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ORIGINAL ARTICLE

Prostate Cancer

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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INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of cancer-related death among American men.[1] In China, the incidence of PCa rapidly increased from 2000 to 2011.[2] The factors driving the increase of PCa include gradual implementation of serum prostate-specific antigen (PSA) screening, improved biopsy techniques,[3] and the impact of a Westernized lifestyle.[4,5] Unlike patients in Western countries, most newly diagnosed Chinese patients already have metastatic prostate cancer (mPCa).[6]

As one of the hormonal therapies, maximal androgen blockade (MAB) offers a survival benefit comparable to that of castration alone.[7] Furthermore, MAB showed much better survival advantages than luteinizing hormone-releasing hormone (LHRH) agonist monotherapy.[8,9] Currently, many indices, including clinical stage, tumor grade, and the circulating concentration of PSA,[10] are used to determine the disease stage in PCa patients. Although PCa is a genetic disease, chronic inflammation promotes cancer progression.[11–13] Inflammatory mediators such as cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species are potential biomarkers.[14] Moreover, the prognostic value of such molecular markers such as Ki-67,[15] p53,[16] B cell leukemia/lymphoma (Bcl)-2,[17] and interleukin (IL)-1β and interferon (IFN)-β[18] in PCa specimens has been evaluated by immunohistochemistry. However, these biomarkers are not commonly applied in clinical practice due to high costs and the lack of standardization. In addition, due to the high proportion of newly diagnosed mPCa patients in China and the poor prognosis of mPCa compared to that of localized PCa, blood parameters that are simple, easy to access, and labor-saving are essential for predicting the therapeutic efficacy in mPCa.

Globulin (GLB) and albumin (ALB) are major components of human serum proteins that play significant roles in inflammatory responses. GLB functions as a carrier of the sex hormones and is of great importance to immunity and inflammation. Hypoalbuminemia is an indicator of poor nutritional status and is related to chronic inflammation in cancer patients.[19,20] Low serum ALB has been used to evaluate the progression and prognosis of several types of cancers, including PCa.[20–22] The serum albumin/globulin ratio (AGR) may be used as a prognostic marker for colorectal cancer, lung cancer, breast cancer, and nasopharyngeal carcinoma.[23–26] However, the prognostic value of the AGR in mPCa has not been confirmed.

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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}.[7] 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%

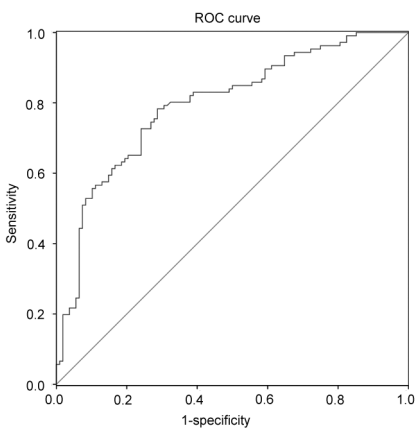

Figure 1: The receiver operating characteristic curve for the pretherapeutic serum albumin/globulin ratio depending on cancer-specific survival.

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* (%)				
PSA ≤10	17 (7.9)	5 (5.0)	12 (10.5)	0.186
10 <PSA ≤20	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)	

AGR: albumin/globulin ratio; BMI: body mass index; PSA: prostate-specific antigen; ECOG PS: Eastern Cooperative Oncology Group performance status; s.d.: standard deviation

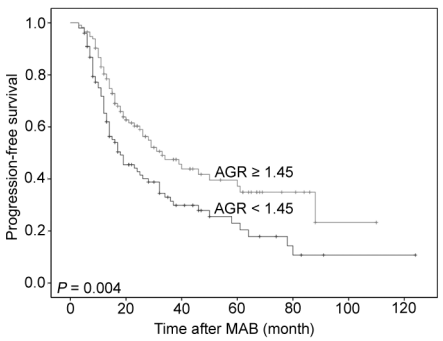

Figure 2: Kaplan-Meier curves and log rank test ($P = 0.004$) showing progression-free survival according to the pretherapeutic optimal value of the serum albumin/globulin ratio in all 214 mPCa patients after MAB. AGR: albumin/globulin ratio; mPCa: metastatic prostate cancer; MAB: maximal androgen blockade.

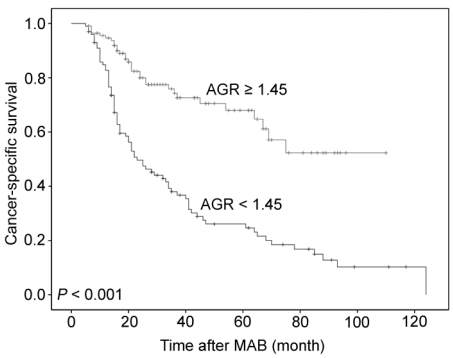

Figure 3: Kaplan-Meier curves and log rank test ($P < 0.001$) showing cancer-specific survival according to the pretherapeutic optimal value of the serum albumin/globulin ratio in all 214 mPCa patients after MAB. AGR: albumin/globulin ratio; mPCa: metastatic prostate cancer; MAB: maximal androgen blockade.

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**).

Relationship between the pretreatment AGR and CSS

A total 108 patients (50.5%) died from mPCa; the proportions of death in the low and high AGR group were 77.0% (77/100) and 27.2% (31/114), respectively.

In the univariate analysis, CSS was closely associated with the following parameters: age, BMI, PSA, GS, ALB, hemoglobin, neutrophil count, AGR, and ECOG PS ($P < 0.05$ for all, **Table 3**). In the multivariate analysis, the pretreatment AGR (HR = 0.412; 95% CI: 0.259–0.654; $P < 0.001$, **Table 3**) was independently associated with CSS. Other independent factors of CSS were PSA ($P = 0.023$), GS ($P = 0.022$), and hemoglobin (HR = 0.983; 95% CI: 0.972–0.994; $P = 0.003$). In addition, Kaplan–Meier analysis and log rank testing indicated that patients with a low AGR had shorter CSS than those with a high AGR ($P < 0.001$, **Figure 3**).

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 ($P = 0.009$).

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.[21] The serum ALB level is accurate for prediction of malnutrition and subsequent survival in cancer patients.[27] Malnutrition, by reducing muscle mass and subsequently affecting the functional status of individuals, is an

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
10 <PSA ≤20	1.283 (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	<0.001	1	<0.001
7	1.988 (0.965–4.094)		2.099 (0.985–4.475)	
>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 (×10^3 μl^{-1})	1.036 (0.966–1.111)	0.327	0.995 (0.882–1.122)	0.930
Neutrophil count (×10^3 μl^{-1})	1.104 (1.003–1.214)	0.042	1.037 (0.874–1.229)	0.678
AGR				
Low	1	0.005	1	0.030
High	0.605 (0.426–0.859)		0.642 (0.430–0.957)	
ECOG PS				
0	1	0.044	1	0.275
>0	1.441 (1.010–2.054)		1.254 (0.836–1.881)	

AGR: albumin/globulin ratio; PFS: progression-free survival; BMI: body mass index; PSA: prostate-specific antigen; HR: hazard ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status

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
10 <PSA ≤20	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	<0.001	1	0.022
7	1.462 (0.704–3.039)		1.302 (0.605–2.805)	
>7	3.203 (1.582–6.482)		2.236 (1.058–4.722)	
Albumin (g l^{-1})	0.881 (0.839–0.925)	<0.001	0.981 (0.924–1.040)	0.512
Hemoglobin (g dl^{-1})	0.978 (0.970–0.987)	<0.001	0.983 (0.972–0.994)	0.003
White blood cell count (×10^3 μl^{-1})	1.035 (0.958–1.119)	0.381	1.039 (0.923–1.170)	0.532
Neutrophil count (×10^3 μl^{-1})	1.115 (1.006–1.237)	0.038	1.007 (0.843–1.202)	0.941
AGR				
Low	1	<0.001	1	<0.001
High	0.298 (0.196–0.454)		0.412 (0.259–0.654)	
ECOG PS				
0	1	0.012	1	0.831
>0	1.645 (1.116–2.426)		0.952 (0.606–1.494)	

AGR: albumin/globulin ratio; BMI: body mass index; PSA: prostate-specific antigen; HR: hazard ratio; CI: confidence interval; ECOG PS: eastern Cooperative Oncology Group performance status

established risk factor for adverse perioperative outcomes.[28] Malnutrition weakens human defense mechanisms such as anatomic barriers, cellular and humoral immunity, and phagocyte function.[29] 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.[30] Malignancy and tissue necrosis decrease the synthesis of ALB.[31] 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.[32] 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.[33]

GLB (total serum protein—ALB), another major protein produced by immune organs that reflects the immune state,[34] consists of various proinflammatory proteins, including C-reactive protein (CRP), complement components, and immunoglobulins. Elevated serum CRP indicates poor prognosis in mPCa patients.[35] High levels of alpha GLB and complement 3 are correlated with a poor prognosis in several cancer types.[36,37] Furthermore, the serum GLB level increased with stimulation of inflammation, and it was associated with poor survival in cancer patients.[38,39]

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.[40–42] In addition, inflammatory mediators and cytokines were also involved in tumor progression and metastasis.[43] 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 indictors, 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*.[44] 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*.[45] 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[46] and the circulating tumor cell count[47] 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*.[48] suggested that regular use of non-aspirin nonsteroidal antiinflammatory 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	33.2	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	36.2	31.5
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

Contd...

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

Contd...

Supplementary Table 1: Contd...

Patient number	*Serum albumin (g l^{-1})*	*Serum globulin (g l^{-1})*
163	44.9	20.2
164	33.2	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