Systematic review

Predictive performance of factors associated with malignancy in intraductal papillary mucinous neoplasia of the pancreas

M. Heckler, L. Brieger, U. Heger, T. Pausch, C. Tjaden, J. Kaiser, M. Tanaka, T. Hackert and C. W. Michalski

Department of Surgery, Heidelberg University Hospital, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

Correspondence to: Dr T. Hackert (e-mail: thilo.hackert@med.uni-heidelberg.de)

Background: Estimation of the risk of malignancy in intraductal papillary mucinous neoplasia (IPMN) of the pancreas is a clinical challenge. Several routinely used clinical factors form the basis of the current consensus guidelines. This study aimed to determine the predictive values of the most commonly assessed risk factors.

Methods: A meta-analysis of individual risk factors of malignancy in IPMN was performed. Contingency tables were derived from these data, and sensitivity, specificity, negative and positive predictive values, and diagnostic odds ratios (DOR) were determined. Hierarchical summary receiver operating characteristic (HSROC) curves for each factor were calculated and the respective area under the curve (AUC) was assessed.

Results: A total of 3443 studies were screened initially. Analysis of recent literature revealed 60 studies with 13 relevant risk factors including clinical, serological and radiological parameters. The largest area under the HSROC curve was found for weight loss (0.84) and jaundice/raised bilirubin level (0.80), followed by increased carcinoembryonic antigen (CEA) (0.79) or carbohydrate antigen (CA) 19-9 (0.78) levels. The most sensitive factors were patient age (71 per cent) and mural nodules (65 per cent), and jaundice/raised bilirubin level (97 per cent) and increased CEA level (95 per cent) were most specific. None of the analysed factors reached a positive or negative level of prediction beyond 90 per cent.

Conclusion: None of the established criteria safely distinguishes malignant from non-malignant lesions.

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Introduction

The clinical management of intraductal papillary mucinous neoplasia (IPMN) is still controversial. The major reason is the absence of factors that clearly predict malignancy. To overcome this issue, consensus conferences in Sendai1 and Fukuoka2 have defined combinations of risk factors that may predict malignancy more sensitively and specifically. A large number of mainly single-centre analyses based on these criteria have been published, but a recent meta-analysis3 of data from these publications demonstrated that both overall sensitivity and specificity of the most recent (Fukuoka) criteria were relatively low.

The present study aimed to assess the predictive values of individual factors that have been associated with malignancy in IPMN. Studies including branch duct (BD), main duct (MD) and mixed-type IPMN were considered, focusing on those that reported sensitivity and specificity of individual risk factors of malignancy. Data were pooled and meta-analysed, allowing for a determination of statistical classifiers.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines4 were followed. Two investigators screened two databases, PubMed and Web of Science, independently. In cases of disagreement, a third investigator decided on inclusion of the study. The search strategy consisted of the following terms: ‘intraductal papillary mucinous neoplasms’ AND biomarker OR marker OR predictor OR malignancy OR
Identification and screening

Records identified and screened through database MEDLINE/PubMed and Web of Science searching after duplicates removed

n = 3443

Records excluded n = 3067
Case series with fewer than ten patients n = 11
Non-English-language article n = 11
No extractable data n = 10
No full text available n = 18
Not in field of interest n = 224

Full text assessed for eligibility n = 376

Eligibility

Included

Studies included in qualitative synthesis n = 65

Studies included in quantitative synthesis n = 60

Not able to create a 2×2 table n = 5

Table 1 Characteristics of included studies

| Reference       | Factor     | Cut-off value | No. of patients | Age (years)* | Male sex (%) | Study type                        | Statistical analysis | Type of IPMN |
|-----------------|------------|---------------|-----------------|--------------|--------------|-----------------------------------|----------------------|-------------|
| Baiocchi et al. | CA19-9     | 37 units/ml   | 44              | 69.3 (38–86) | 45-5         | Prospective uncontrolled case study | Uni BD+MI+MD         |             |
| Hwang et al.    | CA19-9     | 37 units/ml   | 118             | 63-4(8-5) (41–85) | 61          | RCCS                             | Uni BD              |             |
| Roch et al.     | CA19-9     | 37 units/ml   | 171             | IPMA: 68-4   | IPMA: 80-2   | RCCS                             | Multi BD+MI+MD       |             |
| Xu et al.       | CA19-9     | 37 units/ml   | 86              | 62(9) (41–76) | 72-1         | RCCS                             | Uni BD+MI+MD         |             |
| Jang et al.     | Cyst size  | 20 mm         | 138             | 60-6(8-9) (32–82) | 63          | RCCS                             | Multi BD+MI+MD       |             |
| Nagai et al.    | Cyst size  | 30 mm         | 69              | 63(8)        | 62-3         | RCCS                             | Uni BD              |             |
| Akita et al.    | MN         | –             | 32              | IPMA: 65-3(8-5) | IPMA: 65   | RCCS                             | Multi MD             |             |
| Arima et al.    | MN         | –             | 76              | IPMA: 66-3(8) | IPMA: 65-4 | RCCS                             | Uni BD+MI+MD         |             |
| Kawada et al.   | MN         | 10 mm         | 202             | 68(7)        | 54-5         | RCCS Retrospective multicentre case–control study | Multi BD             |             |
| Kwong et al.    | MN         | –             | 284             | 67-3(10-8)  | 43           | RCCS                             | Uni BD              |             |
| Moris et al.    | MN         | –             | 856             | 70-6         | 39           | RCCS Retrospective multicentre case–control study | Uni BD              |             |
| Ogawa et al.    | MN         | > 3-6 mm      | 49              | 64-9 (41–81) | 66-1         | RCCS                             | Uni BD              |             |
| Ohno et al.     | MN on EUS  | –             | 87              | 66-5(9-5)   | 60-9         | RCCS                             | Uni BD+MI+MD         |             |
| Seo et al.      | MN         | –             | 60              | 64-3(0-9)   | 63-3         | RCCS                             | Multi BD             |             |
| Shimizu et al.  | MN         | 7 mm          | 310             | 67-1(8-7)   | 58-3         | RCCS                             | Multi BD+MI+MD       |             |
| Kang et al.     | MPD        | 7 mm          | 375             | 63-8(9-0)   | 62-4         | RCCS                             | Multi BD+MI+MD       |             |
| Rittitid et al. | MPD        | 5–9 mm        | 105             | 65(2-12-5)  | 53           | RCCS                             | Uni BD              |             |
| Sadakari et al. | MPD        | 5 mm          | 73              | 66(8) (46–82) | 65-8        | RCCS                             | Uni BD              |             |
| Ohno et al.     | MPD enlargement on EUS | – | 142 | 65(9) (37–83) | 53-8 | RCCS                             | Uni BD              |             |

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Table 1 continued

| Reference          | Factor                  | Cut-off value | No. of patients | Age (years)* | Male sex (%) | Study type | Statistical analysis | Type of IPMN |
|--------------------|-------------------------|---------------|-----------------|--------------|--------------|------------|----------------------|--------------|
| Kim et al.         | Pancreatitis            | –             | 118             | 61.2 (37–78) | 70.3         | RCCS       | Uni                  | BD+MI+MD    |
| Morales-Oyarvide et al. | Pancreatitis          | –             | 325             | 68(10-9)     | 48.9         | RCCS       | Multi               | BD+MI+MD    |
| Tsuchumi et al.    | Pancreatitis            | –             | 150             | Pancreatitis | 66(8-6)      | RCCS       | Uni                  | BD+MI+MD    |
| Carobogin et al.   | Thickened cyst wall     | –             | 29              | IPMA: 64.7(9-9) | 58.6         | RCCS       | Uni                  | BD          |
| Correa-Gallego et al. | Weight loss            | –             | 123             | 68 (62–75)   | 40.7         | RCCS       | Multi               | BD          |
| Dortch et al.      | Weight loss             | 10 lb         | 66              | 68(8-5)      | 33.36        | RCCS       | Uni                  | BD          |
| Ammori et al.      | Cyst size               | 30 mm         | 184             | 68 (34–88)   | n.a.         | RCCS       | Uni                  | BD+MI+MD    |
| Chiu et al.        | Lymphadenopathy         | 3 mm          | 40              | 60 (32–67)   | 69           | RCCS       | Multi               | BD+MI       |
| Fritz et al.       | CA19-9                  | 37 units/ml   | 142             | n.a.         | 57.75        | RCCS       | Uni                  | BD+MI+MD    |
| Fritz et al.       | CEA                     | 5 ng/ml       | 142             | 160          | 39.91        | RCCS       | Uni                  | BD          |
| Fujino et al.      | CA19-9                  | 35 units/ml   | 64              | IPMA: 66(1-2) | 60.94        | RCCS       | Multi               | BD+MI+MD    |
| Goh et al.         | Jaundice (obstructive) | 5 mm          | 39              | 63 (33–83)   | 66           | RCCS       | Uni                  | BD          |
| Hirono et al.      | Age                     | 70 years      | 54              | 69 (44–81)   | 57.4         | RCCS       | Uni                  | BD+MI+MD    |
| Hirono et al.      | CA19-9                  | 37 units/ml   | 134             | 68(9-7)      | 55.2         | RCCS       | Uni                  | BD          |
| Hwang et al.       | CEA                     | 5 mg/ml       | 237             | 63-1 (38–83) | 57.8         | RCCS       | Uni                  | BD          |
| Jang et al.        | CA19-9                  | 37 units/ml   | 333             | 63-6(8-9)    | 61.7         | RCCS       | Multi               | BD          |
| Kato et al.        | Age                     | 65 years      | 47              | 66-2 (50–77) | 63.8         | RCCS       | Uni                  | BD          |
| Kim et al.         | Cyst size (enlargement) | 5 mm          | 47              | n.a.         | n.a.         | RCCS       | Uni                  | BD+MI+MD    |
| Kim et al.         | MN                      | 10 mm         | 93              | n.a.         | n.a.         | RCCS       | Uni                  | BD+MI+MD    |

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| Reference          | Factor                        | Cut-off value | No. of patients | Age (years)* | Male sex (%) | Study type | Statistical analysis | Type of IPMN |
|--------------------|-------------------------------|---------------|-----------------|--------------|--------------|------------|---------------------|--------------|
| Kim et al.         | CA19-9                        | 37 units/ml   | 324             | 62 (30–83)   | 55-2         | RCCS       | Multi               | BD           |
|                    | Cyst size                     | 37 units/ml   | 324             | 62 (30–83)   | 55-2         | RCCS       | Multi               | BD           |
|                    | Jaundice (bilirubin)          | 1-2 mg/dl     | 187             | 62 (30–83)   | 55-2         | RCCS       | Multi               | BD           |
|                    | Male sex                      | 5 mm          | 324             | 62 (30–83)   | 55-2         | RCCS       | Multi               | BD           |
|                    | MN                            | 5 mm          | 324             | 62 (30–83)   | 55-2         | RCCS       | Multi               | BD           |
|                    | MPD                           | 5 mm          | 324             | 62 (30–83)   | 55-2         | RCCS       | Multi               | BD           |
| Kim et al.         | Cyst size                     | 30 mm         | 177             | 63 (30–87)   | 61           | Retrospective multicentre case–control study | Uni          | BD           |
|                    | Jaundice (obstructive)        | 30 mm         | 177             | 63 (30–87)   | 61           | Retrospective multicentre case–control study | Uni          | BD           |
|                    | MN on EUS                     | 5 mm          | 110             | 63 (30–87)   | 61           | Retrospective multicentre case–control study | Uni          | BD           |
| Kurahara et al.    | Pancreatitis                  | 5 mm          | 55              | 63 (30–87)   | 61           | RCCS       | Multi               | BD           |
|                    | CA19-9                        | 37 units/ml   | 40 mm           | 60 (30–87)   | 72-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Cyst size                     | 37 units/ml   | 40 mm           | 60 (30–87)   | 72-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Lymphadenopathy               | 7 mm          | 129             | 60 (30–87)   | 72-9         | RCCS       | Uni                 | BD+MI+MD    |
| Lou et al.         | Jaundice                      | –             | 51              | 63 (41–78)   | 64-7         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Weight loss                   | –             | 29              | 66 (37–85)   | 51-3         | RCCS       | Uni                 | BD           |
| Maguchi et al.     | Pancreatitis                  | 5 mm          | 30              | 66 (37–85)   | 51-3         | RCCS       | Uni                 | BD           |
|                    | MN                            | 5 mm          | 30              | 66 (37–85)   | 51-3         | RCCS       | Uni                 | BD           |
|                    | CA19-9                        | 37 units/ml   | 40 mm           | 60 (30–87)   | 72-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MPD                           | 6 mm          | 40 mm           | 60 (30–87)   | 72-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Cyst size                     | 37 units/ml   | 40 mm           | 60 (30–87)   | 72-9         | RCCS       | Uni                 | BD+MI+MD    |
| Murakami et al.    | Cyst size                     | 28 mm         | 62              | n.a.         | 64-7         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MN                            | 6 mm          | 62              | n.a.         | 64-7         | RCCS       | Uni                 | BD+MI+MD    |
| Nagai et al.       | Pancreatitis                  | 5 mm          | 57              | 66 (41–85)   | 51-3         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MN                            | 5 mm          | 57              | 66 (41–85)   | 51-3         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Weight loss                   | 57             | 66 (41–85)      | 51-3         | RCCS         | Uni                 | BD+MI+MD    |
| Nara et al.        | Age                           | 70 years      | 123             | 64 (40–84)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | CA19-9                        | 37 units/ml   | 40 mm           | 64 (40–84)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Cyst size                     | 37 units/ml   | 40 mm           | 64 (40–84)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MN                            | 30 mm         | 43              | 64 (40–84)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MPD                           | 6 mm          | 43              | 64 (40–84)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Cyst size                     | 28 mm         | 62              | 67 (33–85)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MN                            | 6 mm          | 62              | 67 (33–85)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | Pancreatitis                  | 5 mm          | 62              | 67 (33–85)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
|                    | MN on EUS                     | 5 mm          | 62              | 67 (33–85)   | 56-9         | RCCS       | Uni                 | BD+MI+MD    |
| Okabayashi et al.  | Pancreatitis                  | 30 mm         | 23              | 66 (53–86)   | 69-6         | RCCS       | Multi               | BD+MI+MD    |
|                    | MN                            | 5 mm          | 23              | 66 (53–86)   | 69-6         | RCCS       | Multi               | BD+MI+MD    |
| Rodriguez et al.   | Jaundice                      | 28 mm         | 23              | 66 (53–86)   | 69-6         | RCCS       | Multi               | BD+MI+MD    |
|                    | MN on EUS                     | 5 mm          | 23              | 66 (53–86)   | 69-6         | RCCS       | Multi               | BD+MI+MD    |
| Sahora et al.      | Jaundice                      | 30 mm         | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | Thickened cyst wall           | 30 mm         | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | Cyst size                     | 30 mm         | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | Age                           | 39 units/ml   | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | CA19-9                        | 39 units/ml   | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | Cyst size                     | 39 units/ml   | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | Male sex                      | 39 units/ml   | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | MN                            | 39 units/ml   | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
|                    | MPD                           | 39 units/ml   | 217             | 67 (21–92)   | 37-8         | RCCS       | Multi               | BD           |
| Shin et al.        | Age                           | 60 years      | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
|                    | CA19-9                        | 37 units/ml   | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
|                    | Cyst size                     | 37 units/ml   | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
|                    | Jaundice (bilirubin)          | 1-2 mg/dl     | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
|                    | MN                            | 1-2 mg/dl     | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
|                    | MPD                           | 1-2 mg/dl     | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
|                    | Pancreatitis                  | 6 mm          | 204             | 61 (35–77)   | 68-1         | RCCS       | Multi               | BD+MI+MD    |
serum OR CA19-9 OR CEA OR ‘pancreatic enzymes’ OR amylase OR lipase OR PLR OR NLR OR Ca24-2 OR bilirubin OR platelet OR neutrophil and ‘pancreatic cancer’ AND enzymes OR ‘serum amylase’ OR ‘serum lipase’ OR amylase OR lipase OR ‘serum enzymes’ and ‘cancer AND platelet lymphocyte ratio OR neutrophil lymphocyte ratio’. The search was conducted to cover articles published between 2006 (publication of the Sendai consensus) and April 2016 (date of search).

Criteria for study inclusion were as follows: patients with histologically confirmed IPMN; studies that analysed one or more of the factors of the consensus guidelines or one of the other factors defined in the primary literature search; and studies that allowed for clear assignment of presence of the respective factor to the histological outcome. Invasive carcinoma and high-grade dysplasia (formerly carcinoma in situ) were considered as malignant lesions.

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Table 1 continued

| Reference       | Factor               | Cut-off value | No. of patients | Age (years)* | Male sex (%) | Study type | Statistical analysis | Type of IPMN |
|-----------------|----------------------|---------------|-----------------|--------------|--------------|------------|---------------------|--------------|
| Suzuki et al.   | Cyst size MN (MN)    | 47 mm         | 96              | 67(10) (34–81)| 66-7         | RCCS       | Multi               | BD+MI+MD     |
|                 | MPD                  | 9 mm          |                 |              |              |            | Multi               |              |
| Takeshita et al.| Cyst size + MPD max. | –             | 46              | 65 (43–78)   | 52-8         | RCCS       | Multi               | BD           |
|                 | diameter MN MPD dilated + max. cyst size |                 |              |              |              | Uni       | Multi               |              |
| Walter et al.   | MN                   | 30 mm         | 60              | 64(12-2)     | 60-3         | RCCS       | Multi               | BD+MI+MD     |
| Woo et al.      | Cyst size DM         | 30 mm         | 85              | 63 (40–82)   | 58-8         | RCCS       | Uni                 | BD           |
| Xu et al.       | CA19-9               | 37 units/ml   | 54              |              |              | RCCS       | Multi               | BD+MI+MD     |
|                 | Jaundice MPD         | 30 mm         |                 |              |              | Uni       | Multi               |              |
| Yamada et al.   | Jaundice (obstructive) | –             | 166             | 66-6(5-8)    | 60-2         | RCCS       | Multi               | BD+MI+MD     |
|                 | Lymphadenopathy      |               |                 |              |              | Uni       | Multi               |              |
| You et al.      | CA19-9 CEA           | 37 units/ml   | 87              | 61-5(9-2)    | 64-4         | RCCS       | Multi               | BD+MI+MD     |
|                 |                      | 5 ng/ml       |                 |              |              |            | Multi               |              |

*Values are mean(s.d.) (range). IPMN, intraductal papillary mucinous neoplasia; CA, carbohydrate antigen; Uni, univariable; BD, branch duct; MI, mixed-type IPMN; MD, main duct; RCCS, retrospective controlled cohort study; IPMA, benign IPMN; IPMC, malignant IPMN; Multi, multivariable; MN, mural nodules; EUS, endoscopic ultrasonography; MPD, main pancreatic duct; n.a., not available; CEA, carcinoembryonic antigen.

Table 2 Results of the pooled analysis

| No. of studies | No. of patients | AUC | Sensitivity (%) | Specificity (%) | DOR | P (%) |
|----------------|-----------------|-----|-----------------|-----------------|-----|-------|
| Age            | 5               | 645 | 0.67 (0.62, 0.72)| 71 (53, 89)     | 59 (47, 71) | 3.64 | 6-03 |
| CA19-9         | 17              | 2747| 0.78 (0.75, 0.82)| 49 (41, 57)     | 89 (86, 92) | 7.29 | 5-91 |
| CEA            | 3               | 456 | 0.79 (0.70, 0.86)| 35 (21, 48)     | 95 (91, 99) | 8.37 | 4-12 |
| Cyst size      | 21              | 2375| 0.68 (0.65, 0.72)| 64 (56, 72)     | 69 (61, 77) | 3.62 | 4-76 |
| Diabetes       | 3               | 231 | 0.71 (0.62, 0.79)| 46 (37, 56)     | 83 (76, 90) | 4.42 | 8-90 |
| Jaundice       | 12              | 1689| 0.80 (0.76, 0.84)| 26 (18, 33)     | 97 (96, 99) | 7.98 | 12-15 |
| Lymphadenopathy| 5               | 945 | 0.51 (0.41, 0.61)| 20 (8, 32)      | 93 (84, 100)| 4.74 | 12-14 |
| Male sex       | 3               | 774 | 0.62 (0.56, 0.69)| 59 (48, 71)     | 59 (47, 71) | 2.14 | 3-12 |
| Dilatation of MPD | 21            | 2991| 0.77 (0.73, 0.80)| 60 (52, 68)     | 80 (75, 86) | 6.59 | 9-26 |
| Mural nodules  | 33              | 5068| 0.77 (0.75, 0.80)| 65 (61, 70)     | 81 (76, 85) | 7.89 | 6-82 |
| Pancreatitis   | 7               | 1127| 0.67 (0.63, 0.72)| 32 (21, 43)     | 86 (80, 91) | 2.67 | 3-68 |
| Thickened cyst wall | 4          | 581 | 0.56 (0.46, 0.66)| 23 (10, 36)     | 95 (88, 100)| 4.93 | 11-35 |
| Weight loss    | 4               | 297 | 0.84 (0.78, 0.89)| 53 (34, 72)     | 90 (83, 96) | 8.72 | 18-07 |

Values in parentheses are 95 per cent confidence intervals. AUC, area under the curve; DOR, diagnostic odds ratio; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; MI, main pancreatic duct.
Fig. 2 Receiver operating characteristic (ROC) curves for clinical parameters associated with malignancy in intraductal papillary mucinous neoplasia: a pancreatitis, b weight loss, c male sex, d age, e diabetes mellitus

Articles with abstracts that did not fit the scope of the search were excluded, along with non-English-language articles, case reports, small case series with ten or fewer patients, reviews and meta-analyses. Only studies that allowed for a quantitative analysis of the results into a $2 \times 2$ contingency table were included in the meta-analysis.

Studies eligible for inclusion were grouped according to the respective factor of interest. All continuous exposures (for example laboratory parameters such as carbohydrate antigen (CA) 19-9) were then converted into a binary form using widely used cut-off values. In the next step, $2 \times 2$ tables were designed for all studies. Sensitivities, specificities, negative predictive values (NPVs), positive predictive values (PPVs) and diagnostic odds ratios (DORs) were calculated. Results were pooled using a random-effects model. Final results for each analysed factor were depicted...
Factors associated with malignancy in intraductal papillary mucinous neoplasia of the pancreas

Summary estimate
Data point for individual study
95% c.i.

0 0.2 0.4 0.6 0.8 1.0
False-positive rate
Sensitivity

0 0.2 0.4 0.6 0.8 1.0
False-positive rate
Sensitivity

0 0.2 0.4 0.6 0.8 1.0
False-positive rate
Sensitivity

Fig. 3 Receiver operating characteristic (ROC) curves for serological parameters associated with malignancy in intraductal papillary mucinous neoplasia: a carbohydrate antigen (CA) 19-9, b jaundice, c carcinoembryonic antigen (CEA)

using forest plots. Heterogeneity was assessed using I² statistics. Study quality and publication bias were investigated using funnel plots. The open-source statistical software R 3.3 and the meta-analysis package metafor 1.9-9 (R Foundation for Statistical Computing, Vienna, Austria) were used for the analysis. The mada 0.5.7 package was used for calculation of the hierarchical summary receiver operating characteristic (HSROC) curves and the corresponding area under the curve (AUC).

Results

A total of 3443 studies were screened. Initial screening for markers derived from the differential blood count (neutrophil : lymphocyte ratio, platelet : lymphocyte ratio) revealed poor study quality for these factors, so these studies were excluded. After further exclusion of non-relevant studies, 60 were included in the final analysis (Fig. 1). Of these studies, 33 investigated mural nodules, 21 examined dilatation of the main pancreatic duct (MPD), 33 investigated age, 5-7 weight loss, 10-12 male sex, 18-23, 15-20, 31, 35 pancreatitis, 15-20, 31, 35, 59-61, thickened cyst wall, 6-8, 32, 62 and weight loss, 10, 57, 63, 64. Other characteristics (age, 13-15, 23, carcinoembryonic antigen (CEA) increase, 19, 50, 56, diabetes mellitus, 38, 40, 48, lymphadenopathy, 6, 32, 41, 54, 58, male sex, 18, 23, 54, pancreatitis, 15, 20, 31, 35, 59-61, thickened cyst wall, 6-8, 32, 62 and weight loss, 10, 57, 63, 64) were assessed in between three and seven studies. The characteristics of included studies are shown in Table 1.

AUC values derived from HSROC curves were calculated for each factor (Table 2). The largest AUCs were 0.84 for weight loss (Fig. 2) and 0.80 for jaundice (Fig. 3), followed by the serological markers CEA (0.79) and CA19-9 (0.78) (Fig. 3). The radiological criteria of lymphadenopathy (0.51) and thickened cyst wall (0.56) had the lowest AUC values (Fig. 4).

Factors with the highest sensitivities were patient age (71 per cent), presence of mural nodules (65 per cent) and cyst size (64 per cent). Jaundice (26 per cent), thickened cyst
wall (23 per cent) and lymphadenopathy (20 per cent) were the least sensitive. Specificity was highest for jaundice (97 per cent), raised CEA level (95 per cent) and thickened cyst wall (95 per cent), and lowest for patient age (59 per cent) and male sex (59 per cent) (Table 2; Fig. S1, supporting information). Jaundice (82 per cent) and lymphadenopathy (71 per cent) had the highest PPVs, and male sex the lowest (26 per cent); NPVs ranged from 86 per cent for male sex to 60 per cent for diabetes mellitus (Fig. S1, supporting information).

The pooled DOR was highest for weight loss (8.72), CEA increase (8.37) and jaundice (7.98), and lowest for male sex (2.14) and pancreatitis (2.67) (Table 2; Figs S2–S4, supporting information).

Fig. 4 Receiver operating characteristic (ROC) curves for radiological parameters associated with malignancy in intraductal papillary mucinous neoplasia: a dilatation of main pancreatic duct (MPD), b thickened cyst wall, c mural nodules, d lymphadenopathy, e cyst size.
Analysis of heterogeneity of the included factors revealed low heterogeneity for the majority (below 30 per cent), with moderate heterogeneity (30–60 per cent) for CA19-9 level, cyst size, lymphadenopathy, dilatation of the MPD and the presence of mural nodules (Table 2). Funnel plots of study quality are shown in Fig. S5 (supporting information).

Discussion

High reliability in the identification or exclusion of malignancy is an important characteristic of a diagnostic test that is clinically useful in patients with suspected cancer. This meta-analysis assessed the diagnostic accuracy of a number of established clinical, radiological and serological markers, and revealed that no single clinically established factor (or the absence of such a factor) sufficiently predicted or excluded malignancy. Several factors provided high specificity, but sensitivity was generally poor.

Although it provides a comprehensive overview of all established factors in the stratification of IPMN of the pancreas, this analysis has several limitations. Studies evaluating BD, MD and mixed-type IPMN were all included. It is conceded that many surgeons would feel that MD IPMN should generally be resected and might wonder why those different entities were investigated in one analysis. Although the dogma that all MD IPMN should be resected is based on an estimated malignancy rate of 61–6 per cent, compared with only 25–5 per cent for BD IPMN\(^5\), IPMN with only minimal MD involvement can be followed up safely without surgical intervention in some patients\(^6\). On the other hand, BD IPMN with high-risk signs according to the Fukuoka consensus should be resected\(^2\). Future biomarkers might provide safe exclusion of malignancy in MD and BD IPMN. Until such reliable biomarkers have been established, the risk of malignancy in MD IPMN, mixed-type IPMN and BD IPMN might be estimated incorrectly. The authors chose to include all three subtypes of IPMN of the pancreas to gain a thorough overview of the current literature, although it is accepted that this approach might represent a source of bias. Other limitations include the retrospective nature of most of the included studies, the conversion of continuous variables into binary variables, and heterogeneity of the studies.

The absence of a single valid criterion to predict malignancy leads to the conclusion that several factors need to be combined to identify sufficiently patients likely to benefit from intervention, or observation. The presence or absence of combinations of factors including jaundice, presence of mural nodules, dilatation of the MPD and others might then be used to guide treatment decisions.

The present study did identify factors with relatively high AUCs, such as the presence of increased levels of tumour markers. CEA and CA19-9 are not included in the recommendations of the current consensus guidelines, but they might be valuable adjuncts where there is diagnostic uncertainty owing to their relatively high specificity. Several potential scoring formulas to improve diagnostic accuracy have been developed over the past decade\(^19,36,66,67\), but none has been validated prospectively.

Until the identification of biomarkers with an adequate ROC curve (such as troponin T for the diagnosis of myocardial infarction), decisions regarding intervention or observation remain largely dependent on the ‘gut feeling’ of treating clinicians. An international prospective study using highly standardized clinical pathways with the collection of high-quality biomaterial should be undertaken.

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References

1. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006; 6: 17–32.
2. Tanaka M, Fernández-Del Castillo C, Adsay V, Chari S, Falconi M, Jang JY et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012; 12: 183–197.
3. Heckler M, Michalski CW, Schaeff S, Kaiser J, Bächler MW, Hackert T. The Sendai and Fukuoka consensus criteria for the management of branch duct IPMN – a meta-analysis on their accuracy. Pancreatology 2017; 17: 255–262.
4. Moher D, Liberati A, Tetzlaff J, Altman DG, Oxman AD, Cook DJ et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336–341.
5. Okabayashi T, Kobayashi M, Nishimori I, Sugimoto T, Namikawa T, Okamoto K et al. Clinicopathological features and medical management of intraductal papillary mucinous neoplasms. J Gastroenterol Hepatol 2006; 21: 462–467.
6. Chiu SS, Lim JH, Lee WJ, Chang KT, Oh DK, Lee KT et al. Intraductal papillary mucinous tumour of the pancreas: differentiation of malignancy and benignancy by CT. Clin Radiol 2006; 61: 776–783.
branch duct type intraductal papillary mucinous neoplasms of the pancreas: a suggested scoring formula. J Korean Med Sci 2011; 26: 740–746.
20. Ohtsuka T, Kono H, Nagayoshi Y, Mori Y, Tsutsumi K, Sadakari Y et al. An increase in the number of predictive factors augments the likelihood of malignancy in branch duct intraductal papillary mucinous neoplasm of the pancreas. Surgery 2012; 151: 76–83.
21. Hirono T, Tani M, Kawai M, Okada K, Miyazawa M, Shimizu A et al. The carcinoembryonic antigen level in pancreatic juice and mural nodule size are predictors of malignancy for branch duct type intraductal papillary mucinous neoplasms of the pancreas. Ann Surg 2012; 255: 517–522.
22. Shimizu Y, Yamaue H, Maguchi H, Yamao K, Hirono S, Osnai M et al. Predictors of malignancy in intraductal papillary mucinous neoplasm of the pancreas: analysis of 310 pancreatic resection patients at multiple high-volume centers. Pancreas 2013; 42: 883–888.
23. Sahara K, Mino-Kenudson M, Brugge W, Thayer SP, Ferrone CR, Sahani D et al. Branch duct intraductal papillary mucinous neoplasms. Ann Surg 2013; 258: 466–475.
24. Kawada N, Uehara H, Nagata S, Tsuchishima M, Tsutsumi M, Tomita Y. Predictors of malignancy in branch duct intraductal papillary mucinous neoplasm of the pancreas. JOP 2014; 15: 459–464.
25. Ammori JB, Do RKG, Brennan MF, D’Angelica MI, Dematteo RP, Fong Y et al. Uncinate duct dilation in intraductal papillary mucinous neoplasms of the pancreas: a radiographic finding with potentially increased malignant potential. J Gastrointest Surg 2014; 18: 911–916.
26. Jang JY, Park T, Lee S, Kang MJ, Lee SY, Lee KB et al. Validation of international consensus guidelines for the resection of branch duct-type intraductal papillary mucinous neoplasms. Br J Surg 2014; 101: 686–692.
27. Kato Y, Takahashi S, Gotohda N, Konishi M. Risk factors for malignancy in branched-type intraductal papillary mucinous neoplasms of the pancreas during the follow-up period. World J Surg 2015; 39: 244–250.
28. Walter TC, Steffen IG, Stelter LH, Maurer MH, Bahra M, Faber W et al. Implications of imaging criteria for the management and treatment of intraductal papillary mucinous neoplasms: benign versus malignant findings. Eur Radiol 2015; 25: 1329–1338.
29. Arima K, Okabe H, Hashimoto D, Chikamoto A, Kuroki H, Taki K et al. The neutrophil-to-lymphocyte ratio predicts malignant potential in intraductal papillary mucinous neoplasms. J Gastrointest Surg 2015; 19: 2171–2177.
30. Kim SH, Lee JM, Lee ES, Baek JH, Kim JH, Han JK et al. Intraductal papillary mucinous neoplasms of the pancreas: evaluation of malignant potential and surgical resectability by using MR imaging with MR cholangiography. Radiology 2015; 274: 723–733.
31. Kim TH, Song TJ, Hwang JH, Yoo KS, Lee WJ, Lee KH et al. Predictors of malignancy in pure branch duct type

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intraductal papillary mucinous neoplasm of the pancreas: a nationwide multicenter study. *Pancratologia* 2015; 15: 405–410.

32 Kim JR, Jang JY, Kang MJ, Park T, Lee SY, Jung W et al. Clinical implication of serum carcinoembryonic antigen and carbohydrate antigen 19–9 for the prediction of malignancy in intraductal papillary mucinous neoplasm of pancreas. *J Hepatobiliary Pancreat Sci* 2015; 22: 699–707.

33 Kwong WT, Lawson RD, Hunt G, Fehmi SM, Proudfoot JA, Xu R et al. Rapid growth rates of suspected pancreatic cyst branch duct intraductal papillary mucinous neoplasms predict malignancy. *Dig Dis Sci* 2015; 60: 2800–2806.

34 Moris M, Raimondo M, Woodward TA, Skinner V, Arcidiacono PG, Petrone MC et al. Risk factors for malignant progression of intraductal papillary mucinous neoplasms. *Dig Liver Dis* 2015; 47: 495–501.

35 Kurahara H, Maemura K, Mataka Y, Sakoda M, Iino S, Kijima Y et al. Predictors of early stages of histological progression of branch duct IPMN. *Langenbecks Arch Surg* 2015; 400: 49–56.

36 Suzuki Y, Nakazato T, Yokoyama M, Kogure M. Development and potential utility of a new scoring formula for prediction of malignant intraductal papillary mucinous neoplasm of the pancreas. *Pancratologia* 2016; 45: 1229–1232.

37 Seo N, Byun JH, Kim JH, Kim HJ, Lee SS, Song KB et al. Validation of the 2012 international consensus guidelines using computed tomography and magnetic resonance imaging: branch duct and main duct intraductal papillary mucinous neoplasms of the pancreas. *Ann Surg* 2016; 263: 557–564.

38 Fujino Y, Matsumoto I, Ueda T, Toyama H, Kuroda Y. Proposed new score predicting malignancy of intraductal papillary mucinous neoplasms of the pancreas. *Am J Surg* 2007; 194: 304–307.

39 Sadakari Y, Ienaga J, Kobayashi K, Miyasaka Y, Takahata S, Nakamura M et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. *Pancratologia* 2010; 39: 232–236.

40 Mimura T, Masuda A, Matsumoto I, Shiomi H, Yoshida S, Sugimoto M et al. Predictors of malignant intraductal papillary mucinous neoplasm of the pancreas. *J Clin Gastroenterol* 2010; 44: e224–e229.

41 Lee JH, Lee KT, Park J, Bae SY, Lee KH, Lee JK et al. Predictive factors associated with malignancy of intraductal papillary mucinous pancreatic neoplasms. *J Hepatobiliary Pancreat Surg* 2010; 16: 533–538.

42 Ohno E, Itoh A, Kawashima H, Ishikawa T, Matsubara H, Itoh Y et al. Malignant transformation of branch duct-type intraductal papillary mucinous neoplasms of the pancreas based on contrast-enhanced endoscopic ultrasonography morphological changes: focus on malignant transformation of intraductal papillary mucinous neoplasm. *Pancratologia* 2012; 41: 855–862.

43 Xu B, Ding W-X, Jin D-Y, Wang D-S, Lou W-H. Decision making for pancreatic resection in patients with intraductal papillary mucinous neoplasms. *World J Gastroenterol* 2013; 19: 1451–1457.

44 Goh BKP, Thng CH, Tan DMY, Low ASC, Wong JS, Cheow PC et al. Evaluation of the Sendai and 2012 International Consensus Guidelines based on cross-sectional imaging findings performed for the initial triage of mucinous cystic lesions of the pancreas: a single institution experience with 114 surgically treated patients. *Am J Surg* 2014; 208: 202–209.

45 Kang MJ, Jang JY, Lee S, Park T, Lee SY, Kim SW. Clinicopathological meaning of size of main-duct dilatation in intraductal papillary mucinous neoplasm of pancreas: proposal of a simplified morphological classification based on the investigation on the size of main pancreatic duct. *World J Surg* 2015; 39: 2006–2013.

46 Ridtitid 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: 436–445.

47 Jang J-Y, Kim S-W, Lee SE, Yang SH, Lee KU, Lee YJ et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? *Ann Surg Oncol* 2008; 15: 199–205.

48 Woo SM, Ryu JK, Lee SH, Yoon WJ, Kim YT, Yoon YB. Branch duct intraductal papillary mucinous neoplasms in a retrospective series of 190 patients. *Br J Surg* 2009; 96: 405–411.

49 Nagai K, Doi R, Ito T, Kida A, Koizumi M, Masui T et al. Single-institution validation of the international consensus guidelines for treatment of branch duct intraductal papillary mucinous neoplasms of the pancreas. *J Hepatobiliary Pancreat Surg* 2009; 16: 353–358.

50 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: 104–110.

51 Xu B, Zheng W-Y, Jin D-Y, Ding W, Lou W-H, Ramosok L. Predictive value of serum carbohydrate antigen 19–9 in malignant intraductal papillary mucinous neoplasms. *World J Surg* 2011; 35: 1103–1109.

52 Hwang DW, Jang JY, Lee SE, Lim CS, Lee KU, Kim SW. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: a 15-year experience at a single academic institution. *Langenbecks Arch Surg* 2012; 397: 93–102.

53 Baiochhi GL, Bertagna F, Gheza F, Grazioli L, Calanducci D, Giubbini R et al. Searching for indicators of malignancy in pancreatic intraductal papillary mucinous neoplasms: the value of 18FDG-PET confirmed. *Ann Surg Oncol* 2012; 19: 3574–3580.

54 Fritz S, Klauss M, Bergmann F, Strobel O, Schneider L, Werner J et al. Pancreatic main-duct involvement in branch-duct IPMNs. *Ann Surg* 2014; 260: 848–856.
Abnormal serum pancreatic enzymes, but not pancreatitis, are associated with an increased risk of malignancy in patients with intraductal papillary mucinous neoplasms. *Surgery* 2014; **156**: 923–929.

Roch AM, Parikh JA, Al-Haddad MA, DeWitt JM, Ceppa EP, House MG *et al*. Abnormal serum pancreatic enzymes, but not pancreatitis, are associated with an increased risk of malignancy in patients with intraductal papillary mucinous neoplasms. *Surgery* 2014; **156**: 923–929.

You L, Ma L, Zhao WJ, Zhao YP, Dai MH. Emerging role of tumor markers and biochemistry in the preoperative invasive assessment of intraductal papillary mucinous neoplasm of the pancreas. *Clin Chim Acta* 2016; **454**: 89–93.

Lou W, Jin D, Wang D, Xu X, Kuang T, Qin X. An analysis of clinico-pathologic features of intraductal papillary mucinous neoplasm of the pancreas. *Front Med China* 2007; **1**: 173–176.

Yamada S, Fujii T, Murotani K, Kanda M, Sugimoto H, Nakayama G *et al*. Comparison of the international consensus guidelines for predicting malignancy in intraductal papillary mucinous neoplasms. *Surgery* 2016; **159**: 878–884.

Kim SC, Park KT, Lee YJ, Lee SS, Seo DW, Lee SK *et al*. Intraductal papillary mucinous neoplasm of the pancreas: clinical characteristics and treatment outcomes of 118 consecutive patients from a single center. *J Hepatobiliary Pancreat Surg* 2008; **15**: 183–188.

Tsutsumi K, Ohtsuka T, Oda Y, Sadakari Y, Mori Y, Aishima S *et al*. A history of acute pancreatitis in intraductal papillary mucinous neoplasms of the pancreas is a potential predictive factor for malignant papillary subtype. *Pancreatology* 2010; **10**: 707–712.

Morales-Oyarvide V, Mino-Kenudson M, Ferrone CR, Gonzalez-Gonzalez LA, Warshaw AL, Lillemoe KD *et al*. Acute pancreatitis in intraductal papillary mucinous neoplasms: a common predictor of malignant intestinal subtype. *Surgery* 2015; **158**: 1219–1225.

Carbognin G, Zamboni G, Pinali L, Dalla Chiara E, Girardi V, Salvia R *et al*. Branch duct IPMTs: value of cross-sectional imaging in the assessment of biological behavior and follow-up. *Abdom Imaging* 2006; **31**: 320–325.

Correa-Gallego C, Do R, Lafemina J, Gonen M, D’Angelica MI, DeMatteo RP *et al*. Predicting dysplasia and invasive carcinoma in intraductal papillary mucinous neoplasms of the pancreas: development of a preoperative nomogram. *Ann Surg Oncol* 2013; **20**: 4348–4355.

Dortch JD, Stauffer JA, Ashun HJ. Pancreatic resection for side-branch intraductal papillary mucinous neoplasm (SB-IPMN): a contemporary single-institution experience. *J Gastrointest Surg* 2015; **19**: 1603–1609.

Sahora K, Castillo CF, Dong F, Marchegiani G, Thayer SP, Ferrone CR *et al*. Not all mixed-type intraductal papillary mucinous neoplasms behave like main-duct lesions: implications of minimal involvement of the main pancreatic duct. *Surgery* 2014; **156**: 611–621.

Jang JY, Park T, Lee S, Kim Y, Lee SY, Kim SW *et al*. Proposed nomogram predicting the individual risk of malignancy in the patients with branch duct type intraductal papillary mucinous neoplasms of the pancreas. *Ann Surg* 2017; **266**: 1062–1068.

Hijioka S, Shimizu Y, Mizuno N, Hara K, Imaoka H, Mekky MA *et al*. Can long-term follow-up strategies be determined using a nomogram-based prediction model of malignancy among intraductal papillary mucinous neoplasms of the pancreas? *Pancreas* 2014; **43**: 367–372.
Graphical Abstract

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The diagnosis of intraductal papillary mucinous neoplasia (IPMN) is still accompanied by a high grade of uncertainty–for patients and treating physicians. The authors meta-analysed the current literature and found that none of the established diagnostic parameters safely excludes malignancy.