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Abstract

Background: Recently, the use of separate gender-partitioned patient medians of serum sodium has revealed potential for monitoring analytical stability within the optimum analytical performance specifications for laboratory medicine. The serum albumin concentration depends on whether a patient is sitting or recumbent during phlebotomy. We therefore investigated only examinations requested by general practitioners (GPs) to provide data from sitting patients.

Methods: Weekly and monthly patient medians of serum albumin requested by GP for both male and female patients were calculated from the raw data obtained from three analysers in the hospital laboratory on examination of samples from those >18 years. The half-range of medians were applied as an estimate of the maximum bias. Further, the ratios between the two medians were calculated (females/males).

Results: The medians for male and female patients were closely related despite considerable variation due to the current analytical variation. This relationship was confirmed by the calculated half-range for the monthly ratio between the genders of 0.44%, which surpasses the

optimum analytical performance specification for bias of serum albumin (0.72%). The weekly ratio had a half-range of 1.83%, which surpasses the minimum analytical performance specifications of 2.15%.

Conclusions: Monthly gender-partitioned patient medians of serum albumin are useful for monitoring of long-term analytical stability, where the gender medians are two independent estimates of changes in (delta) bias: only results requested by GP are of value in this application to ensure that all patients are sitting during phlebotomy.

Keywords: analytical stability; medians of serum albumin; partitioning by gender; ratio between gender medians; raw data for serum albumin; requests by general practitioners.

Introduction

Examinations of serum albumin concentrations are important in the diagnosis and monitoring of liver, nutritional and kidney diseases and many other disorders; in consequence, good analytical quality with optimum analytical bias is required to facilitate good quality patient care. A valuable tool for monitoring of analytical stability in the laboratory is the calculation of the medians of the results of examinations on samples from patients [1]. In a previous study, we applied the half-range of medians as an estimate of the maximum bias, and this was estimated as 2.25% for serum albumin [2]. In a recently published model for serum sodium, we improved the approach by separating the medians for the two genders and found a very close relationship, which was independent of the achieved analytical quality [3]. A requirement for obtaining a reliable half-range of the ratio between the monthly medians of the genders was the application of the raw data generated by the analysers in order to quantitate the small variations in the ratios. The advantage of using the two gender medians was that these are totally independent estimates of the actual analytical quality and thus could be used to confirm (or refute) each other in the assessment of the ongoing analytical bias.

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The model using partitioning of the medians by gender could also be applied to serum albumin, but this would have limitations if all patient data were used because changes of concentrations of serum proteins and protein-bound moieties, including albumin, occur with approximately 6.5% higher concentrations when sitting as compared to when recumbent [4]. Further, the frequent requests for serum albumin in hospitalised patients with low serum albumin concentrations results in more unstable patient medians. Therefore, we decided to use only serum albumin results requested by general practitioners (GP). This also solved the problem of the influence of posture on serum albumin because all these patients undergo phlebotomy in a sitting position.

The purpose of the current investigation was to examine the usefulness of raw data for serum albumin medians from samples obtained from patients of GP and partitioned according to gender to generate two independent estimates of analytical bias, thereby providing a tool for assessing and improving analytical stability in individual medical laboratories.

Materials and methods

Analysers and results of examination of samples from patients

The Department of Clinical Biochemistry, Nordsjællands Hospital, University of Copenhagen, generated 145,000 serum albumin results in 2016 from patients >18 years: 30.0% were requested by GP. Serum albumin concentrations were examined by use of bromocresol purple (BCP) (from Siemens Healthcare Diagnostics Inc., Newark, DE, USA) on three Siemens Dimension Vista® 1500 instruments (Siemens Healthcare Diagnostics Inc.), and the study included all results from patients of GP that were >18 years of age and had a Danish personal identification number. The study included only weeks with more than 75 serum albumin examination results on each of the three analysers. Siemens Healthcare Diagnostics Inc. provided the reagents and calibrators. The routine procedures for serum albumin examinations were not changed during the investigation nor during the subsequent assessment of the model. However, the results of the examinations were retained as the raw data from the analysers to allow the computations and calculations of medians used in the model. The overall within-day analytical coefficient of variation (CV_A) was 1.7% over the course of this study ($n=1041$, $\text{mean}=44.8$ g/L).

Calculations

The calculations were performed as documented for serum sodium [3]. Briefly, the raw results from the examinations on samples from patients were used for calculation of weekly and monthly medians of results from patients of GP for each gender on each analyser and for the three analysers combined.

The model

The medians of serum albumin examination results requested by GP for both males and females were calculated for each individual analyser and for the combination of all three analysers for every working week with sufficient number of results for the analyser and for every working month. The gender medians for the whole year were used as targets, and the half-ranges of medians, in g/L, were used as estimates of bias (median – target) or, more correctly, for Δbias , as documented previously [2, 3]. Additionally, the ratios of medians between genders (females/males) of serum albumin were calculated for the weekly and monthly medians, and the half-range in percentage for these ratios was compared to the analytical performance specifications for bias suggested by Fraser et al. [5]. This was derived from the median estimates of published within-subject (CV_I) and between-subject (CV_G) biological variation as documented in the most recent biological variation database [6]. The medians as well as the ratios between medians were grouped with the following numbers: “1” for half-range <0.72%, “2” for half-range <1.43%, “3” for half-range <2.15% and “4” for larger half-ranges. In the figures, the target values for medians are based on the combined gender medians for samples from patients of GP in 2016 and the ratio between these.

Lyophilised control serum

Lyophilised human serum pool (HK12) was obtained from the Danish Institute for External Quality Assurance for Laboratories in Health Care, DEKS (DEKS, Rigshospitalet-Glostrup, Nordre ringvej 29-57, DK-2600 Glostrup, Denmark). This lyophilised human serum pool is produced by Aalto Scientific (CA, USA) from healthy blood donors, and selected purified human analytical components are added to obtain clinically relevant concentrations. It was handled according to manufacturer's instructions. In brief, it was stored at -20 °C, transferred to 4 °C 4–5 days before reconstitution, reconstituted with 2 – 5 °C sterile distilled water by weighing (5.000 ± 0.003 g) and mixed gently for 30 min before distribution to the analysers. This HK 12 is denoted lyophilised control serum; the overall median result for 2016 was 44.9 g/L. During weeks 22–35, the ratio (ratio = median of HK12/median of all patient results) between weekly median of lyophilised control serum and weekly median of combined male and female patient results for each analyser was calculated.

Results

The combined mean of results of examinations of samples from both genders from the three instruments was 38.3 g/L, and the ratio between genders (females/males) was 0.987.

Weekly medians

Figure 1 shows the combined weekly medians from the three analysers for serum albumin of 2016 for both males and females. The individual medians with at least

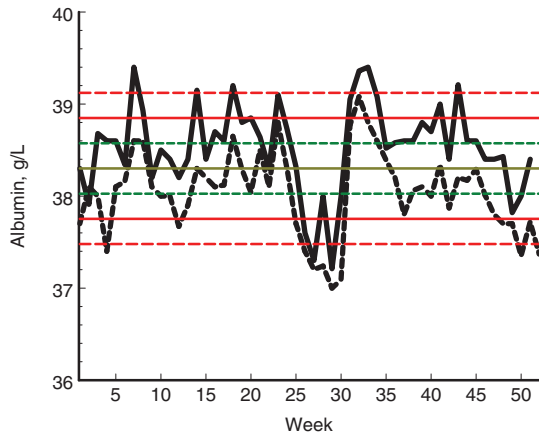


Figure 1: Weekly median serum albumin concentrations for males and females during 2016. The horizontal lines are the true median (dark yellow =38.3 g/L) and the three levels of \pm acceptable examination bias: optimum (green dotted lines), desirable (red lines) and minimum (red dotted lines). Combined weekly medians derived from three analysers. Males (solid black line) and females (dotted black line).

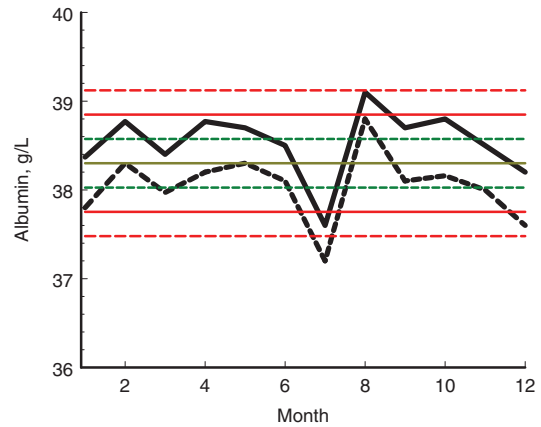


Figure 2: Monthly median serum albumin concentrations for males and females during 2016. The horizontal lines are the true median (dark yellow =38.3 g/L) and the three levels of \pm acceptable examination bias: optimum (green dotted lines), desirable (red lines) and minimum quality (red dotted lines). Combined monthly medians derived from three analysers. Males (solid black line) and females (dotted black line).

75 patient results obtained from the three analysers are shown in the Supplementary Figure 1. Detailed weekly performance characteristics for serum albumin medians of 2016 for both males and females are listed in Table 1A. The half-range of all weekly medians was 2.74%.

three analysers are shown in the Supplementary Figure 2. Detailed monthly performance characteristics for serum albumin medians of 2016 for both males and females are listed in Table 1B. The half-range of all monthly medians was 2.09%.

Monthly medians

Figure 2 shows the combined monthly medians from the three analysers for serum albumin of 2016 for both males and females. The individual medians obtained from the

Ratio between genders (females/males)

Figure 3 shows the ratios of medians between genders (females/males) of serum albumin. The weekly ratios during 2016 are shown in Figure 3A, whereas the monthly

Table 1A: Weekly performance characteristics for serum albumin medians for samples from males and females requested by general practitioners during 2016.

| Gender | All analysers | | | Analyser 1 | | Analyser 2 | | Analyser 3 | |
|-----------------|---------------|---------|------|------------|---------|------------|---------|------------|---------|
| | Males | Females | Both | Males | Females | Males | Females | Males | Females |
| Median, g/L | 38.6 | 38.1 | 38.3 | 38.8 | 38.2 | 38.5 | 38.3 | 38.5 | 37.8 |
| SD, g/L | 0.48 | 0.46 | 0.46 | 0.59 | 0.57 | 0.68 | 0.57 | 0.66 | 0.69 |
| CV, % | 1.23 | 1.21 | 1.19 | 1.51 | 1.49 | 1.77 | 1.48 | 1.73 | 1.81 |
| Minimum, number | 100 | 138 | 238 | 81 | 92 | 79 | 77 | 79 | 85 |
| Median, number | 386 | 510 | 893 | 149 | 193 | 114 | 154 | 126 | 167 |
| Maximum, number | 494 | 623 | 1117 | 248 | 298 | 173 | 217 | 171 | 222 |
| Minimum, g/L | 37.2 | 37.0 | 37.1 | 37.2 | 36.9 | 37.5 | 36.8 | 36.5 | 36.4 |
| Maximum, g/L | 39.4 | 39.1 | 39.2 | 40.1 | 39.5 | 40.1 | 39.4 | 39.7 | 38.9 |
| Range, g/L | 2.2 | 2.1 | 2.1 | 2.9 | 2.6 | 2.6 | 2.6 | 3.2 | 2.5 |
| Half-range, % | 2.84 | 2.73 | 2.74 | 3.74 | 3.40 | 3.43 | 3.35 | 4.16 | 3.24 |
| Classification | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

CV, % calculated as $100 \cdot SD / \text{median}$. Classification according to allowable examination bias [5].

Table 1B: Monthly performance characteristics for serum albumin medians for samples from males and females requested by general practitioners during 2016.

| Gender | All analysers | | | Analyser 1 | | Analyser 2 | | Analyser 3 | |
|-----------------|---------------|---------|------|------------|---------|------------|---------|------------|---------|
| | Males | Females | Both | Males | Females | Males | Females | Males | Females |
| Median, g/L | 38.6 | 38.1 | 38.3 | 38.8 | 38.3 | 38.6 | 38.2 | 38.6 | 37.9 |
| SD, g/L | 0.38 | 0.40 | 0.40 | 0.56 | 0.45 | 0.45 | 0.44 | 0.54 | 0.57 |
| CV, % | 0.98 | 1.04 | 1.05 | 1.43 | 1.18 | 1.17 | 1.16 | 1.40 | 1.52 |
| Minimum, number | 937 | 1208 | 2145 | 341 | 479 | 302 | 375 | 294 | 354 |
| Median, number | 1628 | 2138 | 3773 | 621 | 835 | 459 | 652 | 499 | 650 |
| Maximum, number | 1758 | 2355 | 4016 | 731 | 922 | 562 | 719 | 626 | 835 |
| Minimum, g/L | 37.6 | 37.2 | 37.3 | 37.3 | 37.0 | 37.8 | 37.5 | 37.4 | 36.7 |
| Maximum, g/L | 39.1 | 38.8 | 38.9 | 39.3 | 38.7 | 39.5 | 39.1 | 38.9 | 38.5 |
| Range, g/L | 1.5 | 1.6 | 1.6 | 2.0 | 1.7 | 1.7 | 1.6 | 1.5 | 1.8 |
| Half-range, % | 1.94 | 2.10 | 2.09 | 2.58 | 2.22 | 2.19 | 2.07 | 1.95 | 2.38 |
| Classification | 3 | 3 | 3 | 4 | 4 | 4 | 3 | 3 | 3 |

CV, % calculated as $100 \cdot \text{SD} / \text{median}$. Classification according to allowable examination bias [5].

ratios are shown in Figure 3B. The performance characteristics of ratios between the gender-partitioned medians of serum albumin of 2016 are presented in Table 2. Table 2A documents the characteristic for weekly ratios of medians, and the characteristics for monthly ratios of medians are shown in Table 2B.

Focusing on 3 months: June, July and August of 2016

Analytical stability problems in relation to changes of lot number of reagents and the requirement for recalibration during 3 months of 2016 are illustrated in Figure 4. The weekly medians for both genders for the three instruments are shown together with daily lyophilised control serum results in Figure 4A (some results for individual weekly medians in July are lacking due to fewer than 75 results being generated, the preset criterion for adequate data). The ratio for combined weekly medians of lyophilised control serum divided by the collective weekly medians (analysers and genders combined) is shown together with the ratios for weekly medians of females divided by males in Figure 4B; the half-ranges of ratios were 1.89% and 1.83%, respectively.

Discussion

Importance of using raw data for serum albumin concentrations to calculate patient medians

The traditional way to report serum albumin results from laboratory medicine is in grams per litre and often

without significant figures after the decimal points. This is insufficient for control of analytical quality and especially for calculation of monthly patient medians, where the median values vary within a range of ± 1.0 g/L and the monthly half-range in percentage of the ratio between genders is below 1.50% for individual analysers and below 0.50% for combined data (Table 2B). This is compared to the analytical performance specifications for the bias of serum albumin examinations [5, 6]: 0.72% for optimum quality, 1.43% for desirable quality and 2.15% for minimum quality, ordered as 1, 2 and 3, respectively. Consequently, we used the raw serum albumin examination data available from the analysers to obtain sufficient number of significant figures after the decimal points to obtain a detailed assessment of any small changes in medians over time.

Importance of using the gender medians and their ratio

Each gender median is determined by the population (here patients from GP) and of the analytical performance.

Variation of gender medians

If the gender groups are homogeneous and constant over time, then the “target median” for each gender is considered stable, with minor variation, which reduces with increasing size of the group. Therefore, the weekly medians have larger variation than the monthly (Figures 1 and 2 and Table 1A and B together with Supplementary Figures 1 and 2).

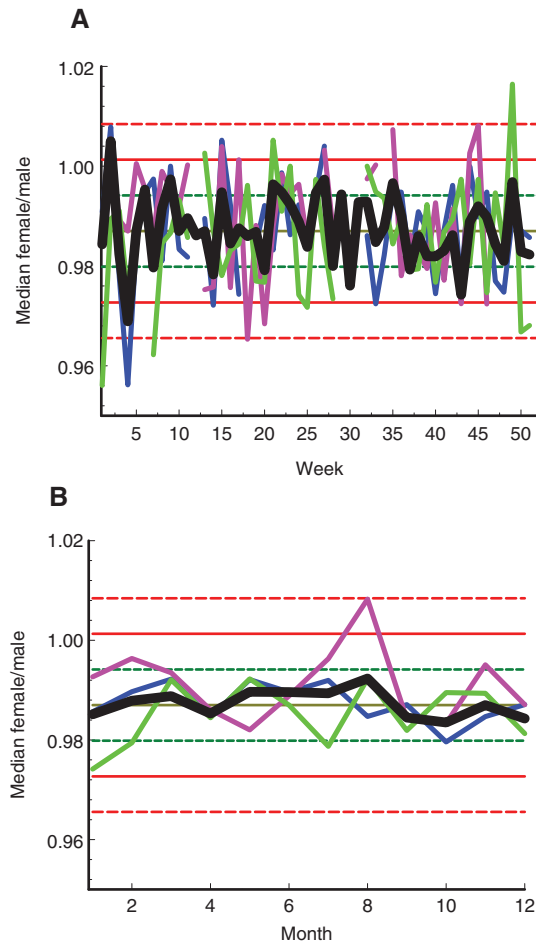


Figure 3: Ratios between median serum albumin concentrations from genders (females/males) measured with three analysers. The horizontal lines are the true median (dark yellow = 0.987) and the three levels of \pm acceptable examination bias: optimum (green dotted lines), desirable (red lines) and minimum quality (red dotted lines). (A) The weekly ratios between median serum albumin concentrations during 2016. Combined weekly medians derived from the three analysers (black line) and the individual ratios for analyser 1 (blue line), analyser 2 (purple line) and analyser 3 (green line). (B) The monthly ratios between median serum albumin concentrations during 2016. Combined monthly medians derived from the three analysers (black line) and the individual ratios for analyser 1 (blue line), analyser 2 (purple line) and analyser 3 (green line).

Δ Bias

Because the patient samples are analysed randomly, then both gender medians are influenced equally by changes in analytical performance, both over time with the same reagents and calibrator and on each instrument according to its current individual level of calibration and maintenance. As seen in Figures 1 and 2, the changes in both gender medians over time clearly confirm each other and reveal the relative large analytical dispersion achieved

Table 2A: Weekly performance characteristics of the ratios between serum albumin concentration medians of genders (females/males) from samples requested by general practitioners during 2016.

| | All analysers | Analyser 1 | Analyser 2 | Analyser 3 |
|----------------|---------------|------------|------------|------------|
| Median | 0.9869 | 0.9871 | 0.9887 | 0.9851 |
| SD | 0.00736 | 0.01048 | 0.01100 | 0.01176 |
| CV, % | 0.75 | 1.06 | 1.11 | 1.19 |
| Minimum | 0.96813 | 0.95619 | 0.96533 | 0.95607 |
| Maximum | 1.00501 | 1.00785 | 1.00813 | 1.01644 |
| Range | 0.03688 | 0.05167 | 0.04280 | 0.06037 |
| Half-range, % | 1.83 | 2.56 | 2.12 | 2.97 |
| Classification | 3 | 4 | 3 | 4 |

CV, % calculated as $100 \cdot \text{SD} / \text{median}$. Classification according to allowable bias [5].

Table 2B: Monthly performance characteristics of the ratios between serum albumin concentration medians of genders (females/males) from samples requested by general practitioners during 2016.

| | All analysers | Analyser 1 | Analyser 2 | Analyser 3 |
|----------------|---------------|------------|------------|------------|
| Median | 0.98745 | 0.98710 | 0.99075 | 0.98573 |
| SD | 0.00275 | 0.00385 | 0.00745 | 0.00610 |
| CV, % | 0.2783 | 0.390 | 0.752 | 0.619 |
| Minimum | 0.98351 | 0.97959 | 0.98203 | 0.97416 |
| Maximum | 0.99233 | 0.99221 | 1.00826 | 0.99227 |
| Range | 0.00882 | 0.01262 | 0.02623 | 0.01811 |
| Half-range, % | 0.44 | 0.63 | 1.30 | 0.91 |
| Classification | 1 | 1 | 2 | 2 |

CV, % calculated as $100 \cdot \text{SD} / \text{median}$. Classification according to allowable examination bias [5].

currently. (The variability of individual instruments is demonstrated in Supplementary Figures 1 and 2). Therefore, each gender median variation over time is an estimate of the Δ bias and the two gender medians provides two independent estimates of Δ bias.

Gender medians

Each gender median depends on its target value, but both are changed by the same alterations in analytical characteristics, so differences between the gender medians are nearly constant without effect from Δ bias. As seen from Figure 2, the changes of monthly medians are nearly parallel with a common decrease in July.

Ratio of gender medians

The ratio between the medians from the two genders (females/males) is an estimate of the ratio between the

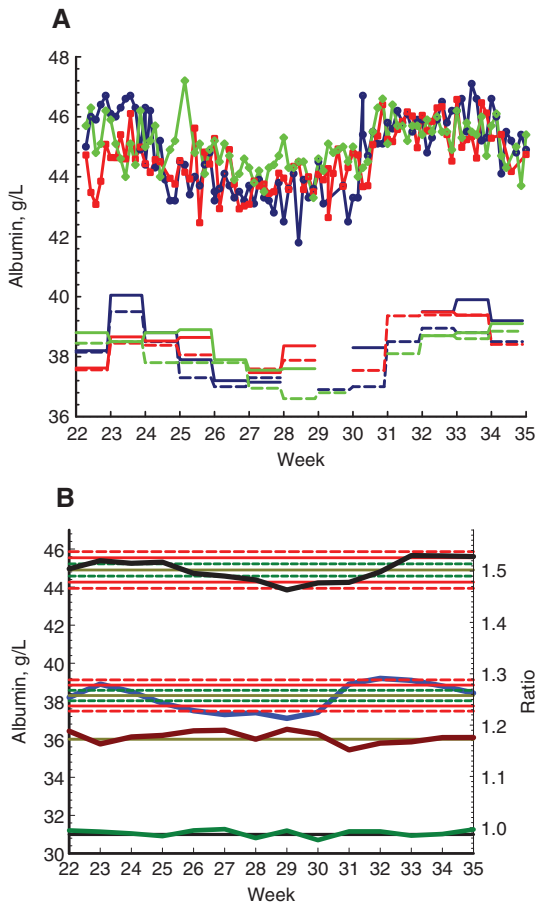


Figure 4: Weekly results for June, July and August of 2016. (A) Individual weekly medians from week 22 to week 35 (as in Figure 1B) for males (solid lines) and for females (dotted lines) together with daily data for lyophilised control serum plotted; the individual patient medians are from analyser 1 (blue line), analyser 2 (purple line) and analyser 3 (green line). (B) The weekly medians of examinations of lyophilised control serum from week 22 to week 35 (black line) and weekly patient median of combined medians from male and female from the three analysers combined are shown (blue line). The horizontal lines are the true medians for lyophilised control serum (44.9 g/L) and for the combined patient median (38.3 g/L) and the three levels of \pm acceptable examination bias: optimum (green dotted lines), desirable (red lines) and minimum quality (red dotted lines). Further, The ratio for weekly medians from the three analysers of lyophilised control serum divided by weekly patient median of combined male and female from the combined analysers is shown (brown line) and the weekly ratio between gender median of the combined analysers (green line).

two target values. Ideally, the ratio is a constant and, with a very large population of patients, the ratio approximates to a constant. This is illustrated in Figure 3A (Table 2A) with weekly ratios and Figure 3B (Table 2B) with (more constant) monthly ratios. Nevertheless, the ratio variation has impact on the estimated Δ bias.

Ranges of ratios

For each gender, the size of the difference between the current ratio and its target is a valuable estimate of range of the two Δ bias. Therefore, the mean of the two gender ratio ranges gives an even better estimation of the range of Δ bias and this is an important benefit as compared to the overall patient median.

The half-range of ratio is the maximum interval for the estimated Δ bias (i.e. Δ bias% \pm half-range of the ratio [%]), and consequently, it can be compared to the analytical performance specifications for bias. An essential point is the stability of the gender medians (Table 2A and B), where we have estimated the monthly half-range of ratios as the maximum deviation from the mean for patients from GP as 0.44%. This surpasses the optimum analytical quality specification for bias of 0.72% [5, 6].

Estimation of Δ bias

The difference between the mean of the gender medians and the targets is an estimate of the magnitude of Δ bias: in addition, the \pm half-range of the ratio is the maximum range for the estimated Δ bias. In practice, the weekly gender medians for individual instruments and combined for all instruments are used in troubleshooting to localise any concerns to a single instrument or to the reagents and calibration over all instruments, as shown in the example below.

Focusing on 3 months: June, July and August of 2016

A change of reagent lot and renewed calibration of all three analysers in week 25 (over 3 days) reduced the found examination serum albumin concentrations. In Figure 4A, it is evident from the weekly medians that the change in performance was found for all three analysers and, therefore, is likely related to the change of reagent lot and recalibration; thus, in such a case, it is relevant to combine the results from the three analysers. The target values for medians (estimated from the first 5 months) were as follows: male, 38.6 g/L; female, 38.1 g/L; and overall, 38.4 g/L. The comparable values from week 26 for the three instruments were as follows (as percentages): instrument 1, -3.8% , -3.0% and -3.4% ; instrument 2, <75 results for both genders; instrument 3, -1.9% , -0.8% and -1.3% . These results indicate a bias of -2.3% ,

which is confirmed in week 27 where the corresponding means of all instruments were -3.5% , -2.5% and -3.0% . This indicated a common source of variation for all three instruments such as problem reagents and/or calibrator resulting in approximately 3% lower concentrations. If the percentage half-ranges calculated for the whole year (Tables 1 and 2) are applied, then the change is just greater than the weekly half-range of 2.7% (Table 1A), and with a weekly half-range of the ratio of 1.8% (Table 2A), the change is not clearly documented ($\Delta\text{bias}\% \pm \text{half-range of ratio } [\%] = \text{approx. } -3\% \pm 1.8\%$). By contrast, with the mean of all monthly medians for both genders and all instruments from July being -2.6% and with the yearly half-range of ratio = 0.44% (Table 2B), this gives a better estimate of Δbias for July of approximately -2.6% (i.e. $\Delta\text{bias}\% = -2.6\% \pm 0.4\%$). In week 30, the reagent lot was changed again, and the previous examination results were restored and the data from the medians and the reference serum became comparable. The number of medians from the individual weeks is somewhat limited due to our criterion that >75 data points were required, but the combined weekly medians clearly demonstrate the general aspects of the systematic change, constant for the lot number of reagents and calibrator over the 5–6 weeks (Figure 4B). The results from the lyophilised control serum further confirmed the systematic change, but less obviously. If our investigation had been prospective, the change would have been observed after 1 week. However, the change was not observed by the routine internal control system because the deviation lay within the acceptance limits set according to the accreditation rules (rejection limits $>7.5\%$).

Use of patient results in internal control

Recently, a novel internal control system using “moving average” of patient results was advocated [7]. Truncation limits were applied, and for some measurands, ambulatory and hospitalised patients were separated, which resulted in removing 58% of patient results for serum albumin. The purpose for the investigation was to optimise the number of patient results needed to detect systematic errors, and for serum albumin, the suggested control limits were $\pm 9.3\%$. This concept differs in application and is different from our model, but it illustrates that there is an increasing interest in finding control procedures based on real patient results and free of the problems with control materials, which may suffer from lack of commutability.

Trueness

There are two dominating reagents for routine examination of serum albumin: bromocresol green (BCG) and bromocresol purple (BCP), which give different examination results with reference materials, and in consequence, harmonisation of methods is difficult but obviously needed [8]. Our method used BCP and our data are not strictly applicable to BCG methods. However, our model can be used by all large hospital laboratories with sufficient number of examinations of serum albumin requested by GP as a tool for assessment of the analytical stability.

Conclusions

- Raw data from analytical systems are necessary for obtaining sufficient number of data after the decimal point to describe the variability of patient medians of serum albumin.
- For serum albumin, only results on samples from patients requested by GP are useful for internal quality monitoring because all these patients are sitting during phlebotomy.
- Weekly and monthly gender-partitioned patient medians are very similar despite the current analytical performance attained, and the deviation of the mean of the two medians from the target gives the best estimate of Δbias in monitoring of analytical stability.
- The ratio between monthly gender medians is almost independent of the current Δbias but determined by the distribution of patients from GP.
- The half-range of the gender ratio is an estimate of the maximum deviation of the Δbias .
- Variation of weekly gender-separated patient medians is a useful tool for troubleshooting when acute analytical problems occur.

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