of EDTA as the gold standard because the urinary clearance of ^{51}Cr -EDTA consistently underestimates inulin clearances by 5 to 15% in most but not all studies, suggesting tubular reabsorption (14); but this choice is based on the wide use of this method as a surrogate of glomerular filtration in Denmark.

With regard to the differences in GFR by gender, it is difficult to say whether the differences between men and women are due to body size alone or not. Besides, the number of men and women in the low and high BSA subgroups, respectively, is low and therefore, the precision of any conclusions drawn is poor.

With regard to the correlation analysis, this study proves that BSA is not a good NI (16), as it does not accomplish with the four statistical requirements for good normalization. The agreement analysis showed BSA as NI of GFR has bias with wide 95% limits of agreement.

This study shows that BSA as a normalization factor has estimation errors, that is why we propose the use of GFR absolute values especially whenever BSA values are <1.6 or ≥ 2 m^2 , in order to calculate the appropriate chemotherapy dose as well as the individual kidney function. This can be easily done by using the following formula:

$$\text{Absolute GFR} = (\text{Indexed GFR} \times \text{Patients BSA}) / 1.73 \text{ m}^2,$$

which results in GFR expressed as ml/min.

This practice can be very relevant as the use of BSA-GFR values based on estimation formula increases from

day to day, adding uncertainty to the results obtained in patients with extreme body sizes.

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