

**Supplementary Table 1. Patient characteristics of concurrent medication cohort by BTC subtype**

Characteristic	Total (N=509)	IHCCA (N=298)	HCCA (N=79)	DCCA (N=27)	GBCA (N=97)	CCA-HCC (N=8)	P-value <sup>†</sup>
Median age, years (range)	62 (20-86)	62 (20-86)	63 (28-81)	63 (33-79)	64 (32-83)	59 (21-64)	0.27
Gender (F, M)	240, 269	131, 167	36, 43	8, 19	60, 37	5, 3	0.01
Race							0.62
African American	35	20	4	0	11	0	
Asian	7	5	1	0	1	0	
Caucasian	436	257	70	25	76	8	
Other/Unknown	31	16	4	2	9	0	
Ethnicity							0.61
Hispanic	11	8	1	0	2	0	
Non-Hispanic	461	266	75	23	90	7	
Unknown	37	24	3	4	5	1	
Stage at Diagnosis							<0.0001
Resectable	80	45	7	11	17	0	
Locally Advanced	141	66	40	12	21	2	
Metastatic	288	187	32	4	59	6	
Resected							0.02
Yes	115	61	21	12	21	0	
No	394	237	58	15	76	8	
Stage at First-Line Systemic Therapy Start							<0.0001
Locally Advanced	132	56	41	12	21	2	
Metastatic	297	195	32	4	60	6	
Recurrent	80	47	6	11	16	0	
Comorbidities*							
CVD	187	104	31	14	36	2	0.44
Diabetes	120	68	16	7	28	1	0.61
Dyslipidemia	131	72	24	10	23	2	0.51
CKD	65	34	9	3	17	2	0.44
Hypertension	308	183	44	20	55	6	0.37
Concurrent Medication*							
ACE-inhibitor	106	62	16	5	20	3	0.83
ARB	49	33	3	3	10	0	0.31
ACE-I/ARB	152	92	19	8	30	3	0.79
Statin	111	55	21	6	27	2	0.27
Aspirin	109	65	18	7	17	2	0.85
One or more	245	148	34	14	45	4	0.85
First-Line Systemic Therapy Included*							
Gemcitabine	417	246	63	22	78	8	0.69
Fluoropyrimidine	103	58	19	8	18	0	0.34
Platinum	393	233	58	15	79	8	0.02
Immunotherapy	34	21	4	0	8	1	0.83
Other	52	37	6	3	6	0	0.53

\*Groups are not mutually exclusive and should not necessarily sum to the row or column total. <sup>†</sup>P-value compares biliary tract cancer subtypes, thereby describing variation between BTC subtypes.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BTC, biliary tract cancer; CCA-HCC, mixed cholangiocarcinoma and hepatocellular carcinoma; CKD, chronic kidney disease; CVD, cardiovascular disease; DCCA, distal cholangiocarcinoma; HCCA, hilar cholangiocarcinoma; IHCCA, intrahepatic cholangiocarcinoma; GBCA, gallbladder carcinoma.

**Supplementary Table 2. Univariate analysis of variables predicting PFS and OS in BTC and anatomic subtypes**

**Supplementary Table 2. Univariate analyses of variables predicting PFS and OS in BTC and anatomic subtypes**

Characteristic	BTC (N=509)				IHCCA (N=298)				HCCA (N=79)				DCCA (N=27)				GBC (N=97)			
	PFS		OS		PFS		OS		PFS		OS		PFS		OS		PFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at diagnosis	1.01 (1.00-1.02)	0.24	1.01 (1.00-1.02)	0.03	1.00 (0.99-1.01)	0.67	1.02 (1.01-1.03)	0.02	1.02 (0.99-1.05)	0.15	1.00 (0.98-1.02)	0.93	1.01 (0.97-1.04)	0.76	1.00 (0.97-1.03)	0.98	1.00 (0.98-1.02)	0.96	1.01 (0.99-1.03)	0.38
Gender (F)	0.89 (0.72-1.11)	0.30	0.86 (0.71-1.03)	0.10	0.75 (0.57-0.99)	0.04	0.75 (0.59-0.96)	0.03	1.21 (0.63-2.35)	0.56	0.76 (0.46-1.24)	0.27	2.20 (0.79-6.11)	0.13	0.99 (0.39-2.56)	0.99	1.15 (0.7-1.9)	0.58	1.26 (0.81-1.96)	0.30
Race																				
African American	1.05 (0.70-1.57)	0.81	1.15 (0.80-1.64)	0.45	0.84 (0.48-1.49)	0.56	1.03 (0.64-1.64)	0.81	2.73 (0.82-9.10)	0.10	8.40 (2.70-26.18)	0.0002	None	None	0.97 (0.49-1.92)	0.93	0.93 (0.48-1.81)	0.83		
Asian	1.51 (0.67-3.41)	0.32	1.46 (0.69-3.09)	0.32	2.25 (0.83-6.08)	0.11	2.71 (1.11-6.62)	0.03	0.48 (0.06-3.92)	0.49	0.85 (0.12-6.21)	0.88	None	None	9.64 (1.22-76.39)	0.03	0.53 (0.07-3.84)	0.53		
Caucasian	Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference			
Other/Unknown	1.56 (0.98-2.49)	0.06	0.93 (0.61-1.43)	0.75	1.79 (0.97-3.30)	0.06	1.11 (0.64-1.95)	0.83	1.81 (0.43-7.69)	0.42	2.19 (0.67-7.17)	0.19	2.05 (0.46-9.24)	0.35	0.58 (0.08-4.37)	0.60	0.91 (0.33-2.53)	0.85	0.50 (0.20-1.23)	0.13
Ethnicity																				
Hispanic	1.09 (0.54-2.21)	0.80	0.87 (0.45-1.68)	0.68	0.85 (0.38-1.93)	0.70	1.22 (0.60-2.48)	0.65	17.44 (1.95-156.05)	0.01	1.76 (0.24-12.91)	0.58	None	None	1.65 (0.23-12.06)	0.62	Unable to calculate	0.98		
Non-Hispanic	Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference			
Unknown	1.20 (0.77-1.87)	0.42	1.22 (0.84-1.75)	0.30	1.06 (0.63-1.80)	0.83	0.97 (0.62-1.52)	0.70	Unable to calculate	0.99	1.51 (0.36-6.27)	0.57	1.65 (0.53-5.14)	0.39	1.47 (0.41-5.31)	0.56	1.59 (0.38-6.72)	0.53	3.31 (1.17-9.42)	0.02
Type of Cancer																				
IHCCA	Reference		Reference		Not applicable		Not applicable		Not applicable		Not applicable		Not applicable		Not applicable		Not applicable			
HCCA	0.59 (0.42-0.83)	0.0027	0.75 (0.57-0.99)	0.04																
DCCA	1.30 (0.82-2.06)	0.26	1.20 (0.79-1.83)	0.39																
GBC	1.04 (0.79-1.37)	0.80	0.94 (0.74-1.20)	0.64																
CCA-HCC	0.68 (0.22-2.13)	0.51	0.78 (0.39-1.58)	0.49																
Stage at Diagnosis																				
Resectable	1.01 (0.76-1.34)	0.96	0.81 (0.62-1.06)	0.12	0.90 (0.62-1.31)	0.58	0.69 (0.48-0.98)	0.02	0.85 (0.29-2.49)	0.76	0.89 (0.34-2.30)	0.80	2.97 (0.65-13.63)	0.16	1.13 (0.32-3.99)	0.84	0.87 (0.47-1.60)	0.66	0.87 (0.49-1.55)	0.64
Locally Advanced	0.50 (0.38-0.66)	<.0001	0.57 (0.46-0.71)	<.0001	0.58 (0.40-0.83)	0.0026	0.63 (0.46-0.86)	0.04	0.28 (0.13-0.59)	0.0008	0.33 (0.19-0.58)	<.0001	0.67 (0.15-2.92)	0.59	0.55 (0.17-1.80)	0.32	0.53 (0.26-1.09)	0.08	0.70 (0.41-1.22)	0.21
Metastatic	Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference			
Resected	0.77 (0.59-1.01)	0.06	0.59 (0.47-0.74)	<.0001	0.73 (0.51-1.03)	0.08	0.54 (0.40-0.74)	0.0001	0.32 (0.11-0.91)	0.03	0.38 (0.21-0.70)	0.002	3.38 (1.12-10.23)	0.03	1.19 (0.51-2.78)	0.68	0.91 (0.50-1.66)	0.75	0.79 (0.47-1.32)	0.37
Stage at First-Line Systemic Therapy Start																				
Locally Advanced	0.48 (0.36-0.64)	<.0001	0.56 (0.45-0.70)	<.0001	0.60 (0.41-0.89)	0.01	0.64 (0.46-0.89)	0.007	0.28 (0.13-0.59)	0.0008	0.33 (0.19-0.57)	<.0001	0.67 (0.15-2.92)	0.59	0.55 (0.17-1.80)	0.32	0.41 (0.19-0.88)	0.02	0.65 (0.37-1.14)	0.13
Metastatic	Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference		Reference			
Recurrent	1.03 (0.78-1.36)	0.83	0.83 (0.64-1.08)	0.16	0.91 (0.63-1.30)	0.59	0.70 (0.50-0.99)	0.05	0.85 (0.29-2.49)	0.76	0.89 (0.34-2.32)	0.81	2.97 (0.65-13.63)	0.16	1.13 (0.32-3.99)	0.84	1.01 (0.55-1.87)	0.97	0.91 (0.51-1.62)	0.75
Comorbidities																				
CVD	0.95 (0.76-1.18)	0.61	1.09 (0.90-1.31)	0.40	0.89 (0.67-1.18)	0.41	1.03 (0.80-1.33)	0.80	1.08 (0.56-2.10)	0.82	1.32 (0.81-2.16)	0.27	0.74 (0.30-1.84)	0.52	0.62 (0.26-1.49)	0.29	0.88 (0.52-1.47)	0.61	1.23 (0.79-1.91)	0.36
Diabetes	1.13 (0.88-1.44)	0.33	1.02 (0.82-1.26)	0.89	0.83 (0.60-1.15)	0.26	1.02 (0.77-1.36)	0.89	1.60 (0.74-3.43)	0.23	0.97 (0.52-1.81)	0.92	0.87 (0.30-2.52)	0.80	1.16 (0.44-3.03)	0.76	2.27 (1.33-3.89)	0.003	1.08 (0.68-1.73)	0.74
HLD	1.02 (0.80-1.30)	0.87	1.19 (0.96-1.46)	0.11	0.97 (0.70-1.32)	0.82	1.13 (0.86-1.49)	0.39	1.08 (0.53-2.20)	0.84	1.13 (0.67-1.91)	0.65	0.99 (0.38-2.56)	0.98	1.46 (0.60-3.54)	0.40	1.12 (0.66-1.93)	0.67	1.72 (1.03-2.87)	0.04
CKD	0.74 (0.53-1.03)	0.07	0.79 (0.60-1.05)	0.10	0.78 (0.51-1.20)	0.26	0.83 (0.57-1.21)	0.33	0.23 (0.05-0.95)	0.04	0.62 (0.28-1.37)	0.24	0.35 (0.05-2.64)	0.31	0.15 (0.02-1.12)	0.06	1.24 (0.67-2.27)	0.49	1.40 (0.80-2.45)	0.25
HTN	0.97 (0.78-1.21)	0.78	1.08 (0.89-1.30)	0.44	0.92 (0.69-1.22)	0.56	0.92 (0.72-1.18)	0.52	0.73 (0.38-1.42)	0.36	1.28 (0.78-2.09)	0.34	1.14 (0.40-3.26)	0.80	2.57 (0.84-7.83)	0.10	1.07 (0.66-1.75)	0.78	1.26 (0.81-1.94)	0.31
Concurrent Medication																				
ACE-inhibitor	0.86 (0.66-1.12)	0.26	0.99 (0.79-1.24)	0.89	0.97 (0.70-1.34)	0.83	0.91 (0.68-1.23)	0.56	0.53 (0.22-1.27)	0.15	0.88 (0.48-1.63)	0.69	0.72 (0.21-2.48)	0.60	1.90 (0.67-5.35)	0.23	1.01 (0.57-1.8)	0.97	1.16 (0.69-1.95)	0.57
ARB	1.14 (0.80-1.64)	0.47	1.28 (0.94-1.75)	0.12	1.04 (0.67-1.62)	0.87	1.25 (0.86-1.83)	0.25	2.65 (0.62-11.28)	0.19	3.60 (1.09-11.91)	0.04	0.52 (0.07-3.97)	0.53	0.28 (0.04-2.07)	0.21	1.14 (0.54-2.41)	0.73	1.40 (0.71-2.73)	0.33
ACE-I/ARB	0.93 (0.74-1.18)	0.55	1.08 (0.88-1.31)	0.48	0.99 (0.74-1.33)	0.95	1.01 (0.78-1.31)	0.94	0.68 (0.31-1.49)	0.33	1.07 (0.61-1.88)	0.82	0.61 (0.20-1.86)	0.38	0.95 (0.36-2.49)	0.91	1.07 (0.64-1.77)	0.80	1.30 (0.82-2.05)	0.27
Statin	1.08 (0.85-1.39)	0.53	1.27 (1.02-1.58)	0.04	1.04 (0.75-1.45)	0.80	1.23 (0.90-1.67)	0.19	1.15 (0.55-2.39)	0.72	1.63 (0.95-2.82)	0.08	0.54 (0.17-1.68)	0.29	1.60 (0.61-4.19)	0.34	1.20 (0.71-2.04)	0.49	1.17 (0.74-1.87)	0.50
Aspirin	1.17 (0.90-1.51)	0.25	1.14 (0.91-1.43)	0.25	1.14 (0.91-1.43)	0.12	1.29 (0.94-1.78)	0.12	1.02 (0.46-2.25)	0.96	1.13 (0.62-2.04)	0.70	0.57 (0.19-1.74)	0.32	0.95 (0.34-2.62)	0.91	1.36 (0.73-2.53)	0.33	1.26 (0.74-2.16)	0.39
One or more	1.08 (0.87-1.33)	0.51	1.14 (0.94-1.37)	0.18	1.04 (0.79-1.37)	0.77	1.08 (0.85-1.37)	0.53	1.12 (0.58-2.17)	0.74	1.10 (0.67-1.80)	0.70	0.46 (0.17-1.24)	0.13	1.31 (0.55-3.14)	0.55	1.27 (0.78-2.06)	0.33	1.37 (0.89-2.11)	0.15
First-Line Systemic Therapy Included																				
Gemcitabine	0.73 (0.55-0.96)	0.02	1.07 (0.84-1.36)	0.61	0.64 (0.44-0.92)	0.02	1.01 (0.73-1.38)	0.97	1.41 (0.55-3.63)	0.48	1.35 (0.75-2.43)	0.32	0.20 (0.06-0.66)	0.01	0.20 (0.06-0.67)	0.01	0.85 (0.47-1.51)	0.57	1.16 (0.67-2.00)	0.60
Fluoropyrimidine	0.88 (0.67-1.15)	0.35	0.85 (0.67-1.07)	0.16	1.01 (0.72-1.42)	0.96	0.84 (0.62-1.15)	0.28	0.45 (0.17-1.15)	0.09	0.78 (0.45-1.35)	0.37	2.71 (0.94-7.85)	0.07	4.01 (1.5-10.73)	0.01	0.71 (0.36-1.40)	0.33	0.67 (0.38-1.20)	0.18
Platinum	0.83 (0.65-1.06)	0.13	0.96 (0.77-1.19)	0.68	0.77 (0.57-1.06)	0.11	0.78 (0.59-1.03)	0.08	1.86 (0.81-4.26)	0.14	1.66 (0.92-2.99)	0.09	0.65 (0.26-1.60)	0.35	0.57 (0.25-1.29)	0.18	0.58 (0.32-1.08)	0.08	1.14 (0.65-1.99)	0.66
Immunotherapy	1.18 (0.80-1.76)	0.40	1.20 (0.83-1.73)	0.33	1.05 (0.63-1.75)	0.86	1.03 (0.65-1.65)	0.90	1.78 (0.54-5.86)	0.34	2.93 (0.89-9.64)	0.08	None	None	1.49 (0.71-3.15)	0.30	1.31 (0.63-2.73)	0.47		
Other	0.93 (0.66-1.32)	0.70	0.82 (0.60-1.13)	0.22	0.97 (0.64-1.46)	0.88	0.75 (0.51-1.09)	0.12	1.62 (0.63-4.20)	0.32	1.51 (0.46-4.90)	0.50	0.55 (0.07-4.21)	0.57	0.50 (0.11-2.23)	0.37	0.51 (0.18-1.41)	0.19	0.93 (0.40-2.13)	0.86

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BTC, biliary tract cancer; CCA-HCC, mixed cholangiocarcinoma and hepatocellular carcinoma; CKD, chronic kidney disease; CVD, cardiovascular disease; DCCA, distal cholangiocarcinoma; HCCA, hilar cholangiocarcinoma; IHCCA, intrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma.

**Supplementary Table 3. Factors predicting PFS and OS of patients who received one or more concurrent medication by BTC subtype (multivariate)**

Characteristic	BTC (N=509)		IHCCA (N=295)		HCCA (N=76)		GBCA (N=96)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Progression-free Survival</b>								
Age	1.01 (1.00-1.02)	0.05	1.01 (1.00-1.02)	0.16	1.06 (1.02-1.10)	0.0041	1.00 (0.98-1.03)	0.86
Gender (F)	0.87 (0.70-1.09)	0.23	0.75 (0.56-1.00)	0.05	0.74 (0.34-1.63)	0.45	1.07 (0.62-1.84)	0.80
≥1 Concurrent Med	0.97 (0.76-1.25)	0.82	1.03 (0.76-1.40)	0.86	0.87 (0.29-2.55)	0.79	0.86 (0.43-1.71)	0.67
Stage at First-Line Systemic Therapy Start								
Locally Advanced	0.46 (0.34-0.63)	<.0001	0.58 (0.38-0.87)	0.01	0.17 (0.07-0.43)	0.0002	0.38 (0.17-0.85)	0.02
Metastatic	Reference		Reference		Reference		Reference	
Recurrent	0.98 (0.73-1.30)	0.86	0.88 (0.61-1.28)	0.52	0.68 (0.18-2.52)	0.56	1.14 (0.60-2.16)	0.69
Comorbidities								
CVD	0.84 (0.66-1.07)	0.17	0.80 (0.59-1.09)	0.15	1.68 (0.70-4.04)	0.25	0.56 (0.30-1.07)	0.08
Diabetes	1.18 (0.90-1.54)	0.23	0.90 (0.63-1.29)	0.57	2.32 (0.87-6.20)	0.09	2.22 (1.18-4.17)	0.01
HLD	1.15 (0.86-1.52)	0.34	1.22 (0.85-1.75)	0.29	0.73 (0.28-1.92)	0.52	1.25 (0.64-2.47)	0.52
CKD	0.76 (0.53-1.08)	0.12	0.76 (0.48-1.21)	0.25	0.11 (0.02-0.67)	0.02	1.67 (0.79-3.50)	0.18
Hypertension	0.87 (0.67-1.12)	0.28	0.84 (0.60-1.17)	0.29	0.60 (0.23-1.58)	0.30	1.07 (0.58-1.98)	0.82
Type of Cancer								
IHCCA	Reference		<i>Not applicable</i>		<i>Not applicable</i>		<i>Not applicable</i>	
HCCA	0.77 (0.54-1.10)	0.14						
DCCA	1.67 (1.03-2.69)	0.04						
GBCA	1.02 (0.77-1.35)	0.91						
CCA-HCC	0.86 (0.27-2.73)	0.80						
<b>Overall Survival</b>								
Age	1.01 (1.00-1.02)	<.0001	1.02 (1.01-1.04)	0.0002	1.02 (0.99-1.04)	0.20	1.00 (0.98-1.02)	0.99
Gender (F)	0.88 (0.73-1.06)	0.18	0.78 (0.61-1.00)	0.05	0.68 (0.40-1.17)	0.16	1.09 (0.68-1.73)	0.73
≥1 Concurrent Med	1.04 (0.83-1.30)	0.76	1.05 (0.79-1.39)	0.74	0.76 (0.39-1.47)	0.41	1.20 (0.66-2.16)	0.56
Stage at First-Line Systemic Therapy Start								
Locally Advanced	0.52 (0.41-0.67)	<.0001	0.56 (0.40-0.79)	0.001	0.29 (0.16-0.54)	<.0001	0.58 (0.32-1.06)	0.08
Metastatic	Reference		Reference		Reference		Reference	
Recurrent	0.78 (0.59-1.01)	0.06	0.68 (0.48-0.96)	0.03	0.62 (0.21-1.81)	0.38	0.85 (0.47-1.55)	0.59
Comorbidities								
CVD	0.99 (0.80-1.22)	0.90	0.89 (0.67-1.17)	0.40	1.35 (0.72-2.52)	0.35	1.09 (0.67-1.79)	0.72
Diabetes	0.95 (0.74-1.21)	0.67	1.12 (0.82-1.54)	0.47	0.70 (0.33-1.50)	0.36	0.90 (0.52-1.57)	0.72
HLD	1.29 (1.02-1.65)	0.04	1.28 (0.94-1.75)	0.12	1.00 (0.50-1.98)	0.99	1.74 (0.95-3.20)	0.07
CKD	0.73 (0.54-0.98)	0.04	0.72 (0.48-1.07)	0.10	0.59 (0.25-1.42)	0.24	1.21 (0.66-2.22)	0.53
Hypertension	0.94 (0.75-1.18)	0.57	0.69 (0.51-0.94)	0.02	1.42 (0.74-2.71)	0.29	0.99 (0.58-1.70)	0.97
Type of Cancer								
IHCCA	Reference		<i>Not applicable</i>		<i>Not applicable</i>		<i>Not applicable</i>	
HCCA	0.92 (0.69-1.24)	0.59						
DCCA	1.51 (0.98-2.35)	0.06						
GBCA	0.94 (0.73-1.21)	0.64						
CCA-HCC	0.90 (0.44-1.83)	0.77						

*ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BTC, biliary tract cancer; CCA-HCC, mixed cholangiocarcinoma and hepatocellular carcinoma; CKD, chronic kidney disease; CVD, cardiovascular disease; DCCA, distal cholangiocarcinoma; HCCA, hilar cholangiocarcinoma; IHCCA, intrahepatic cholangiocarcinoma; GBCA, gallbladder carcinoma.*