Research Article

Murat Keleş*

Evaluation of the clinical chemistry tests analytical performance by using different models and specifications

Klinik kimya testlerinin analitik performansının farklı modeller ve spesifikasyonlar kullanılarak değerlendirilmesi

https://doi.org/10.1515/tjb-2018-0250
Received June 18, 2018; accepted February 17, 2019; previously published online November 29, 2019

Abstract

Background: The importance of managing analytical quality in clinical laboratories is known. Goal-setting models are critical for analytical quality management, along with correctly implemented error models. However, the methods used to determine analytical performance and more importantly, the relevant analytical quality goals are open to discussion. Our aim was to compare the analytical performance characteristics of routine clinical chemistry tests with different goal-setting models which was proposed by various establishments. In addition, to provide a perspective to Turkish total analytical error (TAE) circular letter that compulsory to calculate from 2016.

Materials and methods: This study was performed by the data obtained from the internal and external quality control of clinical chemistry tests which were measured by Roche Cobas c501 biochemistry analyzer. TAE calculated with TAE% = 1.65 ×(CV%) + Bias% formula. Nordtest uncertainty model was used in the calculation of measurement uncertainty (MU). In this context, total analytical error was evaluated with biological variation (BV), RCPA, CLIA and Turkish allowable total error (ATE) goals. Measurement uncertainty was evaluated with only permissible measurement uncertainty (pU%) goal.

Results: In our study, RCPA goals are the most stringent, followed by the $BV_{EuBIVAS}$, BV_{Ricos}, pU%, CLIA and finally the ATE_{Turkey} goals coming in last. In cumulatively, $BV_{EuBIVAS}$ goals were 18.3% lower than BV_{Ricos} for evaluated parameters.

Conclusion: The balance between applicability and analytical assurance of goals should be well ensured when determining goal-setting models. Circular letter (2016/18) creates awareness to the analytical quality management but still open to development. Biological variation dependent total allowable error model never designed to be used as benchmarks for measurement uncertainty and it is not methodologically appropriate for assessing measurement uncertainty which was estimated by the Nordtest method. Also considered that, the use of "permissible MU" is more methodologically appropriate in the evaluation of measurement uncertainty.

Keywords: Total analytical error; Measurement uncertainty; Allowable total error; Analytical quality management; Clinical Chemistry.

ÖZ

Amaç: Klinik laboratuvarlarda analitik kalite yönetiminin önemi bilinmektedir. Analitik kalite yönetiminde doğru uygulanan hata modelleriyle birlikte amaca uygun olarak seçilen hedef belirleme modelleri kritik bir öneme sahiptir. Ancak, analitik performansı belirlemek için kullanılan yöntemler ve daha da önemlisi, ilgili hedef belirleme modelleriyle alakalı tartışmalar günümüzde devam etmektedir. Çalışmamızda, rutin klinik kimya testlerinin analitik performans karakteristiklerini çeşitli kuruluşlar tarafından önerilen farklı hedef belirleme modelleri ile karşılaştırmayı amaçladık. Ayrıca, ülkemizde 2016 yılından itibaren uygulanmaya başlanan toplam analitik hata modeline bir bakış açısı sağlamayı amaçladık.

***Corresponding author: Murat Keleş,** Bursa Halk Sağlığı Laboratuvarı, Esentepe Mahallesi İstiklal Caddesi Ağaçlı Sokak No: 17 Nilüfer/Bursa, Bursa, Turkey,
e-mail: muratkeles23@gmail.com.
https://orcid.org/0000-0003-2251-6406

Gereç ve Yöntem: Çalışmamız, Roche Cobas c501 biyokimya analizörü kullanılarak elde edilen iç ve dış kalite kontrol verileriyle gerçekleştirilmiştir. Toplam analitik hata TAH% = 1.65 × (CV%) + Bias% formülü ile hesaplanmıştır. Ölçüm belirsizliği Nordtest kılavuzuna bağlı kalınarak hesaplanmıştır. Toplam analitik hata biyolojik varyasyon (BV), RCPA, CLIA ve Türkiye izin verilen toplam hata hedefleriyle, ölçüm belirsizliği ise sadece ilgili kalite hedefi olan Alman Klinik Kimya ve Laboratuvar Tıp Derneği izin verilebilir ölçüm belirsizliği (%pU) ile değerlendirildi.

Sonuç: Çalışmamızda, en zorlayıcı hedef belirleme modelinin RCPA olduğu ve bunu sırasıyla $BV_{EuBIVAS}$, BV_{Ricos}, %pU, CLIA ve son olarak da Türkiye izin verilen hata genelgesi sınırlarının olduğunu gözlemlendi. Biyolojik Varyasyon temelli modeller incelendiğinde, $BV_{EuBIVAS}$ hedeflerinin değerlendirilen parametreler için BV_{Ricos}'dan kümülatif olarak %18,3 oranında daha zorlayıcı hedefler belirlediği gözlemlendi.

Tartışma: Analitik kalite hedefleri belirlenirken, hedeflerin uygulanabilirliği ile analitik güvencesi arasındaki denge iyi sağlanmalıdır. İzin verilen toplam hata genelgesi (2016/18), ülkede analitik kalite yönetiminde farkındalık sağladığı, ancak yine de gelişime açık noktaların bulunduğu düşünülmektedir. Biyolojik varyasyona bağlı toplam izin verilen hata modellerinin ölçüm belirsizliğini değerlendirmek için bir kriter olarak tasarlanmadığı ve Nordtest yöntemiyle hesaplanan ölçüm belirsizliğini değerlendirmek için metodolojik olarak uygun olmadığı düşünülmektedir. Ölçüm belirsizliğinin değerlendirilmesinde "İzin verilebilir ölçüm belirsizliğinin" kullanılmasının metodolojik olarak uygun olduğu düşünülmektedir.

Anahtar Kelimeler: Toplam Analitik Hata; Ölçüm Belirsizliği; İzin Verilen Toplam Hata; Analitik Kalite Yönetimi; Klinik Kimya.

Introduction

Clinical laboratories play a significant role in the diagnosis, treatment and follow-up of diseases and expected to provide the highest possible quality of service. Therefore, quality of test results is fundamental for clinical laboratories. But how to define the required level of quality is a question that has been subject to much debate. Clinical laboratories generally use total analytical error (TAE), bias, coefficient of variation (CV) and measurement uncertainty (MU) as bases to determine analytical performance characteristics (APC) for quality management in the analtyical phase [1].

Total analytical error provides a quantitative approach to determine the adequacy of method performance. In the indirect conventional TAE model, bias and imprecision are added linearly to obtain a value $TAE = bias + k \times CV$ [2].

Measurement uncertainty is a non-negative parameter characterizing the dispersion of the values attributed to assessed amount [3]. There are two main approaches in estimating measurement uncertainty, the bottom-up and the top-down. Guide to the expression of uncertainty in measurement (GUM) mainly describes a bottom-up approach to estimating MU, in which an uncertainty budget for a given measurement procedure is assembled by identifying all potential sources of uncertainty and attributing to each an uncertainty estimate as an SD obtained from experimentation or available information [4]. The top-down approach estimates the MU, typically by evaluation of quality control (QC) data or method verification experiment data [5]. To managing analytical quality, goal-setting models should be used which was defined for these analytical performance characteristics.

A consensus conference was held in Milan in 2014 to set analytical performance specifications (APS), and proposed three models [6].

- Model 1. Based on the effect of analytical performance on clinical outcomes; this model is ideal for APS but difficult to implement, and impractial except for a few measurands such as HbA1c, cholesterol, etc.
- Model 2. Based on components of biologic variation of the measurand; in this model there is no direct link to the clinical use of the test, but uses "signal-to-noise" ratio between analytical variation and biological variation.
- Model 3. Based on state-of-the-art models; State-of-the-art models was defined by various establishments – most of PT/EQA programs – and are expressed in the form of allowable total error (ATE). Among the State-of-the-art models, CLIA is most widely used for ATE and written into law with no documentation of origin. It was updated after a long time in 2019 [7]. This model should be temporarily used for measurands that cannot be included in model 1 or 2.

As mentioned above, goal setting models have a central position in the evaluation of analytical performance. According to the Milan hierarchy, the most reasonable model for clinical laboratories is based on components of biological variation (BV), except some analtytes. However, there is also the need to consider availability of reliable biological data to evaluation of analitical performance. Therefore, after the Milan concensus EFLM (European Federation of Clinical Chemistry and Laboratory Medicine) has handled biological variation data to update. Biological Variation Working Group (WG-BV) which established by the EFLM was developed the critical appraisal checklist for studies of biological variation. Ricos BV data was last updated in 2014 by the Spanish Society of

Laboratory Medicine [8], but a systematic review of those publications revealed that they do not meet all of the requirements of the recently published EFLM checklist for BV studies [9]. For these reasons, EFLM Working Group on Biological Variation [10] has designed and implemented the European Biological Variation Study (EuBIVAS) to deliver BV estimates based on best methodological practice and contemporary analytical technologies [11]. The preliminary data of study has started to come and evaluation has been made by already available EuBİVAS data which presented in EFLM website [11–13].

The international standard ISO 15189:2012 requires that "Clinical laboratories shall determine the measurement uncertainty for each measurement procedure in the examination phases" [14]. But methods to calculate "permissible MU" procedures based on MU theory are poorly developed and the ISO standard does not clarify how and within which limits the measurement uncertainty should be. The most common concept for establishing permissible uncertainty limits is to correlate them with foremost, biological variability dependent ATE goals. However, the important point here is to evaluate the selected performance characteristics with methodologically appropriate goal-setting models. The work on BV goals was begun in the US by Cotlove et al. in 1970 [15]. Fraser and Hyltoft Petersen proposed to combine both imprecision and bias in a single expression (95% acceptance range for each laboratory from the target value) in 1993 by using Westgard's linear addition model, and it was later associated with the Ricos biodatabase [16]. As mentioned above, bias and imprecision are added linearly to obtain BV dependent ATE and never designed to be used as benchmarks for measurement uncertainty. In this context, working group (guide limits) of the DGKL (German Society of Clinical Chemistry and Laboratory Medicine) under the leadership of Haeckel R. has proposed a new concept for MU targets "Permissible limits for uncertainty of measurement in laboratory medicine" in Milan consensus. This proposal is based on a non-linear relationship between biological and analytical variation [17].

In the framework of these discussions "Total Analytıcal Error Circular Letter (2016/18) for Medical Laboratories" was published in Turkey [18]. In circular letter, total allowable error limits are defined based on "Minimum analytical quality specifications for Spanish EQAP organizers study" which conducted by Ricós et al. [19].

In this study, we aim to evaluate the analytical performance of clinical chemistry tests that were compulsory to calculate in circular letter (2016/18) by using TAE and MU as well comparing them to related analytical performance goals (BV_{Ricos}, $BV_{EuBIVAS}$, CLIA, RCPA, DGKL's permissible MU (pU%) and ATE_{Turkey}).

Materials and methods

Roche Cobas c501 biochemistry analyzer was used to measure Albumin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), creatinine, chloride, cholestrol, glucose, high density lipoprotein (HDL), lactate dehydrogenase (LDH), urea, potassium, sodium, total protein and triglyceride. The internal quality control (IQC) data of 15 clinical chemistry parameters between November 2017 and January 2018 were used for MU and TAE calculation. Two levels of internal control materials were used from Roche Diagnostic, PreciControl ClinChem Multi 1 (lot no: 186373) and PreciControl ClinChem Multi 2 (lot no: 186387). Twelve data points (February 2017 to January 2018) used from EQC (Randox International Quality Assessment Scheme), which is performed once a month to estimate bias. EQC results for all analties were within the acceptable limits and no exclusion was made.

Analytical performance characteristics

Total analytical error

TAE was calculated by following formulas, using IQC data to estimate within-laboratory reproducibility, and EQC data to estimate bias for each analyte.

$$CV\% = (SD / x_{mean}) \times 100 \quad (1)$$

$$Bias\% = \frac{1}{n}\left(\sum_{i=1}^{n} \frac{(\text{laboratory result} - \text{mean of peer group}) \times 100}{\text{mean of peer group}}\right) \quad (2)$$

$$TAE\% = Bias\% + (1.65 \times CV\%) \quad (3)$$

Measurement uncertainty

The six-step measurement uncertainty calculation model was used, based on the European accreditation guide/12, Eurolab Technical Report No:1/3 and ISO/ DTS 21748 Guide/8 defined in the Nordtest guide [20].

- Step 1: Defining the Measurand;
- Step 2: Imprecision of Measurement;
- Step 3: Bias of Measurement;
- Step 4: Converting the components to a standard uncertainty;

- Step 5: Calculate combined standard uncertainty;
- Step 6: Calculate Expanded Uncertainty / Expression of MU.

Expanded MU is calculated as the following formula according to the Nordtest guide (with k:1.96, for a coverage probability of 95%) considering the within-laboratory reproducibility and the RMS_{bias} value, respectively as the random and systematic variation components.

$$U = k \times \sqrt{\text{imprecission}^2 + \text{RMSbias}^2} \quad (4)$$

Analytical performance goals

Total allowable error

ATE values of evaluated parameters were taken from the Clinical Laboratories Improvement Act (CLIA), Royal College of Pathologists of Australasia (RCPA) and Turkish ATE circular letter. BV_{Ricos} goals were taken from Westgard's website which presents Ricos studies [8, 21, 22]. $BV_{EuBIVAS}$ goals were taken from EuBIVAS studies currently published on EFLM website [13].

Permissible limits of measurement uncertainty

This scientifical approach was based on CV_E (Empirical Coefficient of Variation) which is derived from the reference interval as a surrogate of the biological variation [17]. Appropriately with this proposal, we used the reference ranges of the Turkish population which was made by Ozarda et al. [23]. Permissible limits of measurement uncertainty was performed by an Excel program (dependent log-normal distribution) which is available on the home page of the German Society of Clinical Chemistry and Laboratory Medicine [24]. In our study, we used EQUAS targets for MU because the RMSD model is unique to the German quality management.

Results

Total analytical error was evaluated by different quality goals; According to ATE_{Turkey} all performance goals were achieved. Albumin, chloride, sodium and total protein were found higher according to both of $BV_{EuBIVAS}$ and BV_{Ricos} goals. Solely, creatinine was higher than the acceptable limit of $BV_{EuBİVAS}$ differently to BV_{Ricos}. Albumin, AST, chloride, creatinine, sodium and total protein values were found unacceptable when compared to RCPA goals. Sodium was within acceptable limits only for ATE_{Turkey}, when all quality targets were evaluated.

Measurement uncertainty was evaluated by related quality goal; Albumin, chloride uncertainties were found unacceptable in both levels, and sodium was found unacceptable in only level 2 according to pU% goals. The CV% and bias values are presented in Table 1. Analytical performance characteristics of tests are shown in Table 2. ATE% values of the tests according to BV_{Ricos}, $BV_{EuBIVAS}$, CLIA,

Table 1: Results of CV% values calculated from IQC data, Bias% and RMS_{Bias}% estimated from EQC data.

	$CV_{Level\ 1}$ (%)	$CV_{Level\ 2}$ (%)	Bias (%)	RMS_{Bias} (%)
Albumin	3.07	3.50	0.87	2.41
ALT	2.93	3.14	2.98	5.34
ALP	3.46	3.66	1.35	4.48
AST	4.50	4.30	5.30	7.62
Chloride	1.93	1.50	0.93	2.88
Cholesterol	2.26	2.17	0.83	1.88
Creatinine	4.57	4.49	0.83	2.95
Glucose	2.15	2.09	1.56	2.40
HDL	2.60	2.45	1.02	4.70
LDH	2.23	1.89	2.36	4.79
Potassium	1.68	1.78	0.72	1.60
Total protein	1.99	3.03	0.27	2.21
Sodium	1.82	1.35	0.68	1.24
Triglyceride	3.47	3.80	0.10	3.52
Urea	3.29	2.75	1.40	2.07

RMS_{Bias}, Root Mean Square Bias; CV%, coefficient of variation.

Table 2: Analytical performance characteristics of tests.

	Total analytical error (%)		Measurement uncertainty (%)	
	Level 1	Level 2	Level 1	Level 2
Albumin	5.94	6.65	7.65	8.34
ALT	7.82	8.17	11.95	12.15
ALP	7.07	7.39	11.11	11.34
AST	12.73	12.41	17.35	17.16
Chloride	4.12	3.41	6.80	6.36
Cholesterol	4.57	4.43	5.77	5.64
Creatinine	8.38	8.24	10.67	10.53
Glucose	5.12	5.00	6.33	6.24
HDL	5.31	5.07	10.52	10.39
LDH	6.04	5.48	10.37	10.10
Potassium	3.50	3.65	4.56	4.69
Total protein	3.55	5.26	5.83	7.36
Sodium	3.70	2.91	4.33	3.60
Triglyceride	5.84	6.37	9.69	10.15
Urea	6.85	5.94	7.63	6.75

Table 3: ATE% values of the tests according to BV_{Ricos}, $BV_{EuBIVAS}$, ATE_{Turkey}, CLIA, RCPA and pU%.

Tests	BV_{Ricos} (%)	$BV_{EuBIVAS}$ (%)	ATE_{Turkey}		CLIA 2019	RCPA		pU%
			ATE%	CV%		Lower goal	Upper goal	
Albumin	4.0	3.5	15	7.5	8%	2.0 g/L	6%	8.1
ALT	27.5	15.3	20	10	20%	5.0 U/L	12%	23.9
ALP	12.0	10.6	30	10	20%	15 U/L	12%	19.5
AST	16.7	13.5	20	10	20%	5.0 U/L	12%	17.9
Chloride	1.5	1.2	9	5	5%	3 mmol/L	3%	5.2
Cholesterol	9.0	8.8	11	5	10%	0.3 mmol/L	6%	15.9
Creatinine	8.9	7.4	20	10	10%	0.09 mg/dL	8%	12.8
Glucose	6.9	5.9	11	5	8%	0.4 mmol/L	8%	12.4
HDL	11.6	11.6	30	10	20%	0.2 mmol/L	10%	15.9
LDH	11.3	7.5	21	10	15%	30 U/L	15%	14.7
Potassium	5.6	4.9	9	5	0.3 mmol/L	0.2 mmol/L	5%	10.3
Total protein	3.6	3.4	15	7.5	8%	3.0 g/L	5%	9.0
Sodium	0.7	0.7	9	5	4.0 mmol/L	3 mmol/L	2%	4.0
Triglyceride	26.0	26.5	15	7.5	15%	0.2 mmol/L	12%	25.0
Urea	15.5	17.3	15	7.5	9%	0.5 mmol/L	12%	19.2

BV, Biological variability; pU%, permissible expanded uncertainty; ATE, allowable total error.

Table 4: Analytical performance characteristics were compared with related analytical performance goals.

Tests	BV_{Ricos} (%)[a]		$BV_{EuBIVAS}$ (%)[a]		Turkey ATE (%)[a]		CLIA[a]		RCPA[a]		pU%[b]	
	Lvl 1	Lvl 2	Lvl 1	Lvl 2	ATE[c]	CV%	Lvl 1	Lvl 2	Lower	Upper	Lvl 1	Lvl 2
Albumin	×	×	×	×	✓	✓	✓	✓	✓	×	✓	×
ALT	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ALP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AST	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	✓
Chloride	×	×	×	×	✓	✓	✓	✓	×	×	×	×
Cholesterol	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Creatinine	✓	✓	×	×	✓	✓	✓	✓	✓	×	✓	✓
Glucose	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HDL	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LDH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Potassium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total protein	✓	×	×	×	✓	✓	✓	✓	✓	×	✓	✓
Sodium	×	×	×	×	✓	✓	×	✓	×	×	×	✓
Triglyceride	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urea	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]Compared with total analytical error. [b]Compared with measurement uncertainty. [c]Level 1 and Level 2 evaluated in same column.
✓, Acceptable. ×, Unacceptable.

RCPA, ATE_{Turkey} and pU% are depict in Table 3. Analytical Performance Characteristics are evaluated to different analytical performance goals in Table 4.

Discussion

The importance of analytical performance assessment within the scope of quality management in clinical laboratories is known. From the Aspen conference until today, there is an ongoing contest on proper specifications for analytical quality management and debate on MU and TAE was revitalized in the Milan consensus. After the consensus, the EFLM Task and Finish Group was established and began to deal with unresolved issues that required further development [25]. TAE has been used in worldwide clinical laboratories for many years because of its applicability and simple mathematical model. Since, the

international standard ISO 15189:2012 specifies that "Clinical laboratories shall determine the Measurement Uncertainty for each measurement procedure in the examination phases", measurement uncertainty is gaining momentum globally.

There are two approaches in estimating MU, in fact, the bottom-up approach is impractical and its routinely use in clinical laboratories is currently utopian aside from experimental studies. The ISO guide to the expression of uncertainty in measurement also endorses the top-down approach based on measurement of control samples [26]. Therefore, the top-down approach is unrivaled to determine measurement uncertainty in clinical laboratories, although it lacks standardization for calculation. CLSI (The Clinical Laboratory Standards Institute) was released "C51A Expression of Measurement Uncertainty in Laboratory Medicine" document in January 2012 [27]. Currently, there is no requirement under CLIA to estimate measurement uncertainty for US laboratories, but this document has been drawn attention to the measurement uncertainty.

The main difference between TAE and MU is the concept of bias and how to deal with it [28]. But both the top-down MU and TAE do not provide guidance on how to deal with bias, and the only difference is the evaluation of same data with different mathematical concepts. Regardless of the debate on the pros and cons of the TAE and MU, it is first and foremost necessary to implement the analytical performance characteristies correctly, and secondarily its evaluation by appropriate goal-setting models. Goal-setting models are more sophisticated and important matter that sets limits for analytical quality and this subject will be discussed below.

We evaluated our study in two subgroups. First, comparison between TAE and MU; in our study, measurement uncertainty was found to be higher than the total analytical error in all analytes. This may be due to use of the RMS_{Bias} (Root Mean Square) method in estimating the bias in measurement uncertainty. In contradistinction to measurement uncertainty, total analytical error uses "Mean Bias Error" to estimate bias. Methodologically, RMS_{Bias} is a system that highly punishes deviations from the target, so gives more accurate results in a large number of data sets, and is equal to variance in unbiased systems. It is important to distinguish between short-term (within day) bias and long-term (several months) bias in clinical chemistry laboratories. Many effects causing within-day bias become random effects in the long term. Therefore, during extended periods (weeks and months) of observations many bias components vary and thus increasingly contribute to the random error component (intermediate precision) [29]. However, when bias evaluation is made from External Quality Control data by using RMS_{Bias} method, considered that it causes excessive bias estimation by disproportionate punishment of short-term (within day) bias, because each bias value is obtained from only single EQC measurement which is open to within-day variations. In this direction, in our study, observed that RMS_{Bias} values were higher than the TAE's "Mean Bias Error" for all parameters. Within-day variations are added as a systematic component in a disproportionate frame in Nordtest method so that this situation causes overestimation of MU. Surely, the best way to estimate bias is to use the reference material/reference method. But for many analytes, there is a no reference method or material and it is difficult to reach for laboratories. In addition, it is thought that the use of the bidirectional coverage factor as a result of the systematics of measurement uncertainty contributes to this difference.

Secondarily, APC's were evaluated according to different goal setting models. In our study, RCPA goals are the most stringent, followed by the $BV_{EuBIVAS}$, BV_{Ricos}, pU%, CLIA and finally the Turkish total allowable goals coming in last. In our study when we make a comparison between $BV_{EuBIVAS}$ and BV_{Ricos} goals, both specifications were flaged in albumin, chloride, sodium and total protein. Differently, creatinine was unacceptable for $BV_{EuBIVAS}$ in both levels, and total protein was borderline acceptable for BV_{Ricos} in lower level. We were observed that $BV_{EuBIVAS}$ goals slightly stringent than BVRicos goals when two APS were evaluated. In cumulatively, $BV_{EuBIVAS}$ goals were 18.3% lower than BV_{Ricos} for evaluated parameters. BV_{Ricos} was more tight in only triglyceride and urea analyties.

If we evaluate the some notable measurands individually in the framework of Turkish Total Analytıcal Error Circular Letter; in our study, Creatinine (Cr) was within the permissible limits of BV_{Ricos}, CLIA, ATE_{Turkey} and pU% goals. Creatinine analytical performance was unacceptable for $BV_{EuBIVAS}$ in both levels and borderline-unacceptable for RCPA in upper level control, so these specifications informed laboratory professionals to check and improve the analytical quality. Although creatinine was within the goals according to most of quality targets, the remarkable point is that ATE_{Turkey} goal is 20% for creatinine. An acceptable ATE for Cr yields an ATE for corresponding eGFR with various consequences. If we assume that a patient has a 100 µmol/L Cr value, according to this goal Cr values between 80 and 120 µmol/L would be acceptable for this sample. For a 75 years old non African-American male acceptable eGFR by using CKD-EPI corresponds to ranging between 50.7 and 82.7 mL/min/1.73 m^2. Hence, wide goals may complicate the diagnosis of chronic kidney disease for clinicians. In this context, the analytical quality goal

has been reduced from 15% to 10% for creatinine in CLIA 2019 document [7].

Sodium, chloride, calcium, etc. are rigorously controlled physiologically. Therefore, Ricos BV model has been criticized over years for biologic goals are too demanding. In our study, all goal-setting models were flagged for sodium, except the ATE_{Turkey}. If this situation assessed detailedly, ATE_{Turkey} analytical error limit is 9% for sodium. Hypothetically, a hyponatremic patient with a sodium value 134 mEq/L is likely to be reported as 146 mEq/L and falsely diagnosed as hypernatremic within these error limits and vice versa. Strikingly, this limit is greater than the reference interval. Also, Turkish goal is about five times higher than desirable BV goals for total protein and three times higher than minimum BV goals. Albumin goal is about three times higher than desirable BV goals. Only, ALT and triglyceride were observed to be lower than the desirable level of BV goals by the reason of relatively large biological variation.

There are some major disparities in tolerance limits recommended by various organizations. The methods used to set goals are one of the most important factor in this difference. One end of the scale consists of BV-dependent strict model using the "signal-to-noise" ratio, while the other end consists of "state of art" models designed for use only in external quality assessment programs. According to the study of "Minimum analytical quality specifications for EQAP organizers study" which is the basis for determining ATE_{Turkey} goals; as author suggests, "These consensus minimum quality specifications are the lowest level of quality required and only applied for inter-laboratory comparisons. They never replace the specifications based on biological variability and for intra-laboratory quality management, models higher in the Stockholm hierarchy are to be preferred" [19]. The balance between the applicability and analytical assurance of goals should be well established. While tight limits could cause difficulties in terms of applicability, wide limits could create quality assurance problems. In addition, it is important that the limits contribute to the development of existing methods by forcing in vitro diagnostic (IVD) manufacturers.

Consequently, considered that circular letter (2016/18) creates awareness to the analytical quality management but still open to development. The circular letter (2016/18) should be seen as the first step in the implementation of analytical quality management in country and thought that it will develop with the spread of practice. In this direciton, national standardization and harmonization studies have been started in order to increase the reliability of the test results and analytical quality [30].

When make a general assessment for analytical performance spesifications, it is a pragmatic apporach to apply the same quality standard criteria to all analytes in a program. BV dependent models allows to switch quality goals (desirable to optimal or desirable to minimal) for each analyte in the program, if a few analytes do not qualify at the desirable level or the targets are too wide. In addition, for analytes that do not meet the BV model's minimum goals, laboratories can temporarily reduce the quality standard to state-of-the-art. In this manner, if different quality criteria applied to each analytes, we can aware of the need for possible improvements for analyte-based. Therefore, considered that the utilization of analyte-based goals in accordance with quality expectations of clinical laboratories by following Milan hierarchy is the most reasonable way. This should be viewed as a dynamic situation that needs to be changed by improving analytical performance.

Also an issue that should not be forgotten is that low assay bias or imprecision compared to biological variation criteria can be viewed as the highest level in the hierarchy, as further improvements will not change clinical decision-making. The same may not be true for ATE based on biological variation [22]. An acceptable ATE may hide an unacceptable level of its constituents. For example, if an assay has very low imprecision compared with within-subject biological variation, a significant bias may not be flagged by total error limits applied to the data. However, in our study APC was compared with goals that were expressed by a single value, separately performance was not evaluated.

"Permissible limits for uncertainty of measurement" is a new topic and specification for clinical laboratories. The use of BV-dependent total allowable error goals for assessment of measurement uncertainty leads to comparison of data obtained by different methodologies, thus creating question marks. In accordance with the basic of measurement uncertainty methodology, only if uncertainty values calculated with assumption that bias eliminated or not existence could evaluated with the BV-dependent allowable imprecision. Therefore, measurement uncertainty which was estimated with Nordtest methodology evaluated only with relevant quality goal "permissible MU" in our study. "Permissible MU" was flagged for the same analytes as BV goals, except creatinine and total protein. It was also observed that it presents more reasonable targets than BV goals for physiologically tightly controlled analytes. Theoretically similar to our study, six sigma (based on CLIA goals), Ricos BV imprecision/bias specifications and measurement uncertainty (based on pU% goals) were compared by Westgard and published in his website [31].

He was stated that "permissible MU" is the most stringent specification in evaluated models. As a result, considered that it is appropriate to apply in the evaluation of measurement uncertainty.

References

1. Westgard JO. Useful measures and models for analytical quality management in medical laboratories. Clin Chem Lab Med 2016;54:223–33.
2. Westgard JO, Carey RN, Wold S. Criteria for judging precision and accuracy in method development and evaluation. Clin Chem 1973;20:825–33.
3. JCGM 200: 2008 International vocabulary of metrology – basic and general concepts and associated terms (VIM). Geneva: International Organization for Standardization, 2008:104. (accessed May 5 2018).
4. White GH. Basics of estimating measurement uncertainty. Clin Biochem Rev 2008;29(Suppl 1):S53–60.
5. Barwick V. Evaluatig measurement uncertainity in clinical chemistry. UK National Measurement Systems: Report no: LGC/R/2010/17, 2012.
6. Sandberg S, Fraser CG, Horvath AR, Jansen R, Jones G, Oosterhuis W, et al. Defining analytical performance specifications: consensus statement from the 1st strategic conference of the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2015;53:833–5.
7. Clinical Laboratory Improvement Amendments of 1988 (CLIA) Proficiency Testing Regulations Related to Analytes and Acceptable Performance. Fed Reg 2019;84:1536–67.
8. https://www.westgard.com/biodatabase1.htm (accessed 13 Nov 2019).
9. Bartlett WA, Braga F, Carobene A, Coskun A, Prusa R, Fernandez-Calle P, et al. A checklist for critical appraisal of studies of biological variation. Clin Chem Lab Med 2015;53:879–85.
10. Carobene A, Strollo M, Jonker N, Barla G, Bartlett WA, Sandberg S, et al. Sample collections from healthy volunteers for biological variation estimates' update: a new project undertaken by the Working Group on Biological Variation established by the European Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem Lab Med 2016;54:1599–608.
11. Carobene A, Røraas T, Sølvik UØ, Sylte MS, Sandberg S, Guerra E, et al. Biological variation estimates obtained from 91 healthy study participants for 9 enzymes in serum. Clin Chem 2017;63:1141–50.
12. Aarsand AK, Díaz-Garzón J, Fernandez-Calle P, Guerra E, Locatelli M, Bartlett WA. EuBIVAS: within- and between-subject biological variation data for electrolytes, lipids, urea, uric acid, total protein, total bilirubin, direct bilirubin, and glucose. Clin Chem 2018;64:1380–93.
13. EFLM database, https://biologicalvariation.eu/meta_calculations (accessed 13 Nov 2019).
14. ISO 15189. Medical laboratories – requirements for quality and competence. Geneva: ISO, 2012.
15. Cotlove E, Harris EK, Williams GZ. Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. III. Physiological and medial implications. Clin Chem 1970;16:1028–32.
16. Fraser CG, Hyltoft Petersen P. Quality goals in external quality assessment are best based on biology. Scand J Clin Lab Invest 1993;53(Suppl 212):8–9.
17. Haeckel R, Wosniok W, Gurr E, Peil B. Permissible limits for uncertainty of measurement in laboratory medicine. Clin Chem Lab Med 2015;53:1161–71.
18. Türkiye Toplam Analitik Hata Genelgesi (2016/18) https://dosyamerkez.saglik.gov.tr/Eklenti/2581,genelge-201618izin-verilen-toplam-hata-sinirlaripdf.pdf (accessed 13 Nov 2019).
19. Ricós C, Ramón F, Salas A, Buño A, Calafell R, Morancho J, et al. Minimum analytical quality specifications of interlaboratory comparisons: agreement among Spanish EQA organizers. Clin Chem Lab Med 2012;50:455–61.
20. Magnusson B, Naykki T, Hovind H, Krysell M. Handbook for calculation of measurement uncertainty in environmental laboratories, NordTest Report TR 537. NORDTEST, Finland, 2004.
21. CLIA Requirements for Analytical Quality, https://www.westgard.com/clia.htm (accessed 13 Nov 2019).
22. Jones GR, Sikaris K, Gill J. 'Allowable Limits of Performance' for External Quality Assurance Programs – an Approach to Application of the Stockholm Criteria by the RCPA Quality Assurance Programs. Clin Biochem Rev 2012;33:133–9.
23. Ozarda Y, Ichihara K, Aslan D, Aybek H, Ari Z, Taneli F, et al. A multicenter nationwide reference intervals study for common biochemical analytes in Turkey using Abbott analyzers. Clin Chem Lab Med 2014;52:1823–33.
24. https://www.dgkl.de/en/activities/workinggroups/entscheidungsgrenzen-richtwerte/#c699 (accessed 13 Nov 2019).
25. Panteghini M, Sandberg S. Defining analytical performance specifications 15 years after the Stockholm conference. Clin Chem Lab Med 2015;53:829–32.
26. Guide to the expression of uncertainty in measurement (GUM). Switzerland: JCGM, 2008:100.
27. Clinical and Laboratory Standards Institute. Expression of measurement uncertainty in laboratory medicine. Wayne, PA: CLSI, 2012.
28. Burnett D, Ceriotti F, Cooper G, Parvin C, Plebani M, Westgard J. Collective opinion paper on findings of the 2009 convocation of experts on quality control. Clin Chem Lab Med 2010;48:41–52.
29. Theodorsson E, Magnusson B, Leito I. Bias in clinical chemistry. Bioanalysis 2014;6:2855–75.
30. Mercan F, Serdar MA, Senes M, Konukoglu D, İnal TC, Alatas O, et al. National External Quality Assessment follow-up: 2010–2017 Turkish experience. Turk J Biochem 2019;44:1–8.
31. Sten Westgard. Comparing Verdicts from Different Goals, Models, and Specifications-Roche cobas 8000 c701, 2016. https://www.westgard.com/goal-verdict-comparison1.htm (accessed 13 Nov 2019).