European Journal of Internal Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Original Article

Nonalcoholic fatty liver and the severity of acute pancreatitis

I. Mikolasevic [a,*], L. Orlic [b], G. Poropat [a], I. Jakopcic [c], D. Stimac [a], A. Klanac [c], F. Carovic [c], S. Milic [a]

[a] Department of Gastroenterology, UHC Rijeka, Croatia
[b] Department of Nephrology, Dialysis and Kidney Transplantation, UHC Rijeka, Croatia
[c] School of Medicine, Rijeka, Croatia

ARTICLE INFO

Article history:
Received 15 July 2016
Received in revised form 24 October 2016
Accepted 25 October 2016
Available online xxxx

Keywords:
Nonalcoholic fatty liver
Acute pancreatitis
Severity
Prognosis

ABSTRACT

Aim: To explore the effect of nonalcoholic fatty liver as a hepatic manifestation of metabolic syndrome on the severity of acute pancreatitis. We hypothesized that patients with nonalcoholic fatty liver would have a more severe form of acute pancreatitis.
Patients and methods: We retrospectively analyzed 822 patients hospitalized with acute pancreatitis. We diagnosed acute pancreatitis and determined its severity according the revised Atlanta classification criteria from 2012. We assessed nonalcoholic fatty liver with computed tomography.
Results: There were 198 (24.1%) patients out of 822 analyzed who had nonalcoholic fatty liver. Patients with nonalcoholic fatty liver had statistically higher incidence of moderately severe (35.4% vs. 14.6%; $p = 0.02$) and severe acute pancreatitis (20.7% vs. 9.6%; $p < 0.001$) compared to patients without nonalcoholic fatty liver. At the admission patients with nonalcoholic fatty liver had higher values of C-reactive protein as well as at day three, higher APACHE II score at admission and significantly higher incidence of organ failure and local complications as well as higher values of computed tomography severity index compared to patients without nonalcoholic fatty liver. We found independent association between the occurrence of moderately severe and severe acute pancreatitis and nonalcoholic fatty liver (OR 2.13, 95%CI 1.236–3.689). Compared to patients without nonalcoholic fatty liver, patients with nonalcoholic fatty liver had a higher death rate, however not statistically significant (5.6% vs. 4.3%; p = NS).
Conclusion: Presence of nonalcoholic fatty liver at admission can indicate a higher risk for developing more severe forms of acute pancreatitis and could be used as an additional prognostic tool.

1. Introduction

Around 15 to 25% of all patients with acute pancreatitis progresses to severe form of acute pancreatitis. Consequently, the death rate is much higher in this subgroup of patients. The possibility to predict the severity of this disease could help identify patients with increased risk of morbidity and mortality and assist in appropriate early triage to intensive care units and selection of patients for specific interventions. Therefore, research with intention to detect and develop not only a more accurate diagnostic, but prognostic tool as well, is increasing worldwide [1]. Use of a clinical scoring systems and specific laboratory tests are the two most common approaches in determining prognosis in acute pancreatitis. The majority of research to evaluate methods for prediction of acute pancreatitis severity is focused on death as the outcome of interest as ~~a~~ well-defined relevant outcome. Patients with severe acute pancreatitis often need intensive care treatment, therefore early evaluation and risk stratification for patients with acute pancreatitis is important to differentiate patients with mild versus severe disease. Also, predictions of outcome should be applied accurately and reliably, preferably within the first 24 h of admission to hospital. The Acute Physiology and Chronic Health Evaluation scale (APACHE II) ~~scale~~, Bedside Index of Severity in Acute Pancreatitis (BISAP), Ranson's criteria, the Imrie scoring system and the Computed Tomography (CT) Severity Index are systems for classifying severity of acute pancreatitis. Even though serum lipase and amylase levels remain the most common used laboratory test for diagnosing acute pancreatitis, other biomarkers and inflammatory mediators have been investigated as potential biomarkers to help predict the outcome of acute pancreatitis. The most studied, and widely available as well, is the C-reactive protein. Other markers of systemic inflammation that were studied were interleukins 6 and 8 and some others [1,2,3,4,5,6,7]. In the revised Atlanta classification system measures of severity of acute pancreatitis were revised [8].

Incidence of nonalcoholic fatty liver disease is increasing together with higher incidence of obesity and metabolic syndrome. Nonalcoholic fatty liver disease as the most common chronic liver disease today is closely related to metabolic syndrome and its individual components: diabetes mellitus type 2, arterial hypertension, obesity and dyslipidemia [9]. Recently, we have conducted a study in which we have explored the influence of metabolic syndrome on acute pancreatitis course. We discovered that the existence of metabolic syndrome at admission indicates on higher risk for moderately severe and severe acute pancreatitis,

* Corresponding author.
E-mail address: ivana.mikolasevic@gmail.com (I. Mikolasevic).

http://dx.doi.org/10.1016/j.ejim.2016.10.019
0953-6205/

Please cite this article as: Mikolasevic I, et al, Nonalcoholic fatty liver and the severity of acute pancreatitis, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.10.019

as well as for the higher death rate [10]. According to the literature, there are very few studies about the relationship between fatty liver (FL) and severity and clinical outcomes in AP [11].

Thus, we aimed to explore the effect of nonalcoholic fatty liver (NAFL) as a hepatic manifestation of metabolic syndrome on the severity of acute pancreatitis. Our hypothesis was that patients with nonalcoholic fatty liver would have a more severe form of disease.

2. Patients and methods

We analyzed 1070 patients with acute pancreatitis admitted to our hospital between January 1st, 2008 and June 30th, 2015. We defined acute pancreatitis as an occurrence of typical upper abdominal pain (nausea or vomiting) within the first 48 h prior to admission and elevation of serum lipase or amylase levels at least 3 times the upper limit of normal. We excluded patients with a relapse of acute pancreatitis or with an exacerbation of chronic pancreatitis, patients with incomplete medical data, patients with active malignancy, those who were younger than 18 years and those who were receiving medications that can cause liver steatosis (corticosteroids, amiodarone, etc.). Patients with other causes of chronic liver disease were not a part of this analysis. All patients had a CT scan performed on the fifth day of hospitalization in order to confirm diagnosis and evaluate local complications. CT severity index (CTSI) was calculated for all patients. Out of 1070 initially analyzed patients we excluded 215 patients' cause of alcoholic etiology of acute pancreatitis and 8 due to missing data. From the rest of 847 patients, 6 were excluded because of uncertain etiology of acute pancreatitis and 19 because of other exclusion criteria (taking the medications that can lead to liver steatosis). In the end, we had 822 patients that we included in final analysis, Fig. 1.

We extracted history, demographic and laboratory data from medical record. Details such as gender, age, weight, height, waist circumference, and previous alcohol consumption were acquired. Respectively, consummation of more than 14 alcohol drinks/week in women and more than 21 alcohol drinks/week in men was considered as excessive alcohol consumption. Relevant conditions assessed from medical records included arterial hypertension (AH), obesity, type 2 diabetes mellitus, dyslipidemia, coronary artery disease, and chronic kidney disease. Obesity was defined according to the World Health Organization (WHO) Western Pacific Region as a BMI > 25 kg/m^2 [12]. Use of all medications was noted at admission as well. Initial laboratory tests taken at admission included full and differential blood count, arterial blood gasses and biochemistry.

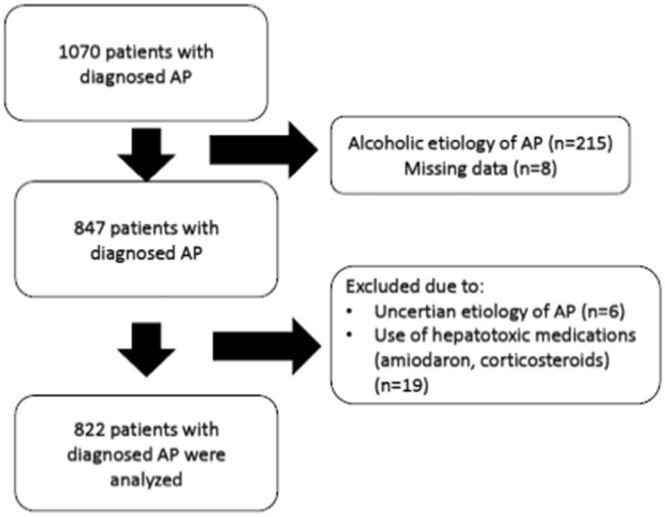

Fig. 1. Flow-chart of included and excluded patients.

According to its severity, defined by the revised Atlanta classification from 2012, acute pancreatitis was divided into three groups. Mild acute pancreatitis defined by absence of organ failure, local or systemic complications; moderate acute pancreatitis characterized by the existence of transient organ failure (lasting continuously less than 48 h), exacerbation of concomitant diseases and/or development of local complications; and severe acute pancreatitis (SAP) defined by presence of persistent organ failure (lasting continuously for more than 48 h) affecting respiration, renal function or the cardiovascular system. Local complications included peripancreatic fluid collections, pseudocysts, pancreatic and peripancreatic necrosis (sterile or infected), and walled-off necrosis (sterile or infected). Walled-off necrosis was not separately analyzed due to small number of patients with this complication [8,13,14]. We initially assessed acute pancreatitis severity by calculating the APACHE II score. We calculated the correlation of nonalcoholic fatty liver presence with severity of acute pancreatitis using a score of 8 or more as a cut-off value for severe acute pancreatitis.

Nonalcoholic fatty liver was diagnosed according to the presence of all following criteria: (A) steatosis detected by imaging (CT scan or abdominal ultrasound). Fatty liver was diagnosed if liver density showed attenuation of 10 HU compared to the spleen, or if liver density was less than 40 HU; (B) absence of alcoholic liver disease; (C) absence of medications and diseases that can cause liver steatosis; and (D) absence of other causes of chronic liver disease [15,16].

The primary endpoint is to evaluate the association between nonalcoholic fatty liver and severity of acute pancreatitis.

Secondary endpoints:

- association between the presence of nonalcoholic fatty liver and acute pancreatitis severity according to the APACHE II and CTSI scores.
- association between the presence of nonalcoholic fatty liver and acute pancreatitis severity according to the levels of C-reactive protein measured at admission and on the third day of hospital stay.
- number of local (peripancreatic fluid collections, pseudocysts, pancreatic and peripancreatic necrosis) complications of acute pancreatitis in accordance with presence of nonalcoholic fatty liver.
- incidence of organ failure in acute pancreatitis patients in accordance with presence of nonalcoholic fatty liver.
- length of hospital stay in high dependency unit, intensive care unit (ICU) and total length of hospital stay in acute pancreatitis patients with nonalcoholic fatty liver compared to patients without nonalcoholic fatty liver.
- association of nonalcoholic fatty liver presence and acute pancreatitis severity independently from other components of metabolic syndrome (obesity, arterial hypertension, type 2 diabetes mellitus and dyslipidemia).
- compare the survival rate between acute pancreatitis patients with and without nonalcoholic fatty liver.

We used descriptive statistics (mean and SD) to analyze statistical data and $\chi 2$ test or Fisher's exact test to test the differences between categorical variables. The importance of the difference between two independent groups was tested by using Student's t-test or ANOVA, where appropriate. We used the logistic regression analysis to analyze multivariable regression (the results were presented as odds ratio [OR] and 95% confidence intervals [CI]). As statistically significant we considered P value <0.05. For statistical analysis we used MedCalc statistical software package, version 10 (MedCalc,Mariakerke, Belgium) and IBM SPSS v22.

3. Results

Out of 822 analyzed patients with acute pancreatitis 198 of them (24.1%) had nonalcoholic fatty liver. Demographic and clinical characteristics of analyzed patients are shown in Table 1. The mean age of our

Please cite this article as: Mikolasevic I, et al, Nonalcoholic fatty liver and the severity of acute pancreatitis, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2016.10.019