Pancreatology xxx (2017) 1–5

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Evaluation of the prognostic value of neutrophil to lymphocyte ratio in patients with hypertriglyceridemia-induced acute pancreatitis

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ARTICLE INFO

Article history:
Received 21 July 2017
Received in revised form
23 September 2017
Accepted 3 October 2017
Available online xxx

Keywords:
Hypertriglyceridemia
Acute pancreatitis
Neutrophil lymphocyte ratio

ABSTRACT

Introduction: Recent studies attribute promising prognostic values to various inflammatory biomarkers in acute pancreatitis, including the following: the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and red cell distribution width (RDW). We aimed to determine the performance of these biomarkers for detecting disease severity in patients with hypertriglyceridemia-induced acute pancreatitis (HTG-AP).

Methods: We retrospectively reviewed 110 patients with HTG-AP and compared the NLR, PLR, and RDW in different severity groups. We performed receiver-operating characteristic (ROC) analysis to identify the optimal cut-off value for NLR to predict severe AP.

Results: NLR was significantly higher in patients with severe AP than mild and moderately severe AP (14.6 vs. 6.9, $p < 0.001$), and higher with organ failure upon presentation (9.1 vs. 7.1, $p = 0.026$). After dichotomization by the optimal cut-off value of 10 as determined by the ROC curve, the high-NLR group had a significantly longer length of stay (9.1 vs. 6.6 days, $p = 0.001$), duration of nil per os (4.9 vs. 3.7 days, $p = 0.007$), and higher rates of complications, including systemic inflammatory response syndrome (81.5% vs. 44.6%, $p = 0.001$) and persistent acute kidney injury (25.9% vs. 3.6%, $p < 0.001$). High NLR independently predicted severe acute pancreatitis in multivariate analysis (Odds ratio 6.71, $p = 0.019$).

Conclusion: NLR represents an inexpensive, readily available test with a promising value to predict disease severity in HTG-AP. Among the three inflammatory biomarkers, NLR has the highest discriminatory capacity for severe HTG-AP, with an optimal cut-off value of 10.

Introduction

Severe hypertriglyceridemia (**HTG**) at a level higher than 1000 mg/dl accounts for up to 4% of all events of acute pancreatitis (**AP**) [1,2]. It is hypothesized that free fatty acid overproduction from triglyceride (**TG**) metabolism leads to a micellar-mediated platelet activation and vascular damage, resulting in local and systemic inflammation [3–5]. In comparison with AP of other etiologies, hypertriglyceridemia-induced AP (**HTG-AP**) has been reported to be associated with higher disease severity and rates of complications, including systemic inflammatory response syndrome (**SIRS**), a hallmark for poor prognosis [6–9].

Recently, various serum markers, including the neutrophil–lymphocyte ratio (**NLR**), platelet–lymphocyte ratio (**PLR**), and red cell distribution width (**RDW**), have been proposed as surrogate markers of inflammation with prognostic value in several entities [10–15]. In AP specifically, cumulative evidence has demonstrated the value of these markers in the prediction of local and systemic complications, disease severity, and short- and long-term mortality rates [14–18]. However, there is a paucity of data regarding their utilities in HTG-AP patients. In the present study, we aim to determine the performance of these biomarkers in detecting disease severity in patients with HTG-AP.

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https://doi.org/10.1016/j.pan.2017.10.001
1424-3903/

Methods and materials

Database setup

We retrospectively reviewed the electronic medical records of patients who were diagnosed with HTG-AP during hospitalization at John H. Stroger Hospital in Cook County, Chicago, IL, from January 1st, 2010 to July 31st, 2016. We identified potential patients using the discharge diagnoses of AP (i.e., ICD 9 code [577.0] and ICD 10 code [K85.9]). We confirmed the diagnosis of AP based on the American College of Gastroenterology guidelines, which require at least two of the following three criteria to be fulfilled: 1) abdominal pain characteristic of AP, 2) serum lipase equal to or higher than three times the upper normal limit, and 3) characteristic findings of AP on computed tomography (**CT**) scan [19]. We included patients who had an admission serum TG level of $\geq$1000 mg/dl on admission [8]. We excluded patients < 18 years of age, those who had gallstones identified by abdominal imaging, and those who had missing data as outlined in the *Variables* section.

The present study was approved by the Institutional Review Board of the Cook County Health & Hospitals System, Chicago. The database was set up and maintained by the Department of Medicine, Cook County Health & Hospitals System [20].

Variables

Demographic variables, including age, gender, medical history, and alcohol, tobacco, and illicit substance use were abstracted. We obtained biochemical data at diagnosis and 48 h after presentation. We calculated NLR based on laboratory results upon initial presentation for each patient. CT results were reviewed to identify local pancreatic compilations. We calculated the Ranson criteria and APACHE II score to assess their correlations with inflammatory biomakers [21,22].

Definition of severity and clinical outcomes

We assessed three organ systems to define organ failure: respiratory, cardiovascular and renal. Organ failure was defined by modified Marshall scoring system as a score of 2 or more [23,24]. Transient organ failure was defined as organ failure that resolved within 48 h [23,24]. Persistent organ failure was defined as organ failure that persisted beyond 48 h. Local pancreatic complications were defined as the development of acute peri-pancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and wall-off necrosis as demonstrated on computed tomography [23,25]. Systemic complications were defined as the exacerbation of pre-existing co-morbidity, such as coronary artery disease, or chronic lung disease.

Mild acute pancreatitis (**MAP**) was defined by the absence of organ failure and the absence of local or systemic complications. Moderately severe acute pancreatitis (**MSAP**) was defined by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure. Severe acute pancreatitis (**SAP**) was defined by the presence of persistent organ failure [26].

Besides the primary end-point of severe acute pancreatitis, we collected length of stay (**LOS**), duration of nil per os (**NPO**), need for medical intensive care unit (**MICU**) admission, and in-hospital mortality as related clinical parameters. We also documented complications of AP, including transient and persistent acute kidney injury (**AKI**; defined as at least 50% elevation of creatinine from baseline), SIRS, and concurrent infections.

Statistical analysis

We performed analyses to describe and summarize the distributions of variables. We use the Student's *t*-test, Wilcoxon rank sum test, or Kruskal–Wallis test to compare continuous nonparametric variables, and the Chi-square test or Fisher's exact test to compare categorical variables. Receiver-operating characteristic (**ROC**) curves were plotted for NLR for SAP prediction, and the optimal cut-off value was determined. We dichotomized according to the optimal cut-off value and compared clinical courses between NLR groups. Finally, we performed univariate and multivariate analysis to assess the independent predictability of NLR for severe acute pancreatitis. All statistical analyses were performed using STATA (Version 14.0, College station, TX). We considered p-values of <0.05 to be statistically significant.

Results

Cohort characteristics

We identified 110 patients with a confirmed diagnosis of HTG-AP (Table 1). Most patients were male (82; 74.6%); the mean age at diagnosis was 39.5 years. There were no significant differences in the prevalence of diabetes, hypertension, hyperlipidemia, metabolic syndrome, or substance abuse between severity groups. Laboratory values at initial presentation revealed that as the severity of AP increased, there was a significant increase in serum lipase, and a significant decrease in lymphocyte counts. There were no consecutive changes in serum triglyceride, serum glucose, neutrophil counts and platelet counts as severity increased.

Comparison of inflammatory biomarkers

NLR was significantly higher among patients with APACHE II scores $\geq$8 (9.3 vs. 7.0, $p = 0.049$) and Ranson criteria scores $\geq$3 (8.9 vs. 5.7, $p < 0.001$). Similarly, we observed higher NLR in patients with organ failure upon presentation (9.1 vs. 7.1, $p = 0.026$) and patients with SAP (14.9 vs. 6.9, $p < 0.001$). PLR was only significantly higher in patients with Ranson criteria scores $\geq$3 (168.2 vs. 135.1 $p = 0.038$). In contrast, the average values of RDW did not show significant differences in any of the above categorizations (Table 2). Therefore, among the three inflammatory biomarkers, NLR correlated most efficiently with AP severity. Interestingly, NLR was not higher with as compared to without local pancreatic complications (8.0 vs. 7.3, $p = 0.448$). This suggested that the differences between the severity groups were mainly driven by persistent organ failure, a demonstration and result of systemic inflammation, rather than local involvement.

Description of clinical course by NLR subcategorization

NLR significantly predicted SAP, as demonstrated in ROC analysis ($p = 0.048$, area under the curve [**AUC**] = 0.891). The optimal cut-off value was determined to be 10, corresponding to a sensitivity of 90%, specificity of 82%, positive likelihood ratio of 5, and negative likelihood ratio of 0.12 (Fig. 1).

After dichotomization, patients with NLR equal to or above 10 had significantly more SIRS upon presentation (81.5% vs. 44.6%, $p = 0.001$), AKI upon presentation (62.9% vs. 38.6%, $p = 0.027$), and persistent AKI (25.9% vs. 3.6%, $p < 0.001$). There was also a higher prevalence of persistent organ failure (22.2% vs 4.8%, $p = 0.011$). Patients with high NLR had longer hospital stays (9.1 vs. 6.6 days, $p = 0.001$) and longer NPO periods (4.9 vs. 3.7 days, $p = 0.007$). There were no differences regarding MICU admission, in-hospital mortality, or re-admission rates for AP between the NLR groups

Please cite this article in press as: Wang Y, et al., Evaluation of the prognostic value of neutrophil to lymphocyte ratio in patients with hypertriglyceridemia-induced acute pancreatitis, Pancreatology (2017), https://doi.org/10.1016/j.pan.2017.10.001