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CLDN18.2 expression is associated with clinicopathological features and prognosis of Chinese patients with digestive system cancers: a retrospective analysis

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Introduction

Claudin18.2 (CLDN18.2) is a promising therapeutic target in solid tumors. Understanding its expression profile and characteristics will be important to instruct clinical trials and clinical practice. This study investigated the prevalence of CLDN18.2 expression in Chinese patients with digestive system cancers and its correlation with clinicopathological features and prognosis.

Methods

- We retrospectively collected formalin-fixed paraffin-embedded tissue from patients with digestive system cancers who were screened for CT041-CG4006 (NCT03874897) and CT041-ST-01 (NCT04581473) trials between June 2019 to April 2021.
- Corresponding clinical and survival data were obtained from medical records. CLDN18.2 expression was detected by immunohisto-chemistry (clone 14F8; prediluted mouse monoclonal antibody; CARsgen). CLDN18.2 positivity was defined as expression of CLDN18.2 in any percentage of tumor cells with intensity ≥ 1+ (**Fig 1**).
- Univariable logistic regression analysis or Wilcoxon rank sum test was used to explore the factors associated with CLDN18.2 expression. P values are reported for the exploratory purpose without adjustment for multiplicity. OS is analyzed using Kaplan-Meier method. Log-rank test is used to compare the survival curve.

Results

A total of 875 cases with GI cancers were analyzed, including 536 gastric cancer (GC), 165 pancreatic cancer (PC), 142 colorectal cancer (CRC), and 32 biliary tract carcinoma (BTC).

- CLDN18.2 expression was observed in
  - 73.1% of GC patients.
  - 61.8% of PC patients.
  - 10.6% of CRC patients.
  - 65.6% of BTC patients.
- In patients with GC (**Table 1**):
  - CLDN18.2-positive expression was associated with younger age, female sex, greater presentation in the stomach, Lauren diffuse type, and higher incidence of uterine adnexa metastasis.
  - Moreover, a lower positive rate of programmed cell death ligand 1 (PD-L1) expression was found in the tumors of patients with CLDN18.2-positive GC.
  - The median OS of patients with CLDN18.2-negative GC was significantly longer than that of patients with CLDN18.2-positive GC (1112 vs. 633 days, *P*=0.017) (**Fig 2**).
- In patients with PC (**Table 2**):
  - There was no significant association between CLDN18.2 positivity and clinicopathological characteristics.
  - No significant difference in OS was observed between patients with CLDN18.2-positive PC and those with CLDN18.2-negative PC (*P*=0.252) (**Fig 3**).

Table 1. CLDN18.2 expression and characteristics in patients with GC

Characteristics	Total N=536	CLDN18.2 positive N=392	CLDN18.2 negative N=144	Univariate analysis *P*
Age, median	54.0	52.0	59.0	<0.001
Sex, n (%)				
Male	336 (62.7)	230 (58.7)	106 (73.6)	ref.
Female	198 (36.9)	161 (41.1)	37 (25.7)	0.001
Unknown	2 (0.4)	1 (0.3)	1 (0.7)	-
Primary tumor location, n (%)				
EGJ	57 (10.6)	33 (8.4)	24 (16.7)	0.007
Stomach	479 (89.4)	359 (91.6)	120 (83.3)	ref.
Tumor stage, n (%)				
IV	353 (65.9)	262 (66.8)	91 (63.2)	0.431
Non-IV	183 (34.1)	130 (33.2)	53 (36.8)	ref.
Metastatic sites, n (%)				
Peritoneum	201 (37.5)	154 (39.3)	47 (32.6)	0.160
Liver	142 (26.5)	92 (23.5)	50 (34.7)	0.009
Uterine adnexa	87 (16.2)	78 (19.9)	9 (6.2)	<0.001
Bone	59 (11.0)	46 (11.7)	13 (9.0)	0.376
Lung	51 (9.5)	34 (8.7)	17 (11.8)	0.275
Lauren type, n (%)				
Diffuse	189 (35.3)	154 (39.3)	35 (24.3)	ref.
Mixed	100 (18.7)	77 (19.6)	23 (16.0)	0.366
Intestinal	148 (27.6)	96 (24.5)	52 (36.1)	0.001
Unknown	99 (18.5)	65 (16.6)	34 (23.6)	-
HER2 positive, n (%)				
No	398 (74.3)	300 (76.5)	98 (68.1)	ref.
Yes	51 (9.5)	29 (7.4)	22 (15.3)	0.006
Unknown	87 (16.2)	63 (16.1)	24 (16.7)	-
PD-L1 expression, n (%)				
CPS<1	143 (26.7)	114 (29.1)	29 (20.1)	ref.
CPS≥1	193 (36.0)	128 (32.7)	65 (45.1)	0.007
CPS<5	224 (41.8)	169 (43.1)	55 (38.2)	ref.
CPS≥5	112 (20.9)	73 (18.6)	39 (27.1)	0.049
Unknown	200 (37.3)	150 (38.3)	50 (34.7)	-
MMR, n (%)				
pMMR	460 (85.8)	344 (87.8)	116 (80.6)	ref.
dMMR	8 (1.5)	5 (1.3)	3 (2.1)	0.435
Unknown	68 (12.7)	43 (11.0)	25 (17.4)	-
TMB, n (%)				
<10 mutations/Mbp	97 (18.1)	73 (18.6)	24 (16.7)	ref.
≥10 mutations/Mbp	22 (4.1)	13 (3.3)	9 (6.2)	0.131
Unknown	417 (77.8)	306 (78.1)	111 (77.1)	-

Table 2. CLDN18.2 expression and characteristics of patients with PC

Characteristics	Total N=165	CLDN18.2 positive N=102	CLDN18.2 negative N=63	Univariate analysis *P*
Age, median	60.0	60.0	60.0	0.997
Sex, n (%)				
Male	106 (64.2)	39 (63.9)	67 (64.4)	ref.
Female	59 (35.8)	22 (36.1)	37 (35.6)	0.399
Unknown	0	0	0	-
Primary tumor location, n (%)				
Pancreatic body	59 (35.8)	40 (39.2)	19 (30.2)	-
Pancreatic head	41 (24.8)	19 (18.6)	22 (34.9)	-
Pancreatic tail	21 (12.7)	12 (11.8)	9 (14.3)	-
Other parts of the pancreas	9 (5.5)	9 (8.8)	0	-
Unknown	35 (21.2)	22 (21.6)	13 (20.6)	-
Tumor stage, n (%)				
IV	31 (18.8)	20 (19.6)	11 (17.5)	ref.
Non-IV	109 (66.1)	64 (62.7)	45 (71.4)	0.561
Unknown	25 (15.1)	18 (17.6)	7 (11.1)	-
Metastatic sites, n (%)				
Liver	97 (58.8)	56 (54.9)	41 (65.1)	0.198
Peritoneum	38 (23.0)	28 (27.5)	10 (15.9)	0.248
Lungs	24 (14.5)	19 (18.6)	5 (7.9)	0.066
KRAS mutation, n (%)				
Negative	2 (1.2)	1 (1.0)	1 (1.6)	ref.
Positive	37 (22.4)	20 (19.6)	17 (27.0)	0.911
Unknown	126 (76.4)	81 (79.4)	45 (71.4)	-
PD-L1 expression				
CPS<1	10 (6.1)	6 (5.9)	4 (6.3)	ref.
CPS≥1	20 (12.1)	10 (9.8)	10 (15.9)	0.606
CPS<5	22 (13.4)	13 (12.7)	9 (14.3)	ref.
CPS≥5	8 (4.8)	3 (2.9)	5 (7.9)	0.301
Unknown	135 (81.8)	86 (84.3)	49 (77.8)	-
MMR				
pMMR	49 (29.7)	28 (27.5)	21 (33.3)	-
dMMR	1 (0.6)	1 (1.0)	0	-
Unknown	137 (83.1)	85 (83.3)	52 (82.5)	-
TMB, n (%)				
<10 mutations/Mbp	28 (17.0)	17 (16.7)	11 (17.5)	-
≥10 mutations/Mbp	2 (1.2)	0	2 (3.2)	-
Unknown	135 (81.8)	85 (83.3)	50 (79.4)	-

CLDN18.2: claudin 18.2; CPS: combined positive score; dMMR: deficient mismatch repair; EGJ: esophagogastric junction; HER2: human epidermal growth factor receptor 2; KRAS: KRAS proto-oncogene, GTPase; MMR: mismatch repair; PD-L1: programmed cell death ligand 1; pMMR: proficient mismatch repair; TMB: tumor mutational burden.

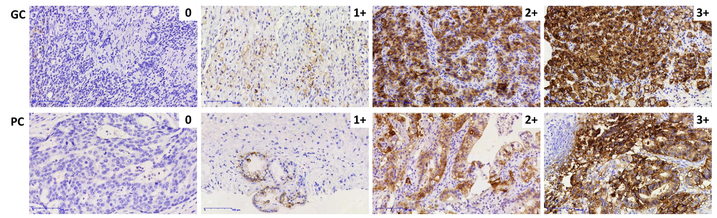

Figure 1. Expression level of CLDN18.2 by immunohistochemistry.

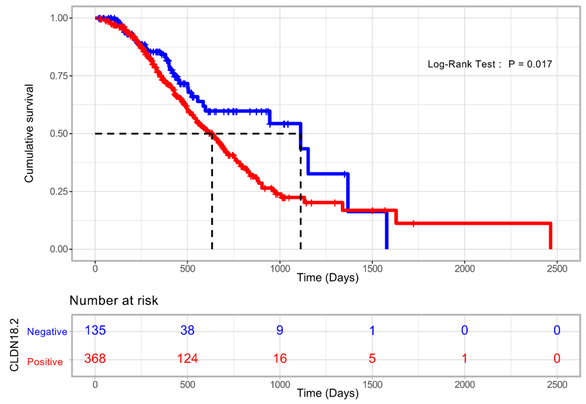

Figure 2. Log-rank analysis of CLDN18.2 expression and overall survival in GC.

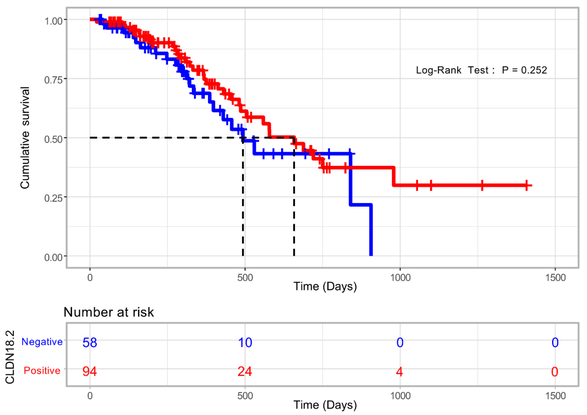

Figure 3. Log-rank analysis of CLDN18.2 expression and overall survival in PC.

Conclusion

We observed a high prevalence of CLDN18.2 expression in Chinese patients with digestive system cancers. Patients with CLDN18.2-positive GC showed different clinicopathological characteristics, metastatic patterns, and a trend for poorer OS compared to CLDN18.2 negative GC. More comprehensive characteristics of CLDN18.2-positive GC are in progress and will be reported in the future.

Acknowledgements

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