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Causal association between immune cells and lung cancer risk: a two-sample bidirectional Mendelian randomization analysis

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Background: Previous studies have highlighted the crucial role of immune cells in lung cancer development; however, the direct link between immunophenotypes and lung cancer remains underexplored.

Methods: We applied two-sample Mendelian randomization (MR) analysis, using genetic variants as instruments to determine the causal influence of exposures on outcomes. This method, unlike traditional randomized controlled trials (RCTs), leverages genetic variants inherited randomly at conception, thus reducing confounding and preventing reverse causation. Our analysis involved three genome-wide association studies to assess the causal impact of 731 immune cell signatures on lung cancer using genetic instrumental variables (IVs). We initially used the standard inverse variance weighted (IVW) method and further validated our findings with three supplementary MR techniques (MR–Egger, weighted median, and MR-PRESSO) to ensure robustness. We also conducted MR–Egger intercept and Cochran's Q tests to assess heterogeneity and pleiotropy. Additionally, reverse MR analysis was performed to explore potential causality between lung cancer subtypes and identified immunophenotypes, using R software for all statistical calculations.

Results: Our MR analysis identified 106 immune signatures significantly associated with lung cancer. Notably, we found five suggestive associations across all sensitivity tests (*P*<0.05): CD25 on IgD- CD24- cells in small cell lung carcinoma (OR_{IVW} =0.885; 95% CI: 0.798-0.983; *P*_{IVW} =0.022); CD27 on IgD+ CD24+ cells in lung squamous cell carcinoma (OR_{IVW} =1.054; 95% CI: 1.010- 1.100; *P*_{IVW} =0.015); CCR2 on monocyte cells in lung squamous cell carcinoma (OR_{IVW} =0.941; 95% CI: 0.898-0.987; *P*_{IVW} =0.012); CD123 on CD62L+ plasmacytoid dendritic cells (OR_{IVW} =0.958; 95% CI: 0.924-0.992; *P*_{IVW} =0.017) as well as on plasmacytoid dendritic cells (OR_{IVW} =0.958; 95% CI: 0.924-0.992; *P*_{IVW} =0.017) in lung squamous cell carcinoma.

Conclusion: This study establishes a significant genomic link between immune cells and lung cancer, providing a robust basis for future clinical research aimed at lung cancer management.

KEYWORDS

Mendelian randomization, lung cancer, immune cells, causal relationship, genome-wide association studies

1 Introduction

Lung cancer remains one of the most prevalent malignancies globally, ranking second in incidence and leading in cancer-related deaths (1-3). Due to its significant incidence and mortality, lung cancer represents a critical public health challenge, emphasizing the need for effective preventive strategies (4, 5). Identifying potential causal relationships between risk factors and lung cancer is essential for developing these strategies.

Recent advancements in tumor immunology have underscored the importance of understanding the role of immune cells within the lung cancer microenvironment. This understanding is crucial for advancing immunotherapy drug development. The immune system plays a complex role in tumorigenesis; it can suppress tumor growth by eliminating cancer cells, yet it can also promote tumor progression by providing growth and survival factors. For instance, the presence of CD3+ tumor-infiltrating lymphocytes is associated with improved overall survival (OS) in non-small cell lung cancer (NSCLC) (6) and hepatocellular carcinoma (7). Elevated levels of FoxP3+ Tregs are linked to poorer outcomes in several cancers, including melanoma and breast cancer. Conversely, an improvement in OS has been reported in colorectal and head and neck cancers, with variable results in lung cancer regarding disease-free survival (DFS) (8). B-cell infiltration has shown mixed outcomes across different cancers, enhancing survival in breast cancer (9) but presenting inconsistent results in melanoma, hepatocellular carcinoma, ovarian and head and neck cancers (10). Despite significant progress in immune cell research, the links between immunophenotypes and lung cancer remain inconsistent, often limited by small sample sizes, study design flaws, and unaddressed confounders (11-13). The introduction of genome-wide association studies (GWAS) has been transformative, providing new pathways to investigate cancer etiology (14, 15).

In this context, Mendelian randomization (MR), which uses genetic variants as instrumental variables (IVs) to establish causal relationships between exposures and outcomes, offers a powerful epidemiological tool (16). MR is advantageous because it uses genotypes that are fixed at conception, thus reducing bias from confounding factors and reverse causation (17, 18). This study employs a two-sample MR approach, using single nucleotide polymorphisms (SNPs) to evaluate the causal impact of immune cells on lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung carcinoma (SCLC).

2 Materials and methods

2.1 Study design

Our two-sample MR study design is depicted in Figure 1. The validity of our MR analysis was ensured by meeting three essential criteria: the first criterion confirmed a significant link between the IVs and immunophenotypes. Second, the IVs were free from any relationships with confounding elements. Finally, outside of exposure elements, there was no impact of the IVs on outcomes through other pathways (19).

2.2 Genome-wide association study data sources for lung cancer

We obtained GWAS summary data for lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung carcinoma (SCLC) from J. D. McKay et al. (20) via the IEU-OpenGWAS platform. The study involved 21,363 lung cancer patients, namely, 11,273 LUAD, 7,426 LUSC and 2,664 SCLC patients and 55,483, 55,627, and 21,444 controls (Supplementary Table 1). In the quality assurance stage, SNPs exhibiting suboptimal imputation (R2 < 0.3 or Info < 0.4) or a minor allele frequency greater than 0.01 were excluded. Approximately 8 million SNPs were retained for the GWAS.

2.3 Sources of immunity-wide GWAS data

We sourced comprehensive GWAS data for 731 immunophenotypes from the largest study to date, involving 3,757 Europeans (21). Approximately 22 million SNPs, adjusted for sex and age (including age squared), were genotyped with high-density arrays and imputed employing a reference panel based on Sardinian sequences (22).



Illustrative schematic of the study methodology. GWAS, genome-wide association study; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier test; IV, instrumental variables.

2.4 Selection criteria for IVs for 731 immunophenotypes

To identify sufficient SNPs (number >3) for both exposure and outcome analyses, we selected SNPs with genome-wide suggestive significance ($P < 1 \times 10^{-5}$). This method is frequently utilized in MR research as it encompasses a wider array of variations, particularly when there are limited genome-wide significant SNPs available for analysis (23). Independent SNPs were identified using a clumping process with stringent criteria (r2 < 0.001, window size 10,000 kb) using the European 1000 Genomes reference panel (17). Following steps evaluated the robustness of these IVs in predicting causal effects using the F-test (24). The formula used in the design is outlined in Supplementary Table 2. An F-statistic greater than 10 typically signifies strong IVs, and any immunophenotypes with an F-statistic below 10 were discarded (25). The PhenoScannerV2 database (http://www.phenoscanner.medschl.cam.ac.uk/) was employed to identify and remove SNPs directly linked to cancer and other recognized confounders in cancer progression, such as smoking (26, 27) and alcohol consumption (28). In the reverse MR analysis, the threshold for statistical significance was established at $P < 5 \times 10^{-8}$, using a clumping parameter analogous to that used in the forward-direction analysis.

2.5 MR statistical analysis

In this MR study, we investigated the causal associations between immune cell profiles and different subtypes of lung

cancer (LUAD, LUSC, SCLC) using the standard inverse variance weighted (IVW) approach. We also applied MR-Egger and weighted median methods as supplementary analyses to IVW, especially in scenarios where a significant fraction of variants (up to 50% or less) might originate from potentially invalid IVs (29, 30). Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). To identify any potential horizontal pleiotropy or outliers among the SNPs, we implemented the MR-Egger intercept test (29) and the Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) test (31). The reliability of our MR results was verified using the Cochran Q statistic to evaluate SNP heterogeneity (32). A sensitivity analysis called "leave-one-out" was conducted, where SNPs were sequentially removed. This analysis was complemented by applying the IVW-random method to the remaining set of SNPs to determine the influence of outlying variants on the findings (33). For thorough analysis of heterogeneity, we generated forest and scatter plots. A metaanalysis was then undertaken to elucidate the causal connections between the identified immunophenotypes and lung cancer subtypes by synthesizing MR data from two distinct cohorts (34). In instances of significant heterogeneity or pleiotropy, adjustments were made to the ORs and CIs for the meta-analysis. Based on the degree of heterogeneity observed, the choice was between a fixedeffects model (I2 \leq 50%) and a random-effects model (I2 > 50%). The conclusions from the meta-analysis were considered the definitive causal relationships (35). To address concerns of multiple testing, a Bonferroni-corrected significance threshold of 6.84×10^{-5} (0.05/731 for the 731 immunophenotypes evaluated) was employed. P values between $6.84 \times 10-5$ and 0.05 were deemed indicative of suggestive causal links between the exposures and

outcomes. All analyses were conducted using the "TwoSampleMR" and "MRPRESSO" packages in R (version 4.2.0).

3 Results

3.1 Selection of IVs

Our two-sample MR analysis identified 106 immunophenotypes with IVs ranging from 4 to 103 SNPs, indicating suggestive associations at P<0.05. The IVs for each phenotype showed high potency, with F-statistics ranging from 19.546 upwards, confirming their reliability for MR studies.

3.2 Causal effects of immunophenotypes on 3 lung cancer subtypes

Using the IVW method, significant associations were found between 36 immunophenotypes and lung adenocarcinoma (LUAD), 33 with lung squamous cell carcinoma (LUSC), and 37 with small cell lung carcinoma (SCLC), as detailed in Figure 2 and Supplementary Table 3. Notably, certain immunophenotypes such as CD4 Treg %T cells in LUAD (OR_{IVW} =1.071; 95% CI: 1.015-1.131; P_{IVW} =0.013), Unsw mem AC in LUSC (OR_{IVW} =1.134; 95% CI: 1.047–1.228; P_{IVW} =0.002), and CD25 on CD4+ T cells in SCLC (OR_{IVW} =1.174; 95% CI: 1.053–1.310; P_{IVW} =0.004) were associated with increased risk, while CD27 on IgD- CD38br cells (OR_{IVW} =0.909; 95% CI: 0.841–0.984; P_{IVW} =0.018), SSC-A on HLA DR+ CD8br cells (OR_{IVW} =0.897; 95% CI: 0.824–0.977; P_{IVW} =0.012) and CD25 on resting Treg cells (OR_{IVW} =0.840; 95% CI: 0.733-0.963; $P_{\rm IVW}$ =0.013) showed protective effects across different subtypes (Table 1; Supplementary Figures 1-4). Additionally, the presence of CD27 on CD24+ CD27+ cells was associated with an increased risk across all three lung cancer subtypes (for LUAD, OR_{IVW} =1.039; 95% CI: 1.006–1.072; P_{IVW} =0.019; for LUSC, OR_{IVW} =1.041; 95% CI: 1.003–1.080; P_{IVW} =0.032; for SCLC, OR_{IVW} =1.072; 95% CI: 1.010– 1.137; P_{IVW} =0.022). Similarly, CD27 on memory B cells also showed increased risks for lung cancer subtypes (for LUAD, OR_{IVW} =1.047; 95% CI: 1.009–1.086; *P*_{IVW} =0.014; for LUSC, OR_{IVW} =1.053; 95% CI: 1.008–1.099; P_{IVW} =0.020; for SCLC, OR_{IVW} =1.093; 95% CI: 1.002– 1.192; P_{IVW} =0.045). The results imply a shared biological pathway among these subtypes of lung cancer, influenced by CD27 expression on CD24+ CD27+ cells and memory B cells, as outlined in Table 2 and Supplementary Figures 5-8. The genetic variants that clarify the links between these immunophenotypes and lung cancer are detailed in Supplementary Tables 4-15.

3.3 Sensitivity and pleiotropy analysis

Due to potential biases from weak instruments in the IVW approach, we expanded our study to incorporate additional sensitivity and pleiotropy assessments, with detailed findings listed in Supplementary Table 3. Noteworthy, pleiotropic effects were observed for SSC-A on HLA DR+ CD8br cells in LUSC (P_{MR} -

PRESSO Global =0.039). The combined outcomes from IVW, MR-Egger, and weighted median methods across immunophenotypes with suggestive links are displayed in Figure 3. Furthermore, we discerned five immunophenotypes with suggestive links that passed all sensitivity analyses (P<0.05) (Table 3; Supplementary Figures 9-12): CD25 on IgD- CD24- cells in SCLC (OR_{IVW} =0.885; 95% CI: 0.798–0.983; P_{IVW} =0.022), CD27 on IgD+ CD24+ cells in LUSC (OR_{IVW} =1.054; 95% CI: 1.010-1.100; P_{IVW} =0.015), CCR2 on monocyte cells in LUSC (OR_{IVW} =0.941; 95% CI: 0.898-0.987; P_{IVW} =0.012), CD123 on CD62L+ plasmacytoid dendritic cells (DCs) of LUSC (OR_{IVW} =0.958; 95% CI: 0.924-0.992; P_{IVW} =0.017), and CD123 on plasmacytoid DCs of LUSC (OR_{IVW} =0.958; 95% CI: 0.924-0.992; P_{IVW} =0.017). Additional validation through MR analysis utilized GWAS data for SCLC (ieua-988: 2,791 patients and 20,580 controls) and LUSC (ieu-a-989: 7,704 patients and 54,763 controls), with results detailed in Supplementary Tables 16, 17. Genetic variants clarifying the associations between these five immunophenotypes and lung cancer are summarized in Supplementary Tables 18-22. In reverse MR analyses, a suggestive link was observed for LUSC risk and CCR2 on monocyte cells (OR_{IVW} =0.888; 95% CI: 0.790-0.999; $P_{\rm IVW}$ =0.048). Lung cancer subtypes with at least two robust MR findings were included in the meta-analysis, whose results are compiled in Supplementary Table 23. Four immunophenotypes demonstrated a suggestive correlation with LUSC risk: CD27 on IgD+ CD24+ cells (OR = 1.0567; 95% CI: 1.0263 to 1.0880; P = 0.0002), CCR2 on monocyte cells (OR = 0.9483; 95% CI: 0.9238 to 0.9735; P < 0.0001), CD123 on CD62L+ plasmacytoid DCs (OR = 0.9629; 95% CI: 0.9414 to 0.9850; P = 0.0011), and CD123 on plasmacytoid DCs (OR = 0.9630; 95% CI: 0.9414 to 0.9850; P = 0.0011). Additionally, CD25 on IgD- CD24- cells was linked to a decreased risk of SCLC (OR = 0.8701; 95% CI: 0.8175 to 0.9260; P < 0.0001). The findings indicate the reliability of the causal relationship between the identified immune phenotype and subtypes of lung cancer.

4 Discussion

This MR study marks a significant advance in understanding the causal effects of immune cell signatures on lung cancer, focusing on three specific subtypes. Leveraging a robust two-sample MR framework that incorporates IVW, MR-Egger, and weighted median approaches, our study advances beyond earlier observational research that predominantly concentrated on correlations (36, 37). By utilizing the most comprehensive GWAS datasets currently available for the immunophenotyping of peripheral blood, our research significantly enhances the investigation into the connections between immune cells and disease, expanding the scope further than prior studies (38, 39). Moreover, we utilized meta-analysis to consolidate data from multiple studies, thereby enhancing the robustness of our conclusions. The discovery of 106 immune signatures, particularly five key associations such as CD25 on IgD- CD24- cells in SCLC and CCR2 on monocyte cells in LUSC, enriches our understanding of these cells' causal involvement in lung cancer.

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0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 0.001 <td< td=""><td>CD20 on momony B coll</td><td>20</td><td>0.0255</td><td>lan lan</td><td>1 0212 (1 0028 1 0506)</td><td>Granulocyte %leukocyte</td><td>23</td><td>0.0365</td><td></td><td>0.9441 (0.8945 - 0.996</td></td<>	CD20 on momony B coll	20	0.0255	lan lan	1 0212 (1 0028 1 0506)	Granulocyte %leukocyte	23	0.0365		0.9441 (0.8945 - 0.996
Dubble state Dubble state<	CD20 on memory B cell	22	0.0200		1.0515 (1.0030 - 1.0350)	CD28+ CD45RA- CD8br AC	27	0.0145	101	0.9662 (0.9400 - 0.993
Control Si Bit File 1 (Sing 1100-1100) Control Sing 1100-1100 Sing 1100-1100 Sing 1100-1100 Control Control Sing 1100-1100 Control Control Control Control Sing 1100-1100 Control Contro Control Control	CD25 on unsw mem	15	0.0188		1.0536 (1.0087 - 1.1005)	CD27 on CD24+ CD27+	28	0.0322		1.0411 (1.0034 - 1.080
CDT of CDT of Up: CDT	CD27 on CD20-	28	0.0191	101	1.0386 (1.0062 - 1.0720)	CD27 on InD+ CD24+	29	0.0103	and a second	1 0543 (1 0104 - 1 100
Corr a go Colles Corr a go Co	CD27 on CD24+ CD27+	14	0.0181		0.9095 (0.8407 - 0.9839)	0007 - 1-D- 0000	20	0.0100	has	1.0540 (1.0104 1.100
Carry many and Carry many and phot maximum 24 0.019 400 0.009 400 0.009 400 0.009 400 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 <	CD27 on IgD- CD38br	28	0.0247		1.0416 (1.0052 - 1.0792)	CD27 on IgD+ CD38- unsw mem	23	0.0045		1.0532 (1.0162 - 1.091
Card P = memory E ad 2 4 Cost P = memory E ad 2 5 Cost P = memory E	CD27 on InD- CD38dim	24	0.0141		1 0471 (1 0093 - 1 0863)	CD27 on IgD- CD38-	28	0.0219		1.0606 (1.0086 - 1.115
Market Markt Markt Markt <td>CD27 on memory B cell</td> <td>24</td> <td>0.0360</td> <td></td> <td>0.0424 (0.9025 0.0004)</td> <td>CD27 on IaD- CD38dim</td> <td>29</td> <td>0.0438</td> <td>101</td> <td>1.0424 (1.0012 - 1.085</td>	CD27 on memory B cell	24	0.0360		0.0424 (0.9025 0.0004)	CD27 on IaD- CD38dim	29	0.0438	101	1.0424 (1.0012 - 1.085
up on instructural up on i	CD27 on memory B cell	24	0.0369		0.9431 (0.8923 - 0.9964)	CD27 on momony B coll	22	0.0202	-	1 0509 (1 0090 1 000
Cd on MxT 17 0.029 0.081 (022 - 010) 0.027 (0 mm mm 2 2 0.002) 0.003 (022 - 010) Cd on MxT CDB 20 0.029 0.029 0.027 (0 mm mm 2 2 0.002) 0.029 (0 mm 2 1 0 0.002) Cd on MxT CDB 20 0.029 0.029 0.027 (0 mm mm 2 2 0.002) 0.029 (0 mm 2 1 0 0.002) Cd on MxT CDB 20 0.029 0.029 0.029 (0 mm 2 1 0 0.002) 0.029 (0 mm 2 1 0 0.002) Cd on MxT CDB 20 0.029 0.029 (0 mm 2 1 0 0.002) 0.029 (0 mm 2 1 0 0.002) 0.029 (0 mm 2 1 0 0.002) Cd on MxT CDB 30 0.029 (0 mm 2 1 0 0.002) 0.029	igu on transitional	14	0.0161		0.9280 (0.8733 - 0.9862)	CD27 OF Memory B Cell	20	0.0203		1.0020 (1.0000 - 1.099
HAM and Dother 9 00444 0 0.0556 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-101) 00040 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (0004-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-1000) 0.0056 (000-10000) 0.0056 (000-1000) 0.0056 (000-1	CD3 on NKT	17	0.0239	101	0.9581 (0.9232 - 0.9944)	CD27 on unsw mem	26	0.0031		1.0773 (1.0254 - 1.131)
0277 must CDB/ 0285 multiple 0 0.000 1.005 (1003-1.108) 0.017 (1073-1.108) 0.017 (1073-1.08) 0.017 (1073-1.08) 0.010	HVEM on EM CD8br	16	0.0146	101	0.9595 (0.9283 - 0.9919)	CD27 on sw mem	27	0.0089	1-0-1	1.0575 (1.0141 - 1.102)
CO30	CCR7 on naive CD8br	20	0.0240		1.0635 (1 0081 - 1 1218)	CD38 on IoD- CD38dim	16	0.0422		0.9550 (0.9134 - 0.009
Control Control <t< td=""><td>CD25 on CD45RA+ CD4 not Tree</td><td>21</td><td>0.0052</td><td>lane.</td><td>1.0591 (1.0172 1.1020)</td><td>In Directory (Inc.)</td><td></td><td>0.0422</td><td></td><td>0.0477 /0.0700 0.000</td></t<>	CD25 on CD45RA+ CD4 not Tree	21	0.0052	lane.	1.0591 (1.0172 1.1020)	In Directory (Inc.)		0.0422		0.0477 /0.0700 0.000
Cube of Emily (10) 19 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 00.000 <th< td=""><td>OD25 OIL CD45RAT CD4 NOL Treg</td><td>21</td><td>0.0052</td><td>and a second</td><td>1.0091 (1.0173 - 1.1026)</td><td>IgD on transitional</td><td>2/</td><td>0.0140</td><td></td><td>0.9177 (0.8569 - 0.982)</td></th<>	OD25 OIL CD45RAT CD4 NOL Treg	21	0.0052	and a second	1.0091 (1.0173 - 1.1026)	IgD on transitional	2/	0.0140		0.9177 (0.8569 - 0.982)
FSC-Ad spatialized 19 0.0245 0.0242 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.0243 0.024	CD25 on resting Treg	19	0.0238	H	0.9417 (0.8939 - 0.9920)	CD28 on CD39+ activated Treg	18	0.0164		1.0521 (1.0093 - 1.096
CitC2: Distancy Sub Cit 19 0.027 1.0661 (001-1.006) CitC2: Distancy Sub Cit 10 0.022 1.0661 (001-1.006) 10 0.017 0.017 0.017 0.017 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 <td>FSC-A on granulocyte</td> <td>19</td> <td>0.0245</td> <td>Here</td> <td>0.9482 (0.9053 - 0.9932)</td> <td>CD28 on resting Treg</td> <td>4</td> <td>0.0156</td> <td></td> <td>1 1061 (1 0193 - 1 200</td>	FSC-A on granulocyte	19	0.0245	Here	0.9482 (0.9053 - 0.9932)	CD28 on resting Treg	4	0.0156		1 1061 (1 0193 - 1 200
C1C22 crO204 - plasmagned DC 19 00024 - plasmagned DC 19 00024 - plasmagned DC 19 0014 - 0004 19 0014 - 0004 0014 - 0	CCR2 on plasmacytoid DC	19	0.0237	104	1.0465 (1.0061 - 1.0886)	CD122 on plasma trid DC	16	0.0474		0.0577 (0.0044 0.000
CD22 CD23 CD23 <th< td=""><td>CCR2 on CD62L+ plasmacytoid DC</td><td>18</td><td>0.0252</td><td></td><td>1.0465 (1.0057 - 1.0890)</td><td>CD 123 ON plasmacytola DC</td><td>10</td><td>0.0174</td><td></td><td>0.9577 (0.9241 - 0.992</td></th<>	CCR2 on CD62L+ plasmacytoid DC	18	0.0252		1.0465 (1.0057 - 1.0890)	CD 123 ON plasmacytola DC	10	0.0174		0.9577 (0.9241 - 0.992
Contact Contact (Contact (CCR2 on granulocyte	17	0.0232		1 0547 (1 0073 - 1 1043)	CD123 on CD62L+ plasmacytoid DC	16	0.0174	101	0.9576 (0.9240 - 0.9924
La un manu cut la de la cut Size ALA DE CO H 19 00029 ALD CO H 10 0001 ALD CO H 10 00001 ALD CO H 10 0000 ALD CO H 10 0000 ALD CO H 10	CD4 as asias CD4 :	49	0.0232	-	0.0119 (0.0075 - 0.0563)	CCR2 on monocyte	19	0.0120	HEH	0.9414 (0.8980 - 0.986
Colls and Colls Hu, Dire Hu, Dire Colls Hu, Dire Co	CD4 on naive CD4+	18	<0.001	and a little state	0.9118 (0.8675 - 0.9584)	CD8 on pairs CD8br	16	0.0284		1 0841 (1 0042 1 170
Calis an Calis And Annu Calis And Annu Calis And Annu Annu Annu Annu Annu Annu Annu	CD45 on CD33br HLA DR+ CD14-	15	0.0279	-	0.9469 (0.9020 - 0.9941)	CDo on haive CDobi	10	0.0304		1.0041 (1.0043 - 1.170
Chill to make yield 15 0.0044 0.0487 (0.0877 - 0.980) SSC-A on HLA DR* TOR 17 0.0124 0.0577 (0.2528 - 0.677 HLA DR* Toroll 16 0.0346 0.0487 (0.0978 - 0.086) HLA DR* Toroll 21 0.0377 10734 (1.522 - 1.12 SpC Collex FLA 20 0.0356 0.0565 (0.788 - 0.884) 10757 (1.004 - 1.150) 10757 (1.007 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.978) 0.557 (0.778 - 0.988) 0.577 (0.778 - 0.988) 0.577 (0.778 - 0.988) 0.577 (0.778 - 0.988)	CD45 on CD33br HLA DR+ CD14dim	14	0.0494	-	0.9505 (0.9036 - 0.9999)	SSC-A on lymphocyte	18	0.0109		0.9033 (0.8352 - 0.976
HADRen HADRen Table 19 0.004 0.004 0.004 0.004 0.004 10734 (10232 - 112 Rek Anders ADLO. Nember of SHP pol 004 (95% C) 10736 (1008 - 1150) 004 (95% C) 10736 (1008 - 1150) GOD Colds Nok 20 0.005 0.004 10736 (1008 - 1150) 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.005 0.004 0.004 0.005 0.004 0.004 0.005 0.004 0.004 <td>CD11b on basophil</td> <td>15</td> <td>0.0094</td> <td></td> <td>0.9403 (0.8977 - 0.9850)</td> <td>SSC-A on HLA DR+ CD8br</td> <td>17</td> <td>0.0124</td> <td></td> <td>0.8971 (0.8238 - 0.976</td>	CD11b on basophil	15	0.0094		0.9403 (0.8977 - 0.9850)	SSC-A on HLA DR+ CD8br	17	0.0124		0.8971 (0.8238 - 0.976
Reduction (notice from the Construction of the Construc	HIADR on HIADR+T cell	18	0.0346	-	0.9478 (0.9019 - 0.9961)	HIADR on B cell	21	0.0037	and and	1 0734 (1 0232 - 1 126
2020-CD38-Nymphocyte 1 0.0109 0.8721 (0.797 - 0.976) CD42L-monocyte AC 17 0.0017 0.874 (0.877 - 0.976) CD42L-monocyte AC 17 0.0017 0.874 (0.877 - 0.976) EN CD8H*/NCD8H 22 0.0032 0.933 (0.874 - 0.966) CD4+ CD8Im AC 17 0.0024 0.9016 (0.817 - 0.917) CD4+ CD8Im AC 17 0.0024 0.9016 (0.817 - 0.917) CD4+ CD8Im AC 17 0.0024 0.8031 (0.808 - 1.128) NK AC 0.0024 0.8031 (0.808 - 1.128) 0.8031 (0.808 - 1.128) CD20 mb2 CD3E-mW 10.0024 (1.008 - 1.0043) 0.8073 (0.808 - 0.9710) CD25 mb2 CD3E-mW 10.0024 (1.008 - 1.0043) 0.8073 (0.810 - 0.9710) CD25 mb2 CD3E-mW 10.0024 (1.008 - 1.0043) 0.8073 (0.810 - 0.9710) CD25 mb2 CD3E-mW 10.0024 (1.008 - 1.0043) 0.8073 (0.810 - 0.9710) CD25 mb2 CD3E-mW 10.0024 (1.008 - 1.0043) 0.8073 (0.810 - 0.9710) CD25 mb2 CD3E-mW 10.0024 (1.008 - 1.0041) 1.8081 (1.008 - 1.0083) CD25 mb2 CD3E-mW 10.0024 (1.008 - 1.0041) 1.8081 (1.008 - 1.0042) CD25 mb2 CD3E-mW 10.0024 1.8074 (1.0040 - 1	IgD- CD38br AC	20 0.	.0365	_	OR (95% CI) 1.0763 (1.0046 - 1.1530)					
LCub Class minipality 2 2 0010 0077 (0077-0080) Secreting Trey AC 19 0008 0077 (0078-0080) Clobe MCOBE* (SCORE * 17 0007 Clobe MCOBE* AC 2 0082 0000 0078 (0087-0097) Clobe MCOBE* AC 2 0082 0000 0078 (0088-10980) Clobe MCOBE* MCOBE* (SCORE * 17 0003 Clobe MCOBE* MCOBE* Tell 00000 0078 (0089-11280) NK AC 19 0002 0008 0078 0081 1008 11280) Clobe MCOBE* MCOBE* Tell 00000 0078 (0089-11280) Clobe MCOBE* MCOBE* Tell 00000 0078 (0089-11180) Clobe MCOBE* MCOBE* Tell 00000 0078 (0089-11180) Clobe MCOBE* MCOBE* Tell 00000 0078 (0089-11180) Clobe MCOBE* Tell 00000 0078 (0089-0000) HYEM MCOBE* Tell 00000 0078 (00890) HYEM MCOBE* Tell 00000 00000 0078 (00890) HYEM MCOBE* Tell 00000 00000 0000000000000000000000	IgD- CD38br AC CD20- CD38- %B cell	20 0. 21 0.	.0365 .0258		OR (95% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) 1.1554 (1.0333 - 1.2030)					
Cubac. Monocyle AC 17 0 0.017 0 0.027 1 0.0270 1 0.0276 (0.002-0.0036) EM COBer K-CoBer 2 0 0.033 0 0.039 0 0.0336 (0.6745-0.0966) EM COBer K-CoBer 3 0 0.039 0 0.039 0 0.0396 (0.689-0.0927) CO4-AC 3 0 0.033 0 0.049 0 0.036 0 0.0470 0 0.0397 (0.689-0.0927) CO4-COBer K-CoBer X-C 3 0 0.024 0 0.0336 0 0.0474 0 0.0563 (0.008-1.0265) HLA DR-COBer X-C 3 0 0.024 0 0.036 0 0.0474 0 0.0563 (0.008-1.0265) CO4-COBer M-CoBer X-C 3 0 0.024 0 0.036 0 0.0771 0 0.0431 CO25 on igD-COB- maine 18 0 0.025 0 0.0274 0 0.0376 (0.089-1.0043) CO25 on igD-COB- maine 19 0.0268 0 0.0271 0 0.0258 (0.008-1.0043) CO25 on igD-COB- maine 19 0.0268 0 0.0271 0 0.044 0 0.0775 0.0813) CO25 on igD-COB- maine 19 0.0268 0 0.0271 0 0.0061 (0.004-1.0365) CO25 on igD-COB- maine 19 0.0268 0 0.0271 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0 0.0071 0	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38dim AC CD20- CD38 %lymphoside	20 0. 21 0. 17 0.	.0365 .0258		OR (95% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) 1.1554 (1.0333 - 1.2920) 0.8721 (0.7372 - 0.9768)					
Secreting Treg AC EM COBer (ACDE) EM COBer (ACDE) EM COBER (ACDE) EM COBER (ACDE) EM COBER (ACDE) EM COBER (ACDE) EM COBER (ACDE) CO4 AC CO4 ACDE CO4 ACDE	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38dim AC CD20- CD38- %lymphocyte	20 0. 21 0. 17 0. 21 0.	.0365 .0258		OR (95% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) → 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9768) 0.6724 (0.2027 - 0.9768)					
EM COBer % COBer % COBer % COBer % COBer % COBer % COB	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38dim AC CD20- CD38- %lymphocyte CD62L- monocyte AC	20 0. 21 0. 17 0. 21 0. 17 0. 17 0.	0365 0258		OR (95% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) → 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9768) 0.8764 (0.8070 - 0.9519)					
EM CBer % Teal 13 0.279 0 0.279 0.0829 0.0869 0.0920 C04 AC 204 AC 20 0.050 0 0.001 0.0970 C04 AC 204 AC 205 AC	IgD- CD38br AC CD20- CD38-%B cell IgD- CD38dim AC CD20- CD38-%lymphocyte CD62L- monocyte AC Secreting Treg AC	20 0. 21 0. 17 0. 21 0. 17 0. 17 0. 19 0.	0365 0258		OR (95% Cl) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) ■ 1.1554 (1.0333 - 1.2920) 0.8724 (0.7787 - 0.9768) 0.8764 (0.8070 - 0.9519) 1.0508 (1.0126 - 1.0905)					
C04 + AC 20 0.030 0.032 0.0310 0.032 HLA DR* COBer AC 30 0.024 0.035 0.035 0.035 NK AC 19 0.022 0.0330 0.035 0.035 0.035 OLSPRA-CD28-CD8b* r%T cell 10 0.044 0.0237 0.075 0.9810 CD25 nigb*-CD28-unswmm 18 0.098 0.08710 0.088710 0.08710 CD25 nigb*-CD24- 28 0.021 0.08710 0.088710 0.088710 CD25 nigb*-CD24- 28 0.021 0.088710 0.088710 0.088710 CD27 cn igb*-CD38- 27 0.0070 0.088710 1.09801 0.088710 CD27 cn igb*-CD34- 28 0.021 0.04111.11880 0.02871 0.0211 0.0087 CD27 cn igb*-CD34- 27 0.042 0.0412 1.0871(10001-1.1374) 0.021 0.0411.11880 0.0231 CD27 cn igb*-CD34- 27 0.042 0.0411 0.0451 0.0411 0.0411.021 0.0411.021 0.0411.021 0.0411.021 0.0411.021 0.0411.021.0111.0111.011.011.011.011.011.011	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38dim AC CD20- CD38- %lymphocyte CD62L- monocyte AC Secreting Treg AC EM CD8br %CD8br	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0.	0365 0258 0112 0180 0017 0088 0392		OR (95% Cl) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) → 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9768) 0.8764 (0.8070 - 0.9519) 1.0508 (1.0126 - 1.0005) 0.9335 (0.8745 - 0.9966)					
C04-C08im AC 17 0.032 1.1039 (1.009 - 1.2095) HLA DR* C08im AC 19 0.024 0.9735 (0.775 - 0.9813) C045RA-C122-C08im K/LC22-C08im K/LC22-C08im K/LC22-C08im K/LC22-C08im K/LC22-C08im K/LC22-C08im K/LC22-C08im K/LC22-C02im LC22-C02im C02-C02im C02im	IgD- CD38br AC CD20- CD38-%B cell IgD- CD38aim AC CD20- CD38-%lymphocyte CD62L- monocyte AC Secreting Treg AC EM CD8br %CD8br EM CD8br %T cell	20 0. 21 0. 17 0. 17 0. 17 0. 19 0. 22 0. 13 0.	0365 0258 ••• 0112 0180 ••• 00017 ••• 0088 0392 •• 0279 ••		OR (95% Cl) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) → 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9768) 0.8764 (0.8070 - 0.9519) 1.0508 (1.0126 - 1.0905) 0.9335 (0.8745 - 0.9966) 0.9289 (0.8698 - 0.9920)					
HA DR: COBin AC 90 0.0249 0.0053 (10000 - 1.1289) NK AC 193 0.0044 0.0527 (10000 - 1.043) CD25 Angb - CD38- max mmm 18 0.0034 0.8873 (0.816 - 0.971) CD25 Angb - CD38- max mmm 18 0.0034 0.8873 (0.816 - 0.971) CD25 Angb - CD38- max mmm 18 0.0034 0.8873 (0.816 - 0.971) CD25 Angb - CD38- max mmm 19 0.0064 0.8873 (0.816 - 0.971) CD25 Angb - CD38- max mmm 19 0.0064 0.8873 (0.816 - 0.987) CD25 Angb - CD38- max mmm 19 0.0064 0.8873 (0.816 - 0.987) CD25 Angb - CD38- max mmm 19 0.0064 0.8873 (0.716 - 0.987) CD27 Angb - CD38- 27 0.0070 1.081 (1.024 + 1.189) CD27 Angb - CD38- 27 0.0070 1.087 (1.000 - 1.134) CD27 Angb - CD38- 18 0.4452 0.9491 (0.886 - 0.9980) HVEM AN CD CD4+ 14 0.4452 0.9491 (0.886 - 0.9980) CD28 An CD28 - CD4+ 13 0.0031 0.8573 (0.776 - 0.9890) CD28 An CD28 - CD4+ 13 0.0031 0.8593 (0.7864 - 0.9983) CD28 An CD28 - C	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38lim AC CD20- CD38- %Wymphocyte CD82L- monocyte AC Secreting Treg AC EM CD8br %CD8br EM CD8br %CD8br CD49- KC CD40- CD4- AC	20 0 21 0 17 0 21 0 17 0 19 0 22 0 13 0 20 0	0365 0258		OR (85% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7558 - 0.9854) 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9788) 0.8764 (0.8070 - 0.5619) 0.8764 (0.8070 - 0.5619) 0.8355 (0.8745 - 0.9986) 0.9328 (0.8686 - 0.9920) 0.9316 (0.8197 - 0.9917)					
NK AC 19 0.022 0.873 (0.1004 - 1.043) CD4 FAR-CD28-CD8br WT cell 103 0.044 1.0025 (1000 - 1.043) CD25 on 1g0- CD38- unsw mem 18 0.087 (0.0114 - 1.080) CD25 on 1g0- CD38- aniav 19 0.0064 0.087 (0.0114 - 1.080) CD25 on 1g0- CD24- 25 0.021 0.884 (0.7977 - 0.827) CD27 on 1g0- CD34- 25 0.021 0.884 (0.7977 - 0.827) CD27 on 1g0- CD34- 25 0.021 0.884 (0.7977 - 0.827) CD27 on 1g0- CD34- 25 0.021 0.885 (0.776 - 0.823) CD3 on HLD AFT cell 21 0.0367 1.0874 (1.0004 - 1.134) CD3 on macry B cell 22 0.485 0.9980) HVEM on CD4+ 14 0.4926 0.9401 (0.885 - 0.9980) HVEM on CD4+ 13 0.081 0.8968 (0.8208 - 0.9799) CD28 on CD4+ 23 0.047 0.8986 (0.8208 - 0.9799) CD26 on costs/ 17 0.018 0.8973 (0.8176 - 0.9893) CD26 on CD4+ 13 0.0397 0.8910 (0.8776 - 0.893) CD26 on CD4+ 13 0.9307 (0.8176 - 0.9893)	IgD- CD38r AC C222- CD38- %B cell IgD- CD38dim AC CD20- CD38- %lymphocyte CD22- monocyte AC CD22- monocyte AC EM CD8br %CD8br EM CD8br %C cell CD4+ CD8tim AC	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0. 13 0. 20 0. 17 0.	0365 0258 - 0112 0180 - 0017 - 0088 0392 - 00279 - 00330 - 00352		OR (65% CI) 1.0783 (1.0046 - 1.1530) 0.8855 (0.7958 - 0.9854) 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9768) 0.8724 (0.7477 - 0.9768) 0.8754 (0.8070 - 0.9519) 1.0508 (1.0128 - 1.0905) 0.9335 (0.8474 - 0.9966) 0.9326 (0.8474 - 0.9966) 0.9326 (0.8698 - 0.9920) 0.9016 (0.8197 - 0.9917) 1.1036 (1.0069 - 1.2095)					
CD4RA-CD28-CD8br %T cell 103 0.0044 10025 (1000 - 1.0043) CD25 on 1g0- CD38- 22 0.038 0.8873 (0.816 - 0.971) CD25 on 1g0- CD38- 22 0.038 0.8854 (0.7977 - 0.9827) CD27 on CD28- rusy 28 0.0221 0.8854 (0.7977 - 0.9827) CD27 on CD28- rusy 28 0.0221 0.8854 (0.7977 - 0.9827) CD27 on CD28- rusy 28 0.0221 0.8854 (0.7977 - 0.9827) CD27 on CD28- rusy 28 0.0221 0.8854 (0.7977 - 0.9827) CD27 on CD29- DD3 22 0.0452 0.0452 CD3 on HLA DR+ T cell 21 0.0367 0.990() HVEM on CD4+ 14 0.0465 0.9357 (0.876 - 0.990) HVEM on CD4+ 14 0.0426 0.9305 (0.8864 - 0.9963) CD28 on CD28+ CD4+ 23 0.0479 0.9305 (0.8864 - 0.9963) CD28 on CD28+ CD4+ 13 0.0469 0.9305 (0.8864 - 0.9963) CD25 on CD4+ 13 0.0379 0.9307 (0.8614 - 0.9833) CD25 on CD4+ 13 0.0399 0.9210 (0.8876 - 0.9863) CD25 on CD4+ 13 0.0399 0.9210 (0.8	IgD- CD38br AC CD20- CD38- %B cell [gD- CD38im AC CD20- CD38- %Wymphocyte CD82L- monocyte AC Secreting Treg AC EM CD8br %CD8br MCD8br %CD8br EM CD8br %C CB8C CD4- CD8dim AC HLA DR+ CD8br AC	20 0. 21 0. 17 0. 21 0. 17 0. 17 0. 18 0. 22 0. 13 0. 20 0. 17 0. 30 0.	0365 0258 0112 0180 0017 0088 0392 0279 0330 0352 0249		OR (85% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7586 - 0.9864) 1.1554 (1.0333 - 1.2920) 0.8764 (0.8070 - 0.9519) 0.8764 (0.8070 - 0.9519) 0.8764 (0.8688 - 0.9920) 0.9269 (0.8688 - 0.9920) 0.9016 (0.8197 - 0.9917) 1.1056 (1.0068 - 1.2925) 1.0656 (1.0060 - 1.1258)					
Conserved Case Could and Case	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38im AC CD20- CD38- %Iymphocyte CD82L - monocyte AC Secreting Treg AC EM CD8br %T cell CD4+ AC CD4+ CD8br %T cell CD4+ CD8br AC HLA RF+ CD8br AC NK AC	20 0. 21 0. 17 0. 19 0. 22 0. 13 0. 20 0. 17 0. 13 0. 20 0. 17 0. 30 0. 19 0.	0365 0258 • • • • • • • • • • • • • • • • • • •		OR (85% CI) 10733 (1046 - 11530) 0.855 (0.7958 - 0.9854) ■ 11554 (1033 - 12920) 0.8721 (0.7787 - 0.9768) 0.8724 (0.8777 - 0.9768) 0.8764 (0.8070 - 0.9519) 1.0508 (10128 - 1.9905) 0.9335 (0.8745 - 0.9966) 0.9229 (0.8698 - 0.9920) 0.9016 (0.8197 - 0.9917) 1.1036 (1.068 - 1.2085) 1.6533 (1.0080 - 1.2288) 0.8735 (0.775 - 0.813)					
Cu2co ingbr Cu2se uniwmem 16 0.003 0.0033 (0.010 - 0.971) C025 in gbr C038- 2 0.023 1.0491 (1060 - 1.036) C025 in gbr C038- 25 0.0221 0.0824 (0.977 - 0.9827) C027 on C024 + C027+ 28 0.0221 0.0824 (0.977 - 0.9827) C027 on memory Bell 22 0.0462 1.0927 (1000 - 1.1374) C027 on memory Bell 22 0.0462 0.9357 (0.876 - 0.9860) HVEM on CLO14 14 0.0467 0.9357 (0.876 - 0.9860) HVEM on CLO24+ 22 0.021 0.9471 (0.968 - 0.9860) HVEM on CLO4+ 14 0.0465 0.9357 (0.876 - 0.9860) HVEM on CLO4+ 14 0.0465 0.9357 (0.876 - 0.9860) HVEM on CLO4+ 14 0.0465 0.9357 (0.876 - 0.9860) CD26 on myeloid DC 16 0.222 (0.022 - 0.0276 - 0.8631) CD26 on CD28+ CD4+ 13 0.0081 0.9305 (0.8664 - 0.9983) CD25 on cSID 17 0.016 0.9470 (0.858 - 0.9893) CD25 on CD4+ 13 0.028 0.9210 (0.877 - 0.8631) CD25 on CD4+ 13 0.028 (0.278 - 0.8982)	IgD- CD38r AC CD20- CD38- %B cell IgD- CD38im AC CD20- CD38- %Wmphocyte CD20- CD38- %Wmphocyte CD20- CD38- %D00F CD24- monocyte AC Secreting Treg AC EM CD8br %CD8br CD4- CD36- %T cell CD4+ AC CD4+ AC CD4- CD8br AC NK AC CM45Ba- CD38- CD38- CP38- 54-54-54	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0. 13 0. 20 0. 17 0. 30 0. 19 0. 19 0. 17 0. 19 0. 19 0. 10	0365 0258 0112 00180 0017 0088 0392 0279 0330 0352 0249 0227		OR (85% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7558 - 0.98634) 1.1554 (1.0333 - 1.2920) 0.8724 (0.8370 - 0.9768) 0.8764 (0.8070 - 0.9619) 1.0558 (1.0128 - 1.0905) 0.9335 (0.8745 - 0.9966) 0.9259 (0.6868 - 0.9927) 1.1056 (1.069 - 1.2995) 1.0653 (1.0906 - 1.2295) 0.9755 (0.1775 - 0.9813) 0.9755 (0.9775 - 0.9813)					
Cu22 on igth Cu38- C025 on igth Cu38- C025 on igth Cu38- C025 on igth Cu38- C024 (D24- C024 (D27- C024 (D27-	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38im AC CD20- CD38- %Wymphocyte CD62L- monocyte AC Secreting Treg AC EM CD8br %CD8br EM CD8br %CD8br CD4- AC CD4+ AC CD4+ AC CD4+ CD8br AC NK AC CD45K-CD8br AC CD45K-CD8br AC CD45K-CD8br AC CD45K-CD8br AC	20 0. 21 0. 17 0. 17 0. 19 0. 22 0. 13 0. 20 0. 17 0. 30 0. 19 0. 19 0. 20 0. 17 0. 30 0. 19 0. 20 0. 20 0. 20 0. 20 0. 20 0. 21 0. 22 0. 20	Vali 03865 00158 0112 0180 0017 0088 0392 0279 0330 0352 0249 0227 0044 0227 0044		OR (65% CI) 1.0763 (1004 - 1.1530) 0.855 (0.7958 - 0.9854) 1.1554 (1.033 - 1.2920) 0.8721 (0.7767 - 0.9768) 0.8724 (0.8707 - 0.9678) 0.8754 (0.8707 - 0.9678) 0.8754 (0.8707 - 0.9678) 0.9335 (0.8745 - 0.9966) 0.9235 (0.8745 - 0.9966) 0.9239 (0.8698 - 0.9920) 0.9316 (1917 - 0.917) 1.1036 (1.0069 - 1.2295) 1.6653 (1.0069 - 1.2295) 0.8673 (0.775 - 0.813) 0.0255 (1.0068 - 1.0043) 0.925 (0.0025 - 1.0043)					
CD25 on igD- CD3+ 19 0.096 1.103 (1.024 - 1.180) CD25 on igD- CD24+ 25 0.022 0.885 (0.797. 0.8927) CD27 on mCD9 Sell 27 0.007 1.091 (1.024 - 1.198) CD27 on mCD9 Sell 22 0.0452 1.0927 (1.001 - 1.194) CD3 on secreting Treg 18 0.0465 0.9357 (0.885-0.9990) HVEM on CD4+ 14 0.0465 0.9357 (0.885-0.9990) HVEM on CD4+ 14 0.0465 0.9401 (0.885-0.9890) HVEM on CD4+ 14 0.0465 0.9401 (0.885-0.9890) HVEM on CD4+ 14 0.0465 0.9401 (0.885-0.9890) HVEM on CD4+ 14 0.0465 0.9357 (0.876-0.9890) CD25 on cD24- CD4+ 23 0.047 0.8360 (0.776-0.9890) CD26 on CD4+ 13 0.0381 0.8360 (0.776-0.9890) CD25 on cS10 17 0.038 0.9471 (0.942-1.148) CD25 on CD4+ 13 0.0392 0.8401 (0.722-0.9633) CD25 on CD4+ 13 0.028 0.9271 (0.857-0.9829) CD25 on CD4+ 13 0.028 0.9271 (0.857-0.9829) CD	IgD- CD38r AC CD20- CD38- %B cell IgD- CD38im AC CD20- CD38- %Wmphocyte CD20- CD38- %Wmphocyte CD24- cnorecyte AC Secreting Treg AC EM CD8br %CD8br MCD8br %CD8br CD4- AC CD4- CD8br AC HLA DR+ CD8br AC NK AC CD45RA- CD38- CD8br %T cell CD26 on IgD+ CD38- unsw mem	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 19 0. 13 0. 20 0. 17 0. 30 0. 19 0. 10 0. 17 0. 10 0. 19 0. 10	0365 0258 - 012 0180 - 012 0180 - 0017 - 0088 0392 - 00279 - 0 0330 - 00352 0249 - 00244 0227 - 0044		OR (65% CI) 1.0763 (1.0046 - 1.1530) 0.8855 (0.7956 - 0.98634) 1.1554 (1.0333 - 1.2920) 0.8721 (0.7787 - 0.9768) 0.8724 (0.7877 - 0.9769) 0.8724 (0.7477 - 0.9769) 0.8724 (0.7477 - 0.9769) 0.8356 (0.4787 - 0.9969) 0.9335 (0.4745 - 0.9969) 0.9326 (0.4745 - 0.9969) 0.9326 (0.475 - 0.9969) 0.9326 (0.4069 - 1.29957) 1.1036 (1.0080 - 1.1258) 0.8735 (0.7775 - 0.9813) 1.0025 (1.0088 - 1.02837) 0.873 (0.8108 - 0.9710)					
CD25 on igD- CD24+ 25 0.021 0.0221 0.021 CD27 on igD- CD34+ 28 0.0221 1.0718 (1.0100 - 1.1374) CD27 on igD- CD38+ 27 0.0070 1.0917 (1.0284 - 1.1939) CD27 on igD- CD34+ 22 0.445 0.9937 (0.8765 - 0.9990) CD3 on HLA DR+ T cell 21 0.0465 0.9937 (0.8765 - 0.9990) HVEM on CD4 14 0.426 0.9937 (0.8765 - 0.9990) HVEM on CD4+ 22 0.021 0.9357 (0.8765 - 0.9990) HVEM on CD4+ 22 0.021 0.9357 (0.8765 - 0.9990) HVEM on CD4+ 14 0.0465 0.9935 (0.866 - 0.9993) CD26 on myelot DC4 16 0.0222 0.9726 (0.778 - 0.9871) CD26 on myelot DC4 16 0.0222 0.9782 (0.778 - 0.9871) CD27 on CD28+ CD4+ 17 0.038 0.9726 (0.778 - 0.9872) CD25 on resing Treg 15 0.126 0.8986 (0.8208 - 0.9799) CD25 on resing Treg 15 0.0126 0.9210 (0.876 - 0.9882) HLA DR on CD4+ 12 0.0041 0.9210 (0.876 - 0.9882) CD4 on naive CD4+ 16 0.9	IgD- CD38br AC CD20- CD38- %B cell IgD- CD38im AC CD20- CD38- %Wmphocyte CD82- monocyte AC Secreting Treg AC EM CD8br %CD8br EM CD8br %CD8br EM CD8br %CD8br CD4- AC CD4- AC CD4- CD8br MC HLA DR+ CD8br AC NK AC CD45- CD8br AC CD26- on IgD+ CD38- unsw mem CD26- on IgD+ CD38-	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0. 13 0. 17 0. 13 0. 17 0. 30 0. 19 0. 19 0. 17 0. 30 0. 18 0. 22 0.	Vali 0365 0365 0112 0180 0017 0088 0392 0330 0352 0227 0227 0227 0227 0227 0227 0227 0227 0227 0227 0227 0227 0228 0227 0228 0278 0278 0278 0392 0278 0392 0278 0392 0278 0392 0278 0392 0278 0392 0278 0392 0278 0392 0278 0392 0279 0392 0279 0392 0279 0392 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279 0279		OR (65% CI) 1.0763 (1004 - 1.1530) 0.8855 (0.7958 - 0.9854) 1.1564 (1033 - 1.2920) 0.8721 (0.787 - 0.9768) 0.8724 (0.870 - 0.9519) 1.0568 (10126 - 1.9965) 0.9235 (0.8745 - 0.9965) 0.9236 (0.8745 - 0.9965) 0.9299 (0.8698 - 0.9920) 0.9016 (0.817 - 0.9175) 0.9016 (0.817 - 0.9175) 0.8016 (0.817 - 0.9175) 0.9036 (0.817 - 0.9175) 0.9036 (0.817 - 0.9175) 0.9036 (0.817 - 0.9175) 0.9036 (0.817 - 0.9175) 0.8735 (0.775 - 0.8133) 1.0025 (1.0008 - 1.0043) 0.8737 (0.8108 - 0.9710) 0.9371 (0.8068 - 0.9730) 0.9375 (0.9133 - 0.936)					
CD27 on 224 - CD27+ 28 0.021 1078 (1010 - 1.134) CD27 on memory Bell 22 0.0452 10927 (1030 - 1.198) CD3 on setting Treg 18 0.0465 0.9357 (1376 - 0.9980) HVEM on CM CD4+ 14 0.0428 0.9401 (0.886 - 0.9980) HVEM on CD4 12 0.021 0.9357 (1376 - 0.9890) HVEM on CD4+ 13 0.0081 0.9357 (0.376 - 0.9890) HVEM on CD4+ 13 0.0081 0.9357 (0.376 - 0.9890) CD26 on CD28+ CD4+ 13 0.022 0.8690 (176 - 0.8931) CD26 on CD28+ CD4+ 17 0.338 0.872 (0.7763 - 0.9807) CD26 on CD4+ 13 0.0397 0.872 (0.7763 - 0.9831) CD25 on CD4+ 17 0.338 0.847 (0.0761 - 0.9832) CD25 on CD4+ 17 0.038 0.847 (0.0761 - 0.9832) CD25 on CD4+ 13 0.039 0.850 (0.7761 - 0.9832) CD25 on CD4+ 13 0.029 0.921 (0.876 - 0.9892) HLA DR on CD14- CD16+ monorgt 10 0.8997 (0.8145 - 0.9938) CD4 on naive CD4+ 16 0.0433 0.9377 (0.8761 - 0.9892)	IgD-CD38r AC CD20-CD38-%B cell (IgD-CD38im AC CD20-CD38-%Wymphocyte CD28-monocyte AC D624-monocyte AC Secreting Treg AC EM CD8br %CD8br EM CD8br %CD8br EM CD8br %CD8br CD4+CD8br AC CD4+CD8br AC CD4+CD8br AC CD4+CD8br AC CD4+CD8br AC CD4+CD8br %CT cell CD20 on IgD+CD38-maive CD25 on IgD+CD38-maive	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0. 13 0. 20 0. 17 0. 13 0. 19 0. 103 0. 18 0. 22 0. 19 0.	Vali 0365 0258 0112 0180 0017 0008 0392 0392 0392 0392 0392 0392 0392 0392 0392 0035 00352 00249 0027 0044 0093 0093 0093 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0095 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 0005 000		OR (65% CI) 10763 (10046 - 11530) 0.855 (0.7958 - 0.9854) 11554 (1033 - 12920) 0.872 (10747 - 0.9768) 0.872 (10747 - 0.9768) 0.872 (10747 - 0.9768) 0.872 (10747 - 0.9768) 0.872 (10747 - 0.9768) 0.872 (10747 - 0.9768) 0.933 (10745 - 0.9966) 0.932 (0.8698 - 0.9920) 0.9016 (0.8197 - 0.9977) 1.1036 (10060 - 1.2288) 0.873 (0.775 - 0.9613) 1.025 (10008 - 1.0935) 1.0326 (1008 - 0.9710) 1.4104 (10064 - 1.0936)					
CD27 on IgD- CD38- 27 0.0070 Image: 1084 - 11939 CD27 on memory B cell 22 0.442 1.0927 (1.0019 - 1.1918) CD30 m HL DAF T cell 1 0.0367 1.0937 (0.376 - 0.9990) HVEM on TO CD4+ 14 0.0426 0.9407 (0.885 - 0.9990) HVEM on TO CD4+ 22 0.0479 0.9305 (0.866 - 0.9990) HVEM on TO CD4+ 23 0.0479 0.9305 (0.866 - 0.9990) CD23 on CL28 + CD4+ 23 0.0479 0.9305 (0.866 - 0.9993) CD266 on myelod DC 16 0.0222 0.9305 (0.866 - 0.9993) CD27 on CD28 + CD4+ 17 0.0180 0.8860 (0.7783 - 0.9897) CD25 on CD4+ 17 0.0180 0.8986 (0.2778 - 0.9893) CD25 on reling Treg 15 0.0126 0.8986 (0.2778 - 0.9892) CD25 on reling Treg 15 0.0126 0.9210 (0.876 - 0.9892) HLA DR on CD1+ CD14+ 12 0.0041 0.9307 (0.816 - 0.9892) HLA DR on CD14+ CD14+ 16 0.0433 0.9307 (0.816 - 0.9892) HLA DR on CD14+ LD R+ CD14+ 0.0373 0.9897 (0.814 - 0.9838) CD45 on C354* 14	IgD-CD38br AC CD20-CD38-%B cell [1gD-CD38lm AC CD20-CD38-%Wmphocyte CD82L-monocyte AC Secreting Treg AC EM CD8br %CD8br MCD8br %CD8br MCD8br %T cell CD4+ AC CD4+ CD8br AC HLA DR+ CD8br AC NK AC CD45KA-CD28-CD8br %T cell CD20 on IgD+ CD38-unsw mem CD25 on IgD+ CD38-naive CD25 on IgD+ CD38-naive CD25 on IgD+ CD34-	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0. 13 0. 19 0. 17 0. 13 0. 14 0. 103 0. 113 0. 12 0. 19 0. 103 0. 12 0. 18 0. 19 0. 19 0. 12 0. 13 0. 14 0. 22 0.	Vali 0365 0258 0112 0180 0017 0008 0008 00279 0030 0227 0044 00227 0044 00238 0096 0221		OR (65% CI) 10763 (1004 - 1.1530) 0.865 (0.7958 - 0.9654) 11554 (1.033 - 1.2920) 0.8721 (0.777 - 0.5768) 0.8724 (0.877 - 0.9676) 0.8754 (0.877 - 0.9676) 0.9535 (0.8745 - 0.9966) 0.9239 (0.8668 - 0.9920) 0.9335 (0.8745 - 0.9966) 0.9239 (0.8668 - 0.9920) 0.9016 (0.817 - 0.9617) 1.1036 (1.0069 - 1.2055) 0.8673 (0.0775 - 0.9613) 0.825 (0.7775 - 0.9613) 0.825 (1.0008 - 1.0043) 0.8874 (0.877 - 0.9877) 0.8873 (0.977 - 0.9873) 0.873 (0.977 - 0.9873) 0.8873 (0.977 - 0.9873) 0.8873 (0.977 - 0.9873) 0.8873 (0.977 - 0.9873) 0.8873 (0.977 - 0.9873) 0.8873 (0.977 - 0.9873) 0.8873 (0.977 - 0.9873) 0.8874 (0.977 - 0.9873) 0.8884 (0.977 - 0.9873) 0.8884 (0.977 - 0.9873) 0.8884 (0.977 - 0.9873)					
CD27 on memory B cell 22 0.0452 •••••••••••••••••••••••••••••	IgD-CD38br AC CD22-CD38-%B cell IgD-CD38lm AC CD22-CD38-%9mphocyte CD52L-monocyte AC Secreting Trep AC EM CD8br %CD8br EM CD8br %CD8br EM CD8br %CD8br CD4+CD8br AC CD4+CD8br AC CD4+CD8br AC CD4+CD8br AC CD4+CD8br AC CD45RA-CD28-CD8br %T cell CD25 on IgD-CD38-unaw mem CD25 on IgD-CD38-unaw CD25 on IgD-CD38-unav CD25 on IgD-CD38-unav CD27 on CD24-CD27+	20 0. 21 0. 17 0. 21 0. 17 0. 19 0. 22 0. 13 0. 20 0. 177 0. 30 0. 19 0. 19 0. 19 0. 19 0. 19 0. 19 0. 22 0. 23 0. 24 0. 25 0. 28 0.	Vali 03665 0258 0112 0180 0017 0008 0392 0008 0392 0330 0352 0249 0044 0093 0093 0093 0093 0093 0093 0093 0093 0093 00221 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 0003 000		OR (65% CI) 10763 (1004 - 11530) 0.855 (0.7958 - 0.9854) 11554 (1033 - 1.2920) 0.872 (10778 - 0.9768) 0.872 (10787 - 0.9768) 0.872 (10787 - 0.9768) 0.875 (10787 - 0.9768) 0.875 (10787 - 0.9768) 0.875 (10787 - 0.9619) 0.9335 (0.8745 - 0.9966) 0.928 (0.8698 - 0.9920) 0.9016 (0.8787 - 0.9913) 1.1036 (10069 - 1.2265) 0.663 (1.0069 - 1.2268) 0.873 (0.777 - 0.9813) 0.025 (1.0068 - 1.0043) 0.873 (0.8108 - 0.9710) 1.4030 (10241 - 1.1880) 0.884 (0.7977 - 0.9827) 1.0105 (1000 - 1.3744)					
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This research offers insightful hypotheses regarding the mechanistic roles of these immune signatures in lung cancer. The diverse interactions of immune cell subsets within the tumor microenvironment hint at their potential influence on tumor growth, apoptosis, and microenvironment dynamics. The distinct responses observed across lung cancer subtypes emphasize the specificity of immune reactions and suggest potential avenues for therapeutic intervention. Of the 106 immune signatures studied, five showed significant links to lung cancer subtypes, including CD25 on IgD- CD24- cells in SCLC, CD27 on IgD+ CD24+ cells in

LUSC, CCR2 on monocyte cells in LUSC, CD123 on CD62L+ plasmacytoid DCs in LUSC, and CD123 on plasmacytoid DCs in LUSC, pointing to their roles in cancer development.

Significantly, our results emphasize the association of CCR2 with monocyte cells in LUSC. CCR2-positive monocytes are attracted to the LUSC tumor microenvironment in response to signals from cancer-associated fibroblasts via CCL2, contributing to an immunosuppressive environment (40, 41). Additionally, these monocytes, once present in inflamed lung areas, tend to reduce local CCL2 levels (42). Concurrent studies, like that by Lei Li and

Trait	Exposure	IVW	MR-Egge			Weighted median	
Tat	Exposure	OR (95% CI)	P- value	OR (95% CI)	P- value	OR (95% CI)	P- value
Lung adenocarcinoma	CD4 Treg %T cells	1.071 (1.015-1.131)	0.013	1.044 (0.965-1.129)	0.303	1.028(0.960-1.101)	0.427
Lung squamous cell carcinoma	Unsw mem AC	1.134 (1.047-1.228)	0.002	1.050 (0.862-1.280)	0.634	1.075(0.961-1.203)	0.205
Small cell lung carcinoma	CD25 on CD4+ T cells	1.174 (1.053-1.310)	0.004	0.985 (0.829-1.170)	0.866	1.195(1.037-1.378)	0.014
Lung adenocarcinoma	CD27 on IgD- CD38br cells	0.909 (0.841-0.984)	0.018	0.869 (0.608-1.243)	0.457	0.915(0.823-1.019)	0.105
Lung squamous cell carcinoma	SSC-A on HLA DR+ CD8br cells	0.897 (0.824-0.977)	0.012	0.973 (0.848-1.117)	0.703	0.954(0.860-1.059)	0.379
Small cell lung carcinoma	CD25 on resting Treg cells	0.840 (0.733-0.963)	0.013	0.794 (0.516-1.223)	0.315	0.772(0.639-0.934)	0.008

TABLE 1 The most detrimental and protective factors for lung cancer subtypes.

colleagues, have shown high CCL2 levels in the tumor microenvironment as predictors of survival in lung cancer patients (43). There is also evidence that CD24 facilitates interactions among B cells, with CD24-deficient mice displaying B-cell anomalies (44). High CD24 levels have been identified as adverse prognostic factors for progression-free and cancer-specific survival in NSCLC patients (45, 46). Moreover, this research highlights the essential role of DCs in LUSC, where tumor-infiltrating mature DCs correlate with better NSCLC prognosis (47, 48).

Despite its strengths, this study has limitations. Firstly, the cohort comprised mainly European individuals, which might limit the generalizability of the findings to more diverse populations. Second, the selection criteria for IVs were relatively permissive, establishing a significance level at $P < 1 \times 10^{-5}$, potentially leading to the incorporation of false-positive variants, potentially introducing bias into the results. Nevertheless, the F-statistics for all IVs

exceeded 10, mitigating the concern for weak instrument bias. Third, despite our thorough examination for possible secondary phenotypes of IVs and the ability to conduct multiple sensitivity analyses, the potential for pleiotropy cannot be entirely dismissed. Fourthly, no immunophenotypes showed a statistically significant association with lung cancer risk after Bonferroni correction.

With further validation in larger populations and additional SNP analysis, identifying these immune signatures as biomarkers could enhance risk prediction, early detection, and prevention strategies in clinical settings. These advances may pave the way for more personalized cancer treatments. Additionally, the identified immune cells serve as promising targets for experimental investigation to determine their impact on lung cancer and the development of innovative immunotherapies. Specifically, focusing on the pathways that regulate these immune cells might facilitate the development of new immunotherapies for lung cancer. As immunotherapy

TABLE 2 Causal effects between CD27 on CD24+ CD27+ cells and CD27 on memory B cells with lung cancer subtypes.

Troit	Evpoqueo	IVW	IVW			Weighted median	
Trait	Exposure	OR (95% CI)	P- value	OR (95% CI)	P- value	OR (95% CI)	P- value
Lung adenocarcinoma	CD27 on CD24+ CD27 + cells	1.039 (1.006-1.072)	0.019	1.045 (0.992-1.101)	0.113	1.035(0.985-1.088)	0.175
Lung squamous cell carcinoma	CD27 on CD24+ CD27 + cells	1.041 (1.003-1.080)	0.032	1.021 (0.961-1.085)	0.507	1.042(0.987-1.099)	0.135
Small cell lung carcinoma	CD27 on CD24+ CD27 + cells	1.072 (1.010-1.137)	0.022	1.021 (0.923-1.130)	0.689	1.026(0.941-1.118)	0.563
Lung adenocarcinoma	CD27 on memory B cells	1.047 (1.009-1.086)	0.014	1.037 (0.978-1.100)	0.235	1.043(0.993-1.097)	0.093
Lung squamous cell carcinoma	CD27 on memory B cells	1.053 (1.008-1.099)	0.02	1.057 (0.986-1.133)	0.134	1.074(1.012-1.140)	0.018
Small cell lung carcinoma	CD27 on memory B cells	1.093 (1.002-1.192)	0.045	1.089 (0.946-1.254)	0.248	1.077(0.980-1.183)	0.123



increasingly becomes a cornerstone of cancer therapy, our results could provide significant contributions to the domain.

In summary, our research offers critical insights into the links between immune signatures and lung cancer, potentially leading to new therapeutic strategies. Continued investigation is essential to fully decipher these interactions and their implications for treating and preventing lung cancer.

5 Conclusion

In conclusion, this investigation marks the first comprehensive MR study to explore the causal links between immunophenotypes and specific lung cancer subtypes using genome-wide data, providing initial insights into how immune cell signatures might affect lung cancer risk. Utilizing the IVW method and various

TABLE 3 Statistically significant association between five potential immune cell signatures and lung cancer.

Troit	Evposuro	IVW		MR-Egger		Weighted median	
Trait	Exposure	OR (95% CI)	P- value	OR (95% CI)	P- value	OR (95% CI)	P- value
Small cell lung carcinoma	CD25 on IgD- CD24- cells	0.885 (0.798-0.983)	0.022	0.790 (0.676-0.923)	0.007	0.772(0.672-0.887)	0
Lung squamous cell carcinoma	CD27 on IgD+ CD24+ cells	1.054 (1.010-1.100)	0.015	1.081 (1.015-1.152)	0.023	1.079(1.018-1.144)	0.011
Lung squamous cell carcinoma	CCR2 on monocyte cells	0.941 (0.898-0.987)	0.012	0.919 (0.864-0.978)	0.017	0.928(0.868-0.992)	0.029
Lung squamous cell carcinoma	CD123 on CD62L+ plasmacytoid dendritic cells	0.958 (0.924-0.992)	0.017	0.938 (0.896-0.981)	0.014	0.950(0.904-0.999)	0.047
Lung squamous cell carcinoma	CD123 on plasmacytoid dendritic cells	0.958 (0.924-0.992)	0.017	0.938 (0.896-0.981)	0.014	0.950(0.903-1.000)	0.049

sensitivity analyses, we identified strong associations between specific immune signatures such as CD25 on IgD- CD24- cells, CD27 on IgD+ CD24+ cells, CCR2 on monocyte cells, and CD123 on both CD62L+ and plasmacytoid dendritic cells with the development of lung cancer. Our results indicate that these immune cell signatures hold potential as valuable biomarkers for the early detection and prevention of lung cancer in clinical settings. These insights open avenues for further studies aimed at understanding the mechanisms through which these immune cells influence lung cancer and developing targeted therapies. While our study has successfully linked numerous immune cell signatures with the incidence of lung cancer, additional research is required to fully understand their roles in the pathogenesis of lung tumors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

SX, HF, TS, YZ, DZ, YK, ZC, and ZL assure that, for the manuscript "Causal association between immune cells and lung cancer risk: a two-sample bidirectional Mendelian randomization analysis", the following is fulfilled: 1) This material is the authors' original work, which has not been previously published elsewhere. 2) The paper is not currently being considered for publication elsewhere. 3) The paper reflects the authors' research and analysis truthfully and completely. 4) The paper properly credits the meaningful contributions of co-authors. 5) All the authors have been personally and actively involved in substantial work leading.

Author contributions

SX: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. HF: Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. TS: Formal analysis, Investigation, Writing – review & editing. YZ: Validation, Writing – review & editing. DZ: Writing – review & editing. YK: Writing – review & editing. ZC: Writing – review & editing. ZL: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1433299/ full#supplementary-material

SUPPLEMENTARY FIGURE 1

Scatter plots illustrating genetic associations of six distinct immunophenotypes with lung cancer risk across different subtypes: (A) CD4 Treg %T cells in LUAD, (B) Unsw mem AC in LUSC, (C) CD25 on CD4+ T cells in SCLC, (D) CD27 on IgD- CD38br cells in LUAD, (E) SSC-A on HLA DR+ CD8br cells in LUSC, (F) CD25 on resting Treg cells in SCLC.

SUPPLEMENTARY FIGURE 2

Forest plots for six immunophenotypes in lung cancer. (A) CD4 Treg %T cells in LUAD, (B) Unsw mem AC in LUSC, (C) CD25 on CD4+ T cells in SCLC, (D) CD27 on IgD- CD38br cells in LUAD, (E) SSC-A on HLA DR+ CD8br cells in LUSC, (F) CD25 on resting Treg cells in SCLC.

SUPPLEMENTARY FIGURE 3

Leave-one-out plots for six immunophenotypes in lung cancer. (A) CD4 Treg %T cells in LUAD, (B) Unsw mem AC in LUSC, (C) CD25 on CD4+ T cells in SCLC, (D) CD27 on IgD- CD38br cells in LUAD, (E) SSC-A on HLA DR+ CD8br cells in LUSC, (F) CD25 on resting Treg cells in SCLC.

SUPPLEMENTARY FIGURE 4

Funnel plots for six immunophenotypes in lung cancer. (A) CD4 Treg %T cells in LUAD, (B) Unsw mem AC in LUSC, (C) CD25 on CD4+ T cells in SCLC, (D) CD27 on IgD- CD38br cells in LUAD, (E) SSC-A on HLA DR+ CD8br cells in LUSC, (F) CD25 on resting Treg cells in SCLC.

SUPPLEMENTARY FIGURE 5

Scatter plots depicting the genetic correlations between two immune markers and the risk of lung cancer among different subtypes. (A) CD27 on CD24+ CD27+ cells in LUAD, (B) CD27 on CD24+ CD27+ cells in LUAD, (C) CD27 on CD24+ CD27+ cells in SCLC, (D) CD27 on memory B cells in LUAD, (E) CD27 on memory B cells in LUSC, and (F) CD27 on memory B cells in SCLC.

SUPPLEMENTARY FIGURE 6

Forest plots for assessing the association of two immune phenotypes with lung cancer risk. (A) CD27 on CD24+ CD27+ cells in LUAD, (B) CD27 on CD24+ CD27+ cells in LUSC, (C) CD27 on CD24+ CD27+ cells in SCLC, (D) CD27 on memory B cells in LUAD, (E) CD27 on memory B cells in LUSC, and (F) CD27 on memory B cells in SCLC.

SUPPLEMENTARY FIGURE 7

Leave-one-out sensitivity plots for two immunophenotypes across lung cancer subtypes. (A) CD27 on CD24+ CD27+ cells in LUAD, (B) CD27 on CD24+ CD27+ cells in LUSC, (C) CD27 on CD24+ CD27+ cells in SCLC, (D) CD27 on memory B cells in LUAD, (E) CD27 on memory B cells in LUSC, and (F) CD27 on memory B cells in SCLC.

SUPPLEMENTARY FIGURE 8

Funnel plots for two immunophenotypes of lung cancer. (A) CD27 on CD24+ CD27+ cells in LUAD, (B) CD27 on CD24+ CD27+ cells in LUSC, (C) CD27 on CD24+ CD27+ cells in SCLC, (D) CD27 on memory B cells in LUAD, (E) CD27 on memory B cells in LUSC, and (F) CD27 on memory B cells in SCLC.

SUPPLEMENTARY FIGURE 9

Scatter plots depicting the genetic correlations between four immune markers and the risk of lung cancer among different subtypes. (A) CD25 on IgD- CD24- cells in SCLC, (B) CD27 on IgD+ CD24+ cells in LUSC, (C) CCR2 on monocyte cells in LUSC, and (D) CD123 on CD62L+ plasmacytoid dendritic cells in LUSC.

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SUPPLEMENTARY FIGURE 10

Forest plots for assessing the association of five immune phenotypes with lung cancer risk. (A) CD25 on IgD- CD24- cells in SCLC, (B) CD27 on IgD+ CD24+ cells in LUSC, (C) CCR2 on monocyte cells in LUSC, (D) CD123 on CD62L+ plasmacytoid dendritic cells in LUSC, and (E) CD123 on plasmacytoid dendritic cells in LUSC.

SUPPLEMENTARY FIGURE 11

Leave-one-out sensitivity plots for five immunophenotypes across lung cancer subtypes. (A) CD25 on IgD- CD24- cells in SCLC, (B) CD27 on IgD+ CD24+ cells in LUSC, (C) CCR2 on monocyte cells in LUSC, (D) CD123 on CD62L+ plasmacytoid dendritic cells in LUSC, and (E) CD123 on plasmacytoid dendritic cells in LUSC.

SUPPLEMENTARY FIGURE 12

Funnel plots for five immunophenotypes of lung cancer. (A) CD25 on IgD-CD24- cells in SCLC, (B) CD27 on IgD+ CD24+ cells in LUSC, (C) CCR2 on monocyte cells in LUSC, (D) CD123 on CD62L+ plasmacytoid dendritic cells in LUSC, and (E) CD123 on plasmacytoid dendritic cells in LUSC.

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