Principles of acute liver failure detection and its management in early postoperative period (review)

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Abstract. *In spite of implementation in clinical practice of the studies results of liver functional reserves with volumetry principles application and calculation of the volume of future residual liver stump (RLS), as well as application of portal vein (PV) embolization or associated liver section and portal vein ligation (ALPPS), acute liver failure (ALF) remains the main cause of complications and patients' mortality.* ***The aim*** *of this review was searching for new approaches in ALF preventions and control after liver resections.* ***Conclusions****: ALF determination and scale (Nuh N. Rahbari et al., 2015) will be applied in future research, aiming to standardize surgical complications in postoperative period and to be able to provide stratified comparison of immediate results of studies with liver resections conducting. And investigation of physiological alterations in the tissues of operated liver of oncologic patients will allow in the future to improve algorithms of ALF diagnostics and management.*

Introduction. Liver resection is routinely used in the treatment of malignant and benign neoplasms [2, 13, 26]. The latter was achieved due to long-term efforts of scientists and clinicians in the field of oncology and hepatology for the last twenty years [16, 33]. Such types of operative interventions as extended liver resections, including those at pathological conditions of organ parenchyma or after chemotherapy, and also repeated, simultaneous and staged resections were developed, and they are applied for the purpose of surgical treatment radicality and achievement of better long-term treatment outcomes. Resulting from postsurgical reduction of functioning parenchyma content in operated patients there is a growing threat of acute liver failure (ALF) development in postoperative period. In spite of implementation in clinical practice of the results of studies of liver functional reserves with application of volumetry principles and calculation of the volume of future residual liver stump (RLS), as well as application of portal vein (PV) embolization or associated liver section and portal vein ligation (ALPPS), ALF remains the main cause of complications and patients' mortality [1,5].

Rate of ALF development is within 1.2 – 32%, and it depends on criteria of patient's selection and operative intervention scope [21,22]. In addition, the cause of the broad diapason of ALF diagnosing after liver resection may be the fact of absence of clear and generally recognized criteria of this pathology determination. Therefore the development of unified protocols with the aim of conduction of reliable comparison of different surgical centers results is extremely important. For application of scientifically-based criteria of ALF development and its severity these protocols should be accessible and simple for use in wide spectrum of patients.

It is important to emphasize that metabolic and functional alterations, including ALF after liver resection, are unique, and they often cause significant difficulties during patient's condition correction. Deep understanding of liver physiology and its alterations should allow surgeons and anesthesiologists to resolve postoperative issues properly. Strategies that are needed for realization in postoperative period to improve treatment outcomes include adequate nutritive support, appropriate glycemic control and measures for reduction of postoperative infectious complications.

Consensus in ALF grade diagnostics in postoperative period at liver resection. Meta-analysis of literature data revealed 1928 scientific papers dedicated to examination of ALF problem [25]. In their publication the authors used different interpretations of ALF term determination. This confirms the fact that there is no generally accepted scientifically-based determination of ALF term. Qualitative variants of ALF determination included one or several symptoms of liver function disorder in postoperative period, namely: coagulopathy, hyperbilirubinemia, ascite and encephalopathy, etc. [29,30]. Most commonly the authors provided ALF assessment basing on laboratory tests, using serum bilirubin levels and international normalized ratio (INR) or prothrombin index as diagnostic criteria. Some authors for ALF detection assessed clinical symptoms/syndromes in combination with the results of liver functional state [7, 26]. In the frames of a number of scientific papers the principles of ALF severity assessment were developed [8, 10], and some authors dedicated their work to examination of markers and factors for prognostication of ALF effect on postoperative patient’s mortality. In that way Balzan and others in 2005 in the frames of their investigation analyzed treatment outcomes of 704 patients that underwent liver resection and had ALF signs in postoperative period. The latter was diagnosed by INR level < 50% and serum bilirubin > 50 mM/L on the day 5 of postoperative period that became stable correlation marker of mortality development in postoperative period [35]. In the other study Mullen and others (1059 patients without cirrhosis and liver insufficiency in preoperative period) discovered that peak bilirubin concentrations in blood serum (>7 mg/mL) are potent predictors of ALF terminal stages development and postoperative mortality, and high levels of postoperative complications in patients that underwent “major” liver resections (≥ 3 segments) [20]. In contrast to the above-mentioned results Schindl and co-authors proposed classification of ALF severity grades. Differential diagnosis criteria comprised 4 parameters (level of total bilirubin in blood serum, INR, lactate serum concentration and degree of encephalopathy), according to these levels the authors proposed to determine 4 grades of ALF.

Standard biochemical analysis of liver values and coagulograms in postoperative period in patients that were subjected to operative liver interventions demonstrates that in majority of such patients the overall level of serum bilirubin fractions and INR are normalized on the day 5 of postoperative period, including the patients that underwent extended “major” resections [17].

Considering these data and their own experience authors of consensus 2015 [21] claim that ALF after liver resection is a loss of liver ability to perform synthetic, excretory and detoxication functions that is accompanied with increased INR levels and simultaneous growth in total bilirubin concentration in blood serum on the day ≥5 of postoperative period.

It is recommended to determine pathological values of coagulogram and blood serum bilirubin according to laboratory standards. Such criteria should be applied to patients both with physiological liver parenchyma condition and with pathologically altered liver condition. It is important to emphasize that in case of presence of pathological INR or bilirubin values in individual patient at preoperative stage ALF diagnosis on the day ≥5 of postoperative period is made comparing levels of serum bilirubin and INR with the same indices on the day 4. The necessity of administration of blood coagulation factors to patients, for example, fresh frozen plasma (FFP), to achieve INR normalization on the day ≥5 of postoperative period in combination with hyperbilirubinemia should be also considered as ALF.

Grades of ALF severity in postoperative period in patients that underwent liver resection. ALF may have transient nature because after liver resection its function may recover resulting from organ's ability for regeneration, and thus to restore its function. In other cases the loss of liver function may become potential life threat for operated patient. In addition to previous recommendations on ALF diagnosing in postoperative period, it is recommended to assess severity grade of this pathology.

Table 1.

ALF severity grades in postoperative period in patients that were subjected to liver resection (International Study Group of Liver Surgery (ISGLS)).

Determination	ALF – is a loss of liver ability (in patients both with normal and pathologically altered liver function before operation) to perform synthetic, excretory and detoxification functions that is accompanied by increase of INR levels (or require administration of blood coagulation factors for INR normalization) and hyperbilirubinemia (according to local laboratory data) on the day 5 of postoperative period and later. In case of detection of increased levels of INR and blood serum bilirubin ALF is determined by increase of INR level (decrease of prothrombin index) and

	hyperbilirubinemia on the day ≥5 after liver resection, comparing with previous day. Other causes of hyperbilirubinemia should be excluded, in particular, mechanical obstruction..
Grades	
A	ALF leading to abnormality of normal laboratory values although without need of additional correction of patient's therapy.
B	ALF leading to abnormality of normal laboratory values, and non-invasive correction of patient's condition is possible.
C	ALF leading to abnormality of normal laboratory values and requires invasive tactics in patient's treatment.

Grade of ALF severity in operated patients should be determined by most pronounced criteria (it is reasonable to consider 1 criterion of invasive or non-invasive treatment methods when differential diagnosis is discerned between grades C and B).

ALF of Grade A in postoperative period suggests liver function impairment, although it does not have impact on changes in patient's therapy tactics. This ALF grade can be determined basing on detected deterioration of initial level of routine laboratory tests. Such patients do not have new symptoms comparing with standard disease course and can be treated in usual in-patient regimen.

ALF of Grade B in postoperative period suggests the need for adjustment of conservative treatment tactics, although patient's condition can be stabilized without application of invasive methods. Non-invasive treatment can comprise indication of FFP, albumin, diuretics and non-invasive methods of lungs ventilation. In addition, alteration in treatment tactics and application of intensive therapy are possible only in case of determination of parenchyma dysfunction of residual liver stump (RLS) that is classified as Grade B of ALF. These patients require additional diagnostic measures, in particular, ultrasound and spiral CT, to exclude mechanical obstruction of bile ducts and presence of abscesses and circumscribed fluid collections. It the signs of infectious complications are present (leucocytosis, etc.) it is necessary to perform plain radiography of thoracic organs and bacterial inoculation of discharges, blood and urine. Brain CT should be performed to exclude other cases of patient's condition deterioration. Patients with ALF Grade B may have clinically significant ascites, in addition the increase of body weight and moderate respiratory insufficiency can be registered. Such patients usually require moderate/intensive therapy, although experienced nurses can provide appropriate care to such patients also in in-patient conditions without resuscitation use.

Grade C of ALF. Such patients require invasive methods of postoperative condition correction. Invasive procedures include hemodialysis, tracheal intubation and mechanical ventilation, extracorporal liver support, "rescue" hepatectomies and transplantation. Even more, for patients, receiving cardiologic support (including vasoactive preparations) due to ALF, the latter should be classified with Grade C as well as in patients, receiving glucose solution infusion for persistent hypoglycemia. Patients with ALF Grade C are in severe condition therefore the provision of medical aid to such patients should be performed in resuscitation conditions. Clinical picture of such patients is characterized with abundant ascites, generalized edemas, hemodynamics instability, pronounced respiratory disorders and encephalopathy. In addition, ALF Grade C is a risk factor for generalized infections development, therefore antibiotic therapy should be applied for prophylactic purposes, although such a tactics should be confirmed with subsequent clinical studies.

Control of fluids and electrolytes. Early postoperative period after liver resection is characterized by imbalance of fluid and electrolytes that is caused by functional disorder of residual liver stump. Maintenance of adequate balance of fluids and normal kidneys function is crucial considering vasodilation-induced hypotension. In such conditions colloid solutions lead to restoration of intravascular volume. Limited indication of infusion solutions with high sodium content and rational use of diuretics is also recommended [19].

It is believed that hyperlactatemia and hypophosphatemia are the most frequent disorders in patients that underwent liver resection. Because of ALF conditions the liver produces lactate, but it does not metabolize it. In these conditions lactate and bilirubin levels in blood serum can be the criteria of assessment of cellular hypoxia level and predictors of mortality and treatment quality. Therefore it is not recommended to prescribe lactate-containing solutions in postoperative period to such patients.

Hypophosphatemia is found in almost all the patients after major liver resections. Pathogenesis of hypophosphatemia after liver resection is poorly examined. Cellular hypoxia caused by glycolysis both of tumor genesis and liver trauma determines accumulation of organic phosphate compounds at simultaneous reduction of intracellular organic phosphate. With phosphate diffusion in cells decrease of its level in blood occurs that leads to hypophosphatemia. Decrease of intracellular inorganic phosphate due to this mechanism is a critical element and it can lead to ATP depletion and initiate generation of superoxide radicals by intracellular and extracellular sources. It is known that in uncomplicated cases phophorylated compounds are metabolized in tricarboxylic acid cycle, providing restoration of ATP levels. At more severe phosphates depletion ATP deficit may become a cause of cellular dysfunction development in different organs and systems. Hypophosphatemia and energy exchange deteriorations, induced by it, lead to pathological alterations, causing, in particular, cardiac arrhythmias, alterations in hematopoiesis system, insulin-resistance and neuromuscular dysfunctions [18].

Standard treatment at liver resections should include adequate phosphate restoration by infusion of solutions, containing potassium phosphate and also, in case when the patent can take meals - his/her ration should be corrected. Assessment of above described changes is possible by measuring phosphates levels in serum, in particular, serum 2,3 diphosphoglycerol levels, and also nucleotide products in urine that are more sensitive physiological markers. Low levels of 2,3 diphosphoglycerol in serum and high levels of nucleotides and theirs degradation products in urine indicate insufficient intracellular phosphate level. In general, hypophosphatemia after liver resection may lead to perilous consequences and therefore it should be properly corrected. Further studies that in prospect will help to discover pathophysiology of hypophosphatemia after liver resection may promote treatment improvement.

Diet. In post-resection period liver parenchyma is characterized by catabolic condition, and frequently - with disproportion of glucose and electrolytes levels that does not promote prompt liver regeneration. Nutritional support in this critical period is paramount for provision of adequate regeneration and postoperative rehabilitation. Individual diet plans should be developed for patients considering liver function since these patients demonstrate changes in amino acids metabolism. In such patients' blood low level of circulating amino acids with branched chain (leucine, isoleucine, valine), methionine and aromatic amino acids is registered. Therefore introduction of amino acids with branched chain into the diet may facilitate acceleration of patients' rehabilitation after liver resection [3]. Enteral nutrition does not influence patients' mortality, but it improves immune indices and reduces postoperative infectious complications. We support enteral nutrition application in case when contraindications are absent.

Glycemic control. It is known that non-alcoholic fatty liver disease (NFLD) in one of the leading causes of transaminases level rise in blood serum in case of liver cirrhosis exclusion [9]. NFLD is accompanied with steatosis (excessive triglycerides accumulation), steatohepatitis (impairment of hepatocytes, infiltration with anti-inflammatory cells and fibrosis) and cirrhosis [31], the latter changes may be histologically confirmed. NFLD is often associated with diabetes mellitus and obesity, which incidence rate requires to consider situation in the world as epidemic [4]. It is noteworthy to mention that not all the patients with diabetes mellitus and obesity have NFLD.

It is known that a number of chemotherapeutic preparations have hepatotoxic effects. In particular, irinotecan- and 5-fluorine uracil-based chemotherapy results in steatohepatitis development in 20 and 5% of cases, respectively [20, 27]. Whereas oxaliplatin prescription is associated with development of sinusoidal obstruction syndrome [22, 27, 32]. Alcohol intake also is a common cause of liver steatosis development [34]. Liver steatosis is associated with increased risks of complications in postoperative period, and moderate or pronounced steatosis correlates with high mortality rates and ALF after surgical treatment [6]. Diabetes mellitus and obesity are independent risk factors of postoperative complications (infectious, cardiovascular, renal) at major" liver resections.

Hyperglycemia, induced by surgical stress, causes disorders of liver metabolism regulation and immune function that may become an adverse factor for postoperative outcomes. Control of blood glucose level and intensive insulin therapy of patients reduce complications and mortality. Insulin resistance after liver resection can make the control of adequate blood glucose level challenging.

Coagulation system control. Control of such blood coagulation indices as INR/PTI, especially on the day 2-5 of postoperative period is a critically important procedure. Pathological changes of these indices correlate with liver resection volume and develop due to reduction of organ stump synthetic function, and also in cases of peri- and postoperative hemotransfusion and application of blood coagulation factors. Prophylactic administration of fresh frozen plasma (FFP) is recommended at INT ≥ 2.0 to prevent bleeding. There is evidence that prophylactic FFP transfusions at PTI > 16 sec. in patients that underwent liver resection are important for prevention of repeated liver metastatic spread at colorectal cancer. And combination of administration of FFP, vitamin K preparations, octreotide and VIIa coagulation factor can be used for coagulopathy correction and bleeding prevention at ALF signs.

Postoperative infections prevention. Infections after liver resections are one of the main reasons of postoperative morbidity and mortality that also influence the results of long-term prognosis. Risk factors for prognostication of postoperative infectious complications are obesity, presence of preoperative bile drainage, operative blood loss, concomitant diseases and bilomas in postoperative period. Early postoperative infections detection, application of broad-spectrum antibiotics and infection control are paramount. In patients that underwent liver resection functional impairment of intestinal barrier and intestinal-microbial balance was found, leading to systemic inflammations and infectious complications. Therefore early enteral feeding is aimed at intestinal barrier function protecting and infectious complications reduction.

It is believed that for prevention of postoperative complications it is necessary to apply synbiotic treatment. It is known that probiotics are the bacteria that in symbiosis with host provide host with benefit improving intestinal microbial balance. Whereas probiotics is a group of microorganisms, not affecting the digestion of food components, but selectively altering the growth and activity of large bowel microflora. And combination of pro- and prebiotics is a synbiotic therapy

Sinusoidal obstruction syndrome and its effect on liver function. In 1920 the disease, leading to occlusion of liver parenchyma veins as a result of pyrrolysine alkaloids poisoning was described, at that moment morphologists determined central veins affection, and also liver sinusoid veins [14]. In 1999 DeLeve et al. presented the model of the disease with liver veins occlusion in rat model, this pathology was induced by monocrotaline [11]. Pathomorphological alterations that are macroscopically described as “blue liver” are well known under the term “sinusoidal obstruction syndrome” (SOS). According to resent years publications SOS is often determined in patients with colorectal cancer with liver metastatic affection which were prescribed with chemotherapy. Under the term SOS sinusoidal membrane impairment, collagen deposition in perisinusoidal space and sinusoidal dilatation is implied. SOS pathophisiology comprises the process of increase of superoxide radicals levels and nitrogen oxide radicals, F-actin depolimerization in vascular endothelial cells, and increased activity of matrix metalloproteinases (MMP-9 and MMP-2) in vascular endothelial cells [12, 24]. Accordingly, SOS is associated with fibrosis development, and further – with portal hypertension, liver insufficiency.

In 2004 Rubbia-Brandt et al. were the first who published clinical data on SOS that had developed after neoadjuvant polychemotherapy (nPCT) in patients with metastatic colorectal cancer [22]. The authors proposed classification of SOS (0 – changes are absent, 1 – mild degree, central lobule affected up to 1/3 of the surface; 2 – moderate degree, central lobule affected up to 2/3 of its surface; 3 – pronounced changes, complete lobule affection). According to this study data SOS was diagnosed in 34 of 43 patients (79.1 %) that were prescribed with oxaliplatin. In the studies [15, 23, 28] correlation between SOS and prescription of chemotherapy schemes based on oxaliplatin and 5-fluorine uracil was demonstrated: in 8.3–51.6 % cases chemotherapy-associated SOS of 2-3 degree developed. Severity of acute liver failure in postoperative period correlates with number of courses of neoadjuvant chemotherapy provided [15], and postoperative complications, associated with liver dysfunction, are more specific for patients with already existing liver diseases [13]. Short course of PCT on the base of oxaliplatin is not associated with early postoperative complications rise. At SOS that resulted from toxic chemotherapy effect increase of resistance to blood flow between portal vein system and hepatic veins occurs. Therefore arising portal hypertension leads to splenomegaly, refractory thrombocytopenia, bleeding from esophageal varices, hemorrhoidal veins. Thus, SOS development is accompanied with decrease of efficacy of oxaliplatin-based neoPCT which in turn worsens long-term outcomes of surgical treatment. And cellular hypoxia is the most important factor, influencing disease course.

Thereby, we consider that proposed ALF determination and scale (Nuh N. Rahbari et al., 2015) will be applied in future research, aiming to standardize surgical complications in postoperative period and to be able to provide stratified comparison of immediate results of studies with liver resections conducting. And investigation of physiological alterations in the tissues of operated liver of oncologic patients will allow in the future to improve algorithms of ALF diagnostics and management.

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