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Article

Quantitative Indicators of Hepatic Preservation in Surgical Hepatobiliary Diseases and Postoperative Recovery

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Abstract: This study aimed to develop and clinically validate a quantitative indicator of hepatic preservation by using a mitochondrial enzymatic coefficient derived from the ratio of cytochrome C–dependent respiration to TMPD-dependent respiration, and to compare its informativeness with conventional biochemical and morphological assessments in surgical hepatobiliary disease. We used an experimental–clinical approach. Hepatocellular damage was experimentally evoked in rats by DL-galactosamine-plus-carbon tetrachloride (CCl_4) at specific times. Twenty-four surgical patients with hepato-biliary disease were studied in an Operating Unit by taking coagulation biopsies of liver, with transcutaneous needle biopsy, followed by processing in the cold-room, preparing a homogenate and measuring oxygen consumption using a Clark-type electrode system; under the microscope morphological viability was cmpared by examination of live cells stained with trypan-blue vital dye. Routine laboratory tests (bilirubin, ALT/AST, thymol and sublimate test, total protein) had been performed. The estimated coefficient increased uniformly as the viable hepatocytes percentage decreased between both experimental models and clinic observations. Comparable coefficient–viability pairs were also found between experimental and clinical datasets, suggesting cross-context transposable predictions. The traditional liver tests did not significantly correlate with the coefficient, particularly when ALT/AST was fluctuant and/or the bilirubin level largely indicated cholestasis rather than parenchymal preservation. The study introduces a mitochondrial-function–based quantitative coefficient that reflects preserved parenchymal mass more directly than routine biochemical panels. Intraoperative coefficient measurement from biopsy material may support risk stratification, perioperative decision-making, and prediction of postoperative course. Sample size was limited, and the method requires biopsy and specialized polarographic equipment; larger prospective studies are needed to define universal cut-offs and outcome-based thresholds.

Keywords: acute liver failure; liver parenchyma; quantitative coefficient; ischemia; mitochondria; postoperative outcomes; hepatobiliary surgery.

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1. Introduction

Accurate assessment of hepatic function and hepatic reserve remains a central problem in hepatobiliary surgery and perioperative medicine. The liver performs essential metabolic, synthetic, detoxification, and immunologic functions; therefore, its impairment influences not only disease progression but also the tolerance to surgical intervention and the risk of postoperative complications. Clinicians routinely rely on biochemical tests and composite scoring systems to diagnose hepatobiliary pathology, estimate severity, and predict outcomes. Over recent years, numerous clinical and biochemical parameters and prognostic scales have been proposed to improve evaluation of hepatocellular dysfunction in diffuse and focal liver lesions [1-2]. Nevertheless, translating these tools into a direct quantitative measure of "how much functioning liver remains" is still challenging.

From a common perspective, the tests used for daily surgical practice can be subdivided in screening, diagnostic and quantitative measurements. Screening tests: screen for liver disease Diagnostic tests: identify the cause Quantitative test: try to estimate functional reserve Nevertheless, a limitation of persisting is that routine liver function tests do not continuously correlate with regenerative capacity or remaining hepatic viable parenchyma after surgical trauma, ischemic injury or toxic lesions [3-4-5]. This issue is even more challenging in the setting where liver tests are confounded by cholestasis, systemic inflammation, sepsis, malignancy or perioperative hemodynamic instability.

ALT and AST are commonly used in making an inference on hepatocyte injury. However, their absolute values can differ dramatically and may not accurately reflect the amount of injured tissue, especially when injury is heterogeneous or patchy necrosis develops or when mitochondrial failure precedes outright cytolysis. Similarly, total bilirubin is an important marker for hepatobiliary disease but is dependent on the degree of bile outflow obstruction rather than functional status of hepatocellular mitochondria. ESR and Tpr can be influenced by nutritional status, inflammation and protein-losing states and may not adequately differentiate hepatic reserve in a surgical patient. Indeed, the assessment of liver failure based on only clinical signs or isolated laboratory tests, is still both a complex and incompletely resolved issue [6-7-8-9]..

Mitochondria are the major energy-producing organelles in hepatocytes, and mitochondrial respiration is closely tied to hepatocyte viability, ATP generation, and resistance to ischemia and toxic injury[10]. A mitochondrial-function–based indicator may therefore provide a more direct link to the preserved functional cell mass than serum markers alone. Polarographic techniques allow measurement of oxygen consumption in tissue homogenates, offering quantitative information about the activity of respiratory chain components. Earlier biochemical work demonstrated that electron transport initiated by substituted phenylenediamines (including TMPD) can be coupled to phosphorylation and respiration [11], while mitochondrial adaptive responses have been related to hepatic functional reserve [12].

In this context, the present study proposes a prognostic coefficient derived from the ratio of cytochrome C–dependent to TMPD-dependent oxidase activities. The rationale is that this ratio reflects mitochondrial respiratory capacity of the remaining parenchyma and may correlate with the proportion of viable hepatocytes. The aim of this work was to evaluate whether this coefficient provides a quantitative characterization of hepatic preservation in experimental models of hepatocellular injury and in surgical patients with hepatobiliary diseases, and to compare its behavior with conventional biochemical tests and morphological measures of cell viability.

2. Materials and Methods

This work employed a combined experimental and clinical methodology. In the experimental arm, hepatocellular injury was modeled in laboratory rats using two toxic agents: DL-galactosamine (time points: 12, 18, 24, and 48 hours) and carbon tetrachloride

(CCl_4; time points: 12 and 24 hours). At each time point, liver tissue was collected for biochemical polarographic analysis and morphologic viability assessment.

The clinical arm comprised 24 adult surgical patients operated on for hepatobiliary operations. The remaining eight patients had complicated hepatobiliary pathology (cholelithiasis with obstructive jaundice, cirrhosis syndromes, biliary obstruction with stenosis of the papilla Vateri). The lower-risk clinical comparison group consisted of patients with uncomplicated disease (e.g., chronic uncomplicated cholecystitis or duodenal ulcer disease). Intra-operative liver biopsies were collected and placed on ice until being immediately processed in a cold room.

Liver specimens were rapidly washed, and homogenates were prepared in a medium containing 0.25 M sucrose, 2×10^{-4} M EDTA, and 0.01 M Tris–HCl buffer (pH 7.4), with a tissue-to-medium ratio of 1:2. Polarographic analysis was conducted using a closed-type Clark platinum electrode system connected to an LP-7 polarograph, following established technical guidance. In a 1.1 mL polarographic cuvette, homogenate was introduced to achieve 1–2 mg protein; sodium ascorbate was added to a final concentration of 2 mM, followed by TMPD (1 μM) and cytochrome C (1 μM). Oxygen consumption rate was expressed as nmol O_2/min/mg protein.

The prognostic coefficient (PC) was calculated as a ratio reflecting cytochrome C–dependent respiration relative to TMPD-dependent respiration under standardized substrate conditions. Hepatocyte viability was assessed via microscopy after vital staining with 0.2% trypan blue, using hepatocyte preparations obtained by the Berry–Friend method (Archakov modification) [13]. Statistical processing applied variation statistics methods [14].

3. Results

Before presenting tabulated data, it is important to clarify that the primary measured outcome was the coefficient value derived from polarographic respiration indices, and the primary morphological comparator was the percentage of viable hepatocytes assessed by microscopy. Conventional biochemical tests were recorded as supportive clinical context.

Table 1 summarizes the paired values of coefficient levels and viable hepatocyte percentages obtained in experimental injury models and in clinical hepatobiliary diseases. The table is presented to demonstrate whether the same coefficient ranges correspond to similar viability ranges across experimental and clinical settings.

Table 1. Coefficient values and percentage of viable hepatocytes in experimental models and clinical material

No.	Experimental (rats): Coefficient (units)	Experimental: Viable hepatocytes (%)	Clinical: Coefficient (units)	Clinical: 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	—	—

The coefficient range observed in planned surgical patients with uncomplicated hepatobiliary conditions and non-complicated surgical diagnoses was typically lower (approximately 2.5–3.4 units), while higher values (up to about 8.0 units in the clinical material presented) were recorded in more severe hepatobiliary pathology, including obstructive jaundice and cirrhosis-associated syndromes.

Figure 1 is included to show time-dependent changes in the DL-galactosamine model and the associated coefficient behavior. The figure is presented to allow visualization of the direction and magnitude of coefficient increase as cell viability declines.

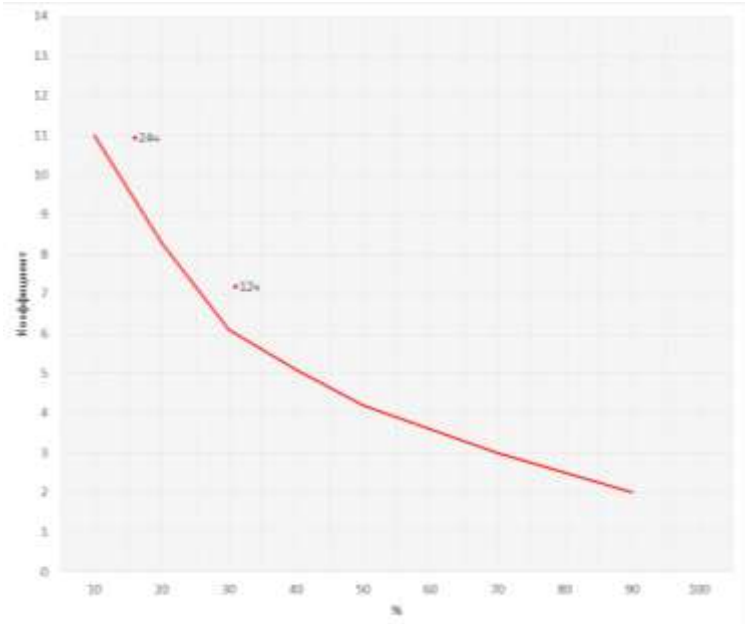

Figure 1. DL-galactosamine model: viable hepatocytes (%) at 12, 18, 24, 48 hours and corresponding coefficient values

Quantitative assessment demonstrated that viability decreased over time following DL-galactosamine administration. At 12 hours, viable hepatocytes were approximately 50%, with a coefficient value of 5.05. By 48 hours, viable hepatocytes decreased to 10–12%, and the coefficient increased to 13.2.

Figure 2 is provided to present analogous data for the CCl_4 model. The figure is included to depict viability and coefficient values at 12 and 24 hours after exposure.

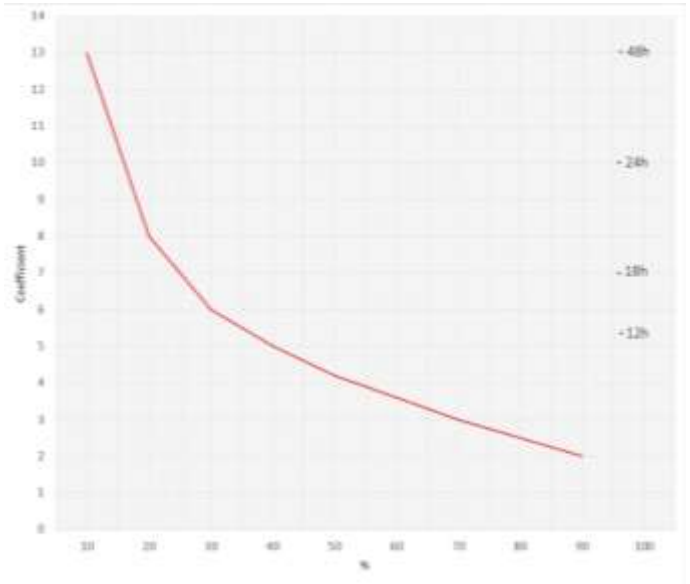

Figure 2. CCl_4 model: viable hepatocytes (%) at 12 and 24 hours and corresponding coefficient values

At 12 hours after CCl_4 exposure, approximately 30% of intact liver cells remained, with a coefficient value of 7.2. At 24 hours, viable hepatocytes were approximately 15%, and the coefficient increased to 10.9.

Before presenting clinical laboratory context, the following **Table 2** provides individual patient examples with diagnoses, preserved hepatocyte proportions, coefficient values, and accompanying biochemical indices. The table is intended to document how coefficient levels are distributed across representative hepatobiliary diagnoses.

Table 2. Coefficient values, preserved hepatocytes, and biochemical indices in hepatobiliary surgical patients

No.	Age	Clinical diagnosis	Preserved hepatocytes (%)	Coefficient (units)	Total bilirubin	ALT	AST	Thymol test	Sublimate test	Total protein (g/L)
1	62	Pancreatic cancer, obstructive jaundice	25	8.0	154.7	0.89	1.22	10	2.0	49.5
2	62	Cholelithiasis, gallbladder empyema	40	5.0	10.9	0.33	1.66	6	2.0	70
3	73	Exacerbation of chronic cholecystitis	37	6.0	9.58	0.27	0.11	5	2.1	58
4	68	Cholelithiasis, choledocholithiasis, Vater's papilla stenosis	35	7.0	59.9	0.56	1.00	5	2.1	73
5	58	Cholelithiasis, choledocholithiasis, obstructive jaundice	40	5.0	137.3	1.66	2.11	5	5.0	81
6	28	Chronic calculous cholecystitis	80	3.0	16.8	0.44	0.56	4	2.2	74

4. Discussion

The current work here illustrates a stable and interpretable relationship between a respiration-based mitochondrial coefficient and morphological estimates of viable hepatocyte proportion in both experimental toxic injury models and clinical surgical material. Such inter-model concordance is essential: It implies the coefficient signifies a core biological characteristic, that is mitochondrial respiratory competency of the preserved parenchymal mass - instead of a COT-specific laboratory artefact [15], [16].

A significant finding is the sense of changes; in both DL-galactosamine and CCl_4 models, the coefficient rose when cell viability fell. This is consistent with the notion that progressive damage shifts the relative contribution of Cytochrome C-dependent and TMPD-dependent respiration, potentially due to loss of electron transport chain integrity, altered permeability/availability of cytochrome-related pathways in mitochondria that suffer injury [17]. Although the current article does not make such a mechanistic claim, the monotonically increasing coefficient with deteriorating morphology lends support to this coefficient as a quantitative proxy for the amount of compromised parenchyma.

The DL-galactosamine series is particularly informative because it provides a multi-time-point trajectory. The decline from ~50% viability at 12 hours to ~10–12% at 48 hours, accompanied by a coefficient increase from 5.05 to 13.2, indicates that the coefficient is

sensitive to progressive hepatocellular injury across a clinically meaningful range. The CCl_4 model, with fewer time points, corroborates the trend by showing reduction from ~30% to ~15% viability and coefficient increase from 7.2 to 10.9 by 24 hours. Importantly, Table 1 shows that similar coefficient "bands" correspond to similar viability ranges in clinical material, suggesting that the indicator may support translation from controlled models to heterogeneous clinical pathology [18], [19].

The clinical considerations support the potential importance of the coefficient when conventional testing is equivocal. As shown in Table 2, total bilirubin levels vary greatly and are more a function of the level of biliary obstruction than remaining parenchyma. This is predictable in patients with obstructive jaundice and periampullary/pancreatic head cancer, where cholestasis can overwhelm laboratory indexes [20]. Similarly, aminotransferases (ALT/AST) are variable between patients and do not correlate well with preserved hepatocyte fractions. This also corresponds with the established deficiencies of ALT/AST as measurements of hepatic reserve; release may vary due to timing from insult, reperfusion, systemic illness and necrotic pattern, and it will do not correlate linearly with viable parenchymal mass.

The clinical case descriptions (e.g., severe obstructive jaundice with high coefficient values and reduced preserved parenchyma) illustrate that the coefficient can stratify patients by parenchymal preservation even when bilirubin is elevated due to obstruction. In lower-risk elective cases (uncomplicated cholecystitis, duodenal ulcer disease), the coefficient range (2.5–3.4) corresponds to high preserved parenchyma proportions and smoother postoperative courses, supporting clinical plausibility. From a surgical decision-making perspective, such quantitative stratification could be valuable in anticipating postoperative hepatic dysfunction, selecting perioperative protective strategies (hemodynamic optimization, minimization of ischemia time), and planning postoperative monitoring intensity.

However, the study also has methodological and interpretative constraints. The coefficient requires intraoperative biopsy material and specialized polarographic measurement, limiting immediate generalizability in low-resource settings. Standardization is essential: homogenate preparation, temperature control, protein concentration, substrate concentrations, and electrode calibration must be tightly controlled to ensure reproducibility. A further limitation is the modest clinical sample size and that the outcome validation (e.g., post operative liver failure outcomes) are underpowered to conclusively define cut-off values. Accordingly, while threshold-like ranges of coefficients may be suggested (e.g., low coefficient ≈ intact parenchyma and higher coefficient ≈ loss of preserved parenchyma), clinically applicable 'outcome thresholds' must await such validation in large prospective cohorts.

Notwithstanding the limitations, the current results do support that coefficient is a suitable quantitative biomarker candidate to enhance, but not replace, the standard liver tests. In this it specifically addresses an absence in standard care that provides an approximation of preserved parenchymal viability consistent with preservation of mitochondrial function. Further research should validate the test in a prospective fashion, against standardized definitions and (2) to combine with imagevolumetry and functional tests such as ICG clearance; (3) develop simplified assay variants to reduce reliance on specialized instrumentation while maintaining the quantitative link to mitochondrial respiration.

5. Conclusion

This study developed and evaluated a mitochondrial respiration–based quantitative coefficient intended to characterize hepatic preservation in surgical hepatobiliary diseases and during postoperative recovery. Across experimental models of toxic liver injury and clinical intraoperative biopsy material, the coefficient demonstrated a consistent association with morphological estimates of hepatocyte viability. Specifically, higher coefficient values corresponded to lower percentages of viable hepatocytes, and similar coefficient ranges mapped to comparable viability ranges in both animal models and clinical cases. These observations indicate that the coefficient can serve as a quantitative

surrogate marker of preserved parenchymal mass, reflecting mitochondrial functional status in damaged liver tissue.

A clinically relevant point is that standard laboratory tests often used in surgical patients were not constantly correlated to coefficient values. The aminotransferases (ALT and AST) varied greatly even when levels of coefficient were similar, precluding their independent utility in predicting preserved parenchymal mass; T. bilirubin, essential for clinical evaluation, instead mostly reflected the severity of biliary outflow obstruction rather than hepatocellular preservation. Sedimentation tests and total protein were of little use in grading the severity of parenchymal compromise. Its above mentioned behavior is in contrast with the proposed coefficient which directly quantitatively correlated to viable hepatocyte ratio and therefore might convey additional information for perioperative risk stratification.

From a practical perspective, the coefficient—measured from intraoperative biopsy material under standardized polarographic conditions—may support objective evaluation of hepatic reserve, inform intraoperative and postoperative management, and contribute to prediction of postoperative course in patients with severe hepatobiliary pathology, including obstructive jaundice and cirrhosis-associated syndromes. At the same time, broader implementation is constrained by the need for biopsy material and specialized measurement technology, and by the limited clinical sample size of the current study. Therefore, the coefficient should be viewed as a promising quantitative indicator requiring further validation. Future prospective studies with larger patient cohorts should establish outcome-based threshold values, evaluate reproducibility across centers, and determine how the coefficient integrates with existing functional tests and clinical scoring systems. Within these boundaries, the present work supports the feasibility and potential clinical utility of a mitochondrial-function–driven quantitative approach to hepatic preservation assessment in surgical practice.

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