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CAUSAL ASSOCIATIONS BETWEEN INFLAMMATORY FACTORS AND LIVER CANCER

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ABSTRACT – *Objective:* Emerging evidence indicates a correlation between inflammation and liver cancer. However, the causality remains elusive.

Materials and Methods: In this study, we performed a two-step, two-sample Mendelian randomization (MR) analysis to understand the causal associations of C-reactive protein and other inflammatory regulators with liver cancer. Summary-level data for genetic variants associated with inflammation, and liver cancer were extracted from the largest genome-wide association studies. The principal MR analysis was performed by using an inverse-variance weighted (IVW) method with a random-effects model. Besides, MR-egger and weighted median were used as sensitivity analyses.

Results: Using the IVW method, the only association was between the levels of TRAIL and a higher risk of liver cancer (Odds ratio: 0.699, 95% Confidence interval: 0.519-0.941, $p = 0.018$). Most importantly, the sensitivity analysis also revealed similar results. No other causal associations were observed between the genetically predicted systemic inflammatory regulators and the risk of liver cancer.

Conclusions: This study provides genetic evidence of relationships between systemic inflammatory factors and liver cancer. Interventions that target TRAIL levels may be promising targets for the development of cancer therapies for liver cancer.

KEYWORDS: Mendelian randomization, Inflammatory factors, Liver cancer.

INTRODUCTION

Liver cancer is the sixth most common cancer of all primary cancers and the 2nd cause of cancer-related mortality [1], the incidence of which is more in patients with cirrhosis and inflammation [2]. It has been estimated that there will be an incidence of >1 million liver cancer patients by 2025 [3]. However, most patients with liver cancer are asymptomatic in their early stages and will not present typical liver symptoms, including jaundice, liver failure, and ascites, which will only present until they progress to advanced stages [4].

The liver is the primary site for the synthesis of crucial factors for blood coagulation. Besides, the liver is also responsible for the secretion of various chemokines [5,6]. By regulating a balance between pro- and anti-inflammatory cytokines, the liver can help to create a tolerogenic environment to keep the organism healthy [7]. However, if the balance is broken, the tissue homeostasis will be disrupted and chronic inflammation will be established, which may result in carcinogenesis if this unbalances persisting for many years [8].

The relationship between liver malignancy and inflammation is a well-established and complex one. Inflammation in the liver can arise from a variety of causes, including viral hepatitis, alcohol abuse, and non-alcoholic fatty liver disease. Chronic liver inflammation also results in harm to hepatic epithelial cells, including both hepatocytes and biliary epithelial cells. Despite this harm, the liver has a remarkable ability to regenerate, leading to substantial cell growth. At the same time, the inflammation triggers the production of reactive oxygen species (ROS) and DNA damage, increasing the risk of genomic DNA mutations [9]. The combination of high cell proliferation and DNA mutations increases the likelihood of malignant transformation. Additionally, chronic inflammation also causes changes in the liver's immune system, making it easier for cancer cells to avoid detection by the immune system.

The changes brought on by chronic inflammation include a decrease in the proportion of M1/M2 tumor-associated macrophages, an increase in myeloid-derived suppressor cells (MDSCs), the release of protumorigenic cytokines, the disruption of the senescence-associated secretome, and the transfer of gut-derived metabolites and pathogens to the liver [10]. Although the underlying molecular mechanisms may differ, chronic liver inflammation and the resulting cirrhotic environment are commonly believed to promote the initiation and progression of liver cancer.

Several studies have shown that individuals with chronic liver inflammation are at a higher risk of developing hepatocellular carcinoma, the most common type of liver cancer [11]. Another study found that there was a significant correlation between the presence of inflammation and an increased risk of liver cancer [12]. These findings highlight the importance of addressing inflammation in the liver as a means of reducing the risk of liver cancer.

Nevertheless, the exploration of the correlation between hepatocellular carcinoma and inflammatory factors is relatively scarce, and a comprehensive understanding of the causal relationship between inflammatory factors and liver malignancies remains elusive. The Mendelian Randomization (MR) approach is instrumental in adopting single nucleotide polymorphisms (SNPs) as genetic variables to assess the causality of the occurrence of a particular disease [13,14]. This approach takes advantage of the random distribution at meiosis of genetic variation which has been determined during pregnancy and is not susceptible to reverse causal bias or confounders. Therefore, MR is considered a powerful predictive tool to assess causality.

This MR study was designed to analyze the causal associations between inflammatory factors and liver cancer.

MATERIALS AND METHODS

Overall study design

A brief description of our study design is shown in Figure 1. This study used a two-sample MR approach to elucidate the association between 40 inflammatory factors and the risk of liver malignancy at the genome-wide significant SNP level. The whole study can be divided into two parts. In the first step, we ex-

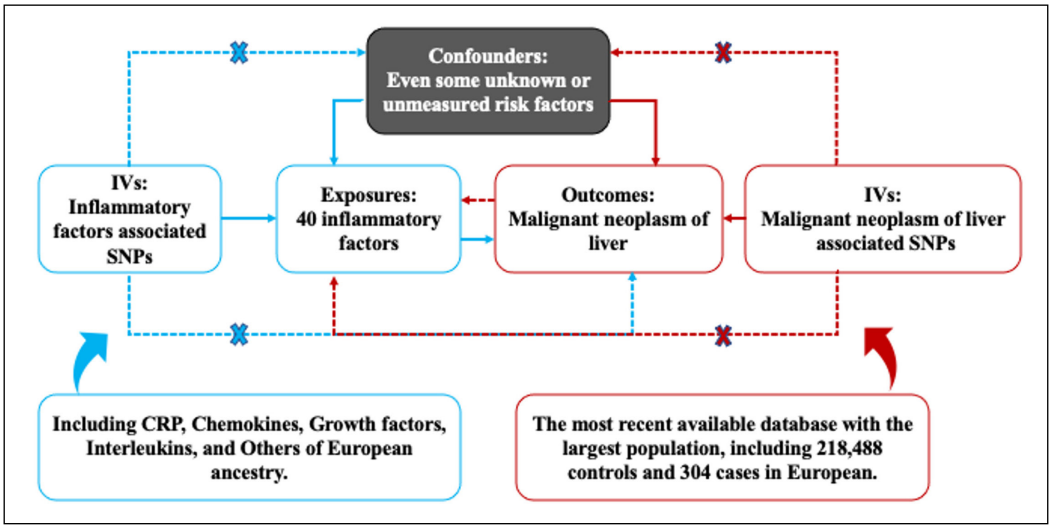

Figure 1. The design of this MR study.

plored the causal effects of 40 inflammatory factors on the risk of liver malignancy. In the second step, we explored the causal effects of liver malignancy on the levels of 40 inflammatory factors. The ethical approval was waived because the study used publicly available summary statistics and all of which have been approved by the Institutional Review Board.

Data sources

Instrumental variables for genetic inflammatory factors

The inflammatory factors used in this study included C-reactive protein (CRP) and inflammatory regulators. Genetic variation in CRP was obtained from the most recent meta-analysis of genome-wide association studies (GWASs), which included 3,301 individuals and 10,534,735 SNPs. Besides, other inflammatory regulators were also selected from the newest and largest GWASs summary statistics which were available to the public at the time of the analysis.

Genetic instrumental variables for liver cancer

Summary-level data for liver cancer were obtained from the public database and available at https://gwas.mrcieu.ac.uk/datasets/finn-b-C3_LIVER_INTRAHEPATIC_BILE_DUCTS/, including 304 cases and 218,488 controls based on the European populations.

MR assumption and IV selection

MR was based on three assumptions: (1) IVs were significantly correlated with the exposure variable (inflammatory factors); (2) IVs were not associated with potentially confounding factors for liver cancer; and (3) IVs were only associated with outcomes (the liver cancer) resulting from the exposure variable (inflammatory factors).

The enrolled SNPs were selected based on the following criteria: (1) as IVs, SNPs had significant genome-wide associations with the exposure variable at a genome-wide significance threshold ($p < 5\times10^{-8}$). In addition, IVs with a low threshold of $p < 5\times10^{-6}$ were also selected for exposure when exploring the causal relationship between the inflammatory factor and liver cancer; (2) the potential SNPs were further filtered using a clumping r^2 cutoff of 0.001 on a 10-Mb window; (3) no association between the selected SNPs and the confounding factors for outcomes should be found in PhenoScanner database ($p < 5 \times 10^{-8}$); (4) no SNP was strongly associated with outcomes ($p < 5 \times 10^{-8}$).

Two sample MR analysis

Considering that no individual-level GWAS data were available, two-sample MR analyses were performed to explore the causal association between inflammatory factors and liver cancer. The principal analyses for inflammatory factors and liver cancer were conducted using inverse-variance weighted (IVW) meta-analysis with a random-effects model. The MR-Egger and weighted median were used in the sensitivity analysis. All three MR methods are based on different models of horizontal pleiotropy. The consistency of these three methods suggested that the results of our MR analysis were reliable. All statistical analyses were performed using R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria) and TwoSample MR version 0.5.5 (GitHub Inc., San Francisco, CA, USA). A two-tailed p-value of < 0.05 was considered statistically significant.

RESULTS

Genetic instrumental variables for inflammatory factors and liver cancer

A total of 29 SNPs associated with the 15 inflammatory factors (**Table S1**) were extracted based on the genome-wide significance threshold ($p < 5 \times 10^{-8}$). However, due to the IVW as the principal analysis,

only IVs ≥ 2 can be included in the analysis. Therefore, only 4 of 15 inflammatory factors can be further analyzed. Based on the relatively relaxed GWAS significance levels ($p < 5 \times 10^{-6}$), a total of 227 SNPs associated with 40 inflammatory factors were extracted (**Table S2**). In the opposite direction, 7 SNPs for liver cancer were extracted (**Table S3**) based on the relatively relaxed GWAS significance levels ($p < 5 \times 10^{-6}$), while no SNP was extracted based on the GWAS significance levels ($p < 5 \times 10^{-8}$). All SNPs met the three basic assumptions of MR and the screening criteria for IVs.

The causal relationship between CRP and the risk of liver cancer

First, we explored the relationship between genetically predicted inflammatory factors and the risk of liver cancer. Four SNPs associated with the CRP level were selected as IVs using the genome-wide significance threshold ($p < 5 \times 10^{-8}$, **Table S1**). The result of IVW showed that a genetically predicted SD increase in CRP levels was associated with a lower risk of liver cancer with an odds ratio [OR] of 0.678 (95% confidence interval [CI]: 0.396-1.161, $p = 0.156$, Table 1). Besides, similar results were revealed in

Table 1. The results of the MR analysis based on a GWAS significant threshold of 5×10^{-8}

Exposure	Method	N_{snp}	*p*	OR (95% CI)
TRAIL levels	MR Egger	6	0.57	0.761 (0.321-1.807)
	Weighted median	6	0.045	0.694 (0.486-0.992)
	Inverse variance weighted	6	0.018	0.699 (0.519-0.941)
Interleukin-12	MR Egger	4	0.838	0.924(0.474-1.801)
	Weighted median	4	0.408	0.842 (0.560-1.266)
	Inverse variance weighted	4	0.334	0.826 (0.560-1.218)
Eotaxin	MR Egger	3	0.732	1.283 (0.432-3.811)
	Weighted median	3	0.903	0.972 (0.621-1.523)
	Inverse variance weighted	3	0.950	0.987 (0.657-1.483)
C-reactive protein	MR Egger	3	0.596	0.025 (0.000-468.347)
	Weighted median	3	0.167	0.638 (0.338-1.207)
	Inverse variance weighted	3	0.157	0.678 (0.396-1.161)

OR: odds ratio; CI: confidence interval; TRAIL: TNF-related apoptosis-inducing ligand.

the sensitivity analysis, including MR Egger (OR: 0.025, 95%CI: 0.000-468.347, $p = 0.596$, Table 1) and weighted median (OR: 0.638, 95%CI: 0.338-1.207, $p = 0.167$, Table 1). In the relaxed threshold of $p < 5 \times 10^{-6}$, the result of IVW also showed that genetically predicted high CRP levels were associated with a lower risk of liver cancer with an OR of 0.610 (95% CI: 0.446-0.835, $p = 0.002$, Table 2 and **Table S4**).

In further analysis, no causal association was observed between the genetically predicted liver cancer and the levels of CRP based on the relaxed threshold of $p < 5 \times 10^{-6}$ (**Table S5**).

Effects of systemic inflammatory regulators on the liver cancer

When exploring the causal relationship between systemic inflammatory regulators and the risk of liver cancer, only a causal relationship was found between the levels of TRAIL (TNF-related apoptosis-inducing ligand) and a lower risk of liver cancer (OR: 0.699, 95% CI: 0.519-0.941, $p = 0.018$, Table 1 and Figure 2-3) by using the IVW method. Most importantly, the sensitivity analysis also revealed similar results (Table 2). No other causal associations were observed between the genetically predicted systemic inflammatory regulators and the risk of liver cancer (Table 1 and **Table S4**).

In the inverse analysis, we explored the relationship between genetically predicted liver cancer and the levels of inflammatory factors. Whether based on GWAS significance levels ($p < 5 \times 10^{-8}$) or the relatively relaxed GWAS significance levels ($p < 5 \times 10^{-6}$), no causal association was observed between the genetically predicted liver cancer and the levels of inflammatory factors (**Table S5**).

Table 2. The results of the MR analysis based on a relatively relaxed GWAS significant threshold of 5×10^{-6}

Exposure	Method	N_{snp}	*p*	OR (95% CI)
TRAIL levels	MR Egger	17	0.088	0.729 (0.520-1.023)
	Weighted median	17	0.037	0.701 (0.502-0.979)
	Inverse variance weighted	17	0.003	0.670 (0.512-0.870)
Interleukin-12	MR Egger	14	0.993	0.997 (0.559-1.780)
	Weighted median	14	0.389	0.836 (0.557-1.256)
	Inverse variance weighted	14	0.401	0.867 (0.621-1.210)
Eotaxin	MR Egger	19	0.388	1.254 (0.760-2.067)
	Weighted median	19	0.863	1.032 (0.723-1.472)
	Inverse variance weighted	19	0.428	0.903 (0.703-1.162)
C-reactive protein	MR Egger	16	0.136	0.438 (0.157-1.219)
	Weighted median	16	0.028	0.624 (0.410-0.950)
	Inverse variance weighted	16	0.002	0.610 (0.446-0.835)

OR: odds ratio; CI: confidence interval; TRAIL: TNF-related apoptosis-inducing ligand.

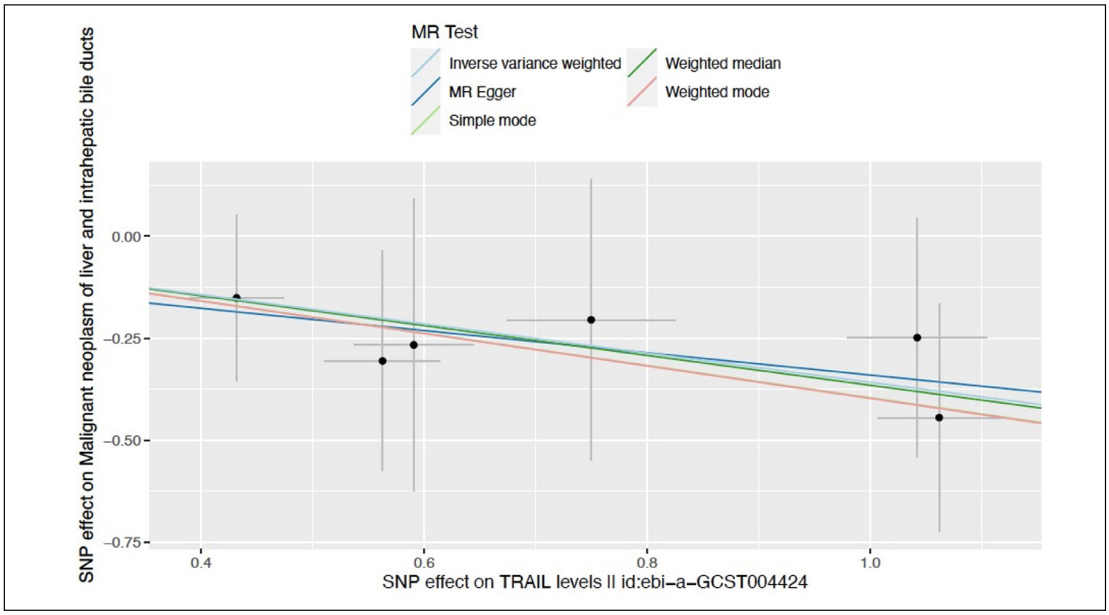

Figure 2. Scatter plot to visualize the causal effect of TRAIL levels on the risk of liver cancer. The slope of the straight line indicates the magnitude of the causal association. IVW indicates inverse-variance weighted; and MR, Mendelian randomization; TRAIL: TNF-related apoptosis-inducing ligand.

Analysis of horizontal pleiotropy

Funnel plots display the individual Wald ratios for each SNP plotted against their precision, where asymmetry is indicative of directional horizontal pleiotropy. It should be noted, however, that assessing funnel plots with respect to symmetry is difficult when using a small number of genetic instruments (Figure 4). The MR-Egger intercepts show no evidence of significant directional pleiotropy, for the causal estimation between the levels of TRAIL and a lower risk of liver cancer (p = 0.303). This result suggests that directional pleiotropic effects are not present between the TRAIL levels and the risk of liver cancer.

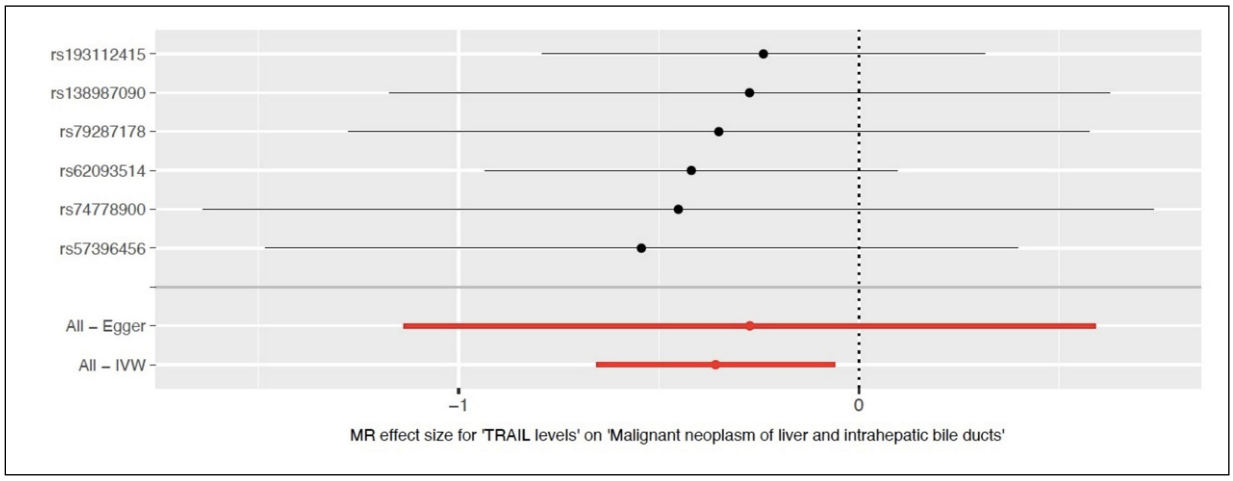

Figure 3. Forest plot to visualize the causal effect of every single SNP on the risk of liver cancer. (TRAIL: TNF-related apoptosis-inducing ligand).

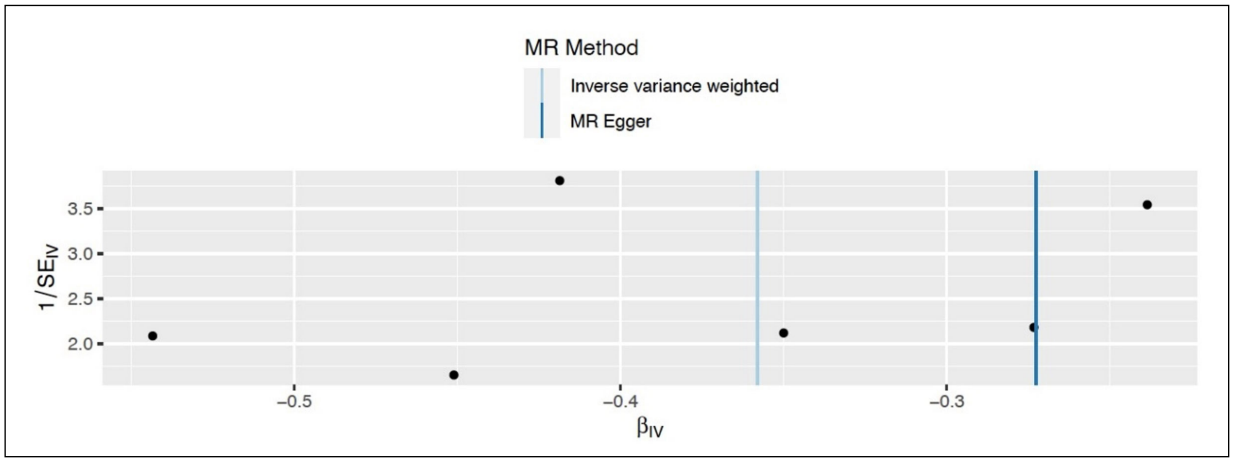

Figure 4. The plot of leave-one-out to visualize the causal effect of every single SNP of TRAIL on the risk of liver cancer. (TRAIL: TNF-related apoptosis-inducing ligand).

Effects of individual genetic instruments about the risk of liver cancer

To verify the influence of each SNP on the overall causal estimate, leave-one-out analyses were performed. No substantial difference appeared in the estimated causal effect when systematically removing individual SNP and repeating the MR analyses (Figure 5). Therefore, not any single genetic instrument resulted in the estimated effects.

Current clinical studies conducted on TRAIL

As is shown in **Table S6**, TRAIL has demonstrated the ability to induce apoptosis in a diverse range of cancer cells, including those originating from advanced solid tumors, metastatic colorectal cancer, non-small cell lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, breast cancer, head and neck cancer, liver cancer, glioblastoma, prostate cancer, sarcoma, relapsed hematologic malignancies, rectal cancer, melanoma.

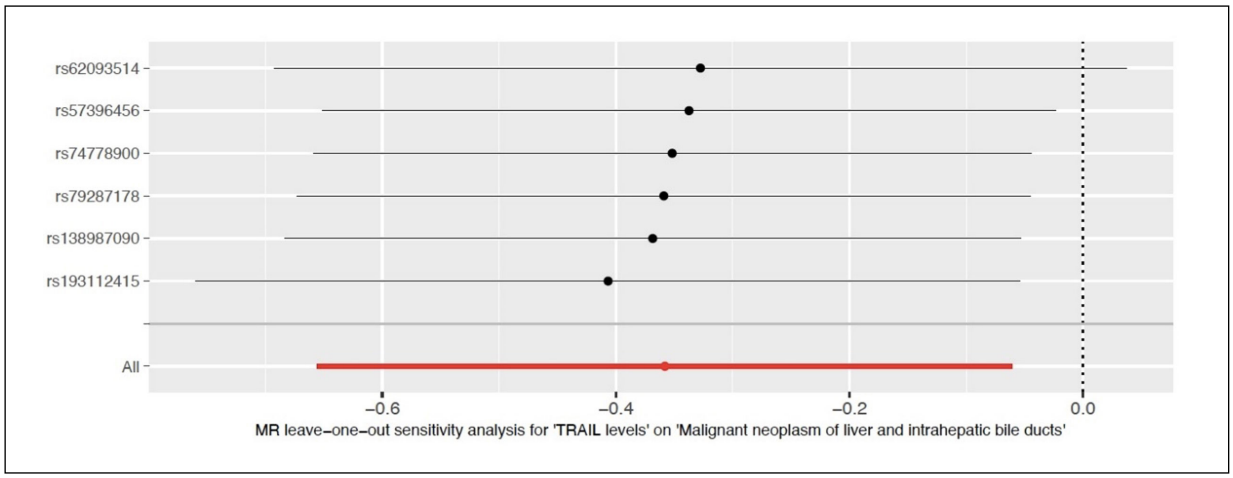

Figure 5. Funnel plots to visualize the overall heterogeneity of MR estimates for the effect of TRAIL levels on the risk of liver cancer. (TRAIL: TNF-related apoptosis-inducing ligand).

DISCUSSION

This study represents the inaugural endeavor to systematically investigate the causal associations between inflammatory factors and liver cancer by using a two-sample MR design. We found that genetically predicted TRAIL levels were causally associated with a lower risk of liver cancer, where a 1 SD increase in TRAIL levels conferred a 30% lower risk of liver cancer. And no other causal association was found in the present MR analysis.

The delicate interplay between cell survival and cell death is vital to sustaining cellular homeostasis in normal cells. Any perturbations in this equilibrium can result in pathological disorders, including the devastating disease known as cancer [15]. Cancer, a highly diverse and genetically intricate disease, is a major contributor to mortality globally [16]. Liver cancer is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths [17]. The incidence of liver cancer is increasing, particularly in countries with high rates of hepatitis B and C virus infections, alcohol consumption, and non-alcoholic fatty liver disease [18]. Although the rapid virologic response (SVR) induced by direct-acting antivirals (DAAs) can reach up to 99% in chronic hepatitis C patients, its role in the incidence or recurrence of hepatocellular carcinoma (HCC) remains uncertain [19]. Therefore, the burden of liver cancer is high, particularly in Asia, where the majority of cases occur [20]. The mortality rate for liver cancer is high, with five-year survival rates ranging from 11% to 46% [21]. It is imperative that strategies to address liver cancer be developed, including the development of effective screening and early detection methods, the implementation of prevention and control programs, and the advancement of innovative therapies.

Conventional cancer therapies, such as radiotherapy and chemotherapy, continue to be the cornerstone of cancer treatment, often in conjunction with surgical resection of the affected tumor [22]. The ultimate objective of cancer treatment is to selectively induce the death of cancerous cells while minimizing harm to normal, healthy cells [22]. However, the indiscriminate nature of these conventional therapies can result in adverse effects, including dose-limiting toxicities, as a result of their lack of specificity toward cancer cells [23]. In light of this, targeted cancer therapy, utilizing modalities such as monoclonal antibodies, small molecule inhibitors, and immunotoxins, has emerged as a promising therapeutic approach due to its specificity towards cancer cells [24].

TRAIL (TNF-related apoptosis-inducing ligand) is a member of the tumor necrosis factor (TNF) family, a group of cytokines that are known for their role in inducing apoptosis or programmed cell death [25,26]. TRAIL is widely recognized for its ability to selectively induce apoptosis in cancer cells while leaving normal cells largely unharmed [23]. This selective toxicity has made TRAIL an attractive target for the development of cancer therapies.

TRAIL has been found to be expressed by several immune cells, including T cells, natural killer cells, and dendritic cells [27]. Despite its established role in the induction of apoptosis, the precise mechanisms underlying its function are yet to be fully understood. Nonetheless, current evidence suggests that the activation of specific death receptors on the surface of cancer cells through TRAIL signaling is a crucial step that leads to the subsequent activation of caspases and other pro-apoptotic signaling pathways [28,29].

One of the key advantages of TRAIL-based therapies is their selectivity for cancer cells. Unlike traditional chemotherapy and radiation therapy, which can harm normal, healthy cells in addition to cancer cells, TRAIL has the potential to specifically target and kill cancer cells while leaving normal cells unscathed [25]. Therefore, TRAIL may be a promising option for the treatment of cancer, as it is less likely to cause the severe side effects that are associated with traditional cancer treatments [30,31].

TRAIL-based therapies are currently in various stages of development and clinical testing [32]. Some of the most promising approaches include the use of recombinant TRAIL protein, as well as the development of small molecule drugs that can mimic the effects of TRAIL [23]. A number of clinical trials have been conducted to evaluate the safety and efficacy of TRAIL-based therapies in human patients, and results so far have been encouraging (**Table S6**).

Despite its potential as a cancer therapy, TRAIL has also been implicated in a number of diseases beyond cancer. For example, it has been shown to play a role in the development of autoimmune diseases such as rheumatoid arthritis [33] and multiple sclerosis [34], as well as in the development of certain inflammatory disorders [30]. In these diseases, the excessive production of TRAIL or overactive TRAIL signaling can contribute to tissue damage and inflammation [35].

To establish causality from MR studies, it is crucial to guarantee that any potential violations of the MR hypothesis do not result in bias and to evaluate the consistency of MR results with those obtained from observational studies. However, observational studies are more prone to confounding and reverse causality. Therefore, the two-sample MR design may offer the most convincing evidence for examining the causal relationship between liver cancer and inflammatory factors, utilizing summary statistics from the largest genome-wide association studies. To minimize the possibility of pleiotropy, a sensitivity analysis was conducted utilizing three distinct methods, namely IVW, MR-Egger, and weighted median regression, to estimate the direction of pleiotropy. The consistency of results obtained through these three methods enhances the robustness of our findings.

Besides, several strategies [20] were used to ensure the fulfill requirement of MR assumptions: First, we just used the SNPs with a genome-wide significant level in this MR analysis. Besides, all the enrolled GWASs were performed in the East Asian ancestry populations. Most importantly, all three MR approaches analysis showed a positive correlation between inflammatory factors and liver cancers, making our results more reliable.

Our study also has some limitations. Firstly, our results were robust in European ancestry populations, but the results were less applicable to non-European ancestry populations [21]. Secondly, we could not explore the further causal association between subgroups (such as different types of liver cancer) because we only used aggregate-level data in our study.

CONCLUSIONS

Controlling inflammatory factors may help prevent liver cancers and ultimately reduce the disease burden and mortality associated with liver cancers. TRAIL is a promising target for the development of cancer therapies for liver cancer due to its ability to selectively induce apoptosis in cancer cells. Although it has also been implicated in a number of diseases beyond cancer, ongoing research is likely to further clarify its role in these conditions and pave the way for the development of new treatments in the liver cancer.

Ethical Approval and Informed consent:

Ethical approval and informed consent were waived because the study used publicly available summary statistics and all of which have been approved by the Institutional Review Board.

Conflict of interests:

The authors declare that they have no competing interests.

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Authors' contributions:

Conception and design: XL, Manuscript writing and data analysis: LW. All authors approved the MS for this publication.

Availability of data and materials:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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