Immune cells, serum metabolites, and ovarian cancer: a Mendelian randomization mediation study

Guansheng Chen, Yongjun Wang, Lingyu Liu, Wenjing Li*

Department of Gynecology and Obstetrics, Beijing Jishuitan Hospital, Capital Medical University, Beijing, China

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***Corresponding author:**
Wenjing Li
Department of Gynecology and Obstetrics
Beijing Jishuitan Hospital
Capital Medical University
Beijing, China
E-mail: liwenjing@jst-hosp.com.cn

Abstract

Introduction: Recent studies have highlighted the potential roles of immune cells and serum metabolites in the progression of ovarian cancer (OC). Therefore, this study used Mendelian randomization (MR) methodology to investigate potential causal associations among serum metabolites, immune cells, and OC.

Material and methods: This study used data from multiple sources to obtain genetic data related to immune cell phenotypes, serum metabolites, and OC. Causal effects were estimated using the inverse variance weighted, MR-Egger, weighted median, simple mode, and weighted mode methods to assess potential causal effects. Finally, mediation analysis was conducted to investigate the potential mediating roles of immune cell phenotypes and serum metabolites in OC.

Results: Thirty-six causal associations between immune cell phenotypes and OC were identified. "Resting CD4 regulatory T cell %CD4 regulatory T cell" (OR = 0.977, p = 0.018) was associated with a lower risk of OC, while "IgD-CD38dim B cell %B cell" (OR = 1.027, p = 0.021) was associated with a higher risk of OC. Additionally, 89 causal associations were identified between serum metabolites and OC. "Gluconate levels" (OR = 0.925, p = 0.047) was associated with a lower risk of OC, while "fructose levels" (OR = 1.097, p = 0.019) was associated with a higher risk of OC. Mediation analysis identified 3 serum metabolites that potentially mediated the influence of immune cell phenotypes on OC, alongside 2 immune cell phenotypes acting as potential mediators between serum metabolites and OC. Notably, sensitivity analysis supported the robustness of these findings.

Conclusions: This work provides novel insights into the potential causal associations among immune cells, serum metabolites, and OC.

Key words: ovarian cancer, immune cells phenotype, serum metabolites, Mendelian randomization, mediation analysis.

Introduction

Ovarian cancer (OC) remains a lethal gynecological malignancy with a 5-year survival rate of approximately 47%. This is mostly due to the absence of early symptoms, resulting in the majority of patients being detected at an advanced stage [1]. Moreover, the etiology of OC remains unclear, further complicating early diagnosis [2]. While current therapies partially control progression, high recurrence rates persist, highlighting an urgent need for improved early diagnostic biomarkers and therapeutic targets [3].

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Recent studies have linked the immune system to OC progression: macrophage homeostasis dysregulation drives tumor microenvironment immunosuppression [4, 5]; and altered lymphocyte subsets (e.g., T/B cells) correlate with prognosis [6]. In particular, regulatory T cells (Tregs) and regulatory B cells (Bregs) inhibit the proliferation of other immune cells by expressing different immune checkpoint molecules and secreting immunosuppressive substances, thereby promoting tumor growth and progression [7–10]. In parallel, the rapid advancement of metabolomics has offered a new lens to clarify OC pathogenesis while being widely used in OC studies over recent years [11, 12]. Serum metabolites, as indicators of biochemical activities in the body, are potentially relevant to risk assessment and prognostic evaluation of female cancers [13]. Fatty acids (such as C16 and C22), amino acids, and various chemical substances have been recognized as possible serum biomarkers for OC [14, 15]. These findings underscore the potential relevance of serum metabolites in OC, but their causal relationship with OC – and whether they mediate the relationships between immune cells and OC pathogenesis – has not been established. Traditional observational studies, limited by confounding factors and reverse causality, cannot resolve these uncertainties.

Based on this, the present study aims to systematically evaluate the causal relationships between immune cells and serum metabolites with OC through Mendelian randomization (MR) analysis, which leverages genetic variants as instrumental variables (IVs) to infer causal associations while potentially reducing confounding and reverse causality [16, 17]. We further integrated mediation analysis to investigate the potential pathways: specifically, whether serum metabolites may mediate the association of immune cells with OC, or vice versa. This approach aims to clarify the potential immunometabolic relationships in OC, providing a theoretical basis for future research into diagnostic strategies and therapeutic interventions.

Material and methods

Data collection

This study incorporated 731 immune phenotypes, all retrieved from the GWAS catalog (https://www.ebi.ac.uk/gwas/) (GCST90001391 to GCST90002121) and encompassing 3,757 individuals of European ancestry with no cohort overlap [18]. Additionally, 1,400 serum metabolites (GCST90199621 to GCST90201020) were retrieved from the GWAS catalog, originating from the Canadian Longitudinal Study on Aging (CLSA) cohort. This cohorts contained 8,299 randomly selected European-descent individuals with no blood relations [19]. Meanwhile, the GWAS data for OC (ieu-a-1120) were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), comprising 40,941 controls and 25,509 case samples of European origin, totaling 470,825 single nucleotide polymorphisms (SNPs).

Acquisition of IVs

MR analysis was conducted based on the following three fundamental assumptions: (1) IVs must demonstrate a consistent correlation with the exposure factors being examined; (2) IVs must be unaffected by any identifiable or unidentifiable confounding variables; (3) IVs must affect the outcome only via the exposure factor, rather than through alternative direct causal mechanisms. Based on these assumptions, we followed the initial step of selecting IVs by setting the SNP selection threshold at $p < 1 \times 10^{-5}$ when regarding immune cells and serum metabolites as exposure factors [20, 21]. Second, the ieugwasr package (v 1.0.0) [22] was used to eliminate SNPs with linkage disequilibrium, (parameters: $r^2 = 0.001$, kb = 10000). Subsequently, we calculated the F-statistic for each genetic variant and retained only those with an F-statistic > 10. Based on GWAS catalog, SNPs potentially associated with outcome GWAS traits were excluded at a threshold of $p < 1 \times 10^{-5}$ to reduce potential bias from SNPs associated with the outcome. Additionally, the Steiger method was employed for directionality testing to assess the direction of the causal associations. To ensure that the effects of SNPs on the exposure and outcome corresponded with those of the same allele, palindromic SNPs were omitted.

MR analysis

This study followed the Mendelian reporting specifications for randomized studies (STROBE-MR) [23]. This study employed multiple MR analysis methods to assess causal associations. The inverse variance weighted (IVW) [24] method, which typically has the highest statistical power [24, 25], was chosen as the primary method, supplemented by other approaches including MR-Egger [26], weighted median [27], simple mode [28], and weighted mode [28]. Moreover, the mediating roles of immune cells and serum metabolites in OC were explored. First, the overall effect of the main exposure on OC was assessed (*a*), reflecting the combined direct and indirect effects of the exposure on OC without considering mediating variables. Subsequently, the effects of exposure on the mediator (*c*) and the mediator on the outcome (*b*) were analyzed. In quantifying mediating

effects, $c \times b$ was used to represent the mediating effect. Additionally, the direct effect was computed using the formula $a - c \times b$, while the proportion of mediation was quantified as $c \times b/a$.

Statistical analysis

Sensitivity analyses were conducted to assess the robustness of causal inferences. Heterogeneity was evaluated using the mr_heterogeneity function and pleiotropy was assessed through MR-Egger regression and MR-PRESSO methods; outliers with $p < 0.05$ were excluded. Additionally, leave-one-out analysis was conducted to assess the dependence of the results on individual SNPs: one SNP was removed sequentially to check whether any single SNP influenced the causal estimates. All analyses were completed using the TwoSampleMR (v 0.6.0) [29] and MRPRESSO packages (v 1.0) [30], and the delta method was used to compute standard errors for mediating effects, direct effects, and proportions mediated [31].

Results

Selection of IVs

SNPs were screened to meet the necessary assumptions for MR analysis. In the analysis of immune cells phenotype and OC, a total of 17,757 SNPs were included for further study, with F-statistics ranging from 19.537 to 3159.289 (Supplementary Table SI). For the analysis of serum metabolites and OC, 34,513 SNPs were used, with F-statistics ranging from 19.503 to 2297.785 (Supplementary Table SII). In the analysis of immune cell phenotypes and serum metabolites, 17,836 SNPs were included, with F-statistics ranging from 19.537 to 3159.289 (Supplementary Table SIII). Finally, in the analysis of serum metabolites and immune cell phenotypes, 34,856 SNPs were included, with F-statistics ranging from 19.503 to 2297.785 (Supplementary Table SIV). All selected SNPs had *F*-statistics exceeding 10, supporting the strength of the genetic instruments.

Investigating the mediating role of serum metabolites in immune cells and OC

Given that immune cells are essential for ovarian development, pathogenic processes, and functional maintenance [32], we investigated the causal associations between immune cells and OC. Among the 731 immune cell phenotypes analyzed in relation to OC, 36 significant causal associations were identified, with 15 associated with a lower risk and 21 associated with a higher risk. Specifically, "resting CD4 regulatory T cell %CD4 regulatory T cell" [odds ratio (OR) = 0.977, 95% confidence interval (CI) = 0.958–0.996, $p = 0.018$) and "CD25 on CD39$^+$ resting CD4 regulatory T cell" (OR = 0.946, 95% CI = 0.899–0.995, $p = 0.032$) were associated with a lower risk of OC. Conversely, "CD19 on IgD$^+$ CD38$^-$ unswitched memory B cell" (OR = 1.037, 95% CI = 1.014–1.060, $p = 0.002$) and "IgD$^-$ CD38^{dim} B cell %B cell" (OR = 1.027, 95% CI = 1.004–1.050, $p = 0.021$) were associated with a higher risk of OC (Figure 1). Subsequently, reverse MR analysis was performed to assess potential bidirectional effects, with no significant associations found, providing no evidence for reverse causality in the identified associations.

Considering the substantial associations between immune cells and OC, we further explored their potential relationships with OC through serum metabolites. This involved analyzing the causal associations between 1,400 serum metabolites and OC, leading to the identification of 89 significant associations (Figure 2). On this basis, we investigated the causal associations between immune cells phenotype and serum metabolites, finding 156 associations between 36 immune cells phenotype and 80 serum metabolites, including 78 protective and 78 risk factors (Supplementary Table SV). In the mediation analysis, 4 significant associations were identified: "2R,3R-dihydroxybutyrate levels" potentially mediated an increased risk associated with "CD11c$^+$ CD62L$^-$ monocyte Absolute Count" and OC (11.300%). "N-lactoyl phenylalanine (Lac-Phe) levels" potentially mediated a reduced risk associated with "CD27 on IgD$^-$ CD38$^+$ B cell" and OC (21.230%), and "X-12221 levels" potentially mediated a reduced risk associated with "CD19 on IgD$^+$ CD38$^-$ unswitched memory B cell" and OC (12.342%). "Pseudouridine levels" potentially mediated an attenuated protective association between "CD4+CD8+ T cell Absolute Count" and OC (14.010%) (Figure 3). Due to the unclear levels of X-12221, three mediating associations were finally retained for further analysis, suggesting potential relationships between metabolites and immune cell phenotypes as well as their influence on OC risk.

Exploring the influence of serum metabolites on OC via immune cell phenotypes

Metabolomics, an emerging branch of systems biology, has made significant progress in cancer research in recent years, substantially enhancing the understanding, diagnosis, and treatment of diverse cancers, including OC [33]. Metabolomics can provide detailed information on metabolic changes during disease onset and progression, offering new perspectives for early diagnosis. Therefore, MR analysis was conducted on 1,400 serum metabolites and OC. In this process, 89 significant associations were identified, including

Exposure	Outcome	Method	nsnp	*P*-value	OR (95% CI)	pleio *P*
IgD+ CD38- B cell Absolute Count	Ovarian cancer II ieu-a-1120	IVW	17	0.022	0.940 (0.892 to 0.991)	0.430
Plasma Blast-Plasma Cell %B cell		IVW	26	0.018	1.039 (1.007 to 1.072)	0.389
Plasma Blast-Plasma Cell Absolute Count		IVW	23	0.021	0.968 (0.942 to 0.995)	0.600
IgD- CD24- B cell Absolute Count		IVW	18	< 0.001	1.081 (1.033 to 1.133)	0.633
IgD- CD38+ B cell %lymphocyte		IVW	27	0.036	0.976 (0.953 to 0.998)	0.835
IgD– CD38dim B cell %B cell		IVW	24	0.021	1.027 (1.004 to 1.050)	0.468
CD11c+ CD62L- monocyte Absolute Count		IVW	22	0.018	1.042 (1.007 to 1.079)	0.509
HLA DR++ monocyte %monocyte		IVW	20	0.008	0.957 (0.927 to 0.989)	0.657
CD4 regulatory T cell %CD4+ T cell		IVW	18	< 0.001	1.077 (1.033 to 1.123)	0.352
Resting CD4 regulatory T cell %CD4 regulatory T cell		IVW	30	0.018	0.977 (0.958 to 0.996)	0.772
Resting CD4 regulatory T cell %CD4+ T cell		IVW	32	0.009	0.974 (0.954 to 0.993)	0.142
Central Memory CD4-CD8- T cell Absolute Count		IVW	4	0.003	1.079 (1.027 to 1.134)	0.340
CD4+CD8+ T cell Absolute Count		IVW	18	0.023	0.945 (0.900 to 0.992)	0.085
CD28- CD25++ CD8+ T cell Absolute Count		IVW	25	0.042	1.030 (1.001 to 1.061)	0.658
CD25++ CD8+ T cell %T cell		IVW	17	0.028	1.048 (1.005 to 1.093)	0.934
CD25++ CD8+ T cell %CD8+ T cell		IVW	22	0.006	1.059 (1.017 to 1.103)	0.171
CD28+ CD45RA+ CD8+ T cell Absolute Count		IVW	53	0.021	1.009 (1.001 to 1.016)	0.548
CD19 on IgD+ CD38- unswitched memory B cell		IVW	24	0.002	1.037 (1.014 to 1.060)	0.535
CD20 on IgD+ CD24- B cell		IVW	23	0.037	1.027 (1.002 to 1.053)	0.744
CD25 on CD20- CD38- B cell		IVW	14	0.028	1.064 (1.007 to 1.125)	0.481
CD27 on IgD- CD38+ B cell		IVW	11	0.037	1.079 (1.005 to 1.159)	0.793
CD38 on IgD+ CD24- B cell		IVW	17	0.044	1.047 (1.001 to 1.095)	0.867
CD62L on CD62L+ Dendritic Cell		IVW	24	0.042	1.040 (1.001 to 1.080)	0.136
CD3 on CD4 regulatory T cell		IVW	11	0.017	1.042 (1.007 to 1.078)	0.257
HVEM on Effector Memory CD8+ T cell		IVW	18	0.003	0.962 (0.937 to 0.987)	0.282
CD45 on HLA DR+ T cell		IVW	16	0.031	1.042 (1.004 to 1.082)	0.784
CD127 on CD45RA+ CD4+ T cell		IVW	21	0.035	1.039 (1.003 to 1.077)	0.389
CD25 on CD39+ resting CD4 regulatory T cell		IVW	15	0.032	0.946 (0.899 to 0.995)	0.941
CD25 on CD39+ activated CD4 regulatory T cell		IVW	12	0.044	1.061 (1.002 to 1.123)	0.457
CD33 on CD33+ HLA DR+ CD14dim		IVW	27	0.046	1.017 (1.000 to 1.034)	0.121
FSC-A on HLA DR+ CD4+ T cell		IVW	16	0.007	0.941 (0.901 to 0.984)	0.902
CCR2 on granulocyte		IVW	17	0.041	0.966 (0.934 to 0.998)	0.667
CD80 on CD62L+ myeloid Dendritic Cell		IVW	26	0.023	0.968 (0.941 to 0.996)	0.985
SSC-A on plasmacytoid Dendritic Cell		IVW	24	0.039	0.967 (0.936 to 0.998)	0.441
SSC-A on HLA DR+ T cell		IVW	22	0.036	0.958 (0.920 to 0.997)	0.217
CD45RA on naive CD4+ T cell		IVW	31	0.031	0.976 (0.954 to 0.998)	0.051

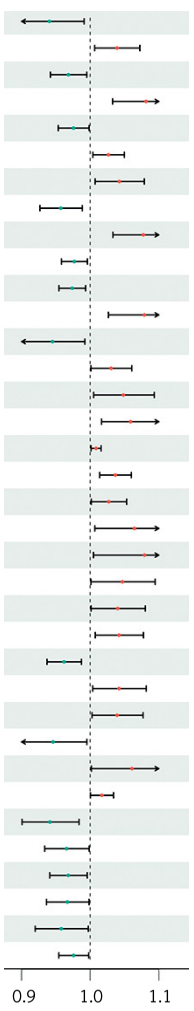


Figure 1. Results of Mendelian randomization (MR) analysis of immune cells phenotypes and ovarian cancer (OC)

IVW – inverse variance weighted, nsnp – number of single nucleotide polymorphisms, OR – odds ratio, CI – confidence interval, pleio_P – pleiotropy p-value.

Exposure	Outcome	Method	nsnp	*P*-value	OR (95% CI)	pleio_*P*
Ribitol levels	Ovarian cancer II ieu-a-1120	IVW	33	0.046	1.057 (1.001 to 1.115)	0.812
Alpha-hydroxyisocaproate levels		IVW	21	0.023	1.105 (1.014 to 1.206)	0.572
Palmitoylcarnitine levels (Metabolon platform)		IVW	28	0.043	0.932 (0.870 to 0.998)	0.349
Tartronate (hydroxymalonate) levels		IVW	20	0.008	0.909 (0.847 to 0.975)	0.520
1-linoleoyl-gpc (18:2) levels		IVW	28	0.006	1.098 (1.027 to 1.173)	0.646
5-acetylamino-6-amino-3-methyluracil levels		IVW	34	< 0.001	1.116 (1.061 to 1.173)	0.555
N1-methylinosine levels		IVW	25	0.048	1.083 (1.001 to 1.171)	0.626
5,6-dihydrouridine levels		IVW	29	0.034	0.930 (0.870 to 0.995)	0.370
Phenol sulfate levels		IVW	19	0.049	0.918 (0.842 to 1.000)	0.943
5-methyluridine (ribothymidine) levels		IVW	24	0.004	0.935 (0.894 to 0.978)	0.571
N6-acetyllysine levels		IVW	17	0.012	0.925 (0.870 to 0.983)	0.720
N-acetylserine levels		IVW	25	0.045	0.923 (0.854 to 0.998)	0.211
Glycocholenate sulfate levels		IVW	33	0.026	0.941 (0.891 to 0.993)	0.274
5alpha-pregnan-3beta,20alpha-diol monosulfate (2) levels		IVW	30	0.048	0.944 (0.892 to 0.999)	0.126
4-hydroxycoumarin levels		IVW	20	0.033	0.920 (0.851 to 0.993)	0.969
2R,3R-dihydroxybutyrate levels		IVW	30	< 0.001	0.905 (0.857 to 0.955)	0.997
2-o-methylascorbic acid levels		IVW	26	0.035	0.922 (0.854 to 0.994)	0.222
Imidazole propionate levels		IVW	22	0.048	0.920 (0.847 to 0.999)	0.885
Trimethylamine n-oxide levels		IVW	14	0.025	1.134 (1.016 to 1.266)	0.102
Margaroylcarnitine (C17) levels		IVW	23	0.024	0.916 (0.849 to 0.988)	0.090
Gamma-CEHC glucuronide levels		IVW	30	0.046	1.056 (1.001 to 1.114)	0.483
Sphingomyelin (d18:1/20:0, d16:1/22:0) levels		IVW	23	0.006	1.083 (1.023 to 1.145)	0.417
Dopamine 3-o-sulfate levels		IVW	24	0.020	0.910 (0.840 to 0.985)	0.800
1-stearoyl-2-linoleoyl-gpc (18:0/18:2) levels		IVW	22	0.034	1.078 (1.006 to 1.155)	0.988
1-palmitoyl-2-stearoyl-gpc (16:0/18:0) levels		IVW	28	0.006	0.919 (0.865 to 0.976)	0.066
Myristoyl dihydrosphingomyelin (d18:0/14:0) levels		IVW	29	0.029	0.931 (0.873 to 0.992)	0.368
1-palmitoyl-2-dihomo-linolenoyl-GPC (16:0/20:3n3 or 6) levels		IVW	27	0.013	1.071 (1.015 to 1.130)	0.312
1-linoleoyl-2-linolenoyl-GPC (18:2/18:3) levels		IVW	22	0.039	1.067 (1.003 to 1.135)	0.491
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1] levels		IVW	19	0.008	0.928 (0.878 to 0.981)	0.368
Gamma-glutamyl-alpha-lysine levels		IVW	31	0.002	0.902 (0.846 to 0.963)	0.094
Ceramide (d18:1/14:0, d16:1/16:0) levels		IVW	26	< 0.001	1.122 (1.055 to 1.194)	0.144
Linoleoylcholine levels		IVW	20	0.047	1.090 (1.001 to 1.186)	0.401
Linolenoylcarnitine (018:3) levels		IVW	21	< 0.001	0.876 (0.810 to 0.947)	0.680
Dihomo-linoleoylcarnitine (C20:2) levels		IVW	28	0.043	0.946 (0.896 to 0.998)	0.0117
Eicosenoylcarnitine (C20:1) levels		IVW	30	0.024	0.928 (0.870 to 0.990)	0.858
Arachidonoylcarnitine (C20:4) levels		IVW	33	0.019	0.954 (0.918 to 0.992)	0.181
3-carboxy-4-methy1-5-penty1-2-furanpropionate (3-CMPFP) levels		IVW	27	0.027	1.077 (1.008 to 1.151)	0.079
Glucuronide of C12H2204 (1) levels		IVW	19	0.027	1.087 (1.010 to 1.170)	0.894
Glycine conjugate of C10H1202 levels		IVW	26	0.011	0.922 (0.866 to 0.981)	0.225
3-amino-2-piperidone levels		IVW	24	0.037	1.087 (1.005 to 1.176)	0.705
N-lactoyl phenylalanine levels		IVW	16	0.001	0.849 (0.769 to 0.937)	0.596
N-lactoyl isoleucine levels		IVW	16	0.011	0.883 (0.803 to 0.972)	0.787
Sulfate of piperine metabolite C18H21NO3 (1) levels		IVW	24	0.039	0.925 (0.860 to 0.996)	0.891
Sulfate of piperine metabolite C16H19NO3 (2) levels		IVW	26	0.023	0.918 (0.852 to 0.988)	0.102
3-hydroxy-2-methylpyridine sulfate levels		IVW	20	0.030	0.911 (0.838 to 0.991)	0.810
Hydroxypalmitoyl sphingomyelin (dl8:1/16:0(OH)) levels		IVW	30	0.002	1.096 (1.035 to 1.160)	0.733
Metabolonic lactone sulfate levels		IVW	29	0.040	0.959 (0.922 to 0.998)	0.897
Bilirubin degradation product, C17H2ON205 (1) levels		IVW	22	0.049	1.082 (1.000 to 1.170)	0.943
Eicosapentaenoate (EPA; 20:5n3) levels		IVW	27	0.013	0.919 (0.860 to 0.982)	0.536
N-acetylputrescine levels		IVW	23	0.025	1.053 (1.006 to 1.103)	0.512
Gluconate levels		IVW	23	0.047	0.925 (0.857 to 0.999)	0.168
Fructose levels		IVW	26	0.019	1.097 (1.015 to 1.186)	0.370
Alpha-ketobutyrate levels		IVW	15	0.042	0.902 (0.817 to 0.996)	0.958
Pseudouridine levels		IVW	22	0.011	0.895 (0.822 to 0.974)	0.332
Dihydroorotate levels		IVW	29	0.040	1.056 (1.002 to 1.112)	0.390
Caproate (6:0) levels		IVW	21	0.025	1.085 (1.010 to 1.165)	0.513
X-11847 levels		IVW	19	0.030	1.098 (1.009 to 1.195)	0.067
X-11795 levels		IVW	15	0.042	0.911 (0.832 to 0.996)	0.686
X-12221 levels		IVW	23	0.001	1.130 (1.050 to 1.217)	0.286
X-12410 levels		IVW	25	< 0.001	1.114 (1.045 to 1.187)	0.385
X-12730 levels		IVW	19	0.034	0.914 (0.841 to 0.993)	0.696
X-13553 levels		IVW	22	0.025	0.908 (0.834 to 0.988)	0.926
X-16087 levels		IVW	23	0.024	1.070 (1.009 to 1.134)	0.536
X-17351 levels		IVW	18	0.043	1.091 (1.003 to 1.186)	0.111
X-21752 levels		IVW	22	0.043	0.926 (0.860 to 0.998)	0.088
X-23678 levels		IVW	19	0.008	0.906 (0.842 to 0.974)	0.730
X-24951 levels		IVW	19	0.009	1.128 (1.030 to 1.236)	0.302
X-24588 levels		IVW	31	0.040	0.944 (0.893 to 0.997)	0.354
5-acetylamino-6-formylamino-3-methyluracil levels		IVW	21	0.006	1.062 (1.017 to 1.108)	0.387
1-stearoy1-2-arachidonoyl-gpc (18:0/20:4) levels		IVW	34	0.040	0.963 (0.930 to 0.998)	0.572
1-palmitoy1-2-arachidonoyl-gpc (16:0/20:4n6) levels		IVW	27	0.036	0.957 (0.919 to 0.997)	0.691
Ethylmalonate levels		IVW	33	0.023	0.931 (0.876 to 0.990)	0.718
N-acetylputrescine to (N(1) + N(8))-acetylspermidine ratio		IVW	33	0.020	1.048 (1.007 to 1.091)	0.103
Histidine to trans-urocanate ratio		IVW	22	0.021	1.097 (1.014 to 1.186)	0.176
Oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [1] ratio		IVW	23	0.013	1.058 (1.012 to 1.106)	0.912
Oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio		IVW	25	0.015	1.059 (1.011 to 1.109)	0.169
Spermidine to (N(1) + N(8))-acetylspermidine ratio		IVW	23	0.045	1.073 (1.002 to 1.150)	0.271
Spermidine to N-acetylputrescine ratio		IVW	20	< 0.001	0.893 (0.841 to 0.947)	0.129
Adenosine 5'-monophosphate (AMP) to tyrosine ratio		IVW	16	0.029	1.115 (1.011 to 1.229)	0.666
Adenosine 5'-monophosphate (AMP) to acetoacetate ratio		IVW	25	0.041	0.929 (0.866 to 0.997)	0.681
Tryptophan to tyrosine ratio		IVW	25	0.028	1.086 (1.009 to 1.169)	0.869
Tyrosine to pyruvate ratio		IVW	23	0.038	0.924 (0.857 to 0.996)	0.499
Mannose to mannitol to sorbitol ratio		IVW	18	0.033	1.104 (1.008 to 1.208)	0.871
Adenosine 5'-diphosphate (ADP) to N-acetylneuraminate ratio		IVW	13	0.030	1.089 (1.008 to 1.177)	0.847
Arachidonate (20:4n6) to paraxanthine ratio		IVW	20	0.033	0.923 (0.857 to 0.994)	0.793
Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [1] ratio		IVW	22	0.023	1.071 (1.009 to 1.137)	0.663
Cholesterol to linoleoyl-arachidonoyl-glycerol (18:2 to 20:4) [2] ratio		IVW	30	0.027	1.064 (1.007 to 1.125)	0.867
Salicylate to oxalate (ethanedioate) ratio		IVW	18	0.034	0.908 (0.831 to 0.993)	0.683
Paraxanthine to 5-acetylamino-6-formylamino-3-methyluracil ratio		IVW	25	0.009	0.954 (0.920 to 0.988)	0.495

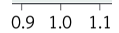


Figure 2. Results of MR analysis between serum metabolites and OC

IVW – inverse variance weighted, nsnp – number of single nucleotide polymorphisms, OR – odds ratio, CI – confidence interval, pleio_P – pleiotropy p-value.

Outcome (Y)	Expouse (X)	Mediate (M)	beta	nsnp	*P*-value	OR (95% CI)	pleio *P*	Mediated effect	Direct effect	Mediated proportion (%)
Ovarian cancer	CD11c+ CD62L- monocyte Absolute Count	2R,3R dihydroxybutyrate levels	a	22	0.018	1.042 (1.007 to 1.079)	0.509	c*b	a-c*b	c*b/a
			c	23	0.008	0.954 (0.921 to 0.988)	0.191	1.005 (1.000 to 1.009)	1.038 (1.002 to 1.074)	11.300 (0.656 to 21.944)
			b	30	< 0.001	0.905 (0.857 to 0.955)	0.997	pval=0.0374	pval=0.0376	pval=0.0374
	CD19 on IgD+ CD38- unswitched memory B cell	X-12221 levels	a	24	0.002	1.037 (1.014 to 1.060)	0.535	c*b	a-c*b	c*b/a
			c	22	0.007	0.964 (0.939 to 0.990)	0.690	0.996 (0.991 to 1.000)	1.041 (1.018 to 1.065)	12.342 (0.380 to 24.303)
			b	23	0.001	1.130 (1.050 to 1.217)	0.286	pval=0.0431	pval=0.000463	pval=0.0431
	CD27 on IgD CD38+ B cell	N lactoyl phenylalanine levels	a	11	0.037	1.079 (1.005 to 1.159)	0.793	c*b	a-c*b	c*b/a
			c	15	0.003	1.104 (1.033 to 1.179)	0.776	0.984 (0.969 to 0.999)	1.097 (1.020 to 1.180)	21.230 (1.620 to 40.840)
			b	16	0.001	0.849 (0.769 to 0.937)	0.596	pval=0.0338	pval=0.0132	pval=0.0338
	CD4+CD8+ T cell Absolute Count	Pseudouridine levels	a	18	0.023	0.945 (0.900 to 0.992)	0.085	c*b	a-c*b	c*b/a
			c	19	0.001	0.931 (0.892 to 0.972)	0.442	1.008 (1.000 to 1.016)	0.938 (0.892 to 0.985)	14.010 (0.005 to 28.015)
			b	22	0.011	0.895 (0.822 to 0.974)	0.332	pval=0.0499	pval=0.0106	pval=0.0499

Figure 3. The impact of immune cells phenotype on OC regulated by serum metabolites

Nsnp – number of single nucleotide polymorphisms, OR – odds ratio, CI – confidence interval, pleio_P – pleiotropy p-value, a – the total effect of immune cells phenotype on OC, b – the effect of serum metabolites on OC, c – the effect of immune cells phenotype on serum metabolites.

Outcome (Y)	Expouse (X)	Mediate (M)	beta	nsnp	*P*-value	OR (95% CI)	pleio *P*	Mediated effect	Direct effect	Mediated proportion (%)
Ovarian cancer	Arachidonate (20:4n6) to paraxanthine ratio	IgD- CD24- AC	a	20	0.033	0.923 (0.857 to 0.994)	0.793	c*b	a-c*b	c*b/a
			c	21	0.002	1.220 (1.075 to 1.385)	0.829	1.016 (1.002 to 1.030)	0.909 (0.843 to 0.980)	19.450 (2.179 to 36.721)
			b	18	< 0.001	1.081 (1.033 to 1.133)	0.633	pval=0.0273	pval=0.0125	pval=0.0273
	Gamma-CEHC glucuronide levels	CD4 Treg %CD4	a	30	0.046	1.056 (1.001 to 1.114)	0.483	c*b	a-c*b	c*b/a
			c	31	0.010	0.879 (0.797 to 0.970)	0.684	0.990 (0.981 to 1.000)	1.066 (1.010 to 1.126)	17.580 (0.495 to 34.666)
			b	18	< 0.001	1.077 (1.033 to 1.123)	0.352	pval=0.0437	pval=0.021	pval=0.0437

Figure 4. Results of mediation analysis of serum metabolites via immune cells phenotype for OC

Nsnp – number of single nucleotide polymorphisms, OR – odds ratio, CI – confidence interval, pleio_P – pleiotropy p-value, a – the total effect of immune cells phenotype on OC, b – the effect of serum metabolites on OC, c – the effect of immune cells phenotype on serum metabolites.

49 associated with a lower risk and 40 associated with a higher risk for OC (Figure 2). "Mannose to mannitol to sorbitol ratio" (OR = 1.104, 95% CI = 1.008–1.208, p = 0.033) and "Oleoyl-linoleoylglycerol (18:1 to 18:2) to linoleoyl-arachidonoylglycerol (18:2 to 20:4) ratio" (OR = 1.058, 95% CI = 1.012–1.106, p = 0.013) were associated with a higher risk of OC. Conversely, "Adenosine 5'-monophosphate (AMP) to acetoacetate ratio" (OR = 0.929, 95% CI = 0.866–0.997, p = 0.041) and "sulfate of piperine metabolite C18H21NO3 (1) levels" (OR = 0.925, 95% CI = 0.860–0.996, p = 0.039) were associated with a lower risk of OC. Similarly, to exclude the possibility of bidirectional effects, the causal impact of OC on these serum metabolites was assessed, with no significant reverse associations found.

Subsequently, the role of serum metabolites in influencing OC through immune cells phenotype was explored. By calculating the causal associations between 731 immune cells phenotype and OC, 36 significant associations were identified (Figure 1). Based on these significant results, the causal associations between serum metabolites and immune cells phenotype were evaluated, identifying 143 significant associations between 69 serum metabolites and 34 immune cells phenotype, including 68 associated with a lower risk and 75 associated with a higher risk of OC (Supplementary Table SVI). Subsequently, mediation analysis was conducted to explore whether these serum metabolites were potentially associated with OC through specific immune cells. The results identified two significant associations: "IgD$^-$ CD24$^-$ AC" potentially mediated an attenuated protective association between "arachidonate (20:4n6) to paraxanthine ratio" and OC (19.450%), and "CD4 Treg %CD4" potentially mediated a reduced risk associated with "Gamma-CEHC glucuronide levels" and OC (17.580%) (Figure 4). These findings suggest that certain metabolites may be associated with OC through their relationships with immune cell phenotypes.

Sensitivity analysis

To assess the robustness of the causal estimates in this study, comprehensive sensitivity analyses were performed. The causal results were consistent with the MR-PRESSO analysis, with no outliers detected. The MR-Egger test results showed p-values exceeding 0.05, indicating no evidence of horizontal pleiotropy (Supplementary Table SVII). Subsequently, where heterogeneity was detected in the MR analysis, a random-effects IVW model was employed (Supplementary Table SVII), still yielding consistent results. Furthermore, leave-one-out analysis revealed that the causal inference conclusions remained largely unaffected

despite the removal of one SNP in each iteration. These findings supported the robustness of the analysis results.

Discussion

Given the unclear interrelationships among immune cells, serum metabolites, and OC, this study used MR analysis to investigate the potential causal associations between immune cells/serum metabolites and OC, further investigating the mediating roles of these factors in OC development. We ultimately identified 3 significant pairs of relationships mediated by serum metabolites and 2 associations mediated by immune cells. These findings provide further insight into the potential relationships among immune cells, serum metabolites, and OC and may inform future research into its early identification and treatment

Through MR analysis, we identified "HLA DR^{++} monocyte %monocyte" as being associated with a lower risk of OC. Monocytes' HLA-DR surface expression denotes their activation state [34], which aids in determining their immunological status [35]. Some studies indicate that a certain monocyte subpopulation may possess immunosuppressive properties by suppressing T cell proliferation and differentiation, facilitating the development of regulatory T cells, and secreting anti-inflammatory mediators. This immune regulatory mechanism can safeguard the ovaries from autoimmune injury, therefore potentially reducing the chance of premature ovarian failure (POF) [36], which may be consistent with our findings. Besides, our research revealed that "$CD28^-$ $CD25^{++}$ $CD8^+$ T cell Absolute Count" is associated with a higher risk of OC, which is consistent with existing research findings. Studies have shown that an increased relative count of $CD28^-$ CD25CD8 T cells correlates with an elevated risk of infertility in women [37]. Another MR analysis revealed that the greatest risk factor for infertility is $CD28^-CD25^{++}$ $CD8^+$ %T cells [38]. The results suggest that immune factors may be associated with the onset and progression of OC.

Metabolites, as products and substrates of cellular metabolic processes, are closely linked to cancer [39]. Therefore, we further investigated the link between serum metabolites and OC and ultimately identified 89 significant causal associations. Among these associations, "palmitoylcarnitine levels" were associated with a lower risk of OC. The primary role of palmitoylcarnitine is to ferry long-chain fatty acids into the mitochondria for β-oxidation, thereby providing cell energy [40]. Consequently, focusing on palmitoylcarnitine and leveraging its capacity to provoke oxidative stress in cancer cells may offer a possible supplementary approach for the treatment of OC [41, 42]. In contrast, "Trimethylamine N-oxide (TMAO) levels" were associated with a higher risk of OC. Studies have shown that TMAO can upregulate macrophage scavenger receptors, promote cholesterol accumulation and foam cell formation, and activate MAPK and nuclear factor-κB pathways, thereby promoting plaque formation and inflammatory responses [43]. Moreover, heightened plasma levels of TMAO may correlate with the pathophysiology of polycystic ovarian syndrome (PCOS) without hyperandrogenism (HA) and are significantly linked to increased systemic inflammation [44]. This suggests that TMAO may be associated with the onset and progression of OC via many pathways, which may be consistent with our results. In summary, this investigation provides further evidence of an association between OC and serum metabolites.

To explore the mediating role of immune cells in the relationship between serum metabolites and OC, mediation analysis revealed that "CD4 Treg %CD4" potentially mediated an attenuated risk associated with "Gamma-CEHC glucuronide levels" – a vitamin E metabolite and OC risk factor. Research has suggested that the anticancer efficacy of tumor-infiltrating cytotoxic CD8+ T cells in OC seems to be impacted by the presence of CD4 Tregs [45], suggesting that CD4 Tregs may be involved in the progression of OC. However, studies have certified that depleting Tregs during OC can boost immunity and perhaps have therapeutic benefits [46, 47]. Additionally, studies have reported that an elevated number of CD4+ T cells is positively connected with the clinical features and tumor size of OC [48, 49]. This suggested that modulating the ratio of CD4 Tregs to CD4+ T cells might provide a potential target for developing novel immunomodulatory therapeutic strategies. Additionally, we also addressed the mediating function of serum metabolites in the interaction between immune cells and OC. Mediation analysis showed that "Lac-Phe levels" potentially mediated a reduced risk associated with "CD27 on IgD^- $CD38^+$ B cell" – a factor associated with a higher risk of OC. Higher IgD^- $CD38^+$ B cells are associated with stronger inflammation [50], which may promote OC via the tumor microenvironment. In both mice and humans, plasma Lac-Phe concentrations rise in response to stimuli that enhance circulating lactate or phenylalanine levels or increase glycolytic flux [51]. Research indicates that elevated levels of Lac-Phe may be associated with a lower risk of OC [52]. These findings suggest that the potential protective association mediated by Lac-Phe may be related to its role in modulating immune cell function and suppressing inflammation, offering a potential hypothesis regarding OC's underlying immunometabolic mechanisms.

We have expanded beyond the traditional single-variable research model in terms of perspective and are the first to use MR mediation analysis to systematically evaluate the potential causal relationship among immune cell phenotypes, serum metabolites and OC. Specific targets such as "CD4 Treg %CD4" and "Lac-Phe levels" have been proposed and may warrant further investigation as potential targets for regulatory therapies. For instance, strategies involving the selective depletion of CD4 Treg cells or the development of Lac-Phe or its analogs as metabolic intervention agents warrant further investigation and validation. Despite making progress in investigating the immunometabolic mechanisms of OC, our research has several limitations. The principal constraint is the substantial dependence on data from European populations, potentially introducing population-specific biases. Furthermore, the outcomes of our mediation study have not been corroborated by further experimental studies, necessitating further research to evaluate these potential causal relationships. The stratification of the research subjects is not clear, and only some immune cells and serum metabolites were included, which may limit the generalizability of the conclusions and result in missed key mediator pathways.

In conclusion, our MR study investigated the potential causative associations among immune cell phenotypes, serum metabolites, and OC. The research identified 36 notable causal associations between immune cell phenotypes and OC, along with 89 associations between serum metabolites and OC. Furthermore, mediation analysis identified potential mediating roles of serum metabolites and immune cells in OC. These findings provide further insight into the potential roles of immune cells and serum metabolites in OC and may provide a basis for future research into its early identification.

Data sharing statement

The genome-wide association study (GWAS) dataset for OC was obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/). Immune phenotypes were obtained from the GWAS catalog (https://www.ebi.ac.uk/gwas/).

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Siminiak N, Czepczyński, R, Zaborowski MP, Iżycki D. Immunotherapy in ovarian cancer. Arch Immunol Ther Exp 2022; 70: 19.
2. Auersperg N. The origin of ovarian cancers: hypotheses and controversies. Front Biosci 2013; 5: 709-19.
3. Chen J, Yang L, Ma Y, Zhang Y. Recent advances in understanding the immune microenvironment in ovarian cancer. Front Immunol 2024; 15: 1412328.
4. Brown MB, Von Chamier M, Allam AB, Reyes L. M1/M2 macrophage polarity in normal and complicated pregnancy. Front Immunol 2014; 5: 606.
5. Zhang M, He Y, Sun X, et al. A high M1/M2 ratio of tumor-associated macrophages is associated with extended survival in ovarian cancer patients. J Ovarian Res 2014; 7: 19.
6. Gasparri ML, Attar R, Palaia I, et al. Tumor infiltrating lymphocytes in ovarian cancer. Asian Pac J Cancer Prev 2015; 16: 3635-8.
7. Toker A, Nguyen LT, Stone SC, et al. Regulatory T cells in ovarian cancer are characterized by a highly activated phenotype distinct from that in melanoma. Clin Cancer Res 2018; 24: 5685-696.
8. Cao X, Cai SF, Fehniger TA, et al. Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance. Immunity 2007; 27: 635-46.
9. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol 2002; 3: 944-50.
10. Zhang Y, Morgan R, Podack ER, Rosenblatt J. B cell regulation of anti-tumor immune response. Immunol Res 2013; 57: 115-24.
11. Ha JH, Jayaraman M, Nadhan R, et al. Unraveling autocrine signaling pathways through metabolic fingerprinting in serous ovarian cancer cells. Biomedicines 2021; 9: 1927.
12. Garg G, Yilmaz A, Kumar P, et al. Targeted metabolomic profiling of low and high grade serous epithelial ovarian cancer tissues: a pilot study. Metabolomics 2018; 14: 154.
13. Cao Z, Long X, Yuan L. Associations between serum metabolites and female cancers: a bidirectional two-sample mendelian randomization study. J Steroid Biochem Mol Biol 2024; 243: 106584.
14. Ke C, Hou Y, Zhang H, et al. Large-scale profiling of metabolic dysregulation in ovarian cancer. Int J Cancer 2015; 136: 516-26.
15. Ahn HS, Yeom J, Yu J, Kwon YI, Kim JH, Kim K. Convergence of plasma metabolomics and proteomics analysis to discover signatures of high-grade serous ovarian cancer. Cancers 2020; 12: 3447..
16. Liang G, Miao D, Du C. Causal associations between blood metabolites and breast cancer. Arch Med Sci 2024; 21: 206-14.
17. Luo M, Li M, Zhou M, Wang L, Yang X. Investigating causal relationships between coffee consumption and gynecological diseases: a mendelian randomization study. Arch Med Sci 2025; doi:10.5114/aoms/200788.
18. Orrù V, Steri M, Sidore C, et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. Nat Genet 2020; 52: 1036-45.
19. Zhao G, Cai Y, Wang Y, Fang Y, Wang S, Li N. Genetically predicted blood metabolites mediate the association between circulating immune cells and pancreatic cancer: a mendelian randomization study. J Gene Med 2024; 26: e3691.

20. Liang X, Fan Y. Bidirectional two-sample mendelian randomization analysis reveals a causal effect of interleukin-18 levels on postherpetic neuralgia risk. Front Immunol 2023; 14: 1183378.
21. Wootton RE, Lawn RB, Millard LAC, et al. Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: mendelian randomisation study. BMJ 2018; 362: k3788.
22. Fan JC, Lu Y, Gan JH, Lu H. Identification of potential novel targets for treating inflammatory bowel disease using mendelian randomization analysis. Int J Colorectal Dis 2024; 39: 165.
23. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement. JAMA 2021; 326: 1614.
24. Ding M, Zhang Z, Chen Z, Song J, Wang B, Jin F. Association between periodontitis and breast cancer: two-sample mendelian randomization study. Clin Oral Investig 2023; 27: 2843-49.
25. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013; 37: 658-65.
26. Burgess S, Thompson SG. Interpreting findings from mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017; 32: 377-89.
27. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016; 40: 304-14.
28. Zeng Y, Cao S, Yang H. Roles of gut microbiome in epilepsy risk: a mendelian randomization study. Front Microbiol 2023; 14: 1115014.
29. Hemani G, Zheng J, Elsworth B, et al. The MR-base platform supports systematic causal inference across the human phenome. eLife 2018; 7: e34408.
30. Zhu S, Hu X, Fan Y. Association of triglyceride levels and prostate cancer: a mendelian randomization study. BMC Urol 2022; 22: 167.
31. Carter AR, Gill D, Davies NM, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. BMJ 2019; 365: l1855.
32. Gu X, Li S, DeFalco T. Immune and vascular contributions to organogenesis of the testis and ovary. FEBS J 2022; 289: 2386-408.
33. Turkoglu O, Zeb A, Graham S, et al. Metabolomics of biomarker discovery in ovarian cancer: a systematic review of the current literature. Metabolomics 2016; 12: 60.
34. Kim OY, Monsel A, Bertrand M, Coriat P, Cavaillon JM, Adib-Conquy M. Differential down-regulation of HLA-DR on monocyte subpopulations during systemic inflammation. Crit Care 2010; 14: R61.
35. Asmussen A, Busch HJ, Helbing T, et al. Monocyte subset distribution and surface expression of HLA-DR and CD14 in patients after cardiopulmonary resuscitation. Sci Rep 2021; 11: 12403.
36. Lu Y, Yao Y, Zhai S, et al. The role of immune cell signatures in the pathogenesis of ovarian-related diseases: a causal inference based on mendelian randomization. Int J Surg 2024; 110: 6541-50.
37. Shen HH, Zhang YY, Wang XY, et al. Potential Causal association between plasma metabolites, immunophenotypes, and female reproductive disorders: a two-sample mendelian randomization analysis. Biomolecules 2024; 14: 116.
38. Peng D, Zhong W, Wang Y, Fu Y, Shang W. The causal relationship between immune cells and infertility: a mendelian randomisation study. Am J Reprod Immunol 2024; 92: e13932.
39. Johnson CH, Patterson AD, Idle JR, Gonzalez FJ. Xenobiotic metabolomics: major impact on the metabolome. Annu Rev Pharmacol Toxicol 2012; 52: 37-56.
40. Tarasenko TN, Cusmano-Ozog K, McGuire PJ. Tissue acylcarnitine status in a mouse model of mitochondrial κoxidation deficiency during metabolic decompensation due to Influenza virus infection. Mol Genet Metab 2018; 125: 144-52.
41. Turnbull PC, Hughes MC, Perry CGR. The fatty acid derivative palmitoylcarnitine abrogates colorectal cancer cell survival by depleting glutathione. Am J Physiol Cell Physiol 2019; 317: C1278-88.
42. Wenzel U, Nickel A, Daniel H. Increased carnitine-dependent fatty acid uptake into mitochondria of human colon cancer cells induces apoptosis. J Nutr 2005; 135: 1510-4.
43. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011; 472: 57-63.
44. Huang J, Liu L, Chen C, Gao Y. PCOS without hyperandrogenism is associated with higher plasma trimethylamine N-oxide levels. BMC Endocr Disord 2020; 20: 3.
45. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci 2005; 102: 18538-43.
46. Cannioto RA, Sucheston-Campbell LE, Hampras S, et al. The association of peripheral blood regulatory T-cell concentrations with epithelial ovarian cancer: a brief report. Int J Gynecol Cancer 2017; 27: 11-6.
47. Barnett B, Kryczek I, Cheng P, Zou W, Curiel TJ. Regulatory T cells in ovarian cancer: biology and therapeutic potential. Am J Reprod Immunol 2005; 54: 369-77.
48. Wu M, Chen X, Lou J, et al. Changes in regulatory T cells in patients with ovarian cancer undergoing surgery: preliminary results. Int Immunopharmacol 2017; 47: 244-50.
49. Zhang S, Ke X, Zeng S, et al. Analysis of CD8+ Treg cells in patients with ovarian cancer: a possible mechanism for immune impairment. Cell Mol Immunol 2015; 12: 580-91.
50. Wang C, Li ZY, Gong Y, You R, Ming-Hui Z, Chen M. Increased frequency of IgD-CD27(Hi)CD38(Hi) B cells and its association with the renal involvement in ANCA-associated vasculitis. Arthritis Res Ther 2022; 24: 109.
51. Xiao S, Li VL, Long JZ. Lac-Phe (N-Lactoyl-Phenylalanine). Trends Endocrinol Metab 2024; 35: 758-9.
52. Guo J, Wang C, Li H, Ding C. Exploring the causal associations of the gut microbiota and plasma metabolites with ovarian cancer: an approach of mendelian randomization analysis combined with network pharmacology and molecular docking. J Ovarian Res 2025; 18: 27.