Am J Cancer Res 2024;14(4):1577-1593
www.ajcr.us /ISSN:2156-6976/ajcr0155831

Original Article

Causal relationship between circulating cytokines and follicular lymphoma: a two-sample Mendelian randomization study

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Received February 7, 2024; Accepted March 27, 2024; Epub April 15, 2024; Published April 30, 2024

Abstract: Follicular lymphoma (FL), derived from germinal centre (GC) B cells, is a kind of systemic neoplasm. Even though FL is indolent, it remains an incurable haematology Neoplasm. Accumulating evidence has suggested that the circulating cytokine is associated with the development of FL, yet the causal relationship between FL and circulating cytokines remains undetermined. Therefore, we conducted a two-sample Mendelian randomization (MR) to confirm the causal link between FL and levels of circulating cytokines with the use of summary data on circulating cytokines and FL. All these data from genome-wide association study were derived from the Genome-wide pQTL mapping which contains 14,824 individuals. FL data were acquired exclusively from FinnGen, where 218,792 individuals (522 cases vs. 218,270 controls) were involved. Various statistical methods, including the inverse variance weighted method (IVW), weighted median (WME), simple model, weighted model (WM) and MR-Egger, were used to evaluate the potential causal connection between circulating cytokines and FL. Sensitivity analysis, which involves the examination of the heterogeneity, pleiotropy, and leave-one-out method, was also performed to ensure more trustworthy results. A bidirectional MR test was performed to evaluate the direction of causal association between circulating cytokines and FL. Combining all the steps of MR analysis, we revealed four causal cytokines: C-X-C motif chemokine ligand 5 (CXCL5), interleukin-15 receptor A (IL15RA), interleukin-20 (IL20), and neurotrophin-3 (NT-3). The risk of FL may be inversely linked to CXCL5 (OR=0.73, CI: 0.545-0.979, P=0.036), IL-15RA (OR=0.669, CI: 0.451-0.993, P=0.046), and IL-20 (OR=0.565, CI: 0.325-0.981, P=0.043) but positively linked to NT-3 (OR=1.872, CI: 1.063-3.297, P=0.03). In addition, in our study, no causal effect of FL on cytokines was demonstrated and no significant heterogeneity and pleiotropy were found. Our research revealed the causal relationship between cytokines and FL, along with both the anti-protective effect of CXCL5, IL-15RA, and IL-20 and the protective effect of neurotrophin-3 on FL. These findings aim to provide new clues regarding the pathogenesis of FL and to extend the potential of circulating cytokines to therapeutic interventions.

Keywords: Circulating cytokines, follicular lymphoma, Mendelian randomization, genome-wide association study

Introduction

FL, also called follicle-related B cell lymphoma, ranks the second most common incident lymphoma in western countries [1]. FL represents the majority of low-grade non-Hodgkin lymphoma (NHL) subtype with the characteristics of indolence and recurrence [2]. Despite being indolence, FL can convert to aggressive lymphoma which leads to early death [3]. Since the application of anti-CD20 (rituximab) based combination therapy, the overall survival of FL has improved remarkably [4]. However, a great proportion of patients still suffer reoccurrence, hindering the treatment of FL [5]. Therefore, the exploration of new therapies for FL is of great importance to overcome the aforementioned dilemma. The pathogenesis of FL, which is associated with the gene characteristics, deregulation of immune system, and tumor

microenvironments, has yet to be elucidated. Several researches suggest that signals in microenvironment contribute to the development and prognosis of FL [6-8].

In the immune microenvironment of tumor exists series of signals, most of which are cytokines. Cytokines, the majority of which are secreted proteins, are produced by lymphoma cells and surrounding immune cells before released into blood. Moreover, cytokines are indispensable in regulating the immune system and inflammatory response, regulating both the balance of T cells and the growth, development, and survival of B cells [9-11]. Cytokines are also indispensable in the evolvement and development of tumors and function as messengers mediating cellular communication between tumor cells and non-tumor cells. When evoked by tumor cells, cytokines project various effects on the biological behaviour of tumor cells, such as the promotion or inhibition of cell growth and apoptosis, the promotion of invasion, and angiogenesis [12, 13].

Cytokines also affect the development and evolvement of FL [14]. They play a key role in immune pathway, exhibiting the necessity in immunoregulation and in the pathogenesis of lymphoma. In a large cohort study, Muhammad A Mir et al. discovered that over 10% of individuals with FL possess the elevated levels of six cytokines - hepatocyte growth factor (HGF), interleukin-8 (IL-8), Interleukin-1 receptor antagonist (IL-1RA), C-X-C Motif Chemokine ligand 9 (CXCL9), interleukin-12 (IL-12), and IL-2 receptor (IL-2R) [15]. The elevated concentrations of various cytokines and VEGF were identified as the biomarkers of early diagnosis and prognosis for Hodgkin [16] and non-NHLs [17, 18]. Additionally, because cytokines play a crucial role in the maturation of lymphocytes, the genes that encode the cytokine produced in microenvironment have the potential to disturb the biology of lymphoma [19]. Multiple researches suggest that various cytokines are involved in the pathogenesis of FL. Sugimoto et al. found the association of CXCL9, IL-2R, and IL-1RA levels with poor outcome in FL patients [7]. Sana Intidhar Labidi et al. evaluated the prognostic significance of ten cytokines in FL and detected high levels of IL-1RA, IL-6, interleukin-7 (IL-7), interleukin-10 (IL-10), interleukin-13 (IL-13), tumor necrosis factor α (TNF-α), vascular endothelial growth factor a (VEGFa), and platelet-derived growth factor (PDGF) in the blood of individuals with FL. Multivariate analyses revealed that elevated levels of tumor necrosis factor β (TNF-β) in the blood were a significant predictor for better prognosis, whereas high levels of LDH and VEGF were linked to worse progression-free survival outcome [20]. In addition, levels of cytokines in serum may be predicators or biomarkers for chemotherapeutic effect in FL patients who received chemotherapy. Various researches have indicated that the secretion of cytokines, such as IL-12, IL-10, interleukin-4 (IL-4), and interleukin-17 (IL-17), into microenvironment can influence the efficacy of chemotherapy. Studies have shown that increased levels of IL-2R, IL-1RA, and CXCL9 are linked to reduced event-free survival in recently diagnosed FL patients receiving chemoimmunotherapy and to higher levels of IL-12 and IL-1RA [15]. Conversely, a high level of chemoattractant cytokine ligand-9 (CCL9) in the blood is a positive factor for FL patients receiving rituximab and chemotherapy and is associated with improved outcomes [21].

Although series of researches have implied the significance of the serum cytokines in FL patients, the causal association between circulating cytokine and FL has not been established.

MR is a methodology that uses single-nucleotide polymorphisms (SNPs) as instrumental variables (IVS) to uncover risk factors and reveal the potential causal link between exposure and outcome [22]. In MR, causality bias can be reversed or assessed free from confounding [23]. The exposure involved in this research can be explored with less limit than that involved in randomized controlled trials.

In our study, we utilized MR approach to investigate the causality between the circulating cytokine and FL. The objective of this study was to provide a new therapeutic regime for FL and to develop profound understanding with respect to development and evolvement of FL.

Methods

Statement of ethics and study design

Using a two-sample MR study, we evaluated the connection between cytokines and follicular lymphoma. Previously published summary sta-

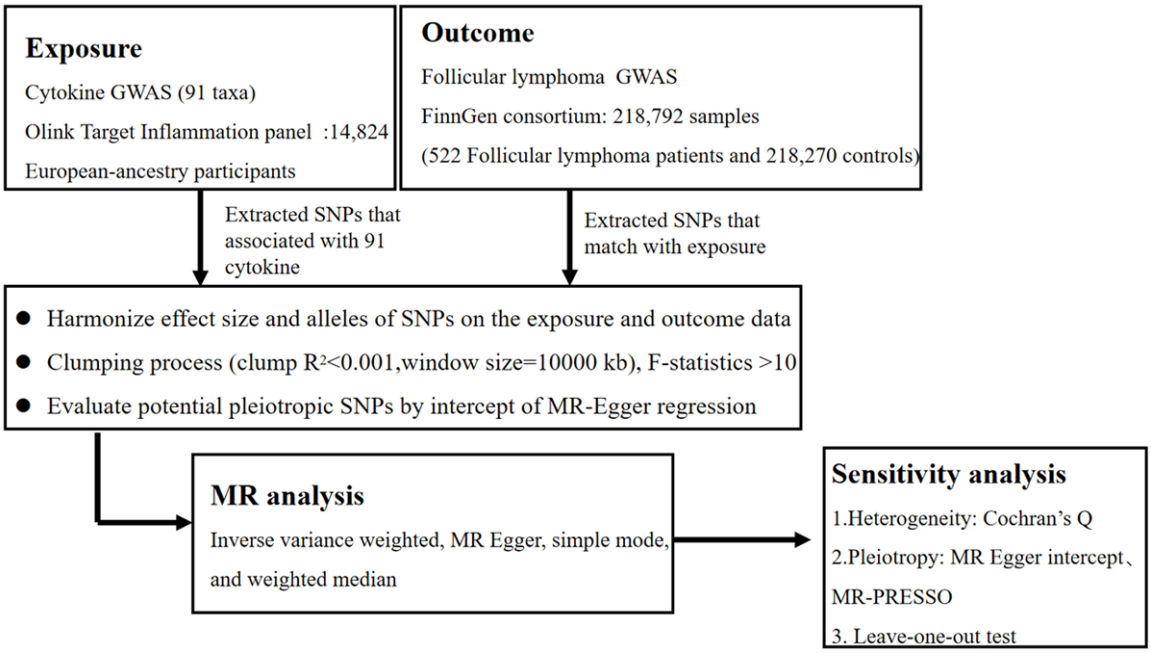

Figure 1. Flow chart of this Mendelian randomization study. MR denotes Mendelian randomization, and SNP denotes single-nucleotide polymorphisms.

Table 1. Summary of datasets from genome-wide association studies (GWAS)

Trait	Year	Population	Sources	Sample sizes	Cases	Control	Reference
Exposure							
Cytokine	2023	European	Olink Target Inflammation panel	14,824	-	-	[25]
Outcome							
Follicular lymphoma	2021	European	FinnGen	218,792	522	218,270	[76]

tistics of the Genome-Wide Association Study (GWAS) was used; no fresh data was gathered, and no fresh ethical analysis was performed. The full details of the trial procedure are provided in **Figure 1**. MR validity relies on three key assumptions [24]: (1) Relevance: the genetic variants and exposure are closely related; (2) Independence: the genetic variants are not affected by confounding factors; (3) Exclusion: the genetic variants impact the outcome risk through exposure rather than other pathways. Cytokines and follicular lymphomas were evaluated for bidirectional causal relationships by means of an inverse variance weighted MR, MR-Egger regression, weighted median, and simple mode. MR pleiotropy residual sum and outlie (MR-PRESSO), leave-one-out sensitivity analysis, pleiotropy test, and heterogeneity test were performed thereafter.

Data sources

The GWAS summary statistics are provided; all individuals are of European ancestry (**Table 1**).

Cytokines: We obtained summary-level information on genome-wide association studies for follicular lymphoma and 91 circulating cytokines. The Olink Target Inflammation panel was used to conduct a comprehensive pQTL analysis of 91 plasma proteins across the genome. A total of 14,824 European ancestries in 11 cohorts were involved in the study [25]. In the ARISTOTLE cohort consisting of 1,585 participants with Olink plasma proteomic data, we examined the discovery meta-analysis for validation [26]. After the adjustment for age, sex, and body mass index, a linear regression analysis was performed to identify the association between cytokine levels and SNPs.

Follicular lymphoma: Summary statistics were derived from publicly accessible GWAS analyses for follicular lymphoma in patients of European ancestry. The study investigated follicular lymphoma cases (522) and controls (218,270), covering over 16 million genetic variants. The study design has been described in detail previously [27]. All the participants provided written informed consent, which was approved by the regional institutional review boards.

Confounders

Numerous risk factors impact the likelihood of developing FL. In addition to family history and genetic susceptibility [28-30], medical exposures, lifestyles, and personal behaviours were demonstrated in several studies to be associated with the risk of FL. According to the findings of the International Agency for Research on Cancer (IARC), there is a clear link between HCV infection and FL, and treating HCV can help mitigate FL [31]. As for HBV infection, the evidence which can prove the causal association between FL and HBV is limited [32]. However, the risk of FL increased in the high HBV prevalent area [33] and was demonstrated to be associated with Sjögren Syndrome [34], rheumatoid arthritis, autoimmune haemolytic anemia, and aplastic anemia [35]. It is important to note that FL risk is negatively associated with the number of pregnancies but is positive associated with the use of hormonal contraceptive [36]. As for personal lifestyles and behaviours, female smoking is positively associated with FL [37] and alcohol abuse is negatively associated with FL [38]. To exclude the possible cofounders, we omitted the selection of SNPs which were associated with HBV, HCV, auto-immune disease, smoking, pregnancy, and alcohol abuse.

Selection of genetic instrumental variables

We identified SNPs with a moderately significant degree of association ($p < 5 \times 10^{-8}$) linked to cytokines. Additionally, the SNPs were filtered by PhenoScanner website (http://www.phenoscanner.medschl.cam.ac.uk/) to eliminate potential confounding factors such as HBV, HCV, autoimmune disorders, tobacco use, gestation, and alcohol misuse. The SNPs selected were proved to be related to variant ($r^2 > 0.8$), if the SNPs were independent with data in outcome pooled. The MR analysis shut down in the absence of sufficient SNPs. Prior to utilizing this organization as the primary genetic method, we employed a threshold of linkage disequilibrium for individual independence by setting the chain disequilibrium $r^2 < 0.001$ within a 10000 kb range [39]. All pairs of combinations were retrieved for further investigation after coordinating with responsive findings. An F statistic was computed for IVs ($F=R^2(n-k-1)/k(1-R^2)$, with n representing the sample size, k being the number of IVs included, and R^2 indicating the exposure variance explained by the chosen SNPs), in order to detect any bias from weak instrumental factors [40]. F > 10 was considered acceptable, given that poor instrumental variables were not the source of bias [22]. In our study, a nominal causal effect was deemed to be the one that falls within the range of a *p*-value from 0.05 to the adjusted value.

Statistical analysis

An IVW method was used in the primary study to evaluate the causal connection between cytokines and follicular lymphoma. Specifically, the direction of causal association between circulating cytokines and FL was assessed by bidirectional MR test. Typically, the effects of causality were assessed with the use of exponential odds ratios (ORs) and corresponding confidence intervals (CIs). $p < 0.05$ was considered to be statistically significant. Additionally, we used the weighted median, simple mode, MR Egger, and techniques to quantify causal effects. When trustworthy IVs contribute at least half of the weight, the weighted median method can generate a reliable estimate by combining data from multiple genetic variants into a single causal estimate [22]. The causal effect may be measured via the MR-Egger approach if genetic alterations exhibit directional pleiotropy [41]. The *p* value greater than 0.05 indicates that pleiotropy has minimal influence on the causal analysis. Horizontal pleiotropy was assessed via the calculation of the intercept of the MR-Egger regression and MR-PRESSO [42, 43]. Cochran's Q test was developed with IVW estimation method to detect heterogeneity among instrumental variables [43]. Additionally, the Mendelian randomization residual sum method was applied to

assess horizontal pleiotropy and to remove anomalies. The impact of an individual SNP's causal association was determined via leave-one-out approach, in which methodical removal of single SNP and the utilization of the remaining SNPs were used as instrumental variables for two-sample MR analysis. MR Steiger's directionality test was used to comprehensively assess the relationship between exposure and outcomes. MR Steiger suggests that genetic diversity should account for a greater proportion of variability during exposure rather than during outcome [44]. This approach validates the appropriateness of genetic instruments for conducting a valid MR study and facilitates the identification of potential reciprocal effects.

A robust association between systemic cytokines and follicular lymphoma is most likely to exist when the Cochran's Q test, MR-Egger, and MR-PRESSO results are not statistically significant ($P > 0.05$). All five methods provided consistent estimates, the MR Steiger directionality tests were positive, and the IVW method showed a significant discrepancy ($P < 0.05$) [45]. The 'Two Sample MR' package (version 4.2.2) for the R program was used for all MR analyses.

Result

Causal relationship between circulating cytokines and the risk of FL

The overview of the causal relationship of 91 circulating cytokines with the risk of FL is shown in **Figure 2**. Of all the circulating cytokines, ten cytokines were selected for the further MR analyses because of their association with FL risk. The details of SNP message (SD, R^2, F) of the ten significant cytokines in MR analyses are shown in Tables S1, S2, S3, S4, S5, S6, S7, S8, S9, S10.

Through MR-PRESSO analysis and primary IVW method test for ten cytokines, we discovered that four cytokines - CXCL5, IL15RA, IL20, and Neurotrophin-3 - showed causal association with FL (**Table 2**). The risk of FL may be inversely linked to CXCL5 (OR=0.73, CI: 0.545-0.979, P=0.036), IL-15RA (OR=0.669, CI: 0.451-0.993, P=0.046), and IL-20 (OR=0.565, CI: 0.325-0.981, P=0.043) and positively associated with Neurotrophin-3 (OR=1.872, CI: 1.063-3.297, P=0.03). In summary, CXCL5, IL15RA, and IL20 functioned as protective factors; however, Neurotrophin-3 functioned as an anti-protective factor (**Figure 3**). The steiger test displayed that FL had little causal effect on the screened cytokines (**Table 3**). We also analysed the causal effect of FL on circulating cytokines, the result of which demonstrated that FL had no causal effect on four cytokines (**Table 4**).

Sensitivity analysis

No heterogeneity was found in the IVs for all four cytokines via a Cochrane's Q test; neither the MR-Egger regression intercepts nor the MR-PRESSO identified any pleiotropic SNP pleiotropy or outliers (**Table 2**). The scatter plots indicated that CXCL5, IL15RA, and IL20 could potentially provide protection against FL, whereas Neurotrophin-3 may have a detrimental effect on FL. The MR analysis includes IVW method, MR-Egger, weighted median, and simple mode, all of which are depicted in scatter plots with assigned weights. A positive association between the cytokines and FL is indicated by lines sloping upwards, whereas a protective association is indicated by lines moving downwards (**Figure 4**). No outliers detected for any of the four cytokines for FL were observed with the use of leave-one-out analysis (**Figure 5**), suggesting that the revealed causal associations were not impacted by individual IVs. Furthermore, the absence of horizontal pleiotropy was confirmed in the funnel plots for any outcomes (**Figure 6**).

Discussion

Follicular lymphoma, the malignancy derived from B cells in germinal center, is the most common indolent non-Hodgkin lymphoma, and the pathological character of FL is irregular follicle-like structure called neoplastic follicles [46]. The process of FL, also called "a waxing and waning clinical course", is somewhat complicate, since FL may progress slowly or degrade spontaneously. In addition, the large interpatient and intratumoral heterogeneity suggest that there is an active interaction between malignant cells and non-malignant cells [47]. Because of the induction of anti-CD20 based immunochemotherapy (rituximab) in FL, the prognosis of FL has been improved immensely and the life span of most FL patients exceeded 10 years. Nevertheless, a great proportion of

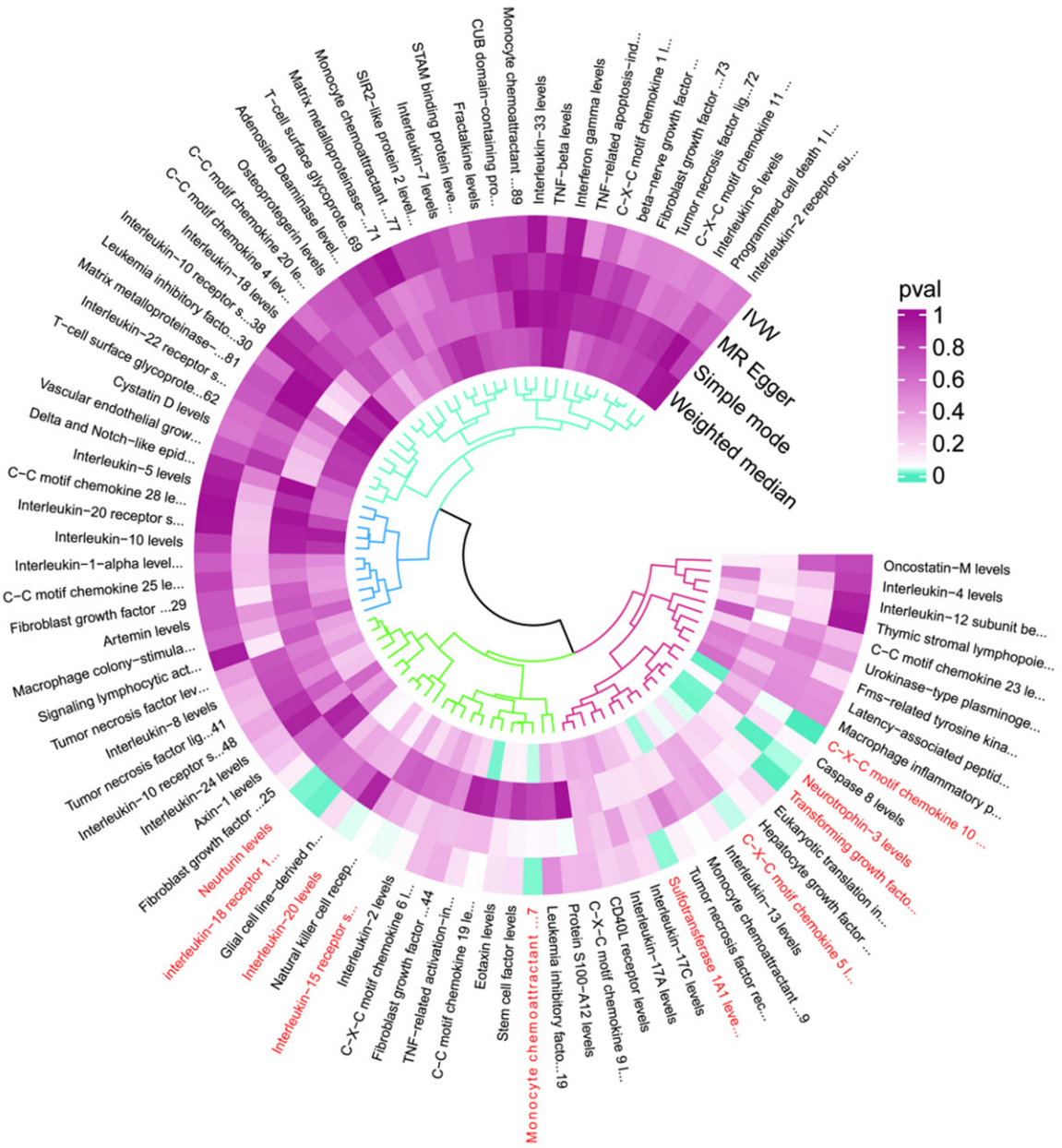

Figure 2. Summary of the impact of cytokines on FL. The Cyan Process color shows that there is statistical significance with a *P*-value less than 0.05. IVW, the inverse variance weighted method.

patients suffer from relapses of FL and receive chemotherapy, causing accumulating side effects and economic burden [48-50]. Additionally, a fifth of patients suffer from progression or relapse within the initial 48 months after treatment, resulting in a poor 60% progression-free survival rate for five years. FL can undergo the transformation into transformed FL (t-FL), which is similar to GC-derived diffuse large B-cell lymphoma (DLBCL) derived from GC and is linked to worse prognosis [48]. Therefore, new treatment strategies or therapeutic targets are required urgently. Tumor intrinsic features, such as microenvironment and clinical features, can markedly influence patients' prognosis. The microenvironment, in which the FL cells residue, is inflammatory and contains a large number of infiltrating inflammatory cells, including tumor-reactive T cells, macrophages, and stromal cells [51]. Cytokines secreted by tumor cells and non-tumor cells can be released into blood and bond to their receptors in the tumor

Table 2. Association of circulating inflammatory regulators with follicular lymphoma using Mendelian randomization

Exposure	No. SNP	MR method	OR	95% CI	*P* value	P for MR-PRESSO
CXCL10	23	Inverse variance weighted	2.274969217	1.58-3.26	8.97E-06	
		Weighted median	2.061603596	1.21-3.51	0.007894293	
		Simple mode	1.639128966	0.66-4.07	0.299399088	
		MR Egger	2.005583459	1.05-3.82	0.046618776	
		MR-PRESSO				0.000205674
CXCL5	15	Inverse variance weighted	0.730317615	0.55-0.98	0.035767505	
		Weighted median	0.706494783	0.50-0.99	0.045267686	
		Simple mode	0.742778518	0.41-1.36	0.35191275	
		MR Egger	0.803951994	0.50-1.29	0.385385519	
		MR-PRESSO				0.054377322
IL-15RA	14	Inverse variance weighted	0.669321365	0.45-0.99	0.04587254	
		Weighted median	0.793243104	0.57-1.10	0.162373349	
		Simple mode	0.820490881	0.34-1.38	0.681803778	
		MR Egger	0.68734896	0.33-2.07	0.314959396	
		MR-PRESSO				0.067252748
IL18R1	23	Inverse variance weighted	0.768884037	0.63-0.94	0.009445163	
		Weighted median	0.797977794	0.63-1.02	0.068357216	
		Simple mode	0.775374989	0.45-1.32	0.359886432	
		MR Egger	0.903339228	0.64-1.28	0.569511189	
		MR-PRESSO				0.007378916
IL-20	13	Inverse variance weighted	0.564846538	0.33-0.98	0.042508482	
		Weighted median	0.518567783	0.24-1.11	0.090327575	
		Simple mode	0.520739805	0.16-1.71	0.303775535	
		MR Egger	0.940592406	0.32-2.80	0.914374362	
		MR-PRESSO				0.065299836
MCP-2	22	Inverse variance weighted	1.223578079	1.04-1.44	0.016202369	
		Weighted median	1.204887452	1.01-1.43	0.034191598	
		Simple mode	1.101851883	0.57-2.14	0.777866137	
		MR Egger	1.218822832	1.00-1.49	0.069993471	
		MR-PRESSO				0.001397391
Neurturin	14	Inverse variance weighted	1.690299937	1.11-2.58	0.015304729	
		Weighted median	1.620270064	0.94-2.80	0.084554469	
		Simple mode	1.690368181	0.70-4.07	0.262892449	
		MR Egger	1.243426609	0.58-2.67	0.58645324	
		MR-PRESSO				0.00541123
Neurotrophin-3	17	Weighted median	2.419336949	1.19-4.90	0.014288427	
		Inverse variance weighted	1.871855786	1.06-3.30	0.029949601	
		Simple mode	3.122061393	0.84-11.66	0.109835158	
		MR Egger	6.579923797	2.19-19.73	0.004272941	
		MR-PRESSO				0.06364232
SULT1A1	23	Inverse variance weighted	0.697517225	0.51-0.95	0.021190208	
		Weighted median	0.553352001	0.26-1.18	0.140093683	
		Simple mode	0.767962621	0.49-1.20	0.242931597	
		MR Egger	0.646702494	0.31-1.36	0.261356795	
		MR-PRESSO				0.022036175
TGFα	14	Inverse variance weighted	0.45332765	0.26-0.78	0.004357798	
		Weighted median	0.423735742	0.22-0.82	0.01106885	
		Simple mode	0.412697583	0.14-1.20	0.128760872	
		MR Egger	0.335574574	0.09-1.19	0.116267095	
		MR-PRESSO				0.013630046

OR, odds ratio; CI, confidence interval; SNP, single nucleotide polymorphism; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlie.

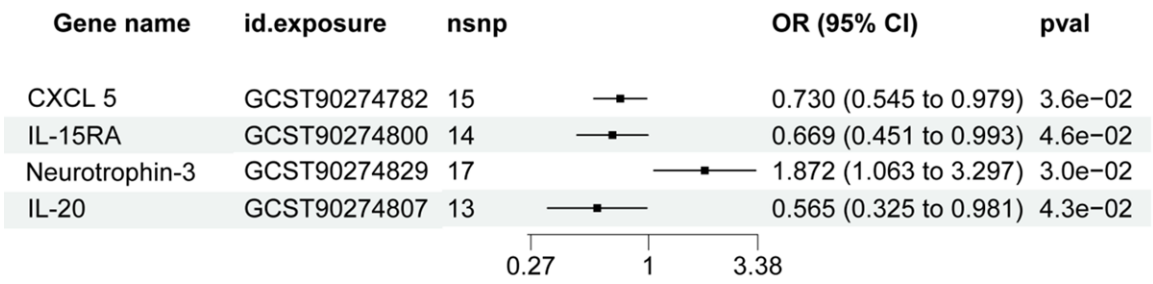

Figure 3. Forest plot of cytokines linked to FL by the inverse variance weighted method. CXCL5 denotes C-X-C motif chemokine 5, IL-15RA denotes Interleukin-15 receptor subunit alpha, and IL-20 denotes Interleukin-20.

Table 3. Sensitivity and steiger analysis of 10 circulating inflammatory cytokines associated with follicular lymphoma

Exposure	MR-Egger intercept		Cochrane's Q IVW		Cochrane's Q Egger		Correct causal direction	steiger_pval
	Intercept Value	*P* value	Q value	*P* value	Q value	*P* value		
CXCL5	0.01905975	0.618035399	15.89560328	0.319791197	15.58281375	0.272393223	TRUE	3.91E-09
IL15RA	0.00571636	0.928456574	29.61959113	0.005341302	29.59885416	0.003207787	TRUE	9.19E-12
IL-20	0.07833119	0.311091424	12.01244977	0.4446803	10.88507412	0.452941117	TRUE	0.484578104
NT-3	0.12838619	0.024056602	21.19991391	0.170953475	14.90298032	0.458428084	TRUE	0.41716229

IVW denotes inverse-variance weighted, and MR denotes Mendelian randomization.

Table 4. Reverse causal association between follicular lymphoma and cytokines

Cytokines (outcome)	MR method	No. SNP	OR	95% CI	*P* value	P for MR-PRESSO global test
CXCL5	IVW	16	0.99	0.96-1.03	0.330	
	Weighted median		0.99	0.94-1.03	0.600	
	MR-Egger		1.04	0.96-1.13	0.330	
	Simple mode		0.99	0.91-1.07	0.727	
	MR-PRESSO					0.396
IL15RA	IVW	16	1.01	0.97-1.05	0.631	
	Weighted median		0.99	0.95-1.04	0.831	
	MR-Egger		0.97	0.88-1.07	0.554	
	Simple mode		0.99	0.91-1.08	0.811	
	MR-PRESSO					0.792
IL-20	IVW	16	1.04	0.99-1.08	0.069	
	Weighted median		1.01	0.96-1.07	0.609	
	MR-Egger		1.01	0.92-1.11	0.837	
	Simple mode		1.00	0.91-1.10	0.993	
	MR-PRESSO					0.133
NT-3	IVW	13	1.01	0.94-1.09	0.812	
	Weighted median		0.99	0.91-1.09	0.873	
	MR-Egger		1.06	0.86-1.31	0.602	
	Simple mode		1.02	0.87-1.19	0.831	
	MR-PRESSO					0.738

SNPs denotes single-nucleotide polymorphism, IVW denotes inverse-variance weighted, MR denotes Mendelian randomization, and MR-PRESSO denotes MR pleiotropy residual sum and outlie.

cells, a mechanism which influences the development and evolvement of FL. Labidi et al. found elevated levels of IL-1R1, IL-6, IL-7, IL-10, IL-13, TNF-α, VEGF, and PDGF in the serum of

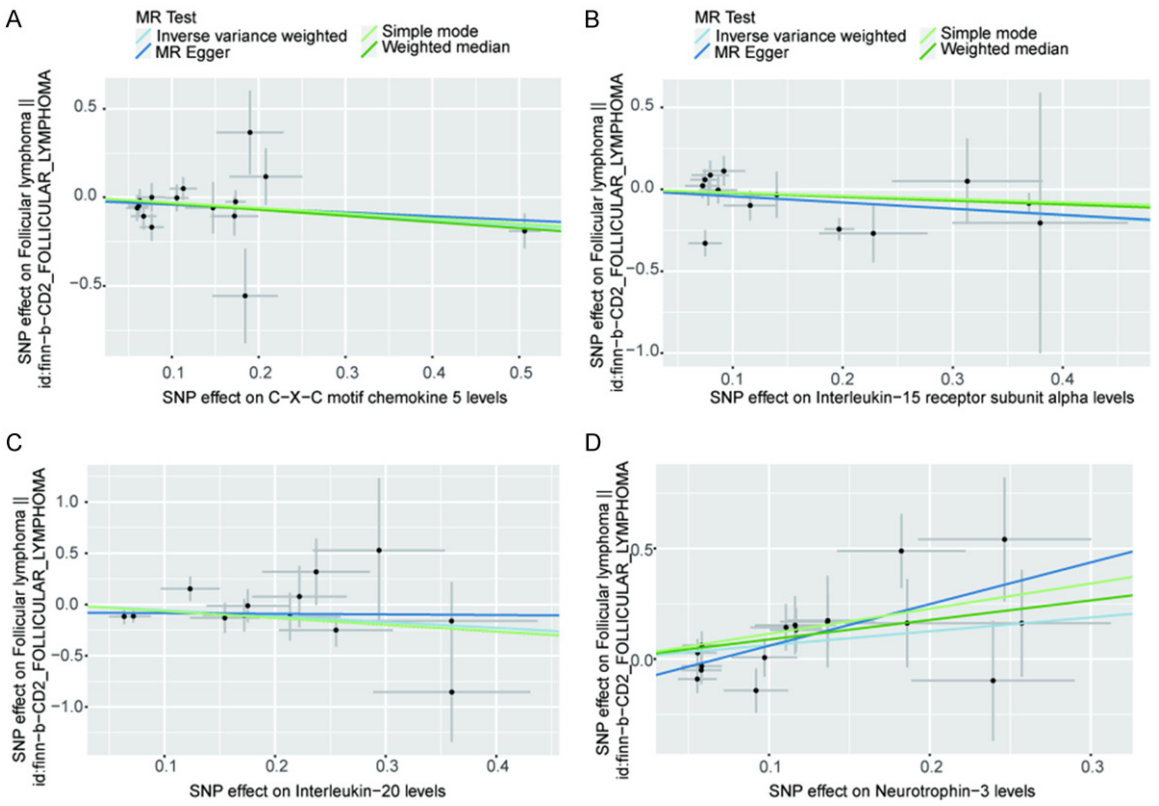

Figure 4. Scatter plots of each cytokine associated with the risk of FL. (A) CXCL5, (B) IL-15RA, (C) IL-20, (D) NT-3.

FL patients. They demonstrated that elevated levels of lactate dehydrogenase and VEGF were independently associated with poorer progression-free survival [20]. Mir et al. identified that the improved levels of IL-2R, IL-1R1, and CXCL9 in the blood of FL patients were associated with worse event-free survival (EFS) in patients treated with chemotherapy or immune-chemotherapy. Additionally, increased levels of IL-1R1 and IL-12 were also associated with shorter EFS in patients who stood in observation cohort or underwent rituximab monotherapy [15]. The fact aforementioned demonstrates that the outcome of FL can be affected by circulating cytokines. Nevertheless, there is a lack of researches to illustrate the causal effect between circulating cytokines and FL.

In our study, the causal impact of 91 circulating cytokines on FL was thoroughly assessed by means of extensive GWAS summary statistics. Finally, we revealed four cytokines that were formally linked to FL. CXCL5, IL-15RA, and IL-20 were identified to prevent FL, whereas NT-3 was associated with an increased risk of FL. Pleiotropy analysis of the datasets did not reveal any significant pleiotropic variants among the chosen circulating cytokines. The results from four MR analysis techniques indicate a potential cause-and-effect connection between FL and circulating cytokines. Moreover, we performed the steiger test to confirm the bi-directionality of the causal relationship between FL and circulating cytokines.

CXCL5, known as neutrophil-activating peptide ENA-78, is a member of chemokine family that is mainly implicated in the chemotaxis of inflammatory cells [52]. By binding to C-X-C motif chemokine receptor 2 (CXCR2), CXCL5 promotes neutrophil migration and inflammatory response [53]. Recent studies have shown that CXCL5 are abnormally expressed in over 14 types of cancer, such as liver cancer, prostate cancer, and pancreatic cancer [54], with its expression of CXCL5 being linked to inflammatory invasion and to migration capabilities. In gastric cancer, CXCL5 is overexpressed and associated with late stage [55]. In pancreatic cancer, CXCL5 is overexpressed in tumor tissue and associated with poorer differentiation, poorer clinical stage, and shorter survival time

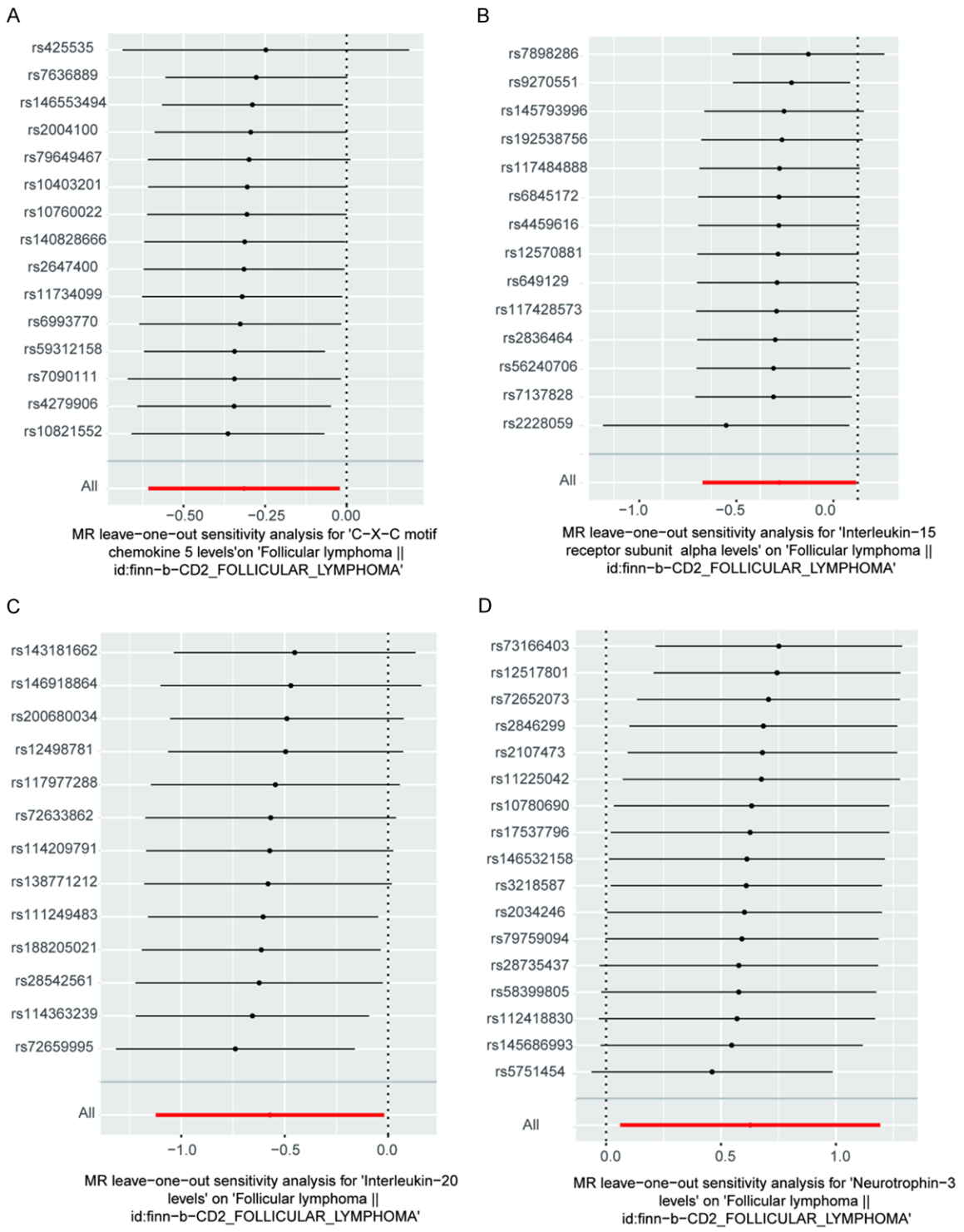

Figure 5. Leave-one-out analysis of each cytokine associated with the risk of FL. (A) CXCL5, (B) IL-15RA, (C) IL-20, (D) NT-3.

[56]. Besides, CXCL5 was involved in the development and evolvement of malignancies and could be identified as a potential biomarker for breast cancer, gastric cancer, and colon cancer [57]. However, insufficient researches have been conducted to explore the causal relation-

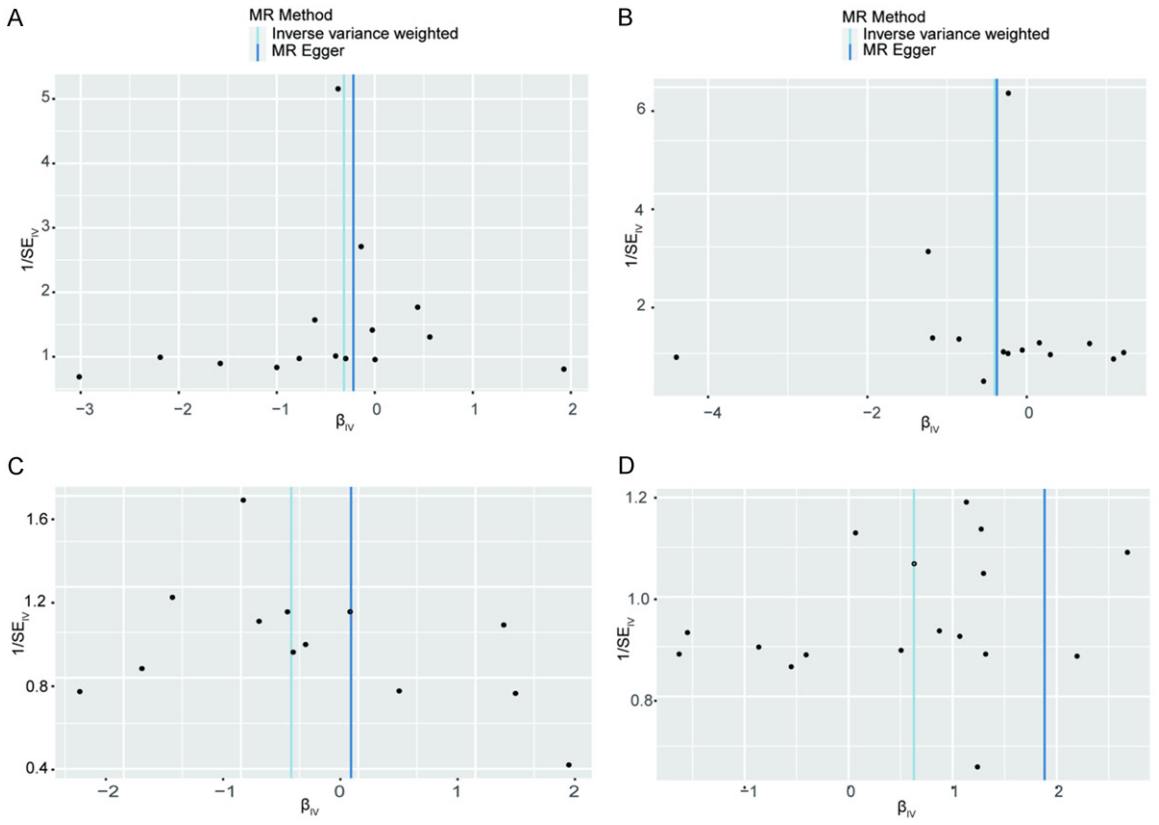

Figure 6. Funnel plots of each cytokine associated with the risk of FL. (A) CXCL5, (B) IL-15RA, (C) IL-20, (D) NT-3.

ship between the CXCL5 level and FL. In present study, we utilized MR analysis to identify that CXCL5 is a protective factor; this result indicates CXCL5 may function as a tumor suppressor in FL, a finding which is contrary to previous investigations of CXCL5 in cancer. Profound further researches need to be conducted to illustrate the underlying mechanism for the causal effect.

IL15RA, a soluble IL15 receptor subunit protein, is one of the three subunits which compose IL15 receptor. IL15 receptor is made up of a heterotrimeric protein composed of the β-chain subunit (IL-2R/IL-15Rβ, CD122), common γ chain (γc, CD132), and special α subunit (IL-15RA) [58]. However, IL15RA losing β and γ subunits can bind IL15 with high affinity. The receptor can function in cis (with all three subunits located on the same cell) or in trans (where the IL15RA subunit is attached to IL15 on one cell while the β and γ subunits on an neighboring cell). As a consequence, the IL15RA complex is presented to the β and γ subunit, leading to the activation of intracellular signaling [59]. IL-15RA plays key roles in various immune pathways, including regulating the immune system by promoting the growth, development, and balance of CD8+ T cells and naive T cells [60]; activating and sustaining different lymphocyte populations by interacting with mature NK cells in periphery, which is essential for NK cells survival; and preventing apoptosis in multiple systems. The IL15/IL15RA complex can initiate signal transduction processes in both immune and non-immune cells. These cascades may inhibit apoptosis and promote proliferation [61-64]. In present study, we identified IL-15RA as a protective factor for FL, and this finding indicates that the level of IL-15RA is negatively associated with the risk of HL. The IL-15RA's feature that enhances NK and CD8+ T cells survival but prevents immune cell apoptosis is believed to hinder FL progression.

IL-20, the member of IL-10 family, is mainly expressed by monocytes, dendritic cells (DCs), epithelial cells, and endothelial cells [65]. IL-20 is involved in multiple pathological or physiolog-

ical processes. IL-20 promotes the CD86 expression in DCs derived from monocytes, a process which may indirectly regulate the T cell activation in process of antigen presentation. Moreover, IL-20 can inhibit the shed of CD18 integrin, and this process attenuates the DCs' ability to migrate into lymphoid organ [66-68]. As for the development and evolvement of cancer, IL-20 displays a double-edge-sword function. Prostate cancer cells experience enhanced migration and colony formation when IL-20 activates the downstream signals like p38, extracellular regulated protein kinases1/2 (ERK1/2), Serine/Threonine Protein Kinase (AKT), and Nuclear factor B (NF-B) by affecting N-cadherin, STAT3, vimentin, fibronectin, RANKL, and cathepsin [68]. A recent research identified that IL-20 is widely expressed in reactive germinal centers of lymphoma, especially in FL (94%); however, Mucosa-Associated Lymphoid Tissue (MALT) lymphoma, lymphoplasmacytic lymphoma, plasmacytoma, and T-cell lymphomas are negative for extranidal marginal zone lymphoma. Additionally, the study found a correlation of IL-20 levels with decreased rates of extranodal and bone marrow involvement and improved overall survival in DLBCL. This connection is probably due to the fact that IL-20 arrests the cell cycle of DLBCL cells in the G1 phase and thus leads to apoptosis [69]. Moreover, IL-20 can inhibit the cyclooxygenase-2/Prostaglandin-E2 pathway to decrease the angiogenesis in tumor and thus inhibits the tumor [70]. The IL-20 plays a bidirectional role in tumor progression. Our study demonstrates that IL-20 is negatively associated with FL, given that the tumor suppressor role of IL-20 dominates the battlefield in FL. However, the underlying mechanism need to be further explored.

NT-3, member of the nerve growth factor (NGF) family, functions as neurotrophic factor. NT-3 functions by interacting with two types of receptors on the membrane: the Tyrosine kinase (Trk) family of receptor tyrosine kinases (also referred to NTRKs, neurotrophic tyrosine kinase receptors) and the shared neurotrophin receptor $p75^{NTR}$. Three NTRKs, namely TrkA, TrkB, and TrkC, exhibit specificity towards neurotrophins. As for NT-3, TrkC can bind to NT-3 with higher affinity than can $p75^{NTR}$ [71]. Noticeably, opposite effects are yielded when NT-3 binds to different receptor. Upon binding to TrkC, NT-3 activates the TrkC receptor, leading to the activated and auto-phosphorylate tyrosine residues in their intracellular tails and generating various downstream as signaling pathways. The activated TrKC pathway promotes survival of cancer cells, proliferation, and apoptosis inhibition [72]. NT-3 is reported to be increased in the majority of aggressive human neuroblastomas (NBs), where it inhibits the TrkC-induced apoptosis, stimulates growth, and facilitates migration of NB cells by interacting with TrKC receptor [73]. Despite these functions, the binding of NT-3 to p75NTR leads to the activation of c-Jun N-terminal kinase (JNK) signaling cascade, which in turn activates p53 and induces the expression of pro-apoptotic genes like Bcl-2 [74]. Studies indicate that liver cancer with decreased NT-3 level is associated with shorter survival rates(OS), recurrence-free survival (RFS), progression-free survival (PFS), and disease-specific survival (DSS). Experiments conducted *in vivo* and *in vitro* showed that NT-3 binding to the $p75^{NTR}$ leads to the activation of the JNK and P38 MAPK pathways, ultimately causing apoptosis [75]. In our study, we revealed that NT-3 functioned as tumor promoter in development and evolvement of FL. It is reasonable to assume that TrkC receptor activation is dominant in the FL.

To the best of our knowledge, this MR study is the initial investigation into the genetic link between FL and cytokines. The main strength of our study is the utilization of MR analysis to minimize bias related to confounding, as opposed to the analyses used in traditional observational researches. By targeting certain cytokines, these findings offered insight into prevention, development, and treatment of FL. Further clinical trials and mechanism studies are needed to investigate the precise processes underlying the connections between cytokines and FL.

Several limitations of our study should be mentioned. First, additional research involving diverse ethnic populations is necessary to validate our results, given that the majority of participants in GWAS were of European descent. Second, the statistical power of causal assessment in MR was lowered due to the limited size of the cytokine GWAS dataset. Third, validation was not performed with multiple databases, since GWAS databases do not include extra FL

data. The current GWAS research methods on cytokines restrict the extent of our investigation. Using advanced analytical methods can enhance the precision and accuracy of the results, leading to improved generalizability and the precision of the study. To delve deeper into the connection between cytokines and FL, it is essential to combine data from cohort studies, clinical trials, and functional research. It is useful to investigate the pathophysiology of FL with this research. Fourth, the cytokines may exhibit complex interaction during the development and evolvement of disease. We expect that the advanced algorithm for MR analysis will be developed to untangle the complex network of cytokines.

Conclusion

In conclusion, our MR analysis revealed a possible causal relationship between certain circulating cytokines and FL. This study would strengthen the diagnostic, therapeutic, and prognostic profile of FL and provide a solid basis for further research into the pathophysiology of circulating cytokines that cause FL.

Acknowledgements

We gratefully acknowledge the support to this study by the Key R&D plan of the Ministry of Science and Technology (2023YFC2505900) and the National Natural Science Foundation of China (No. 82172837, No. 82071799, No. 81972683).

Disclosure of conflict of interest

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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Table S1. Details of C-X-C motif chemokine 10 (CXCL10) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs112202639	A	G	1.68E-06	22.93155648	4.079875763	0.00155311
rs1563171	A	G	3.14E-06	21.72881146	1.541886701	0.001472169
rs12476448	T	C	3.15E-06	21.7237051	1.39605453	0.001472123
rs12629593	T	G	1.37E-06	23.32571549	2.209932705	0.001579763
rs72651343	T	C	6.98E-23	96.9859041	7.391025894	0.006757664
rs115140093	T	C	5.02E-35	152.4636961	5.099844704	0.010236266
rs12646113	T	C	6.78E-13	51.6073205	1.651322282	0.003488724
rs72682331	A	G	1.88E-07	27.14958449	2.536660819	0.001839883
rs2523495	T	C	2.31E-08	31.21160454	2.379846819	0.002112859
rs71534595	T	C	7.99E-07	24.36057739	6.560212408	0.002074766
rs12174864	A	G	1.51E-06	23.13530497	1.446696565	0.00161603
rs12155428	T	C	2.52E-06	22.15271111	4.551733873	0.001501558
rs2349689	A	G	1.50E-06	23.14548632	1.960880455	0.001616627
rs143796249	C	G	4.03E-06	21.24912591	7.413084648	0.00148437
rs10481754	T	C	4.12E-06	21.20641198	1.422833989	0.001481391
rs4367871	T	C	1.89E-06	22.70242215	1.422833989	0.00158573
rs12779465	A	C	3.27E-06	21.65351111	1.627206195	0.001836965
rs55732300	A	G	2.60E-06	22.09	3.034180285	0.001497618
rs741344	A	G	3.92E-06	21.30177515	1.554356458	0.001488042
rs3184504	T	C	3.72E-18	75.46436688	1.422602098	0.006359465
rs1077965	A	G	3.71E-06	21.41022695	1.432181706	0.0014515
rs74956615	A	T	3.86E-06	21.33560091	3.437537718	0.001558443
rs4804148	T	C	1.31E-06	23.41071006	1.578523361	0.00158551
rs150519056	T	C	9.77E-07	23.9735245	4.394698552	0.00175207

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S2. Details of C-X-C motif chemokine 5 (CXCL5) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs4279906	T	C	7.15E-07	24.57326531	5.09517301	0.001667163
rs7636889	A	G	2.07E-08	31.42543556	1.662900108	0.002128745
rs146553494	A	G	1.00E-06	23.92429413	4.576009787	0.001621445
rs11734099	A	G	5.00E-07	25.26212141	1.856981365	0.001712191
rs425535	T	C	3.52E-172	782.4538018	2.196821092	0.050443615
rs79649467	T	G	4.50E-10	38.88155062	3.299094858	0.002714267
rs77914035	A	G	1.20E-08	32.47893298	2.150012437	0.002973314
rs2647400	C	G	1.21E-06	23.55982249	1.577987959	0.001596674
rs6993770	A	T	4.61E-15	61.41914952	1.613687702	0.00428085
rs2004100	T	C	4.39E-06	21.0849646	1.690436086	0.001592149
rs10760022	A	C	3.13E-07	26.17041186	1.468742639	0.001773283
rs10821552	A	C	3.97E-13	52.65548981	1.547548306	0.005323223
rs7090111	C	G	1.08E-49	219.6476003	1.420237357	0.014689546
rs140828666	A	G	4.70E-06	20.95478569	3.585784829	0.001687187
rs59312158	A	G	8.01E-07	24.35486591	4.501702123	0.00177846
rs10403201	A	G	2.22E-06	22.39450679	1.541363585	0.001518231

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S3. Details of Interleukin-15 receptor subunit alpha (IL-15RA) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs56240706	A	T	1.92E-06	22.67338721	1.816764677	0.002552828
rs6845172	C	G	1.57E-06	23.0637098	1.757681336	0.001955701
rs9270551	A	G	9.81E-07	23.96518433	1.629575699	0.002108504
rs117428573	A	C	4.67E-06	20.966759	7.127069939	0.001927806
rs649129	T	C	4.33E-06	21.11344336	1.650929896	0.00193044
rs12570881	A	T	6.27E-07	24.82788347	1.853242952	0.00218424
rs2228059	T	G	8.39E-18	845.1152582	1.352654339	0.06934498
rs7898286	T	G	4.34E-48	212.2956927	1.437860911	0.018373746
rs145793996	A	G	3.66E-06	21.43765285	5.339730195	0.001816991
rs7137828	T	C	1.87E-08	31.63005258	1.416559268	0.002780999
rs117046642	A	T	5.91E-07	24.94121107	1.515099667	0.003130981
rs4459616	T	C	1.92E-06	22.67573696	2.925115321	0.002285935
rs192538756	A	T	1.52E-06	23.12771819	2.344150893	0.002439085
rs117484888	A	G	2.05E-06	22.54764012	6.883931016	0.003029152
rs2836464	A	G	2.48E-06	22.1846574	1.835109672	0.001878275

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S4. Details of interleukin-18 receptor 1 (IL18R1) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs7512350	A	G	4.60E-06	20.99554466	2.180734214	0.001780793
rs76046089	C	G	2.70E-18	76.0999654	2.032548892	0.005296084
rs11465700	A	G	0	1608.678403	1.456950239	0.098404089
rs1005042	A	G	4.09E-152	690.175237	1.432764921	0.044726032
rs17027623	A	T	3.39E-23	98.41482034	4.574767235	0.006640042
rs72828028	T	C	8.91E-13	51.07019631	3.980979658	0.003455342
rs17413812	T	C	2.21E-06	22.40444444	3.460491547	0.001517566
rs7642750	A	C	2.94E-06	21.855625	2.171451128	0.001850939
rs35021151	A	G	1.49E-06	23.16367429	4.151463043	0.001569763
rs62257659	A	G	1.61E-06	23.01714853	5.096903766	0.001560694
rs78199195	A	G	1.07E-06	23.79050396	2.343409311	0.00166172
rs78035061	A	C	2.87E-06	21.90408652	2.65426973	0.00153016
rs117145942	A	G	3.63E-06	21.45302599	7.446267497	0.001627269
rs80317525	A	G	2.49E-06	22.17496449	3.62887962	0.00150337
rs73176827	T	C	2.03E-06	22.5625	2.670350539	0.001529292
rs536613714	T	G	8.43E-07	24.25626131	4.273328231	0.001985735
rs117195704	A	G	1.52E-06	23.11981341	3.798793716	0.001567326
rs1760941	A	C	3.71E-06	21.40691331	1.697776134	0.00149548
rs28929474	T	C	2.86E-09	35.27559147	5.403223644	0.002387313
rs117599131	A	C	2.89E-06	21.8858681	3.646326863	0.001651653
rs78357146	A	G	3.65E-19	80.05041852	4.589704579	0.00540113
rs34174304	A	G	9.62E-07	24.00342327	1.808064504	0.001627681
rs79097546	T	C	8.75E-07	24.18531888	6.686315577	0.001693865
rs116935210	A	G	3.13E-06	21.73526382	6.214633981	0.001473304

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S5. Details of Interleukin-20 (IL-20) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs72633862	T	G	4.65E-06	20.97445111	4.079903215	0.001778555
rs114363239	T	C	1.11E-06	23.72310041	5.286137681	0.002009798
rs114209791	A	G	3.50E-06	21.52153119	4.993490162	0.001823314
rs146918864	T	C	7.29E-07	24.53615232	5.507852168	0.002140925
rs12498781	A	G	3.57E-06	21.48356332	1.485865899	0.001823348
rs143181662	T	C	4.05E-06	21.24264464	1.445590647	0.002468283
rs111249483	A	G	8.10E-07	24.33336336	6.207848568	0.002238305
rs200680034	A	G	4.03E-07	25.68062686	6.446158779	0.003106522
rs138771212	A	G	3.80E-06	21.36388208	8.283416822	0.001881391
rs188205021	T	C	2.00E-07	27.03025849	4.633294342	0.002290888
rs72659995	T	C	3.95E-06	21.29113889	2.842766441	0.001874997
rs28542561	T	C	2.45E-06	22.20638947	4.036499989	0.001882822
rs117977288	T	G	9.96E-07	23.9356273	3.430310633	0.002027423

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S6. Details of monocyte chemoattractant protein 2 (MCP-2) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs78743764	A	C	3.53E-06	21.50640625	5.609226685	0.001572622
rs12075	A	G	4.95E-17	70.35738704	1.408003011	0.004753442
rs6685547	A	G	4.22E-07	25.5916955	3.325258665	0.001929615
rs7538845	C	G	3.50E-06	21.52351518	1.458295553	0.001504349
rs79965992	A	G	2.78E-06	21.96511264	2.641340453	0.001706563
rs138884871	T	C	3.37E-06	21.59399988	5.530662608	0.001577172
rs407595	A	C	2.12E-06	22.48178999	1.757065118	0.001571331
rs145516279	A	G	3.56E-06	21.48708767	5.737556274	0.001501807
rs12523126	A	T	1.35E-06	23.34722429	2.773152199	0.001631607
rs79567569	A	C	9.16E-07	24.09650528	7.740188335	0.001797161
rs4722985	T	C	2.52E-06	22.15365481	1.589781218	0.001548324
rs181726805	A	G	3.75E-06	21.390625	6.5066073	0.001449682
rs948962	A	C	4.84E-06	20.89795918	1.444563934	0.00141634
rs75573205	C	G	2.99E-06	21.82355344	4.950941729	0.001480082
rs112168535	T	C	8.90E-07	24.15287013	3.694633297	0.001763994
rs9889517	A	G	4.83E-07	25.33167133	1.446342311	0.001770043
rs9893096	A	T	7.57E-45	197.4385273	1.419996373	0.013228323
rs76263310	A	G	7.74E-11	42.32145876	5.521645747	0.002865886
rs11080270	A	G	0	4502.703873	1.661771034	0.234348562
rs881323	T	C	4.01E-15	61.6938843	3.338277999	0.004169719
rs35904471	T	C	3.99E-06	21.27166208	1.756843263	0.00187312
rs80131163	A	G	8.77E-07	24.17977274	4.842551734	0.001639064
rs75580960	T	C	1.52E-06	23.12177456	2.161918259	0.001745682
rs74350159	A	G	4.19E-06	21.17816179	7.142641573	0.001532409

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S7. Details of neurotrophin-3 (NT-3) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs145686993	C	G	4.84E-06	20.89795918	6.435804454	0.001463863
rs79759094	A	G	3.60E-06	21.46900843	3.046110188	0.001455776
rs12517801	A	G	4.50E-06	21.03852196	1.468343849	0.00142682
rs2034246	A	C	1.23E-06	23.5225	1.434790577	0.001642917
rs3218587	A	G	3.49E-06	21.52454996	3.569891292	0.001457955
rs112418830	T	C	2.06E-07	26.97676705	3.144582681	0.001883724
rs2107473	A	G	2.36E-06	22.27765523	5.867635219	0.001660742
rs17537796	A	C	3.33E-06	21.61493285	6.602273461	0.001514328
rs73166403	T	C	4.22E-06	21.16	2.391317628	0.001478153
rs72652073	C	G	3.48E-06	21.5296	1.494573518	0.001503933
rs10780690	T	G	3.46E-06	21.54506944	1.434790577	0.001505012
rs146532158	T	C	1.46E-06	23.19445488	4.68652327	0.001571206
rs11225042	A	C	1.64E-06	22.97384067	2.261605863	0.001847815
rs2846299	A	G	3.22E-06	21.678336	1.516626602	0.001470647
rs58399805	A	T	4.98E-07	25.27347107	2.670713013	0.001712263
rs540074689	A	C	8.96E-07	24.13994704	2.265671165	0.002250782
rs28735437	C	G	1.06E-12	50.72218917	1.990895155	0.003430484
rs376150779	C	G	1.92E-06	22.67310032	1.795238413	0.002077305
rs11151953	C	G	3.23E-09	35.03876171	1.48261693	0.002445297
rs5751454	T	C	4.64E-06	20.98008257	4.655068979	0.001531507

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S8. Details of neurturin predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs4360502	A	G	3.76E-06	21.38242543	1.501633451	0.001882027
rs62120726	A	G	4.88E-06	20.88277447	1.831860562	0.001837968
rs908372	C	G	4.80E-06	20.91717128	1.475647004	0.001773857
rs76777800	T	C	4.44E-06	21.06287593	6.148474611	0.003026248
rs143131035	T	C	4.91E-07	25.30078397	7.550868205	0.003325418
rs7712604	C	G	5.90E-07	24.9432141	1.630922782	0.002897024
rs29630	T	C	3.25E-06	21.66053558	1.693405985	0.001906291
rs192427410	T	G	1.92E-06	22.67746797	7.366208162	0.002575909
rs77216559	T	C	9.44E-07	24.03883218	3.691936619	0.002034941
rs182274799	A	G	4.46E-07	25.48621228	3.015297829	0.002687147
rs4753678	A	G	1.02E-06	23.88902916	1.58629861	0.002999669
rs8033310	T	C	3.20E-06	21.69084063	3.046000703	0.001908953
rs28759830	T	C	1.54E-06	23.09192111	3.598903861	0.002435319
rs7202385	A	T	2.02E-06	22.57762992	1.527021742	0.002381461
rs10412462	A	C	2.25E-06	22.36824778	3.974092651	0.00189395
rs113580784	A	G	3.80E-06	21.36493827	5.369780442	0.001812529

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S9. Details of sulfotransferase 1A1 (SULT1A1) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs1698742	T	C	1.78E-06	22.81685361	2.236784388	0.001931861
rs2712255	A	G	1.79E-06	22.80549771	1.458859284	0.002310633
rs710446	T	C	1.33E-07	27.81585734	1.46604033	0.002353523
rs149869672	T	C	3.24E-06	21.66875278	7.127398156	0.00199204
rs371387526	A	C	9.72E-07	23.98253123	2.00943607	0.002713268
rs66530140	T	C	5.64E-35	152.2320502	1.420728151	0.013760179
rs2731674	T	G	4.75E-08	29.81734765	1.65044285	0.002523084
rs55793562	A	G	3.43E-06	21.55945557	2.15995227	0.001826986
rs2691531	T	C	1.77E-06	22.82716049	1.46604033	0.001932241
rs7812322	T	C	4.08E-06	21.22576531	7.877650594	0.001951395
rs2213907	A	G	2.25E-06	22.36873541	3.452900172	0.001893991
rs55939507	A	G	3.72E-06	21.40455799	1.61455802	0.002258007
rs77919742	T	C	5.94E-07	24.93036215	3.056920517	0.002193043
rs76833948	A	T	2.58E-06	22.10649431	3.035617935	0.00194512
rs72656644	C	G	1.52E-06	23.11720743	2.385889184	0.00203387
rs10842189	T	C	3.76E-06	21.383942	1.877986518	0.001811679
rs9804965	A	C	9.40E-08	28.49371168	3.474800807	0.003066645
rs703595	T	C	1.15E-06	23.65796659	1.596084274	0.002003103
rs232928	T	C	4.80E-06	20.91717128	1.448575576	0.001840666
rs11074902	A	G	5.73E-07	25	1.480529449	0.002199156
rs149278	T	C	3.58E-44	194.3442524	1.437860911	0.01684626
rs117222566	A	G	3.10E-06	21.75636403	5.925915189	0.002087391
rs72643498	A	C	1.69E-06	22.91760978	4.08232812	0.001940704

SD, standard deviation; SNP, single nucleotide polymorphism.

Table S10. Details of transforming growth factor alpha (TGFα) predicting SNPs with follicular lymphoma

SNP	Effect allele	Other allele	*P*-value	F	SD	R^2
rs78912149	C	G	1.53E-06	23.10862245	6.578033749	0.001672222
rs72912115	A	T	9.65E-14	55.43773629	2.233005078	0.003750497
rs34007466	A	G	7.96E-08	28.815424	6.068978497	0.001952289
rs11242125	A	C	4.55E-06	21.01614893	1.613960557	0.002218762
rs9262670	T	C	9.06E-07	24.11751736	1.654509208	0.00187479
rs1963491	C	G	2.60E-06	22.09	2.448608993	0.001945554
rs34630685	C	G	3.35E-06	21.60575809	4.314667409	0.001510406
rs74130123	T	C	3.05E-07	26.21520631	6.166082153	0.001776433
rs4934441	A	G	1.60E-06	23.02061014	2.149007027	0.00195073
rs12270510	T	C	4.48E-07	25.47592798	2.30605529	0.001726658
rs653178	T	C	6.50E-08	29.20948663	1.421938473	0.00247345
rs3859189	A	G	1.64E-08	31.88354637	1.407668484	0.002160734
rs111613293	A	T	1.91E-06	22.67945445	1.458142448	0.001585346
rs78464136	A	T	3.19E-06	21.69678193	3.669260096	0.001516759
rs149146289	A	G	5.19E-07	25.19369535	6.800680764	0.001760788

SD, standard deviation; SNP, single nucleotide polymorphism.