Journal of Critical Care 31 (2016) 36–40

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

# Low total cholesterol and high total bilirubin are associated with prognosis in patients with prolonged sepsis

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ARTICLE INFO

*Keywords:*
Sepsis
Cholesterol
Bilirubin
Classification and regression tree
Nutrition
Biomarker

ABSTRACT

*Purpose:* Nutritional biochemical indexes are generally used as markers for critically ill patients. However, they are easily influenced by acute phase changes after injury and are difficult to use as common and practical biomarkers. The objective of this study was to determine the most valuable prognostic markers among 15 common laboratory tests in patients with sepsis.
*Methods:* We included all sepsis patients who stayed in the intensive care unit for more than 2 weeks. We evaluated 15 biochemistry indexes including serum albumin, total protein, C-reactive protein, cholinesterase, total cholesterol (T-Cho), triglyceride, sodium, potassium, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total bilirubin (T-Bil), and prothrombin time. The minimum and maximum values of these indexes during the first 14 days from admission were analyzed by classification and regression tree and multivariate logistic regression analyses.
*Results:* This study comprised 91 patients with sepsis. The primary split was the minimum value of serum T-Cho (T-Cho (Min)), and the cutoff value was 73.5 mg/dL by classification and regression tree analysis. The second split was the maximum value of T-Bil (T-Bil (Max)), and the cutoff value was 1.35 mg/dL. The rate of mortality was 63% (17/27) in the group with T-Cho (Min) less than 73.5 mg/dL and T-Bil (Max) greater than 1.35 mg/dL. Multivariate logistic regression revealed that T-Cho (Min) and T-Bil (Max) were the biomarkers most closely associated with prognosis.
*Conclusions:* Total cholesterol and T-Bil could be associated with prognosis in patients with sepsis.


## 1. Introduction

Management of nutrition is important from the early stage to improve the prognosis of critically ill patients. Although the importance of nutrition in the hospital setting cannot be overstated, it is particularly noteworthy in the intensive care unit (ICU). Critical illness is typically associated with a catabolic stress state in which patients commonly demonstrate a systemic inflammatory response. This response is coupled with complications of increased infectious morbidity, multiorgan dysfunction, prolonged hospitalization, and disproportionate mortality [1].

As biochemical indexes in nutrition management, serum albumin, total protein, blood glucose, triglyceride, cholesterol, rapid turnover protein, and others are generally used. Albumin is a useful preoperative marker related to mortality in the surgical field [2], but traditional nutrition markers including albumin, prealbumin, transferrin, and retinol binding protein are a reflection of the acute phase response and do not accurately represent nutritional status in the ICU setting. Anthropometrics are also not reliable in the assessment of nutritional status or the adequacy of nutrition therapy.

The objectives of this study were to determine the most valuable prognostic factors among 15 common laboratory tests and the thresholds of the biochemical indexes in patients with sepsis using classification and regression tree (CART) and multivariate logistic regression (MVLR) analyses.

## 2. Methods

### 2.1. Patients

Subjects included all patients with sepsis who were admitted to the Trauma and Acute Critical Care Center, Osaka University Hospital, Osaka, Japan, and treated in the ICU for more than 2 weeks during the period of July 2006 to December 2010. To evaluate patients in need of

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http://dx.doi.org/10.1016/j.jcrc.2015.09.033
0883-9441/

long-term treatment, we excluded patients who died within 2 weeks of admission to the ICU. Among the blood tests that have been performed frequently, we retrospectively evaluated 15 different blood biochemistry indexes including many related to nutritional status. They included serum albumin, total protein, C-reactive protein, cholinesterase, total cholesterol (T-Cho), triglyceride, sodium, potassium, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), total bilirubin (T-Bil), and prothrombin time.

Sepsis was diagnosed according to the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine [3]. Enteral nutrition (Lifelon-Q10; Nisshin Pharma, Inc, Tokyo, Japan; protein 5 g, fat 3.4 g, and carbohydrate 12.5 g per 100 kcal, osmolarity 370 mOsm/L) was initiated as quickly as possible through a nasogastric tube at 20 mL/h and advanced by 20 mL/h per day to the calorie goal, which was 25 to 30 kcal/kg ideal body weight per day during the study period. When it was difficult to continue enteral nutrition due to gastrointestinal complications, we used parenteral nutrition in addition to enteral nutrition to reach the target calorie goal. Infections in these patients were initially treated empirically for the underlying clinical syndrome and then according to the results of antibiotics susceptibility testing of the bacterial infection isolated. Antibiotics were administered under the same policy for the entire study period.

This study was carried out according to the principles of the Declaration of Helsinki and was approved by the institutional review board at Osaka University Hospital (approval no. 13217). The board waived the need for informed consent because this was a retrospective study using clinical data.

### 2.2. Statistical analysis

Analysis was performed using mortality as the binary outcome variable. As potential predictor covariates, age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score recorded on admission, and the 15 blood biochemistry indexes were used.

Classification and regression tree analysis is a type of binary recursive partitioning using nonparametric approaches. It is a popular method for identifying high-risk and poor prognosis groups. The overall study group is split into 2 subgroups using the most powerful predictor of outcome. This splitting is repeated within the subgroups until no further significant splits are found or the subgroups become too small. The results are displayed in a binary tree structure, which is pruned as necessary in a final step [4].

First, to evaluate the changes in the biochemical indexes, the maximum and minimum values during the first 14 days after admission were taken as representative values of the changes in these biochemistry indexes. Second, recursive partitioning was used to create a tree using all of the independent covariates. Third, the 2 predominant covariates were selected. Predictive accuracy of CART was evaluated using sensitivity and specificity for mortality.

We also determined the most valuable prognostic indicators with MVLR. First, univariate analysis was performed to find potential prognostic variables, and variables with a $P$ value greater than .20 were excluded. To find the strong prognostic indicators, variables were then selected on forward stepwise logistic regression, where $P = .20$ for entry into the model and $P = .05$ to remain in the model for the stepwise algorithm.

Data are expressed as group means ± SD of the mean, medians with ranges, or actual number. Continuous variables were compared between groups with the Student $t$ test or nonparametric test as appropriate. Categorical variables were analyzed with the $\chi^2$ test or Fisher exact test as appropriate. All statistical tests were 2 sided at a significance level of 0.05. Statistical analysis for CART was performed with Statistica version 10.0 (StatSoft, Inc, Tulsa, OK) and In-House validated Fortran Program, and MVLR was performed with IBM SPSS Statistics for Windows, version 19 (SPSS, Chicago, IL).

**Table 1**
Patient characteristics

| | Total | Survivors | Nonsurvivors | *P* |
|---|---|---|---|---|
| n | 91 | 72 | 19 | – |
| Sex: male (%) | 56 (61.5) | 42 (58.3) | 14 (73.7) | NS |
| Age (y)[a] | 64 ± 18 | 62 ± 19 | 68 ± 13 | NS |
| APACHE II[a] | 18 ± 9 | 17 ± 8 | 21 ± 11 | NS |
| ICU stay (d)[b] (IQR) | 28 (18-50) | 28 (18-49.8) | 31 (18-50) | NS |
| Initial nutritional therapy | | | | |
| Initial day[b] (IQR) | 3 (2-5) | 2 (2-4.8) | 4 (3-6) | <.05 |
| EN:PN | 58:33 | 50:22 | 8:11 | <.05 |

NS indicates not significant; IQR, interquartile range; EN, enteral nutrition; PN, parenteral nutrition.
[a] Mean ± SD.
[b] Median (interquartile range).

## 3. Results

The study group comprised 56 men and 35 women with a mean (±SD) age of 64 ± 18 years. Patient characteristics are listed in Table 1. Median length of ICU stay was 28 days, and the APACHE II score on admission was 18 ± 9. The median day of initial nutritional therapy was the third day from admission. Enteral nutrition was the initial nutritional therapy 63.7% of the time. Nineteen patients (21%) died of sepsis. There were no significant differences between survivors and nonsurvivors in sex, age, length of ICU stay, or APACHE II score, but the day of initial nutritional therapy was later and the percentage of enteral nutrition was lower in nonsurvivors. Origins of sepsis in the study patients are listed in Table 2. There was no significant difference between survivors and nonsurvivors.

Results of biochemical indexes are listed in Table 3. The minimum values of T-Cho, albumin, total protein, cholinesterase, and sodium were significantly lower in nonsurvivors, whereas the maximum values of T-Bil, potassium, BUN, creatinine, and LDH were significantly higher in nonsurvivors than survivors.

Classification and regression tree analysis detected the minimum value of T-Cho (T-Cho (Min)) and the maximum value of T-Bil (T-Bil (Max)) as the most valuable prognostic indicators. The primary split was determined to be T-Cho (Min), and the cutoff value was 73.5 mg/dL. The second split was T-Bil (Max), with a cutoff value of 1.35 mg/dL. The mortality in each partition is shown in Fig. 1. Patients were then classified into 3 groups according to these values: group A, T-Cho (Min) less than or equal to 73.5 mg/dL and T-Bil (Max) greater than 1.35 mg/dL; group B, T-Cho(Min) less than or equal to 73.5 mg/dL and T-Bil (Max) less than or equal to 1.35 mg/dL; and group C, T-Cho (Min) greater than 73.5 mg/dL. The rates of mortality were 63% (17/27) in group A, 13% (2/15) in group B, and 0% (0/49) in group C. A scatter plot of the T-Cho (Min) and T-Bil (Max) values, in which patients are distinguished by outcome, is shown in Fig. 2.

If patients in group A were predicted to be nonsurvivors and patients in both groups B and C were predicted to be survivors, sensitivity, specificity, positive predictive value, negative predictive value, and total predictive value for mortality were 89.5% (17/19), 86.1% (62/72), 63.0% (17/27), 96.9% (62/64), and 86.8% (79/91), respectively.

**Table 2**
Origins of sepsis

| | All patients | Survivors, n (%) | Nonsurvivors, n (%) | *P* |
|---|---|---|---|---|
| | N = 91 | n = 72 | n = 19 | |
| Necrotizing fasciitis | 33 | 28 (38.9) | 5 (26.3) | .423 |
| Pneumonia | 24 | 16 (22.2) | 8 (42.1) | .141 |
| Abdominal infection | 17 | 14 (19.4) | 3 (15.8) | >.999 |
| CNS infection | 7 | 6 (8.3) | 1 (5.3) | >.999 |
| Mediastinitis | 5 | 4 (5.6) | 1 (5.3) | >.999 |
| Bloodstream infection | 4 | 3 (4.2) | 1 (5.3) | >.999 |
| Urinary tract infection | 1 | 1 (1.4) | 0 (0) | >.999 |

CNS indicates central nervous system.