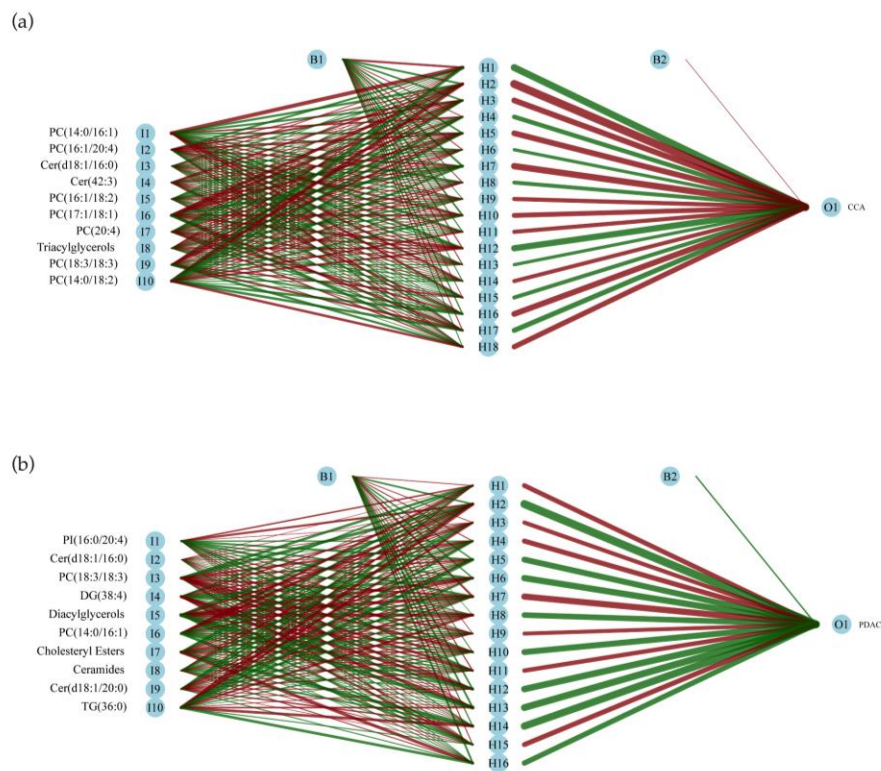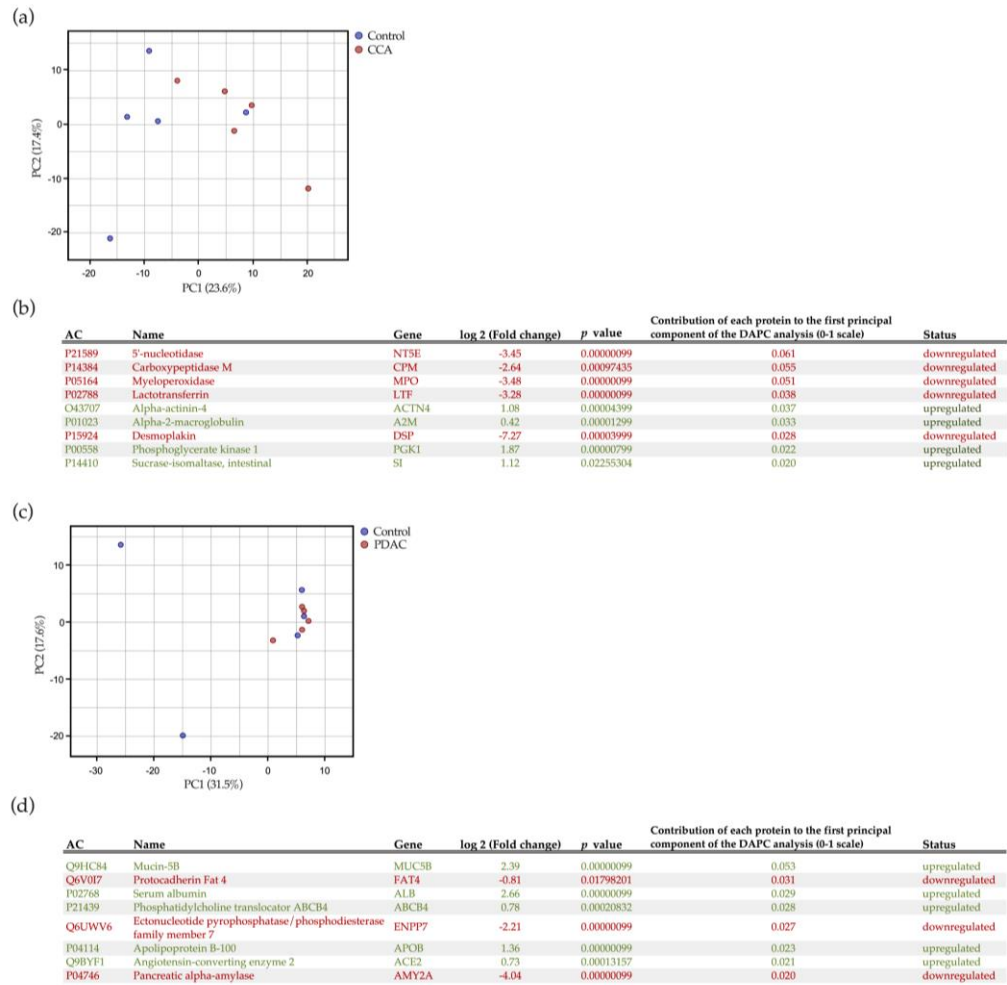**Figure S1.** Analysis of the correlation between serum levels of bilirrubin and total bile acids levels in bile from patients with benign stenoses and those with CCA or PDAC-associated stenoses.

Figure S2. Graphic representation of machine-learning NNs implemented in the analysis of (**a**) bile lipidomic data in control *vs* CCA patients, (**b**) bile lipidomic data in control *vs* PDAC patients. Features (lipids) selected by DAPC analysis of synthetic data are indicated on the left and labels within the nodes indicate the layer and node (I: input, H: hidden, B: bias, O: output). Green lines are positive predictors, red lines are negative (disease) predictors, and the thickness of the lines represent the weight (importance) of the feature to the outcome.

(a)

(b)

AC	Name	Gene	log 2 (Fold change)	p value	Contribution of each protein to the first principal component of the DAPC analysis (0-1 scale)	Status
P21589	5'-nucleotidase	NT5E	-3.45	0.00000099	0.061	downregulated
P14384	Carboxypeptidase M	CPM	-2.64	0.00097435	0.055	downregulated
P05164	Myeloperoxidase	MPO	-3.48	0.00000099	0.051	downregulated
P02788	Lactotransferrin	LTF	-3.28	0.00000099	0.038	downregulated
O43707	Alpha-actinin-4	ACTN4	1.08	0.00004399	0.037	upregulated
P01023	Alpha-2-macroglobulin	A2M	0.42	0.00001299	0.033	upregulated
P15924	Desmoplakin	DSP	-7.27	0.00003999	0.028	downregulated
P00558	Phosphoglycerate kinase 1	PGK1	1.87	0.00000799	0.022	upregulated
P14410	Sucrase-isomaltase, intestinal	SI	1.12	0.02255304	0.020	upregulated

(c)

(d)

AC	Name	Gene	log 2 (Fold change)	p value	Contribution of each protein to the first principal component of the DAPC analysis (0-1 scale)	Status
Q9HC84	Mucin-5B	MUC5B	2.39	0.00000099	0.053	upregulated
Q6V0I7	Protocadherin Fat 4	FAT4	-0.81	0.01798201	0.031	downregulated
P02768	Serum albumin	ALB	2.66	0.00000099	0.029	upregulated
P21439	Phosphatidylcholine translocator ABCB4	ABCB4	0.78	0.00020832	0.028	upregulated
Q6UWV6	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7	ENPP7	-2.21	0.00000099	0.027	downregulated
P04114	Apolipoprotein B-100	APOB	1.36	0.00000099	0.023	upregulated
Q9BYF1	Angiotensin-converting enzyme 2	ACE2	0.73	0.00013157	0.021	upregulated
P04746	Pancreatic alpha-amylase	AMY2A	-4.04	0.00000099	0.020	downregulated

Figure S3. PCA plots and proteins selected by the DAPC analysis of real proteomic data. (**a**) PCA analysis of proteomic data from control and CCA patients, (**b**) proteins selected by DAPC analysis of the differential bile proteome of control and CCA patients, (**c**) PCA analysis of proteomic data from control and PDAC patients, (**d**) proteins selected by DAPC analysis of the differential bile proteome of control and PDAC patients.

Figure S4. Graphic representation of machine-learning NNs implemented in the analysis of (**a**) bile proteomic data in control *vs* CCA patients, (**b**) bile proteomic data in control *vs* PDAC patients. Features (proteins, UniProt accession number), selected by DAPC analysis of synthetic data are indicated on the left and labels within the nodes indicate the layer and node (I: input, H: hidden, B: bias, O: output). Green lines are positive predictors, red lines are negative (disease) predictors, and the thickness of the lines represent the weight (importance) of the feature to the outcome.