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CORRELATION OF APOPTOSIS MARKERS LEVELS WITH THE DEVELOPMENT OF HEPATIC FAILURE IN MALIGNANT OBSTRUCTIVE JAUNDICE

Obstructive jaundice (OJ) is a common diagnosis in everyday clinical practice, which requires a thorough understanding of pathophysiological changes occurring in the liver to plan ongoing treatment and predict its effectiveness in the postoperative period. The study **aimed** to determine the dynamics of changes in the levels of apoptosis markers (caspase-3 and BCL-2) at the time of preoperative biliary decompression (PBD) and major surgery depending on the severity of the hepatic failure (HF) and to evaluate their correlation with the severity grade of HF in patients with malignant obstructive jaundice (MOJ). **Materials and Methods.** The study included 104 patients with MOJ who underwent PBD. All patients were diagnosed with HF of moderate severity (n = 65) or severe HF (n = 39). During PBD and main surgical intervention, the levels of caspase-3 and BCL-2 were determined in blood serum and bile by the Sandwich-ELISA method. **Results.** The values of apoptosis markers in patients with moderate and severe HF were significantly different at the time of PBD and major surgery ($p < 0.001$). PBD significantly reduced the levels of caspase-3 and increased the levels of BCL-2 in sera of patients with MOJ and HF, which was confirmed by further intraoperative values of the indicators, $p < 0.001$. Imbalance of serum caspase-3 ($R^2_{Nagelkerke} = 0.553$, $p = 0.013$) and BCL-2 ($R^2_{Nagelkerke} = 0.327$, $p = 0.003$) levels was associated with severe HF. **Conclusions.** The indicators of apoptosis after PBD can serve as additional markers of the effectiveness of a patient's treatment in the preoperative period and can be included in the diagnostic and therapeutic algorithm for patients with MOJ.

Keywords: apoptosis, jaundice, biliary decompression, hepatic failure.

Obstructive jaundice (OJ) is a common diagnosis in everyday clinical practice, which requires a thorough understanding of pathophysiological changes to plan current and future treatment. Clinically, mortality in patients with OJ is due to prolonged biliary obstruction with the development of necrobiotic and degenerative changes in liver parenchyma and progressive endotoxemia in the setting of general comorbidity. Biliary decompression is often performed against an unfavorable background due to the long course of the disease, and existing methods of correcting hepatic metabolic disorders do not comprehensively take into account all pathophysiological mechanisms leading to the development of hepatic failure (HF) [1]. In this regard, the main task of OJ treatment is a pathogenetically based method of restoring the functional activity of the liver [2—4]. Therefore, more and more attention has been paid recently to the study of pathophysiological processes occurring in the liver to determine the optimal management of patients in the preoperative period and predict postoperative treatment outcomes.

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Caspase-3 is a "cell death" protease that induces apoptosis in cells. It is expressed in almost all tissues but mostly in the structural components of the liver: hepatocytes, sinusoidal cells, portal zones and intrahepatic focal necrosis, and bile duct epithelium. This fact illustrates the close interconnection of all liver tissue elements with the development of pathological processes [5]. The expression of caspase-3 as an apoptotic effector caspase can serve as an early marker of liver damage [6]. BCL-2 (B-cell/lymphoma 2) is one of the most important antiapoptotic proteins, whose overexpression and phosphorylation may be involved in regulating cell proliferation, cell cycle, DNA repair, tumorigenesis, and chemoresistance [7]. Apoptotic signaling is regulated by the balance between pro- and antiapoptotic factors. The severity of liver damage may result from an imbalance between these factors [8].

In our previous research [9], we studied the changes in the hepatocyte apoptosis markers levels in malignant OJ complicated by cholangitis. In the present work, we aimed to determine the dynamics of changes in the levels of apoptosis markers (caspase-3 and BCL-2) at the time of preoperative biliary decompression (PBD) and major surgery depending on different severity of HF; a possible correlation between the levels of apoptosis markers and the presence of HF in patients with malignant obstructive jaundice (MOJ) was another focus of the present investigation.

Materials and Methods

We have conducted a single-center prospective cohort study, which included 104 patients with MOJ who underwent treatment at the First Department of General Surgery, Bogomolets National Medical University in the period from 2016 to 2023 (including 84 from the previous study [9]). The main endpoints were:

- to determine the dynamics of changes in the levels of apoptosis markers (caspase-3 and BCL-2) at the time of PBD and major surgery in patients with HF of different severity;
- to analyze the relationship between the levels of apoptosis markers and the development of HF.

Research inclusion, non-inclusion, and exclusion criteria were similar to the study [9]. The following inclusion criteria were applied: MOJ, tumor resectability, age of patients over 18 years, patient's consent to participate in the study, and further outpatient monitoring. Non-inclusion criteria: any invasive biliary tract surgery for the underlying disease before hospitalization, V—VI risk ASA class of surgery, acute surgical pathology not related to the underlying disease, decompensated comorbidities, diagnosed viral hepatitis and medical history of viral hepatitis, chronic HF, ascites, and neoadjuvant chemotherapy. We excluded patients who refused diagnosis and treatment at any stage of the study or cases of death not related to the underlying disease. The patients included in the study were examined in accordance with the international and national standards for the diagnosis and treatment of cancer patients [10, 11]. Permission to conduct the study was approved by the expert decision of the bioethical commission dated 20.06.2022, protocol No. 159. All study procedures were carried out following the current legislation of Ukraine on ethics, the principles of Good Clinical Practice (ICH 6CP), and the recommendations of the Declaration of Helsinki 2013.

The decision concerning PBD intervention and its type was made based on the results of the survey and multidisciplinary discussion. A cumulative classification was used to confirm the diagnosis of HF. It was based on previous literature data analysis and clinical guidelines, taking into account the levels of alanine aminotransferase and aspartate aminotransferase (hepatocellular damage at a value of > 1.5 x upper limit of normal [12, 13]: > 1.5—5 x upper limit of normal value — moderate severity of HF, and > 5 x upper limit of normal value — severe HF). Bilirubin level ≥ ≥ 171 μmol/L, INR ≥ 1.5; prothrombin index: 40—70% — moderate, < 40% — severe HF; and albumin level: 30—35 g/L — moderate, <30 g/L — severe HF [14]. All patients enrolled in the study underwent PBD. Of the 104 patients, 76 (73%) underwent endobiliary stenting (EBS) and 28 (27%) underwent percutaneous transhepatic biliary drainage (PTBD). The main indications for biliary decompression were acute ascending cholangitis, severe skin pruritus, hyperbilirubinemia > 250 μmol/L, severe nutritional deficiency, and delayed surgical treatment [15].

The clinicopathological characteristics of the study group patients are presented in Tables 1 and 2.

The method for taking biological material for the experiment and its processing was identical to the one previously published [9]. The samples were collected at the stage of PBD and intraoperatively. The levels of caspase-3 and BCL-2 were determined in serum and bile during PBD and

Table 1. **Characteristics of patients in the study group**

Characteristics	PBD group (*n* = 104)
Age, years	62 (56—69)
Males, *n* (%)	63 (60.6%)
Females, *n* (%)	41 (39.4%)
BMI*, kg/m^2	27.2 (25.7—28.7)
Comorbidities, *n* (%)	62 (59.6%)
ASA, class	
II	4
III	76
IV	24

Notes: * Median (QI—QIII); PBD — preoperative biliary decompression; BMI — body mass index; ASA — American Society of Anesthesiologists (Physical Status Classification System).

Table 2. **Clinicopathological characteristics of the study group of patients**

Characteristics	PBD group (*n* = 104)
Histological type of tumor	
Adenocarcinoma	104
Histological grade	
G2	85
G3	19
Localization of the primary tumor	
Pancreas	73
Choledochus	12
Papilla Vateri	16
Duodenum	3
TNM classification	
T1	18
T2	49
T3	37
N0	67
N1	31
N2	6
M0	104
Stage of the disease	
I	53
II	45
III	6

major surgery by the Sandwich-ELISA technique. The following reagents were used: an ELISA kit for the quantitative determination of caspase-3 concentration E-EL-H0017 and an ELISA kit for the quantitative determination of BCL-2 concentration E-EL-H0114 (Elabscience, USA).

The statistical analysis of the results was performed using the Mann — Whitney U-test, Wilcoxon's and Friedman's analyses, correlation analysis with Spearman's coefficient, linear regression analysis, and binary logistic regression analysis using the statistical program SPSS 22.0 for Windows and MedStat.

Results

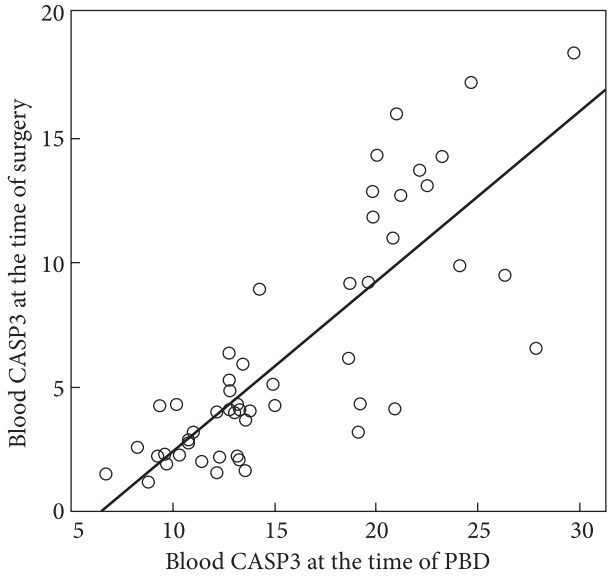
All patients included in the study group were diagnosed with HF of moderate severity grade (62%, n = = 65), or severe (38%, n = 39). The mean values of apoptosis markers depending on the stage of sampling in patients with moderate HF are shown in Table 3.

First, we analyzed patients with moderate HF. Using Friedman's analysis, we found that the values of apoptosis markers in patients with moderate HF at the time of PBD and major surgery significantly differed ($p < 0.001$). A further posteriori analysis of the results revealed a significant decrease in the levels of serum and bile caspase-3 ($p < 0.001$) and an increase in the levels of serum and bile BCL-2 in the dynamics ($p < 0.001$). A strong correlation was also found between the levels of serum caspase-3 ($r = 0.812$, $p < 0.001$), bile caspase-3 ($r = 0.811$, $p < 0.001$), serum BCL-2 ($r = 0.753$, $p < 0.001$), and bile BCL-2 ($r = 0.734$, $p < 0.001$) compared at the time of PBD and major surgery. The linear regression analysis showed a correlation between these parameters at the time of PBD and the main surgical intervention: serum caspase-3 ($R^2_{Nagelkerke} = 0.656$, $p < 0.001$), bile caspase-3 ($R^2_{Nagelkerke} = 0.624$, $p < 0.001$), serum BCL-2 ($R^2_{Nagelkerke} = 0.554$, $p < 0.001$), and bile BCL-2 ($R^2_{Nagelkerke} = 0.591$, $p < 0.001$) (Figs. 1—4).

Table 3. **Comparison of mean values (M (QI—QIII)) of apoptosis markers in moderate HF**

Indicator	Period of sampling		p^*
	PBD	Intraoperative	
Serum caspase-3	13.46 (11.61—19.96)	4.26 (2.62—9.40) ↓	< 0.001
Bile caspase-3	13.02 (10.54—19.48)	5.17 (2.19—9.12) ↓	
Serum BCL-2	4.19 (1.21—6.18)	11.11 (8.12—13.23) ↑	
Bile BCL-2	3.26 (2.19—5.97)	10.11 (7.54—11.97) ↑	

Note: * the Wilcoxon test.



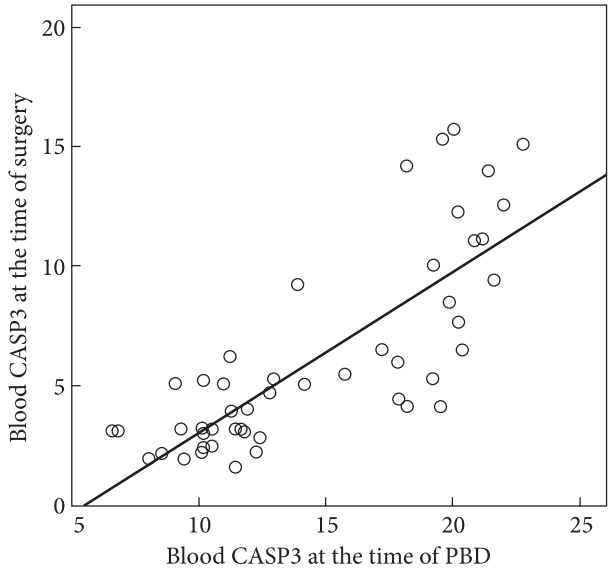
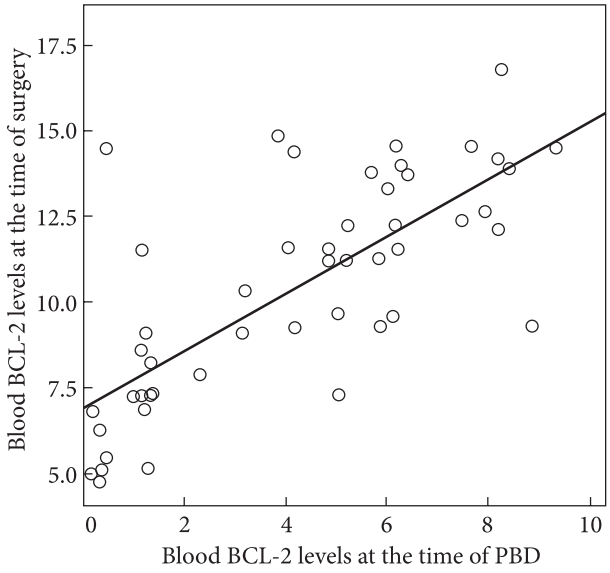


Fig. 1. Linear univariate model of the relationship between serum caspase-3 levels at the time of PBD and at the time of surgery in patients with moderate HF

Fig. 2. Linear univariate model of the relationship between bile caspase-3 levels at the time of PBD and at the time of surgery in patients with moderate HF



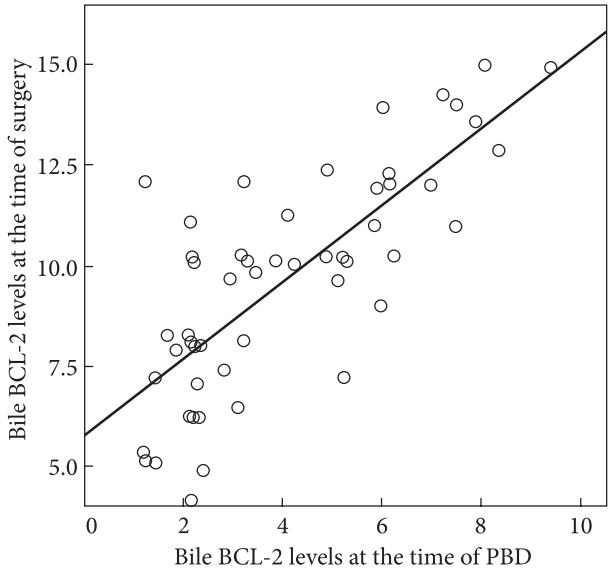


Fig. 3. Linear single-factor model of the relationship between serum BCL-2 levels at the time of PBD and at the time of surgery in patients with moderate HF

Fig. 4. Linear single-factor model of bile BCL-2 levels at the time of PBD and at the time of surgery in patients with moderate HF

Next, we analyzed patients with severe HF. The Friedman analysis showed that the values of apoptosis markers in patients with severe HF at the time of PBD and major surgery significantly differed ($p < 0.001$) (Table 4).

We revealed a significant decrease in serum and bile caspase-3 levels ($p < 0.001$) and an increase in serum and bile BCL-2 levels in the dynamics ($p < < 0.001$). Also, a strong significant correlation (Spearman's coefficient) was established between the levels of serum caspase-3 ($r = 0.732$, $p < 0.001$), bile caspase-3 ($r = 0.735$, $p < 0.001$), serum BCL-2 ($r = = 0.613$, $p < 0.001$), and bile BCL-2 ($r = 0.703$, $p < < 0.001$) at the time of PBD and major surgery. The linear regression analysis showed a correlation between these parameters at the time of PBD and the main surgical intervention: serum caspase-3 ($R^2_{\text{Nagelkerke}} = 0.572$, $p < 0.001$), bile caspase-3

($R^2_{Nagelkerke}$ = 0.598, p < 0.001), serum BCL-2 ($R^2_{Nagelkerke}$ = 0.385, p < 0.001), and bile BCL-2 ($R^2_{Nagelkerke}$ = 0.510, p < 0.001) (Figs. 5—8).

The comparison of the mean values of apoptosis markers at the time of PBD depending on the severity of HF found that they did not differ statistically significantly, p > 0.05, except for the value of serum caspase-3, p = 0.02 (Table 5).

The binary logistic analysis established a statistically significant relationship between the apoptosis markers at the time of PBD and severe HF serum caspase-3 ($R^2_{Nagelkerke}$ = 0.553, p = 0.013) and serum BCL-2 ($R^2_{Nagelkerke}$ = 0.327, p = 0.003) levels. At that time, there was no statistically significant relationship between the levels of apoptosis markers in bile samples and the severity of HF: bile caspase-3 (p = = 0.193) and bile BCL-2 (p = 0.393).

The comparison of the mean values of apoptosis markers at the time of surgery depending on the severity of HF revealed that they did not differ significantly, p > 0.05 (Table 6).

The binary logistic analysis did not reveal a significant relationship between the levels of apoptosis markers at the time of radical surgery and the severity of HF: caspase-3 blood (p = 0.149); caspase-3 bile (p = 0.097); BCL-2 blood (p = 0.839); BCL-2 bile (p = 0.786).

Discussion

Apoptosis is a highly regulated form of programmed cell death. In healthy organisms, the number of cells destroyed by apoptosis is equal to the number of cells formed as a result of mitosis, ensuring proper organ homeostasis. In addition, "physiological" apoptosis allows the removal of cells with virtually no release of proinflammatory cytokines and minimal immune response. However, in pathophysiological processes, the balance between cell proliferation and cell death often changes, leading to the loss of tissue homeostasis and the occurrence of liver diseases. Excessive and/or prolonged apoptosis can lead to acute or chronic HF. Hence, strategies aimed at inhibiting apoptosis in liver dysfunction have the potential to become a powerful tool for the treatment of liver diseases [16, 17].

The increased concentrations of bile acids accumulating in hepatocytes due to a decreased bile flow in cholestatic liver injury cause liver damage. Although the mechanisms of liver damage are associated with cholestasis, bile acid-mediated hepatotoxicity can play a key role in the pathogenesis of liver diseases. Hydrophobic bile acids (in particular, glycocholic acid) induce hepatocyte apoptosis in vitro and in vivo. Ursodeoxycholic acid is cytoprotective, stabilizes the hepatocyte cell membrane, increases protection against oxidative stress, and in-

Table 4. **Comparison of mean values (M (QI—QIII)) of apoptosis markers in severe HF**

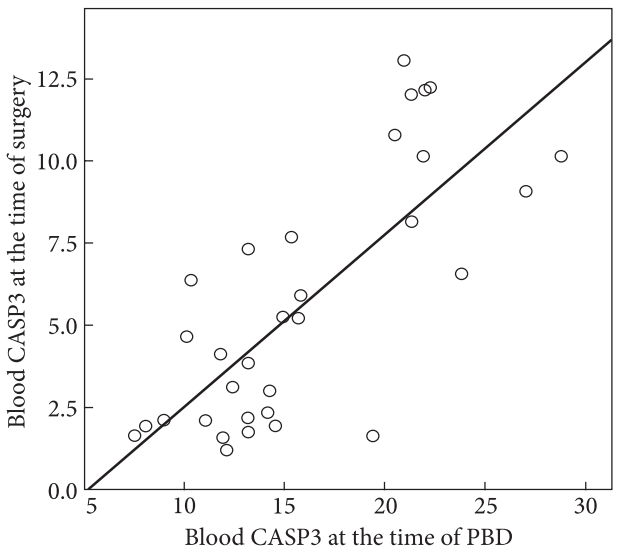
Indicator	Period of sampling		p^*
	PBD	Intraoperative	
Serum caspase-3	21.32 (19.84—23.83)	4.93 (2.11—8.85) ↓	< 0.001
Bile caspase-3	13.54 (10.99—18.32)	6.07 (3.06—8.22) ↓	
Serum BCL-2	1.32 (1.01—4.19)	10.0 (7.31—13.15) ↑	
Bile BCL-2	3.93 (2.19—6.12)	9.30 (7.40—11.56) ↑	

Note: * the Wilcoxon test.

Table 5. **Comparison of mean values (M (QI—QIII)) of apoptosis markers at the time of PBD depending on the severity of HF**

Indicator	Severity degree of HF		p^*
	Moderate	Severe	
Serum caspase-3	13.46 (11.61—19.96)	21.32 (19.84—23.83)	0.024
Bile caspase-3	13.02 (10.54—19.48)	13.54 (12.82—18.24)	0.772
Serum BCL-2	4.19 (1.21—6.18)	1.32 (1.01—4.19)	0.062
Bile BCL-2	3.26 (2.19—5.97)	3.93 (2.19—6.12)	0.916

Note: * The Mann — Whitney test.



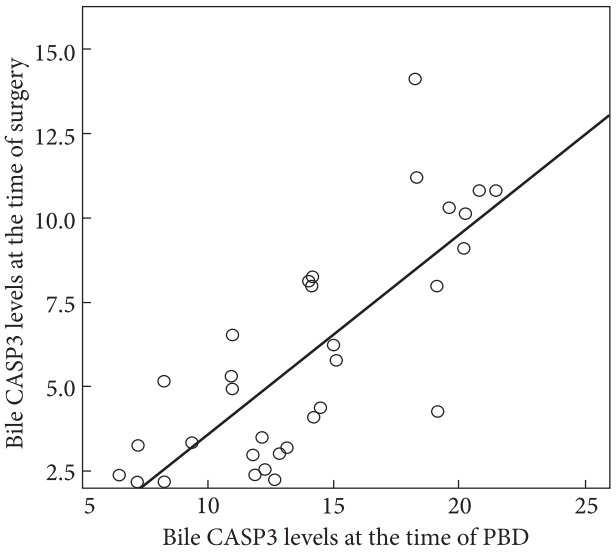
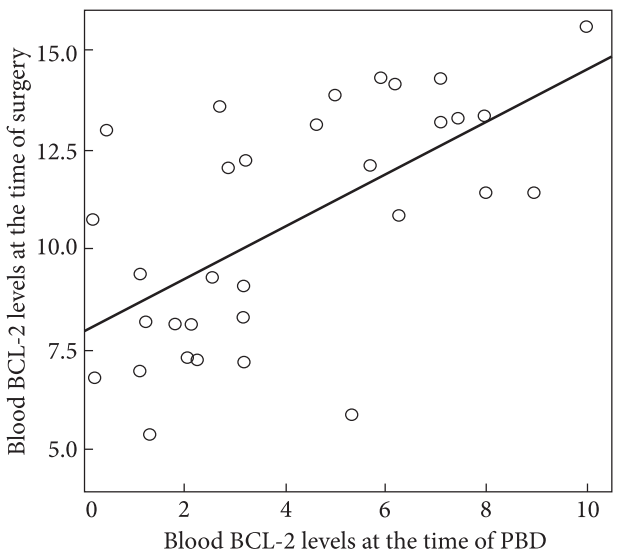


Fig. 5. Linear single-factor model of the relationship between serum caspase-3 levels at the time of PBD and at the time of surgery in severe HF

Fig. 6. Linear single-factor model of the relationship between serum BCL-2 levels at the time of PBD and at the time of surgery in severe HF



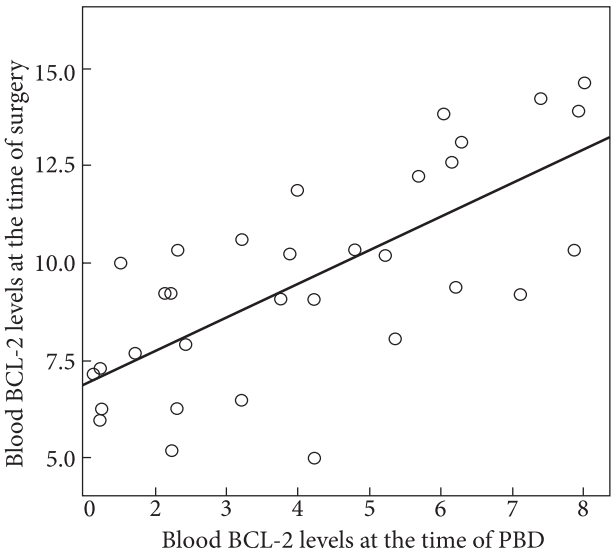


Fig. 7. Linear single-factor model of the relationship between serum BCL-2 levels at the time of PBD and at the time of surgery in severe HF

Fig. 8. Linear univariate model of the relationship between serum BCL-2 levels at the time of PBD and at the time of surgery in severe HF

Table 6. **Comparison of the mean values (M (QI—QIII)) of apoptosis markers at the time of surgery depending on the severity of HF**

Indicator	Severity degree of HF		p^*
	Moderate	Severe	
CASP3 blood	4.26 (2.62—9.40)	4.93 (2.11—8.85)	0.537
CASP3 bile	5.17 (2.19—9.12)	6.07 (3.06—8.22)	0.908
BCL-2 blood	10.0 (7.31—13.15)	11.11 (8.12—13.23)	0.761
BCL-2 bile	10.11 (7.54—11.97)	9.30 (7.40—11.56)	0.854

Note: * The Mann — Whitney test.

hibits apoptosis of hepatocytes [18, 19]. Bile acids trigger hepatocyte apoptosis by the ligand-independent activation of death receptors and subsequent apoptotic death of cholangiocytes [20, 21].

BCL-2 is one of the most important antiapoptotic proteins that acts at the mitochondrial level, integrating death and survival signals, which prevents excessive apoptosis [7]. Hepatic overexpression of BCL-2 can cause a drastic accumulation of serum bile acid and bilirubin and dysregulate bile acid synthetic enzymes and transporters. BCL-2 reactivation triggered severe liver injury, fibrosis, and inflammation [22]. There is a high level of BCL-2 protein in many human tumors, such as liver, prostate, colon, lung, stomach, and breast cancer, lymphoma, and neuroblastoma. However, studies on the role of BCL-2 in hepatocellular carcinoma are scarce. The study [8] demonstrated that normal hepatocytes did not express BCL-2, and the expression of BCL-2 by hepatocytes during cholestasis suggested an adaptive phenomenon to resist apoptosis by toxic bile salts. Hepatocytes in the ligated bile duct of rats expressed BCL-2, which prevented hepatocellular apoptosis caused by cholestasis.

In the presence of massive hepatocyte apoptosis, the ability of phagocytic cells to remove effectively and rapidly dead cells in the tissue is overloaded with accumulation and subsequent autolysis of apoptotic bodies and release of their proinflammatory contents. Moreover, some studies have demonstrated that the uptake of apoptotic bodies by Kupffer cells, the main phagocytes in the liver, enhances the expression of Fas ligands and the proinflammatory cytokine TNF-α, thus accelerating hepatocyte apoptosis and causing liver inflammation [23].

Apoptosis is mediated by the activation of caspases. Expression of caspase-3 as an apoptotic effector caspase is an early marker of liver damage [24, 25].

In conclusion, our data have shown that PBD significantly reduces the levels of caspase-3 and increases the levels of BCL-2 in sera of patients with MOJ and HF, which was confirmed by further intraoperative values of indicators, $p < 0.001$. The imbalance of serum caspase-3 levels ($R^2_{\text{Nagelkerke}} = 0.553$, $p = 0.013$) and BCL-2 ($R^2_{\text{Nagelkerke}} = 0.327$, $p = 0.003$) was associated with severe HF. Given the topic of our analysis and the results obtained, the levels of apoptosis markers may indicate the presence and severity of HF. The dynamics of the values of indicators after PBD can serve as an additional marker of the effectiveness of the patient's treatment in the preoperative period and can be included in the diagnostic and therapeutic algorithm in patients with MOJ. However, these suggestions should be confirmed by further observational studies in a larger cohort of patients.

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КОРЕЛЯЦІЙНИЙ АНАЛІЗ ЗВ'ЯЗКІВ РІВНІВ МАРКЕРІВ АПОПТОЗУ З РОЗВИТКОМ ПЕЧІНКОВОЇ НЕДОСТАТНОСТІ ПРИ ОБТУРАЦІЙНІЙ ЖОВТЯНИЦІ ПУХЛИННОГО ГЕНЕЗУ

Обтураційна жовтяниця (ОЖ) є поширеним діагнозом у повсякденній клінічній практиці, що потребує глибокого розуміння патофізіологічних змін, які відбуваються в печінці, для планування поточного лікування та прогнозування його ефективності в післяопераційному періоді. **Метою** дослідження було визначити динаміку змін рівнів маркерів апоптозу (каспази-3 та BCL-2) на час проведення передопераційної біліарної декомпресії (ПБД) та основного оперативного втручання при різних ступенях тяжкості печінкової недостатності (ПН) та оцінити кореляційний зв'язок рівнів маркерів апоптозу з наявністю ПН у пацієнтів з ОЖ пухлинного генезу. **Матеріали та методи.** У дослідження було включено 104 пацієнти з ОЖ пухлинного генезу, яким була виконана ПБД. У всіх пацієнтів встановлено діагноз ПН: середнього ступеня тяжкості у 65 пацієнтів (62%) і тяжкого у 39 (38%) пацієнтів. Рівні каспази-3 та BCL-2 визначали в сироватці крові та в жовчі під час проведення ПБД та основного оперативного втручання шляхом застосування імуноферментного аналізу непрямого типу. Бінарний логістичний аналіз встановив статистично значимий зв'язок тільки між значеннями каспази-3 сироватки крові ($R^2_{Nagelkerke}$ = = 0,553; p = 0,013) і BCL-2 сироватки крові ($R^2_{Nagelkerke}$ = 0,327; p = 0,003) та тяжкою ПН на момент виконання ПБД; рівень маркерів апоптозу в зразках жовчі (каспаза-3 жовчі (p = 0,193); BCL-2 жовчі (p = 0,393)) був статистично недостовірним. **Висновок**. Виконання ПБД статистично значимо зменшує рівень маркерів апоптозу в пацієнтів з ОЖ пухлинного генезу та ПН, що підтверджено подальшими інтраопераційними значеннями показників (p < 0,001). Дисбаланс каспази-3 та BCL-2 крові асоціюється з тяжкою ПН. Етапне хірургічне втручання з виконанням ПБД за чіткими показами є необхідною стратегією лікування подібних когорт пацієнтів.

Ключові слова: апоптоз, жовтяниця, біліарна декомпресія, печінкова недостатність.