

Non-Alcoholic Fatty Liver Disease and Sepsis

Nealkoholna masna bolest jetre i sepsa

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Sepsis and non-alcoholic fatty liver disease (NAFLD) are both inflammation-related entities and major disease burdens with high impact on modern healthcare systems. Sepsis is a heterogeneous syndrome, with an outcome dependent on the culprit pathogen, infection site and host factors (e.g. comorbidities, genetic factors, immunosuppression, including the degree and types of the host immune response). Only recently has the role of liver in sepsis begun to be revealed. Evidence has shown that liver dysfunction in sepsis in patients without pre-existing liver disease is an independent predictor of mortality (54-68%), higher than the mortality rates of sepsis complicated with respiratory or kidney failure^[1]. On the other hand, chronic liver disease is a risk factor for the progression of infection to sepsis. The patients with liver cirrhosis are exposed to an increased risk of developing bacterial infections, have ten times more common bloodstream infections with a fourfold increase in mortality in comparison to patients without cirrhosis. Progression to septic shock in these patients is associated with an in-hospital mortality rate as high as 70%^[2]. These clinical findings highlight the critical role of liver as an immunomodulatory organ in sepsis.

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease^[3, 4]. Although the pathogenesis of NAFLD is linked with systemic changes in immune response, the question remains whether patients with NAFLD are more prone to bacterial infections and what is the impact of

persistent local inflammation to the systemic response to infection, sepsis course and outcome.

There are only several clinical studies that examined the role of NAFLD in infectious diseases: (1) it was shown that the post-transplant risk for infection is significantly higher in patients transplanted due to non-alcoholic steatohepatitis (NASH) when compared to other transplant indications^[5]; (2) in patients suffering from advanced liver disease, the presence of steatosis measured by the controlled attenuation parameter (CAP) ≥ 220 dB/m is associated with an increased risk of decompensation and bacterial infection^[6]; (3) NAFLD was associated with an increase in all-cause mortality in patients with community acquired pneumonia even in the absence of advanced fibrosis^[7]; (4) bacteraemia of gastrointestinal origin was more common in patients with NAFLD^[8]. More recently, NAFLD was identified as a risk factor for *Clostridioides difficile* infection^[9].

In this issue of the Croatian Journal of Infection, *Gjurašin et al.*^[10] have shown that invasive Group B Streptococcus (GBS) disease in patients with NAFLD is associated with higher mortality than in patients without NAFLD. Moreover, this appears to be independent of other components of metabolic syndrome, such as obesity and diabetes mellitus. Furthermore, the authors have found that nosocomial infections and acute renal failure are more common in the NAFLD group. This highlights the need for further prospective studies to evaluate the association of NAFLD with the outcomes of bacterial infections.

The study is a part of the ongoing Installation Research Project „The role of immune semaphorins in NAFLD and sepsis“, SepsisFAT, financed by the Croatian Science Foundation^[11]. The researchers plan to conduct the first comprehensive interdisciplinary clinical, microbiological, immunological and biomarker study of the impact of NAFLD on sepsis.

The impact of NAFLD on severe bacterial infections, sepsis and pneumonia has not been established so far. Although there is an abundance of data on the gut-liver axis and changes in gut microbiome shown to be associated with NAFLD and progression to NASH, there are no data on the incidence, clinical course and outcome of gastrointestinal infections in this population, specifically the risk for *Clostridioides difficile* infection. In addition, there is a question if NAFLD gut microbiome profile contributes to the colonization with MDR bacteria. Therefore, significant gaps in our understanding of the role of NAFLD in infectious diseases exist, and „SepsisFAT” might provide the insight into these clinical questions. Importantly, the profile of pro-inflammatory and anti-inflammatory mediators in the presence of NAFLD to bacterial infections will be described. There are critical gaps in our knowledge of biomarkers of sepsis severity, treatment response and prognosis in this group. This integrated approach could identify new diagnostic and prognostic biomarkers and new targets for prevention and more promising treatment options.

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