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ABSTRACT

PROGNOSTIC SIGNIFICANCE OF CT-PLANIMETRIC CHARACTERISTICS OF THE PANCREAS IN THE DEVELOPMENT OF PANCREATIC FISTULA AFTER PANCREATODUODENECTOMY

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Introduction. The study investigates the prognostic significance of preoperative computed tomography (CT) parameters, particularly pancreatic parenchymal density and duct-to-parenchyma (D/P) ratio, in predicting the risk of postoperative pancreatic fistula (POPF) following pancreatoduodenectomy (PD). POPF remains a major postoperative complication, with incidences between 6–60%, prolonging hospital stays and escalating treatment costs. This research addresses the limitations of subjective intraoperative assessments, proposing objective, preoperative CT-based criteria to forecast POPF risk.

Methods. A prospective study was conducted with 234 patients undergoing PD between January 2022 and November 2023. The research employed multiphase contrast-enhanced CT imaging to assess pancreatic density (in Hounsfield Units, HU) and D/P ratio at the expected resection site above the superior mesenteric vein. Density was measured using unenhanced CT, while D/P ratios were calculated based on duct and parenchymal measurements in two planes. The radiologists were blinded to patient outcomes, and logistic regression models were utilized to assess the prognostic value of these metrics.

Results. The study identified a significant association between lower pancreatic density and increased POPF risk. Patients with POPF had a median density of 22 HU compared to 39.65 HU in patients without POPF. Similarly, lower ventrodorsal and craniocaudal D/P ratios correlated with higher POPF incidence. Logistic regression models demonstrated that low pancreatic density and D/P ratio are independent predictors of POPF, with an area under the ROC curve (AUC) of 0.91 for pancreatic density and 0.86 for the D/P ratio. A combined model achieved the highest prognostic accuracy (AUC = 0.92), suggesting

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these parameters are valuable for preoperative POPF risk stratification.

Conclusions The study concludes that low pancreatic density and a low D/P ratio, identified through preoperative CT planimetry, are reliable predictors of POPF following PD. These parameters enable a more objective risk assessment, potentially guiding individualized surgical strategies to mitigate POPF risk. Future studies with larger cohorts are warranted to validate these findings and explore histological correlations.

Keywords: pancreatoduodenectomy, pancreatic fistula, computed tomography, pancreatic density, pancreas, duct-to-parenchyma ratio, risk factors.

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ПРОГНОСТИЧНЕ ЗНАЧЕННЯ КТ-ПЛАНІМЕТРИЧНИХ ХАРАКТЕРИСТИК ПІДШЛУНКОВОЇ ЗАЛОЗИ У РОЗВИТКУ ПІДШЛУНКОВОЇ НОРИЦІ ПІСЛЯ ПАНКРЕАТОДУОДЕНЕКТОМІЇ

Вступ. Метою дослідження було вивчення прогностичного значення планіметричних характеристик підшлункової залози, визначених за допомогою комп'ютерної томографії (КТ), таких як щільність паренхіми та співвідношення діаметра протоки до товщини паренхіми (співвідношення D/P), у розвитку клінічно значущої післяопераційної панкреатичної фістули (POPF) після панкреатодуоденектомії (ПД).

Матеріали і методи. Це проспективне дослідження включало 234 пацієнтів, які пройшли ПД в період з січня 2022 року по листопад 2023 року в Національному науковому центрі хірургії та трансплантології імені О. О. Шалімова. Основні показання до операції включали рак підшлункової залози (n = 119; 50,9 %), дистальний холангіокарциному (n = 30; 12,8 %), рак ампули Фатера (n = 26; 11,1 %), внутрішньопротокову папілярну муцинозну неоплазію (n = 17; 7,3 %), рак дванадцятипалої кишки (n = 12; 5,1 %) та хронічний панкреатит (n = 30; 12,8 %).

Передопераційні КТ-зображення в аксіальній площині на рівні передбачуваної лінії резекції вище верхньої брижової вени використовувалися для вимірювання щільності паренхіми підшлункової залози в одиницях Хаунсфілда (HU). Співвідношення D/P визначали шляхом вимірювання максимального діаметра головної протоки підшлункової залози та товщини підшлункової залози у двох перпендикулярних напрямках: вентродорсальному та краніокаудальному. Товщину паренхіми визначали як відстань від зовнішнього краю залози до стінки протоки. POPF визначали відповідно до критеріїв ISGPS. Прогностичне значення КТ-критеріїв оцінювали за допомогою логістичної регресії та ROC-аналізу.

Результати. Частота клінічно значущої POPF (ступінь B/C) становила 18,8% (n = 44). Медіана щільності паренхіми була значно нижчою в групі POPF у порівнянні з групою без POPF (22 проти 39,65 HU, p<0,001). Медіанні співвідношення D/P також були нижчими в групі POPF у вентродорсальній (0,14 проти 0,33, p<0,001) та краніокаудальній площинах (0,12 проти 0,255, p<0,001).

Мультифакторна модель, яка включала щільність паренхіми та співвідношення D/P, мала найвищу прогностичну точність (AUC 0,92; 95% CI 0,87–0,96). Порогові значення щільності ≤26,6 HU та співвідношення D/P ≤0,2 забезпечували чутливість 81,8%, специфічність 91,7%, позитивну прогностичну цінність 62,5% і негативну прогностичну цінність 98,2% для POPF. Виявлено помірну позитивну кореляцію між щільністю паренхіми та співвідношенням D/P (r=0,29, p<0,001). Збільшення співвідношення D/P на 0,1 у вентродорсальній і краніокаудальній площинах було пов'язане зі зниженням ймовірності POPF на 86,4% (OR 0,136; 95% CI 0,058-0,318; p<0,001) і 72,6% (OR 0,274; 95% CI 0,117-0,639; p=0,003) відповідно.

Висновки. Низька щільність паренхіми підшлункової залози (≤26,6 HU) та співвідношення D/P ≤0,2, визначені за допомогою КТ-планіметрії площини резекції, є незалежними предикторами клінічно значущої POPF після ПД. Прогностична модель, заснована на цих критеріях, дозволяє точно стратифікувати ризик виникнення POPF до операції. Виявлений зв'язок між щільністю паренхіми та співвідношенням D/P свідчить про загальні патофізіологічні механізми, що впливають на цілісність панкреатоеюностомії. Результати дослідження відкривають перспективи для впровадження персоналізованих профілактичних стратегій при ПД на основі передопераційної КТ-планіметрії.

Ключові слова: панкреатодуоденектомія, панкреатична фістула, комп'ютерна томографія, щільність підшлункової залози, підшлункова залоза, співвідношення діаметра протоки до паренхіми, фактори ризику.

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INTRODUCTION

PD remains a complex surgical procedure associated with a high incidence of postoperative complications, despite significant advances in surgical techniques and perioperative patient management. Among these complications, POPF holds a prominent place, occurring in 6-60% of cases following PD, according to literature [1, 2, 3, 4]. POPF not only prolongs hospitalization and increases treatment costs but can also lead to severe intra-abdominal complications and fatalities.

Numerous studies have focused on identifying risk factors for POPF to improve PD outcomes. Among the primary factors influencing the integrity of the pancreatojejunostomy are the texture of the pancreatic parenchyma and the diameter of the main pancreatic duct [5, 6]. A soft, fatty gland with a small duct is considered the most unfavorable for forming a reliable anastomosis, whereas a dense, fibrous gland with a dilated duct provides optimal conditions for healing [7].

However, the intraoperative assessment of these pancreatic characteristics is subjective and depends on the surgeon's experience. Objective preoperative risk criteria for POPF based on radiological methods could significantly aid in the prediction and prevention of this complication.

The most promising imaging method for the pancreas is computed tomography (CT). Previous studies have shown that low parenchymal density in HU on native CT images correlates with a high incidence of POPF [6, 8]. This is because low HU values reflect fatty infiltration of the gland, which worsens the conditions for anastomotic healing.

Meanwhile, the role of pancreatic duct diameter as a predictor of POPF remains controversial. Although most authors believe that a small duct is associated with an increased risk of fistula [5, 6, 9], some studies have not found such a correlation [10, 11]. Perhaps, the relative diameter of the duct compared to the thickness of the parenchyma, rather than the absolute size of the duct, has greater prognostic significance. This parameter, which can be represented as the duct-to-parenchyma diameter ratio (D/P ratio), reflects the

degree of duct dilation and, consequently, the conditions for pancreatic secretion outflow. Theoretically, a low D/P ratio (a narrow duct relative to thick parenchyma) may be a more informative predictor of POPF than isolated values of duct diameter or gland thickness.

A recent study demonstrated that a D/P ratio <0.25 is an independent risk factor for clinically significant POPF after PD. However, this study used an indirect measurement method along the duct's course, while direct planimetry of the expected resection plane above the superior mesenteric vein could yield more accurate results [9].

Additionally, it remains unclear which parameter—D/P ratio or parenchymal density in HU—has greater prognostic value and whether there is a correlation between them. Comparing these parameters in the same cohort of patients would provide a better understanding of their relative diagnostic and prognostic roles and the potential for combined use in POPF risk stratification.

Given the above, we initiated a prospective study to investigate the prognostic significance of preoperative CT criteria, such as pancreatic parenchymal density and the D/P ratio, determined by direct planimetry of the resection plane, for the development of POPF after PD. We hypothesize that these parameters may be reliable predictors of POPF both individually and in combination and may correlate with each other, reflecting common pathophysiological mechanisms. Confirming their diagnostic value will enable objective preoperative risk assessment of POPF and individualize surgical strategies for patients undergoing PD.

MATERIALS AND METHODS

This prospective study is based on the analysis of data from patients who underwent PD between January 2022 and November 2023 at the National Scientific Center of Surgery and Transplantology named after O.O. Shalimov. The study included patients with periampullary and pancreatic head tumors, as well as those with chronic pancreatitis, who underwent standard PD. All surgeries were performed by experienced surgeons specializing in hepatopancreatobiliary surgery. The standard surgical technique was the classical PD with Child's modification [10]. Intraoperatively, surgeons assessed the texture of the pancreatic parenchyma in the resection area by palpation, categorizing it as either soft or firm. To prevent complications, drains were placed in the area of the pancreatojejunostomy and hepaticojejunostomy.

The antibiotic prophylaxis protocol included the administration of first-generation cephalosporins or antibiotics selected based on preoperative bile bacteriological studies, administered immediately before the skin incision and intraoperatively every 3 hours. Postoperatively, the amylase levels in the drain output were regularly measured on days 1, 3, 5, and 7. Drains were removed on postoperative days 5-7 in the absence of signs of pancreatic fistula or bacterial contamination.

The diagnosis of POPF was established according to the criteria of the International Study Group on Pancreatic Fistula (ISGPS) when any measurable volume of drain output with an amylase concentration more than three times the upper normal limit in serum was observed on the third postoperative day or later. POPF was classified by severity into types B and C [12]. Type A was excluded from the analysis as it is considered clinically insignificant.

All patients underwent multiphase contrast-enhanced computed CT of the abdomen at the preoperative stage. CT images were acquired using a 128-slice multidetector CT scanner (SOMATOM Edge Plus; Siemens Healthineers). The tube voltage was automatically selected, and current modulation was applied. The general scanning parameters included a detector configuration of 128 x 0.6 mm, a gantry rotation time of 0.5 seconds, a tube current of 20-800 mAs, a tube voltage of 70-140 kVp, a slice thickness of 1 mm, and a reconstruction interval of 1 mm. CT scans were performed in the native, arterial, venous, and delayed phases. Primary axial images were reconstructed with multiplanar reconstructions in the coronal and sagittal planes.

Two experienced radiologists independently performed CT planimetry of the pancreas at the expected resection line in the axial plane above the superior mesenteric vein. Native phase images were used for this purpose, while the arterial phase was utilized to identify and exclude vascular structures and the ductal system from the analysis. Attenuation (HU) was measured on preoperative unenhanced CT images at the neck of the pancreas (at the level of the anticipated surgical margin of the pancreas). Attenuation values were calculated using regions of interest (ROI) of 0.2-0.3 cm^2 (Fig. 1). The average value of three ROIs obtained in the neck area was considered the parenchymal density of the pancreas. To determine the D/P ratio, a CT planimetry technique was used. On axial plane images in the native phase at the level of the anticipated resection line above the superior mesenteric vein, the maximum diameter of the main pancreatic duct (MPD) and the thickness of the pancreas (PT) were measured in two perpendicular directions: anteroposterior (MPD1 and PT1) and mediolateral (MPD2 and PT2) (Fig. 2). Then, two D/P ratio indicators were calculated: D1/P1 and D2/P2,

where D1 and D2 are the diameters of the MPD in the corresponding directions, and P1 and P2 are the thicknesses of the parenchyma in the respective directions. The arithmetic mean of D1/P1 and D2/P2 was used for further analysis. All measurements were performed independently by two radiologists, and the average values of the obtained indicators were calculated. In cases where the MPD was not visualized, the diameter was assumed to be 0, and the D/P ratio was not calculated.

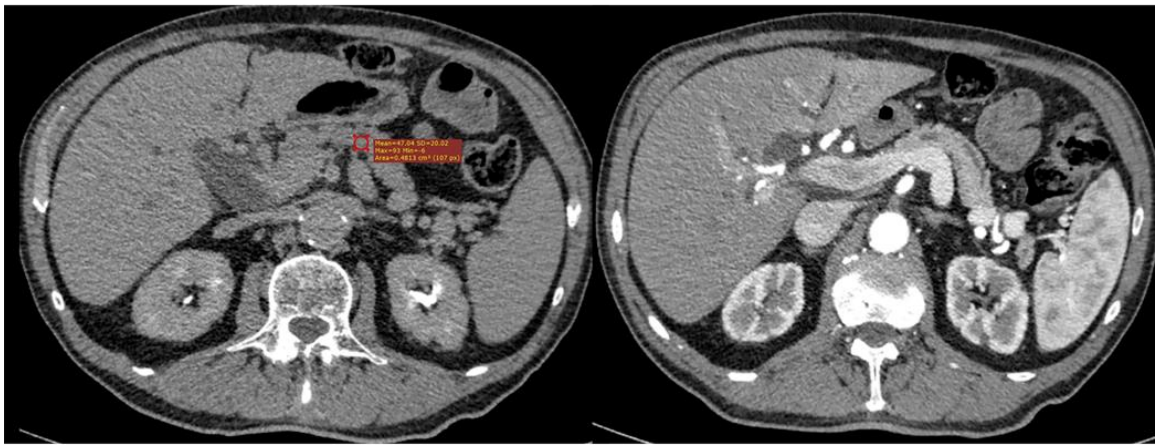

Fig. 1. CT. Measurement of pancreatic density in the native phase. Enhanced images in the late arterial phase for the identification and exclusion of ducts and vessels of the pancreas

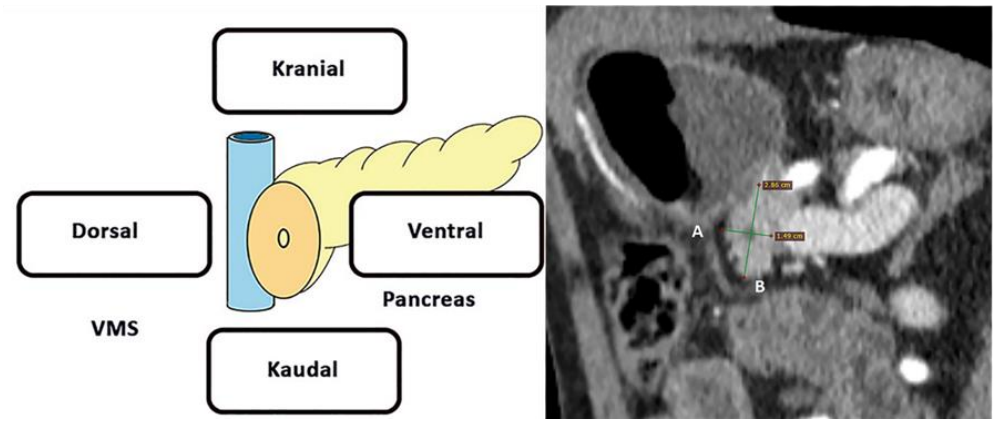

Fig. 2. Orthograde planimetry of the pancreatic resection plane anterior to the superior mesenteric/portal vein. SMV – superior mesenteric vein. Measurement of pancreatic diameter in the ventrodorsal (A) and craniocaudal (B) directions

All patients provided informed consent to participate in the study. The radiologists who analyzed the CT results were blinded to the patients' clinical data and postoperative outcomes.

To evaluate the effectiveness of the logistic regression model in predicting POPF and to investigate the relationship between pancreatic density, the D/P ratio, and the presence of POPF, we conducted a series of statistical analyses. Descriptive statistics were used to characterize the sample and calculate the median, interquartile range, and minimum and maximum values of the D/P ratio in the groups with and without POPF. Comparisons of pancreatic density and the D/P ratio between groups were made using the independent samples t-test or the Mann-Whitney U test.

ROC analysis was performed to assess the prognostic ability of the models, with the construction of ROC curves and calculation of the area under the curve (AUC) with 95% confidence intervals. Optimal classification thresholds were determined using the Youden index, calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The Spearman correlation coefficient was used to assess the relationship between pancreatic density and the D/P ratio. Additionally, residual analysis of logistic regression was conducted to check model adequacy, and multivariate

regression analysis was performed to evaluate the impact of all variables on the development of POPF.

RESULTS

The study included 234 patients who underwent pancreatoduodenectomy (PD). Among them, there were 150 (64.1%) men and 84 (35.9%) women. The median age was 68 years. The main indications for surgery were pancreatic cancer (n = 119; 50.9%), distal cholangiocarcinoma (n = 30; 12.8%), ampullary cancer (n = 26; 11.1%), intraductal papillary mucinous neoplasia (n = 17; 7.3%), duodenal cancer (n = 12; 5.1%), and chronic pancreatitis (n = 30; 12.8%). Preoperative biliary drainage was performed in 122 (52.1%) patients.

The incidence of POPF in the studied population was 18.8% (n=44). Among the patients with POPF, 28 (63.6%) had type B fistula, and 16 (36.4%) had type C fistula, according to the ISGPS classification.

The analysis of the relationship between pancreatic density, measured in HU, and the development of POPF showed significant differences between patient groups. In the group without POPF, the median pancreatic density was 39.65 HU, with a range from 11.0 to 59.84 HU. Conversely, in the POPF group, the median density was significantly lower at 22.0 HU, with a range from -10.0 to 38.0 HU. Statistical analysis using the t-test (t = -9.59, p = 1.48e-18) and the Mann-Whitney U test (U = 1135.0, p = 5.29e-14) confirmed the significance of this difference between the groups. These results allow for the rejection of the null hypothesis of no difference in mean pancreatic density between the groups with and without POPF.

Similarly, the analysis of the relationship between the ventrodorsal D/P ratio and the development of POPF showed significant differences between the patient groups. In the group without POPF, the median ventrodorsal D/P ratio was 0.33, with a range from 0.06 to 0.54. Conversely, in the POPF group, the median ratio was significantly lower at 0.14, with a range from 0.05 to 0.33. Statistical analysis using the Mann-Whitney U test (U = 1037.0, p = 7.59e-15) confirmed the significance of this difference between the groups. These results allow for the rejection of the null hypothesis of no difference in the ventrodorsal D/P ratio between the groups with and without POPF.

Additionally, the analysis of the relationship between the craniocaudal D/P ratio and the development of POPF also revealed significant differences between the patient groups. In the group without POPF, the median craniocaudal D/P ratio was 0.255, with a range from 0.05 to 0.39. In the POPF group, the median ratio was lower at 0.12, with a range from 0.04 to 0.29. Statistical analysis using the Mann-Whitney U test (U = 1199.5, p = 1.67e-13) confirmed the significance of this difference between the groups. These results also allow for the rejection of the null hypothesis of no difference in the craniocaudal D/P ratio between the groups with and without POPF.

The logistic regression model based on pancreatic density demonstrated excellent prognostic ability for the risk of developing POPF, with an area under the ROC curve (AUC) of 0.91 (95% CI 0.89-0.96). The optimal threshold value for density, determined using the Youden index, was 26.62 HU, providing a sensitivity of 81.8%, specificity of 91.7%, positive predictive value (PPV) of 62.5%, and negative predictive value (NPV) of 98.2% (Fig. 3). Logistic regression models incorporating the D/P ratio in the ventrodorsal or craniocaudal planes had an AUC of 0.86 (95% CI 0.76-0.94). At a threshold D/P ratio value of 0.25, the sensitivity was 90.9%, specificity was 75.0%, PPV was 43.5%, and NPV was 97.9% (Fig. 4).

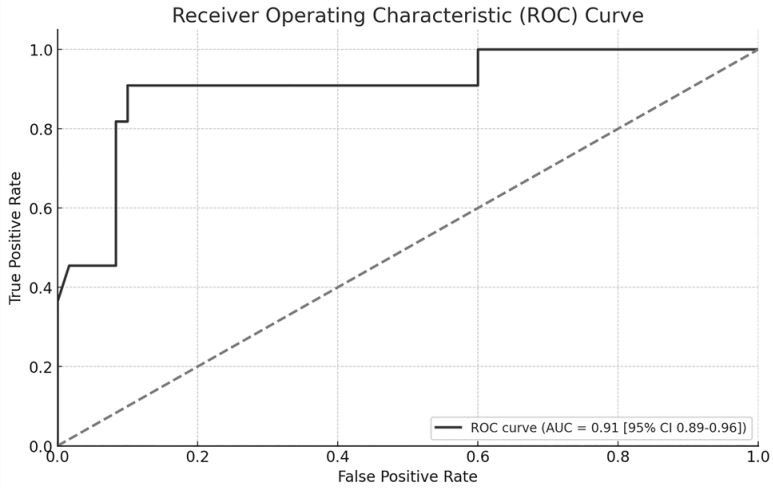

Fig. 3. Receiver Operating Characteristic (ROC) Curve for the Logistic Regression Model Assessing the Probability of Developing POPF Based on Pancreatic Density (HU). AUC = 0.91 (95% CI 0.89-0.96), Indicating High Model Accuracy

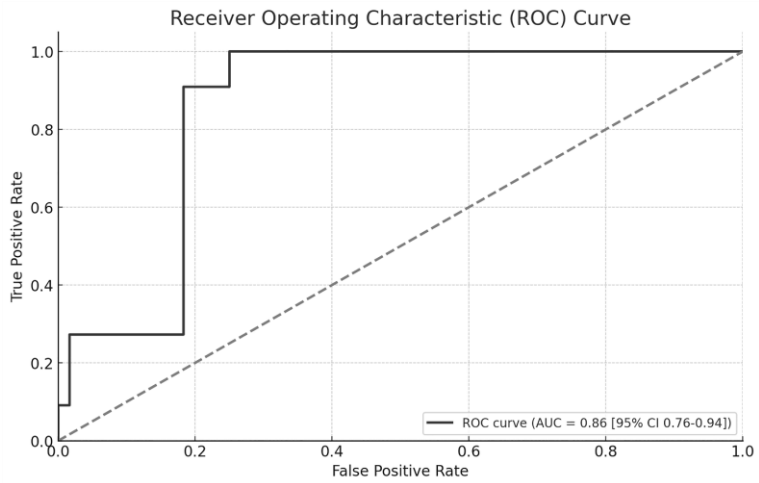

Fig. 4. Receiver Operating Characteristic (ROC) Curve for the Logistic Regression Model Assessing the Probability of Developing POPF)Based on the D/P Ratio in the Ventrodorsal or Craniocaudal Planes. AUC = 0.86 (95% CI 0.76-0.94), Indicating High Model Accuracy

The combined model, which included both pancreatic density and the D/P ratio, demonstrated the highest prognostic accuracy with an AUC of 0.92 (95% CI 0.87-0.96, Fig. 5). At an optimal probability threshold of 0.3, the model provided a sensitivity of 81.8%, specificity of 91.7%, PPV of 62.5%, and NPV of 98.2%. Residual analysis confirmed the adequate fit of the model.

Regression analysis demonstrated that an increase in pancreatic density by each HU reduced the odds ratio (OR) of developing POPF by 9.5% (OR 0.905; 95% CI 0.854-0.958; p<0.001). An increase in the D/P ratio in the ventrodorsal and craniocaudal planes by 0.1 was associated with a reduction in the OR by 86.4% (OR 0.136; 95% CI 0.058-0.318; p<0.001) and 72.6% (OR 0.274; 95% CI 0.117-0.639; p = 0.003), respectively.

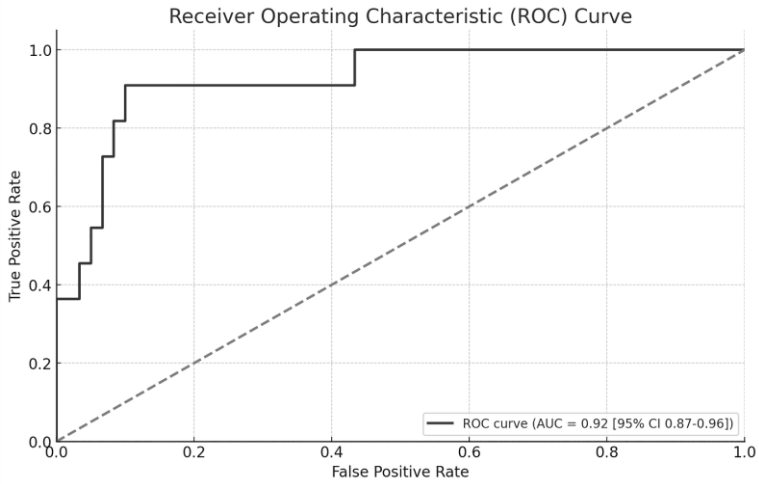

Fig. 5. Multivariate Logistic Regression Model Including Pancreatic Density and D/P Ratio (Ventrodorsal and Craniocaudal) Showing an Area Under the Curve (AUC) of 0.92 (95% CI 0.87-0.96). This Indicates High Prognostic Accuracy of the Model

A significant moderate positive correlation was found between pancreatic density and the D/P ratio (Spearman correlation coefficient r = 0.29; p<0.001 for the ventrodorsal D/P ratio and r = 0.29; p<0.001 for the craniocaudal D/P ratio). These data indicate an interrelationship between the parenchymal structure and the ductal system's patency of the pancreas, which together determine the risk of POPF.

The obtained results confirm the hypothesis that low pancreatic density and a low duct-to-parenchyma ratio are independent predictors of clinically significant POPF after PD. The prognostic model

based on these CT criteria, determined by direct planimetry of the resection plane, allows for an objective and accurate preoperative risk stratification of patients. This opens up opportunities for a personalized approach to the prevention and treatment of POPF in patients undergoing PD.

DISCUSSION

Our study demonstrated that low pancreatic parenchymal density and a low duct-to-parenchyma ratio (D/P ratio) are significant predictors of POPF after PD. These results align with previous findings that have also identified soft texture and fatty infiltration of the pancreas, as well as a narrow duct, as being associated with an increased risk of POPF [1, 6].

However, unlike earlier studies, our research uniquely highlights the prognostic value of direct planimetry of the expected resection plane on preoperative CT images. This method offers a more precise and objective assessment of pancreatic anatomy compared to the indirect or subjective approaches used previously. Direct planimetry avoids distortions caused by the variability in duct course and pancreatic curvature, providing a reliable evaluation of parenchymal and ductal system characteristics.

The data suggest several pathophysiological mechanisms that explain the association between low parenchymal density and a narrow duct with the risk of POPF. First, the replacement of normal parenchyma with fatty tissue impairs conditions for pancreatojejunostomy healing due to weak suture fixation in the soft, lipomatous gland [1, 10]. Second, a narrow duct hinders the adequate outflow of pancreatic secretions, increasing pressure in the remaining part of the gland and promoting leakage at the anastomosis site [13].

The threshold values of the D/P ratio (<0.2 in both ventrodorsal and craniocaudal planes) identified in our study are close to those reported by Akamatsu et al., 2010, who used a different measurement method but reached similar conclusions. Despite different methodological approaches, both studies confirm the reliability of the D/P ratio as a predictor of POPF, enhancing the potential for extrapolating these findings and their implementation in clinical practice [13].

We acknowledge several limitations of our study, including its retrospective design, a relatively small patient sample, and the absence of histological data on the degree of pancreatic fibrosis. Future prospective studies with larger patient cohorts and the inclusion of morphological examination of pancreatic tissue could help address these limitations. Such studies would refine the correlations between parenchymal characteristics, ductal system parameters, and histological changes in predicting POPF risk.

The clinical significance of our findings lies in the ability of preoperative CT planimetry to stratify patients by POPF risk and individualize surgical strategies and preventive measures. For instance, in patients with low parenchymal density and a D/P ratio <0.2, modified pancreatojejunostomy techniques, external duct drainage, or preventive octreotide therapy could be considered. Early identification of risk factors through CT planimetry could substantially improve PD outcomes and reduce the incidence of life-threatening complications.

Our study results show that low pancreatic parenchymal density (<30 HU) and a D/P ratio <0.2, determined by direct CT planimetry of the anticipated resection plane, are independent risk factors for clinically significant POPF after PD. The prognostic model developed based on these CT criteria allows for an objective and accurate preoperative assessment of POPF risk, opening opportunities for a personalized approach to the prevention of this serious complication.

The novelty of our work lies in the development and validation of a direct CT planimetry method, providing a reliable assessment of pancreatic anatomy at the resection plane. The observed correlation between parenchymal density and the D/P ratio indicates common pathophysiological mechanisms determining the integrity of the pancreatojejunostomy.

Future research directions include studying the correlation of CT parameters with histological characteristics of the gland, such as the degree of fibrosis and fatty infiltration, and validating the developed prognostic model in larger patient cohorts. Widespread implementation of CT planimetry in preoperative assessment for patients undergoing PD could significantly improve the outcomes of this complex surgery.

CONCLUSIONS

Low pancreatic parenchymal density (≤26.6 HU) and a D/P ratio of ≤0.2, determined by CT planimetry of the resection plane, are independent predictors of clinically significant POPF after PD. A prognostic model based on these criteria allows for accurate preoperative risk stratification of patients for POPF. The identified relationship between parenchymal density and the D/P ratio suggests common pathophysiological mechanisms underlying the integrity of the pancreatojejunostomy. The study results provide prospects for the implementation of personalized preventive strategies for PD based on preoperative CT planimetry.

AUTHOR CONTRIBUTIONS

Olexander Usenko – given final approval to the manuscript version submitted for publication
Oleh Symonov – contributed to the conception and design of the study
Romanna Pavliuk – acquisition, analysis and interpretation of data
Serhii Vasyliuk – drafted the manuscript and revised it critically for content
Oleh Tkachuk – acquisition, analysis and interpretation of data

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ARTIFICIAL INTELLIGENCE DISCLOSURE

The authors of this study declare that no AI was involved in the writing of this article.

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