Prediction of Unresectability and Prognosis in Patients Undergoing Surgery on Suspicion of Pancreatic Cancer Using Carbohydrate Antigen 19-9, Interleukin 6, and YKL-40

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Objectives: The aim was to determine whether serum levels of carbohydrate antigen (CA) 19-9, interleukin 6 (IL-6), and YKL-40 could identify advanced disease and poor prognosis in pancreatic cancer (PC) patients intraoperatively diagnosed with locally advanced or metastatic disease.
Methods: Two hundred ninety patients were included with preoperative blood samples. Plasma IL-6 and YKL-40 were determined by enzyme-linked immunosorbent assays.
Results: Interleukin 6 was elevated in patients with unresectable PC compared with resectable PC ($P = 0.03$). Carbohydrate antigen 19-9 and YKL-40 were similar. Patients with resectable tumors and greater than median preoperative CA 19-9, IL-6, and YKL-40 had shorter overall survival than patients with low levels (CA 19-9: hazard ratio [HR], 1.79; 95% confidence interval [CI], 1.13–2.83; $P = 0.01$; IL-6: HR, 1.83; 95% CI, 1.20–2.78; $P = 0.01$; YKL-40: HR, 1.60; 95% CI, 1.02–2.49; $P = 0.04$). Patients with resectable tumors and 2 or 3 high biomarker levels had significantly reduced overall survival compared with patients with low levels (2 high: HR, 2.97; 95% CI, 1.44–6.10; $P = 0.00$; 3 high: HR, 3.10; 95% CI, 1.45–6.65; $P = 0.00$).
Conclusions: Preoperative levels of CA 19-9, IL-6, and YKL-40 may be useful to identify a subgroup of PC patients with poor prognosis.

Key Words: CA 19-9, IL-6, pancreatic cancer, pancreatic ductal adenocarcinoma, unresectability, YKL-40

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Pancreatic cancer (PC) is the fourth most common cause of cancer death in the Western world[1,2] and is projected to be the second leading cause of cancer-related death in 2030 in the United States after lung cancer.[3] If not resected, patients with PC have a dismal prognosis, with 1- and 5-year survival rates of only 20% and 6%, respectively.[1] Systemic chemotherapy prolongs survival after tumor resection,[4] but in patients with metastatic disease,[5,6] surgery is the only curative treatment.[7,8] Only 20% of patients diagnosed with PC present with localized disease (stage Ia–IIb) and thus a resectable tumor,[7,8] and 80% of these patients operated on will later have recurrences.[8,9] Furthermore, a high percentage of patients referred to surgery for PC are not subjected to radical surgery because of the spread of locally advanced disease into major arteries (stage III) or distant metastases (stage IV), most often to liver, lungs, or omentum.[8] A computed axial tomography scan, sometimes supplemented with endoscopic retrograde cholangiopancreaticography, is commonly used to diagnose PC.

No biomarker exists for screening of PC. Carbohydrate antigen (CA) 19-9 is produced by several gastrointestinal cancers, in particular pancreatic adenocarcinomas. Serum CA 19-9 cannot be used for screening because of low sensitivity (~80%) and specificity (~80%)[10] and is often normal in early stages[10] and in patients with small tumors.[11] Serum CA 19-9 is used only in the clinic as a biomarker in patients with PC during treatment with chemotherapy and during follow-up after surgery for PC.[11] A high level of CA 19-9 is associated with short overall survival (OS).[12]

Inflammation is a common finding in cancer,[13] including patients with PC.[14] Interleukin (IL) 6 plays a major role in the development and progression of PC[15] and the development of cachexia.[16] Plasma IL-6 in patients with PC is elevated compared with healthy individuals[17]; it increases with stage,[17,18] and a high plasma IL-6 is associated with poor prognosis[12,15,17–20] and presence of liver metastases.[21]

YKL-40 (chitinase 3-like 1, CHI3LI) is a highly conserved glycoprotein produced by cancer cells, including PC, macrophages, neutrophils, and by fetal and embryonic stem cells.[22–24] Production of YKL-40 is stimulated by IL-6 and hypoxia,[25–27] and YKL-40 regulates vascular endothelial growth factor and plays a major role in inflammation, angiogenesis,[27–29] remodeling of the extracellular matrix,[30] and fibrosis.[31,32] The protein regulates cellular and tissue responses via IL-13 receptor α2[33] and may be a potential new target for inhibition in both cancer[27,28] and inflammatory diseases.[29] High plasma YKL-40 in subjects from the general population is associated with an increased risk of developing cancer[34] and increased risk of death from gastrointestinal cancer, including PC.[35] High plasma YKL-40 in patients with advanced PC is associated with short OS.[12]

We hypothesized that preoperative serum CA 19-9 in combination with the inflammatory biomarkers IL-6 and YKL-40 could predict unresectability and prognosis in patients subjected to surgery for PC. The aim was therefore to study circulating levels of these 3 biomarkers before and after surgery in a large cohort of patients in a single Danish hospital who underwent surgery due to suspicion of PC.

MATERIALS AND METHODS

Patients

The BIOPAC Study: From December 23, 2010, through December 31, 2015, pretreatment blood samples were collected from

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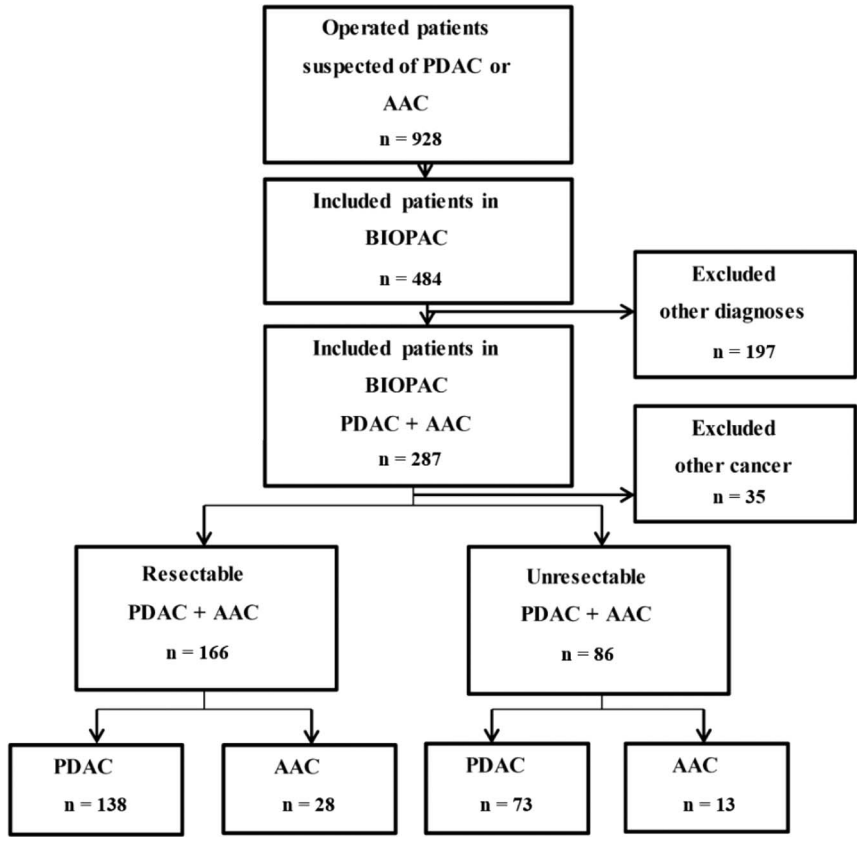


FIGURE 1. Flowchart of included patients. The patients were subjected to surgery because of suspicion of PDAC or AAC.

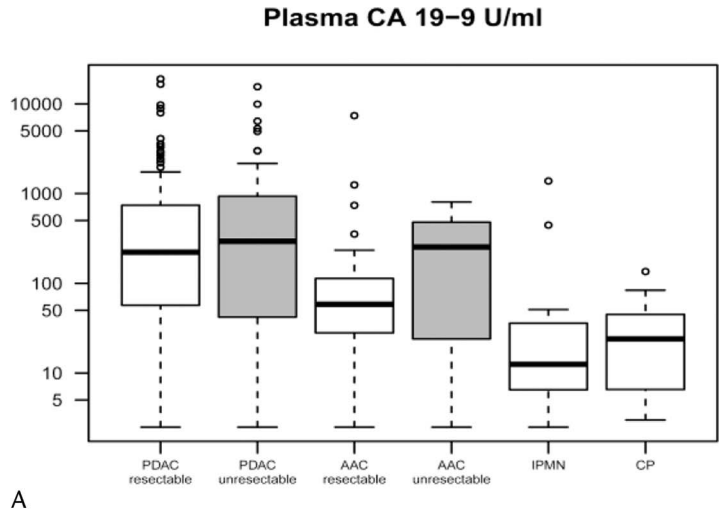
487 patients operated on due to suspicion of PC and included in the Danish multicenter BIOPAC Study "BIOmarkers in patients with Pancreatic Cancer—Can They Provide New Information of the Disease and Improve Diagnosis and Prognosis of the Patients?" Patients were recruited consecutively during the same period and represented 52% of all patients (n = 941) operated on at Rigshospitalet, Copenhagen, Denmark, due to suspicion of PC. Clinical eligibility criteria for inclusion were age older than 18 years and suspicion of PC. After surgery, 211 were diagnosed with pancreatic ductal adenocarcinoma (PDAC), 41 patients with periampullary adenocarcinoma (AAC), 26 patients with intraductal papillary mucinous neoplasm (IPMN), and 12 patients with chronic pancreatitis (CP) (Fig. 1). Patients with other cancers within 5 years before surgery were excluded. Patients with previous cancer and 5 years or more without relapse were included. One hundred thirty-eight patients with local PDAC underwent a pancreaticoduodenectomy, a distal pancreatectomy, or a total pancreatectomy. Patients were followed until death or July 29, 2016. At follow-up, investigations were undertaken to ensure that patients in the study had not developed other types of cancer. A computed axial tomography scans were obtained every third month or on suspicion of disease progression.

Supplementary Table 1, http://links.lww.com/MPA/A763, gives the number of patients operated on annually for PDAC and AAC at Rigshospitalet and the number of patients included in the BIOPAC study. Patients with resectable and unresectable tumors are included. Supplementary Table 2, http://links.lww.com/MPA/A763, gives the types of chemotherapy used for treatment of the patients in the different disease groups. All patients provided written informed consent. The BIOPAC Study was approved by the Regional Ethics Committee (VEK ref. KA-2006-0113) and

TABLE 1. Clinical Characteristics of the Patients According to Type of Disease

	PDAC (n = 211)	AAC (n = 41)	IPMN (n = 26)	Chronic Pancreatitis (n = 12)
Age, y				
<60	49 (23)	9 (22)	5 (19)	6 (50)
>60	162 (77)	32 (78)	21 (81)	6 (50)
Sex				
Male	118 (56)	25 (61)	12 (46)	10 (83)
Female	93 (44)	16 (39)	14 (54)	2 (17)
Tumor stages				
IA	7 (3)	2 (5)		
IB	4 (2)	5 (12)		
IIA	24 (11)	4 (10)		
IIB	103 (49)	17 (42)		
III	15 (7)	12 (29)		
IV	58 (28)	1 (2)		
Resectability				
Resectable	138 (65)	28 (68)		
Unresectable	73 (35)	13 (32)		

Values are presented as number (%).



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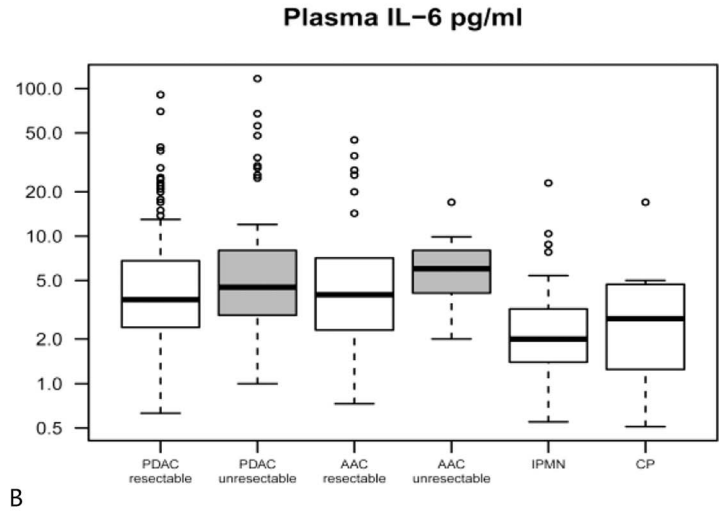

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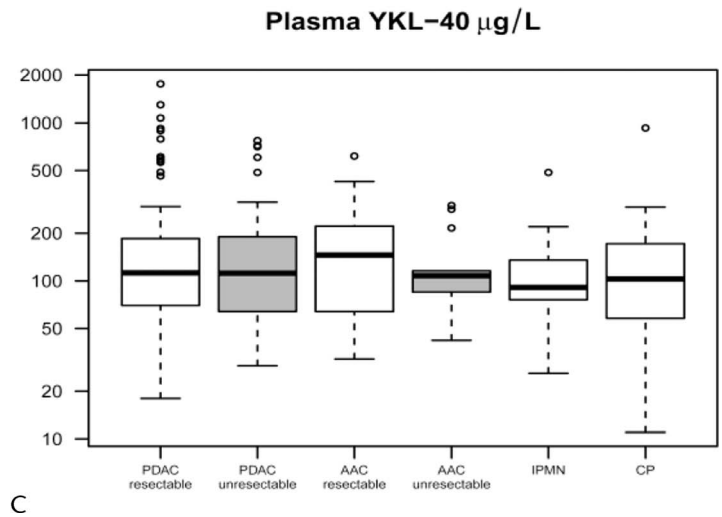

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FIGURE 2. Boxplots of serum CA 19-9 (A), plasma IL-6 (B), and plasma YKL-40 (C) in patients operated on for PDAC, AAC, IPMN, and CP.

the Danish Data Protection Agency (jr. no. 2006-41-6848, jr. no. 2012-58-004, and HGH-2015-027, I-suite 03960).

Biomarker Analyses and Cutoff Levels

Standard operating procedures were used for handling blood samples. Within ½ to 2 hours after sampling, blood was centrifuged at 2330*g* for 10 minutes at 4°C, and serum was then stored at −80°C until analysis. Serum CA 19-9 was analyzed using the Immulite 2000 GI-MA assay (catalog number L2KG12; Siemens, Ballerup, Denmark), a solid-phase, 2-site sequential chemiluminescent immunometric assay. Elevated serum CA 19-9 is defined as greater than 37 U/mL. Plasma IL-6 was determined in duplicate by an enzyme-linked immunosorbent assay (ELISA) (catalog no. HS600; R&D Systems, Abingdon, United Kingdom) according to the manufacturer's instructions. Median plasma IL-6 in healthy subjects is 1.3 pg/mL (range, 2.5%–97.5%; reference level, 0.33–26 pg/mL).[36] Elevated plasma IL-6 is defined as greater than 4.5 pg/mL (95% percentile for healthy individuals). The detection limit of the IL-6 ELISA is 0.01 pg/mL, and intra-assay and interassay coefficients of variation are ≤8% and ≤11%. Plasma YKL-40 was determined in duplicate by ELISA (Quidel, Santa Clara, Calif, according to the manufacturer's instructions. Median plasma YKL-40 in healthy subjects is 40 ng/mL (range, 2.5%–97.5%; reference level, 14–155 ng/mL). Elevated plasma YKL-40 is defined as greater than 95% limit of the age-adjusted reference levels. The YKL-40 percentile can be calculated as a function of age in years, and plasma YKL-40 in ng/mL was derived: percentile = 100/(1 + (YKL-40^ −3) * (1.062^age) * 5000).[37] The detection limit of the YKL-40 ELISA is 20 ng/mL, and the intra-assay and interassay coefficients of variation are 5% or less and 6% or less.

Statistical Analysis

Discriminations between cancer and noncancer patients and resectable and unresectable patients were evaluated by the receiver operating characteristic curve and the area under the curve (AUC), with 95% confidence intervals (CIs) for each biomarker separately as well as for the number of elevated biomarkers.

For the prognostic study, the probability of disease-free survival (DFS) for resectable patients or progression-free survival (PFS) for unresectable patients and OS with respect to CA 19-9, IL-6, and YKL-40 levels was illustrated by Kaplan-Meier curves by dichotomizing the protein levels using the median as cutoff. The association was tested by means of univariate Cox proportional hazards regression both on the continuous variables and on the dichotomized variables and presented as hazard ratios (HRs) log-rank and corresponding 95% CIs, as well as HRs adjusted for age, stage, diagnosis, sex, and R0/R1 (aHR).

All analyses were done in R version 3.2.2 (R Foundation, Vienna, Austria)[38] using a 5% significance level.

RESULTS

Patient Characteristics

The clinical patient characteristics are given in Table 1. The majority (77%) of patients with PC were older than 60 years at time of surgery, and approximately 60% were men. Stage IIB was the most frequent (PDAC: 49%, AAC: 42%). Thirty-five percent of included patients with PDAC and 32% with AAC were unresectable.

Preoperative Biomarker Levels According to Diagnosis and Resectability

Boxplots for each biomarker in the different groups of patients are shown in Figure 2. Plasma IL-6 was significantly elevated in patients with unresectable tumors (PDAC and AAC combined) compared with patients with resectable tumors (P = 0.03). No significant differences in serum CA 19-9 (P = 0.49) and plasma YKL-40 (P = 0.82) were found between the 2 groups. Interleukin 6 could predict resectability, with AUC of 0.58 (95% CI, 0.50–0.65; P = 0.05), whereas CA 19-9 and YKL-40 could

TABLE 2. Univariate and aHRs of DFS and OS for the Preoperative Levels of CA 19-9, IL-6, and YKL-40 in Patients Subjected to Surgery for PC

	DFS Unadjusted		DFS Adjusted*	
Preoperative Biomarker†	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CA 19-9	1.65 (1.11–2.47)	0.01	1.52 (0.97–2.37)	0.07
IL-6	1.63 (1.09–2.42)	0.02	1.38 (0.92–2.09)	0.12
YKL-40	1.80 (1.20–2.71)	0.01	1.61 (1.05–2.46)	0.03
1 High biomarker	2.15 (1.12–4.13)	0.02	2.32 (1.16–4.65)	0.02
2 High biomarkers	3.25 (1.70–6.19)	0.00	2.86 (1.46–5.60)	0.00
3 High biomarkers	3.07 (1.53–6.15)	0.00	2.46 (1.18–5.14)	0.02
	OS Unadjusted		**OS Adjusted***	
Preoperative Biomarker†	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CA 19-9	2.00 (1.31–3.04)	0.00	1.79 (1.13–2.83)	0.01
IL-6	1.85 (1.23–2.79)	0.00	1.83 (1.20–2.78)	0.01
YKL-40	1.81 (1.19–2.75)	0.01	1.60 (1.02–2.49)	0.04
1 High biomarker	1.81 (0.89–3.66)	0.10	1.95 (0.92–4.11)	0.08
2 High biomarkers	3.15 (1.57–6.32)	0.00	2.97 (1.44–6.10)	0.00
3 High biomarkers	3.92 (1.92–7.99)	0.00	3.10 (1.45–6.65)	0.00

Patients with PDAC and AAC are combined.

*Adjusted for age, stage, diagnosis, sex, and R0/R1.

†The biomarkers are dichotomized according to median levels.

not (CA 19-9: AUC, 0.53; 95% CI, 0.45–0.60; $P = 0.49$; and YKL-40: AUC, 0.51; 95% CI, 0.43–0.58; $P = 0.82$).

Seventy-five percent of the patients with unresectable PDAC had elevated levels of CA 19-9, 70% had elevated IL-6, and 26% had elevated YKL-40. Eighty-one percent of the patients with resectable PDAC had elevated levels of CA 19-9, 53% had elevated IL-6, and 28% had elevated YKL-40. Few patients with IPMN and CP had elevated biomarkers (IPMN: 23% had elevated levels of CA 19-9, IL-6, and YKL-40; CP: 33% had elevated levels of CA 19-9, 25% had elevated IL-6, and 33% had elevated YKL-40).

Preoperative Biomarker Levels and Prediction of DFS and OS in Resectable Patients

During the follow-up period, 99 patients (61%) with resectable tumors had disease recurrence and 93 (58%) died. Operated patients (PDAC + AAC combined) with high (median level used

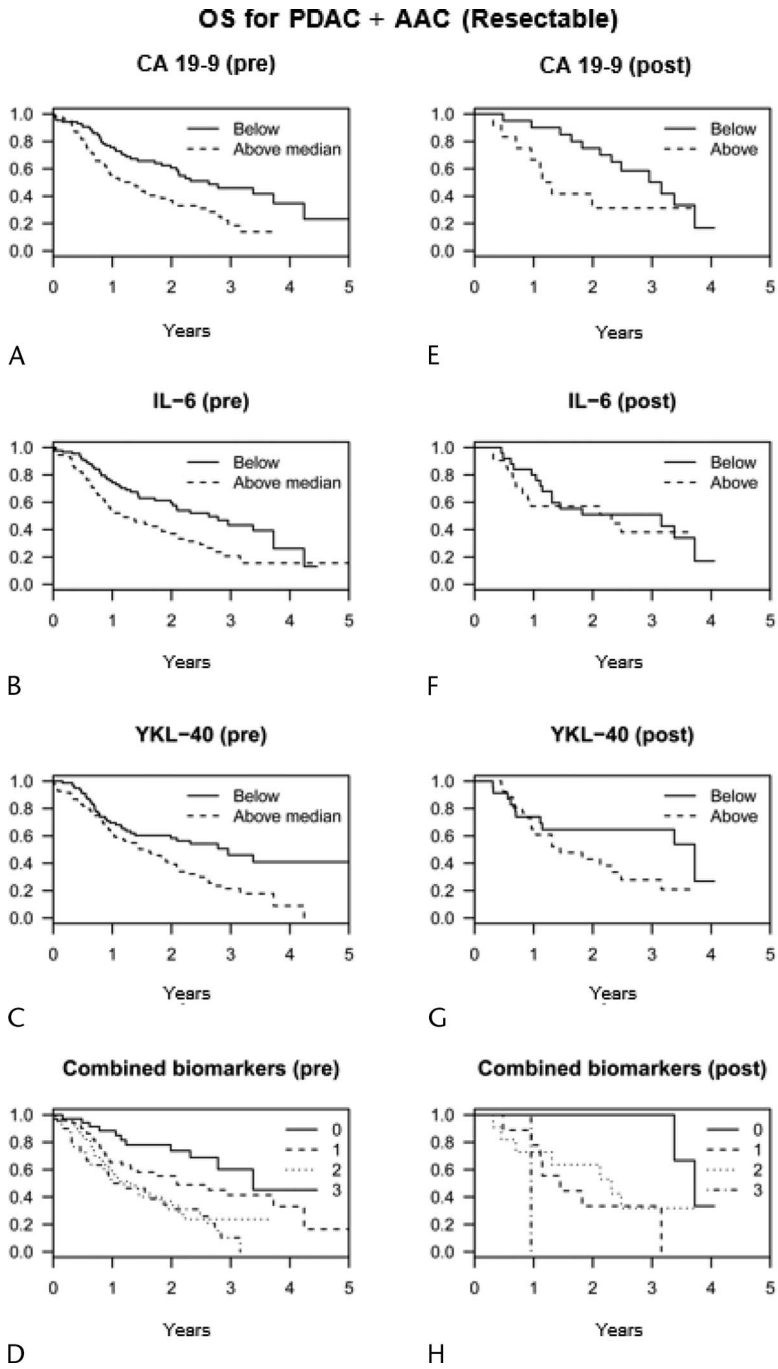

FIGURE 3. Kaplan-Meier plots of OS for resectable PDAC + AAC for a single biomarker (A, CA-19-9; B, IL-6; and C, YKL-40, respectively) and combined biomarkers (D) preoperatively and postoperatively for a single biomarker (E, CA-19-9; F, IL-6 and G, YKL-40, respectively) and combined biomarkers (H).

as cut-off) preoperative plasma YKL-40 had significantly shorter DFS than patients operated on with low levels (aHR, 1.61; 95% CI, 1.05–2.46; $P = 0.03$). The aHR was adjusted for age, stage, diagnosis, sex, and R0/R1. High preoperative serum CA 19-9 and plasma IL-6 were not associated with shorter DFS (Table 2, top). Similar results were found in patients operated on for PDAC (Supplementary Table 3, top, http://links.lww.com/MPA/A763). Patients with high levels of 1 (aHR, 2.32; 95% CI, 1.16–4.65; $P = 0.02$), 2 (aHR, 2.86; 95% CI, 1.46–5.60; $P = 0.00$), or 3 (aHR, 2.46; 95% CI, 1.18–5.14; $P = 0.02$) biomarkers had significantly shorter DFS than patients with low levels of all 3 biomarkers (Table 2, top). The Kaplan-Meier plots of DFS according to preoperative biomarker levels in patients with PDAC and AAC combined are shown in Supplementary Figure 1 (left figures), http://links.lww.com/MPA/A763. The corresponding Kaplan-Meier plots of DFS among patients with resectable PDAC are shown in Supplementary Figure 2 (left figures), http://links.lww.com/MPA/A763.

Patients operated on (PDAC + AAC combined) with high preoperative biomarkers (median level used as cutoff) had significantly shorter OS than patients operated on with low biomarker levels (CA 19-9: aHR, 1.79; 95% CI, 1.13–2.83; $P = 0.01$; IL-6: aHR, 1.83; 95% CI, 1.20–2.78; $P = 0.01$; YKL-40: aHR, 1.60; 95% CI, 1.02–2.49; $P = 0.04$) (Table 2, bottom). Significantly shorter OS was found in patients with high preoperative levels of 2 (aHR, 2.97; 95% CI, 1.44–6.10; $P = 0.00$) or 3 (HR, 3.10; 95% CI, 1.45–6.65; $P = 0.00$) biomarkers compared with patients with low levels of all biomarkers (Table 2, bottom). Similar results were found in patients operated on for PDAC (Supplementary Table 3, bottom, http://links.lww.com/MPA/A763). Figure 3 (left figures) shows the Kaplan-Meier plots of OS according to preoperative biomarker levels in patients with PDAC and AAC combined. Supplementary Figure 3 (left figures), http://links.lww.com/MPA/A763, shows the Kaplan-Meier plots of OS for resectable PDAC with preoperative biomarker levels (median level used as cutoff).

Preoperative Biomarker Levels and Prediction of PFS and OS in Unresectable Patients

During the follow-up period, 62 patients (73%) with unresectable tumors had disease progression, and 71 (84%) died. Preoperative levels of CA 19-9, IL-6, and YKL-40 in patients with unresectable tumors (PDAC + AAC combined) (median level used as cutoff) could not predict disease progression (Table 3, top). Similar results were found in patients with unresectable PDAC (Supplementary Table 4, top), http://links.lww.com/MPA/A763. Neither 1 nor 2 nor 3 elevated biomarkers predicted short PFS. The Kaplan-Meier plots of PFS according to preoperative biomarker levels in patients with unresectable tumors (PDAC and AAC combined) are shown in Supplementary Figure 4, http://links.lww.com/MPA/A763.

Patients with unresectable tumors (PDAC and AAC combined) and high preoperative IL-6 and YKL-40 levels (median level used as cutoff) had significantly shorter OS than patients with unresectable tumors and low levels (IL-6: aHR, 2.12; 95% CI, 1.24–3.64; $P = 0.01$; YKL-40: aHR, 2.04; 95% CI, 1.27–3.30; $P = 0.00$) (Table 3, bottom). Patients with 3 high biomarkers had shorter OS than patients with low biomarker levels (aHR, 3.78; 95% CI, 1.48–9.66; $P = 0.01$). Similar results were found when only the patients with unresectable PDAC were studied (Supplementary Table 4, bottom), http://links.lww.com/MPA/A763. Figure 4 shows the Kaplan-Meier plots of OS according to preoperative biomarker levels in patients with unresectable tumors (PDAC + AAC combined), and Supplementary Figure 5, http://links.lww.com/MPA/A763, shows the corresponding Kaplan-Meier plots when only the patients with unresectable PDAC were studied.

Postoperative Biomarkers and Prediction of DFS and OS in Resectable Patients

Blood samples were available just before start of adjuvant chemotherapy in 54 (34%) of the patients operated on. The

TABLE 3. Univariate and Adjusted HRs of PFS and OS for the Preoperative Levels of CA 19-9, IL-6, and YKL-40 in Patients With Unresectable PC

	PFS Unadjusted		PFS Adjusted*	
Preoperative Biomarker†	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CA 19-9	0.73 (0.44–1.23)	0.24	0.69 (0.40–1.22)	0.20
IL-6	0.96 (0.57–1.60)	0.87	0.85 (0.49–1.49)	0.58
YKL-40	0.96 (0.56–1.65)	0.87	1.07 (0.61–1.88)	0.81
1 High biomarker	0.40 (0.18–0.87)	0.02	0.32 (0.13–0.75)	0.01
2 High biomarkers	0.53 (0.25–1.11)	0.09	0.41 (0.18–0.97)	0.04
3 High biomarkers	0.51 (0.20–1.26)	0.14	0.40 (0.14–1.16)	0.09
	OS Unadjusted		**OS Adjusted***	
Preoperative Biomarker†	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CA 19-9	1.01 (0.63–1.60)	0.99	0.93 (0.57–1.52)	0.77
IL-6	2.08 (1.26–3.44)	0.00	2.12 (1.24–3.64)	0.01
YKL-40	2.05 (1.28–3.29)	0.00	2.04 (1.27–3.30)	0.00
1 High biomarker	1.62 (0.73–3.63)	0.24	1.43 (0.62–3.27)	0.40
2 High biomarkers	2.41 (1.12–5.18)	0.02	1.98 (0.89–4.38)	0.09
3 High biomarkers	3.00 (1.29–6.93)	0.01	3.78 (1.48–9.66)	0.01

PDAC and AAC are combined.

*Adjusted for age, stage, diagnosis, and sex.

†The biomarkers are dichotomized according to median levels.

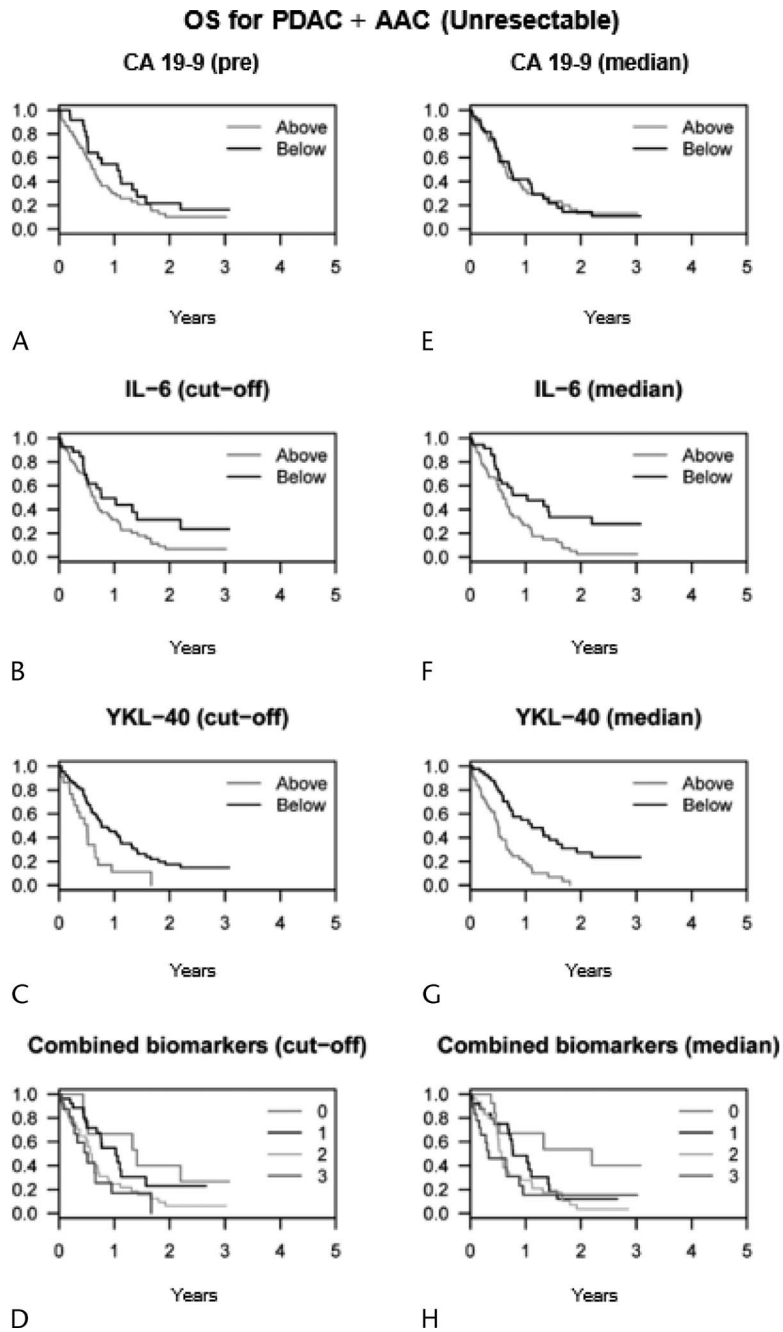

FIGURE 4. Kaplan-Meier plots of OS for unresectable PDAC + AAC for a single preoperative biomarker above cutoff (A, CA-19-9; B, IL-6; and C, YKL-40, respectively) and combined biomarkers (D) and for a single preoperative biomarker above the median (E, CA-19-9; F, IL-6 and G, YKL-40, respectively) and combined biomarkers above the median (H).

Kaplan-Meier plots of DFS according to postoperative biomarker levels are shown in Supplementary Figure 6, http://links.lww.com/MPA/A763 (median level used as cutoff). None of the postoperative biomarkers (just before chemotherapy) could predict short DFS (Table 4, top).

Figure 3 (right figures) shows the Kaplan-Meier plots of OS according to postoperative biomarker levels in patients with resectable tumors (PDAC + AAC combined) (median level used as cutoff). None of the postoperative biomarkers (just before chemotherapy) could predict short OS (Table 4, bottom). Adjusted HRs for 1, 2, or 3 high biomarkers could not be estimated, because too few patients with blood sample results from all 3 biomarkers were available.

DISCUSSION

Less than 20% of patients with PC have resectable disease at the time of diagnosis.[7,39] Better biomarkers for early diagnosis of PC are needed, including markers to identify patients with a risk of early recurrence of disease, because these patients may benefit from neoadjuvant chemotherapy.

TABLE 4. Univariate and Adjusted HRs of PFS and OS for Postoperative Levels of CA 19-9, IL-6, and YKL-40 in Patients With Resectable PC

	DFS Unadjusted		DFS Adjusted*	
Postoperative Biomarker†	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CA 19-9	1.79 (0.80–4.01)	0.16	1.71 (0.71–4.11)	0.23
IL-6	1.21 (0.62–2.37)	0.57	1.08 (0.52–2.22)	0.84
YKL-40	2.42 (1.22–4.79)	0.01	1.72 (0.75–3.94)	0.20
1 High biomarker	3.34 (0.86–12.89)	0.08	21.03 (1.12–396.28)	0.04
2 High biomarkers	3.70 (0.97–14.11)	0.06	19.07 (1.36–267.30)	0.03
3 High biomarkers	7.55 (0.70–81.50)	0.10	64.44 (1.61–2582.46)	0.03
	OS Unadjusted		**OS Adjusted***	
Postoperative Biomarker†	**HR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CA 19-9	2.31 (0.91–5.86)	0.08	2.06 (0.77–5.52)	0.15
IL-6	1.16 (0.54–2.51)	0.71	1.01 (0.44–2.30)	0.98
YKL-40	2.08 (0.93–4.65)	0.08	1.36 (0.54–3.43)	0.52
1 High biomarker	9.11 (1.07–77.72)	0.04		
2 High biomarkers	5.41 (0.66–44.16)	0.12		
3 High biomarkers	33.42 (1.74–641.40)	0.02		

PDAC and AAC are combined. Adjusted OS for 1, 2, or 3 high biomarkers could not be analyzed.

*Adjusted for age, stage, diagnosis, sex, and R0/R1.

†The biomarkers are dichotomized according to median levels.

In the present study, we analyzed whether serum CA 19-9 in combination with plasma IL-6 and YKL-40 could predict resectability and poor prognosis after surgery. Thirty-four percent of our study population were diagnosed with stage III or IV disease and did not have significantly higher biomarker levels preoperatively than patients with stage I or II PC. However, we found that preoperative plasma IL-6 was significantly elevated in patients with unresectable PC (PDAC and AAC combined) compared with patients with resectable tumors, and plasma IL-6 could predict resectability (AUC, 0.58). However, this is not reliable enough to be used in clinical practice.

Fifty-nine percent of all patients with PDAC had elevated levels of IL-6, and 53% of patients with resectable PDAC had elevated plasma IL-6. Thus, the clinical utility of IL-6 to detect unresectability is debatable.

Interestingly, we found that high preoperative levels of YKL-40 were associated with shorter DFS and that high preoperative levels of all 3 biomarkers were related to short OS. Increasing numbers of elevated biomarkers were associated with shorter DFS and OS after surgery in patients with resectable tumor. However, these results need to be validated in other cohorts of patients operated on for PC.

A strength of our study is that all patients were from 1 hospital, but a limitation is that only 52% of all patients operated on during the study period were included in the BIOPAC Study, and the sample size of patients with AAC was small.

In conclusion, our study indicates that determination of serum CA 19-9 in combination with plasma IL-6 and YKL-40 can identify a subgroup of patients with low stages of PC but with very poor prognosis. If these 3 biomarkers are high before a planned operation, the patient is likely to have a short DFS and OS. These patients may benefit from neoadjuvant chemotherapy such as FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin) or gemcitabine in combination with nab-paclitaxel or capecitabine.

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