Original Article

Comparison of test performance of biochemical parameters in semiautomatic method and fully automatic analyzer method

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Abstract

Background: The primary health-care center (PHC) and community health center (CHC) are not well equipped with laboratory services. Semiauto analyzer-based reporting could be an effective modality, provided that the performance standard is comparable to that of the fully automatic analyzer. So, the objective of this study was to analyze the test results of biochemical parameters in semiauto and fully automatic analyzer and to compare the quality performance. **Materials and Methods:** One hundred forty-nine patients undergoing routine biochemical investigations in the department laboratory were enrolled in this study. Two millimeter of venous blood was collected from all the participants and processed for urea, cholesterol, triglyceride (TG), serum glutamate-oxaloacetate transaminase (SGOT) (aspartate aminotransferase), and serum glutamate-pyruvate transaminase (SGPT) (alanine aminotransferase) by using standard kits (ERBA) in semiauto analyzer (Transasia Erba Chem5X by Calbiotech Inc. USA, semiautomated clinical chemistry analyzer) and the fully automatic analyzer (Cobas Integra 400 Roche, Germany) method. **Results:** There was high variability in the distribution of urea, TG, SGOT, and SGPT values in both measurement methods, whereas cholesterol data followed a normal distribution (skewness: 1.522, 1.037; kurtosis: 2.373, 0.693 in semiauto and automated methods, respectively). A significant positive correlation between both the methods of assessment was observed in urea, cholesterol, TGs, SGOT, and SGPT. The mean difference for urea was −9.85 ± 23.997 (LOA: 37.189, −56.88), whereas it was highest for TG −24.34 ± 38.513 (LOA: 51.144, −99.829), suggesting that both methods can measure urea with less difference in absolute values, whereas for TG the measurement values are highly variable. **Conclusion:** The test performance of biochemical parameters such as urea, total cholesterol, TGs, SGOT, and SGPT taken by semiauto analyzer and fully automatic analyzer method of assessment were highly related and comparable.

Keywords: Auto analyzer, biochemical parameters, performance standard, semiauto analyzer

Introduction

To ensure the reliability and accuracy of test results, the quality assurance is of paramount importance to provide the best possible patient care. The health outcomes depend on the accuracy of the testing and reporting as nowadays these test results are widely used in clinical and public health setups.[1] Hence, it is important to assure good laboratory performance by analyzing the complexity that involves many steps of activity and many people along with different laboratory processes and procedures.[2]

Clinical biochemistry is the most predominant diagnostic services in the field of laboratory Medicine and clinical medicine. It involves the measurement of substances in body fluids especially in the blood for

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the purpose of diagnosis, prevention, or treatment of disease.[3] These biochemical quantitative investigations give an accurate measure of extent of disease progression and hence help in greater understanding of the disease process. Reliability of the test performance depends on its accuracy, precision, specificity, and sensitivity of which precision and accuracy of the performance of analytical methods are the key measure of the quality performance.[4] Precision is measured by repeating the test run and it represents the reproducibility of an analytical method; accuracy being another important dimension defines how close the measured value is to the actual value.[5] The precision and accuracy of the test parameters should be acceptable for every biochemical method.[6] Specificity refers to the ability of an analytical method to determine solely the parameter of interest and sensitivity is the ability to detect even small quantities of the measured analyte.[7] Bias and imprecision are the major determinants of the test performance. Bias, an analytical characteristic, represents how the reported results differ from the actual value, whereas imprecision, or lack of reproducibility, is due to both physiological and analytical factors.[8] A number of factors broadly divided as preanalytical and analytical affect these determinants of quality performance. Deviation would result in laboratory errors, that is, use of unstable/deteriorated calibrators, unstable reagent blanks, error in calibration, or impure calibration material resulting in inadequate control on analytical variables causing systemic errors and inadequate control on preanalytical variables such as patient identity, sample collection and labeling, handling and transport, and fault in measuring devices causing the random errors.[9] Manual methods, semiauto analyzers, and fully automatic analyzer-based methods are in use in the Biochemistry laboratories. There has been a considerable increase in the demand of the biochemical parameters in clinical practice. To maintain the turnaround time and to meet the huge clinical need, mono-step methods (automated methods) are introduced to replace multistep cumbersome methods (Manual methods). Mono-step method using fully automatic chemistry analyzers performs many tests with the least manual involvements. The function of auto analyzer is to replace with automated devices the steps of pipetting and increase the accuracy and precision of the methods. Automation leads to reduction in variability of results and error of analysis as compared to manual means.[10]

Analytical methods used are the mainstay of the accuracy of the test results. Automation attains improved reproducibility but not improved accuracy. Hence, this study was conducted to analyze the test results of biochemical parameters in semiauto analyzer and fully automatic analyzer method and to compare the quality performance of the respective methodologies.

Materials and Methods

This was a hospital-based cross-sectional study conducted in the Department of Biochemistry from February 2017 to September 2019. One hundred forty-nine patients undergoing routine biochemical investigations in the department laboratory were enrolled in this study. After obtaining informed written consent, 2 mL of venous blood was collected from all the participants and processed for the biochemical analysis. The biochemical parameters such as urea, cholesterol, triglyceride (TG), serum glutamate-oxaloacetate transaminase (SGOT) (aspartate aminotransferase [AST]), and serum glutamate-pyruvate transaminase (SGPT) (alanine aminotransferase [ALT]) were estimated from the serum sample by using standard kits (ERBA) in semiauto analyzer (Transasia, Erba Chem5X, semiautomated clinical chemistry analyzer) and the fully automatic analyzer (Cobas Integra 400 Roche) method.

Estimation of urea by urease method (semiauto analyzer)

The reagent used contains: urease, glutamate dehydrogenase (GLDH), nicotinamide adenine dinucleotide (NADH), α-ketoglutaric acid, buffers, and stabilizers.

1. Urea was hydrolyzed in the presence of urease enzyme and water to yield ammonia and carbon dioxide:

$$NH2\text{-}CO\text{-}NH2 + H2O \xrightarrow{\text{Urease}} 2NH3 + CO2$$

2. The ammonia reacted with α-ketoglutaric acid and reduced NADH in the presence of GLDH to yield glutamic acid and nicotinamide adenine dinucleotide (NAD):

$$NH3 + \alpha\ \text{Keto glutarate} + NADH^{+} + H^{+} \xrightarrow{\text{GLDH}} \text{glutamate} + NAD + H2O$$

The rate of oxidation of NADH to NAD was measured at 340 nm by semiauto analyzer and was proportional to the urea concentration.[11]

Estimation of urea by full automatic analyzer (kinetic ureases and glutamate dehydrogenase method)

The serum sample was used to estimate the urea levels by full automatic analyzer. In the reaction, urea is hydrolyzed by urease to ammonia and carbon dioxide. GLDH catalyzes the condensation of ammonia and α-ketoglutarate to glutamate with the concomitant oxidation of reduced β-NADH to β-NAD. Change in the absorbance was directly proportional to the urea levels.[12]

Estimation of total cholesterol by semiauto analyzer (cholesterol oxidase and peroxidase method)

Cholesterol esterase (CHE) hydrolyzed the esterified cholesterol to free cholesterol. The free cholesterol was oxidized to form hydrogen peroxide (H_2O_2), which further reacted with phenol and 4 amino antipyrine by peroxidase to form red-colored quinoneimine dye complex. The intensity of the color was directly proportional to the cholesterol in the serum sample.[13]

$$\text{Cholesterol esters} + H_2O \xrightarrow{\textit{Cholesterol Esterase}} \text{Cholesterol} + \text{Fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\textit{Cholesterol Oxidase}} \text{Cholestenone} + H_2O_2$$

$$H_2O_2 + \text{4 Aminoantipyrine} + \text{Phenol} \xrightarrow{\textit{Peroxidase}} \text{Red Quinoneimine dye} + H_2O$$

Estimation of total cholesterol by full automatic analyzer (cholesterol oxidase and peroxidase method)

Cholesterol esters in serum were hydrolyzed by CHE. The free cholesterol produced was oxidized by cholesterol oxidase (CHO) to cholest-4-en-3-one with the simultaneous production of H_2O_2, which oxidatively coupled with 4-aminoantipyrine and phenol in the presence of peroxidase to yield a chromophore. The red quinoneimine dye formed was measured at 540/600 nm as an increase in absorbance:[14]

$$\text{Cholesterol ester} \xrightarrow{\text{CH}} \text{Cholesterol + fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{CH}} \text{Cholest-4-en-3-one} + H_2O_2$$

$$2H2O2 + \text{4-aminoantipyrine} + \text{phenol} \xrightarrow{\text{Peroxidase}} \text{Red dye} + 4\,H_2O$$

Estimation of triacylglycerol by semiauto analyzer (enzymatic glycerol phosphate oxidase and peroxidase method)

Lipoprotein lipase hydrolyzed TGs to glycerol and free fatty acid. The glycerol formed with ATP in the presence of glycerol kinase formed glycerol 3 P, oxidized by glycerol phosphate oxidase to form H_2O_2, that reacted with phenolic compound and 4-amino antipyrine by the catalytic action of peroxidase to form a red-colored quinoneimine dye complex, intensity of which was directly proportional to the TGs present in the sample:[15]

$$\text{Triglycerides} \xrightarrow{\text{Lipoprotein Lipase}} \text{Glycerol + free fatty acid}$$

$$\text{Glycerol + ATP} \xrightarrow{\text{Glycerol Kinase}} \text{Glycerol 3 } P + \text{ADP}$$

$$\text{Glycerol 3 } P + O2 \xrightarrow{\text{Glycerol phosphate oxidase}} \text{Dihydroxy acetone phosphate} + H2O2$$

$$H2O2 + \text{4 aminoantipyrine} + \text{phenol} \xrightarrow{\text{Peroxidase}} \text{Red quinoneimine} + H2O$$

Estimation of triacylglycerol by fully automatic analyzer (enzymatic glycerol phosphate oxidase and peroxidase: GPO POD method)

TGs in the sample were hydrolyzed by lipoprotein lipase to glycerol and free fatty acids. Glycerol kinase acted on glycerol to form glycerol 3 P, oxidized by glycerol phosphate oxidase to form H_2O_2, that reacted with chlorophenolic compound and 4-amino antipyrine by the catalytic action of peroxidase to form a red-colored benzoquinone mono imino phenazone complex.[16]

Estimation of SGOT by semiauto analyzer (International Federation of Clinical Chemistry [IFCC] kinetic method)

SGOT (AST) catalyzes the transfer of an amino group from L-aspartate to α-ketoglutarate. The rate of reaction was monitored using a coupling enzyme malate dehydrogenase (MDH), whereby the oxaloacetate formed was converted to malate in the presence of NADH. The oxidation of NADH was measured by monitoring the decrease in absorbance at 340 nm:[17]

$$\text{L-Aspartate} + \text{2-Oxoglutarate} \xrightarrow{\textit{Aspartate aminotransferase}} \text{Oxaloacetate} + \text{L-Glutamate}$$

$$\text{Oxaloacetate} + \text{NADH} \xrightarrow{\textit{Malate Dehydrogenase}} \text{Malate} + \text{NAD}$$

$$\text{Sample pyruvate} + \text{NADH} \xrightarrow{\textit{Lactate Dehydrogenase}} \text{L-Lactate} + \text{NAD}$$

Estimation of SGOT by fully automatic analyzer (IFCC kinetic method)

AST catalyzes the transfer of the amino group from L-aspartate to α-ketoglutarate to yield oxaloacetate and L-glutamate. MDH catalyzed the reduction of oxaloacetate with simultaneous oxidation of NADH + to NAD. The resulting rate of decrease in absorbance at 340 nm was directly proportional to the AST activity. Lactate dehydrogenase (LDH) was added to prevent interference from endogenous pyruvate which is normally present in serum.[17]

Estimation of SGPT by semiauto analyzer (IFCC kinetic method)

ALT or SGPT catalyzes the reversible transfer of an amino group from alanine to oxoglutarate forming glutamate and pyruvate. The pyruvate produced was reduced to lactate by LDH and NADH: [17]

$$\text{L-Alanine} + \text{2-Oxoglutarate} \xrightarrow{\textit{Alanine aminotransferase}} \text{Pyruvate} + \text{L-Glutamate}$$

$$\text{Pyruvate} + \text{NADH} \xrightarrow{\textit{Lactate Dehydrogenase}} \text{L-Lactate} + \text{NAD}$$

Estimation of SGPT by fully automatic analyzer (IFCC kinetic method without pyridoxal phosphate)

ALT transfers the amino group from alanine to α-oxoglutarate to form pyruvate and glutamate. LDH catalyzed the reaction with pyruvate and NADH to produce lactate and NAD+. The decrease in absorbance due to the consumption of NADH was measured at 340 nm and was proportional to the ALT activity in the sample.[17]

The data generated by estimating these biochemical parameters by the semiauto analyzer and the fully automatic analyzer method were registered for statistical analysis.

Statistical analysis

Data were entered in Microsoft Excel 2013 and were analyzed using Statistical Package for the Social Sciences (SPSS SPSS by IBM) software program, version 20.0. Normality of data was assessed using skewness and kurtosis, normality plots, and statistical tests of normality such as Shapiro–Wilk and Kolmogorov–Smirnov tests. Quantitative data were represented in the form mean and standard deviation (SD). Correlation

between two quantitative data was assessed using spearman's correlation as the data was not distributed normally.

Bland–Altman plot analysis was performed to assess the measures of agreement between two different methods of estimation of a biochemical parameter. Scatter plot was plotted between mean on the *x*-axis and difference of two measurement methods on the *y*-axis and limits of agreement were calculated using mean ± 1.96 SD of the differences between two measurements. A scatter that is evenly distributed above and below the zero line of no difference indicates that there is no systematic bias between the two methods and a scatter that is largely above or largely below the zero line of no difference or a scatter that increases or decreases with the mean value indicates a systematic bias between both methods. A Kendall's correlation coefficient between the means and the differences was obtained to confirm the uniformity of variance in the repeated measurements.

The intra-class correlation coefficient (ICC) was used to describe the relative extent to which two continuous measurements taken by two different methods of assessment are related. A high value of ICC of 0.95 indicates that 95% of the variance in the measurement is due to the true variance between the methods and 5% of the variance is due to measurement error or the variance within two methods.

Results

This study was conducted on 149 patients and the biochemical parameters obtained were compared using semiauto and automated methods.

Table 1 represents the mean and SD, skewness, kurtosis of serum urea, cholesterol, TG, PT, and OT values along with correlation between two semiauto and automated methods. Skewness and kurtosis values in Table 1 indicated that there was a very high variability in the distribution of urea, TG, OT, and PT values in both measurement methods, whereas cholesterol data followed a normal distribution (skewness: 1.522, 1.037; kurtosis: 2.373, 0.693 in manual and automated methods, respectively). There was a significant positive correlation between both the methods of assessment in all the aforementioned five parameters.

Table 1 and Figure 1 show that serum urea gave a correlation coefficient of $r = 0.691$; $P = 0.0001$ at 95% confidence interval with a regression equation of $y = 0.8966x + 32.859$ (where y = measurements in automated urea, x = measurement in semiauto urea). Serum cholesterol gave a correlation coefficient of $r = 0.798$; $P = 0.0001$ at 95% confidence interval with a regression equation of $y = 1.3144\times$ =0.133 (where y = measurements in automated cholesterol, x = measurement in semiauto cholesterol).

Table 1: Descriptive statistics, skewness, kurtosis, and correlation between two measurement methods

	Mean	Std. deviation	*n*	Skewness	Kurtosis	Spearman correlation	*P*
Semiauto urea	31.74	26.118	149	3.432	15.801	0.691	0.0001
Auto urea	41.58	41.073	149	2.724	8.032		
Semiauto cholesterol	142.79	61.498	149	1.522	2.373	0.798	0.0001
Auto cholesterol	161.30	67.555	149	1.037	0.693		
Semiauto TG	136.17	67.470	149	2.258	5.989	0.821	0.0001
Auto TG	160.51	92.825	149	2.596	7.402		
Semiauto OT	42.42	76.576	149	4.533	20.42	0.653	0.0001
Auto OT	56.95	102.384	149	4.187	17.455		
Semiauto PT	37.52	41.046	149	5.427	35.923	0.551	0.0001
Auto PT	59.99	104.540	149	7.995	77.454		

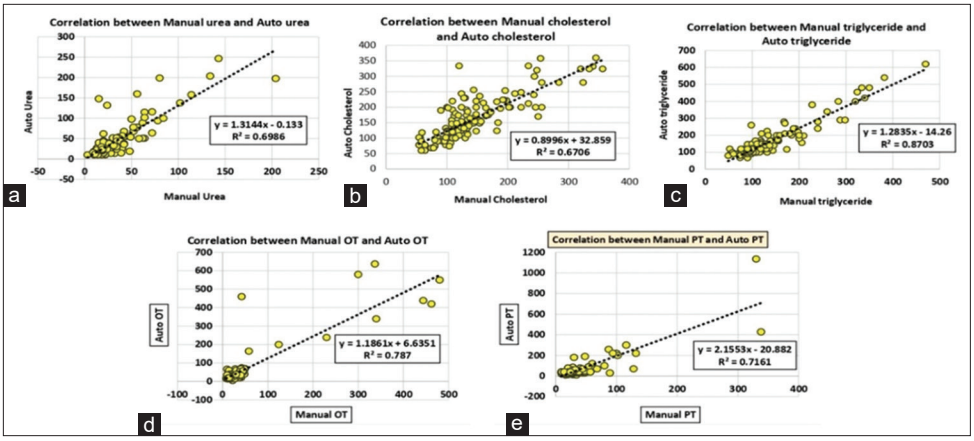

Figure 1: Correlation between two measurement methods. (a) Correlation between manual and automated urea. (b) Correlation between manual and automated cholesterol. (c) Correlation between manual and automated triglyceride. (d) Correlation between manual OT and automated OT. (e) Correlation between manual and automated PT

Serum TG gave a correlation coefficient of $r = 0.821$; $P = 0.0001$ at 95% confidence interval with a regression equation of $y = 1.2835x - 14.26$ (where y = measurements in automated TG, x = measurement in semiauto TG). Serum SGOT gave a correlation coefficient of $r = 0.653$; $P = 0.0001$ at 95% confidence interval with a regression equation of $y = 1.1861x + 6.6351$ (where y = measurements in automated SGOT, x = measurement in semiauto SGOT). Serum PT gave a correlation coefficient of $r = 0.551$; $P = 0.0001$ at 95% confidence interval with a regression equation of $y = 2.1553x - 20.822$ (where y = measurements in automated PT, x = measurement in semiauto PT). Hence, it can be summarized that the measurements in semiauto and automated methods showed significant positive correlation.

After applying Bland–Altman analysis of agreement, on comparison between semiauto and automated methods, the mean difference was found to be less for urea –9.85 ± 23.997 (LOA: 37.189, –56.88) [Table 2], whereas it was highest for TG –24.34 ± 38.513 (LOA: 51.144, –99.829), suggesting that both methods can measure urea with less difference in absolute values, whereas for TG the measurement values are highly variable [Table 3]. The high intra-class correlation of 0.731 (PT) to 0.94 (TG) suggested the two continuous measurements taken by two different methods of assessment are highly related [Figure 2].

The correlation between mean and difference of two methods showed weak correlation between two methods. Correlation coefficient was highest between urea (–0.386) and lowest between cholesterol (–0.181). The weak correlation coefficient suggests that both the methods are similar in measurement.

Discussion

The medical requirements for performance of the biochemical parameters can best and most easily be described in terms of the

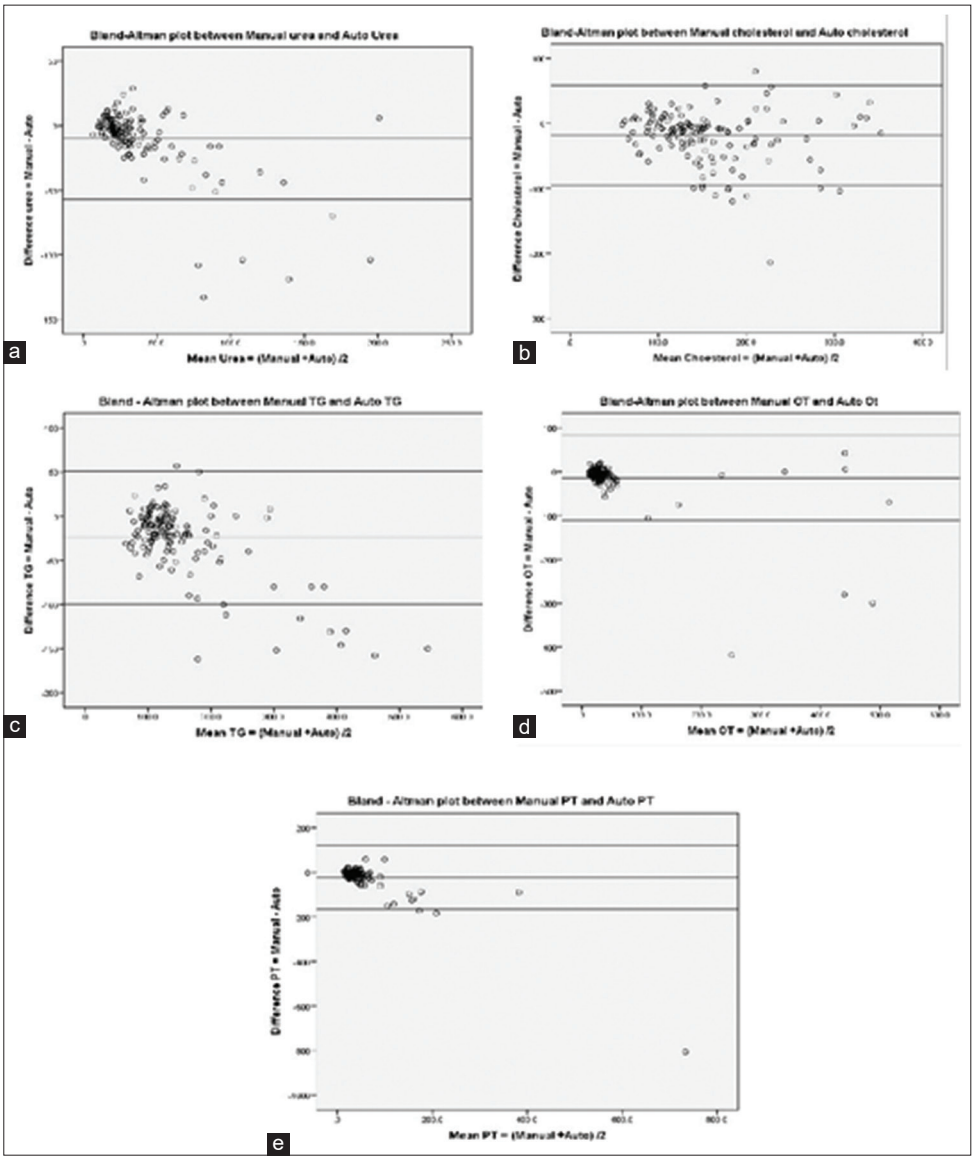

Figure 2: Agreement between manual and auto methods (a) Urea (b) Cholesterol (c) TG (d) OT (e) PT

Table 2: Bland-Altman analysis of agreement between two measurement methods

	Mean	Std. deviation	Limits of agreement (LOA)		Cronbach α	95% CI	
			Upper	Lower		Upper	Lower
Difference urea=Semiauto-auto	-9.85	23.997	37.189	-56.880	0.862	0.809	0.90
Difference Cholesterol=Semiauto-auto	-18.52	39.261	58.434	-95.468	0.898	0.859	0.926
Difference TG=Semiauto-auto	-24.34	38.513	51.144	-99.829	0.94	0.918	0.957
Difference OT=Semiauto-auto	-14.53	49.354	82.204	-111.264	0.919	0.889	0.942
Difference PT=Semiauto-auto	-22.47	73.150	120.905	-165.845	0.731	0.628	0.805

Table 3: Correlation between the means and the differences to confirm the uniformity of variance

	Kendall's tau_b	Difference urea=manual-auto
Mean urea=(manual + auto) /2	Correlation coefficient	-0.386
	P	0.0001
		Difference cholesterol=manual-auto
Mean cholesterol=(manual + auto) /2	Correlation coefficient	-0.181
	P	0.0001
		Difference TG=manual-auto
Mean TG=(manual + auto) /2	Correlation coefficient	-0.224
	P	0.0001
		Difference OT=manual-auto
Mean OT=(manual + auto) /2	Correlation coefficient	-0.222
	P	0.0001
		Difference PT=manual-auto
Mean PT=(manual + auto) /2	Correlation coefficient	-0.231
	P	0.0001

total analytic error that represents both random and systematic components. The performance standard (PS), summarizes the medical specification for total analytic error.[18] The estimates of analytic error in the test method were compared with the defined allowable error (EA). If the errors observed in the test method are comparable to the medically allowable errors, then the method performs acceptably. If larger difference is observed, then the errors need to be decreased by appropriate modifications or else the method is unacceptable.[19]

In this study biochemical parameters obtained were compared using semiauto analyzer and automated methods. High variability in the distribution of urea, TG, SGOT, and SGPT values observed in both measurement methods as compared to cholesterol data indicating significant positive correlation between both the methods of assessment in all the above mentioned five parameters. This is in concordance with the previous study conducted by Swetha and Kavitha,[20] in which significant positive correlation at 95% confidence interval was documented in the SGOT and SGPT levels between semiauto and automated analyzers using the same analytical methodology. Ilanchezhian *et al.*[21] found lesser blood glucose values in glucometer as compared to chemical analyzer with lesser values of glucose in semiauto -analyzer as compared to auto analyzer that they attributed to changes in the temperature, humidity and transport conditions. Bland–Altman analysis of agreement, on comparison between semiautomatic and fully automated methods, the mean difference was found to be less for urea and highest for TG suggesting both methods can measure urea with less difference in absolute values, whereas for TG the measurement values are highly variable that could be attributed to certain variables such as sample capacity of the tubes, sample volume, dead volume, and throughput walkaway time.[22]

Many studies were done to compare the effectiveness of biochemical method with the molecular method with variable and contradictory results.[23,24]

In our study the high intra-class correlation of 0.731 (for SGPT) to 0.94 (for TG) suggested that two continuous measurements taken by two different methods of assessment are highly related, this satisfies the criteria that can be used to judge whether an analytical method has acceptable precision and accuracy. However, factors such as recovery, interference, and running in replicates must be taken into account, while conduction method-evaluation studies were taken into account to evaluate the performance of a new laboratory method. Analytical variations observed in this study could be due to testing methods and equipment, which may cause analyte values to be slightly different each time they are measured.

The district-level health services have an urgent need for improvement in diagnostic laboratory quality reporting by adopting latest technologies. Most of the peripheral health-care institutions are not equipped with fully automated chemistry analyzers. Semiauto analyzer-based biochemical reporting of routine parameters have comparable and dependable results, provided there is continuous, coordinated, and comprehensive care by primary care physicians and staff. The inferior quality of care reemphasizes the role of primary care physicians in the screening, diagnosis and treatment of common metabolic disorders. The district-level health-care facilities need reorganizations for better management of chronic disease management programs.

Conclusion

The test performance of biochemical parameters such as urea, total cholesterol, TG, SGOT, and SGPT taken by semiauto analyzer, and fully automatic analyzer method of assessment were highly related and comparable, with a significant positive correlation. Semiauto analyzer could be an efficient alternative in peripheral setups to provide quality biochemistry laboratory services.

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Conflicts of interest

There are no conflicts of interest.

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