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ORIGINAL ARTICLE

Casual Association between Circulating Cytokines and Colorectal Cancer: A Mendelian Randomization Study

Arzoo Prasai[1#], Qianzi Kou[1#], Ying Li[1#], Vicheth Virak [# 2], Sokheng Phal[3], Nora Iv[3], Rattanaricky Ung[3], Sokhuon Cheat[3], Gechhorng Lim[3], Vahid Say[3], Ratanak Pich[3], Seng An Hong[3], Nita Nouth[3], Dinarong Phan[3], Pengkhun Nov[1*], Juanli Xu [1]*, Jiqiang Li[1]*

[1]Department of Radiation Oncology，Oncology Center, Zhujiang Hospital, Southern Medical University, No.253 Mid Gongye Ave, Haizhu District, Guangzhou, Guangdong Province, Postal code 510282, China

[2]Department of Cardiology, Laboratory of Heart Center, Zhujiang Hospital, Southern Medical University, No. 253, Middle Gongye Avenue, Haizhu District, Guangzhou 510282, Guangdong, The People's Republic of China

[3]School of International Education, Southern Medical University, Guangzhou, Guangdong Province 510515, China

[*]Corresponding Author: Jiqiang Li, Juanli Xu, Dr. Pengkhun Nov

Abstract

Background: Colorectal cancer (CRC) represents a significant health issue globally, and comprehending it's molecular basis is crucial for developing effective intervention strategies. This research explores the causal links among cytokines, and CRC through a Mendelian Randomization (MR) framework.

Methods: A comprehensive two-sample Mendelian randomization (MR) analysis was performed in this research. In summary, publicly accessible genetic data were used to explore the causal relationship between 41 cytokines, 91 cytokines and with colorectal cancer (CRC). For MR analysis, the inverse variance weighted (IVW) method and weighted medians were applied, while to evaluate heterogeneity and pleiotropy, sensitivity analyses were performed.

Results: Our results demonstrated a significant association between the likelihood of developing of colorectal cancer (CRC) and the concentration of the T-cell surface membrane glycoprotein CD5 [odds ratio (OR) = 0.746, 95% confidence interval (CI) = 0.605–0.920, p = 0.006], C-C motif chemokine 4 [OR = 0.886, 95% CI = 0.810–0.969, p = 0.008], CUB domain-containing protein 1 [OR = 0.845, 95% CI = 0.738–0.968, p = 0.0157], TNF-related apoptosis-inducing ligand [OR = 0.858, 95% CI = 0.755–0.975, p = 0.018], Interleukin-6 [OR = 0.719, 95% CI = 0.570–0.9058, p = 0.005], and Tumor necrosis factor beta [OR = 1.102, 95% CI = 1.015–1.197, p = 0.019].

Conclusion: These findings open new avenues for additional research into the clinical use of T-cell surface membrane glycoprotein CD5, C-C motif chemokine 4, CUB domain-containing protein 1, TNF-related apoptosis-inducing ligand, Interleukin-6, and Tumor necrosis factor beta in colorectal cancer, presenting hopeful opportunities for diagnosis and therapy.

Keyword: Colorectal cancer, cytokines, Mendelian randomization, GWAS

Introduction

Colorectal cancer (CRC) ranks as the third most prevalent form of cancer and is the second leading cause of death linked to cancer globally [1]. It has the highest death rate among diseases affecting

the digestive system, and its exact causes and underlying mechanisms remain challenging to identify. Nevertheless, research has established that inflammation contributes to the development of CRC [2-4], with the tumor microenvironment (TME) being a critical factor [5-6]. The tumor microenvironment (TME) consists of a variety of cellular and non-cellular elements that work together to promote tumor development, invasion, metastasis, and the reaction to treatment [7]. It is important to note that a significant number of colorectal cancer cases show abundant inflammatory cell infiltrates, which correlate with elevated cytokine levels within the TME [8]. These cytokines comprise a range of soluble substances, such as cytokines and chemokines, as well as signaling molecules like growth factors [9].

Cytokines are crucial in the onset, advancement, and spread of cancer [10-12]. In recent times, there has been considerable research into cytokines and their receptors as potential targets or therapies for cancer. The discovery of abnormal and unregulated cytokine expression across all types of human cancers supports this approach [13]. For example, interleukin (IL)-17F has been shown to inhibit CRC by inhibiting tumor angiogenesis [14]. Furthermore, inflammation driven by IL-23/IL-17 activation promotes CRC development [15]. Nevertheless, findings related to the relationship between certain cytokines and the risk of colorectal cancer (CRC) remain variable. Research indicated that levels of TNF-α were notably lower in individuals with colorectal cancer when compared to healthy individuals [16-17]. Nevertheless, another study reported that T cells infiltrated colorectal cancer, producing higher number of tumor necrosis factor (TNF)-α [8]. Given the debate over these cytokines and biases in traditional observational study designs, the potential relationship between cytokines and CRC risk remains to be elucidated.

Mendelian randomization (MR) is a statistical technique that leverages genetic differences to determine a causal link between an exposure and its effects [18]. Since genetic variation is random and alleles are not affected by exposure, this approach minimizes the effects of confounding factors. In this study, we first extracted 91 cytokines (circulating inflammatory factors, chemokines, growth factors, and interfering factors) from effective genetic variation using a two-sample MR analysis to explore their correlation with CRC risk. Furthermore, an independent analysis was conducted on the genetic variations of 41 cytokines and colorectal cancer publicly released in 2021. This study aimed to elucidate the cytokines demonstrating a relationship with CRC risk using an MR analysis.

2. Materials and Methods

2.1 Study Design

The relationship between 41 cytokines, 91 cytokines and colorectal cancer (CRC) was assessed using two-sample Mendelian randomization (MR) techniques. This method relied on genetic variations as proxies for the risk factors. To ensure valid causal conclusions, the instrumental variables (IVs) used in the MR analysis had to fulfill three essential criteria: (1) The genetic variation must have a direct link to the exposure; (2) The genetic variant should not be connected to any confounding variables that could influence both the exposure and the outcome; and (3) The genetic variation must affect the outcome exclusively through the exposure, without involving any other pathways **Figure 1**.

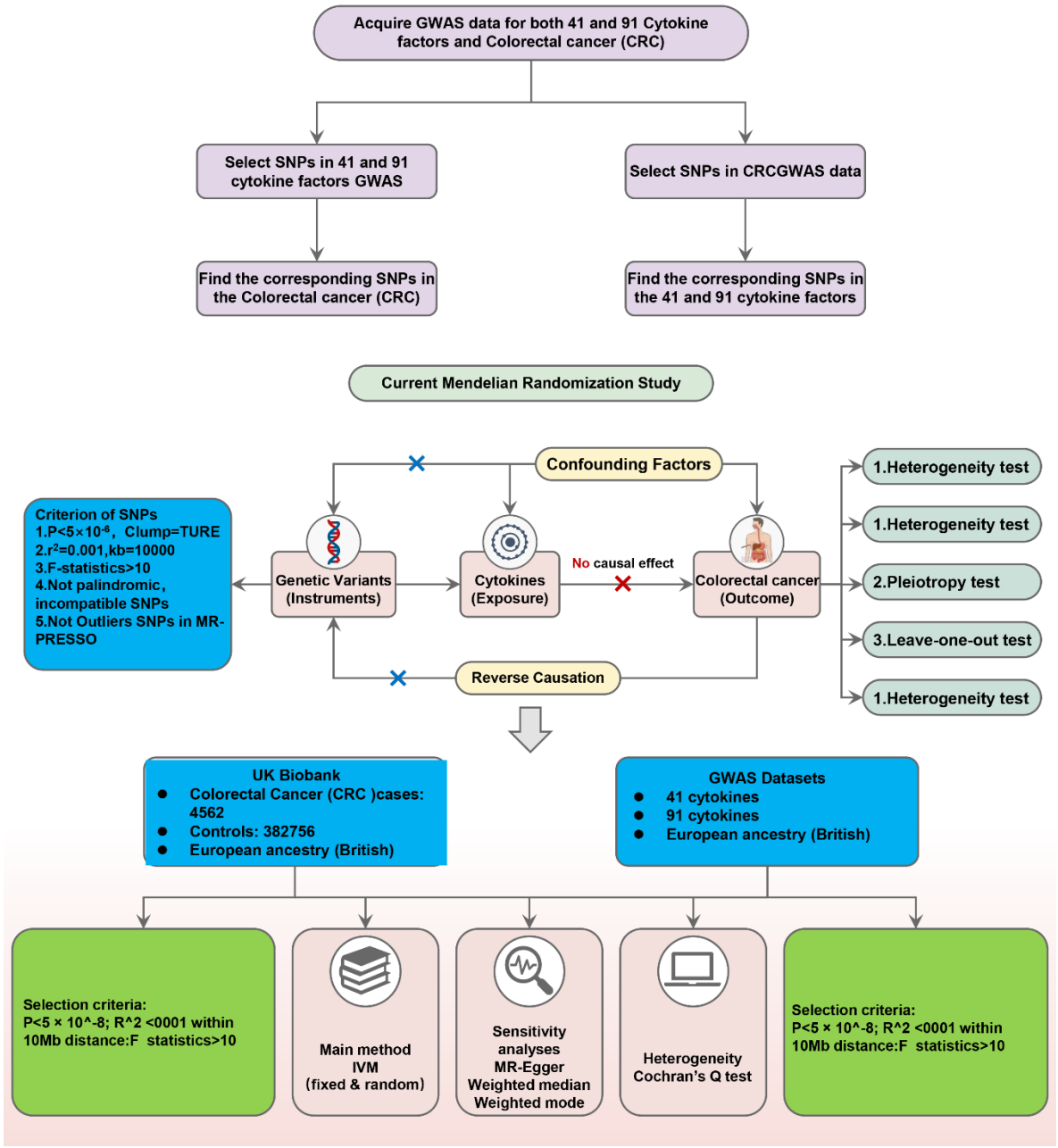

Figure 1 Study Design Flowchart.

2.2 Data Sources for Exposure and Outcome

A compilation of GWAS data for all 41 cytokines, 91 cytokines can be found in the GWAS catalog, which is available to the public (https://www.ebi.ac.uk/gwas/) (accession numbers: GCST90274758 to GCST90274848) [19-20]. Cancer-specific keywords were applied to search relevant data for CRC **(https://pheweb.org/UKB-SAIGE/)** for UK Biobank data include CRC (ukb-saige-153).

2.3 Instrument Selection

Due to the extensive number of single-nucleotide polymorphisms (SNPs) that exhibit genome-wide significance ($p < 5 \times 10^{-8}$) for 91 traits related to inflammatory cytokines, we adopted stricter correlation criteria ($p < 5 \times 10^{-9}$) for the selection of genetic instrumental variables (IVs). These IVs were classified using the Linkage Disequilibrium (LD) reference panel from the 1000 Genomes Project, applying an R^2 threshold of less than 0.001 within a range of 1,000 kilobases (kb). Given the relatively small GWAS dataset for the 91 inflammatory cytokines, we also utilized a p-value threshold of 5×10^{-8} and a more flexible clustering criterion ($R^2 < 0.001$ within 1000 kb). To validate the robustness of our findings, we chose IVs with F-statistics exceeding 10, marking them as strong instruments for

subsequent analysis. These IVs were gathered from summary statistics concerning outcomes related to CRC, omitting any that indicated potential pleiotropic influences (p < 10^-5) on CRC, in line with methodologies from previous studies.

2.4 Statistical Analysis

We utilized the inverse-variance weighted (IVW) method as our main analytical technique, considering its robust performance as a statistical approach [21]. The relationship between circulating cytokine concentrations and the risk of colorectal cancer (CRC) was assessed by integrating beta values along with their standard errors. We evaluated heterogeneity in the analyses using Cochran's Q statistic, where a p-value below 0.05 suggested significant heterogeneity [22]. Furthermore, we performed several sensitivity analyses, such as MR-Egger, weighted median, simple mode, and weighted mode. The MR-Egger approach utilized the regression intercept to assess possible pleiotropic effects, with a significance level set at a p-value below 0.05 [22]. The weighted median approach was utilized to enhance causal estimations, especially in scenarios where nearly fifty percent of the weight in the Mendelian Randomization (MR) analysis came from questionable instrumental variables (IVs). The simple mode denotes fundamental statistical models that lack intricate adjustments or numerous variables, typically employed in initial analyses to evaluate direct connections between variables [23]. In contrast, the weighted mode applies weights according to the data's reliability, enabling a more precise representation of the different variables' impacts [24].

To detect genetic variants exhibiting horizontal pleiotropy, we utilized the MR-pleiotropy residual sum and outlier (MR-PRESSO) approach. We examined potential reverse causal links between SNPs associated with cytokines and colorectal cancer (CRC) through the MR Steiger Filtering Test [21]. We assessed the heterogeneity among causal estimates specific to the variants and identified outliers using scatter plots. In instances where significant heterogeneity was noted among the SNPs, the random-effects model grounded in the inverse variance-weighted (IVW) method was deemed more trustworthy [24].

All evaluations were conducted using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). The "TwoSampleMR" and "MR-PRESSO" packages were employed for statistical evaluations and data visualization.

3 Results

To explore the causal impact of inflammatory cytokines on colorectal cancer (CRC), we performed a two-sample Mendelian Randomization (MR) analysis and inverse variance weighting (IVW) as our primary analytical approach. In summary, we found a strong correlation between CRC risk and levels of T-cell surface glycoprotein CD5 [odds ratio (OR) = 0.746, 95% confidence interval (CI) = 0.605–0.920, p = 0.006], C-C motif chemokine 4 [OR = 0.886, 95% CI = 0.810–0.969, p = 0.008], CUB domain-containing protein 1 [OR = 0.845, 95% CI = 0.738–0.968, p = 0.0157], TNF-related apoptosis-inducing ligand [OR = 0.858, 95% CI = 0.755–0.975, p = 0.018], Interleukin-6 [OR = 0.719, 95% CI = 0.570–0.9058, p = 0.005], and Tumor necrosis factor beta [OR = 1.102, 95% CI = 1.015–1.197, p = 0.019] (see **Figure 2**).

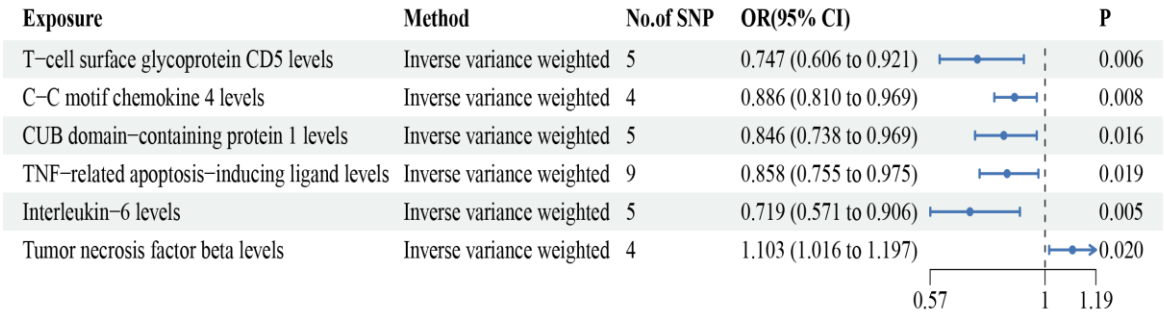

Figure 2. The causal association between cytokines and colorectal cancer. We selected Inverse variance weighted (IVW) as a primary method p<0.05 showed statistically significant; OR value >1 indicated a risk factor; OR value <1 indicated a protective factor.

Additionally, we conducted a sensitivity analysis. Although we observed some degree of heterogeneity, as indicated by significant findings from Cochran's Q test ($P < 0.05$), the causal estimates proved to be stable when assessed using the random-effects IVW model (refer to **Table SI**).

Table SI The heterogeneity of causal association between cytokines and colorectal cancer. The p-values for the Cochran's Q yielded were above 0.05, suggesting that no significant heterogeneity effects were found.

exposure	method	Q	Q_df	Q_pval
T-cell surface glycoprotein CD5 levels	MR Egger	4.677121957	3	0.197025151
T-cell surface glycoprotein CD5 levels	Inverse variance weighted	4.721488973	4	0.31708609
C-C motif chemokine 4 levels	MR Egger	0.289632648	2	0.865181191
C-C motif chemokine 4 levels	Inverse variance weighted	0.478460756	3	0.923597358
CUB domain-containing protein 1 levels	MR Egger	0.076376881	3	0.994513032
CUB domain-containing protein 1 levels	Inverse variance weighted	3.983905256	4	0.408188419
TNF-related apoptosis-inducing ligand levels	MR Egger	12.56142474	7	0.083543052
TNF-related apoptosis-inducing ligand levels	Inverse variance weighted	12.63031304	8	0.125218288
Interleukin-6 levels	MR Egger	5.666296837	3	0.12902372
Interleukin-6 levels	Inverse variance weighted	5.710165393	4	0.221864102
Tumor necrosis factor beta levels	MR Egger	2.057309483	2	0.35748755
Tumor necrosis factor beta levels	Inverse variance weighted	3.613671581	3	0.306315783

The P-values for the MR-Egger intercept were above 0.05, suggesting no notable pleiotropic effects (see **Table SII**).

Table SII The pleiotropy of causal association between cytokines and colorectal cancer. The p-values for the MR-Egger intercept were above 0.05, suggesting that no significant pleiotropy effects were found.

exposure	egger_intercept	se	pval
T-cell surface glycoprotein CD5 levels	0.014634603	0.086752014	0.876769254
C-C motif chemokine 4 levels	0.028250114	0.065011007	0.706284077
CUB domain-containing protein 1 levels	0.045994985	0.023268019	0.142507697
TNF-related apoptosis-inducing ligand levels	-0.004440562	0.022663954	0.850230912
Interleukin-6 levels	0.006046877	0.039677429	0.88854351
Tumor necrosis factor beta levels	0.024722549	0.020098921	0.343732371

Moreover, we further examined the data through scatter plots (**Figure 3A-F**), funnel plots (**Figure 4A-F**), and leave-one-out plots (**Figure 5A-F**), which assisted in mitigating the potential effects of outliers and horizontal pleiotropy on the identified significant cytokines.

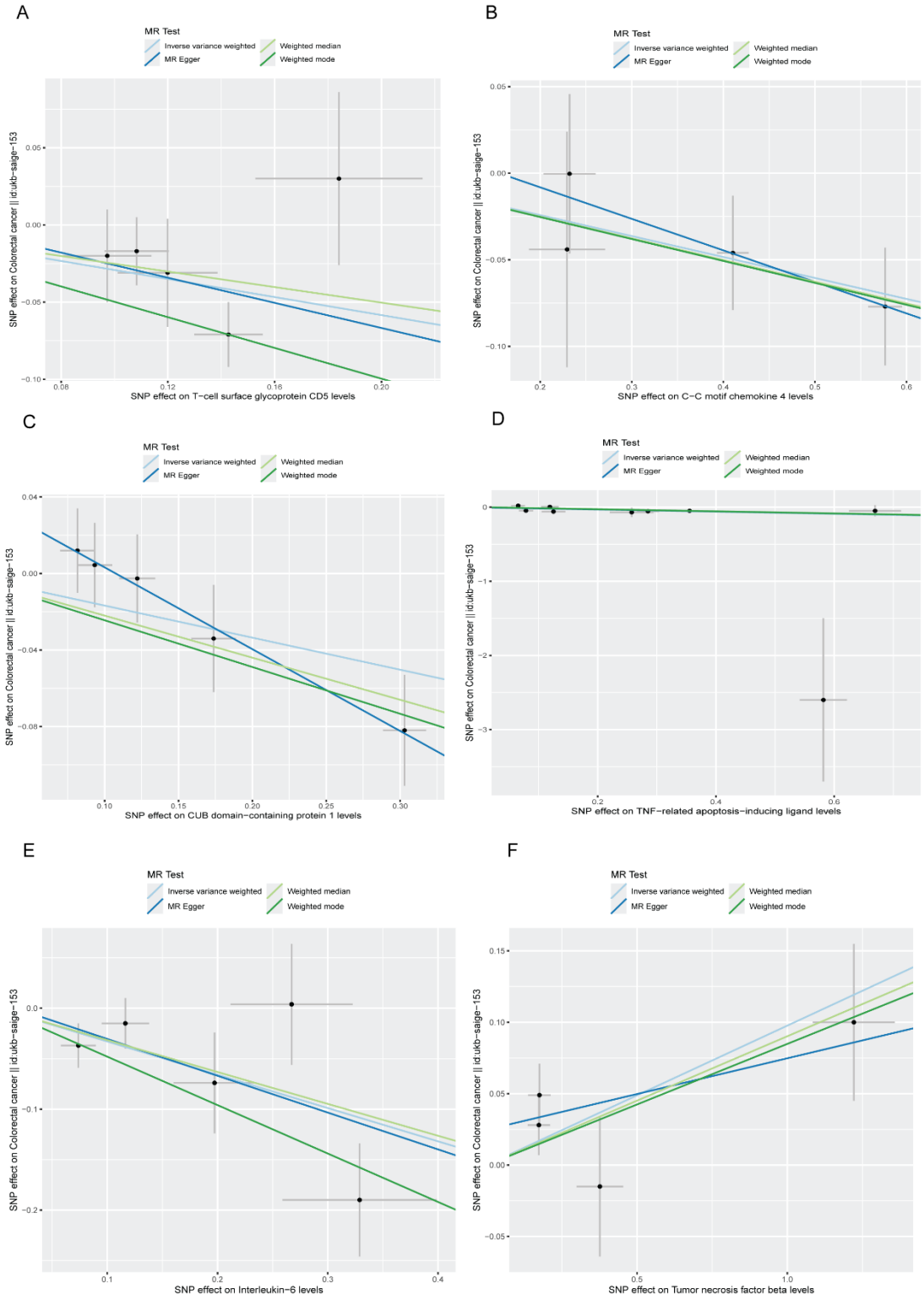

Figure 3 Scatter plot showing the relationship of cytokine with the risk of colorectal cancer (CRC). (A) T-cell surface glycoproteins CD5; (B) C–C motif chemokines 4; (C) CDCP1; (D) TRAIL; (E) IL-6; (F) TNF-beta.

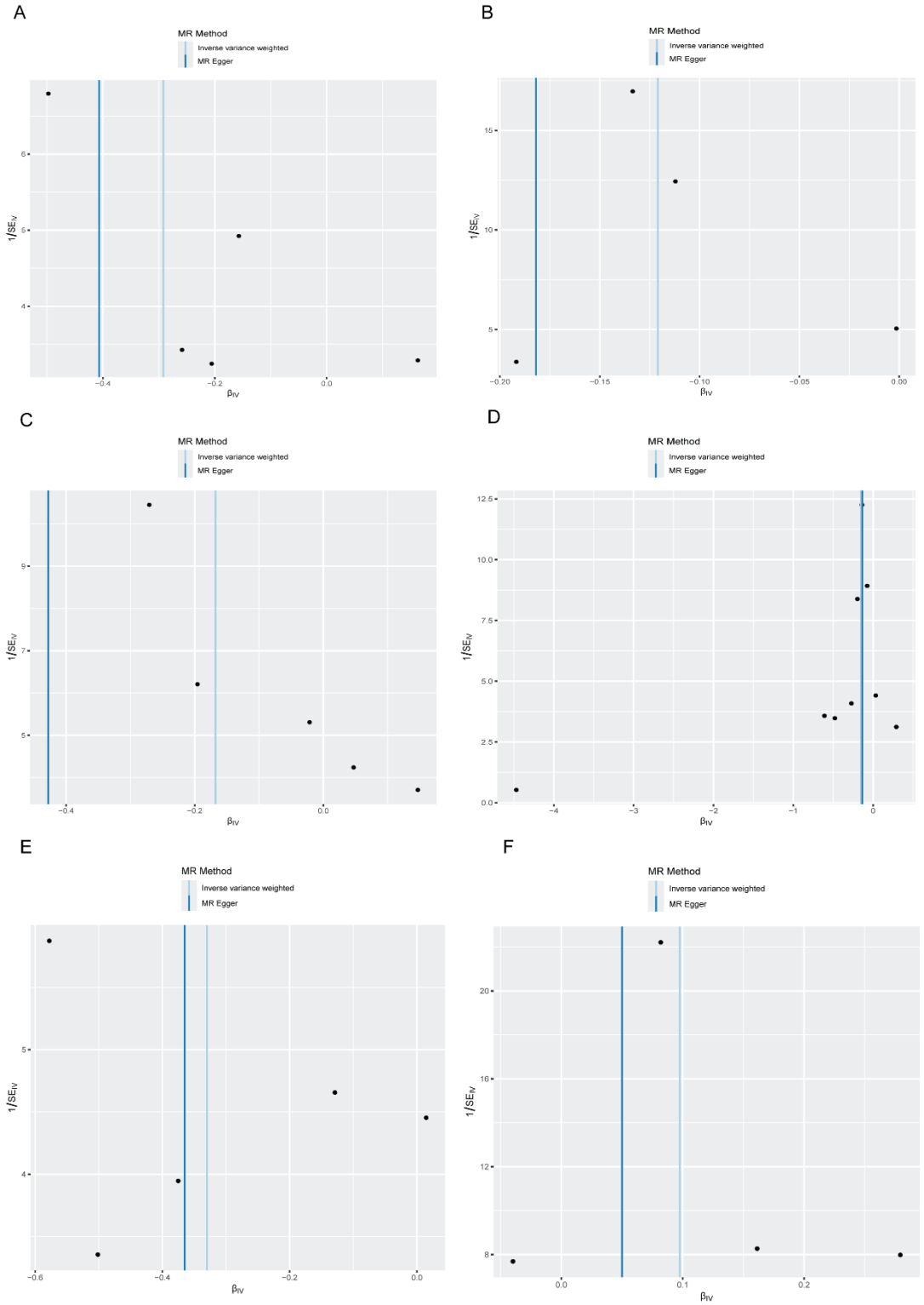

Figure 4 Funnel plot showing the relationship of cytokine with the risk of colorectal cancer (CRC). (A) T-cell surface glycoproteins CD5; (B) C–C motif chemokines 4; (C) CDCP1; (D) TRAIL; (E) IL-6; (F) TNF-beta.

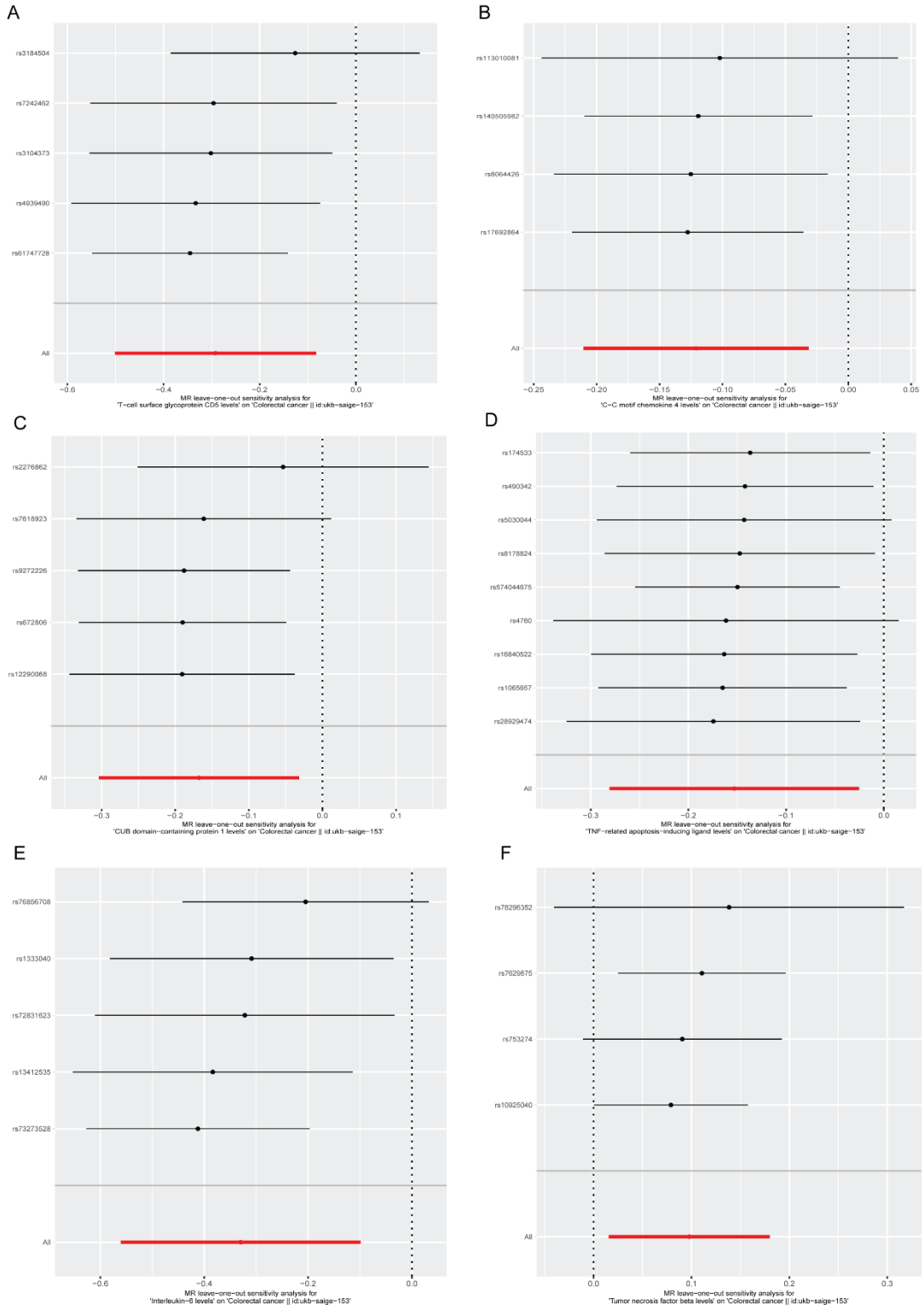

Figure 5 Leave one out showing the relationship of cytokine with the risk of colorectal cancer (CRC). (A) T-cell surface glycoproteins CD5; (B) C–C motif chemokines 4; (C) CDCP1; (D) TRAIL; (E) IL-6; (F) TNF-beta.

4. Discussion

T-cell surface glycoproteins CD5 (CD5) plays a critical role as a receptor that primarily functions to inhibit the activation of T-cells. Interestingly, studies indicate that T-cells with elevated levels of CD5 demonstrate enhanced survival rates for both effector and memory cells when subjected to pathogenic challenges. This suggests a possible compensatory function of CD5. Additionally, NF-κB has emerged as a key regulator that manages the survival, activation, and differentiation of both innate immune cells and inflammatory T-cells [25]. The activation of its canonical pathway is

crucial for chronic inflammation and the development of tumors [26]. One investigation proposed that the NF-κB pathway is influenced by CD5 signaling and provided further evidence supporting the link between CD5 expression and Atopic Dermatitis (AD) [27]. Another previous study was published by Zhao et al. [28] It also showed that CD5 is the protective factor in peripheral artery disease which is line with our study result.

On the other hand, research by He et al. described CD5 as a monomeric cell surface glycoprotein found on thymocytes, mature T cells, and a specific group of B cells called B-1 cells [29-30]. It acts as a receptor based on immunoreceptor tyrosine-based inhibitory motifs, which counteracts the activation of the primary T-cell receptor through the recruitment of inhibitory intracellular mediators like SHP-1, RasGAP, or Cbl. Although CD5 reduces T-cell activation and differentiation, it does not interfere with the adherence of antigen-presenting cells to T cells or the formation of immune synapses [31]. Studies have demonstrated that about 50% of patients with vestibular neuritis (VN) show a reduction in total T lymphocytes and specifically CD8 lymphocytes [32]. T cells, a vital component of lymphocytes, perform various functions including direct cytotoxicity towards target cells, modulation of B-cell antibody production, response to specific antigens and mitogens, and cytokine release, all contributing to immune defense against infections and cancers. Thus, it's hypothesized that the increased expression of CD5, known for its inhibitory properties, might elevate the risk of vestibular neuritis. Additionally, another study noted that children diagnosed with autism spectrum disorder (ASD) had significantly higher serum and plasma levels of CD5 compared to healthy controls, correlating positively with their scores on the Childhood Autism Rating Scale [32-34]. As a universal marker for T cells, CD5 is significantly expressed in various autoimmune diseases, and this meta-analysis offers new insights suggesting that heightened circulating CD5 levels may actively facilitate the onset of ASD. More randomized clinical trials and fundamental experiments are necessary to address these discrepancies.

C–C motif chemokines, a subset of small, secreted proteins, interact with G protein-coupled chemokine receptors located on the cell membrane, characterized by closely positioned cysteine residues [35]. Their well-known role is to coordinate cell movement, especially of leukocytes, significantly contributing to both protective and harmful immune and inflammatory reactions [36]. CCL4, commonly referred to as the macrophage inflammatory protein, is an important member of the CC chemokine family. This protein, which is encoded by the CCL4 gene in humans, interacts with CCR5 and is recognized as a crucial factor in suppressing human immunodeficiency virus (HIV) released by CD8+ T-cells [37]. Furthermore, its role in cardiovascular diseases is gaining attention [36]. While CCL4 shows a protective effect in patients with Type 1 diabetes, it is also observed to be elevated in conditions like atherosclerosis and myocardial infarction [36]. CCL4 enhances the proliferation of porcine uterine luminal epithelial cells by activating the PI3K and MAPK signaling pathways while inhibiting the NF-κB pathway [38]. This mechanism may help clarify CCL4's protective role in colorectal cancer (CRC), as demonstrated in this study, emphasizing its potential as both a biomarker and a target for therapy.

Earlier research has indicated that the CDCP1 protein is found on hematopoietic stem cells, mesenchymal stem cells, and neuronal progenitor cells [39-40]. Additionally, both our team and other scientists have demonstrated that CDCP1 is significantly overexpressed in various human cancer cell types, including those from melanoma [41], lung [42], pancreatic [43], renal cell [44], colon, liver, gastric, kidney, breast, and prostate carcinoma [45]. Analyses of 25 breast cancer tissue samples revealed that the expression of CDCP1 mRNA is influenced by CpG methylation occurring in the promoter region [46]. Furthermore, the levels of CDCP1 mRNA in K562 and Jurkat hematopoietic cells also show an inverse relationship with CpG methylation [47]. CDCP1 staining in colon cancer and surrounding normal tissue indicated a relationship between tumor aggressiveness and the intensity of CDCP1 staining [45]. In a study examining human cancer samples, researchers discovered that certain tumor subsets exhibited relatively elevated levels of CDCP1 expression. This subset included as many as 77 out of 230 cases of renal cell carcinoma, 60 out of 200 lung cancer cases, and 53 out of 145

pancreatic cancer cases, all of which were notably linked to unfavorable prognosis regarding disease-free and overall survival [44-46]. Conversely, a recent study indicated that low levels, but not elevated levels, of CDCP1 expression correlated with poor prognosis in 23 out of 110 cases of endometrial adenocarcinoma [48]. Recently, it has been proposed that kidney cancer tissues with membrane-localized CDCP1 tend to have a poorer prognosis compared to those where CDCP1 is expressed in the cytoplasm [49]. It appears that the overall expression of CDCP1 in various cancers is typically correlated with unfavorable outcomes; however, additional details and more thorough analyses will be necessary to understand the consequences of the protein's subcellular localization and its tyrosine phosphorylation. Furthermore, recent studies have indicated that the CDCP1 gene is activated by hypoxia-inducible factors (HIF)-1 and HIF-2, which are associated with the loss of the von Hippel-Lindau (VHL) tumor suppressor gene in clear cell renal cell carcinoma (CC-RCC) cells [49]. This is the initial report regarding the transcriptional regulation of the CDCP1 gene in cancer cells. The hypoxia-inducible factor (HIF) governs the expression of target genes, even during tumor advancement, and can be subjected to degradation by the proteasome when the VHL protein is present. In cases of clear cell renal cell carcinoma (CC-RCC), the VHL gene is inactive in approximately 80% of instances [50]. Tumor cells that are hypoxic tend to be particularly aggressive, metastatic, and resistant to cancer treatments [51]. Therefore, the expression of CDCP1 could influence the malignancy of hypoxic tumor cells, making the CDCP1 protein a promising therapeutic target for these challenging tumors. Our research indicates that CDCP1 acts as a protective factor in colorectal cancer (CRC), although further investigation is needed to clarify this finding.

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which belongs to the tumor necrosis factor (TNF) family, has attracted considerable attention as a potential cancer treatment because of its unique ability to selectively trigger cell death in cancer cells while leaving healthy tissues largely unharmed, as shown in preclinical studies [52]. This selectivity results from TRAIL's interaction with the death receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2), which initiate apoptotic signaling cascades [53]. In clinical settings, soluble TRAIL formulations and monoclonal antibodies aimed at these death receptors have been investigated in phase I/II trials; however, their effectiveness in treating colorectal cancer (CRC) has been restricted due to the development of resistance in tumor cells, despite initial indications of safety and potential benefit from preclinical studies [54]. Investigations into TRAIL resistance have mainly focused on intrinsic factors, such as the natural resistance of normal cells to apoptosis [55]. Studies also highlight acquired resistance in CRC models. Repeated exposure to sublethal TRAIL doses (10–25 ng/mL) has been shown to generate resistant subpopulations in initially sensitive cell lines like HCT116, underscoring tumor heterogeneity and adaptive survival mechanisms [58-60]. Genetic alterations, including Bax mutations and p53 deficiency, further contribute to TRAIL resistance in CRC, as demonstrated in models of HCT116 cells [59-60]. Contrary to these findings, our study identifies TRAIL as a protective factor in colorectal cancer, suggesting a context-dependent role that may diverge from its conventional pro-apoptotic function. This observation highlights the need to reevaluate TRAIL's complex biological activity in CRC and explore strategies to harness its protective effects while overcoming resistance mechanisms.

In a prior nested case-control study, elevated plasma levels of IL-6 were found to be positively correlated with gastric cancer (OR = 1.73, 95%CI 1.00–3.00) [61]. Conversely, another nested case-control study did not reveal any significant links [62]. Multiple studies have suggested that high IL-6 levels independently indicate a poor prognosis for patients with gastric cancer [63-64]. However, one investigation assessing serum IL-6 levels and the survival of gastric cancer patients did not recognize IL-6 as an independent prognostic factor [65]. The common IL-6–174G>C polymorphism in the IL-6 promoter, associated with increased transcriptional activity, raises serum IL-6 concentrations [66]. Earlier research has also investigated the connection between IL-6 levels and gastrointestinal cancers, specifically considering IL-6 polymorphism as a functional variant. Multiple meta-analyses have shown that IL-6 polymorphism does not correlate with the risk of developing gastric cancer [67-68]. Additionally, among 155 patients diagnosed with gastric cancer, the presence of this polymorphism

does not appear to impact survival [63]. However, some studies suggest that IL-6 polymorphism may be linked to poorer survival outcomes in patients with gastric cancer. [69-70]. In patients diagnosed with colorectal cancer, most research indicates no significant correlation, although a nested case-control study revealed a modest positive connection (OR = 1.76, 95%CI 1.01–3.06) [71-74]. There is a limited amount of research examining the causal link between IL-6 and esophageal cancer; however, IL-6 is believed to be linked with unfavorable outcomes in esophageal cancer [75]. As a cytokine that promotes tumorigenesis, IL-6 plays a role in cancer advancement via various STAT3-mediated oncogenic signaling pathways in cell lines and mouse models [76]. For instance, IL-6 signaling can trigger the expression of several molecular targets, such as the proto-oncogene MYC, which play a role in cell cycle advancement and survival in gastric cancers [77].

Currently, IL-6 inhibitors have emerged as a key treatment approach for immune-mediated inflammatory conditions, including rheumatoid arthritis and Takayasu arteritis, with various drugs designed to block IL-6 signaling pathways [78]. There is growing interest in the potential therapeutic effects of IL-6 inhibitors in oncology, with preliminary studies suggesting that medications like Siltuximab and Elsilimomab might be beneficial [79]. In gastric cancer, inhibiting IL-6 could limit the interaction between malignant epithelial cells and cancer-associated fibroblasts within the tumor microenvironment, thereby mitigating stroma-related chemotherapy resistance [80]. Additionally, recent findings have shown that an IL-6 inhibitor can reduce the toxicity of immunotherapy and enhance tumor immunity in cancer patients[81].

Earlier research has demonstrated that TNF-β (lymphotoxin), which is a member of the tumor necrosis factor family, triggers inflammatory responses in colorectal cancer (CRC) cells with effectiveness comparable to that of TNF-α [82-83]. In these studies, TNF-β activates the NF-κB signaling pathway in CRC cells, leading to increased cancer cell growth, invasion, and the upregulation of genes associated with metastasis. It also encourages epithelial-to-mesenchymal transition, enhances its own expression, and promotes the production of TNF-α [82-83]. The increase, development of colonospheres, and movement of HCT116 cells were notably enhanced in the presence of TNF-β or TNF-α in a manner that depended on both the dosage and duration. These observations align with findings indicating a strong link between inflammation and the onset of tumors in various cancers [84]. It has been established that inflammation creates a microenvironment conducive to tumor development, which is associated with tumorigenic processes, including cellular transformation, promotion, proliferation, and metastasis [85,86]. Our research indicates that TNF-β serves as a risk factor for CRC.

5. Limitation

Our Mendelian randomization (MR) research aimed to explore the causal link between inflammatory cytokines and colorectal cancer (CRC) utilizing data from a comprehensive genome-wide association study (GWAS) and the UK Biobank. This approach effectively tackles the shortcomings of conventional observational studies by minimizing confounding influences and decreasing the likelihood of reverse causation. Moreover, MR helps alleviate challenges related to representativeness and practicality often encountered in randomized controlled trials (RCTs). However, interpreting our results requires careful consideration of several limitations. These include the potential neglect of issues associated with nasopharyngeal carcinoma, the possible impact of unforeseen factors on inflammatory markers, and adopting a low P-value threshold for selecting instrumental variables. Furthermore, the absence of validation across a broader spectrum of ethnic groups limits the applicability of our findings. Our study also encountered difficulties due to restricted access to critical databases, which hindered a more thorough examination of inflammatory markers concerning the personalized profiles of the CRC cohort, encompassing clinical stages, subtypes, age of onset, gender, and treatment modalities such as surgery, immunotherapy, or targeted therapies.

6. Conclusion

This research establishes a causal link between inflammatory cytokines and nasopharyngeal carcinoma, demonstrated through Mendelian randomization analyses. Inflammatory cytokines are closely associated with cancer, and examining

their role in tumor development enhances our understanding of tumor growth mechanisms, potentially leading to new therapeutic targets. In our investigation, we initially discovered that levels of Tumor necrosis factor beta were positively associated with the progression of CRC, whereas T-cell surface glycoprotein CD5, C-C motif chemokine 4, CUB domain-containing protein 1, and IL-6 were negatively linked to the development of nasopharyngeal carcinoma. These findings underscore the promise of targeting inflammatory pathways as a treatment approach for CRC, indicating a need for further exploration of inflammation's role in cancer biology.

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Availability of Data and Materials

All the data for the present article can be found on the GWAS (http://www.ebi.ac.uk/gwas/) and yunshang Gwas (https://gwas.medicineitlab.com/).

Authors' Contributions

Pengkhun Nov, and Arzoo Prasai collected, analyzed, and interpreted the data. Arzoo Prasai wrote the manuscript. SS, ST, SK, PN, QK, YL, AP, WF, KD, and JL designed, revised, and supervised the study. All authors had reviewed and approved the final manuscript.

Ethics Approval and Consent to Participate.

Not applicable.

Patient Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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