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The transition from gel separatory serum tubes to lithium heparin gel tubes in the clinical laboratory

Oğuzhan Zengi

Department of Medical Biochemistry, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey

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ABSTRACT

Aims: To assess the viability of replacing serum samples with plasma samples in various clinical chemistry and immunoassay tests and to examine the implications of turnaround time (TAT) and sample quality during the transition process.

Methods: We compared the results of 27 paired clinical chemistry and 13 immunoassay tests from samples obtained using gel separator serum and gel separator lithium heparinized plasma (LIH) tubes. We used regression analysis, bias values, and Bland-Altman plots to compare the performance of serum and LIH tubes in various clinical chemistry and immunoassay tests. We collected and evaluated sample aspiration errors, hemolysis index values, and TAT data from the laboratory information system before and after switching to plasma in our study.

Results: Most tests showed no significant difference between the serum and LIH. However, for some analytes, total error (TE) values exceeded the total allowable error (TEa) limits derived from the biological variation database. Notably, insulin TE value did not exceed TEa, but it consumed near all its error budget. Consequently, we determined the alternative allowable error limits for some tests and found that plasma tubes could be used instead of serum tubes for most tests, except for lactate dehydrogenase (LDH). Plasma tubes improved the sample quality, reduced the incidence of aspiration errors, and decreased TAT in the emergency laboratory. We observed significant reductions in TAT after switching to plasma tubes.

Conclusion: Our study showed that LIH tubes can replace serum tubes in most clinical chemistry and immunoassay tests. Using LIH tubes in clinical laboratories can improve healthcare quality and reduce the workload of the laboratory staff.

Keywords: Plasma, serum, total error, turnaround time, sample quality

INTRODUCTION

Plasma and serum are the two most common types of samples used in medical laboratories. However, plasma has recently gained popularity because of its advantages over serum. These advantages include no need for clotting before centrifugation, a larger sample volume, and better sample quality with fewer clots and fibrin residues.[1] Turnaround time (TAT) is the time interval between when a lab receives a test sample, processes it, and sends the results to the physician or other medical provider who orders it. The literature measures TAT intervals as the time from request to report or acceptance to report.[2] All laboratory processes require good planning and evaluation to improve TAT targets.[3] One of these improvements is the use of plasma samples instead of serum, particularly in emergency laboratories.[4] Evidence also supports the use of plasma to prevent interference that may result from serum clotting. Plasma is recommended for most laboratory tests because its constituents represent a patient's pathological state more accurately than serum. Anticoagulants can stop the clotting process from having an interferant effect.[1] Our study aimed to assess the viability of replacing serum samples with plasma samples and to examine the implications of TAT and sample quality during the transition process.

METHODS

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: 117). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

The study was conducted in April 2023 and included data from patients who were treated in the year 2022 in our retrospective analysis. The participants were 38 males and 38 females aged 25-65 years, who were randomly recruited from the emergency department of our hospital. A single experienced phlebotomist trained in preanalytical errors

Corresponding Author: Oğuzhan Zengi, oguzhanzengi@gmail.com

sampled the antecubital vein using a 21-gauge blood collection needle. Two tubes were randomly assigned for sampling, and each tube was used to collect samples from the contralateral arms. We applied the inclusion criteria specified in the Clinical and Laboratory Standards Institute (CLSI) GP34-A:2010 document.[5,6] We followed the recommendations of the tube manufacturers for tube inversion, clotting time, and centrifugation characteristics. We centrifuged the samples at 1800g for 10 minutes. After centrifugation, we visually evaluated sample quality indicators such as hemolysis, lipemia, icterus, fibrin, and clots in the serum/plasma. During the analysis, we also measured a semi-quantitative hemolysis index and excluded samples with evident hemolysis (>50 mg/dl free hemoglobin). We used the gel separator-clot activator tube VACUETTE® Greiner Bio-One (Kremsmuenster, Austria) 13*100 mm, catalog number 456073 for serum and gel separator plasma tubes with lithium heparin VACUETTE® 13*100 mm, catalog number 456087, Greiner Bio-One (Kremsmuenster, Austria). We used a pneumatic system to send all tubes to the laboratory after blood collection. Serum tubes were upright for 25-30 minutes before centrifugation. The plasma tubes were centrifuged immediately after receiving the tubes without delay. We compared the results of 27 paired clinical chemistry and 13 immunoassay tests from samples obtained using gel separator serum and gel separator lithium heparinized plasma (LIH) tubes. Measurements were performed randomly on a Roche COBAS 8000 clinical chemistry analyzer with c 701, e 602 and ion-selective electrodes (ISE) modules. (Roche Diagnostics, Basel, Switzerland); the measurement method applied for biochemical testing was spectrophotometry, whereas immunoassays utilized electrochemiluminescence, and electrolyte tests made use of ion-selective electrodes. Analyses were performed in duplicate within a single study cycle, using the averages of the calculated results. Precision and reproducibility studies were conducted using same-brand internal quality control materials, with twice-daily measurements.

Statistical Analysis

The study compared serum and LIH tubes using regression analysis, bias values, and Bland-Altman plots. The Kolmogorov-Smirnov test was used to check for normality, and the paired t-test or Wilcoxon test was used to determine statistical significance. The present study aimed to assess clinically significant differences using biological variation in TEa (Total allowable error) targets.[7,8] MedCalc Statistical Software 19.0.7 (Ostend, Belgium) was used for the statistical analysis.

$$Bias\% = [(compared\ tube\ LIH) - (control\ tube\ serum)/(control\ tube\ serum)]X100$$

$$Total\ error\%: |\%Bias| + 1.65X\%CV$$

CV (%) is the coefficient of variation for measuring between day imprecision.

We followed different sources for the TEa targets depending on the availability of the test parameters. We mainly used the biological variation database from the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) website but also referred to the combined performance specifications from Westgard's website for some parameters. For N-terminal pro B-type natriuretic peptide (PBNP) and Procalcitonin (PCT) tests, we relied on the targets from the literature.[7-9]

RESULTS

Paired statistical analyses performed on the test results obtained from serum and plasma tubes revealed significant differences in K, ALP, ALT, ALB, GGT, Na, CK, TP, AST, LDH, PHOS, Mg, UA, LIP, COL, TG, PBNP, TNT-hs, FER, TSH, CA125, CA15-3, CA19-9, and INS ($p<0.05$). The total error values for the Na, K, Cl, TP, and LDH tests exceeded the TEa limits for biological variation (BV). Some tests did not meet the performance criteria of BV models.[10] Therefore, the alternative TEa limits for Na, K, Cl, TP, and LDH were determined and evaluated. The total protein (TP) test was beyond these limits due to fibrinogen in the plasma, and further evaluation was not required.[4] Analytical performance specifications for BIL-D, CKMB, PBNP, HCG-BETA, PCT, and CA15.3 were obtained from other sources because they were not included in the BV database (**Table 1**).

Table 2 shows the slope and intercept values obtained from the Passing and Bablok regression analyses. The regression lines are shown in **Figure 1**. According to the regression analysis results, considering the 95% confidence interval for the slope, there is no proportional difference between the two groups if the confidence interval covers a value of 1. Except for the Ca and INS tests, the 95% confidence interval for the slope value included 1 for all tests. As is common knowledge, the intercept value is assessed as a measure of the systemic difference between two groups. If the 95% confidence interval of the intercept values from the Passing and Bablok regression analysis covers 0, then we assume that the two sample groups do not differ systematically. This assumption was valid for all tests except for Ca and GGT when we compared serum and plasma samples based on the intercept values obtained in our study. In our study, most test points were within the set limits, as shown in **Figure 2**. We also reported the mean biases (%) from the Bland-Altman analysis in **Table 1**. We collected alerts related to device aspiration errors from the laboratory information system to evaluate the effects of plasma use in our laboratory (**Table 3**).

Table 1. Comparison of the results of clinical chemistry tests using serum and plasma tubes

Test (Unit)	n	Serum (Gel separator tube)	Plasma (Lithium-heparinized plasma tube)	CV%	Mean bias (%)	TE (%)	TE[a] (%)
K (mmol/L)	76	4.44 (4.23-4.75)	4.24 (4.04-4.48)	1.88	-4.66	7.77	4.8
GLU (mg/dl)	75	100.5 (92.73-124.08)	101 (92.68-125.6)	1.32	0.51	2.69	6.5
CREA (mg/dl)	76	0.84 (0.61-0.94)	0.83 (0.61-0.95)	3.12	-0.45	5.60	7.4
Urea (mg/dl)	73	28 (22.13-36.54)	28 (22.04-36.79)	1.56	-0.39	2.97	17.8
ALP (IU/L)	76	74 (59.4-98)	71 (58.68-92.7)	2.1	-3.22	6.68	10.5
BIL-T (mg/dl)	76	0.39 (0.24-0.62)	0.4 (0.26-0.61)	3.9	7.03	13.46	24.8
ALT (IU/L)	76	19.95 (13.0-29.75)	17.95 (13.05-26.75)	1.6	-5.16	7.80	16.1
ALB (g/L)	75	45.4 (39.65-47.85)	44.8 (39.45-47.46)	1.25	-1.15	3.21	3.4
AMY (IU/L)	76	58.95 (46.3-76.9)	59.38 (46.3-77.23)	1.0	0.28	1.93	13.2
GGT (IU/L)	76	18 (12.95-29.95)	20.13 (14.15-30.88)	1.72	13.21	16.05	18.9
CRP (mg/L)	75	3.98 (1.28-20.35)	4.06 (1.25-20.29)	1.64	-1.48	4.19	50.7
Na (mmol/L)	76	139.05 (137.55-140.4)	138.63 (137.23-140.03)	1.3	-0.31	2.46	5.0
CK (IU/L)	71	85.85 (55.74-136.5)	85.2 (56.48-133.25)	1.0	-1.08	2.73	22.6
Cl (mmol/L)	75	102.45 (99.54-104.09)	102.8 (99.96-104.2)	1.59	0.25	2.88	5.0
TP (g/L)	71	71.58±5.6	73.58±5.7	1.9	2.83	5.96	8.0
BIL-D (mg/dl)	76	0.16 (0.11-0.26)	0.16 (0.12-0.25)	1.96	6.55	9.79	44.5
Ca (mg/dl)	76	9.27±0.593	9.26±0.54	1.28	-0.11	2.23	2.3
AST (IU/L)	76	21.55 (16.65-30.75)	22.78 (17.75-29.35)	1.95	4.82	8.04	13.6
LDH (IU/L)	75	181.5 (158.5-218.75)	205 (174.88-250.38)	1.0	13.95	15.60	15
CKMB (ng/ml)	64	1.61 (1.16-2.22)	1.65 (1.17-2.21)	2.44	1.68	5.71	25
PHOS (mg/dl)	74	3.26±0.65	3.11±0.65	1.28	-4.63	6.74	9.7
Mg (mg/dl)	74	2.03 (1.9-2.17)	2.06±0.29	1.89	0.47	3.59	4.0
UA (mg/dl)	74	4.95±1.84	4.7 (3.8-5.8)	1.31	0.46	2.62	12.8
LIP (IU/L)	75	30.7 (23.04-40.03)	30.5 (23.13-39.94)	1.71	0.22	3.04	14.2
CHOL (mg/dl)	70	187±47.49	184.2±46.94	2.6	-1.50	5.79	8.8
HDL (mg/dl)	69	42.7 (35.0-49.05)	44.23±13.33	2.9	0.09	4.87	10.9
TG (mg/dl)	57	121.7 (83.55-186.43)	118.4 (80.0-183.63)	1.9	-2.60	5.73	27
FT3 (pg/ml)	70	2.94 (2.55-3.24)	2.87±0.59	2.07	-0.17	3.59	6.5
PBNP (pg/ml)	66	50.93 (24.8-134)	50.33 (25.1-134)	3.37	-2.53	8.09	30
FT4 (ng/dl)	66	1.26±0.226	1.26±0.23	3.04	-0.06	5.07	6.3
TNT-hs (ng/L)	69	4.92 (3.0-11.33)	5.18 (3.0-11.73)	2.58	7.54	11.79	17.6
FER (ng/ml)	66	99.78 (41.1-184)	96.08 (40.65-180)	2.38	-0.70	4.63	13.8
HCG-BETA (mIU/ml)	66	0.2 (0.2-0.89)	0.2 (0.2-0.9)	3.12	3.62	8.77	18.0
TSH (uIU/ml)	66	1.52 (1.06-2.14)	1.52 (1.07-2.06)	2.76	-0.50	5.05	24.6
PCT (ng/ml)	66	0.05 (0.04-0.07)	0.05 (0.04-0.07)	3.87	2.03	8.41	20.3
CA125 (IU/ml)	64	10.25 (7.38-18.25)	9.99 (7.12-17.75)	2.14	-3.56	7.09	13.9
CA15-3 (IU/ml)	63	15.9 (12.63-21.93)	15.4 (12.28-20.68)	3.63	-3.38	9.37	20.8
CA19-9 (IU/ml)	63	8.04 (4.67-14.78)	8.01 (4.63-14.73)	4.65	-0.92	8.59	17.9
INS (uIU/ml)	66	13.6 (8.08-22.5)	8.73 (5.18-19.6)	4.23	-22.97	29.95	31.5
VITD (ng/ml)	69	12 (8.16-18.2)	13.1 (8.69-18.83)	2.76	4.98	9.53	12.4

[a]Total error targets derived from biological variation. [b]CLIA (Clinical Laboratory Improvement Amendments) [c]Westgard consolidated comparison of chemistry performance specifications, consolidated comparison of immunoassay performance specifications. *Values are presented as mean±standard deviation; percentiles (Q1-Q3) are given in parentheses. CV: Coefficient of variation. TE: Total error. TEa: Total Allowable Error. Alanine aminotransferase (ALT), albumin (ALB), alkaline phosphatase (ALP), amylase (AMY), aspartate aminotransferase (AST), bilirubin direct (BIL-D), bilirubin total (BIL-T), C-reactive protein (CRP), inorganic phosphorus (PHOS), gamma-glutamyl transferase (GGT), glucose (GLU), HDL cholesterol (HDL), calcium (Ca), creatine kinase (CK), creatine kinase-MB (activity) (CKMB), creatinine (CREA), lactate dehydrogenase (LDH), lipase (LIP), magnesium (Mg), total cholesterol (CHOL), total protein (TP), triglycerides (TG), uric acid (UA), chloride (Cl), potassium (K), and sodium (Na), free triiodothyronine (FT3), N-terminal pro-b-natriuretic peptide (PBNP), free thyroxine (FT4), troponin T (TNT-hs), ferritin (FER), chorionic gonadotropin (HCG-BETA), thyroid stimulating hormone (TSH), procalcitonin (PCT), cancer antigen 125 (CA125), cancer antigen 15-3 (CA15-3), cancer antigen 19-9 (CA19-9), insulin (INS), total 25-hydroxy vitamin D (VITD).

Table 2. Results of Passing-Bablok regression analysis comparing the values of 40 clinical chemistry tests in serum and plasma.

Test	Passing-Bablok slope (95% CI)	Passing and Bablok intercept (95% CI)	Measured concentration range
K	0.968 (0.847-1.101)	-0.085 (-0.670-0.456)	2.01-5.47
GLU	1.0 (0.976-1.017)	0.200 (-1.423-2.791)	60.3-562.6
CREA	1.007 (0.989-1.033)	-0.010 (-0.032-0.007)	0.459 -1.965
URE	1.003 (0.996-1.001)	-0.240 (-0.448-0.005)	9.1-103
ALP	0.955 (0.940-0.971)	0.568 (-0.738-1.964)	33-258
BIL-T	0.969 (0.934-1.000)	0.016 (0.000-0.029)	0.04-1.755
ALT	0.981 (0.954-1.011)	-0.127 (-0.731-0.535)	8.4-317.6
ALB	0.969 (0.937-1.000)	0.898 (-0.500-2.334)	29.2-51.2
AMY	1.000 (0.986-1.005)	0.000 (-0.254-0.799)	16-944
GGT	1.000 (0.966-1.023)	1.000 (0.592-1.858)	6-260
CRP	0.981 (0.976-0.988)	0.046 (0.031-0.071)	0.125-197.22
Na	1.038 (0.940-1.150)	-5.579 (-21.197-8.066)	129-143.3
CK	0.996 (0.985-1.002)	-0.530 (-1.200-0.581)	10-805.5
Cl	0.982 (0.922-1.041)	1.972 (-4.018-8.162)	87.5-107.9
TP	1.017 (0.951-1.080)	0.821 (-3.710-5.530)	55.6-83.9
BIL-D	1.000 (0.949-1.043)	0.001 (-0.005-0.010)	0.04-0.8
Ca	0.903 (0.838-0.971)	0.877 (0.224-1.489)	6.89-10.25
AST	1.000 (0.973-1.052)	0.700 (-0.368-1.445)	11.1-636.5
LDH	1.028 (0.938-1.150)	13.649 (-6.870-29.531)	97.6-520.5
CKMB	0.986 (0.964-1.004)	0.026 (0.004-0.052)	0.317-9.18
PHOS	1.042 (1.000-1.081)	0.029 (-0.095-0.170)	1.57-4.73
Mg	1.000 (0.950-1.063)	-0.020 (-0.145-0.079)	0.9-3.56
UA	1.000 (1.000-1.008)	0.005 (-0.024-0.005)	1.6-12.05
LIP	0.999 (0.986-1.007)	-0.251 (-0.528-0.202)	8.4-2435
CHOL	1.011 (0.992-1.031)	0.843 (-2.269-4.360)	75.5-307.3
HDL	1.000 (0.977-1.017)	0.000 (-0.730-0.874)	15.8-92.6
TG	1.001(0.994-1.023)	2.495 (0.897-4.369)	46.3-443.2
FT3	1.007 (0.978-1.042)	-0.023 (-0.126-0.059)	0.855-3.89
PBNP	0.982 (0.972-0.997)	-0.114 (-1.105-0.467)	8.765-10328
FT4	1.015 (0.977-1.058)	-0.023 (-0.076-0.026)	0.854-1.805
TNT-hs	0.966 (0.953-0.991)	0.103 (0.027-0.141)	3-126
FER	0.979 (0.970-0.989)	0.355 (-0.110-1.135)	2.48-2000
HCG-BETA	1.000 (1.000-1.035)	0.000 (-0.007-0.000)	0.2-10000
TSH	0.987 (0.977-0.999)	0.001 (-0.011-0.013)	0.171-14.1
PCT	0.949 (0.902-1.041)	0.002 (-0.002-0.005)	0.02-2.57
CA125	0.968 (0.947-0.983)	0.028 (-0.164-0.207)	2.33-400
CA15-3	0.967 (0.945-0.987)	-0.063 (-0.351-0.291)	3.65-46.9
CA19-9	0.981 (0.972-0.993)	0.037 (-0.006-0.059)	2-64.8
INS	1.179 (1.097-1.306)	0.683 (-0.192-1.384)	0.866-106
VITD	0.989 (0.946-1.027)	0.372 (-0.080-0.951)	3-72.4

CI=Confidence interval

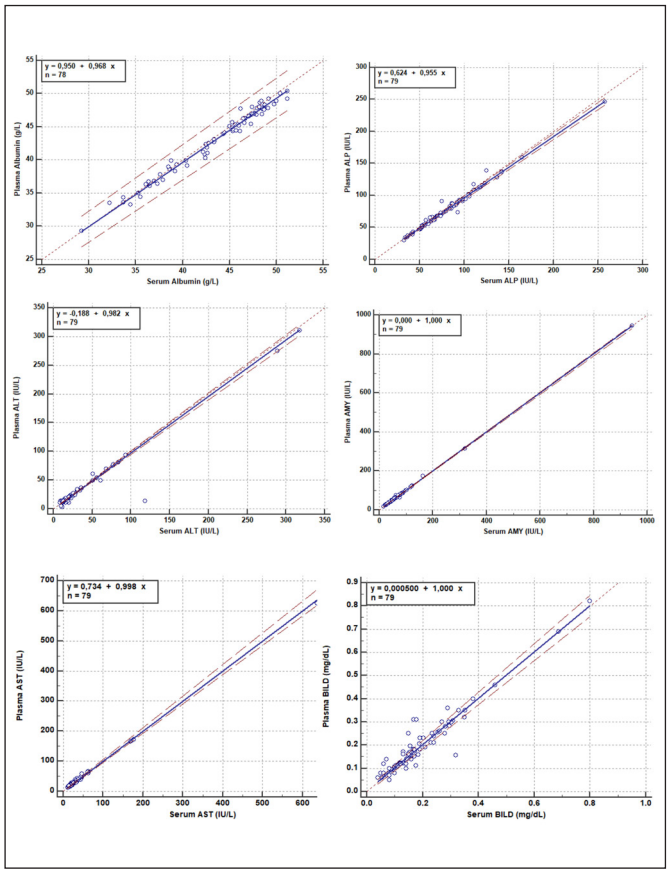
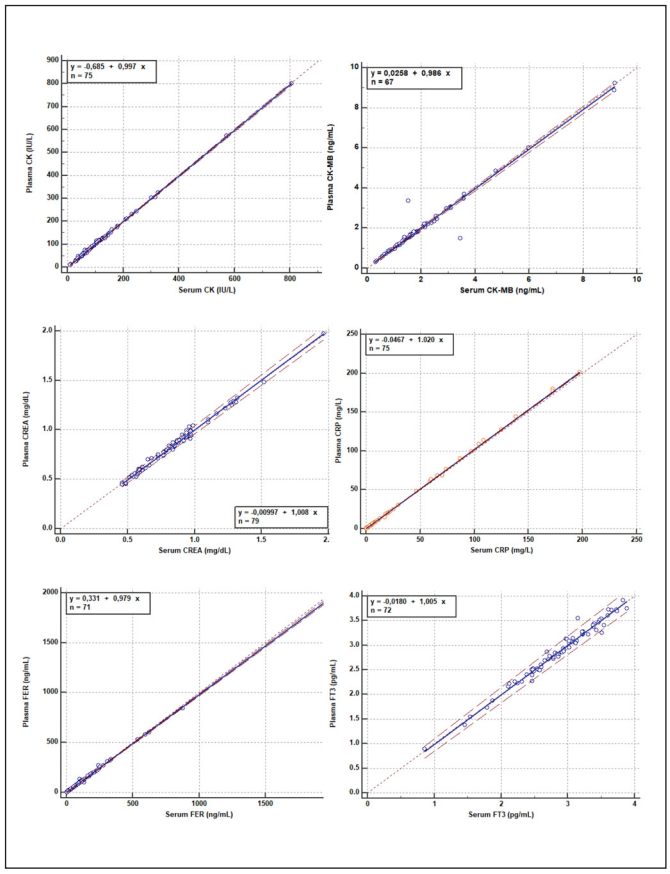


Figure 1A



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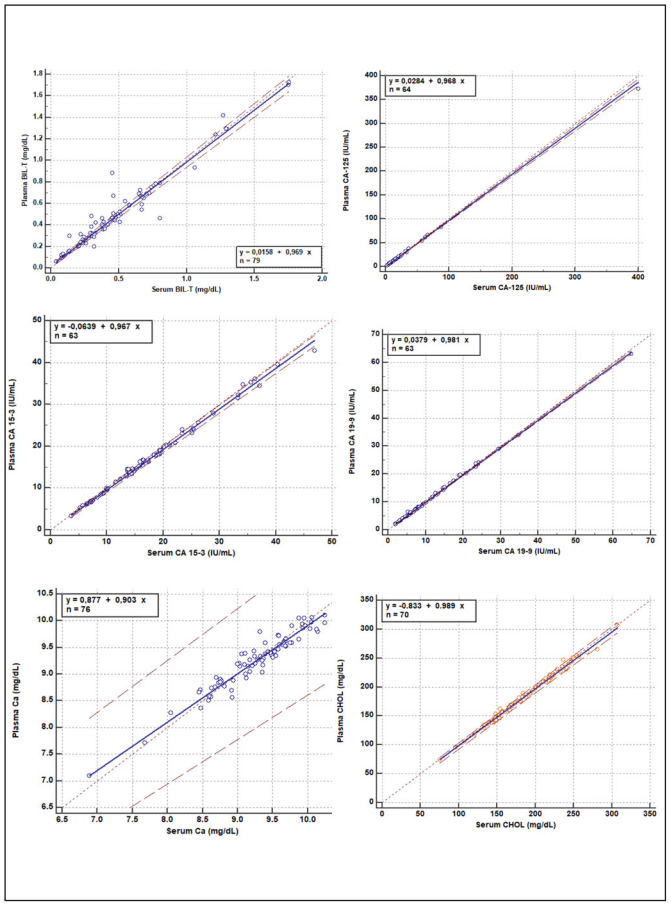


Figure 1B

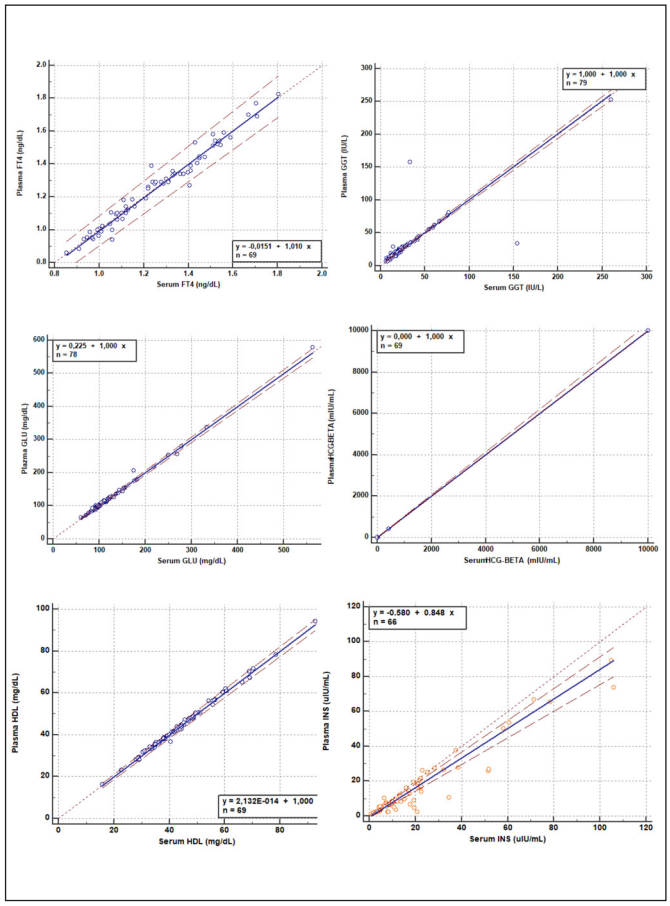


Figure 1D

Figure 1 (A - G): Serum and heparinized plasma test results shown on the Passing-Bablok regression analysis.

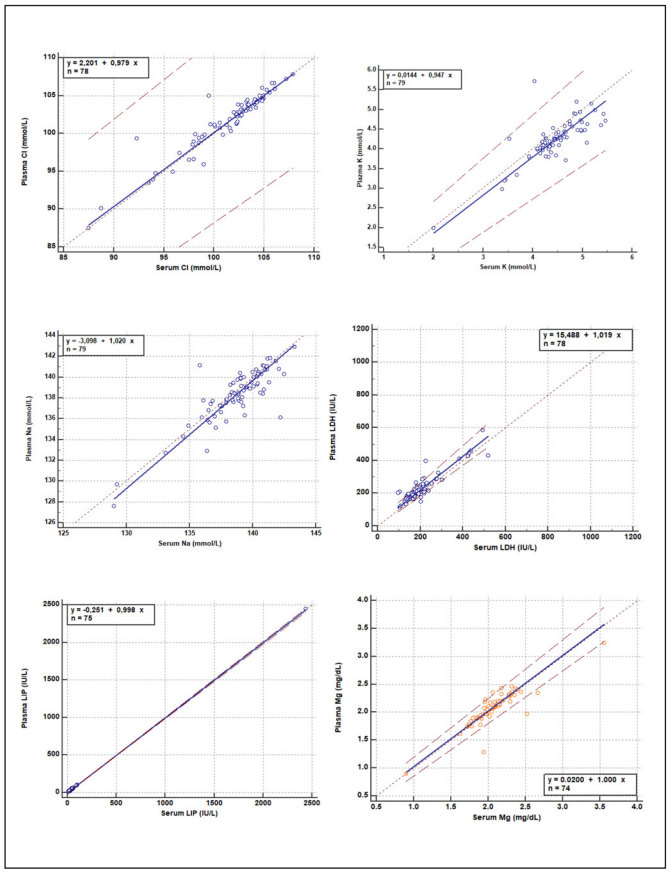
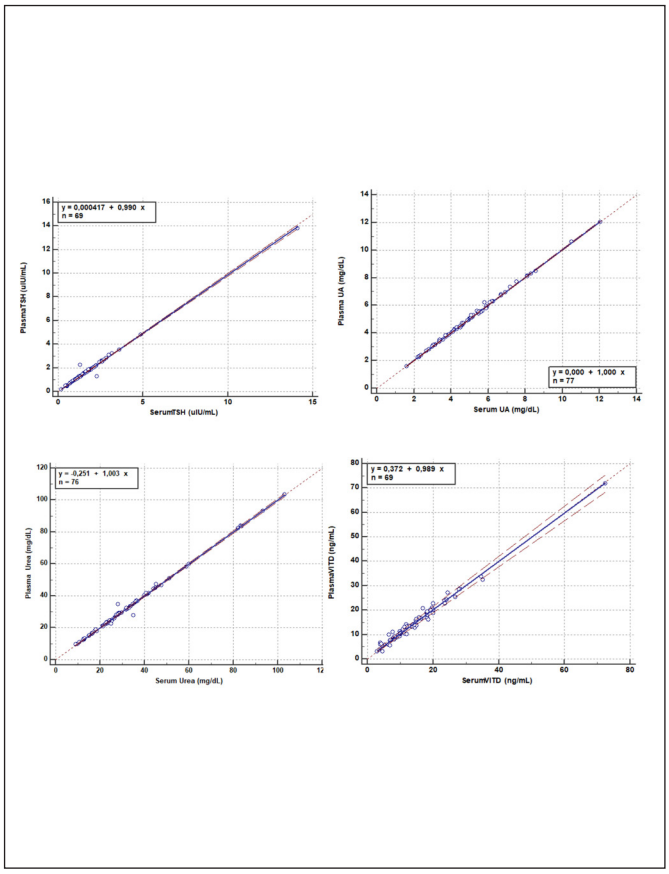


Figure 1E



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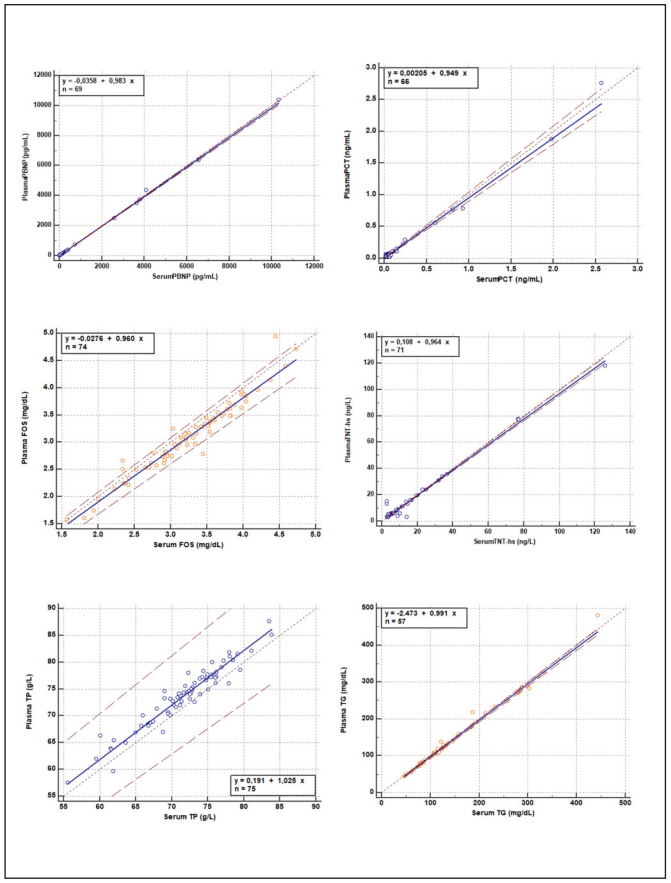

Figure 1F

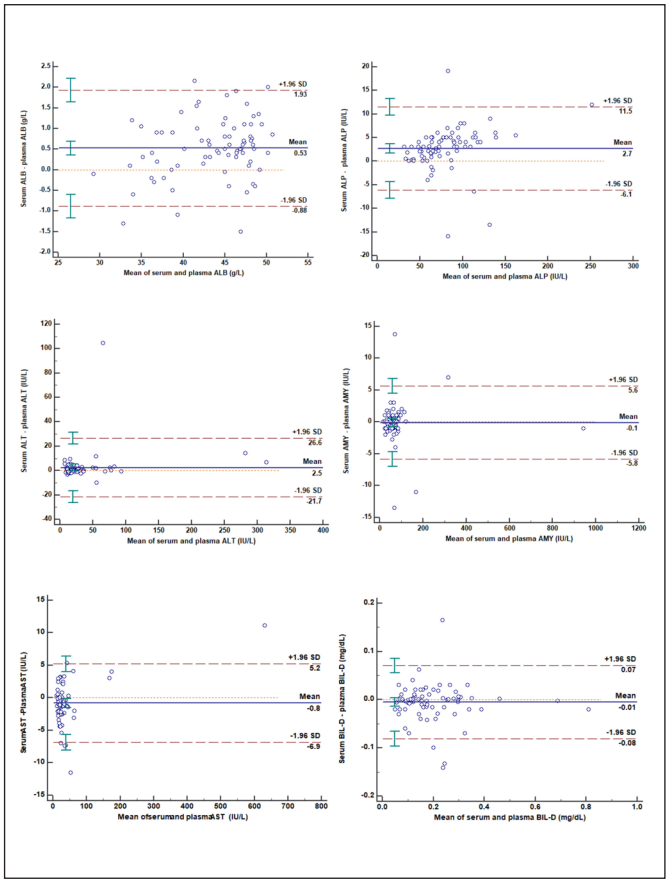

Figure 2A

Figure 1 (A - G): Serum and heparinized plasma test results shown on the Passing-Bablok regression analysis.

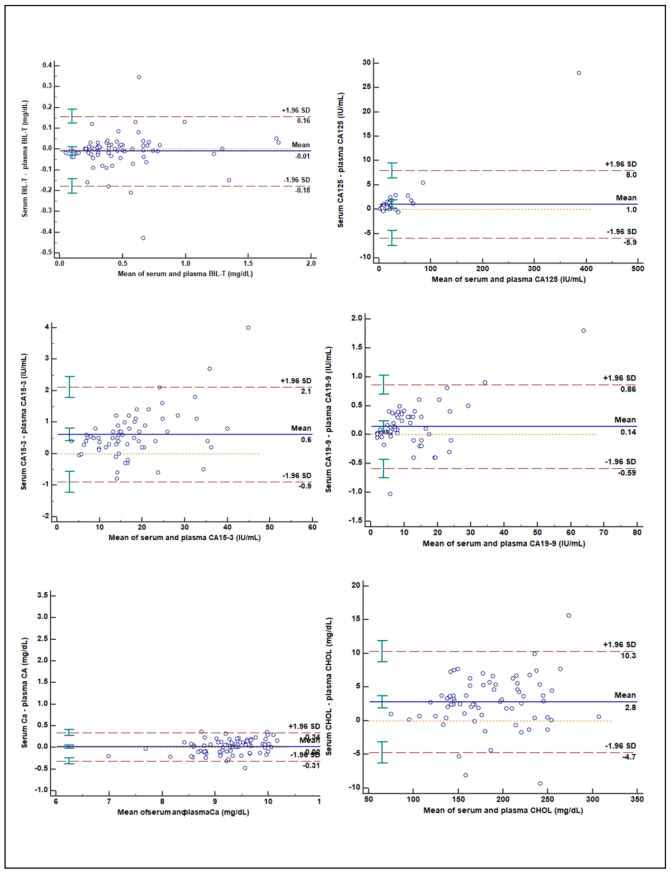

Figure 2B

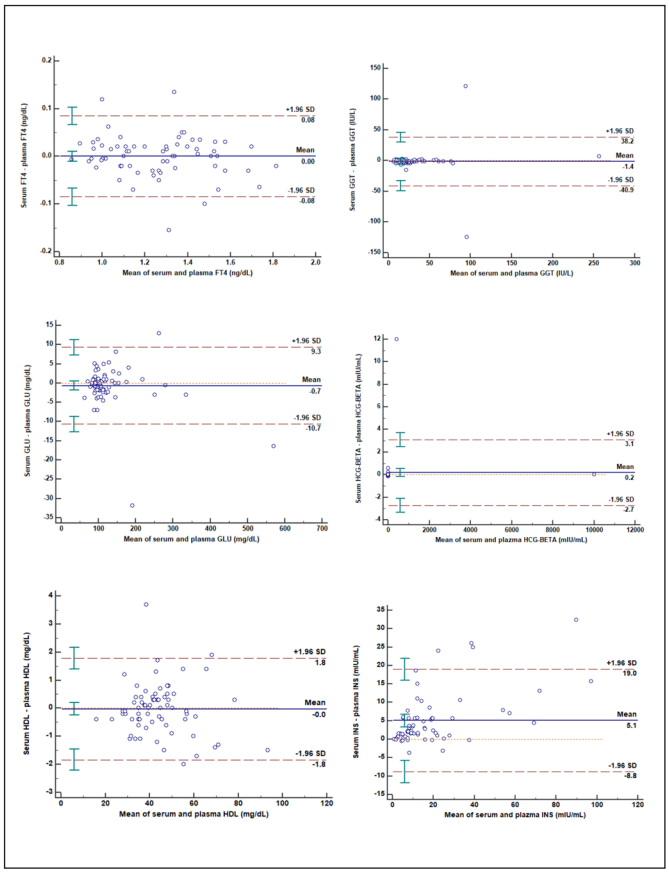

Figure 2D

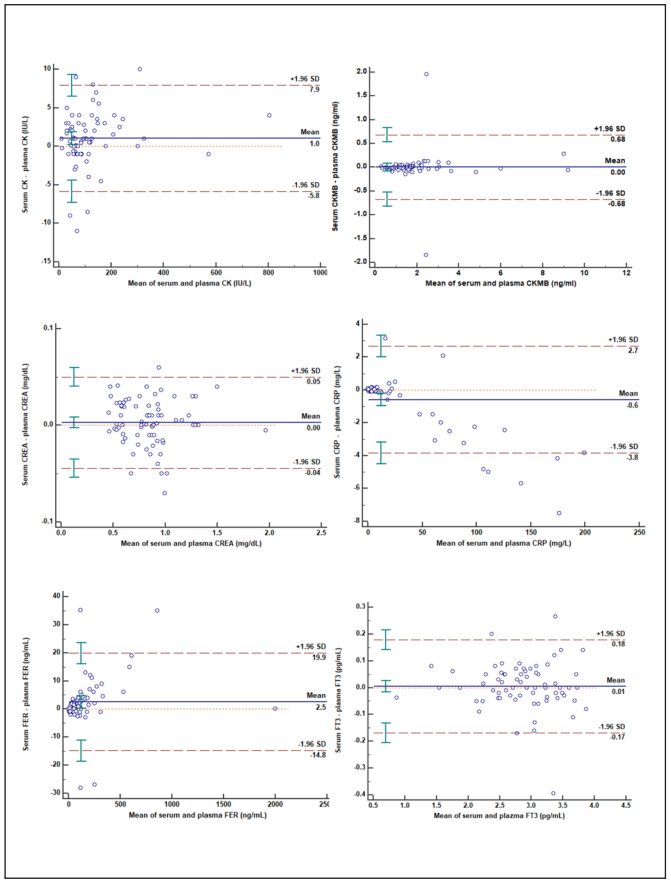

Figure 2C

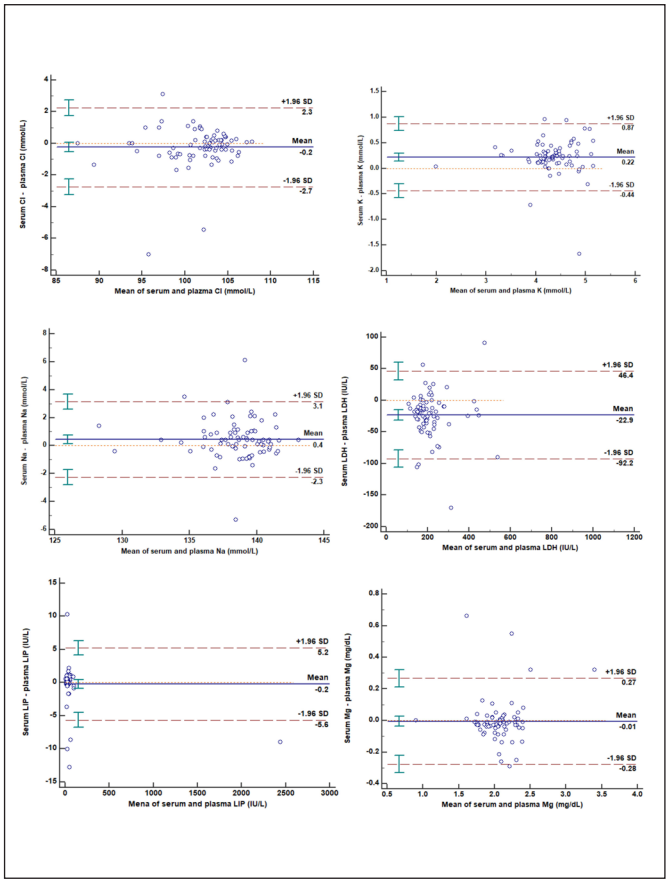

Figure 2E

Figure 2 (A - G): Bland-Altman plots for serum and plasma test results

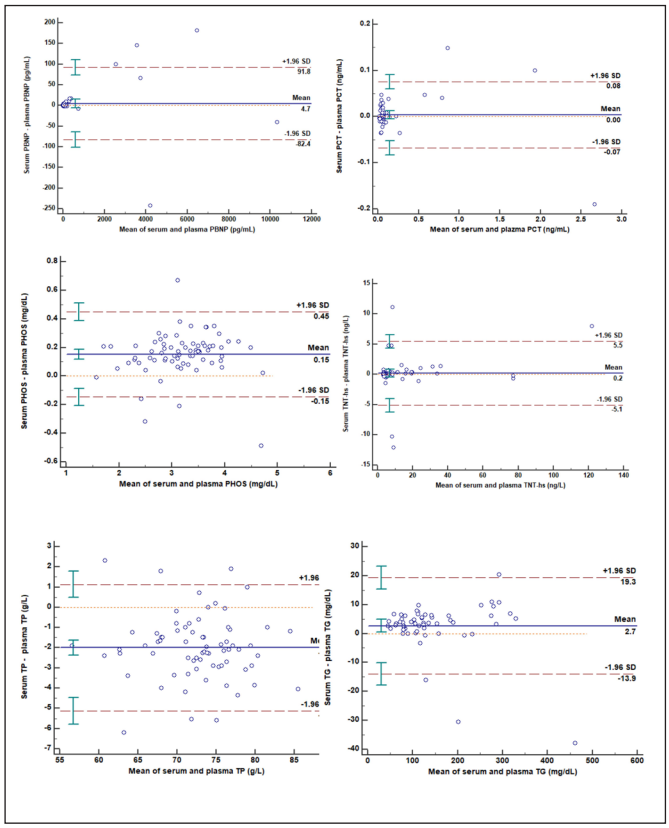

Figure 2F

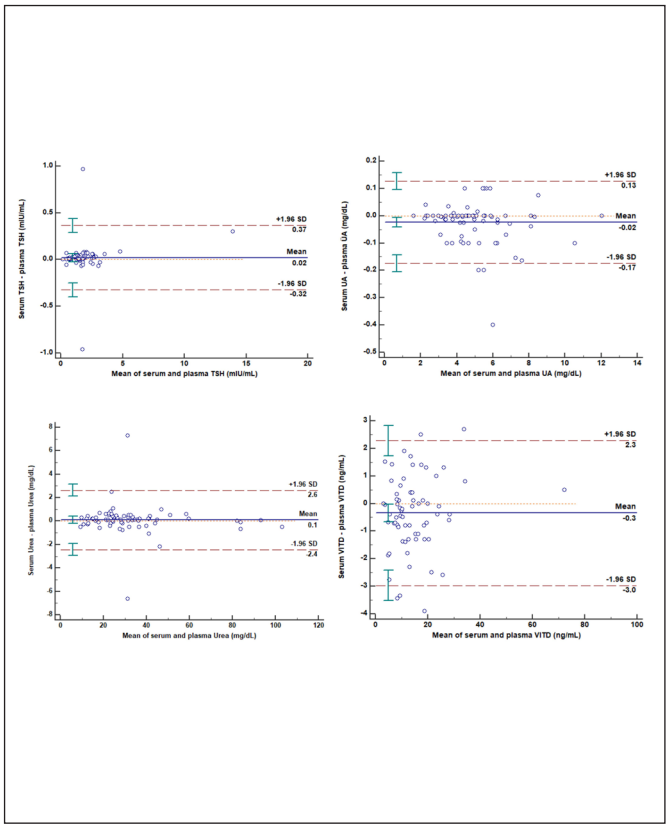

Figure 2G

Figure 2 (A - G): Bland-Altman plots for serum and plasma test results

Table 3. Sample probe errors and hemolysis index values

		Before the use of LIH	After the use of LIH
Total number of samples		15866	45059
Sample probe aspiration errors[a]		141 (0.88%)	200 (0.44)
Hemolysis[b]	Negative	12996 (81.9%)	35979 (79.8%)
	+	1558 (9.8%)	5084 (11.3%)
	++	1142 (7.2%)	3486 (7.7%)
	+++	118 (0.7%)	352 (0.8%)
	++++	52 (0.3%)	158 (0.4%)

[a]X^2=41.718, df=1, p<0.001[b]X^2=34.130, df=4, p<0.001. LIH: Lithium heparin tubes

Before the introduction of the LIH tube (February-March 2023), 141 aspiration errors appeared as instrument alerts in the system. The proportion of tubes with aspiration errors in the total number of samples was 0.88%. The proportional reduction in total aspiration errors and related device warnings was statistically significant two months after switching to plasma tubing. The proportion of specimens with aspiration errors to the total number of specimens was 0.44% between April and May 2022 (X 2=41.718, p<0.001). A medical laboratory technician takes approximately 15 minutes on average to deal with a tube with an aspiration failure warning. This involves identifying the specimen, locating it (removing it from the instrument), checking for clots visually, re-centrifuging, aliquoting, ensuring that the rerun is programmed in the instrument, and transferring the results to the LIS. These steps can divert the technician's attention from other tasks.[11] Therefore, aspiration errors can significantly impact TAT goals. We retrospectively assessed the specimen reception-device result output times of serum K and TNT-hs tests to measure the effect of switching to plasma use on TAT (March-April 2023). These were the two most common tests requested by the emergency department (Figure 3). LIH reduced the percentage of K orders that lasted more than 90 minutes between order-result time from 5.48% to 4.09% (X2=36.75, p<0.001).

Similarly, for TNT-hs orders, the percentage of time outliers decreased from 6.97% to 4.86% (X2=23.93, p<0.001). LIH successfully lowered the percentage of samples that exceeded the TAT out of the total number of samples. Using plasma reduced the order-result time for 95% of the emergency biochemistry and immunoassay samples from the emergency department. Before the intervention, 95% of 20957 samples took less than 110 minutes, while after the intervention, 95% of 21433 samples took less than 102 minutes (Figure 4).

We compared the median time from sample acceptance to device entry before and after plasma use (Figure 5). The median and interquartile values for this period decreased after plasma use in March and April 2023. Before plasma use (n=6838), the median and interquartile range were 21 (16-28) minutes, while after plasma use (n=12682), they were 17 (15.3-21.2) minutes (p<0.001).

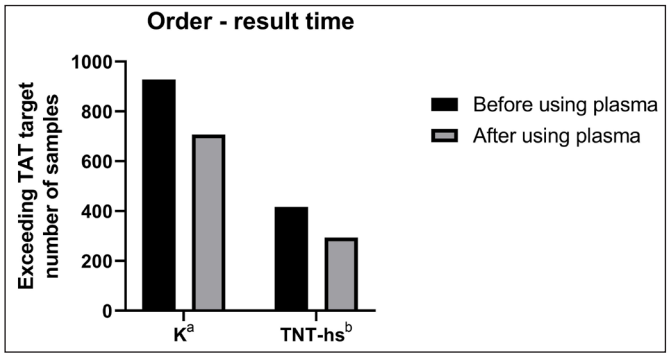

Figure 3. Order - result time analysis K and TNT-hs tests

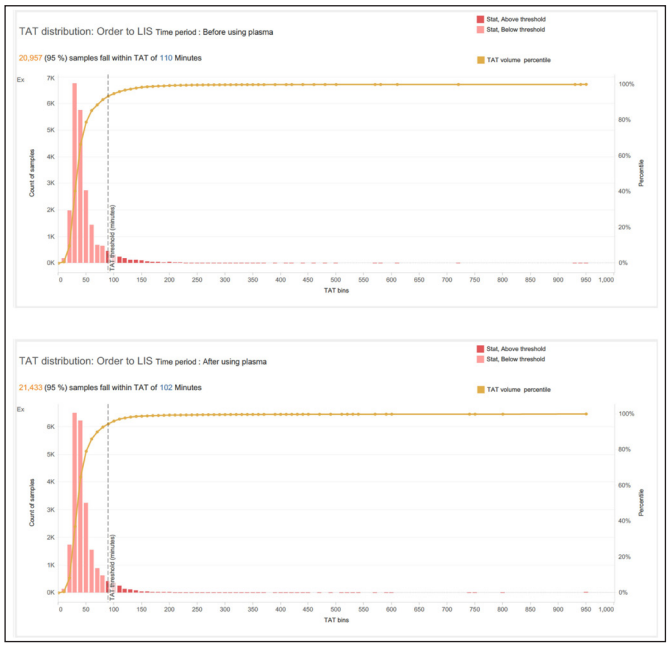

Figure 4. Sample Turnaround Time (TAT) distribution analysis.

DISCUSSION

Sample quality defects and clotting problems can cause errors in laboratory processes, especially with new-generation high-performance analyzers. Plasma is often a more suitable sample for laboratory tests than serum because it reduces TAT and avoids false results caused by fibrin remnants. Correct sample processing is essential for accurate and reliable test results, and the CLSI recommends validating plasma tubes locally before routine use.[1,6,12,13]

Our study found a mean bias of -4.66% for K and 5.96% for TP. These results are consistent with those of previous studies on these analytes. For example, using gel lithium heparin tubes, Ercan et al.[14] reported mean bias values of -2.63% and 2.37% for K and TP, respectively. The literature has previously documented a negative bias for K and a positive bias for TP in plasma tubes compared to serum tubes.[4,5,15] Consistent with the studies in the literature, our study found a positive bias of 13.95% for LDH compared to serum tubes.

Additionally, our study found no statistically significant differences between the hemolysis indices of plasma and serum tubes. In contrast to our findings, Arslan et al.[16] reported a negative bias for LDH. According to Hetu et al.[11] a positive bias for LDH in a Barricor mechanical separator heparinized plasma tube was consistent with our findings. The reason for this phenomenon is not fully understood. It is believed that LDH may be released from platelets and other cells into plasma during centrifugation.[17]

The observed total error (TE%) values for Na and Cl analytes exceeded the TEa% limits derived from the BV database. The mean bias (%) for Na and Cl analytes was -0.31% and 0.25%, respectively, while the calculated TE% values were 2.46% and 2.88%, respectively. Although these bias% values were consistent with the literature, the TE% values obtained by researchers in previous studies also exceeded the TEa% targets derived from BV. According to Oosterhuis et al.[10] analytes, such as Na and Cl, which are tightly regulated by homeostatic mechanisms, can be accurately measured. However, they recommend questioning the quality criteria set

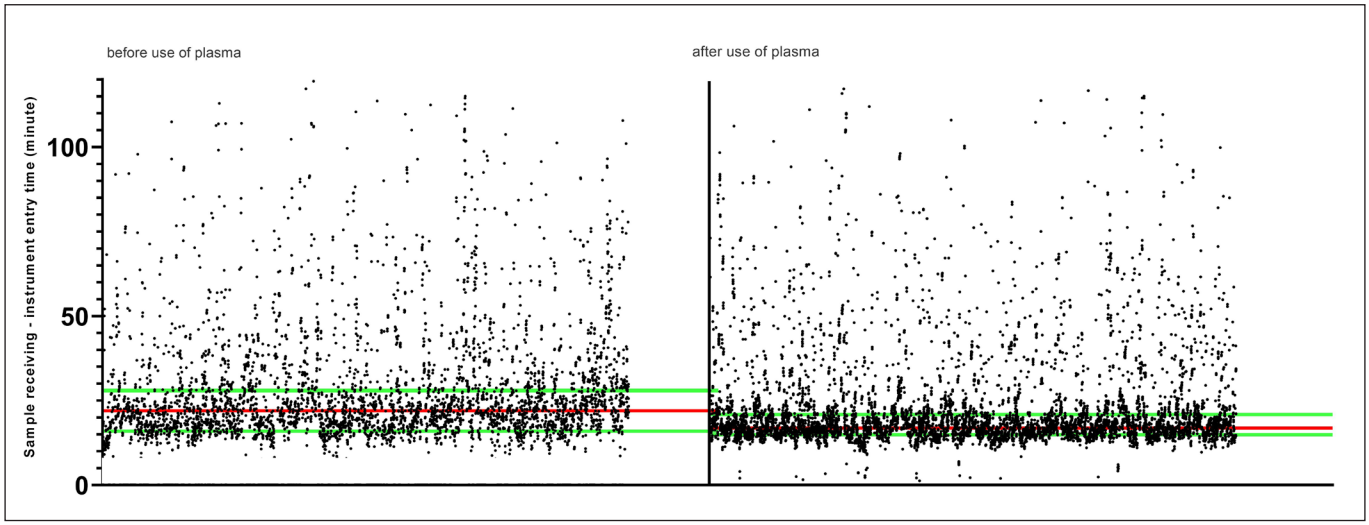

Figure 5. The median of the times for sample reception and instrument entry (Pre and post plasma period)

by BV and using alternative methods to determine the performance specifications for sodium.[10] Based on the limitations of BV targets, alternative targets for allowable bias were set for Na and K; the targets were±4 mmol/L and±3 mmol/L, respectively. For Cl TEa% was 5%, while for TP, the chosen limit was 8%.18 Table 4 summarizes the alternative targets for Na, K, Cl, TP, and LDH, according to Westgard's consolidated quality requirement targets. Upon re-evaluation using alternative targets, it was determined that a plasma sample could be used instead of a serum sample for these tests, except for LDH. Although our comparison results for LDH were close to the alternative error limit, the total error budget was used. Therefore, it is recommended that a reference interval transfer be performed if a plasma sample is used in the LDH assay.[6]

Table 4. Alternative TEa limits

Test	Mean bias (%)	TE (%)	TEa (%)-BV	TEa (%) -Westgard
Na	- 0.31 (0.4 mmol/L)*	2.46	0.7	± 4 mmol/L**
K	- 4.66 (0.2 mmol/L)*	7.77	4.8	± 3 mmol/L**
Cl	0.25	2.88	1.3	5
TP	2.83	5.96	3.5	8
LDH	13.95	15.60	15	15

*Mean bias (mmol/L),** Allowable absolute bias,TE: Total error, TEa: Total allowable error, BV: Biological variation

Many studies have compared serum and plasma samples using statistical and medical criteria. They used Bland-Altman differences plots and Passing-Bablok regression analyses to assess the statistical difference and agreement between the samples and TEa% targets from various sources to assess the medical significance of the differences. The regression analysis and the difference plot have different ways of interpreting the agreement and significance of the difference based on the confidence intervals of certain values.[4,14,19] Ercan et al.[14] used the Turkish Ministry of Health Total Error Guideline for TEa limits to compare with serum and gel plasma tubes. They found that the TE values for all the tests were below the TEa limits. They concluded that heparinized lithium plasma with a gel separator could replace the serum.[14] In a similar study, Arslan et al.[16] used BV TEa targets and obtained larger differences than the desired bias values for the K, LDH, and TP analytes in the plasma tube. However, when assessing this difference in the assays, a clinically significant difference was considered to be present when the difference between the mean concentration in one tube and the reference tube exceeded±2.8x (long-term standard deviation). Since they found clinically significant differences for K, LDH, and TP analytes, they reported that they could be used with reference value transfer.[4] Orhan et al.[20] observed that the K test in tubes with mechanical separators exceeded the TEa limit they set. Still, they suggested its use in the laboratory because of the benefits of using plasma. Hetu et al.[11] compared 65 different analytes and found that, except for K, TP, LDH, progesterone, and rheumatoid factor, the TE values obtained in plasma tubes with mechanical separators were within the BV TEa limits.[11]

Numerous research have been undertaken in the academic literature to investigate the disparities observed in the lactate dehydrogenase (LDH) test results when comparing plasma and serum samples, as well as to identify the underlying causes contributing to these discrepancies. There are several factors that contribute to this disparity, including variations in tube brands, plasma contamination with platelets, fragmentation of platelets, and fragmentation of erythrocytes. The literature has highlighted the notable issue of the impact of platelet residues and platelet lysis on plasma LDH levels, specifically in terms of their amplifying influence. These findings offer significant criteria that necessitate consideration when evaluating LDH levels. It has been noted that LDH measurements can be influenced by many processes that take place during serum preparation, including hemolysis and coagulation. In summary, it is important to consider the type of sample, preparation process, and tube selection when aiming to achieve accurate evaluation and interpretation of LDH measurement outcomes. The acquisition of this information holds significant value in enhancing the precision and dependability of outcomes in laboratory testing.[12,16,21-27]

In the Passing-Bablok regression analysis (Figure 1), the slope value for all tests, except for Ca and INS, had a 95% confidence interval that included 1. The slope value for Ca was 0.90 95% CI (0.84-0.97), and for INS, it was 0.84 95% CI (0.77-0.91). The intercept value confidence interval for all tests, except GGT and Ca, passed through 0. The intercept values and 95% CI for GGT and Ca were calculated as 1.00 (0.59-1.86) and 0.88 (0.22-1.49), respectively. The systematic error and proportional difference observed for the Ca, GGT, and INS analytes were not clinically significant, as all three tests remained within the BV %TEa limits (Table 1). Kösem et al.[23] similarly interpreted their findings on parathormone. According to Ercan et al.[14] the confidence interval for the CRP intercept did not contain a value of 0. However, they reported that this bias was not clinically significant. Our study, following that of Ferrari et al.[15] represents the second investigation examining insulin in various tubes. However, our findings concerning insulin did not correspond with the earlier report. We observed a negative bias compared to the serum tube. We believe future research should focus on evaluating insulin values at low, normal, and high levels for a more comprehensive understanding.

We collected and evaluated sample aspiration errors, hemolysis index values, and TAT data from the LIS before and after switching to plasma in our study. During the 2-month period we measured, the proportion of aspiration errors in all samples was 0.88% before the implementation phase, while this proportion dropped to 0.44% after switching to plasma (Table 3). This decrease was statistically significant and has been reported in similar studies. Ramakers et al.[28] reported a decrease in aspiration errors from 2.3% to 0.4% over six months. Hetu et al.[11] found that aspiration errors dropped from 2.01% before to 0.77% after the implementation. Our findings were consistent with those reported in the literature. However, the reduction rate of aspiration errors was low because of the relatively low number of aspiration errors and the short evaluation period. In our initial implementation phase, as shown in Table 3 with data sourced from actual patient samples, we did not observe a decrease in hemolysis rates. We assume that the utilization of plasma tubes did not influence our hemolysis rates. Such an outcome might be attributed to persistent preanalytical errors during blood collection.

Nevertheless, our reduction rate is significant for high-volume emergency laboratories. These data indicate that the sample quality improved in the plasma phase compared with the previous phase using serum samples. This resulted in a decrease in the time required by the laboratory staff for clotting time and corrective actions related to fibrin. As a result, laboratory staff can spend more time on other critical tasks and less time on non-value-added work.

Previous studies have shown the positive effects of plasma on TAT. Hetu et al.[11] studied TAT for the K test and found significant reductions in the average time between sample acceptance and result confirmation. Similarly, Ramakers et al.[28] reported a significant decrease in median TAT time using Barricor tubes. Badiou et al.[29] reported significant reductions in the median time to specimen acceptance and turnaround time in the first 15-day measurement period using Barricor tubes instead of gel LIH tubes. Their study reduced the time between sample collection from the emergency department and transfer of results to the LIS by 10 minutes for 95% of TAT results for some analytes such as creatinine, CRP, K, Na, and Na and Hs-cTnT measured for eight analytes.[11,28,29] In our laboratory, we performed three separate analyses to measure improvements in TAT after switching to plasma tubing. Using the K and TnT-Hs assays as examples, we observed a significant decrease in the number of samples exceeding the TAT target ($p<0.001$). As shown in Figure 3, the reductions in TAT time after the transition phase are consistent with those reported by Hetu et al.[11] Our second analysis examined sample-based TAT distributions before and after the transition phase. When we analyzed the time between ordering and receiving test results for all patient samples, we found that 95% of the patients received results in 102 minutes instead of 110 minutes when using serum, as shown in Figure 4. In our other sample-based analysis, when we analyzed the median values of the laboratory sample acceptance-device entry times, we decreased from 21 minutes to 17 minutes ($p<0.001$). We think that a partial reduction occurred here due to not having to wait before centrifugation Figure 5. According to our findings, these significant reductions in TAT times are in agreement with the literature. Our study encountered certain limitations concerning insulin. Given the conflicting results for plasma insulin, we propose that examining various plasma/serum insulin levels is essential to determine if these discrepancies are influenced by such variations.

CONCLUSION

In this study, we compared the performance of serum and LIH tubes in various clinical chemistry and immunoassay tests. According to the regression analysis and Bland-Altman plots, most tests had no significant difference between the serum and LIH. However, for some analytes, TE values exceeded the TEa limits derived from the BV database. Therefore, we determined the alternative allowable error limits for some tests and found that plasma tubes could be used instead of serum tubes for most tests, except for LDH. We also observed that the use of lithium heparinized plasma tubes improved the sample quality reduced the incidence of aspiration errors, and decreased TAT times in the emergency laboratory. Our study showed that LIH tubes can replace serum tubes in most clinical chemistry and immunoassay tests. Plasma not only improved the sample quality but also reduced TAT times and the incidence of aspiration errors. Therefore, using LIH tubes in clinical laboratories can improve healthcare quality and reduce the workload of the laboratory staff.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: 117).

Informed consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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