Comparison of Early-Compartment Correction Equations for GFR Measurements

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Measuring the glomerular filtration rate (GFR) remains indicated in specific patients and/or specific clinical contexts.[1,2] For practical reasons, plasma clearances are preferred instead of urinary clearance. In most centers, the plasma clearance is calculated from exogenous marker concentrations obtained during the excretion phase (the *second* or *slow* GFR compartment), which is the most important for GFR determination. However, GFR is systematically overestimated because the part of the area under the curve (AUC) from the first (or *early*) compartment, which corresponds to the distribution of the marker in the body, is neglected. Because the AUC of the first compartment is not measured but estimated, it is prone to some imprecision, notably in high GFR ranges. Moreover, this overestimation can be corrected using various published mathematical models published by Chantler (C), Bröchner-Mortensen (BM), Fleming (F), Jodal-Bröchner-Mortensen (JBM), and Ng (N) (equations are given in Supplementary Table S1).[3–7] Few data are available on the comparison between these models. This is the goal of the current study.

From 6 different cohorts,[8,9] we collected results of measured GFR by plasma clearance (iohexol or ^{51}Cr−ethylenediamine tetraacetic acid [EDTA]) and compared the results obtained with the different correction equations (methods are described in detail in the Supplementary Methods).

Among the 5459 participants, the mean age was 53 ± 17 years, and 42.9% were women. Mean height and body weight were 168 ± 10 cm and 73 ± 17 kg, respectively. Mean body mass index (BMI) and body surface area (BSA) were 26 kg/m^2 ± 6 kg/m^2 and 1.85 m^2 ± 0.24 m^2, respectively. Mean measured GFR (mGFR) with C, BM, F, JBM, and Ng was 63 ml/min per 1.73 m^2 ± 28 ml/min per 1.73 m^2, 64 ml/min per 1.73 m^2 ± 25 ml/min per 1.73 m^2, 63 ml/min per 1.73 m^2 ± 24 ml/min per 1.73 m^2, 64 ml/min per 1.73 m^2 ± 25 ml/min per 1.73 m^2, and 65 ml/min per 1.73 m^2 ± 26 ml/min per 1.73 m^2, respectively. Lin's concordance correlation coefficient and biases are described in detail in Supplementary Table S2 in the Supplementary Material, but all comparisons showed almost perfect correlation (with concordance correlation coefficients >0.99). Regarding bias, all comparisons showed that bias was not relevant from a clinical perspective (the highest bias being 3 ml/min per 1.73 m^2). All concordance within 10% and 5% are given in Table 1. Concordance within 10% is 100% for all comparisons, except when C equation is considered. Within 5% concordance was also close to 100% for all equations, except between F and N and when the C equation is considered in the comparison. Subanalyses (see Supplemental Material) were repeated in subgroups according to GFR levels in Supplementary Table S3 (based on the BM method in 6 categories: >130 ml/min

Table 1. Concordance within 10% (above diagonal) and within 5% (below diagonal)

	C	BM	F	JBM	N
C	—	97.1	96.8	96.2	91.7
BM	51.9	—	100	100	100
F	59.6	100	—	100	100
JBM	54.3	100	100	—	100
N	37.4	98.8	90.7	98.9	—

BM, Bröchner-Mortensen; C, Chantler; F, Fleming; JBM, Jodal-Bröchner-Mortensen; N, Ng. All results are expressed as percentages.

per 1.73 m^2, 90−130 ml/min per 1.73 m^2, 60−90 ml/min per 1.73 m^2, 45−60 ml/min per 1.73 m^2, 30−45 ml/min per 1.73 m^2, and ≤30 ml/min per 1.73 m^2), sex in Supplementary Table S4, BMI in Supplementary Table S5 (<18.5 kg/m^2, 18.5−25 kg/m^2, 25−30 kg/m^2, 30−35 kg/m^2, 35−40 kg/m^2, and ≥40 kg/m^2, respectively), and age in Supplementary Table S6 (categorized in decades). Conclusions were not different from those of the total cohort when analyses were made according to sex or BMI. Only the variable *GFR level* influenced concordance, with less concordance in high GFR levels, even if results were still quite similar between BM and F, BM and JBM, and F and JBM. Excluding results from the C equation which is, once again, the most discrepant, we observed a discordance of more than 5% when the *slow* GFR was above 290, 290, 155, 290, 117, and 128 ml/min per 1.73 m^2 comparing BM-F, BM-JBM, BM-N, F-JBM, F-N, and JBM-N, respectively.

To the best of our knowledge, the current, multicentric study is the largest one comparing the different equations to correct the overestimation of the GFR obtained from the slow compartment. Two important conclusions should be drawn. First, the method proposed by Chantler in 1969 deviated most from all other methods. It can be reasonably presumed that this method was an oversimplification (C correction is just a linear correction), and we recommend that it should be abandoned. Second, all other models give very similar results, except at high GFR levels. The BM correction is the mostly used in the literature with iohexol and ^{51}Cr-EDTA, whereas the F model is mostly used with ^{99}Tc−diethylene triamine pentaacetic acid (DTPA), but obviously all these equations are interchangeable. More discrepancies can be observed at very high GFR levels. However, these discrepancies are observed at GFR levels which are higher than the threshold usually considered for the diagnosis of hyperfiltration, and therefore the clinical impact of such discrepancies is limited. BM correction is known to underestimate renal clearance at such high GFR levels. The performance of other equations at such high levels is not well known.

The main limitation of the current analysis is the absence of renal/urinary clearance and/or plasma samples in the first (or *early*) compartment. Thus, we can assert that all equations, except the C one, are equivalent when measured GFR is lower than 130 ml/min 1.73 m^2, but it remains difficult to know which one is the most accurate in the highest range of GFR. Further studies in this specific range of GFR are still required.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Different equations to correct for the absence of the first compartment.

Table S2. Concordance correlation coefficient (with 95% CI) and bias ± SD between the different methods.

Table S3. Comparison of concordance within 5 and 10% between the different models according to GFR levels.

Table S4. Comparison of concordance within 5 and 10% between the different models according to sex.

Table S5. Comparison of concordance within 5 and 10% between the different models according to BMI levels.

Table S6. Comparison of concordance 5 and 10% between the different models according to age.

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Regulatory B and T Cells and Their Association With Clinical Response in New-Onset Lupus Nephritis Patients

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Systemic lupus erythematosus (SLE) is a multisystem disease characterized by a global loss of self-tolerance with activation of autoreactive T and B cells.[S1] Hyperactive B cells produce a variety of antibodies that form immune complexes leading to the effector phase of the disease, and T cells contribute to tissue injury through proinflammatory cytokines.[S1–S3] The imbalance between these autoreactive T-helper cells (Th1/Th2/Th17) and regulatory T and B cells (Tregs and Bregs, respectively) is among the many immune-mediated responses involved in SLE.[S4] Tregs suppress immune responses by modulation of antigen-presenting cell maturation and function, killing of target cells and production of anti-inflammatory cytokines.[S5] Bregs exert suppressive effects by secretion of anti-inflammatory cytokines such as interleukin (IL)−10 and engaging in cell-to-cell contact via activation of cell death markers or co-stimulatory molecules that can also influence T-helper cell plasticity.[1,S6]

Lupus nephritis (LN) is a serious potential feature of SLE. Studies have shown a quantitative and functional deficiency in Tregs in SLE and LN patients.[2,3,S7,S8] Similarly, abnormalities in Bregs have been reported in SLE.[4–6,S9–S11] However, at present, there is no systematic study reporting the role Bregs in new-onset LN. Therefore, in our study, we aimed to monitor the baseline levels of Breg and Treg populations in new-onset LN patients and changes in their profile in response to immunosuppressive (IS) drugs. We also analyzed the association of regulatory cells with clinical response in LN patients. Unlike Tregs, which are uniformly identified as $CD3^+CD4^+CD25^{hi}$ $FoxP3^+$ $CD127^{lo}$,[S5] Bregs have been reported to have varying phenotypes, the secretion of IL-10 being characteristic, regardless of phenotype. We studied $CD19^+CD5^+CD1d^{hi}IL\text{-}10^+$ Bregs, which have been reported to have potent regulatory function in both murine and human studies.[7,8,S13,S14]

RESULTS

Demographic and Clinical Parameters

During the study period, a total of 25 patients with new-onset LN were recruited. The mean age of the patients was 29.35 ± 9.783 years. There was a female preponderance, with a female:male ratio of