Prognostic implications of tumoral and peritumoral infiltrating T-lymphocytes in pancreatic ductal adenocarcinoma

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Disclosure of COI

- All authors declare that there are no conflicts of interest associated with this study

Aim & Methods

- This study aimed to elucidate the prognostic implications of tumoral and peritumoral infiltrating T-lymphocytes in pancreatic ductal adenocarcinoma (PDAC) through a meta-analysis.

- Fourteen eligible studies and 1,572 PDAC patients were included in the present study. Parameters for tumoral and peritumoral infiltrating T-lymphocytes were CD3, CD4, CD8, FOXP3, and immunoscore. The correlations between these parameters and overall and disease-free survival were investigated and performed the meta-analysis.

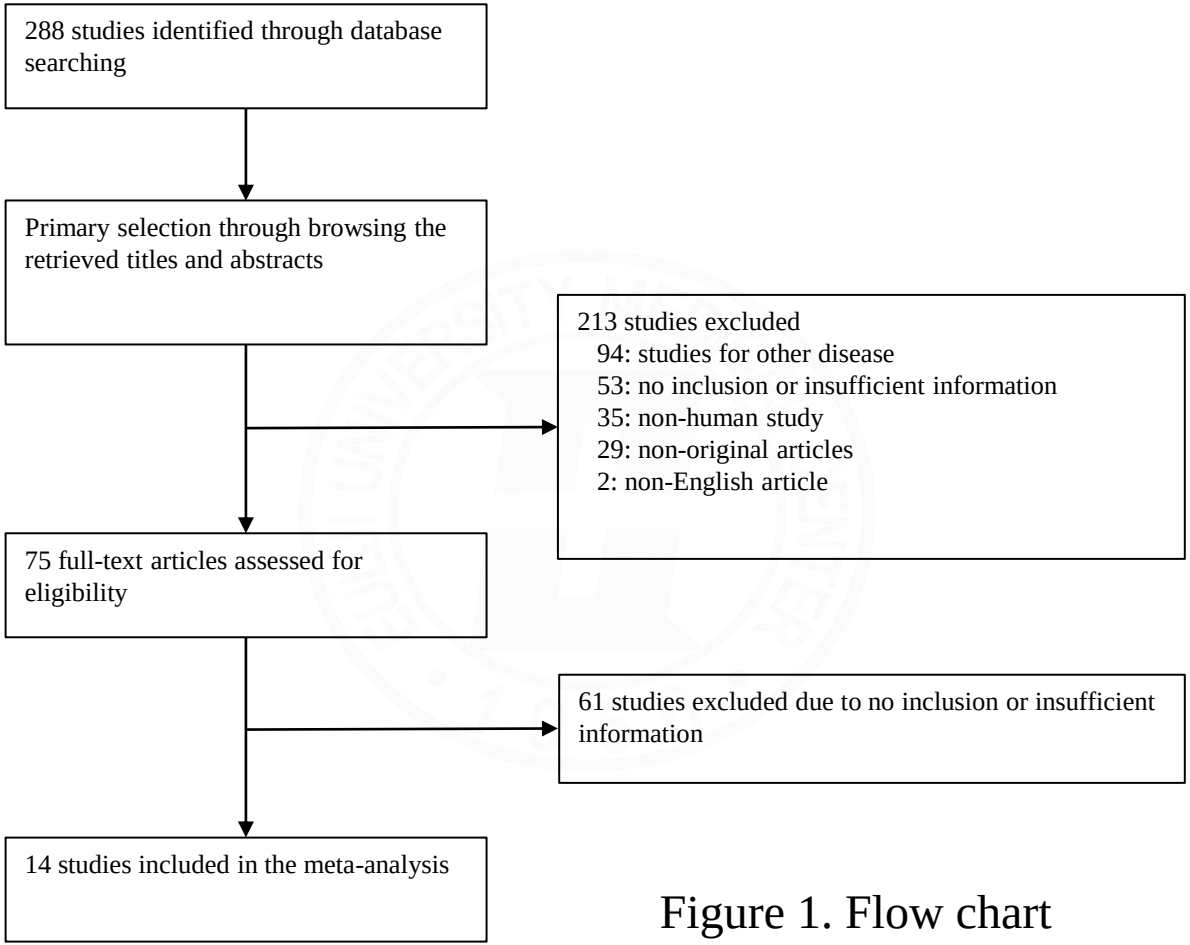


Figure 1. Flow chart

Results

- High intratumoral CD3, CD4, and CD8 infiltrations were significantly correlated with better overall survivals (hazard ratio [HR] 0.721, 95% confidence interval [CI] 0.590-0.880, HR 0.763, 95% CI 0.607-0.959, and HR 0.698, 95% CI 0.505-0.964, respectively).

- However, there survival no significant correlation between intratumoral FOXP3 and immunoscore and prognosis of PDAC (HR 1.336, 95% CI 0.770-2.319 and HR 0.776, 95% CI 0.566-1.065, respectively). In evaluations of disease-free survival, high intratumoral CD4 infiltration was only correlated with better prognosis (HR 0.525, 95% CI 0.341-0.810).

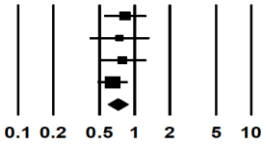
Table 1. Main characteristics of the eligible studies

Authors	Location	No of Patients	Tumor type	Tumor stage	Parameters				
					CD3	CD4	CD8	FOXP3	Immuno-score
Diana 2016	Canada	145	PDAC	ND			O	O	
Fukunaga 2004	Japan	80	PDAC	I-IV		O	O		
Homma 2014	Japan	22	PDAC	I-III			O		
Hwang 2016	Korea	30	PDAC	ND		O			
Liu 2015	China	72	PDAC	ND			O		
Liu 2016	China	92	PDAC	I-III			O		
Mota Reyes 2019	Germany	74	PDAC	ND		O			
Nejati 2017	USA	136	PDAC	ND		O			
Tahkola 2018	Finland	108	PDAC	I-II	O		O		O
Tahkola 2019	Finland	79	PDAC	I-III	O		O		O
Tang 2014	USA	228	PDAC	I-IV		O	O		
Tewari 2013	UK	81	PDAC	ND	O		O		
Wartenberg 2015	Switzerland	120	PDAC	I-IV			O		
Zhang 2019	China	305	PDAC	I-III	O		O	O	

ND, no description

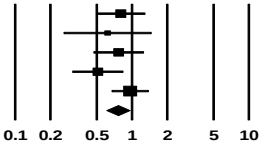
A

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Tahkola 2018	0.827	0.548	1.248	0.366
Tahkola 2019	0.740	0.412	1.328	0.313
Tewari 2013	0.783	0.491	1.249	0.305
Zhang 2019	0.646	0.482	0.865	0.003
	0.721	0.590	0.880	0.001



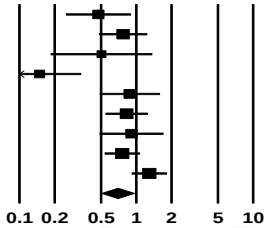
B

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Fukunaga 2004	0.803	0.497	1.295	0.367
Hwang 2016	0.618	0.261	1.463	0.274
Mota Reyes 2019	0.769	0.470	1.257	0.295
Nejati 2017	0.510	0.310	0.840	0.008
Tang 2014	0.965	0.673	1.383	0.845
	0.763	0.607	0.959	0.020



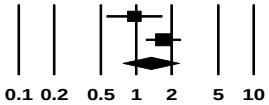
C

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Diana 2016	0.474	0.251	0.894	0.021
Fukunaga 2004	0.771	0.481	1.237	0.281
Homma 2014	0.504	0.186	1.363	0.177
Liu 2015	0.149	0.066	0.336	0.000
Liu 2016	0.880	0.489	1.585	0.670
Tahkola 2018	0.827	0.548	1.248	0.366
Tahkola 2019	0.910	0.487	1.700	0.767
Tang 2014	0.758	0.538	1.067	0.113
Zhang 2019	1.292	0.917	1.821	0.143
	0.698	0.505	0.964	0.029



D

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Diana 2016	0.965	0.561	1.660	0.898
Zhang 2019	1.704	1.215	2.389	0.002
	1.336	0.770	2.319	0.303



E

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Tahkola 2018	0.786	0.521	1.186	0.251
Tahkola 2019	0.763	0.466	1.251	0.284
	0.776	0.566	1.065	0.117

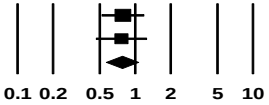


Figure 2. Forest plots for overall survival. (A) CD3. (B) CD4. (C) CD8. (D) FOXP3. (E) Immunoscore

Table 2. The prognostic roles of peritumoral infiltrating T-lymphocytes in pancreatic cancers

Overall survival	Number of subsets	Fixed effect [95% CI]	Heterogeneity test [*P*-value]	Random effect [95% CI]	Egger's Test [*P*-value]
Peritumoral CD3					
High vs. Low	3	1.123 [0.905, 1.395]	0.080	1.000 [0.671, 1.489]	0.072
Peritumoral CD8					
High vs. Low	5	0.905 [0.721, 1.135]	< 0.001	0.749 [0.381, 1.473]	0.083
Peritumoral FOXP3					
High vs. Low	1	1.647 [0.860, 3.154]	1.000	1.647 [0.860, 3.154]	-

CI, Confidence interval

Supplementary Table 1. The prognostic roles of tumor-infiltrating T-lymphocytes in pancreatic cancers

Overall survival	Number of subsets	Fixed effect [95% CI]	Heterogeneity test [*P*-value]	Random effect [95% CI]	Egger's Test [*P*-value]
Intratumoral CD3					
High vs. Low	4	0.721 [0.590,0.880]	0.778	0.721 [0.590, 0.880]	0.303
Intratumoral CD4					
High vs. Low	5	0.768 [0.620, 0.953]	0.354	0.763 [0.607, 0.959]	0.288
Intratumoral CD8					
High vs. Low	9	0.799 [0.679, 0.940]	0.001	0.698 [0.505, 0.964]	0.050
Intratumoral FOXP3					
High vs. Low	2	1.453 [1.091, 1.936]	0.081	1.336 [0.770, 2.319]	-
Immunoscore					
High vs. Low	2	0.776 [0.566, 1.065]	0.930	0.776 [0.566, 1.065]	-

CI, Confidence interval

Supplementary Table 2. The prognostic roles of tumor- or stromal-infiltrating T-lymphocytes in pancreatic cancers

Disease-free survival	Number of subsets	Fixed effect [95% CI]	Heterogeneity test [*P*-value]	Random effect [95% CI]	Egger's Test [*P*-value]
CD3					
Intratumoral, high vs. low	2	0.764 [0.542, 1.078]	0.612	0.764 [0.542, 1.078]	-
Peritumoral, high vs. low	1	0.560 [0.290, 1.081]	1.000	0.560 [0.290, 1.081]	-
CD4					
Intratumoral, high vs. low	2	0.525 [0.341, 0.810]	0.815	0.525 [0.341, 0.810]	-
Peritumoral, high vs. low	0				
CD8					
Intratumoral, high vs. low	3	0.854 [0.644, 1.134]	0.955	0.854 [0.644, 1.134]	0.460
Peritumoral, high vs. low	2	0.810 [0.580, 1.131]	0.959	0.810 [0.580, 1.131]	-
Immunoscore					
High vs. Low	2	0.766 [0.558, 1.052]	0.915	0.766 [0.558, 1.052]	-

CI, Confidence interval

*, Comparison between the results of endoscopic and surgical resection; †, Comparison between malignancies in endoscopic and surgical resection

Conclusions

- Our results showed that high TILs were significantly correlated with a better prognosis of PDAC.

- However, among parameters of TILs, CD3, CD4, and CD8, but not FOXP3 and immunoscore, had the prognostic implications.