Use of Age-Albumin Ratio as a Single Predictor of 30-Day Mortality after Colectomy

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Keywords

Colorectal cancer · Postoperative mortality · Age-albumin ratio · Receiver operating characteristic curve

Summary

Background: Colorectal cancer is among the three leading cancers and causes of mortality worldwide. It is important to develop an effective single-parameter screening technique for reducing the postoperative mortality rate. Previous studies have proved that patient age is a major factor influencing postoperative mortality. A strong association has been reported between serum albumin and patient age. We aimed to identify new predictors on the basis of age-albumin ratio (AAR) for assessing 30-day mortality after colectomy. **Patients and Methods:** Detailed information about patients with colon cancer was retrieved from the Colorectal Section Tumor Registry at Chang Gung Memorial Hospital, Taiwan. The study subjects comprised 3,732 consecutive patients with colon cancer who had undergone elective, potentially curative surgery. **Results:** The area under the receiver operating characteristic curve (AUC) of the AAR was significantly larger than the AUC of serum albumin. The low specificity of AAR was compensated by its substantially high sensitivity. An AAR of ≥ 20 years $g^{-1} dl^{-1}$ was found to be the most prevalent threshold value. **Conclusion:** The present investigation suggests that AAR can be used in clinical practice as a simple parameter for the identification of patients at risk of 30-day mortality after colectomy.

Schlüsselwörter

Kolorektales Karzinom · Postoperative Mortalität · Alters-Albumin-Ratio · «Receiver Operating Characteristic»-Kurve

Zusammenfassung

Hintergrund: Das kolorektale Karzinom gehört zu den drei führenden Krebserkrankungen und Todesursachen weltweit. Die Entwicklung einer effektiven Ein-Parameter-Screening-Technik zur Reduktion der postoperativen Mortalitätsrate ist bedeutend. Frühere Studien haben belegt, dass das Patientenalter ein wichtiger Faktor für die postoperative Mortalität ist. Ein ausgeprägter Zusammenhang von Serumalbumin und Patientenalter ist festgestellt worden. Wir beabsichtigten daher, auf der Grundlage der Alters-Albumin-Ratio neue Prädiktoren zur Beurteilung der 30-Tage-Mortalität nach Kolektomie zu identifizieren. **Patienten und Methoden:** Detaillierte Informationen zu Patienten mit Dickdarmkrebs wurden aus der Colorectal Section Tumor Registry am Chang Gung Memorial Hospital, Taiwan, abgerufen. Die Probandengruppe setzte sich aus 3732 konsekutiven Patienten mit Dickdarmkrebs zusammen, die sich einer elektiven, potenziell kurativen Operation unterzogen hatten. **Ergebnisse:** Die Fläche unter der «Receiver Operating Characteristic»(ROC)-Kurve der Alters-Albumin-Ratio war signifikant größer als die ROC-Kurve des Serumalbumins. Die geringe Spezifität der Alters-Albumin-Ratio wurde durch deren erheblich höhere Sensitivität ausgeglichen. Eine Alters-Albumin-Ratio ≥ 20 Jahre $g^{-1} dl^{-1}$ wurde als der am weitesten verbreitete Schwellenwert identifiziert. **Schlussfolgerung:** Die vorliegende Untersuchung deutet darauf hin, dass die Alters-Albumin-Ratio in der klinischen Praxis als einfacher Parameter zur Identifizierung von Patienten mit dem Risiko einer 30-Tage-Mortalität nach Kolektomie verwendet werden kann.

Background

Colorectal cancer is among the three leading cancers and causes of mortality worldwide, with about 1 million new cases and 528,978 deaths reported in 2002 [1–6]. The statistics and publications of the Department of Health of Taiwan indicate that colorectal cancer is the most commonly diagnosed cancer and the third leading cause of cancer-related deaths among both men and women in Taiwan [7]. It is therefore important to plan health care and to identify the risk factors for postoperative mortality in patients with colorectal cancer.

Despite improvements in surgical techniques, a mortality rate of 5–6.5% has been reported for elective colorectal surgery with resection [8–11]. There is strong evidence that malnutrition increases adverse surgical outcome after major elective surgery [12]. Studies have indicated several malnutrition-related risk factors for postoperative mortality [13, 14]. It is well established that hypoalbuminemia (serum albumin level ≤ 3.5 g/dl), as a marker of malnutrition, is strongly related to a high risk of adverse surgical outcomes [15–18]. Compared with other preoperative parameters, the serum albumin level is a frequently used predictor of malnutrition as well as risk of poor postoperative outcomes in clinical practice. One of the main advantages is the relatively low cost of the serum albumin test [19].

As noted in previous studies, the age of patients with colorectal cancer is another major predictor of adverse surgical outcomes. For example, in a previous study, the patients were divided into age groups of 0–59 years, 60–69 years, 70–79 years, 80 years, and >80 years, and the operative risk significantly increased in the older-age group [20]. Other studies, in which the patients were also divided into several age groups, used odds ratios of postoperative mortality for the different strata of patients. An increasing risk of postoperative mortality is observed with increasing age [21, 22]. Many recent studies can be referred to regarding the association of mortality and age [23–26]. All these studies aimed to discover that an increase in postoperative mortality rates is associated with aging. Overall, preoperative serum albumin level and age can prominently affect the postoperative outcomes of patients with colorectal cancer undergoing surgical treatment [27].

Many studies support the assumption that serum albumin levels decrease with age [28, 29]. The ratio of age to serum albumin can be considered as a single and easy-to-determine index for predicting 30-day mortality; the significance of age can be weighed by dividing it by serum albumin. Use of receiver operating characteristic (ROC) curves is suggested for evaluating the diagnostic value of indices on the basis of a single cut-off value of a continuous variable [30]. Thus, it would be interesting to evaluate whether the application of a new index, based on the ratio of age and serum albumin, will increase the area under the ROC curves (AUC) for assessing 30-day mortality, compared with that of the index based on serum albumin alone. We expected this new index to be more

Table 1. Pathological and clinical characteristics of patients and 30-day mortality

Parameter	Median (IQR)
Age, years	65 (54–74)
Height, cm	159 (153–165)
Weight, kg	59 (52–67)
Preoperative CEA level, ng/ml	3.3 (1.9–7.8)
Serum albumin level, g/nl	4.0 (3.6–4.3)
Hemoglobin level, g%	11.7 (9.8–13.3)
n = 3,732 (%)	
Medical illness – asthma	
Yes	119 (3.19)
No	3,613 (96.81)
Medical illness – diabetes	
Yes	506 (13.56)
No	3,226 (86.44)
Medical illness – liver cirrhosis	
Yes	48 (1.29)
No	3,684 (98.71)
Tumor location	
Right colon	1,449 (38.83)
Left colon	2,283 (61.17)
TNM stage	
I	488 (13.08)
II	1,731 (46.38)
III	1,513 (40.54)
30-day mortality	
Yes	40 (1.07)
No	3,692 (98.93)

IQR = Interquartile range; CEA = carcinoembryonic antigen; TNM = tumor node metastasis.

significantly related to 30-day mortality than serum albumin alone. Finally, we attempted to determine the optimal cut-off value of the new index for predicting the risk of 30-day mortality after colectomy.

Methods

Patients

Detailed information about patients with colon cancer, such as patient- and tumor-related factors and follow-up status, was retrieved from the Colorectal Section Tumor Registry (CRSTR) at Chang Gung Memorial Hospital, Taiwan. All the data in this registry were prospectively collected. Patient demographic data, comorbidities, tumor characteristics, and postoperative mortality were included in the data collection. Patient-related factors comprised age, height, weight, hemoglobin level, serum albumin level, carcinoembryonic antigen (CEA) level, and comorbidities. The following comorbidities that may influence the postoperative outcome were recorded in this study: asthma, diabetes, and liver cirrhosis. Tumor-related factors comprised location and stage. Tumors were staged according to the sixth edition of the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system. With regard to location, the tumors were categorized as those present in the right colon (from the cecum to the transverse colon) and as those present in the left colon (from the splenic flexure to the sigmoid colon).

The study subjects comprised 3,732 consecutive patients with colon cancer who had undergone elective, potentially curative surgery at the Chang Gung Memorial Hospital from January 1995 to December 2008. Patients with metastatic disease (stage IV colon cancer) were excluded from the study since the treatments for these patients vary and are always palliative. Every patient in this study underwent standard oncological resection of the colon and received routine postoperative care.

Statistical Analyses

The pathological and clinical characteristics of the patients are shown in table 1. To exclude the confounding factors, a logistic regression analysis was performed using a multivariate stepwise selection procedure to analyze the factors that significantly differed between patients with 30-day mortality and non-30-day mortality in the univariate analysis (inclusion factors were those with a p value of <0.05 determined by univariate analysis). The univariate analysis included the Wilcoxon test for medians and chi-square test or Fisher's exact test (if one of the cell counts was small or zero) for discrete data. Moreover, we have discussed the way of feature extraction from the significant factors derived from the logistic regression model (the ratio of the first and second significant factors). In order to determine the way having the strongest association with 30-day mortality, we derived the AUCs for the prediction of 30-day mortality by using each of the candidate predictors. Furthermore, we graphically compared the AUCs and tested the equality of the ROC curves by area test [31]. The main aim was to identify the best predictor of 30-day mortality in terms of sensitivity and specificity. The optimal threshold value (cut-off value) of each candidate predictor was calculated as follows:

$$\text{Optimal cut-off value} = \min(\sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2}) \quad (1)$$

Table 2. Surgery-related complications in 40 patients with 30-day mortality

Complications	Incidence
Lung (atelectasis, pneumonia)	15
CV (MI, CVA, embolism)	5
Bladder dysfunction	1
GI (obstruction, bleeding)	4
Anastomosis (leakage, stenosis)	5
Others	6
Combination	4
CV = Cardiovascular; MI = myocardial infarction; CVA = cerebrovascular accident; GI = gastrointestinal.	

Table 3. Comparison of the pathological and clinical characteristics of patients with non-30-day and 30-day mortality

	Univariate analysis		Multivariate analysis		
	Z/odds ratio	p value	odds ratio	95% CI	p value
Height	-1.70	0.089	–	–	–
Weight	-4.09	<0.001	1.000	(0.998–1.003)	0.780
Age	5.66	<0.001	1.064	(1.026–1.103)	0.001
Preoperative CEA level	4.84	<0.001	1.000	(0.996–1.004)	0.947
Hemoglobin level	-2.58	0.010	1.008	(0.928–1.095)	0.853
Serum albumin level	-6.10	<0.001	0.248	(0.146–0.423)	<0.001
Medical illness – asthma	3.46	0.037	2.947	(0.935–9.285)	0.065
Medical illness – diabetes	3.12	0.002	2.668	(1.286–5.542)	0.008
Medical illness – liver cirrhosis	9.21	0.002	3.244	(0.769–13.679)	0.109
Tumor location	0.77	0.420	–	–	–
TNM stage	2.35	0.310	–	–	–
CI = Confidence interval; CEA = carcinoembryonic antigen; TNM = tumor node metastasis.					

We determined the sensitivity and specificity for the prediction of 30-day mortality on the basis of the threshold values of the candidate predictors. All the statistical analyses were conducted using the 'MASS' and 'ucR' packages of R 2.9.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria) and Statistical Analysis System (SAS) 9.1.3 software (SAS Institute, Cary, NC, USA).

Results

Demographic Data

The pathological and clinical characteristics of the patients are shown in table 1. The number of patients with 30-day mortality was 40. The morbidity rate was 10.7% in the non-30-day mortality group and 100% in the 30-day mortality group. Surgery-related complications in 40 patients with 30-day mortality are shown in table 2.

Univariate and Multivariate Analyses of 30-Day Mortality

By performing univariate analysis, we found that weight, age, preoperative CEA level, hemoglobin level, serum albumin level, asthma, diabetes, and liver cirrhosis were statistically significant (table 3). With regard to multivariate analysis, age, serum albumin level, and diabetes were found to be the significant predictors. Moreover, the logistic regression model from SAS revealed that patients whose age increased by 10 years, with the other factors remaining constant, were at a 1.852 times higher risk of mortality than the others. Patients whose serum albumin levels increased by one unit (0.1 g/dl), with the other factors remaining constant, were 0.248 (0.146–0.423) times more susceptible to mortality than the others. Similarly, patients with diabetes were 2.668 (1.286–5.542) times more susceptible to mortality than those without diabetes (table 3).

AUCs of Serum Albumin and AAR for the Prediction of 30-Day Mortality

The ratio of the first and second significant factors was age-albumin ratio (AAR) [32]. In order to assess which predictor

Fig. 1. ROC curves for serum albumin and AAR for the prediction of 30-day mortality.

(serum albumin or AAR) was more significantly related to 30-day mortality, we conducted the area test (results shown in table 4). Testing of the difference between serum albumin and AAR showed that the ROC curves for serum albumin and AAR were unequal. AAR had larger AUCs, while serum albumin had a significantly smaller AUC. Figure 1 shows the ROC curves for serum albumin and AAR for the prediction of 30-day mortality. We found that the ROC curve for AAR was almost consistently higher than that for serum albumin.

The values of sensitivity and specificity for the prediction of 30-day mortality, determined on the basis of the threshold values of serum albumin and AAR, are shown in table 5. The sensitivities are as follows: serum albumin level of ≤ 3.5 g/nl and AAR of ≥ 20 years $\text{g}^{-1} \text{nl}^{-1}$. The specificities are as follows: serum albumin level of ≤ 3.5 g/nl and AAR of ≥ 20 years $\text{g}^{-1} \text{nl}^{-1}$.

Discussion

Our study has several strengths. To begin with, it is the first study that combined age with serum albumin, forming a new index to evaluate the postoperative 30-day mortality in patients with colon cancer. Additionally, by using AUCs, we were able to examine each (or any) combination of the risk factors to determine the one that was most strongly associated with adverse operative outcomes.

Bad food intake habits contribute to hypoalbuminemia [33]. Food intake was measured by a food frequency questionnaire in our study. Frequency of consumption in the recent 5 years was recorded for the following 12 food items: rice, bread, instant noodles, fish/shrimp, red meat, white meat, vis-

Table 4. AUCs for the prediction of 30-day mortality, derived on the basis of the threshold values of serum albumin and the new indices

	AUC	p value
Age-albumin ratio	0.851	–
Serum albumin	0.779	0.0002

AUC = Area under the receiver operating characteristic curve.

Table 5. Sensitivity and specificity for the prediction of 30-day mortality, determined on the basis of the threshold values of serum albumin and the new indices

	Sensitivity	Specificity
Serum albumin level of ≤ 3.5 g/nl	0.625	0.81907
Age-albumin ratio of ≥ 20 years $\text{g}^{-1} \text{nl}^{-1}$	0.800	0.79605

cera, eggs, vegetables, milk, coffee, and fruit. However, we found that all of the 12 items were not statistically significant in regard to mortality. Traditionally, hypoalbuminemia is associated with a high risk of adverse surgical outcomes [15–18]. Serum albumin is a better prognostic predictor of operative outcome than anthropomorphic markers of nutritional status. Older patients often have many coexisting diseases and develop hypoalbuminemia; i.e., serum albumin levels decrease with age, and this association is independent of sex. On the basis of these findings, many studies have suggested preoperative low serum albumin levels and old age as the fundamental factors that increase 30-day mortality after colorectal surgery [8, 24, 25]. In clinical practice, the most important advantage is that the serum albumin test is a relatively low-cost test, and age determination is easy. The AAR is an index that assessed older patients by the stricter criteria. Our results show that the percentage of the AAR of ≥ 0.8 years $\text{g}^{-1} \text{nl}^{-1}$ in cases of mortality has higher values (80%). Hence, a combination of the two parameters of age and serum albumin should be used more frequently as a prognostic tool to predict postoperative mortality. Concomitant medical illnesses such as asthma, diabetes, and liver cirrhosis have also been reported in several studies as significant predictors of 30-day mortality [13, 34, 35]. The results of this study are in accordance with those of the studies cited above. Specific postoperative complications were identical in the 30-day mortality group and the non-30-day mortality group. However, there were more pulmonary complications in the 30-day mortality group than in the non-30-day mortality group (37.5 vs. 0.4%; $p < 0.001$). This implies that postoperative pulmonary complications are frequent in terms of 30-day mortality. Moreover, serum albumin level and the patient's age were parameters having a high correlation with pulmonary complications [23, 36]. In our study, means of AAR were compared in both groups. The values were significantly different between those with and without pulmonary complication (16.54 ± 5.16 vs. 26.65 ± 7.81 ; $p < 0.001$). In multivariate analysis, among the patient-related factors and co-

Table 6. Percentage of the considered measurements in cases of morbidity and mortality

	Percentage, %					
	lung	CV	bladder dysfunction	GI	anastomosis	mortality
Albumin of ≤ 3.5 g/nl	75.9	42.9	45.8	18.2	31.3	62.5
AAR of ≥ 20 years $\text{g}^{-1} \text{nl}^{-1}$	86.2	42.9	50.8	23.6	29.2	80.0

AAR = Age-albumin ratio; CV = cardiovascular; GI = gastrointestinal.

morbidities, preoperative serum albumin level, age, and diabetes were observed to be markedly associated with the postoperative 30-day mortality in patients with colon cancer. Furthermore, patients whose serum albumin levels increased by one unit (0.1 g/dl), with the other factors remaining constant, were 0.248 times more susceptible to mortality than the others. The risk of 30-day mortality was 1.852 times higher in patients whose age increased by 10 years than in others. Similarly, patients with diabetes were 2.668 times more susceptible to mortality than those without diabetes.

The present study mainly showed that combining two continuous predictors (preoperative serum albumin level and age) significantly affected the prediction of postoperative mortality in patients with colon cancer. In this study, we proposed the use of AAR as a screening parameter for identifying the optimal cut-off value in order to predict the 30-day mortality after colon surgery. AAR of ≥ 20 years $\text{g}^{-1} \text{nl}^{-1}$ yielded the minimal value of

$$\sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2} \quad (2)$$

for predicting 30-day mortality. The low specificity was compensated by its substantially high sensitivity. In other words, the new index would offer built-in solutions for situations in which individuals with high risks of 30-day mortality are falsely assumed to have no risk. Moreover, the optimal cut-off values recommended in this study for AAR showed a balance of sensitivity and specificity for the prediction of 30-day mortality (table 5).

Table 6 shows the percentage of the considered measurements in cases of morbidity and mortality. For 30-day mortality, AAR of ≥ 0.8 years $\text{g}^{-1} \text{nl}^{-1}$ has higher values (80%) than

serum albumin of ≤ 3.5 g/nl (62.5%), mGPS (modified Glasgow prognostic score) of ≥ 1 (52.5%), and mGPS of ≥ 2 (32.5%). For pulmonary complications, AAR of ≥ 0.8 years $\text{g}^{-1} \text{nl}^{-1}$ has a higher value (86.2%) than serum albumin of ≤ 3.5 g/nl (75.9%), mGPS of ≥ 1 (65.5%), and mGPS of ≥ 2 (51.7%). This result implies that the use of a combination of serum albumin and age as the predictor of postoperative 30-day mortality in patients with colon cancer is better than that of serum albumin or mGPS alone.

On the basis of the AUCs derived for the prediction of 30-day mortality in patients with colon cancer, we suggest that AAR is a better predictor than serum albumin in Taiwanese subjects. In conclusion, hypoalbuminemia often reflects malnourishment in patients [37]. In the meta-analysis of Braunschweig et al., malnourished patients benefited from parenteral nutrition in terms of mortality [38, 39]. Such an approach has also been shown to reduce the postoperative complication rate by as much as 10% [40]. Hence, in order to reduce AAR as low as possible, our aim should be to initiate preoperative total parenteral nutrition for malnourished colon cancer patients.

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Disclosure Statement

The authors declare that there are no conflicts of interest.

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