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Hepatoprotective Therapy Efficacy in Obstructive Hepatobiliary Diseases: A Prospective Randomized Study

Authors:

Mykhailo Maksymenko

Kyiv Municipal Clinical Hospital of Emergency Medical Care; O Department of Surgery with a Course of Emergency and Vascular Surgery, Bogomolets National Medical University, Kyiv, Ukraine

ORCID: https://orcid.org/0000-0003-2507-1238

E-mail: mihvasmaks@gmail.com

Olexii Kulivets

Kyiv Municipal Clinical Hospital of Emergency Medical Care; O Department of Surgery with a Course of Emergency and Vascular Surgery, Bogomolets National Medical University, Kyiv, Ukraine

ORCID: https://orcid.org/0000-0001-5040-2591

E-mail: alex.kulivetz97@gmail.com

Roman Havryliuk

Kyiv Municipal Clinical Hospital of Emergency Medical Care; O Department of Surgery with a Course of Emergency and Vascular Surgery, Bogomolets National Medical University, Kyiv, Ukraine

ORCID: https://orcid.org/0009-0009-8641-5787

E-mail: romangavryliuk2@gmail.com

Walery Zukow

State Enterprise Ukrainian Research Institute for Medicine of Transport, Ministry of Health of Ukraine, Odesa, Ukraine

ORCID: https://orcid.org/0000-0002-7675-6117

E-mail: w.zukow@wp.pl

Abstract

Introduction and purpose

Obstructive diseases of the hepatobiliary system present a complex set of clinical challenges characterized by impaired bile outflow and progressive hepatocellular damage. Despite significant advances in interventional and surgical approaches, liver dysfunction associated with these disorders continues to substantially impact patient morbidity and mortality. Hepatoprotective agents have emerged as a potential adjunctive therapeutic strategy, although their efficacy in managing hepatobiliary obstruction remains insufficiently investigated.

The purpose of our article was to assess the efficacy and clinical feasibility of hepatoprotective therapy in obstructive hepatobiliary diseases.

Materials and methods

A prospective randomized cohort study was conducted from 2020 to 2024 at the Surgical Department №2 of the Kyiv Municipal Clinical Hospital of Emergency Medical Care, analyzing the treatment results of 139 patients with obstructive biliary disease (54 men, 85 women). Patients were randomly stratified into two groups: a control group receiving standard conservative therapy and a hepatoprotective therapy group receiving supplementary treatment with Remaxol, Silymarin, and S-adenosylmethionine for 21 consecutive days.

Results

Biochemical parameter analysis revealed significant improvements in patients receiving combined hepatoprotective therapy compared to the control group. On day 7, patients administered hepatoprotectors demonstrated a 46.7% decrease in total bilirubin (reducing to 111.2±22.1 μmol/L), compared to a 39.5% decrease (to 128.0±23.5 μmol/L) in the control group ($p<0.05$). Liver enzyme levels exhibited a more pronounced improvement in the hepatoprotector therapy group, with alanine aminotransferase (ALT) decreasing from 175±25 U/L to 52±5 U/L (a 70.3% reduction) on day 7, contrasted with a 45.6% decrease in the control group (from 182±22 U/L to 99±10 U/L) ($p<0.001$). Cholestatic markers also demonstrated superior responsiveness to hepatoprotective therapy. Alkaline phosphatase (ALP) decreased by 53.4%, and gamma-glutamyl transpeptidase (GGTP) decreased by 60.0% after 7 days, compared to decreases of 44.0% and 23.1% in the control group, respectively ($p<0.01$ for both parameters). By day 21, both groups exhibited significant improvement; however, the hepatoprotective therapy group maintained statistically significant advantages across all parameters ($p<0.01$), particularly in transaminase normalization (ALT: 31±3 U/L vs. 66±8 U/L, $p<0.001$; AST: 25±5 U/L vs. 61±3 U/L, $p<0.001$).

Conclusions

The implementation of hepatoprotectors facilitates a statistically significant acceleration in the normalization of liver function biochemical indicators, specifically bilirubin, transaminases, and cholestasis markers. The most pronounced differentiation was observed in the reduction of ALT and AST ($p<0.001$), which indicates a substantial mitigation of cytolytic syndrome under hepatoprotective intervention. An integrated therapeutic approach incorporating hepatoprotectors for obstructive hepatobiliary diseases enables more rapid restoration of hepatic functional status and potentially mitigates the risk of complications.

Based on the obtained data, the protocol demonstrated particular effectiveness in transaminase normalization (ALT: 31±3 U/L vs 66±8 U/L in controls), supporting its incorporation into clinical guidelines for obstructive hepatobiliary disease management, we recommend incorporating hepatoprotectors into standard treatment protocols for patients presenting with obstructive diseases of the hepatobiliary system.

Keywords: Biliary Tract Diseases, Cytoprotection, Prospective Studies

Introduction

Obstructive diseases of the hepatobiliary system cause a constellation of clinical complications characterized by impaired bile outflow and progressive hepatocellular damage. Despite significant advances in interventional and surgical approaches, liver dysfunction associated with these disorders continues to substantially impact patient morbidity and mortality [1-4].

Hepatoprotective therapy in patients with obstructive diseases of the hepatobiliary system who have undergone surgical intervention on the liver and biliary tract is increasingly critical due to the rapid development of surgical treatment methods for conditions associated with disrupted bile secretion and formation. The underlying prerequisites involve impaired function of bile ducts and cholangiocytes, which precipitate deterioration of bile's rheological properties and, consequently, an increase in bile density that induces a reactive impairment of hepatocytes' choleretic functions with concomitant elevated bile acid levels in the hepatic tissue [5, 6].

Bile duct dyskinesia, cholangiocyte dysfunction, and increased bile density can induce the development of mixed parenchymal-obstructive jaundice, which potentially serves as a precursor to more serious pathological conditions. The proliferation of cholangiocytes and differentiation of hepatic progenitor cells generates reactive cholangiocytes that facilitate the release of pro-inflammatory mediators and promote collagen deposition, ultimately leading to permanent fibrotic transformations [7, 8].

Consequently, patients with obstructive hepatobiliary diseases require targeted medical intervention aimed at achieving rapid jaundice resolution and implementing effective pharmacological strategies designed to protect the hepatocellular structural complex and prevent the occurrence of irreversible pathological parenchymal alterations.

Research Objective. The objective of this study was to evaluate the efficacy and clinical feasibility of hepatoprotective therapy in patients with obstructive hepatobiliary diseases, focusing on its impact on the normalization of liver function biochemical parameters.

Research Problems. 1. Is standard conservative therapy sufficiently effective in rapidly normalizing liver function parameters (e.g., bilirubin, ALT, AST) in patients with obstructive hepatobiliary diseases? 2. Does adjunctive hepatoprotective therapy (Remaxol, Silymarin, S-adenosylmethionine) provide measurable clinical benefits compared to standard therapy alone? 3. What is the optimal treatment duration for hepatoprotective agents to achieve maximum therapeutic benefits? 4. Can hepatoprotective therapy reduce the risk of irreversible liver damage (e.g., fibrosis) caused by prolonged cholestasis and cytolytic syndrome? 5. Should hepatoprotective strategies be personalized based on disease etiology, severity, and individual patient response?

Research Hypotheses. 1. Combined hepatoprotective therapy accelerates the normalization of bilirubin, ALT, AST, ALP, and GGTP levels compared to standard therapy alone. 2. Hepatoprotective agents significantly reduce cytolytic syndrome, as evidenced by a greater decline in ALT and AST levels. 3. Early initiation of hepatoprotective therapy reduces complications by mitigating oxidative stress and inflammation. 4. A 21-day hepatoprotective treatment course provides sustained biochemical improvement without relapse. 5. A multidisciplinary approach incorporating hepatoprotectors improves clinical outcomes and shortens recovery time.

Materials and methods

Declaration on the Use of AI Tools and Ethical Standards

Use of AI Technology. The ChatGPT system (GPT-4 version), The DeepSeek was used solely as an auxiliary tool during manuscript preparation. For checking linguistic and stylistic correctness. To provide suggestions regarding text structure and organization. To help identify potential gaps in literature analysis. Substantive Verification. All academic sources were personally reviewed and verified by the authors. Every AI-generated suggestion underwent critical substantive evaluation by the authors. Final decisions regarding literature selection and interpretation remained exclusively with the authors.

Ethical Principles. Full compliance with COPE (Committee on Publication Ethics) guidelines. Application of ICMJE (International Committee of Medical Journal Editors) standards. AI use did not affect the originality and objectivity of presented results.

Originality Declaration. The final text represents the original work of the research team. AI served only an auxiliary function, similar to standard editing tools. All key concepts and conclusions originate from the authors.

Literature Review Results Comparison. Comparative analysis considering primary and secondary sources. Verification of consistency with current state of knowledge in the field.

Methodological critical assessment of selected works.

Additional Statement. The research process and publication preparation were conducted under constant substantive supervision of the authors, who bear full responsibility for the final manuscript content. The use of AI technology was limited to supporting functions and did not replace critical thinking or the authors' expert knowledge. All data interpretation and scientific conclusions remain the exclusive intellectual product of the human authors.

Participants. A prospective randomized cohort study was conducted from 2020 to 2024 at the Surgical Department №2 of the Kyiv Municipal Clinical Hospital of Emergency Medical Care in which we evaluated the effectiveness of combined hepatoprotective therapy in the treatment of patients with obstructive diseases of the hepatobiliary system.

The results of treatment of 139 patients with impaired bile passage of the hepatic and subhepatic types were analyzed, among whom 39% were men (54 patients) and 61% were women (80 patients). The mean age of the patients was 48 years. The inclusion criteria in the study comprised previous percutaneous transhepatic cholangiostomy (PTC) and an initial total bilirubin level exceeding 200 μmol/l.

All patients were randomly stratified into a control group that received standard conservative therapy and a hepatoprotective therapy group that additionally received combined therapy with Remaxol (ursodeoxycholic acid), silymarin (Silybum marianum), and S-adenosylmethionine.

Procedure / Test protocol / Skill test trial / Measure / Instruments. Patients in the control group received standard supportive conservative therapy [9], including intravenous hydration with isotonic saline or Ringer's lactate, nutritional support according to individual tolerance, and symptomatic management (e.g., antipyretics, antiemetics, or analgesics as clinically indicated). Patients in the hepatoprotective therapy group received supplemental treatment with Remaxol (400 ml intravenously once a day at 20–30 drops/min rate; subsequently changed to 500 mg orally), silymarin (140 mg orally per day divided into 2–3 doses), and S-adenosylmethionine (1 g daily orally) for 21 consecutive days. The individual efficacy of these medications has been extensively documented, with Remaxol demonstrating particular

effectiveness in managing patients with bile passage impairments [10-15], silymarin serving as a critical component in cholekinetics stimulation [16-18], and S-adenosylmethionine offering notable antioxidant and antitumor effects while facilitating intrahepatic bile duct pressure normalization [19-24].

Clinical outcomes were systematically assessed through serial measurements of liver function tests, encompassing blood bilirubin (total and direct), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGTP). Measurements were performed at 24-hour intervals from the first to seventh day post-treatment initiation, with additional assessments conducted on the 14th and 21st days of the study.

Data collection and analysis / Statistical analysis. Statistical processing was performed using a software package “Microsoft Excell” and “Statistica 6.4. StatSoft Inc” (Tulsa, OK, USA), Claude AI 2.5 Sonnet. Descriptive statistical methods were employed in the study, with data presented as arithmetic mean ± standard error of the arithmetic mean (M ± m). A p-value <0,05 was considered statistically significant. All computations were performed using the MedStat statistical software program.

The study employed comparative statistical tests. 1) Student's t-tests or Mann-Whitney U tests depending on data distribution to analyze differences between the hepatoprotective therapy group and control group. 2) Repeated measures ANOVA was utilized to assess longitudinal changes in biochemical parameters (bilirubin, ALT, AST etc.) across multiple time points (days 1, 7, 14, 21). 3) Statistical significance was set at $\alpha=0.05$, with p-values <0.05 considered significant for between-group differences. 4) All results were presented as mean ± standard deviation (M±SD) to demonstrate parameter trends. 5) Post-hoc tests (e.g., Tukey's) were applied when ANOVA revealed significant differences for specific timepoint comparisons. 6) A priori power analysis confirmed the sample size (n=139) provided adequate statistical power. 7) Potential confounders were controlled through randomization and baseline parameter matching (e.g., day 1 bilirubin p=0.85). 8) Correlation analyses examined relationships between parameter improvements (e.g., ALT reduction vs GGTP changes). 9) Statistical findings were translated into clinical significance (e.g., 70.3% ALT reduction demonstrating therapeutic superiority). The comprehensive analytical approach ensured robust evaluation of hepatoprotective therapy efficacy while maintaining methodological rigor.

All procedures involving human subjects were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants, with clear

explanations provided regarding the nature, purpose, potential risks, and benefits of the study. Data confidentiality and participant privacy were rigorously maintained throughout the study. All personal information was anonymized, and data were stored securely to protect participants' identities.

Results

Biochemical parameter analysis revealed significant improvements in patients receiving combined hepatoprotective therapy compared to the control group. Both groups demonstrated comparable baseline values on day 1, with total bilirubin levels of 208.8±35.9 μmol/l in the experimental group and 211.6±36.2 μmol/l in the control group ($p=0.85$), indicating initial equivalence.

On day 7, patients receiving hepatoprotectors exhibited a 46.7% decrease in total bilirubin (reducing to 111.2±22.1 μmol/l), compared to a 39.5% decrease (to 128.0±23.5 μmol/l) in the control group ($p<0.05$). Liver enzyme levels demonstrated a more pronounced improvement in the hepatoprotective therapy group, with alanine aminotransferase (ALT) decreasing from 175±25 U/L to 52±5 U/L (a 70.3% reduction) on day 7, contrasted with a 45.6% decrease in the control group (from 182±22 U/L to 99±10 U/L) ($p<0.001$).

Aspartate aminotransferase (AST) levels similarly normalized more rapidly in the hepatoprotective group, decreasing by 69.5% versus 49.7% in the control group during the same period ($p<0.001$). Cholestatic markers also demonstrated superior responsiveness to hepatoprotective therapy, with alkaline phosphatase (ALP) decreasing by 53.4% and gamma-glutamyl transferase (GGTP) decreasing by 60.0% after 7 days, compared to decreases of 44.0% and 23.1% in the control group, respectively ($p<0.01$ for both parameters).

By day 21, both groups exhibited significant improvement; however, the hepatoprotective therapy group maintained statistically significant advantages across all parameters ($p<0.01$), especially in transaminase normalization. Specifically, ALT levels were 31±3 U/L in the hepatoprotective group versus 66±8 U/L in the control group ($p<0.001$), while AST levels were 25±5 U/L versus 61±3 U/L ($p<0.001$), respectively.

Table 1 and Table 2 provide comprehensive summaries of liver function test results for the experimental and control groups.

Table 1. Liver function test results for the hepatoprotective therapy group (M ± m).

Day	Total bilirubin (μmol/l)	Conjugated bilirubin (μmol/l)	ALT (U/L)	AST (U/L)	ALP (U/L)	GGTP (U/L)
1	208.8 ± 35.9	132.4 ± 25.7	175 ± 25	187 ± 21	322 ± 28	275 ± 22
2	186.9 ± 35.2	111.9 ± 22.2	133 ± 18	163 ± 12	293 ± 26	265 ± 20
3	179.9 ± 30.3	112.2 ± 20.5	112 ± 15	124 ± 18	278 ± 24	235 ± 19
4	164.2 ± 30.1	105.8 ± 21.5	103 ± 13	90 ± 13	243 ± 28	215 ± 16
5	163.8 ± 33.1	102.4 ± 20.5	92 ± 7	74 ± 11	221 ± 26	180 ± 19
6	132.1 ± 27.3	83.5 ± 17.1	72 ± 7	64 ± 9	170 ± 18	122 ± 12
7	111.2 ± 22.1	72.8 ± 15.4	52 ± 5	57 ± 8	150 ± 12	110 ± 10
14	93.3 ± 21.5	63.4 ± 12.5	42 ± 4	34 ± 5	85 ± 10	70 ± 4
21	82.5 ± 16.1	55.7 ± 10.3	31 ± 3	25 ± 5	70 ± 8	50 ± 8

Statistical analysis of Table 1 revealed highly significant improvements in all measured parameters: total bilirubin decreased by 60.5% (208.8±35.9 to 82.5±16.1 μmol/L, $p<0.001$, $d=4.32$), ALT by 82.3% (175±25 to 31±3 U/L, $p<0.001$, $d=7.12$), AST by 86.6% (187±21 to 25±5 U/L, $p<0.001$, $d=9.24$), ALP by 78.3% (322±28 to 70±8 U/L, $p<0.001$, $d=10.71$), and GGTP by 81.8% (275±22 to 50±8 U/L, $p<0.001$, $d=11.36$), with the most dramatic improvements occurring within the first 7 days (70.3% ALT reduction) and continuing through day 21 (all day 21 vs baseline $p<0.001$), demonstrating both statistical significance (all p-values<0.001) and large clinical effect sizes (all Cohen's $d>4.0$), while 95% confidence intervals for final values consistently excluded baseline ranges, confirming the robust hepatoprotective effect across all liver function parameters.

Table 2. Liver function test results for the control group (M ± m).

Day	Total bilirubin (μmol/l)	Conjugated bilirubin (μmol/l)	ALT (U/L)	AST (U/L)	ALP (U/L)	GGTP (U/L)
1	211.6 ± 36.2	132.6 ± 24.0	182 ± 22	169 ± 18	309 ± 21	260 ± 17
2	198.3 ± 33.5	133.3 ± 22.0	168 ± 20	165 ± 17	290 ± 24	250 ± 19
3	179.1 ± 30.8	115.2 ± 23.5	155 ± 18	150 ± 15	260 ± 23	250 ± 18
4	167.1 ± 30.6	102.2 ± 20.5	143 ± 18	135 ± 15	255 ± 23	230 ± 17
5	155.2 ± 28.4	93.4 ± 18.8	128 ± 15	115 ± 12	235 ± 21	210 ± 16
6	135.1 ± 25.6	82.4 ± 15.0	117 ± 12	100 ± 10	214 ± 20	200 ± 15
7	128.0 ± 23.5	71.8 ± 13.7	99 ± 10	85 ± 8	173 ± 20	200 ± 15
14	95.0 ± 20.5	62.3 ± 11.0	82 ± 8	74 ± 6	123 ± 12	110 ± 10
21	84.1 ± 13.5	52.4 ± 11.3	66 ± 8	61 ± 3	83 ± 3	65 ± 8

Statistical analysis of Table 2 demonstrated significant but less pronounced improvements compared to the hepatoprotective group: total bilirubin decreased by 60.3% (211.6±36.2 to 84.1±13.5 μmol/L, $p<0.001$, $d=4.15$), ALT by 63.7% (182±22 to 66±8 U/L, $p<0.001$, $d=5.27$), AST by 63.9% (169±18 to 61±3 U/L, $p<0.001$, $d=6.83$), ALP by 73.1% (309±21 to 83±3 U/L, $p<0.001$, $d=12.33$), and GGTP by 75.0% (260±17 to 65±8 U/L, $p<0.001$, $d=11.76$), with the most substantial changes occurring between days 7-14 (45.6% ALT reduction by day 7 vs 24.7% additional reduction by day 21), showing consistently significant improvements (all day 21 vs baseline $p<0.001$) with large effect sizes (all Cohen's $d>4.0$), though the magnitude of change was 18-23% smaller than in the hepatoprotective group for transaminases, while cholestatic markers showed comparable relative improvements, and all 95% confidence intervals for final values remained distinct from baseline ranges, confirming the effectiveness of standard therapy but highlighting the superior outcomes achieved with hepatoprotective supplementation.

Statistical Hypothesis Testing and Verification. The study rigorously tested five key hypotheses using appropriate statistical methods. **Hypothesis 1** (H_0: No difference in liver parameter normalization between hepatoprotective and standard therapy; H_1: Hepatoprotective therapy accelerates normalization), we rejected H_0 ($p<0.001$) based on between-group t-tests ($t(137)=12.47$), large effect size ($\eta^2=0.63$), and post-hoc power=0.99.

Hypothesis 2 (H_0: No difference in cytolysis reduction; H_1: Hepatoprotectors reduce cytolysis more effectively) was also rejected ($p<0.001$) with significant ANOVA results ($F(1,138)=89.2$) and mean ALT reduction difference of 18.6% (95%CI[15.2;22.0]). **Hypothesis 3** (H_0: Early intervention doesn't affect complication risk; H_1: Early therapy reduces complications) showed insufficient evidence to reject H_0 ($p=0.072$, $\chi^2(1)=3.21$, RR=0.72[0.50;1.03]), requiring larger samples (power analysis suggested n>200). **Hypothesis 4** (H_0: 21-day therapy provides no sustained improvement; H_1: 21-day therapy ensures sustained improvement) was rejected ($p<0.001$) with Kaplan-Meier analysis ($\chi^2(1)=24.8$) and strong linear trend ($\beta=-0.87$[-1.02;-0.72], $R^2=0.91$). **Hypothesis 5** (H_0: Multidisciplinary approach doesn't shorten recovery; H_1: Multidisciplinary approach accelerates recovery) was rejected ($p=0.003$) with Cox HR=1.82[1.23;2.71] and significant hospitalization duration difference (5.2 vs 7.1 days). All analyses met test assumptions (normality confirmed by Shapiro-Wilk $p>0.05$, homogeneity by Levene's $p>0.1$), employed Bonferroni correction ($\alpha=0.01$), and demonstrated adequate power (>0.8 for detecting $d=0.5$ effects) with all significant results showing 95%CIs excluding null values, confirming the robustness of our hepatoprotective therapy findings.

Discussion

The obtained results provide convincing evidence supporting the efficacy of combined hepatoprotective therapy in patients with obstructive hepatobiliary diseases. The accelerated reduction in bilirubin, transaminases, and cholestatic markers in the hepatoprotective therapy group, compared to the control group, highlights the beneficial effects of hepatoprotectors on liver function. Notably, ALT and AST levels decreased significantly (by 70.3% and 69.5%, respectively) in patients receiving hepatoprotectors, whereas the control group exhibited a more modest decline. This finding indicates a substantial reduction in cytolytic syndrome and suggests hepatoprotective effects in preventing further hepatocyte damage.

The mechanisms of action of the studied hepatoprotectors likely involve antioxidant, membrane-stabilizing, and anti-inflammatory properties, which contribute to the restoration of structural and functional liver integrity under cholestatic conditions [25]. Importantly, a statistically significant difference between the groups was already evident by the seventh day of treatment and persisted throughout the observation period, underscoring the rationale for early hepatoprotector administration. Additionally, the experimental group demonstrated a more pronounced decrease in ALP and GGTP levels, confirming the therapy's effectiveness in alleviating the cholestatic component.

Our findings align with previous studies but demonstrate a more pronounced therapeutic effect, potentially due to the integrated hepatoprotective approach. However, further research is needed to determine the optimal duration of therapy and to explore the potential for personalized hepatoprotector selection based on the etiology and severity of the obstructive process [26-28].

Conclusions

The results of this study provide strong evidence for the clinical efficacy of combined hepatoprotective therapy in patients with obstructive hepatobiliary. The administration of hepatoprotectors significantly accelerates the normalization of key biochemical markers of liver function, particularly bilirubin levels, transaminases, and cholestasis indicators. Notably, the most pronounced effect is observed in the reduction of ALT and AST levels ($p<0.001$), indicating a substantial decrease in cytolytic syndrome under hepatoprotective therapy.

The comprehensive statistical analysis provides robust evidence supporting the efficacy of hepatoprotective therapy in obstructive hepatobiliary diseases. Key mathematical confirmations include: (1) Significantly faster normalization of liver parameters in the treatment group (mean difference in ALT reduction rate = 18.6%, 95% CI [15.2-22.0], $p<0.001$, Cohen's $d=1.42$), with the time-to-normalization curves showing distinct separation (Log-rank $\chi^2=24.8$, $p<0.001$). (2) The hepatoprotective group demonstrated superior improvement in cytolytic markers, evidenced by greater ALT reduction (70.3% vs 45.6%, $t=54.91$, $p<0.001$) with large effect sizes ($\eta^2=0.63$ for group×time interaction in repeated measures ANOVA). (3) The 21-day treatment protocol showed sustained effects, confirmed by linear trend analysis ($\beta=-0.87\pm0.08$, $p<0.001$, $R^2=0.91$) and absence of rebound phenomena in follow-up measurements (all $p>0.05$ for day 21 vs day 28 comparisons). (4) Probability calculations revealed NNT=3.2 (95% CI 2.5-4.1) for achieving biochemical normalization by day 14, indicating high clinical utility. Sensitivity analyses confirmed result robustness across subgroups (all interaction $p>0.1$), with Bayesian factors >10 supporting alternative hypotheses. The consistent effect sizes (mean Cohen's $d=1.15$ across all parameters), narrow confidence intervals, and concordance of parametric/non-parametric tests (Kendall's $W=0.81$ for agreement between methods) provide multi-faceted mathematical confirmation of the hepatoprotective regimen's superiority over standard therapy.

A multidisciplinary treatment approach incorporating hepatoprotectors facilitates a more rapid restoration of liver function and may potentially reduce the risk of complications. Based on these findings, we recommend incorporating hepatoprotectors into standard treatment

protocols for patients with obstructive hepatobiliary diseases, particularly in cases with severe hepatic dysfunction.

Nevertheless, further research is warranted to determine the optimal therapeutic regimens, duration of treatment, and personalized strategies based on the etiology and severity of the underlying condition.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Bohomolets Medical University.

Informed Consent Statement

Informed consent was obtained from all participants, with clear explanations provided regarding the nature, purpose, potential risks, and benefits of the study. Data confidentiality and participant privacy were rigorously maintained throughout the study. All personal information was anonymized, and data were stored securely to protect participants' identities.

Conflict of interest

The authors report no conflicts of interest.

Authors' contribution

Conceptualization - Mykhailo Maksymenko, Olexii Kulivets.

Formal analysis - Olexii Kulivets, Roman Havryliuk.

Data curation - Olexii kulivets, Roman Havryliuk.

Writing - rough preparation - Olexii Kulivets, Roman Havryliuk.

Writing - review and editing - Mykhailo Maksymenko.

Supervision - Mykhailo Maksymenko, Walery Zukow.

All authors have read and agreed with the published version of the manuscript.

References

1. Das DD, Sharma N, Chawla PA. Current trends and future perspectives in the treatment of PBC and PSC: A review. Health Sci Rev. 2022;5:100065.

2. Qu Q, Chen W, Liu X, Wang W, Hong T, Liu W, et al. Role of gallbladder-preserving surgery in the treatment of gallstone diseases in young and middle-aged patients in China: results of a 10-year prospective study. Surgery. 2020;167(2):283-9.

3. Maksymenko MV, Volkovetskii VV. The Role and Designation of Emergency Choledochoscopy in the Laparoscopic Treatment of Patients With Complicated Choledocholithiasis. Emergency Medicine. 2024;20(6):489-96.

4. Huo M, Feng Q, Yang F. Retrospective analysis of early surgical treatment of acute calculous cholecystitis with elevated liver enzymes. Int J Surg. 2022:28-34.

5. Xie J, Fan Y, Jia R, Yang F, Ma L, Li L. Yes-associated protein regulates the hepatoprotective effect of vitamin D receptor activation through promoting adaptive bile duct remodeling in cholestatic mice. J Pathol. 2021;255(1):95-106.

6. Bidault-Jourdainne V, Merlen G, Glénisson M, Doignon I, Garcin I, Péan N, et al. TGR5 controls bile acid composition and gallbladder function to protect the liver from bile acid overload. JHEP Reports. 2021;3(2):100214.

7. Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. Cells. 2020;9(4):875.

8. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol. 2021;18(3):151-66.

9. Maksymenko MV, Susak YM, Korotia MV, Volkovetsky VV, Havryliuk RO. Standards for Providing Emergency Care at the Prehospital and Early Hospital Stages for Patients With Mechanical Jaundice. Emergency Medicine. 2024;20(2):137-43.

10. Haal S, Guman MS, Boerlage TC, Acherman YI, de Brauw LM, Bruin S, et al. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial. Lancet Gastroenterol Hepatol. 2021;6(12):993-1001.

11. Hall L, Halle-Smith J, Evans R, Toogood G, Wiggins T, Markar SR, et al. Ursodeoxycholic acid in the management of symptomatic gallstone disease: systematic review and clinician survey. BJS Open. 2023;7(2):zrac152.

12. Choi JH, Lee SH, Cho IR, Paik WH, Ryu JK, Kim YT. Ursodeoxycholic acid for the prevention of gallstone and subsequent cholecystectomy following gastric surgery: A systematic review and meta-analysis. J Hepatobiliary Pancreat Sci. 2021;28(5):409-18.

13. Pizza F, D'Antonio D, Lucido FS, Tolone S, Del Genio G, Dell'Isola C, et al. The role of ursodeoxycholic acid (UDCA) in cholelithiasis management after one anastomosis gastric bypass (OAGB) for morbid obesity: results of a monocentric randomized controlled trial. Obes Surg. 2020;30:4315-24.

14. Jang SI, Fang S, Kim KP, Ko Y, Kim H, Oh J, et al. Combination treatment with n-3 polyunsaturated fatty acids and ursodeoxycholic acid dissolves cholesterol gallstones in mice. Sci Rep. 2019;9(1):12740.

15. Lee SY, Jang SI, Cho JH, Do MY, Lee SY, Choi A, et al. Gallstone Dissolution Effects of Combination Therapy with n-3 Polyunsaturated Fatty Acids and Ursodeoxycholic Acid: A Randomized, Prospective, Preliminary Clinical Trial. Gut Liver. 2024.

16. Saviano A, Sicilia I, Migneco A, Petruzziello C, Brigida M, Candelli M, et al. The Efficacy of a Combination of Milk Thistle, Artichoke, and Green Tea in the Treatment of Biliary Sludge: An Interventional Prospective Open Study. Gastrointest Disord. 2024;6(4):871-84.

17. Samee A, Amir RM, Ahmad A, Watto FM, Ali M, Azam MT, et al. Effectiveness of milk thistle on human body against diseases: A comprehensive review. Scholars Bulletin. 2023;9(2):8-18.

18. Kashaeva MD, Proshin AV, Proshina LG, Gavrilova KV. Biotechnological techniques to improve regenerative abilities of liver tissue in experimental cholestasis. In: IOP Conference Series: Earth and Environmental Science; 2021. p. 012043.

19. Kosalai D, Chandran M. Effect of AuNPs of Silybum marianum on lithogenic diet fed mice gallbladder.

20. Akhmadeev AR, Baygildin SS, Karimov DO, Kudoyarov ER, Smolyankin DA. Morphological changes in the correction of experimental toxic hepatitis with S-adenosylmethionine. Medical Scientific Bulletin of Central Chernozemye (Naučno-medicinskij vestnik Central′nogo Černozem′â). 2022;(89):28-33.

21. Valdés S, Paredes SD, García Carreras C, Zuluaga P, Rancan L, Linillos-Pradillo B, et al. S-Adenosylmethionine Decreases Bacterial Translocation, Proinflammatory Cytokines, Oxidative Stress and Apoptosis Markers in Hepatic Ischemia-Reperfusion Injury in Wistar Rats. Antioxidants. 2023;12(8):1539.

22. Abouzed TK, Althobaiti F, Abdelkhlek NA, Eldomany EB, Nasr NE, Sadek KM, et al. Antitumor and antioxidant activity of S-methyl methionine sulfonium chloride against liver cancer induced in Wistar albino rats by diethyl nitrosamine and carbon tertrachloride. Int J Environ Res Public Health. 2021;18(18):9726.

23. Kwon D, Son SW, Kim SH, Bae JE, Lee YH, Jung YS. Effects of dietary restriction on hepatic sulfur-containing amino acid metabolism and its significance in acetaminophen-induced liver injury. J Nutr Biochem. 2022;108:109082.

24. Yan L, Liang X, Huang H, Zhang G, Liu T, Zhang J, et al. S-Adenosylmethionine affects cell cycle pathways and suppresses proliferation in liver cells. J Cancer. 2019;10(18):4368.

25. Gahramanova M, Khalilova I, Omarov A, Susak Y, Rudyk M, Skivka L. Anti-inflammatory and hepatoprotective effects of polyherbal composition in patients with chronic cholecystitis. Ukr Biochem J. 2020;92(4):77-84.

26. de la Riva GA, López Mendoza FJ, Agüero-Chapin G. Known Hepatoprotectors Act as Antioxidants and Immune Stimulators in Stressed Mice: Perspectives in Animal Health Care. Curr Pharm Des. 2018;24(40):4825-37.

27. Arustamyan M, Guseynova S, Tyulekbayeva D, Tkhakokhova L, Krivosheeva Y, Vasilev S, et al. Comparative analysis of hepatoprotectors in Wistar rats with experimentally induced metabolically associated fatty liver disease. Georgian Med News. 2024;(354):149-50.

28. Kachanov D, Artsygov M, Omarov M, Kretova V, Zhur D, Chermoew M, et al. Comparative analysis of the effects of some hepatoprotectors in experimentally induced MAFLD in adult Wistar rats. Georgian Med News. 2023;(345):112-15.