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13TH INTERNATIONAL CONFERENCE ON THROMBOSIS AND HEMOSTASIS ISSUES IN CANCER, 2026 **ABSTRACT N. PO03**

MECHANISMS OF THROMBOSIS AND BLEEDING IN CANCER

HEPATIC FIBROSIS–DRIVEN TISSUE FACTOR EXPRESSION BY MALIGNANT CHOLANGIOCYTES IS ASSOCIATED WITH CANCER-ASSOCIATED THROMBOSIS AND POOR SURVIVAL IN INTRAHEPATIC CHOLANGIOCARCINOMA

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Introduction. Cholangiocarcinoma (CCA) is an aggressive primary liver malignancy with increasing incidence worldwide, particularly the intrahepatic subtype (iCCA). Although hepatic fibrosis has been involved in CCA development, its role in coagulation imbalance and cancer-associated thrombosis (CAT) remains unclear.

Aim. This study investigated the relationship between advanced liver fibrosis, hemostasis activation, CAT, and clinical outcomes in patients with iCCA.

Materials and Methods. Fifty patients with iCCA undergoing curative liver resection were studied. Graft wedge biopsies served as controls (n=10). Fibrosis was assessed on formalin-fixed, paraffin-embedded samples using the Ishak Fibrosis Score (IFS, 0-6). Expression of tissue factor (TF), factor X (FX), fibrinogen, and von Willebrand factor (vWF) was assessed by immunohistochemistry. As readout of CAT, portal vein microthrombosis was quantified using Martius Scarlet Blue staining. Association of TF expression with outcomes was evaluated by Kaplan-Meier survival analysis. Immunofluorescence analysis of TF and FX was performed on patient-derived iCCA organoids (PDOs, n=10). Extracellular vesicles (EVs) isolated from PDO culture media were characterized by flow cytometry (FC) using Calcein-AM, EpCAM-PE, and Annexin V. TF levels in PDO supernatants were quantified by ELISA. EV-induced platelet activation was assessed by FC using CD41, CD62P, and Annexin V.

Results. Compared with controls, iCCA patients exhibited a procoagulant phenotype characterized by increased coagulation activation. Patients with advanced fibrosis (IFS 4–5, n=16) showed significantly higher TF, FX, vWF, and fibrinogen expression than those with IFS ≤3 (n=34). Fibrosis severity correlated with TF expression by malignant bile ducts and with the number of portal vein microthrombi ($p<0.05$). High TF expression by malignant bile ducts was significantly associated with reduced disease-free survival and overall survival (logrank $p<0.05$). PDO analyses confirmed strong TF and FX expression, demonstrated TF release into culture supernatants, and showed that PDO-derived EVs significantly promoted platelet activation.

Conclusions. Advanced hepatic fibrosis is closely associated with CAT in patients with iCCA and is linked to increased TF expression by malignant cholangiocytes, driving platelet activation. By contributing to a prothrombotic tumor microenvironment, TF is associated with disease progression and adverse clinical outcomes in iCCA patients.