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Review

RISK STRATIFICATION IN CIRRHOTIC PATIENTS UNDERGOING NONHEPATIC SURGERY – LITERATURE REVIEW

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ABSTRACT

Liver cirrhosis is a socially significant chronic disease affecting people of working age that leads to severe, life-threatening complications in the absence of adequate treatment. In the course of the disease, numerous pathophysiological changes develop in the body of the affected patients, leading to permanent reorganization of the functional activity of the cardiovascular, respiratory, excretory systems, as well as deviations in the coagulation and immunological status of patients. The above-listed dysfunctions lead to increased mortality rates and development of complications in the perioperative period in these patients, which makes them unsuitable candidates for surgical treatment. Risk stratification in this patient population and careful selection of suitable surgical candidates require a detailed assessment of the clinical condition of patients and its optimization in order to reduce the initially increased levels of morbidity and mortality. The existing scoring systems that are used with the highest frequency in clinical practice – Child – Pugh – Turcotte and MELD, show similar levels of predictive value in terms of surgical risk. The latter can be adequately defined when they are used simultaneously and implemented in daily clinical practice in patients undergoing emergency or elective non-hepatic surgery.

Key words: Child – Pugh – Turcotte, liver dysfunction, MELD, cirrhosis

The incidence of liver cirrhosis is increasing due to the epidemic spread of hepatitis C virus infection and the widespread prevalence of nonalcoholic fatty liver disease associated with metabolic syndrome, as well as alcohol abuse in the affected population. Chronic liver damage is characterized by chronic loss of hepatocytes, leading to the development of inflammatory changes, fibrosis and cirrhosis, characterized by changes in liver architectonics, increased resistance to portal venous flow with subsequent development of portal hypertension (PH), formation of collateral portosystemic venous shunts, varices and accumulation of ascites fluid. As these processes progress, reverse blood flow develops in the portal system, leading to a decrease in the supply of hepatotropic factors with the portal blood flow, worsening the existing hepatocyte loss and deteriorating the liver function. Chronic liver dysfunction increases the risk of developing infections, bleeding, thrombosis and prolongs the half-life of medications due to impaired hepatic metabolism (opioids, benzodiazepines). Splanchnic venous congestion occurs with peripheral vasodilation and reduced myocardial contractility with increased cardiac output which leads to a hyperdynamic type of circulation typical for cirrhotic patients. The renin-angiotensin-aldosterone system (RAAS) is involved with hypersecretion of vasopressin as a compensatory reaction aimed at maintaining adequate arterial pressure, leading to sodium and water retention, dilutional hyponatremia, while in the most severe cases development of hepatorenal syndrome is observed. It is characterized by a sudden decrease in renal function, reduced sodium excretion due to the existing renal vasoconstriction and reduced to absent cortical perfusion. The risk of developing hypoxia is also increased in cirrhotics due to the presence of ascites or pleural effusions and the existing pulmonary shunts and pulmonary hypertension. The central nervous system (CNS) is also affected as hepatic encephalopathy (HE) development, which can range from mild

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cognitive changes to coma. The increased amount of ammonia produced by the metabolism of glutamine by enterocytes and the breakdown of urea by the intestinal flora crosses the blood-brain barrier and lead to cerebral edema. Hemostasis in cirrhosis is also impaired, and this is facilitated by thrombocytopenia and platelet dysfunction due to splenic cell sequestration and bone marrow suppression (alcohol, folate deficiency, viral hepatitis), as well as the compensatory increase in von Willebrand factor and reduced hepatic synthesis of thrombopoietin. All coagulation factors, anticoagulants, and fibrinolytic proteins are secreted by the liver, which explains the hemostatic disorders in advanced liver disease. Reduced bile salt secretion leads to impaired absorption of fat-soluble vitamins, such as vitamin K and further impairs the synthesis of vitamin K-dependent coagulation factors. All of this increases the risk of bleeding, or thrombosis in cirrhotic patients. The above-mentioned pathophysiological mechanisms present in cirrhotic patients require careful preoperative evaluation and therapy in order to improve postoperative outcomes in this population. (1)

Approximately 10% of patients with liver cirrhosis will undergo surgery in the last 2 years of their lives. Surgical treatment in such patients carries a risk of developing perioperative complications that significantly increase morbidity and mortality. Mortality rates in cirrhotic patients undergoing surgery range from 8.3% to 25% compared with 1.1% in noncirrhotic patients. Mortality is determined by the severity of liver disease and the type of surgery, which requires precise stratification of the risk of performing surgical treatment. (2)

The increased incidence of postoperative complications in the population of patients with liver cirrhosis is due to the specific pathophysiological changes associated with chronic liver damage. When performing a laparotomy, hepatic blood flow decreases, hepatic ischemia occurs and the risk of hemorrhagic incidents increases in the presence of concomitant portal hypertension, previous operations and the presence of intra-abdominal adhesions. The most common postoperative complications in cirrhotics are development or reaccumulation of ascites in the peritoneal cavity; development or exacerbation of HE; bleeding from the upper gastrointestinal tract (GIT); development or worsening of renal failure, development of hepatorenal syndrome; development of acute liver failure; development of disseminated intravascular coagulopathy (DIC); surgical site infection, dehiscence, eventration, bleeding; The levels of non-specific complications are also increased – development of acute respiratory distress syndrome (ARDS), ventilator dependence, heart failure, arrhythmia, acute myocardial infarction, thrombotic incidents, death. (2)

The type of surgical treatment is an important determinant in relation to postoperative complications development. Emergency surgical interventions are associated with increased morbidity and mortality, compared to elective procedures, with the risk being highest in open abdominal and cardiac surgery. (2) Emergency surgical interventions, compared to elective surgery in cirrhotic patients show a 4-10-fold higher postoperative mortality and a 5-7-fold higher risk of complications. (3) Arahna et al. reported an 86% mortality rate in advanced cirrhosis and emergency laparotomy. (4, 5) Emergency colorectal surgery in cirrhotic patients has a 20-35% mortality rate, emergency cholecystectomy a 20% mortality rate, and emergency hernioplasty 10-20%. Morbidity in emergency settings compared with elective surgery has also been reported to be 5-7 times higher. In this regard, it is advisable to consider elective surgery after stabilization of the patients condition in order to avoid complications and emergency surgery in the future. (6)

Postoperative mortality and morbidity in patients with cirrhosis are influenced not only by the timing of the surgical intervention, but also by the type and volume of the surgical intervention, with colorectal interventions with the highest mortality rates among abdominal surgeries (13-26%), esophagectomies (11-25%) and duodenopancreatic resections (11.9-17%), and cholecystectomy and elective hernioplasty (11.9-17%), while the lowest mortality rates are reported for cholecystectomy and elective hernioplasty. Regardless of the type of surgical intervention, cirrhotic patients with Child–Pugh–Turcotte (CPT) class C and high MELD are considered high-risk for surgical treatment with unacceptably high mortality. (6)

Traumatic injuries in cirrhotic patients are associated with a 5-fold higher mortality rate compared to noncirrhotic patients, with those undergoing explorative laparotomy having a 2-7-fold higher mortality rate, compared to non-cirrhotic patients. Cirrhotic patients with traumatic injuries carry a higher risk of developing ARDS, coagulopathy, and sepsis. Laparostomy in cirrhotics has mortality rates of 67%, compared to noncirrhotic patients and are at a higher risk of developing coagulopathy, multiple organ failure, and vasoactive drug treatment. (6)

The overall morbidity rate for all surgical procedures in cirrhotic patients is 30.1%, and the 30-day postoperative mortality rate is 11.6. Compared with non-cirrhotic patients, the mortality rate for cholecystectomy, colectomy, and abdominal aortic aneurysm (AAA) in cirrhotic patients is 3.4, 3.7, and 5.0 times higher, respectively, and increases to 12.3, 14.3, and 7.8 times higher in the presence of portal hypertension, respectively. Laparoscopic surgical procedures show morbidity rates of 16% and mortality rates of 0.6%. Hospital stay is prolonged with increasing severity of liver damage. (7) Absolute contraindications for elective surgery in patients with liver disease include acute and fulminant hepatic failure, acute viral and acute alcoholic hepatitis, AAA, ASA class 5, due to high mortality rates. (8)

Several scoring systems exist to assess the risk of surgery, whether it should be postponed until clinical improvement or liver transplantation, or not perfomed at all due to the unacceptably high morbidity and mortality rates in this population. In 1964, Child and Turcotte summarized their experience, which included 128 patients who underwent portal decompression to control acute variceal bleeding. In patients with advanced cirrhosis, a mortality rate of 53% was reported, while in those with minimal or moderate cirrhosis, a mortality rate of 4.3% was reported. Their patients had an increased perioperative risk due to the indications for surgical treatment - unsuccessful conservative therapy of variceal bleeding. Child and Turcotte analyzed the clinical variables that are common in patients with poor postoperative outcomes and noticed 5 constant factors - malnutrition, hepatic encephalopathy and coma, uncontrolled ascites, hypoalbuminemia and hyperbilirubinemia. Thus, they created the Child - Turcotte classification, based on these indicators and divided patients into three classes - class A with minimal, class B with moderate and class C with advanced liver disease. **(Table 1)**

Table 1. *Child – Turcotte classification*

	Class A	Class B	Class C
Nutritional status	Normal	Moderate malnutrition	Severe malnutrition
Ascites	None	Moderate, well controlled by diuretic therapy	Poor diuretic response
Encephalopathy	None	Grade 1	Grade 2 или 3
Prothrombine time	0-2sec>control	2-4sec>control	>4sec>control
Bilirubin	0-2mg/dL	2-3mg/dL	>3mg/dL
Albumin	>3.5g/dL	2.5-3.5g/dL	<2.5g/dL

Ten years later, Pugh and Murray-Lyon reported their results of transthoracic ligation of esophageal varices to control variceal bleeding and as a prerequisite for portal decompression by portocaval shunting. They presented a study of 38 patients, of whom 11 died from ongoing or recurrent bleeding and 10 died from acute liver failure. They divided their patients according to the criteria of Child and Turcotte, with all patients classified as class C not surviving 1 year. Pugh added an additional element and assigned numerical values to calculate a total final score, but removed nutritional status from the classification, although malnutrition is a characteristic feature of advanced cirrhosis. Class A with a score of 5-6 points are considered good candidates for surgical treatment, class B with a score of 7-9 points are at moderate risk, and class C with 10-15 points are at high risk for surgical treatment. (9) **(Table 2)** The Child–Pugh–Turcotte (CPT) scoring system is used to assess perioperative morbidity and mortality in patients with cirrhosis, indicating mortality rates for the three classes, respectively – CPT A 10%, CPT B 30%, CPT C 76-82%. The CPT scoring system has several disadvantages – the use of two subjective parameters (ascites and HE) and the presence of heterogenity between patients classified in the same class. (8)

Table 2. *Child – Pugh – Turcotte classification*

	1point	2 points	3points
Encephalopathy	None	Grade 1 или 2	Grade 3 или 4
Ascites	None	Mild	Moderate
Bilirubin	1-2mg/dL	2-3mg/dL	>3mg/dL
Albumin	>3.5g/dL	2.8-3.5mg/dL	<2.8g/dL
Prothrombine time	1-4sec	4-6sec	>6sec

CPT A – 5-6т., CPT B 7-9т., CPT C 10-15т.

The Model of End-Stage Liver Disease (MELD) classification system was originally developed to assess survival after transjugular intrahepatic portosystemic shunt (TIPS) placement as a decompression option in patients with cirrhosis and portal hypertension. Portal venous shunting to the systemic circulation can be achieved through surgical interventions including mesocaval shunt, distal splenorenal shunt, and portocaval shunt, with reported operative mortality rates of 5–7%. This redirection of portal blood flow can be achieved in a minimally invasive way by placing a percutaneous transjugular portosystemic prosthesis (TIPS). TIPS was introduced in 1980 and it was expected to reduce the frequency and necessity for surgical shunting. A disadvantage of the method is the high incidence of post-interventional complications such as liver capsule lesions, portal, caval or hepatic veins lesions and massive hemorrhage. Another serious disadvantage is worsening of the existing HE due to the diversion of toxic metabolites to the systemic circulation and bypassing the liver, whose functional activity is decreased, as the presence of HE is a contraindication for performing TIPS. The procedure shows high efficacy and safety when planned in patients with preserved liver functional activity. All of the listed shunt procedures are performed for portal decompression, which reduces the risk for variceal bleeding and improves ascites control. The listed interventions are suitable for patients with preserved liver function as a long-term prerequisite for stabilizing the condition before performing liver transplantation or in patients who are contraindicated for transplantation due to advanced age or alcoholism. (9) Since 2002, this scoring system has been used to assess short-term survival of transplant candidates and today – as an estimate of 30-day postoperative mortality, showing a linear relationship with mortality rates. The advantages of this scoring system are the renal function assessment and the usage of objective parameters (bilirubin, creatinine, INR). (10) The calculation is performed using the following equation: MELD = 3.78x ln (bilirubin mg/dL) + 11.2 x ln (INR) + 9.57 x ln (creatinine mg/dL) + 6.43. Any value below 1 is = 1, and if the patient has been dialyzed 2 times in the last week, the serum creatinine value is 4.0 mg/dL. As for MELD <10 = CPT A; for MELD 10-14 = CPT B; and for MELD >14 = CPT C. (11) The MELD score shows a linear relationship with postoperative mortality – there is a 14% increase in 30- and 90-day mortality for each point increase in MELD >8 points. The gray zone MELD - 12-15 points predicts a mortality of 25.4%, in which conservative alternatives to surgery or liver transplantation should be considered. Adding the serum albumin value to the risk assessment in borderline patients with MELD 15 is useful, since with albumin <25 there is a 60% mortality or need for transplantation, in contrast to albumin values >25, in which they are 14%. The disadvantage of MELD is the poor correlation with the severity of the disease, HE and ascites. (8) D'Amico et al. in a review of 118 studies, they believe that CPT is better for calculating the risk in compensated cirrhosis, and MELD is a better predictor in decompensated cirrhosis, and both classifications are comparable in predicting short-term outcomes. (12) MELD and CPT are not mutually exclusive, a combined assessment is recommended in determining clinical behavior, with MELD being more precise. Many authors report a poor prognosis in patients with MELD 8-14 points, undergoing abdominal surgery. (10) The degree of liver damage is classified according to CPT or MELD, as CPT A = MELD <10, CPT B = MELD 10-14, CPT C = MELD >14, CPT A – planned surgical treatment is possible, CPT B – surgical treatment is possible after good preoperative preparation, CPT C – contraindicated for surgical treatment. Individual risk factors – presence of jaundice, prolonged prothrombine time, ascites, encephalopathy, hypoalbuminemia, portal hypertension, renal failure, hyponatremia, infections, anemia, malnutrition. (2) Compensated cirrhosis CPT A or MELD <10 can undergo surgical treatment, CPT B or MELD 11-15 surgical treatment after benefit/risk assessment, CPT C or MELD >15 alternatives to surgical treatment or liver transplantation due to the very high surgical risk, and in MELD >20 elective surgery is postponed until liver transplantation. (6) MELD has an advantage over CPT due to the usage of only objective parameters and a wider range of numerical values, allowing better discrimination of patients with different degrees of liver dysfunction. In a study by Perkins et al., no difference was found in the predictive value of CPT and MELD in cholecystectomized cirrhotic patients, with the authors suggesting cut-off values of MELD 8 points as a predictor of increased morbidity. (13) Suman et al. found that CPT and MELD are comparable predictors of postoperative morbidity and mortality and proposed a cut-off value of CPT 7 points, which is more sensitive to postoperative mortality than MELD 13 points. (14) Befeler et al. found MELD to be a better predictor, comparing MELD and CPT numerically, rather than by class. (15, 16) With regard to increased incidence of complications and mortality, the MELD score is more predictive, with patients with MELD < 8 having a mortality rate of 5.7% for elective surgery, compared to patients with MELD > 20, who have a mortality rate of 50%. (7) According to Douard et al., CPT A are suitable for elective surgery, CPT B require optimization of the condition to conversion to CPT A preoperatively, and CPT C are not suitable for surgical treatment due to a mortality rate exceeding 40%.(17) Northup et al. have determined a 1% increase in mortality for each point increase in MELD score to 20 points and a 2% increase in mortality for each point increase in MELD >20 points.(18) Teh et al. believe that for MELD >20 points, elective surgery should be postponed until transplantation is possible, for MELD 12-19 points, transplantation should be considered, and for MELD <11 points, there is an acceptable postoperative mortality with elective surgery.(19) MELD <12 and CPT A have higher mortality and morbidity with surgical treatment compared to the general population, but do not require therapeutic interventions, as they are suitable for elective surgery. CPT B and MELD >12 require optimization of the condition and require consideration of liver transplantation, and CPT C and MELD >20 are contraindicated for elective surgery until transplantation is possible. The presence of portal hypertension further increases the surgical risk of any procedure, necessitating preoperative intervention. The worst outcomes are observed in emergency surgery procedures and stabilization and elective surgery are preferred whenever possible. (7, 12)

The American Society of Anesthesiologists (ASA) classification system has been used since 1940 to determine the risk of general anesthesia in patients with varying degrees of comorbidity. Class 1 – healthy patient; Class 2 – mild systemic disease; Class 3 – severe systemic disease that is not life-threatening; Class 4 – severe systemic disease that is life-threatening; Class 5 – moribund patient who is not expected to survive without surgical treatment; Class 6 – brain-dead/donor patient. (18) An increased ASA class is associated with increased mortality, and it should be noted that this classification system does not assess the severity of liver damage (21). A high ASA class and age >70 years are predictors of increased mortality. (18) Only ASA class is considered an independent predictor of 7-day mortality, with ASA class 5 indicating 100% mortality and a contraindication to surgery except for liver transplantation. (8) According to Teh et al, cirrhotic patients undergoing surgery and classified preoperatively as ASA 5 have a median survival of 2 days, 90% mortality at 14 days, and 100% mortality at 90 days. (18)(19) The CPT and MELD classification systems traditionally used in clinical practice assess the severity of liver injury but do not take into account the type of surgical intervention and comorbidities. Postoperative mortality can be predicted for 7, 30, 90 days, and 1 year using the Mayo calculator based on MELD score, ASA class, and age. (18)

It has been found that at a cut-off value of portal pressure of >10.5mmHg its value has a sensitivity of 82.8% and a specificity of 93.4% as a predictor of mortality in CPT class A. (22) The diagnosis and staging of portal hypertension is carried out by measuring the hepatic venous pressure gradient (HVPG), with HVPG>10mmHg indicating clinically significant portal hypertension, leading to an increased risk of developing complications, and early detection of portal hypertension is important for the therapeutic approach in these patients. In patients with HVPG>12mmHg there is a severe PH and in patients with HVPG>16mmHg – very severe PH; (23) The study by Reverter et al evaluated the prognostic role of HVPG in cirrhotic patients undergoing elective extrahepatic surgery. The authors reported that ASA class, high-risk surgical interventions (open abdominal and cardiovascular surgery), and elevated HVPG were independently associated with 1-year mortality, with HVPG >16 mmHg increasing, and HVPG >20 mmHg identifying an extremely high-risk population, and no patient with HVPG <10 mmHg developed hepatic decompensation postoperatively. (3, 21) Salman et al. (24) found that portal hypertension was a significant predictor of 30-day mortality in CPT A-C undergoing emergency surgery, and portal pressure had a sensitivity of 83.6% and a specificity of 92%. Nguyen et al. (25) found that mortality was higher in cirrhotic patients with elevated portal pressure undergoing elective colorectal surgery compared with those with normal portal pressure. The impact of portal pressure on surgical outcomes in cirrhotic patients requires preoperative portal decompression by TIPS to improve survival, and Kim et al. (26) found lower short-term mortality rates in such patients. Hemida et al. proved that the MELD score had a sensitivity of 100% and a moderate specificity of 64% as a predictor of increased mortality in cirrhotic patients undergoing non-hepatic abdominal surgery. (22, 27)

When assessing the surgical risk in patients with chronic liver disease and liver cirrhosis, it is necessary to take into account the etiology of the liver disease, the degree of liver damage and decompensation, concomitant diseases, indications and timing of surgical treatment (emergency or elective), and possible alternatives to surgical treatment. This is mandatory for performing safe surgical treatment in this population, since according to data from the world literature, cirrhotics show worse perioperative results, higher levels of perioperative complications and increased mortality rates compared to non-cirrhotics and those operated electively. It is necessary to widely use scoring systems established in clinical practice for assessing liver function in high risk cirrhotic patients indicated for surgical treatment. Concomitant diseases must be well-controlled and compensated for full optimization of the patients clinical condition. Preoperative preparation must be performed so that cirrhotics could tolerate the surgical intervention without significant deviations in the postoperative period or surgical treatment must be postponed whenever possible until the general condition stabilizes and the liver disease is sufficiently compensated.

ABBREVIATIONS

PH – portal hypertension
RAAS – rennin – angiotensine – aldosteron system
CNS – central nervous system
HE – hepatic encephalopathy
GIT – gastrointestinal tract
DIC – disseminated intravascular coagulopathy
ARDS – acute respiratory distress syndrome
CPT – Child – Pugh – Turcotte
MELD – Model of end-stage liver disease
AAA – abdominal aorta aneurysm
ASA – American society of anesthesiologists
HVPG – hepatic venous pressure gradient

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