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ORIGINAL RESEARCH

Causal Involvement of Immune Cells in Chronic Obstructive Pulmonary Disease: A Mendelian Randomization Study

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Background: The immune cells play a substantial role in the development and progression of chronic obstructive pulmonary disease (COPD). We aim to investigate the causal involvement of immune cells in COPD via a Mendelian randomization (MR) analysis.
Methods: Published genome-wide association studies (GWAS) statistics on immune cells were analyzed, with genetic variants identified as instrumental variables (IVs). Inverse-variance weighting (IVW), weighted median, and MR-Egger regression methods were employed, along with simple mode and weighted mode adopted in the two-sample MR analysis. Sensitivity analysis was conducted to examine the heterogeneity, horizontal pleiotropy, and stability of the causal relationship.
Results: IVW results suggested that CCR2 on CD62L+ plasmacytoid dendritic cells (DC), CCR2 on plasmacytoid DC, CD11b on CD66b++ myeloid cells, CD19 on CD20− CD38− CD24+ memory B cell subset, CD25 on transitional B cells, and CD25++CD8br % CD8br T cells were risk factors for the development of COPD. Besides, CD127 on effector memory-like cytotoxic T lymphocytes lacking expression of co-stimulatory molecule 28 (CD28-EM CTLs) and HLA DR+ NK ACs expressing human leukocyte antigen DR molecules while being natural killer cells (%NK ACs) were protective factors for COPD.
Conclusion: This study unveiled a causal relationship between immune cell phenotype and COPD. These findings offer new insights for the prevention and treatment of COPD using COPD-associated immune cells.
Keywords: chronic obstructive pulmonary disease, immune cells, causal inference, Mendelian randomization

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide characterized by progressive airflow restriction and accelerated lung function decline.[1] A long-term course of COPD eventually damages lung epithelial cells and lung tissue, leading to airway inflammation, increased mucus secretion, peribronchial fibrosis, and airway remodeling.[2] Generally, chronic innate and adaptive inflammatory immune responses are triggered by COPD.[3] COPD-induced inflammatory responses involve various components of innate immunity, such as eosinophils, neutrophils, macrophages, mast cells, natural killer (NK) cells, and dendritic cells (DC), as well as components of adaptive immunity like T lymphocytes and B lymphocytes.[4] Although the importance of immune cells in the pathology of COPD has been established, its causal relationship with COPD remains largely unclear. This study aims to investigate the causal involvement of immune cell phenotypes in the development of COPD by a Mendelian randomization (MR) analysis, thus providing novel therapeutic targets for COPD.

Materials and Methods

Data Sources

Genetic signatures in immune cell traits, involving 22 million variants and their impact on 731 immune cell phenotypes in a cohort of 3757 individuals of Sardinian descent were available from a published literature.[5] Additionally, summary data on 13,530 COPD patients and 454,945 controls of European ancestry, with 24,180,654 single nucleotide polymorphisms (SNPs) were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/, accessed on November 5, 2023). An ethical approval of the present study was not necessary because of the publicly available datasets.

Selection of Tool Variables

Optimal instrumental variables (IVs) were selected following the rigorous screening criteria, aiming to ensure the authenticity and accuracy of our findings. Briefly, summary-level genome-wide association study (GWAS) statistics on immune cells were screened, and SNPs with a significance threshold of $P<5\times10^{-5}$ were selected. Following the independence assumption of MR, a coefficient R^2 of 0.001 and clump distance of 10,000 kb maximized their efforts to avoid any potential linkage disequilibrium IVs. Further, palindromic SNPs were excluded to guarantee consistent alleles for each SNP in both the immune cell group and COPD group. The process of selecting the optimal IVs was depicted in (Figure 1).

MR Assumptions

A valid MR analysis required that IVs should adhere to the following three fundamental assumptions: (1) Independence assumption: the selected IVs were independent of confounding factors influencing immune cells and COPD; (2) Association assumption: IVs were robustly associated with COPD; (3) Exclusivity assumption: IVs were associated with COPD through immune cells only (Figure 2).
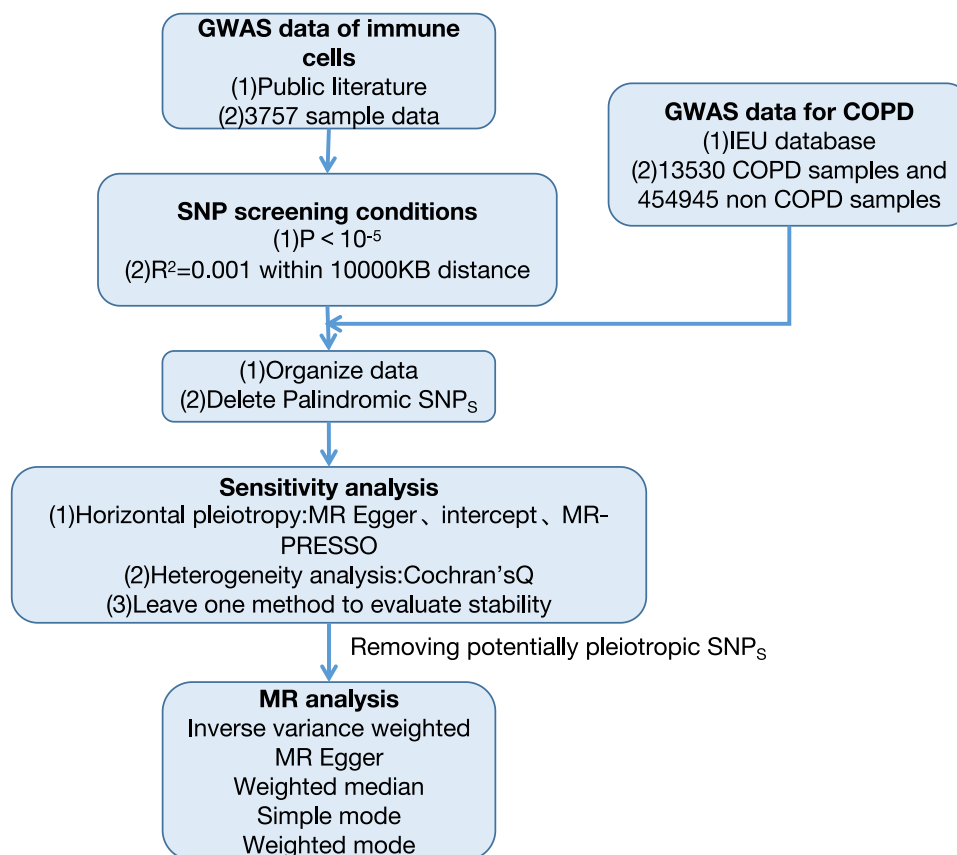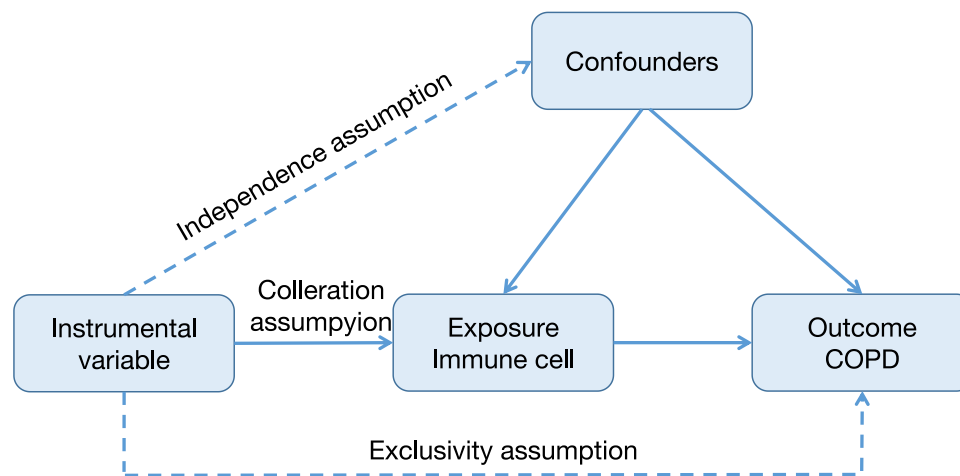

Figure 1 Flowchart of MR analysis.

The dashed line indicates that there is no correlation between variables, and the solid line indicates that there is a correlation between variables

Figure 2 Principal assumptions of MR.

Statistical Processing

Two-sample MR and MR-PRESSO in R 4.320 were utilized for the MR analysis and sensitivity analysis, respectively. The F statistic was employed to assess the strength of correlation between IVs and COPD, where an F value of greater than 10 indicated a satisfaction of the association assumption.

MR Analysis

Inverse-variance weighting (IVW), MR-Egger regression, weighted median, simple model, and weighted model were employed in the present MR analysis of inferring a causal relationship between immune cells and COPD. In the absence of horizontal pleiotropy, IVW method approached a weighed mean of the reciprocal of outcome variance, rather than the consideration of an intercept term in the regression analysis. IVW results were considered as the primary outcomes. Depending on heterogeneity presence or absence, either a fixed-effects or a random-effects model was adopted in IVW. MR-Egger regression provided consistent estimates even when all IVs exhibited gene pleiotropy. The weighted median was excellent in consistently estimating causal relationships even when more than 50% of IVs were invalid. The simple model offered a robustness against genetic pleiotropy,[6] and the weighted model was featured by the high sensitivity to challenge bandwidth selection during model estimation.[7] Therefore, IVW, MR-Egger regression and weighted median method were used in the MR analysis, with the simple and weighted models adopted as supplementary methods. A significance level was determined at $p<0.05$.

Sensitivity Analysis

Heterogeneity was assessed using Cochran's Q test. The MR-PRESSO was employed to identify and remove outliers, followed by reanalysis. MR-Egger analysis allowed the evaluation of horizontal pleiotropy by testing the intercept. The robustness of MR results was evaluated using the leave-one-out approach. A significance level was determined at $p<0.05$.

Results

Optimal IVs

After screening GWAS statistics on immune cells, a total of 18,621 SNPs with F value of greater than 10 were selected as IVs.

MR Analysis

IVW data revealed that CCR2 on CD62L+ plasmacytoid DC (OR=1.039, 95% CI 1.008, 1.065, $P<0.05$), CCR2 on plasmacytoid DC (OR=1.036, 95% CI 1.001, 1.003, $P<0.05$), CD11b on CD66b++ myeloid cells (OR=1.033, 95% CI

1.004, 1.063, $P<0.05$), CD19 on CD20− CD38− (OR=1.084, 95% CI 1.038, 1.131, $P<0.05$), CD24 on memory B cells (OR=1.027, 95% CI 1.004, 1.051, $P<0.05$), CD25++ CD8br %CD8br (OR=1.042, 95% CI 1.002, 1.084, $P<0.05$), CD27 on CD24+ CD27+ (OR=1.040, 95% CI 1.016, 1.065, $P<0.05$), CD27 on switched memory cells (OR=1.033, 95% CI 1.006, 1.061, $P<0.05$), CD27 on unswitched memory cells (OR=1.036, 95% CI 1.007, 1.066, $P<0.05$), CD28+ CD45RA − CD8br %T cells (OR=1.015, 95% CI 1.000, 1.029, $P<0.05$), CD33dim HLA DR+ CD11b− %CD33dim HLA DR+ (OR=1.017, 95% CI 1.003, 1.032, $P<0.05$), CD62L− CD86+ myeloid DC %DC (OR=1.023, 95% CI 1.001, 1.047, $P<0.05$), CD62L− myeloid DC AC (OR=1.044, 95% CI 1.009, 1.080, $P<0.05$), CD62L on monocytes (OR=1.028, 95% CI 1.002, 1.055, $P<0.05$), HLA DR on plasmacytoid DC (OR=1.020, 95% CI 1.003, 1.037, $P<0.05$), IgD+ CD38br %B cells (OR=1.038, 95% CI 1.007, 1.069, $P<0.05$), myeloid DC AC (OR=1.038, 95% CI 1.015, 1.061, $P<0.05$) and NKT % lymphocytes (OR=1.042, 95% CI 1.012, 1.074, $P<0.05$) were risk factors for COPD. In addition, CD127 on CD28− CD8br (OR=0.957, 95% CI 0.917, 0.998, $P<0.05$), CD127 on CD28+ CD45RA− CD8br (OR=0.970, 95% CI 0.946, 0.995, $P<0.05$), CD14+ CD16+ monocyte AC (OR=0.968, 95% CI 0.940, 0.998, $P<0.05$), CD19 on IgD− CD38br (OR=0.955, 95% CI 0.919, 0.992, $P<0.05$), CD19 on PB/PC (OR=0.940, 95% CI 0.903, 0.978, $P<0.05$), CD25hi %T cells (OR=0.965, 95% CI 0.934, 0.997, $P<0.05$), CD3− lymphocyte AC (OR=0.945, 95% CI 0.906, 0.986, $P<0.05$), CD3 on CM CD8br (OR=0.957, 95% CI 0.924, 0.996, $P<0.05$), CD3 on EM CD8br (OR=0.965, 95% CI 0.942, 0.989, $P<0.05$), CD3 on naive CD8br (OR=0.95, 95% CI 0.994, 0.999, $P<0.05$), CD4+ CD8dim %leukocytes (OR=0.943, 95% CI 0.894, 0.995, $P<0.05$), CD4+ CD8dim %lymphocytes (OR=0.943, 95% CI 0.904, 0.984, $P<0.05$), CD45 on Im myeloid derived suppressor cells (MDSCs) (OR=0.965, 95% CI 0.941, 0.990, $P<0.05$), CD62L on granulocytes (OR=0.944, 95% CI 0.908, 0.981, $P<0.05$), CD80 on granulocytes (OR=0.967, 95% CI 0.944, 0.991, $P<0.05$), HLA DR on monocytes (OR=0.978, 95% CI 0.955, 1.000, $P<0.05$), HLA DR+ NK AC (OR=0.951, 95% CI 0.916, 0.987, $P<0.05$), HLA DR+ T cell%T cells (OR=0.977, 95% CI 0.958, 0.996, $P<0.05$), naive CD8br AC (OR=0.964, 95% CI 0.934, 0.996, $P<0.05$), SSC−A on HLA DR+ T cells (OR=0.957, 95% CI 0.926, 0.989, $P<0.05$) and TCRgd %T cells (OR=0.965, 95% CI 0.937, 0.994, $P<0.05$) served as protective factors for COPD (Figure 3).

Sensitivity Analysis

A significance level of $p<0.05$ obtained in the heterogeneity test suggested no significant heterogeneity among the combined IVs, and a fixed-effects model was then employed for all IVW analyses. No outliers and horizontal pleiotropy were detected by MR-PRESSO and MR-Egger, respectively. Additionally, a leave-one-out approach revealed that neither of an individual SNP had a significant impact on the robustness of our findings. Therefore, the MR analysis unveiled a causal involvement of immune cells in the development of COPD.

Discussion

Tissue damage and disease severity of COPD are associated with the formation of tertiary lymphoid organs (TLOs).[2,8] Lymphoid follicles (LFs) are the predominant type of TLOs, consisting of a large population of B lymphocytes surrounded by DC and small numbers of CD4+ and CD8+ cells.[9] B cells in LFs interact with certain subsets of CD4+ T cells and thus experience phenotypic transformation and maturation. Their interactions further trigger the release of inflammatory factors, serving as an inducer for tissue injury. Therefore, an effective suppression of inducers for inflammatory responses is considered as a crucial step in blocking immune responses in LFs and the onset of COPD.[10] Various types of immune cells are involved in the immune reactions that either stimulate or inhibit the pathogenesis of COPD. Using publicly available databases, we investigated the causal relationship between 731 immune cell traits and COPD by an MR analysis. A total of 39 immunophenotypes across 4 immune cell traits of median fluorescence intensity (MFI), relative cell count (RC), absolute cell count (AC) and morphological parameters (MP) that exhibited significant causal effects on COPD.

Seven immune cell phenotypes associated with DC were found as risk factors for the onset of COPD, including CCR2 on CD62L+ plasmacytoid DC, CCR2 on plasmacytoid DC, HLA DR on plasmacytoid DC, CD62L-CD86 + myeloid DC AC, CD62L-CD86 + myeloid DC %DC, CD62L on monocytes, and myeloid DC AC. Two granulocyte phenotypes, namely CD62L on granulocytes and CD80 on granulocytes, were identified as protective factors for COPD. Plasmacytoid (pDC) and myeloid DC (mDC1 and mDC2) are bone-marrow-derived and blood-derived cells, respectively. Both of them
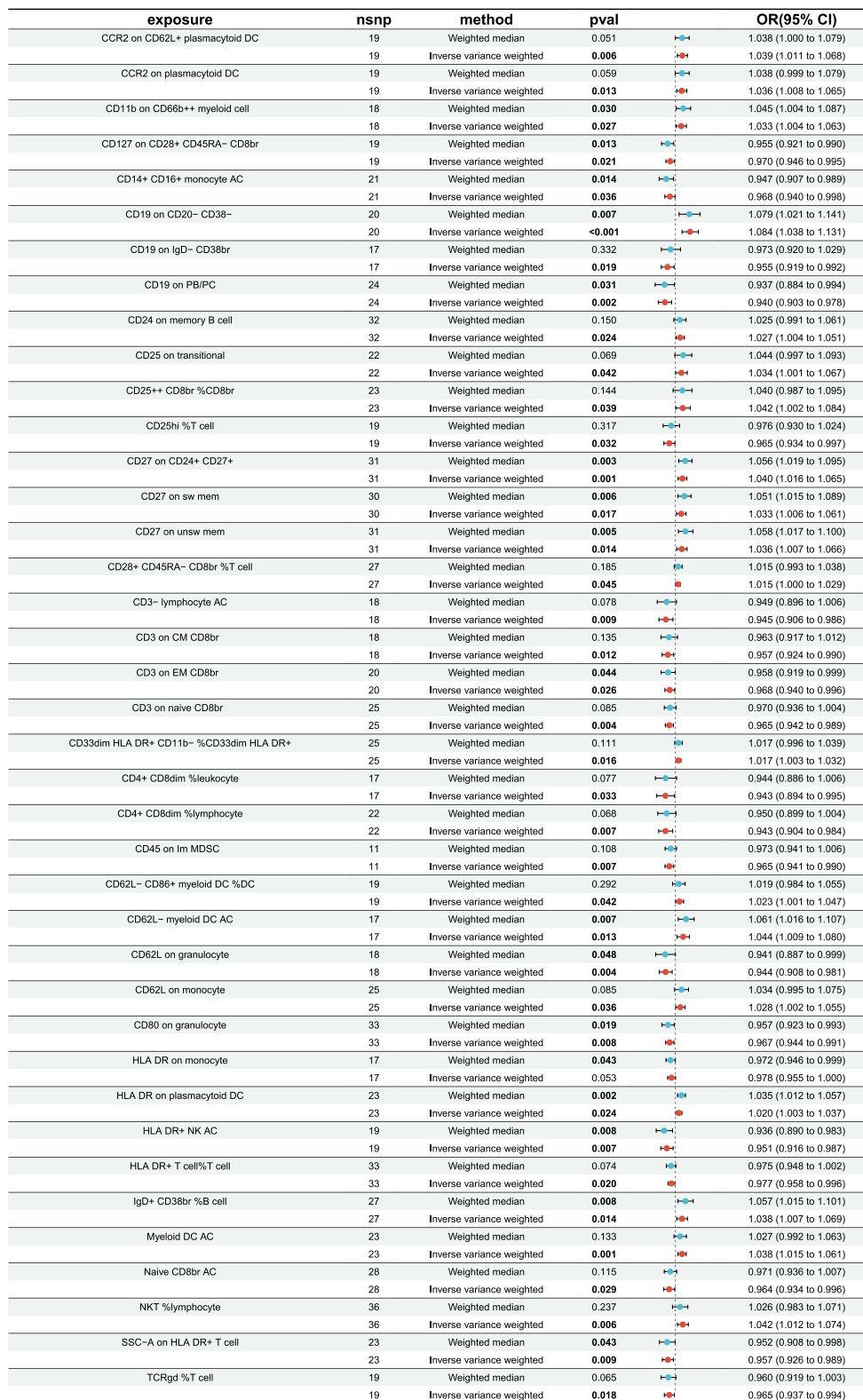
exposure	nsnp	method	pval		OR(95% CI)
CCR2 on CD62L+ plasmacytoid DC	19	Weighted median	0.051		1.038 (1.000 to 1.079)
	19	Inverse variance weighted	**0.006**		1.039 (1.011 to 1.068)
CCR2 on plasmacytoid DC	19	Weighted median	0.059		1.038 (0.999 to 1.079)
	19	Inverse variance weighted	**0.013**		1.036 (1.008 to 1.065)
CD11b on CD66b++ myeloid cell	18	Weighted median	**0.030**		1.045 (1.004 to 1.087)
	18	Inverse variance weighted	**0.027**		1.033 (1.004 to 1.063)
CD127 on CD28+ CD45RA− CD8br	19	Weighted median	**0.013**		0.955 (0.921 to 0.990)
	19	Inverse variance weighted	**0.021**		0.970 (0.946 to 0.995)
CD14+ CD16+ monocyte AC	21	Weighted median	**0.014**		0.947 (0.907 to 0.989)
	21	Inverse variance weighted	**0.036**		0.968 (0.940 to 0.998)
CD19 on CD20− CD38−	20	Weighted median	**0.007**		1.079 (1.021 to 1.141)
	20	Inverse variance weighted	**<0.001**		1.084 (1.038 to 1.131)
CD19 on IgD− CD38br	17	Weighted median	0.332		0.973 (0.920 to 1.029)
	17	Inverse variance weighted	**0.019**		0.955 (0.919 to 0.992)
CD19 on PB/PC	24	Weighted median	**0.031**		0.937 (0.884 to 0.994)
	24	Inverse variance weighted	**0.002**		0.940 (0.903 to 0.978)
CD24 on memory B cell	32	Weighted median	0.150		1.025 (0.991 to 1.061)
	32	Inverse variance weighted	**0.024**		1.027 (1.004 to 1.051)
CD25 on transitional	22	Weighted median	0.069		1.044 (0.997 to 1.093)
	22	Inverse variance weighted	**0.042**		1.034 (1.001 to 1.067)
CD25++ CD8br %CD8br	23	Weighted median	0.144		1.040 (0.987 to 1.095)
	23	Inverse variance weighted	**0.039**		1.042 (1.002 to 1.084)
CD25hi %T cell	19	Weighted median	0.317		0.976 (0.930 to 1.024)
	19	Inverse variance weighted	**0.032**		0.965 (0.934 to 0.997)
CD27 on CD24+ CD27+	31	Weighted median	**0.003**		1.056 (1.019 to 1.095)
	31	Inverse variance weighted	**0.001**		1.040 (1.016 to 1.065)
CD27 on sw mem	30	Weighted median	**0.006**		1.051 (1.015 to 1.089)
	30	Inverse variance weighted	**0.017**		1.033 (1.006 to 1.061)
CD27 on unsw mem	31	Weighted median	**0.005**		1.058 (1.017 to 1.100)
	31	Inverse variance weighted	**0.014**		1.036 (1.007 to 1.066)
CD28+ CD45RA− CD8br %T cell	27	Weighted median	0.185		1.015 (0.993 to 1.038)
	27	Inverse variance weighted	**0.045**		1.015 (1.000 to 1.029)
CD3− lymphocyte AC	18	Weighted median	0.078		0.949 (0.896 to 1.006)
	18	Inverse variance weighted	**0.009**		0.945 (0.906 to 0.986)
CD3 on CM CD8br	18	Weighted median	0.135		0.963 (0.917 to 1.012)
	18	Inverse variance weighted	**0.012**		0.957 (0.924 to 0.990)
CD3 on EM CD8br	20	Weighted median	**0.044**		0.958 (0.919 to 0.999)
	20	Inverse variance weighted	**0.026**		0.968 (0.940 to 0.996)
CD3 on naive CD8br	25	Weighted median	0.085		0.970 (0.936 to 1.004)
	25	Inverse variance weighted	**0.004**		0.965 (0.942 to 0.989)
CD33dim HLA DR+ CD11b− %CD33dim HLA DR+	25	Weighted median	0.111		1.017 (0.996 to 1.039)
	25	Inverse variance weighted	**0.016**		1.017 (1.003 to 1.032)
CD4+ CD8dim %leukocyte	17	Weighted median	0.077		0.944 (0.886 to 1.006)
	17	Inverse variance weighted	**0.033**		0.943 (0.894 to 0.995)
CD4+ CD8dim %lymphocyte	22	Weighted median	0.068		0.950 (0.899 to 1.004)
	22	Inverse variance weighted	**0.007**		0.943 (0.904 to 0.984)
CD45 on lm MDSC	11	Weighted median	0.108		0.973 (0.941 to 1.006)
	11	Inverse variance weighted	**0.007**		0.965 (0.941 to 0.990)
CD62L− CD86+ myeloid DC %DC	19	Weighted median	0.292		1.019 (0.984 to 1.055)
	19	Inverse variance weighted	**0.042**		1.023 (1.001 to 1.047)
CD62L− myeloid DC AC	17	Weighted median	**0.007**		1.061 (1.016 to 1.107)
	17	Inverse variance weighted	**0.013**		1.044 (1.009 to 1.080)
CD62L on granulocyte	18	Weighted median	**0.048**		0.941 (0.887 to 0.999)
	18	Inverse variance weighted	**0.004**		0.944 (0.908 to 0.981)
CD62L on monocyte	25	Weighted median	0.085		1.034 (0.995 to 1.075)
	25	Inverse variance weighted	**0.036**		1.028 (1.002 to 1.055)
CD80 on granulocyte	33	Weighted median	**0.019**		0.957 (0.923 to 0.993)
	33	Inverse variance weighted	**0.008**		0.967 (0.944 to 0.991)
HLA DR on monocyte	17	Weighted median	**0.043**		0.972 (0.946 to 0.999)
	17	Inverse variance weighted	0.053		0.978 (0.955 to 1.000)
HLA DR on plasmacytoid DC	23	Weighted median	**0.002**		1.035 (1.012 to 1.057)
	23	Inverse variance weighted	**0.024**		1.020 (1.003 to 1.037)
HLA DR+ NK AC	19	Weighted median	**0.008**		0.936 (0.890 to 0.983)
	19	Inverse variance weighted	**0.007**		0.951 (0.916 to 0.987)
HLA DR+ T cell%T cell	33	Weighted median	0.074		0.975 (0.948 to 1.002)
	33	Inverse variance weighted	**0.020**		0.977 (0.958 to 0.996)
IgD+ CD38br %B cell	27	Weighted median	**0.008**		1.057 (1.015 to 1.101)
	27	Inverse variance weighted	**0.014**		1.038 (1.007 to 1.069)
Myeloid DC AC	23	Weighted median	0.133		1.027 (0.992 to 1.063)
	23	Inverse variance weighted	**0.001**		1.038 (1.015 to 1.061)
Naive CD8br AC	28	Weighted median	0.115		0.971 (0.936 to 1.007)
	28	Inverse variance weighted	**0.029**		0.964 (0.934 to 0.996)
NKT %lymphocyte	36	Weighted median	0.237		1.026 (0.983 to 1.071)
	36	Inverse variance weighted	**0.006**		1.042 (1.012 to 1.074)
SSC−A on HLA DR+ T cell	23	Weighted median	**0.043**		0.952 (0.908 to 0.998)
	23	Inverse variance weighted	**0.009**		0.957 (0.926 to 0.989)
TCRgd %T cell	19	Weighted median	0.065		0.960 (0.919 to 1.003)
	19	Inverse variance weighted	**0.018**		0.965 (0.937 to 0.994)

Figure 3 A forest map visualizing a causal relationship between immune cells and COPD.

can directly or indirectly participate in the process of lung dysfunction and mediation of downstream T lymphocytes[11]. The activated adaptive immune system is also involved in the pathogenesis of COPD through inducing inflammation responses or antigen presentation.[12] Although ranking the highest proportion, mDC2, alongside mDC1 and pDC in the

lung tissue are quantitatively similar between COPD patients and healthy volunteers. Expression levels of costimulatory molecules, however, are significant different between COPD patients and healthy controls. Specifically, CD40 on mDC1, CD86 on mDC2, CD40 on mDC2, CD80 on pDC and CD40 on pDC increase with the increasing severity of COPD. Upregulation of costimulatory molecules also result in a stronger stimulation towards downstream T cells.[13] It is found that mDC2 exerts an excellent performance in inducing helper T lymphocytes.[8,14] The higher absolute values of mDC and pDC in the lung lavage fluid of COPD smokers compared to those of non-smokers are indicative of the importance of tobacco exposure in the pathogenesis of COPD[14]. After 4 hours of smoking, an increase in alveolar lavage fluid mDC and decrease in blood mDC among smokers suggested that the selective migration of mDC to the airway and its contribution to antigen presentation[15]. Co-stimulatory molecules CD62L, CD80, and CD86 expressed on the surface of immune cells play a vital role in mediating cell-cell interactions with lymphocytes. Human leukocyte antigen (HLA) serves as a key molecule involved in DC-mediated antigen presentation. CCR2 regulates cell-cell interactions by binding to specific chemokines, and the frequency of CCR2-related gene carriers is positively correlated with the incidence of COPD.[16] Overall, DC-induced immune function affects the formation of LFs by mediating downstream immune cell responses, thus influencing the development and progression of COPD.

T cells and B cells are the primary cellular components involved in the adaptive immune response. In our study, most T lymphocyte phenotypes were identified as protective factors for COPD, including CD127 on CD28+ CD45RA− CD8br, CD25hi %T cells, CD28+ CD45RA− CD8br %T cells, CM-CD3 on naive EM-CD8br, naive AC-CD8br, AC-CD3 lymphocytes, leukocyte% of CD4+ and dimly expressed% of lymphocytes in HLA DR+ T cells. However, TCRgd %T cells and highly expressed markers (CD25++ and dimly expressed) were risk factors for COPD. With the increasing severity of COPD, there are increased percentages of small airways containing immune cells (eg, CD4+, CD8+, B lymphocytes) and lymphoid aggregates consisting of follicles macrophages and neutrophils.[2] Differentiated from undifferentiated T lymphocytes after antigen presentation by T cell receptors (TCRs), the phenotype of surface marker helper T cells primarily assists B-cells to produce antibodies and enhance humoral immunity, and secondarily supports other lymphocyte functions of inflammatory cell activity through releasing cytokines.[17] CD8+ cells represent inhibitory and cytotoxic T lymphocytes that suppress B lymphocyte activity, antibody synthesis and secretion, and T cell proliferation.[18] Therefore, an increase in the population of CD8+ cells is not conducive to antibody production or inflammation control, but signifies a subgroup of cells responsible for clearing infected or damaged cells.[19] CD4+ T lymphocytes, predominantly the Th1 subtype, accumulate in the airway and lung tissue of COPD patients. They are inducers of inflammatory cytokines and chemokines and ultimately lead to emphysema.[20] Besides CD4+ T lymphocytes, CD8+ T lymphocytes (particularly the Tc1 population) also increase in the peripheral blood of COPD patients[21]. Influenced by proinflammatory cytokines, CD4+CD25−Foxp3+-labeled T cells promote the proliferation and differentiation of naive CD4+ T cells into proinflammatory Th17 effector cells in COPD. These specific T cell phenotypes are responsible for lung inflammation via assisting leukotriene formation.[21–23] Regulatory T cells (Tregs) are a specialized subset of CD4+ T lymphocytes expressing CD25, presenting anti-inflammatory and immunomodulatory properties. Upon activation, Tregs inhibit the proliferation of both CD4+ and CD8+T cells through cell-contact dependent mechanisms and the secretion of cytokines (primarily IL-10). The protective function of Tregs in regulating the immune system and inhibiting inflammatory responses, however, is diminished in COPD patients.[24] Maturation (CD45RA, CD45R0) and activation (CD28) patterns on both CD4+ and CDS-T lymphocytes are considered as crucial cellular phenotypes involved in the pathogenesis of COPD[2]. A higher proportion of CD8+CD45RA+ T lymphocytes in the bronchoalveolar lavage fluid (BALF) of COPD patients, that is, a maturation pattern, predicts a greater potential of tissue damage. Down-regulation of CD45RA and up-regulation of CD28 may potentially inhibit the development of COPD,[25,26] which were consistent with our identifications of risk and protective factors for COPD. A phenotype analysis of peripheral blood CD4+T cells in patients experiencing acute exacerbation of COPD (AECOPD) revealed that the abnormal activation patterns of Th1, Th17, and Treg cells, and an imbalance between Th1/Th2 cells altogether contribute to a Th1-dominant enhanced immunoinflammatory response.[27] Both CD4+ and CD8+T lymphocytes increase in either stable or acute COPD patients. Further investigation, nevertheless, is needed to determine the causal relationship between different phenotypes of immune cells and the progression of COPD.

Our findings demonstrated that CD19 expression on CD20− CD38− cells, CD24 expression on memory B cells, CD25 expression on transitional B cells, CD27 expression on CD24+CD27+ cells, and IgD+CD38br %B cells were risk factors for COPD, while the presence of CD19 on IgD−CD38br cells was a protective factor. Plasma cells (PCs) and memory

B cells are two distinct types of lung-resident B cells. The former is capable of producing mainly IgA and IgM antibodies and triggering their secretion into the airway lumen, and the latter generated during the primary lung infection elicits a secondary immune response.[28] LFs formed in responsiveness to the activation of B cells reside in B cells and aggregate in small airways, showing a close association with emphysema in patients with chronic COPD.[29] CD27+ LFs can also be found within the pulmonary parenchyma of COPD patients[30]. Characterized by an excessive activation of B cells in the lungs, emphysema eventually Results in the increase in immature, memory, and antibody-producing B cells, and induces a vicious circle to further exacerbates emphysematous pathology.[31,32] Overexpression of B-cell stimulating factor (BAFF) in LFs causes lung inflammation exacerbation and alveolar destruction through promoting B cell proliferation. Produced by B cells, IL-10 is a cytokine that adds immune responses in neutrophils and macrophages (fuel) to the chronic airway inflammation (flame).[33] IgA produced by B cells impairs mucosal immunity and aggravates the progression of COPD.[34] Currently, the relationship between B cell-mediated immune response and the pathogenesis of COPD remains unclear. B-cell-triggered immunoinflammatory response is generally considered as a vital event accelerating the development of COPD. Therefore, inhibiting B cell activation is a promising therapeutic strategy for COPD.

Our findings suggested that the presence of CD14+ CD16+ monocyte antigen-presenting cells (APCs) and high expression of HLA DR on monocytes were protective factors against COPD. Three subsets of myeloid cells reside in the lungs, namely resident alveolar macrophages (AMs), resident interstitial macrophages (IMs), and blood monocytes.[35] Lung AMs show typical phenotypes of positive CD14 and CD16.[36] They are responsible for clearing alveolar surface active substances, inhibiting adaptive immunity, regulating inflammatory cell recruitment, and generating reactive oxygen species (ROS).[37] In COPD patients, AMs exhibit altered secretion patterns of pro-inflammatory mediators like TNF-α, IL-1β, IL-6, and CCL3 upon TLR stimulation.[38,39] Both monocytes and AMs are potent producers of matrix metalloproteinases (MMPs) that contribute to elastolysis and destruction of alveolar tissue in the lungs.[40] Furthermore, the phenotype of CD14+HLA-DR+ macrophages is the major source of TNF-α. Their detection in sputum samples of COPD patients indicates the involvement of high-level TNF-α in the onset of COPD. Consistently, our findings also highlighted the role of activated AMs in inhibiting the development of COPD.

In the present study, we for the first time unveiled a causal relationship between immune cells and COPD via an MR analysis. Rigorous measures were adopted to exclude SNPs associated with COPD and immune cells from the analysis, minimizing potential confounding effects. In addition, our study provided a relatively large sample size for exposures and results, enhancing its reliability. However, limitations of the study existed. First of all, genetic and immune cell statistics were only from European populations. Our findings may not applicable to other countries and populations. Secondly, the immunophenotype of COPD patients varies with disease severity and stage. Finally, it was a methodology-based analysis, and more extensive longitudinal cohort studies and long-term follow-upobservations are needed to fully evaluate the potential of immune cells in the prevention and treatment of COPD.

In recent years, a dynamic balance between pro-inflammatory and anti-inflammatory signals and the relationship between innate immune cells and adaptive immune cells have been well concerned in the prevention and treatment of COPD. COPD breaks the cross-talk among various immune cells and the balance of pro-inflammatory and anti-inflammatory responses, resulting in chronic airway inflammation, airway remodeling and tissue damage.[41] Fibroblasts increase in the lung tissue of COPD patients, and moreover, Th1/Tc1 cells, Th17 cells, activated B cells, and NK cells present within lung fibroblasts induce specific tissue damage and inflammation. Due to the downregulation or loss-of-function of TGF-β1 (transforming growth factor-beta 1), FOXP3 (forkhead box P3), CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and antioxidants in the lung tissue of COPD patients, an anti-inflammatory response is diminished.[28] Although a complex interaction pattern between the immune system and COPD has been established, immune response processes involved with different immune cell phenotypes remain largely unclear. Through an MR analysis, our study identified risk and protective immune cell traits for COPD while minimizing confounding factors, providing new avenues to the prevention and management of COPD.

Data Sharing Statement

The GWAS summary data were acquired from the publicly accessible online platform (https://gwas.mrcieu.ac.uk/). The analyses of the GWAS summary data were conducted using application R version 4.2.1.

Ethical Approval

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Disclosure

The authors report no conflicts of interest in this work.

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