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Small and Stable Pancreatic Cysts Are Reassuring During Surveillance: Results From the PACYFIC Trial

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Abbreviations: BD-IPMN, branch-duct IPMN; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; CT, computed tomography; DM, diabetes mellitus; ECIS, European cancer information system; EUS, endoscopic ultrasound; HGD, high-grade dysplasia; HR, hazard ratio; HRS, high-risk stigmata; IPMN, intraductal papillary mucinous neoplasm; IPNB, intrapapillary neoplasm of the bile duct; IQR, interquartile range; MCN, mucinous cystic neoplasm; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NET, neuro-endocrine tumor; PC, pancreatic cancer; SCA, serous cyst adenoma; SD, Standard deviation; SIR, standardized incidence ratio; WF, worrisome features.

Marco J. Bruno and Djuna L. Cahen share authorship.

For a complete listing of the PACYFIC-study work group, see the Acknowledgments section.

Keywords: cyst size | high-grade dysplasia | intraductal papillary mucinous neoplasm (IPMN) | pancreatic cancer | pancreatic cyst | stable cyst growth | surveillance

ABSTRACT

Background: Pancreatic cysts are increasingly discovered on imaging studies performed for unrelated conditions. Currently, surveillance of these lesions poses a substantial burden on patients, and health care recourses. We hypothesized that individuals with small and stable cysts have a diminutive risk of progressing to high-grade dysplasia (HGD) or pancreatic cancer (PC) that is similar to that in the general population.

Methods: This nested PACYFIC-study is a collaboration among 44 centers in Europe and Northern-America, and investigates the risk of HGD and PC for different cyst sizes and growth rates in participants without baseline worrisome features (WF) or high-risk stigmata (HRS).

Results: Of the 2369 PACYFIC participants, 975 met the inclusion criteria, with a mean age of 67 years (SD 13) and 65% being female. Of these, 438 individuals (45%) had a baseline small cyst size (< 15 mm), and 885 (91%) individuals had a slow growth rate (< 2.5 mm/year). During a median follow-up of 45 months (IQR 27), 20 individuals (2.1%) developed HGD, or PC. Individuals with small cysts had a 1.5-fold lower risk of developing WF or HRS (hazard ratio [HR] 0.7 [0.5–1.0], $p = 0.03$) than those with larger cysts but a similar risk of developing HGD or PC ($p > 0.05$). Slow growth was protective against the development of WF or HRS (HR 0.4 [0.2–0.6], $p < 0.001$) and HGD or PC (HR 0.04 [95% CI 0.02–0.12], $p < 0.001$). Individuals with small, stable sized cysts without baseline WF or HRS did not have a higher risk of HGD or PC than the general population (standardized incidence ratio [SIR] 1.13 [95% CI 0.01–6.30]).

Conclusion: Cyst size < 15 mm and growth rate < 2.5 mm/year appear to be "reassuring" features associated with a negligible risk of developing WF or HRS and HGD or PC. For cysts with these characteristics—and without baseline WF or HRS—less intensive surveillance (than currently recommended) or even cessation may be appropriate.

1 | Introduction

Pancreatic cancer (PC) is a leading cause of cancer-related death with a poor 13% 5-year survival [1]. Most patients are diagnosed with advanced disease, limiting curative treatment options. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are cystic precursor lesions of PC. As a result, intensive imaging-based surveillance programs are being propagated worldwide for presumed neoplastic pancreatic cysts to enable earlier detection of PC within these lesions.

With increased quality (and frequency) of imaging came the detection of more and smaller cystic lesions. Cyst prevalence mounts with age; at 80 years, 76% have a pancreatic cyst, with a median size of just 7 mm [2]. Guidelines [3, 4] recommend surveillance of all neoplastic and undefined cysts, as long as an individual is fit for surgery. They advise surgery when worrisome features (WF) or high-risk stigmata (HRS) are present, with cyst size ≥ 30 mm and growth ≥ 2.5 mm/year being two of these WFs [4]. The most recent international guidelines propagate surveillance frequency based on cyst size [4] yet the European guidelines do not [3].

In the past decade, it has become clear that the malignant potential of cystic neoplasms is lower than originally thought. 33%–72% of resected cysts prove to be benign upon histology, causing unnecessary harm [5–8]. Moreover, current repetitive imaging of (mostly) small pancreatic cysts poses a substantial burden on health care costs and resources. Therefore, it is crucial to identify reassuring characteristics that suggest the presence of "trivial cysts"—cysts with a diminutive risk of developing high-grade dysplasia (HGD) or PC—to help clinicians reduce the frequency of surveillance, or even discontinue it all together.

We hypothesized that small (< 15 mm) and slow-growing (< 2.5 mm/year) pancreatic cysts—without baseline WF or HRS—have a risk of HGD and PC that is similar to that of the general population. To test this hypothesis, we aimed at evaluating the risks of progression for different cyst sizes and growth rates, and compared this to the general population.

2 | Material & Methods

2.1 | PACYFIC Study

This is a nested study of the PACYFIC-registry, which has been running since 2015. It includes individuals with neoplastic and undefined pancreatic cysts—newly or previously diagnosed or operated upon—who are being followed at the discretion of their treating physician.

2.2 | In- and Exclusion Criteria

This study involved participants from 14 academic and 16 community hospitals from Europe (28 centers) and North America (2 centers). All individuals with at least 24 months of follow-up at the time of data extraction in February 2024 were included. In addition, individuals who developed the primary endpoint of malignant progression (HGD or PC) or underwent surgical resection before the 24-months follow-up time were included. Individuals with WF, HRS, or PC at baseline, a

Summary

- What is known?
  - Repetitive imaging of (mostly) small cysts poses a substantial burden on patients and health care recourses.
- What is new here?
  - We confirm that small and stable cysts have a diminutive risk of progressing to high-grade dysplasia and pancreatic cancer. This risk is similar to that of the general population. For cysts with these characteristics, less intensive surveillance (than currently recommended) or even cessation may be appropriate.

missing baseline cyst size, or a history of PC and/or pancreas resection (e.g., for IPMN or MCN) were excluded. Moreover, for cyst growth analysis, individuals were excluded in case of development of the primary endpoint or surgical resection in the first year.

2.3 | Data Collection

Information regarding participant and cyst characteristics, follow-up visits and histological outcomes were prospectively recorded in an online case record form (www.pacyfic.net). The study was conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). All individuals signed informed consent prior to inclusion. All co-authors reviewed and approved the final manuscript.

2.4 | Definitions

Definitions of WF and HRS were based on the recent international Kyoto guidelines [4]. HRS were defined as obstructive jaundice in a patient with a cystic lesion in the pancreatic head, an enhancing mural nodule ≥ 5 mm or solid component, main pancreatic duct (MPD) ≥ 10 mm and suspicious or positive cytology. WF included acute pancreatitis in the past year, an increased serum CA19-9 level (≥ 37 kU/L), new-onset diabetes mellitus (DM) within the past year, an enhancing mural nodule < 5 mm, a thickened or enhancing cyst wall, a MPD ≥ 5 mm and < 10 mm, and/or an abrupt caliber change and lymphadenopathy.

Cyst size and growth were based on the size of the largest cyst and were not considered WF. A follow-up visit was defined as any visit after baseline during which at least an MRI/MRCP, endoscopic ultrasound (EUS), or CT was performed. The last follow-up was defined as the final recorded visit or the time of surgery or HGD or PC diagnosis. Time-to-event was defined as the time (in months) from the first to the last follow-up visit (or the development of WF or HRS, depending on the analysis).

2.5 | Statistical Analysis

Patients were stratified according to size and growth, with cutoffs based on available literature [4, 9–14]. (1) Largest cyst at baseline < 15 mm or ≥ 15 mm. (2) Growth during follow-up (< 2.5 mm/year or ≥ 2.5 mm/year) was calculated as the size difference between the first and last follow-up visits divided by the elapsed time. Descriptive analyses of baseline characteristics were expressed as means with 95% confidence intervals (CI; for normally distributed data) or medians with interquartile ranges (IQR; for non-normally distributed data) or numbers with percentages. Differences between groups were evaluated with a Student's T-test/ANOVA for normally distributed data or a Mann–Whitney U/Kruskal–Wallis test in case of a non-normal distribution. For categorical variables, a χ^2-test was used.

To evaluate the risk of WF or HRS and HGD or PC over time according to cyst size and growth, we performed multiple univariable cox proportional hazards analyses. Depending on the significance ($p < 0.05$) of results from univariable results, multivariable analyses were performed. For the risk of HGD or PC analysis, correction by two variables was accepted, based on the limited number of cases within this low-risk cohort; for the risk of WF or HRS analysis, correction for more variables was accepted, yet only three variables were deemed clinically relevant.

The standardized incidence ratio (SIR) of malignant progression was defined as the ratio of observed HGD and PC in our study population to the expected number of PC cases. Due to the limited number of cases, the expected numbers were calculated using age-standardized incidence data for PC from European Union countries (EU-27) in 2022 (European Cancer Information System [ECIS] [15]) and were adjusted for the total population in Europe in 2013. The Wilson and Hilferty approximation of the exact Poisson distribution was used to calculate the 95% CI of the SIR.

Data were analyzed and graphs visualized using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, version 27). Two-sided p-values of < 0.05 were considered statistically significant.

3 | Results

3.1 | Baseline Characteristics

Of the 2369 PACYFIC participants, 1394 were excluded for the following reasons: less than 24 months of follow-up ($n = 992$), history of pancreatic surgery ($n = 78$), missing baseline cyst size ($n = 49$), history of PC ($n = 15$; Figure 1), and presence of WF or HRS at baseline ($n = 260$). Of 975 included participants, 631 were female (65%), and had a median age of 67 years (IQR 13). Other baseline characteristics are shown in Table 1 and Table S1.

At baseline, the median largest cyst size was 15 mm (IQR 12) and 438 (45%) individuals had cysts smaller than 15 mm. Females had smaller cysts (median 14 mm [IQR 10]) than males (median 16 mm [IQR 12]; $p < 0.001$), and cyst size was positively correlated with age ($r = 0.14$; $p < 0.001$). Participants with

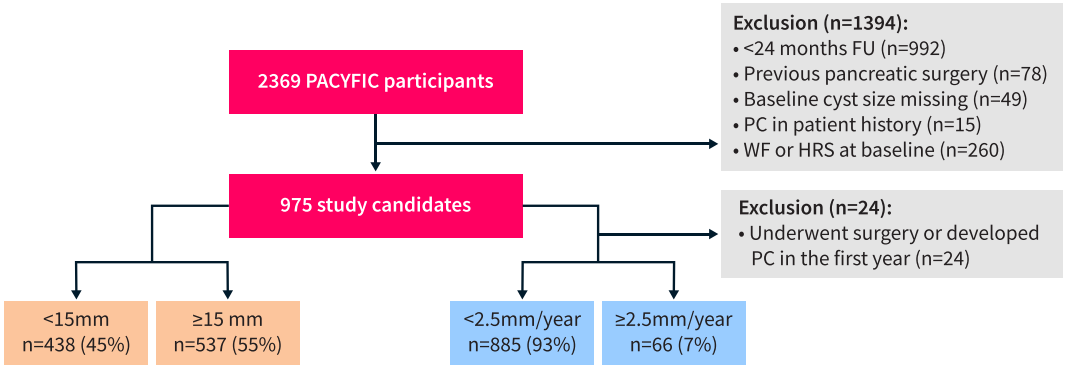

FIGURE 1 | Flowchart showing the in- and exclusion of PACYFIC participants. Nine hundred seventy-five participants were included in the cyst size cohort; this cohort was subdivided into a small cyst size group (< 15 mm) and a larger cyst size group (≥ 15 mm). For the cyst growth analysis, only those 951 participants who had more than 12 months of follow-up were included. Cyst size or cyst growth were not included as worrisome features (WF) or high-risk stigmata (HRS). FU = follow-up, PC = pancreatic cancer.

cysts < 15 mm were less likely to undergo both MRI/MRCP and EUS than those with larger cysts (19% vs. 30%; $p < 0.001$; Table 1).

For the cyst growth analysis, 24 (2.5%) individuals were excluded because they underwent surgery and/or developed PC in the first year. Individuals with slow cyst growth (< 2.5 mm/year) had smaller baseline cysts (median 15 mm [IQR 10]) than those with faster-growing cysts (median 20 mm [IQR 15], $p < 0.001$). The two groups did not differ in age, sex, BMI, race, or selected baseline imaging modality (Table 1).

3.2 | Final (Histological) Diagnosis

A histological diagnosis was established in 65 (6.7%) individuals after a median of 19 months (IQR 35). Twenty (2.1%) cases developed advanced neoplasia; 13 PC (1.3%) and seven HGD (0.7%). Eight individuals with PC were not operated due to co-morbidity or advanced disease. The remaining 12 individuals underwent surgery. For three of these patients, metastases were detected during surgery.

Of the 57 individuals who underwent surgery, the majority ($n = 45$; 78% of operated individuals; 4.6% of total cohort) had benign histological outcomes. Specifically, 22 (2.3%) were diagnosed with low-grade IPMN, 10 (1.0%) low-grade MCN, one neuro-endocrine tumor (NET) grade 1 (0.1%), one intraductal papillary neoplasm of the bile duct (IPNB; 0.1%), seven serous cystic adenoma (SCA), two pseudocysts, one lymphoepithelial cyst, and one lymphangioma.

Thus, the risk of undergoing surgery to receive a benign diagnosis (4.6%) was higher than the risk of harboring HGD or PC (2.1%). Moreover, only nine individuals (0.9%) were diagnosed with early-stage disease, defined as HGD or localized PC.

3.3 | Follow-Up: Cyst Size

The median follow-up duration for the total cohort was 45 months (IQR 27). Participants with a baseline cyst < 15 mm underwent less follow-up visits (median 3 [IQR 3]), as compared to those with a larger cyst (median 4 [IQR 2], $p = 0.006$; Table 2).

After correction for age, sex and cyst count, the risk of developing WF or HRS was 1.5-fold lower in individuals with smaller cysts (< 15 mm) than in those with larger cysts (≥ 15 mm, hazard ratio [HR] 0.7 [0.5–1.0], $p = 0.03$; Table 3, Figure 2a). The risk of HGD or PC was similar ($p < 0.05$). Individuals with smaller cysts had a lower risk of developing an elevated CA19-9 ≥ 37 kU/L (6.6% vs. 11%, $p = 0.03$), new-onset diabetes (0% vs. 0.7%, $p = 0.04$), or a thickened cyst wall (0.2% vs. 1.7%, $p = 0.03$) compared with those with larger cysts (Table 2). However, a smaller cyst size was not associated with a lower risk of HGD or PC ($p > 0.05$, Table 3, Figure 3a).

3.4 | Follow-Up: Cyst Growth

Individuals with a slow growing cyst (< 2.5 mm/year) had a longer median follow-up time (47 months [IQR 26]) than those with a faster growing cyst (≥ 2.5 mm/year, 35 months [IQR 16]; $p < 0.001$; Table 2). During follow-up, after correction for age, sex and cyst count, the risk of developing WF or HRS was 2.8-fold lower in individuals with a slow-growing cyst (< 2.5 mm/year) than in those with a fast-growing one (≥ 2.5 mm/year, HR 0.4 [0.2–0.6], $p < 0.001$; Table 3, Figure 2c). When the growth cutoff was elevated from 2.5 to 5 mm/year, individuals with a slow-growing cyst had a 4.3-fold lower risk of developing WF or HRS than those with faster-growing cysts (HR 0.24 [95% 0.11–0.51]; $p < 0.001$, Table 3, Figure 2d).

A 1-mm faster growth increased the risk of developing HGD or PC within 45 months by 31% (HR 1.31 [95% CI (1.21–1.42)]; $p < 0.001$; Table 3) after correction for age and sex. Individuals with a cyst growing < 2.5 mm/year had a 25-fold lower risk of developing HGD or PC than those with a fast-growing cyst (≥ 2.5 mm/year; HR 0.04 [95% CI 0.02–0.12], $p < 0.001$; Table 3, Figure 3c). Growth < 5 mm/year was associated with a 47-fold lower risk of malignancy than growth ≥ 5 mm/year (HR 0.02 [95% CI 0.01–0.07], $p < 0.001$; Table 3, Figure 3d).

When combining cyst size and cyst growth, the absolute risk of developing WF or HRS was lowest (10%) for those with a

TABLE 1 | Baseline characteristics for the total cohort as well as per baseline cyst size and cyst growth group during follow-up.

	Cyst size cohort (n = 975)	Cyst size < 15 mm (n = 438)	Cyst size ≥ 15 mm (n = 537)	p-value	Cyst growth < 2.5 mm/year (n = 885)	Cyst size ≥ 2.5 mm/year (n = 66)	p-value
Demographics							
Age, median (IQR)	67 (13)	65 (14)	68 (13)	< 0.001	67 (13)	67 (13)	0.69
Female sex, n (%)	631 (65)	317 (73)	314 (59)	< 0.001	572 (65)	44 (67)	0.74
BMI, median (IQR)[a]	25 (6.3)	25 (6.0)	26 (6.4)	0.08	25 (6.2)	24 (6.8)	0.12
Race, n (%)				0.70			0.55
Caucasian	910 (93)	413 (94)	497 (93)	—	827 (93)	62 (94)	—
Other	29 (2.9)	14 (3.2)	15 (2.8)	—	26 (2.9)	2 (3.0)	—
Unknown	36 (3.7)	11 (2.5)	25 (4.7)	—	32 (3.6)	2 (3.0)	—
Cyst morphology							
Cyst size in mm, median (IQR)	15 (12)	—	—	—	15 (10)	20 (15)	< 0.001
Cyst growth in mm/year, median (IQR)	0 (0.7)	0 (0.5)	0 (0.9)	< 0.001	—	—	—
Number of cysts, median (IQR)[b]	1 (1)	1 (1)	1 (1)	0.06	1 (1)	1 (1)	0.53
Multifocality (≥ 2 cysts), n (%)	387 (40)	160 (37)	227 (42)	0.07	357 (40)	24 (36)	0.53
Location of largest cyst, n (%)							
Uncinate process	122 (13)	44 (10)	78 (15)	0.04	113 (13)	7 (11)	0.61
Head	321 (33)	134 (31)	187 (35)	0.16	294 (33)	22 (33)	0.99
Neck	98 (10)	45 (10)	53 (10)	0.84	91 (10)	6 (9)	0.76
Corpus	265 (27)	141 (32)	124 (23)	0.001	240 (27)	19 (29)	0.77
Tail	169 (17)	74 (17)	95 (18)	0.74	147 (17)	12 (18)	0.74
Working diagnosis, n (%)							
Unspecified cyst	89 (9.1)	50 (11)	39 (7.3)	0.03	81 (9.2)	6 (9.1)	0.99
IPMN	866 (89)	385 (88)	481 (90)	0.33	794 (90)	60 (91)	0.95
MCN	20 (2.1)	3 (0.7)	17 (3.2)	0.007	10 (1.1)	0 (0)	0.39
Modality, n (%)							
MRI + EUS (± CT)	241 (25)	81 (19)	160 (30)	< 0.001	219 (25)	14 (21)	0.52
EUS only (± CT)	149 (15)	64 (15)	85 (16)	0.60	130 (15)	13 (20)	0.27
MRI only (± CT)	521 (53)	260 (59)	261 (49)	< 0.001	478 (54)	36 (55)	0.93
CT only	64 (6.6)	33 (7.5)	31 (5.8)	0.27	58 (6.6)	3 (4.5)	0.52

Note: Twenty-four patients were excluded from cyst growth analysis, as they underwent surgery, and/or developed PC in the first year.
Abbreviations: BD-IPMN = branch-duct IPMN, CT = computed tomography, EUS = endoscopic ultrasound, MD-IPMN = main-duct IPMN, MRCP = magnetic resonance cholangio-pancreatography, MRI = magnetic resonance imaging, MT-IPMN = mixed-type IPMN.
[a]Body mass index (BMI): Missing value in 592 (61%) participants.
[b]The eCRF allows to fill out a maximum number of four cysts.

baseline cyst size < 15 mm and growth < 2.5 mm/year, and highest (31%) for cysts ≥ 15 mm and growth ≥ 2.5 mm/year (Figure 2b). The absolute risk of developing HGD or PC was lowest for those with a baseline cyst < 15 mm and growth < 2.5 mm/year (0.2%; n = 416), and highest for those with a baseline cyst size < 15 mm and growth ≥ 2.5 mm/year (19%; n = 21; Figure 3b).

3.5 | Standardized Incidence Ratio

As compared to the general population, an individual with a suspected pancreatic cyst had a higher risk of developing HGD/PC (SIR 8.99 [95% CI 5.49–13.89]). This also applied for individuals with a small (< 15 mm) cyst at baseline (SIR 5.42 [95% CI 1.75–12.65]) and for those with a slow growing cyst

TABLE 2 | Follow-up time and visits as well as the absolute risks of developing worrisome features and high-risk stigmata per baseline cyst size and cyst growth group during follow-up.

	Cyst size cohort (n = 975)	Cyst size < 15 mm (n = 438)	Cyst size ≥ 15 mm (n = 537)	p-value	Cyst growth < 2.5 mm/year (n = 885)	Cyst size ≥ 2.5 mm/ year (n = 66)	p-value
Follow-up time, median (IQR)[a]	45 (27)	45 (26)	45 (29)	0.80	47 (26)	35 (16)	< 0.001
Number of follow-up visits, median (IQR)[b]	3 (2)	3 (3)	4 (2)	0.006	4 (2)	3 (2)	0.04
≥ 1 HRS, n (%)[c]	43 (4.4)	16 (3.7)	27 (5.0)	0.30	25 (2.8)	13 (20)	< 0.001
Jaundice	1 (0.2)	1 (0.2)	0 (0)	0.27	1 (0.1)	0 (0)	0.79
Enhancing mural nodule ≥ 5 mm or solid component	36 (3.7)	12 (2.7)	24 (4.5)	0.15	20 (2.3)	11 (17)	< 0.001
MPD ≥ 10 mm	7 (0.7)	3 (0.7)	4 (0.7)	0.91	4 (0.5)	3 (4.5)	< 0.001
Positive cytology	3 (0.3)	0 (0)	3 (0.6)	0.12	1 (0.1)	1 (1.5)	0.02
≥ 1 WF, n (%)[d]	116 (12)	37 (8.4)	82 (15)	0.003	99 (11)	14 (21)	0.02
Acute pancreatitis	2 (0.2)	0 (0.0)	2 (0.4)	0.20	1 (0.1)	0 (0.0)	0.79
CA19-9 ≥ 37 kU/L[e]	68 (9.3)	21 (6.6)	47 (11)	0.03	58 (8.7)	8 (15)	0.15
New-onset diabetes mellitus	4 (0.4)	0 (0)	4 (0.7)	0.07	3 (0.3)	1 (1.4)	0.15
Enhancing mural nodule < 5 mm	2 (0.2)	1 (0.2)	1 (0.2)	0.89	1 (0.1)	0 (0.0)	0.79
Thickened cyst wall	10 (1.0)	1 (0.2)	9 (1.7)	0.03	8 (0.9)	2 (3.0)	0.10
MPD 5–9 mm	32 (3.3)	14 (3.2)	18 (3.4)	0.89	25 (2.8)	6 (9.1)	0.006
Caliber change MPD	5 (0.5)	2 (0.5)	3 (0.6)	0.82	3 (0.3)	2 (3.0)	0.004
Lymphadenopathy	4 (0.4)	1 (0.2)	3 (0.6)	0.42	4 (0.5)	0 (0.0)	0.58
Cases, n (%)	20 (2.1)	5 (1.1)	15 (2.8)	0.10	8 (0.9)	8 (12)	< 0.001
HGD	7 (0.7)	3 (0.7)	4 (0.7)	—	1 (0.1)	3 (4.5)	< 0.001
PC	13 (1.3)	2 (0.5)	11 (2.0)	—	7 (0.8)	5 (7.6)	< 0.001

Note: Twenty-four patients were excluded from cyst growth analysis, as they underwent surgery, and/or developed PC in the first year.
[a]Time between baseline and last follow-up visit.
[b]Baseline visits not included.
[c]Obstructive jaundice, an enhancing mural nodule ≥ 5 mm or solid component anywhere in the pancreas, main pancreatic duct (MPD) ≥ 10 mm, and a suspicious or positive cytology (if performed) were considered as high-risk stigmata (HRS).
[d]An acute pancreatitis (recurrent or within the past year), increased serum level of CA19-9 (≥ 37 kU/L), new-onset DM within the past year, an enhancing mural nodule < 5 mm in any of the cysts, a thickened or enhancing cyst wall in any of the cysts, a MPD ≥ 5 mm and < 10 mm, an abrupt caliber change, and lymphadenopathy were considered as WF.
[e]In the cyst size cohort, in 242 (25%) patients CA19-9 was not assessed during follow-up (121 [28%] participants with cyst size < 15 mm; 121 [23%] with size ≥ 15 mm); for the cyst growth cohort, CA19-9 was not assessed in 227 (24%) of patients 216 [24%] participants with cyst growth < 2.5 mm/year; 11 [17%] with cyst growth ≥ 2.5 mm/year).

(< 2.5 mm/year, SIR 3.81 [95% CI 1.64–7.51]). However, individuals with a small and stable sized cyst (without baseline WF/HRS) did not have an increased risk of developing HGD/PC (SIR 1.13 [95% CI 0.01–6.30]), as compared to the general population (Table S2).

3.6 | Time to Progression

To assess the required surveillance intervals, we investigated the duration to development of WF or HRS and HGD or PC for smaller cysts. Of 438 individuals with a baseline cyst < 15 mm, five (1.1%) developed HG or PC after a median of 23 months (range 20–60). 47 (11%) individuals developed WF or HRS after a median of 23 months (IQR 23). Of these, 11 (2.5%) developed within the first year, 13 (2.9%) between the first and second year, and 23 (5.3%) after 2 years. Thus, for cysts < 15 mm without WF or HRS, first-time surveillance after 12—or even after 18—months may suffice (rather than 6 months).

Subsequently, we investigated the duration of development of WF or HRS and HGD or PC in slowly growing cysts. Of the 885 individuals with cyst growth < 2.5 mm/year, eight (0.9%) developed HGD or PC after a median period of 41 months (range 19–62), whilst 115 (13%) developed WF or HRS after a median time of 50 months (IQR 32). Of these, 53 developed WF or HRS in the first 2 years, and 62 developed after 2 years. Thus,

TABLE 3 | Results of univariable and multivariable cox proportional hazard analyses showing that cyst growth is associated with high-grade dysplasia (HGD) and pancreatic cancer (PC) independent of age and sex; cyst size was not.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Risk of WF or HRS				
Age at baseline, years	1.04 (1.02–1.06)	< 0.001	1.04 (1.01–1.06)[a]	< 0.001
Age > 65 years	1.76 (1.23–2.53)	0.002	1.62 (1.11–2.36)[a]	0.01
Age > 75 years	2.06 (1.38–3.06)	< 0.001	1.98 (1.31–2.98)[a]	0.001
Male sex	1.34 (0.99–1.87)	0.09	1.10 (0.77–1.56)[b]	0.61
Number of cysts at baseline	1.12 (1.04–1.21)	0.003	1.13 (1.01–1.22)[c]	0.001
Multifocality (≥ 2 cysts)	1.13 (0.81–1.57)	0.49	1.10 (0.77–1.55)[c]	0.61
Cyst growth (mm/year)	1.20 (1.14–1.25)	< 0.001	1.19 (1.13–1.26)[d]	< 0.001
Cyst growth < 2.5 mm/year	0.35 (0.22–0.57)	< 0.001	0.35 (0.21–0.57)[d]	< 0.001
Cyst growth < 5 mm/year	0.24 (0.11–0.51)	< 0.001	0.24 (0.11–0.51)[d]	< 0.001
Cyst size at baseline (mm)[d]	1.04 (1.03–1.06)	< 0.001	1.04 (1.02–1.05)[d]	< 0.001
Cyst size < 15 mm	0.60 (0.42–0.85)	0.004	0.66 (0.47–0.95)[d]	0.03
Cyst size < 20 mm	0.47 (0.34–0.65)	< 0.001	0.51 (0.36–0.71)[d]	< 0.001
Cyst size < 30 mm	0.42 (0.28–0.64)	< 0.001	0.46 (0.30–0.70)[d]	< 0.001
Cyst size < 40 mm	0.25 (0.14–0.46)	< 0.001	0.28 (0.15–0.50)[d]	< 0.001
Risk of HGD or PC				
Age at baseline, years	1.06 (1.00–1.12)	0.04	1.04 (0.98–1.11)[a]	0.24
Age > 65 years	2.16 (0.78–5.93)	0.14	1.04 (0.34–3.22)[a]	0.94
Age > 75 years	3.67 (1.46–9.26)	0.006	4.13 (1.48–11.59)[a]	0.007
Male sex	4.17 (1.60–10.86)	0.003	1.95 (0.67–5.69)[b]	0.22
Number of cysts at baseline	1.07 (0.88–1.30)	0.49	1.06 (0.88–1.27)[c]	0.55
Multifocality (≥ 2 cysts)	2.12 (0.87–5.18)	0.10	2.06 (0.84–5.05)[c]	0.12
Cyst growth (mm/year)[d]	1.34 (1.24–1.46)	< 0.001	1.31 (1.21–1.42)[d]	< 0.001
Cyst growth < 2.5 mm/year	0.05 (0.02–0.13)	< 0.001	0.04 (0.02–0.12)[d]	< 0.001
Cyst growth < 5 mm/year	0.02 (0.01–0.07)	< 0.001	0.02 (0.01–0.07)[d]	< 0.001
Cyst size at baseline (mm) [d]	1.03 (1.00–1.07)	0.09	1.05 (0.99–1.11)[d]	0.14
Cyst size < 15 mm	0.41 (0.15–1.12)	0.08	0.55 (0.20–1.55)[d]	0.26
Cyst size < 20 mm	0.56 (0.23–1.36)	0.20	0.68 (0.28–1.64)[d]	0.39
Cyst size < 30 mm	0.40 (0.14–1.21)	0.11	0.53 (0.17–1.60)[d]	0.26
Cyst size < 40 mm	0.41 (0.06–3.07)	0.39	0.58 (0.07–4.50)[d]	0.60

Note: In multivariable analyses to calculate risk of WF/HRS and HGD/PC, age was corrected for sex, and cyst growth.
[a]In multivariable analysis to calculate the risk of WF/HRS, age was also corrected for the number of cysts.
[b]Sex was corrected for age and cyst growth (and number of cysts for risk of WF or HRS).
[c]The number of cysts was corrected for age and sex (and cyst growth for risk of WF or HRS).
[d]Growth and size were corrected for age and sex (and cyst count for risk of WF or HRS). HR per mm/year or mm increase.

the risk of malignant progression in the first year after observed stability seems very low.

4 | Discussion

Pancreatic cysts are detected more than ever, and current surveillance recommendations impose a heavy burden on both patients and healthcare resources. Historically, studies prioritized identifying high-risk features, such as large cyst size. In contrast, this large prospective study highlights the reassuring aspects of small size and lack of growth. Indolence seems to be the most reassuring feature, more so than small size. Those being small and stable even have a similar risk to that in the general population. This may significantly impact future surveillance recommendations as one could argue its discontinuation for cysts with these characteristics after years of stability.

In a retrospective study [16] of 49 individuals with ≤ 20 mm cysts, none developed PC after over 5 years of follow-up. Ciprani et al. [17] evaluated the risk of malignant transformation in 806 individuals with cysts < 15 mm (median follow-up 58 months). Of these, only 14 (1.7%) developed HGD/PC. Additionally,

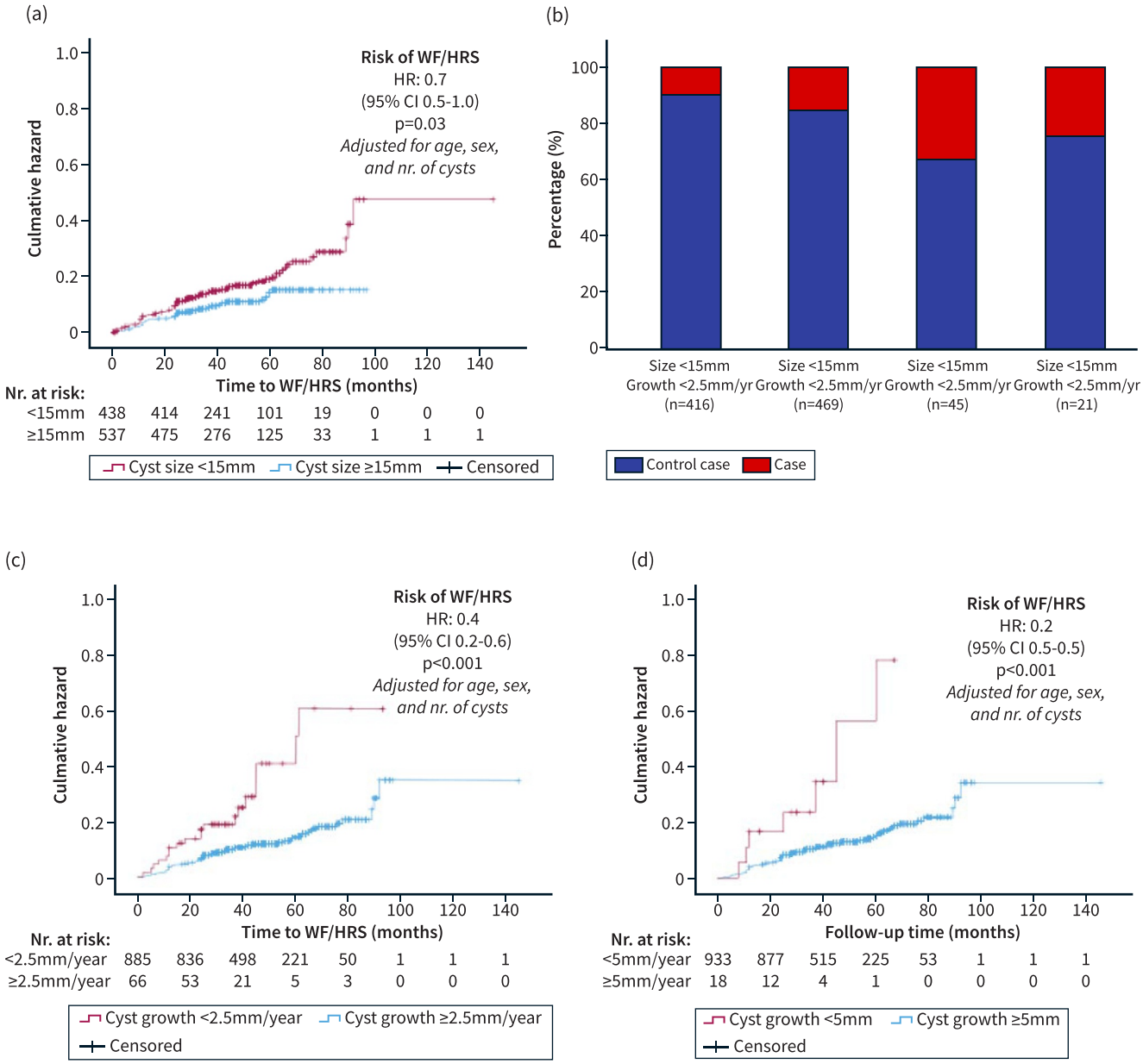

FIGURE 2 | Cox proportional hazard plots showing the risk of developing worrisome features (WFs) or high-risk stigmata (HRS). (a, c, and d). The hazard ratio (HR; adjusted for age and sex) per cyst size (a) and cyst growth group (c, d). (b) The absolute risk per cyst size and growth group.

Oyama et al. [18] showed that every 10 mm increase in baseline cyst size was associated with a 1.5-fold increased risk of developing PC (n = 1404, median follow-up 72 months). More recently, Han et al. [19] (2024; n = 3656, median follow-up 83 months) found no malignancy in patients with cysts < 20 mm after 5-of stability. Therefore, they suggest discontinuing surveillance in cases of limited life expectancy of less than 10 years.

Other studies investigated surrogate endpoints (risk of worrisome features [WF] and high-risk stigmata [HRS]) in relation to cyst size. Capurso et al. (n = 540, median follow-up 52 months) [9] showed a two-fold increased risk of WF or HRS for branch-duct IPMN (BD-IPMN) > 15 mm. The same result was found in an even larger study by Lee et al. (n = 982, median follow-up 96 months) [12]. Also, Marchegiani et al. (2023) [20] stressed that surveillance can be discontinued at a certain age and cyst size (age 65 years at size < 15 mm; age 75 at size < 30 mm) after 5 years without WF or HRS development. In analogy with these results, we now observed that cysts < 15 mm without WF or HRS at baseline harbor a 1.5-fold lower risk of developing WF or HRS during follow-up. Together, these findings endorse that—for individuals without WF or HRS—cyst size < 15 mm can be used as a reassuring feature.

With regard to cyst growth rate, we found a 25-fold lower risk of HGD or PC in individuals with growth < 2.5 mm/year. Similar outcomes on the predictive value of cyst growth rate in trivial cysts were reported by others. In 2019, Marchegiani, Andrianello et al. [21] et al. showed that growth < 2.5 mm/year was associated with a lower 10-years cumulative incidence of PC, as compared to growth ≥ 2.5 mm/year (16.7% vs. 1.8%, p = 0.029).

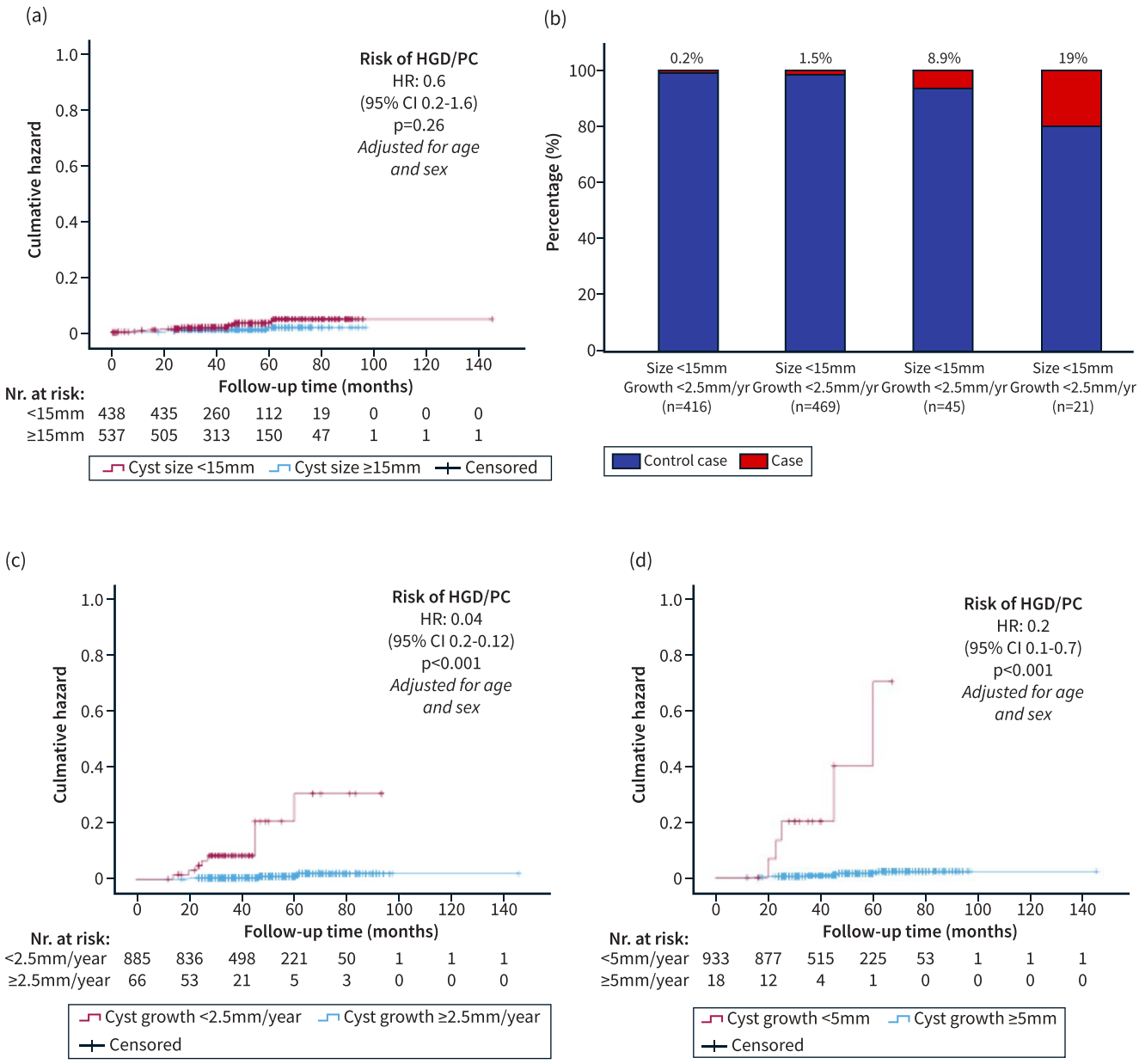

FIGURE 3 | Cox proportional hazard plots showing the risk of developing high-grade dysplasia (HGD) or pancreatic cancer (PC). (a) The absolute risk per cyst size and growth group. (b–d) The hazard ratio (HR; adjusted for age and sex) per cyst size (b) and cyst growth group (c, d).

Kwong et al. (2015) [22] demonstrated a low (0.8%) malignancy rate in cysts growing less than 2 mm/year (n = 286, median follow-up 56 months). Other studies looked at surrogate endpoints. Tsai et al. (2015, 135 individuals, ≥ 1 year follow-up) [23] showed that those with cysts growing > 1 mm/year more often developed morphological changes. Yamazaki et al. (2021, 283 individuals, median 56 months follow-up) [24] demonstrated that cyst growth (but not initial size) was associated with the development of HRS.

Thus, all evidence points toward stable cyst size being a reassuring feature with a very low risk of HGD or PC. Our results pose doubt whether the present growth rate threshold as recommended by the international guidelines [4] is not too low, as we found growth > 2.5 mm/year to be already associated with an increased risk of HGD or PC. This applies even more to the European guidelines. Which use a cutoff of ≥ 5 mm/year. Unfortunately, our sample size did not allow for appraisal of the optimal cutoff to reduce or even discontinue surveillance.

Based on our results, a less intensive follow-up regime may suffice for smaller cysts. The international Kyoto guidelines (2024) [4] already propagate a size-based approach. After 6-months of stable follow-up, they recommend 18-monthly follow-up for cysts smaller than 20 mm; for cysts 10–20 mm, twice 6-monthly and thereafter yearly; and for larger cysts, every 6 months with possible lengthening of intervals when cysts remain stable. We suggest a similar approach for the envisioned future global guidelines.

Compared to other published series, the PACYFIC-study is a unique international registry that prospectively records data of a representative population under real-life cyst surveillance. The large sample size allowed us to use HGD or PC as endpoints and

not only WF or HRS as surrogates. The study also has limitations. First, cyst management was determined by the treating physician and not protocolized based on guideline recommendations. For example, EUS was used more often for cysts ≥ 15 mm, and MRI more often for smaller cysts, perhaps driven by a higher prevalence of WF or HRS in larger cysts. This may have influenced the results, as Huynh (2020) [25] showed EUS to slightly underestimate cyst size by 1–4 mm, whereas MRI overestimates by 3 mm. This also emphasizes the importance of performing surveillance with the same imaging modality to allow for reliable growth estimation. For some patients, the use of MRI and EUS was inconsistent in our cohort. Therefore, we chose to use persistent growth (rather than a single growth measurement) as variable. We also performed a sensitivity analysis, which showed that results were similar after excluding those individuals who only underwent CT at baseline (Table S3).

It is highly remarkable that 78% of surgical patients had no HGD or cancer. This suggests that our current strategy for selecting individuals, that supposedly have presumed HGD or cancer, is deeply flawed. Of surgical patients, 21% had cystic lesions that did not require surveillance at all. It further suggests the need for significant diagnostic improvements, such as biomarkers in cyst fluid or pancreatic juice, and improved imaging tools.

A potential referral bias may be another limitation, as 14 of the 30 participating centers perform tertiary care. However, the absolute malignancy risk was low regardless of this fact. In addition, while we aimed to recruit individuals with neoplastic cysts, other cystic lesions (e.g., SCNs, lymphoepithelial cysts, pseudocysts) may have been misdiagnosed as IPMN. However, we do anticipate that the majority of the cysts are IPMN. One should keep in mind that the 15-mm threshold does not count for other cyst types, such as NET or MCN. Additionally, the current study may underestimate the prevalence of HGD, as this was only confirmed within those individuals who underwent resection. Furthermore, as only 27% had a follow-up time over 5 years, we were unable to draw conclusions beyond this period to assess cessation of surveillance beyond this period.

Our SIRs were comparable to those reported by Oyama et al., but were higher than Marchegiani et al., who analyzed a larger number of PC cases with substantially more person-years. Given the limited number of PC cases in our study, the SIRs should be interpreted with caution. Consequently, we were only able to standardize for age but not for gender.

Finally, when interpreting the presented results, one should not forget the relatively low background risk of malignancy. For instance, a 1-mm larger initial cyst size was associated with a 4% increased risk of WF/HRS. Thus, an assumed 2% risk in individuals without WF/HRS at baseline increases to 2.08%. Similarly, this metric increases to 2.4% in the case of yearly 1 mm growth.

In conclusion, this study shows that both small size and size stability appear to be protective factors for the development of WF or HRS. For those lacking WF or HRS at baseline, and presenting with cysts smaller than 15 mm, yearly growth of less than 2.5 mm is associated with a risk of HGD or PC that is similar to the general population, which is highly reassuring. Evidence is accumulating that for such "trivial" cysts less frequent monitoring will suffice. Low-risk cysts should be a focal point of attention for future studies aiming to alleviate the burden on patients and health care resources by reducing the intensity of follow-up regimes or even discontinuing surveillance after years of stability. However, clinical studies with extended follow-up and more cases are required to draw definite conclusions.

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Ethics Statement

The study was conducted according to the ethical guidelines of the Declaration of Helsinki (1975–2013), the Declaration of Taipei (2016) and the Medical Research involving Human Subjects Act (WMO).

Consent

Written informed consent was obtained from each individual prior to inclusion.

Conflicts of Interest

Iris J.M. Levink, Marloes L.J.A. Sprij, Brechtje D.M. Koopmann, Sanne Jaarsma, Priscilla A. van Riet, Kasper A. Overbeek, Jihane Meziani, Myrte Gorris, Rogier P. Voermans, Riccardo Casadei, Mariacristina Di Marco, Sanne A. Hoogenboom, Neville Azopardi, Reea Ahola, Marcin Polkowski, Pieter Honkoop, Erik J. Schoon, Niels G. Venneman, Laurens A. van der Waaij, Anne-Marie van Berkel, Gemma Rossi, Jilling F. Bergmann, Elizabeth Pando, Georg Beyer, Matthijs P. Schwartz, Frederike G.I. van Vilsteren, Chantal Hoge, Marianne E. Smits, Rutger Quispel, Ellert J. van Soest, Patrick M. Vos, Robert C. Verdonk, Toon Steinhauser, Eva Kouw, Adriaan C.I.T.L. Tan, Laszlo Czako, and Djuna L. Cahen have no conflicts of interest. Jeanin E. van Hooft: Boston Scientific (Lecture), Cook medical (Lecture), Fuji Film (Lecture), Olympus (Consultancy fee). Michael B. Wallace: Consulting: Verily, Boston Scientific, Endiatix, Fujifilm, Medtronic, Surgical Automations; Research grants: Fujifilm, Boston Scientific, Olympus, Medtronic, Ninepoint Medical, Cosmo/Aries Pharmaceuticals' Stock/Stock Options:, Virgo Inc., Surgical Automations. Silvia Carrara: Olympus (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).

Data Availability Statement

The study protocol and more information on the PACYFIC-registry can be found at https://www.pacyfic.net/. Individual participant data will not be shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.