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CHOLESTEROL HOMEOSTASIS AND IMMUNE-INFLAMMATORY PROFILES IN PATIENTS WITH mRCC RECEIVING IMMUNOTHERAPY

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OBJECTIVE: Cholesterol metabolism may modulate antitumor immunity, influencing response to immune-checkpoint inhibitors (ICIs). We evaluated cholesterol transport-related biomarkers, KIM-1, and inflammatory mediators in metastatic renal cell carcinoma (mRCC) patients treated with first-line ICI-based regimens, to characterize the immune–metabolic profiles.

METHODS: LINCHOLM is a prospective, multicentre, observational study. Patients with mRCC receiving ICI-based combinations underwent blood collection at baseline, week 6 and progression. ABCA1- and ABCG1-mediated cholesterol efflux (CE), lipid fractions, and inflammatory mediators were assessed. Primary objective was to investigate associations between baseline cholesterol transporters and inflammatory mediators, and progression-free survival (PFS).

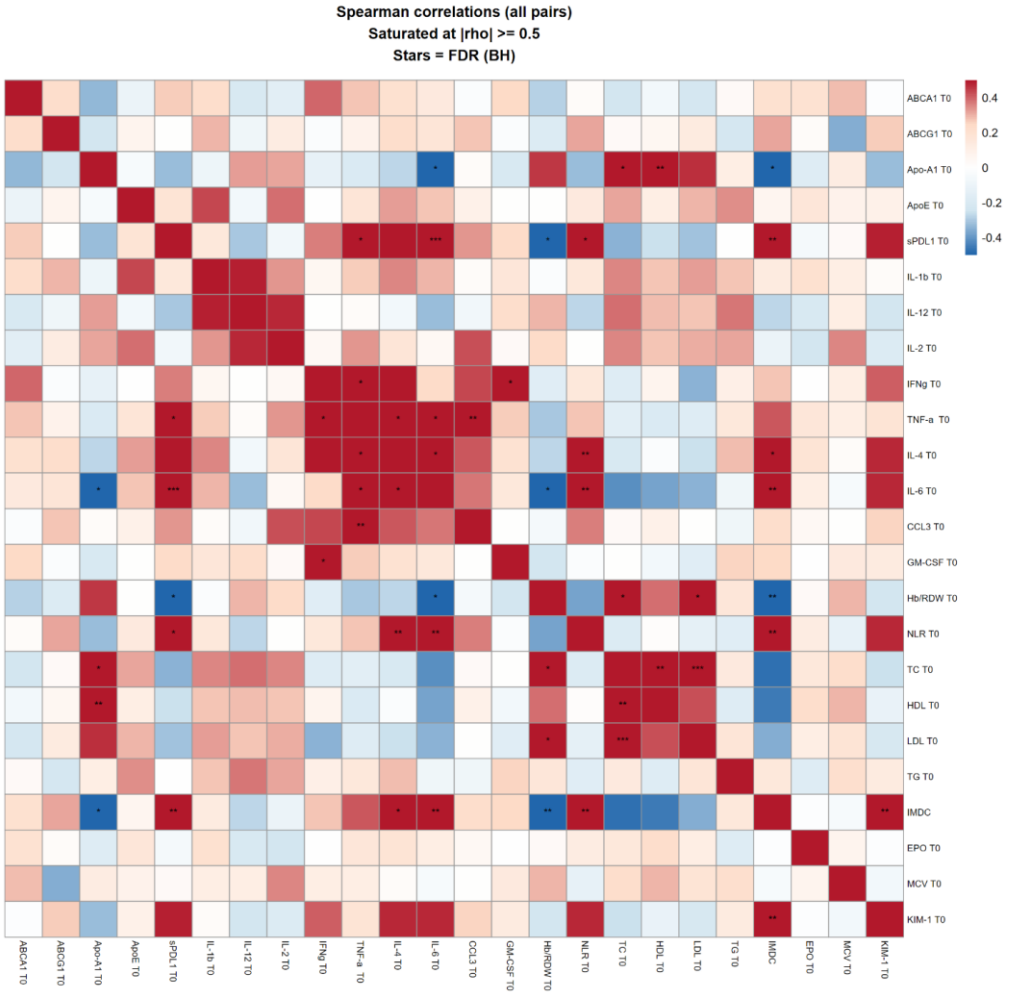
RESULTS: 33 patients were included, 84.8% had ECOG PS 0-1. Across worsening IMDC risk groups Apo-A1, total cholesterol, HDL and LDL decreased (all $p \leq 0.03$), whereas KIM-1, IL-6 and Apo-E increased (all $p \leq 0.02$). High ABCG1-mediated CE correlated with higher levels of ApoE and IL-1β (all $p \leq 0.04$). High KIM-1 was associated with poorer ECOG PS, synchronous metastatic disease, and higher NLR, IL-4, IL-6, and IL-10 (all $p \leq 0.04$), **Figure 1**. High baseline ABCG1-mediated CE, KIM-1, ApoE, NLR, and inflammatory cytokines (IL-4, IL-6, IFN-γ, IL-10, IL-1β, IL-2, and TNF-α) correlated with shorter PFS, **Table 1**. Only ABCG1 remained independently associated with worse PFS at multivariable analysis (HR 10.61, 95%CI 2.35–47.97; $p=0.002$), although estimates were limited by small sample size.

CONCLUSIONS: ABCG1-mediated CE may serve as a prognostic biomarker in mRCC patients receiving first-line ICI-based therapies. The interplay among cholesterol metabolism, KIM-1, and inflammatory mediators suggests a biological profile influencing outcomes and warrants further validation.

Table 1. Selected biomarkers significantly associated with PFS.

Variable	Low group, median PFS, months (95% CI)	High group, median PFS, months (95% CI)	*p*-value
ABCG1	12.07 (6.81–NE)	1.81 (1.15–NE)	<0.001
NLR	16.09 (7.07–NE)	2.57 (1.45–NE)	0.008
KIM-1	16.09 (7.53–NE)	2.62 (1.45–NE)	0.002
ApoE	12.07 (6.81–NE)	1.51 (0.89–NE)	<0.001
IL-6	12.07 (6.78–NE)	1.45 (1.18–NE)	0.009
IL-1β	12.07 (6.81–NE)	1.22 (1.15–NE)	0.002
TNF-α	12.07 (6.81–NE)	1.64 (1.25–NE)	0.002

Figure 1. Heatmap of correlations between baseline biomarkers.


Spearman correlations (all pairs)
Saturated at |rho| >= 0.5
Stars = FDR (BH)
ABCA1 T0
ABCG1 T0
Apo-A1 T0
ApoE T0
sPDL1 T0
IL-1b T0
IL-12 T0
IL-2 T0
IFNg T0
TNF-a T0
IL-4 T0
IL-6 T0
CCL3 T0
GM-CSF T0
Hb/RDW T0
NLR T0
TC T0
HDL T0
LDL T0
TG T0
IMDC
EPO T0
MCV T0
KIM-1 T0
0.4
0.2
0
-0.2
-0.4