# RESEARCH

# Clinicopathological features and prognostic significance of TAF1L in gastric cancer

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## Abstract

**Background** TAF1L may play an important role in the occurrence and development of gastric cancer (GC), but the correlation between the expression of TAF1L and the clinicopathological factors and prognosis of GC is still unclear.

**Methods** A total of 1053 GC patients in Zhejiang Cancer Hospital between January 1st, 2018 to December 31th, 2019 were screened. Finally, 120 patients met the inclusion criteria. TAF1L expression was detected by immunohistochemistry, and the correlations of TAF1L in clinicopathological characteristics and prognosis were analyzed. TCGA GC dataset was used to perform further bioinformatics analysis.

**Results** In this study, TAF1L expression was evaluated in 120 clinical samples of GC. TAF1L expression was higher in tumor tissues and was associated with tumor differentiation (p = 0.046), signet-ring cells (p = 0.043), dMMR status (p = 0.011), lympho-vascular invasion (p = 0.038), and neural invasion (p = 0.005) in our cohort. Cases with high expression of TAF1L presented worse mean OS than those with low expression (40.3 months vs. 51.8 months, p = 0.019), and the difference was also significant in HER2-positive cases (20.9 months vs. 51.2 months, p = 0.007) as well as pMMR cases (38.8 months vs. 51.6 months, p = 0.006). Multivariate Cox regression analysis showed that TAF1L (HR = 2.044, 95%CI = 1.007–4.147, p = 0.048) and HER2 status (HR = 2.383, 95%CI = 1.087–5.222, p = 0.030) were independent prognosis factors of these patients. In subgroup analysis, TAF1L was the independent prognostic risk factor in HER2-positive patients (HR = 6.736, 95%CI = 1.373–33.032, p = 0.019). and pMMR patients (HR = 2.291, 95%CI = 1.126–4.660, p = 0.022). Besides, HER2 status was the independent prognostic risk factor in TAF1L-H patients (HR = 4.832, 95%CI = 1.908–12.239, p = 0.001). TCGA dataset also indicated the higher expression of TAF1L in tumors than normal tissues (p < 0.001). High TAF1L expression is linked to worse survival in MSS (11.0 months vs. 35.0 months, p = 0.0046) groups, and is negatively associated with overall survival in HER2-positive cases (24.0 months vs. 57.0 months, p = 0.0039).

**Conclusion** TAF1L is closely related to the occurrence and development of GC. Our results suggested that TAF1L is a significant biomarker for predicting prognosis of GC and may play an important role in immunotherapy and targeted therapy.

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Keywords TAF1L, Gastric cancer, Clinicopathological features, Prognosis, Biomarker

#### Introduction

Gastric cancer (GC) is a common malignancy globally, and a serious threat to human health [1]. With the continuous improvement of diagnosis and treatment techniques, the comprehensive treatment level of gastric cancer has made some progress, but the overall efficacy is still less than satisfactory, and new therapeutic targets need to be further explored [2, 3].

TAF1 (TATA-box binding proteinassociated factor 1) which is also called TAF(II)250, is located on the X chromosome (Xq13.1), and encodes TATA box binding protein-associated factor 1 protein as a scaffold for TF II D which is involved in the transcription process of numerous genes in eukaryotic cells [4, 5]. As a homologue of TAF1, TAF1L (TATA-box binding protein associated factor 1 like) has been found that presents a similar function with histone acetyltransferase activity like TAF1 [6, 7], but it also varies in individual fields.

Previous studies had proved that TAF1/TAF1L played important roles in different kinds of tumor progression [8–10]. There were also several studies mentioned the potential role of TAF1/TAF1L in GC [8, 11, 12]. Until now, there was no study explored the relationship of TAF1L expression with clinicopathological features and prognosis of GC.

In this study, we evaluated the expression of TAF1L in clinical samples by immunohistochemistry and aims to investigate the clinical significance of TAF1L in GC and to explore a new potential biomarker for evaluating treatment and prognosis.

#### **Materials and methods**

#### **Patient inclusion**

In this study, we screened patients with inclusion and exclusion criteria. Therefore, 120 patients met the inclusion criteria, as well as 30 paired para-cancerous/ normal samples of the enrollment.

Inclusion criteria: (1) histologically confirmed gastric or oesophagogastric junction adenocarcinoma; (2) receive surgical treatment as initial treatment; (3) age 18–80 years; (4) Eastern Cooperative Oncology Group performance status (ECOG) 0–1 [13]; and (5) complete clinicopathologic data. Exclusion criteria: (1) with distant metastasis; (2) previous anti-tumor therapy such as chemotherapy and radiotherapy; (3) combined with other malignancies; and (4) missing data.

#### Immunohistochemistry

Immunohistochemistry (IHC) was carried out according to the manufacturer's instructions (Leica Bond III, Germany). Four-micrometer-thick tissue sections were incubated with the primary rabbit anti-TAF1L antibody (1:250; 55170-1-AP, Proteintech, USA) for 15 min followed by the incubation with the secondary antibody for 8 min, DAB color development for 10 min.

All IHC results were interpreted by two independent pathologists blinded to this study. In case of disagreement between the two pathologists, the result would be re-evaluated by a third one. The degrees of staining intensity were determined as: 0 (none), 1 (weak), 2 (moderate),3 (intense) and 4 (strongly intense). Percentages of positive cell were counted as 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%) and 4 (76-100%). The final staining score was calculated by multiplying the intensity of the positive signal by the percentage of positive cells, following the method of Remmele and Stegner (1987) [14]. A score of <4 was considered as "low expression" and a score  $\geq 4$  as "high expression", and the categories were used for statistical analysis. To ascertain the mismatch repair (MMR) status, postoperative immunohistochemical analysis was conducted on four key MMR proteins: MLH1 (using Dako's ES05 clone), MSH2 (with Dako's FE11 clone), MSH6 (employing Dako's EP49 clone), and PMS2 (via Dako's EP51 clone). Loss of any of the four MMR proteins was defined as MMR deficiency (dMMR).

#### Follow-up

For enrolled patients, follow-up was performed once per 3 months in first 2 years, once per 6 months in 3 to 5 years and once yearly thereafter. The follow-up methods mainly included telephonic follow-ups and regular outpatient reexaminations. Overall survival (OS) was defined as the time from the date of pathological diagnosis of GC to the date of death or the most recent follow-up. The cutoff date for OS was December 31, 2023.

#### **Bioinformatics analysis**

TCGA dataset (https://tcgadata.nci.nih.gov/tcga) was used to gain the RNA-sequencing expression (level 3) profiles and clinicopathological information for stomach adenocarcinoma (STAD) cases. The differences in survival between the groups were compared by Log-rank test. The predictive accuracy of TAF1L mRNA was compared by the timeROC (v 0.4) analysis. R software package ggstatsplot and pheatmap were used to display the two-gene correlation map and the multi-gene correlation respectively. Spearman's correlation analysis was used to describe the correlation between quantitative variable that without a normal distribution. The Genomics Analysis and Visualization Platform tool (http://r2.amc.nl) was used to preform KEGG (Kyoto Encyclopedia of Genes and Genomes) and GO (Gene Ontology) analyses.

#### Statistical analysis

SPSS 26.0 (IBM Corporation, Armonk, NY, USA) and R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses and p < 0.05 was indicated statistical significance. Student t-test or Chi-squared test was used to assess the between-group differences regarding to continuous or discrete variables, respectively. Survival analysis was performed by the Kaplan-Meier method with Logrank test. Univariate and multivariate analyses based on Cox hazard regression models were used to evaluate the prognostic factors, Hazard ratio (HR) and 95% confidence interval (CI). Cox proportional hazards regression model was used for univariate and multivariate analysis to identify the risk factors affecting the survival status of patients and estimated hazard ratio (HR) and 95% confidence interval (95% CI).

#### Results

#### **Baseline characteristics**

In this study, a total of 1053 GC patients in Zhejiang Cancer Hospital (Hangzhou, China) between January 1st, 2018 to December 31th, 2019 were screened, while 479 patients had distant metastasis, 261 patients had received preoperative chemotherapy, 96 patients concurrent with other primary tumors, 47 patients were either under 18 or over 80 years old, 29 patients had incomplete clinicopathologic data and 21 patients were loss to follow-up. Finally, 120 patients met the inclusion criteria. 83 (69.2%) were male and 37 (30.8%) were female, and the median age was 59 years (range 26–80). All the patients received surgical treatment as initial treatment and postoperative pathology showed 72 cases (60.0%) were poorly/undifferentiated adenocarcinoma. The number of stages I, II, III cases was 15 (12.5%), 33(27.5%), 72(60.0%), respectively. The details of patient characteristics were shown in Table 1.

# Clinicopathological features and immunohistochemical expression of TAF1L

TAF1L expression was evaluated by IHC in surgical specimens, and the results showed that TAF1L was higher expressed on the tumor tissues than para-cancerous/normal tissues. (Fig. 1a, expression of TAF1L in tumor tissue; Fig. 1b, expression of TAF1L in para-cancerous/normal tissue; Fig. 1c Representative image of TAF1L IHC staining by scoring). According to the results of IHC, there were 55 GC patients (45.8%) in the high-expression group (TAF1L-H group) while

65 GC patients (54.2%) in the low-expression group (TAF1L-L group).

TAF1L expressions were mainly correlated with tumor differentiation (p=0.046), signet-ring cells (p=0.043), dMMR status (p=0.011), lympho-vascular invasion (p=0.038) and neural invasion (p=0.005) as shown in Table 1.

#### Survival analysis

There was significant difference in OS between the TAF1L-H group and the TAF1L-L group (mean OS: 40.3 months vs. 51.8 months, p = 0.019; Fig. 2). Furthermore, we analyzed the survival differences in subgroups according to the pathological features. The results showed that the TAF1L-H cases presented worse survival in HER2-positive GC (mean OS: 20.9 months vs. 51.2 months, p=0.007, Fig. 3a) while no statistical difference in HER2-negative GC (mean OS: 43.6 months vs. 51.1 months, p = 0.168, Fig. 3b). As for mismatch repair (MMR) status, the survival of TAF1L-H group was significantly worse than that of TAF1L-L group in mismatch repair-proficient (pMMR) cases (mean OS: 38.8 months vs. 51.6 months, p=0.006, Fig. 3c) but not in mismatch repair-deficient (dMMR) cases (p=0.724, Fig. 3d). Besides, TAF1L-H cases showed worse OS both in stage I/II diseases and stage III diseases compared to TAF1L-L cases, although there were no statistical differences (p=0.075 and 0.119, respectively).

#### **Prognostic factors analysis**

Univariate Cox regression showed that the expressions of TAF1L, tumor size, N stage, HER2 status were statistically significant as the prognostic risk factors. Multivariate analysis showed that the expression of TAF1L (HR=2.044, 95%CI=1.007-4.147, p=0.048) and HER2 status (HR=2.383, 95%CI=1.087-5.222, p=0.030) were independent prognostic risk factors (Table 2).

Moreover, in HER2-positive cases (n=18), TAF1L was the independent prognostic risk factor (HR=6.736, 95%CI=1.373-33.032, p=0.019). In HER2-negative cases (n=102), however, TAF1L showed no significant relationship with the prognosis (HR=1.718, 95%CI=0.789-3.741, p=0.173). Besides, HER2 status was also the independent prognostic risk factor in TAF1L-H group (HR=4.832, 95%CI=1.908-12.239, p=0.001), but not in TAF1L-L group (HR=1.023, 95%CI=0.227-4.616, p=0.977). Due to the limited case number, we were unable to analyze the role of TAF1L in the prognosis of dMMR cases. In the pMMR cases, TAF1L was also the independent prognostic risk factor (HR=2.291, 95%CI=1.126-4.660, p=0.022).

### Table 1 Baseline characteristics of 120 GC patients

| Adexing<br>Median (marging)Interpret interpret in           | Variable                | <b>TAF1L-H Group (</b> <i>n</i> <b>=55)</b> | %     | <b>TAF1L-L Group (</b> <i>n</i> <b>= 65)</b> | %    | χ2-value | p-value |
|---|-------------------------|---|-------|--|------|----------|---------|
| <table-container>Meang 50(3431-30)(3431-30)(344)Ream 50(32-37)(344)(34)(34)Sa(32-32)(34)(34)(34)Sa(34)(34)(34)(34)Fande(34)(34)(34)(34)Fande(34)(34)(34)(34)Sa 50(34)(34)(34)(34)Sa 50(34)(34)(34)(34)Na 60(34)(34)(34)(34)Na 61(34)(34)(34)(34)Sa 50(34)(34)(34)(34)Na 61(34)(34)(34)(34)Sa 50(34)(34)(34)(34)Sa 50(34)(34)(34)(34)<td< td=""><td>Age (years)</td><td></td><td></td><td></td><td></td><td></td><td></td></td<></table-container>  | Age (years)             |   |       |  |      |          |         |
| <table-container>Mans205/42.13.35/4.21.3.35/4.21.3.35/4.21.3.35/4.21.3.35/4.21.3.3Bans202.2.3.2.3.2.32.3.2.3.2.3.32.3.2.3.2.33.3.2.3.33.3.2.3.3Social Application Problem Prob</table-container>  | Median (min - max)      | 61.0 (31.0-80.0)                            |       | 57.0 (26.0–79.0)                             |      |          |         |
| BMIUse the set of           | Mean±SD                 | 61.2±9.73                                   |       | 57.4±11.93                                   |      |          |         |
| Menér22±3.3329±2.43.3JendedJendedJendedJendedSame1425.52.4 and 3.4  | BMI                     |   |       |  |      |          |         |
| Series1.37.01.37.01.37.01.37.01.37.0Male1.42.5523.43.43.4Snokiny13.43.43.43.43.4Na3.40.04.03.43.43.4Na3.40.04.03.43.43.4Na3.40.01.43.51.43.43.4Na1.42.551.43.43.43.43.4Stansing3.43.43.43.43.43.43.4Stansing3.43.43.43.43.43.43.4Stansing3.43.43.43.43.43.43.43.4Stansing3.4 <td>Mean±SD</td> <td>22.2±3.23</td> <td></td> <td>22.9±2.87</td> <td></td> <td></td> <td></td>   | Mean±SD                 | 22.2±3.23                                   |       | 22.9±2.87                                    |      |          |         |
| Male14244767681Fondia futore14253310713Sholing history125421.51313Na425.5421.5131313Timofisikory25.51421.514131313State (M)25.51421.514131313Timofisikory125.51423.514131313State (M)2423.423.423.413131313131313131313131415141414151414151414151414151415141514141514151415<  | Sex                     |   |       |  |      | 1.377    | 0.165   |
| Panale1425523254 $-1070$ $-1070$ $-1070$ Smoking biskory2666 $-1070$ $-1070$ Non267 $-1070$ $-1070$ $-1070$ Smoking biskory1255147 $-1070$ $-1070$ Non4255147 $-1070$ $-1070$ $-1070$ Non475147 $-1070$ $-1070$ Standard biskory17 $-1070$ $-1070$ $-1070$ $-1070$ Standard biskory11 $-1070$ $-1070$ $-1070$ $-1070$ $-1070$ Standard biskory111 $-1070$ $-1070$ $-1070$ $-1070$ $-1070$ Standard biskory111 $-1070$ $-10700$ $-10700$ $-10700$ $-10700$ $-10700$ $-10700$ $-10700$ $-10700$ $-107000$ $-107000$ $-1070000$ $-10700000000000000000000000000000000000$  | Male                    | 41  | 74.5  | 42   | 64.6 |          |         |
| Sending history <td>Female</td> <td>14</td> <td>25.5</td> <td>23</td> <td>35.4</td> <td></td> <td></td>   | Female                  | 14  | 25.5  | 23   | 35.4 |          |         |
| Yes2240021323No3360044677No346256013Timing history1425514215Yes1425514215No4125514215Tumor Size (m)12303001State (m)1300001State (m)1300001State (m)1300001State (m)110000State (m)110000State (m)111State (m)111State (m)111State (m)111State (m)111No/1182311No/1182311No/1182311Upper816416246Upper869.13423Upper869.13423State (m)1121Nord State (m)1331Upper869.134231Nord State (m)136930State (m)1111Nord State (m)1311Nord State (m)1111State (m)1111State  | Smoking history         |   |       |  |      | 0.767    | 0.381   |
| No<br>bits<br>bits<br>bits<br>bits3300.04467.7Drinkipistor0.013Yes1474.55178.5No4174.55178.5Tumor Size (m)0.091<br><5   | Yes                     | 22  | 40.0  | 21   | 32.3 |          |         |
| Dirking historyImage of the second seco          | No                      | 33  | 60.0  | 44   | 67.7 |          |         |
| Yea142551421514215142151415No142455123233923393   | Drinking history        |   |       |  |      | 0.255    | 0.613   |
| No47455783  | Yes                     | 14  | 25.5  | 14   | 21.5 | 0.200    | 0.010   |
| Nome is a set of the set of | No                      | 41  | 74.5  | 51   | 78.5 |          |         |
| Num See (N)         Constraint of the sec of                 | Tumor Size (cm)         |   | 7 1.5 |  | 70.5 | 2 303    | 0.001   |
| S3D3P3P4D40D4025P7P7B3B3B3B3B3B3P15tageIID3D2D30IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII   | ~5                      | 28  | 50.0  | 40   | 64.6 | 2.505    | 0.001   |
| 2 J1/21/21/21/21/20/000/11≤↑2 Q121813200> TQ3172200N/1183273147.7N/23376332.73147.7N/23376332.73147.7N/2337631116.9Midde916.41624.6Lower8869.13452.3Pootfy/undifferentated3869.13452.3Signetring cells34.970.043Vellmoderately173031.353.3Negative4785.54670.8Serur CEL (ng/mL)Normal4887.35990.8Serur CA199 (U/mL)Normal4887.34975.4   | ~5                      | 20  | 10.9  | +z<br>22                                     | 25 / |          |         |
| prison         isolation         isolation         isolation         isolation         isolation         isolation           >12         12         12         13         200            >172         43         78.2         52         80.0            pN-stage                 No/1         18   | ≥J<br>nT stage          | 27  | 49.1  | 23   | 55.4 | 0.060    | 0.401   |
| A12A13A3A3A00>T2A3R22S2B00pN-stageN/11832.73147.7.N/233734CarTumo locationUpper814.51116.9Middle91624.6Lower3869.138855Ordy/undifferentiated969.13432.3Well/moderated3869.13432.3Vell/moderated3869.134.4Ponty/undifferentiated3869.134.4Well/moderated3869.134.4Spatring cellsWell/moderated3869.1Spatring cellsNormal4887.359Normal48Normal41Normal41   | pr-stage                | 10  | 21.0  | 10   | 20.0 | 0.000    | 0.491   |
| PA-Stage     Image:   | ≤IZ<br>> T2             | 12  | 21.8  | 13   | 20.0 |          |         |
| prividge         2.762         0.07           N0/1         18         32.7         31         47.7           N2/3         37         67.3         34         52.3           Tumor location         -         1.612         0.447           Upper         8         1         6.9         0.44           Iddle         9         1.64         16         2.46         0.47           Upper         83         69.1         38         58.5         .         .           Ordflemtifitientiated         9         64.1         38         58.5         .         .           Pothylundifferentiated         86         69.1         34         37.0         .         .           Pothylundifferentiated         86         69.1         34         .         .         .           Pothylundifferentiated         86         69.1         34         .         .         .         .         .           Pothylundifferentiated         86         69.1         34         .         .         .         .         .         .         .         .         .         .         .         .         .         .         .   | > IZ                    | 43  | /8.2  | 52   | 80.0 | 2762     | 0.070   |
| NV/1     16     3.7     6.1     4.7.4     1.7       NV23     37     67.3     34     52.3     1.612     0.447       Upper     8     14.5     1     16.9     0.44       Middle     9     63.1     38     2.3     1.5       Differentiation     8     69.1     38     2.6     1.5       Portly/undifferentiated     38     69.1     34     52.3     1.6       Signet-ring construction     17     3.0     3.1     4.7     1.5       Signet-ring construction     17     3.0     3.1     4.7     1.5       Signet-ring construction     17     3.1     4.7     3.497     0.043       Signet-ring construction     17     3.5     4.6     7.8     7.3       Negative     47     8.5.5     4.6     7.8     7.3     0.73       Normal     47     8.5.5     4.6     7.8     7.7     0.73       Normal     48     7.3     59     9.8     7.4     7.7       Saft     12.7     6.7     2.11     1.7     1.7       Normal     47     2.5     2.2     3.8     1.7       Saft     12.7     16     2.6   | pN-stage                | 10  | 227   | 21   | 477  | 2.762    | 0.070   |
| NZ/33/33/33/43/43/43/4Tumor location11116/91/4160.4/7Middle916.41624.611Middle916.41624.611Lower3869.13835.534.70.46Differentiation163452.311Pootly/undifferentiated3869.131.447.71Signet-ring cells1730.93147.71Vegative1730.931.447.7136.9Negative4855.54629.211Serum CEA (ng/mL)12.716.990.8137.3Normal4887.35990.811Softard Af 199 (U/mL)12.716.090.811Normal4887.34975.411Normal4887.34953.6111Normal1425.522.033.8111Normal41.025.523.033.8111MMR atus1415.516.415.5111MMR atus81.115.555.584.6111Morda Africo15.555.584.61111MMR atus16.115.555.584.6 <td>NU/ I</td> <td>18</td> <td>32.7</td> <td>31</td> <td>47.7</td> <td></td> <td></td>   | NU/ I                   | 18  | 32.7  | 31   | 47.7 |          |         |
| Tumo focation1.6120.44/Upper81.541.601.691.7Middle91.641.624.61.7Lower3869.13858.51.7Differentiation82.3.7Poorly/undifferentiated383.093.14.7.7Signet-ring cells885467.08.7Negative478.55467.08.7.7Sormal 488.735990.8.7.7.7Normal488.735990.8.7.7.7Normal488.734975.4.7.7.7Normal1.611.71.6.7.7.7.7Normal488.734975.4.7.7.7.7Normal1.61.71.6.7 <td>N2/3</td> <td>37</td> <td>67.3</td> <td>34</td> <td>52.3</td> <td></td> <td>o 4 47</td>   | N2/3                    | 37  | 67.3  | 34   | 52.3 |          | o 4 47  |
| Upper       8       14.5       11       16.9         Middle       9       16.4       16       24.6         Midder       38       16.1       16       24.6         Differentiation       52.3       52.3       0.046         Poorly/undifferentiated       17       30       31       27.3       0.046         Signet-ring cells       17       38       61.1       34       52.3       13       13         Negative       47       85.5       46       70.8       13 <td>lumor location</td> <td>_</td> <td></td> <td></td> <td></td> <td>1.612</td> <td>0.447</td>   | lumor location          | _   |       |  |      | 1.612    | 0.447   |
| Middle       9       164       16       246         Lower       38       69.1       38       58.5         Doorly/undifferentiated       38       69.1       34       52.3         Poorly/undifferentiated       38       69.1       34       52.3         Well/moderately       17       30.9       31       47.7         Signet-ring cells       -       3.689       0.043         Negative       47       85.5       46       70.8       0.043         Negative       87       6.6       70.8       .       .         Serum CEA (ng/mL)       -       0.377       0.373       0.373         Normal       48       7.3       59       9.8       .       .         Softme CA199 (U/mL)       -       -       0.377       0.373         Normal       48       87.3       69       9.2       .       .         Softme CA125 (U/mL)       -       12.7       16       24.6       .       .         Normal       13       12.7       16       24.6       .       .       .         Normal       14.1       15.       .       .       .       .<   | Upper                   | 8   | 14.5  | 11   | 16.9 |          |         |
| Lower3869.13858.5Differentiated5.4973.49   | Middle                  | 9   | 16.4  | 16   | 24.6 |          |         |
| Differentiation     3497     0.046       Poorly/undifferentiated     38     69.1     34     52.3  | Lower                   | 38  | 69.1  | 38   | 58.5 |          |         |
| Poorly/undifferentiated3869.13452.3Well/moderately173869.147.736890.043Signet-ring cells85.54670.870.870.8Positive814.51920.270.73Serum CEA (ng/mL)11990.870.73Normal4887.35990.870.73Soft CA199 (U/mL)622.770.730.073Normal4887.34975.470.73Normal4887.34975.470.73Normal4887.34975.470.73Normal4887.34975.470.73Normal4887.34975.470.73Normal12.71624.670.7471.74Normal4175.42081.7471.74Normal4175.56463.271.74Normal4185.56485.571.74MMR8214.51015.471.74Normal8314.51015.471.74Normal8314.51015.471.74Normal8314.510.7471.7471.74Normal8415.510.7471.7471.74Normal85.55584.671.7471.74Normal14.510.7415.7471.7471.74 <t< td=""><td>Differentiation</td><td></td><td></td><td></td><td></td><td>3.497</td><td>0.046</td></t<>   | Differentiation         |   |       |  |      | 3.497    | 0.046   |
| Well/moderately       17       30.9       31       47.7         Signet-ring cells       .   | Poorly/undifferentiated | 38  | 69.1  | 34   | 52.3 |          |         |
| Signet-ring cells       3689       0.043         Negative       47       85.5       46       0.28         Positive       0.29       20       20         Serum CEA (ng/mL)       0.373       0.373         Normal       48       57.3       90.8         >5       7       12.70       6       9.2         Serum CA199 (U/mL)       7       2.718       0.071         Normal       48       87.30       49       7.4       0.771         Normal       48       87.30       49       7.4       0.772         Serum CA199 (U/mL)       12.70       16       2.46       2.7       0.071         Normal       48       87.30       49       66.2       2.7       2.7         Sormal Algo Algo Algo Algo Algo Algo Algo Alg  | Well/moderately         | 17  | 30.9  | 31   | 47.7 |          |         |
| Negative       47       85.5       46       70.8         Positive       8       14.50       19.00       29.2  | Signet-ring cells       |   |       |  |      | 3.689    | 0.043   |
| Positive       8       14.5       19       29.2         Serum CEA (ng/mL)   | Negative                | 47  | 85.5  | 46   | 70.8 |          |         |
| Serum CEA (ng/mL)       0.377       0.373         Normal       48       87.3       59       0.08  | Positive                | 8   | 14.5  | 19   | 29.2 |          |         |
| Normal       48       87.3       59       90.8         >5       7       12.7       6       9.2         Serum CA199 (U/mL)        2.718       0.077         Normal       48       87.3       49       75.4          >37       7       12.7       16       24.6           Serum CA125 (U/mL)        12.7       16       66.2           Normal       41       74.5       43       66.2         0.999       0.212         Normal       14       25.5       22       33.8           0.115         pMR status        14.2       25.5       64       98.5       0.011           0.151            0.151   | Serum CEA (ng/mL)       |   |       |  |      | 0.377    | 0.373   |
| >5       7       12.7       6       9.2         Serum CA199 (U/mL)       2.718       0.077         Normal       48       87.3       49       75.4         >37       7       12.7       16       24.6       12         Serum CA125 (U/mL)       12.7       16       24.6       12         Normal       41       74.5       43       66.2       12         >35       14       25.5       22       3.8       12       0.11         pMR status       1       45.5       64       98.5       0.01       11         pMMR       47       85.5       64       98.5       15       15       15         pMMR       47       85.5       64       98.5       15       15       15         pMMR       47       85.5       64       98.5       15       15       15       15         Postive       8       13.5       15.5       15       15       15       15       15         Vestive       13       23.6       10       15       15       15       15       15       15       15       15       15       15       15 <t< td=""><td>Normal</td><td>48</td><td>87.3</td><td>59</td><td>90.8</td><td></td><td></td></t<>  | Normal                  | 48  | 87.3  | 59   | 90.8 |          |         |
| Serum CA199 (U/mL)       2,718       0,077         Normal       48       87,3       49       75,4       1         >37       7       12,7       16       24,6       1         Serum CA125 (U/mL)       12,7       16       62,2       12,7         Normal       41       74,5       43       66,2       1         >35       14       25,5       22       33,8       1         pMMR status       7,265       0,011          | >5                      | 7   | 12.7  | 6  | 9.2  |          |         |
| Normal       48       87.3       49       75.4         >37       7       12.7       16       24.6         Serum CA125 (U/mL)       .       0.999       0.212         Normal       41       74.5       43       66.2         >35       14       25.5       22       33.8       .         MMR status       Y       7.265       0.011         pMMR       47       85.5       64       98.5       .         qMMR       8       14.5       1       .       .         Negative       8       14.5       1       .       .         Negative       47       85.5       55       84.6       .       .         Negative       47       85.5       55       84.6       .       .         Solve       47       85.5       55       84.6       .       .       .         Ke7       Y       10       15.4       .   | Serum CA199 (U/mL)      |   |       |  |      | 2.718    | 0.077   |
| >37712.71624.6Serum CA125 (U/mL)  | Normal                  | 48  | 87.3  | 49   | 75.4 |          |         |
| Serun CA125 (U/mL) $0.999$ $0.212$ Normal4174.543 $66.2$ $$   | >37                     | 7   | 12.7  | 16   | 24.6 |          |         |
| Normal4174.54366.2>351425.52233.8MMR status $7.265$ 0.011pMMR4785.56498.5dMMR81.4511.5HER2 $1.5$ 0.0160.553Negative4785.55584.6Positive814.51015.4Ki-67 $1.5$ $1.958$ 0.115<50% positive  | Serum CA125 (U/mL)      |   |       |  |      | 0.999    | 0.212   |
| >351425.52233.8MMR status7.2650.011 $pMMR$ 4785.56498.55 $dMMR$ 81.4.51.51.55HER27.2650.0160.553Negative4785.55584.65Positive814.51015.41.9580.115Ki-677.26523.623.625.41.9580.115 $< 50%$ positive1323.62335.41.51.9580.138 $< 50%$ positive1323.62335.41.51.3120.038LVNegative1934.53452.31.51.51.5   | Normal                  | 41  | 74.5  | 43   | 66.2 |          |         |
| MMR status       7.265       0.011         pMMR       47       85.5       64       98.5       5         dMMR       8       14.5       1       1.5       1.5         HER2       T       0.016       0.553         Negative       47       85.5       55       84.6       1.5         Positive       8       14.5       10       15.4       1.958       0.115         Ki-67       1.5       1.5       1.5       1.958       0.115         <50% positive   | > 35                    | 14  | 25.5  | 22   | 33.8 |          |         |
| pMMR4785.56498.5dMMR814.511.5HER2 $I$ $0.16$ $0.553$ Negative4785.55584.6Positive814.51015.4Ki-67 $I$ $I$ $I$ $I$ < 50% positive1323.62335.4> 50% positive4276.44264.6LV $I$ $I$ $I$ $I$ Negative1934.53452.3   | MMR status              |   |       |  |      | 7.265    | 0.011   |
| dMMR814.511.5HER2 $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ Negative4785.55584.6 $\cdot$ Positive814.51015.4 $\cdot$ Ki-67 $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ < 50% positive1323.62335.4 $\cdot$ $\cdot$ $\geq$ 50% positive42 $\cdot$ 64.6 $\cdot$ $\cdot$ $\cdot$ LV $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ $\cdot$ Negative1934.53452.3 $\cdot$ $\cdot$ $\cdot$  | pMMR                    | 47  | 85.5  | 64   | 98.5 |          |         |
| HER2       0.016       0.553         Negative       47       85.5       55       84.6       54         Positive       8       14.5       10       15.4       115         Ki-67       1.958       0.115         < 50% positive   | dMMR                    | 8   | 14.5  | 1  | 1.5  |          |         |
| Negative         47         85.5         55         84.6           Positive         8         14.5         10         15.4           Ki-67         1.958         0.115           < 50% positive   | HER2                    |   |       |  |      | 0.016    | 0.553   |
| Positive       8       14.5       10       15.4         Ki-67       1.958       0.115         < 50% positive       13       23.6       23       35.4         ≥ 50% positive       42       64.6       20.115         LVI       3.812       0.038         Negative       19       34.5       34       52.3   | Negative                | 47  | 85.5  | 55   | 84.6 |          |         |
| Ki-67       1.958       0.115         < 50% positive  | Positive                | 8   | 14.5  | 10   | 15.4 |          |         |
| < 50% positive 13 23.6 23 35.4<br>≥ 50% positive 42 76.4 42 64.6<br>LVI   | Ki-67                   |   |       |  |      | 1.958    | 0.115   |
| ≥ 50% positive 42 76.4 42 64.6<br>LVI   | < 50% positive          | 13  | 23.6  | 23   | 35.4 |          |         |
| LVI 3.812 0.038<br>Negative 19 34.5 34 52.3   | ≥50% positive           | 42  | 76.4  | 42   | 64.6 |          |         |
| Negative 19 34.5 34 52.3  | LVI                     |   |       |  |      | 3.812    | 0.038   |
|   | Negative                | 19  | 34.5  | 34   | 52.3 |          |         |

#### Table 1 (continued)

| Variable | TAF1L-H Group (n=55) | %    | <b>TAF1L-L Group (</b> <i>n</i> <b>=65)</b> | %    | χ2-value | p <b>-value</b> |
|----------|----------------------|------|---|------|----------|-----------------|
| Positive | 36                   | 65.5 | 31  | 47.7 |          |                 |
| NI       |                      |      |   |      | 7.762    | 0.005           |
| Negative | 27                   | 49.1 | 49  | 75.4 |          |                 |
| Positive | 28                   | 50.9 | 16  | 24.6 |          |                 |

CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen199; CA125: Carbohydrate antigen 125; LVI: Lympho-vascular invasion; NI: Nerve invasion



Fig. 1 Representative TAF1L immunohistochemical staining images. a Expression of TAF1L in tumor tissue; b Expression of TAF1L in para-cancerous/ normal tissue; c Representative image of TAF1L IHC staining by scoring

#### **Bioinformatics analysis of TAF1L**

As TCGA-GC dataset results showed, the expression of TAF1L was significantly higher in tumors compared with the normal control tissues (p < 0.001, Fig. 4a). Additionally, we further analyzed the relationship between TAF1L and some classical biomarkers associated with treatment. According to the results, TAF1L presented lower expression in microsatellite instability-high (MSI-H) GC than microsatellite-stable (MSS) GC (p = 0.002). Moreover, we analyzed the expression relationship between TAF1L and the main four DNA mismatch repair (MMR) protein genes (MLH1, MSH2, MSH6, PMS2), and the results presented significant positive correlations (p < 0.01). As for HER2 status, the gene correlation analysis suggested a significant correlation between ERBB2 (HER2) and TAF1L (p=0.002). Compared with HER2-negative cases, HER2-positive cases presented higher TAF1L expression (p = 0.005).

Survival analysis found that high expression of TAF1L cases showed worse OS which presented significant difference (p < 0.001, Fig. 4b). Further analysis showed that TAF1L high expression tended to have worse survival both in MSI-H group (34.0 months vs. *NE*, p=0.054, Fig. 5a) and MSS group (11.0 months vs. 35.0 months, p=0.0046, Fig. 5b). In HER2-positive cases, TAF1L expression was negatively correlated with OS (24.0 months vs. 57.0 months, p=0.0039, Fig. 5c), while no significant difference in HER2-negative ones (30.0 months vs. 39.0 months, p=0.16, Fig. 5d).

KEGG analysis revealed the genes showed highly correlation with TAF1L were mainly focused on biological processes such as p53 signaling pathway, mismatch repair, IL-17 signaling pathway, and cell cycle (Fig. 6a). GO analysis showed that the biological functions of TAF1L and its related genes mainly



Fig. 2 Kaplan-Meier analysis of overall survival according to the expression of TAF1L in the whole cohort (p = 0.019)

concentrated in biological processes such as organelle fission, cell cycle checkpoint, nuclear division, and DNA replication (Fig. 6b). These biological behaviors may participate in GC occurrence and progression.

#### Discussion

GC is characterized by high heterogeneity and a comprehensive molecular profile can greatly facilitate the evolution of treatment regimens and the improvement of precision in population selection. Researching GC biomarkers is of great significance to improve the treatment efficacy and prognosis.

TAF1L was first found to present high expression in human testicular germ cells by P. Jeremy et al., and its similarity to TAF1 was greater than 94% [15], which mainly played a role in transcriptional regulation and histone acetyltransferase activity [4, 6, 7]. Currently, only several studies revealed the potential role of TAF1/TAF1L in the occurrence and development of GC [8, 11, 12]. However, its relationship with prognosis and clinicopathological features in GC remains unclear. Thus, this study aims to evaluate the probability of TAF1L as a new potential biomarker of treatment and prognosis evaluation in GC.

In this study, we performed IHC to evaluate the TAF1L expression in GC tissues. According to IHC staining results, TAF1L expression in GC tissue sections was much stronger than those in normal/paracancerous ones. Moreover, the expression of TAF1L were correlated with tumor differentiation, signet-ring cells, dMMR status, lympho-vascular invasion, and neural invasion in this cohort, which suggested that TAF1L is closely related to the occurrence and development of GC. Survival analysis showed that high expression of TAF1L presented worse survival, and the result of TCGA dataset also showed similar tendency. Besides, the multivariate analysis suggested the expression of TAF1L is one of the independent prognostic risk factors. These results revealed that the expression of TAF1L is related to the progression of GC and may act as a potential prognosis biomarker of GC.

Previous study showed that TAF1 and TAF1L genes had mononucleotide repeats in the coding sequences that might be mutation targets in the cancers with MSI [8], which may promoting the tumorigenesis of MSI-H



Fig. 3 Kaplan-Meier analysis of overall survival according to the expression of TAF1L in clinical samples. **a** HER2-positive cases (p = 0.007); **b** HER2-negative cases (p = 0.168); **c** pMMR cases (p = 0.006); **d** dMMR cases (p = 0.724)

GC. MMR is critical for genome stability and dMMR can result in MSI phenotype [16], and the concordance between MSI-H status and dMMR was 97.6–99% [17, 18]. In our cohort, the TAF1L-H group presented higher dMMR proportion (14.5%, 8/55) than TAF1L-L group (1.5%, 1/65) and there was statistical difference (p=0.011). As the prevalence of dMMR/MSI-H was 6-10% in eastern cohorts [19–21], our results suggested that the higher expression of TAF1L may presented more frequency of dMMR status. However, the frameshift mutations would result in premature stops of amino acid synthesis in TAF1L protein [8], indicating that low expression of TAF1L is associated with MSI-H/dMMR status, which is contrary to our results.

Thus, we further explore the relationship between TAF1L and MSI-H/dMMR status.

According to the TCGA dataset, TAF1L presented lower expression in MSI-H cases (p=0.00413). Moreover, TAF1L presented significant positive correlations with MLH1, MSH2, MSH6 and PMS2 expression, suggesting that low expression of TAF1L might cause the deficiency of MMR protein expression and resulting in dMMR status. Although our conclusion was not consistent with the TCGA results due to the rarity of dMMR GC and the limited cases of our cohort, the expression of TAF1L did correlate with MSI-H/dMMR status and was expected to be confirmed by larger sample size studies in the future.

| Variable                  | Univariate          |         | Multivariate        |         |  |
|---------------------------|---------------------|---------|---------------------|---------|--|
|                           | HR (95%CI)          | p-value | HR (95%CI)          | p-value |  |
| Age (≥ 50 years)          | 1.316 (0.677–2.560) | 0.418   |                     |         |  |
| Sex (Male)                | 0.950 (0.465–1.940) | 0.888   |                     |         |  |
| TAF1L Exprssion (High)    | 2.274 (1.145–4.516) | 0.019   | 2.044 (1.007-4.147) | 0.048   |  |
| Tumor Size (≥5 cm)        | 2.328 (1.183-4.582) | 0.014   | 1.870 (0.922-3.791) | 0.083   |  |
| T-stage (>T2)             | 2.316 (0.817–6.566) | 0.114   |                     |         |  |
| N-stage (N2-3)            | 2.214 (1.037-4.727) | 0.040   | 1.465 (0.656–3.274) | 0.352   |  |
| Differentiation           | 1.183 (0.596–2.348) | 0.631   |                     |         |  |
| (Poorly/undifferentiated) |                     |         |                     |         |  |
| Signet-ring cells         | 1.563 (0.750–3.254) | 0.233   |                     |         |  |
| MMR status (dMMR)         | 0.541 (0.074–3.949) | 0.544   |                     |         |  |
| HER2                      | 2.425 (1.133–5.191) | 0.023   | 2.383 (1.087–5.222) | 0.030   |  |
| Ki-67 (≥50% positive)     | 1.122 (0.550–2.291) | 0.751   |                     |         |  |
| LVI                       | 1.696 (0.844-3.410) | 0.138   |                     |         |  |
| NI                        | 1.297 (0.635–2.648) | 0.476   |                     |         |  |
| CEA (>5 ng/mL)            | 1.755 (0.728–4.231) | 0.210   |                     |         |  |
| CA199 (> 37 U/mL)         | 1.648 (0.791–3.432) | 0.182   |                     |         |  |
| CA125 (> 35 U/ml )        | 1.514 (0.762-3.007) | 0.237   |                     |         |  |

 Table 2
 Univariate and multivariate analysis of prognostic factors for OS

CEA: Carcinoembryonic antigen; CA199: Carbohydrate antigen199; CA125: Carbohydrate antigen 125; LVI: Lympho-vascular invasion; NI: Nerve invasion



**Fig. 4** The mRNA expression level of TAF1L in the TCGA GC dataset. **a** TAF1L expression in tumors is higher than that in normal tissues (\*\*\*\* p < 0.001); **b** Kaplan-Meier analysis of overall survival according to the expression of TAF1L in the TCGA GC dataset (p < 0.001)

Through whole-genome sequencing, Zhou et al. found that TAF1 was an important mutated driver gene in HER2-positive GC [12]. Moreover, Cai et al. found that the co-expression of TAF1 and HER2 cases presented worse prognosis in endometrial clear cell carcinoma [22]. These results indicated the potential relationship of TAF1 and HER2 in cancer progression. As TAF1L is an analogue of TAF1, we further analyzed the correlation of TAF1L and HER2 in GC. Survival analysis based on TCGA dataset showed that TAF1L expression was negatively correlated with OS in HER2-positive GC samples (p=0.0039), but not in HER2-negative ones (p=0.16). Moreover, the gene correlation also suggested a significant association between ERBB2 and TAF1L (p=0.002).

In our cohort, the TAF1L-H cases showed worse survival in HER2-positive GC (p=0.007) and TAF1L was the independent prognostic risk factor in HER2 positive cases. However, there was no relationship between TAF1L expression and HER2 status (p=0.553) in this cohort, which may be caused by the limited case number. In conclusion, TAF1L might play an important role in HER2-positive GC progression and the co-expression of TAF1L and HER2 in GC may results in worse prognosis. Further studies are expected to explore the relationship and mechanisms of interaction between TAF1L and HER2 status in GC.

As studies reported previously, immune-checkpoint inhibitors (ICIs) in dMMR/MSI-H GC had been well validated in several phase II and III studies [23–25].



Fig. 5 Kaplan-Meier analysis of overall survival according to the expression of TAF1L in different TCGA dataset. **a** MSI-H GC dataset (*p*=0.054); **b** MSS GC dataset (*p*=0.0046); **c** HER2-positive GC dataset (*p*=0.0039); **d** HER2-negative GC dataset (*p*=0.16)

According to our KEGG analyze results, IL-17 signaling pathway was one of the top-20 enriched pathways related to TAF1L. Several studies had indicated the importance of IL-17 in cancer immunotherapy which involved in tumor microenvironment [26–28]. Targeting the IL-17/TAF1L immune axis may become a new way improving immunotherapy efficacy. Moreover, targeted therapy such as trastuzumab has been wildly used in HER2-positive GC [29, 30]. As our results revealed the relationships between TAF1L together with MSI-H/dMMR and HER2 status, indicating that TAF1L may be associated with immunotherapy and targeted therapy efficacy. However, these were only inferences based on our results and did not conduct further analysis because of the limited cases. The correlation between TAF1L and the efficacy of different treatment regimens needs to be further studied.

Our study also had some limitations. First, it was retrospective study in a single-center as the overall sample size was relatively small, and large-sample studies might be necessary to clarify our result. Second, although we performed preliminary IHC to evaluate the expression of TAF1L in clinical samples and validated by TCGA dataset, some results still need to be validated by wet-experiment and we would like to conduct in future study. In addition, because most of the surgical specimens of stage IV patients were after treatment (such as chemotherapy or immunotherapy), we did not include such patients for analysis, and we expected further studies to discuss the role of TAF1L



Fig. 6 Functional enrichment of TAF1L in the TCGA GC dataset. a KEGG enrichment analysis of pathways associated with TAF1L in the TCGA GC dataset; b GO enrichment analysis of pathways associated with TAF1L in the TCGA GC dataset

in such patients in the future. Despite these, as far as we know, it is the first study focusing on TAF1L expression and revealing its potential relationship with clinicopathological features of GC, which is important for future exploration of new biomarker in therapy and prognosis.

In conclusion, TAF1L presents high expression in GC tissues and is closely related to the occurrence and development of GC. Moreover, high expression of TAF1L is a marker of poor prognosis, especially in HER2 positive GC cases. We suppose that TAF1L might become a significant biomarker for predicting prognosis as well as a potential therapeutic biomarker in GC. However, further in vitro and in vivo experiments were needed to explore the mechanism of TAF1L acting on GC tumor progression. Overall, our findings provide a basis for understanding the function of TAF1L in GC, which will provide theoretical basis and new ideas for the target of gene detection, diagnosis, and treatment in the future.

#### Author contributions

Han Chen, Hang Chen, JF and PY designed the study. Han Chen, JF, XH, and TC analyzed the data. Han Chen and JF drafted the manuscript. Hang Chen, XZ and LH collected and registered the data. PY, XC and LH interpreted the data and revised the manuscript. All authors read and approved the final manuscript.

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#### Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

#### Declarations

#### **Ethics** approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Zhejiang Cancer Hospital Ethics Committee (No. IRB-2022-691). Human Ethics and Consent to Participate declarations: not applicable. Informed consent was waived by the Ethics Committee of the Zhejiang Cancer Hospital because of the retrospective study of this project.

#### **Consent for publication**

Not Applicable.

#### **Competing interests**

The authors declare no competing interests.

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#### References

- Smyth EC, Nilsson M, Grabsch HI, van Grieken NCT, Lordick F. Gastric cancer. Lancet. 2020;396(10251):635–48.
- Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA Cancer J Clin. 2021;71(3):264–79.
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
- Lee D-H, Gershenzon N, Gupta M, Ioshikhes IP, Reinberg D, Lewis BA. Functional characterization of core promoter elements: the downstream core element is recognized by TAF1. Mol Cell Biol. 2005;25(21):9674–86.
- Wassarman DA, Sauer F. TAF(II)250: a transcription toolbox. J Cell Sci. 2001;114(Pt 16):2895–902.
- Filippakopoulos P, Picaud S, Mangos M, Keates T, Lambert J-P, Barsyte-Lovejoy D, Felletar I, Volkmer R, Müller S, Pawson T, et al. Histone recognition and

large-scale structural analysis of the human bromodomain family. Cell. 2012;149(1):214–31.

- Tavassoli P, Wafa LA, Cheng H, Zoubeidi A, Fazli L, Gleave M, Snoek R, Rennie PS. TAF1 differentially enhances androgen receptor transcriptional activity via its N-terminal kinase and ubiquitin-activating and -conjugating domains. Mol Endocrinol. 2010;24(4):696–708.
- Oh HR, An CH, Yoo NJ, Lee SH. Frameshift mutations in the mononucleotide repeats of TAF1 and TAF1L genes in gastric and colorectal cancers with regional heterogeneity. Pathol Oncol Res. 2017;23(1):125–30.
- Wang D, Qi H, Zhang H, Zhou W, Li Y, Li A, Liu Q, Wang Y. TAF1L promotes development of oral squamous cell carcinoma via decreasing autophagydependent apoptosis. Int J Biol Sci. 2020;16(7):1180–93.
- Zhong S, Yan H, Chen Z, Li Y, Shen Y, Wang Y, Li L, Sheng S, Wang Y. Overexpression of promotes cell proliferation, migration and invasion in esophageal squamous cell carcinoma. J Cancer. 2019;10(4):979–89.
- Wang R, Song S, Harada K, Ghazanfari Amlashi F, Badgwell B, Pizzi MP, Xu Y, Zhao W, Dong X, Jin J, et al. Multiplex profiling of peritoneal metastases from gastric adenocarcinoma identified novel targets and molecular subtypes that predict treatment response. Gut. 2020;69(1):18–31.
- 12. Zhou C, Feng X, Yuan F, Ji J, Shi M, Yu Y, Zhu Z, Zhang J. Difference of molecular alterations in HER2-positive and HER2-negative gastric cancers by wholegenome sequencing analysis. Cancer Manag Res. 2018;10:3945–54.
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.
- Flohr AM, Rogalla P, Bonk U, Puettmann B, Buerger H, Gohla G, Packeisen J, Wosniok W, Loeschke S, Bullerdiek J. High mobility group protein HMGA1 expression in breast cancer reveals a positive correlation with tumour grade. Histol Histopathol. 2003;18(4):999–1004.
- Wang PJ, Page DC. Functional substitution for TAF(II)250 by a retroposed homolog that is expressed in human spermatogenesis. Hum Mol Genet. 2002;11(19):2341–6.
- Li G-M. Mechanisms and functions of DNA mismatch repair. Cell Res. 2008;18(1):85–98.
- Hewitt LC, Inam IZ, Saito Y, Yoshikawa T, Quaas A, Hoelscher A, Bollschweiler E, Fazzi GE, Melotte V, Langley RE, et al. Epstein-Barr virus and mismatch repair deficiency status differ between oesophageal and gastric cancer: a large multi-centre study. Eur J Cancer. 2018;94:104–14.
- Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, Fassan M, Rugge M, Valeri N, Okines A, et al. Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the Medical Research Council adjuvant gastric Infusional Chemotherapy (MAGIC) trial. JAMA Oncol. 2017;3(9):1197–203.
- An JY, Choi YY, Lee J, Hyung WJ, Kim K-M, Noh SH, Choi M-G, Cheong J-H. A multi-cohort study of the prognostic significance of microsatellite instability or mismatch repair status after recurrence of resectable gastric cancer. Cancer Res Treat. 2020;52(4):1153–61.

- Kim SY, Choi YY, An JY, Shin HB, Jo A, Choi H, Seo SH, Bang H-J, Cheong J-H, Hyung WJ, et al. The benefit of microsatellite instability is attenuated by chemotherapy in stage II and stage III gastric cancer: results from a large cohort with subgroup analyses. Int J Cancer. 2015;137(4):819–25.
- Zhang Q, Wang L, Ni S, Tan C, Cai X, Huang D, Sheng W. Clinicopathological features and prognostic value of mismatch repair protein deficiency in gastric cancer. Int J Clin Exp Pathol. 2018;11(5):2579–87.
- 22. Cai Y, Han Q, Guo H. Identifying clinical features and molecular characteristics of the endometrial clear cell carcinoma. Front Oncol. 2023;13:1286176.
- Chao J, Fuchs CS, Shitara K, Tabernero J, Muro K, Van Cutsem E, Bang Y-J, De Vita F, Landers G, Yen C-J, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. JAMA Oncol. 2021;7(6):895–902.
- Lu C, Guan J, Lu S, Jin Q, Rousseau B, Lu T, Stephens D, Zhang H, Zhu J, Yang M et al. DNA sensing in mismatch repair-deficient tumor cells is essential for anti-tumor immunity. Cancer Cell. 2021;39(1).
- Palmeri M, Mehnert J, Silk AW, Jabbour SK, Ganesan S, Popli P, Riedlinger G, Stephenson R, de Meritens AB, Leiser A, et al. Real-world application of tumor mutational burden-high (TMB-high) and microsatellite instability (MSI) confirms their utility as immunotherapy biomarkers. ESMO Open. 2022;7(1):100336.
- Lechner M, Cheng M, Patel A, Hoang A, Yakobian N, Astourian M, Pioso M, Rodriguez E, McCarthy E, Hugo W et al. Inhibition of IL-17A protects against thyroid immune-related adverse events while preserving checkpoint inhibitor antitumor efficacy. J Immunol. 2022;209(4):696–709.
- Majchrzak K, Nelson MH, Bailey SR, Bowers JS, Yu X-Z, Rubinstein MP, Himes RA, Paulos CM. Exploiting IL-17-producing CD4 + and CD8 + T cells to improve cancer immunotherapy in the clinic. Cancer Immunol Immunotherapy: Cll. 2016;65(3):247–59.
- Nagaoka K, Shirai M, Taniguchi K, Hosoi A, Sun C, Kobayashi Y, Maejima K, Fujita M, Nakagawa H, Nomura S et al. Deep immunophenotyping at the single-cell level identifies a combination of anti-IL-17 and checkpoint blockade as an effective treatment in a preclinical model of data-guided personalized immunotherapy. J Immunother Cancer. 2020;8(2).
- 29. Guan W-L, He Y, Xu R-H. Gastric cancer treatment: recent progress and future perspectives. J Hematol Oncol. 2023;16(1):57.
- Zhu Y, Zhu X, Wei X, Tang C, Zhang W. HER2-targeted therapies in gastric cancer. Biochim Biophys Acta Rev Cancer. 2021;1876(1):188549.

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