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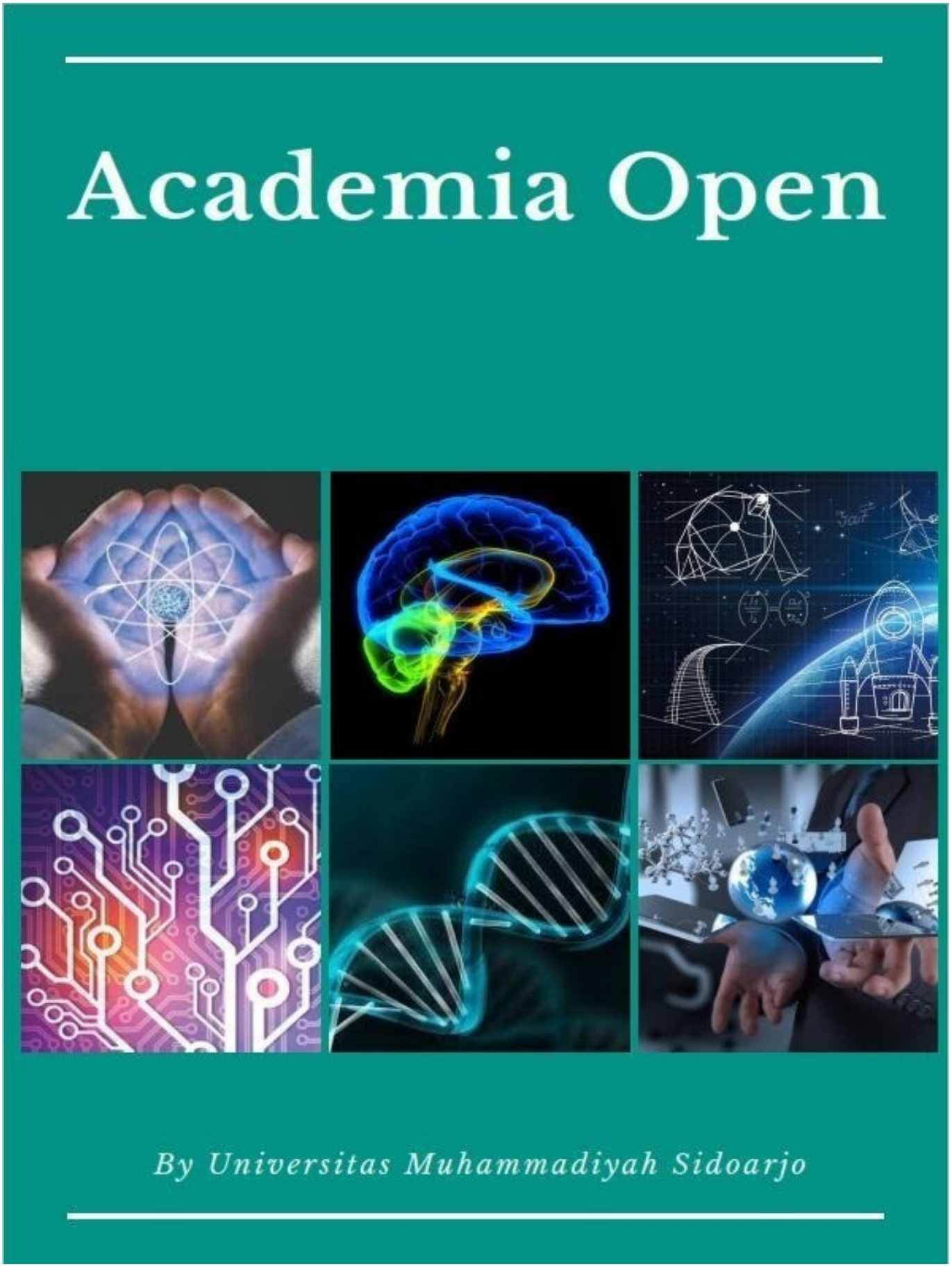

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Quantitative Characterization of Liver Safety in Surgical Diseases and Postoperative Course

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Abstract

General Background: Accurate assessment of liver functional reserve remains critical in surgical practice, as hepatic dysfunction substantially elevates postoperative morbidity and mortality risks. **Specific Background:** Conventional biochemical markers (ALT, AST, bilirubin) predominantly reflect cytolysis and cholestasis but fail to evaluate hepatocellular energetic status or regenerative capacity. **Knowledge Gap:** Current diagnostic approaches lack objective quantitative indicators that directly measure mitochondrial function and viable hepatocyte populations in surgical patients. **Aims:** This study evaluated a novel prognostic coefficient based on the ratio of cytochrome C to TMPD oxidase mitochondrial activities for quantifying liver parenchymal preservation in patients with hepatobiliary surgical diseases. **Results:** Analysis of 24 patients demonstrated strong inverse correlation between coefficient values and viable hepatocyte percentages. Coefficients of 2.5-3.5 units indicated favorable prognosis, 5-7 units signaled elevated complication risk, while values ≥8 units predicted unfavorable outcomes, irrespective of standard biochemical parameters. **Novelty:** Unlike traditional markers, this coefficient directly reflects mitochondrial respiratory chain integrity and hepatocellular viability through objective biochemical measurements. **Implications:** The proposed coefficient serves as an integrated quantitative marker of hepatic functional reserve, enabling improved surgical risk stratification and outcome prediction in hepatobiliary surgery.

Highlight :

- The cytochrome C to TMPD oxidase ratio correlates better with hepatocyte viability than standard biochemical markers in both experimental and clinical contexts.
- Coefficient values predict postoperative outcomes: 2.5-3.5 units indicate favorable prognosis, 5-7 units suggest complications, and ≥8 units correlate with mortality.
- Mitochondrial dysfunction demonstrates universal quantifiable patterns across different etiologies, showing consistent relationships between the coefficient and hepatocyte viability.

Keywords : Liver Functional Reserve, Mitochondrial Dysfunction, Cytochrome C Oxidase, Hepatocyte Viability, Postoperative Prognosis

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Introduction

Assessment of liver functional status remains one of the most complex and pressing tasks in modern surgery. The liver performs key metabolic, detoxification, and synthetic functions, and a reduction in its functional reserve significantly increases the risk of postoperative complications and mortality [2,6,8]. This issue is particularly relevant in patients with hepatobiliary diseases accompanied by chronic inflammation, cholestasis, ischemia, and fibrotic changes. Evaluation of liver function is essential for diagnosing diseases, assessing the severity of liver damage, determining prognosis, understanding the compensatory capacity of liver functions, and monitoring treatment efficacy [1,3,5].

Despite the widespread use of standard biochemical indicators of liver function (ALT, AST, bilirubin, sedimentation tests), their diagnostic and prognostic value remains limited. These indicators typically reflect the degree of cytolysis or bile flow disturbances but do not allow an objective assessment of the hepatocytes' energetic status or their regenerative potential [4,7,15]. In clinical practice, this limitation complicates the prediction of postoperative outcomes, especially in patients with borderline liver functional reserve. Assessment of liver functional reserve thus represents a challenging clinical task [5].

In recent years, increasing attention has been paid to mitochondrial dysfunction as a central element in the pathogenesis of liver failure. According to Sun et al. (2022) [14], mitochondrial damage leads to ATP deficiency, increased oxidative stress, and activation of hepatocyte apoptosis, which clinically manifests as progressive liver failure. The findings of the present study regarding the increase in the coefficient associated with a decrease in the percentage of viable hepatocytes fully align with these pathogenetic mechanisms. In this context, the search for quantitative indicators reflecting the state of the liver mitochondrial apparatus is a promising direction in surgical hepatology.

Materials and Methods

From the 24 patients we examined, 8 were in the surgical department with diagnoses of cholelithiasis, cirrhosis, and mechanical jaundice. The liver study results, obtained during surgery, showed that depending on the duration of the disease, the length of obstruction of the common bile duct, stenosis of the Vater's papilla, and comorbid conditions, the cytochrome C TMFD oxidase activity ratio ranged from 5 to 7 units. In patients with peptic ulcer disease of the duodenum and uncomplicated cholecystitis, the ratio ranged from 2.5 to 3.4 units. These patients underwent surgery, and the postoperative course was smooth.

The liver of the patients was examined in a cold room after intraoperative biopsy. The liver was quickly washed, and a homogenate was prepared in a medium consisting of 0.25 sucrose, $2x10^{-4}$ M EDTA (ethylene diamine tetraacetic acid), and 0.01 M tris-HCl buffer with pH 7.4, in a tissue-to-medium ratio of 1:2. Polarographic analysis was conducted using a standard Clark-type platinum electrode on an LP-7 polarograph [10].

In the polarographic cuvette (volume 1.1 ml), a homogenate was sequentially added, calculated at 1–2 mg of protein, sodium ascorbate at a final concentration of 2 mM, TMFD-[11] (tetramethylene para-phenylene diamine) at 1 μM, and cytochrome C-[12] at 1 μM. The rate of respiration was expressed in nmol O_2/min/mg of protein. The prognostic coefficient (PC) was calculated using the formula: PC = Cytochrome C – Ascorbate Na / TMFD – Ascorbate Na.

The xenogeneic hepatocyte suspension was obtained using the combined Berry-Friend method, modified by A.I. Archakov [13]. The degree of morphological preservation of the obtained hepatocytes was assessed by light and phase-contrast microscopy, with prior staining using the vital dye – 0.2% trypan blue. The digital data were processed using the method of variation statistics.

Results and Discussions

Interesting data were obtained from our clinical material. In patients with various surgical diseases, as well as liver and biliary tract disorders, liver biopsies were performed. The biopsy samples were analyzed using the same methods as in the experiments conducted on laboratory animals. Table 1 presents the values of the prognostic coefficient and the percentage of viable hepatocytes.

Table 1. Values of the Prognostic Coefficient and Percentage of Viable Hepatocytes in Animals with Various Models of Hepatocellular Injury and in Patients with Hepatobiliary Diseases

№№	Experimental Data (Rats and Dogs)		Clinical Material	
	Coefficient (units)	Percentage of Viable Hepatocytes	Coefficient (units)	Percentage of Viable Hepatocytes
1.	1,9-2,0	95-100	2,5	95
2.	5-6	43-45	5-6	40-45
3.	7	35	7	35
4.	8	30	8	25-30
5.	10-11	24-25	-	-
6.	13-14	15-16	-	-

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The maximum values of the ratio of cytochrome C to TMFD oxidase activities reached 8.0 units, while the minimum values of 2.5–3.0 units were observed in elective patients admitted for surgical treatment of chronic uncomplicated cholecystitis or duodenal ulcer disease. High coefficient values were noted in patients with hepatolienal syndrome, liver cirrhosis, intrahepatic portal hypertension, and mechanical jaundice. The data in Table 2 also indicate that both in experiments on laboratory animals and in clinical patients, the values of the percentage of viable hepatic parenchyma and the corresponding coefficient are practically identical. This suggests that in animal cells, the ratio of cytochrome C to TMFD oxidase activity is a constant value, which apparently changes in a similar manner in humans, and that the same biochemical processes underlie these changes.

The values of the ratios of cytochrome C to TMFD oxidase activities and the percentage of viable liver parenchyma obtained in our experiments and clinical studies were compiled and are presented in Figure 1 and Figure 2.

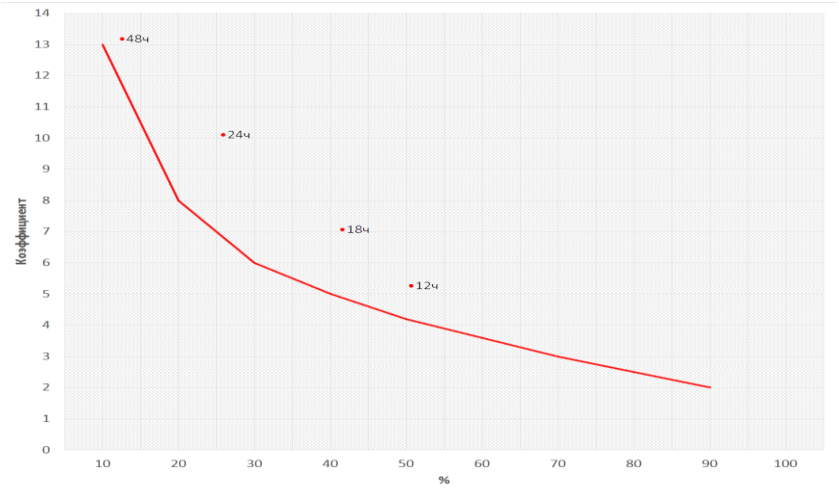

Figure 1. Counting of Viable Liver Cells After DL-Galactosamine Challenge (at 12, 18, 24, and 48 Hours) and Their Ratio to the Coefficient.

The number of viable liver cells decreases over time following the challenge. At 12 hours, the percentage of viable cells is 50% with a coefficient of 5.05, whereas at 48 hours, the percentage drops to 10–12% with a coefficient of 13.2 (Figure 1).

Observations of these animals showed that the severity of their clinical condition increased with the duration of time after the challenge. By 48 hours, the animals exhibited pronounced hypodynamia, bleeding tendencies, and reduced pain sensitivity, ultimately resulting in 100% mortality.

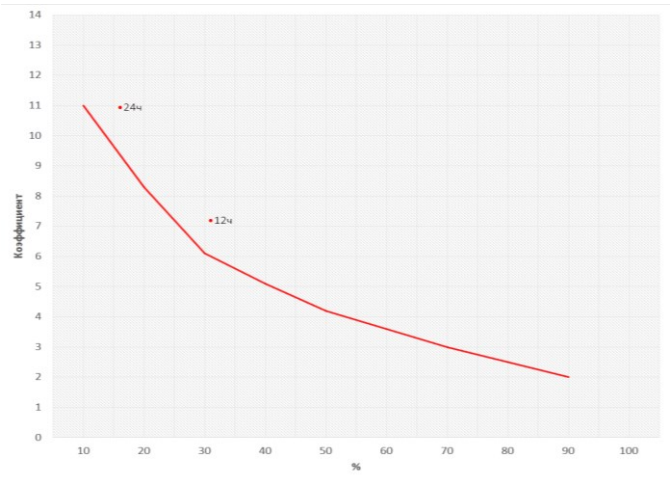

Figure 2. Counting of Viable Liver Cells After CCl_4 Challenge (at 12 and 24 Hours) and Their Ratio to the Coefficient

Counting of viable liver cells (Figure 2) showed that 12 hours after the CCl_4 challenge, 30% of intact cells remained (coefficient 7.2), while at 24 hours, only 15% remained (coefficient 10.9).

The clinical condition of the rats gradually deteriorated, reaching its peak at 24 hours, when 50% mortality was observed. In the surviving animals, by 48 hours, mobility partially recovered, reflexes were activated, appetite appeared, bleeding tendencies decreased, and the number of viable cells slightly increased.

The curve representing the relationship between these values is parabolic, and it can be used to estimate the amount of preserved liver parenchyma by determining the coefficient values in a liver biopsy.

Thus, the results of this series of experiments demonstrated that the method we used allows for a quantitative assessment of the degree of liver parenchymal damage caused by DL-galactosamine and CCl_4 intoxication. The highest coefficient values corresponded to the most pronounced morphological changes, the lowest number of viable cells, and the most severe clinical condition of the animals.

The results convincingly demonstrate that the ratio of cytochrome C to TMFD oxidase activity is a sensitive and quantitative indicator of the extent of liver parenchymal damage. A clear inverse relationship was observed between the coefficient level and the percentage of viable hepatocytes,

both in experimental models of toxic liver injury (DL-galactosamine, CCl_4) and in patients with hepatobiliary surgical pathology.

Of particular interest is the fact that at similar coefficient values, the percentage of preserved liver parenchyma in experimental animals and patients was almost identical. This indicates the presence of universal mechanisms of mitochondrial dysfunction in hepatocellular injury, regardless of the etiological factor. Similar conclusions were reported by Ozawa et al. [14], who showed that the state of the mitochondrial respiratory chain directly reflects the functional reserve of the liver.

In clinical practice, various scales and tests are widely used to assess the severity of liver failure (Child–Pugh, MELD, indocyanine green test). However, most of these either include subjective parameters or do not provide a direct quantitative assessment of hepatocyte viability. In contrast, the proposed coefficient is based on objective biochemical processes and directly reflects the state of the mitochondrial apparatus of the liver.

Of the 24 patients we examined, 8 were admitted to the surgical department with diagnoses of cholelithiasis, cirrhosis, and mechanical jaundice. Liver study results obtained during surgery showed that, depending on the duration of the disease, the length of obstruction of the common bile duct, stenosis of the Vater's papilla, and associated comorbidities, the ratio of cytochrome C to TMFD oxidase activities ranged from 5 to 7 units (Table 2).

Table 2. Ratio of Cytochrome C to TMFD Oxidase Activities, Number of Preserved Hepatocytes, and Biochemical Test Results in Patients with Hepatobiliary Diseases

Age	Clinical Diagnosis	Preserved Hepatocytes	Coefficient (units)	Biochemical Tests					
				Total Bilirubin	ALT	AST	Thymol Test	Sublimate Test	Total Protein (g/L)
2 years	Pancreatic Cancer with Complicated Mechanical Jaundice	25	8	154,7	0,89	1,22	10	2,0	49,5
2 years	Cholelithiasis with Gallbladder Empyema	40	5	10,9	0,33	1,66	6	2,0	70
3 years	Exacerbation of Chronic Cholecystitis	37	6	9,58	0,27	0,11	5	2,1	58
8 years	Cholelithiasis, Choledocholithiasis, and Stenosis of the Vater's Papilla	35	7	59,9	0,56	1,00	5	2,1	73
8 years	Cholelithiasis, Choledocholithiasis, and Obstructive Jaundice	40	5	137,3	1,66	2,11	5	5,0	81
28 years	Chronic Calculous Cholecystitis	80	3	16,8	0,44	0,56	4	2,2	74

Analysis of Clinical Material showed that with coefficient values of 2.5–3.5 units, the postoperative course was generally favorable. In patients with coefficients of 5–7 units, an increased risk of complications was observed, and with values ≥8 units, the prognosis was unfavorable, as evidenced by the fatal outcomes in the presented clinical cases. It is important to emphasize that standard biochemical liver parameters in some cases did not correlate with the coefficient level. Identical values of ALT and AST were associated with fundamentally different mitochondrial activity and percentages of viable hepatocytes. This confirms modern literature data that transaminases reflect the degree of cytolysis but not the functional reserve of the liver. For example, patient K.M.P., 68 years old, medical record № I25I2, with cholelithiasis, stenosis of the Vater's papilla, and obstructive jaundice, underwent suprapapillary choledocho-duodenostomy before admission to the hospital. Her coefficient reached 7 units, and the amount of preserved parenchyma was 37.2% (0.95×10^6 cells).

Patient D.L.N., 62 years old, medical record № 9255, was admitted with an exacerbation of chronic hepatocystitis. Upon liver examination, the coefficient was 8.0 units. The patient passed away on the 4th day after the Monastyrsky operation. The post-mortem diagnosis was: pancreatic head cancer complicated by obstructive jaundice, cancerous intoxication, bilateral pneumonia, and hepatorenal failure.

In patients with peptic ulcer disease of the duodenum, sigmoid colon cancer, and uncomplicated cholecystitis, the coefficient ranged from 2.5 to 3.4 units. These patients underwent surgery, and their postoperative course was smooth.

Table 2 presents data obtained from a series of patients. These data indicate that liver function tests used in surgical patients do not always correlate with the coefficient values. With identical coefficient values, AST and ALT activity levels may vary. It is difficult to assess the severity of the disease based solely on sedimentation tests or protein levels. The total bilirubin content primarily reflects the degree of bile flow obstruction into the duodenum.

In summary, the ratio of cytochrome C to TMFD oxidase activities allows for an assessment of the amount of preserved liver parenchyma both in various pathological processes of the hepatobiliary system and during the progression of disease and surgical treatment. Moreover, the coefficient level enables a more reliable prediction of disease outcome and the postoperative course.

Fundamental studies by Ozawa et al. [10] have shown that a decrease in the activity of mitochondrial respiratory chain components directly correlates with a reduction in the liver's functional reserve and a poorer prognosis in surgical patients. The authors emphasize that it is the impairment of mitochondrial oxidative phosphorylation, rather than changes in traditional biochemical markers, that serves as an early and highly sensitive indicator of hepatocellular insufficiency. These findings are fully consistent with the results of the present study, in which an increase in the cytochrome C to TMFD oxidase activity ratio reflected progressive suppression of mitochondrial respiration and decreased hepatocyte viability.

Current clinical guidelines from EASL (2023) also highlight the limitations of standard laboratory indicators (ALT, AST, bilirubin) in assessing the true functional state of the liver. According to these guidelines, these parameters primarily reflect acute hepatocyte injury or cholestasis but do not allow evaluation of the liver's adaptive and regenerative capacity after surgical intervention. In the present study, it was confirmed that patients with similar transaminase and bilirubin levels exhibited fundamentally different levels of mitochondrial activity and percentages of viable hepatocytes, underscoring the diagnostic advantage of the proposed coefficient.

Thus, the proposed indicator can be considered an integrated quantitative marker of liver functional reserve, enabling an objective assessment of hepatocellular damage, prediction of postoperative outcomes, and justification for the choice of surgical strategy

Conclusion

1. Standard biochemical liver tests do not always reflect the true functional capacity of the hepatic parenchyma in surgical patients.
2. The ratio of cytochrome C to TMFD oxidase activity reliably correlates with the percentage of viable hepatocytes.
3. High coefficient values are associated with an unfavorable postoperative course and a high risk of mortality.
4. The proposed method can be used as a quantitative indicator of liver functional reserve and as a prognostic criterion in surgical practice.

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