RISK STRATIFICATION OF POSTOPERATIVE COMPLICATIONS IN JAUNDICED PATIENTS WITH FOCAL DISEASES OF THE BILIOPANCREATODUODENAL ZONE

P. Muraviov[1,2], B. Zaporozhchenko[1,2], I. Borodaev[1,2], V. Shevchenko[1,2],

M. Zaporozhchenko[1,2], Makrem Harhouri[1]

[1]Odessa National Medical University, Department of Surgery, Odessa

[2]MUI 'Odessa Regional Clinical Medical Center' of the Odessa Regional Council,

Department of Surgery, Odessa;

Correspondence to: Dr Petro Muraviov, Department of Surgery, Odessa National Medical University, 2 Valikhovsky Lane, 65082 Odesa, Ukraine
E-mail: gemostatik@gmail.com
[*]Contributed equally

Abstract

The risk stratification was performed by mathematical modeling taking into account genetic factors and the results of instrumental research as ultrasonic elastography. The results of 272 jaundiced patients' surgical treatment as pancreaticoduodenal resection (PDR) for malignant tumors of biliopancreatoduodenal area (218 patients) and chronic pseudotumoral pancreatitis (54 patients) were analyzed. In the main group (n=112) the optimized algorithm of preoperative preparation and risk stratification was used and in the comparison group (n=160) preparation for PDR was carried out conservatively according to generally accepted standards. radical surgery is defined as inexpedient and too risky, while shunt decompression surgery is performed as a first step for pancreatoduodenal resection. Thanks to the preoperative preparation according to our algorithm, mental status evaluation in the main

group compared to the comparison one was significantly better. By MoCA scale before surgery it was 24.9 ± 3.2 and 22.8 ± 2.4 points, and by the DSST test - 40.2 ± 3.8 and 23.6 ± 2.6 points in the main and comparison groups respectively. The level of bilirubinemia in patients of the main group on the day before PDR was 112.3 ± 2.7 µmol/l, while in the comparison one it was 198.3 ± 3.3 µmol/l ($p < 0.05$). On the eve of the PDR, the activity of alkaline phosphatase was in the main group 104.8 ± 1.3 U / l, and in the comparison group - 270.8 ± 1.9 U / l ($p < 0.05$). Before PDR, γ-glutamiltransferase activity significantly decreased to 529 ± 29 U / l in the comparison group and to 485 ± 33 U / l in the main group ($p < 0.05$).

Key words: postoperative complications; mechanical jaundice; biliary decompression; biliopancreatoduodenal zone; risk stratification; phenotype.

Introduction. Despite the significant advances in surgery achieved in the treatment of the pancreatobiliary zone diseases, obstructive jaundice stays one of the main causes of death in patients with such pathology (1, 2, 3, 4). Surgical interventions at the height of obstructive jaundice increase as the number of postoperative complications so mortality, which reaches 50%, while in patients who underwent radical surgery after jaundice relief, complications are much less common (5, 6). In this regard, the prediction of the risk of developing various intra- and, most importantly, postoperative complications occupies a special place in the diagnostic and treatment algorithm (4, 7, 8).

The Aim. The aim of the present article was to optimize the approach of the diagnosis and surgical treatment of patients with focal lesions of the pancreatobiliary area complicated by obstructive jaundice.

Patients and methods. This study is based on the analysis of the results of 272 jaundiced patients surgical treatment who underwent radical surgery as pancreaticoduodenal resection (PDR) for malignant tumors of biliopancreatoduodenal area (218 patients) and chronic pseudotumoral pancreatitis (54 patients). All patients were divided into two groups: the main group, for whom the optimized algorithm of preoperative preparation and risk stratification was used (n=112) and the comparison group- preparation for PDR was carried out according to generally accepted standards (n=160). There were 59 men (52.7%) in the main and 82 (51.3%) in the comparison group, women, respectively, 53 (47.3%) and 78 (48.7%). The mean age of patients was 49.6 ± 4.1 and 47.3 ± 3.3 years in the main group and in the comparison group, respectively. The diagnosis verification was carried out on the base of a comprehensive examination of patients with the mandatory involvement of general clinical, laboratory and instrumental methods of ultrasound, CT, MRI, FEGDS.

In patients of the main group in the genetic analysis as additional predictor of the malignant transformation probability and postoperative period course severity the detection of type-specific mutations in genes (polymorphisms) PRSS 1 (Arg122His), SPINK 1 (Asn34Ser), TNF (CF30he) was used with obvious determination of the phenotype of the patient, which has certain features of the postoperative period course.

Results and discussion

The risk stratification was performed by mathematical modeling taking into account genetic factors and the results of instrumental research as ultrasonic elastography.

In patients after definition of planned radical surgery risk index according to the developed formula (taking into account pathomorphological parameters of a condition of the patient) the decision on stages of surgical treatment carrying out was made.

$$X = 904.3 + 1.7(Bil) - 0.2(AlcPh) - 3,2(GP) - 7.5(CEA) - 13.0(CA50) - 6.8(Alb) - 24.9(CD) - 4.6(Dens) - 83.0(INR),$$

where indications are: X - the degree of PDR performing risk; Bil - the level of total bilirubin before surgery; AlcPh - alkaline phosphatase level; GP - the level of total protein; CEA - the level of cancer embryonic antigen; CA50 - tumor marker CA50; Alb - serum albumin level; CD - diameter of the choledochus; Dens - tissue density of the parenchyma on CT in HU; INR - international normalized ratio; in the case where we get a negative number, the result must be multiplied by "-1".

So, at X≥60 values, radical surgery is defined as inexpedient and too risky, while shunt decompression surgery is performed as a first step for pancreatoduodenal resection.

In studying the dynamics of biochemical parameters after PDR in patients of the main group with chronic pancreatitis and pancreatic cancer, we tried to identify certain features that give rise to several phenotypes (for predominant changes in homeostasis and related complications), primarily as options for complicated period in patients with severe mechanical jaundice in the preoperative stage. In Figure 2 the distribution of patients who participated in the study by different phenotypes of the postoperative period is described. The most common were mixed phenotype (51.1%), slightly less often - pro-inflammatory (16.2%) and dyscholegenic (22.1%) variants. Obviously, the prevalence of certain symptoms in the postoperative period may be genetically determined.
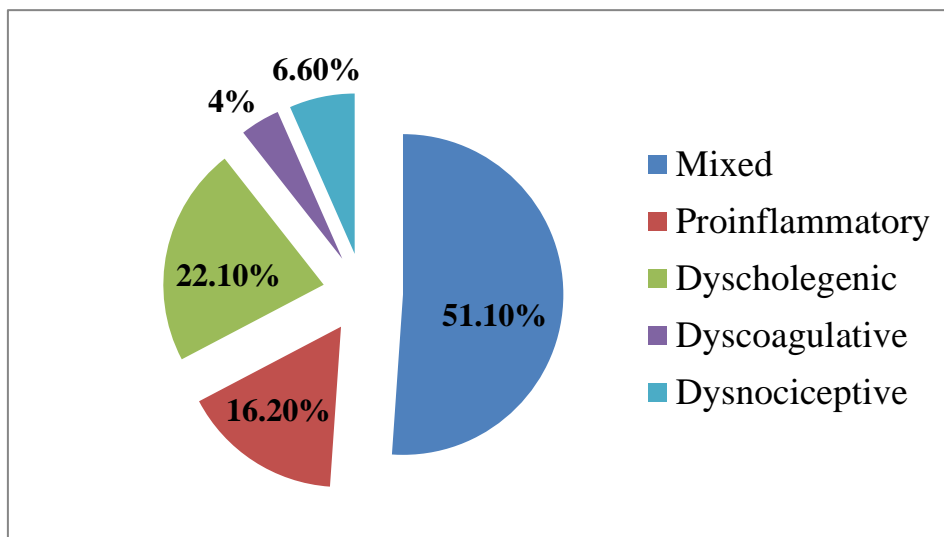
Fig. 2. Patient's phenotypes of the postoperative period course

Attempts to determine the possibility of genetic analysis using in combination with ultrasonoelastography for screening and differential diagnosis between benign (CPTP) and malignant (biliopancreatoduodenal area cancer) genesis of mechanical jaundice were also made (Fig. 3, Fig. 4).

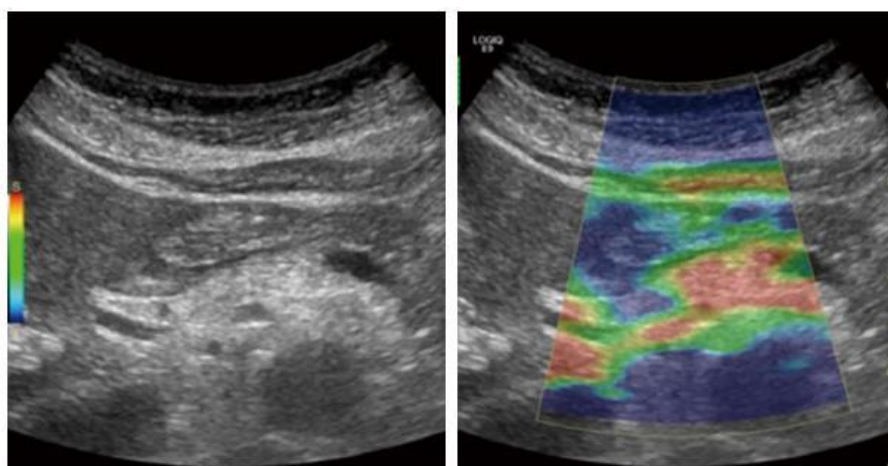Fig. 3. The method of sonoelastography reflects the partial replacement of the normal pancreatic parenchyma with soft and dense fibrous tissue (from red, through yellow and green, to blue) at the beginning of the development of chronic pancreatitis.

If the surgery performance was risky, then at the first step in patients of the main group resorted to rapid detoxification, the comparison group - the usual conservative preparation.
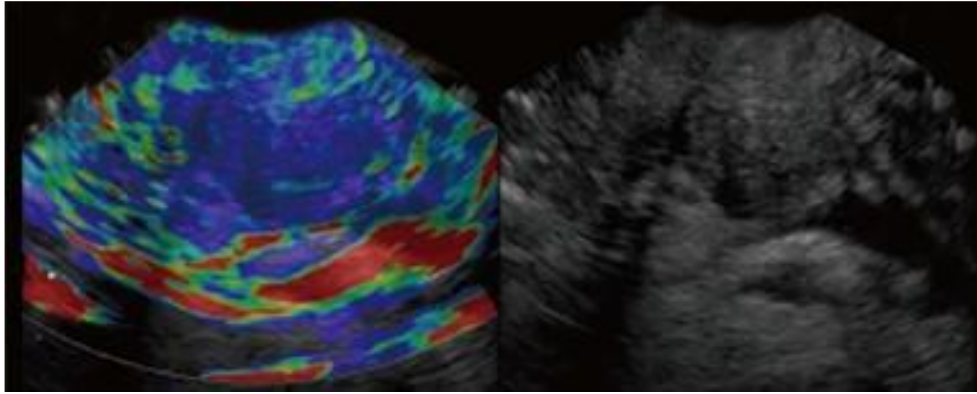
Fig. 4. Sonographic picture of adenocarcinoma of the pancreas, as evidenced mainly by the blue (dense) solid spectrum of the focus

Patients came mainly in an abandoned state with severe mechanical jaundice and the initial manifestations of multiorgan failure syndrome. Most of the studied patients sought medical help only after 7 - 10 days or more, and some in general a month after the appearance of external signs of biliary obstruction (Table 1).

Table 1

Duration of jaundice in patients before hospitalization

The jaundice duration	The main group (n=112)	The comparison group (n=160)	p
Up to 7 days, (n)	6 (5,4%)	13 (8,1%)	0,38
8-14 days, (n)	37 (33,0%)	70 (43,8%)	0,08
15-28 days, (n)	51 (45,5%)	56 (35,0%)	0,10
More than 28 days, (n)	18 (16,1%)	21 (13,1%)	0,35

Among the main criteria for satisfactory preparation of patients to perform PDR in addition to the positive dynamics in the main indicators of the syndrome of mesenchymal cytolysis was necessarily present stabilization of mental status.

The dynamics of the mental state of patients under conditions of certain preparation for surgery during the preoperative period was assessed taking into account the gradation of hepatic encephalopathy (HE) according to the criteria of West Heaven and ISHEN (Table 2).

According to the results of laboratory-diagnostic search of cases of severe HE (stage II-IV) during admission to the hospital and during preoperative preparation, none of the patients was detected (Table 2).

Table 2

Criteria of pancreatic encephalopathy (by Vilstrup et al., 2014)

West Haven	ISHEN	The Main group (n=112)	The Comparison group (n=160)
No damage		-	-
Minimal	Reversible	70 (62,5%)	127 (79,4%)
Grade I		42 (37,5%)	33 (20,6%)
Grade II		-	-
Grade III		-	-
Grade IV	Irreversible	-	-

On admission to the hospital in 197 patients (70 (62.5%) patients of the main and 127 (79.4%) patients of the comparison group, respectively) with the help of psychometric instruments just minimal changes in neuropsychiatric activity were revealed (Table 2). One was the Montreal Cognitive Test (MoCA), the other was the Digital Short Symbolic Test (DSST).

Thus, the results of the DSST test in patients of the main group averaged 38.8 ± 2.2 points, the comparison group - 37.1 ± 3.0 points. Taking into account the patient's age, its results were worse than the medieval indicators, but did not go beyond moderate cognitive impairment. The average levels of results on the MoCA scale in patients of the main group and the comparison group were corresponding - 24.6 ± 2.5 and 24.2 ± 2.2 points.

In 75 patients (42 (37.5%) patients of the main and 33 (20.6%) patients of the comparison group, respectively) during admittion to the hospital stage I of HE according to West Haven (Table 2) were diagnosed. They had time orientation disorders, respectively, the results of testing on the MoCA scale were 22.2 ± 2.2 and 23.0 ± 2.3 points in patients of the main group and the comparison group, respectively. The average results of the DSST test in these patients did not exceed 30 points - 23.1 ± 2.2 and 23.7 ± 2.4 points in the main and comparison groups, respectively. Focal neurological symptoms were generally unsimilar, but in 68 (26 (23.2%) patients of the main and 42 (26.2%) patients of the comparison group) there were manifestations of vestibulo-atactic syndrome. Postural tremor was determined in 33 patients (14 (12.5%) patients of the main and 19 (11.9%) patients of the comparison group) with HE of the I degree.

Thanks to the preoperative preparation according to our algorithm, more significant positive changes were achieved in the main group compared to the comparison one. The number of points on the MoCA scale before surgery in the main and comparison groups was 24.9 ± 3.2 and 22.8 ± 2.4, respectively. According to the results of the DSST test, patients

were distributed as follows - 40.2 ± 3.8 and 23.6 ± 2.6 points in the main and comparison groups.

In the main group of patients the changes in the indicators of total bilirubin, alkaline phosphatase and GGT were noted as the most positive from the point of view of dynamics.
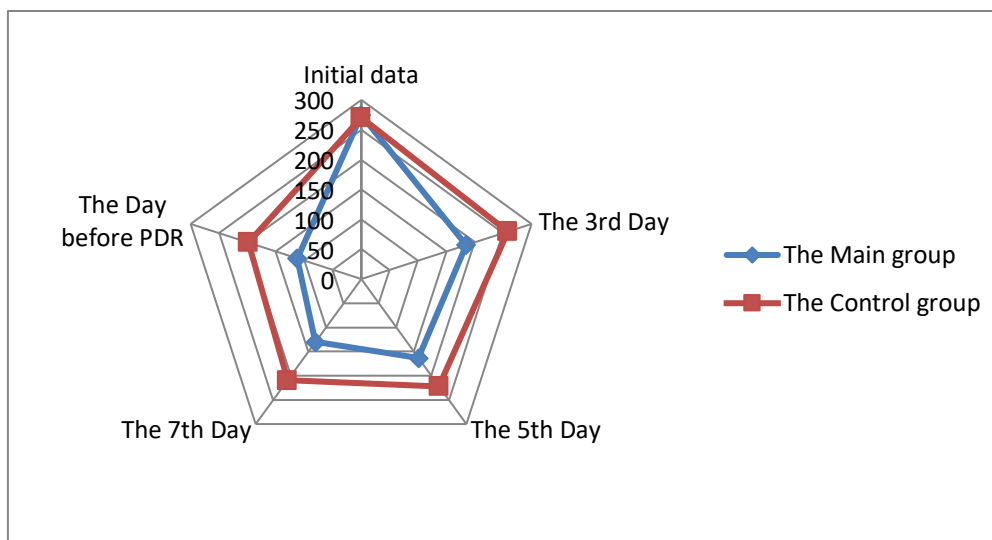

Fig. 5. The dynamics of total bilirubin decrease

Due to the application of the developed detoxification algorithm with the use of biliary decompression in patients of the main group on the third day the level of bilirubinemia averaged 185.1±2.4 μmol/l, while on the fifth day it was already 163.2±2.6 μmol/l and on the day before PDR the level was 112.3±2.7 μmol/l (p<0.05). In the control group, which followed the usual volume of patient preparation for radical surgery, the level of total bilirubin on the third day was 258.4±2.9 μmol/l, on the fifth day it was 222.2±3.8 μmol/l, and on the day before PDR the level was 198.3±3.3 μmol/l (Fig.5) (p <0.05). Thus, in the main group after decompression, the total bilirubin level decrement was Δ= -59.1%, direct one was Δ=-62.5%, indirect one was Δ=-47.6%. While in the control group of patients on the day before PDR, the total bilirubin level decrement was Δ=-26.7%, direct one was Δ=-27.2%, indirect one was Δ=-25.0%.

Alkaline phosphatase (AP) activity was closely correlated with the dynamics of bilirubinemia (Fig. 6).

However, if in general, the bilirubin concentration showed a stable pattern of decrease over time, with differences only in the decrement of reduction depending on the applied means of preoperative preparation, the content of AP was more fluctuating (Fig. 7).
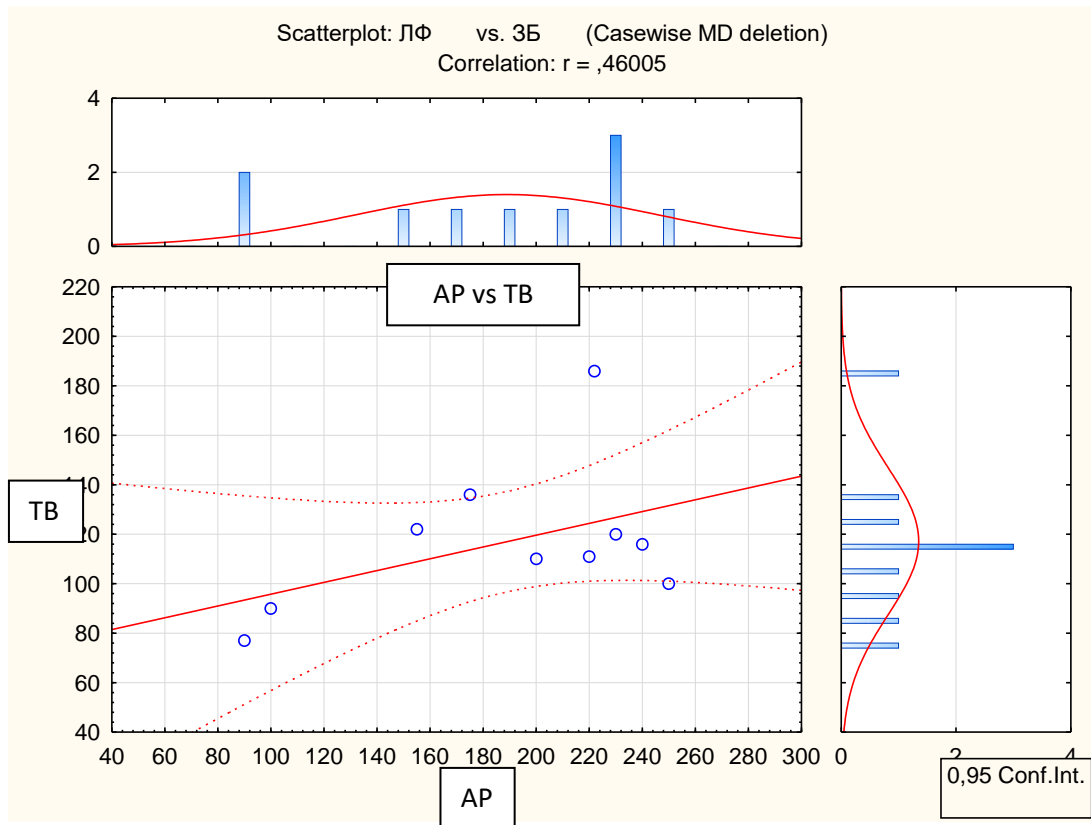
Fig. 6. Alkaline phosphatase (AP) and total bilirubin (TB) correlation
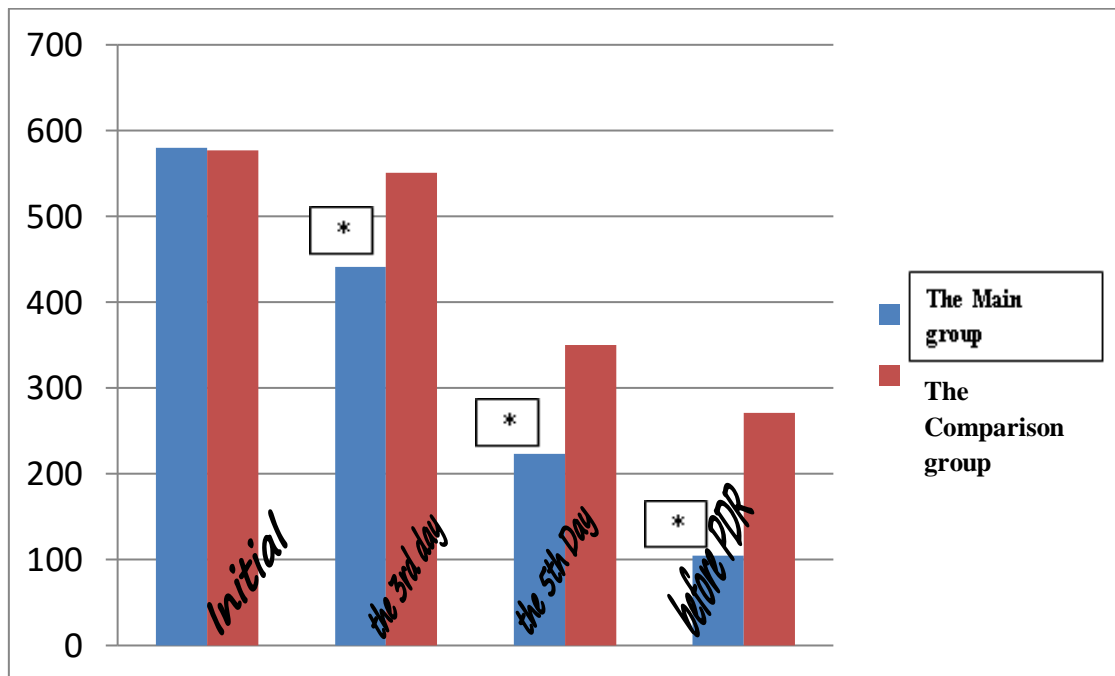

Fig. 7. Dynamics of AP activity in patients of different clinical groups.

Note: * - p <0,05

As can be seen from the figure, at the beginning of treatment, the average content of AP in the serum was, respectively, in the main group - 580.2 ± 1.7 U / l, and in the comparison group - 577.0 ± 1.9 U / l, which corresponds with coefficients of variation of 6.4% and 8.8%. The greater variance in the comparison group that exceeds the baseline in the number of observation units may be due to the heterogeneity of the data set. On the 3rd day of observation, the AP content in both groups decreased to 440.9 ± 2.1 and 550.7 ± 1.4 U / l. On the 5th day of observation, the values of the indicator were even smaller, and in the main group there was a more significant decrease in the activity of LF (223.2 ± 2.7 U / l) compared with the comparison group (350.3 ± 1.1 U / l) (p <0.05). Finally, on the eve of the PDR, the activity of AP was in the main group 104.8 ± 1.3 U / l, and in the comparison group - 270.8 ± 1.9 U / l, while the variability of indicators in both groups increased - cv = 18, 7% in the main and cv = 34.5% in the comparison group (p <0.05).
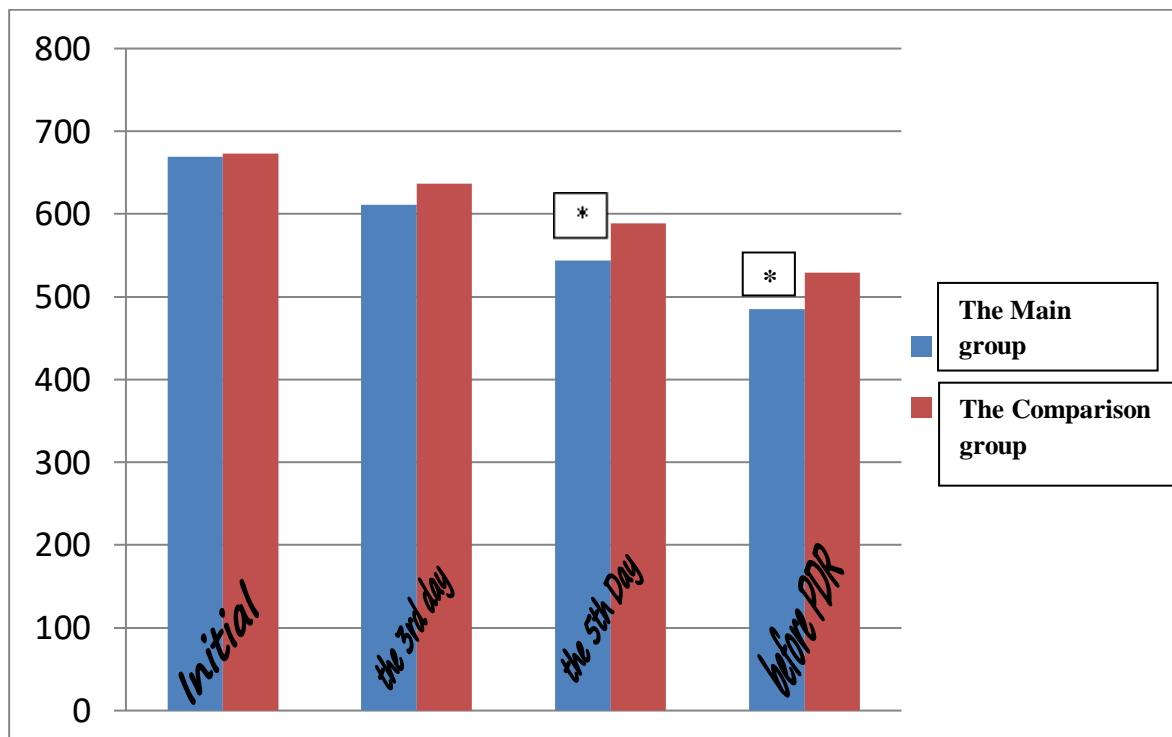

Fig. 8. Dynamics of GGT content in patients of different clinical groups.

Note: * - p <0,05

Thus, at the beginning of the study, the activity of γ-glutamiltransferase (GGT) averaged 673 ± 28 U / l in the comparison group and 669 ± 41 U / l - in the main group. On the 3rd day of the study, the values of the indicator decreased to 637 ± 31 U / l (comparison group) and to 611 ± 38 U / l (main group), on the 5th day - to 303 ± 29 U / l and 321 ± 35 U / l (p <0.05). On the eve of PDR, GGT activity significantly decreased to 529 ± 29 U / l in the

comparison group and to 485 ± 33 U / l in the main group (p <0.05).

After preoperative preparation, PDR was performed in 272 of patients.

Mortality rate in the main group was 6.3% (7 patients), and in the comparison group 11.9% (19 patients) (p <0.05).

Conclusions

1.   Clinical monitoring of single nucleotide genetic mutations by genes (polymorphisms) PRSS 1 (Arg122His), SPINK 1 (Asn34Ser), TNF (G308A) and CFTR (Phe508del) is promising in patients with high levels of cholemia to assess the possible course of the disease.

2.   The combination of detected genetic mutations with the results of ultrasonic elastography creates a basis for screening in jaundiced patients with already diagnosed focal diseases of the pancreatobiliary zone, and increases the likelihood of malignancy of its genesis. (CI 95%; 2.2-5.8).

3.   The efficiency of the developed mathematical model in patients with focal diseases of the pancreatobiliary zone of benign and malignant origin, complicated by obstructive jaundice, is 92% and 87%, respectively.

4.   The application of the proposed preoperative preparation algorithm allowed to reduce the rates of postoperative mortality significantly from 19 (11.9%) in the comparison group to 7 (6.3%) in the main group (p <0.05).

Authors' contributions

PM and BZ contributed to the conception of the study, collected, analyzed and interpreted data from the literature and critically revised the manuscript. PM and IB contributed to the conception of the study, performed the literature research, drafted the manuscript and were responsible for confirming the authenticity of all the raw data. IB and MH contributed to the interpretation of the data from the literature, collected, analyzed and interpreted the data corresponding to the patients and critically revised the manuscript. PT, MZ and SV collected analyzed and interpreted the data corresponding to the patients

introduced in this study and critically revised the manuscript. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

The Ethics Committee of Odessa National Medical University (Odessa, Romania) approved the study. Informed consent was obtained from all patients prior to surgery and all data were collected according to the principles of The Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

There are no competing interests to declare regarding this study.

References

1.   Wang L. Obstructive jaundice and perioperative management / L. Wang, Y. Wei-Feng. // Acta Anaesthesiologica Taiwanica. – 2014. – Vol. 52. – P. 22–29.

2.   Pavlidis E. T. Pathophysiological consequences of obstructive jaundice and perioperative management / E. T. Pavlidis, T. E. Pavlidis. // Hepatobiliary & Pancreatic Diseases International. – 2018. – Vol. 17. – P. 17–21.

3.   Kutovy OB Experience in the treatment of patients with tumors of the pancreatoduodenal zone / OB Kutovy et al. // Clinical surgery. – 2018. – №6 (2). – P. 49–51.

4.   Ceniceros L., Prados S., Alvarez Gallego R. (2021) Jaundice in Pancreatic Cancer. In: Søreide K., Stättner S. (eds) Textbook of Pancreatic Cancer. Springer, Cham. https://doi.org/10.1007/978-3-030-53786-9_78

5.   S. Blacker et al.. (2021) Which patients benefit from preoperative biliary drainage in resectable pancreatic cancer?, Expert Review of Gastroenterology & Hepatology, 15:8, 855-863

6.   S. Dindyal, D.Spalding (2019) Pancreatic cancer Medicine Volume 47, Issue 7, Pages 433-439

7.   Fekaj E. Obstructive Jaundice / E. Fekaj, N. Jankulovski, N. Matveeva. // Austin Dig Syst.. – 2017. – Vol. 2 (1). – CP. 1006.

8.   Zhang, H., Ren, D., Jin, X. et al. The prognostic value of modified Glasgow Prognostic Score in pancreatic cancer: a meta-analysis. Cancer Cell Int 20, 462 (2020). https://doi.org/10.1186/s12935-020-01558-4