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Background

- High YAP1 expression correlates with the 'T-cell inflamed' expression phenotype in small cell lung cancer (SCLC), but its association with other biomarkers of immune checkpoint vulnerability and in tumor types beyond SCLC is not known.
- We examined whether YAP1 expression correlates with other established markers of immune checkpoint blockade (ICB) efficacy (PDL1 expression and TMB) in a tumor agnostic manner to determine clinical relevance

Methods

- Next-generation sequencing of DNA (592 gene panel or whole exome) and RNA (whole transcriptome) was performed for patient samples (n = 57,134), representing 13 cancer types, submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ).
- The 'T-cell inflamed' signature (TIS) score was calculated as an 18-gene weighted coefficient composite value (Cristescu, 2018).
- PDL1 expression was assessed by immunohistochemistry (IHC) with cancer type-specific antibodies and thresholds, and high tumor mutational burden was defined as ≥10 mut/Mb.
- Patients were stratified into subgroups based on median YAP1 expression (YAP1-High/YAP1-Low) within each cancer type.
- Significance was tested by Chi-square, Fisher's exact test, or Mann-Whitney U test.

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Results

Table 1 – Demographics of YAP-High and YAP1-Low tumors stratified by median YAP1 expression for cancer types included in the study.

Cancer Type (abbreviation)	Samples (N)	Median Age (range)		Gender, Male % (N)	
		YAP1-High	YAP1-Low	YAP1-High	YAP1-Low
Total	57134				
Lung Small Cell Cancer (SCLC)	882	67.0 (32 – 90+)	66.0 (18 – 90+)	51.9% (229/441)	51.7% (228/441)
Bladder cancer (BLCA)	3399	72.0 (24 – 90+)	72.0 (18 – 90+)	73.8% (1254/1700)	70.8% (1203/1699)
Breast Carcinoma (BRCA)	9910	61.0 (19 – 90+)	61.0 (23 – 90+)	1.1% (56/4955)	1.3% (64/4955)
Cervical Cancer (CECA)	1773	52.0 (19 – 90+)	52.0 (23 – 90+)	0.1% (1/887)	0.0% (0/886)
Esophagogastric Junction Carcinoma (EGJ)	1005	66.0 (26 – 90+)	67.0 (26 – 90+)	83.3% (419/503)	83.3% (418/502)
Endometrial carcinoma (ENCA)	6271	66.0 (26 – 90+)	66.0 (18 – 90+)	0.1% (3/3136)	0.0% (0/3135)
Esophageal Carcinoma (ESCA)	2179	66.0 (14 – 90+)	67.0 (28 – 90+)	83.2% (907/1090)	80.5% (877/1089)
Gastric Adenocarcinoma (GACA)	1925	66.0 (21 – 90+)	64.0 (19 – 90+)	57.3% (552/963)	59.5% (572/962)
Liver Hepatocellular Carcinoma (HCC)	532	66.0 (13 – 90+)	67.0 (17 – 90+)	76.3% (203/266)	75.2% (200/266)
Melanoma (MM)	2899	68.0 (3 – 90+)	67.0 (5 – 90+)	60.3% (874/1450)	63.7% (923/1449)
Lung Non-small cell lung cancer (NSCLC)	19891	69.0 (21 – 90+)	69.0 (24 – 90+)	50.0% (4973/9946)	50.7% (5044/9945)
Pancreatic Adenocarcinoma (PAAD)	5135	67.5 (17 – 90+)	68.0 (13 – 90+)	53.7% (1380/2568)	52.5% (1348/2567)
Kidney Cancer (RCC)	1333	63.0 (4 – 90+)	64.0 (4 – 90+)	67.2% (448/667)	75.4% (502/666)

Figure 1 – YAP1-High tumors were positively associated with TIS score.

- YAP1-High tumors were associated with significantly increased TIS scores compared to YAP1-Low across all 13 cancer types examined, with the largest fold increase observed in SCLC (1.33-fold, p < 0.0001), followed by pancreatic cancer (1.28-fold, p < 0.0001), while the smallest occurred in melanoma (1.13-fold, p < 0.0001).
- Spearman correlation strength (range 0.23-0.57) between YAP expression and TIS scores was consistent with increased TIS scores in YAP1-High samples.

Cancer Type	N YAP1-High	N YAP1-Low	YAP1-High (TIS Median)	YAP1-Low (TIS Median)	Fold change (High/Low)	p-value	Spearman Correlation (YAP1 vs TIS)	p-value
PAAD	2568	2567	4.23	3.30	1.28	1.22E-302	0.60	0
HCC	266	266	4.01	3.17	1.26	4.11E-24	0.48	1.00E-32
EGJ	503	502	4.40	3.50	1.26	1.06E-56	0.55	5.38E-80
GACA	963	962	4.48	3.70	1.21	1.35E-72	0.46	1.25E-102
BRCA	4955	4955	4.30	3.56	1.21	0	0.43	0
ESCA	1090	1089	4.35	3.62	1.20	3.57E-71	0.43	9.50E-101
ENCA	3136	3135	4.16	3.48	1.20	1.55E-163	0.40	1.18E-244
NSCLC	9946	9945	4.63	3.88	1.19	0	0.38	0
CECA	887	886	4.69	3.96	1.18	2.41E-41	0.36	8.36E-57
BLCA	1700	1699	4.24	3.57	1.19	1.78E-67	0.36	6.15E-102
RCC	667	666	4.77	3.98	1.20	1.45E-33	0.38	3.94E-48
MM	1450	1449	4.58	4.07	1.13	2.50E-25	0.23	5.19E-35

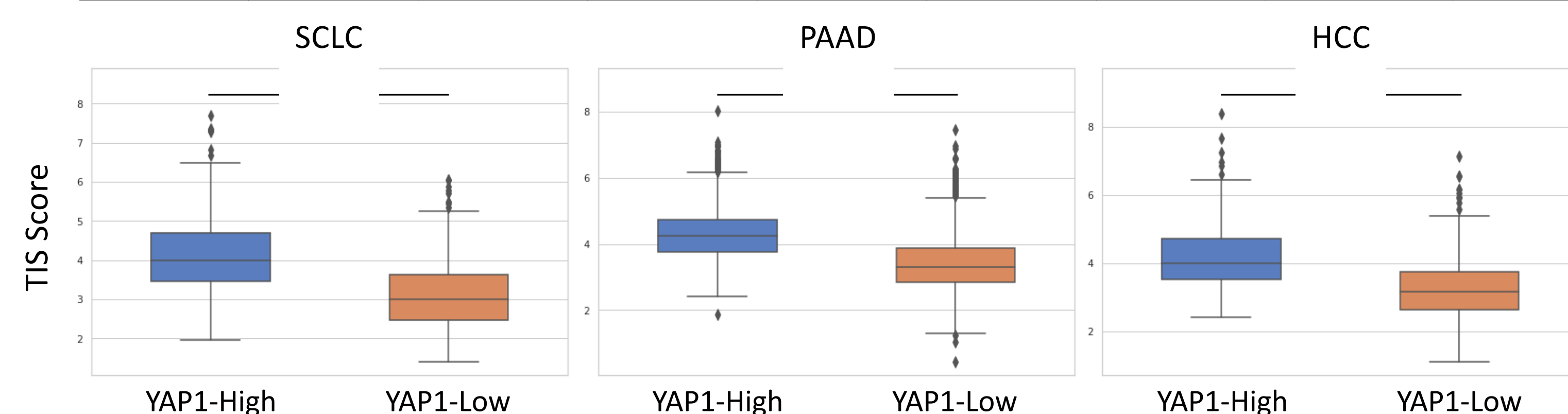


Figure 2 – YAP1 expression was not significantly increased in PDL1+ (IHC) tumors for most cancer types. However, significantly decreased YAP1 expression was associated with PDL1+ samples in RCC (Renal Cell Carcinoma) (0.91-fold change, P < 0.05), MM (0.90-fold change, P < 0.001), and ENCA (0.80-fold change, P < 0.0001)

Cancer Type	PDL1+ Threshold	N PDL1+	N PDL1-	PDL1+ YAP1 Median	PDL1- YAP1 Median	Fold Change	p-value
SCLC	CPS ≥1	212	323	11.05	9.46	1.17	0.13485197
EGJ	CPS ≥1	759	187	48.69	45.71	1.07	0.13619984
BLCA	CPS ≥10	59	95	67.27	64.94	1.04	0.33575845
GACA	CPS ≥1	337	1481	45.82	44.93	1.02	0.64857824
NSCLC	TPS ≥1	2571	1901	55.95	55.60	1.01	0.92192104
CECA	CPS ≥1	1433	283	47.80	49.75	0.96	0.95754635
ESCA	CPS ≥10	559	1470	46.99	50.68	0.93	0.18273689
BRCA	CPS ≥10	177	829	39.86	43.31	0.92	0.95727302

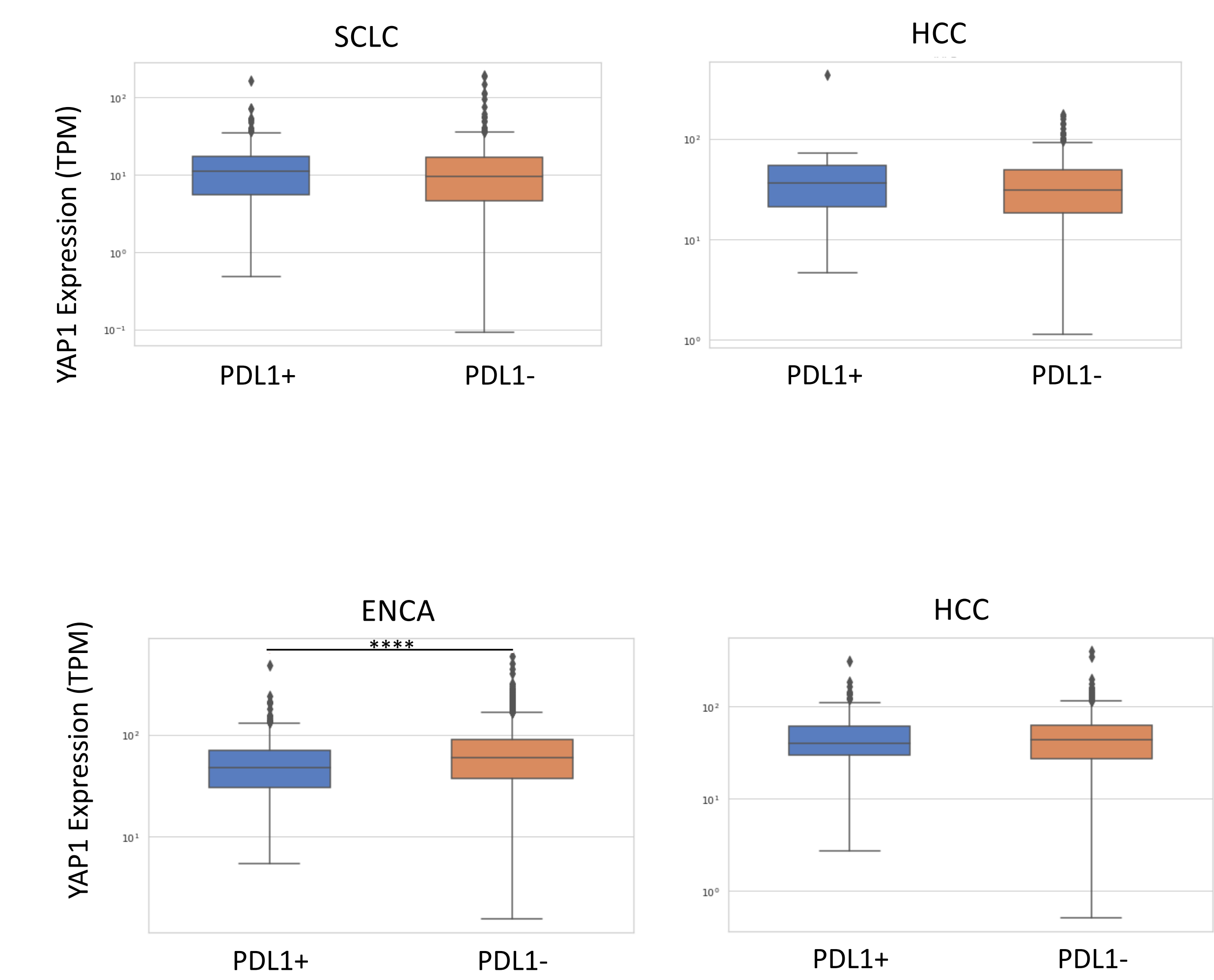
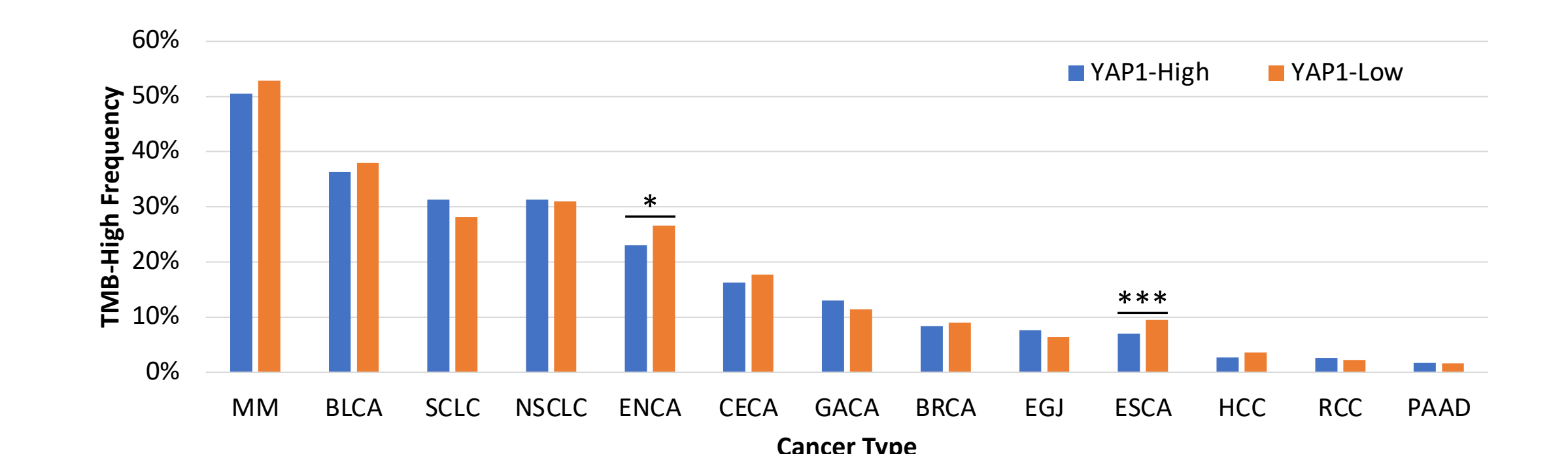
Cancer Type	PDL1+ Threshold (SP142, TC)	N PDL1+	N PDL1-	PDL1+ YAP1 Median	PDL1- YAP1 Median	Fold Change	p-value
HCC	2+ [5%	28	465	35.99	30.85	1.17	0.53203459
PAAD	2+ [5%	767	4105	49.07	48.43	1.01	0.1336948
RCC	2+ [5%	242	1038	35.42	38.77	0.91	0.04126015
MM	1+ [1%	1103	1429	35.80	39.97	0.90	0.00062939
ENCA	2+ [5%	454	5698	47.34	59.30	0.80	1.54E-11
BRCA	2+ [5%	2	78	28.30	38.78	0.73	0.39556962

Cancer Type	PDL1+ Threshold (SP142, IC)	N PDL1+	N PDL1-	PDL1+ YAP1 Median	PDL1- YAP1 Median	Fold Change	p-value
BRCA	IC ≥5%	610	7649	37.90	35.34	1.07	0.26373675
BLCA	IC ≥5%	846	2280	47.33	52.31	0.90	0.05647143

Figure 3 – TMB-High (≥10 mut/Mb) rates in YAP-High and YAP1-Low tumors.

For most cancer types, TMB-High rates were similar in YAP-High and YAP1-Low tumors, with slightly lower rates in YAP1-High tumors observed for ENCA (23.0 vs 26.6%, p < 0.001***) and ESCA (7.0 vs 9.5%, p < 0.05*) cancers.

Cancer Type	YAP1-High			YAP1-Low			p-value
	N TMB-High	N TMB-Low	% TMB-High	N TMB-High	N TMB-Low	% TMB-High	
MM	720	705	50.5%	751	668	52.9%	0.20064
BLCA	603	1059	36.3%	633	1031	38.0%	0.29381
SCLC	135	296	31.3%	122	312	28.1%	0.30134
NSCLC	782	1718	31.3%	583	1299	31.0%	0.83062
ENCA	703	2356	23.0%	820	2260	26.6%	0.00095
CECA	142	731	16.3%	154	714	17.7%	0.41231
GACA	123	821	13.0%	107	832	11.4%	0.27879
BRCA	397	4306	8.4%	426	4300	9.0%	0.32469
EGJ	37	452	7.6%	31	456	6.4%	0.46122
ESCA	75	989	7.0%	101	962	9.5%	0.04009
HCC	7	252	2.7%	9	243	3.6%	0.57293
RCC	17	629	2.6%	14	636	2.2%	0.57359
PAAD	43	2446	1.7%	40	2445	1.6%	0.74542



Conclusions

- Our analyses provide confirmation that YAP1 expression positively correlates with the 'T-cell inflamed' phenotype across many cancer types, including those with approvals for (ICB) therapy.
- YAP1 expression was independent of established markers of ICB response, including TMB and PDL1.
- Further analysis of YAP1 expression as an additional tumor agnostic predictive biomarker is warranted.

References

1. Owonikoko, T. K., Dwivedi, B., Chen, Z., Zhang, C., Barwick, B., Ernani, V., Zhang, G., Gilbert-Ross, M., Carlisle, J., Khuri, F. R., Curran, W. J., Ivanov, A. A., Fu, H., Lonial, S., Ramalingam, S. S., Sun, S. Y., Waller, E. K., & Sica, G. L. (2021). YAP1 Expression in SCLC Defines a Distinct Subtype With T-cell-Inflamed Phenotype. *Journal of thoracic oncology* : official publication of the International Association for the Study of Lung Cancer, 16(3), 464–476. <https://doi.org/10.1016/j.jtho.2020.11.006>