Invited critical review
Serum albumin: Accuracy and clinical use
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Abstract

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Albumin is the major plasma protein and its determination is used for the prognostic assessment of several diseases. Clinical guidelines call for monitoring of serum albumin with specific target cut-offs that are independent of the assay used. This requires accurate and equivalent results among different commercially available methods (i.e., result standardization) through a consistent definition and application of a reference measurement system. This should be associated with the definition of measurement uncertainty goals based on medical relevance of serum albumin to make results reliable for patient management. In this paper, we show that, in the current situation, if one applies analytical goals for serum albumin measurement derived from its biologic variation, the uncertainty budget derived from each step of the albumin traceability chain is probably too high to fulfill established quality levels for albumin measurement and to guarantee the accuracy needed for clinical usefulness of the test. The situation is further worsened if non-specific colorimetric methods are used for albumin measurement as they represent an additional random source of uncertainty.

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1. Introduction

The available scientific evidence supports the importance of albumin measurement in serum for the prognostic assessment of several diseases. Particularly, the determination of serum albumin is strongly recommended in hemodialysis patients as an indicator of therapy adequacy, in patients with multiple myeloma for disease staging and in patients undergoing replacement albumin therapy (Table 1) [1].

The “Kidney Disease Outcomes Quality Initiative” (KDOQI) guidelines call for monitoring of serum albumin as a valid and clinically useful measure of protein-energy nutritional status in dialysis patients, identifying the maintenance of concentrations >40 g/L as treatment goal [2]. Values below this concentration are highly predictive of mortality risk when present at the time of initiation of chronic dialysis as well as during the course of maintenance dialysis therapy [3]. In some countries (e.g., United States of America) monitoring of serum albumin concentrations is recommended in the dialyzed population with a target value of 40 g/L as a quality indicator of the performance of dialysis centres in order to obtain the reimbursement from the healthcare system.

The “International Myeloma Working Group” strongly recommends albumin measurement in serum of patients with multiple myeloma for disease staging [4]. Particularly, an albumin concentration ≥35 g/L, associated with a concentration of β2-microglobulin in serum lower than 3.5 mg/L, allows to classify individuals with multiple myeloma at stage 1 of disease [5].

Plasma albumin measurement in patients undergoing replacement therapy with human albumin, for calculation of the dose to be administered and for therapy monitoring, is recommended by the Italian Society of Transfusion Medicine and Immunohematology, which identifies, for some clinical situations, specific decision levels [6]. For instance, in the case of cirrhotic patients with spontaneous bacterial peritonitis or with ascites refractory to diuretic therapy, or in subjects with protein-losing enteropathy or undergoing major surgery, a concentration of serum albumin <20 g/L represents the decision level for albumin infusion.
From what briefly described, it is clear that currently available national and international guidelines recommend the monitoring of serum albumin concentrations using specific decision-making levels, which are independent of the method used for measurement, therefore considering results from different laboratories using different assays substantially equivalent to allow their consistent and reliable interpretation.

2. Standardization of serum albumin measurement

The production of accurate and equivalent results among laboratories and different methods of measurement is a primary goal of Laboratory Medicine and an absolute priority for public health [7]. In fact, an inadequate laboratory performance and a lack of comparability of results obtained in different situations can result in a wrong interpretation and decision by clinicians, with serious consequences for clinical practice, for the health care, and, ultimately, for the patient himself. The application of the concept of reference measurement system, based on the implementation of the metrological traceability of results obtained on biological samples to higher-order reference methods and/or materials, is now universally accepted as the best approach to obtain accurate and equivalent results [8]. For sure, the standardization of results for a given analyte is the only approach that allows the effective use of clinical guidelines, which, as previously mentioned for serum albumin, often recommend the use of specific and method-independent decision levels for diagnosis and therapeutic intervention [9].

The definition and the application of reference measurement system concept for result standardization should be strictly linked to the definition of goals for acceptable measurement uncertainty to fit the intended clinical use [10]. Using the consensus established at the IFCC-IUPAC Stockholm Conference for setting quality specifications in Laboratory Medicine [11], the best scientific approach of defining analytical performance goals should rely on (in a hierarchical order): 1) the evaluation of the effect of analytical performance on clinical outcome in the specific clinical setting, 2) data based on components of biological variation, and, if the previous information is lacking, 3) data based on clinical and laboratory experts’ opinion and published recommendations. As data on the impact of quality of albumin measurement on clinical outcome are lacking, it is possible to derive analytical goals from biological variation components of the analyte in serum. Using this approach, to be acceptable, the degree of uncertainty (expanded) of albumin measurement for clinical laboratories using unbiased assays should stay within ± 1.55% or ± 2.33% (desirable or minimum quality level, respectively), which are clearly stringent requirements [12]. It is vital to define the uncertainty sources across the entire traceability chain, starting with the employed reference materials, extending through the assignment of calibrator values by diagnostic manufacturers, and ultimately to the final result that the clinical laboratory provides on the patient’s biological sample, in order to compare the expanded uncertainty (usually obtained by multiplying the relative combined standard uncertainty by a coverage factor of 2 (95% level of confidence)) with an appropriate analytical goal [13].

Fig. 1 shows the reference measurement system for albumin measurement in serum, as currently defined [13,14]. In particular, the availability (in the past) of the ERM-DA470 reference material (also known as BCR-470) and, more recently, of the ERM-DA470k/IFCC material, together with immunochemical methods based on turbidimetry–nephelometry principles, recognized as reference measurement procedures by the Joint Committee on Traceability in Laboratory Medicine (JCTLM) [15], ensure the traceability of measurements in clinical laboratories to the US National Reference Preparation no. 12-0575C, representing the highest level of the albumin traceability chain. The ERM-DA470k/IFCC secondary reference material was released in 2008 by the Institute for Reference Materials and Measurements (IRMM) to replace the ERM-DA470 (BCR-470), sold out at that time [16,17]. The new material was characterized for 12 proteins, including albumin, through the use of a value-transfer protocol, according to which the certified values of the ERM-DA470 (considered as “reference material”) were transferred to the ERM-DA470k/IFCC (“target material”) (Fig. 2) [18]. The certified value and the associated expanded uncertainty for albumin, reported in the ERM-DA470k/IFCC certificate of analysis, are 37.2 g/L and 1.2 g/L, respectively [17]. This reference material should then be used by the diagnostic manufacturers for directly assign value to their method calibrators (Fig. 1). However, this works in transferring trueness only if the commutability of the material is demonstrated in order to not break the metrological traceability chain [19,20]. In a recent work [21], we showed that, when albumin is tested, the

| U.S. National Reference |
| Preparation no. 12-0575C |
| value transfer protocol |
| ERM-DA470 |
| value transfer protocol using immunochemical methods based on turbidimetry–nephelometry principles |
| ERM-DA470k/IFCC |
| value transfer protocol using immunochemical methods based on turbidimetry–nephelometry principles |
| Manufacturer’s working calibrator (master lot) |
| Manufacturer’s standing immunoassay |
| Manufacturer’s product calibrator |
| Commercial assay |
| Routine sample result |

Fig. 1. Metrological traceability chain for albumin measurement in serum. ERM, European Reference Material.
ERM-DA470k/IFCC has the same behavior (within well defined statistical limits [22]) of native human sera, confirming that this material is commutable (at least for the evaluated methods, i.e. turbidimetry and nephelometry) and can therefore be used to ensure the traceability of commercial assays to the reference measurement system (Fig. 3). A further limitation to be mentioned is the fact that, while there is a reference measurement procedure for serum albumin, accredited reference measurement services are not available in the JCTLM database [15]. This can make it difficult for manufacturers to establish metrological traceability and/or assess whether their assay performs good enough on native samples.

3. Accuracy of serum albumin measurement

According to the European Union (EU) directive on in vitro diagnostic medical devices, diagnostic manufacturers are obliged to implement the traceability of their commercial systems to recognized higher-order references (methods and/or materials) [23]. Our profession should verify that this is correctly applied and adequate for the clinical use [10,13].

For serum albumin, almost all commercial systems declare in their package inserts the traceability to the BCR-470 reference material, even if manufacturers do not clarify whether this is done directly or through the ERM-DA470k/IFCC material (see Fig. 1). As mentioned above, being the former sold out from years, the ERM-DA470k/IFCC should now be used to drive the metrological alignment of commercial systems for albumin measurement in serum. Considering this confused situation, we evaluated as a paradigm the performance of the Roche Diagnostics Tina-quant Albumin Gen. 2 immunoturbidimetric assay, carried out on the Roche Cobas c501 analyzer, by measuring the albumin concentration of the ERM-DA 470 k/IFCC in two identical experiments carried out five months apart using two different lots of assay reagents [24]. In each experiment, a) the reference material was reconstructed according to the procedure recommended by the IRMM and determined in duplicate for three consecutive days, b) the analytical system was used in strict accordance with the manufacturer’s instructions without any procedural change, and c) the system control materials (Precinorm and Precipath Protein) were measured to check the correct alignment of the system to the manufacturer’s established parameters. Quite surprisingly, the values obtained on the ERM-DA470k were markedly lower than expected, with an average bias between the experimental mean of the means (34.9 g/L) and the target value (37.2 g/L) of −6.2%. The need of a more careful alignment of commercial albumin assays to higher-order references was recently confirmed in an intercomparison exercise with single-donation sera [25]. Importantly, in our study, even eliminating the bias component, the expanded uncertainty associated with albumin result (which basically includes the combined uncertainty of the corresponding traceability chain and the uncertainty due to imprecision of measurements) remained about two times higher than the minimum goal for albumin measurement in serum derived from biological variation of the analyte (≤2.33%), showing that the uncertainty of albumin measurement was probably too high to fulfill the established quality level needed for clinical application of the test [24].

In summary, if from one hand, depending from the biology and strict homeostatic control of serum albumin, the analytical quality required for its measurement is extremely high and, consequently, the performance of commercial assays should be extremely good to allow their application in the clinical setting, on the other hand the currently available reference materials probably have too high associated uncertainty and the commercial methods are still too imprecise. In other words, we should probably recognize that the accuracy associated with each step of the traceability chain should be significantly reduced in order to obtain a final combined uncertainty associated to the patient’s sample results that fulfills quality levels for albumin measurement [13].

Limiting the evaluation to albumin measurement imprecision, few years ago we demonstrated that the use of methods with poor analytic selectivity, such as those based on protein dye-binding, e.g. the bromocresol green methods, or those methods based on semiquantitative measurements (peak quantitation at serum protein electrophoresis) could be associated with a better precision in comparison with more specific nephelometric measurements [26]. However, in the case of serum albumin the lack of selectivity of the measurement procedure becomes a hardly tolerable factor, as it adds an additional source of uncertainty in a metrological system that, as seen above, has in itself a too high uncertainty budget even when specific and relatively precise commercial methodologies, such as immunoturbidimetry, are used. On the other hand, reducing the uncertainty coming from reference materials may not be feasible if the characterization approach of the materials includes contributions caused by different selectivities of the different albumin methods, as in the case of ERM-DA470 k/IFCC [14,17]. As for serum

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**Fig. 2.** Approach used to the value transfer from the ERM-DA470 (BCR-470) to the ERM-DA470k/IFCC reference material.

**Fig. 3.** Evaluation of commutability of the ERM-DA470k/IFCC reference material. The behavior of the ERM-DA470k/IFCC was compared with those of 20 selected human serum samples. The commutability of the material was estimated from Deming’s regression analysis of the results obtained in native samples using the 95% prediction interval (95PI) (dashed lines in the figure), in accordance with the C53-A Clinical and Laboratory Standards Institute standard (22). As the ERM-DA470 k/IFCC results fall well inside the 95PI, its commutability is shown. Adapted from ref. [21].
albumin it is worth to try to reduce uncertainties of reference materials, alternative characterization ways should be considered. For instance, assigning values to a pure albumin reference preparation to be used at the top of the traceability chain using dry mass and amino acid analysis, together with a performance improvement of the reference method used to assign values to the secondary reference material could work as an alternative. The use of liquid chromatography-mass spectrometry (LC-MS) methods could be another alternative, even if their repeatability in measuring digested peptides of the protein is still high compared to immunoassays [27,28]. Overall, we strongly believe that the specifications of reference materials and calibration materials should be defined by the performance needs of analyze measurements in clinical setting; therefore, stakeholders should be prepared to provide new suitable reference materials together with improved commercial assay methods whenever the clinical application of the test is made questionable.

4. Final remarks

The implementation of measurement standardization in laboratory practice is the only way to allow equivalence of results produced in different places with different methods, permitting their unambiguous interpretation, by eliminating the need of method-specific reference intervals and decision limits, and allowing a more correct use in clinical practice of the information derived from scientific evidence [29]. For serum albumin, the reference measurement system is well defined in all its components and the uncertainty associated to each step of the traceability chain is known. However, if this is undoubtedly useful for ensuring equivalence of patient results (provided that the metrological approach is properly implemented by manufacturers), it is possibly not yet enough to guarantee the accuracy required for optimal clinical use of the test. In particular, if from one hand the uncertainty associated with the reference materials already uses an important portion of the uncertainty budget provided to fulfill the analytical goals of albumin measurement, on the other hand commercial assays are still relatively imprecise and offer performances not fully in line with the request of high analytical quality. To this difficult situation, one should also add the still widespread use of analytical methods known for having low selectivity for albumin measurement. Considering the data of the Lombardy External Quality Assessment Scheme (EQAS) (October 2012) as an example, only less than 13% of the participating laboratories employ methods based on immunoturbidimetry or immunonephelometry principles. As recently demonstrated also for creatinine measurement in serum [30], the use of non-specific methods for the measurement of analytes having high clinical impact makes the standardization of measurements very difficult, or even impossible, with important negative effects on patient care. On the other hand, the lack of EQAS fulfilling the necessary prerequisites to objectively assess the laboratory performance and the analytical quality of measurements is another factor of difficulty in highlighting issues such as those reported in this paper [10,13,25].

References


