Preoperative Serum Albumin Level as a Predictor of Operative Mortality and Morbidity

Results From the National VA Surgical Risk Study

James Gibbs, PhD; William Cull, PhD; William Henderson, PhD; Jennifer Daley, MD; Kwan Hur, MS; Shukri F. Khuri, MD

**Objective:** To improve the precision and reliability of estimates of the association between preoperative serum albumin concentration and surgical outcomes.

**Design:** Prospective observational study. Patients were followed up for 30 days postoperatively. Multiple logistic regression models were developed to evaluate serum albumin level as a predictor of operative mortality and morbidity in relation to 61 other preoperative patient risk variables.

**Setting:** Forty-four tertiary care Veterans Affairs (VA) medical centers.

**Patients:** A total of 54,215 major noncardiac surgery cases from the National VA Surgical Risk Study.

**Main Outcome Measures:** Thirty-day operative mortality and morbidity.

**Results:** A decrease in serum albumin from concentrations greater than 46 g/L to less than 21 g/L was associated with an exponential increase in mortality rates from less than 1% to 29% and in morbidity rates from 10% to 65%. In the regression models, albumin level was the strongest predictor of mortality and morbidity for surgery as a whole and within several subspecialties selected for further analysis. Albumin level was a better predictor of some types of morbidity, particularly sepsis and major infections, than other types.

**Conclusions:** Serum albumin concentration is a better predictor of surgical outcomes than many other preoperative patient characteristics. It is a relatively low-cost test that should be used more frequently as a prognostic tool to detect malnutrition and risk of adverse surgical outcomes, particularly in populations in whom comorbid conditions are relatively frequent.

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**Hypoalbuminemia** has been shown to be associated with increased mortality and morbidity rates in both hospitalized patients and samples of community-dwelling elderly persons. In surgery, an association between hypoalbuminemia and adverse outcome has been recognized for many years. In an early series of 26 patients, most operated on for diseases of the digestive tract, Jones and Eaton found that postoperative edema was associated with low concentrations of serum albumin and serum protein, which they attributed to preoperative and postoperative undernutrition. More recently, Rich et al. found that patients undergoing cardiac surgery who had lower serum albumin levels showed a trend toward having higher postoperative mortality rates and had significantly higher rates of several complications than did patients with higher serum albumin levels, while controlling for other risk factors. Albumin also has been found to predict postoperative mortality and morbidity for patients undergoing elective surgery and postoperative morbidity for those undergoing gastrointestinal tract surgery.

Although it is well established that hypoalbuminemia, as a marker of malnutrition and disease, is associated with greater risk of adverse surgical outcome, previous studies have been based on relatively small samples and selected types of operations and have failed to adequately separate the predictive ability of albumin level from other risk factors. We used a large database, the National VA Surgical Risk Study, which included all major surgical procedures, to improve the precision and reliability of estimates of the association between albumin levels and mortality and morbidity. This database was sufficiently large and detailed to allow separate as well as summary analysis for

From the Cooperative Studies Program Coordinating Center, the Edward Hines, Jr, VA Hospital, Hines, Ill (Drs Gibbs, Cull, and Henderson and Mr Hur); Institute for Health Services Research and Policy Studies, Northwestern University, Evanston, Ill (Drs Gibbs, Cull, and Henderson); Brockton/West Roxbury VA Medical Center, West Roxbury, Mass (Drs Daley and Khuri); and Harvard Medical School (Drs Daley and Khuri), Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center (Dr Daley), and Brigham and Women’s Hospital (Dr Khuri), Boston, Mass.
MATERIALS AND METHODS

OVERVIEW OF THE NATIONAL VA SURGICAL RISK STUDY

The National VA Surgical Risk Study was initiated in 44 academically affiliated Veterans Affairs (VA) medical centers with the aim of developing and validating risk-adjusted models for the prediction of surgical outcome (30-day mortality and morbidity).11-14 Clinical nurse reviewers at each site prospectively collected 46 preoperative, 12 operative, and 24 postoperative variables for 87,078 major surgery cases between October 1, 1991, and December 31, 1993. Preoperative variables included health risk behaviors, comorbidities, and 14 laboratory test results. All surgical operations conducted under general, spinal, and epidural anesthesia were eligible for inclusion as the index operation except (1) operations on patients who had been enrolled in the study for an index operation within the previous 30 days, (2) operations with very low mortality rates (eg, ophthalmologic procedures), and (3) organ transplantation, because this is performed at a limited number of VA medical centers. The study protocol is described in detail elsewhere.11

ALBUMIN STUDY DATABASE

The analyses presented here were based on 54,215 (62%) of the 87,078 cases from the National VA Surgical Risk Study database for which preoperative serum albumin values were reported. The omitted cases, those not tested for albumin level (38%), were similar in age to those included in the analysis but were somewhat less likely to have comorbid conditions or severe disease. For example, 33% of the omitted cases vs 38% of the included cases had hypertension requiring medication, 12% vs 13% had diabetes mellitus requiring an oral agent or insulin, and 51% vs 64% were assigned an American Society of Anesthesiology (ASA) class of 3 or higher. (An ASA class of 1 indicates a healthy patient; 2, mild systemic disease but no functional limitations; 3, severe systemic disease with definite functional limitations; 4, severe systemic disease that is a constant threat to life; and 5, moribund patient unlikely to survive 24 hours with or without operation.) An analysis using all cases, in which missing albumin values were imputed from scores on the other preoperative variables, yielded very similar results to those reported here for cases tested for albumin level.

INDEPENDENT VARIABLES

Preoperative serum albumin values closest to the day of surgery were used in the analysis. Only those measurements that occurred within 30 days prior to surgery were considered valid. The number of days intervening between the last albumin measurement and surgery (mean=5.03 days, SD=6.15 days) was not found to affect the association between serum albumin level and mortality as indicated by a lack of statistical interaction between time of measurement and albumin level ($\chi^2=1.47, P=.23$). The predictive ability of serum albumin levels was evaluated against 61 other preoperative patient characteristics. These variables are listed in a previous publication.11 They include age, sex, tobacco use, alcohol use, substance abuse, functional status, weight loss, emergency operation, presence or absence of comorbidities covering all major organ systems, and 14 preoperative laboratory values.

DEPENDENT VARIABLES

Operative mortality was defined as death due to any cause occurring within 30 days of the operation. Operative morbidity

RESULTS

SAMPLE CHARACTERISTICS

Reflecting the composition of all VA hospital patients, 97.1% of the albumin study cases were male, and the mean age was 61.0 years (SD=13.0 years). Seventy-six percent were white, 18% were black, and 6% were of other racial backgrounds (eg, Hispanic, Asian American). The most frequent subspecialty was general surgery (28.3%), followed by orthopedics (18.0%), urology (14.8%), vascular surgery (11.7%), neurosurgery (8.4%), thoracic surgery (7.3%), otolaryngology (5.9%), plastic surgery (3.7%), and other (2.0%). The 30-day mortality rate was 3.9%, and the 30-day morbidity rate (1 or more of the 21 complications) was 19.6%. The mean preoperative serum albumin level was 38 g/L (SD=6.5 g/L). Twenty-three percent of the cases had albumin values less than 35 g/L, which is generally considered the lower boundary of the normal range.

UNIVARIATE ANALYSES

Table 1 shows the 10 strongest predictors of 30-day mortality and morbidity, ranked by the $c$ index, from the set of 62 preoperative variables. For both outcomes, albumin level was the best predictor, with ASA class and hematocrit ranking second and third, respectively. Albumin level alone correctly discriminated between survivors and nonsurvivors 78% of the time. In general, the $c$ values are higher for mortality than morbidity, indicating that the variables predict mortality better than the occurrence of 1 or more complications. Figure 1 and Figure 2 display the relationship between serum albumin and mortality and morbidity for all operations and for the 3 selected subspecialties. For all operations, the mortality rate increases from less than 0.00 to 0.04 for albumin levels of 30-34 g/L. The morbidity rate increases from less than 0.25 to 0.40 for albumin levels of 30-34 g/L.
included 21 predefined complications recorded in the 30 days after the operation. The summary measure used in this analysis was the presence or absence of 1 or more of the 21 complications. In other analysis of the National VA Surgical Risk Study database, this score was found to be strongly correlated with summary scores based on several weighting schemes, including the total number of morbidities reported ($r=0.74$), weights based on the regression relationship between postoperative length of stay and the 21 morbidities ($r=0.75$), weights based on the relative proportion of a morbidity occurring with other morbidities ($r=0.96$), and the mean ratings by the chiefs of surgery at the 44 participating VA medical centers on a scale of 1 to 5 as to the likelihood that the morbidity could result in death, permanent sequelae, prolonged length of stay, or patient dissatisfaction ($r=0.97$).

### STATISTICAL ANALYSIS

First, the association between preoperative serum albumin levels and mortality and morbidity was assessed univariately. We compared the predictive ability of albumin level with that of each of the 61 other preoperative variables. The predictive ability of each variable was determined by the $c$ index from logistic regressions with 1 independent variable. A $c$ index of 0.5 or less indicates prediction no better than chance, and values from 0.5 to 1.0 (perfect prediction) indicate improvement over chance.

Second, multivariate logistic regression models were developed to assess the predictive ability of albumin level independent of the effects of other variables. The large number of candidate predictor variables was reduced in several steps. First, the variables were screened for significant univariate association ($P<.001$) with the dependent variables, which eliminated only 10 of the 62 candidate variables for mortality modeling and only 4 for morbidity modeling. Next, we eliminated variables that predicted the dependent variables with a $c$ index less than 0.57, a cutoff level that substantially reduced the number of variables but retained a diverse set of variables. We further reduced the number of remaining variables by developing separate stepwise regression models for the remaining comorbidity and laboratory variables, requiring $P\leq.0001$ (Wald $\chi^2$) to enter the models and $P\leq.0005$ (Wald $\chi^2$) to stay, and then eliminating variables that did not increase the $c$ index for the model by at least 0.01. These steps identified a diverse set of 7 strong predictors of mortality, including serum albumin level, that were forced in a final model to assess their relative predictive ability. Likewise, 6 variables were selected for a final morbidity model. These variables were tested for intercorrelation, and none of the correlations between pairs of predictor variables exceeded $r=0.37$.

In addition to analysis of all operations in the database, we assessed the predictive ability of albumin levels within 3 subspecialties chosen to represent variation in mortality and morbidity rates as well as different types of surgery—general surgery and noncardiac thoracic surgery, which had the highest subspeciality 30-day mortality rates (6.4% and 6.0%, respectively) and higher than average morbidity rates (26.3% and 23.6%, respectively), and orthopedics, with a mortality rate of 2.5% and a morbidity rate of 13.7%. The model development process described for all operations was also used for the subspecialty analyses except that less stringent screening and model entry criteria were used owing to smaller sample sizes. Split-sample cross-validation of the all operations and subspecialty models showed little degradation of the $c$ values, ranging from no decrease from learning to test samples in 3 of the models to a decrease of 0.03 in the $c$ value for the orthopedic mortality model.

1% for albumin levels of 46 g/L or higher to 28% for albumin levels below 21 g/L. The increase in mortality seems to be exponential as albumin level decreases from a level of approximately 40 g/L. Figure 2 shows that morbidity increases from approximately 10% to 65% as albumin values decline from 46 g/L to less than 21 g/L. The subspecialties show similar trends except that the mortality and morbidity rates are lower for orthopedics than the other subspecialties.

### MULTIVARIATE ANALYSES

**Table 2** presents the final models developed from the 62 preoperative variables for all operations and for 3 selected subspecialties. The models predict mortality very well for all operations, general surgery, and orthopedics, with $c$ values ranging from 0.86 to 0.91. The $c$ values for the morbidity models are not as high, ranging from 0.67 to 0.76. The predictive variables are listed in Table 2 in order of the magnitude of their Wald $\chi^2$ values, which indicates their relative importance in the models. Albumin level appears in all of the models and is the strongest predictor in both the mortality and morbidity models for all operations and in several of the subspecialty models. The odds ratios for albumin level in the all operations models indicate that a decrease of 10 g/L in albumin value was associated with more than a 2-fold increase in the odds of dying and almost a 2-fold increase in the odds of a complication. The ASA class was also a strong predictor, particularly in the mortality models. Both serum albumin levels and weight loss appear in the mortality model for thoracic surgery, indicating that albumin level detects risk not associated with weight loss of greater than 10% of body weight in the 6 months prior to surgery.

**COMPLICATION-SPECIFIC ANALYSIS**

In addition to analysis of morbidity using the summary measure of complications, we analyzed the association between preoperative serum albumin and each of the 21 predefined complications. **Table 3** gives the mortality rate, incidence, and regression results for each of the complications, listed in order of the magnitude of the $c$ index for the regression of the complication on serum albumin level. The complications with the higher $c$ values...
tend to have higher mortality rates. They also are characterized by incidence rates that are markedly higher for cases with albumin levels below normal (<35 g/L) than for cases in the normal range (≥35 g/L).

The last column of Table 3 shows the entry step of albumin level in stepwise logistic regression using all 62 preoperative variables and an entry criterion of P<.05. In these multivariate analyses, albumin level was a relatively strong predictor of most of the complications, entering the models at the first, second, or third step. Albumin level was the first variable to enter for the major infection complications (systemic sepsis, pneumonia, deep wound infection). For several complications, albumin level was not a significant predictor in the regression analyses.

The variation in the predictive ability of albumin level for different complications partially explains why albumin level was not as strong a predictor of most of the complications, serum albumin level was a strong predictor of complications combined and for selected surgical subspecialties. The association between albumin concentration and operative mortality persisted in a subset of patients who were classified as low risk on admission for the total sample. Within the last 6 months prior to surgery. There were 15,555 patients in our sample who met these criteria. The 30-day death rate for these low-risk patients was 0.32%. As shown in Figure 3, there was a negative association (c index=0.72, P<.001) between serum albumin level and mortality even within this lower-risk subgroup. Likewise, for the women in the sample (n=1575), there was a strong association between serum albumin level and mortality (c index=0.86, P<.001), with a graded increase in mortality rates as albumin values declined, similar to the finding for the total sample.

We used a large national sample of VA patients to determine the association between preoperative serum albumin level and 30-day postoperative mortality and morbidity. We found large, graded increases in mortality and morbidity as albumin level declined from high to low levels. We found that for all major operations combined and for selected surgical subspecialties, serum albumin level was a strong predictor of mortality and morbidity independent of the effects of a large, diverse set of prospectively determined patient risk variables. The association between albumin concentration and operative mortality persisted in a subsample of patients who were classified as low risk on

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Table 1. Preoperative Predictors of 30-Day Mortality and Morbidity After Major Surgery, Ranked by c Index Magnitude (Albumin Study Database)*

<table>
<thead>
<tr>
<th>Variable†</th>
<th>c Index</th>
<th>Variable</th>
<th>c Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin, g/L</td>
<td>0.78</td>
<td>Albumin, g/L</td>
<td>0.68</td>
</tr>
<tr>
<td>ASA class</td>
<td>0.77</td>
<td>ASA class</td>
<td>0.67</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>0.72</td>
<td>Hematocrit, %</td>
<td>0.66</td>
</tr>
<tr>
<td>Serum urea nitrogen, mmol/L</td>
<td>0.69</td>
<td>Functional status</td>
<td>0.60</td>
</tr>
<tr>
<td>Functional status</td>
<td>0.67</td>
<td>Age, y</td>
<td>0.60</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>0.67</td>
<td>Prothrombin time, s</td>
<td>0.59</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.64</td>
<td>Serum urea nitrogen, mmol/L</td>
<td>0.58</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>0.64</td>
<td>Alkaline phosphatase, U/L</td>
<td>0.58</td>
</tr>
<tr>
<td>WBC, &gt;11 000/µL</td>
<td>0.63</td>
<td>Emergency operation</td>
<td>0.57</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>0.62</td>
<td>WBC, &gt;11 000/µL</td>
<td>0.57</td>
</tr>
</tbody>
</table>

*ASA indicates American Society of Anesthesiology; WBC, white blood cell count.
†All variables were examined using single-variable logistic regression models, and all variables were significant at P<.001.
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c index of 0.70.

c index of 0.68.

c index of 0.67.

c index of 0.66.

c index of 0.62.

As with mortality, the basis of clinically recognizable risk factors. With regard to operative morbidity, we showed that albumin level was a better predictor of some types of complications than others. Although serum albumin level may also be affected by acute factors such as trauma and surgical stress, it is predictive of operative outcome because it is a marker of disease and malnutrition as well as possibly conferring a direct protective effect through several biological mechanisms. It is a better prognostic indicator than anthropomorphic markers of nutritional status because of its ability to detect protein-energy malnutrition, which is not necessarily accompanied by lower body weight and may not be clinically recognizable, but is associated with significantly increased risk of morbidity and mortality. Protein-energy malnutrition results from increased protein and energy requirements associated with the stress of illness, injury, or infection. If the increased needs are not met from dietary or therapeutic sources, visceral protein stores are depleted, leading to
abnormal function in organ systems, including gastrointestinal malabsorption, impaired immunologic response, and impaired production of albumin and other plasma proteins in the liver.24,25 However, albumin infusion usually is not an effective therapy because the albumin will degrade quickly and infusion does not address the underlying causes of adverse operative outcome.26

There was wide variation in the rate of preoperative serum albumin testing among the 44 participating hospitals, ranging from 20% to 98% of cases, with a median testing rate of 60%. Even if the analysis is restricted to cases with an ASA score of 3 or higher (severe systemic disease with functional limitation; 59% of all cases), the variation by hospital in the proportion tested remains large (from 27% to 97% of cases, with a median of 72%). In contrast, the ordering of blood counts and portions of the SMA-7 (eg, serum sodium and potassium) was consistently high (>90%) across hospitals.

These findings suggest that preoperative serum albumin testing is underutilized by some surgeons. The cost of the test ($2-$4, based on cost data from 2 VA hospitals and 1 large community hospital) is low in relation to its prognostic value. In addition to its value as a prognostic tool, serum albumin level is a key element in accurate nutritional assessment,9,10,17,27 and it has been shown that nutritional therapy is more effective in reducing operative mortality and morbidity when the diagnosis of malnutrition is based on objective nutritional indices that include serum albumin rather than on subjective assessment.28,29 Particularly in patient populations with high rates of comorbidities, such as VA patients, it would seem that the test should be used more frequently as a prognostic tool and for detecting malnutrition.

This research was supported by a grant from the American Association for Clinical Chemistry Inc, Washington, DC, to the Institute for Health Services Research and Policy Studies at Northwestern University, Evanston, Ill; and by the Office of Patient Care Services and Cooperative Studies Program, US Department of Veterans Affairs Headquarters, Washington. Dr Daley is a Senior Research Associate in the Health Services Research and Development Program in the Department of Veterans Affairs.
Dyspepsia in the Community Is Linked to Smoking and Aspirin Use but Not to Helicobacter pylori Infection
Sanjay Nandurkar, FRACP; Nicholas J. Talley, MD, PhD, FRACP; Harry Xia, PhD; Hazel Mitchell, PhD; Stuart Hazel, PhD; Michael Jones, PhD

Background: The relationship between Helicobacter pylori infection and symptoms remains controversial. We aimed to determine if an association exists between unexplained dyspepsia (pain or discomfort centered in the upper part of the abdomen) and H pylori.

Methods: A validated questionnaire was completed by 592 healthy blood donors. Helicobacter pylori serologic values (via enzyme-linked immunosorbent assay), blood group status, and Rh status were measured; 4.9% of subjects who had a history of peptic ulcer disease were excluded from the analyses.

Results: The prevalence of dyspepsia and no ulcer history was 11% (95% confidence interval [CI], 8.6%-13.8%); 15.4% of subjects with dyspepsia had H pylori while 14.6% of subjects without dyspepsia were infected (P = .90). The mean dyspepsia impact scores (combining frequency and severity) in those with and without H pylori were 4.7 and 5.4, respectively (P = .20). The median H pylori optical density values in dyspepsia vs no dyspepsia were not significantly different (P = .30). Independent risk factors for dyspepsia were the use of aspirin (odds ratio [OR], 2.2; 95% CI, 1.3-3.7) and smoking (OR, 2.1; 95% CI, 1.3-3.6) but not age, sex, marital status, educational level, income, or the use of alcohol, coffee, or nonsteroidal anti-inflammatory drugs. Independent risk factors for H pylori were increasing age (OR, 1.8 per decade; 95% CI, 1.5-2.3), male sex (OR, 2.1; 95% CI, 1.3-3.4), and net family income (OR, 1.8; 95% CI, 1.2-3.3).

Conclusion: Dyspepsia in the community is linked to smoking and aspirin use, but not to H pylori infection. (1998;158:1427-1433)

Reprints: Nicholas J. Talley, MD, PhD, Department of Medicine, University of Sydney, Nepean Hospital, Penrith, New South Wales 2751, Australia.