Review

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Critical appraisal and meta-analysis of biological variation estimates for kidney related analytes

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Abstract

Objective: Kidney markers are some of the most frequently used laboratory tests in patient care, and correct clinical decision making depends upon knowledge and correct application of biological variation (BV) data. The aim of this study was to review available BV data and to provide updated BV estimates for the following kidney markers in serum and plasma; albumin, creatinine, cystatin C, chloride, potassium, sodium and urea.

Content: Relevant studies were identified from a historical BV database as well as by systematic literature searches. Retrieved publications were appraised by the Biological Variation Data Critical Appraisal Checklist (BIVAC). Meta-analyses of BIVAC compliant studies with similar design were performed to deliver global estimates of within-subject (CV_I) and between-subject (CV_G) BV estimates. Out of the 61 identified papers, three received a BIVAC grade A, four grade B, 48 grade C, five grade D grade and one was

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not appraised as it did not report numerical BV estimates. Most studies were identified for creatinine (n=48). BV estimates derived from the meta-analysis were in general lower than previously reported estimates for all analytes except urea. For some measurands, BV estimates may be influenced by age or states of health, but further data are required.

Summary: This review provides updated global BV estimates for kidney related measurands. For all measurands except for urea, these estimates were lower than previously reported.

Outlook: For the measurands analyzed in this review, there are sufficient well-designed studies available to publish a trustworthy estimate of BV. However, for a number of newly appearing kidney markers no suitable data is available and additional studies are required.

Keywords: albumin; analytical performance specifications; biological variation; creatinine; cystatin C; electrolytes; kidney markers; meta-analysis; urea.

Introduction

Reduced kidney function correlates strongly with increased morbidity and mortality, and biochemical measurements have a central role in diagnosing and monitoring of kidney disease and the effectiveness of treatment. Essential for interpretation of laboratory test results in these settings is knowledge of the within-subject biological variation (CV_I) of the analytes. Furthermore, data that characterize the CV_I and between-subject biological variation (CV_G) can be used e.g. for the development of analytical performance specifications [1] for internal quality control [2] and for external quality assurance [3, 4].

Serum creatinine and urea are used to assess patients either at risk for kidney disease, or to monitor those having chronic kidney disease (CKD). When reviewing whether a change in serial measurements is potentially of clinical significance or consistent with normal biological variation (BV), it is important to assess the BV in a setting that is comparable to the clinical setting, thus delivering a valid point of reference to enable safe application of the data. This means that if a patient has their kidney function measured every three months, BV data based on weekly measurements may not be applicable. Thus, for the calculation of reference change values (RCV) [1], appropriate CV_I estimates must be applied. The RCV also takes into account the analytical (CV_A) variation of the measurement method to describe the maximum expected change between two measurements at a predetermined level of probability. Changes in serial results over time exceeding the RCV greater than might be expected given relevant estimates of CV_I and CV_A are likely to represent clinical important changes in renal function.

Many other important laboratory applications of BV data also depend upon the availability of estimates of the components of variance that are well characterized and are of sufficient quality and thus transferable to the population to which the laboratory tests are to be deployed. As a consequence, concerns have been raised around the quality of existing BV studies and the veracity of the published BV data estimates that were collated in the historical BV database, last revised in 2014 [5, 6]. With this background the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group on Biological Variation and the Task Group on the Biological Database have developed the recently published Biological Variation Data Critical Appraisal Checklist (BIVAC) [7]. The BIVAC enables an objective assessment of the quality of BV publications by verifying whether all essential elements that may impact upon veracity and utility of the derived BV estimates are present [7, 8]. It thus both provides a tool to review historical data and to assess new studies and has been applied here to enable a systematic review process applied to measurands commonly used in renal medicine.

The aims of the present study were:

- To perform a systematic literature review of BV studies published for the following analytes used in the diagnosis and management of kidney related disorders; albumin, creatinine, cystatin C, chloride, potassium, sodium and urea in serum and plasma,
- To critically appraise relevant publications on these markers by application of the BIVAC [7].
- To review the effect of different study population characteristics and sampling intervals on associated BV estimates, and
- To perform a meta-analysis of BIVAC compliant studies with comparable study design to deliver global BV estimates for kidney related analytes

Materials and methods

The initial source material identified for review was the historical BV database, from which relevant publications on kidney markers were retrieved (references 7–246 in Supplementary Table 1) [5, 6]. Furthermore, multiple systematic literature searches were performed in PubMed, as described in detail in [7] with cut-date Feb 7th, 2020, identifying more than 200 additional publications on BV, 26 of which addressing kidney markers (references

248–483 in Supplementary Table 1). The retrieved publications are identified in this review by the article number they have been assigned in the EFLM BV database [9] (Supplementary. Table 1). When one study included estimates for several different subpopulations, such as for instance based on sex, age or health status, a subscript (a, b, c etc.) was added to the article number as illustrated in Supplementary Table 1. All publications were independently assessed by groups of two assessors, and separately for each measurand and/or subgroup in the same publication. In the BIVAC, each study is appraised with regards to 14 different quality items (QI), including the assessment of pre-analytical procedures, the measurement procedure, applied statistical methods and the presentation of data [7]. The QI may be assigned either an A, B, C or D score, indicating increasing non-compliance. Based on the individual scores for each of the 14 QI, an overall BIVAC grade is given, equal to the lowest score given to any of the QI. When there was disagreement on the score for any QI between the two assessors, all involved assessors reviewed the study until consensus was reached.

The results of the BIVAC review were registered in an Excel-file (Microsoft), together with data on the study population, study design characteristics and associated BV data (see Supplementary Table 2, exemplified for cystatin C). Confidence intervals (CI) for CV_I and CV_G were calculated from the available data at a 95% probability level, using the method described by Burdick [10] and Sahai [11], when the necessary data on the mean number of subjects and samples and estimates of CV_A were reported.

The global CV_I and CV_G estimates were obtained using a meta-analysis approach, which takes into consideration the inverse of each study's CI and weights based on the BIVAC grade; i.e. for an A grade paper multiplied by 4, B grade by 2 and C grade by 1 [5]. When publications reported separate estimates for different subgroups, these estimates were first combined to provide a common estimate by applying the weighted mean on the point estimates and corresponding CIs. For the global CV_I, a percentile bootstrap approach [12] was used to indicate measures of uncertainty.

Only studies reporting BV estimates from healthy adults (age range 18–75 years) were included in the meta-analysis. Further exclusion criteria were applied which included: studies in which CI could not be calculated, sampling intervals shorter than twice per week or greater than one month, and studies only including two samples per subject. Additionally, papers were excluded if they had greatly differing estimates derived from non-standard methodologies (i.e. for albumin–electrophoretic separation, for electrolytes–dry chemistry).

Results

In total, 61 BV publications on kidney markers were included. The highest number of published studies were identified for creatinine (n=48) (Table 1). Overall, 259 BV estimates were identified, when included for all analytes and the different subgroups (Table 1). Of the 61 papers reviewed, only three received a BIVAC A grade [13–15] (Table 1), all of which are recent papers published according to the BIVAC. Four papers received a B grade [16–19] and the majority, 48 papers, were awarded a C grade. The most common reasons for C scores were, in order of frequency, the following: failure to report homogeneity of variances (homoscedasticity, QI 10), failure to report the number data points used to calculate the BV estimates (QI 12), and failure to report and perform appropriate testing for outliers (QI 8). Five papers (110, 220, 270, 271, 309) were given a D score because the time between phlebotomies was not standardized (QI 3) or multiple analyzers were used throughout the study (QI 4). One study was not appraised as it did not report numerical BV estimates (288). For each analyte, CV_I estimates from all the different subgroups with 95% CI for the point estimate are presented (Figures 1–6). The number of studies available to be included in the meta-analysis ranged from three for cystatin C to 11 for creatinine (Table 2). For several of the measurands, in particular for creatinine, meta-analysis derived estimates appeared slightly lower than those reported in the historical BV database [6] (Table 2). However, direct comparisons are difficult due to the lack of measures of uncertainty for the estimates reported in the historical database. Smaller differences were observed for the CV_G estimates (Table 2).

Table 1: Overview of the number of studies identified by the systemic search for each measurand with the associated BIVAC grade and number of subgroups. The subgroups were based on age, sex, health status, sampling interval, and in the case of creatinine analytical method.

Analyte	No. of papers	A	B	C	D	No. of subgroups
Albumin	35	1	1	29	3	56
Creatinine	49	1	4	40	4	78
Cystatin C	11	1	1	8	1	18
Chloride	27	1	1	22	2	33
Potassium sodium	31	1	1	26	2	34
Urea	33	1	2	27	2	40
Total	61[a]	3	4	48	5	259

[a]one paper did not provide a numerical estimate and was therefore not appraised.

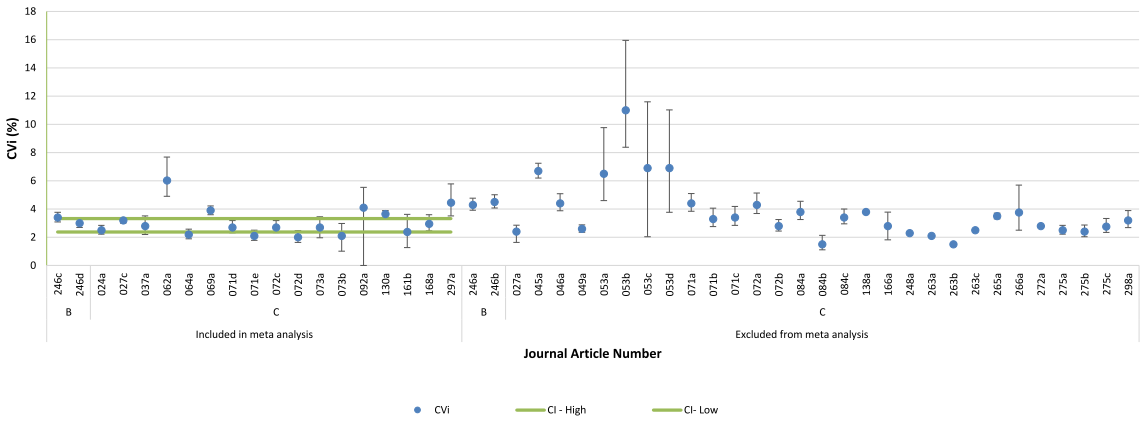


Figure 1: CV_I estimates for albumin. Confidence intervals (CI) for individual papers are shown as error bars around the CV_I data point. Numbers on the *x*-axis represent the reference id number in the EFLM BV database (as listed in Supplementary Table 1) and letters different subgroups. 95% CI limits for the global BV estimate are shown in green.

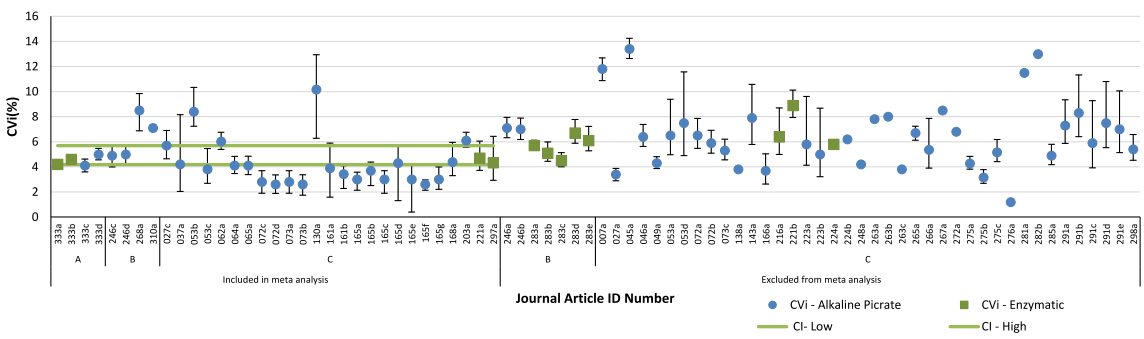


Figure 2: CV_I estimates for creatinine. Confidence intervals (CI) for individual papers are shown as error bars around the CV_I data point. Numbers on the *x*-axis represent the reference id number in the EFLM BV database (as listed in Supplementary Table 1) and letters different subgroups. 95% CI limits for the global BV estimate are shown in green.

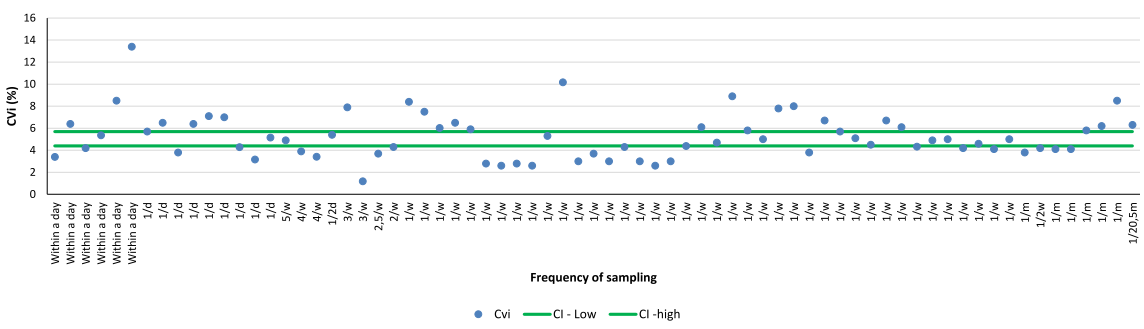


Figure 3: CV_I estimates for creatinine ranked according to sample frequency, based on studies from healthy subjects. In green the upper and lower confidence interval for the meta-analysis derived estimate for the CV_I of creatinine.
Values of *x*-axis are ordered according to sampling interval.
D: day, W: week; m: month.

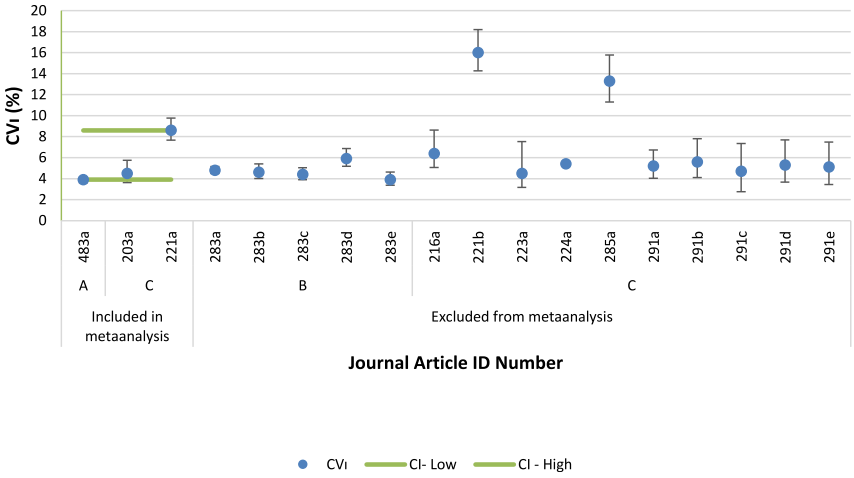
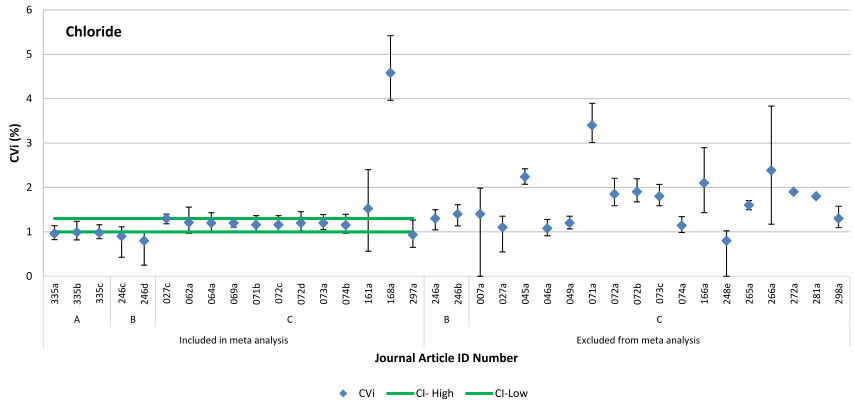
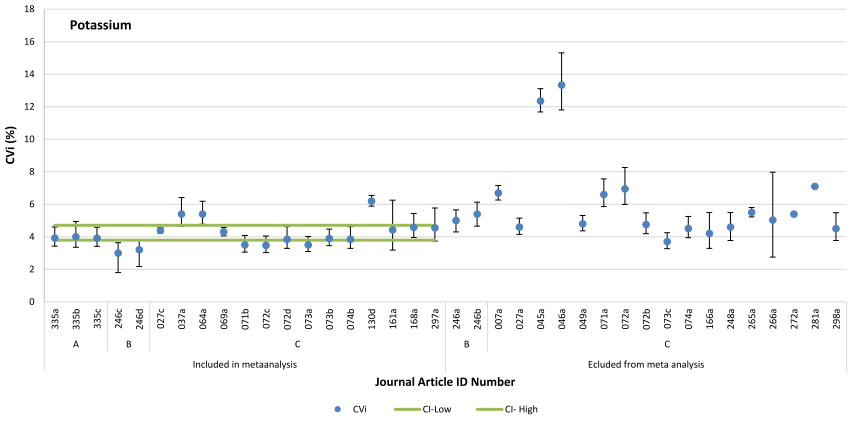


Figure 4: CV_I estimates for cystatin C. Confidence intervals (CI) for individual papers are shown as error bars around the CV_I data point. Numbers on the *x*-axis represent the reference id number in the EFLM BV database (as listed in Supplementary Table 1) and letters different subgroups. 95% CI limits for the global BV estimate are shown in green.





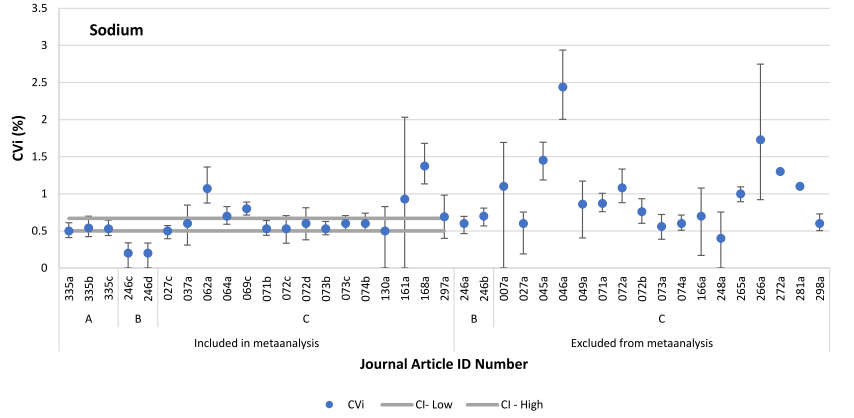


Figure 5: CV_I estimates for electrolytes. Confidence intervals (CI) for individual papers are shown as error bars around the CV_I data point. Numbers on the *x*-axis represent the reference id number in the EFLM BV database (as listed in Supplementary Table 1) and letters different subgroups. 95% CI limits for the global BV estimate are shown in green.

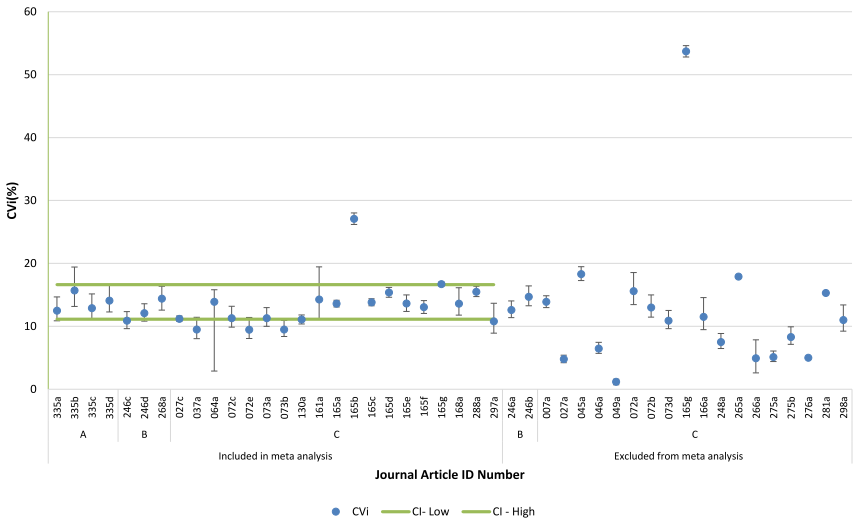


Figure 6: CV_I estimates for urea. Confidence intervals (CI) for individual papers are shown as error bars around the CV_I data point. Numbers on the *x*-axis represent the reference id number in the EFLM BV database (as listed in Supplementary Table 1) and letters different subgroups. 95% CI limits for the global BV estimate are shown in green.

Table 2: Estimates for CV_I and CV_G resulting from the meta-analysis of BIVAC compliant studies of similar study design, accompanied by the estimates reported in the historical BV database.

Analyte	No of studies included in meta-analysis	Meta-analysis based estimates		Historical BV database	
		CV_I (95% CI)	CV_G (95% CI)	CV_I	CV_G
Albumin	10	2.6 (2.2–3.9)	5.1 (2.2–6.3)	3.2	4.7
Chloride	7	1.1 (0.9–2.1)	1.3 (0.8–1.4)	1.3	1.3
Creatinine	11	4.5 (4.4–5.7)	14.2 (7.0–17.4)	5.9	14.7
Cystatin C	3	4.0 (3.9–8.6)	12.1 (12.0–15.1)	5.0	13.0
Potassium	7	4.1 (3.1–5.4)	4.1 (4.1–7.7)	4.6	5.6
Sodium	7	0.5 (0.2–1.4)	1.2 (0.5–1.4)	0.6	0.7
Urea	9	13.9 (9.5–14.4)	19.0 (1.1–22.5)	12.1	18.7

Discussion

The availability of robust and contextually relevant BV estimates is in many ways an essential requirement for delivery and effective application of clinical laboratory results. The BIVAC may be an important improvement in the assessment of BV studies compared with previous approaches [20]. This is because it specifies essential criteria to be met in reported studies to produce reliable estimates of BV. In addition, BIVAC provides a framework that will help those planning and performing BV studies in the future to produce valid estimates of BV that are transportable into clinical practice across populations. Furthermore, they will be immediately suitable to be included as a fully BIVAC compliant study in the online BV database published by the EFLM [9].

Application of BIVAC to historical publications indicates many fundamental issues that are often not addressed. As an example, the classical method for estimating components of BV put forward by Fraser and Harris [21] required testing the raw data for outliers and variance homogeneity prior to further analysis; many authors studying BV appear not to have addressed this requirement. Users may not be aware of these issues, but they are clearly identified and simply communicated when BIVAC is applied to deliver a grading against 14 QIs that address fundamental requirements, as is done in this systematic review. This review identified only three recent BIVAC grade A papers describing BV of analytes important in the diagnosis, management and monitoring of kidney disease. All the other included studies were graded B, C or D because of failure to comply with one or more of the BIVAC 14 QIs. Most of the included studies in our review had been performed in healthy individuals, whereas a smaller number of studies had addressed BV in different health states and age groups, as detailed for all analytes in the following.

Albumin

Most studies had analysed albumin in serum. Only the recently published European Biological Variation Study (EuBIVAS) paper received a BIVAC grade A [15]. Paper 53 was excluded from the meta-analysis because it was visually a clear outlier, possibly related to the use of a different measurement method (electrophoretic separation). Most other studies had applied either an immunoassay, or bromcresol green/purple method.

Four studies performed in non-healthy individuals were identified, including the following disease groups: chronic liver disease, diabetes mellitus, myocardial infarction and renal disease. The CV_I estimates derived from these non-healthy populations did not differ significantly from those reported in healthy subjects.

There are insufficient data to draw any conclusions on whether age influences estimates of CV_I for albumin. However, based on one study (paper 246, with a BIVAC grade C) estimates derived from elderly participants (80–92 years) were slightly higher, with CV_I estimates of 4.0, 95% CI (3.9–4.8) in males and 4.5% (4.1–5.0) in females, as compared to 3.4% (3.1–3.8) and 3% (2.7–3.4) in healthy adults.

Only one study performed in children was identified (paper 248a), which reported a CV_I estimates of 2.3% in a one-day study with samples taken every 2.5 h. However, this represents within-day BV variation, and results may be different in pediatric studies with longer sampling intervals.

Creatinine

The majority of studies had performed analysis of creatinine in serum (n=48 out of 61 papers). A comparison with studies in plasma was not possible, because all studies in plasma were excluded from the meta-analysis for reasons such as using only two samples per subject, having a study duration of only one day or studying non-healthy subjects.

The only A paper (number 333), delivering BV estimates for male and female subgroups assessed with two different analytical methods, reported some of the lowest CV_I values and the narrowest CI [13]. This A-paper is the EuBIVAS, set up by the ELFM Working Group on BV, in which 91 subjects were included and a strict protocol was followed throughout. Due to the narrow CI and the high weight given due to the BIVAC grade, this paper, reporting a CV_I of 4.2% for males and 4.6% for females, has a large influence on the global CV_I estimate (4.5%) provided by the meta-analysis, which is lower than the previously often used estimate of 5.9% derived from the historical BV database. Some B papers and many of the C papers in healthy subjects reported similar or lower CV_I values compared to this A paper; however, the associated CIs are much wider, reflecting the smaller scale study design of these papers, and thus they have less weight on the meta-analysis result (Figure 2).

Regarding the analytical method for creatinine testing, the majority of papers applied alkaline picrate methods, and only five papers used the enzymatic method which is considered to be the state of the art for creatinine testing [22, 23]. There appears, however, to be no difference between CV_I estimates delivered by the two different methods, as exemplified by the EuBIVAS, where BV estimates based on both methods were derived from the same study [14]. Furthermore, six studies performed after the 2009 global restandardisation of creatinine (NIST SRM 967a) were included in the meta-analysis. Because the restandardisation resulted in generally lower creatinine results, BV estimates reported from post-standardisation studies could theoretically be higher than those from pre-standardisation studies. However, no such effects were observed. Excluding the studies performed pre-standardisation did not lead to different BV estimates and meta-analyses performed separately for pre- and post-standardisation studies produced similar BV estimates with overlapping CIs.

Creatinine production is related to muscle mass which changes with age and exercise and theoretically this might impact BV within stratified groups. Two of the reviewed studies delivered BV estimates from children (248a, 270a,b), however, in both within-day BV estimates were reported. Three papers reported studies of elderly subjects (over 75 years old) (papers number 49, 246 and 263). These CV_I estimates (4.3% (paper 49), 3.8% (paper 246) and 7.1% for men; 7.0% for women (paper 263), respectively), appear not to differ significantly from non-elderly, but equality is yet to be proven.

Creatinine is the analyte that has been studied the most in non-healthy populations (Tables 1 and 2). Given that creatinine is most often used to monitor disease, the impact of different pathologies and interventions on BV, such as renal disease, renal post-transplant patients, diabetes mellitus and myocardial infarction is of importance. Some of these disease states appear to have a very distinct effect, for example paper 7 (BIVAC grade C), which was performed in renal post-transplant patients, reported a high CV_I, as does paper 45 (BIVAC grade C), which studied BV in patients with myocardial infarction. However, it is unclear if the patients in these studies were in a stable condition, or how to adequately define a stable condition for these groups of patients.

Many factors, such as sampling intervals, may impact BV estimates. This is important to take into

consideration as creatinine may be measured several times per day for hospitalized patients and less frequently for patients being monitored for CKD progression (e.g. every three months) [22]. Figure 3 illustrates that based on the studies identified in our review, there are no apparent differences in CV_I values between shorter (once per week or less) and longer (once per month or more) sampling intervals.

Cystatin C

Only three papers (203, 221 and 483) out of the 11 identified studies on cystatin C could be included in the meta-analysis. One study received a D-grade because different analytical platforms were used to analyze the samples throughout the study (paper 309). Four were performed in non-healthy subjects, one in children, two had included only two samples per subject and one reported a greatly differing estimate and had been derived with an older version of the turbidimetric analytical method (paper 285) (Figure 4). Only the recent EuBIVAS paper 483 received an A grade [15]. The CV_I estimate based on meta-analysis of 4.0% (3.9–8.6%) is slightly lower than that provided in the historical database (CV_I=5.0%) [6]. This is caused by the exclusion of the eight papers mentioned and the inclusion of one A-grade paper that had a strong influence on the new estimate (Figure 4).

Cystatin C clearly demonstrates the challenges of attempting a meta-analysis for a relatively new analyte with few studies available for inclusion. The analytical methods differ greatly (nephelometry, turbidimetry), and their influence on BV is unknown since it is possible that they measure different measurands. Given the increasing importance of this analyte in renal medicine, further high-quality BV studies for cystatin C are needed.

Chloride

Critical appraisal with the BIVAC identified only the recently published EuBIVAS paper as an A paper (335), and the remaining 26 papers as C. Eight studies fulfilled the criteria to be included in the meta-analysis, which delivered a CV_I estimate of 1.1%, a little lower than that reported in the historical database (1.3%) (Table 2) [6].

Estimates derived from studies performed in non-healthy persons varied, but most showed only slightly higher estimates than the meta-analysis derived point estimates for healthy subjects (Figure 5). Data from one study (168) was a clear outlier on visual inspection of the data. This was a 1970 study using a Technicon electrometry chloride analysis on samples obtained from nine healthy volunteers. Review of the study did not reveal any obvious reason for the highly increased result [24].

As for age, CV_I estimates of 1.3% (1.0–1.5%) and 1.4% (1.1–1.6%%) for elderly men and women respectively were reported in paper 246, which did not appear different from those in non-elderly adults (Table 2).

Potassium and sodium

The estimates for the BV of sodium and potassium in serum and plasma delivered by this meta-analysis were slightly lower than those reported by the historical database [6] (Table 2), although the historical values were within the CI found in this study.

Based on paper 246, old age (>75 years) did not appear to influence the CV_I of potassium and sodium. Two studies had assessed BV of these electrolytes in children (248, 270a,b), but the study 248 was a within-day study and study 270 included only two samples per subject.

Focusing on studies of non-healthy subjects; two papers (72 and 74) reported data for sodium and potassium that did not differ from the estimates derived from healthy individuals. This was, however, not the case for the papers studying patients with renal transplantation (paper 7), myocardial infarction (paper 45) and renal disease (paper 46) where higher CV_I values than healthy subjects were observed. These observations were evident for both sodium and potassium studies (Figure 5).

Two studies performed in healthy adults reported results for sodium based on within-day sampling (paper 46; CV_I 2.4%, and 266; CV_I 2.2%) that were not within the 95% CI for the point estimate derived from our meta-analysis (Table 2). This might be relevant for clinical settings in which high frequent analysis of electrolytes is performed.

Urea

Within-day studies BV of urea (papers 27, 248), performed in healthy individuals, demonstrated significant differences in CV_I (4.8 and 7.5%) as compared to the estimates based on biweekly to monthly samplings (Figure 6). As with creatinine, urea is frequently measured in patients with differing sampling intervals depending on the clinical setting, and this may need to be taken into account when monitoring patients. However, standardized studies are required to

clearly conclude on this issue. The meta-analysis derived CV_I estimate of 13.9% (95% CI; 9.5–14.4) is highly influenced by the estimate from the EuBIVAS A-graded paper, and this may be the main reason for the meta-analysis estimates being slightly higher than the estimate reported in the historical database (median CV_I=12%) [6].

Opportunities for additional research

Although Kashani et al. [25] state that there are also other important biomarkers of acute kidney injuries, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM-1), liver-type fatty acid-binding protein (L-FABP), interleukin 18 (IL-18), insulin-like growth factor-binding protein 7, tissue inhibitor of metalloproteinase 2 (TIMP-2) and calprotectin, they have not been included in this review because none or only one study on BV was available for these analytes [18]. All these markers are candidates for early detection of acute kidney injury and appropriate BV studies are therefore warranted.

Electrolyte measurements also offer an opportunity for additional research. Electrolytes are commonly measured in intensive care settings multiple times per day, often as a standard part of blood gas analysis. Because of the tight regulation of sodium concentration within one patient, there is a risk of interpreting analytical variation as a clinically significant change. The only papers that report within-day variation arrived at slightly higher estimates for CV_I. For sodium in intensive care unit patients, appropriately powered BIVAC compliant studies, or studies based on a big data design, are needed to deliver data on hour-to-hour BV of sodium.

Conclusions

Extensively researched measurands such as the electrolytes, creatinine and urea have produced many papers with comparable values for BV components. The recently published BIVAC compliant EuBIVAS grade A study has confirmed the accuracy of these data, and further A studies do not appear necessary. However, for cystatin C for instance, more data are required.

Some data indicate that BV estimates may be different in some groups of non-healthy subjects as compared to the healthy population. However, proving equality between a group of healthy and non-healthy subjects may require a fully BIVAC compliant study that directly compares both groups.

There are few studies of BV in children and the elderly for most of the measurands. This and differing clinical scenarios are drivers for delivery of appropriately designed BIVAC compliant BV studies for a range of old and new measurands; targets should include elderly, children, specific disease states, analytes in clinical scenarios where within day BV and/or long term BV are required, analytes with few, conflicting or no associated BV data.

Clinicians and Laboratory Medicine Specialists should recognize BV data as reference data that might vary in quality and applicability to their local populations and clinical scenarios. Many BV estimates are the result of well characterized rigorous studies reproduced by multiple groups around the world, but many target measurands appear to require more extensive study. The recent publication of the new EFLM BV database [9] updated with newly published studies, combined with the future delivery of new studies that appropriately powered and BIVAC compliant will provide a useful tool for better healthcare by enabling effective application of appropriately specified laboratory test.

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