

# Anti-thyroid peroxidase (TPO) antibodies – Comparative analysis of two automatic methods, ECLIA and CMIA

Ion Bogdan Manescu<sup>1,2#</sup>, Andreea Luca<sup>3#</sup>, Adina Hutanu<sup>1,2\*</sup>, Andreea Truta<sup>3</sup>, Minodora Dobreanu<sup>1,2</sup>

1. Department of Laboratory Medicine, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania
2. Department of Immunology, Center for Advanced Medical and Pharmaceutical Research, Romania
3. Department of Laboratory Medicine, County Emergency Clinical Hospital of Targu Mures, Romania

## ABSTRACT

**Introduction:** Anti-thyroid peroxidase autoantibodies (TPO) is an essential diagnostic tool for autoimmune disorders of the thyroid gland. However, TPO results are not always comparable due to differences between methods. Here, we aimed to investigate the differences between two modern laboratory methods for TPO measurement: electrochemiluminescence (ECLIA) and chemiluminescence microparticle (CMIA) immunoassays.

**Methods:** A total of 234 serum samples were tested on two methods: Cobas-e601 (ECLIA) and Alinity i (CMIA). TPO results were compared statistically both quantitatively and qualitatively (results were coded as positive/ negative, according to ECLIA/ CMIA reference ranges).

**Results:** The precisions of both methods were acceptable compared with the claims of the manufacturer. There was a very strong, but unsatisfactory correlation between the two methods (Pearson  $r=0.85$ ). Passing-Bablok regression revealed a significant deviation from linearity (Cusum  $p<0.01$ ) and an unacceptable quantitative relationship: intercept -7.61, slope 1.10. Moreover, a visual analysis of overall and medical decision level-focused Bland-Altman plots confirmed the lack of quantitative agreement. As for the qualitative analysis, the concordance rate between methods was 218/234 (93.1%). The agreement was considered good to very good according to the inter-rater agreement test: weighted Cohen  $\kappa = 0.805$ .

**Conclusions:** The qualitative agreement between Cobas-e601 (ECLIA) and Alinity i (CMIA) was good, therefore the two methods may be used indiscriminately for initial testing of patients suspected of thyroid gland autoimmune diseases. However, due to poor quantitative agreement, the two methods should not be used interchangeably for monitoring as the results may mislead both physicians and patients, possibly leading to medical errors.

**Keywords:** CMIA, ECLIA, method comparison, thyroid peroxidase antibodies, TPO

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## INTRODUCTION

Hashimoto thyroiditis (HT) is an autoimmune disease characterized by an enlarged thyroid gland and elevated serum anti-thyroid peroxidase (TPO) autoantibodies. HT is more prevalent in women than in men (ratio of 4 to 1) and also in individuals who suffer from other autoimmune diseases or with relatives who suffer from HT [1]. Eventually, HT leads to hypothyroidism and is associated with a higher risk of malignancy [2]. Hashimoto thyroiditis significantly adds to the global burden of disease due to its high estimated prevalence of 7.5% in adults, with variations depending on sex, geographic region, and socio-economic status [3]. Diagnosis of HT is based on clinical findings and blood tests, mainly anti-TPO antibodies which are found in patients suffering from HT and also in

Graves disease. Anti-TPO antibodies can also be present in individuals without apparent thyroid impairment. At the same time, the presence of these antibodies can predict future thyroid dysfunction, and adverse outcomes during pregnancy, while detectable TPO antibodies levels have been associated with increased mortality in men [4]. Early diagnosis and treatment of HT is essential. Delayed diagnosis allows for the complications of hypothyroidism to occur, such as mental health disorders, sexual dysfunction, infertility, heart problems, etc [5].

Given the relevance of TPO antibody testing for the diagnosis of HT, it is important to understand current testing methods in the clinical laboratory, as well as the differences between them. Two of the most popular methods for testing TPO antibody levels are the automat-

\* Adina Hutanu, Department of Laboratory Medicine, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania. E-mail: adina\_hutanu03@yahoo.com

# Authors with equal contribution

ed electrochemiluminescence immunoassay (ECLIA) and chemiluminescence microparticle assay (CMIA). Despite their similarities and high sensitivities and specificities, such modern immunoassays are not always comparable to one another. Moreover, all immunoassays are more or less prone to immune interferences which are typically patient-specific and sometimes difficult to suspect and detect. Thus, knowing the advantages and limitations of each method, as well as the differences between methods is important in order to increase diagnostic accuracy. Another aspect, quite frequent in large clinical laboratories, relates to inter-method comparability and agreement. When more than one TPO antibody immunoassay are present in a clinical laboratory, studying the comparability and agreement between the methods in use is essential as it enables both laboratory doctors and physicians to establish a proper strategy for the diagnosis, monitoring, and overall management of patients.

The objective of this study was to investigate the comparability and agreement of two automated methods for measuring TPO antibody levels – ECLIA (Cobas e601 analyzer) and CMIA (Alinity i analyzer).

## METHODS

### General data

Between January and June 2023, we conducted a prospective, observational study at the Central Laboratory of the County Emergency Clinical Hospital of Târgu Mureș (Romania), using the Cobas e601 (Roche Diagnostics, Switzerland) and Alinity i (Abbott, U.S.) analyzers. This study was approved by the Ethics Committee of the County Emergency Clinical Hospital of Targu Mures, Romania (approval no. 32245/ 15.12.2022).

### Sample collection and processing

The study included a total of 234 consecutive blood samples of patients tested for TPO antibodies at the request of the physicians. After centrifugation (10 minutes at 3000 rotations per minute), each sample was initially tested on Cobas e601, then again on Alinity i within less than one hour. Because residual sera were used, patients were not subjected to additional interventions or blood collections. Blood samples originated from both outpatient and inpatient individuals across various hospital departments. Hemolyzed, hyperbilirubinemic, and lipemic samples were excluded, as well as those improperly stored or transported.

### Assessment of methods precision

Reproducibility and repeatability for both devices were estimated from the quality control (QC) results. For reproducibility, the internal control chart was used throughout the study period. For repeatability, 15 de-

terminations of internal control were conducted at all levels in a single analytical run (within-run imprecision), specifically 2 on Cobas e 601 and 3 on Alinity i. Results were expressed as mean, standard deviation (SD), and coefficient of variation (CV%).

### Statistical analysis

All statistical processing and graph generation were performed using MedCalc Statistical Software version 20.104. For quantitative comparability, Pearson correlation coefficient ( $r$ ), Bland-Altman plots, and Passing-Bablok regression were used. For qualitative comparability, numerical data were transformed into binary data and labeled as “negative” (within the reference range) or “positive” (above the upper limit of the reference range), with respect to the reference range of each method as declared by the manufacturer (Cobas e601/ ECLIA negative  $\leq 30$  IU/mL; Alinity i/ CMIA negative  $\leq 5.8$  IU/mL). Only negative/ negative and positive/ positive pairs were considered concordant, while negative/ positive and positive/ negative pairs were considered discordant. For the qualitative analysis, the concordance rate (concordance rate = number of concordant pairs / total number of pairs) and Cohen kappa for inter-rater agreement with linear weights were used.

## RESULTS

A final number of 234 samples were introduced in the study and analyzed on both methods. For the quantitative method comparison, 11 pairs of data where the concentration was below or above the detection limits on at least one method, were excluded. Thus, the quantitative method comparison was performed on 223 pairs of data.

### Methods precision

Results of the repeatability and reproducibility experiments are shown in Tables 1 and 2 for the Cobas e601/ ECLIA and the Alinity i/ CMIA analyzers/ methods, respectively.

### Quantitative method comparison

TPO antibody results from the two methods showed a very strong correlation: Pearson  $r=0.85$  (95% CI: 0.81-0.88;  $p<0.0001$ ). With an intercept of -7.61 (95% CI: -10.31 to -4.23) and a slope of 1.10 (95% CI: 0.67-1.39), the Passing-Bablok regression equation was  $y=-7.61+1.10x$  (where  $x$  is Cobas e601/ ECLIA and  $y$  is Alinity i/ CMIA) and a significant deviation from linearity was observed (Cusum test for linearity  $p<0.01$ ).

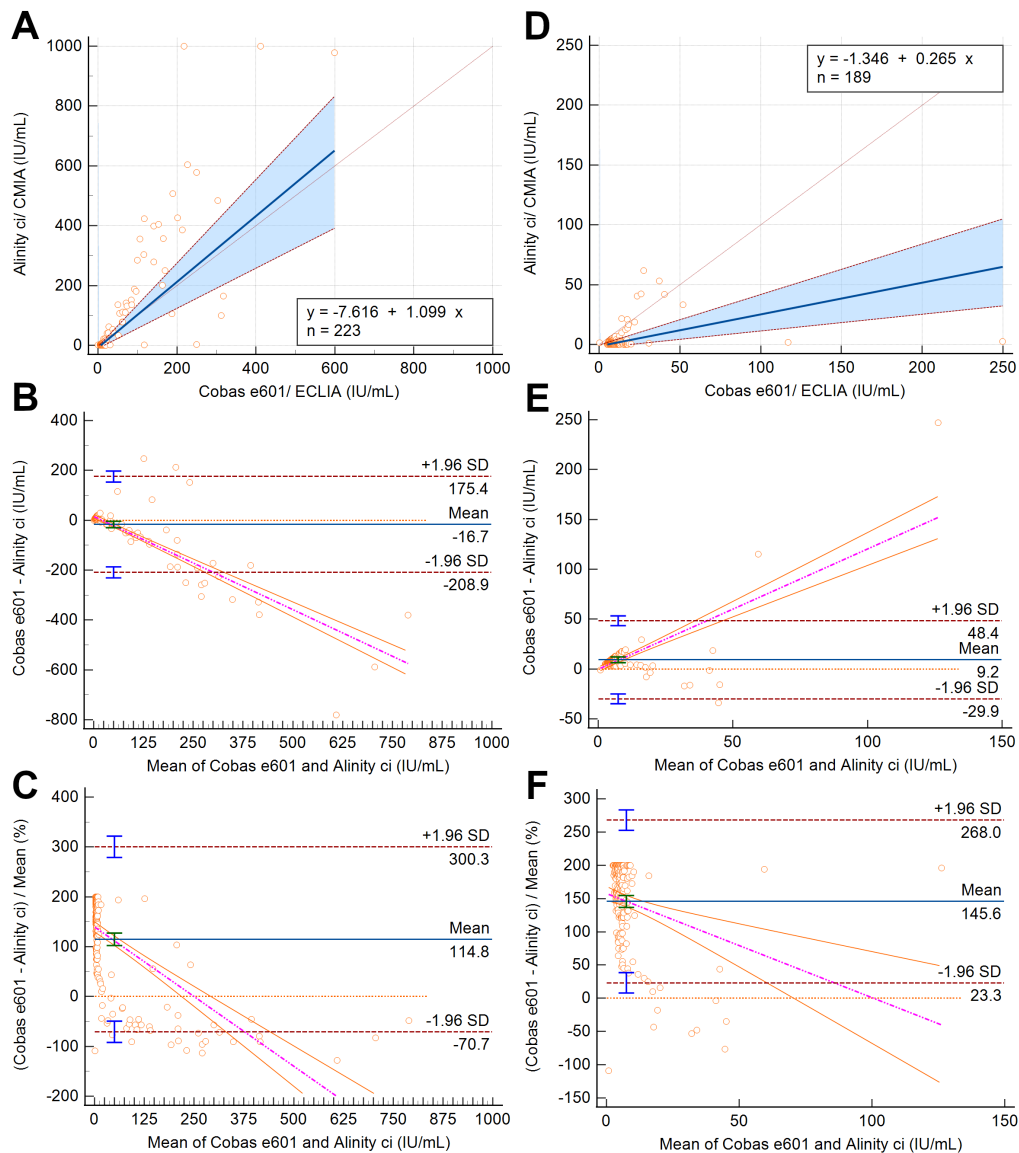
The Passing-Bablok and Bland-Altman scatter plots were first generated from all data ( $n=223$ , figure 1A-C), then again for samples within the 0-50 IU/mL range ( $n=189$ , figure 1D-F).

**Table 1. Results of the TPO antibody repeatability and reproducibility experiments on the Cobas e601 analyzer (ECLIA method), compared with the claims of the manufacturer. CV – coefficient of variation, SD – standard deviation.**

		Measured values		Claims of the manufacturer	
		Level 1	Level 2	Level 1	Level 2
<b>Repeatability</b>	Mean/ Target	49.65	114.46	50.10	115.00
	SD	1.84	1.81	5.01	8.05
	CV (%)	3.70	1.58	10.00	7.00
<b>Reproducibility</b>	Mean/ Target	43.88	104.80	43.88	104.80
	SD	2.04	4.09	4.73	7.84
	CV (%)	4.64	3.90	10.77	6.81

**Table 2. Results of the TPO antibody repeatability and reproducibility experiments on the Alinity i analyzer (CMIA method), compared with the claims of the manufacturer. CV – coefficient of variation, SD – standard deviation.**

		Measured values			Claims of the manufacturer		
		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
<b>Repeatability</b>	Mean/ Target	19.70	36.31	56.17	20.32	37.38	58.73
	SD	0.37	0.47	1.91	0.22	0.59	1.74
	CV (%)	1.87	1.29	3.40	1.08	1.57	2.96
<b>Reproducibility</b>	Mean/ Target	20.10	36.20	56.20	20.32	37.38	58.73
	SD	1.33	2.41	3.75	1.14	1.91	2.77
	CV (%)	6.61	6.65	6.67	5.61	5.11	4.71



**Fig. 1. Graphs based on all paired samples: A – the Passing Bablok regression plot, B – the Bland-Altman plot with differences plotted in absolute units of measurement (IU/mL), C – the Bland-Altman plot with differences plotted in percentages (%). Graphs based on samples within the 0-50 IU/mL range: D – idem A, E – idem B, F – idem C.**

## Qualitative method comparison

A qualitative comparison was also performed after labeling each result as either “negative” (within reference range) or “positive” (above the reference range). There were 47/234 positive results on Cobas e601/ ECLIA and 59/234 positive results on Alinity i/ CMIA. The concordance rate between methods was 218/234, that is 93.1%. Results of the inter-rater agreement statistical test are shown in Table 3.

## DISCUSSION

### Methods precision

In this study we first looked at the repeatability and reproducibility of the two methods, by performing small studies based on internal QC material and by comparing the results with the claims of the manufacturer. Firstly, it should be noted that the manufacturer of Alinity i/ CMIA (Abbott, U.S.) has more stringent coefficient of variation (CV) targets than the manufacturer of Cobas e601/ ECLIA (Roche, Switzerland) in terms of both repeatability and reproducibility (compare Tables 1 and 2). This may explain why, in practice, the mean and standard deviations (SDs)/ (CVs) obtained in this study for Alinity i/ CMIA failed to meet the claims of the manufacturer. In both repeatability and reproducibility experiments (exception: repeatability for level 2 of the internal QC material). However, the differences between our results and the claims of Alinity i manufacturer were minor for both means and SDs/ CVs (see Table 2) and therefore not considered to be a problem in practice.

Secondly, despite the more permissive claims of the Cobas e601 manufacturer, the repeatability and reproducibility experiments actually showed better results for Cobas e601/ ECLIA than for Alinity i/ CMIA – means closer to targets and lower CVs (compare Tables 1 and 2). However, without context, these results are just numbers and there are better ways of judging whether the analytical performance of a method is satisfactory than comparing it with the claims of the manufacturer. According to Westgard, TPO antibodies show a 11.3% within-subject biological variation and a 147.0% between-subject biological variation, which leads to the following desirable analytical performance specifications: imprecision (CV) 5.7%, bias 36.9%, and total allowable error (TEa) 46.2% [6]. Also, according to Westgard, the short-term imprecision (within-run or within-day; repeatability in the present study) should not exceed 1/4 of the total allowable error (TEa), while the long-term imprecision (day-to-day, between-day, or total; reproducibility in the present study) should not exceed 1/3 of the TEa [7]. Thus, it can be calculated that, in order to meet the desired specifications, the repeatability CB of any TPO antibody assay should not exceed  $0.25 \times 46.20\%$  (that is 11.55%) and reproducibility CV should not exceed  $0.33 \times 46.20\%$  (that is 15.24%). Finally, by comparing the CVs of the two methods reported in Tables 1 and 2 against the calculations above, it becomes apparent that in both cases (Cobas e601/ ECLIA and Alinity i/ CMIA) the CVs obtained in practice (ranging from 1.29% to 6.67%) are well within the desired analytical performance specifications as derived from biological variation (11.55% or 15.24%). This is all the more welcome since analytical performance specifications derived from biological variation are generally more stringent and difficult to meet in practice [8]. A limitation of this study was the lack of bias estimation, but this was not necessarily needed for a method comparison study. Moreover, while Alinity i had been recently introduced, the Cobas e601 analyzer had been a well-established analyzer in our laboratory at the time this study was performed and had also been part of a continuous external quality control program.

Correlation is a good initial statistical test for method comparison. Correlation does not assess agreement, but association. Thus, while high correlation does not guarantee good agreement, it shows that the two methods are linearly related and allows for subsequent statistical analysis using ordinary linear regression [9]. In the present study, the correlation was indeed very strong and statistically significant, but the correlation coefficient ( $r=0.85$ ) was much below the ideal value ( $r \geq 0.99$ ) for a wide range analyte such as TPO antibody [9]. Thus, simple linear regression could not be applied.

### Quantitative method comparison

An ideal regression equation would be  $y = x$ . Such cases are exceptionally rare, but in theory they are possible if the constant error/ intercept is 0 and the proportional error/ slope is 1. Thus, in practice, it is desired that the

**Table 3. Inter-method agreement according to the inter-rater agreement statistical test.**

Cobas e601/ ECLIA	Alinity i/ CMIA		
	Negative	Positive	
Negative	173	14	187 (79.9%)
Positive	2	45	47 (20.1%)
	175 (74.8%)	59 (25.2%)	234 (100.0%)
<b>Weighted Cohen's kappa (95% CI)</b>	<b><math>\kappa = 0.805 (0.714-0.896)</math></b>		

intercept and slope have as close values as possible to 0 and 1, respectively. It is considered that the intercept and slope are significantly different from their ideal values when their 95% CIs do not include the values of 0 and 1, respectively.

In the present study, the Passing-Bablok regression ( $y = -7.61 + 1.10x$ ; 95% CI for intercept -10.31 to -4.23 and 95% CI for slope 0.67-1.39) showed a significant deviation from linearity. The constant error was significant as the 95% CI of the intercept did not include the value of 0. The proportional error was technically acceptable as the 95% CI of the slope included the value of 1. However, these are purely statistical criteria for accepting a regression equation and should never replace clinical judgment. What is statistically acceptable may not be clinically acceptable and vice versa.

Let us look at the following hypothetical regression equation calculated between two methods for the measurement of plasma glucose concentration (mg/dL):  $y = 0.2 + 1.010x$ ; with constant error/ intercept 95% CI 0.1-0.3 mg/dL and proportional error/ slope 95% CI 1.008-1.012. While this equation violates both statistical criteria (CIs not including the values of 0 and 1), it is more than acceptable clinically where it translates to a "1% + 0.2 mg/dL" difference between methods. Thus, it becomes apparent that, despite meeting the statistical criteria, the value of the slope in the Passing-Bablok equation between ECLIA and CMIA is far from being acceptable clinically, as it translates to a proportional error of anywhere between -33% and 39%. Overall, the Passing-Bablok regression equation clearly reflected the lack of qualitative agreement between ECLIA and CMIA methods. To further support this observation, a brief calculation will show that, for an ECLIA result at the upper limit of the reference range for CMIA (5.8 IU/mL), the estimated calculated concentration for CMIA would be an absurd -1.23 IU/mL.

Bland-Altman plots are great visual aids in establishing whether two methods are comparable. In Figure 1B, the differences between methods are shown in absolute units (IU/mL) and in figure 1C they are shown in percentages (%). At first sight, with a mean of differences of -16.7 UI/mL ( $\pm 2SD$  range of -208.9 IU/mL to 175.4 IU/mL) or 114.8% ( $\pm 2SD$  range of -70.7% to 300.3%), the Bland-Altman plots confirm the conclusion of the Passing-Bablok regression analysis, that is the two methods do not agree quantitatively.

Further visual inspection of the two plots determines that Cobas e601/ ECLIA generates roughly up to three times higher results than Alinity i/ CMIA at low concentrations of up to 25-30 IU/mL. At higher concentrations, the trend changes, with Alinity i/ CMIA generating

increasingly higher results. Since the main clinical role of TPO antibody assays is to diagnose autoimmune diseases of the thyroid gland, we should focus on data pairs close to the upper reference limits of the two methods, that is 5.8 IU/mL for CMIA and 30 IU/mL for ECLIA. As most data sets are found in this range, it makes the analysis more reliable for this purpose. Therefore, regardless of the graph as a whole, the two methods display significant disagreement at the clinically important low levels of TPO antibody to be considered comparable.

Together, Passing-Bablok regression and Bland-Altman plots have so far shown that the two methods do not agree quantitatively, especially at the lower but clinically more relevant concentrations (<50 IU/mL, an arbitrarily chosen value fairly higher, but still close to the highest upper limit of reference range). To further verify this major finding, we decided to "zoom into" the 0-50 IU/mL range by removing all data pairs where both results were higher than 50 IU/mL (34 pairs removed). Then, a secondary statistical analysis was performed. A brief look at Figures 1D-F concludes that the two methods do not agree quantitatively.

As to why ECLIA and CMIA methods are not quantitatively comparable, the answer is most likely complex. Firstly, the disagreement between methods may simply be caused by the inherent differences between the two technologies, recombinant antigen, polyclonal TPO antibodies and tag(/label/probe) used in competition method. Secondly, the methods use different calibrators. Thirdly, other factors may generate differences between methods, such as preanalytical errors (collection, transport, preparation), endogenous analytical errors (type 1: hemolysis, hyperbilirubinemia, hyperlipemia; type 2: treatment, disease), non-reproducible analytical errors (carry-over, pipetting), or immune interferences (heterophilic antibodies, anti-streptavidin antibodies, anti-ruthenium antibodies, paraproteinemia, Hook effect, etc) [10]. Each of the two methods may be more or less susceptible to any number of interfering factors, thus giving rise to unpredictable and difficult to detect differences for the same patient sample. In the present study, we tried to minimize variability and interferences by excluding hemolyzed/ hyperbilirubinemic/ hyperlipemic samples, by processing the samples in virtually identical conditions, and by reducing the time between tests to less than an hour. However, other possible interfering factors may have played a role in the differences observed in this study.

### Qualitative method comparison

Given the unsatisfactory result of the quantitative analysis, we proceeded to perform a qualitative method comparison in order to establish whether the different

reference ranges of the two methods would compensate for inter-method quantitative disagreement. Continuous data were converted into binary data as detailed above. The concordance rate between methods, as defined above, was high (93.1%). However, concordance rate can be misleading due to agreement by chance, especially when the number of categories being used is small, as is the case in this study (two categories: negative and positive). Hence, the inter-rater agreement test was performed, which accounts for this limitation. The computed Cohen kappa was 0.805 which reflects a good (0.61-0.80) to very good (0.81-1.00) strength of qualitative agreement. Table 3 shows that it is more likely for Alinity i/ CMIA to give a positive result to a negative result on Cobas e601/ ECLIA (14/187, that is 7.48%) than is for Cobas e601/ ECLIA to give a positive result to a negative result on Alinity i/ CMIA (2/175, that is 1.14%). Therefore, the qualitative agreement is highest when the tested sample is negative on Alinity i/ CMIA.

A small-scale (n=71) yet to be reviewed study published as a preprint on Research Square compared Thermo Fisher Phadia Cap TPO antibody assay with three other methods: Abbott Architect, Roche Cobas, and Phadia EliA [11]. Briefly, the quantitative analysis revealed unsatisfactory correlation coefficients (0.95, 0.85, and 0.77, respectively) and Passing-Bablok regression equations ( $y=-1.77+1.85x$ ;  $y=10.76+1.21x$ ;  $y=-1.56+1.43x$ ; respectively). The qualitative analysis revealed that, out of 18 patients negative on Phadia Cap, 3 were positive on Abbott Architect and 4 were positive on Roche Cobas and Phadia EliA [11]. A direct comparison between Abbott Architect and Roche Cobas was not performed in this study.

There is a fair amount of literature on TPO antibodies. However, to our knowledge, method comparison studies on TPO antibody assays are scarce and mostly outdated. There is an acute need for such comparative studies for TPO and other assays, given the unprecedented pace at which new analyzers and improved technologies are introduced in the clinical laboratory. Comparison studies are important for method validation, benchmarking, and appropriate patient care. Running two or more chemistry/ immunology/ hematology analyzers at the same time is a common practice in large clinical laboratories. Thus, as we have previously discussed on multiple occasions, QC studies of various designs (comparative included) are essential for understanding the particularities of each method, establishing appropriate QC plans, deciding if/ when methods can be used interchangeably etc [8, 9, 11-14]. In such cases, the responsibility of studying method agreement rests primarily with the laboratory. If two methods are shown to agree, they may be declared comparable and therefore used interchangeably.

Regardless of the outcomes of such comparative studies, physicians should also be advised in order to enable them to make informed medical decisions.

## CONCLUSIONS

We studied the comparability of two TPO antibody assays – Cobas e601/ ECLIA and Alinity i/ CMIA. As the qualitative agreement was good to very good, the two methods may be used indiscriminately for initial testing of patients suspected of thyroid gland autoimmune pathologies. The highest agreement is achieved when the patient is negative on Alinity i/ CMIA. However, the two methods showed a poor quantitative agreement and therefore, if a patient is diagnosed based on one method, the monitorization of TPO antibody concentration should continue to be performed on the same method. Thus, for monitorization purposes, the two methods should not be used interchangeably as the results may mislead both physicians and patients, possibly leading to medical errors.

## ABBREVIATIONS

- CI – confidence interval (95%)
- CMIA – chemiluminescence microparticle immunoassay
- CV – coefficient of variation (%)
- ECLIA – electrochemiluminescence immunoassay
- HT – Hashimoto thyroiditis
- SD – standard deviation
- TEa – total allowable error
- TPO – thyroid peroxidase
- QC – quality control

## AUTHORS CONTRIBUTION

- AH – conceptualization, methodology, writing the original draft and reviewing it for important intellectual content
  - AL – data acquisition, analysis, and interpretation; writing the original draft
  - AT – data acquisition, analysis, and interpretation, writing the original draft
  - IBM – data acquisition, analysis, and interpretation; writing the original draft
  - MD – conceptualization, methodology, writing the original draft and reviewing it for important intellectual content
- All authors have read and agreed to the published version of the manuscript.

## CONFLICT OF INTEREST

None to declare.

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