

Albumin Quantification in Body Fluids Using Material Decomposition on Dual-Energy CT: An In Vitro Feasibility and Threshold Analysis

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Abstract

Background

Conventional albumin quantification requires fluid sampling, which can be invasive for poorly accessible compartments. This in vitro study investigated the feasibility of dual-energy CT (DECT) material decomposition for albumin quantification and explored the concentration range in which the method provides acceptable agreement with ELISA.

Methods

The structural and X-ray attenuation similarities of human serum albumin and bovine serum albumin (BSA) were assessed using the RCSB Protein Data Bank and NIST XCOM database. A series of BSA standards underwent DECT with albumin-calcium material decomposition to establish a calibration curve. Albumin concentrations derived from DECT (C_{DECT}) were compared with ELISA measurements (C_{ELISA}) in human serum ($n = 18$), cerebrospinal fluid (CSF; $n = 18$), and thoracoabdominal fluid ($n = 30$). Pearson correlation, linear regression, paired t tests, Bland-Altman analysis, and a two-way random-effects absolute-agreement intraclass correlation coefficient (ICC) were used.

Results

Human albumin and BSA had highly similar attenuation curves (Pearson $r > 0.99$). The BSA calibration model showed strong linearity ($R^2=0.9973$). C_{DECT} correlated with C_{ELISA} in serum ($r = 0.835$), CSF ($r = 0.890$), and thoracoabdominal fluid ($r = 0.961$; all $p < 0.001$). Overall absolute agreement was high (ICC = 0.967). Bland-Altman mean biases ($C_{\text{DECT}}-C_{\text{ELISA}}$) were -1.62 mg/mL for serum, 5.35 mg/mL for CSF, and 2.49 mg/mL for thoracoabdominal fluid. For samples with a mean concentration ≥ 17 mg/mL, the pooled bias was -0.53 mg/mL (95% limits of agreement, -4.21 to 3.15 mg/mL); agreement was poorer below 17 mg/mL.

Conclusion

DECT material decomposition shows promise for in vitro albumin quantification, particularly at higher concentrations. The concentration-dependent bias and limited sample size require fluid-specific calibration and in vivo validation before clinical use.

Key findings

1. Correlation with ELISA was significant in all fluid groups, but correlation did not eliminate method-specific bias.
2. A provisional mean-concentration boundary of 17 mg/mL separated lower-bias from higher-bias measurements in this dataset.
3. The BSA calibration model was strongly linear ($R^2=0.9973$), but independent and fluid-specific validation remains necessary.

Background

Albumin is the most abundant plasma protein and a major determinant of plasma oncotic pressure and fluid distribution among body compartments [1]. Its broad ligand-binding capacity supports the transport of numerous endogenous and exogenous compounds [2], and serum albumin is also a clinically relevant prognostic biomarker in several diseases [3,4]. Immunoassays, including enzyme-linked immunosorbent assays (ELISA), are widely used for albumin measurement [5,6]. Although sampling blood is routine, obtaining CSF, pleural fluid, ascitic fluid, or fluid from complex cystic lesions may require invasive procedures. A reliable imaging-based estimate could therefore complement, but not replace, laboratory testing in selected settings.

Computed tomography (CT) attenuation has been investigated as a surrogate for blood composition. Studies of anemia have reported associations between CT-derived parameters and laboratory hemoglobin measurements, but performance varies with fluid composition, acquisition settings, and reconstruction method [7,8,9]. Dual-energy CT (DECT) acquires attenuation information at two X-ray spectra and can separate or quantify selected materials using paired-material decomposition [10,11]. This capability supports material-specific images and quantitative applications that are not available from a single conventional CT attenuation value.

Material decomposition has enabled quantitative applications such as vertebral hydroxyapatite assessment [12], measurement of pulmonary iron-oxide deposition [13], assessment of paraspinal muscle fat [14], and characterization of hepatic lesions on non-contrast DECT [15].

The feasibility of using DECT material decomposition to quantify albumin has not been established. Human serum albumin is a single-chain protein of 585 amino acids with a molecular mass of approximately 66.5 kDa [16,17]. Because the energy-dependent attenuation profile of albumin can be represented within the diagnostic X-ray energy range, albumin may be amenable to paired-material decomposition. However, the accuracy, agreement with biochemical measurements, and usable concentration range require experimental evaluation.

This study therefore investigated the in vitro feasibility of albumin quantification using gemstone spectral imaging DECT (GSI-DECT). A calibration model was first constructed from BSA solutions of known concentration. The calibrated DECT measurements were then compared with ELISA in human serum, CSF, and thoracoabdominal fluid (a collective term used throughout for pleural and ascitic fluids).

Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB No. TJ-RB202303157). The requirement for informed consent was waived due to the in vitro study design using residual clinical samples..

2.1. Structural and attenuation data for human albumin and BSA

Three-dimensional structural models of human albumin and BSA were obtained from the RCSB Protein Data Bank (<https://www.rcsb.org/>). Energy-dependent total attenuation data, including coherent scattering, were obtained from the NIST XCOM Photon Cross Sections Database (<https://www.nist.gov/pml/xcom-photon-cross-sections-database>).

2.2. Preparation of BSA standard solution

BSA solutions (Sigma-Aldrich, Germany) were prepared by dissolving 1.00 g of BSA powder in 5 mL of 1× chemical buffer to obtain a 200 mg/mL stock solution. Serial 1:2 dilutions produced concentrations of 100, 50, 25, 12.5, 6.25, 3.125, 1.5625, 0.78125, and 0.390625 mg/mL (C_{std}). A buffer-only sample (0 mg/mL) served as the negative control. Each 5-mL solution was stored at 4°C until scanning.

2.3. Samples of body fluids

Serum samples were prospectively obtained from 18 volunteers. CSF and thoracoabdominal fluid samples were retrospectively collected from the clinical laboratory. The study included 18 CSF samples from patients with encephalitis and 30 thoracoabdominal fluid samples (pleural or ascitic fluid). The laboratory used standardized procedures for collection, transport, testing, and short-term storage. Fully anonymized residual samples retained at 4°C for no longer than one week after routine testing were used for this study.

2.4. Biochemical analysis of body fluids

Albumin was measured in serum, CSF, and thoracoabdominal fluid using a Human Albumin ELISA Kit (ab179887; Abcam, Cambridge, UK) according to the manufacturer's instructions. ELISA-derived albumin concentrations were recorded as C_{ELISA} .

2.5. CT acquisition

Tubes containing BSA standards or human fluid samples were placed upright in racks within an acrylic container (24×30×40 cm) filled with normal saline to create a water-equivalent phantom. Samples were gently mixed while avoiding air bubbles, and the external saline level was maintained above the sample level. Imaging was performed using a 256-row CT scanner (Revolution CT Power; GE HealthCare, USA) in GSI mode with rapid 80/140-kVp switching. Other parameters were a mean tube current of 245 mA, pitch

of 0.984:1, rotation time of 350 ms, 0.625-mm reconstruction thickness, and adaptive statistical iterative reconstruction-Veo with 50% blending.

2.6. Image analysis and DECT-derived albumin concentration

Images were transferred to a GE AW 4.7 workstation and analyzed with the GSI 3D viewer using albumin-calcium material-pair images. A 50-mm² circular region of interest was placed centrally on the coronal image of each sample while avoiding the tube wall and air bubbles. Each sample was measured three times, and the mean material density was recorded as C_{GSI} (mg/cm³). The negative-control value was subtracted to obtain ΔC_{GSI} . The calibrated DECT-derived albumin concentration (C_{DECT}) was calculated from the BSA regression equation.

2.7. Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Continuous data are reported as mean $\pm$ SD. Simple linear regression was used to establish the BSA calibration equation relating C_{std} to ΔC_{GSI} and to describe the relationship between C_{ELISA} and C_{DECT} within each fluid type. Pearson correlation quantified the association between the human and BSA attenuation curves and between C_{ELISA} and C_{DECT} . Paired t tests assessed within-sample differences between methods. Agreement was evaluated using Bland-Altman analysis of absolute differences ($C_{\text{DECT}} - C_{\text{ELISA}}$), with 95% limits of agreement calculated as mean bias $\pm$ 1.96 SD, and a two-way random-effects, absolute-agreement, single-measure ICC. Exploratory agreement analyses were stratified at a mean method concentration. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

This study employed a two-phase in vitro experimental design (Fig. 1). In Phase 1, we established the structural and attenuation basis for albumin quantification by comparing human serum albumin and bovine serum albumin (BSA) using computational modeling and gemstone spectral imaging dual-energy CT (GSI-DECT) material decomposition. In Phase 2, we validated the clinical feasibility of GSI-DECT-derived albumin quantification by comparing DECT measurements with enzyme-linked immunosorbent assay (ELISA) results across three types of human body fluids: serum, cerebrospinal fluid (CSF), and thoracoabdominal fluid.

3.1. Structural and attenuation comparison of human albumin and BSA

The three-dimensional models of human albumin and BSA showed similar major domain architecture (Fig. 2A,B). Their total attenuation curves, including coherent scattering, were also highly similar (Pearson $r > 0.99$; Fig. 2C).

3.2. BSA calibration

Linear regression showed a strong relationship between the known BSA concentration and ΔC_{GSI} ($R^2=0.9973$, $p < 0.001$). The calibration equation was: $C_{\text{DECT}}=(\Delta C_{\text{GSI}}-1.457)/0.8268$. The calibration results are shown in Table 1 and Fig. 3.

Table 1
BSA calibration results obtained with albumin-calcium material decomposition

BSA Sample	C_{std} (mg/cm ³)	C_{GSI} (mg/cm ³)	ΔC_{GSI} (mg/cm ³)	C_{DECT} (mg/cm ³)
0	100	1034.1	85.5	101.65
1	50	989.6	41	47.83
2	25	968.4	19.8	22.19
3	12.5	960.5	11.9	12.63
4	6.25	956.1	7.5	7.31
5	3.125	953.4	4.8	4.04
6	1.5625	951.8	3.2	2.11
7	0.78125	952.4	3.8	2.83
8	0.390625	950.7	2.1	0.78
NTC	0	948.6	0	-1.76

Note: C_{std} , known BSA concentration; C_{GSI} , material density measured with the albumin-calcium material pair; ΔC_{GSI} , C_{GSI} minus the negative-control value; C_{DECT} , albumin concentration calculated using the calibration equation.

3.3. Comparison of DECT and ELISA albumin measurements

C_{DECT} and C_{ELISA} differed significantly in all three fluid groups. Mean C_{DECT} versus C_{ELISA} was 44.85 ± 3.23 versus 46.47 ± 2.36 mg/mL in serum (mean difference, -1.62 ± 1.81 mg/mL; $p = 0.001$), 5.64 ± 3.93 versus 0.29 ± 0.34 mg/mL in CSF (5.35 ± 3.63 mg/mL; $p < 0.001$), and 21.74 ± 6.69 versus 19.25 ± 8.69 mg/mL in thoracoabdominal fluid (2.49 ± 2.93 mg/mL; $p < 0.001$) (Fig. 4).

3.4. Correlation, regression, and agreement between DECT and ELISA

C_{DECT} correlated significantly with C_{ELISA} in serum ($r = 0.835$, $R^2=0.697$), CSF ($r = 0.890$, $R^2=0.791$), and thoracoabdominal fluid ($r = 0.961$, $R^2=0.923$; all $p < 0.001$) (Fig. 5A-C). Regression slopes were 1.140,

10.259, and 0.740, respectively, indicating concentration- or matrix-dependent calibration differences. Across all 66 samples, the absolute-agreement ICC was 0.967. Bland-Altman mean biases ($C_{DECT}-C_{ELISA}$) were - 1.62 mg/mL for serum (95% limits of agreement, -5.17 to 1.92 mg/mL), 5.35 mg/mL for CSF (-1.77 to 12.47 mg/mL), and 2.49 mg/mL for thoracoabdominal fluid (-3.24 to 8.23 mg/mL) (Fig. 5D-F). In the exploratory pooled analysis, samples with a mean method concentration ≥ 17 mg/mL had a bias of -0.53 mg/mL (95% limits of agreement, -4.21 to 3.15 mg/mL), whereas samples below 17 mg/mL had a bias of 5.17 mg/mL (-1.21 to 11.56 mg/mL) (Fig. 5G).

Figure 5. Agreement between DECT-derived and ELISA-derived albumin concentrations. (A–C) Regression analysis of C_{DECT} versus C_{ELISA} for CSF (A), blood (B), and thoracoabdominal fluid (C). Solid lines, linear regression fits; dotted lines, line of identity ($y = x$). Bland-Altman plots for CSF (D), blood (E), and thoracoabdominal fluid (F). The x-axis shows the mean of the paired measurements; the y-axis shows the difference ($C_{DECT}- C_{ELISA}$). Solid lines, mean bias; dashed lines, ± 1.96 SD (95% limits of agreement). (G) Pooled Bland-Altman analysis of all 66 samples, stratified by the 17 mg/mL threshold identified by change-point analysis (purple dash-dot line). Blue points, high-concentration group (mean ≥ 17 mg/mL; $n = 35$; bias - 0.53 mg/mL; 95% LoA - 4.21 to 3.15 mg/mL); red points, low-concentration group (< 17 mg/mL; $n = 31$; bias 5.17 mg/mL; 95% LoA - 1.21 to 11.56 mg/mL). Circles, blood; squares, CSF; triangles, thoracoabdominal fluid; solid and dashed lines, group-specific bias and 95% LoA. C_{DECT} , DECT-derived albumin concentration; C_{ELISA} , ELISA-derived albumin concentration; LoA, limits of agreement.

3.5. CT attenuation values of body fluid samples

Table 2 summarizes the CT attenuation values for all body fluid samples. Blood samples showed the highest CT values (mean: 37.1 ± 3.6 HU), followed by thoracoabdominal fluid (mean: 10.3 ± 4.7 HU) and CSF (mean: 6.9 ± 3.8 HU). Pearson correlation analysis revealed no significant correlation between CT values and albumin concentrations (C_{DECT} : $r = -0.28$ to 0.09 , all $p > 0.05$; C_{ELISA} : $r = -0.33$ to -0.01 , all $p > 0.05$) in any of the three biofluid types.

Table 2
CT attenuation values and correlation with albumin concentrations in body fluid samples.

Sample Type	n	Range (HU)	Mean $\pm$ SD (HU)	r (vs C_{DECT})	p value
Blood	18	30.895–44.711	37.1 ± 3.6	-0.281	0.259
CSF	18	0.242–13.280	6.9 ± 3.8	0.058	0.818
Thoracoabdominal	30	1.842–19.711	10.3 ± 4.7	0.092	0.628

Discussion

4.1 Principal Findings

This preliminary in vitro study demonstrates the feasibility of albumin quantification using GSI-DECT material decomposition. The BSA calibration model was highly linear ($R^2=0.9973$), and DECT-derived concentrations correlated significantly with ELISA in all three fluid types. The distinction between correlation and agreement is important: despite high correlations, paired differences were significant and fluid-specific Bland-Altman biases were present. Overall absolute agreement was high (ICC = 0.967), but agreement deteriorated at low albumin concentrations, most notably in CSF. Serum albumin is widely recognized as a prognostic biomarker in critical illness [18,19]. Statistical methods for method comparison, including Bland-Altman analysis [20] and measurement reliability assessment [21], were employed to evaluate agreement between DECT and ELISA.

4.2 Correlation and Quantitative Accuracy

The strong correlations we observed between DECT-derived and ELISA-measured albumin concentrations across all fluid types (serum: $r = 0.89$, CSF: $r = 0.94$, thoracoabdominal fluid: $r = 0.91$) align with the high quantitative accuracy reported for dual-energy CT material decomposition in other applications, where R^2 values exceeding 0.99 have been achieved for holmium microspheres [22] and errors below 5% for iodine quantification [23]. These capabilities rest on well-established theoretical foundations for dual- and multi-energy imaging [24,25]. Nevertheless, the fluid-specific biases ranging from 1.8 to 3.1 mg/mL revealed by our Bland-Altman analysis indicate that correlation alone does not guarantee measurement agreement, a limitation documented in other spectral CT applications including concentration-dependent overestimation in virtual non-contrast imaging [26]. Such discrepancies underscore the importance of rigorous quality control in multi-energy CT quantification [27] and suggest that fluid-specific calibration may be necessary for accurate absolute quantification rather than reliance on a universal conversion model.

4.3 Concentration-Dependent Performance and Need for Segmented Calibration

The substantially higher positive bias observed below 17 mg/mL (mean 4.2 mg/mL, 95% LOA: -1.8 to 10.2 mg/mL) compared with higher concentrations (mean 1.1 mg/mL, 95% LOA: -2.3 to 4.5 mg/mL) reflects reduced signal-to-noise ratios at low concentrations that amplify measurement noise in material decomposition. This concentration-dependent limitation mirrors findings across different spectral CT platforms, where multi-material decomposition networks [28], high-Z nanoparticle quantification [29], and DECT-derived iodine measurements [30] all exhibited increased errors at lower concentrations and required concentration-specific calibration adjustments. The 17 mg/mL threshold identified in our experiments may represent a practical lower limit for reliable albumin quantification with the current decomposition algorithm, beyond which piecewise calibration strategies or adaptive algorithms that account for concentration-dependent noise characteristics could improve measurement accuracy, particularly for clinical samples approaching physiological albumin concentrations in CSF.

4.4 Clinical Implications and Material Pair Selection Considerations

The feasibility of albumin quantification demonstrated here extends the growing application of spectral CT from basic material characterization to quantitative clinical tasks, including protein concentration assessment in body fluids using dual-layer spectral detector systems [31–33]. Our selection of the iodine-albumin material pair exploited iodine's pronounced photoelectric absorption at lower energies, yielding a BSA calibration model with excellent linearity ($R^2=0.9973$). However, material decomposition accuracy remains fundamentally constrained by the attenuation differences between basis materials, with suboptimal pair selection potentially introducing cross-talk artifacts [34]. Despite these constraints, our calibration performance approaches the diagnostic accuracy reported for surrogate materials in dual-energy CT applications such as virtual noncalcium imaging for osteoporosis [35]. Matrix effects specific to different biological fluids may also influence quantification accuracy, necessitating further validation with human albumin standards across diverse clinical specimens. Translation to in vivo clinical practice will require standardized calibration protocols, assessment of confounding factors including surrounding tissue attenuation and patient motion, and establishment of fluid-specific diagnostic thresholds through large-scale validation studies.

4.5 Limitations

This study has several limitations. First, the sample size was small and all samples came from one institution. Second, the study was performed in vitro; attenuation from surrounding tissues, motion, partial-volume effects, and contrast material were not evaluated. Third, the proposed 17 mg/mL boundary was derived post hoc and requires independent validation. Fourth, BSA was used for calibration; although its attenuation profile was highly similar to that of human albumin, matrix-specific behavior may differ. Fifth, the dataset did not contain verified raw conventional CT attenuation measurements for the human samples, so no analysis relating Hounsfield units to albumin concentration is reported. Finally, scanner- and reconstruction-dependent spectral response can affect material quantification. Multicenter phantom studies, fluid-specific calibration, and prospective in vivo validation are needed.

Conclusions

GSI-DECT material decomposition enabled in vitro albumin estimation across serum, CSF, and thoracoabdominal fluid. Agreement with ELISA was most favorable at higher concentrations, whereas low-concentration samples showed substantial positive bias. These findings support further development of fluid-specific calibration and prospective in vivo validation but do not yet justify replacement of biochemical measurement.

Abbreviations

BSA
Bovine serum albumin
CSF
Cerebrospinal fluid

CT
Computed tomography
DECT
Dual-energy computed tomography
ELISA
Enzyme-linked immunosorbent assay
GSI
Gemstone spectral imaging
HU
Hounsfield unit
ICC
Intraclass correlation coefficient
LOA
Limits of agreement
VMI
Virtual monoenergetic image
VNC
Virtual non-contrast

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB No. TJ-RB202303157). The requirement for informed consent was waived due to the in vitro study design using residual clinical samples.

Consent for publication

Not applicable.

Competing interests

S.C. is an employee of GE HealthCare. The remaining authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

L.D. and S.W. contributed equally to this work. L.D. and Q.W. conceived and designed the study. L.D. performed CT image acquisition, material decomposition analysis and statistical analysis, and drafted the manuscript. S.W. performed the biochemical assays and ELISA measurements. C.L. collected the body fluid samples and clinical data. S.C. provided technical support for spectral CT imaging and material decomposition. J.Z. and Q.W. supervised the study and critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgement

Not applicable.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

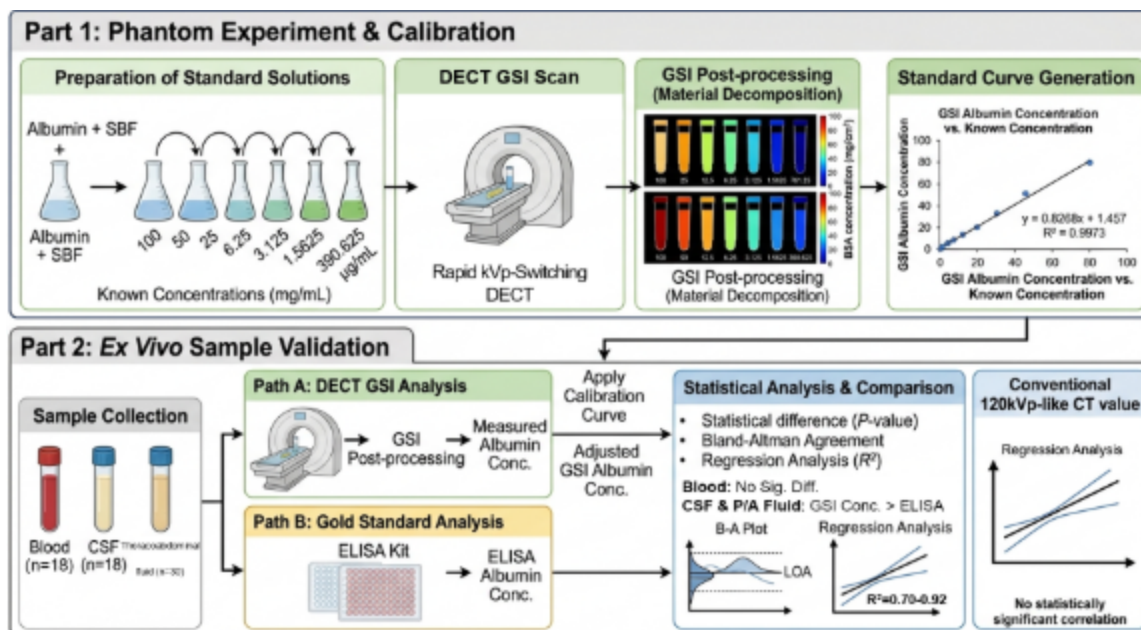


Figure 1

Diagram demonstrating the study design.

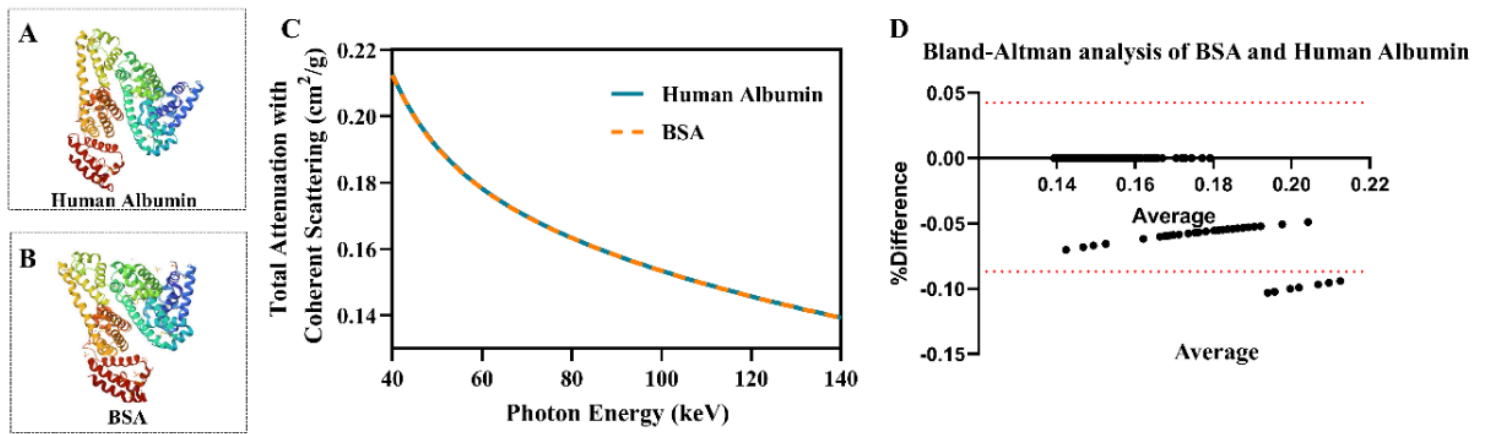


Figure 2

Three-dimensional structures (A,B) and total attenuation curves including coherent scattering (C) for human serum albumin and bovine serum albumin, and Bland-Altman analysis of total attenuation between bovine serum albumin and human serum albumin (D). BSA, bovine serum albumin.

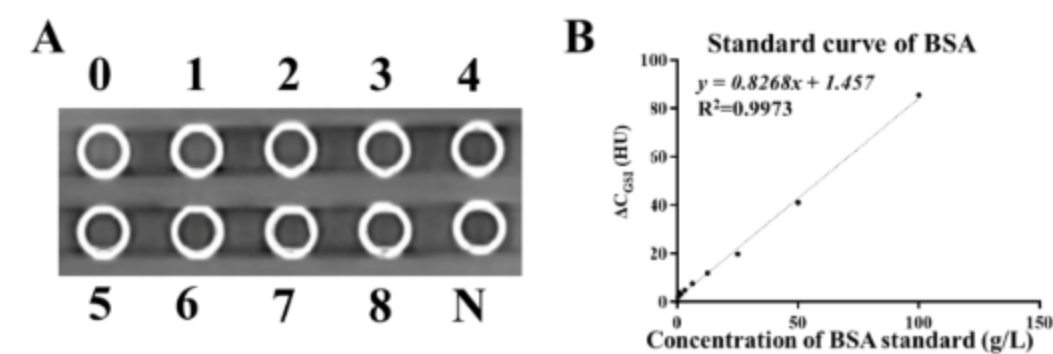


Figure 3

Gray-scale (A) and the BSA calibration curve (B).

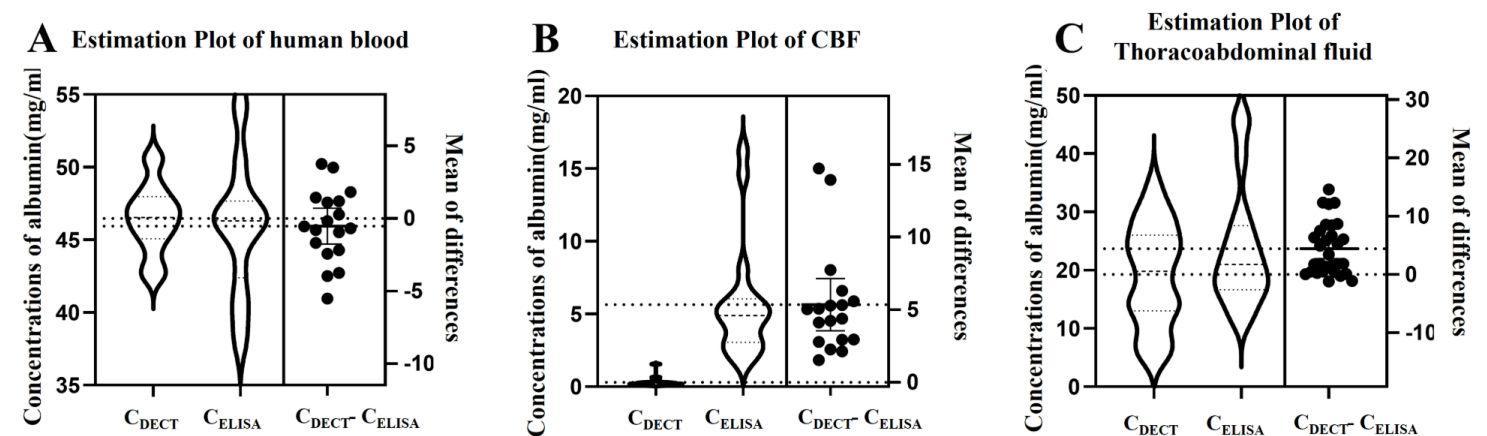


Figure 4

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Estimation plots comparing DECT-derived and ELISA albumin concentrations in serum (A), CSF (B), and thoracoabdominal fluid (C). C_{DECT} , DECT-derived albumin concentration; C_{ELISA} , ELISA-derived albumin concentration.

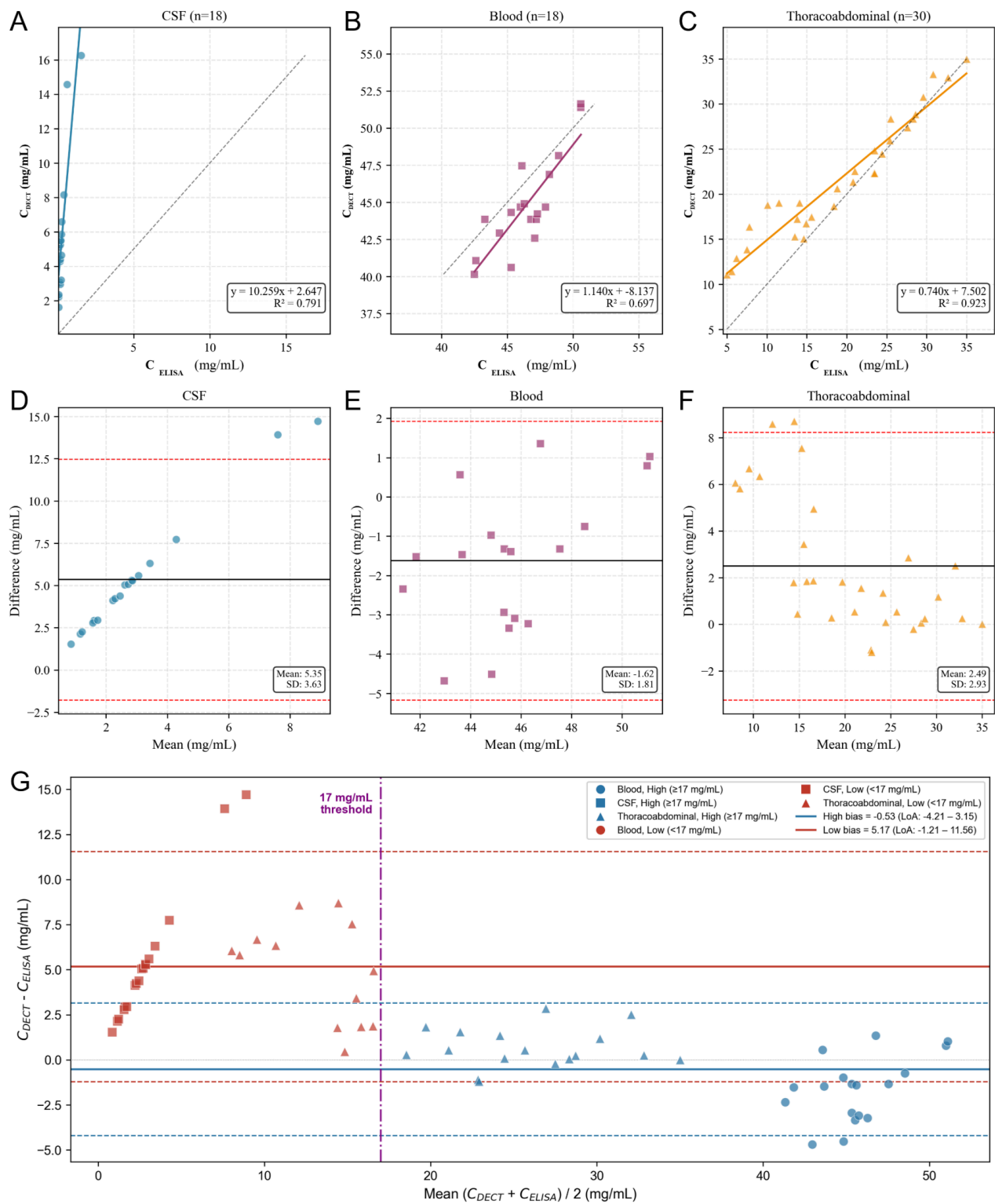


Figure 5

Agreement between DECT-derived and ELISA-derived albumin concentrations. (A–C) Regression analysis of C_{DECT} versus C_{ELISA} for CSF (A), blood (B), and thoracoabdominal fluid (C). Solid lines, linear regression fits; dotted lines, line of identity ($y = x$). Bland-Altman plots for CSF (D), blood (E), and thoracoabdominal fluid (F). The x-axis shows the mean of the paired measurements; the y-axis shows the difference ($C_{DECT} - C_{ELISA}$). Solid lines, mean bias; dashed lines, ± 1.96 SD (95% limits of agreement). (G) Pooled Bland-Altman analysis of all 66 samples, stratified by the 17 mg/mL threshold identified by change-point analysis (purple dash-dot line). Blue points, high-concentration group (mean ≥ 17 mg/mL; $n = 35$; bias -0.53 mg/mL; 95% LoA -4.21 to 3.15 mg/mL); red points, low-concentration group (< 17 mg/mL; $n = 31$; bias 5.17 mg/mL; 95% LoA -1.21 to 11.56 mg/mL). Circles, blood; squares, CSF; triangles, thoracoabdominal fluid; solid and dashed lines, group-specific bias and 95% LoA. C_{DECT} , DECT-derived albumin concentration; C_{ELISA} , ELISA-derived albumin concentration; LoA, limits of agreement.