

RESEARCH

Open Access



# Intraductal papillary neoplasm of the bile duct: a clinical analysis of 62 cases and evaluation of prognostic factors

Ling-Yan Fang<sup>1</sup>, Wen-Wen Tang<sup>1</sup>, Jie Bai<sup>1</sup>, Ping Zheng<sup>1</sup>, Deng Huang<sup>1</sup>, Li Cao<sup>1</sup>, Jie Shu<sup>1,2\*</sup> and Lang Gan<sup>1\*</sup>

## Abstract

**Objective** To investigate the clinicopathological characteristics of intraductal papillary neoplasm of the bile duct (IPNB) and the prognostic factors influencing survival in patients with malignant IPNB.

**Methods** A retrospective analysis was performed on the clinicopathological data and postoperative follow-up records of 62 IPNB patients who underwent surgical treatment at the First Affiliated Hospital of Army Medical University from September 2010 to March 2021. Clinical and pathological characteristics were compared among patients with different histopathological grades (e.g., low-grade vs. high-grade intraepithelial neoplasia) and anatomical subtypes (e.g., intrahepatic, extrahepatic, and diffuse types). Prognostic factors affecting survival in malignant IPNB cases were analyzed using multivariate statistical methods.

**Results** Based on pathological findings, the 62 IPNB patients were categorized into three groups: low-grade intraepithelial neoplasia (LGIN group,  $n = 20$ ), high-grade intraepithelial neoplasia (HGIN group,  $n = 23$ ), and associated invasive carcinoma (IC group,  $n = 19$ ). The LGIN group exhibited a significantly lower proportion of patients with elevated CA19-9 ( $> 37$  U/mL) compared to the other two groups ( $p = 0.009$ ). No statistically significant differences were observed in demographic or perioperative parameters among the three groups. Patients in the HGIN and IC groups demonstrated inferior overall survival rates compared to the LGIN group ( $p = 0.007$ ). After merging HGIN and IC groups into a malignant cohort, the malignant group showed significantly worse overall survival than the LGIN group ( $p = 0.002$ ). Multivariate Cox regression analysis identified postoperative recurrence, abdominal pain, and non-radical surgery as independent predictors of poor prognosis in the malignant group ( $p < 0.05$ ). According to the modified anatomical classification system, the 62 patients were stratified into intrahepatic ( $n = 43$ ), extrahepatic ( $n = 15$ ), and diffuse ( $n = 4$ ) subtypes. The intrahepatic group had a significantly higher rate of radical resection compared to the extrahepatic and diffuse groups ( $p = 0.006$ ). Surgical approaches differed markedly among subtypes: intrahepatic cases predominantly underwent partial hepatectomy ( $p < 0.001$ ), whereas extrahepatic cases more frequently required extrahepatic bile duct resection ( $p < 0.001$ ).

\*Correspondence:

Jie Shu  
shujiecn@163.com  
Lang Gan  
ganlang1122@163.com

Full list of author information is available at the end of the article



© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

**Conclusion** The modified anatomical classification system provides partial guidance for determining the optimal surgical resection extent in IPNB patients. Radical resection demonstrates superior prognosis compared to palliative treatment. Postoperative recurrence, abdominal pain, and non-radical surgery are identified as independent risk factors for adverse prognosis in malignant IPNB cases. In patients with suspected IPNB, radical resection should be pursued aggressively, especially in those presenting with abdominal pain or elevated CA19-9.

**Keywords** IPNB, Survival analysis, Prognosis, Malignant tumor, Pathological classification, Anatomical classification

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare tumor originating from the biliary mucosal epithelium, which can occur anywhere in the biliary system. It is characterized by bile duct dilatation, multifocal papillary epithelial hyperplasia, or cystic biliary changes, with 28%–37% of cases demonstrating mucin hypersecretion [1–3]. The pathogenesis of IPNB is associated with chronic cholangitis induced by factors such as pancreaticobiliary reflux, biliary stones, and *Clonorchis sinensis* infection, predominantly affecting middle-aged and elderly populations [4]. IPNB exhibits an insidious onset, and clinical manifestations such as jaundice and abdominal pain may emerge when tumor progression or mucin secretion causes biliary obstruction. According to the 2019 WHO Classification of Digestive System Tumors [1], IPNB is histologically categorized into three subtypes based on cellular architectural atypia: low-grade intraepithelial neoplasia (LGIN), high-grade intraepithelial neoplasia (HGIN), and associated invasive carcinoma (IC). This study included 62 IPNB patients from the First Affiliated Hospital of Army Medical University, all confirmed by surgical resection and postoperative pathological examination. We systematically analyzed clinicopathological features and postoperative follow-up data to compare distinctions in clinical characteristics among different pathological subtypes and anatomical classifications. By merging HGIN and IC groups into a malignant cohort, we further identified prognostic factors influencing outcomes in malignant IPNB patients, aiming to provide evidence-based recommendations for clinical diagnosis and therapeutic decision-making.

## Materials and methods

### Inclusion and exclusion criteria

Inclusion criteria: (1) Underwent either laparoscopic or open surgical resection of lesions; (2) Postoperative pathological confirmation of intraductal papillary neoplasm of the bile duct (IPNB); (3) Availability of complete preoperative abdominal imaging data; (4) Child–Pugh class A or B liver function; Exclusion criteria: (1) Incomplete clinical records; (2) Patients who did not undergo surgical resection but received endoscopic biopsy only.

### General information

This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical

University (Third Military Medical University)(No. KY2025084). Between September 2010 and March 2021, 62 IPNB patients meeting the aforementioned inclusion criteria underwent surgical treatment at our institution. Clinicopathological data, perioperative parameters, and postoperative follow-up records were systematically collected. Classification was performed according to the 2019 WHO Classification of Digestive System Tumors and the modified anatomical classification system for IPNB proposed by Kim [5] et al.: Intrahepatic type: Lesions localized to intrahepatic bile ducts. Extrahepatic type: Lesions involving the common hepatic duct or common bile duct. Diffuse type: Lesions spanning both intrahepatic and extrahepatic bile ducts. The intrahepatic IPNB subgroup was further stratified based on biliary dilatation morphology: Ductal dilatation subtype: Characterized by cylindrical or fusiform diffuse dilatation of bile ducts with dominant lesions. Cystic subtype: Defined by cystic mass formation accompanied by adjacent bile duct dilatation.

All patients underwent laboratory investigations including complete blood count (CBC), liver and renal function tests, coagulation profiles, and tumor marker levels. Cardiopulmonary function assessment was conducted to determine fitness for anesthesia and surgical intervention. Abdominal ultrasonography, computed tomography angiography (CTA), and magnetic resonance cholangiopancreatography (MRCP) were performed to delineate tumor location, biliary duct dilatation, and presence of biliary stones. When indicated, endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTBD) was utilized for preoperative biliary decompression.

### Follow-up methods

Through outpatient visits and/or telephone follow-ups, information regarding postoperative tumor recurrence, the time of follow-up termination, and survival status is collected. The follow-up period extended until May 2024. Overall survival (OS) was defined as the time interval from the date of surgery to either the end of follow-up or death from any cause, whichever occurred first.

### Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 24.0. Normally distributed continuous variables

were expressed as mean  $\pm$  standard deviation (SD) and analyzed with Student's t-test or one-way ANOVA. Non-normally distributed variables were presented as median with interquartile range [M (Q1, Q3)] or range [M (range)], with intergroup comparisons conducted using Mann-Whitney U test. Categorical variables were described as absolute numbers or percentages (%) and compared via Chi-square test or Fisher's exact probability method. Survival outcomes were evaluated using Kaplan-Meier curves with log-rank test for comparing survival differences across treatment modalities. Prognostic factors (including pathological subtypes, radical resection status, and lymph node dissection) were assessed through multivariate Cox proportional hazards regression model. A two-tailed  $p$ -value  $< 0.05$  was considered statistically significant.

## Results

### Comparative analysis of clinicopathological features and prognosis among IPNB pathological subtypes

The baseline characteristics of the three cohorts are summarized in Table 1 (LGIN:  $n = 20$ ; HGIN:  $n = 23$ ; IC:  $n = 19$ ). No significant intergroup differences were observed in age (mean  $\pm$  SD:  $56.0 \pm 9.9$  vs.  $59.3 \pm 10.7$  vs.  $51.3 \pm 12.4$  years,  $p > 0.05$ ) or clinical presentations. Abdominal pain was the most common preoperative symptom (56.5%–75.0%), followed by jaundice (20.0%–30.4%), and then fever and vomiting ( $p > 0.05$ ). Elevated serum CA19-9 ( $> 37$  U/mL) was significantly more prevalent in HGIN (43.5%) and IC (52.6%) groups compared to LGIN (10.0%,  $p = 0.017$ ). No significant differences were noted in abnormal levels of CEA ( $> 5$  ng/mL), ALT ( $> 41$  U/L), AST ( $> 45$  U/L), ALP ( $> 143$  U/L), GGT ( $> 54$  U/L), TBIL ( $> 22$   $\mu$ mol/L), or DBIL ( $> 8$   $\mu$ mol/L) ( $p > 0.05$ ). The preoperative CT or MRCP findings of the three groups showed the following: Biliary stones were predominantly detected in LGIN (60.0% vs. 13.0% in HGIN vs. 21.1% in IC,  $p = 0.002$ ). Biliary masses showed higher prevalence in HGIN (65.2%) and IC (63.2%) versus LGIN (20.0%,  $p = 0.005$ ). Biliary duct dilatation rates were comparable (LGIN: 85.0% vs. HGIN: 78.3% vs. IC: 73.7%,  $p = 0.682$ ). Surgical approaches (partial hepatectomy, combined hepatectomy-bile duct resection, extrahepatic bile duct resection, pancreaticoduodenectomy), anatomical subtypes, minimally invasive/open surgery ratios, lymphadenectomy rates, and mucin secretion profiles showed no intergroup disparities. The overall incidence of postoperative complications, including fever, bile leakage, pulmonary and intra-abdominal infections, showed no statistically significant differences among the three groups of patients ( $p > 0.05$ ). Using the log-rank test to compare the overall survival rates among three groups of patients, the Kaplan-Meier survival curve (Fig. 1) showed that the

total survival rates of the HGIN and IC groups were significantly lower than that of the LGIN group ( $P = 0.007$ ). The Kaplan-Meier survival curve (Fig. 2) demonstrated that the malignant cohort (HGIN+IC) had a significantly worse overall survival rate compared to the benign (LGIN) group ( $P = 0.002$ ).

### Comparison of clinicopathological characteristics of IPNB patients based on modified anatomical classification

According to the modified anatomical classification, patients were divided into three groups: intrahepatic type (43 cases), extrahepatic type (15 cases), and diffuse type (4 cases). Their clinical characteristics are summarized in Table 2. No statistically significant differences were observed among the three groups in demographic data (age, clinical presentation) or laboratory results (CA19-9, CEA, total bilirubin et al.) ( $p > 0.05$ ). The radical resection rates for intrahepatic, extrahepatic, and diffuse types were 93.0% (40/43), 66.7% (10/15), and 50.0% (2/4), respectively. The intrahepatic group had a significantly higher radical resection rate ( $p = 0.006$ ). Intrahepatic type predominantly underwent hepatectomy ( $p < 0.001$ ). Extrahepatic and diffuse types required higher rates of extrahepatic bile duct resection ( $p < 0.001$ ). Extrahepatic type showed a higher lymph node dissection rate compared to intrahepatic type ( $p = 0.044$ ). The diffuse type had a higher overall complication rate (e.g., fever, bile leakage, pulmonary/abdominal infections) compared to the intrahepatic type ( $p = 0.038$ ). No significant differences in overall survival rates were observed among the three anatomical subtypes ( $p > 0.05$ ) (Fig. 3).

### Survival analysis of the malignant cohort (HGIN+IC Groups, $n = 42$ )

The median follow-up duration was 45 months (95% CI: 37.3–71.5), with a median overall survival (OS) of 57 months (95% CI: 42.8–71.2) and a 5-year survival rate of 41.4%. Univariate Cox regression analysis identified elevated CA19-9 levels, postoperative recurrence, abdominal pain, and non-radical surgery as significant predictors of poor prognosis ( $P < 0.05$ ). These variables were subsequently incorporated into multivariate analysis, which confirmed postoperative recurrence, abdominal pain, and non-radical surgery as independent risk factors for adverse outcomes ( $P < 0.05$ , Table 3).

### Recurrence

In this study, postoperative recurrence occurred in 11 patients at different sites with varying frequencies. The specific recurrence patterns were as follows: Bilioenteric anastomosis: 6 cases (54.6%), Liver parenchyma: 5 cases (45.5%), Intra- and extrahepatic bile ducts: 3 cases (27.3%), Duodenum: 3 cases (27.3%), Other sites

**Table 1** Comparison of clinical characteristics among LGIN, HGIN, and IC groups

|                                          | LGIN(n=20) | HGIN(n=23) | IC(n=19)  | Statistical value | P value |
|------------------------------------------|------------|------------|-----------|-------------------|---------|
| Age(years) (mean, SD)                    | 56.0±9.9   | 59.3±10.7  | 51.3±12.4 | 2.776             | 0.070   |
| Sex (%)                                  |            |            |           |                   |         |
| Male                                     | 6(30.0%)   | 9(39.1%)   | 9(47.4%)  | 1.242             | 0.538   |
| Female                                   | 14(70.0)   | 14(60.9%)  | 10(52.6%) |                   |         |
| Manifestations (%)                       |            |            |           |                   |         |
| Abdominal pain                           | 15(75.0%)  | 13(56.5%)  | 11(57.9%) | 1.860             | 0.395   |
| Fever                                    | 6(30.0%)   | 2(8.7%)    | 4(21.1%)  | 3.171             | 0.071*  |
| Vomiting                                 | 1(5.0%)    | 3(13.0%)   | 1(5.3%)   | 1.106             | 0.610*  |
| Jaundice                                 | 4(20.0%)   | 7(30.4%)   | 5(25.8%)  | 0.652             | 0.717*  |
| CA19-9>37U/mL (%)                        | 2(10.0%)   | 10(43.5%)  | 10(52.6%) | 9.212             | 0.009*  |
| CEA>5ng/mL (%)                           | 2(10.0%)   | 2(8.7%)    | 1(5.3%)   | 0.495             | 1.000*  |
| ALT>41U/L (%)                            | 11(55.0%)  | 10(43.5%)  | 9(47.4%)  | 0.580             | 0.748   |
| AST>45U/L (%)                            | 10(50.0%)  | 11(47.8%)  | 7(36.8%)  | 0.786             | 0.675   |
| ALP>143U/L (%)                           | 10(50.0%)  | 13(56.5%)  | 10(52.6%) | 0.187             | 0.911   |
| GGT>54U/L (%)                            | 15(75.0%)  | 21(91.3%)  | 12(63.2%) | 4.846             | 0.010*  |
| TBIL>22μmol/L (%)                        | 10(50.0%)  | 9(39.1%)   | 7(36.8%)  | 0.811             | 0.667   |
| DBIL>8μmol/L (%)                         | 8(40.0%)   | 10(43.5%)  | 7(36.8%)  | 0.192             | 0.909   |
| Modified anatomical classification (%)   |            |            |           | 5.395             | 0.208*  |
| Intrahepatic                             | 15(75.0%)  | 13(56.5%)  | 15(78.9%) |                   |         |
| Extrahepatic                             | 5(25.0%)   | 8(34.8%)   | 2(10.5%)  |                   |         |
| Diffuse                                  | 0(0.0%)    | 2(8.7%)    | 2(10.5%)  |                   |         |
| Imaging data                             |            |            |           |                   |         |
| Biliary dilatation (%)                   | 17(85.0%)  | 18(78.3%)  | 14(73.7%) | 0.820             | 0.682*  |
| Biliary stones (%)                       | 12(60.0%)  | 3(13.0%)   | 4(21.1%)  | 12.284            | 0.002   |
| Biliary masses (%)                       | 4(20.0%)   | 15(65.2%)  | 12(63.2%) | 10.646            | 0.005   |
| Mucin secretion (%)                      | 5(25.0%)   | 7(30.4%)   | 4(21.1%)  | 0.523             | 0.822   |
| Treatment Modality (%)                   |            |            |           | 0.617             | 0.832*  |
| Palliative                               | 3(15.0%)   | 3(13.0%)   | 4(21.1%)  |                   |         |
| Radical                                  | 17(85.0%)  | 20(87.0%)  | 15(78.9%) |                   |         |
| Lymphadenectomy (%)                      | 1(5.0%)    | 6(26.1%)   | 4(21.1%)  | 3.572             | 0.169*  |
| Preoperative Diagnosis: IPNB (%)         | 3(15.0%)   | 6(26.1%)   | 4(21.1%)  | 0.820             | 0.682*  |
| Surgical approach (%)                    |            |            |           | 0.982             | 0.630*  |
| Laparoscopic surgery                     | 2(10.0%)   | 4(17.4%)   | 4(21.1%)  |                   |         |
| Open surgery                             | 18(90.0%)  | 19(82.6%)  | 15(78.9%) |                   |         |
| Resection Site (%)                       |            |            |           | 9.417             | 0.104*  |
| Partial hepatectomy                      | 14(70.0%)  | 9(39.1%)   | 11(57.9%) |                   |         |
| Combined hepatectomy-bile duct resection | 2(10.0%)   | 7(30.4%)   | 7(36.8%)  |                   |         |
| Extrahepatic bile duct resection         | 4(20.0%)   | 5(21.7%)   | 1(5.3%)   |                   |         |
| Pancreaticoduodenectomy                  | 0(0.0%)    | 2(8.7%)    | 0(0.0%)   |                   |         |
| Complications (%)                        |            |            |           | 1.797             | 0.407   |
| Fever                                    | 5(25.0%)   | 2(8.7%)    | 3(15.8%)  |                   |         |
| Bile leakage                             | 1(5.0%)    | 2(8.7%)    | 0(0.0%)   |                   |         |
| Pulmonary infection                      | 2(10.0%)   | 1(4.3%)    | 2(10.5%)  |                   |         |
| Abdominal infection                      | 0(0.0%)    | 2(8.7%)    | 3(15.8%)  |                   |         |
| Incision infection                       | 0(0.0%)    | 0(0.0%)    | 1(5.3%)   |                   |         |
| Hepatic and renal dysfunction            | 0(0.0%)    | 2(8.7%)    | 2(10.5%)  |                   |         |
| Total                                    | 8(40.0%)   | 9(39.1%)   | 11(57.9%) |                   |         |

LGIN Low-grade intraepithelial neoplasia, HGIN High-grade intraepithelial neoplasia, IC Associated invasive carcinoma

\*Fisher's exact test

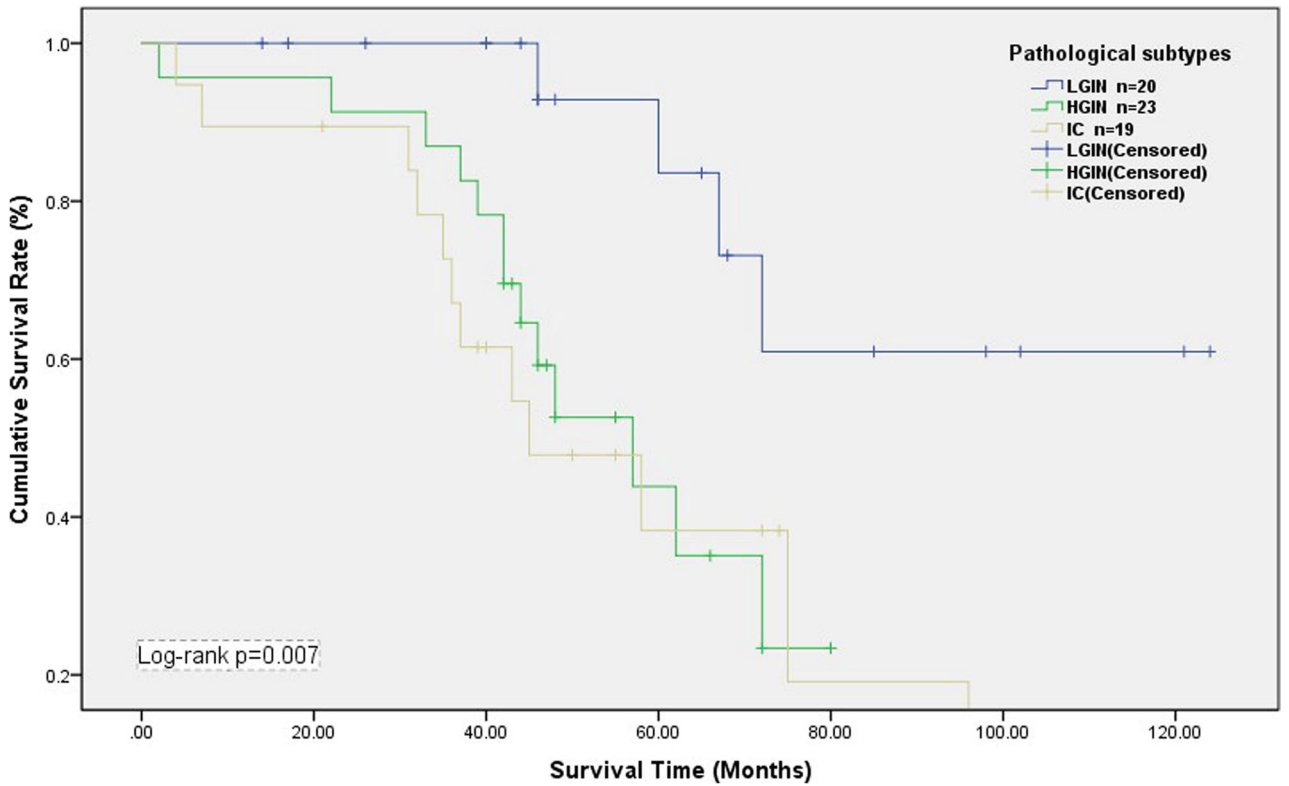


**Fig. 1** Kaplan-Meier survival curves for the LGIN, HGIN, and IC groups

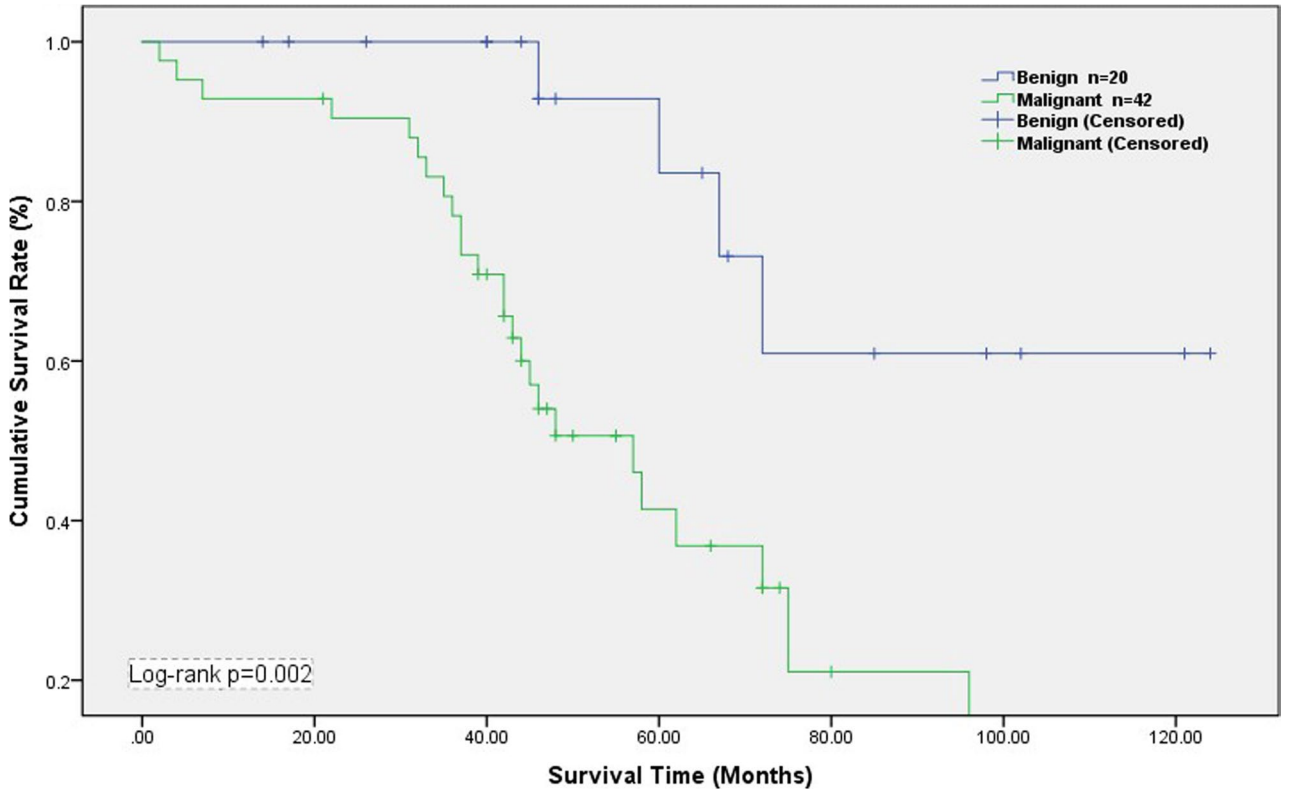


**Fig. 2** Kaplan-Meier survival curves comparing the benign (LGIN) and malignant (HGIN + IC) groups

**Table 2** Comparison of clinical characteristics among intrahepatic, extrahepatic, and diffuse subtypes

|                                          | Intrahepatic (n = 43) | Extrahepatic(n = 15) | Diffuse(n = 4) | Statistical value | P value |
|------------------------------------------|-----------------------|----------------------|----------------|-------------------|---------|
| Age(years) (mean, SD)                    | 54.9 ± 11.3           | 58.9 ± 10.4          | 53.5 ± 15.9    | 0.766             | 0.470*  |
| Sex (%)                                  |                       |                      |                | 2.407             | 0.314*  |
| Male                                     | 14(32.6%)             | 8(53.3%)             | 2(50.0%)       |                   |         |
| Female                                   | 29(67.4%)             | 7(46.7%)             | 2(50.0%)       |                   |         |
| Manifestations (%)                       |                       |                      |                |                   |         |
| Abdominal pain                           | 28(65.1%)             | 8(53.3%)             | 3(75.0%)       | 0.962             | 0.670*  |
| Fever                                    | 10(23.3%)             | 2(13.3%)             | 0(0.0%)        | 1.057             | 0.649*  |
| Vomiting                                 | 2(4.7%)               | 2(13.3%)             | 1(25.0%)       | 3.473             | 0.111*  |
| Jaundice                                 | 11(25.6%)             | 4(26.7%)             | 1(25.0%)       | 0.229             | 1.000*  |
| CA19-9 > 37U/mL (%)                      | 14(32.6%)             | 6(40.0%)             | 2(50.0%)       | 0.904             | 0.739*  |
| CEA > 5ng/mL (%)                         | 3(7.0%)               | 2(13.3%)             | 0(0.0%)        | 1.016             | 0.714*  |
| ALT > 41U/L (%)                          | 18(41.9%)             | 9(60.0%)             | 3(75.0%)       | 2.593             | 0.285*  |
| AST > 45U/L (%)                          | 19(44.2%)             | 8(53.3%)             | 1(25.0%)       | 1.050             | 0.631*  |
| ALP > 143U/L (%)                         | 20(46.5%)             | 11(73.3%)            | 2(50.0%)       | 3.283             | 0.234*  |
| GGT > 54U/L (%)                          | 33(76.7%)             | 13(86.7%)            | 2(50.0%)       | 2.446             | 0.285*  |
| TBIL > 22μmol/L (%)                      | 16(37.2%)             | 9(60.0%)             | 1(25.0%)       | 2.774             | 0.288*  |
| DBIL > 8μmol/L (%)                       | 15(34.9%)             | 9(60.0%)             | 1(25.0%)       | 3.212             | 0.210*  |
| Pathological subtypes (%)                |                       |                      |                | 5.395             | 0.208*  |
| LGIN                                     | 15(34.9%)             | 5(33.3%)             | 0(0.0%)        |                   |         |
| HGIN                                     | 13(30.2%)             | 8(53.3%)             | 2(50.0%)       |                   |         |
| IC                                       | 15(34.9%)             | 2(13.3%)             | 2(50.0%)       |                   |         |
| Imaging data                             |                       |                      |                |                   |         |
| Biliary dilatation (%)                   | 34(79.1%)             | 12(80.0%)            | 3(75.0%)       | 0.373             | 1.000*  |
| Biliary stones (%)                       | 14(32.6%)             | 4(26.7%)             | 1(25.0%)       | 0.229             | 0.897*  |
| Biliary masses (%)                       | 20(46.5%)             | 8(53.3%)             | 3(75.0%)       | 1.239             | 0.585*  |
| Mucin secretion (%)                      | 13(30.2%)             | 2(13.3%)             | 1(25.0%)       | 1.660             | 0.383*  |
| Treatment Modality (%)                   |                       |                      |                | 8.959             | 0.006*  |
| Palliative                               | 3(7.0%)               | 5(33.3%)             | 2(50.0%)       |                   |         |
| Radical                                  | 40(93.0%)             | 10(66.7%)            | 2(50.0%)       |                   |         |
| Lymphadenectomy (%)                      | 5(11.6%)              | 6(40.0%)             | 0(0.0%)        | 5.762             | 0.044*  |
| Preoperative Diagnosis: IPNB (%)         | 12(27.9%)             | 1(6.7%)              | 0(0.0%)        | 3.364             | 0.151*  |
| Surgical approach (%)                    |                       |                      |                | 3.823             | 0.171*  |
| laparoscopic surgery                     | 7(16.3%)              | 1(6.7%)              | 2(50.0%)       |                   |         |
| open surgery                             | 36(83.7%)             | 14(93.3%)            | 2(50.0%)       |                   |         |
| Resection Site (%)                       |                       |                      |                | 54.926            | 0.000*  |
| Partial hepatectomy                      | 34(79.1%)             | 0(0.0%)              | 0(0.0%)        |                   |         |
| Combined hepatectomy-bile duct resection | 9(20.9%)              | 3(20.0%)             | 4(100.0%)      |                   |         |
| Extrahepatic bile duct resection         | 0(0.0%)               | 10(66.7%)            | 0(0.0%)        |                   |         |
| Pancreaticoduodenectomy                  | 0(0.0%)               | 2(13.3%)             | 0(0.0%)        |                   |         |
| Complications (%)                        |                       |                      |                | 6.032             | 0.038*  |
| Fever                                    | 6(14.0%)              | 3(20.0%)             | 1(25.0%)       |                   |         |
| Bile leakage                             | 1(2.3%)               | 2(13.3%)             | 0(0.0%)        |                   |         |
| Pulmonary infection                      | 4(9.3%)               | 1(6.7%)              | 0(0.0%)        |                   |         |
| Abdominal infection                      | 3(7.0%)               | 2(13.3%)             | 0(0.0%)        |                   |         |
| Incision infection                       | 0(0.0%)               | 0(0.0%)              | 1(25.0%)       |                   |         |
| Hepatic and renal dysfunction            | 2(4.7%)               | 0(0.0%)              | 2(50.0%)       |                   |         |
| Total                                    | 16(37.2%)             | 8(53.3%)             | 4(100.0%)      |                   |         |

LGIN Low-grade intraepithelial neoplasia, HGIN High-grade intraepithelial neoplasia, IC Associated invasive carcinoma

\*Fisher's exact test

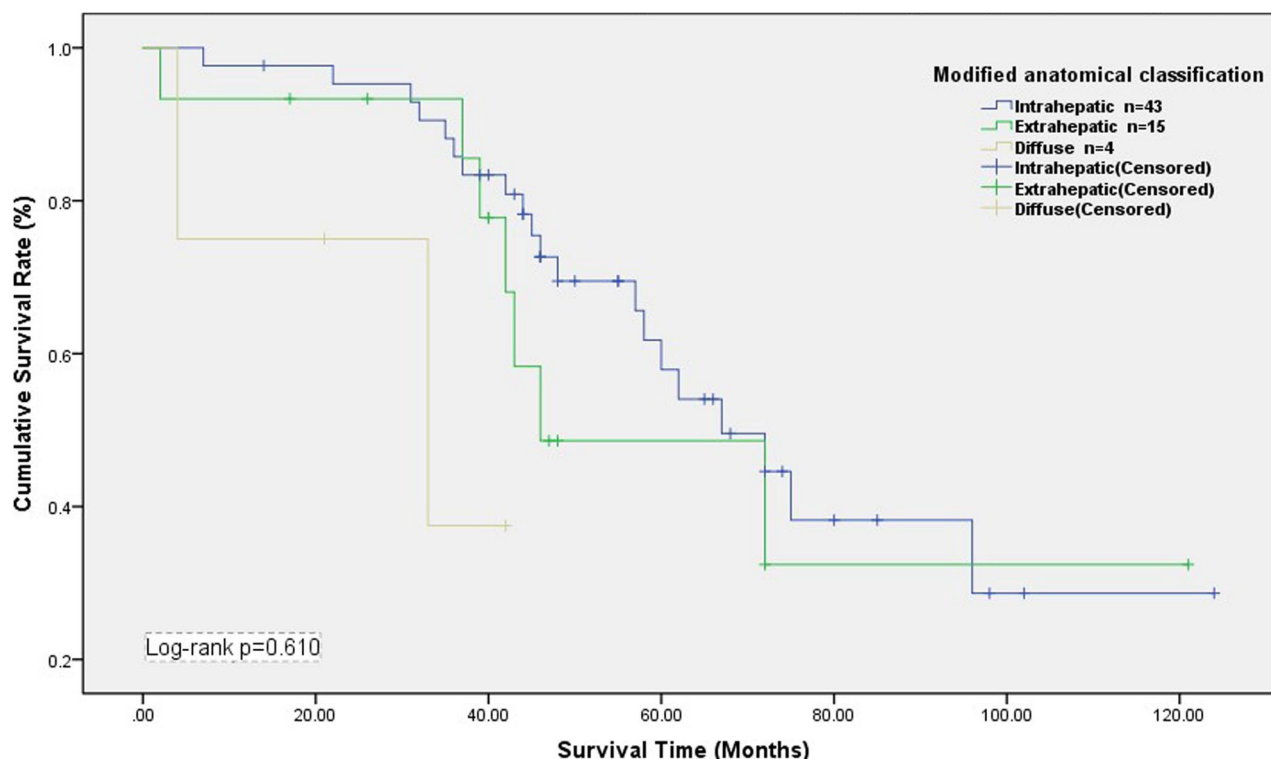


**Fig. 3** Kaplan-Meier survival curves stratified by anatomical subtypes (Intrahepatic, Extrahepatic, Diffuse)

(including abdominal wall, retroperitoneum, lung, adrenal gland): 3 cases (27.3%).

## Discussion

The pathogenesis of IPNB remains unclear. Previous studies suggest associations between IPNB and chronic biliary inflammation induced by factors such as biliary stones and prolonged pancreaticobiliary reflux, which promote biliary epithelial hyperplasia [6]. In this study, 19 patients (30.6%) exhibited concomitant biliary stones. This pathological condition may induce cholestasis through mechanical obstruction, leading to recurrent chronic inflammatory responses in the bile duct wall. Persistent inflammatory microenvironments can stimulate reactive oxygen species (ROS) generation, subsequently causing oxidative DNA damage and epigenetic alterations, ultimately driving abnormal proliferation and dysdifferentiation of biliary epithelial cells. The incidence of IPNB is significantly higher in Asian countries compared to Western populations, potentially attributable to the elevated prevalence of biliary stone disease and *Clonorchis sinensis* infections in these regions [7–10]. Choi [11] et al. reported no statistically significant differences in biliary stone coexistence among IPNB patients based on tumor location (common bile duct, hilar region, or intrahepatic bile ducts). In contrast, Han [12] et al. observed lower intrahepatic stone rates in malignant intrahepatic IPNB subgroups. Our study revealed

no significant differences in biliary stone detection rates across anatomical subtypes. However, marked disparities were noted among pathological subtypes, with the LGIN group demonstrating higher stone prevalence (60.0%) compared to HGIN (13.0%) and IC (21.1%) groups ( $p < 0.05$ ). The precise mechanisms underlying these associations require further investigation.

IPNB predominantly occurs in individuals aged 50–70 years. While previous studies report a male predominance [4], our cohort included 24 males and 38 females, potentially influenced by the limited sample size. The clinical manifestations of IPNB are non-specific and correlate with lesion location and biliary obstruction severity [6, 13]. In this study, among the 62 included patients, 62.9% (39 cases) presented with abdominal pain, while other symptoms included obstructive jaundice, fever, and recurrent cholangitis. In IPNB patients, abdominal pain arises from multiple causes, including coexisting bile duct stones, cholangitis, and elevated biliary pressure due to tumor cells secreting large amounts of mucus into the bile ducts [8]. Jaundice in these patients is primarily caused by mucus accumulation within the bile ducts, with secondary factors including acute biliary obstruction from tumor tissue detachment or concurrent bile duct stones.

Relatively low preoperative diagnosis rate of IPNB (6.7% in our cohort) reflects the diversity of its imaging manifestations and the complexity of diagnosis,

**Table 3** Univariate and Multivariate Cox Regression Analysis of Prognostic Factors in 42 Malignant Cases (HGIN + IC Groups)

| Variables                                | Univariate Analysis |           |                  | Multivariate Analysis |                 |
|------------------------------------------|---------------------|-----------|------------------|-----------------------|-----------------|
|                                          | Cases(%)            | p value   | HR(95%CI)        | p value               | HR(95%CI)       |
| Age ≥ 65 years                           | 10(23.8%)           | 0.636     | 1.24(0.51–3.03)  |                       |                 |
| Male                                     | 18(42.9%)           | 0.145     | 0.5(0.2–1.27)    |                       |                 |
| Abdominal pain                           | 24(57.1%)           | 0.015     | 3.02(1.24–7.36)  | 0.017                 | 3.05(1.22–7.61) |
| Vomiting                                 | 4(9.5%)             | 0.077     | 2.67(0.9–7.93)   |                       |                 |
| Jaundice                                 | 12(28.6%)           | 0.610     | 0.77(0.28–2.1)   |                       |                 |
| Asymptomatic                             | 14(33.3%)           | 0.074     | 0.43(0.17–1.09)  |                       |                 |
| CA19-9 > 37U/mL                          | 20(47.6%)           | 0.024     | 2.68(1.14–6.28)  | 0.202                 | 1.84(0.72–4.67) |
| CEA > 5ng/mL                             | 3(7.1%)             | 0.537     | 0.53(0.07–3.96)  |                       |                 |
| ALT > 41U/L                              | 19(45.2%)           | 0.837     | 0.92(0.41–2.07)  |                       |                 |
| AST > 45U/L                              | 18(42.9%)           | 0.761     | 1.13(0.51–2.54)  |                       |                 |
| ALP > 143U/L                             | 23(54.8%)           | 0.075     | 2.22(0.92–5.32)  |                       |                 |
| GGT > 54U/L                              | 33(78.6%)           | 0.311     | 1.79(0.58–5.51)  |                       |                 |
| TBIL > 22μmol/L                          | 16(38.1%)           | 0.698     | 1.18(0.51–2.76)  |                       |                 |
| DBIL > 8μmol/L                           | 17(40.5%)           | 0.903     | 1.05(0.45–2.46)  |                       |                 |
| Modified anatomical classification (%)   |                     |           |                  |                       |                 |
| Intrahepatic                             | 28(66.7%)           | Reference |                  |                       |                 |
| Extrahepatic                             | 10(23.8%)           | 0.298     | 1.62(0.65–4.05)  |                       |                 |
| Diffuse                                  | 4(9.5%)             | 0.101     | 3.66(0.78–17.28) |                       |                 |
| Biliary dilatation (%)                   | 32(76.2%)           | 0.517     | 1.43(0.49–4.22)  |                       |                 |
| Biliary masses (%)                       | 27(64.3%)           | 0.872     | 0.93(0.4–2.17)   |                       |                 |
| Mucin secretion (%)                      | 11(26.2%)           | 0.612     | 1.28(0.5–3.27)   |                       |                 |
| Radical surgery (%)                      | 35(83.3%)           | 0.019     | 0.32(0.12–0.83)  | 0.026                 | 0.30(0.11–0.87) |
| Lymphadenectomy (%)                      | 10(23.8%)           | 0.387     | 0.65(0.24–1.74)  |                       |                 |
| Laparoscopic surgery                     | 8(19.0%)            | 0.384     | 0.58(0.17–1.97)  |                       |                 |
| Resection Site (%)                       |                     |           |                  |                       |                 |
| Partial hepatectomy                      | 20(47.6%)           | Reference |                  |                       |                 |
| Combined hepatectomy-bile duct resection | 14(33.3%)           | 0.335     | 1.62(0.61–4.29)  |                       |                 |
| Extrahepatic bile duct resection         | 6(14.3%)            | 0.068     | 2.61(0.93–7.3)   |                       |                 |
| Pancreaticoduodenectomy                  | 2(4.8%)             | 0.869     | 1.19(0.15–9.46)  |                       |                 |
| Postoperative recurrence                 | 11(26.2%)           | 0.030     | 2.59(1.1–6.1)    | 0.030                 | 2.72(1.11–6.72) |

HR Hazard Ratio, CI Confidence Interval, HGIN High-grade intraepithelial neoplasia, IC Associated invasive carcinoma

potentially leading to interpretive variability among radiologists. In this study, we employed a comprehensive diagnostic approach based on multimodal imaging rather than relying on a single modality. Our standard diagnostic pathway involves the combined use of at least two of the following: color Doppler ultrasound, contrast-enhanced CT, and MRI (including MRCP). For cases with high clinical suspicion, endoscopic methods such as ERCP or EUS are further utilized for auxiliary diagnosis and tissue acquisition. In our cohort, 57 patients (90%) underwent contrast-enhanced CT, 53 (85%) underwent MRI, and 45 (72%) underwent ultrasound, reflecting our multi-modal diagnostic strategy. Despite this, significant overlap exists between the imaging features of IPNB and those of cholangiocarcinoma or stones. Therefore, achieving a definitive preoperative diagnosis remains challenging even with combined modalities. This explains the suboptimal overall diagnostic rate in our series and underscores the need for future integration of

more specific tumor markers or molecular imaging techniques to improve diagnostic accuracy.

Preoperative laboratory findings in IPNB patients are non-specific, primarily manifesting as abnormal liver function tests and hyperbilirubinemia. Existing studies indicate that patients with concurrent biliary obstruction and cholangitis may exhibit elevated AST, ALT, TBil, DBil, GGT, and ALP levels – a pattern corroborated by varying degrees of elevation observed in our cohort [14]. While no tumor biomarkers currently demonstrate sufficient diagnostic or prognostic utility for IPNB, preoperative elevations in CEA and CA19-9 are frequently detected. In this study, 8.1% ( $n = 5$ ) and 35.5% ( $n = 22$ ) of patients showed CEA > 5 ng/mL and CA19-9 > 37 U/mL, respectively. However, both markers exhibit limited sensitivity and specificity for IPNB diagnosis. Notably, CA19-9 elevation may correlate with mucin-induced obstructive jaundice but cannot independently determine tumor malignancy or grade [15]. Fuks [16] et al. revealed paradoxically higher serum CEA levels in simple hepatic

cysts compared to papillary cystic neoplasms, suggesting CEA has no diagnostic value for IPNB. Furthermore, cholestasis, cholangitis, and obstructive jaundice may all elevate serum CA19-9 [17]. Despite its diagnostic limitations, CA19-9 demonstrates prognostic significance. Youn [18] et al. identified CA19-9 > 37 U/mL as an independent risk factor for tumor recurrence and reduced survival in malignant IPNB. Beyond conventional markers, emerging evidence suggests tumor-associated glycoproteins are overexpressed in mucinous IPNB compared to simple cysts, indicating potential diagnostic value for mucin-producing subtypes [16].

IPNB exhibits significant malignant potential, and radical resection demonstrates superior prognosis over palliative treatment [19]. Therefore, radical resection is strongly recommended for eligible patients. Studies consistently report worse long-term survival in HGIN and IC subtypes compared to LGIN, underscoring the critical importance of early malignancy detection [20–22]. Current clinical guidelines advocate surgical intervention for all IPNB cases to prevent disease progression, with postoperative 5-year survival rates ranging from 68% to 80% [23]. Our study revealed a 100% 5-year survival rate in the LGIN group versus 41.4% in HGIN/IC patients. We note that the 5-year overall survival rate for malignant IPNB in our study (41.4%) is considerably lower than the rate reported by Kubota et al. in 2014 (84%). We have carefully considered several key factors that may account for this discrepancy. Differences in Cohort and Follow-up: Our study had a relatively small sample size (malignant IPNB,  $n = 42$ ) and a median follow-up of 45 months, which may be insufficient for precise estimation of 5-year survival, particularly for assessing long-term outcomes. In contrast, the study by Kubota et al. included a larger cohort with longer follow-up. Impact of Treatment Strategy: In our cohort, 7 patients (16.6%) underwent palliative resection rather than radical resection. The poorer prognosis in this subgroup may lower the overall survival rate. This underscores the critical importance of pursuing R0 radical resection whenever feasible. Tumor Biological Heterogeneity: The study by Kubota et al. clearly demonstrated that pancreatobiliary-type IPNB has a significantly worse prognosis than intestinal or gastric types. Regrettably, limited by our sample size, we were unable to adequately validate the independent prognostic impact of different histologic subtypes in our multivariate analysis. Our cohort may have included a higher proportion of aggressive subtypes (e.g., pancreatobiliary type), which could be an underlying biological reason for the lower survival rate.

Surgical strategies should be tailored according to Kim [4] et al.'s modified anatomical classification system. Intrahepatic IPNB: Segmentectomy or lobectomy was predominantly performed for localized lesions.

Intrahepatic IPNB with extrahepatic involvement: Combined hepatic resection and extrahepatic bile duct resection. Distal extrahepatic IPNB: Pancreaticoduodenectomy for lesions involving the distal bile duct. Hilar IPNB: Hepatic resection with bile duct resection or selective bile duct segmentectomy based on tumor extent.

The recurrence site and frequency data from this study indicate that the bilioenteric anastomosis and the liver parenchyma are common sites of recurrence following IPNB surgery. This finding underscores the critical importance of ensuring a negative bile duct margin during the initial radical resection and imposes higher demands on anastomotic technique. Recurrence in the liver parenchyma may suggest a risk of micrometastasis via portal venous or lymphatic pathways, which can aid in formulating more targeted postoperative monitoring and adjuvant therapy strategies. Given the propensity of IPNB for mucosal spreading, intraoperative frozen section analysis is mandatory to ensure negative resection margins, as margin positivity is an independent risk factor for recurrence and reduced survival [6, 24, 25]. Chang [26] et al., through analyzing tumor spread patterns in papillary extrahepatic cholangiocarcinoma, proposed an optimal surgical margin of 16 mm. The necessity of routine lymphadenectomy remains controversial. Jar-nagin [27] et al. recommend systematic regional lymphadenectomy for hilar and distal bile duct IPNB, whereas Luvira [20] et al. reported significantly lower 5-year overall survival rates in node-positive patients, though lymphadenectomy itself conferred no survival benefit. For patients with unresectable lesions, surgical contraindications, or refusal of surgery, palliative options include: biliary drainage (percutaneous or endoscopic), radiofrequency ablation (RFA), argon plasma coagulation, Chemotherapy, Photodynamic therapy. Delaney [28] et al. successfully treated an 87-year-old IPNB patient using endoscopic RFA, demonstrating its safety and efficacy in select cases. However, long-term oncological outcomes, thermal injury risks, biliary stricture incidence, and cholangitis rates require further validation through large-scale studies [29].

Based on the morphological features of epithelial cells and supportive immunohistochemical staining (e.g., for MUC1, MUC5AC, MUC2, CDX2), IPNB was classified into pancreatobiliary, intestinal, gastric, and oncocytic types. Among these, the pancreatobiliary type was the most common, followed by the intestinal, gastric, and oncocytic types. The coexistence of two or more subtypes within a single tumor was frequently observed, and the predominant subtype (constituting > 50% of the tumor) was assigned as the final classification for each case. Pancreatobiliary and gastric type IPNBs were more frequently associated with high-grade intraepithelial neoplasia (HGIN) and invasive carcinoma, demonstrating a

more aggressive biological tendency. In contrast, intestinal type IPNB was more commonly found in cases with low-grade intraepithelial neoplasia (LGIN). It is less aggressive, has a lower propensity for invasion, and, when malignant transformation occurs, often presents as colloid carcinoma, correlating with a relatively better overall prognosis. Research by Kubota [23] et al. indicates that epithelial cell type may be an important factor in assessing malignancy potential. No statistically significant correlation was observed between histologic subtypes and the modified anatomical classification. Various histologic subtypes could be found in tumors from different anatomical locations.

The Kaplan-Meier survival curves in our study demonstrated significantly inferior overall survival in the malignant cohort (HGIN + IC groups) compared to the LGIN group ( $p = 0.002$ ), aligning with findings by Krawczyk [19] et al. showing superior prognosis in IPNB patients without invasive carcinoma (5-year survival: 100% vs. 22.2%). Our analysis revealed a 5-year survival rate of 41.4% for malignant IPNB cases. Multivariate Cox regression identified postoperative recurrence, abdominal pain, and non-radical resection as independent predictors of adverse prognosis ( $p < 0.05$ ). Other studies suggest additional prognostic determinants [22, 30, 31]. Anatomic factors: Extrahepatic/hilar location. Molecular markers: IPNB-NM subtype, pancreatobiliary phenotype, high MUC1/CEA expression, low MUC5AC. Pathological features: Advanced histologic grade, tumor infiltration. Surgical outcomes: Positive resection margins (R1), lymph node metastasis. Youn [18] et al. confirmed R1 resection as an independent risk factor for recurrence and mortality. Uemura [32] et al., through multivariate analysis of 83 resected IPNB cases, showed that lymph node metastasis (HR, 5.78;  $p = 0.002$ ) and bile duct margin status with carcinoma in situ (HR, 5.10;  $p = 0.002$ ) were independent prognostic factors, whereas MUC6 expression showed only a marginal influence on prediction of prognosis. For a disease with diverse biological behaviors like IPNB, particularly for indolent subtypes such as low-grade intraepithelial neoplasia (LGIN), the median follow-up of 45 months in this study is indeed insufficient to accurately assess its 5-year long-term survival outcomes. This limitation may lead to an overestimation of survival rates in patients with indolent tumors like LGIN. The current findings primarily reflect mid-term prognosis. To obtain more conclusive survival analysis data, multicenter, large-scale clinical studies with a follow-up period of no less than 5 years are required. IPNB is a lesion with considerable molecular heterogeneity, and molecular markers—such as the expression of MUC1 and MUC5AC, as well as mutations in genes like KRAS and GNAS—are becoming increasingly critical for its precise biological subtyping, risk stratification, and prognosis prediction. As a

retrospective analysis focusing on clinicopathological and imaging features, our study indeed did not include systematic molecular profiling data, which represents a major limitation.

This study compared the clinical characteristics of IPNB patients with different pathological subtypes and anatomical classifications. In terms of prognosis, malignant cohort (HGIN+IC groups) had relatively shorter survival periods. Postoperative recurrence, abdominal pain, and non-radical surgery were significantly associated with poor prognosis in malignant IPNB patients. In principle, all suspected IPNB patients require surgical treatment. However, due to the low incidence and preoperative diagnostic rates, there is no unified standard for surgical approaches across medical centers. The small overall sample size in this study, combined with the fact that some IPNB patients in clinical practice did not undergo surgery (making pathological confirmation impossible), may introduce bias into the results. Multi-center, prospective RCT studies are needed to generate high-quality evidence for guiding clinical practice and ultimately improving outcomes for IPNB patients.

#### Abbreviations

|      |                                                 |
|------|-------------------------------------------------|
| IPNB | Intraductal papillary neoplasm of the bile duct |
| LGIN | Low-grade intraepithelial neoplasia             |
| HGIN | High-grade intraepithelial neoplasia            |
| IC   | Invasive carcinoma                              |
| CBC  | Complete blood count                            |
| CTA  | Computed tomography angiography                 |
| MRCP | Magnetic resonance cholangiopancreatography     |
| ERCP | Endoscopic retrograde cholangiopancreatography  |
| PTBD | Percutaneous transhepatic biliary drainage      |
| OS   | Overall survival                                |
| CEA  | Carcinoembryonic antigen                        |
| ALT  | Alanine Aminotransferase                        |
| AST  | Aspartate Aminotransferase                      |
| ALP  | Alkaline Phosphatase                            |
| GGT  | Gamma-Glutamyl Transferase                      |
| TBIL | Total Bilirubin                                 |
| DBIL | Direct Bilirubin                                |

#### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12893-026-03620-w>.

Supplementary Material 1.

#### Acknowledgements

Not applicable.

#### Clinical trial number

Not applicable.

#### Authors' contributions

LY F, WW T, and J B, P Z, wrote the main manuscript text, and D H, L C, prepared Figures 1-3, and J S, L G, prepared Tables 1-3. All authors reviewed the manuscript. The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. The authors have no relevant financial or non-financial interests to disclose.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Data availability

The datasets generated and analyzed during the current study are available as Supplementary Material (Additional File 1: Data.xlsx) submitted alongside this manuscript. The data file includes all raw data underlying the findings reported in this study. The datasets can be also available from the corresponding author. Researchers interested in obtaining the raw data may contact Dr. Shu at shuijecn@163.com for further information.

## Declarations

### Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University, PLA (Approval No.: KY2025084). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained in writing from all individual participants involved in the study. The authors affirm that human research participants provided informed consent for publication of the images and data.

### Consent for publication

Human research participants have provided informed consent for publication of the images and data. All authors have consented to publication.

### Competing interests

The authors declare no competing interests.

### Author details

<sup>1</sup>Institute of Hepatobiliary Surgery, First Affiliated Hospital (Southwest Hospital), Army Medical University, 30 Gaotanyan Main Street, Shapingba District, Chongqing 400038, China

<sup>2</sup>Institute of Surgery, 954th Hospital of PLA Army, 80 Naidong Street, Naidong District, Shannan 856000, China

Received: 30 November 2025 / Accepted: 17 February 2026

Published online: 26 February 2026

## References

1. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system[J]. *Histopathology*. 2020;76(2):182–8.
2. Ozcan K, Klimstra DS. A review of mucinous cystic and intraductal neoplasms of the pancreatobiliary tract. *Arch Pathol Lab Med*. 2022;146(3):298–311.
3. Lee SS, Kim MH, Lee SK, et al. Clinicopathologic review of 58 patients with biliary papillomatosis. *Cancer*. 2004;100(4):783–93.
4. Kim JR, Jang KT, Jang JY, et al. Clinicopathologic analysis of intraductal papillary neoplasm of bile duct: Korean multicenter cohort study[J]. *HPB (Oxford)*. 2020;22(8):1139–48.
5. Kim JR, Lee KB, Kwon W, et al. Comparison of the clinicopathologic characteristics of intraductal papillary neoplasm of the bile duct according to morphological and anatomical classifications. *J Korean Med Sci*. 2018;33(42):e266.
6. Gordon-Weeks AN, Jones K, Harriss E, et al. Systematic Review and Meta-analysis of Current Experience in Treating IPNB: Clinical and Pathological Correlates[J]. *Ann Surg*. 2016;263(4):656–63.
7. Yang CY, Huang WJ, Tsai JH, et al. Targeted next-generation sequencing identifies distinct clinicopathologic and molecular entities of intraductal papillary neoplasms of the bile duct. *Mod Pathol*. 2019;32(11):1637–45.
8. Rocha FG, Lee H, Katabi N, et al. Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? [J]. *Hepatology*. 2012;56(4):1352–60.
9. Jung G, Park KM, Lee SS, et al. Long-term clinical outcome of the surgically resected intraductal papillary neoplasm of the bile duct[J]. *J Hepatol*. 2012;57(4):787–93.
10. Ohtsuka M, Kimura F, Shimizu H, et al. Similarities and differences between intraductal papillary tumors of the bile duct with and without macroscopically visible mucin secretion[J]. *Am J Surg Pathol*. 2011;35(4):512–21.
11. Choi SC, Lee JK, Jung JH, et al. The clinicopathological features of biliary intraductal papillary neoplasms according to the location of tumors[J]. *J Gastroenterol Hepatol*. 2010;25(4):725–30.
12. Han SY, Kim DU, Nam HS, et al. Comparison of the malignant predictors in intrahepatic and extrahepatic intraductal papillary neoplasm of the bile duct. *J Clin Med*. 2022. <https://doi.org/10.3390/jcm11071985>.
13. Kim JR, Jang KT, Jang JY. Intraductal papillary neoplasm of the bile duct: review of updated clinicopathological and imaging characteristics[J]. *Br J Surg*. 2023;110(9):1229–40.
14. Valente R, Capurso G, Pierantognetti P, et al. Simultaneous intra-ductal papillary neoplasms of the bile duct and pancreas treated with chemoradiotherapy[J]. *World J Gastrointest Oncol*. 2012;4(2):22–5.
15. Yeh TS, Tseng JH, Chen TC, et al. Characterization of intrahepatic cholangiocarcinoma of the intraductal growth-type and its precursor lesions[J]. *Hepatology*. 2005;42(3):657–64.
16. Fuks D, Voitot H, Paradis V, et al. Intracystic concentrations of tumour markers for the diagnosis of cystic liver lesions[J]. *Br J Surg*. 2014;101(4):408–16.
17. Marrelli D, Caruso S, Pedrazzani C, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions[J]. *Am J Surg*. 2009;198(3):333–9.
18. Youn JM, Hwang S, Ahn CS, et al. Clinicopathological Features and Long-Term Outcomes of Intraductal Papillary Neoplasms of the Bile Duct of the Liver: Single-Institution Experience with 146 Patients[J]. *J Gastrointest Surg*. 2022;26(7):1394–405.
19. Krawczyk M, Ziarkiewicz-Wroblewska B, Podgorska J, et al. Intraductal papillary neoplasm of the bile duct - A comprehensive review[J]. *Adv Med Sci*. 2021;66(1):138–47.
20. Luvira V, Pughkhem A, Bhudhisawasdi V, et al. Long-term outcome of surgical resection for intraductal papillary neoplasm of the bile duct[J]. *J Gastroenterol Hepatol*. 2017;32(2):527–33.
21. Tsuyuguchi T, Sakai Y, Sugiyama H, et al. Endoscopic diagnosis of intraductal papillary mucinous neoplasm of the bile duct[J]. *J Hepatobiliary Pancreat Sci*. 2010;17(3):230–5.
22. Kim KM, Lee JK, Shin JU, et al. Clinicopathologic features of intraductal papillary neoplasm of the bile duct according to histologic subtype[J]. *Am J Gastroenterol*. 2012;107(1):118–25.
23. Kubota K, Nakanuma Y, Kondo F, et al. Clinicopathological features and prognosis of mucin-producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association[J]. *J Hepatobiliary Pancreat Sci*. 2014;21(3):176–85.
24. Kim JE, Lee JM, Kim SH, et al. Differentiation of intraductal growing-type cholangiocarcinomas from nodular-type cholangiocarcinomas at biliary MR imaging with MR cholangiography[J]. *Radiology*. 2010;257(2):364–72.
25. Nanashima A, Sumida Y, Tamaru N, et al. Intraductal papillary neoplasm of the bile duct extending superficially from the intrahepatic to extrahepatic bile duct[J]. *J Gastroenterol*. 2006;41(5):495–9.
26. Chang YR, Lee KB, Jang JY, et al. Analysis of microscopic tumor spread patterns according to gross morphologies and suggestions for optimal resection margins in bile duct cancer. *J Gastrointest Surg*. 2014;18(6):1146–54.
27. Jarnagin WR, Bowne W, Klimstra DS, et al. Papillary phenotype confers improved survival after resection of hilar cholangiocarcinoma[J]. *Ann Surg*. 2005;241(5):703–12.
28. Delaney S, Zhou Y, Pawa S, et al. Intraductal papillary neoplasm of the left hepatic duct treated with endoscopic retrograde cholangiopancreatography guided radiofrequency ablation[J]. *Clin J Gastroenterol*. 2021;14(1):346–50.
29. Arai J, Kato J, Toda N, et al. Long-term survival after palliative argon plasma coagulation for intraductal papillary mucinous neoplasm of the bile duct[J]. *Clin J Gastroenterol*. 2021;14(1):314–8.
30. Zhu X, Ni Q, Wang Q, et al. Intraductal papillary mucinous neoplasm of the biliary tract in the caudate lobe of the liver: a case report and literature review[J]. *Front Oncol*. 2023;13:114514.
31. Lee S, Kim MJ, Kim S, et al. Intraductal papillary neoplasm of the bile duct: assessment of invasive carcinoma and long-term outcomes using MRI. *J Hepatol*. 2019;70(4):692–9.

32. Uemura S, Higuchi R, Yazawa T, et al. Prognostic factors for surgically resected intraductal papillary neoplasm of the bile duct: a retrospective cohort study. *Ann Surg Oncol*. 2021;28(2):826–34.

### **Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.