Peer Review File

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Reviewer Comments

1. exclusion of AoV cancer is not reasonable. Authors already commented that BTC contain AoV cancer in Introduction session--> please change Title or Introduction.

Response: Thank you for your suggestion. We have reviewed some articles and found that our introduction is inappropriate. There are many articles aimed to study biliary tract cancers (BTCs) and these articles did not include ampulla of Vater cancer. [1-6] So, we would like to learn the classification in their introduction. We have modified our text as advised (see page 4, line 64-65).

References

1. Simone V, Brunetti O, Lupo L, Testini M, Maiorano E, Simone M, Longo V, Rolfo C, Peeters M, Scarpa A et al: Targeting Angiogenesis in Biliary Tract Cancers: An Open Option. Int J Mol Sci 2017, 18(2).

2. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX: New Horizons for Precision Medicine in Biliary Tract Cancers. Cancer Discov 2017, 7(9):943-962.

3. Blair AB, Murphy A: Immunotherapy as a treatment for biliary tract cancers: A review of approaches with an eye to the future. Curr Probl Cancer 2018, 42(1):49-58.

4. Feng K, Liu Y, Guo Y, Qiu J, Wu Z, Dai H, Yang Q, Wang Y, Han W: Phase I study of chimeric antigen receptor modified T cells in treating HER2-positive advanced biliary tract cancers and pancreatic cancers. Protein Cell 2018, 9(10):838-847.

5. Kaavya J, Mahalaxmi I, Devi SM, Santhy KS, Balachandar V: Targeting phosphoinositide-3-kinase pathway in biliary tract cancers: A remedial route? J Cell Physiol 2019, 234(6):8259-8273.

6. Tella SH, Kommalapati A, Borad MJ, Mahipal A: Second-line therapies in advanced biliary tract cancers. The Lancet Oncology 2020, 21(1): e29-e41.

2. Authors are dealing with only patients with resected BTC. Please change title.

Response: We are grateful for this suggestion. The patients included in the study all

underwent surgery. We have changed the title to "Controlling nutritional status score as a prognostic marker to predict overall survival in **resected** biliary tract cancers" as advised (see page 1, line 2).

3. About 40% patients could not enrolled due to missing data. Selection bias is highly suspected.

Response: Thank you for putting forward the question. We have carefully reviewed the data. There were no cholesterol values for the most of excluded cases because these patients did not have blood lipid examination in the process of diagnosis and treatment, which may generate potential selection bias. To further explain the possible selection bias, we have analyzed the basic characteristics of the included and excluded cases. The results showed no significant differences as below. However, selection bias is an inherent disadvantage of retrospective analysis. More cases from multi-center were needed to verify our results in the future.

Table. Basic clinicopathological characteristics of included and excluded cohort

Characteristic	Total (n=593)	Included Cohort (n=371)	Excluded Cohort (n=222)	P value
Sex				0.676
Male	271	172	99	
Female	322	199	123	
Age, y				0.288
< 65	363	221	142	
≥65	230	150	80	
Jaundice				0.250
No	265	157	108	
Yes	327	213	114	
Surgical situation				0.211
Radical and R0 resection	340	220	120	
The others	253	151	102	
TNM stage (AJCC7)				0.774
0-I	188	116	72	
II	175	115	60	
III	165	101	64	
IV	65	39	26	
T stage (AJCC7)				0.096
0-I	153	86	67	

II	54	106	54	
III	85	136	85	
IV	16	43	16	
N stage				0.053
0	374	223	151	
1&2	219	148	71	
M stage				0.198
0	578	364	214	
1	15	7	8	

4. No probability for Individual bile duct cancers to impact survival of the patients as shown in periampullary cancer ? Please check it.

Response: Thank you for your suggestion. Our description about carcinoma of ampulla is unprecise. Since we have changed the introduction, we have deleted this description.

5. Patients without resection need to be excluded for avoiding heterogeneity of the patients group.

Response: Thank you for raising this issue. The patients included in the study all underwent surgery as our inclusion criteria said. However, some had curative resection and others had non-curative resection. The subgroups for the different surgical methods were tested, and the result showed that our risk stratification had a satisfactory prognostic classification.

6. "There were also 16 stage N1 cases with either a clear or vague preoperative diagnosis, in which about half (seven cases) obtained a curative resection." I cannot get it.

Response: We are sorry we didn't make it clear. We had wanted to explain why the stage IV patients had undergone the surgery. We have changed the description to better explain this (see page 9, line 168-170).

7. How about correlation perineural invasion, lymphovascular invasion , lymph node metastasis, individual diagnosis and tumor size with CONUT?

Response: We appreciate this suggestion. We have carefully reviewed the data and investigated the correlation between these characteristics and COUNT. The results

showed that the CONUT score was not associated with perineural invasion, lymphovascular invasion, lymph node metastasis, individual diagnosis and tumor size. These results have been added to **Table 1.**

Table 1 Basic clinicopathological characteristics by CONUT score group

	Total	The COUNT score		P value
	(n=371)	≤1 (n=201)	≥2 (n=170)	
Age				0.630
< 65	221	122	99	
≥65	150	79	71	
Sex				0.705
Male	199	106	93	
Female	172	95	77	
Individual diagnosis				0.408
GC	96	56	40	
ICC	69	33	36	
ECC	206	112	94	
DM				0.635
Absent	290	159	131	
Present	81	42	39	
Hyper				0.152
Absent	237	135	102	
Present	134	66	68	
Jaundice				0.077
Absent	158	94	64	
Present	213	107	106	
CA19-9 (U/ml)				0.369
＜40	100	58	42	
≥40	271	143	128	
Differ				**0.011***
Well and moderate	233	138	95	
Poor	138	63	75	
Size (cm)				0.412
≤2	181	102	79	
＞2	190	99	91	
Lymphovascular invasion				0.270
Negative	223	126	97	
Positive	148	75	73	
Perineural invasion				0.277
Negative	285	150	135	
Positive	86	51	35	
Lymph node metastasis				0.617
Negative	342	184	158	

Positive	29	17	12	
TNM stage (AJCC7)				0.247
0-I	117	59	58	
II	115	70	45	
III	107	58	49	
IV	**32**	14	18	
Surgical method				0.224
Radical and R0 resection	222	126	96	
the others	149	75	74	
Complications (Clavien-Dindo≥II)				0.927
Absent	154	83	71	
Present	217	118	99	
Hospital stays (day)				**0.046***
Median (IQR)	21 (16-29)	20 (15-28)	22 (16-32)	

8. CA 19-9 is a value after biliary decompression? Please provide the adjusted CA 19-9 (value adjusted to serum bilirubin level).

Response: We are grateful for your suggestion. We have carefully reviewed the data and found that CA 19-9 is not a value after biliary decompression. We have reviewed the relevant articles and some revised adjust the value as CA19-9/ bilirubin when the bilirubin > 2 mg/dl, which means jaundice. In our article, we have already analyzed the impact of jaundice on the overall survival. And in the multivariate analysis of the whole cohort (shown in the table below), both jaundice and CA19-9 were included. The result showed that CA19-9 was an independent prognostic index. In addition, our nomogram had a good discrimination and calibration power. So, we believe the unadjusted CA19-9 value could represent the total effects of jaundice and adjusted CA19-9 value on prognosis.

Table. Univariate and multivariate cox hazards analysis between clinicopathological features and OS in the whole cohort.

	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	P value	HR (95%CI)	P value
Age				
⩾65 vs. < 65	1.136 (0.878-1.469)	0.332		
Sex				
Female vs. Male	1.044 (0.809-1.346)	0.741		
DM				

Present vs. Absent	1.063 (0.783-1.443)	0.696		
Hyper				
Present vs. Absent	0.971 (0.745-1.265)	0.827		
Jaundice				
Present vs. Absent	**1.328 (1.022-1.725)**	**0.033***	0.969 (0.720-1.304)	0.833
CA19-9 (U/ml)				
⩾40 vs. < 40	**2.229 (1.597-3.113)**	**<0.001***	**1.865 (1.284-2.709)**	**0.001***
COUNT				
⩾2 vs. ⩽1	**1.417 (1.099-1.826)**	**0.007***	**1.371 (1.061-1.772)**	**0.016***
Surgical method				
The others vs. Radical and R0 resection	**2.855 (2.205-3.697)**	**<0.001***	**2.579 (1.964-3.386)**	**<0.001***
TNM stage (AJCC7)		**<0.001***		**<0.001***
0-I	**Reference**		**Reference**	
II	**1.558 (1.106-2.196)**	**0.011***	**1.919 (1.348-2.730)**	**<0.001***
III-IV	**2.308 (1.673-3.184)**	**<0.001***	**2.215 (1.600-3.067)**	**<0.001***

9. Developing nomogram and risk stratifications are good trial, but external validation should be done by extra data set. This approach is one of the circular reasoning because potential variables for nomogram were extracted from whole data analysis.

Response: Thank you for your suggestion. Indeed, we have analyzed the potential variables for nomogram from development cohort and the whole cohort. We showed the results of the whole data in our article because we care more about the prognostic value of COUNT in the whole cohort. However, this approach is one of the circular analysis as revised. We have changed the results of univariate and multivariate analysis as shown in **Table 2**.

Table 2 Univariate and multivariate cox hazards analysis between clinicopathological features and OS in the development cohort.

	Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	P value	HR (95%CI)	P value
Age				
⩾65 vs. < 65	1.060 (0.776-1.446)	0.716		
Sex				
Female vs. Male	1.012 (0.741-1.381)	0.943		
DM				
Present vs. Absent	1.264 (0.884-1.809)	0.199		
Hyper				
Present vs. Absent	0.824 (0.592-1.147)	0.251		
Jaundice				

Present vs. Absent	1.273 (0.929-1.744)	0.133		
CA19-9 (U/ml)				
⩾40 vs. < 40	**2.368 (1.591-3.524)**	**＜0.001***	**2.078 (1.385-3.119)**	**＜0.001***
COUNT				
⩾2 vs. ⩽1	**1.431 (1.050-1.949)**	**0.023**	**1.478 (1.078-2.025)**	**0.015***
Surgical method				
The others vs. Radical and R0 resection	**2.549 (1.867-3.480)**	**＜0.001***	**2.282 (1.645-3.165)**	**＜0.001***
TNM stage (AJCC7)		**＜0.001***		**＜0.001***
0-I	**Reference**		**Reference**	
II	1.488 (0.985-2.249)	＜0.059	**1.993 (1.299-3.057)**	**0.002***
III-IV	**2.246(1.535-3.287)**	**＜0.001***	**2.418 (1.648-3.547)**	**＜0.001***