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ORIGINAL RESEARCH

# Mendelian Randomization Analysis Supports a Causal Relationship Between Circulating Inflammatory Proteins and Basal Cell Carcinoma

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**Background:** It has been shown that the Basal cell carcinoma (BCC) is associated with chronic inflammation of skin conditions, the circulating inflammatory protein levels may be a more intuitive index in response to inflammation, however, the cause-and-effect relationship between circulating inflammatory proteins and BCC is currently unknown.

**Methods:** This study performed a Mendelian randomization (MR) analysis using the plasma inflammatory protein levels from a large genome-wide protein quantitative trait loci study as the exposure data, and the outcome data from a GWAS for BCC. Inverse variance weighed, MR-Egger, maximum likelihood ratio, and weighted median for assessing causality between inflammatory proteins and BCC. MR-Egger regression and Cochran's Q statistic were applied for sensitivity analysis and MRPRESSO was applied to exclude outliers. Inverse MR analysis was performed on inflammatory proteins found to be causally associated with BCC.

**Results:** Six circulating inflammatory proteins with a causal relationship with BCC were obtained, including CCL4, was of a significant protective effect on BCC development. IL-18 and CCL28, were of suggestive protective effects on BCC development. CX3CL1, IL-17A, and CSF-1 were potential risk factors in the development of BCC. According to the results of reverse MR analysis, there is no significant causal relationship between BCC and the above-mentioned inflammatory proteins.

**Conclusion:** This two-sample MR study revealed a strong association between circulating inflammatory proteins and the development of BCC. Specifically, CCL4, CCL28, IL-18, CX3CL1, IL-17A, and CSF-1 emerged as potential targets for prognostic evaluation and treatment of BCC. However, further experimental studies are needed to elucidate the specific mechanisms.

**Keywords:** Mendelian randomization, basal cell carcinoma, circulating inflammatory proteins, GWAS

## Introduction

Basal cell carcinoma (BCC) has the highest incidence of non-melanoma skin cancer in the world, with a percentage of approximately 80%.[1] There are approximately 3.6 million diagnosed cases each year worldwide, with approximately 2000 deaths from BCC and squamous cell carcinoma (SCC) in the United States each year.[2] First time BCC occurs in patients typically over the age of 60 years of age, and is frequently seen in body parts exposed to direct sunlight, which is due to the fact that ultraviolet (UV) rays cause damage to the DNA double strand, production of reactive oxygen species (ROS), and mutations in tumor-associated genes.[3] Certain genetic syndromes are also associated with an increased risk of developing multiple BCCs. The most common among them is Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Gorlin Syndrome. Gorlin Syndrome is caused by germline mutations in the PTCH1 gene, which lead to sustained activation of the Hedgehog (Hh) signaling pathway, thereby promoting the formation of tumor.[4]

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As is known, the role of inflammation in tumorigenesis is important; the development of tumors and the strength of their response to treatment are regulated by inflammation. Within the blood circulation, the inflammation can be measured by the concentrations of circulating proteins, and some circulating inflammatory proteins are significantly elevated prior to the diagnosis of pulmonary tumors, suggesting that circulating protein concentrations might be expected to be a marker of early carcinogenesis.[5] Observational studies have shown that skin chronic inflammation is closely associated with BCC development, for example, chronic radiodermatitis,[6] psoriasis,[7] and seborrheic keratosis,[8] etc. The majority of previous observational studies were based on a case-controlled analysis that was affected by confounding factors such as the age, environment, dietary patterns, and lifestyle. It is the limitations of the traditional observational studies themselves that also limit the inferences on the causal relationship between inflammatory proteins and BCC.

Mendelian randomization (MR) is the inference of a causal relationship between exposure and outcome based on genetic variation. As genetic variation is inherent, the traditional confounders such as environment, diet, and lifestyle have little impact on the causality obtained from MR analysis. MR analysis has been widely used for association analysis of several tumors, including colorectal cancer (CRC),[9] hepatocellular carcinoma,[10] and melanoma,[11] among others. In this study, we used 91 circulating inflammatory proteins as an exposure factor for MR analysis of BCC, and various statistical methods were used to evaluate the causal relationship between circulating inflammatory proteins and BCC, with correction of the results.

# Materials and Methods

## Methods

This study was based on the MR analysis performed, which needed to obey the following three assumptions: Firstly, the instrumental variables (IVs) used for MR analysis must be closely associated with exposure factors (p<5e-6). Secondly, IVs must not be directly related to outcomes. And finally, IVs are not related to any potential confounding factors. In this study, the exposure genome-wide association study (GWAS) summary data used were taken from published articles, and the outcome GWAS summary data were released by the IEU Open GWAS project. Ethical review was not required for this study due to the fact that the data used in this study were public, anonymous, and de-identified.

## Data Source

Genetic variation in circulating inflammatory proteins was obtained from Zhao et al[12] who used the Olink Target platform to perform a large-scale genome- wide protein quantitative trait loci (pQTL) study of 91 plasma proteins. This study included 14,824 individuals from 11 cohorts, all of European ancestry, and this study identified genetic variation in plasma protein levels associated with inflammation. The summary data for the outcome were obtained from a GWAS of BCC conducted by Christelle et al,[13] which included 17,416 cases and 375,455 controls, totaling 392,871 European individuals.

## Instrumental Variables (IVs)

The following criteria were applied to filter the GWAS data for circulating inflammatory proteins to obtain IVs with confidence and validity: (1) Single nucleotide polymorphism (SNP) loci within the significant threshold (p=1e-5) were selected as potential IVs.[14] Furthermore, using a stricter threshold for the p- value used for filtering, respectively, and we found that the circulating inflammatory proteins could still maintain a cohort of 91 when the threshold value (p=5e-6) was taken. Based on our aim to minimize the influence of confounding factors, we selected a p- value of 5e-6 to filter for circulating inflammatory proteins. (2) We calculated the linkage disequilibrium (LD) between SNPs using the reference panel from the 1000 Genomes Project Europe sample data, and used the plink package in R software to filter the SNPs based on a clumping window size of 10 mb and a threshold of R2<0.001. Only the SNPs with the most significant p-values were retained. (3) Remove SNPs with a major effect allele frequency (EAF) less than 0.01 in order to reduce statistical bias caused by low confidence. (4) The strength of association of IVs was assessed for the F statistic by using the equation F=beta^2/se^2, with beta as the effect value of each IVs on exposure and se represents the standard error of beta.[15] The IVs with an F statistic greater than 10 were included in the MR analyses to avoid weak IVs effect.[16] (5) When

palindromic SNP loci exist in both the exposure and outcome data, they should be removed. (6) If no SNP identical to the exposure data is found in the outcome data, a threshold of r^2 = 0.8 was applied to find a proxy SNP. (7) SNPs significantly associated with outcome were searched for and eliminated by using PhenoScannerV2.[17]

## Statistical Analysis

In this study, inverse variance weighted (IVW),[18] MR-Egger regression,[19] and weighted median (WM)[20] were used as traditional methods of MR analysis. To obtain an overall estimate of the effects of the exposure factors on the outcome, a meta-analysis was conducted using the IVW method, which incorporates the wald-estimates for each SNP. It is important to note that the validity of the IVW analysis relies on the assumptions of no heterogeneity and no horizontal pleiotropy. If these assumptions are met, the results obtained from the IVW analysis are considered unbiased.[18] In addition to the traditional methods of MR analysis mentioned earlier, Maximum Likelihood Ratio (ML) is accurate when ensuring no heterogeneity and horizontal pleiotropy between the IVs.[21] Furthermore, our study utilized MRPRESSO to examine the causal relationship between circulating inflammatory proteins and BCC, by using MRPRESSO, we were able to assess and account for any potential bias caused by pleiotropy in our analysis.[22] Without the presence of horizontal pleiotropy among IVs, the MR-Egger analysis method, which assumes that instrumental strength and direct effects (InSIDE) are independent, yielded results consistent with the IVW method.[19] Additionally, when up to 50% of the IVs are invalid, the WM method can provide an unbiased estimate of the causal relationship.[20]

## Sensitivity Analyses

The Cochran's IVW Q statistic was used to assess heterogeneity among the IVs. Additionally, MR-Egger regression was employed to test for the presence of horizontal pleiotropy among the IVs.[23] The MRPRESSO method was utilized to assess pleiotropy between the IVs, and to identify and eliminate outliers among the IVs. Of course, we conducted a leave-one-out analysis for each IV used in the analysis by eliminating each SNP one by one in turn and thus looking for outliers. To control for multiple testing, we calibrated the false discovery rate (FDR) using q- values. A causal relationship was considered significant when the p-value was less than 0.05 combined with a q-value less than 0.1. The suggestive relationship was considered when the p-value was less than 0.05 combined with a q-value greater than 0.1.[24] A reverse MR analysis of circulating inflammatory proteins identified in the forward MR analysis with BCC was also performed, with the methods used as described previously.

Statistical software All statistical analyses for this study were completed for the R software (version 4.2.1), using the TwoSampleMR (version 0.5.6), MR-PRESSO (version 1.0),[22] and q-value[24] R packages for MR analysis.

# Results

Based on the criteria of a filtering threshold of 5e-6 and removal of linkage disequilibrium, a total of 1818 SNPs were used as IVs for 91 circulating inflammatory proteins. Previous studies have suggested that body mass index (BMI),[25] telomere length,[26] height,[27] and birth weight[28] may be potential risk factors for BCC development. After filtering the 410 IVs using PhenoscannerV2, we obtained 1408 IVs that were not significantly associated with BCC. The details of the associated IVs are displayed in the Supplementary File 1, Table S1.

In at least one MR method, nine circulating inflammatory proteins were found to be associated causally with BCC ($p<0.05$) as shown in Table 1, Supplementary File 1, Table S2. The nine proteins are C-C motif chemokine 28 (CCL28),

**Table 1** MR Estimates for the Association Between Circulating Inflammatory Proteins and BCC

| Exposure | MR method | Num of SNP | F-statistic | OR (95% CI) | P-value | Q-value |
|---|---|---|---|---|---|---|
| C-C motif chemokine 28 levels (CCL28) | IVW | 14 | 25.73 | 0.9(0.81–1) | 5.38E-02 | 0.76 |
| C-C motif chemokine 28 levels (CCL28) | ML | 14 | | 0.9(0.82–0.99) | 3.93E-02 | 0.54 |
| C-C motif chemokine 28 levels (CCL28) | MR-Egger | 14 | | 0.97(0.76–1.22) | 7.83E-01 | 0.73 |

(*Continued*)

**Table 1** (Continued).

| Exposure | MR method | Num of SNP | F-statistic | OR (95% CI) | P-value | Q-value |
|---|---|---|---|---|---|---|
| C-C motif chemokine 28 levels (CCL28) | WM | 14 | | 0.87(0.76–1) | 4.44E-02 | 0.86 |
| C-C motif chemokine 4 levels (CCL4) | IVW | 14 | 117.56 | 0.93(0.89–0.97) | 9.41E-04 | 0.09 |
| C-C motif chemokine 4 levels (CCL4) | ML | 14 | | 0.93(0.89–0.97) | 9.53E-04 | 0.04 |
| C-C motif chemokine 4 levels (CCL4) | MR-Egger | 14 | | 0.9(0.84–0.96) | 6.85E-03 | 0.47 |
| C-C motif chemokine 4 levels (CCL4) | WM | 14 | | 0.91(0.87–0.96) | 4.25E-04 | 0.04 |
| C-X-C motif chemokine 9 levels (CXCL9) | IVW | 18 | 31.16 | 0.92(0.77–1.11) | 3.99E-01 | 0.82 |
| C-X-C motif chemokine 9 levels (CXCL9) | ML | 18 | | 0.91(0.84–0.99) | 3.12E-02 | 0.54 |
| C-X-C motif chemokine 9 levels (CXCL9) | MR-Egger | 18 | | 1.02(0.65–1.59) | 9.41E-01 | 0.73 |
| C-X-C motif chemokine 9 levels (CXCL9) | WM | 18 | | 1.02(0.9–1.14) | 7.88E-01 | 1 |
| Fms-related tyrosine kinase 3 ligand levels (Flt3L) | IVW | 20 | 48.44 | 0.9(0.8–1) | 5.97E-02 | 0.76 |
| Fms-related tyrosine kinase 3 ligand levels (Flt3L) | ML | 20 | | 0.89(0.84–0.95) | 2.36E-04 | 0.02 |
| Fms-related tyrosine kinase 3 ligand levels (Flt3L) | MR-Egger | 20 | | 0.99(0.83–1.19) | 9.46E-01 | 0.73 |
| Fms-related tyrosine kinase 3 ligand levels (Flt3L) | WM | 20 | | 0.97(0.88–1.06) | 4.43E-01 | 0.92 |
| Fractalkine levels (CX3CL1) | IVW | 18 | 39.17 | 1.09(1.01–1.18) | 3.72E-02 | 0.76 |
| Fractalkine levels (CX3CL1) | ML | 18 | | 1.09(1.01–1.19) | 3.45E-02 | 0.54 |
| Fractalkine levels (CX3CL1) | MR-Egger | 18 | | 1.3(1.05–1.62) | 2.67E-02 | 0.55 |
| Fractalkine levels (CX3CL1) | WM | 18 | | 1.07(0.95–1.2) | 2.70E-01 | 0.86 |
| Interleukin-17A levels (IL-17A) | IVW | 11 | 22.76 | 0.98(0.86–1.12) | 8.07E-01 | 1 |
| Interleukin-17A levels (IL-17A) | ML | 11 | | 0.98(0.88–1.09) | 7.50E-01 | 0.93 |
| Interleukin-17A levels (IL-17A) | MR-Egger | 11 | | 1.35(1.07–1.7) | 3.18E-02 | 0.55 |
| Interleukin-17A levels (IL-17A) | WM | 11 | | 0.98(0.85–1.14) | 8.38E-01 | 1 |
| Interleukin-18 levels (IL-18) | IVW | 12 | 48.97 | 0.96(0.89–1.03) | 2.80E-01 | 0.77 |
| Interleukin-18 levels (IL-18) | ML | 12 | | 0.96(0.9–1.03) | 2.53E-01 | 0.57 |
| Interleukin-18 levels (IL-18) | MR-Egger | 12 | | 0.82(0.7–0.96) | 3.11E-02 | 0.55 |
| Interleukin-18 levels (IL-18) | WM | 12 | | 0.94(0.86–1.02) | 1.35E-01 | 0.86 |
| Interleukin-1-alpha levels (IL-1α) | IVW | 9 | 34.07 | 1.06(0.92–1.23) | 4.31E-01 | 0.82 |
| Interleukin-1-alpha levels (IL-1α) | ML | 9 | | 1.07(0.96–1.18) | 2.09E-01 | 0.57 |
| Interleukin-1-alpha levels (IL-1α) | MR-Egger | 9 | | 1.32(1.06–1.65) | 4.32E-02 | 0.55 |
| Interleukin-1-alpha levels (IL-1α) | WM | 9 | | 0.99(0.85–1.16) | 9.27E-01 | 1 |
| Macrophage colony-stimulating factor 1 levels (CSF-1) | IVW | 12 | 34.77 | 1.13(1.04–1.22) | 5.57E-03 | 0.25 |
| Macrophage colony-stimulating factor 1 levels (CSF-1) | ML | 12 | | 1.13(1.04–1.23) | 5.66E-03 | 0.17 |
| Macrophage colony-stimulating factor 1 levels (CSF-1) | MR-Egger | 12 | | 1.13(0.89–1.43) | 3.34E-01 | 0.68 |
| Macrophage colony-stimulating factor 1 levels (CSF-1) | WM | 12 | | 1.13(1.01–1.26) | 2.63E-02 | 0.86 |

**Abbreviations**: MR, Mendelian randomization; BCC, basal cell carcinoma; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; ML, maximum likelihood, WM: weighted median.

CCL4, Macrophage colony-stimulating factor-1 (CSF-1), Fractalkine (CX3CL1), C-X-C motif chemokine 9 (CXCL9), Fms-related tyrosine kinase 3 ligand (Flt3L), Interleukin-17A (IL-17A), IL-18, IL-1α, and IL-7.

As shown in Table 1, the results of IVW analysis showed that a significant protective effect of CCL4 (Odds ratio (OR) =0.93, 95% confidence interval (CI): 0.89–0.97, p= 9.41E-04, q= 0.09) was associated with BCC. CSF-1 (OR =1.13, 95% CI: 1.04–1.23, p=5.57E-03, q= 0.25) and CX3CL1 (OR=1.09, 95% CI: 1.01–1.18, p= 3.72E-02, q= 0.76) are potential risk factors for the development of BCC. Analysis of MR-Egger showed that CCL4 (OR=0.90, 95% CI: 0.84–0.96, p= 6.84E-03, q= 0.47) and IL-18 (OR=0.82, 95% CI: 0.70–0.96, p= 3.11E-02, q= 0.55) had a suggestive protective effect against BCC. IL-1α (OR=1.32, 95% CI: 1.06–1.65, p= 4.32E-02, q= 0.55), CX3CL1 (OR=1.30, 95% CI: 1.05–1.62, p= 2.67E-02, q= 0.55), and IL-17A (OR=1.35, 95% CI: 1.07–1.70, p= 3.18E-02, q= 0.55) had a potential promotion of BCC development. Our results of WM analysis showed that CCL4 (OR=0.91, 95% CI: 0.87–0.96, p=4.25E-04, q=0.04) significantly protective against the development of BCC, as well as CCL28 (OR=0.87, 95% CI: 0.76–1.00, p=4.44E-02, q= 0.86) with suggestive protective effect. The suggestive contribution of CSF-1 (OR=1.13, 95% CI: 1.01–1.26, p=2.63E-02, q=0.86) to the development of BCC. The results of ML analysis showed that Flt3L (OR=0.89, 95% CI: 0.84–0.95, p=2.36E-04, q=0.02) and CCL4 (OR=0.93, 95% CI: 0.89–0.97, p=9.53E-04, q=0.04) had significant protective effects against BCC, with CXCL9 (OR= 0.91, 95% CI:

0.84–0.99, p=3.12E-04, q=0.28) and CCL28 (OR=0.91, 95% CI: 0.83–1.00, p=4.35E-02, q=0.32) had suggestive protective effects against the development of BCC. CSF-1 (OR=1.13, 95% CI: 1.04–1.23, p=5.66E-03, q=0.17) and CX3CL1 (OR=1.09, 95% CI: 1.01–1.19, p=3.45E-02, q=0.54) played suggestive promotional roles in the development of BCC.

For these 9 cause-and-effect relationships, the F statistics of all available IVs ranged from 20.88–934.22, which indicates that we were able to avoid the bias caused by weak IV effects (F<10). The IVW Q-test by Cochran showed the presence of heterogeneity for CXCL9, Flt3L, and IL-1α, with no significant heterogeneity for the rest (Supplementary File 1: Table S3). Furthermore, based on the results of the MR-Egger regression intercept analysis, IL-17A and IL-18 were shown to be horizontally pleiotropic, and the rest were not significantly horizontally pleiotropic (Supplementary File 1: Table S4). Separate analysis of the nine circulating inflammatory proteins by a further MRPRESSO method showed significant outliers for IL-1α, CXCL9, and Flt3L, and no significant outliers for the rest (Supplementary File 1: Table S5). By removing outliers from these circulating inflammatory protein IVs, the MR analysis was again performed, and IL-1α, CXCL9, and Flt3L lost their original causality after removing the outliers (Supplementary File 1: Table S6). Furthermore, we obtained six circulating inflammatory proteins that were found to be causally associated with BCC in the forward MR analysis of circulating inflammatory proteins as exposure and BCC as outcome, namely CCL28, CCL4, IL-18, CX3CL1, CSF-1, and IL-17A. The scatter plots (Figure 1) and leave-one-out plots (Figure 2) of the relationship between these six circulating proteins and BCC are shown graphically. In addition, the forest and funnel plots obtained from MR analysis are shown in Supplementary Figures 1 and 2.

In addition, in order to explore the reverse causal relationship between circulating inflammatory proteins and BCC, a reverse causality analysis was performed with the six circulating inflammatory proteins obtained in the forward causality analysis as the outcome and BCC as the exposure. The results of MR analysis showed no significant causal relationship between BCC and these six circulating inflammatory proteins (Supplementary File 1: Table S7). The IVW Q-test of Cochran showed heterogeneity for CX3CL1 and CSF-1, and no significant heterogeneity for the rest (Supplementary File 1: Table S8). No significant horizontal pleiotropy was observed for all six circulating inflammatory proteins as shown by MR-Egger regression intercept analysis (Supplementary File 1: Table S9). Further MRPRESSO test showed that CX3CL1 and CSF-1 had outliers (Supplementary File 1: Table S10), after removing the outliers and again performing MR analysis, there was no causal relationship between BCC and CX3CL1 and CSF-1 (Supplementary File 1: Table S11). In conclusion, none of the six circulating inflammatory proteins associated with BCC obtained by forward MR analysis showed reverse causality with BCC, which ensured the reliability of the results. The results of forward and reverse MR are shown in Figure 3.

## Discussion

Chronic inflammation and systemic oxidative stress are two closely related and significant pathological processes within organisms. They play a pivotal role in the initiation and progression of various diseases.[29] The research shows that cumulative UV exposure can disrupt redox balance and trigger inflammation and skin immunosuppression. These processes can independently or through their interplay promote skin carcinogenesis.[30] During chronic inflammation, immune cells like macrophages and neutrophils are activated. While phagocytosing pathogens and clearing damaged cells, they produce large amounts of reactive oxygen species (ROS), which can oxidatively damage surrounding healthy tissues and trigger systemic oxidative stress. In chronic skin inflammation, inflammatory cells like macrophages and neutrophils release multiple inflammatory cytokines, such as tumor necrosis factor - alpha (TNF - α) and interleukin - 6 (IL - 6).[31] These cytokines not only participate in the inflammatory response of skin tissue but may also enter the systemic circulation, leading to elevated levels of inflammatory proteins in the blood. Thus, exploring the links among chronic skin inflammation, blood inflammatory protein levels, and BCC is crucial for understanding BCC's pathogenesis and finding prevention and treatment strategies. Based on this, we conducted a two-sample MR analysis in this study. We utilized the summary statistics of circulating inflammatory proteins obtained from the published study by Zhao et al[12] as the exposure factor. Additionally, we used the summary statistics of BCC from the published study by Christelle et al[13] as the outcome. This analysis aimed to evaluate the causal relationship between circulating inflammatory proteins and BCC. To our knowledge, this is the first two-sample MR study to investigate the causal relationship between circulating inflammatory proteins and the risk of BCC using a European cohort. Our findings indicate that CCL4 has a significant protective effect on the development of BCC, and this association remained significant even after conducting the q-value test. Additionally, we observed suggestive protective causal

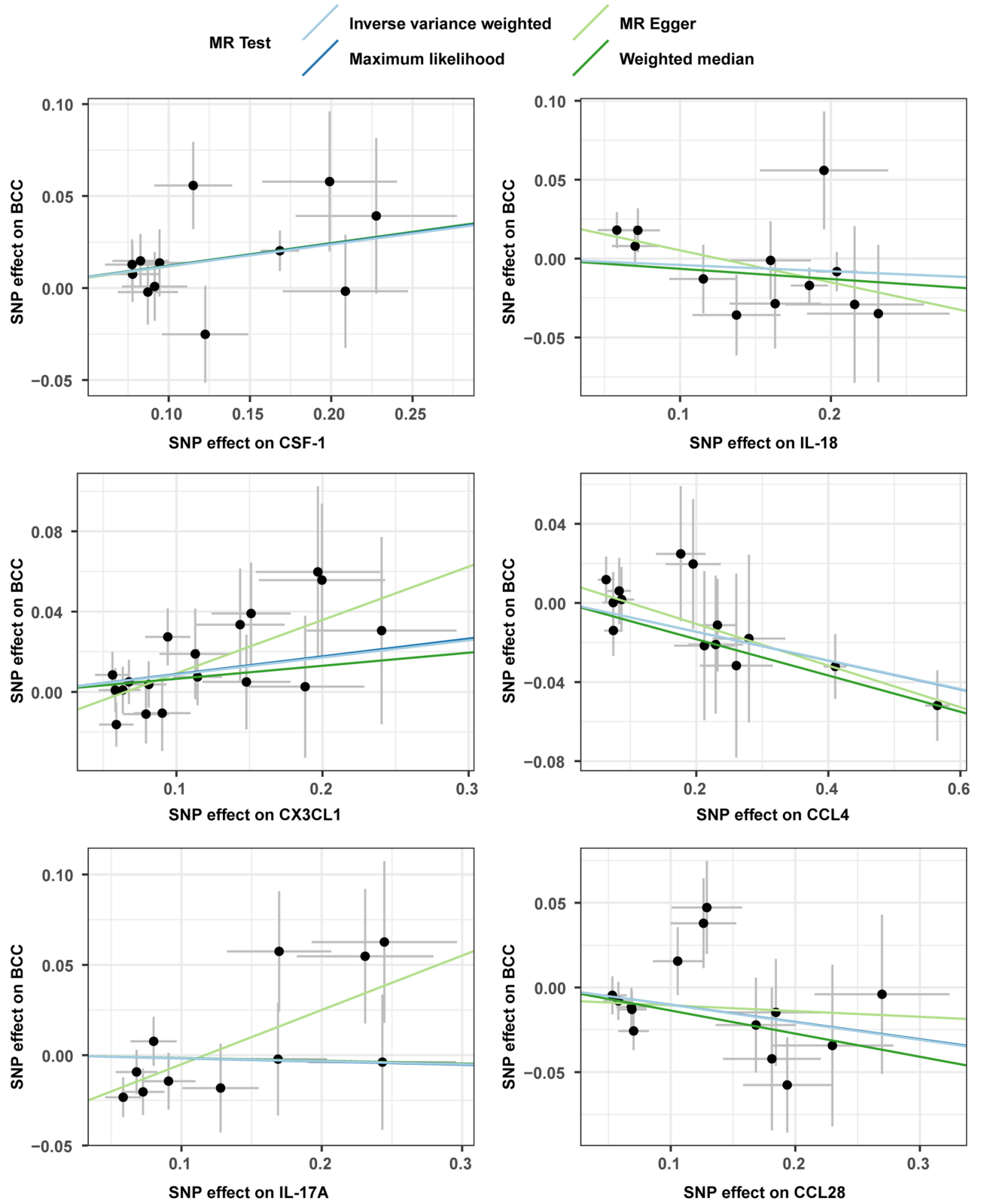


**Figure 1** The scatter plot of the causal relationship between circulating proteins and BCC.
**Abbreviations**: MR, Mendelian randomization; SNP, Single nucleotide polymorphism; BCC, Basal cell carcinoma; CCL4, C-C motif chemokine 4; CCL28, C-C motif chemokine 28; IL-17A, Interleukin-17A; IL-18, Interleukin-18; CX3CL1, Fractalkine; CSF-1, Macrophage colony- stimulating factor-1.


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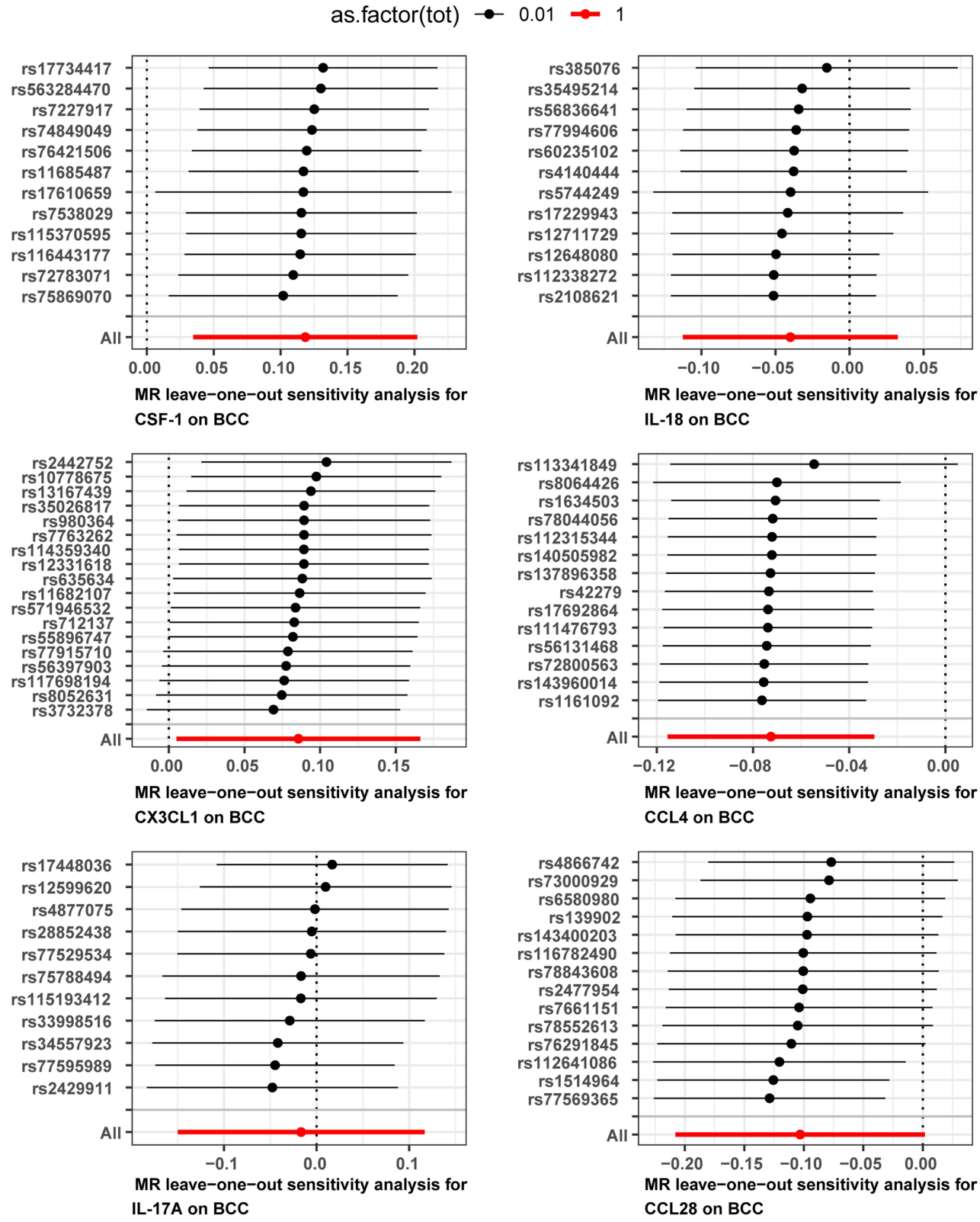


**Figure 2** The leave-one-out plot of the casual relationship between circulating proteins and BCC.
**Abbreviations**: MR, Mendelian randomization; BCC, Basal cell carcinoma; CCL4, C-C motif chemokine 4; CCL28, C-C motif chemokine 28; IL- 17A, Interleukin-17A; IL-18, Interleukin-18; CX3CL1, Fractalkine; CSF-1, Macrophage colony-stimulating factor-1.

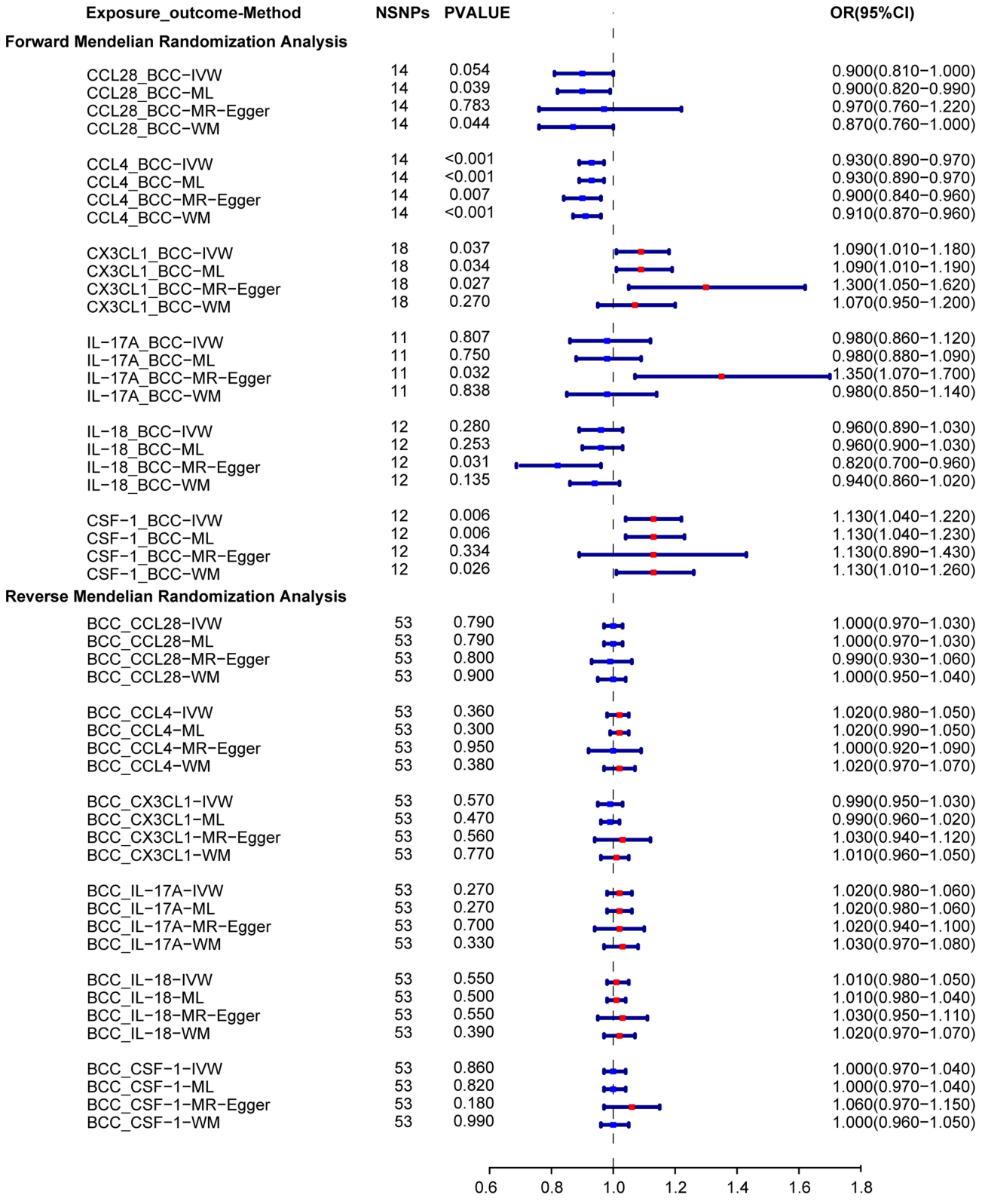


**Figure 3** The forest plot of the result in forward and reverse MR.
**Abbreviations**: MR, Mendelian randomization; BCC, Basal cell carcinoma; IVW, Inverse variance weighted; WM, Weighted median; ML, Maximum Likelihood.

associations between two other circulating inflammatory proteins, CCL28 and IL-18, and BCC. On the other hand, IL- 17A, CSF-1 and CX3CL1 as potential risk factors for BCC development were identified. The findings of this study contribute to a deeper understanding of the role of inflammatory proteins in influencing BCC, may provide valuable insights for the development of preventive and diagnostic strategies for BCC.

Chemokines, an important component of the immune system, play a crucial role in the migration and homing of immune cells.[32] It is worth noting that BCC is an immunogenic tumor, as evidenced by the increased risk observed in immunosuppressed individuals and the presence of tumor-infiltrating lymphocytes (TIL) around the tumor.[33,34] Chemokine families play a crucial role in recruiting various immune cells to the tumor site, thereby initiating and facilitating a potent anti-tumor immune response.[32] It has been demonstrated that the WNT-β-catenin signaling pathway-induced reduction in the expression of the chemokine CCL4 hinders the recruitment of dendritic cells (CD103+ cells) and T cells to the tumor microenvironment (TME).[35] This finding suggests that the downregulation of CCL4 may impede the immune cell recruitment and hinder an effective anti-BCC response at the BCC site, which is consistent with the results of our study. Additionally, our study also revealed that CCL28 may function as a potential protective factor for BCC. Furthermore, we also found that CCL28 functions as a potential protective factor for BCC. Previous studies have also found that CCL28 expression is down-regulated in breast tumors[36] and CRC,[37] suggesting that CCL28 may have anti-cancer functions. In tumors, with high expression of CCL4 and CCL28 may promote the infiltration of immune cells, such as T cells and natural killer (NK) cells, into the TME.[35] Cells expressing C-C motif chemokine receptor 10 (CCR10), such as regulatory T cells (Treg), are attracted by CCL28 through chemotaxis.[38] High expression of CCL28 may enhance the recruitment of Treg to tumor sites. Studies have indicated a negative association between the expression of Treg cells and the invasion depth of BCC,[39] which suggests an anti-BCC effect of CCL28 possibly through promotion of Treg cell recruitment. Several studies have suggested a close association between CX3CL1- CX3CR1 and the development of various cancers. In pancreatic carcinoma cells, CX3CL1 has been found to be associated with glucose uptake and lactate secretion, it may promote tumorigenesis by reprogramming the glucose metabolism of the tumor cells.[40] Migration and proliferation of pancreatic ductal adenocarcinoma (PDAC) may be facilitated by CX3CL1-CX3CR1 axis through the JAK/STAT signaling pathway.[41] Additionally, CX3CL1-CX3CR1 axis has been found to play a role in the development of human glioblastoma by regulating immune subpopulations within the tumor microenvironment.[42] Moreover, CX3CL1 inhibits lipopolysaccharide- induced macrophage M1-type polarization by activating the WNT-β-catenin signaling pathway,[43] which may facilitate tumorigenesis.[44] These findings are consistent with our own research.

It has been demonstrated that chemokines play a bi-directional role in tumor immunity. Specifically, high expression of CCL4 in CRC might induce infiltration of pro- tumorigenic macrophage profiles (CD163 cells), leading to the development of CRC.[45] The KRAS-driven activation of Fos-like antigen 2 (FOSL2) has been found to promote PDAC progression by transcriptionally activating CCL28.[46] These suggest that high level of expression of CCL4 and CCL28 might also be risk factors for tumorigenesis. In addition, there is growing evidence that the CX3CL1-CX3CR1 axis plays a role in controlling tumor growth by recruiting anti-tumor immune cells (eg NK cells and T cells) into the TME, thereby exerting anti- tumor effects.[47–49] CX3CL1 has been shown to play a role in the development and progression of clear cell renal cell carcinoma (ccRCC) by acting as a tumor suppressor.[50] However, the bi-directional regulation of CCL4, CCL28, and CX3CL1 in BCC is still unclear. In our present study, the role of CCL4 as a significant protective factor in the development of BCC, CCL28 acts as a suggestive protective factor, and CX3CL1 has a promoting effect on BCC. Further experiments are needed subsequently to conduct the relevant mechanisms to be explored. The association between pro-inflammatory factors and tumors has been reported in numerous observational studies. Specifically, IL-17, as a pro-inflammatory factor, has been implicated in the induction and mediation of inflammatory responses, and its association with tumorigenesis has been extensively documented.[51,52] High levels of IL-17 have been found to promote the development of human non-melanoma skin cancer (NMSC),[53] and the risk of BCC was reduced in psoriasis patients who were treated with IL-17 inhibitors.[54] These findings are consistent with our own research. Our findings suggest that CSF-1 is a risk factor that promotes the development of BCC. The overexpression of CSF-1 and CSF-1R has been associated with a poor tumor prognosis,[55,56] this may be due to the relationship of polarization of M2-type macrophages and CSF-1 overexpression.[57] Several studies have demonstrated significant anti-tumor activity of CSF-1R inhibitors.[58,59] As a powerful pro- inflammatory factor, the IL-18 has been reported to enhance the antibody-dependent cell-mediated cytotoxicity (ADCC) effect of NK cells, effectively killing the tumor cells.[60,61] The study showed that IL-18 expression correlated positively with prognostic survival in melanoma patients, and this might be related to

CD8 + T and NK cells infiltration.[62] In tumor cells, the IL-18 decoy receptor (IL-18BP) binding to IL- 18 expresses to prevent NK cells from activating the IL-18 pathway to kill tumors.[63,64] Decoy-resistant IL-18 (DR-18) modified by Aaron's team, can be unaffected by IL-18BP and maintain the function of IL-18.[65] This novel modification opens up new possibilities for tumor immunotherapy. During tumor development, many types of cells are recruited to the microenvironment surrounding tumor cells. These cells include, but are not limited to, macrophages, dendritic cells (DCs), neutrophils, B-cells, T-cells, tumor-associated fibroblasts, and other cell types. These immune cells, combined with the extracellular matrix and other elements, together make up the Tumor Immunity Microenvironment (TIME).[66,67] The TIME resembles a field of battle between promotion and suppression of tumor immunity. The tumor cell associated antigens stimulate the immune system, leading to the production of massive amounts of immune cells. However, tumor cells also employ various mechanisms to evade immunity through a variety of effects, these corporately lead to tumor cell immunological escape.[68] Inflammatory protein expression plays a significant role in the process of tumor immunity.[69] Our study suggests that up- regulation of CCL4, CCL28, and IL-18 around BCC tumors may inhibit the progression of BCC, while the over-expression of IL-17A, CSF-1, and CX3CL1 may promote BCC development. Further follow- up experiments should be conducted to explore the specific mechanisms underlying these associations.

## Strengths

This study possesses several strengths: (1) All the data utilized in this study were derived from GWAS conducted on European populations, which reduces bias due to ethnicity and provides an accurate representation of the cause-and-effect relationship with circulating inflammatory proteins and BCC in European populations. (2) Three major assumptions of MR analysis were satisfied in this study. Firstly, through setting strict filtering criteria for closely related (p=5e-06) SNPs of circulating inflammatory proteins, the IVs with strong statistical strength (F>10) were selected, which satisfied the first hypothesis. Next, the second assumption is satisfied through setting a threshold of clump, which eliminates the LD between IVs as much as possible. Finally, several risk factors associated with the development of BCC, like telomere length,[26] birth weight[28] BMI,[25] and height,[27] among others, by reviewing previous studies were identified. Confounding effects from outcome were efficiently avoided through the removal of confounding-associated SNPs in IVs by phenoscannerV2. The IVW Q- test of Cochran was used to detect IVs heterogeneity, and in this study, MR-Egger regression and MRPRESSO analysis were also applied to test for horizontal pleiotropy and to eliminate outliers, the third hypothesis was fulfilled. (3) A reverse MR analysis of BCC and circulating inflammatory proteins was performed in this study, which aimed to determine the direction of causality between circulating inflammatory proteins and BCC. (4) MR analysis was performed based on genetic variation, effectively avoiding interference from external confounders. This study used non-overlapping exposure and outcome summary data for MR analysis to effectively avoid bias.[70]

# Limitations

This study has several limitations that should be considered. Firstly, the results of this study were based on the analysis of European populations, may introduce the potential confounding effect of population stratification. Therefore, caution should be exercised when generalizing these findings to other populations worldwide. In the future, it would be beneficial to extend the analysis to include diverse populations to enhance the generalizability of the findings regarding the association between circulating inflammatory proteins and BCC. Secondly, for this study, it used data that were summarized from GWAS, rather than raw data, which would not allow for association analyses between BCC subgroups, such as to differentiate between nodular BCC and superficial BCC. Finally, in order to conduct tests for heterogeneity and pleiotropy, it was necessary to include more SNPs as IVs. However, the filtering threshold for this study did not meet the traditional GWAS analysis threshold (p=5e-8), for this purpose, the q-value test was used to minimize the FDR.[24]

This two-sample MR study establishes a causal link between circulating inflammatory proteins and BCC. CCL4, CCL28, and IL-18 may protect against BCC by modulating immune cell migration and activation, but their exact mechanisms in the BCC microenvironment are unclear. Conversely, CX3CL1, IL-17A, and CSF-1 might promote BCC development. For instance, CX3CL1 might influence tumor-associated macrophage polarization via interaction with CX3CR1, and IL-17A could drive BCC development by inducing inflammatory responses and cytokine network activation. However, the specific pathways and targets of these proteins in BCC require further investigation. Additionally, though reverse MR estimates do not support a causal link

from BCC to inflammatory proteins, a potential reverse causality where BCC affects inflammatory protein expression via unknown mechanisms cannot be ruled out. This possibility demands more experimental and clinical research.

## Conclusion

In summary, this study offers vital causal proof of the relationship between circulating inflammatory proteins and BCC, yet many crucial questions remain. Future research should explore the specific mechanisms of these proteins, confirm potential reverse causality, and study their roles in different BCC stages and subtypes. These efforts could provide new theoretical foundations and potential targets for BCC prevention, diagnosis, and treatment.

## Ethics Statement

According to Article 32, Items 1 and 2 of the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" (National Science and Technology Ethics Committee, China), this research is exempt from ethical review. The exemption is based on the use of anonymous data from public and legitimate databases.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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