Pretreatment serum albumin/globulin ratio as a prognostic biomarker in metastatic prostate cancer patients treated with maximal androgen blockade

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The pretreatment serum albumin/globulin ratio (AGR) has been used as a prognostic biomarker for various cancer types. However, the prognostic value of the AGR for prostate cancer, especially for metastatic prostate cancer (mPCa) after maximal androgen blockade (MAB), remains unclear. The aim of this study was to evaluate the prognostic value of the pretreatment serum AGR for mPCa treated with MAB. This retrospective study included 214 mPCa patients receiving MAB from October 2007 to March 2017. The correlation of the AGR with survival was estimated using Kaplan–Meier analysis and Cox proportional hazards models. The cutoff value of the AGR was 1.45 according to the receiver operating characteristic curve. Kaplan–Meier analysis demonstrated that patients with a low AGR (<1.45) had poor outcomes in terms of progression-free survival (PFS) and cancer-specific survival (CSS). Multivariate Cox analyses showed that the AGR was an independent predictor of PFS (hazard ratio [HR] = 0.642; 95% confidence interval [CI]: 0.430–0.957; P = 0.030) and CSS (HR = 0.412; 95% CI: 0.259–0.654; P < 0.001). Furthermore, in a subset of 79 patients with normal serum albumin levels (≥40.0 g l−1), the serum AGR remained an independent predictor of CSS (P = 0.009). The pretreatment AGR was an independent prognostic biomarker for PFS and CSS in patients with mPCa receiving MAB. In addition, the AGR remained effective for the prediction of CSS in patients with normal albumin levels (≥40 g l−1). However, further prospective studies are needed to confirm our conclusions.

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Keywords: albumin/globulin ratio; maximal androgen blockade; metastatic prostate cancer; prognosis; survival
We conducted a retrospective study to evaluate whether the pretreatment AGR could be used as a predictor of mortality in mPCa patients receiving MAB.

PATIENTS AND METHODS

Patients
Two hundred and fourteen mPCa patients who received MAB as the first-line therapy between October 2007 and March 2017 were included in this study. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (Changsha, China). All patients gave informed written consent before they were enrolled in this study. The diagnosis of mPCa was confirmed by needle biopsy and pathohistological examination. The Gleason score (GS) was assessed by senior pathologists. The serum PSA level was determined. Clinical staging was performed according to the results of a clinical examination, bone scanning, and computed tomography and/or pelvic magnetic resonance imaging (MRI). MAB was defined as continuous hormonal therapy using an LHRH agonist and an oral antiandrogen. No patient received any other first-line treatment such as radiotherapy or chemotherapy. Patients with any evidence of active infection or coexisting hematologic disease were excluded.

Data collection
General clinical data were acquired from patient records and included demographic parameters and clinical characteristics. Peripheral blood was collected before breakfast between 7 a.m. and 8 a.m. during the stay in hospital 1 day before starting MAB therapy. Serum chemical analysis and complete blood counts were performed in the central laboratory of the Third Xiangya Hospital. Blood counts were conducted using a Sysmex XE-5000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Serum ALB and total serum protein levels were determined using an automated immunoturbidimetric analyzer (Hitachi High-Technologies, Tokyo, Japan). The AGR was calculated using the equation AGR = ALB/(total serum protein − ALB).

Follow-up
All patients were followed up at 3-month intervals during the first 3 years after diagnosis, at 6-month intervals in years 4–5, and at 12-month intervals in years 6–11. mPCa was evaluated by measuring serum PSA levels and digital rectal examinations. PSA relapse was defined as three consecutive increases in PSA, 1 week apart, resulting in two 50% increases over the nadir with a PSA level > 2.0 ng ml⁻¹. Patients with PSA relapse were further examined for local and/or distant recurrences by isotope bone scan, chest X-ray, and abdominal and pelvic MRI.

Statistical analyses
The first endpoint for progression-free survival (PFS) was defined as the duration from the start of MAB to the occurrence of the first evidence of biochemical or clinical progression. The second endpoint for cancer-specific survival (CSS) was defined as the time from diagnosis to death due to mPCa. The ideal cutoff value of the pretreatment serum AGR was determined by the receiver operating characteristic (ROC) curve, according to the surviving and deceased patients, as the value with the highest Youden’s index. Differences in continuous variables were analyzed using the Mann–Whitney U-test, and differences in categorical data were analyzed using the Chi-square test. Clinical endpoints were calculated using Kaplan–Meier analysis and were compared by the log rank test. Univariate and multivariate Cox proportional hazards analyses were performed to assess the relative effect of the AGR on PFS and CSS. All statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). P < 0.05 was considered statistically significant.

RESULTS
Identification of the optimal cutoff value for the AGR
Using ROC curve analysis, we found that an AGR = 1.45 was the strongest prognostic point for CSS (Figure 1). The area under the curve (AUC) for the AGR was 0.795 (95% confidence interval [CI]: 0.735–0.855, Youden’s index = 0.487, sensitivity = 0.774, specificity = 0.713, P < 0.001). According to the optimal cutoff value, of the total 214 patients, 100 (46.7%) were in the low AGR group (< 1.45) and 114 (53.3%) were in the high AGR group (≥ 1.45).

Clinicopathological features
The distribution of clinicopathological features in the AGR subgroups is described in Table 1, while the actual serum ALB and GLB values of patients are shown in Supplementary Table 1. Patients with a pretreatment AGR ≥ 1.45 had a higher prevalence of younger age (P = 0.024) and high body mass index (BMI, P = 0.020). Serum ALB and hemoglobin level were lower in the low AGR group than in the high AGR group (P < 0.001 and P = 0.002, respectively). In addition, patients in the low AGR group had significantly higher neutrophil counts than patients in the high AGR group (P < 0.001). No differences were found for the PSA, GS, white blood cell count, and Eastern Cooperative Oncology Group performance status (ECOG PS) (P > 0.05).

Relationship between the pretreatment AGR and PFS
The mean follow-up duration was 34.79 months. During follow-up, 126 of 214 patients (58.9%) experienced tumor progression, including 68 of 100 (68.0%) patients in the low AGR group and 58 of 114 (50.9%) patients in the high AGR group.

The Kaplan–Meier curve showed significantly higher PFS rates in the high AGR group than in the low AGR group (P = 0.004, Figure 2). Univariate Cox regression analyses showed that the risk of disease progression was higher in the low AGR group (P = 0.005, Table 2). The univariate analysis also showed that PFS was significantly associated with BMI, PSA, GS, ALB, hemoglobin, neutrophil count, and ECOG PS (P < 0.05 for BMI, PSA, GS, ALB, hemoglobin, neutrophil count, and ECOG PS). In the multivariate analysis, after adjusting for the effects of these parameters, we found that only the pretreatment AGR (hazard ratio [HR] = 0.642; 95%
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CI: 0.430–0.957; \( P = 0.030 \), PSA (\( P = 0.012 \)), GS (\( P < 0.001 \)), and hemoglobin (HR = 0.981; 95% CI: 0.971–0.992; \( P < 0.001 \)) were independent predictors of PFS (Table 2).

**Table 1: The clinicopathological characteristics stratified by the albumin/globulin ratio level in 214 patients**

|                         | Values | Low AGR group (AGR <1.45) | High AGR group (AGR ≥1.45) | \( P \) |
|-------------------------|--------|---------------------------|-----------------------------|-------|
| Total, \( n \) (%)      | 214 (100) | 100 (46.7) | 114 (53.3) |       |
| Age (year), mean ± s.d. | 70.75 ± 7.58 | 71.99 ± 7.67 | 69.66 ± 7.36 | 0.024 |
| BMI (kg m\(^{-2}\)), mean ± s.d. | 22.57 ± 2.92 | 22.08 ± 2.68 | 23.01 ± 3.06 | 0.020 |
| PSA (ng ml\(^{-1}\)), \( n \) (%) | \( ≤10 \) 17 (7.9) 5 (5.0) 12 (10.5) 0.186 | \( <10 \) 12 (5.6) 4 (4.0) 8 (7.0) |       |
| PSA >20                  | 185 (86.4) | 91 (91.0) | 94 (82.5) |       |
| Gleason score, \( n \) (%) | <7 24 (11.2) 12 (12.0) 12 (10.5) | 0.443 |       |
|                         | 7 89 (41.6) 37 (37.0) 52 (45.6) |       |       |
|                         | >7 101 (47.2) 51 (51.0) 50 (43.9) |       |       |
| Albumin (g l\(^{-1}\)), mean ± s.d. | 38.56 ± 4.49 | 36.29 ± 4.06 | 40.55 ± 3.88 | <0.001 |
| Hemoglobin (g dl\(^{-1}\)), mean ± s.d. | 119.57 ± 20.18 | 115.03 ± 20.08 | 123.54 ± 19.50 | 0.002 |
| White blood cell count \( (×10^3 \) µl\(^{-1}\)), mean ± s.d. | 6.64 ± 2.33 | 6.96 ± 2.66 | 6.37 ± 1.97 | 0.064 |
| Neutrophil count \( (×10^3 \) µl\(^{-1}\)), mean ± s.d. | 4.43 ± 1.63 | 4.88 ± 1.66 | 4.03 ± 1.52 | <0.001 |
| ECOG PS, \( n \) (%) | 0 110 (51.4) 48 (48.0) 62 (54.4) 0.351 |       |       |
|                         | >0 104 (48.6) 52 (52.0) 52 (45.6) |       |       |

**Figure 2:** Kaplan–Meier curves and log rank test (\( P = 0.004 \)) showing progression-free survival according to the pretherapeutic optimal value of the serum albumin/globulin ratio in all 214 mPCa patients after MAB. AGR: albumin/globulin ratio; mPCa: metastatic prostate cancer; MAB: maximal androgen blockade.

**Figure 3:** Kaplan–Meier curves and log rank test (\( P < 0.001 \)) showing cancer-specific survival according to the pretherapeutic optimal value of the serum albumin/globulin ratio in all 214 mPCa patients after MAB. AGR: albumin/globulin ratio; mPCa: metastatic prostate cancer; MAB: maximal androgen blockade.

**DISCUSSION**

In the present study, the pretreatment serum AGR level was an independent prognostic factor for PFS and CSS in mPCa patients treated with MAB. Furthermore, patients with a low AGR had a 1.56-fold and 2.43-fold increased risk of progression and cancer-related death, respectively, compared to that of patients with a high AGR.

Serum ALB produced by the liver is a major serum protein. Serum ALB can maintain intravascular oncotic pressure, facilitate the transport of substances, and act as a free radical scavenger. The serum ALB level is accurate for prediction of malnutrition and subsequent survival in cancer patients. Malnutrition, by reducing muscle mass and subsequently affecting the functional status of individuals, is an independent predictor of CSS (\( P = 0.009 \)).

**Additional analyses for normal serum ALB**

The aim of the additional analyses was to determine whether the pretreatment AGR had prognostic value for patients with a normal serum ALB level. Therefore, survival analysis was performed including only patients with ALB \( ≥40.0 \) g l\(^{-1}\) (\( n = 79 \)). Similarly, among these patients, the 5-year CSS was 33.0% in the low AGR group and 70.0% in the high AGR group. Moreover, in this subset of 79 patients with normal serum ALB level, the multivariate analysis indicated that the serum AGR remained an independent predictor of CSS (\( P = 0.009 \)).
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28 Malnutrition weakens human defense mechanisms such as anatomic barriers, cellular and humoral immunity, and phagocyte function. Consequently, patients may be ineligible for therapy, resulting in poorer survival than patients who have higher serum ALB levels. Moreover, serum ALB should also be considered as an inflammatory response marker and a reliable indicator of morbidity and mortality, reflecting disease severity.

Table 2: Prognostic value of the albumin/globulin ratio by univariate and multivariate analyses regarding progression-free survival in 214 patients

|                      | Univariate analysis |                      | Multivariate analysis |                      |
|----------------------|---------------------|----------------------|-----------------------|----------------------|
|                      | HR (95% CI)         | P                    | HR (95% CI)           | P                    |
| Age (year)           |                     |                      |                       |                      |
| 1.017 (0.993–1.041)  | 0.177               |                       | 0.996 (0.968–1.025)   | 0.773                |
| BMI (kg m⁻²)         |                     |                      |                       |                      |
| 0.926 (0.873–0.983)  | 0.012               |                       | 0.995 (0.932–1.063)   | 0.892                |
| PSA (ng ml⁻¹)        |                     |                      |                       |                      |
| PSA ≤10              | 1                   | 0.002                | 1                     | 0.012                |
| 2.83 (0.320–5.144)   |                      |                       | 2.368 (0.563–9.950)   |                      |
| PSA >20              | 4.025 (1.484–10.919)|                      | 4.303 (1.546–11.979)  |                      |
| Gleason score        |                     |                      |                       |                      |
| <7                   | 1.988 (0.965–4.094) | <0.001               | 2.099 (0.985–4.475)   | <0.001               |
| >7                   | 4.490 (2.208–9.128) |                      | 3.994 (1.877–8.498)   |                      |
| Albumin (g l⁻¹)      | 0.933 (0.893–0.974) | 0.002                | 1.002 (0.953–1.054)   | 0.923                |
| Hemoglobin (g dl⁻¹)  | 0.978 (0.969–0.986) | <0.001               | 0.981 (0.971–0.992)   | <0.001               |
| White blood cell count (x10⁴ μl⁻¹) | 1.036 (0.966–1.111) | 0.327                | 0.995 (0.882–1.122)   | 0.930                |
| Neutrophil count (x10⁴ μl⁻¹) | 1.104 (1.003–1.214) | 0.042                | 1.037 (0.874–1.229)   | 0.678                |
| AGR                  |                      |                      |                       |                      |
| Low                  | 0.933 (0.893–0.974) | 0.002                | 1.002 (0.953–1.054)   | 0.923                |
| High                 | 0.605 (0.426–0.859) |                      | 0.642 (0.430–0.957)   |                      |
| ECOG PS              |                      |                      |                       |                      |
| 0                    | 1.037 (0.874–1.229) | 0.042                | 1.037 (0.874–1.229)   | 0.678                |

Table 3: Prognostic value of the albumin/globulin ratio by univariate and multivariate analyses regarding cancer-specific survival in 214 patients

|                      | Univariate analysis |                      | Multivariate analysis |                      |
|----------------------|---------------------|----------------------|-----------------------|----------------------|
|                      | HR (95% CI)         | P                    | HR (95% CI)           | P                    |
| Age (year)           |                     |                      |                       |                      |
| 1.047 (1.020–1.074)  | 0.001               |                       | 1.030 (0.999–1.061)   | 0.056                |
| BMI (kg m⁻²)         |                     |                      |                       |                      |
| 0.896 (0.839–0.956)  | 0.001               |                       | 0.963 (0.894–1.037)   | 0.315                |
| PSA (ng ml⁻¹)        |                     |                      |                       |                      |
| PSA ≤10              | 1                   | 0.007                | 1                     | 0.023                |
| 1.176 (0.237–5.833)  |                      |                       | 3.992 (0.735–21.696)  |                      |
| PSA >20              | 4.077 (1.291–12.876)|                      | 5.308 (1.590–17.713)  |                      |
| Gleason score        |                     |                      |                       |                      |
| <7                   | 1.988 (0.965–4.094) | <0.001               | 2.099 (0.985–4.475)   | <0.001               |
| >7                   | 4.490 (2.208–9.128) |                      | 3.994 (1.877–8.498)   |                      |
| Albumin (g l⁻¹)      | 0.933 (0.893–0.974) | 0.002                | 1.002 (0.953–1.054)   | 0.923                |
| Hemoglobin (g dl⁻¹)  | 0.978 (0.969–0.986) | <0.001               | 0.981 (0.971–0.992)   | <0.001               |
| White blood cell count (x10⁴ μl⁻¹) | 1.036 (0.966–1.111) | 0.327                | 0.995 (0.882–1.122)   | 0.930                |
| Neutrophil count (x10⁴ μl⁻¹) | 1.104 (1.003–1.214) | 0.042                | 1.037 (0.874–1.229)   | 0.678                |
| AGR                  |                      |                      |                       |                      |
| Low                  | 0.933 (0.893–0.974) | 0.002                | 1.002 (0.953–1.054)   | 0.923                |
| High                 | 0.605 (0.426–0.859) |                      | 0.642 (0.430–0.957)   |                      |
| ECOG PS              |                      |                      |                       |                      |
| 0                    | 1.037 (0.874–1.229) | 0.042                | 1.037 (0.874–1.229)   | 0.678                |

Malignancy and tissue necrosis decrease the synthesis of ALB. A decreased serum ALB concentration in cancer patients may result from the production of cytokines such as IL-6, which inhibits the production of albumin by hepatocytes. In addition, the serum level of tumor necrosis factor (TNF)-α is elevated in patients with cachexia-associated chronic diseases, such as cancer, and inhibits albumin synthesis at the transcriptional level even before the onset of weight loss.
GLB (total serum protein—ALB), another major protein produced by immune organs that reflects the immune state, consists of various proinflammatory proteins, including C-reactive protein (CRP), complement components, and immunoglobulins. Elevated serum CRP indicates poor prognosis in mPCA patients. High levels of alpha GLB and complement 3 are correlated with a poor prognosis in several cancer types. Furthermore, the serum GLB level increased with stimulation of inflammation, and it was associated with poor survival in prostate cancer patients.

Chronic inflammation has been associated with PCA development due to the paracrine actions of cytokines, adhesion molecules, and mediators of angiogenesis generated by the inflammatory response. In addition, inflammatory mediators and cytokines were also involved in tumor progression and metastasis. We propose that both the nutritional status and systemic inflammatory response play important roles in the survival of mPCA patients treated with MAB.

Since the serum ALB level is affected by various factors, including stress, tissue necrosis, and cancers, ALB alone may be insufficient to be widely used in clinical practice to predict the survival of mPCA patients, and the same applies to GLB. Compared to other nutritional or inflammatory indicators, the AGR may be a superior predictor for mPCA patients by combining two aspects of adverse outcomes. Many studies have indicated that the AGR might be used to predict the long-term survival of cancer patients. For example, Zhou et al. suggested that small-cell lung cancer patients with a pretreatment serum AGR <1.29 had a 1.35 times higher risk of death than those with an AGR ≥1.29. Mao et al. showed that a serum AGR <1.50 indicated poorer overall survival in patients with gastric cancer. In our study, a pretreatment serum AGR <1.45 was an independent prognostic factor for poor PFS and CSS in mPCA patients treated with MAB. The formation of urokinase plasminogen activator receptor and the circulating tumor cell count in the peripheral blood has been associated with the prognosis of mPCA, but these markers are difficult to widely apply in clinical practice due to the lack of standardization. However, compared to these markers, the serum AGR is a more general biochemical index and does not impose an additional financial burden on patients.

We also showed that the AGR remained a predictor of CSS in patients with normal ALB values (≥40.0 g·L⁻¹). A low AGR is not only useful for determining malnutrition but also useful for indicating chronic inflammation. As a consequence, the AGR should be evaluated before therapeutic modalities are determined for mPCA patients, and nutritional support and anti-inflammatory treatment may be administered in advance for patients with an AGR <1.45. Daugherty et al. suggested that regular use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), but not aspirin, was associated with a reduction of bladder cancer risk. Further research should be designed to evaluate the therapeutic effect of anti-inflammatory treatment for mPCA patients.

CONCLUSIONS
We found that the AGR had significant prognostic value for mPCA patients; however, there were some limitations. First, specific inflammatory markers, such as CRP and cytokine levels, were not included in the study. Second, prospective and multi-institutional studies are needed to confirm our results, since the present study was a retrospective analysis that only included a small number of patients.

AUTHOR CONTRIBUTIONS
NW designed and conducted this study and drafted the manuscript. JYL and XL participated in the design of the study. MHD and ZL collected patient data. JT, KY, and YCZ performed the statistical analysis. LYH supervised the research and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declared no competing interests.

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Supplementary information is linked to the online version of the paper on the Asian Journal of Andrology website.

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Supplementary Table 1: The actual values of the patients’ pretreatment serum albumin and globulin

| Patient number | Serum albumin (g l\(^{-1}\)) | Serum globulin (g l\(^{-1}\)) |
|----------------|-------------------------------|------------------------------|
| 1              | 32.9                          | 30.3                         |
| 2              | 37.2                          | 31.1                         |
| 3              | 33.7                          | 34.4                         |
| 4              | 43.5                          | 26.4                         |
| 5              | 48.0                          | 25.0                         |
| 6              | 38.1                          | 22.8                         |
| 7              | 43.2                          | 46.8                         |
| 8              | 38.9                          | 23.7                         |
| 9              | 38.9                          | 24.6                         |
| 10             | 42.5                          | 28.7                         |
| 11             | 38.2                          | 34.2                         |
| 12             | 37.3                          | 39.4                         |
| 13             | 41.2                          | 31.8                         |
| 14             | 34.0                          | 37.2                         |
| 15             | 44.4                          | 14.4                         |
| 16             | 36.4                          | 25.0                         |
| 17             | 27.8                          | 23.6                         |
| 18             | 29.3                          | 28.9                         |
| 19             | 39.1                          | 29.7                         |
| 20             | 31.2                          | 33.9                         |
| 21             | 41.7                          | 30.8                         |
| 22             | 37.4                          | 30.3                         |
| 23             | 41.0                          | 26.5                         |
| 24             | 37.5                          | 29.2                         |
| 25             | 38.2                          | 23.1                         |
| 26             | 39.3                          | 24.2                         |
| 27             | 40.9                          | 31.6                         |
| 28             | 40.6                          | 30.4                         |
| 29             | 32.2                          | 24.4                         |
| 30             | 39.1                          | 23.6                         |
| 31             | 46.2                          | 29.1                         |
| 32             | 32.6                          | 23.3                         |
| 33             | 33.5                          | 18.7                         |
| 34             | 33.5                          | 23.5                         |
| 35             | 37.4                          | 22.9                         |
| 36             | 45.7                          | 25.5                         |
| 37             | 33.0                          | 30.4                         |
| 38             | 33.0                          | 30.4                         |
| 39             | 38.6                          | 26.7                         |
| 40             | 34.6                          | 30.8                         |
| 41             | 38.7                          | 22.0                         |
| 42             | 38.2                          | 37.8                         |
| 43             | 35.3                          | 39.2                         |
| 44             | 37.5                          | 26.5                         |
| 45             | 34.7                          | 21.1                         |
| 46             | 38.2                          | 23.4                         |
| 47             | 37.7                          | 27.9                         |
| 48             | 39.0                          | 31.6                         |
| 49             | 41.5                          | 29.3                         |
| 50             | 31.4                          | 24.2                         |
| 51             | 43.7                          | 31.9                         |
| 52             | 38.8                          | 23.4                         |
| 53             | 39.7                          | 21.3                         |
| 54             | 39.7                          | 21.3                         |
| 55             | 36.8                          | 28.0                         |

Contd...

Supplementary Table 1: Contd...

| Patient number | Serum albumin (g l\(^{-1}\)) | Serum globulin (g l\(^{-1}\)) |
|----------------|-------------------------------|------------------------------|
| 56             | 40.2                          | 28.4                         |
| 57             | 41.5                          | 28.9                         |
| 58             | 30.7                          | 26.1                         |
| 59             | 32.1                          | 25.3                         |
| 60             | 39.3                          | 30.2                         |
| 61             | 40.4                          | 31.0                         |
| 62             | 40.3                          | 23.5                         |
| 63             | 34.3                          | 30.1                         |
| 64             | 41.1                          | 26.7                         |
| 65             | 41.3                          | 31.5                         |
| 66             | 37.5                          | 30.5                         |
| 67             | 38.1                          | 23.3                         |
| 68             | 43.6                          | 29.0                         |
| 69             | 38.9                          | 25.3                         |
| 70             | 35.9                          | 22.4                         |
| 71             | 36.3                          | 20.9                         |
| 72             | 36.3                          | 20.9                         |
| 73             | 42.0                          | 28.0                         |
| 74             | 28.2                          | 28.5                         |
| 75             | 38.9                          | 29.2                         |
| 76             | 40.3                          | 24.7                         |
| 77             | 40.4                          | 21.3                         |
| 78             | 43.7                          | 27.2                         |
| 79             | 40.1                          | 24.9                         |
| 80             | 33.5                          | 29.0                         |
| 81             | 40.4                          | 22.0                         |
| 82             | 41.6                          | 28.4                         |
| 83             | 44.3                          | 30.0                         |
| 84             | 36.3                          | 23.2                         |
| 85             | 37.1                          | 29.5                         |
| 86             | 44.8                          | 29.8                         |
| 87             | 38.0                          | 22.7                         |
| 88             | 34.9                          | 26.7                         |
| 89             | 39.8                          | 20.7                         |
| 90             | 37.9                          | 25.1                         |
| 91             | 39.2                          | 37.1                         |
| 92             | 44.6                          | 21.6                         |
| 93             | 37.9                          | 18.6                         |
| 94             | 36.1                          | 24.6                         |
| 95             | 38.7                          | 23.9                         |
| 96             | 37.6                          | 25.5                         |
| 97             | 40.2                          | 33.5                         |
| 98             | 34.2                          | 30.5                         |
| 99             | 31.1                          | 21.6                         |
| 100            | 29.7                          | 25.2                         |
| 101            | 35.6                          | 28.8                         |
| 102            | 36.7                          | 24.6                         |
| 103            | 35.1                          | 25.5                         |
| 104            | 38.3                          | 27.6                         |
| 105            | 41.1                          | 33.0                         |
| 106            | 43.4                          | 28.4                         |
| 107            | 35.4                          | 28.3                         |
| 108            | 40.9                          | 23.1                         |
| 109            | 44.5                          | 31.0                         |
| 110            | 44.5                          | 31.0                         |
| 111            | 36.5                          | 24.0                         |
### Supplementary Table 1: Contd...

| Patient number | Serum albumin (g l\(^{-1}\)) | Serum globulin (g l\(^{-1}\)) |
|----------------|-----------------------------|-------------------------------|
| 112            | 34.2                        | 30.6                          |
| 113            | 40.1                        | 25.6                          |
| 114            | 43.6                        | 31.2                          |
| 115            | 44.7                        | 31.2                          |
| 116            | 41.3                        | 25.0                          |
| 117            | 29.4                        | 28.6                          |
| 118            | 37.8                        | 29.6                          |
| 119            | 41.2                        | 20.9                          |
| 120            | 41.3                        | 24.2                          |
| 121            | 38.4                        | 23.5                          |
| 122            | 38.3                        | 28.5                          |
| 123            | 35.6                        | 21.3                          |
| 124            | 37.8                        | 25.8                          |
| 125            | 41.9                        | 28.8                          |
| 126            | 36.8                        | 23.9                          |
| 127            | 37.6                        | 28.0                          |
| 128            | 34.9                        | 28.3                          |
| 129            | 34.5                        | 21.9                          |
| 130            | 40.6                        | 23.1                          |
| 131            | 36.1                        | 26.4                          |
| 132            | 34.7                        | 32.5                          |
| 133            | 41.3                        | 20.7                          |
| 134            | 46.3                        | 25.5                          |
| 135            | 35.1                        | 24.2                          |
| 136            | 44.1                        | 23.9                          |
| 137            | 35.7                        | 23.6                          |
| 138            | 39.0                        | 30.7                          |
| 139            | 42.6                        | 27.6                          |
| 140            | 41.4                        | 20.2                          |
| 141            | 46.9                        | 26.1                          |
| 142            | 40.2                        | 25.2                          |
| 143            | 37.7                        | 28.4                          |
| 144            | 43.7                        | 20.4                          |
| 145            | 39.5                        | 22.3                          |
| 146            | 32.0                        | 25.1                          |
| 147            | 35.4                        | 21.6                          |
| 148            | 36.1                        | 22.0                          |
| 149            | 35.6                        | 28.7                          |
| 150            | 44.4                        | 25.4                          |
| 151            | 37.9                        | 35.4                          |
| 152            | 46.4                        | 24.7                          |
| 153            | 38.8                        | 23.3                          |
| 154            | 43.2                        | 25.3                          |
| 155            | 43.2                        | 25.3                          |
| 156            | 45.3                        | 27.8                          |
| 157            | 44.3                        | 29.3                          |
| 158            | 36.6                        | 32.4                          |
| 159            | 37.3                        | 22.3                          |
| 160            | 38.5                        | 30.6                          |
| 161            | 40.9                        | 27.4                          |
| 162            | 48.3                        | 26.4                          |

### Supplementary Table 1: Contd...

| Patient number | Serum albumin (g l\(^{-1}\)) | Serum globulin (g l\(^{-1}\)) |
|----------------|-----------------------------|-------------------------------|
| 163            | 44.9                        | 20.2                          |
| 164            | 43.2                        | 25.4                          |
| 165            | 34.5                        | 19.4                          |
| 166            | 41.8                        | 22.6                          |
| 167            | 36.2                        | 25.5                          |
| 168            | 39.8                        | 21.8                          |
| 169            | 39.6                        | 24.0                          |
| 170            | 47.2                        | 24.8                          |
| 171            | 47.0                        | 26.4                          |
| 172            | 37.2                        | 37.7                          |
| 173            | 38.4                        | 33.2                          |
| 174            | 45.3                        | 22.1                          |
| 175            | 41.3                        | 25.9                          |
| 176            | 35.4                        | 24.3                          |
| 177            | 29.0                        | 16.0                          |
| 178            | 35.1                        | 20.3                          |
| 179            | 35.4                        | 33.9                          |
| 180            | 44.8                        | 21.9                          |
| 181            | 47.8                        | 23.6                          |
| 182            | 43.2                        | 24.8                          |
| 183            | 47.4                        | 24.0                          |
| 184            | 34.4                        | 28.8                          |
| 185            | 36.2                        | 28.3                          |
| 186            | 37.9                        | 26.5                          |
| 187            | 38.8                        | 26.7                          |
| 188            | 35.4                        | 23.4                          |
| 189            | 47.7                        | 21.1                          |
| 190            | 45.7                        | 21.9                          |
| 191            | 39.9                        | 30.7                          |
| 192            | 39.5                        | 19.0                          |
| 193            | 41.3                        | 27.9                          |
| 194            | 43.6                        | 23.2                          |
| 195            | 39.4                        | 27.4                          |
| 196            | 39.8                        | 33.4                          |
| 197            | 31.1                        | 21.2                          |
| 198            | 32.3                        | 25.5                          |
| 199            | 41.3                        | 25.8                          |
| 200            | 38.5                        | 24.3                          |
| 201            | 38.9                        | 32.2                          |
| 202            | 28.7                        | 32.8                          |
| 203            | 31.2                        | 26.9                          |
| 204            | 36.1                        | 30.5                          |
| 205            | 45.5                        | 22.5                          |
| 206            | 25.4                        | 31.1                          |
| 207            | 34.8                        | 24.7                          |
| 208            | 37.2                        | 32.7                          |
| 209            | 27.3                        | 19.1                          |
| 210            | 32.3                        | 28.4                          |
| 211            | 32.0                        | 37.6                          |
| 212            | 40.9                        | 21.7                          |
| 213            | 38.7                        | 30.0                          |
| 214            | 41.8                        | 22.9                          |

Contd...