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TYMS presents a novel biomarker for diagnosis and prognosis in patients with pancreatic cancer

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Abstract

Pancreatic cancer is one of the most malignant tumors worldwide. DNA replication plays a critical role in the occurrence and development of pancreatic cancer. *TYMS* encodes thymidylate synthase, which is important for DNA synthesis. The *TYMS* gene has been assessed in some tumors. However, the specific role of *TYMS* in pancreatic cancer has not been identified. This study was designed to clarify the diagnostic and prognostic significance of *TYMS* in pancreatic cancer.

The Cancer Genome Atlas (TCGA) database was used to compare *TYMS* expression in pancreatic cancer, and ROC curve analysis was used to investigate its diagnostic value. The correlation between clinical characteristics and *TYMS* expression was analyzed, and the prognostic value of *TYMS* expression in the patients with pancreatic cancer was assessed by Kaplan–Meier curves and Cox analysis.

TYMS was upregulated in pancreatic cancer and associated with poor overall survival (OS) and recurrence-free survival (RFS). Univariate and multivariate survival analysis demonstrated that *TYMS* is an independent risk factor for OS and RFS in patients with pancreatic cancer.

The upregulation of *TYMS* in pancreatic cancer leads to unfavorable OS and RFS in patients, and represents a diagnostic and prognostic biomarker for patients with pancreatic cancer.

Abbreviations: OS = overall survival, RFS = recurrence-free survival, TCGA = The Cancer Genome Atlas.

Keywords: diagnosis, pancreatic cancer, prognosis, *TYMS*

1. Introduction

Pancreatic cancer is one of the most lethal malignant tumors worldwide, with an estimated five-year survival rate of only about 5%.[1] This means that early and accurate diagnosis of pancreatic cancer may help improve the survival of patients and is urgently required. To date, the diagnosis of pancreatic cancer relies on imaging methods, which are insufficient in some situations.[2] Therefore, identifying a diagnostic and prognostic biomarker has great clinical significance for patients with pancreatic cancer.

Cancer is regarded as a disease involving genome changes.[3] DNA replication, which affects genomic stability, plays an important role in the initiation and progression of tumors. *TYMS*, located on chromosome 18p, encodes thymidylate synthase (TS), an enzyme involved in the replication and repair of DNA.[4] TS plays an important role in DNA replication by catalyzing the methylation of dUMP to produce dTMP.[5] Some studies have described *TYMS* expression, suggesting that it plays a role in cancer.[4,6] However, the role of *TYMS* expression in the diagnostic and prognostic evaluation of patients with pancreatic cancer remains unclear.

In this study, we compared *TYMS* expression in patients with pancreatic cancer and healthy people, and evaluated the diagnostic value of *TYMS* in pancreatic cancer using ROC. We also investigated the correlation between clinical characteristics and *TYMS* expression, and discussed the prognostic role of *TYMS* in overall survival (OS) and recurrence-free survival (RFS) in patients. Finally, we explored whether *TYMS* could be a biomarker for the diagnostic and prognostic evaluation of patients with pancreatic cancer.

2. Methods

2.1. Data mining and collection

Data generated from patients with pancreatic cancer and RNA-seq results were downloaded using the RTCGAToolbox package in R (version 3.5.1) from The Cancer Genome Atlas (TCGA) database.[7,8] As a public database, ethics approval and patient consent were not applicable. The number of patients included in our analysis was 173, and the number of normal individuals was 4.

2.2. Statistical analysis

Box-plots were used to compare *TYMS* expression between different groups. ROC was applied to test the diagnostic value of *TYMS*, and patients were divided into 2 groups (high *TYMS*

Editor: Raffaele Pezzilli.

This study was supported by the Project of Talent Development Funds of Jilin Province (grant number: 802160100428). The funding sources had no involvement in design, analysis or submission of this article.

The authors have no conflicts of interests to disclose.

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How to cite this article: Fu Z, Jiao Y, Li Y, Ji B, Jia B, Liu B. TYMS presents a novel biomarker for diagnosis and prognosis in patients with pancreatic cancer. Medicine 2019;98:51(e18487).

Received: 17 May 2019 / Received in final form: 16 September 2019 / Accepted: 18 November 2019

http://dx.doi.org/10.1097/MD.0000000000018487

expression and low *TYMS* expression) based on thresholds set using pROC packages.[9] Chi-square and Fisher exact tests were used to examine the correlation between *TYMS* expression and clinical characteristics in patients. Kaplan–Meier curves were used to investigate OS and RFS, grouped by *TYMS* expression, using the Survival package in R.[10,11] Univariate Cox analysis was used to select the variables related to OS and RFS. Finally, Multivariate Cox analysis was used to check the effects of *TYMS* expression on the survival of patients, and other pathological features. $P < .05$ was considered statistically significant.

3. Results

3.1. Patients' characteristics

A total of 173 patients and 4 normal individuals were included in this analysis, and their clinical data were mined and downloaded from the TCGA database. Included in this study were 77 (44.51%) females and 96 (55.49%) males. There were 140 (80.92%) patients older than 55 years, and 33 (19.08%) patients younger than 55 years. Detailed patient characteristics are presented in Table 1.

Table 1

Clinical characteristics of the patients with pancreatic cancer.

Characteristics	Numbers of cases
Age	
<55	33 (19.08)
≥55	140 (80.92)
Gender	
Female	77 (44.51)
Male	96 (55.49)
Alcohol history	
	12 (6.94)
No	64 (36.99)
Yes	97 (56.07)
Anatomic subdivision	
Body of pancreas	14 (8.09)
Head of pancreas	134 (77.46)
Other	11 (6.36)
Tail of pancreas	14 (8.09)
Histological type	
Pancreas adenocarcinoma-other subtype	26 (15.03)
Pancreas adenocarcinoma ductal type	147 (84.97)
Histologic grade	
G1	30 (17.34)
G2	93 (53.76)
G3	48 (27.75)
G4	1 (0.58)
GX	1 (0.58)
Stage	
NA	2 (1.16)
I	20 (11.56)
II	143 (82.66)
III	3 (1.73)
IV	5 (2.89)
T classification	
NA	1 (0.58)
T1	6 (3.47)
T2	23 (13.29)
T3	139 (80.35)
T4	3 (1.73)
TX	1 (0.58)
N classification	
NA	1 (0.58)
N0	48 (27.75)
N1	121 (69.94)
NX	3 (1.73)
M classification	
M0	77 (44.51)
M1	5 (2.89)
MX	91 (52.6)
Lymphnodes positive	
No	47 (27.65)
Yes	123 (72.35)
Max dimension	
<=5	139 (86.34)
>5	22 (13.66)
Residual tumor	
NA	9 (5.2)
R0	103 (59.54)
R1	52 (30.06)
R2	5 (2.89)
RX	4 (2.31)
Radiation therapy	
NA	16 (9.25)
NO	115 (66.47)
YES	42 (24.28)
Targeted molecular therapy	
NA	13 (7.51)
NO	46 (26.59)
YES	114 (65.9)
Surgery performed type	
NA	
Distal pancreatectomy	22 (12.72)
Other method	13 (7.51)
Total pancreatectomy	3 (1.73)
Whipple	133 (76.88)
Therapy outcome	
NA	40 (23.12)
Complete remission/response	64 (36.99)
Partial remission/response	10 (5.78)
Progressive disease	51 (29.48)
Stable disease	8 (4.62)
Vital status	
Deceased	91 (52.6)
Living	82 (47.4)
Sample type	
Metastatic	1 (0.58)
Primary tumor	172 (99.42)
Overall survival	
Survival	81 (47.09)
Death	91 (52.91)
Recurrence status	
Null	93 (61.59)
New tumor	58 (38.41)
TYMS	
High	86 (49.71)
Low	87 (50.29)
Characteristics	Numbers of cases
Age	
<55	33 (19.08)
≥55	140 (80.92)
Gender	
Female	77 (44.51)
Male	96 (55.49)

NA = not applicable.

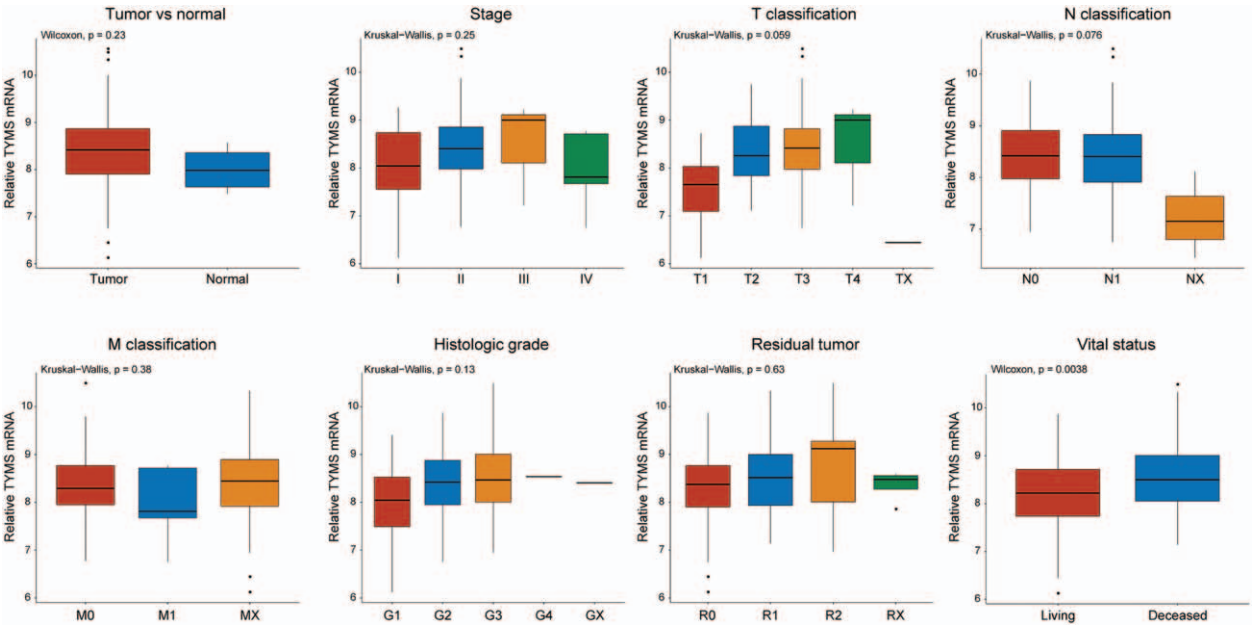

Figure 1. *TYMS* was upregulated in pancreatic cancer. Expression of *TYMS* in normal tissues and pancreatic cancer samples with different stages, T classification, N classification, M classification, histologic grade, residual tumor, and vital status.

3.2. TYMS is upregulated in pancreatic cancer

TYMS expression was compared between pancreatic cancer samples and normal tissues (Fig. 1). Our results show that *TYMS* is highly expressed in pancreatic cancer. Moreover, *TYMS* expression significantly differed in vital status (P=.0038) subgroups.

3.3. Diagnostic value of TYMS

We performed ROC analysis of data from patients and healthy people to measure the diagnostic value of *TYMS*. The AUC was 0.675, representing a moderate diagnostic value for pancreatic cancer (Fig. 2). Subgroup analysis further demonstrated the diagnostic value of PES1 expression in distinct stage, with AUC of 0.562 for stage I, 0.691 for stage II, 0.667 for stage III and 0.450 for stage IV.

3.4. Correlation between clinical characteristics and TYMS expression in pancreatic cancer

We divided patients into *TYMS* high and low expression groups and examined the correlation between clinical characteristics and *TYMS* expression in patients with pancreatic cancer (Table 2). The correlation between *TYMS* expression and clinical characteristics, including therapy outcome (P=.0401), vital status (P=.027), and OS (P=.0325) was significant.

3.5. High TYMS expression is associated with poor OS in patients with pancreatic cancer

Kaplan–Meier curves of OS showed that higher *TYMS* expression was associated with worse OS (P=.014) (Fig. 3). Subgroup analysis further indicated that high *TYMS* expression significantly affected the OS of patients in histologic grades G1/G2 (P=.025) and clinical stages I/II (P=.023). Univariate analysis revealed that histological type (P=.001), T classification (P=.009),N classification (P=.002), residual tumor (P=.018), and TYMS expression (P=.014) were associated with poor OS. Multivariate analysis including age, gender, histological type, stage, T/N/M classification, residual tumor, and *TYMS* expression parameters further showed that *TYMS* is an independent risk factor for OS in patients with pancreatic cancer (HR=1.62, 95% CI: 1.05–2.48, P=.028; Table 3).

3.6. High TYMS expression is associated with poor RFS in patients with pancreatic cancer

We generated Kaplan–Meier curves of RFS (Fig. 4). Upregulation of *TYMS* was associated with poor RFS in patients with pancreatic cancer (P=.021). Subgroup analysis revealed that *TYMS* upregulation was associated with poor RFS in clinical stage I/II (P=.0038). Univariate analysis revealed that N classification (P=.017), residue tumor (P=.002), and *TYMS* expression (P=.013) were associated with poor RFS (Table 4). Multivariate analysis further confirmed *TYMS* as an independent risk factor for RFS in patients with pancreatic cancer (HR=1.92, 95% CI: 1.13–3.28, P=.016).

4. Discussion

Our team has been working toward developing novel biomarkers for distinct tumors.[12,13] In this study, we report that *TYMS* is upregulated in pancreatic cancer and that elevated *TYMS*

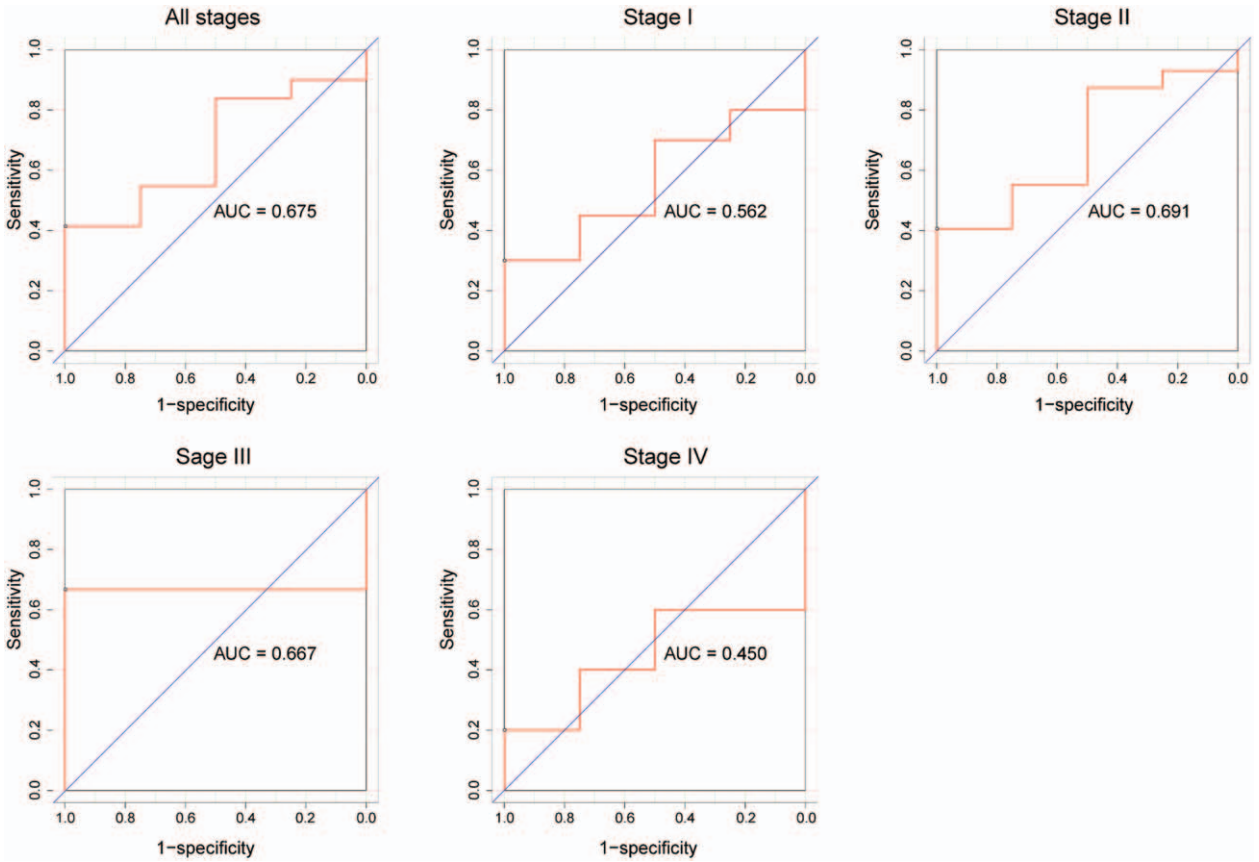

Figure 2. *TYMS* represented a moderate diagnostic value. The ROC of normal tissues and all pancreatic cancer samples, and subgroup analysis for stage I, II, III, and IV pancreatic cancer.

expression is associated with therapy outcome, vital status, and OS of patients. Kaplan–Meier curves of OS and RFS also showed that high *TYMS* expression is correlated with poor survival in patients. Moreover, univariate and multivariate analyses suggest that *TYMS* expression plays a prognostic role in patients with pancreatic cancer. Our results indicate that *TYMS* is insufficient for use as a diagnostic biomarker, but the prognostic capacity of *TYMS* is sufficient.

High *TYMS* expression has been reported in breast cancer,[14] non-small cell lung cancers,[15] and prostate cancer.[6,16] However, *TYMS* expression levels in pancreatic cancer were unknown. Our results demonstrate that *TYMS* is upregulated in pancreatic cancer. This result is consistent with those previously reported in other tumors. Moreover, different *TYMS* expression levels were found in distinct histologic grades and vital status, suggesting that *TYMS* plays an important role in the progress and prognosis of pancreatic cancer. However, because the AUC of ROC was relatively low, the diagnostic value of *TYMS* was moderate.

TYMS, encodes an enzyme that participates in the synthesis of DNA and its role in the proliferation of tumor cells has been reported. Patients with advanced clinical stage prostate cancer more commonly express *TYMS* than do those with less advanced disease.[16] In colorectal cancer, knockdown of *TYMS* inhibits the proliferation of tumor cells and promotes apoptosis.[17] Our results, that patients with poorer vital status or OS had higher *TYMS* expression levels, are consistent with these observations.

TYMS expression is associated with decreased survival in lung carcinoma,[15,18] metastatic colorectal cancer,[19] and hepatocellular carcinoma.[20] Our results, consistent with those reported in other cancers, show that high *TYMS* expression correlates with poorer OS in patients with pancreatic cancer. We also found that high *TYMS* expression affects the OS of patients in histologic grades G1/G2 and clinical stages I/II, but not in histologic grades G3/G4 and clinical stages III/IV. These data suggest that *TYMS* has different roles in patients with distinct stages.

Surgery is the only way to cure pancreatic cancer.[21] However, tumor recurrence adversely impacts the effectiveness of surgery, which complicates treatment choice. Here, we also show that high *TYMS* expression leads to poorer RFS in patients with pancreatic cancer, indicating that *TYMS* expression levels can be used to inform treatment choice. Moreover, we found high *TYMS* expression significantly affected the RFS of patients in clinical stages I/II, rather than in clinical stages III/IV, indicating a powerful prognostic capacity during an early stage. However, the prognostic role of *TYMS* in patients was limited in histologic grades G3/G4. Exploring more potential grade G1/G2 biomarkers in patients with pancreatic cancer in the near future is important. Limitations of our study included the small sample size in some comparison groups, and that

Table 2

Association between the clinical features and TYMS expression in patients with pancreatic cancer.

Features	Variables	N	TYMS (%)		X^2	P
			High	Low		
Age	<55	33	14 (16.28)	19 (21.84)	0.5434	.461
	≥55	140	72 (83.72)	68 (78.16)		
Gender	Female	77	45 (52.33)	32 (36.78)	3.6249	.0569
	Male	96	41 (47.67)	55 (63.22)		
Alcohol history	No	64	34 (43.04)	30 (36.59)	0.456	.4995
	Yes	97	45 (56.96)	52 (63.41)		
Anatomic subdivision	Body of pancreas	14	7 (8.14)	7 (8.05)	6.1303	.1054
	Head of pancreas	134	72 (83.72)	62 (71.26)		
	Other	11	4 (4.65)	7 (8.05)		
	Tail of pancreas	14	3 (3.49)	11 (12.64)		
Histological type	Pancreas adenocarcinoma other subtype	26	9 (10.47)	17 (19.54)	2.1238	.145
	Pancreas adenocarcinoma ductal type	147	77 (89.53)	70 (80.46)		
Histologic grade	G1	30	10 (11.63)	20 (22.99)	5.7579	.218
	G2	93	48 (55.81)	45 (51.72)		
	G3	48	26 (30.23)	22 (25.29)		
	G4	1	1 (1.16)	0 (0)		
	GX	1	1 (1.16)	0 (0)		
Stage	I	20	9 (10.59)	11 (12.79)	0.7345	.8651
	II	143	72 (84.71)	71 (82.56)		
	III	3	2 (2.35)	1 (1.16)		
	IV	5	2 (2.35)	3 (3.49)		
T classification	T1	6	1 (1.18)	5 (5.75)	4.0855	.3946
	T2	23	11 (12.94)	12 (13.79)		
	T3	139	71 (83.53)	68 (78.16)		
	T4	3	2 (2.35)	1 (1.15)		
	TX	1	0 (0)	1 (1.15)		
N classification	N0	48	25 (29.07)	23 (26.74)	3.0916	.2131
	N1	121	61 (70.93)	60 (69.77)		
	NX	3	0 (0)	3 (3.49)		
M classification	M0	77	36 (41.86)	41 (47.13)	0.7936	.6725
	M1	5	2 (2.33)	3 (3.45)		
	MX	91	48 (55.81)	43 (49.43)		
Lymphnodes positive	No	47	24 (28.24)	23 (27.06)	0	1
	Yes	123	61 (71.76)	62 (72.94)		
Max dimension	≤5	139	68 (87.18)	71 (85.54)	0.0053	.942
	>5	22	10 (12.82)	12 (14.46)		
Residual tumor	R0	103	49 (59.04)	54 (66.67)	1.7263	.6311
	R1	52	28 (33.73)	24 (29.63)		
	R2	5	3 (3.61)	2 (2.47)		
	RX	4	3 (3.61)	1 (1.23)		
Radiation therapy	No	115	61 (79.22)	54 (67.5)	2.1851	.1394
	Yes	42	16 (20.78)	26 (32.5)		
Targeted molecular therapy	No	46	24 (30.38)	22 (27.16)	0.0757	.7832
	Yes	114	55 (69.62)	59 (72.84)		
Surgery performed type	Distal pancreatectomy	22	8 (9.52)	14 (16.09)	5.0306	.1696
	Other Method	13	6 (7.14)	7 (8.05)		
	Total pancreatectomy	3	0 (0)	3 (3.45)		
	Whipple	133	70 (83.33)	63 (72.41)		
Therapy outcome	Complete remission/response	64	33 (47.14)	31 (49.21)	8.3073	**.0401**
	Partial remission/response	10	2 (2.86)	8 (12.7)		
	Progressive disease	51	28 (40)	23 (36.51)		
	Stable disease	8	7 (10)	1 (1.59)		
Vital status	Death	91	53 (61.63)	38 (43.68)	4.8921	**.027**
	Living	82	33 (38.37)	49 (56.32)		
Sample type	Metastatic	1	0 (0)	1 (1.15)	0	1
	Primary tumor	172	86 (100)	86 (98.85)		
Overall survival	Survival	81	33 (38.37)	48 (55.81)	4.5736	**.0325**
	Death	91	53 (61.63)	38 (44.19)		
Recurrence survival	Null	93	41 (54.67)	52 (68.42)	2.4653	.1164
	New tumor	58	34 (45.33)	24 (31.58)		

Bold values indicate $P < .05$ and is statistically significant.

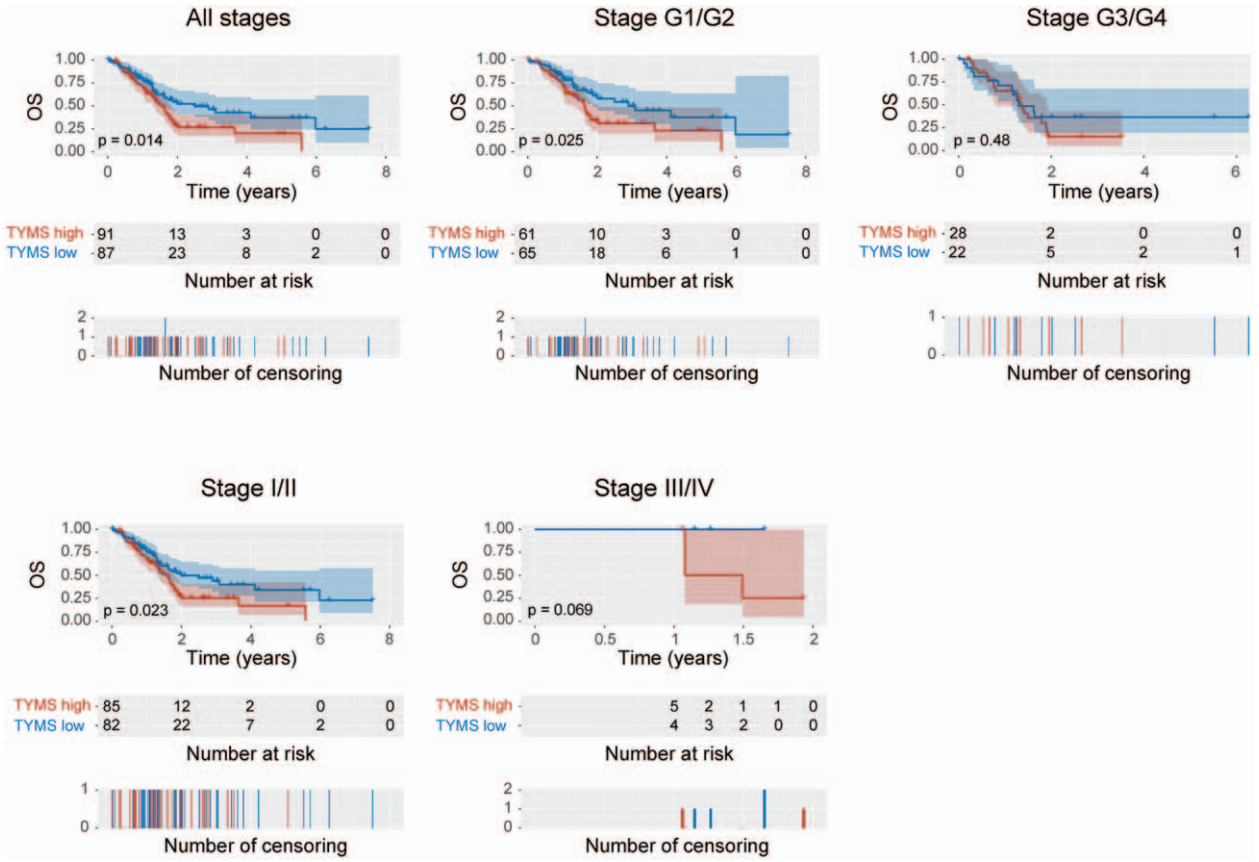

Figure 3. Kaplan–Meier curves of overall survival in patients with pancreatic cancer: in all tumors; histologic grades G1/G2 and G3/G4; and clinical stages I/II and III/IV.

tissue collection was very difficult in some cases given that operations were not suitable for patients with late stage pancreatic cancer. In addition, some types of pancreatic cancer were rarely observed.

Our results show that *TYMS* plays a significant role in the diagnosis and prognosis of patients with pancreatic cancer. These results contribute to the collective understanding of the role of *TYMS* in the diagnosis and prognosis of patients with cancer. The application of *TYMS* in prognosis is limited in histologic grades G3/G4, and a novel biomarker in histologic grades G1/G2 of patients with pancreatic cancer is urgently required in the future.

In conclusion, we show that, in patients with pancreatic cancer, higher *TYMS* expression is associated with advanced clinical stages and undesirable prognosis, and that *TYMS* could be used as a biomarker for diagnostic and prognostic evaluation in patients with pancreatic cancer.

Table 3

Univariate and multivariate analysis of overall survival in patients with pancreatic cancer.

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	1.30	0.77–2.20	.330			
Gender	0.82	0.54–1.24	.347			
Histological type	4.37	1.9–10.06	**.001**	3.33	1.40–7.92	**.006**
Stage	1.38	1.00–1.91	.050			
T classification	1.80	1.16–2.79	**.009**	1.19	0.72–1.94	.501
N classification	2.18	1.34–3.53	**.002**	1.49	0.88–2.51	.134
M classification	0.78	0.19–3.26	.734			
Residual tumor	1.37	1.05–1.77	**.018**	1.36	1.04–1.78	**.024**
TYMS	1.70	1.12–2.60	**.014**	1.62	1.05–2.48	**.028**

Bold values indicate $P < .05$ and is statistically significant. CI = confidence interval, HR = Hazard Ratio.

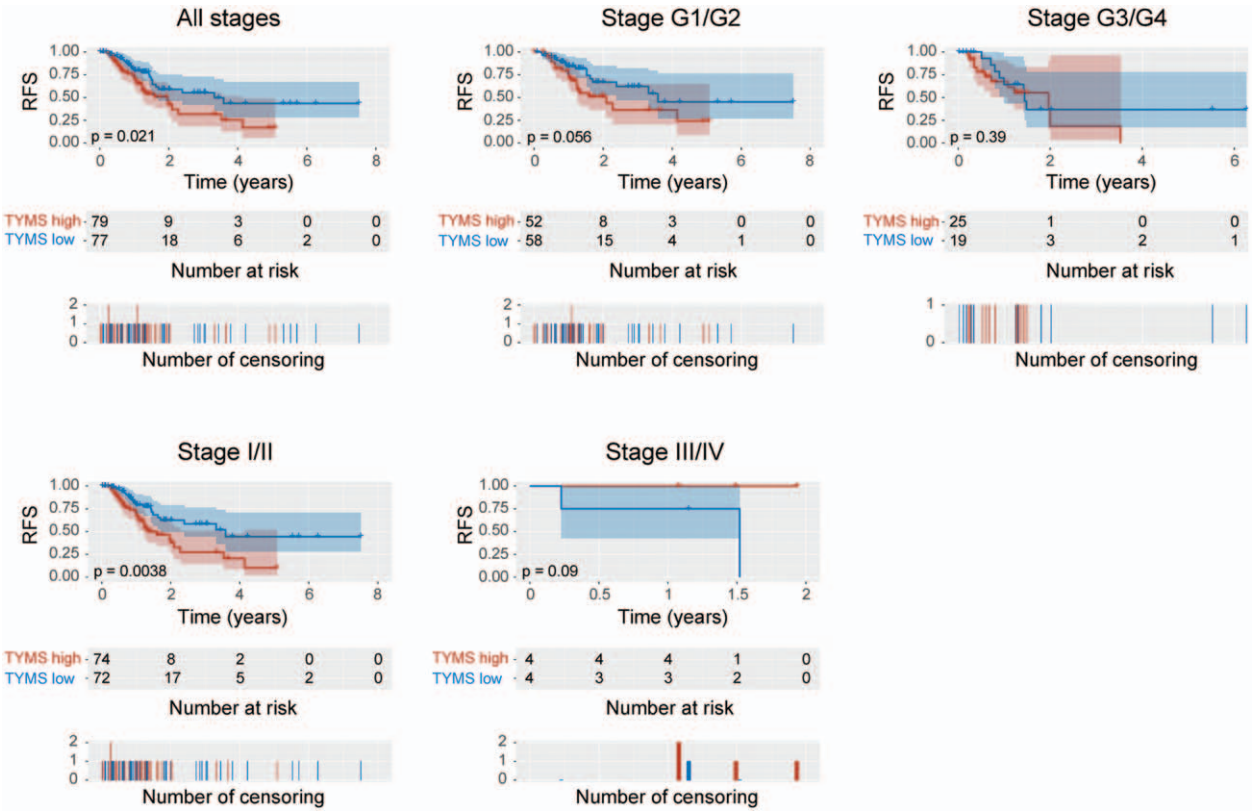

Figure 4. Kaplan–Meier curves of recurrence-free survival in patients with pancreatic cancer: in all tumors; histologic grades G1/G2 and G3/G4; and clinical stages I/II and III/IV.

Table 4

Univariate and multivariate analysis of recurrence-free survival in patients with pancreatic cancer.

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	0.95	0.52–1.74	.868			
Gender	1.15	0.68–1.94	.601			
Histological type	1.50	0.77–2.94	.235			
Stage	1.41	0.98–2.03	.062			
T classification	1.52	0.95–2.43	.081			
N classification	1.96	1.13–3.40	**.017**	1.96	1.11–3.47	**.021**
M classification	0.79	0.19–3.34	.747			
Residual tumor	1.70	1.21–2.38	**.002**	1.58	1.13–2.21	**.008**
TYMS	1.95	1.15–3.30	**.013**	1.92	1.13–3.28	**.016**

Bold values indicate $P < .05$ and is statistically significant. CI = confidence interval, HR = Hazard Ratio.

Acknowledgments

We thank Rebecca Porter, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

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References

[1] Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol 2016;22:9694–705.
[2] Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol 2018;24:2047–60.
[3] Hanahan D, Weinberg RA. The hallmark of cancer. Cell 2000;100:57–71.

[4] Gallegos-Arreola MP, Zuniga-Gonzalez GM, Sanchez-Lopez JY, et al. TYMS 2R3R polymorphism and DPYD [IVS]14+1G>A gene mutation in Mexican colorectal cancer patients. Acta Biochim Pol 2018; 65:227–34.
[5] Carreras CW, Santi DV. The catalytic mechanism and structure of thymidylate synthase. Annu Rev Biochem 1995;64:721–62.
[6] Burdelski C, Strauss C, Tsourlakis MC, et al. Overexpression of thymidylate synthase (TYMS) is associated with aggressive tumor features and early PSA recurrence in prostate cancer. Oncotarget 2015;6:8377–87.
[7] Team RDCR: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Computing 2012;1:12–21.
[8] Samur MK. RTCGAToolbox: a new tool for exporting TCGA firehose data. Plos One 2014;9:e106397.
[9] Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. Bmc Bioinformatics 2011;12:1–8.
[10] Therneau TM, April. A Package for Survival Analysis in S. 2015.
[11] Therneau TM, Grambsch PM. Modeling survival data: extending the cox model. Technometrics 2000;97:353–4.
[12] Jiao Y, Fu Z, Li Y, et al. High EIF2B5 mRNA expression and its prognostic significance in liver cancer: a study based on the TCGA and GEO database. Cancer Manag Res 2018;10:6003–14.
[13] Jiao Y, Fu Z, Li Y, et al. Aberrant FAM64A mRNA expression is an independent predictor of poor survival in pancreatic cancer. PLoS One 2019;14:e0211291.
[14] Gupta P, Suman S, Mishra M, et al. Autoantibodies against TYMS and PDLIM1 proteins detected as circulatory signatures in Indian breast cancer patients. Proteomics Clin Appl 2016;10:564–73.
[15] Sun S, Shi W, Wu Z, et al. Prognostic significance of the mRNA expression of ERCC1, RRM1, TUBB3 and TYMS genes in patients with non-small cell lung cancer. Exp Ther Med 2015;10:937–41.
[16] Russo GI, Bier S, Hennenlotter J, et al. Expression of tumour progression-associated genes in circulating tumour cells of patients at different stages of prostate cancer. BJU Int 2018;122:152–9.
[17] Xu W, Jiang H, Zhang F, et al. MicroRNA-330 inhibited cell proliferation and enhanced chemosensitivity to 5-fluorouracil in colorectal cancer by directly targeting thymidylate synthase. Oncol Lett 2017;13:3387–94.
[18] Jiang H, Wang H, Wang S, et al. Expression of ERCC1, TYMS, RRM1, TUBB3, non-muscle myosin II, myoglobin and MyoD1 in lung adenocarcinoma pleural effusions predicts survival in patients receiving platinum-based chemotherapy. Mol Med Rep 2015;11:3523–32.
[19] Abdallah EA, Fanelli MF, Buim ME, et al. Thymidylate synthase expression in circulating tumor cells: a new tool to predict 5-fluorouracil resistance in metastatic colorectal cancer patients. Int J Cancer 2015; 137:1397–405.
[20] Yeh HW, Lee SS, Chang CY, et al. Pyrimidine metabolic rate limiting enzymes in poorly-differentiated hepatocellular carcinoma are signature genes of cancer stemness and associated with poor prognosis. Oncotarget 2017;8:77734–51.
[21] Kamisawa T, Wood L, Itoi T, et al. Pancreatic cancer. Lancet 2016; 388:73–85.