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Biological variations of thirteen plasma biochemical indicators

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ABSTRACT

Background: Reports on biological variation of plasma biochemical indicators are limited. We evaluated biological variations of 13 plasma biochemical indicators.
Methods: Plasma samples were collected from 40 healthy individuals over 5 days. Intra-individual coefficient of variation (CV_I), inter-individual coefficient of variation (CV_G), index of individuality (II), reference change value (RCV), and analytical goal parameters were calculated.
Results: Albumin (Alb) showed the lowest CV_I (2.50%) and the lowest CV_G (5.08%), while C-reactive protein (hsCRP) presented the highest CV_I (26.87%) and CV_G (61.73%). II values were all less than 1.0. Alb presented the lowest 95% RCV (7.67), while hsCRP showed the highest 95% RCV (74.61). Alb, urea, creatinine (Cr), creatine kinase (CK), and creatine kinase isoenzyme MB (CKMBmass) CV_I differed with gender ($P < 0.05$). The CV_G of the 13 indicators presented a significant gender difference ($P < 0.0001$). Alb showed the lowest desirable imprecision CV (1.3%), the lowest desirable bias (1.4%), and the lowest desirable total error (3.5%), while hsCRP presented the highest desirable imprecision (13.4%), the highest desirable bias (16.8%), and the highest desirable total error (39.0%).
Conclusion: Our findings add to the database of biological variations of plasma indicators.

1. Introduction

The results of blood analysis are affected by the patient's health status as well as by pre-analytical variations, total random analytical errors, and variations in homeostatic set-points of the patient [1]. To accurately evaluate longitudinal changes in detection parameters, intra-individual and inter-individual biological variations should be considered. Variations caused by different homeostatic points within the same individual are referred to as intra-individual biological variations, whereas variations in the results among different individuals are referred to as inter-individual biological variations.

To provide rapid test report, plasma samples with added heparin are gradually replacing serum for the detection of biochemical indicators. This replacement is based on the fact that serum samples increase the turnaround time because of coagulation, especially for patients receiving anticoagulant therapy, and increase the risk of blockage by fibrinogen in sampling probes when automatic biochemical analyzers are used, especially when the sampling probe or instrument does not have the capacity to detect such blockage [2]. Results provided by the 2014 edition of the biological variation database mostly included information on serum biochemical indicators [3], whereas reports on biological variation of plasma biochemical indicators are limited. The results obtained in this study could be used to effectively supplement the current database and provide information to establish biological variation database for plasma biochemical indicators.

2. Materials and methods

2.1. Study subjects

A total of 40 healthy volunteers were recruited, including 21 male subjects and 19 female subjects with ages ranging from 21 to 68 years (median age, 46 years). To reduce pre-analytical variations to the minimum, strict inclusion and exclusion criteria were established before selection of the subjects [4]. The inclusion criteria included the following: a healthy life style, non-smoking, no alcohol consumption, no infection, no participation in strenuous exercise, and no consumption of medicine. Qualified subjects were interviewed and asked to answer a health questionnaire survey. Menstruating or pregnant women were excluded. Subjects should not have a family history of cancer or a history of cancer. Additionally, their routine blood and urine detection indicators such as fasting blood glucose, blood lipids, and liver and kidney function indicators should not show abnormalities. In addition, the subjects were asked to maintain their daily life habits during the study period. This study

Abbreviations: CV_I, intra-individual coefficient of variation; CV_G, inter-individual coefficient of variation; II, index of individuality; RCV, reference change value.

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Table 1
CV_A, CV_I, CV_G, and corresponding CIs of the 13 plasma biochemical indicators.

Indicator	Units	Group	Median	Range	CV_A (%)	CV_I (%)	CV_G (%)
ALT	U/l	All	13	6–40	1.74 (1.51–2.04)	3.57 (3.06–4.3)	12.56 (9.49–18.57)
		Male	14	9–40	1.51 (1.25–1.91)	3.04 (2.43–3.97)	8.18 (5.63–14.94)
		Female	11	6–22	1.98 (1.64–2.5)	4.14 (3.35–5.39)	14.56 (9.83–27.89)
Alb*	g/l	All	48.4	43.4–57.2	1.19 (1.01–1.42)	2.50 (2.05–3.18)	5.08 (3.87–7.42)
		Male	50.7	45.7–57.2	1.16 (0.97–1.43)	2.40 (1.97–3.08)	2.74 (1.91–4.81)
		Female	46.5	43.4–52.0	1.20 (1.00–1.48)	2.76 (2.33–4.06)	5.02 (3.39–9.62)
TBil	μmol/l	All	8.52	4.20–18.90	1.51 (1.32–1.76)	9.93 (8.59–11.77)	14.26 (10.70–21.38)
		Male	8.95	4.40–18.90	1.73 (1.44–2.18)	9.47 (8.17–11.26)	14.46 (10.85–21.69)
		Female	6.60	4.20–18.30	1.18 (0.98–1.47)	10.00 (8.19–12.84)	14.43 (9.75–27.65)
DBil	μmol/l	All	2.80	1.40–5.80	2.73 (2.39–3.17)	13.12 (11.33–15.57)	33.48 (25.47–48.91)
		Male	3.01	1.40–5.80	2.62 (2.20–3.24)	11.00 (9.05–14.03)	31.23 (21.82–54.81)
		Female	2.10	1.50–3.70	2.84 (2.36–3.58)	16.53 (13.44–21.47)	23.72 (16.02–45.43)
Urea*	mmol/l	All	4.58	2.59–7.88	1.87 (1.64–2.19)	7.99 (6.87–9.56)	14.64 (11.13–21.38)
		Male	5.18	3.34–7.88	1.68 (1.40–2.10)	5.12 (4.18–6.63)	14.17 (7.8–19.59)
		Female	3.83	2.59–6.21	2.14 (1.77–2.71)	8.30 (5.61–15.91)	11.18 (9.04–14.65)
Cr*	μmol/l	All	73	53–93	1.59 (1.38–1.87)	4.28 (3.65–5.17)	13.98 (10.63–20.42)
		Male	82	75–93	1.52 (1.25–1.95)	3.16 (2.21–5.55)	3.41 (2.71–4.62)
		Female	64	53–79	1.64 (1.37–2.06)	5.16 (4.21–6.68)	6.42 (4.34–12.3)
AMY	U/l	All	56	30–112	2.11 (1.85–2.46)	4.29 (3.70–5.11)	25.60 (19.47–37.38)
		Male	53	43–112	2.05 (1.71–2.57)	4.15 (3.16–5.22)	26.80 (18.73–47.04)
		Female	51	30–93	2.17 (1.8–2.72)	5.04 (4.11–6.53)	21.07 (14.23–40.36)
Lipa	U/l	All	127	14–331	2.89 (2.52–3.38)	15.97 (13.73–19.08)	21.00 (15.97–30.68)
		Male	135	83–331	3.19(2.67–3.95)	9.52 (7.82–12.19)	18.15 (12.68–31.85)
		Female	115	14–206	2.26 (1.86–2.88)	11.56 (9.29–15.57)	22.67 (15.31–43.42)
CK*	U/l	All	119	53–195	4.16 (3.61–4.90)	26.27 (23.05–32.50)	48.47 (36.1–73.77)
		Male	127	91–195	3.97 (3.28–5.01)	26.43 (22.26–35.80)	36.06 (24.35–69.07)
		Female	70	53–160	3.84 (3.14–4.93)	14.89 (11.14–18.47)	17.40 (11.51–35.42)
CKMBmass*	μg/l	All	0.66	0.10–2.40	6.37 (5.6–7.4)	18.38 (15.94–21.73)	47.63 (35.99–70.43)
		Male	0.82	0.30–2.40	5.58 (4.70–6.86)	16.58 (13.72–20.94)	35.61 (24.88–62.50)
		Female	0.44	0.10–1.90	8.03 (6.66–10.11)	21.79 (17.76–28.19)	37.91 (25.07–77.16)
hsCRP	mg/l	All	0.40	0.05–2.02	1.63 (1.43–1.89)	26.87 (23.29–31.75)	61.73 (46.94–90.15)
		Male	0.38	0.05–1.69	1.40 (1.19–1.71)	26.43 (22.04–33.02)	59.56 (41.62–104.52)
		Female	0.26	0.16–2.02	2.05 (1.69–2.61)	26.79 (21.61–35.26)	64.71 (43.71–123.96)
NT-proBNP	pg/ml	All	19	4–64	3.87 (3.38–4.53)	12.76 (10.96–15.26)	20.86 (15.86–30.47)
		Male	14	4–59	4.50 (3.74–5.63)	11.82 (9.61–15.35)	21.79 (15.23–38.25)
		Female	22	5–64	3.19 (2.64–4.03)	13.48 (10.93–17.58)	20.36 (13.75–39.0)
Glu	mmol/l	All	5.17	3.80–5.89	1.14 (1.00–1.34)	4.66 (3.99–5.60)	5.26 (4.52–6.27)
		Male	5.29	4.19–5.80	1.32 (1.10–1.65)	4.15 (3.16–6.07)	4.36 (3.32–6.37)
		Female	5.03	3.80–5.89	0.86 (0.71–1.10)	5.00 (4.01–6.65)	5.83 (3.94–11.16)

* Significant gender difference for CV_I ($P < 0.05$).

was approved by the Ethics Committee of Peking Union Medical College Hospital and all subjects signed an informed consent form.

2.2. Specimen collection

Venous blood samples were collected at 8 a.m. every day from day 1 to day 5 by the same phlebotomist. The venous blood samples were placed in vacuum blood collection tubes containing lithium heparin. Once specimens were collected from all subjects, the specimens were immediately centrifuged (3000 r/min × 10 min) and the separated plasma samples were stored at −80 °C. Detection was performed once all specimens were collected.

2.3. Sample detection

The plasma ALT, Alb, TBil, DBil, Urea, Cr, Glu, AMY, Lipa, CK, CKMBmass, and NT-proBNP were detected using the Siemens Dade Dimension EXL automatic biochemical and immunological analyzer (Dade Behring Inc.). To ensure the traceability of the results, all reagents (ALT, BA6119; Alb, BA6016; TBil, GB6050; DBil, FD6047; Urea, GB6019; Cr, BB5353; Glu, BA5352; AMY, EB6006; Lipa, FA6038; CK, FA6041; CKMBmass, GA6071; and NT-proBNP, EA6097) and calibrators (ALT, Enzy2 4BD069; Alb, TP/Alb 4MD026; TBil, TBil/DBil Cal 4MD050; DBil, TBil/DBil Cal 4MD050; Urea, Chem 1 Cal 4KD055; Cr, Chem 1 Cal 4KD055; Glu, Chem 1 Cal 4KD055; AMY, Enzy Verifier 4GJ041; Lipa, LIPL Cal 4KD0027; CK, CK Verifier 4JD028; CKMBmass, MMB Cal 4GD009; and NT-proBNP, NTP Cal 5AD070) were from Siemens Inc. High and low values of ALT, Alb, TBil, DBil, Urea, Cr, Glu, AMY, Lipa, CK were detected using Bio-Rad 2-level internal control samples, while CKMBmass and NT-proBNP were detected using Bio-Rad 3-level internal control samples.

The Beckman AU5800 automatic biochemical analyzer (Beckman Coulter Biomedical Co.) was used to detect plasma hsCRP. To ensure the traceability of the results, the reagent (hsCRP) and calibrator (hsCRP) were from Beckman. High and low values of plasma hsCRP were detected using Bio-Rad 2-level internal control samples. Before detection, the internal quality control samples were measured to assure that they were within the accepted range. Data on the internal quality control are shown in Supplementary Table 1. To avoid multiple freeze–thaw cycles and to minimize analytical variability, the detection of each sample was completed in the same analysis batch in the same day and each indicator for each sample was repeated twice in random order in the same instruments.

2.4. Statistical analysis

The statistical software SAS9.3 was used to perform the statistical analysis (SAS Institute Inc.). A normality test was performed using the Shapiro–Wilk test and a logarithmic conversion was conducted on skewed indicator [5]. Outliers more than 3 SD from the mean were excluded. The intra-individual coefficient of variation (CV_I), inter-individual coefficient of variation (CV_G), and analytical coefficient of variation (CV_A) were calculated using a nested analysis of variance. CV_I and CV_G were evaluated by using the method of Fraser et al. [4]. A nested analysis of variance was also applied to compare biological variation between male and female subjects.