

Biologia vascolare

EXTRACELLULAR VESICLE PROFILES REFLECT THROMBO-INFLAMMATORY ACTIVATION AND ARE ASSOCIATED WITH CLINICAL OUTCOMES IN LIVER CIRRHOSIS

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Background and aims. Cirrhosis is characterized by progressive immune dysregulation, endothelial dysfunction, and haemostatic imbalance. Circulating extracellular vesicles (EVs) have emerged as potential biomarkers reflecting these pathophysiological processes. We aimed to determine whether EVs mirror disease severity and predict liver-related outcomes in cirrhosis.

Methods. In this prospective single-centre study, patients with compensated, stable decompensated, or acutely decompensated cirrhosis were enrolled. A group of 32 healthy controls was included. EVs were isolated from platelet-poor plasma and quantified by flow cytometry to characterize platelet-, endothelial-, anticoagulant-, immune-, hepatocyte-, and fibrosis- derived EVs. Primary endpoints were first hepatic decompensation in compensated cirrhosis and a composite of further decompensation, acute-on-chronic liver failure, or liver-related mortality in acutely decompensated cirrhosis. Associations were analysed using Fine-Gray competing-risk models.

Results. We included 228 patients, including 75 compensated, 44 stable decompensated, and 109 acutely decompensated. Median follow-up was 418 days. EV profiling showed progressive increases in total, platelet-derived, endothelial-, immune-derived, and fibrosis- associated EVs across Child–Pugh stages, indicating increasing thrombo-inflammatory and endothelial activation. First hepatic decompensation occurred in 7 patients with compensated cirrhosis and was associated with higher MELD and Child–Pugh scores, alcohol-related aetiology, and lower platelet count. In univariate competing-risk analyses, higher levels of several EV subpopulations were associated with first decompensation, but these associations disappeared after adjustment for MELD. Among patients with decompensated cirrhosis, 36 developed further decompensation, ACLF, or liver-related death; higher CRP levels were associated with these events, whereas no EV subpopulation could predict the composite outcome.

Conclusions. Circulating EVs reflect cirrhosis severity and progressive thrombo- inflammatory, endothelial, and pro-fibrotic alterations, supporting their role as markers of underlying pathophysiological processes. However, EVs were not independently associated with clinical outcomes and therefore have limited value for prognostic stratification.

Table 1 Circulating MVs across disease severity

Variable (MV subset)	Healthy controls	Child–Pugh A	Child–Pugh B	Child–Pugh C	p overall
Total MVs (Calcein)	3867 (3407–4362)	4582 (3803–5380)	5579 (4069–6289)	5830 (4832–7234)	<0.001
Platelet MVs (CD41$^+$)	3085 (2654–3715)	3447 (2544–4447)	4117 (3076–5587)	4631 (2971–6337)	<0.001
Activated platelet MVs (CD41$^+$CD62P$^+$)	822 (574–1005)	600 (452–928)	830 (549–1204)	966 (617–1483)	<0.001
Activated endothelium (CD62E$^+$)	1311 (833–1550)	808 (530–1169)	1016 (703–1427)	1141 (733–1754)	<0.001
Activated endothelium + TF (CD62E$^+$TF$^+$)	272 (211–320)	4 (2–9)	5 (2–10)	10 (4–22)	<0.001
Monocytes/Macrophages (CD45$^+$)	3610 (2895–4740)	3589 (2466–4280)	4240 (3191–5475)	4776 (3612–6198)	<0.001
Monocytes/Macrophages (CD45$^+$CD14$^+$)	2716 (2118–3560)	2501 (1790–3067)	2979 (2255–3911)	3376 (2692–4351)	<0.001
Angiogenesis/HCC (CD105$^+$)	3134 (2568–3988)	3842 (2697–4948)	4229 (3588–5561)	4729 (3775–6175)	<0.001
Angiogenesis/HCC (CD147$^+$)	2174 (1879–2681)	3161 (2597–4238)	4197 (3187–5282)	4381 (3419–5974)	<0.001
Angiogenesis/HCC (CD105$^+$CD147$^+$)	1525 (1346–1913)	2017 (1515–2546)	2636 (2051–3377)	2868 (2127–3862)	<0.001
Hepatocyte damage (CK18$^+$)	121 (97–195)	154 (69–265)	186 (111–270)	190 (133–328)	0.011
Hepatocyte damage + TF (CK18$^+$TF$^+$)	113 (90–194)	58 (37–91)	65 (46–90)	67 (47–96)	<0.001
T-lymphocytes (CD11a$^+$)	2110 (1733–2550)	2964 (2150–3716)	3494 (2771–4402)	3962 (3166–5045)	<0.001
T-lymphocytes (CD11a$^+$CD4$^+$)	529 (410–662)	602 (428–797)	719 (525–953)	878 (683–1107)	<0.001
Endothelial cells (CD144$^+$)	2594 (2303–2994)	3672 (2486–4180)	3988 (3043–5105)	4885 (3731–5760)	<0.001
Endothelial cells + VEGFR2 (CD144$^+$VEGFR2$^+$)	1397 (1245–1619)	2055 (1356–2410)	2755 (2074–3282)	3025 (2354–3842)	<0.001
EPCR$^+$ endothelial MVs (EPCR)	974 (831–1298)	752 (481–960)	906 (573–1222)	1010 (718–1384)	<0.001
Thrombomodulin$^+$ endothelial MVs (CD141$^+$)	1358 (1185–1516)	19 (10–61)	26 (14–55)	42 (19–83)	<0.001
Anticoagulant endothelial MVs (CD141$^+$EPCR$^+$)	325 (288–481)	7 (2–30)	14 (7–31)	19 (7–41)	<0.001

MVs: microvesicles; TF: tissue factor; EPCR: endothelial protein C receptor; HCC: hepatocellular carcinoma¸ VEGFR: vascular endothelial growth factor receptor