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Fibronectin Expression Correlates with Microvascular Invasion in Hepatocellular Carcinoma

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Background

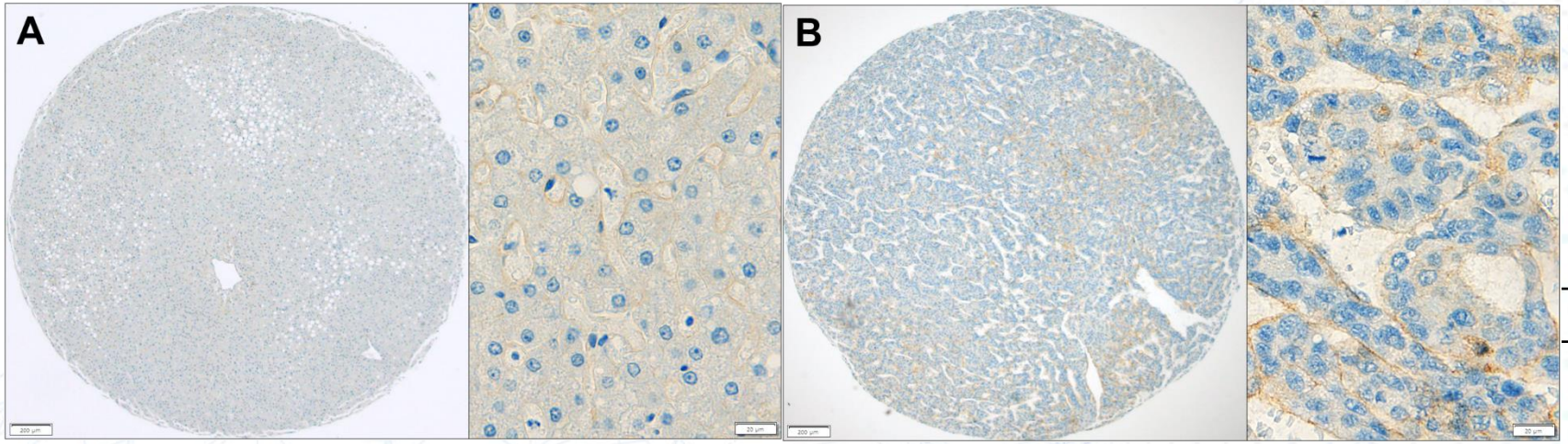
- Fibronectin (FN), an extracellular matrix glycoprotein involved in cell adhesion and migration, has recently been shown to be overexpressed in hepatocellular carcinomas (HCCs) and suggested as a potential biomarker of vascular invasion.
- We aimed to evaluate the patterns of FN expression in HCCs, its clinicopathological implications, including vascular invasion status, and patterns of angiogenesis.

Methods

- Immunohistochemistry for FN was performed on tissue microarrays of comprising 258 surgically resected HCCs and their adjacent liver tissues.
- Three patterns of FN expression were seen in HCCs: cytoplasmic, membranous, sinusoidal pattern.
- Moderate or strong expression was regarded as FN-positive.

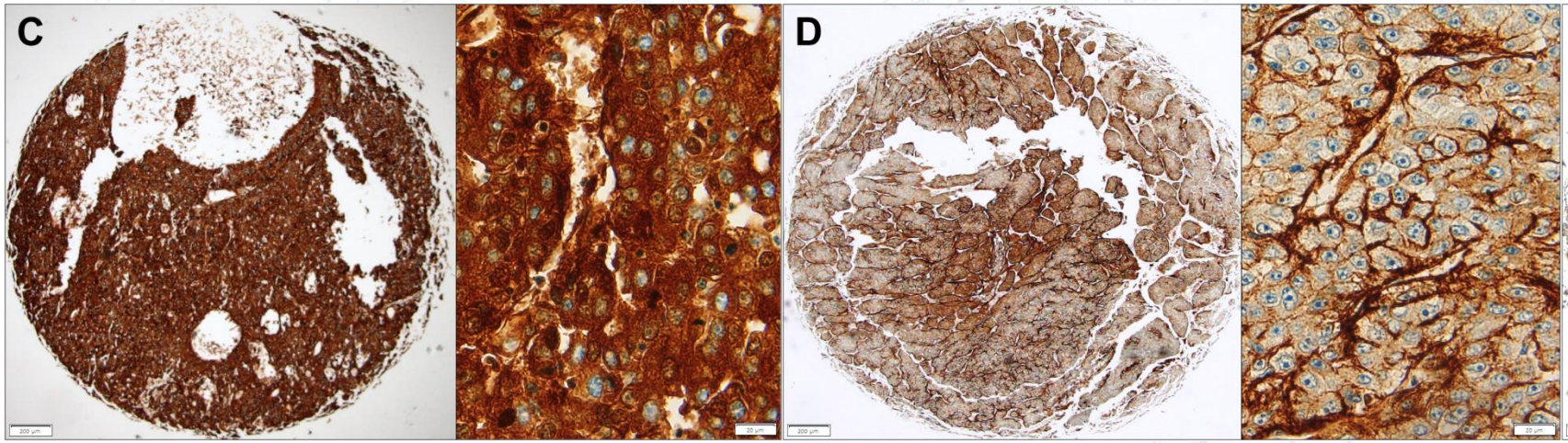
Fibronectin stain in non-neoplastic liver tissue (A) and HCC (B-E).

A: Faint sinusoidal staining. **B**: Weak sinusoidal staining. **C**: Strong cytoplasmic staining.
D: Strong membranous and sinusoidal staining with VETC pattern. **E**: Moderate sinusoidal staining.
(left: 40x, right: 400x)



Intensity of FN staining		
Negative	No staining	
	Faint staining	Discernable at 100x
	Weak staining	Discernable at 40x
Positive	Moderate staining	Discernable at 12.5x
	Strong staining	Discernable at scan view

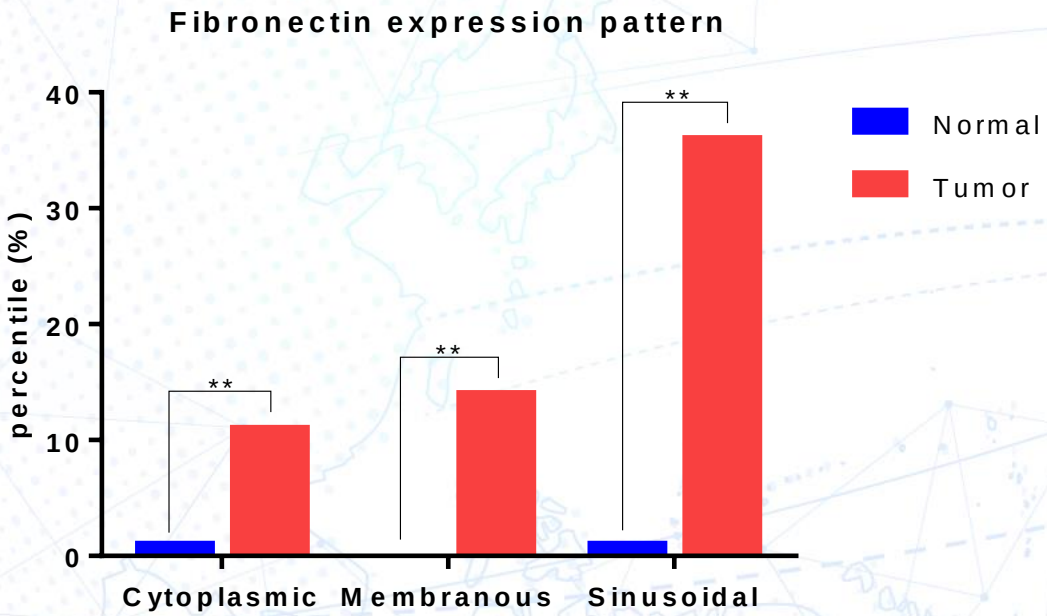
Pattern of FN staining	
Cytoplasmic	Stained at cytoplasm of hepatocytes/tumor cells
Membranous	Stained at membrane of hepatocytes/tumor cells
Sinusoidal	Stained at endothelial cells of hepatic sinusoids



Results

Fibronectin expression in HCCs and non-neoplastic livers

- Cytoplasmic FN expression was seen significantly more frequently in the HCC (10.9%) than the adjacent parenchyme (1.1%).
- Membranous FN expression was only seen in the tumor cells (14.2%) and not in the non-neoplastic hepatocytes.
- Sinusoidal FN expression was seen significantly more frequently in the HCC (36.5%) compared to the adjacent liver tissue (1.5%).

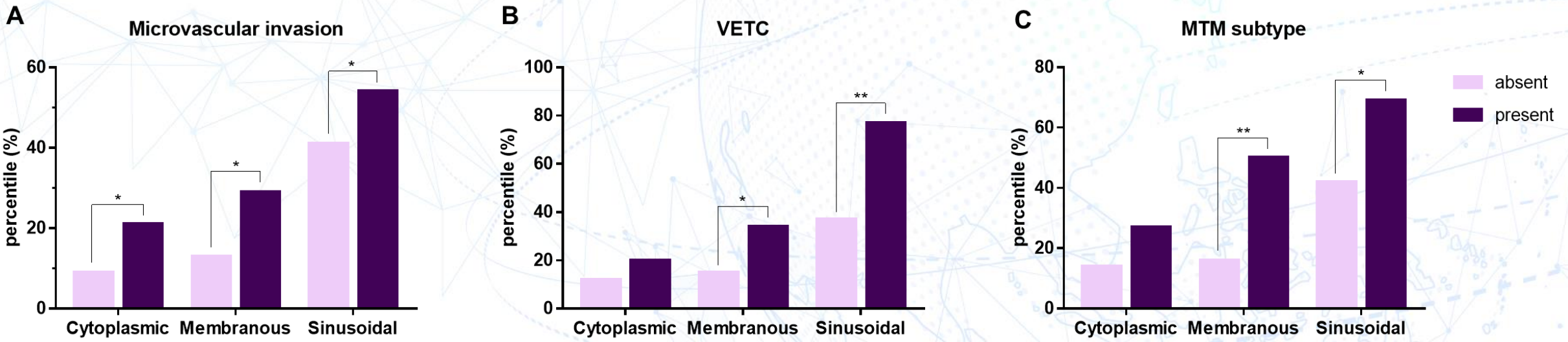


(* indicates p<0.05, ** indicates p<0.001)

Results

Clinicopathological features according to fibronectin expression pattern

- Cytoplasmic FN expression was significantly associated with microvascular invasion (MVI).
- Membranous and sinusoidal FN expression was significantly associated with not only MVI but also with vessels encapsulating tumor clusters (VETC) pattern and macrotrabecular massive (MTM) subtype.

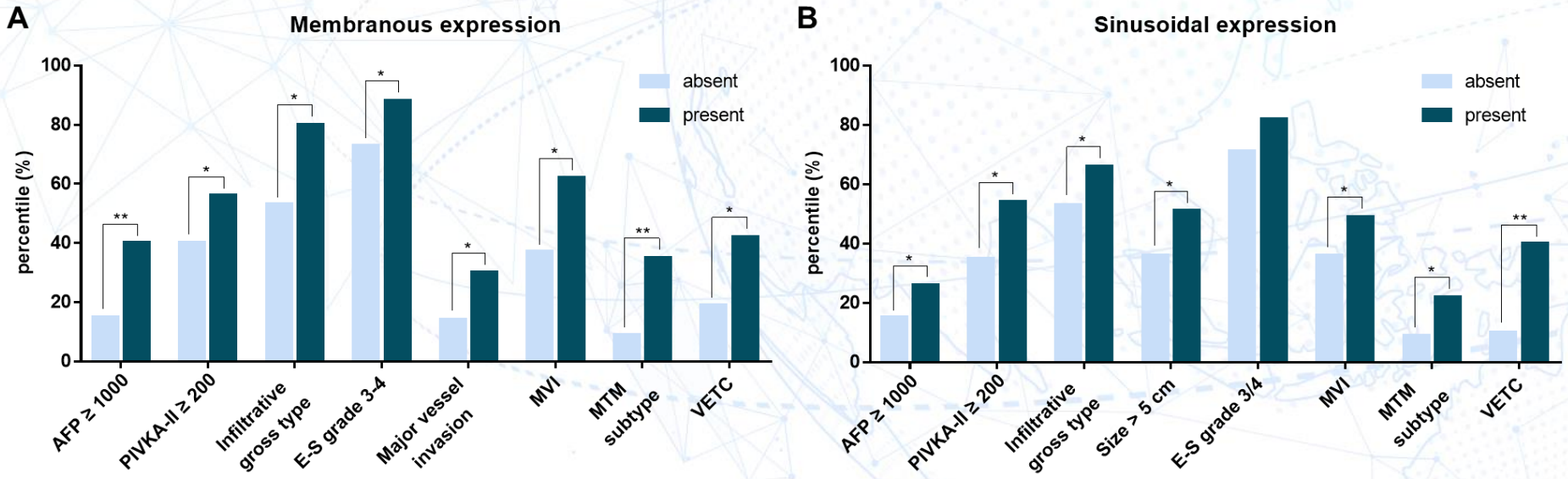


(* indicates p<0.05, ** indicates p<0.001)

Results

Clinicopathological features according to fibronectin expression pattern

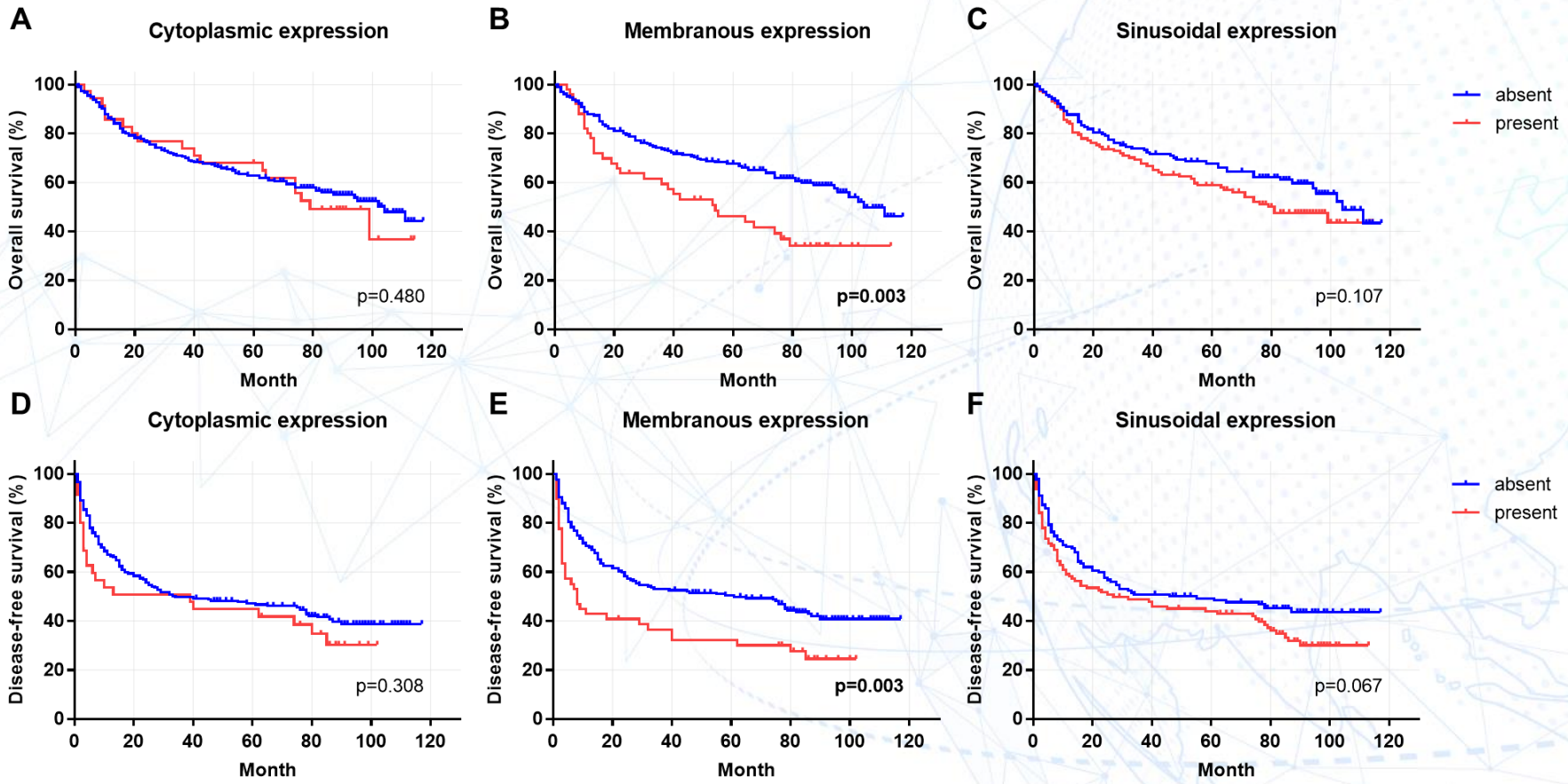
- FN positivity in the membrane of tumor cells was significantly associated with high serum alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II) levels, infiltrative gross type, poor Edmonson-Steiner (ES) grade, major vessel invasion, MVI, MTM subtype, higher T stage, and VETC pattern.
- Sinusoidal FN expression in HCC was significantly associated with high serum AFP and PIVKA-II levels, infiltrative gross type, large tumor size MVI, MTM subtype and VETC pattern



(AFP: ng/mL, PIVKA-II: mAU/mL, * indicates p<0.05, ** indicates p<0.001)

Results

Survival according to fibronectin expression pattern



- Overall survival and disease-free survival in the patients with HCCs showing membranous FN expression were significantly shorter than those without membranous FN expression.

Conclusion

- FN expression in tumor cells and sinusoidal endothelial cells of HCC was associated with microvascular invasion and aggressive clinicopathological parameters, and sinusoidal FN expression was also associated with VETC pattern of angiogenesis.
- Evaluating FN expression in HCC may potentially be useful for identifying an aggressive group of HCCs with vascular invasion, especially in the biopsy setting.