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ORIGINAL ARTICLE

Standardized Estimation of Measurement Uncertainty in Clinical Chemistry Using ISO 20914

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ABSTRACT

Background: **The degree to which one is certain of results for a particular measurement/testing process is expressed as a confidence level within a range. Measurement uncertainty (MU) is a critical parameter in clinical chemistry, reflecting the degree of confidence in laboratory test results and directly influencing diagnostic accuracy and patient care.**
Methods: **The study calculated MU for 27 general chemistry analytes using the ISO 20914:2019 top-down approach, which uses long-term internal quality control (IQC) data and manufacturer calibrator traceability certificate values. The study was conducted at Nad al Hammar Health Center, Dubai Health, Dubai, using Roche Cobas Pure analyzers. The study compared calculated MU values with maximum allowable uncertainty (MAU) thresholds obtained from the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) biological variation database.**
Results: **The results show that 17 analytes met the desirable MAU criteria at IQC level 1, confirming robust analytical performance. However, 10 analytes - including albumin, alkaline phosphatase, calcium, magnesium, phosphorus, transferrin, troponin T hs, uric acid, urine albumin, and vitamin D - exceeded the desirable MAU limits, suggesting potential areas for method optimization or high signal to noise ratio at quality control level 1.**
Conclusions: **The findings underscore the importance of MU estimation in ensuring metrological traceability, fulfilling ISO 15189 accreditation requirements, and supporting risk-based quality management in clinical laboratories. This study highlights the practicality of ISO 20914 for routine MU assessment and advocates for its broader adoption to enhance result reliability and inter-laboratory comparability.**
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INTRODUCTION

Measurement uncertainty represents the degree of doubt about a measurement's true value. It arises from various influencing factors, including random and systematic errors, which cause variability in repeated measurements. This variability, or dispersion, around the estimated value indicates the level of uncertainty - smaller

dispersion corresponds to lower uncertainty [1]. In clinical chemistry, accurate and reliable laboratory results are crucial for effective clinical decision-making, thus necessitating the evaluation and management of MU [2].

The accuracy of clinical laboratory results is crucial for the diagnosis and treatment of diseases. All tests are known to exhibit variability based on biological variation, matrix effect, interference, calibrator traceability, environmental conditions, and multiple operators. In clinical laboratories, knowing measurement uncertainty is critical for ensuring the reliability, equivalence, and accuracy of patient laboratory test results [3]. According to ISO 15189:2012, section 5.5.1.4, laboratories "shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients' samples." Additionally, "Upon request, the laboratory shall make its estimates of measurement uncertainty available to laboratory users".

As per Joint Committee for Guides in Metrology (JCGM), MU is "non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used" [4].

The ISO Technical Specification 20914:2019 offers primary guidelines for medical laboratories to estimate measurement uncertainty. It advises using a "top-down" strategy, which combines all MU sources within the chosen traceability chain. The MU of clinical samples should represent the total uncertainty from all sources. The bottom-up model, as detailed in the Guide to the Expression of Uncertainty in Measurement, identifies every potential uncertainty source significantly affecting a measurement method's result. This model accounts for each source's uncertainty, rendering it impractical for laboratory medicine due to the need to describe variation from numerous sources and apply complex mathematical formulas. Therefore, the top-down MU estimation model, based on quality control or method validation data, is favored [5].

ISO advises laboratories to determine MU values for each measurement procedure. The ISO 15189 guideline offers adaptability to laboratories by not specifying a particular method for MU calculation. Several organizations propose varying MU estimation methods. In practice, clinical biochemistry relies on quality control materials to assess the imprecision inherent in the entire measurement process; this approach allows for the estimation of random effects contributing to the overall measurement uncertainty, predicted on the assumption that the measurand exhibits comparable behavior.

The Nordtest MU guideline also provides a clear and practical method for laboratories to easily implement MU calculations using data from quality control or method validation studies.

The ISO 20914 guideline, employing a "top-down approach," suggests a practical method for calculating the MU value, primarily using data from long-term imprecision (uRw), bias (ubias), and calibrator uncertainty (ucal). A key difference between this guideline and the Nordtest method lies in how bias is handled. The Nord test method estimates potential bias for all measurements, necessitating the inclusion of ubias in the MU calculation. In contrast, ISO 20914 advises that if bias remains within specified limits, laboratories may disregard ubias, as the long-term imprecision already accounts for it [6].

Particularly, the MU at the level of clinical samples (u result) must be the combination of all uncertainty contributions accumulated across the entire traceability chain (u result = $\sqrt{[ucal^2 + uRw^2]}$ [7,8].

How do you define maximum allowable MU?

ISO Technical Specification 20914 explains that determining a measurement's uncertainty is only valuable when compared to the acceptable measurement uncertainty, which is based on the quality of results needed for medical decisions. Acceptable performance specifications play a key role in risk management by ensuring the effectiveness of laboratory tests in diagnosis and treatment. In 2014, during a conference in Milan, the European Federation of Clinical Chemistry and Laboratory Medicine suggested three models for defining acceptable performance specifications. These models consider: 1) the direct influence of analytical performance on clinical results; 2) the biological variation components of the measurands; and 3) the state of the art in measurement, which represents the highest level of analytical performance currently achievable.

According to ISO 20914, clinical laboratories must determine measurement uncertainty for tests generating quantitative results, crucial for reliable patient results. The EFLM Biological Variation Database offers the maximum allowable measurement uncertainty for different measurands, utilizing biological variation data. Ideally, bias should be eliminated, and any remaining variation sources should be combined linearly as variances. Consequently, a measurement result can have two uncertainties: one related to bias correction and another due to imprecision. Therefore, the maximum allowable standard measurement uncertainty can be defined as 0.5 times the CVI (within subject biological variation), while the maximum expanded allowable measurement uncertainty is k x 0.5 x CVI, where "k" represents the coverage factor (e.g., 2 or 3) for a specific confidence level. The 0.5 factor corresponds to desirable APS, with optimum and minimum performance specifications factors set at 0.25 and 0.75, respectively. Accurate MU estimation, aligned with internationally recognized methodologies, is important for the metrological traceability of patient results and for inter-laboratory result comparability [9].

MATERIALS AND METHODS

This study was conducted in the Clinical Chemistry Laboratory at Nad al Hammar Health Center of Dubai Health, Dubai. The Roche Cobas c303, a clinical chemistry module, and the Cobas e402 immunoassay module of Cobas Pure, an automated, multi-channel, selective analyzer designed for clinical chemistry laboratories, were utilized for analysis. The laboratory employs Roche quality control materials for internal quality control purposes. We followed ISO 20914 guidelines for expanded measurement uncertainty and percentage of expanded measurement of uncertainty for 27 analytes. The results were compared with desirable MAU and minimum MAU determined from EFLM database.

Evaluation of MU

In line with ISO 20914:2019 recommendations, the 'top-down' method, incorporating commercial calibrator data and internal quality control data, was employed to estimate measurement uncertainty. The long-term QC data and calibrator certificate data were extracted to estimate the MU.

Statistical analysis

Statistical calculations were performed using Microsoft Excel.

The MU was calculated using the formula mentioned below.

The combined standard uncertainty, denoted as *u-(combined)*, was determined by taking the square root of the sum of the squares of the uncertainty due to laboratory imprecision and the uncertainty associated with the calibrator. This calculation effectively combines these two sources of uncertainty to provide a comprehensive measure of the overall uncertainty in the measurement process [10,11].

MU calculation according to ISO 20914 guidelines

1) The ISO 20914 guideline outlines the procedure for calculating the *u*(y) value of analyte Y measured. This calculation considers the uncertainty of the measurement procedure (*u*Rw), the uncertainty of the value assigned to the calibrator (*u*cal), and the uncertainty caused by the deviation of the determined value (*u*bias). To calculate the *u*Rw component, we based our calculations on the 12-month normal (level 1) and pathological (level 2) IQC results. We also included the *u*cal values of the analytes in the calculations, as declared by the manufacturer Roche in traceability certificate. The ISO 20914 guideline recommends that the *u*bias value should be included in the MU calculation only if it constitutes a significant medical difference [12].

$u(y)=\sqrt{u_{rw}^2 + u_{cal}^2}$

2) The expanded uncertainty (*U*(y)) was calculated by multiplying the *u*(y) value for each analyte by k, and the relative percentage of the expanded uncertainty (%*U*(y) rel) was calculated divided by the mean value.

$$U(y) = u(y)x2$$

$$U(\mathrm{y})rel\% = \frac{U(y)x100}{mean}$$

The maximum allowable measurement uncertainty desirable and minimum (MAU) target were extracted from the European Federation of Laboratory Medicine Biological Variation and were compared with relative percentage of expanded uncertainty (%*U*(y)rel) [13].

Quality control in clinical chemistry is essential for ensuring reliable and accurate laboratory results, as errors can arise from various sources, including pre-analytical, analytical, and post-analytical phases. Implementing a comprehensive quality control program helps minimize errors and improve the overall quality of laboratory testing and decreases the variability of measurands.

Ten analytes with quality control level 1 measurement of uncertainty percentage, namely albumin, alkaline phosphatase, calcium, phosphorous, magnesium, transferrin, troponin T high sensitive, uric acid, albumin in urine, and vitamin D, showed measurement uncertainty percentages exceeding the desirable maximum allowable uncertainty (MAU), defined as k x 0.5 x CVI, where *k* is the coverage factor and *CVI* is the within-subject biological variation. These findings indicate that the analytical uncertainty for these analytes may not meet the desirable performance specifications derived from biological variation and therefore warrant further evaluation and potential quality improvement measures. (Table 1, Figure 1).

Applying the less stringent minimum MAU criterion based on biological variation (k x 0.75 x CVI) reduced the number of non-conforming analytes to seven. These analytes exceeding the allowable uncertainty limits were calcium, magnesium, phosphorus, high-sensitivity troponin T, uric acid, urinary albumin, and vitamin D. (Table 1, Figure 1).

The vitamin D percentage of expanded measurement of uncertainty exceeds the permissible limit of maximum allowable uncertainty for both levels of quality controls. Calcium failed for quality control level 2 (Figure 1).

The detailed calculation of measurement uncertainty for each analyte is expressed in Supplementary Table 1. Analytical performance specifications and maximum allowable measurement uncertainty as per biological variation EFLM level are listed in Supplementary Table 2.

DISCUSSION

This study applied the ISO 20914:2019 guideline to estimate measurement uncertainty (MU) for 27 general chemistry analytes using a top-down approach. The results underscore the practical utility of this method in routine clinical laboratory settings, particularly when long-term internal quality control (IQC) and calibrator data are readily available.

Table 1. Percentage of relative measurement of uncertainty Urel% comparison with desirable and minimum specifications of (MAU) maximum allowable uncertainty (MAU) for analytes exceeding quality control level 1.

Analyte name	Urel %	MAU % (desirable)	Analyte name	Urel %	MAU % (minimum)
Albumin	4.6	4.2	Calcium	6.0	1.2
Alkaline phosphatase	7.1	6	Magnesium	94.6	4.1
Calcium	6.07	0.8	Phosphorus	50.4	11.6
Magnesium	94.6	2.7	Troponin T (high sensitivity)	197.9	17.1
Transferrin	4.5	3.9	Uric acid	25.0	12.1
Phosphorus	50.4	7.7	Urine albumin	47.4	15.6
Troponin T (high sensitivity)	197.9	11.4	Vitamin D	26.8	10.2
Uric acid	25.0	8.1			
Urine albumin	47.4	12.4			
Vitamin D	26.8	6.8			

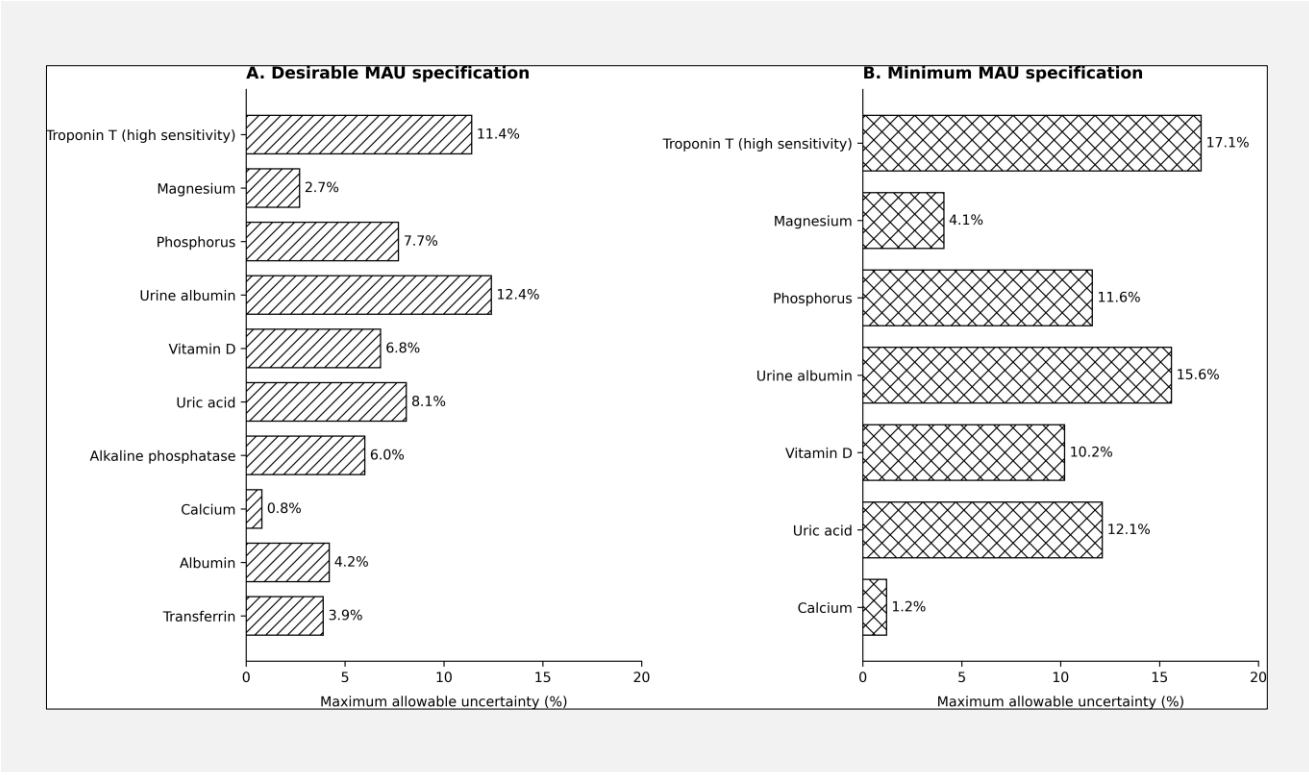

Figure 1. Comparison of relative measurement uncertainty (Urel%) with desirable (A) and minimum (B) maximum allowable uncertainty specifications for analytes exceeding the respective limits at quality control level 1. Urel, relative measurement uncertainty, MAU: maximum allowable uncertainty, QC: quality control.

Analytes within acceptable limits

Out of the 27 analytes tested, 17 met the desirable maximum allowable uncertainty (MAU) at both IQC levels. These include: amylase, total cholesterol, creatinine, iron, ferritin, GGT, bicarbonates, glucose, ALT (SGPT), AST (SGOT), HDL and LDL cholesterol, total biliru-bin, total protein, transferrin, triglycerides, and urea.

Analytes exceeding MAU

However, 10 analytes exceeded the MAU at IQC Level 1, including: albumin, alkaline phosphatase, calcium,

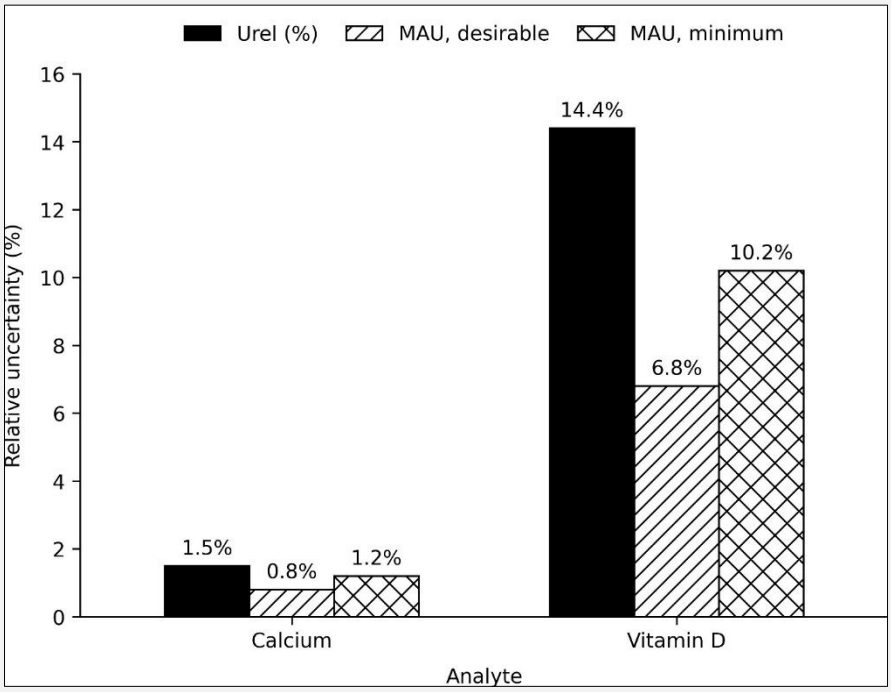

Figure 2. Bar graphs for analytes exceeding percentage of relative measurement of uncertainty in comparison to desirable and minimum specifications of maximum allowable uncertainty (MAU) for quality control level 2.

phosphorus, transferrin, troponin T hs, uric acid, urine albumin, vitamin D.

The elevated MU values in these tests may be due to high variability in calibrator uncertainty (e.g., troponin T hs). Analytical method limitations (e.g., colorimetric assays for calcium and phosphorus), inherent biological variability, matrix effects, and assay cross-reactivity (particularly for urinary albumin and vitamin D) may have contributed to the observed measurement uncertainty values exceeding the maximum allowable uncertainty (MAU).

For vitamin D, cross-reactivity is commonly the key reason for increased MU. These findings highlight the need for method optimization and enhanced QC protocols.

This indicates that the laboratory's analytical performance for these tests is robust and aligns with international standards, ensuring reliable patient results.

The study confirms that long-term imprecision (uRw) is the dominant contributor to overall MU, consistent with findings from other laboratories [14]. This emphasizes the importance of maintaining stable analytical performance over time and regularly reviewing IQC trends and shifts.

By comparing MU values with the EFLM Biological Variation Database, the study ensures that the uncertainty estimates are not only statistically valid but also clinically meaningful. This approach supports risk-based quality management and aligns with ISO 15189: 2022 requirements for metrological traceability and patient safety [15].

CONCLUSION

This study successfully applied the ISO 20914:2019 top-down approach to estimate measurement uncertainty (MU) for 27 general chemistry analytes in a clinical laboratory setting. By utilizing long-term internal quality control (IQC) data and manufacturer calibrator certificates, the study demonstrated a practical and efficient method for MU estimation that aligns with international standards and supports metrological traceability.

The study underscores the value of integrating MU estimation into routine laboratory practice to enhance result reliability, support accreditation requirements (ISO 151 89), and improve inter-laboratory comparability.

Limitations:

The study has several limitations that should be acknowledged:

1) Single-center scope: Conducted at a single laborato-

ry using Roche Cobas analyzers, the findings may not be generalizable to other platforms or institutions with different QC practices or environmental conditions.
2) Bias consideration: Following ISO 20914, bias was excluded from MU calculations unless it was deemed medically significant. While this simplifies the process, it may underestimate total uncertainty in borderline cases [18].
3) Analyte selection: The study focused on general chemistry analytes and the analytes based on the scope of the primary health center laboratory.

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Declaration of Generative AI in Scientific Writing:
The authors declare that generative AI was not used for writing this manuscript.

Declaration of Interest:
The authors declare that there is no conflict of interest.

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