

TITLE: PROGNOSTIC SIGNIFICANCE OF LIVER INJURY IN SARS-CoV-2 PATIENTS

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SARS-CoV-2 infection represents a public health issue that has caught global interest since the beginning of 2020. As a result of the research performed in the specialty literature, an unpredictable character of COVID-19 has been established. The character led to an absence until present times of a therapeutic protocol guide of surpassing the infection. SARS-CoV-2 associated liver injury presents a prognostic significance, most of the time in COVID-19 patients with increased severity of the disease or the presence of preexisting liver disease.

The choice of studying the prognostic significance of liver injury in SARS-CoV-2 patients is fully sustained because it represents a current novelty theme by referring to a newly diagnosed disease at the beginning of 2020, and also due to the possibility of guiding the management of liver injury associated with this disease. In Romania, the innovation of the study is the multidisciplinary assessment of SARS-CoV-2 patients, including Gastroenterology, Infectious Disease, and Intensive Care Unit physicians, and the presentation of the experience in two COVID-19 support hospitals which were designated at the beginning of the Emergency State in Romania.

In the general part, we presented the current state of knowledge regarding epidemiology, physiopathology, diagnostic tools and stabilization of the disease, possible complications, general and therapeutic resources in COVID-19. It was based on 119 references.

The personal contribution included four studies that allowed obtaining the proposed objectives.

In the first study, we followed up retrospectively 1207 patients with COVID-19 admitted in two COVID-19 support hospitals – Mures County Clinical Hospital and Colentina Clinical Hospital. We followed up clinical and paraclinical data, previously administered medication, and medication administered during hospitalization. We tried to identify predictive markers for a poor outcome. In the retrospective analysis, we included 134 COVID-19 patients who presented liver function tests abnormalities above the upper limit of normal. Most of the patients presented with mild elevation of liver function tests, with a predominant cholestatic pattern. The patients who received lopinavir/ritonavir present a high risk of developing ALT elevation ($p > 0.0001$). Sixteen patients included in the study presented with preexisting liver disease and developed severe forms of COVID-19. We concluded that preexisting liver disease is a risk factor for a negative outcome, but the

severity of COVID-19 was the only predictor of death. In the same study, we included histopathological correlations by including the results of autopsies performed in 2 patients with signs of liver injury without a preexisting liver disease in which death was noted in the first four days from admission. The microscopic assessment showed micro and macrovacuolar hepatic steatosis and minimal portal activity.

The second study underlines the necessity of a multidisciplinary team in the management of COVID-19 patients and the significance of establishing a therapeutic plan in the management of SARS-CoV-2 associated liver injury. We performed a retrospective analysis of 146 patients admitted in Mures County Clinical Hospital in the following departments: Gastroenterology, Infectious Disease, and Intensive Care Unit. The patients presented abnormal liver function tests in the first seven days from admission, and patients with preexisting liver disease were excluded. Almost 70% of patients developed mild liver injury, and the median duration of abnormality of liver function tests was five days. The median duration of hospitalization was approximately 16 days (16.21 ± 7.43) and was not statistically significant longer in patients with severe liver injury. The study highlights the importance of standardized definitions and practical guidelines for consultant Hepatologists (Gastroenterologists) to clarify differential diagnosis and applying a unitary measure of care.

The objective of the third study was to establish the impact of liver injury as an additional prognostic factor in COVID-19 patients admitted to the Intensive Care Unit. We performed a retrospective study of 156 patients admitted to the Intensive Care Unit. We excluded patients with a history of preexisting liver disease. We divided the patients into two groups (Group 1 – mild/moderate liver injury and Group 2 – severe liver injury). We noted statistically significant differences between the two groups in the duration of hospitalization, the null hypothesis being partially upheld ($p=0.009$). None of the patients presented with normal liver function tests at discharge, regardless of the severity of the liver injury. Our study highlighted the mandatory follow-up of COVID-19 patients who presented abnormality of liver function tests and the necessity of proper management in critical COVID-19 patients who associate liver injury.

The primary objective in the fourth study was the assessment of the impact of liver injury, as a supplementary long-term prognostic factor in COVID-19 patients. We followed up patients at 6 months prior to the SARS-COV-2 infection diagnosis. We performed a prospective study of 154 patients admitted in Mures County Clinical Hospital, Gastroenterology Department with SARS-COV-2 infection confirmed by RT-PCR and associated liver injury and we excluded patients with pre-existing liver disease. Patients were divided into two groups: Group 1 - patient who presented at index hospitalisation (T0) a non-severe form of COVID-19 and Group 2 - patients with a severe form of COVID-19. We performed paraclinical examinations, clinical examination and imagistic assessments with abdominal ultrasonography and computed tomography of the abdomen and pelvis, with or without oral or intravenous contrast solution. We obtained statistically significant

differences regarding serum levels of ALT ($p=0.03$), total bilirubin ($p<0.001$) and inflammatory markers (ferritin levels, $p=0.001$), results which were similar to index hospitalisation. Our study underlined the significance of liver enzymes monitoring in COVID-19 patients, and the importance of etiological complete diagnosis with the need for implementing an individualised therapeutic management in the long-term follow-up of post-SARS-CoV-2 infection patients.