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ORIGINAL ARTICLE

Alanine Transaminase Mediates the Causal Link between Chronic Heart Failure and Nonalcoholic Fatty Liver Disease

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ABSTRACT

Background: **Clinical evidence suggests an association between chronic heart failure (CHF) and liver disease; however, the causal relationship remains unclear. This study aimed to investigate the causal effects of CHF on common liver diseases, including non-alcoholic fatty liver disease (NAFLD), hepatitis, and cirrhosis, using a two-sample Mendelian randomization (MR) approach. Additionally, we evaluated whether four liver function indicators-alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (BL), and albumin (AL)-mediate this relationship.**

Methods: **Genome-wide association study (GWAS) summary data were obtained from the UK Biobank database. CHF was treated as the exposure, while NAFLD, hepatitis, and cirrhosis were considered outcomes. ALT, AST, BL, and AL were analyzed as potential mediators. Five MR methods-Inverse Variance Weighted (IVW), MR-Egger, Weighted Median, MR-RAPS, and MR-PRESSO were applied to evaluate causal associations and mediation effects.**

Results: **MR analysis demonstrated a causal association between CHF and NAFLD by 48 SNPs (p = 0.0182), OR_{IVW} [95% CI] = 1.1352 [1.0218 - 1.2612]. No significant causal associations were observed between CHF and hepatitis or cirrhosis. Among the four liver function indicators, ALT was identified as a significant mediator in the CHF-NAFLD relationship, with a mediation effect of 0.0021 [0.0001 - 0.0040], and a mediation proportion of 1.6561 [0.0698, 3.1788] % (p = 0.0406). Sensitivity analyses, including funnel plots and leave-one-out analysis, confirmed the robustness of the findings.**

Conclusions: **These findings suggest that CHF may increase the risk of NAFLD, partially mediated through ALT levels, highlighting the potential role of liver function indicators in the pathophysiological link between CHF and NAFLD.**

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Supplementary Data

Table S1. SNPs associated with key confounding factors.

Exposure-outcome	SNP	Disease	PMID
ALT	-	-	-
CHF	rs12452647	Severe COVID-19 infection	36662838
CHF	rs600038	Severe COVID-19 infection	32558485
CHF	rs10938398	BMI	39024449, 28443625
CHF	rs11642015	BMI	39024449, 28443625
CHF	rs2472610	BMI	28443625, 39024449
CHF	rs34860124	BMI	39024449
CHF	rs62477737	BMI	37106081, 39024449, 28443625
CHF	rs11642015	Hypertension	39024449
CHF	rs16998073	Hypertension	30487518, 39024449, 40465716
CHF	rs62477737	Hypertension	39024449
CHF	rs880315	Hypertension	39024449, 31545351
CHF	rs10938398	DM	39024449, 32541925, 35551307
CHF	rs11642015	DM	39024449, 32541925, 35551307
CHF	rs2472610	DM	39024449, 32541925
CHF	rs28435470	DM	32541925
CHF	rs600038	DM	39024449, 35551307
CHF	rs72932523	DM	29632382
CHF	rs903678	DM	32541925
CHF	rs11642015	Breast cancer	37380357, 25751625, 27117709
CHF	rs28435470	Prostate cancer	29892016, 37945903, 29892016
CHF	rs35661955	Breast cancer	37340002, 39024449
CHF	rs72932523	Prostate cancer	38632662, 37945903
CHF	rs7857118	Skin cancer, Colorectal cancer	39024449, 34594039, 37340002
CHF	rs9819329	Prostate cancer	38632662
CHF	rs11642015	Alcohol consumption	39024449, 37282553, 36301540
CHF	rs2472610	Alcohol consumption	30643258, 31046077

SNPs: Single Nucleotide Polymorphisms, COVID-19: Coronavirus Disease 2019, BMI: body mass index, DM: diabetes mellitus.

Table S2. The MR results of CHF -> ALT, ALT -> NAFLD and CHF -> NAFLD.

MR info								Cochran's Q			Horizontal pleiotropy		
Expo-sure	Out-comes	Snps (n)	Method	β	SE	OR [95% CI]	p	Q	df	p	Inter-cept	SE	p
CHF	ALT	13	MR Egger	-0.0038	0.0388	0.9962 [0.9232 - 1.0749]	0.923	19.9131	11	0.0467	0.0075	0.0057	0.2159
			IVW	0.0412	0.0187	1.0420 [1.0045 - 1.081]	0.0279	23.0342	12	0.0274	-	-	-
			Weighted median	0.0635	0.0197	1.0656 [1.0253 - 1.1075]	0.0012	-	-	-	-	-	-
			MR-RAPS	0.0337	0.0182	1.0342 [0.9979 - 1.0719]	0.0649	-	-	-	-	-	-
			MR-PRESSO	0.0412	0.0187	1.0420 [1.0045 - 1.081]	0.0483	-	-	-	-	-	-
ALT	NAFLD	3	MR Egger	0.0330	0.0290	1.0330 [0.9760 - 1.0940]	0.4610	1.3620	1	0.2430	0.0060	0.0090	0.6380
			IVW	0.0500	0.0090	1.0510 [1.0320 - 1.0710]	< 0.0001	1.9170	2	0.3830	-	-	-
			Weighted median	0.0520	0.0110	1.0530 [1.0310 - 1.0750]	< 0.0001	-	-	-	-	-	-
			MR-RAPS	0.0590	0.0160	1.0610 [1.0290 - 1.0940]	0.0730	-	-	-	-	-	-
			MR-PRESSO	0.0480	0.0080	1.0490 [1.0330 - 1.0660]	0.0090	-	-	-	-	-	-
CHF	NAFLD	48	MR Egger	0.1187	0.1249	1.1260 [0.8815 - 1.4385]	0.3470	50.1371	46	0.4099	0.0007	0.0098	0.9428
			IVW	0.1268	0.0537	1.1352 [1.0218 - 1.2612]	0.0182	50.1428	47	0.4490	-	-	-
			Weighted median	0.1467	0.0754	1.1580 [0.9989 - 1.3424]	0.0517	-	-	-	-	-	-
			MR-RAPS	0.0042	0.0121	1.0042 [0.9807 - 1.0282]	0.7310	-	-	-	-	-	-
			MR-PRESSO	0.0041	0.0120	1.0041 [0.9808 - 1.0279]	0.736	-	-	-	-	-	-

OR and 95% CI were calculated from unrounded Beta estimates.

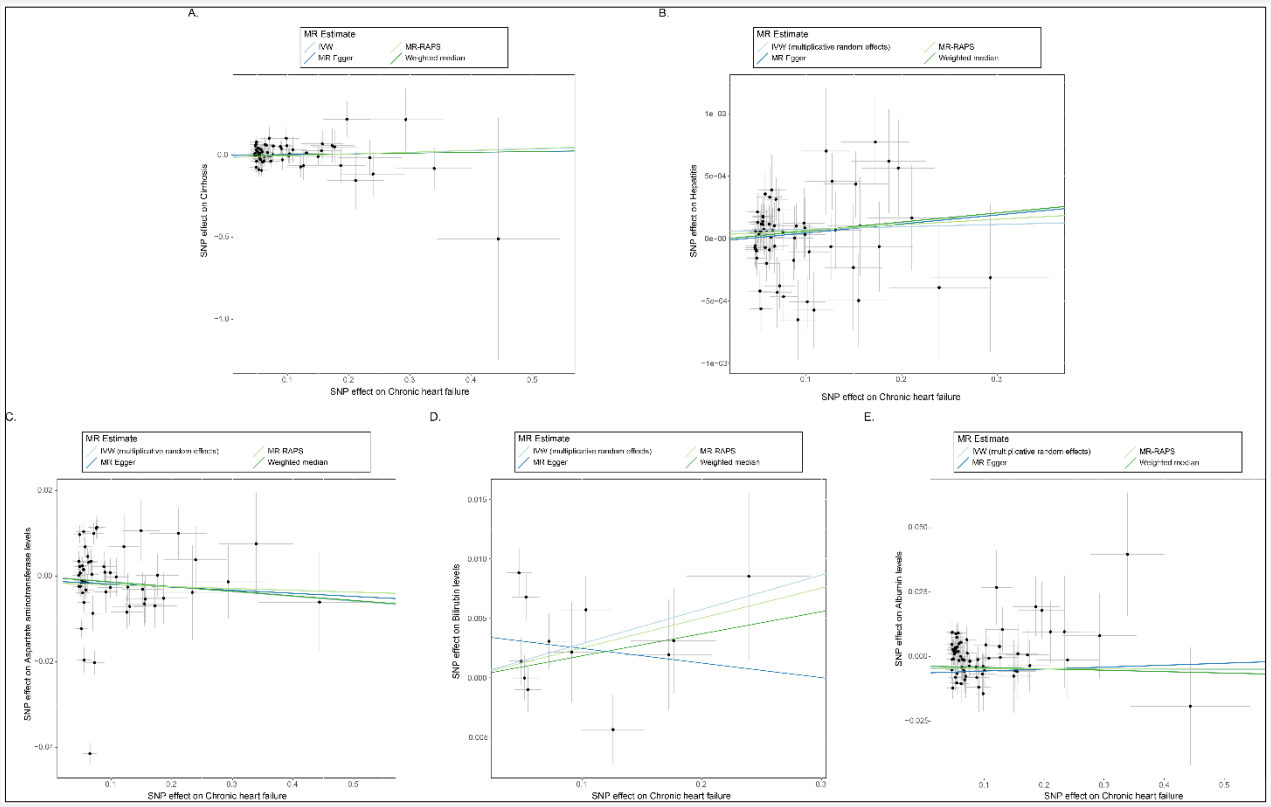


Figure S1. Scatter plot for the main results of the mendelian randomization analysis.
A: result of cirrhosis, B: result of hepatitis, C: result of AST, D: result of BL, E: result of AL.