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The additive value of CA19.9 monitoring in a pancreatic cyst surveillance program

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Abstract

Background: Surveillance of pancreatic cysts focuses on the detection of (mostly morphologic) features warranting surgery. European guidelines consider elevated CA19.9 as a relative indication for surgery. We aimed to evaluate the role of CA19.9 monitoring for early detection and management in a cyst surveillance population.

Methods: The PACYFIC-registry is a prospective collaboration that investigates the yield of pancreatic cyst surveillance performed at the discretion of the treating physician. We included participants for whom at least one serum CA19.9 value was determined by a minimum follow-up of 12 months.

Results: Of 1865 PACYFIC participants, 685 met the inclusion criteria for this study (mean age 67 years, SD 10; 61% female). During a median follow-up of 25 months (IQR 24, 1966 visits), 29 participants developed high-grade dysplasia (HGD) or pancreatic cancer. At baseline, CA19.9 ranged from 1 to 591 kU/L (median 10 kU/L [IQR 14]), and was elevated (≥37 kU/L) in 64 participants (9%). During 191 of 1966 visits (10%), an elevated CA19.9 was detected, and these visits more often led to an intensified follow-up (42%) than those without an elevated CA19.9 (27%; $p < 0.001$). An elevated CA19.9 was the sole reason for surgery in five participants with benign disease (10%). The baseline CA19.9 value was (as continuous or dichotomous variable at the 37 kU/L threshold) not independently associated with HGD or

pancreatic cancer development, whilst a CA19.9 of ≥ 133 kU/L was (HR 3.8, 95% CI 1.1–13, $p = 0.03$).

Conclusions: In this pancreatic cyst surveillance cohort, CA19.9 monitoring caused substantial harm by shortening surveillance intervals (and performance of unnecessary surgery). The current CA19.9 cutoff was not predictive of HGD and pancreatic cancer, whereas a higher cutoff may decrease false-positive values. The role of CA19.9 monitoring should be critically appraised prior to implementation in surveillance programs and guidelines.

KEYWORDS
biomarkers, CA19.9, early detection, follow-up, GICA, pancreatic cancer, pancreatic cysts, pancreatic lesions, surgical intervention, surveillance

INTRODUCTION

Pancreatic cancer (PC) is a leading cause of cancer-related death, with a mere 5-year survival of 9%.[1] Timely detection is expected to increase the chance of curative surgery and prolonged survival.[2,3] Intraductal Papillary Mucinous Neoplasms (IPMNs) of the pancreas are neoplastic cystic lesions with a potential for malignant progression. They are increasingly being detected in asymptomatic individuals who undergo cross-sectional imaging for unrelated reasons. As precursor lesions of PC, surveillance is recommended by seeking (mostly) morphological changes (so called relative [RI] and absolute [AI] indications for surgery).[4]

Serum carbohydrate antigen 19.9 (CA19.9) is a tumor marker that is used to monitor the disease course in patients with PC. In the latest update of the European guidelines on cystic neoplasms,[4] an elevated CA19.9 level was added as an RI, meaning that surgery should be considered in the presence of a second RI. This recommendation was based on retrospective surgical studies,[4–7] but the yield of CA19.9 monitoring in a surveillance population has not yet been investigated. Conversely, CA19.9-related harm, due to unnecessary shortening of surveillance intervals and surgery, is unclear.

The aim of this study was to evaluate the role of serum CA19.9 monitoring in individuals undergoing pancreatic cyst surveillance within the PACYFIC-registry by assessing 1. The range and variability of CA19.9 levels at baseline and during follow-up; 2. The clinical impact of an elevated value; 3. The diagnostic performance of CA19.9 for the detection of HGD or PC; 4. The risk of developing HGD or PC over time for different CA19.9 cutoffs.

Key Summary

Summarize the established knowledge on this subject

- Surveillance of pancreatic cysts focuses on the detection of (mostly morphologic) features warranting surgery.
- European guidelines consider elevated CA19.9 as a relative indication for surgery.
- Surgery is recommended in individuals with two or more relative indications for surgery.

What are the significant and/or new findings of this study?

- In a pancreatic cyst surveillance program, CA19.9 monitoring may cause substantial harm by shortening surveillance intervals (and performance of unnecessary surgery).
- The current CA19.9 cutoff is not predictive of HGD and PC in individuals with pancreatic cysts, whereas a higher cutoff may decrease false-positive values.

MATERIAL AND METHODS

The PACYFIC registry

The PACYFIC-registry is an ongoing prospective multicenter cohort study (http://www.pacyfic.net) that follows individuals who undergo pancreatic cyst surveillance at the discretion of their treating physician. The study has been running since 2015 and includes individuals with a pancreatic cyst (either newly or previously diagnosed, or previously operated upon) for whom cyst surveillance is warranted according to the treating physician. Exclusion criteria were a history of chronic pancreatitis, suspected pseudocyst or walled-off necrosis, suspected serous cystadenoma, Von Hippel-Lindau disease and limited life expectancy (<2 years). It was designed to investigate the long-term yield of this surveillance. The surveillance period ends if the cyst appears to be benign (due to new insights) or is no longer present, or if the participant is no longer fit for surgery, is lost to follow-up, withdraws participation, or has passed away. A total of 23 academic and community hospitals from Europe ($n = 22$) and The United States ($n = 1$) contributed to this study.

The PACYFIC registry was approved by the ethical review board of Erasmus University Medical Center in 2014 (MEC-2014-021).

Written informed consent was obtained from each participant prior to inclusion. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

PACYFIC data are prospectively collected at each follow-up visit and stored in a digital case record form. Registered patient information includes sex, age, body mass index (BMI), presence of symptoms, and diabetes mellitus (DM). Cyst characteristics include the working diagnosis, size, presence of AI or RI and histological outcomes (of fine-needle aspiration or biopsy or surgery). Per study participant, each CA19.9 value was tested at the same center (using the same laboratory technique).

In- and exclusion criteria for the current study

All PACYFIC-participants were considered for inclusion in the current study. As surveillance within the PACYFIC-registry is performed at the discretion of the treating physician, CA19.9 is not always determined. Participants without a recorded CA19.9 value were excluded, as well as those with less than 12 months of follow-up. However, participants—for which a definitive dysplasia grade was established within 12 months after the first recorded CA19.9 value—were included. Individuals with a history of PC or jaundice at baseline were also excluded as these conditions may influence CA19.9 levels.[8]

Definitions

Definitions regarding the presence of RI and AI were based on the European evidence-based guidelines on pancreatic cystic neoplasms.[4] A solid mass (tumor-related) jaundice, enhancing mural nodules ≥5 mm, main pancreatic duct (MPD) dilation >10 mm were considered as "AI"; RI was defined as MPD dilation 5–9 mm, new-onset DM (DM developed within 2 years prior to visit), acute pancreatitis, enhancing mural nodules <5 mm and a cyst size ≥40 mm (based on the largest cyst). Cyst growth ≥5 mm/year was not included as RI at baseline as growth is not assessable at that time. Individuals with ≥2 RI were considered to have an "AI, " as the guideline recommends surgery in this case, regardless of co-morbidity. "Baseline" is defined as the first visit during which CA19.9 was recorded, whilst the follow-up is the period from "baseline" until the time of analysis or the end of the study. "Cases" were defined as individuals who developed pathology-proven HGD or PC and "controls" as those who did not. Time-to-event was defined as the time (in months) from the first CA19.9 value determination to development of HGD/PC or the last follow-up visit.

Statistical analysis

Patients were stratified according to baseline CA19.9 values (threshold 37 kU/L). Results were expressed as mean with standard deviation (SD; for normally distributed data), median with interquartile range (IQR; for non-normally distributed data), or numbers with percentages. Differences between groups were assessed with a student's *t*-test/ANOVA for normally distributed data or a Mann–Whitney-U/Kruskal-Wallis-test for non-normally distributed data. For categorical variables, a χ^2-test was used. Correlation between variables was performed using Spearman.

To evaluate the impact of an elevated value on cyst management (regarding surveillance intervals or interventions) were described as proportions (of visits), and compared by a χ^2-test. General surveillance intervals were based on recommendations by the European guidelines[4] (6 months' interval during the first year and 12 months' thereafter).

Median CA19.9 values were compared with the Mann–Whitney *U* test. An ROC-curve was generated for different cutoffs; besides 37 kU/L, two other cutoffs were selected upon visualization of clear angles on the ROC curve (aiming for high specificity). Subsequently, the diagnostic performance (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy) for these thresholds were calculated; 95% of the CIs were "exact" Clopper-Pearson CIs. For individuals with a pathological diagnosis, CA19.9 levels from the last visit before this diagnosis were used. Otherwise, levels from 12 months prior were used to minimize the risk of occult PC.

To evaluate the risk of HGD or PC related to baseline CA19.9 values, multiple (univariable and multivariable) proportional hazards models were generated, with CA19.9 as a continuous and dichotomous variable (at thresholds selected by performed ROC analyses).

Two-sided *p*-values of less than 0.05 were considered statistically significant. Data were analyzed and graphs visualized using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois, version 27) and GraphPad (GraphPad Prism version 9, La Jolla, CA).

RESULTS

Characteristics of study participants

Of the 1865 PACYFIC participants, 1180 were excluded; 521 for lack of CA19.9 determination, 648 for insufficient follow-up duration, seven for a history of PC and four for jaundice at baseline (Figure 1). The mean age of 685 included individuals was 67 years (SD 10) and 61% were female. BD-IPMN was the most common working diagnosis (77%), followed by unspecified cyst (9.5%) and mixed-type (MT-IPMN) or main-duct IPMN (MD-IPMN; 9.3%; Table 1).

During the follow-up, a pathological diagnosis was established in 77 individuals (11%), by surgery in 64 (9.3%) and by fine-needle aspiration (FNA) in 13 (1.9%). Of these, 15 (2.2%) had PC (7 resected, 8 irresectable), 14 (2.0%) HGD IPMN (all resected), 27 (4.0%) LGD IPMN (23 resected), 6 (0.9%) LGD MCN (all resected), and 15

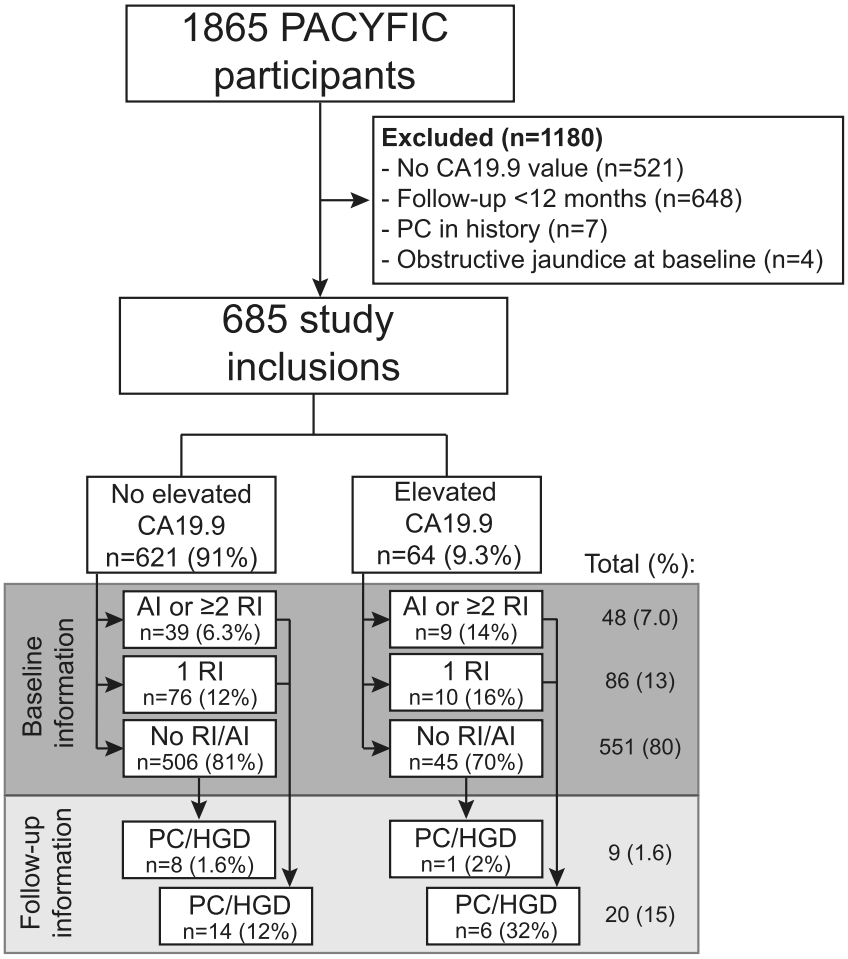


FIGURE 1 Flowchart of patient in- and exclusion, baseline information and follow-up information. All PACYFIC participants were considered for inclusion in the current study. Participants without a recorded CA19.9 value as well as those with less than 12 months of follow-up (with the exception of those participants for which a pathological cyst diagnosis was established within the first 12 months after the first recorded CA19.9 value) were excluded. Additionally, individuals with a history of PC or jaundice at baseline were excluded as these conditions may influence CA19.9 levels. CA19.9 values and (baseline) cyst growth were not included as absolute (AI) or relative (RI) indications for surgery[9]; HGD, high-grade dysplasia; PC, pancreatic cancer.

(2.2%) other diagnoses: lympho-epithelial cyst (n = 1), lymphangioma (n = 1), pseudocyst (n = 2), neuroendocrine tumor grade 1 (NET; n = 6, 5 resected), SCN (n = 4), SPN (n = 1).

CA19.9 outcomes

At baseline, CA19.9 values ranged from 1 to 591 kU/L (median 10 kU/L; IQR 14) and were elevated in 64 participants (9.3%). Those with an elevated CA19.9 at baseline were older (p = 0.05), had a larger cyst size (p = 0.03) and more often an AI or RI (p = 0.03), ≥1AI (p = 0.004), weight loss (p = 0.04), a solid component (p = 0.03) or diabetes mellitus (DM; p = 0.01; Table 1).

During a median follow-up of 25 months (IQR 24; 0–72 months), a median of three surveillance visits took place (IQR 2; range: 1–11 visits) in which a median of three CA19.9 values were determined (IQR 2; range 1–11). Serum CA19.9 ranged from 1 to 1470 kU/L (median 10, IQR 14) and levels were elevated at 191 of 1966 visits (9.7%) in 96 individuals (14%).

The clinical impact of an elevated value

Figure 2 depicts the impact of elevated CA19.9 levels on cyst management. A shortened interval was chosen more often during visits with an elevated value (42%) as compared to those without (27%, p < 0.001). Ten of 96 participants with an elevated value underwent surgery (10%). Of these, four had HGD or PC (40%, Figure 3a) and six had benign disease (60%; Figure 3b). In the latter group, an elevated value was the sole reason for surgery in 5 of 48 participants. Thus, the omission of CA19.9 testing may have prevented unnecessary surgery for this group.

Seven (5 PC, 2 HGD) of 29 individuals with HGD or PC had an elevated CA19.9 value (24%; Figure 3a). Of these, five had at least

TABLE 1 Baseline characteristics.

	Total cohort	CA19-9		
	(*n* = 685)	<37 kU/L (*n* = 621)	≥37 kU/L (*n* = 64)	*p*-value
Age, mean (SD)	67 (10)	67 (10)	69 (8)	0.05
Female sex, *n* (%)	416 (61)	379 (61)	37 (58)	0.62
BMI, mean (SD)[a]	26 (5.1)	26 (5.0)	27 (6.2)	0.89
Previously operated cyst, *n* (%)	18 (2.6)	18 (2.9)	-	0.17
AI or RI[b,c], *n* (%)	134 (20)	115 (19)	19 (30)	0.03
≥1 AI[b], *n* (%)	48 (7.0)	39 (6.3)	9 (14)	0.004
1 RI[c], *n* (%)	86 (13)	76 (12)	10 (16)	0.10
Symptoms				
Acute pancreatitis, *n* (%)	20 (2.9)	19 (3.1)	1 (1.6)	0.50
Steatorrhea, *n* (%)	4 (0.6)	4 (0.6)	-	0.52
Abdominal pain, *n* (%)	70 (10)	66 (11)	4 (6.3)	0.25
Weight loss, *n* (%)	23 (3.4)	18 (2.9)	5 (7.8)	0.04
Size largest cyst, median mm (IQR)	16 (13)	16 (13)	18 (13)	0.03
Cyst size ≥40 mm, *n* (%)	42 (6.1)	37 (6.0)	5 (7.8)	0.53
Diabetes mellitus, *n* (%)	122 (18)	103 (17)	19 (30)	0.01
New-onset diabetes mellitus[c], *n* (%)	8 (1.2)	7 (1.1)	1 (1.6)	081
MPD dilation, *n* (%)	87 (13)	75 (12)	12 (19)	0.14
MPD 5–9 mm, *n* (%)	60 (8.8)	52 (8.4)	8 (13)	0.29
MPD ≥10 mm, *n* (%)	18 (2.6)	14 (2.3)	4 (6.3)	0.06
Dilated, unknown PD diameter, *n* (%)	9 (1.3)	9 (1.4)	-	0.33
Solid component, *n* (%)	22 (3.2)	17 (2.7)	5 (7.8)	0.03
Mural nodule <5 mm, *n* (%)	8 (1.2)	5 (0.8)	3 (4.7)	0.006
Mural nodule ≥5 mm, *n* (%)	4 (0.6)	4 (0.6)	-	0.52
Enhancing solid mass (other), *n* (%)	10 (1.5)	8 (1.3)	2 (3.1)	0.31
Working diagnosis, (%)				
Unspecified cyst[d]	65 (9.5)	56 (9.0)	9 (14)	0.20
BD-IPMN[d]	525 (77)	481 (78)	44 (69)	0.15
MT-IPMN or MD-IPMN[d]	64 (9.3)	57 (9.2)	7 (11)	0.19
MCN	12 (1.8)	12 (1.9)	-	0.26
NET	3 (0.4)	3 (0.5)	-	-
PC	2 (0.3)	1 (0.2)	1 (1.6)	-
No visible cyst (previous surgery)	8 (1.2)	8 (1.3)	-	0.38
Unknown	6 (0.9)	3 (0.5)	3 (4.7)	-

Note: *p*-values compare the values in column CA19.9 <37 kU/L to ≥37 kU/L.

Abbreviations: BD-IPMN, branch-duct IPMN; IQR, interquartile range; MCN, mucinous cystic neoplasm; MD-IPMN, main-duct IPMN; MT-IPMN, mixed-type IPMN; NET, neuroendocrine tumor; PC, pancreatic cancer; SD, standard deviation.

[a]Body mass index (BMI) was a missing value for 349 individuals.

[b]Absolute indications for surgery (AI): solid mass, enhancing mural nodule (≥5 mm), main pancreatic duct dilation ≥10 mm or ≥2 relative indications for surgery (RI); Patients with baseline jaundice were excluded.[9]

[c]RI: main pancreatic duct (MPD) 5–9 mm, cyst diameter ≥40 mm, new-onset diabetes mellitus, (recent or recurrent) acute pancreatitis, mural nodule <5 mm.

[d]Not pathology-proven, upon imaging interpretation of the radiologist or endosonographer. Growth-rate (as a rate cannot be calculated from one single time point) and serum CA19.9 value were not included as RIs.

[Correction added on 25 July 2023, after first online publication: Bold emphasis for the bold values have been removed in the 'p value' column.]

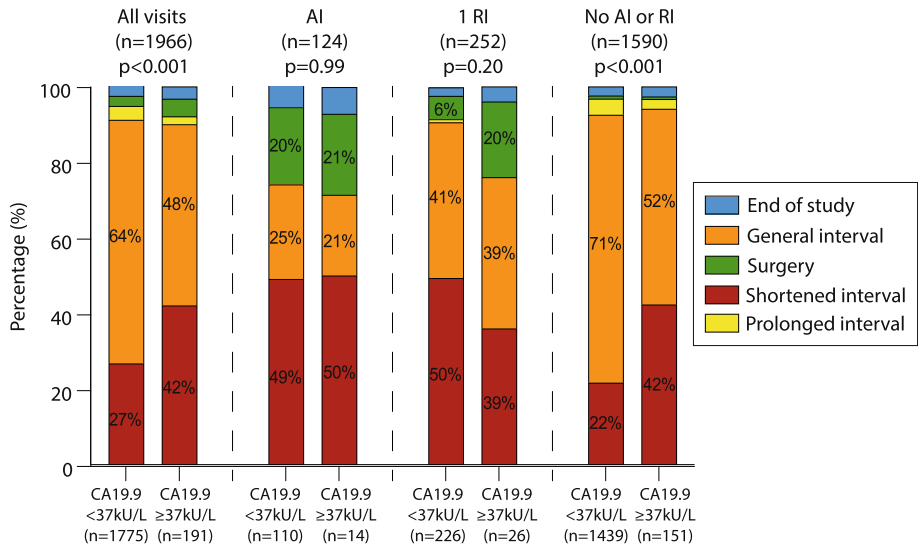


FIGURE 2 Clinical consequences of an elevated value at all visits, and at those visits with and without absolute (AI) or relative (RI) indications for surgery. For visits without AI or RI, an elevated CA19.9 value more often led to a shortened surveillance interval, as compared to a normal value <37 kU/L (χ^2-test). Management was based on the decision of the physician after imaging. A general surveillance interval was 6 months' interval during the first year of surveillance and 12 months' interval during follow-up afterward (as based on the recommendations in the European Guidelines[9]).

one AI (4 resectable, 1 irresectable), and two had 1 RI (#1 and #8; both were unresectable at time of diagnosis). Thus, in this study, no malignancy was detected in a resectable stage due to an elevated CA19.9 value (alone or in addition to 1 RI). Of 542 controls with at least two CA19.9 values, 79 (14%) had at least one elevated CA19.9 value during follow-up. Figure 3c depicts the variation in these values.

The diagnostic performance of CA19.9

The 29 individuals with HGD or PC (n = 29) did not have a higher median CA19.9 level (11 kU/L [IQR 24], range 1–1470) than the benign group (n = 656; 10 kU/L [IQR 12], range 1–605; p = 0.18). However, those with HGD or PC more often had a CA19.9 value ≥37 kU/L (24% vs. 8%; p = 0.002; Figure 4a). Subgroup analysis showed no difference in median CA19.9 levels between dysplasia grades (p = 0.58, Figure 5b) and the presence or absence of AI and/or RI (Figure 5c).

To determine the most reliable cutoff for PC detection, a ROC-curve was created (AUC 0.57 [95% CI 0.44–0.71]; Figure 4d). The cutoff of ≥37 kU/L was able to differentiate between HGD/PC and controls with a sensitivity of 24% (95% CI 10%–44%), specificity of 92% (95% CI 90%–94%) and accuracy of 90% (95% CI 87%–92%; Figure 4e).

Two alternative higher and lower cut-off values were chosen based on this ROC curve. A higher cutoff (A; 133 kU/L) significantly increased specificity (99% [95% CI 98–100]) and PPV (50% [95% CI 23–77]) without changing the NPV (96% [95% CI 96%–97%]). In contrast, a lower cutoff of 27 kU/L increased sensitivity to 41% (95% CI 24%–61%), yet decreased specificity (86% [95% CI 83–89]) and accuracy (84% [95% CI 81–88]), without changing the PPV and NPV Figure 5e.

The risk of future development of HGD or PC for different CA19.9 cutoffs

The univariable model showed a 1% higher risk of HGD or PC for each 1 kU/L increase in CA19.9 (HR 1.01, 95% CI 1.00–1.01; p < 0.001). When evaluating CA19.9 as a binary parameter, the HRs were 2.8 (95% CI 1.3–6.0; p = 0.009) for the 27 kU/L threshold, 2.6 (95% CI 1.0–6.3, p = 0.04) for 37 kU/L, and 11 (95% CI 3.4–37, p < 0.001) for the 133 kU/L threshold (Supplemental Table S1). Multivariable analysis showed that the 37 kU/L threshold, continuous or dichotomous, was not independently (of the presence of AI or RI) associated with HGD/PC, whereas the 27 kU/L (HR 2.3; 95% CI 1.1–5.0, p = 0.04) and 133 kU/L thresholds were (HR 3.8; 95% CI 1.1–13, p = 0.03; Figure 5a–c, Supplemental Table S1).

DISCUSSION

Surveillance of (presumed neoplastic) pancreatic cysts by seeking morphologic changes on imaging remains a challenge. The current study aimed to evaluate the additive value of CA19.9 monitoring and its potential harm using data extracted from the PACYFIC registry. It shows that—for individuals under pancreatic cyst surveillance—serum CA19.9 (at a cutoff level of 37 kU/L or as a continuous variable) is not independently associated with the development of HGD

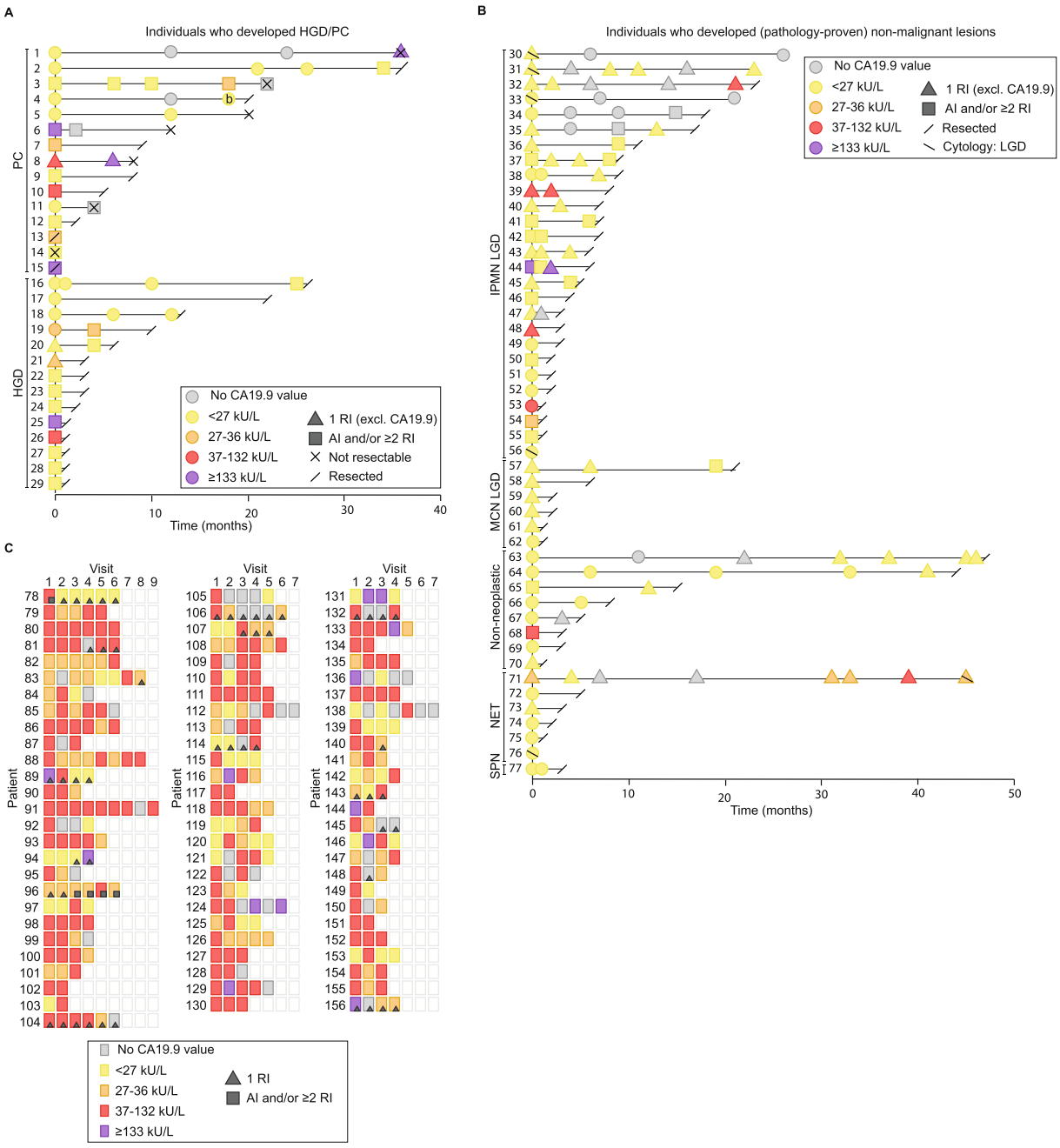
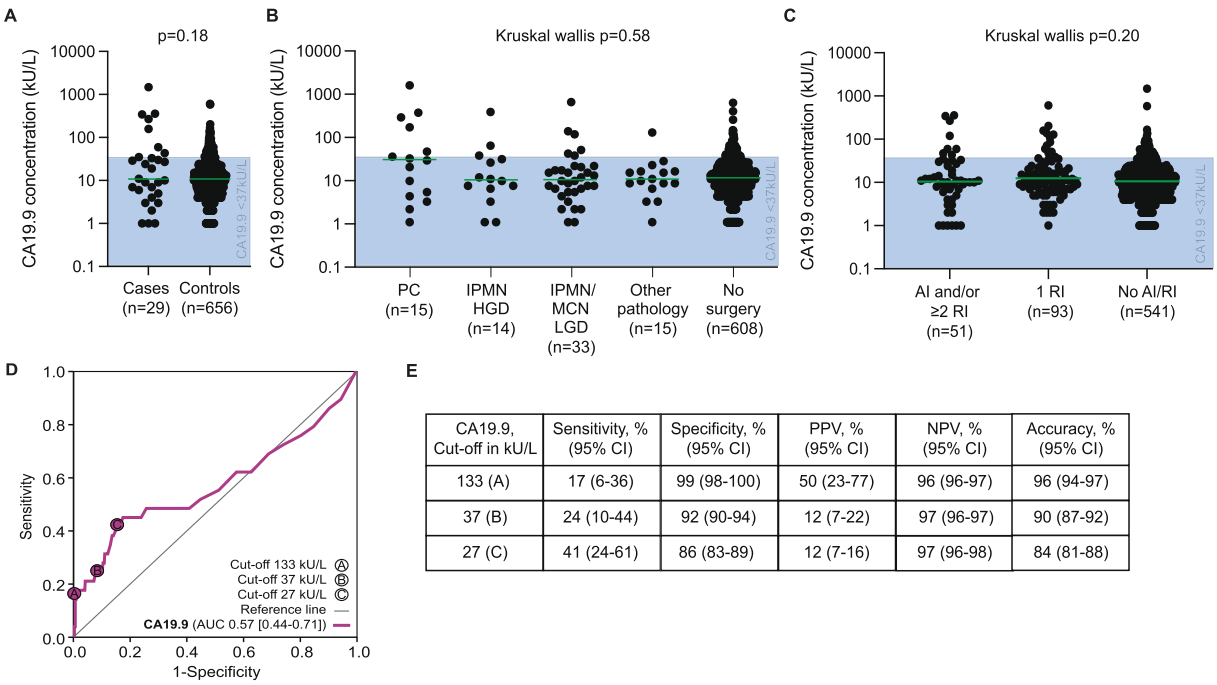


FIGURE 3 The role of CA19.9 monitoring on treatment management. ((a)–(b)) Presence of relative indications for surgery other than (excl.) CA19.9 elevation (RI), absolute indications for surgery (AI)[9] and elevated CA19.9 values over time for individuals who develop high-grade dysplasia (HGD) or pancreatic cancer (PC; (a)) and other pathology-proven lesions (b); (c) Overview of participants with two or more available CA19.9 values who did not undergo surgery, showing the high frequency of elevated values. IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NET, neuro-endocrine tumor; PA-proven, pathology proven; SPN, solid pseudopapillary neoplasm.

or PC. Moreover, CA19.9 monitoring led to substantial unnecessary shortening of surveillance internals and even surgery. Without CA19.9 determination, surgery might have been prevented in 6 of 37 individuals with IPMN harboring LGD. An alternative threshold of 133 kU/L was associated with a 4-fold increased risk of developing HGD or PC (independent of presence of baseline AI or other RI) with high specificity but low sensitivity.

Our observed CA19.9 values were in accordance with previous literature.[5,7,10,11] CA19.9 is a marker for advanced disease and seems less suitable for early detection. Data by Ciprani et al. (2020)[10] support this hypothesis. In their study, individuals who underwent surgery for IPMN ($n = 594$) did not show a higher proportion of HGD (relative to LGD) in the elevated CA19.9 group ($n = 128$). However, it did show a higher proportion of T3-tumors (relative to T1) and CA19.9 was independently associated with advanced disease (perineural invasion and lymphogenic metastases). The majority (72%) of their HGD/PDAC cases had normal CA19.9 levels. This percentage was lower in our cohort (53%), perhaps because of the smaller number of participants



CA19.9, Cut-off in kU/L	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
133 (A)	17 (6-36)	99 (98-100)	50 (23-77)	96 (96-97)	96 (94-97)
37 (B)	24 (10-44)	92 (90-94)	12 (7-22)	97 (96-97)	90 (87-92)
27 (C)	41 (24-61)	86 (83-89)	12 (7-16)	97 (96-98)	84 (81-88)

FIGURE 4 Subgroup analyses do not show differences in median CA19.9 values. However, CA19.9 is able to differentiate cases from controls with high specificity, yet low sensitivity. (a) The median CA19.9 value is not higher in cases with high-grade dysplasia (HGD) or pancreatic cancer (PC) than controls; (b) Individuals with PC, HGD, low-grade dysplasia (LGD), other pathologies (heterogeneous group of SPN, NET, SCN, lympho-epithelial cyst, lymphangioma and pseudocyst); (c) The median CA19.9 level was not higher in individuals with absolute (AI) or relative (RI) indications for surgery,[9] as compared to those without; (d) Receiver operator curve (ROC) of serum CA19.9 with three cut-offs (37 kU/L and two selected based on visualized angles in the curve); (e) Diagnostic performance at the three cut-offs. Described data do not have equal variances; therefore, nonparametric tests were used ((a)–(c)). 95% confidence intervals (CIs) are "exact" Clopper-Pearson confidence intervals ((d)–(e)). AUC, area under the curve; NPV, negative predictive value.

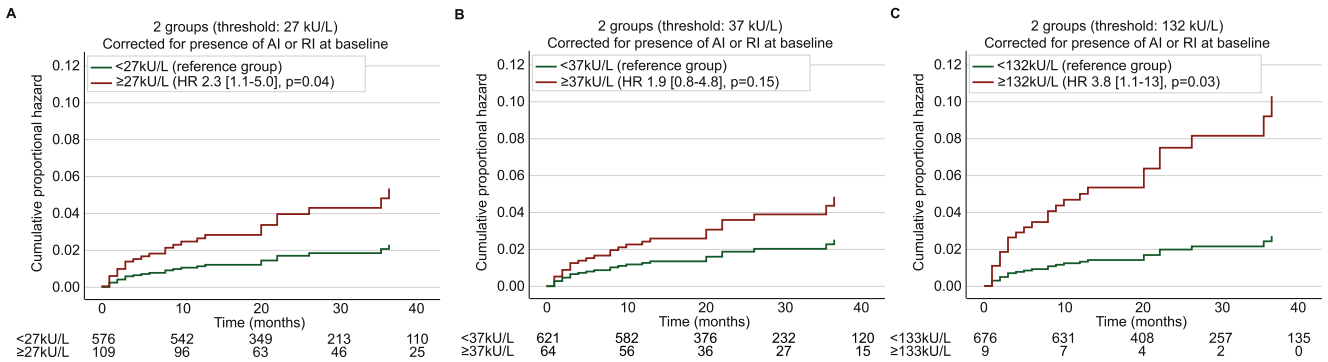


FIGURE 5 Cox proportional hazards model. ((a)–(c)) The risk of developing high-grade dysplasia (HGD) and pancreatic cancer (PC) for three different thresholds ((a), (b), (c); corrected for the presence of absolute indications for surgery (AI) and relative indications for surgery (RI)[9] at baseline). Intervals are 95% confidence intervals.

with advanced disease. Our percentage is similar to 51% observed by Oyama et al. (2020),[12] who performed surveillance in 1404 individuals with BD-IPMN. Of 22 cases with resectable disease, none had an elevated CA19.9 value without having ≥1 AI and/or ≥2 RI (similar to the current study). Manen et al. (2020)[11] also showed higher CA19.9 levels in patients with (locally) advanced (n = 224), as compared to resectable (n = 151) PC. Interestingly, Fahrmann et al. (2020)[13] evaluated the predictive value of CA19.9 determination at 6-month' intervals in healthy individuals. In this study, 175 patients developed PC and were compared to 875 controls with prostate, lung, colorectal, or ovarian cancer. CA19.9 was able to catch localized (early) PC in 50% of cases, as long as it was measured frequently (every 0–6 months). Thus, based on these studies, CA19.9 may be a marker for late-stage disease requiring short interval determination to be of value for the detection of early stage disease.

A surveillance protocol ideally involves diagnostic tests with a small number of false positives (high specificity), which is not the case for current CA19.9 testing. Elevated CA19.9 values are not only seen in PC, yet also in obstructive jaundice, as well as hepatic (cirrhosis and hepatitis), gastrointestinal cancer, pulmonary,

gynecological and endocrine (DM or hypothyroidism) diseases.[14–16] Thus, false positive outcomes are common, as our results show. Also, we established that this often leads to an intensified follow-up regimen, which could cause harm due to unnecessary diagnostic procedures (such as EUS/FNA) and psychological distress.[17–19] Moreover, in the current study, 45% of operated individuals underwent surgery for benign disease, while we know that pancreatic surgery is associated with substantial grade III-IV (Clavien-Dindo) morbidity (4%–31%) and mortality (2%–6%).[20–24]

We found CA19.9 levels >37 kU/L not to be associated with the development of HGD or PC. The first cutoff for PC detection was set by Pleskow et al. at 70 kU/L. Recently, the current cutoff was debated by our group, Levink et al. (2022),[25] as well as Ciprani et al. (2020)[10] and others. Ciprani et al.[10] proposed 100 kU/L as a new cutoff, which would alter the sensitivity and specificity for PC detection from 41% to 85% (cutoff 37 kU/L), to 23% and 97%. Fahrmann et al. (2020)[13] observed a sensitivity of 27% and specificity of 99% for invasive IPMN at a cutoff of 97 kU/L. These results are similar to our cross-sectional analysis, showing that individuals with a CA19.9 value ≥133 kU/L had a higher risk of developing HGD or PC.

Based on these results, we propose using this higher threshold to reduce false positive results. Future research (in a larger cohort with more cases) is needed to evaluate if the threshold of 133 kU/L is indeed optimal to detect early stage PC. Additionally, as CA19.9 value <27 kU/L had a lower risk of HGD or PC development, one may argue that a value below this threshold may be a soothing feature. However, we believe this is unlikely as CA19.9 is not generated by all pancreatic cells and 6%–22% of the Caucasian population is not able to produce CA19.9.[26]

This study has limitations. Whilst the PACYFIC cohort is unique in its size, it is still too small to draw definite conclusions on CA19.9-related risk of HGD or PC. Also, the low number of malignant cases does not allow us to correct for confounding variables. The follow-up duration is short (especially for those with HGD or PC) and solely allows short-term predictions. Thus, other multicentric efforts with longer follow-up durations are needed to validate our results. In addition, the choice to determine CA19.9 was at the discretion of the treating physician. This may have caused the selection of individuals at higher risk and overestimation of the role of CA19.9 in a surveillance population. Moreover, two individuals already had a suspicion of PC at the time of the first CA19.9 value.

A general limitation related to prospective cyst surveillance studies is their mixed population. Other lesions (e.g., SCNs, lymphoepithelial cysts, pseudocysts) often show similar morphological changes on imaging and are therefore misdiagnosed as IPMN. Thus, these results cannot be extrapolated to IPMN, yet can be extrapolated to other neoplastic cyst populations. Critical appraisal of the differential diagnosis by the treating physician is required for each patient undergoing pancreatic surveillance. As all controls had at least 12 months of follow-up, the presence of PC was unlikely within this group.

In conclusion, CA19.9 monitoring in its current form does not contribute to early stage PC detection and causes harm by unnecessary shortening of surveillance intervals and surgery. This calls for critical appraisal of current recommendations and may lead to either omitting CA19.9 monitoring altogether or exploring the potential of higher cutoff values, aiming for a higher specificity in combination with the highest achievable sensitivity.

AUTHOR CONTRIBUTIONS

Iris J. M. Levink: Conceptualization, Methodology, Resources, Formal analysis, Writing – Original Draft, Visualization, Project administration. **Sanne C. Jaarsma:** Conceptualization, Methodology, Formal analysis, Writing – Original Draft; Visualization. **Brechtje D. M. Koopmann, Priscilla A. van Riet, Kasper A. Overbeek, Jihane Meziani, Marloes L. J. A. Sprij:** Data Curation, Resources, Writing – Review and Editing, Project administration. **Riccardo Casadei, Carlo Ingaldi, Marcin Polkowski, Megan M. L. Engels, Laurens A. van der Waaij, Silvia Carrara, Elizabeth Pando, Marlies Vornhülz, Pieter Honkoop, Erik J. Schoon, Johanna Laukkarinen, Jilling F. Bergmann, Gemma Rossi, Frederike G. I. van Vilsteren, Anne-Marie van Berkel, Trevor Tabone, Matthijs P. Schwartz, Adriaan C. I. T. L. Tan, Jeanin E. van Hooft, Rutger Quispel, Ellert van Soest, Laszlo Czacko:** Validation; Investigation; Writing – Review and Editing. **Marco J. Bruno, Djuna L. Cahen:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – Review and Editing, Supervision, Project administration, Funding acquisition.

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CONFLICT OF INTEREST STATEMENT

Silvia Carrara: Olympus (lecture). Jeanin E. van Hooft: Boston Scientific (Lecture), Cook medical (Lecture), Abbvie (Lecture), Medtronic (Lecture). Marco J. Bruno: Boston Scientific (Consultant, support for industry and investigator-initiated studies), Cook Medical (Consultant, support for industry and investigator-initiated studies), Pentax Medical (Consultant, support for investigator-initiated studies), Mylan (Support for investigator-initiated studies), ChiRoStim (Support for investigator-initiated studies). Other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

As this manuscript does not cover the main objective of the PACYFIC-study, it was decided to not upload the PACYFIC study protocol or the database. Information can be requested at pacyfic@erasmusmc.nl.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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