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Epithelial-to-mesenchymal transition in extranodal extension of distal extrahepatic bile duct carcinoma with AI-assisted analyses

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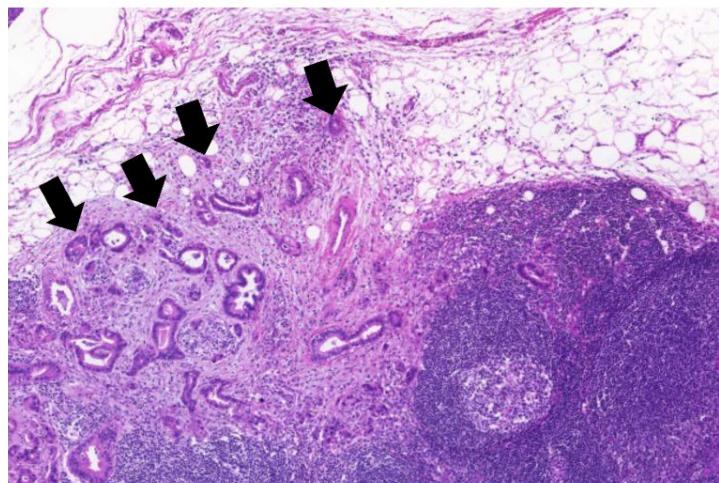
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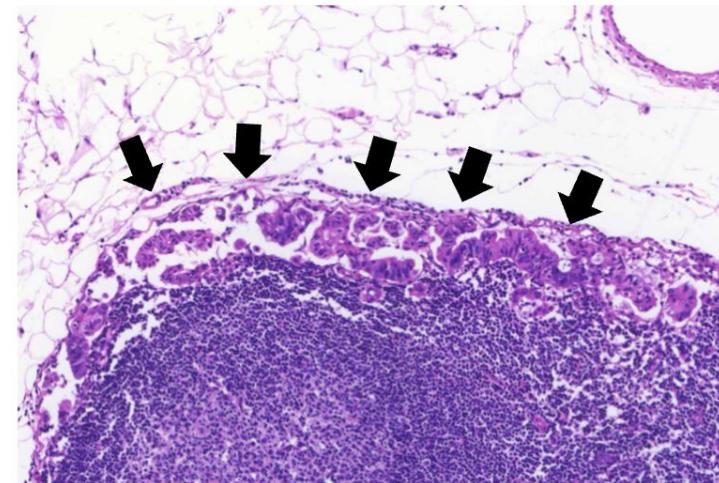


Distal extrahepatic bile duct (EBD) carcinoma

- Aggressive nature, complex location
- Often leads to advanced disease presentation
- Lymph node metastasis (NM): Critical in progression and staging
- Extranodal extension (ENE): Impact on distal EBD carcinoma under-explored

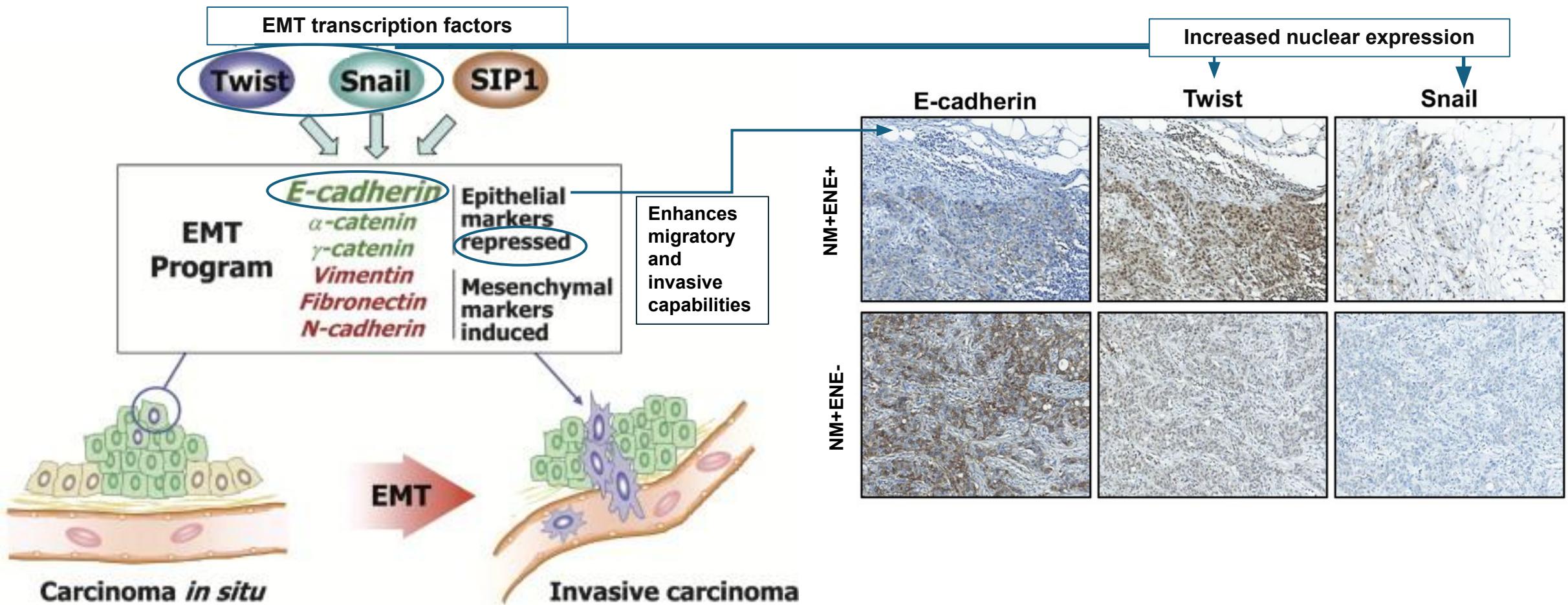


Lymph node metastasis with ENE



Lymph node metastasis without ENE

Epithelial-Mesenchymal Transition (EMT)



Objectives

1. Evaluate the impact of ENE on prognosis in distal EBD carcinoma
2. Analyze EMT markers in nodal metastasis with/without ENE using AI-assisted techniques : a novel assessment

Methods

Study cohort: 595 surgically resected distal EBD carcinoma cases

Clinicopathological analysis:

- Age, sex, growth pattern, depth of invasion (DOI, mm), pT category, differentiation, pancreas and duodenum invasion, histologic type, cancer size (cm), lymphovascular invasion (LVI), perineural invasion (PNI)

Survival analysis: Overall survival (OS) and Recurrence-free survival (RFS)

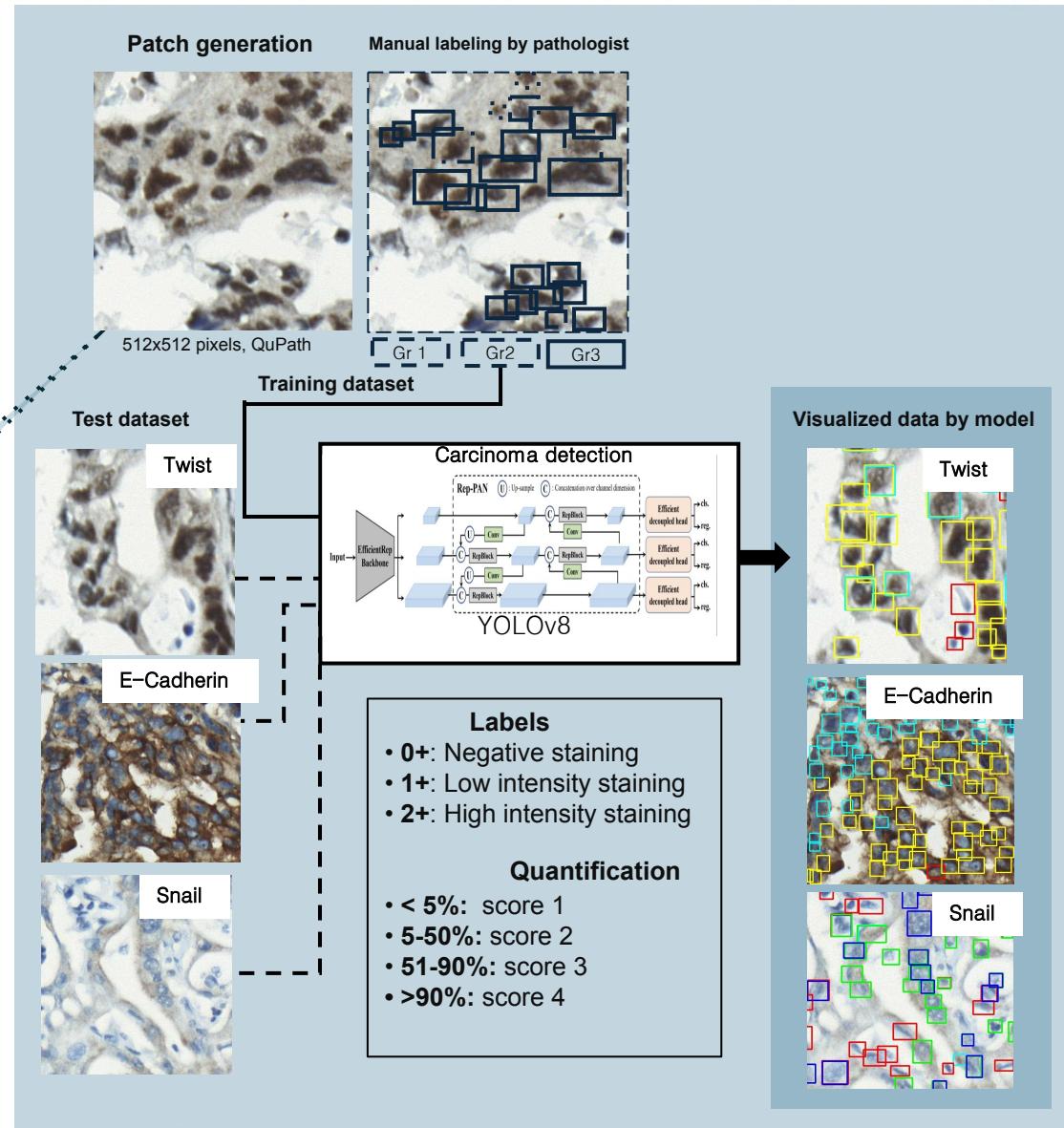
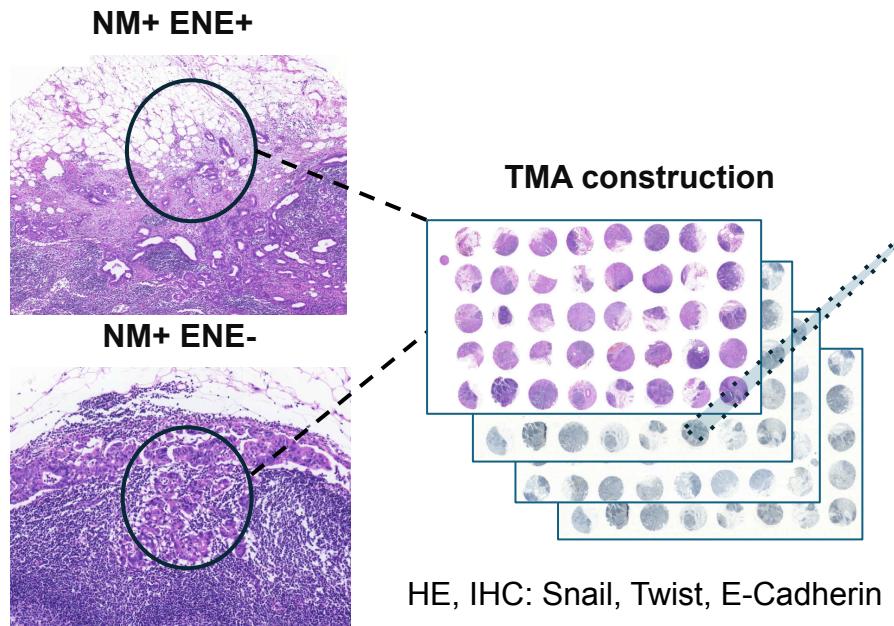
Immunohistochemistry for EMT markers:

- E-cadherin, Twist, Snail

AI-assisted analysis:

- YOLOv8 model-assisted objective quantification of IHC markers

AI-Driven Immuno-Index



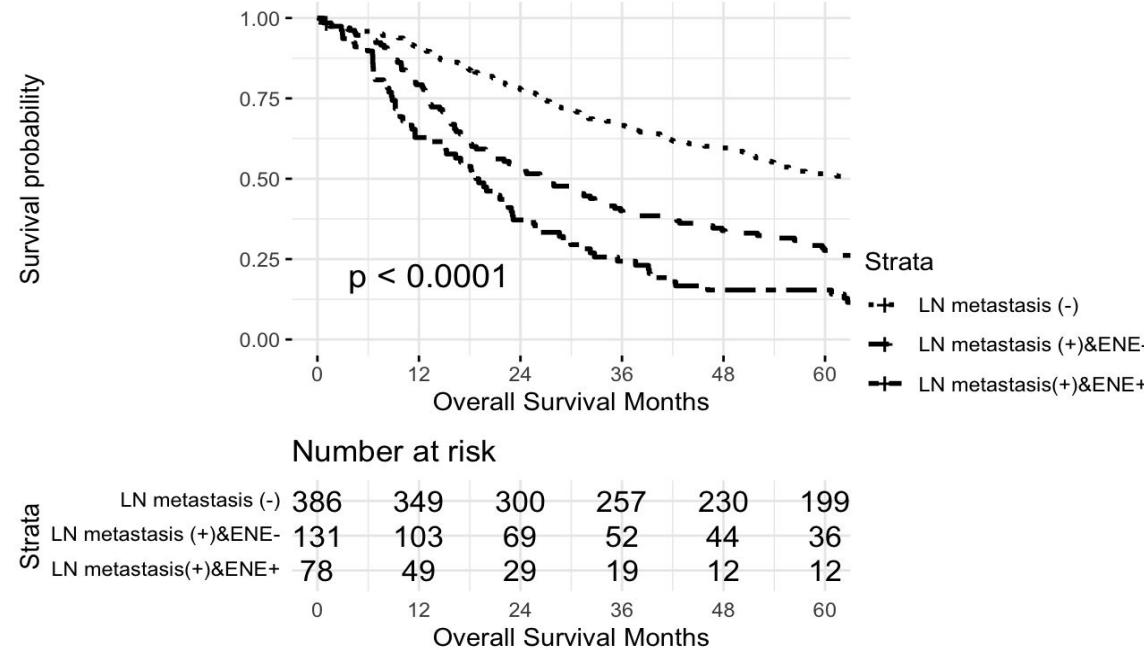
Results

Characteristic	Patients without ENE (N=131)	Patients with ENE (N=78)	p-value	Characteristic	Patients without ENE (N=131)	Patients with ENE (N=78)	p-value
Growth pattern			0.302	Differentiation			0.147
- Papillary	5 (3.8%)	1 (1.3%)		- WD	17 (13.7%)	8 (10.3%)	
- Nodular	24 (18.3%)	10 (12.8%)		- MD	83 (66.9%)	51 (65.4%)	
- Flat	102 (77.9%)	67 (85.9%)		- PD	24 (19.4%)	19 (24.4%)	
DOI (mm)	9.2 ± 4.7	11.1 ± 4.9	0.008	LVI			0.004
Size (cm)	3.1 ± 1.4	3.2 ± 1.3	0.643	- Absent	52 (39.7%)	15 (19.2%)	
Histology			NA	- Present	79 (60.3%)	63 (80.8%)	
- Tubular	121 (92.4%)	77 (98.7%)		PNI			0.34
- Papillary	3 (2.3%)	0 (0.0%)		- Absent	19 (14.5%)	7 (9.0%)	
- Mucinous	0 (0.0%)	1 (1.3%)		- Present	112 (85.5%)	71 (91.0%)	
- Adenosquamous	7 (5.3%)	0 (0.0%)		Number of LNs with Nodal metastasis	1.8 ± 1.3	3.9 ± 2.5	0.001
pT category			0.046	Age	65.8 ± 8.6	66.3 ± 8.5	0.66
- pT1	23 (17.6%)	6 (7.7%)		Sex			0.02
- pT2	73 (55.7%)	41 (52.6%)		- Male	77 (58.8%)	59 (75.6%)	
- pT3	35 (26.7%)	31 (39.7%)		- Female	54 (41.2%)	19 (24.4%)	
Pancreas invasion			0.114	DOI: Depth of Invasion; LVI: Lymphovascular Invasion; LN: Lymph Node; ENE: Extranodal Extension; WD: Well Differentiated; MD: Moderately Differentiated; PD: Poorly Differentiated; PNI: Perineural Invasion			
- Absent	47 (35.9%)	19 (24.4%)					
- Present	84 (64.1%)	59 (75.6%)					
Duodenum invasion			0.003				
- Absent	95 (72.5%)	40 (51.3%)					
- Present	36 (27.5%)	38 (48.7%)					



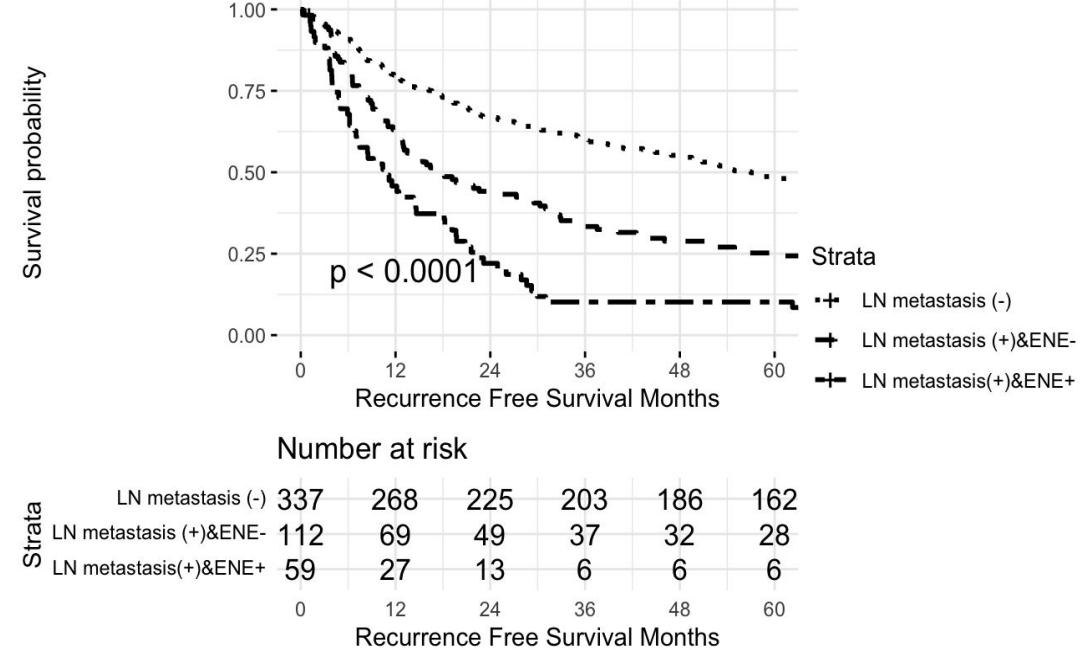
Kaplan-Meier survival analyses

(A) Overall survival by nodal metastasis and ENE status



5-year OS: LN (+) ENE (+) vs. LN (+) ENE (-):
15.4% vs. 27.5%, $p=0.020$

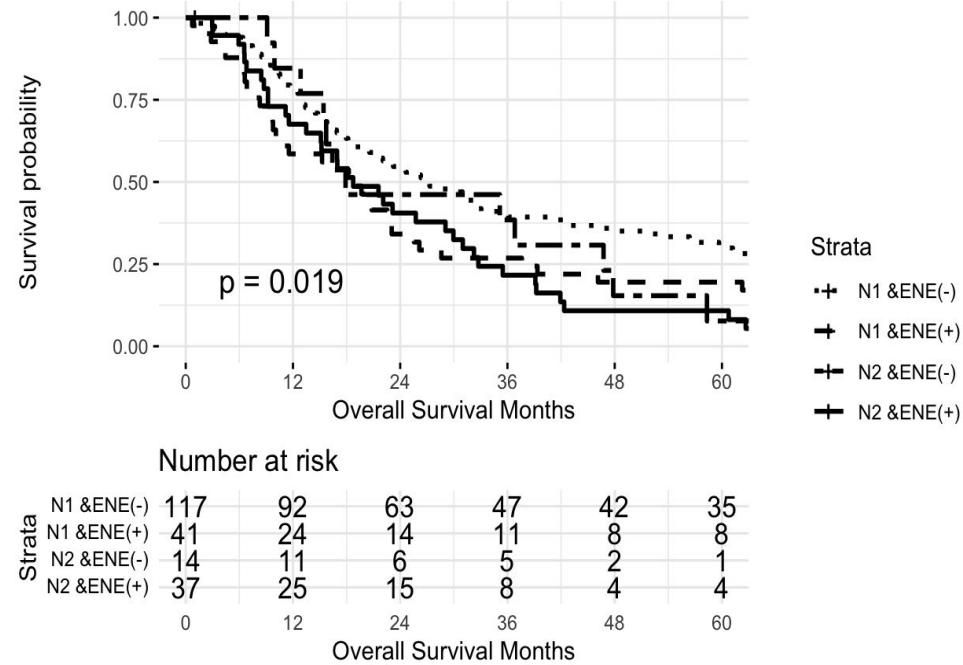
(B) Recurrence-free survival by nodal metastasis and ENE status



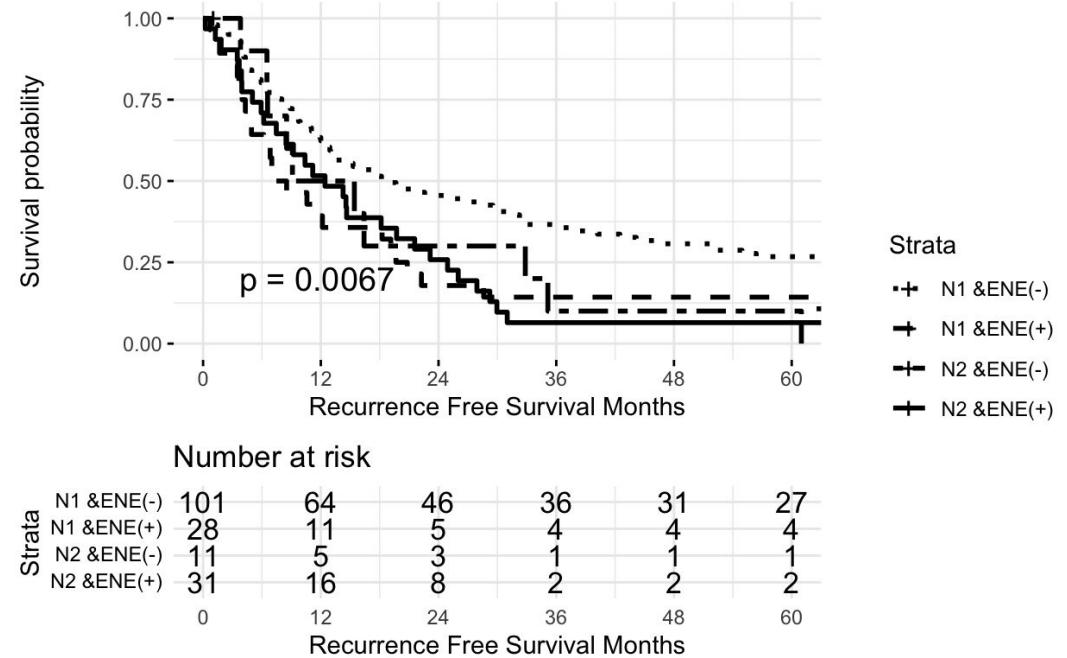
5-year RFS: LN (+) ENE (+) vs. LN (+) ENE (-):
10.2% vs. 25.0%, $p=0.0016$



(C) Overall survival in node-positive patients: Impact of ENE



(D) Recurrence-free survival in node-positive patients: Impact of ENE



5-yr OS:

N1: LN(+)ENE(+) vs. LN(+)ENE(-): 19.5% vs. 29.9%, p=0.005
 N2: LN(+)ENE(+) vs. LN(+)ENE(-): 10.8% vs. 7.1%, p=0.16

5-yr RFS:

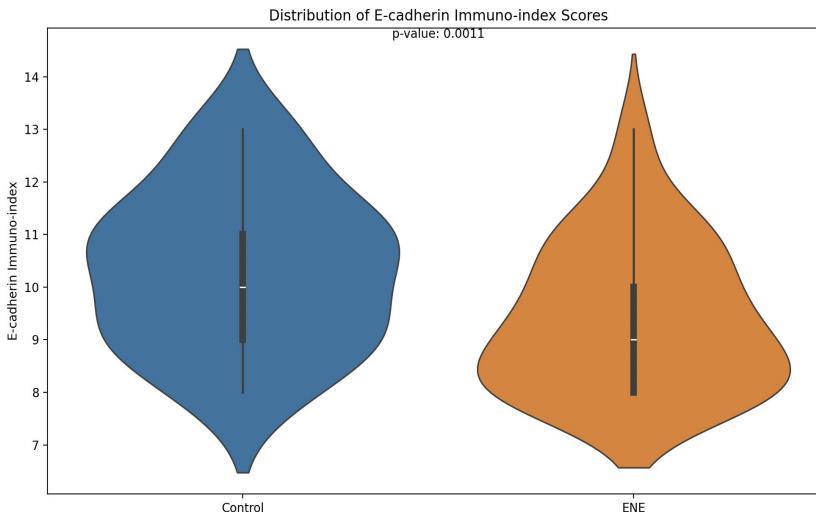
N1: LN(+)ENE(+) vs. LN(+)ENE(-): 14.3% vs. 26.7%, p<0.001
 N2: LN(+)ENE(+) vs. LN(+)ENE(-): 6.5% vs. 9.1%, p=0.31

Multivariate Cox regression analysis results

Characteristics		Patients ^a (n=209)	OS Hazard ratio ^b (multivariable)	Patients ^a (n=171)	RFS Hazard ratio ^b (multivariable)
ENE	Absent	131 (62.7%)		112 (65.5%)	
	Present	78 (37.3%)	1.91 (1.46-2.51, p<.001)	59 (34.5%)	2.13 (1.57-2.91, p<.001)
Sex	Male	136 (65.1%)	0.87 (0.71-1.07, p=.192)	109 (63.7%)	
	Female	73 (34.9%)		62 (36.3%)	
LVI	Absent	67 (32.1%)		58 (33.9%)	
	Present	142 (67.9%)	1.28 (1.05-1.57, p=.015)	113 (66.1%)	1.21 (0.97-1.51, p=.095)
PNI	Absent	26 (12.4%)		25 (14.6%)	
	Present	183 (87.6%)	0.98 (0.75-1.28, p=.858)	146 (85.4%)	1.02 (0.77-1.37, p=.872)
pT	1	29 (13.9%)		26 (15.2%)	
	2	114 (54.5%)	1.26 (0.99-1.61, p=.061)	93 (54.4%)	1.21 (0.94-1.57, p=.145)
	3	66 (31.6%)	2.00 (1.48-2.69, p<.001)	52 (30.4%)	1.99 (1.44-2.76, p<.001)
Differentiation	WD	25 (12.0%)	1.46 (1.11-1.92, p=.008)	19 (11.1%)	
	MD	137 (65.6%)	1.68 (1.19-2.37, p=.003)	116 (67.8%)	1.39 (1.02-1.88, p=.036)
	PD	43 (20.6%)	2.66 (0.82-8.58, p=.102)	33 (19.3%)	1.60 (1.09-2.34, p=.016)
	AdSq	4 (1.9%)	1.08 (0.43-2.70, p=.868)	3 (1.8%)	2.35 (0.73-7.58, p=.151)

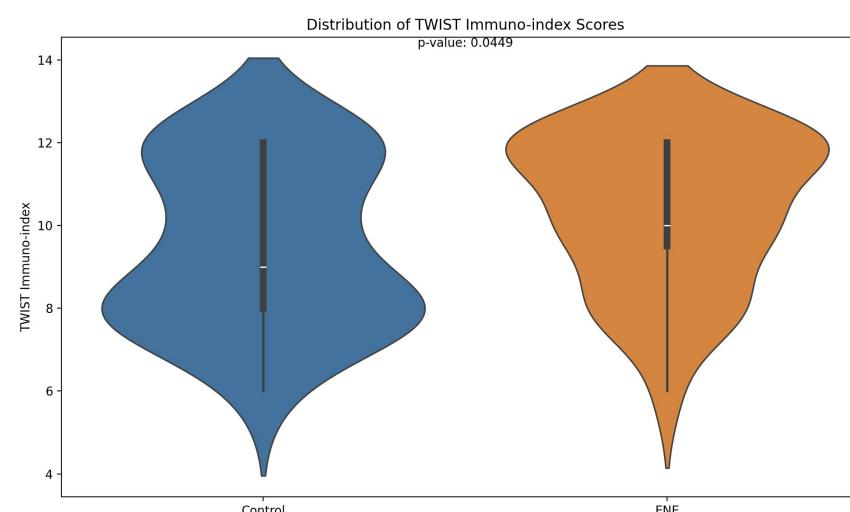
Immunoindex comparison: NM+ENE+ vs. NM+ENE-

E-Cadherin



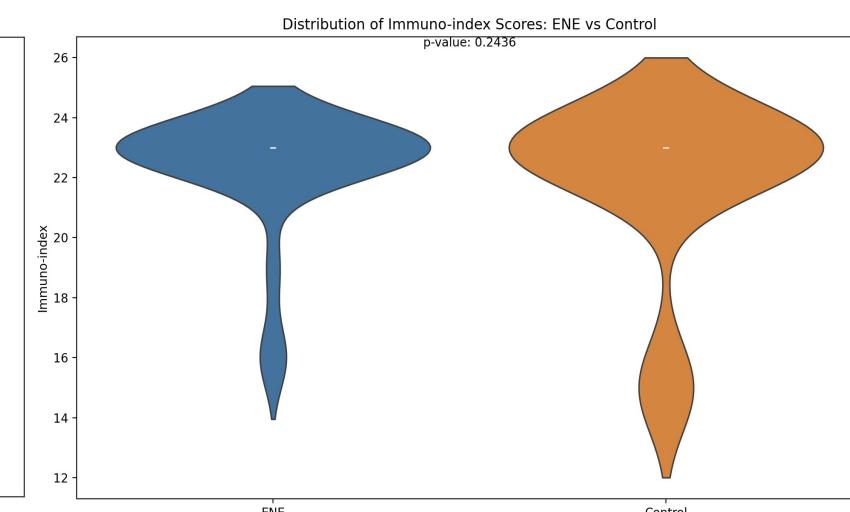
Significantly reduced in NM with ENE (p=0.001)

Twist



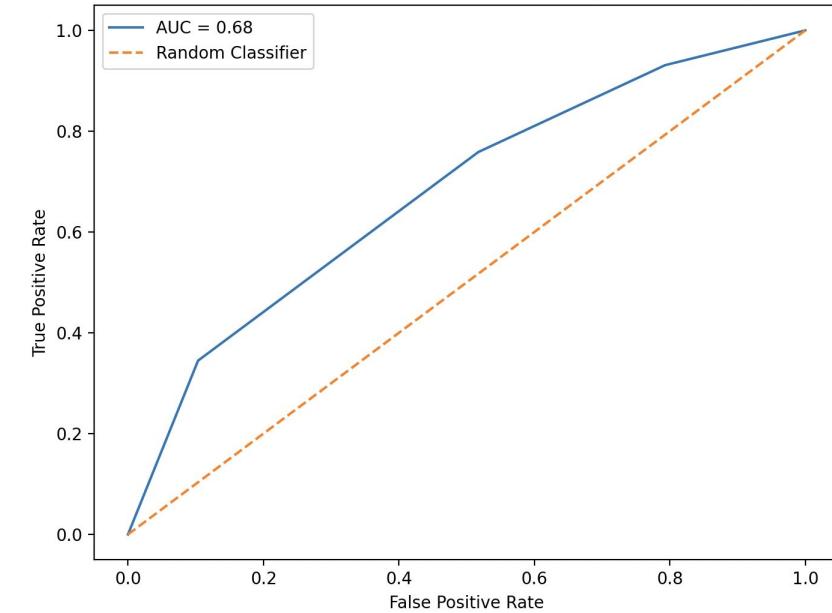
Significantly elevated in NM with ENE (p=0.045)

Snail

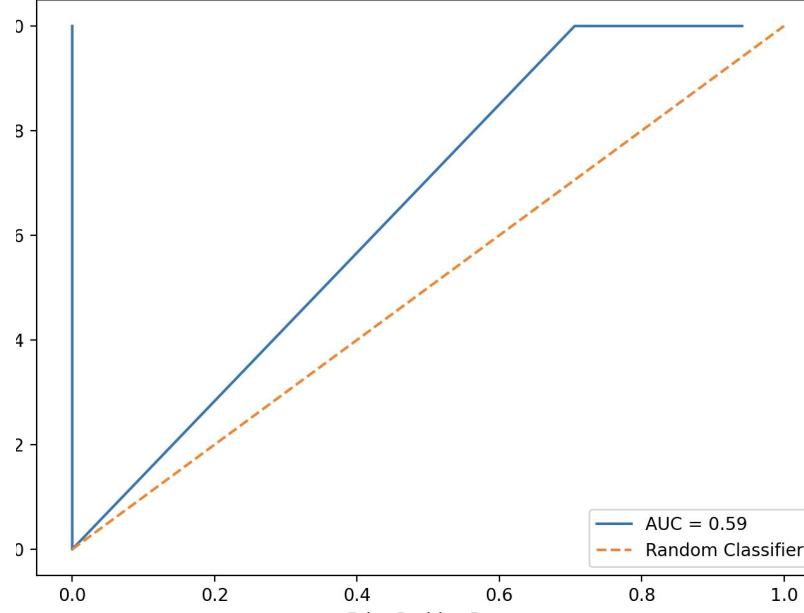


No significance (p=0.24)

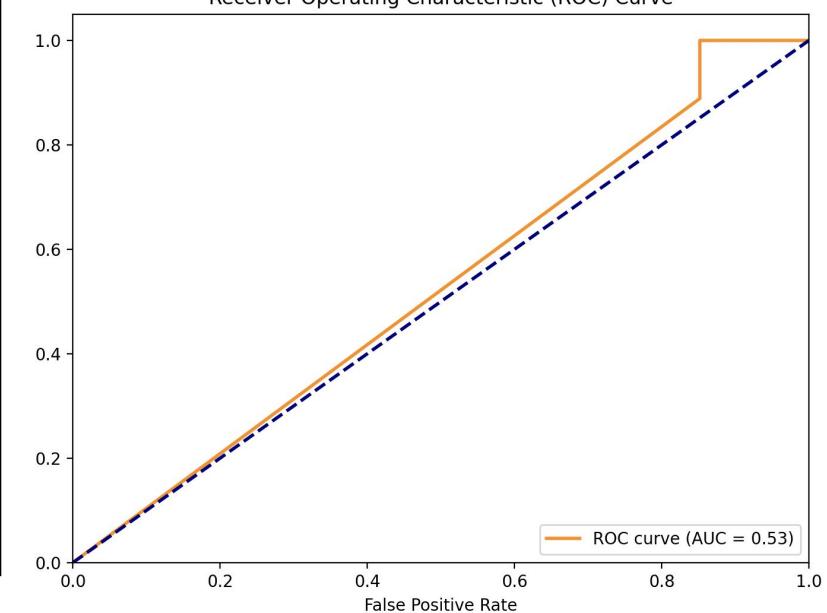
ROC Curve for E-cadherin Immuno-index (ENE vs Control)



ROC Curve for TWIST Immuno-index (ENE vs Control)



Receiver Operating Characteristic (ROC) Curve



Literature Review

Authors	Year	Origin	Purpose	Research design	Target population	Major findings
Noji et al.	2012	Japan	To evaluate incidence and prognostic significance of ENE in EBDCa	Retrospective	228 patients with surgically-treated EBDCa (110 hilar, 118 distal)	<ul style="list-style-type: none"> ENE present in 22% of NM cases (7% overall); no impact on survival ENE was more frequent in the distal cholangiocarcinomas NM was the only significant independent prognostic factor
Yoshizawa et al.	2017	Japan	To investigate the prognostic impact of ENE and myofibroblastic activity in EBDCa	Retrospective	32 cases of EBDCa with lymph node metastasis	<ul style="list-style-type: none"> ENE present in 65.6% of EBDCa; associated with poor disease-free and overall survival Higher myofibroblast density in ENE cases
Our study	2024	South Korea	To investigate the prognostic impact of ENE in distal EBDCa and its association with EMT	Retrospective	595 cases of EBDCa with NM (n=209) and NM+ENE+ (n=78) cases.	<ul style="list-style-type: none"> Largest cohort (595 cases vs. previous maximum of 228) First study to analyze EMT markers in distal EBD carcinoma using IHC in ENE Unique employing AI-assisted analysis for objective quantification

Conclusions

- First and largest study (n=595) to analyze ENE's prognostic impact and molecular mechanisms through EMT markers using AI-assisted quantification
- ENE: crucial determinant of poor 5-year OS and RFS in distal EBD carcinoma
- EMT marker alterations in NM with ENE: potential cause of worse outcome and aggressive course
- AI-assisted analysis: valuable tool for objective quantification of IHC markers

Thank you for your attention!

Thank
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