Prognostic value of an index for serum globulin compensation in colon and breast cancers

F S Al-Joudi

ABSTRACT

Introduction: Decreased serum albumin (SA) levels have been used extensively as prognostic indicators in many chronic debilitating diseases. The decrease may be partly compensated by globular proteins. The failure of globulins to compensate may reflect advanced disease. We examined the prognostic value of the level of serum globulins in colorectal and breast cancers.

Methods: Data of 80 patients with advanced colon and breast cancers were analysed. Of these, 46 patients died within six months of measurement of their serum proteins, and the rest were followed-up for more than six months after measurements of their serum proteins were taken. A mathematical formula, representing the globulin compensation index (GCI), was recently developed from the measured SA levels and globulins. Patients were then classified into three categories: negative GCI and negative compensation; GCI of 0 to less than 1.0 with partial compensation; and GCI equal or greater than 1.0 with full compensation.

Results: Among the deceased patients, 45.7 percent had negative GCI, compared to 26.5 percent of patients in the survivors group. For partial compensation, 30.4 percent of patients were from the deceased group, and 32.4 percent were from the survivors group. For full compensation (elevated GCI), 23.9 percent of patients were from the deceased group, compared to 41.1 percent from the survivors group (p-value equals 0.031).

Conclusion: Patients with low GCI are more likely to have bad prognoses, whereas those with higher GCI have more favourable prognoses. Globulin compensation may be a reliable prognostic factor in advanced colorectal and breast cancers, and possibly in other chronic illnesses. The GCI may serve as a useful tool in the measurement of this compensation.

Keywords: breast cancer, colon cancer, globulin compensation index, serum albumin, serum globulin

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INTRODUCTION

Reduced serum albumin (SA) levels are used as prognostic indicators in several diseases, including cancer, kidney diseases, human immunodeficiency virus infections, chronic liver diseases, autoimmune diseases, and even in healthy geriatric individuals[1-14]. Other non-disease-specific parameters have been considered, such as haematocrit, lymphocyte count, C-reactive protein, interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), beta-2-microglobulin, tumour necrosis factor-alpha (TNF-α) and its receptor. Age, body mass index, performance status and physical disability are the main non-specific clinical parameters. A prognostic inflammatory and nutritional index (PINI) has also been used in advanced malignancies[15].

Measurement of SA and total serum protein (TSP) is routinely performed in medical laboratories, in addition to the albumin/globulin (A/G) ratio, which is calculated spontaneously by most clinical chemistry autoanalysers. In response to reduced SA, the A/G ratio is lowered due to an increase in globular proteins (G) mainly immunoglobulins synthesised by lymphocytes to compensate for the reduced SA. The failure of these cells to raise G to levels that are high enough to compensate for the reduced SA may indicate advanced disease, where protein synthesis is reduced and/or protein catabolism has accelerated[16,17]. This implies that the reduction in SA is further aggravated by the failure of G to compensate. This study examines the feasibility of using G as a supplementary parameter in determining the prognosis of patients with advanced cases of colorectal and breast cancers. A mathematical index, the globulin compensation index (GCI), was recently developed to express the extent of globulin compensation for reduced SA and was tested for its prognostic value[18].

Department of Chemical Pathology School of Medical Sciences Universiti Sains Malaysia Kubang Kerian 16150 Kota Bharu Kelantan, Malaysia

F S Al-Joudi, PhD
Lecturer

Correspondence to:
Dr Fawwaz Shakir Al-Joudi
Tel: (60) 9766 3777
Fax: (60) 9764 2026
Email: fajoudi@hotmail.com

Table I. The distribution of GCI in the deceased group and the survivors group.

	Number	Mean (SD)	95% confidence interval	IQR	Significance
Deceased	46	0.29 (0.84)	0.04, 0.54	1.09	0.031
Survivors	34	0.72 (0.92)	0.40, 1.0	1.31	

Independent t-test, $p<0.05$; SD: standard deviation; IQR: interquartile range.

Table II. The distribution of SA in the deceased group and the survivors group.

	Number	Mean (SD)	95% confidence interval	IQR	Significance
Deceased	46	22.09 (4.82)	22.66, 23.52	7.25	0.010
Survivors	34	24.68 (3.51)	23.45, 25.9	6.00	

Independent t-test, $p<0.05$; SD: standard deviation; IQR: interquartile range.

METHODS

The records of 46 patients who died from colon cancer and breast cancer were analysed. All had low SA levels, which were measured within the six-month period preceding their demise. The control subjects comprised 34 patients who suffered from similar malignancies, but were followed-up ≥6 months after their SA levels were measured: the survival periods obtained ranged from six to 23 months with a median period of 15 months. All breast cancer cases were of the histological grades 2 and 3 (World Health Organisation [WHO] Classification of Breast Tumours, 1981), and all colon cancers were of stages II and III (American Joint Committee on Cancer, 2002). Patients who received blood or blood components before measuring their SA levels, those with fluid loss from haemorrhage or severe diarrhoea, and those with reported sudden deaths were excluded. For all patients, the TSP levels were recorded and the G levels were calculated by subtracting the SA values from TSP values.

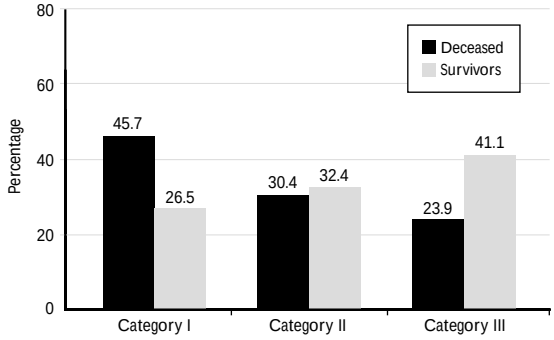
GCI is based on the ratio of deviation of G from normal, which is 25 g/L, to the deviation of SA from normal, which is 35 g/L. Hence, the following equation was obtained:

$$\mathbf{GCI = G - 25 / 35 - SA}$$

where G and SA are the measured concentrations and 25 and 35 represent the minimum of their normal ranges, respectively[19].

Based on their GCI scores, the patients were classified into three categories: negative GCI (G <25 g/L) with negative compensation; GCI of 0 to <1.0 (G ≥25 g/L) and TSP <60 g/L with partial compensation; and GCI ≥1.0 (G values >25 g/L) and TSP ≥60 g/L, with full compensation. The mean GCI and mean SA values were analysed by the Independent t-test using Statistical Package for Social Sciences (SPSS) version 11.0 (Chicago, IL, USA). The p-value <0.05 was considered significant.

Fig. 1 Bar chart shows the percentages of the three categories in each of the two test groups.



RESULTS

The GCI for each case was calculated individually for the two study groups. In the negative GCI category, the percentage of the dead was high (45.7%) whereas it was 26.5% in the survivors group. In the full compensation GCI category, the percentage of the dead was 23.9%, and that of the survivors was 41.1% (Fig. 1). The descriptive statistics of GCI is shown in Table I, with a significant difference between the two groups, the survivors and the deceased, p-value = 0.031. The differences in the distribution of the GCI values among the deceased and the survivors is shown in Figs. 2a-b.

The albumin levels were taken alone and plotted in a scattering graph against the outcome of death or survival (Fig. 2c). The descriptive statistics of SA are shown in Table II, with a significant difference between the two groups, the survivors and the deceased, p-value = 0.010. The ratio of the mean GCI of the survivors to that of the deceased was 2.5, whereas the

Fig. 2 The distribution of the two study groups, survivors and deceased according to their GCI values (2a and 2b). The dotted lines mark the cut-off points for the negative GCI values. Fig. 2c shows the distribution of the two groups according to their SA levels.

Fig. 2a The distribution of GCI among the survivors.

Fig. 2b The distribution of GCI among the deceased.

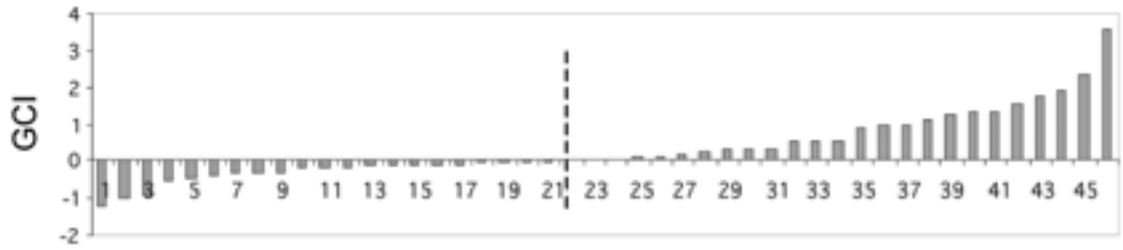


Fig. 2c The distribution of the two study groups according to the SA levels.

ratio of the mean SA of survivors to that of the deceased was 1.12. This means that, comparing mean values, GCI is 2.23 times (2.5/1.12) more sensitive than SA.

DISCUSSION

Depressed compensation, expressed as lowered GCI, was obtained mostly in patients with bad prognoses. The controls had higher GCI values previously. Hence, their protein-synthesising capacities were preserved and they survived for more than 6 months despite their reduced SA. The SA levels showed a lower difference between the two groups compared to the GCI, indicating a higher sensitivity of the latter over the former. Albumin helps to maintain oncotic pressure, and confers anti-oxidant[20], nitrovasodilatory[21], and anti-apoptotic protective effects on endothelial cells[22]. It also acts as a reserve for amino acids. When albumin is reduced, globular proteins serve in the compensation for its reduction. Hence, when the efficiency of globular proteins is compromised, the concomitant reduction in globulins and albumins may magnify the loss of their functions. This loss is represented by the GCI.

Nevertheless, in systemic debilitating diseases, the hepatic protein-synthesising capacity is mostly not affected and can be restored following feeding[23]. In contrast to this, the infusion of exogenous albumin does not improve the outcome in critically ill hypoalbuminaemic patients[24], nor alleviate the underlying systemic illness. This may lead to a persistently lowered GCI, since the systemic capacity is not likely to show any progress. This is found in terminal cancer syndrome and is associated with anorexia and cachexia[25]. Thus, determining the compensation by globulins may be a useful parameter in determining the prognosis.

The direct causes of death among cancer patients are variable. However, deaths due to infections are likely to occur in such immunocompromised patients. A lowered globulin level may be an early marker of this immunosuppression. Death from cardiac failure, pulmonary embolism, therapy, syncope or bleeding may also be due to a lowered nutritional status[26]. Moreover, terminal cancer is usually associated with a general lowering of the functional and metabolic statuses, and the presence of symptoms associated with anorexia-cachexia, independent of the primary tumour and metastatic diffusion[25].

The GCI aids the measurement of globulin compensation. It is easy to use and all components can be obtained from the patients' data. The mathematical equation can be easily programmed into autoanalysers to yield the GCI spontaneously. However, one limitation of the test is that it can only function when the SA is <35 g/L. Nevertheless, when SA is not reduced, no compensation would be necessary. Another limitation is that a G value of 25 g/L always yields a GCI of zero, which is a real value in terms of compensation regardless of the extent of reduction in albumin. Not withstanding these limitations, the test is a good alternative to PINI[15] in determining the prognosis of cancer patients. It may also prove useful in the nutritional management of cancer patients, especially in hospitals where PINI is not routinely used, such as for interleukin-6 and alpha-1 acid glycoprotein. Finally, it may prove to be effective in measuring response to therapy.

A prospective study utilising larger numbers of patients is required to further assess the usefulness of this parameter in different diseases and in other types of cancer. Confounding factors such as nature and duration of illnesses, management and response to therapy, can be considered. They may also provide a better understanding of the mechanisms underlying these changes, where improvement or deterioration can be associated with relevant changes in the GCI.

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