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Opinions

Ruptured hepatocellular carcinoma and non-alcoholic fatty liver disease, a potentially life-threatening complication in a population at increased risk

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The prevalence of overweight and obesity is a global health concern. [1] Obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia are essential components of the metabolic syndrome (MS). [2] The prevalence of obesity is directly related to the increased incidence of non-alcoholic fatty liver disease (NAFLD), the liver component of MS, and which represents the leading cause of liver disease in industrialized countries. [3] Increased body weight and obesity have been associated with the development of cancer at different organs, and MS is considered an independent risk factor for the development of hepatocellular carcinoma (HCC). [3,4] Recently, Saitta et al. [5] highlighted the impact of NAFLD and its association with HCC. Non-alcoholic steatohepatitis (NASH) may be present in up to 20% of NAFLD patients, and is defined as the coexisting hepatic fat accumulation and necroinflammatory changes. Between 26% and 37% of patients with NASH will progress to fibrosis, and up to 9% will develop cirrhosis, which are recognized risk factors for HCC. [6]

HCC is the most common primary liver malignancy, representing the fifth most frequent cancer in the world, the third leading cause of cancer-related mortality in global population and the second leading cause in men. [5,7] Approximately 80% of HCC cases originate in the setting of liver cirrhosis, which is mainly caused by chronic hepatitis B virus and hepatitis C virus infections, heavily alcohol intake and NASH. [5] Nevertheless, regional variations of these entities and a genetic susceptibility for NAFLD/NASH progression have been described. [8] More advanced forms of liver disease and higher rates of HCC have been observed in Latino patients. [9]

HCC is a hypervascular tumor with a high growth and vascular invasion potential. Causes of death are tumor progression, liver failure, and spontaneous rupture with intraperitoneal hemorrhage. Spontaneous rupture of HCC is a potentially life-threatening complication, with geographic incidences between 2.3% and 26%. The mortality rate in the acute phase is reported in 25-75%. [10,11] To date, there are no defined guidelines for ruptured HCC management.

The mechanisms of spontaneous rupture of HCC are not completely understood. HCC is highly capable of vascular invasion and angiogenesis. [11] Tumor dimension, localization, subcapsular position, increased intratumoral pressure, vascular congestion,

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; TAE, transcatheter arterial embolization; TACE, transcatheter arterial chemoembolization.

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hypertension, liver cirrhosis, portal vein thrombosis and extrahepatic growth are risk factors for HCC spontaneous rupture. [12]

In a recent review, the mean age of spontaneous rupture of HCC was 55.6 years (± 6.64) with male predominance (77.9%). [13] An initially epigastric and further generalized abdominal pain, hemodynamic instability and peritoneal irritation constitute the most common clinical presentation. A sudden onset of abdominal pain and shock has been reported in 66-100% and 33-90% of patients, respectively. Peritoneal irritation due to bleeding may not be evident when the HCC is in a more central localization. Liver failure in the acute phase has been reported in 12-42% of cases. [11,12]

Diagnosis may be difficult particularly in hemodinamically unstable patients with no previous history of liver disease. A high suspicion index based on clinical findings and hemoglobin level at presentation are required.

On ultrasound, a hyperechoic area may be observed around the ruptured tumor in 66% of patients. Computed tomography can be diagnostic in 75-100% of patients. On triple-phase computed tomography, the modality of choice, a ruptured HCC is suggested by a peripherally located liver tumor with a contour bulge, discontinuity of the liver capsule, hemoperitoneum, subcapsular hematoma, extravasation of contrast material, and “enucleation sign”, which is a non-enhancing low-attenuating lesion with a peripheral rim enhancement. A peripherically located large tumor, a small localized or intraperitoneal collection and a “pseudo retraction sign” at the liver capsule underneath the fluid collection have 100% sensitivity for a confined HCC rupture. Hepatic artery angiography finding of active extravasation of contrast from the tumor may be observed in 13.2-35.7% of cases. [12] In hemodynamic unstable patients diagnosis may be confirmed until emergency surgical exploration.

Initial management of ruptured HCC requires hemodynamic stabilization, blood transfusion and coagulopathy correction. Hemostasis is the priority over tumor treatment and should be individualized according to the hemodynamic state, liver functional status, HCC characteristics and stage. [10–12] Conservative management is rarely used alone in hemodinamically stable patients, as outcomes are poor with a re-bleeding rate of 65.6% and mortality rates of 85-100%. A definitive treatment should be offered, such as transcatheter arterial embolization (TAE) / transcatheter arterial chemoembolization (TACE) or surgery. Conservative management should be considered for patients with poor prognosis, poor liver function or advanced stage. [12,13]

Direct hemostatic measures are indicated for patients who remain hemodynamically unstable or show signs of active bleeding. Success rate with TAE alone or in combination with TACE has been reported in 53-100% and in-hospital mortality rates of 0-55.5%, due to recurrent bleeding and liver failure. (10) A recent review reported in-hospital and 1-month survival ranges from 30.3% to 66.7% and from 44.4% and 87.5%, respectively. [13]

Emergency surgical procedures are indicated when bleeding persists or when TAE is not feasible. Perihepatic packing, Pringle maneuver or hepatic artery clamping are temporary measures. [10,13] Emergency hepatic resection can be particularly demanding in hemodinamically unstable or advanced cirrhotic patients, with mortality rates in the range between 16.5% and 100%. [10] Recently, in patients who underwent hepatic resection (either emergent or staged) in-hospital and 1-month survival rates at 94% and 95.5%, respectively, have been reported. [13] A recent multicenter study showed that staged partial hepatectomy offers significantly higher overall survival. [14] Although there are no randomized trials to determine the best treatment option for ruptured HCC, TAE / TACE or surgery seem to be the best options. [12,13] The most appropriate treatment should be selected on individual basis.

Surveillance is recommended for all patients with liver cirrhosis, with an ultrasound being performed every six months. [5,7,15] NAFLD represents the largest proportion among new HCC patients without advanced fibrosis or cirrhosis in the United States, but surveillance in non-cirrhotic patients is yet to be determined. [15] Detection of HCC at an early stage allows timely treatment and the rate of spontaneous rupture of HCC rate may lower.

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