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Alimentary Tract

A simplified prognostic model to predict mortality in patients with acute variceal bleeding

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ABSTRACT

Background: Acute variceal bleeding (AVB) is a major cause of death in patients with liver cirrhosis. The aim of this study was to investigate mortality predictors and develop a new simple prognostic model using easily verified factors at admission in AVB patients.
Methods: Between January 2009 and May 2015, 333 consecutive patients with AVB were included. A simplified prognostic model was developed using multiple logistic regression after identifying significant predictors of 6-week mortality. Mortality prediction accuracy was assessed with area under the receiver operating characteristic (AUROC) curve. We compared the new model to existing models of model for end-stage liver disease (MELD) and Child–Pugh scores.
Results: The 6-week overall mortality rate was 12.9%. Multivariate analysis showed that C-reactive protein (CRP), total bilirubin, and the international normalized ratio were independent predictors of mortality. A new logistic model using these variables was developed. This model's AUROC was 0.834, which was significantly higher than that of MELD (0.764) or Child–Pugh scores (0.699). Two external validation studies showed that the AUROC of our model was consistently higher than 0.8.
Conclusions: Our new simplified model accurately and consistently predicted 6-week mortality in patients with AVB using objective variables measured at admission. Our system can be used to identify high risk AVB patients.

1. Introduction

Patients with cirrhosis are at risk for developing one or more critical complications, such as ascites, spontaneous bacterial peritonitis, encephalopathy, or hepatorenal syndrome [1–4]. When these are accompanied by multiple organ failure and culminate in high short-term mortality, this becomes a distinct disease entity known as acute-on-chronic liver failure (ACLF) [5,6]. ACLF is an increasingly recognized disease entity. It has been postulated that ACLF could allow for early identification of patients at high risk for cirrhosis-related death.

Acute variceal bleeding (AVB) is a major complication of portal hypertension in patients with cirrhosis. Endoscopic ligation therapy combined with vasoactive drugs and prophylactic antibiotics is the current standard of care for AVB patients [7,8]. Despite advances in diagnosis and management of esophageal and gastric varices, AVB is a main cause of upper gastrointestinal bleeding (UGIB). Mortality remains high in this situation (16%–24%) [7,9]. Development of sensitive and specific risk prediction models for AVB patients is important for reducing mortality in high-risk patients. Early transjugular intrahepatic portosystemic shunt (TIPS) use in selected high-risk patients reduces mortality [10,11]. Furthermore, rigorous application of treatments such as restricted blood transfusion or nonselective beta-blockers can improve AVB patient survival [12].

Although there are several AVB prognostic models, they have limited ability to predict patient outcomes. Rockall and Glasgow Blatchford scores are widely used UGIB risk predictors. However, these scores are poor at predicting clinical outcomes of patients with AVB [13]. The Child–Pugh score has subjective components that are inconsistently predictive, such as ascites or encephalopathy [14]. Model for end-stage liver disease (MELD) score is composed of objective variables [15]. However, this model

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was developed based on patients treated with TIPS more than 10 years ago and so might not apply to AVB patients. The chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score has received the most attention recently and adequately predicts ACLF in chronic liver disease patients [6]. However, this score is complex and includes subjective components.

The aim of the present study was to develop a new and simple prognostic model based on initial objective components in AVB patients. To achieve this aim, we first investigated mortality predictors in AVB patients. Based on this analysis, a new and simple prognostic model was produced using exclusively objective and easily verified factors. Finally, this new model was validated externally to ensure generalizability and implementation in clinical practice.

2. Patients and methods

2.1. Study population

A consecutive database that included all patients admitted to Seoul St. Mary's Hospital, a tertiary care center, for acute gastrointestinal (GI) bleeding from January 2009 to May 2015 was created. This study was approved by Seoul St. Mary's Hospital Institutional Review Board (KC14RISI0606). From the total GI bleeding patient cohort, those who were found to have cirrhosis and variceal bleeding were identified and selected for this study.

Patients with cirrhosis and acute bleeding from both esophageal and gastric varices were considered eligible for this study. Cirrhosis diagnosis was based on definite clinical data combined with imaging findings such as abdominal sonography or computed tomography. Only patients presenting with variceal bleeding confirmed by esophagogastroduodenoscopy (EGD) were included. According to Baveno guideline, antibiotic prophylaxis was instituted as early as possible on presentation of AVB and continued for 5–7 days in all patients with AVB in our institution. Vasoconstrictors were also administered as soon as possible when there is a clinical suspicion of AVB. We excluded the following cases: those under 18 years of age, those who did not undergo EGD, and follow-up loss within 6 weeks from initial endoscopic examination.

2.2. Data collection

Baseline demographic characteristics, Child–Pugh and MELD scores, cirrhotic complications, previous episodes of variceal bleeding, and major comorbidities were recorded. Initial systolic blood pressure (SBP), diastolic blood pressure (DBP) and laboratory tests including measures of hemoglobin, serum blood urea nitrogen, creatinine, prothrombin time or international normalized ratio (INR), total bilirubin, albumin, serum CRP, and white blood cell count were also recorded. Bleeding focus and endoscopic findings were described by the endoscopist who performed the EGD.

Endoscopic therapy was performed as soon as safely possible. Sclerotherapy or ligation choice was left to the endoscopist's discretion according to recommended standards. A Sengstaken–Blakemore tube was placed when necessary. Transfusion requirements were defined as number of packed red blood cells (pRBC) products transfused on the day of bleeding or transfused continuously during the following hospital stay with initiation at the day of bleeding.

Outcome data, including hospital stay, rebleeding, readmission, and 6-week mortality were also recorded. The primary outcome of the present study was 6-week mortality because it is a thoroughly validated end point during which most AVB deaths occur [7,11]. Rebleeding was defined as a new hematemesis or melena after 24 h of stable vital signs and hemoglobin level [12].

2.3. Definitions

This study's definitions were based on the criteria of the Baveno II consensus workshops [16]. Time zero of a variceal bleeding episode was defined as the first time a patient was admitted to the hospital presenting with AVB symptoms. The endoscopic findings of variceal bleeding were classified as active bleeding, stigmata, and no definite stigmata. Active bleeding was defined as a spurting or oozing lesion. Stigmata of recent hemorrhage was defined as presence of a white nipple on varices, adherent clots on varices or ulcers, or a visible vessel in an ulcer's base. If varices were seen in the context of a recent UGIB with neither active bleeding nor stigmata and there were not any causative lesion for bleeding such as peptic ulcer or angioectasia, no definite stigmata was recorded.

Bacterial infection was defined by one of the following criteria during the first 5 days after hemorrhage: spontaneous bacterial peritonitis, pneumonia, urinary tract infection (UTI), bacteremia, or other infection. Other infections were diagnosed according to clinical, radiologic, and bacteriologic data. Mean arterial pressure (MAP) was calculated as follows: MAP = DBP + [0.333 (SBP − DBP)].

2.4. External validation

External validation studies were performed in 2 series of cirrhotic patients presenting with variceal bleeding. The first validation was performed in 555 consecutive AVB patients in Uijeongbu St. Mary's Hospital from June 2009 to October 2015. This facility is located in Gyeonggi-do, and is a tertiary care center reporting high variceal bleeding occurrence. The second sample included 105 consecutive AVB patients admitted to St. Paul's Hospital from January 2009 to October 2013. This facility is located in Seoul, is a secondary care center, and reports a low variceal bleeding volume. Data from which to calculate the model was available for all patients in both series.

2.5. Statistical analysis and prognostic model generation

Descriptive statistics were used to characterize the demographic features of the study population. For the univariate analysis, continuous variables were expressed as mean (±standard deviation) or median (interquartile range) and were compared using the Mann–Whitney *U* test. Categorical variables were expressed as number (percentage) and were compared between groups using Chi-square or Fisher's exact test as appropriate.

A logistic regression model was used to assess predictive factors of 6-week mortality. This model was considered a suitable alternative to the Cox model because the follow-up time was relatively short. Variables showing *P*-values <0.05 after univariate analysis and those that were considered clinically relevant were included in a multivariate logistic regression model to identify independent factors associated with 6-week mortality. Backward step-wise multivariate analyses were performed. For significant variables, coefficients and odds ratios with 95% confidence intervals were reported. After multivariate analysis, significant variables were selected for the final prognostic model of the outcome of interest. We decided to exclude variables that were subjective and hard to verify at initial presentation. To test discriminatory ability of the newly developed model, a prognostic index (PI) was computed for the model with the equation, $PI = bxi + byi + \ldots bzi + constant\ term$. *b* was the regression coefficient for each variable in the final model, and xi, yi, zi, and so forth represented each variable's value for patient i [9]. PI was subsequently used to compute individual probabilities for death and to produce receiver operating characteristic (ROC) curves. This new prognostic model then was validated by comparing the area under the receiver operating characteristic curve with other known prognostic models. Statistical analysis was

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