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ABSTRACT N. CO46

ALTERAZIONI DELLE PIASTRINE E CONDIZIONI GENETICHE

COMPARISON OF RETICULATED PLATELET PROCOAGULANT ROLE IN LIVER CIRRHOSIS *VS* FIBROSIS.

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Background and aims: Reticulated platelets (RePLTs) are bigger and more reactive than mature platelets (PLTs), with an increased content of ribonucleic acid (RNA) and directly released by megakaryocytes. In liver cirrhosis the increased platelet turnover implies the release of these "emergency platelets'' which would contrast bleeding events that can occur due to reduced synthesis of hepatic-dependent coagulation factors and to contrast peripheral platelet destruction. Although the role of RePLTs in the hemostatic balance in cirrhotic patients is not well defined, even less is known about their role in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).
The aim of this study is to compare the percentage and activation of RePLTs vs PLTs in patients with cirrhosis and MASLD.

Methods: Platelet rich plasma from consecutive patients with liver cirrhosis of different severity (n=37), from patients with MASLD (n=29) and healthy subjects (n=22) was collected for analysis. CD41 and SYTO-13 positivity defines RePLTs in the morphological gate set between the 3 µm and 10 µm beads population diameter using new generation flow cytometry (CytoFLEX SRT). To evaluate RePLTs and PLTs activation, samples were stained with annexin V and CD62P after activation with Thrombin Receptor Activating Peptide (TRAP), Adenosine Diphosphate (ADP) and arachidonic acid (ASPI). The project is Funded by the European Union-Next Generation EU-NRRP M6C2-Investment 2.1 Enhancement and strengthening of biomedical research in the NHS.

Results: The proportion of circulating RePLTs was slightly lower in healthy controls than in cirrhotic patients (p=0.4), but significantly higher than in MASLD patients (p<0.0001) (Fig. 1A). RePLT levels showed an inverse correlation with platelet count (r = –0.5, p<0.0001), and in cirrhotic patients, they were positively associated with both Child-Pugh score (r = 0.38, p = 0.037) and MELD score (r = 0.58, p = 0.008).
Activated RePLTs expressing $CD41^+/CD62P^+/AnnexinV^+$ were significantly more abundant than PLTs with the same activation profile in cirrhosis, MASLD, and healthy controls (p<0.0001 for all comparisons) (Fig. 1B). No correlation was observed between RePLT levels and fibrosis severity in MASLD patients.
Upon stimulation with TRAP (p<0.0001), ADP (p<0.0001), and ASPI (p=0.0023), RePLTs from MASLD patients and healthy controls exhibited significantly increased expression of CD62P and Annexin V (Fig. 1C, 1E). Interestingly, in MASLD patients only, PLTs also showed a significant activation response to TRAP (p<0.0001), ADP (p<0.0001), and ASPI (p=0.0016) (Fig. 1D, 1F). In MASLD, RePLT activation after stimulation with TRAP and ADP—but not with ASPI—was significantly associated with fibrosis severity (p = 0.015 and p = 0.032, respectively).

Conclusions: Circulating RePLTs are increased in cirrhosis compared to healthy controls but reduced in MASLD patients. Across all groups— cirrhosis, MASLD, and healthy controls—RePLTs consistently show greater expression of activation markers than PLTs. Upon stimulation with agonists, RePLTs exhibit a similar increase in activation in both healthy controls and MASLD patients. Notably, in MASLD, RePLT activation following TRAP and ADP stimulation correlates with fibrosis severity. In contrast, PLTs show enhanced activation only in MASLD, suggesting a condition-specific increase in platelet reactivity.

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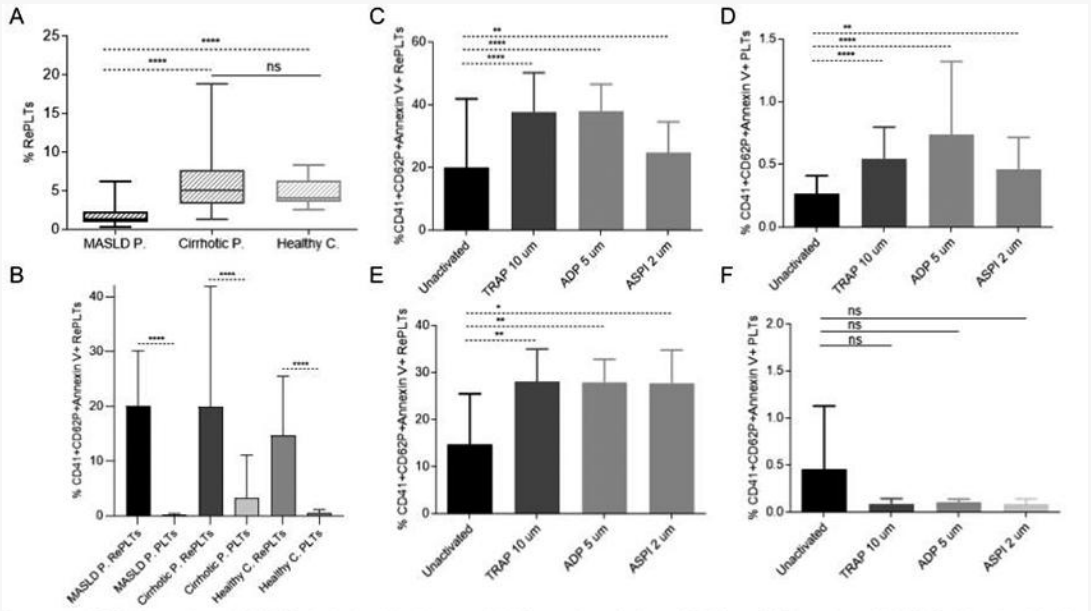

Percentage of RePLTs in patients with MASLD, cirrhosis and healthy controls (A). Comparison of activated RePLTs *vs.* PLTs in patients with MASLD, cirrhosis and healthy subjects (B). Activation of RePLTs (C,E) and PLTs (D,F) after addition of TRAP, ADP and ASPI in MASLD patients (C,D) and healthy controls (E,F).