Low HDL-Cholesterol is Associated with Malignant Intraductal Papillary Mucinous Neoplasms: A Multicenter Study

Chen Wang

Nanjing Drum tower Hospital, the Affiliated Hospital of Nanjing University medical school

Tingting Lin

the affiliated hospital of nanjing university of chinese medicine

Xinru Wang

the affiliated hospital of nanjing university of chinese medicine

Zhicheng Yu

the affiliated hospital of nanjing university of chinese medicine

Xiaoling Zhuge

the first affiliated hospital, college of medicine zhejiang university

Wenjing Cui

the affiliated hospital of nanjing university of chinese medicine

Miaomiao Wang

the affiliated hospital of nanjing university of chinese medicine

Zhongqiu Wang

the affiliated hospital of nanjing university of chinese medicine

Chuangeng Guo

the first affiliated hospital, college of zhejiang university

Xiao Chen (✉ chxwin@163.com)

affiliated hospital of nanjing university of Chinese medicine

Research Article

Keywords: HDL-cholesterol, intraductal papillary mucinous neoplasms, pancreas, malignancy

Posted Date: July 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-739674/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Intraductal papillary mucinous neoplasms (IPMNs) has the potential of malignant transformation. Previous studies showed that HDL-c was related to risk of cancer. In this study, we showed the association between HDL-c and the incidence of malignancy in IPMNs.

Material and methods: 226 patients with histologically proven IPMNs who underwent surgery were included in the present study. 151 patients were assigned to training group and other 75 patients was set as a validation. Patients' demographic information, clinical data, and pathological features were obtained from medical records. Those with high grade dysplasia and invasive carcinoma were defined as malignant IPMNs. Logistic regression analyses were used to show the association between HDL-c and malignant IPMNs. Receiver operating characteristic (ROC) curves were performed to show the predictive performance.

Results: Prevalence of low HDL-c in patients with malignant IPMNs was higher than those with non-malignant IPMNs ($p < 0.01$) both in training group and validation group. Prevalence of malignant IPMNs was decreased with the increase of HDL-c both in all IPMNs and Branch-Duct IPMNs (BD-IPMNs). Logistic analysis showed that low HDL-c was associated with malignant IPMNs (OR = 20.56, 95% CI: 2.58 - 163.64) in all IPMNs and BD-IPMNs (OR = 17.6, 95% CI: 1.16-268.46). The predictive performance of mural nodule plus low HDL-c was higher than that of mural nodule alone or mural nodule plus cyst size in identifying malignant BD-IPMNs.

Conclusion: HDL-c may be a potential biomarker for identifying malignant IPMNs. Moreover, HDL-c may improve the predictive ability of malignancy in BD-IPMNs.

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are common cystic neoplasms of pancreas. IPMNs has the potential of malignant transformation. The neoplastic transformation may culminate in invasive carcinoma in some patients [1], and IPMNs have the potential to progress from low-grade dysplasia to invasive carcinoma over the time [2, 3]. The incidence of high-grade dysplasia or pancreatic cancer in IPMNs was 42% [4]. IPMNs include three types considering the degree of involvement of the pancreatic ductal system: main duct (MD), branch duct (BD), and mixed type (features of MD and BD). Surgical intervention is recommended for MD IPMNs and mixed IPMNs because the high risk of malignancy [5]. Management of BD-IPMNs remains challenging.

High-risk stigmata and worrisome features have been applied to identify high-grade dysplasia or invasive carcinoma [6], such as diameter of main pancreatic duct (MPD) and enhanced mural nodule > 5 mm. Several studies also have shown the elevated tumor biomarkers was associated with invasive carcinoma in IPMNs, including carcinoembryonic antigen (CEA) and serum carbohydrate antigen 19-9 (CA19-9) [5]. However, those approaches are still not satisfied because of inadequate sensitivity and specificity [6]. There are inconsistencies among published guidelines [7]. In addition, some efforts were also made to predict malignant IPMN by using novel approach, such as extracellular vesicle [8]. However, few biomarkers have been used to identify malignancy in BD-IPMNs.

Cholesterol plays a critical role in cancer progression by enhancing cell proliferation, migration, and invasion [9]. High-density lipoprotein (HDL) is the main lipoprotein cholesterol transporter to the major steroidogenic organs [10, 11]. HDL protects against cancer development through its pleiotropic properties, including anti-oxidation and modulating cytokine production, and by blocking apoptosis, cell-growth stimulation and migration [12, 13]. HDL potentially antagonizing two main hallmarks of cancer progression via its potent antioxidant and anti-inflammatory properties [14, 15]. The association between high density lipoprotein-cholesterol (HDL-c) and cancer risk was also reported, including breast cancer [11, 16], prostate and ovarian cancer [11]. In addition, similar correlation was also found between HDL-c levels and risk of gastrointestinal cancer, such as liver cancer [17, 18], biliary tract cancer [19, 20] and pancreatic cancer [11, 21, 22]. However, to the best of our knowledge, the role of HDL-c in IPMNs has not been investigated. In the present multicenter study we observed the association between HDL-c and the incidence of malignancy in IPMNs, particularly to BD-IPMN.

Materials And Methods

Patients

226 patients with biopsy proven IPMN who underwent surgery during 2011-2020 in three centers were included in the present study after excluding those patients with data missing or receiving chemotherapy/radiotherapy. 151 patients in center 1 and center 2 were set as training group. Other 75 patients in center 3 was considered as validation group. Patients' demographic information, clinical data, and pathological features were obtained from medical records. We collected the data of preoperative symptoms (such as abdominal symptoms and overt jaundice), serum carbohydrate antigen 19-9 (CA19-9) level, serum carcinoembryonic antigen (CEA) levels, HDL-c, low density lipid (LDL), triglyceride (TG) and total cholesterol (TC). The medical history of pancreatitis and diabetes were collected. Fasting plasma glucose levels and 2-h plasma glucose levels were determined within one week before the operation. The diabetes mellitus (DM) was defined according to plasma

glucose levels and history of DM. Imaging information was obtained from PACS. This retrospective study was approved by the Institutional Ethic Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine. Informed consent was waived.

Imaging analysis

All patients underwent magnetic resonance imaging (MRI) examinations. T1 weighted imaging (T1WI), T2WI, MRCP and contrast-enhanced imaging were obtained. The following imaging findings were recorded: MPD diameter, enhanced mural nodule, cyst location, cyst size and the communication with MPD.

Malignant IPMN

IPMN was classified into three types considering the degree of involvement of the pancreatic ductal system: MD, BD, and mixed type. IPMN was classified into low-intermediate dysplasia, high-grade dysplasia, and invasive adenocarcinoma. Malignant IPMNs were defined as those with high grade dysplasia and associated invasive carcinoma.

Statistical analysis

HDL-c was divided into two groups: < 0.7 mmol/L and ≥ 0.7 mmol/L. The two-tailed t tests or Mann-Whitney U-test were used to compare the variables. Univariable and multivariable logistic regression analyses were used to show the association between low HDL-c and malignant IPMNs. The results were additionally adjusted with diabetes and pancreatitis. Receiver operating characteristic (ROC) curves were performed to show the performance of mural nodule plus low HDL-c in evaluating malignant IPMN. P values less than 0.05 were considered as statistically significant.

Results

The clinical data of patients

The clinical data of patients in training group and validation group is shown in Table 1. There were 47 patients (31.1%) with malignant IPMN in training group and 19 malignant IPMN (25.3%) in validation group. Prevalence of low HDL-c in patients with malignant IPMN was higher than those with non- malignant IPMN ($p < 0.01$) both in training group and validation group. 77.8% patients with low HDL-c had malignant IPMNs. Similar data was observed in validation group (75.0%). The prevalence of malignant IPMN was decreased with the increase of HDL-c both in all IPMNs and BD-IPMNs (Fig.1).

The association between low HDL-c and malignant IPMNs

Univariable and multivariable logistic regression were used to identify the associated factors for malignant IPMNs (Table 2). Compared with MD involved IPMN, BD IPMN had a lower risk for malignancy (OR = 0.13, 95% CI: 0.05 - 0.34). However, this association was disappeared when adjusting to high risk stigmata (diameter of main pancreatic duct and mural nodule). Low HDL-c was associated with the presence of malignant IPMNs (OR = 8.93, 95% CI: 1.78 - 44.80), and such association was remained after adjusting for diabetes, pancreatitis and serum LDL level (OR = 20.56, 95% CI: 2.58 - 163.64). Similar trend was found in validation group (OR = 6.66, 95%CI: 1.08 - 41.06).

Subsequently, we showed the association between low HDL-c and malignancy in BD-IPMNs (Table 3). Subgroup analysis also showed that low HDL-c was associated with the presence of malignant IPMNs (OR =17.6, 95% CI: 1.16 - 268.46) in BD- IPMNs

ROC analysis

ROC curve showed that the area under the curve (AUC) of mural nodule plus MPD diameter and low HDL-c (AUC = 0.82, 95% CI: 0.74 - 0.89) was slightly higher than that of mural nodule plus MPD diameter and Ca19-9 (AUC = 0.81, 95% CI: 0.73 - 0.89) in identifying malignant IPMNs (Fig.2). Moreover, the area under the curve (AUC) of mural nodule plus low HDL-c (AUC = 0.81, 95% CI: 0.62 - 0.99) was higher than that of mural nodule alone (AUC = 0.71, 95% CI: 0.49 - 0.92) or mural nodule plus cyst size (AUC= 0.76, 95%CI: 0.57-0.95) in identifying malignant BD-IPMNs (Fig.2).

Discussion

The diagnosis and clinical management strategies of them still remains controversial currently because of the absence of factors that predict malignancy clearly [23]. Tumor biomarkers, such as CEA and CA19-9, were also used to predict the malignancy [5]. Our study demonstrated a reverse association between HDL-c and IPMN. Low HDL-c in malignant IPMN were significantly higher than non- malignant IPMNs. Multivariable logistic analysis further showed that low HDL-c was associated with occurrence of malignant IPMN. In addition, the combination

of mural nodule and low HDL-c showed higher performance than mural nodule alone or combination of mural nodule plus cyst size in predicting malignant BD-IPMNs. Low HDL-c may be a potential biomarkers for malignant IPMNs.

An inverse relationship between serum total cholesterol levels and cancer risk has been reported [24–26]. Moreover, the associations between HDL-c and cancer risk, disease free survival (DFS) or overall survival (OS) have been reported in many malignancies [11, 16–22, 27]. Low HDL-C levels were associated with high TNM stage and occurrence of distant metastasis [28]. It is noteworthy that, in several studies, the HDL-c had shown the reverse correlation with the gastrointestinal cancer. The randomized controlled intervention studies showed [21] that the inverse associations of HDL-c with pancreatic cancer were not materially affected by other lipids, and the inverse association was unchanged after exclusion of the first 3 years of follow-up. Michalaki et.al [22] reported that serum HDL concentration was significantly lower in pancreatic cancer patients than in the controls. Serum apolipoprotein A-II, transthyretin, and apolipoprotein A-I were also decreased at least 2-fold in pancreatic cancer compared with the control group [29]. HDL-c levels were inversely associated with the risk of developing liver cancer [17], and pre-operative HDL-c levels was associated with the risk of cancer recurrence [18]. Patients in the lowest quintile of HDL-c (< 30 mg/dL) had a 11.6-fold higher risk of gallbladder cancer and a 16.8-fold higher risk of bile duct cancer, relative to the reference group [20]. Moreover, alteration for HDL levels may be a therapeutic strategy for cancer [30]. However, the association between HDL-c and malignant IPMNs has not been clarified.

Interestingly, our data showed that low serum HDL-c was an independent risk factor for malignancy in IPMN both in training population and validation population even after adjustment for confounding factors. In addition, the diagnostic performance of mural nodule plus MPD diameter and low HDL-c was similar with mural nodule plus MPD diameter and CA19-9. Management of BD-IPMNs remains challenging [31]. Few biomarkers have been used to identify malignancy in BD-IPMNs. Our data showed that low serum HDL-c improved the diagnostic performance of mural nodule in predicting malignant BD IPMN. The AUC was increased from 0.71 to 0.81. Interestingly, we also observed a reverse association between low HDL-c (< 0.8 mmol/L) and grade 3 pancreatic neuroendocrine neoplasms (PNENs) (n = 197, OR = 2.37, 95%CI: 1.001–5.62, data not shown). These data further support that low HDL-c is associated with malignant pancreatic diseases. However, conflicting evidence was also reported between HDL and cancer incidence or mortality because this association may be tumor-type-dependent [30]. Anyway, there is increasing evidence that supports this association [30].

The possible mechanism of HDL on cancer development or progression has not been totally clarified. HDL-associated proteins may have antioxidant, anti-inflammatory, anti-angiogenesis, and immunomodulatory activities which can result in anti-tumorigenesis effects [27]. In addition, cancer cells expressed high level of scavenger receptor type B-I (SR-BI) which can promote lipid internalization and lipoprotein consumption by cancer cells [31]. Meanwhile, a large amount of cholesterol is demanded in cancer cells because of the formation of new membranes [31]. Consequently, low levels of circulating HDL-c occurred.

Our study has several limitations. First, the sample size was relatively small, especially for number of malignant IPMNs or carcinoma in BD-IPMNs. Second, it would be better to perform a longitudinal study to show the baseline serum HDL-c and developing malignant IPMNs. Third, whether low HDL-c level is a consequential or causal factor in malignant IPMNs need further exploration. Fourth, some confounding factors were not considered, such as lifestyle and diet habits. Finally, HDL-associated proteins and enzymes were not easily affected by covariates. We did not observed the association between malignant IPMNs and them. Our study is an exploration.

In conclusion, our data shows that low HDL-c is associated with malignant IPMNs. Low HDL-c may be a potential biomarker for identifying malignant IPMNs. Moreover, HDL-c may improve the predictive ability of malignancy in BD-IPMNs. Prospective study is needed to evaluate the role of HDL-c in malignancy of IPMNs.

Abbreviations

AUC: area under the curve; BD: branch duct; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; HDL-c: highdensitylipoprotein-cholesterol; IPMN: intraductal papillary mucinous neoplasms; LDL: low density lipoprotein; MD: main duct; MPD: main pancreatic duct; MT: mixed-type; OR: odds ratio; ROC: receiver operating characteristic.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Ethic Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine. Informed consent was waived.

Consent for publication

Not applicable

Data availability statement

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

Disclosure of potential conflicts of interest

None

Funding

This study was funded by Zhejiang Provincial Natural Science Foundation (LY18H180004) and Zhejiang Medical Science and Technology Project (2017KY331).

Authors contributions

Cheng Wang: Data curation, Formal analysis, Writing – original draft, Writing - review & editing; T. Lin: Data curation, Formal analysis, Writing - review & editing; X. Wang: Data curation, Formal analysis, Writing - review & editing; Z. Yu: Data curation, Formal analysis, Writing -draft; X. Zhuge: Data curation, Formal analysis, Writing – original draft, Writing - review & editing. W.Cui: Formal analysis, Writing – original draft, Writing - review & editing. M. Wang: Data curation, Formal analysis, Writing - review & editing; Z.Wang: Formal analysis, Writing- review & editing. X. Chen: Conceptualization, Methodology, Data curation, Visualization, Writing - review & editing. C. Guo: Conceptualization, Methodology, Writing - review & editing.

Acknowledgments

Not applicable

References

1. Fernández-del Castillo C, Adsay NV. Intraductal papillary mucinous neoplasms of the pancreas. *Gastroenterology*. 2010;139(3): 708-13.
2. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol*. 2004;28(8): 977-87.
3. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg*. 2004;239(6): 788-97.
4. Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148(4): 824-48.
5. Fritz S, Hackert T, Hinz U, Hartwig W, Büchler MW, Werner J. Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas. *Br J Surg*. 2011;98(1): 104-10.
6. Tanaka M, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5): 738-53.
7. Tjaden C, Sandini M, Mihaljevic AL, Kaiser J, Khristenko E, Mayer P, et al. Risk of the Watch-and-Wait Concept in Surgical Treatment of Intraductal Papillary Mucinous Neoplasm. *JAMA Surg*. 2021, e210950.
8. Yang KS, Ciprani D, O'Shea A, Liss AS, Yang R, Fletcher-Mercaldo S, et al. Extracellular Vesicle Analysis Allows for Identification of Invasive IPMN. *Gastroenterology*. 2021;160(4): 1345-58.
9. Huang B, Song BL, Xu C. Cholesterol metabolism in cancer: mechanisms and therapeutic opportunities. *Nature metabolism*. 2020;2(2): 132-41.
10. Rigotti A, Miettinen HE, Krieger M. The role of the high-density lipoprotein receptor SR-BI in the lipid metabolism of endocrine and other tissues. *Endocr Rev*. 2003;24(3): 357-87.
11. Revilla G, Cedó L, Tondo M, Moral A, Pérez JI, Corcoy R, et al. LDL, HDL and endocrine-related cancer: From pathogenic mechanisms to therapies. *Semin Cancer Biol*. 2021;73:134-57.
12. Ramadori P, Kroy D, Streetz KL. Immunoregulation by lipids during the development of non-alcoholic steatohepatitis. *Hepatobiliary surgery and nutrition*. 2015;4(1): 11-23.
13. Inoue M, Kurahashi N, Iwasaki M, Tanaka Y, Mizokami M, Noda M, et al. Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). *Cancer Causes Control*. 2009;20(5): 741-50.
14. Georgila K, Vyrla D, Drakos E. Apolipoprotein A-I (ApoA-I), Immunity, Inflammation and Cancer. *Cancers (Basel)*. 2019;11(8):1097.

15. Bacchetti T, Ferretti G, Sahebkar A. The role of paraoxonase in cancer. *Semin Cancer Biol.* 2019;56:72-86.
16. Johnson KE, Siewert KM, Klarin D, Damrauer SM, Chang KM, Tsao PS, et al. The relationship between circulating lipids and breast cancer risk: A Mendelian randomization study. *PLoS Med.* 2020;17(9): e1003302.
17. Nderitu P, Bosco C, Garmo H, Holmberg L, Malmström H, Hammar N, et al. The association between individual metabolic syndrome components, primary liver cancer and cirrhosis: A study in the Swedish AMORIS cohort. *Int J Cancer.* 2017;141(6): 1148-60.
18. Tian L, Yu Q, Gao XH, Wu J, Ma XL, Dai Q, et al. A new use for an old index: preoperative high-density lipoprotein predicts recurrence in patients with hepatocellular carcinoma after curative resections. *Lipids Health Dis.* 2017;16(1): 123.
19. Hsing AW, Gao YT, Han TQ, Rashid A, Sakoda LC, Wang BS, et al. Gallstones and the risk of biliary tract cancer: a population-based study in China. *Br J Cancer.* 2007;97(11): 1577-82.
20. Andreotti G, Chen J, Gao YT, Rashid A, Chang SC, Shen MC, et al. Serum lipid levels and the risk of biliary tract cancers and biliary stones: A population-based study in China. *Int J Cancer.* 2008;122(10): 2322-9.
21. Kabat GC, Kim MY, Chlebowski RT, Vitolins MZ, Wassertheil-Smoller S, Rohan TE. Serum lipids and risk of obesity-related cancers in postmenopausal women. *Cancer Causes Control.* 2018;29(1): 13-24.
22. Michalaki V, Koutroulis G, Syrigos K, Piperi C, Kalofoutis A. Evaluation of serum lipids and high-density lipoprotein subfractions (HDL2, HDL3) in postmenopausal patients with breast cancer. *Mol Cell Biochem.* 2005;268:19-24.
23. Heckler M, Brieger L, Heger U, Pausch T, Tjaden C, Kaiser J, et al. Predictive performance of factors associated with malignancy in intraductal papillary mucinous neoplasia of the pancreas. *BJS open.* 2018;2(1): 13-24.
24. Pirro M, Ricciuti B, Rader DJ, Catapano AL, Sahebkar A, Banach M. High density lipoprotein cholesterol and cancer: Marker or causative? *Prog Lipid Res.* 2018;71:54-69.
25. Ahn J, Lim U, Weinstein SJ, Schatzkin A, Hayes RB, Virtamo J, et al. Prediagnostic total and high-density lipoprotein cholesterol and risk of cancer. *Cancer Epidemiol Biomarkers Prev.* 2009;18(11): 2814-21.
26. Chandler PD, Song Y, Lin J, Zhang S, Sesso HD, Mora S, et al. Lipid biomarkers and long-term risk of cancer in the Women's Health Study. *Am J Clin Nutr.* 2016;103(6): 1397-1407.
27. Ridditid W, DeWitt JM, Schmidt CM, Roch A, Stuart JS, Sherman S, et al. Management of branch-duct intraductal papillary mucinous neoplasms: a large single-center study to assess predictors of malignancy and long-term outcomes. *Gastrointest Endosc.* 2016;84(3): 436-45.
28. Ganjali S, Banach M, Pirro M, Fras Z, Sahebkar A. HDL and cancer - causality still needs to be confirmed? Update 2020. *Semin Cancer Biol.* 2021;73:169-77.
29. Ehmann M, Felix K, Hartmann D, Schnölzer M, Nees M, Vorderwülbecke S, et al. Identification of potential markers for the detection of pancreatic cancer through comparative serum protein expression profiling. *Pancreas.* 2007;34(2): 205-14.
30. Ganjali S, Ricciuti B, Pirro M, Butler AE, Atkin SL, Banach M, et al. High-Density Lipoprotein Components and Functionality in Cancer: State-of-the-Art. *Trends Endocrinol Metab.* 2019;30(1): 12-24.
31. Morin EE, Li X-A, Schwendeman A. HDL in Endocrine Carcinomas: Biomarker, Drug Carrier, and Potential Therapeutic. *Front Endocrinol (Lausanne).* 2018;9:715.

Tables

Table 1 Clinical data in malignant and non-malignant IPMNs

	Training group (center 1 and Center 2)				Validation group (center 3)			
	Total (n=151)	Malignant IPMN (n = 47)	Non-malignant IPMN(n = 104)	p	Total (n=75)	Malignant IPMN (n = 19)	Non-malignant IPMN(n = 56)	p
Age	63.28 ± 9.47	63.59 ± 8.99	62.60±10.50	0.55	64.8±8.90	68.42±8.25	63.68±8.86	0.44
Size	3.69±1.98	3.93±1.63	3.58±2.11	0.34	3.1±1.12	3.8±1.33	2.5±0.93	0.02
Sex(male/female)	95/56	34/13	61/43	0.11	49/26	11/8	38/18	0.43
Dysplasia	/				/			
Low-intermediate grade	104	/	104		56	0	56	
High-grade	24	24	0		11	11	0	
Invasion	23	23	0		8	8	0	
Type	<0.01				<0.01			
Main	24	16	8		14	8	6	
Branch	73	9	64		46	6	40	
Mixed	54	22	32		15	5	10	
Location	0.11				0.94			
Head-neck	95	34	61		41	9	32	
Body and Tail	56	13	43		34	10	24	
CEA (ng/ml)	3.57±3.61	4.75±5.65	3.03±1.95	0.09	3.99±10.03	8.51±19.29	2.43±1.59	0.03
CA19-9 (U/ml)	48.68±228.65	99.04±396.08	26.19±70.67	0.002	71.37±204.27	132.83±270.4	50.15±174.53	0.13
HDL-c (mmol/L)	1.19±0.39	1.10±0.52	1.21±0.31	0.38	1.02±0.39	0.84±0.41	1.08±0.37	0.02
HDL-c< 0.7	9	7	2	<0.01	12	9	3	<0.01
LDL (mmol/L)	2.51±0.82	2.52±0.69	2.51±0.89	0.95	2.27±0.69	1.91±0.65	2.40±0.67	0.01
MPD diameter	0.61±0.41	0.90±0.49	0.48±0.29	<0.001		0.97±0.42	0.43±0.21	<0.01
Pancreatitis	3	0	3	0.24	1	0	1	0.25
Diabetes	23	9	14	0.13	4	1	3	1.0
Lymph node metastasis (yes vs no)	2	2	0	0.09		0	0	/
Peripancreatic extension	5	5	0	0.003	1	1	0	0.45
Mural nodule	17	13	4	< 0.01	8	5	3	0.01

Malignant intraductal papillary mucinous neoplasms (IPMNs) were defined as those with high grade dysplasia and associated invasive carcinoma

CA 19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, MPD: main pancreatic duct, HDL-c: high density lipoprotein-cholesterol, LDL: low density lipoprotein

Table 2 Associated factors with malignant IPMNs

	Training group (center 1 and center 2)			Validation group (center 3)	
variables	Univariable	Multivariable		Multivariable	
		Model 1	Model 2	Model 1	Model 2
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Mural nodule	9.56(2.92-31.30)	15.14(3.10-74.07)	14.51(3.05-69.02)	16.11(2.78-93.5)	25.2(3.43-185.4)
Duct(cm)	18.0(5.84-55.52)	10.45(1.78-61.17)	11.61(1.88-71.65)	15.4(2.36-89.6)	18.76(3.32-165.3)
Size (cm)	1.09(0.91-1.30)	0.99(0.79-1.23)	0.95(0.76-1.19)	1.07(0.86-1.28)	1.06(0.86-1.31)
Type					
MD+MT	1	1	1	1	1
Branch-duct	0.15(0.07-0.34)	0.39 (0.10-1.53)	0.38 (0.09-1.53)	0.21 (0.10-0.37)	0.16 (0.09-0.28)
Location					
Head-neck	1	1	1	1	1
Body-Tail	0.54(0.26-1.15)	0.57(0.22-1.50)	0.62(0.23-1.63)	0.47(0.18-1.21)	0.50(0.20-1.27)
HDL-c (< 0.7 vs ≥ 0.7)	8.93(1.78-44.80)	17.92(2.40-134.17)	20.56 (2.58-163.64)	6.63(1.14-38.47)	6.66(1.08-41.06)

Model 1 was adjusted with BMI, age and gender, Model 2 was additionally adjusted with pancreatitis, LDL and diabetes.

Table 3 Associated factors with malignant IPMNs in BD-IPMN

variables	Univariable	Multivariable	
		Model 1	Model 2
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Mural nodule	24.80 (3.61-170.3)	50.6(5.12-499.6)	52.8(5.29-528.2)
Duct (cm)	1.24(0.01-170.5)	19.45(0.04-1000.0)	17.6(0.04-820.7)
Size (cm)	1.12(0.86-1.46)	1.08(0.77-1.52)	1.11(0.78-1.56)
HDL-c (<0.7 vs ≥ 0.7)	8.86(1.07-73.1)	15.27(1.19-196.26)	17.6(1.16-268.46)

Model 1 was adjusted with BMI, age and gender, Model 2 was additionally adjusted with pancreatitis, LDL and diabetes.

Figures

Figure 1

The association between the prevalence of malignant intraductal papillary mucinous neoplasms (IPMNs) and HDL-c. The prevalence of malignancy increased with HDL-c both in all IPMNs (A) and BD-IPMNs (B). malignant branch duct intraductal papillary mucinous neoplasm (BD-IPMN).

Figure 2

The receiver operating characteristic (ROC) curves of variables in predicting malignantintraductal papillary mucinous neoplasms (IPMNs). A: mural nodule plus MPD diameter and Ca19-9 or low HDL-c in predicting malignant IPMN. B: mural nodule alone, mural nodule plus cyst size, and mural nodule plus low HDL-c in predicting malignant branch duct IPMNs (BD-IPMNs).