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Neutrophil-lymphocyte ratio predicts hospital-acquired bacterial infections in decompensated cirrhosis

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ABSTRACT

Background: Bacterial infection is a frequent complication and severe burden in cirrhotic patients. We determined the utility of neutrophil-to-lymphocyte ratio (NLR) to predict the hospital-acquired (HA) bacterial infections episode in patients with decompensated cirrhosis.
Methods: We retrospectively included 2066 consecutive decompensated cirrhotic patients from two separate tertiary hospitals, divided into training (n = 1377) and validation (n = 689) set. All data were collected on admission and all overt bacterial infections occurring after > 48 h of hospital stay were registered.
Results: The incidence of HA bacterial infections in training and validation cohort was 35.87% and 31.05% respectively. Multivariate analysis showed that total bilirubin (TBil), albumin, white blood cell count (WBC) and NLR were independent predictors of HA bacterial infections. We established a Model_NTWA using these four variables and a Model_TWA which did not include NLR. Areas under the curves (AUC) of Model_NTWA (0.859) and NLR (0.824) were higher than which of Model_TWA (0.713), WBC (0.675), TBil (0.593) and Albumin (0.583). Consistent with training cohort, validation cohort showed similar results. Patients with NLR of at least 4.33 had a significantly lower survival ($P < 0.001$).
Conclusions: NLR can be used as a novel noninvasive marker to predict the occurrence of HA bacterial infections in decompensated cirrhotic patients.

1. Introduction

Bacterial infections occur in 25–35% of cirrhotic patients admitted to hospital, and infections can further deteriorate their liver function [1]. Bacterial infections are classified as community-acquired (CA), health care–associated (HCA), or hospital-acquired (HA). Compared with CA infections, multidrug-resistant bacteria or antibiotic-resistant infections are more frequently found in cirrhotic patients with HA infections [2], which can ultimately lead to both a longer hospital stay and increase the mortality in patients with advanced cirrhosis [2–4]. Therefore, the early predictors to assess HA infections in cirrhotic patients are needed. Several variables included invasive procedures performed, placement in a room with another patient, decompensated status, use of antibiotics and proton pump inhibitors (PPIs) have been proved to be associated with increased risk of acquiring a HA infection [5,6]. Furthermore, prognosticate value of individual baseline parameters, such as C reactive protein (CRP), model for end stage liver disease (MELD) score, albumin, creatinine, bilirubin, white blood cell count, neutrophil count, platelet count for predicting HA infection in cirrhotic patients have also been researched in a few studies [2,7,8].

The neutrophil-to-lymphocyte ratio (NLR), which is calculated from the complete blood count, is an easily accessible biomarker of systemic inflammation, and has been used to predict outcomes in various disease including cardiac disease, gastric malignancy and renal failure [9–12]. Recently, NLR was used to predict the outcomes in patients with liver cirrhosis, acute-on-chronic liver failure (ACLF), nonalcoholic fatty liver disease (NAFLD), and liver transplantation [13–16]. As we know, spontaneous increased pro-inflammatory response occurred in patients with advanced cirrhosis because of an imbalance pro-inflammatory and anti-inflammatory signaling pathways in immune cells [17]. In blood

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routine test, the neutrophil count reflects ongoing inflammation and the lower lymphocyte count represents the malnutrition as well as inflammation [18,19]. Thus, elevated NLR might be commonly seen in cirrhotic patients. Though NLR has been proved as an indicator of systemic inflammatory response syndrome (SIRS), the relationship between NLR and infection has not been determined. Overt infection was a severe complication in cirrhosis and accounted for increased mortality. Therefore, we aimed to investigate the predictors of HA bacterial infections in cirrhotic patients, and, in particular, whether HA bacterial infections episode was related to NLR.

2. Materials and methods

2.1. Patients

In this retrospective follow-up study, patients with decompensated cirrhosis were recruited from two separated tertiary medical centers (training cohort: the First Affiliated Hospital of Wenzhou Medical University from January 2006 to January 2015; validation cohort: Ningbo First Hospital from January 2010 to January 2015). The study protocol was approved by the ethics committees of the First Affiliated Hospital of Wenzhou Medical University and Ningbo First Hospital. The ethics committees decided that no informed consent was required, because all the data were analyzed anonymously.

2.2. Inclusion and exclusion criteria

All consecutive patients with cirrhosis admitted to our hospitals were included if they fulfilled the following criteria: (i). cirrhosis diagnosis by liver biopsy (fibrosis grade 5 or more) or combination of clinical (presence of hepatocellular jaundice/ascites/hepatic encephalopathy), laboratory [hyperbilirubinaemia (Tbil > 17.1 μmol/l), hypoalbuminemia (albumin < 35 g/l), prolonged prothrombin time (> 15 s) and/or thrombocytopaenia (< 100 × 10^9/l)] or radiological (ultrasound, computed tomography or magnetic resonance imaging) findings. (ii). admission to hospital with decompensated status such as refractory ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome or spontaneous bacterial peritonitis. Patients who met the following criteria were excluded: (i). age younger than 18 years. (ii). patients were diagnosed with bacterial infection and received treatment with any antibiotics on admission. (iii). cirrhosis complicated with systematic inflammatory disease such as systemic lupus erythematosus, hematological disorders. (iv). ongoing corticosteroid, pegylated interferon or immunosuppressive therapy, and (v). concurrence of liver cancer or other malignancies.

Baseline demographic, clinical and laboratory characteristics were retrieved from electronic medical records for each patient in both the training and validation cohorts before treatment commenced. The thickness of spleen and width of portal vein were measured by an experienced sonographer. Overt hepatic encephalopathy was diagnosed according to the West Haven criteria [20]. Upper gastrointestinal hemorrhage was recorded when the patient had recently hematemesis or melena. MELD score was calculated as follows: MELD Score = [9.6 × ln(Serum Creatinine) + 0.38 × ln(Serum bilirubin) + 11.2 × ln(INR) + 0.64 × (etiology: 0 if cholestatic or alcoholic, 1 otherwise)] [21].

2.3. Infection diagnosis

HA bacterial infection was defined as diagnosing of bacterial infection after > 48 h of hospital stay. All participants enrolled needs a systemic detection for HA bacterial infection. Spontaneous bacterial peritonitis (SBP) is a common and frequently bacterial infection of ascites occurring in patients with cirrhosis who have diverse symptomatology [22]. The only way to diagnose an episode of SBP is by examining a sample of ascitic fluid [23] and the diagnosis of SBP is established by a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute polymorphonuclear cell count (≥ 250 cells/mm^3) [24]. Patient with ascites in our hospital would achieve this examination and it is available to exclude the SBP. Of course, SBP is not the only infection in cirrhosis and non-SBP infections represent more than two thirds of infections [25]. Here's some diagnostic criteria of infections [26]: 1) Bronchitis: symptoms include coughing up mucus, wheezing, shortness of breath, and chest discomfort, no radiographic infiltrates and positive sputum culture; 2) Pneumonia: clinical signs of respiratory system and new infiltrates on chest X-ray; 3) urinary infection: abnormal urinary sediment (> 10 leukocytes/field) and positive urinary culture or uncountable leukocytes per field if negative cultures; 4) spontaneous bacteremia: positive blood cultures and no cause; 5) secondary bacteremia: catheter-related infection (positive blood and catheter cultures) or bacteremia occurring within 24 h after an invasive procedure; 6) cellulitis: clinical signs of infection associated with swelling, erythema, heat and tenderness in the skin; 7) cholangitis: cholestasis, compatible symptoms (right upper quadrant pain and/or jaundice) and radiological data of biliary obstruction; 8) secondary peritonitis: polymorphonuclear cell count in ascitic fluid ≥ 250/mm^3 and evidence of an intraabdominal source of infection demonstrated by abdominal CT or surgery; 9) suspected bacterial infection: presence of signs of infection (fever and leukocytosis requiring antibiotic therapy).

2.4. Calculation of NLR

Blood routine test (BRT) was measured by a Sysmex XE-2100 automated hematology analyzer (Sysmex Corporation). NLR was calculated at admission as the ratio of absolute neutrophil count (NC) and absolute lymphocyte count (LC), given by the differential white blood cell count (WBC). The normal range of WBC, NC and LC was 3.5 × 10^9–9.5 × 10^9/l, 1.8 × 10^9–6.3 × 10^9/l and 1.1 × 10^9–3.2 × 10^9/l, respectively.

2.5. Statistical analysis

Continuous variables were expressed by mean ± SD or median (P25, P75), and categorical variables were described as frequency (percentage). Student's *t*-tests or Mann-Whitney *U* tests were used for comparison of continuous data. Categorical data were compared using the Pearson's χ^2 the fisher's exact tests.

A univariate analysis was performed for determining the association between HA bacterial infections and baseline parameters. Variables showing significant differences ($P < 0.05$) were subsequently entered into multivariate analysis to identify independent predictors of HA bacterial infections. Based on the results of multivariate analysis, Model_NTWA and Model_TWA were developed. Receiver-operating characteristic (ROC) curves were then constructed to evaluate the accuracy of Model_NTWA, Model_TWA and 4 independent factors for predicting HA bacterial infections, and the area under the ROC curve (AUROC) was calculated to determine the clinical utility of NLR to distinguish between the infection and non-infection groups. We also plotted decision curves to assess the net benefits of Model_NTWA, Model_TWA and four independent factors assisted decisions [27]. Optimal cut-off values were calculated using a common optimization step that maximized the Youden index. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the IBM SPSS software v.19.0 (IBM Corp) and MedCal v.13.0 software.

3. Results

3.1. Baseline characteristics of included patients

A total of 2639 patients diagnosed with decompensated cirrhosis were initially enrolled in this study. After exclusion of 573 patients who meet the exclusion criteria, 2066 patients (1377 in the training cohort and 689 in validation cohort) were finally included (Supplementary Fig.