PIN1 mRNA expression in biliary tract cancer: A multiomic analysis of its prognostic relevance and association with tumor-immune states in a large real-world cohort.

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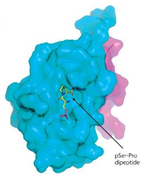
INTRODUCTION

- *PIN1* (peptidyl-prolyl cis-trans isomerase NIMA-interacting 1) overexpression is seen in many tumor types and has been correlated with poor prognosis[1]
- Previous studies in pancreatic cancer have associated higher *PIN1* expression with an immunosuppressive tumor microenvironment (TME)[2]
- Inhibition of *PIN1* in animal models renders pancreatic cancer eradicable by chemo/immunotherapy[2-3]
- Like pancreatic cancer, biliary tract cancers (BTCs) carry a poor prognosis and are characterized by desmoplastic stroma[4]
- We hypothesized that *PIN1* expression may have similar roles and implications in BTCs



PIN1 structure[5]

METHODS

- Tempus Lens was used to identify pts with primary diagnosis of BTC (intrahepatic or extrahepatic cholangiocarcinoma or gallbladder adenocarcinoma) who had Tempus xT DNA and xR RNA sequencing
- RNA-Seq data normalized to correct for assay/batch effects, quantified as transcripts per million (TPM) and reported as $\log_2$(TPM+1)
- *PIN1*-High (n=2240) vs. Low (n=2239) split on median mRNA expression
- Immune cell proportions and cytolytic, cytotoxic, and interferon-γ immune scores estimated from RNA expression
- Somatic alterations assessed: pathogenic/likely pathogenic short variants (SNVs and indels), copy number alterations in *IDH1*, *IDH2*, *PBRM1*, *FGFR2*, *BRAF*, *ERBB2* (amplification), *KRAS*, *NRAS*, *TP53*, *PIK3CA*, *BRCA1*, *BRCA2*, *ATM*, *POLE*, *MET* (amplification), *BAP1*, *ARID1A*, *CDKN2A*, *CDKN2B*, *KMT2C*, *TERT*, *KMT2D*, *SMAD4*, *LRP1B*; and gene fusions in *FGFR2*, *NTRK1/2/3*, *ROS1*, and *RET*.
- Real-world overall survival (rwOS) defined as time from sample collection to death or loss to follow up

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

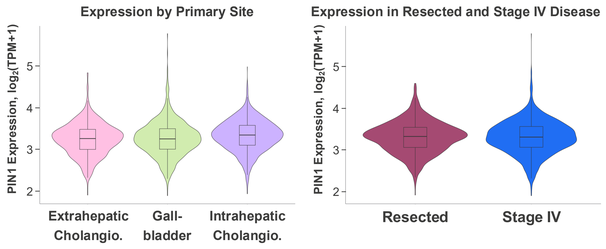
	Overall N = 4,479[1]	PIN1 PIN1-High N = 2,240[1]	PIN1 PIN1-Low N = 2,239[1]	p-value[2]
Age at Sample Collection				0.009
Median (Q1, Q3)	67 (59, 74)	67 (58, 74)	68 (60, 74)	
Sex				0.069
Female	2,474 (55%)	1,207 (54%)	1,267 (57%)	
Male	2,005 (45%)	1,033 (46%)	972 (43%)	
Race				0.11
White	1,955 (77%)	1,032 (79%)	923 (75%)	
Black or African American	265 (10%)	122 (9.3%)	143 (12%)	
Asian	129 (5.1%)	64 (4.9%)	65 (5.3%)	
Other Race	197 (7.7%)	93 (7.1%)	104 (8.4%)	
Ethnicity				0.3
Hispanic or Latino	307 (18%)	141 (17%)	166 (19%)	
Not Hispanic or Latino	1,379 (82%)	682 (83%)	697 (81%)	
Staging Closest to Sample Collection (within 90 days)				0.5
Stage 1	111 (4.1%)	51 (3.9%)	60 (4.3%)	
Stage 2	226 (8.4%)	103 (7.8%)	123 (8.9%)	
Stage 3	377 (14%)	193 (15%)	184 (13%)	
Stage 4	1,991 (74%)	976 (74%)	1,015 (73%)	
Unknown	1,774	917	857	
Tumor Site				<0.001
Intrahepatic biliary tract	2,054 (46%)	1,122 (50%)	932 (42%)	
Extrahepatic duct	667 (15%)	307 (14%)	360 (16%)	
Gallbladder	1,050 (23%)	462 (21%)	588 (26%)	
Biliary tract (unspecified)	708 (16%)	349 (16%)	359 (16%)	
Resection Status				0.8
Non-Resected	3,426 (76%)	1,709 (76%)	1,717 (77%)	
Resected	1,053 (24%)	531 (24%)	522 (23%)	

[1] *n (%)*

[2] *Pearson's Chi-squared test*

PIN1 mRNA EXPRESSION

	Overall N = 4,479	PIN1 PIN1-High N = 2,240	PIN1 PIN1-Low N = 2,239	p-value
mRNA expression level of PIN1				<0.001
Median (Q1, Q3)	3.31 (3.06, 3.54)	3.54 (3.42, 3.71)	3.06 (2.85, 3.19)	
Min, Max	1.82, 5.78	3.31, 5.78	1.82, 3.31	



TUMOR IMMUNE ENVIRONMENT

	Overall N = 4,479	Median % (Q1, Q3) PIN1-High N = 2,240	PIN1-Low N = 2,239	p-value[1]
Cell types				
B cells	4.23 (3.22, 5.69)	4.23 (3.29, 5.63)	4.23 (3.18, 5.75)	0.2
CD4 T cells	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.2
CD8 T cells	0.27 (0.00, 1.09)	0.27 (0.00, 1.22)	0.26 (0.00, 1.00)	0.1
Treg cells	3.51 (2.42, 5.17)	3.73 (2.63, 5.47)	3.33 (2.24, 4.89)	<0.001
NK cells	2.67 (2.08, 3.35)	2.82 (2.22, 3.49)	2.51 (1.96, 3.17)	<0.001
M1 macrophages	7.31 (5.29, 9.97)	7.71 (5.52, 10.39)	6.93 (5.07, 9.48)	<0.001
M2 macrophages	4.14 (2.77, 5.76)	4.14 (2.72, 5.72)	4.15 (2.83, 5.84)	0.2
Monocytes	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	<0.001
Neutrophils	6.80 (5.18, 8.92)	6.55 (4.94, 8.75)	7.03 (5.39, 9.10)	<0.001
Dendritic Cells	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.002
Other Cells	68.23 (61.39, 73.34)	67.79 (60.47, 72.84)	68.50 (62.10, 73.78)	<0.001
Immune Scores				
Cytolytic Score	3.56 (2.89, 4.26)	3.63 (2.93, 4.38)	3.49 (2.85, 4.16)	<0.001
Cytotoxic Score	3.73 (3.26, 4.26)	3.76 (3.28, 4.32)	3.71 (3.25, 4.21)	0.012
FNgamma Score	3.59 (3.00, 4.21)	3.62 (3.00, 4.23)	3.56 (3.00, 4.17)	0.048

[1] *Wilcoxon rank sum test*

SOMATIC ALTERATIONS

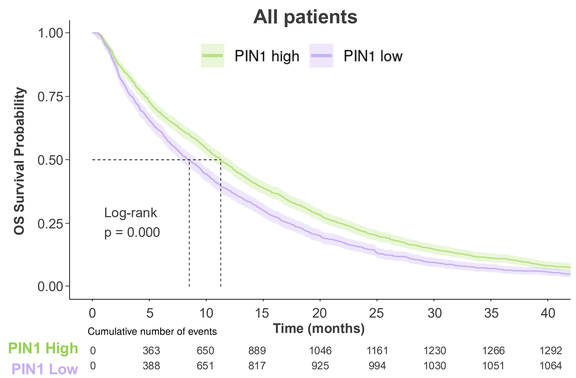
Gene	Overall N = 4,479[1]	PIN1 PIN1-High N = 2,240[1]	PIN1 PIN1-Low N = 2,239[1]	p-value[2]	q-value[3]
TP53	1,956 (44%)	892 (40%)	1,064 (48%)	<0.001	**<0.001**
IDH1	422 (9.4%)	262 (12%)	160 (7.1%)	<0.001	**<0.001**
ERBB2	171 (3.8%)	53 (2.4%)	118 (5.3%)	<0.001	**<0.001**
LRP1B	163 (3.6%)	55 (2.5%)	108 (4.8%)	<0.001	**<0.001**
SMAD4	517 (12%)	226 (10%)	291 (13%)	0.002	**0.011**
ARID1A	749 (17%)	406 (18%)	343 (15%)	0.012	**0.048**
IDH2	127 (2.8%)	77 (3.4%)	50 (2.2%)	0.015	0.052
BAP1	417 (9.3%)	231 (10%)	186 (8.3%)	0.021	0.063
FGFR2	100 (2.2%)	61 (2.7%)	39 (1.7%)	0.026	0.07
KRAS	897 (20%)	420 (19%)	477 (21%)	0.033	0.078
BRCA2	96 (2.1%)	58 (2.6%)	38 (1.7%)	0.039	0.086
ATM	174 (3.9%)	75 (3.3%)	99 (4.4%)	0.063	0.13
KMT2D	186 (4.2%)	82 (3.7%)	104 (4.6%)	0.1	0.2
PBRM1	367 (8.2%)	196 (8.8%)	171 (7.6%)	0.2	0.3
BRAF	155 (3.5%)	84 (3.8%)	71 (3.2%)	0.3	0.4
MET	58 (1.3%)	25 (1.1%)	33 (1.5%)	0.3	0.4
KMT2C	243 (5.4%)	116 (5.2%)	127 (5.7%)	0.5	0.6
NRAS	123 (2.7%)	65 (2.9%)	58 (2.6%)	0.5	0.6
BRCA1	36 (0.8%)	20 (0.9%)	16 (0.7%)	0.5	0.6
POLE	1 (<0.1%)	0 (0%)	1 (<0.1%)	0.5	0.6
TERT	332 (7.4%)	162 (7.2%)	170 (7.6%)	0.6	0.7
PIK3CA	291 (6.5%)	142 (6.3%)	149 (6.7%)	0.7	0.7
CDKN2B	745 (17%)	377 (17%)	368 (16%)	0.7	0.8
CDKN2A	1,018 (23%)	505 (23%)	513 (23%)	0.8	0.8

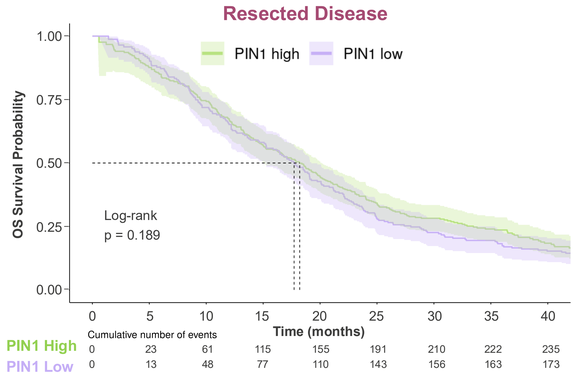
[1] *n (%)*

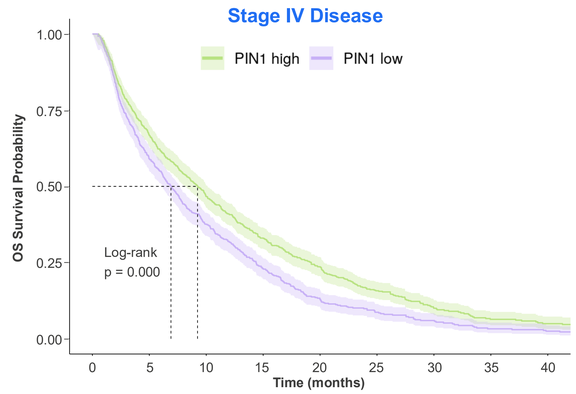
[2] *Pearson's Chi-squared test; Fisher's exact test*

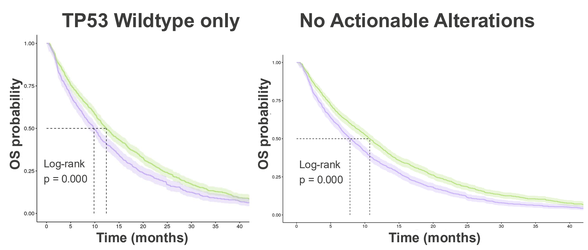
[3] *False discovery rate correction for multiple testing*

REAL-WORLD OVERALL SURVIVAL









RESPONSE TO 1ST-LINE THERAPY

	Overall N = 558[1]	PIN1 PIN1-High N = 285[1]	PIN1 PIN1-Low N = 273[1]	p-value[2]
Response within 90 Days				0.14
Complete Response	8 (2.3%)	1 (0.6%)	7 (4.0%)	
Partial Response	96 (28%)	51 (29%)	45 (26%)	
Stable Disease	93 (27%)	50 (28%)	43 (25%)	
Progressive Disease	152 (44%)	74 (42%)	78 (45%)	
Unknown	209	109	100	
Response within 180 Days				0.7
Complete Response	13 (2.6%)	5 (2.0%)	8 (3.2%)	
Partial Response	143 (29%)	75 (31%)	68 (27%)	
Stable Disease	122 (25%)	62 (25%)	60 (24%)	
Progressive Disease	215 (44%)	103 (42%)	112 (45%)	
Unknown	65	40	25	

[1] n (%)

[2] Fisher's exact test; Pearson's Chi-squared test

KEY RESULTS & CONCLUSIONS

- Median real-world OS was significantly longer for *PIN1*-High vs. *PIN1*-Low (11.3 vs. 8.5 mo), driven primarily by stage IV disease
- No statistical difference in survival seen when restricting to patients who underwent surgical resection
- *PIN1*-High status associated with lower rates of *TP53* (40 vs. 48%) and *ERBB2* alterations (2.4 vs 5.3%) and higher rates of *IDH1* alterations (12 vs 7.1%) (all q<0.001)
- However, significant difference in survival favoring *PIN1*-High persists after stratifying by *TP53* status or presence/absence of actionable alterations
- The TME of the *PIN1*-High group showed significantly higher enrichment in M1 macrophages (p<0.001) as well as cytolytic (p<0.001), cytotoxic (p=0.012), and interferon-γ (p=0.048) signatures compared to the *PIN1*-L group, though these differences were numerically small
- These findings stand in contrast with much of the literature on the role of *PIN1* in malignancy, particularly pancreatic cancer, though a recent study in lung adenocarcinoma also showed improved OS and immune response with PIN overexpression[6]
- Follow-up studies using mouse models of biliary tract cancers and clinically-annotated tumor microarrays are underway to reconcile these findings and better understand nuances and context of *PIN1*'s role in biliary tract cancers, e.g. based on cell type, patterns of expression, and cancer stage

REFERENCES

1. Lu Z and Hunter T. *Cell Research*, 2014
2. Koikawa K et al. *Cell*, 2021
3. Liu J et al. *Nature Communications*, 2022
4. Sirica AE and Gores GJ. *Hepatology*, 2015
5. Lu KP and Zhou XZ. *Nature Reviews Molecular Cell Biology*, 2007
6. Yu J et al. *Functional & Integrative Genomics*, 2025

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