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The systemic inflammatory response syndrome in cirrhotic patients: Relationship with their in-hospital outcome☆

Massimo Cazzaniga*, Elena Dionigi, Giulia Gobbo, Alessia Fioretti, Valentina Monti, Francesco Salerno

University of Milan, Department of Internal Medicine, IRCCS Policlinico San Donato, Via Morandi 30, 20097 San Donato Milanese, Milan, Italy

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***Background/Aims*: Some evidence suggests that the systemic inflammatory response syndrome (SIRS) contributes to the poor outcome of cirrhotic patients. We studied 141 cirrhotic patients consecutively admitted to a tertiary referral centre assessing prevalence of SIRS and its relationship with in-hospital outcome.**

***Methods*: Presence of SIRS was assessed on admission and during hospital stay. Main clinical outcomes were death and development of portal hypertension-related complications.**

***Results*: Thirty-nine patients met SIRS criteria. SIRS was present on admission in 20 of 141 patients (14.1%), whereas it occurred during hospital stay in 19 of 121 (15.7%). SIRS was correlated with bacterial infection at admission ($p = 0.02$), jaundice ($p = 0.011$), high serum creatinine levels ($p = 0.04$), high serum bilirubin levels ($p = 0.002$), high international normalized ratio ($p = 0.046$), high model of end-stage liver disease (MELD) score ($p = 0.001$), and high SOFA score ($p = 0.003$). During a follow-up of 14 ± 8 days, 16 patients died (11%), 7 developed portal hypertension-related bleeding (5%), 16 hepatic encephalopathy (11%), and 5 hepatorenal syndrome type-1 (3.5%). SIRS was correlated both to death ($p < 0.001$) and to portal hypertension-related complications ($p < 0.001$). On multivariate analysis, SIRS and MELD were independently associated with death.**

***Conclusions*: SIRS frequently occurs in patients with advanced cirrhosis and is associated with a poor outcome.**

***Keywords*: Cirrhosis; Infection; Portal hypertension; Systemic inflammatory response syndrome; Survival**

1. Introduction

There is growing evidence that systemic inflammation is quite frequent in patients with advanced cirrhosis and portal hypertension, and might be associated with a negative outcome [1]. Systemic inflammation can be caused by overt or occult bacterial infection and can affect clotting function [2,3]. In cirrhotic patients inflammation has been shown to favor serious complications such as variceal bleeding, encephalopathy and acute-on-chronic liver failure [4]. Accordingly, Thabut et al. [1] showed that inflammation increases the risk of complications and death in cirrhotic patients with acute renal damage.

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* Corresponding author. Tel./fax: +39 02 52774462.

E-mail address: massimo.cazzaniga@unimi.it (M. Cazzaniga).

Abbreviations: SIRS, systemic inflammatory response syndrome; HCC, hepatocellular carcinoma; SBP, spontaneous bacterial peritonitis; WBC, white blood cell; PMNCs, polymorphonuclear neutrophil cells; MELD, model of end-stage liver disease; HRS, hepatorenal syndrome; PRCs, packed red cells; ICU, intensive care unit; INR, international normalized ratio; TNF, tumor necrosis factor; PPV, positive predictive value; NPV, negative predicting value; LR, likelihood ratio.

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Excluding hepatocellular carcinoma (HCC), the in-hospital outcome of patients with advanced cirrhosis is mainly driven by liver and/or renal dysfunction [5,6]. In this setting the role of systemic inflammation has been poorly investigated, even if inflammation can affect both renal and hepatic function.

The aim of this prospective study was to determine (i) the prevalence of systemic inflammation in a cohort of cirrhotic patients consecutively admitted to a tertiary referral centre, (ii) its relationship with liver and kidney function, and (iii) its relationship with the in-hospital outcome. The main endpoints were death and development of portal hypertension-related complications.

2. Patients and methods

2.1. Patients

Cirrhotic patients consecutively admitted to our ward from February to September 2004 were enrolled in this study. Inclusion criteria were diagnosis of cirrhosis based on liver biopsy or on obvious clinical, biochemical and imaging features. Exclusion criteria were age <18 years; ongoing cardiac failure (NYHA classes II–IV); organic kidney disease; treatment for chronic obstructive pulmonary disease; diagnosis of HCC or of extrahepatic malignancy; human immunodeficiency virus-positivity; use of nephrotoxic (e.g.: aminoglycosides) or hepatotoxic drugs; refusal of the patient to participate.

2.2. Definition of systemic inflammation.

The systemic inflammation response syndrome (SIRS) was assessed according to the recommendations of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [7]. Patients were considered to have SIRS if they fulfilled at least 2 of the following criteria: (a) a core temperature of >38 °C (100.4 °F) or <36 °C (96.8 °F); (b) a heart rate of ⩾90 beats/minute; (c) a respiratory rate of ⩾20 breaths/minute; or (d) a white blood cell (WBC) count of ⩾12,000/mm^3 or ⩽4000/mm^3, or a differential count showing ⩾10% immature polymorphonuclear neutrophil cells (PMNC).

2.3. Diagnosis of infection

Patients were considered to have a bacterial infection when one or more of the following events were recognized: (a) positive blood cultures in the absence of any recognized source of infection (spontaneous bacteremia); (b) ascitic fluid PMNC >250/mm^3 (spontaneous bacterial peritonitis, SBP) [8]; (c) pleural effusion with a fluid PMNC count >250/mm^3 (empyema); (d) urinary WBC count >15 cells per high-power field and positive urine culture (urinary tract infection) [9]; (e) radiographic evidence of pulmonary infiltration associated with purulent sputum (pneumonia); (f) fever and cellulites associated with leukocytosis (skin infection). Other infections (e.g. cholangitis, diverticulitis) were diagnosed according to clinical, radiological, and bacteriologic data. Furthermore, patients who showed fever (>37.5 °C), leukocytosis (WBC count > 10,000/mm^3), negative cultures, and no evidence of organ involvement were considered to have undetermined infection [10].

We distinguished community-acquired infections (recognized before admission or within the first 48 h) and hospital-acquired infections (recognized after the first 48 h of admission).

Patients with SIRS and infection were considered to have sepsis.

2.4. Patient evaluation and management

Medical history was recorded upon admission by one of the authors (ED). Clinical events (infection, bleeding, ascites, encephalopathy) and treatments on admission were carefully evaluated. Any use of nephrotoxic or hepatotoxic drugs was investigated. Within the first 24 h after admission patients underwent physical examination, laboratory tests (blood and urine), and abdominal ultrasound scanning. During hospitalization, cultures of blood, urine, ascites, sputum or swab were performed when an infection was suspected. Triplicate blood cultures were performed at intervals of 30 min. Samples of ascitic or pleuric fluid for culture were collected at the patients' bed (10 ml in blood culture bottles for aerobic and anaerobic bacteria). Severity of liver disease was assessed according to Child–Pugh classes [11] and to the Model of End-stage Liver Disease (MELD) [12].

Patients were followed up by residents and a consultant expert in hepatology. Physical examination, blood cell count and urinary sediment evaluation were performed daily. The presence and number of SIRS criteria were accurately assessed both on admission and during hospitalization. Any significant cirrhosis-related event was recorded, in particular encephalopathy, bleeding from gastroesophageal varices or from hypertensive gastropathy (portal hypertension-related bleeding), and acute renal failure. Overt hepatic encephalopathy was diagnosed when there was an increase in stage according to the West Haven criteria [13]. Portal hypertension-related bleeding was defined according to international criteria [14]. Hepatorenal syndrome (HRS) was diagnosed according to the International Ascites Club criteria [15].

Patients with encephalopathy were treated with lactulose enema, neomycin, dietary regimen or infusion of branched chain aminoacid-enriched solutions. Patients with hematemesis and/or melena were urgently submitted to endoscopy and, in case of variceal bleeding, treated with band ligation, large-spectrum antibiotic, packed red cells (PRCs) and terlipressin or somatostatin according to Baveno IV recommendations [14]. If patients showed hemodynamic instability they were treated with crystalloids and inotropic agents to raise mean blood pressure to ⩾70 mm Hg and with PRCs to obtain hemoglobin levels higher than 9 g/dl. Patients with suspected infection were treated with empiric large-spectrum antibiotics (cefotaxime, ceftriaxone or ciprofloxacin) started as early as the diagnosis of infection was made. The antibiotic treatment was then modified according to the results of cultures and to the clinical response. Patients with community-acquired pneumonia received ceftriaxone and azithromicin whereas patients with hospital-acquired pneumonia received teicoplanin, levofloxacin or imipenem. Patients with urinary tract infection received a quinolone agent and patients with SBP received cefotaxime. Prophylactic albumin was given to patients with SBP and bilirubin > 4 mg/dl to prevent renal failure. Biliary infections were treated with piperacillin-tazobactam or third-generation caphalosporins; cellulites were treated with amoxicillin and clavulanic acid. Duration of antibiotic therapy was individually established according to the clinical response, negativity of cultures and correction of inflammatory symptoms.

In patients with functional renal failure diuretics were withdrawn and saline and albumin solution were given. When a HRS type-1 was diagnosed, terlipressin combined with albumin infusion was given according to the International Ascites Club recommendations [16].

When patients showed respiratory failure they were transferred to the intensive care unit (ICU) to be monitored and adequately supported with non-invasive or mechanical ventilation. Patients listed for liver transplantation who developed acute on chronic liver failure (encephalopathy, renal failure and severe hyperbilirubinemia), and patients who developed septic shock and/or multiorgan failure, were treated with inotropes and transferred to the ICU where organ replacement therapy, conventional dialysis or extracorporeal albumin dialysis, could be performed.

The study was approved by the local institutional review board and complied with the Declaration of Helsinki. Each patient gave an informed consensus to participate in this study. Individual data were treated in compliance with Italian legislation regarding protection of personal data.

2.5. Statistical analysis

The data are reported as means ± standard error of means or frequencies. χ^2 or Mann–Whitney U tests were used to compare patients with and without SIRS. Univariate analysis was performed to correlate variables, including SIRS, with the in-hospital survival, as well as with