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Finding order in measuring disorders: Measurement Uncertainty of Thyroid Function Tests at a tertiary care hospital in Eastern India

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ABSTRACT

Background: Quantitative estimation of analytes in the laboratory is the mainstay of disease diagnosis. However, the true value of the analyte cannot be measured. Hence, the clinical validity of a test requires a concurrent statement of uncertainty. The International Organization for Standardization further mandates that measurement uncertainty (MU) for all parameters be included in medical reports for laboratory accreditation. Yet, studies regarding the uncertainty of measurement across instruments and parameters remain elusive in India. Thyroid disorders constitute a global health menace but can be efficiently managed if diagnosed early via reliable immunoassays. However, such immunoassays may be altered by different variables, necessitating the addition of the uncertainty statement for proper evaluation of the hormonal status. **Aims and Objectives:** Present study aimed to determine the uncertainty of measurement in estimating free thyroxine and thyroid-stimulating hormone (TSH) levels in the immunoassay laboratory of a tertiary care hospital in Eastern India. **Materials and Methods:** In this hospital-based descriptive study, MU was calculated using internal quality control and external quality assurance data, adapting a top-down approach as per the Guide to the expression of uncertainty in measurement documents. **Results:** Using three levels of immunoassay controls, MU for free thyroxine was 0.08, 0.08, and 0.21, while it was 0.03, 0.21 and 0.53 for TSH. **Conclusion:** Incorporation of uncertainty data alongside individual patient reports can help physicians gain more comprehensive information regarding diseases. The present study can act as a stepping stone for further research in India to facilitate greater quality of patient care laboratory services.

Key words: Quality control; Thyroxine; Thyroid stimulating hormone; Traceability; Uncertainty

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INTRODUCTION

In the era of evidence-based medicine, the measured values assigned by clinical laboratories to various biological quantities provide essential information in the field of patient care. These results are indispensable for appropriate diagnostic and therapeutic decisions, clinical correlations, and the optimization of healthcare processes. Therefore, these values must be reliable as well as traceable across different periods of time and place.[1,2] Measurand has been termed by the International Vocabulary of Metrology as a quantity "*intended to be measured*" along with the inclusion of

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a specific measuring system plus the conditions needed to influence the measurement.[3] However, due to the variability of laboratory procedures, the "true" value of a quantity cannot be exactly known. Hence, supplementation of a measured quantity with a statement of its uncertainty is often of paramount importance for the completion and clinical validity of a test report.[4] Measurement uncertainty (MU), preferably reported as (x±U), has been included as a reflection of the dispersion of the measured values in ISO 15189:2003 (3.17).[5] Proper knowledge regarding MU and its allowable limits for clinical application represent one of the mainstays for various measurements. Incorporation of MU into a test report confers higher confidence in the clinical decisions based on the results obtained with the analyzer; fewer re-determinations are called for and long- term costs are lowered.[6] Furthermore, the inclusion of MU can pave the way for validation of the generated data and aid in the accreditation process of the laboratories as per International guidelines ISO 15189: 2012 and ISO 17025:2017.[7,8] With the adoption of the guidelines laid down by the International Organization for Standardization (ISO 15189:2012), clinical pathology laboratories have been mandatorily required to provide estimates of MU for all quantitative test results.[7]

Recent reports demonstrate that thyroid disorders affect more than 300 million people worldwide, out of whom, India harbors a disease burden of approximately 42 million populations.[9] Determination of the uncertainty of serum thyroid levels will ensure a broader perspective in the context of diagnostics as well as rationality in treatment and patient care. However, data regarding the declaration of uncertainty of measurement while estimating the hormones of thyroid function remain scarce, if any, in the Indian subcontinent, and more so in the eastern parts of the country. Therefore, the present study aimed to evaluate the uncertainty of measurement for free thyroxin (fT4) and thyroid-stimulating hormone (TSH) based on laboratory data to validate the results of these hormones for clinical utilization.

Aims and objectives

The study aimed at quantifying the Measurement Uncertainty associated with the estimation of free T4 and TSH based on the regular quality control and assurance protocol performed in the laboratory so as to aid in a more informed decision-making about the hormonal status of the patients.

MATERIALS AND METHODS

Study design and setting

This descriptive, observational, hospital-based cross-sectional study was done in the immunoassay laboratory at the Department of Biochemistry in the Institute of Post Graduate Medical Education and Research and SSKM Hospital, Kolkata from February 2021 to July 2022. The study was approved by the Institutional Ethics committee vide Memo No. IPGME&R/IEC/2022/096. Formal calculation of sample size was not relevant in this study, nor was there a requirement to select cases and controls.

Materials and inclusion criteria

After obtaining proper informed consent from the Head of the Department of Biochemistry of IPGME&R, suitable materials were selected for the study purpose. Serum levels of fT4 and TSH were serum levels of fT4 and TSH were estimated by the electrochemiluminescence immunoassay method using the ADVIA Centaur CP instruments (Siemens, Germany).[10] Adequate quality control (QC) was maintained during the procedure by following the Westgard multi- rule QC System, proper calibration, and analyte-specific analytical measurement range. ADVIA centaur FT4 and TSH3UL reagent packs, automated fixed and variable pipettes, disposable microtips for pipettes, Eppendorf tubes, and clot vials were used for the estimation. As part of the internal QC (IQC) measures, Siemens ADVIA Centaur CAL Calibrator A (for fT4), Siemens ADVIA centaur CP TSH3 ultra calibrator (available with kit), and RANDOX IA premium plus tri-level control materials were utilized. The calibrator values were internally assigned by the assay manufacturer. As per the Clinical Laboratory Improvement Amendments recommendations, the present study participated in the external quality assessment (EQA) or proficiency testing (PT) scheme (external quality assurance service [EQAS] program) guided by the Christian Medical College (CMC) Vellore. The EQA material received from the aforementioned setup for the cycle of April 2021 was used for the calculation of bias during the estimations. A proper annual maintenance contract and procurement of machines were performed according to standard guidelines. The quality and integrity of the reference materials were ensured before performing the assay.

Exclusion criteria

Reference materials for IQC, EQA, and calibrators, if received in inadequate quantities or with their homogenous nature disrupted or were transported through improper means, were excluded from the study. The bottom-up approach, which excludes all parameters starting from pre-analytical patient sample collection, transport, temperature fluctuations, environmental fluctuations, humidity and air pressure changes in the laboratory, and electrical and instrumental perturbations, was not considered in this study.

Methodology

The calibrators and reference materials were initially refrigerated at 2–8°C. Following reconstitution, these

materials were stored at −20°C until use. Proper pre-requisites, such as air temperature, humidity, and pressure, were taken into consideration, and strict.

Biomedical waste medical guidelines were followed. No additional human and financial resources were required, as study parameters were measured by reagents and machines procured within departmental resources according to strict standard guidelines and standard operating procedures.

Data collection and statistical analysis

IQC data worth 12 months were collected from February 2021 to January 2022 over three levels (Levels 1, 2, and 3) of RANDOX IA controls. Similarly, the EQAS results were obtained for this period. The EQAS data for the April 2021 cycle were considered in this study. Subsequently, MU was calculated using Microsoft Office Excel 2010 and its interpretation was performed based on the results generated. The guidelines provided by ISO 17025:2017, ISO 15189:2012, and other international recommendations were followed. All QC data were found to have a Gaussian distribution and passed the goodness-of-fit test using the MEDCALC software.

The present study used the top-down approach to estimate the uncertainty of the measurement of fT4 and TSH. The guide to the expression of uncertainty in measurement (GUM) document was considered during uncertainty of measurement calculation.[11] MU was determined by "Type-A evaluation"- referring to the estimation of uncertainty using statistical analysis of a series of observations.[12] While making certain assumptions, internal QC materials were used as a common practice. The IQC Material represented a matrix similar to that of the clinical samples. Analyte concentrations were representative of levels found routinely in clinical samples. Both the controls and clinical samples shared a common analysis pathway and were treated identically. The analytical method was stable and remained consistent under the control. As per present guidelines, it was recommended to use at least 6 months' worth of data when calculating uncertainty.[13]

The total MU of any parameter depends on the combination of random and systematic uncertainties. To identify random uncertainties, the intra-assay precision within a run was determined. L1, L2, L3 of Immunoassay control were consecutively used to generate 30 data sets on two occasions for each level, resulting in 60 data points. Inter-assay precision for the same QC material was measured by running each level of RANDOX Immunoassay control in a replicate manner, with one replicate every working day, from February 2021 to January 2022. This process identified systematic uncertainty. As Tri-level QC was used in the immunoassay laboratory, the MU was calculated for each and a judgment was made as to whether they were sufficiently different to warrant their use with patient results that were in the range considered to be covered by each QC level. The standard error of the mean of the intra-assay precision (A) and the standard deviation (SD) of the inter-assay precision (B) were calculated.

The standard uncertainty (u) was calculated as:

$$u=\sqrt{(A^2+B^2)}$$

Multiplying the standard uncertainty, u, by a coverage factor (k) gave the expanded uncertainty, usually denoted by the symbol U. A particular value of coverage factor indicated a particular confidence level for the expanded uncertainty. The reported uncertainty was an expanded uncertainty calculated using a coverage factor (k) of 2, indicating the confidence interval of approximately 95%.

$$U=k.u \text{ (k=coverage factor, 2 for 95\% C.I).}$$

The bias needed to be calculated and incorporated within the overall calculation of uncertainty. To calculate this, the study determined the uRef, uncertainty of the analyte value assigned to the EQA sample of April 2021, as per the EQA or PT scheme (CMC, Vellore) and uRep, the uncertainty of the analyte value in the reference material of EQA when measured in replicate in the Departmental Immunoassay Laboratory. uRep was obtained by the SD values of running the particular EQA sample of April 2021 for 10 times. The uncertainty bias was then calculated using the following formula: $uBias = \sqrt{(uRef^2+uRep^2)}$.

Bias uncertainty and the expanded uncertainty of QC imprecision were combined to get the total MU. Hence, the overall uncertainty was derived from these normally distributed QC data by using the coverage factor k=2, to give a level of confidence of approximately 95%.

RESULTS

To estimate the intra-assay precision within a run, the standard error of the mean (A) was determined by running 30 repeated replicates of the same QC material at the same time. It allowed the identification of random uncertainties. Furthermore, to estimate the systematic uncertainty, the SD of the inter-assay precision (B) of the same QC material was calculated by running one replicate per working day for 30 days (Table 1).

Table 1: Calculation of MU in fT4 and TSH estimation

Analyte	Free T4 (ng/dL)			TSH (μIU/mL)		
QC level	L1	L2	L3	L1	L2	L3
QC lot no.	1862	1877	1867	1862	1877	1867
Assigned range	0.52–0.86	1.89–3.15	3.2–5.32	0.089–0.173	1.75–3.41	16.7–32.5
Mean within-run (n=60)	0.6247	2.325	4.453	0.1018	2.4067	23.915
SEM* (A)	0.018	0.022	0.052	0.0013	0.046	0.1984
Mean Between-run (n=30)	0.68	2.36	4.76	0.0923	2.2066	24.023
SD** (B)	0.0191	0.0161	0.0776	0.0072	0.0868	0.1631
MU [u= √ (A^2+B^2)]	0.026	0.027	0.093	0.0073	0.0982	0.2568
Expanded uncertainty U=k. u***	0.052	0.054	0.186	0.0146	0.1964	0.5136

fT4: free thyroxin, TSH: Thyroid-stimulating hormone, QC: quality control, MU: Measurement uncertainty. *SEM: Standard Error of Mean calculated to estimate within-run precision, **SD: Standard deviation calculated to estimate the Between-run precision, ***k=coverage factor, indicative of a 95% CI. RANDOX IA premium plus Tri level immunoassay control used as reference material

The uncertainty of measurement (u) was calculated as:

$$u=\sqrt{(A^2+B^2)}$$

The expanded uncertainty (U) was deduced for a particular confidence interval by a particular coverage factor.

$$U=k.\ u\ (k=2,\ CI:\ 95\%)$$

The reported uncertainty was an expanded uncertainty calculated using a coverage factor k=2, with the level of confidence being approximately 95%.

The standard (u) and expanded uncertainty (U) were calculated for each level of immunoassay control in fT4 as well as TSH estimation (Table 1).

Bias was calculated from the EQAS material of April 2021 (CMC Vellore). For that purpose, the uncertainty of the analyte value of the EQA material (uRef) was obtained. Uncertainty of the same EQA material after running in replicates for 10 times (uRep) was deduced from the SD values. The uncertainty bias was calculated as:

$$uBias = \sqrt{(uRef^2+uRep^2)}$$

EQA uncertainty (uRef) was 0.02 for fT4 and 0.01 for TSH (Table 2).

EQA uncertainty on the replicate run (uRep) was 0.016 for fT4 and 0.0069 for TSH. The bias obtained in the estimation of fT4 and TSH was 0.0256 and 0.0122, respectively (Table 2).

Combining it with the expanded uncertainty, the total MU for fT4 and TSH estimation was obtained (Table 3).

Hence, from the calculations of uncertainty at tri-level immunoassay controls and the values obtained the dispersion when declared and combined with the test results has the potential ability to affect clinical decision limits.

Table 2: Calculation of uncertainty bias in fT4 and TSH estimation

Analyte	Free T4 (ng/dL)	TSH (μIU/mL)
Method	ECLIA	ECLIA
No. of participants	173	283
DV	2.12	1.73
Participants		
CV	6.80	6.07
SD	0.14	0.10
Present lab value	1.96	1.21
SDI	1.11	4.95
uRef	0.02	0.01
EQA material: Replicate-run Mean (n=10)	1.958	1.206
EQA: Replicate-run SD (uRep)	0.016	0.007
Uncertainty bias √ ($uRef^2$+$uRep^2$)	0.0256	0.0122

fT4: free thyroxin, TSH: Thyroid-stimulating hormone, ECLIA: electrochemiluminescence, *CMC external quality assurance scheme (EQA), *Month: April, Year: 2021, *Constituent group: Thyroid hormones and cortisol

Table 3: Estimation of total measurement uncertainty for fT4 and TSH

Analyte	IQC level	Expanded uncertainty (U)	uBias	Total uncertainty U+uBias (upto 2-decimals)
Free T4 (ng/dL)	L1	0.052	0.0256	0.08
	L2	0.054		0.08
	L3	0.186		0.21
TSH (μIU/mL)	L1	0.0146	0.0122	0.08
	L2	0.1964		0.21
	L3	0.5136		0.53

fT4: Free thyroxin, TSH: Thyroid-stimulating hormone, IQC: Internal quality control

DISCUSSION

Thyroid disorders are common worldwide as well as in India. A population-based study in Cochin revealed the prevalence of hypothyroidism among adult Indians to be 3.9%.[14] A hospital-based study on women in Pondicherry revealed the presence of subclinical and overt hyperthyroidism in 0.6% and 1.2% of subjects, respectively.[15] Besides, thyroid hormones are one of the most important endocrine hormones that reflect the

metabolic status of the individual. There is evidence that thyroid function profoundly impacts the metabolic and energy homeostasis of the human body at many levels.[16]

As no value can be truly measured, a small swing in the data has a robust capability to alter the diagnostic spectrum. The uncertainty component has the potential to provide a broad horizon in the understanding and follow-up of patients with these diagnostic dilemmas. Identification of thyroid anomalies, both diagnostically and for therapeutic supplementation, is heavily dependent on the Laboratory test results.[17]

Free T4 and TSH levels in serum, estimated through the immunoassay method, remain the main diagnostic indicators of thyroid function and confer the necessary sensitivity as per the guidelines, thus allowing the identification of patients having both overt and subclinical cases.[18] However, these automated immunoassays are greatly variable and can be altered by different factors such as inter- and intra-individual variations, circadian and diurnal variations, hook effect, macro-TSH, instrument calibration, interferences due to heterophile antibodies, TSH isoforms and paraproteins, sample-related factors (such as hemolyzed, icteric or lipemic sample), etc.[19,20] Hence, quantification of the uncertainty of measurement in FT4 and TSH assays can provide relevant contextual information for proper diagnosis of the thyroid disorders while avoiding over- or under-diagnosis, and also for the rationalistic decision making of treatment planning and implementation.[21]

The "Guide to the Expression of Uncertainty in Measurement" (GUM) approach was adopted by National Measurement Institutes and international laboratory accreditation standards such as ISO/IEC 17025.[11] The ISO and International Electro technical Commission (IEC) 17025:2017 for testing and calibration laboratories as well as ISO 15189:2012 for medical laboratories requires the laboratories to estimate the uncertainties of measurement results.[7,8] An uncertainty, if too large, may affect the reliability of the result. In contrast, an uncertainty that is too small makes the tests more costly.

Therefore, it is essential for laboratories to achieve an appropriate estimate of the MU. The expression of uncertainty in a result allows comparison between different laboratories within the same laboratory, or against reference values assigned in specifications or standards.

The present study found that MU was useful in providing objective information on the performance of individual laboratories, as well as to serve as a management tool. Rounding the data obtained through the study to two decimal places, the total MU in the fT4 estimation for L1, L2 and L3 controls were 0.08, 0.08 and 0.21, respectively. For TSH estimation, the MU was 0.03, 0.21 and 0.53 for the respective control levels.

Çubukçu *et al*., following a study performed on the measurement uncertainties of 14 immunoassay analytes with internal and external QC data, suggested that tests with high uncertainties must be informed by the laboratories to the clinicians, thus assisting and guiding them into making the appropriate clinical diagnosis.[22]

Padoan *et al.* did a study on the uncertainty of measurement along with laboratory reports. It was used to improve the interpretation of the results. Reporting of MU was evaluated with respect to various test purposes, such as patient monitoring and comparison with reference intervals (RI), or clinical decision limits.[23]

The present study preferred the use of the "top-down" approach, rather than the 'bottom-up" one, for estimating the uncertainty of measurement. This approach had been strongly recommended by Braga and Panteghini as a simpler and effective way of estimating the MU of laboratory results in view of its recent endorsement in the recently released ISO/TS 20914:2019 Proposal for MU calculation according to different test purposes.[24]

The present study used three levels of IQC and EQA data for the calculation of MU, similar to a prior research by Oguz.[25]

Reliable immunoassay methods and RI s for their measurement may have significant clinical relevance in the detection of thyroid disease, particularly in the early stages, due to the lack of obvious signs and symptoms.[26] However, the measurement results of TSH and fT4 without its MU cannot be compared meaningfully with a similar previous result, unless the measurement uncertainties during the two estimations are similar. It is, therefore, critical for every medical laboratory to have optimum knowledge of the magnitude of the MU to assess whether the measurement results produced by immunoassay procedures are suitable for clinical applications. However, although significant research has been conducted on the estimation of MU, data to shed light on the MU of both fT4 and TSH have been scarce. An extensive literature search did not reveal any similar studies previously performed in India. Hence, it was difficult to compare the results obtained in the present study with those of other studies. Therefore, further studies are warranted.

Limitations of study

The present study also had a few limitations. Measurement uncertainties due to calibration and RI could not be

included due to the lack of adequate data at the time of study. Any measurement being an ongoing procedure, may have also led to minuscule shifts in the dispersion values. Further studies in these regards are in the pipeline for the future.

CONCLUSION

It can be concluded that the test result imparts complete clinical validity only when accompanied by a statement of uncertainty. In addition, in the present era, the accreditation of laboratories as per the guidelines of ISO 15189:2012 mandates the estimation of the MU of each parameter. Thyroid disorders influence the metabolic setup of an individual and are prevalent in developing countries such as India. Hence, the present study estimated the MU of fT4 and TSH levels in a diagnostic laboratory of a government-sponsored tertiary care hospital. This was probably the first-of-its-kind study in the state of West Bengal, India. It is recommended that all clinical laboratories in the region conduct such studies to incorporate information regarding the MU of thyroid hormone estimation in their reports. Such reports can constitute part of the total quality management in the laboratory and assess the reliability of the immunoassay platforms used for the estimation of these hormones. The statement of uncertainty associated with free T4 and TSH tests can assist in the alleviation of delay in diagnosis as well as the prevention of over- and/or under-diagnosis of thyroid disorders. It can also guide clinicians with a holistic view of the results, aiding better patient management.

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AB- Definition of intellectual content, literature survey, data collection, implementation of study protocol, preparation of first draft of manuscript; **KM**- Concept and design, manuscript preparation editing and review; **AD**- Data analysis, statistical analysis and interpretation, review of manuscript, submission of article; **DM**- Literature survey, data collection and review manuscript; **MM**: Supervision, coordination and manuscript revision.

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