Evaluation of visual serum indices measurements and potential false result risks in routine clinical chemistry tests in Addis Ababa, Ethiopia

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Background:
Serum indices (SI) including hemolyzed, lipemic, and icteric samples, affects the accuracy of test result. The aim of this study was to evaluate SI values done by visual inspections and potential false result risks by comparing with actual measurements done by Cobas 6000 Chemistry analyzer at Ethiopian Public Health Institute (EPHI), Addis Ababa, Ethiopia.

Methods:
An observational, cross-sectional study was conducted from April to May 2017 on samples referred to Clinical Chemistry laboratory of EPHI, Ethiopia. These samples SI values, after visual inspection by three trained observers, was analyzed again on Roche Cobas 6000 analyzer (RCA). The generated data was analyzed by using weighted kappa methods on STAT statistical software version 20.

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ABSTRACT

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Key words: hemolysis, icteric, lipemic, serum indices
Results:
From a total of 1509 samples, SI values identified by the RCA as hemolysis, icteric, and lipemic were 933 (62%), 74(5%) and 59(4%) respectively. The SI average weighted kappa between RCA and visual inspection were: 0.1870, 0.3421, and 0.1259 for hemolysis, icteric, and lipemic samples, respectively. Combined inter-observers variability among observers for hemolysis, icterus, and lipemic samples were 0.4758, 0.3258, and 0.3628 respectively. The best agreement among observers was in the case of hemolysis (0 grades), while the lowest agreement was observed in the case of icterus (+3 grades). In addition, test parameters, such as CK-MB (22%), and LDH (20%) were falsely accepted, whereas Cl⁻ and Na⁺ (up to 25%) were falsely rejected tests by observers. On the other hand, results rejected by Cobas SI assessments included CK-MB (22%), LDH (20%), and BIL-D (4%).

Conclusion:
Visual inspection of SI showed poorly agreement with automated system. Thus, there is genuine need for more training of Laboratory professionals on identification of SI, and as much as possible SI should be done by automated system to improve quality of test results.

Abbreviations
AAU: Addis Ababa University
ALT: Alanine Amino Transferase
AST: Aspartat Amino Transferase
CCH: Clinical Chemistry
CK-MB: Creatine Kinase
EPHI: Ethiopian Public Health Institute
LDH: Lactate Dehydrogenase
RPM: Revolution Per Minute
SI: Serum Indices

SMLS: School of Medical Laboratory Sciences
SOPS: Standard Operating Procedures
UIBC: Unsaturated Iron Binding Capacity
HIL: Hemolysis, Icterus, Lipemia

BACKGROUND
In clinical laboratory activities, 68-77 percent of errors occur in the pre-analytical phase [1, 2]. Efficient management and monitoring of the pre-analytical sources of interference is critical to the quality of clinical laboratory analytical process and to the quality of patient results. Clinical laboratory errors can lead to incorrect results dispatched to physicians that result in erroneous patient laboratory report interpretation and conclusion. This in turn highly affects the whole healthcare system [3]. Among the main causes of pre-analytical error, serum indices (SI) which includes Hemolysis, Icterus and Lipemia (HIL) are the leading ones.

Hemolysis is one of the major causes of pre-analytical source of error. It accounts for 40% to 70% of unsuitable samples [4]. Hemolyzed samples (>95 percent) are attributable to in vitro processes resulting from inappropriate sample collection technique or transport [5]. The hemolyzed sample affect different clinical tests by mechanism of leakage of constituents of red blood cells into plasma or serum, spectrophotometric/colorimetric interference by hemoglobin, participation of the hemoglobin in the reaction through inhibition, and dilution of serum or plasma components [6].

Lipemia, the other cause of pre analytical errors, results from increased concentration of triglyceride-rich lipoproteins in blood. This lipemic serum causes cloudy/turbid appearance of serum or plasma. Lipemic sample test interference is associated with light scattering effects, and may
increase absorbance during end point reactions and non-blanked reactions for some analytes. In addition, lipemia is associated with volume displacement effect, and greatly decreases the value of some analytes [7].

Icterus, another main cause of pre-analytical errors, result from diseases associated with increased bilirubin production or inappropriate bilirubin excretion. Icterus samples interfere in laboratory tests by direct interaction with different test analytes or reagents resulting in decreased analyte values, and creating spectral interferences during color measurement [6, 8].

Different studies have showed that visual assessments have limitations, including subjectivity, difficult in identification by the naked eye, time consumption, and inability to inspect by naked eye when the sample is covered by multiple barcodes.

In Ethiopia medical laboratories, common interferences are usually determined by using visual assessments. But up to the knowledge of this study groups, there is no study conducted on comparison of serum indices value against visual inspection of the samples.

Thus, the aim of this study was to compare Serum Indices value measurements and visual assessment using Cobas 6000 chemistry analyzer, and identify potential false result risks at the routine clinical chemistry laboratory at Ethiopian Public Health Institute (EPHI), Addis Ababa, Ethiopia.

**MATERIALS AND METHODS**

This research was observational, cross-sectional study, conducted from April to May 2017 at EPHI Clinical Chemistry Laboratory, Addis Ababa, Ethiopia. All patient samples referred to EPHI Clinical chemistry department, during the study periods, were used as a source of samples. During actual study, all referred samples except those that were unlabeled and with insufficient volume, were utilized. Accordingly, a total of 1509 samples were analyzed visually and using serum indices (Roche Serum Indices Gen 2). Visual inspection was done by laboratory technologists who took intensive training for three days from experienced laboratory technologist to identify interferences. In addition, to standardize the visual assessment, colored photo and categories of HIL in serum or plasma grading were prepared (Table 1).

| Grading | Hemolysis SI indices value, hemoglobin, mg/dl | Icteric SI indices value, bilirubin in mg/dl | Lipemic SI indices value, intralipid, mg/dl |
|---------|---------------------------------------------|-------------------------------------------|-----------------------------------------|
| 0       | <9                                          | <2.5                                     | <40                                     |
| +1      | 10-199                                      | 2.5-4.9                                  | 40-99                                   |
| +2      | 200-299                                     | 5.0-9.9                                  | 100-199                                 |
| +3      | 300-399                                     | 10-119.9                                 | 200-299                                 |
| +4      | >400                                        | >40                                      | >300                                    |

SI=Serum indices; *adapted from Lim et al [9].
Laboratory analysis

Blood samples (3-5 ml) without anticoagulant were collected from each patients, and centrifuged at 2500 revolution per minute (RPM) for 5 minutes according to EPHI clinical chemistry standard operating procedure (SOP). Then the separated serum samples were inspected visually by three laboratory technologists who participated in the study. Visual inspection was performed with grading according to standardized colored photos and a consensus was reached when doubtful samples were interpreted according to these photos.

Those samples which were evaluated visually were analyzed again for serum indices using Roche serum indices of Roche Gen 2 without delay by Cobas 6000 (Roche Diagnostics, Mannheim, Germany). In addition, the Cobas 6000 instrument was used to perform 22 different routine clinical chemistry tests (as requested by the physicians), and assessed the degree of interfaces on the test parameters.

Description of Roche serum indices

The Serum Indices Gen. 2 assay is based on calculations of absorbance measurements of diluted samples at different dichromatic wavelength pairs to provide a semi-quantitative representation of levels of lipemia, hemolysis and icterus present in serum and plasma samples. The analyzers take an aliquot of the patient specimen and dilute it in saline solution (0.9 % sodium chloride) to measure the absorbance for lipemia at 660 nm (primary wavelength) and 700 nm (secondary wavelength), for hemolysis at 570 nm (primary wavelength) and 600 nm (secondary wavelength), and for icterus at 480 nm (primary wavelength) and 505 nm (secondary wavelength). From these absorbance values the instrument calculates the SI [10].

Quality control and quality assurance

Before running patient samples, two levels of quality control materials were run to assess the functionality of the instrument and test procedures. In addition, well-trained and experienced laboratory professionals participated in the analysis procedure.

Data management and statistical analysis

The statistical analyses were performed by STATA version 14. Prior to analyses, the entered data were cross-checked against the original paper data collection form. Agreement between serum indices and observers were assessed by weighted kappa. Interpretation of kappa coefficient was as follows: - <0 = Less than chance agreement, 0.00-0.20 = Slight agreement, 0.21-0.40 = Fair agreement, 0.41-0.60 = Moderate agreement, 0.61-0.80 = Substantial agreement, 0.81-1.00 = Almost perfect agreement [11].

Ethical consideration

Before the research work, ethical clearance was obtained from the School of Medical Laboratory Sciences, College of Health Sciences, Addis Ababa University. In addition, the project was presented to EPHI scientific and Ethical Review Office (SERO) and got additional ethical approval. In order to protect patient confidentiality patient identifiers like name and telephone number were not collected. Moreover, Patient’s registration (sample ID) coding system and patient detail information’s were secured.

RESULTS

Comparison of visual inspection and serum indices of Roche for hemolysis among observers

From a total of 1509 samples, cobas automated SI measurement revealed that 933 (62%) were hemolyzed. These values when assessed by visual inspection, observer one, two and three
recognized 257 (17%), 343 (23%) and 336 (22%) samples, respectively. The weighted kappa between observers and serum indices was 0.1709 for observer 1, 0.1764 for observer 2, and 0.2136 for observer 3. Accordingly, there was slight agreement with Cobas by observer 1 and 2, and fair agreement between observer 3 and serum indices, as shown in Table 2.

Comparison of visual inspection and serum indices of Roche for Icterus among observers

From a total of 1509 samples, automated serum indices revealed that 74 (5%) were icteric. Meanwhile, when icterus assessed by Visual inspection, observer one, two and three reported 158 (11%), 76 (5%) and 81 (5.4%) samples, respectively. The weighted kappa shows fair agreement for observer one, and moderate agreement for observer two and three, with Kappa values of 0.2682, 0.4136, and 0.3445, respectively, as shown in Table 3.

Comparison of visual inspection and serum indices of Roche for lipemia among observers

From a total of 1509 samples, Cobas 6000 SI value revealed 59 (4%) as lipemic. Meanwhile, observer one, two and three upon visual assessment identified 207 (14%), 208 (14%) and 148 (10%) samples, respectively as lipemic. The weighted k coefficient was 0.1169 for observer 1, 0.1221 for observer 2, and 0.1386 for observer 3 with slight agreement between serum indices and visual inspection for all observers, see Table 4.

Inter-observers variability for visual inspection among observers

In the present study, agreement among Inter-observers variability was assessed. Accordingly, the best overall agreement among observers was in the assessment of hemolysis (0 grade) with the kappa value of 0.6600 and the lowest degree of agreement was observed in assessing icterus (+3 grade) with kappa value 0.1016, as shown in Table 5.

Potential risk introduced by observers

One of the objectives of this study was to assess risk of false result delivery following poor visual SI evaluations. Accordingly, test parameters which were falsely accepted by visual observers while rejected by Cobas SI assessments included CK-MB (22%), LDH (20%), and BIL-D (4%), as shown in Figure 5.

On the other hand, routine clinical chemistry tests which were falsely rejected by visual observers while accepted by cobas serum indices analysis, included Cl\(^-\) and Na\(^+\) (n=178, 25%), and BIL-T (n=17, 7%), as shown in Figure 2.

DISCUSSION

Efficient laboratory service is the cornerstone of modern health care systems. In this regard, mainly in the clinical chemistry areas, scientific innovations contributed a lot to substantial improvements in reducing laboratory diagnostic errors. Nevertheless, shortage of advanced clinical chemistry instruments, affordability of instrument running costs, along with shortage of experienced laboratory professionals are still a challenge in most developing countries to produce quality laboratory results.

In the present study, out of the 1509 specimens submitted to EPHI for clinical chemistry tests, hemolysis was detected in 933 (62%) samples. For hemolysis, visual inspection showed a fair agreement with automated detection, at a kappa value of less than 0.21 for observers. A similar study performed by Giuseppe L. et al, compared detection of hemolysis in 800 serum samples, where 8% of samples were hemolytic and the automation versus visual inspection difference showed a weighted kappa value of 0.42. Hemolysis was overestimated using visual assessment of serum samples and
### Table 2: Comparison of visual inspection and serum indices of Roche for hemolysis, EPHI, Ethiopia, 2017

| Serum Indices | Visual Inspection of hemolysis |  |  |  |  |  | Level of agreement | Kappa |
|---------------|-------------------------------|---|---|---|---|---|------------------|-------|
| Observer 1    |                              | 0 | +1 | +2 | +3 | +4 | Total            |       |
| 0             | 576                           | 8 | 0  | 0  | 1  |    | 576              |       |
| +1            | 667                           | 168| 57 | 21 | 4  |    | 917              |       |
| +2            | 0                             | 2 | 2  | 2  | 2  |    | 8                |       |
| +3            | 0                             | 1 | 3  | 0  | 1  |    | 5                |       |
| +4            | 0                             | 0 | 1  | 0  | 2  |    | 3                |       |
| Total         | 1234                          | 179| 63 | 23 | 10 |    | 1509             |       |
| Observer 2    |                              | 0 | +1 | +2 | +3 | +4 | Total            |       |
| 0             | 517                           | 9 | 3  | 2  | 1  |    | 576              |       |
| +1            | 604                           | 143| 98 | 52 | 20 |    | 917              |       |
| +2            | 0                             | 1 | 1  | 3  | 3  |    | 8                |       |
| +3            | 1                             | 0 | 1  | 2  | 1  |    | 5                |       |
| +4            | 0                             | 0 | 0  | 0  | 3  |    | 3                |       |
| Total         | 1166                          | 153| 103| 59 | 28 |    | 1509             |       |
| Observer 3    |                              | 0 | +1 | +2 | +3 | +4 | Total            |       |
| 0             | 565                           | 8 | 2  | 0  | 1  |    | 576              |       |
| +1            | 607                           | 208| 78 | 13 | 11 |    | 917              |       |
| +2            | 0                             | 1 | 3  | 0  | 4  |    | 8                |       |
| +3            | 0                             | 1 | 2  | 1  | 1  |    | 5                |       |
| +4            | 1                             | 0 | 0  | 2  | 6  |    |                  |       |
| Total         | 1173                          | 218| 85 | 14 | 19 |    | 1506             |       |
| Observer | Serum Indices | Visual inspection of hemolysis | Level of agreement | Kappa |
|----------|---------------|-------------------------------|--------------------|-------|
| 1        | 0             | 1327             | 4                 | 83.26%| 0.2682 |
| 1        | +1            | 11               | 2                 | 89%   | 0.2682 |
| 1        | +2            | 9                | 3                 | 75%   | 0.2682 |
| 1        | +3            | 4                | 0                 | 50%   | 0.2682 |
| 1        | +4            | 0                | 0                 | 0%    | 0.2682 |
| Total    | 1351          | 95               | 39                | 10    | 14    | 1509 |
| 2        | 0             | 1404             | 4                 | 84.44%| 0.4136 |
| 2        | +1            | 14               | 3                 | 46.67%| 0.4136 |
| 2        | +2            | 10               | 7                 | 21.43%| 0.4136 |
| 2        | +3            | 4                | 0                 | 4.29% | 0.4136 |
| 2        | +4            | 1                | 1                 | 0.81% | 0.4136 |
| Total    | 1433          | 31               | 29                | 14    | 6     | 1509 |
| 3        | 0             | 1392             | 4                 | 83.33%| 0.3445 |
| 3        | +1            | 15               | 5                 | 11.11%| 0.3445 |
| 3        | +2            | 15               | 7                 | 16.67%| 0.3445 |
| 3        | +3            | 5                | 1                 | 1.43% | 0.3445 |
| 3        | +4            | 1                | 0                 | 0%    | 0.3445 |
| Total    | 1428          | 50               | 21                | 8     | 2     | 1509 |
Table 4  Comparison of visual inspection and serum indices of Roche for lipemia, EPHI, Ethiopia, 2017

| Observer | Serum Indices | Visual inspection of hemolysis |  |  |  |  |  | Level of agreement | Kappa |
|----------|---------------|-------------------------------|---|---|---|---|---|-------------------|-------|
| 1        | 0             | 1280                          | 81 | 63 | 21 | 5  | 1450          |       |
|          | +1            | 22                            | 4  | 13 | 8  | 7  | 54           |       |
|          | +2            | 0                             | 1  | 0  | 0  | 4  | 5           | 85.15%| 0.1169         |
|          | +3            | 0                             | 0  | 0  | 0  | 0  | 0           |       |
|          | +4            | 0                             | 0  | 0  | 0  | 0  | 0           |       |
|          | Total         | 1302                          | 85 | 76 | 29 | 16 | 1509        |       |
| 2        | 0             | 1279                          | 123| 41 | 6  | 1  | 1450          |       |
|          | +1            | 20                            | 7  | 18 | 8  | 1  | 54           |       |
|          | +2            | 2                             | 0  | 0  | 2  | 1  | 5           | 81.22%| 0.1221         |
|          | +3            | 0                             | 0  | 0  | 0  | 0  | 0           |       |
|          | +4            | 0                             | 0  | 0  | 0  | 0  | 0           |       |
|          | Total         | 1301                          | 130| 59 | 16 | 3  | 1509        |       |
| 3        | 0             | 1332                          | 97 | 18 | 2  | 1  | 1450          |       |
|          | +1            | 29                            | 7  | 10 | 3  | 5  | 54           |       |
|          | +2            | 0                             | 1  | 0  | 1  | 3  | 5           | 88.73%| 0.1386         |
|          | +3            | 0                             | 0  | 0  | 0  | 0  | 0           |       |
|          | +4            | 0                             | 0  | 0  | 0  | 0  | 0           |       |
|          | Total         | 1361                          | 105| 28 | 6  | 9  | 1509        |       |
Table 5  Inter-observers variability among different technologist, EPHI, Ethiopia, 2017

| Interferences | Visual grading value | 0     | +1    | +2    | +3    | +4    | Combined |
|---------------|----------------------|-------|-------|-------|-------|-------|----------|
| Kappa Value   |                      |       |       |       |       |       |          |
| Hemolysis     |                      | 0.6600| 0.3563| 0.2619| 0.1486| 0.4847| 0.4758   |
| Icterus       |                      | 0.4643| 0.1310| 0.3238| 0.1016| 0.2692| 0.3258   |
| Lipemic       |                      | 0.5022| 0.2265| 0.2489| 0.2067| 0.2812| 0.3628   |

Figure 1  Total number of tests performed and the number of tests falsely accepted by observers, EPHI, Ethiopia, 2017
underestimated in plasma samples [5]. Studies indicated that following damage to red cell membrane and a resultant hemoglobin concentration greater than 0.3g/l, hemolysis can be recognized by the naked eye [12]. But the visual inspection of hemolysis varies from person to person due to factors, including differences in laboratory work experiences, individual ability to differentiate color intensity, and on job training opportunities.

Hemolysis affects result of different test parameters. In the present study, our observers falsely accepted a number of samples that were (+1) hemolytic as per the automated approach. If the tests were run just by visual inspection, test parameters including CK-MB, DBIL, LDH, AST, UIBC, TBIL and $K^+$ were labeled as false laboratory results. Similar study done by Jeffery et al. indicated that use of the automated hemolysis indices is highly recommended and that potassium in neonatal and adult specimens should be reported with a correction formula, since it might be beneficial to the clinical management of the patient [13]. The most probable cause of poor identification of hemolytic samples by visual inspection might be due to poor knowledge and lack of observer experience on hemolysis. In addition differences on sensitivity of the naked eye as compared to spectrophotometers could be another reasoning.

Another finding of the present study was that the automated approach identified a total of 74 (5%) samples with icterus; whereas the icterus indices recorded by observer 1, 2, and 3 were 158 (11%), 76 (5%) and 81 (5.4%), respectively. Upon statistical analysis, kappa value agreement
between the automated machine and the three visual observers were 0.3421, i.e., fair agreement. A similar study conducted in Croatia indicated that from the total of 1727 routine biochemistry samples, 101 samples were identified as icteric using visual inspection while automated serum indices detected only 74 samples, with moderate agreement between the two icterus indices detection approaches at weighted kappa values of 0.529 with moderate agreement [3].

The only parameter affected by grade icterus (+1) was the triglyceride assay. Similar findings were reported in a study conducted by Fatuma et al. on the study of assessment of serum indices implementation on cobas 6000. In this study, a total of 717 samples with no interferences by visual inspection were analyzed. From this, they found 102, 4 and 2 samples were hemolytic, lipemic and icteric, respectively [14].

In this present study a total of 207 (14%) lipemic samples were identified by the automated approach, and upon visual assessment observer one, observer two and observer three reported lipemia in 208 (14%), 148 (10%) and 59 (4%) samples, respectively. The average weighted kappa for the three observers was 0.1258, with slight agreement with the automated approach. The findings were similar to results reported by other researchers [3, 7]. Test results from lipemic samples may be inaccurate and can lead to medical errors, and as such represent a considerable risk to patient health [15, 16]. Studies indicate that lipemia is associated with diet and alcohol intake; as well as due to different pathological conditions including diabetes mellitus, hypertriglyceridemia, chronic renal failure and lupus erythematosus [17].

Studies showed that lipemic indices estimation ensures that the sample is fit for analysis. The use of automated lipemic estimation overcomes the limitations associated with visual estimation by providing a more objective and accurate estimate of lipemia [14, 18].

**STRENGTH AND LIMITATION**

Strength of this study include its large sample size, and to the best of authors’ knowledge this study is the first of its kind in Ethiopia. However, there are certain limitations that need to be considered when interpreting our finding, since the numbers of observers and the analytes measured were limited.

**CONCLUSION**

Ethiopia and most other developing countries are now delivering quality laboratory services, and also apply for local/international laboratory accreditation. In this regard the present study demonstrates that visual inspection will introduce significant pre-analytical errors with regards to SI evaluations, and lead to false results. Thus, as a recommendation:

- Further studies are needed in the area in order to study the level of agreement between visual inspection and automated serum indices value for more specific parameters.
- Continued training on visual inspection for medical laboratory technologists in order to increase the potential of identifying interferences.
- Medical laboratories should be encouraged to implement automated serum indices measurement to detect interferences.

*Authors’ contributions*

TG, AA, FM, MS, AA, WH, ZG, FG: designed the study, monitored data collection, and prepared the manuscript.

MW, FC: Principle advisors of the study, and participated in conception and designing of the
study, and revised the manuscript critically for important intellectual content.
All authors have read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Ethical clearance and consent to participate
Ethical clearance for the study was obtained from the Department of Medical Laboratory Sciences, College of Health Sciences Addis Ababa University, Ethiopia.

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