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Original Article

The Causal Role of Immune Cells in Upper Gastrointestinal Cancers: A Mendelian Randomization (MR) Study

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Abstract:

Objective: Upper gastrointestinal (UGI) cancers, particularly esophageal cancer (EC) and gastric cancer (GC), are significant global health concerns characterized by high morbidity and mortality rates. The role of the adaptive immune system in controlling the growth and recurrence of human UGI tumors remains controversial. Here, Mendelian randomization (MR) was employed to explore the causal relationship between immune cells and UGI cancers.

Methods: An extensive two-sample MR analysis was enrolled in this study. Briefly, the publicly available genetic data were utilized for investigation of the causal relationship between 731 immune cells and various UGI cancers; the inverse variance weighted model and weighted medians were employed for MR analyses; and sensitivity analyses were adopted for heterogeneity and pleiotropy assessments.

Results: Our analysis revealed a total of 20 immune cells associated with EC and 25 immune cells associated with GC. Of them, CD62L− HLA-DR++ monocytes, myeloid dendritic cell (DC) % DCs, CD20+ % B cells, CD4+ CD8dim % T lymphocytes, Naive double negative (DN) T cells (CD4- CD8-), CD4+ ACs, and SSC−A on CD14+ monocytes were strongly associated with EC; HLA-DR++ monocytes, IgD+CD24− lymphocytes, CD62L− HLA-DR++ monocyte ACs, and DN (CD4−CD8−) ACs were significantly correlated with GC. CD62L− HLA-DR++ cells were all correlated with all UGI cancers. Interestingly, CD62L− HLA-DR++ cells were negatively correlated with EC but positively correlated with GC.

Conclusion: Our analysis for the relationships between immune cells and UGI cancers provides a framework for characterizing immune status and suggests a dynamic immune cell environment in the setting of UGI cancers. Our results also highlight multiple aspects of the immunosuppressive states found in UGI cancers, all of which may serve as promising potential new therapeutic targets.

Keywords: Esophageal cancer, Gastric cancer, Immune cells, Mendelian randomization, Genome wide association study

1. Introduction

In 2018, gastrointestinal (GI) cancers accounted for approximately 4.8 million new cases and 3.4 million cancer-associated deaths globally, making up more than one-fourth (26%) of cancer cases and over a third (35%) of cancer-related mortality worldwide [1]. Upper GI (UGI) cancers, particularly esophageal cancer (EC; 570,000 newly diagnosed cases in 2018) and gastric cancer (GC; about one million newly diagnosed cases in 2018), present substantial global health challenges, marked by significant morbidity and mortality rates [2]. The prognosis of UGI cancers in many countries remains poor, largely due to the absence of effective screening programs [3-4]. Understanding the mechanisms underlying the initiation and progression of UGI cancers is crucial for developing effective prevention and treatment approaches.

Economic evaluation is currently a cornerstone in guiding the development of cancer screening strategies [5]. However, in screening programs devoid of therapeutic interventions, government budgets are predominantly allocated to the screening phase. Consequently, the burden of high treatment costs falls squarely on the patients and/or local insurance sectors. This scenario often leads to unforeseen challenges that traditional cost-effectiveness analysis may fail to fully capture. For instance, even with medical reimbursements, patients from low-income backgrounds may suffer financial ruin due to the catastrophic expenses associated with cancer treatment, causing a significant decrease in their quality of life [6-7]. Additionally, the financial strain can impede timely access to treatment, thereby undermining the real-world effectiveness of screening programs [8]. Recent research suggests that more than half of UGI cancers can be attributed to alterable risk factors, including alcohol consumption, smoking, infections, diet, and obesity [9]. Changes in UGI cancer morbidity throughout the last few decades are largely due to changes in the prevalence of these risk factors [10]. The magnitude of this burden underscores the necessity of planning future clinical interventions for UGI cancer patients, as well as enforcing preventative measures to avert future diagnoses and mortality.

The close link between cancer and inflammation, keenly observed by Virchow [11] in the 19th century, foreshadowed contemporary concerns about a possible immunological role in neoplastic pathogenesis. As Harold Dvorak [12] has observed, inflammation bears a striking resemblance to a wound that cannot heal. At present, approximately 20% of global cancer deaths are estimated to be linked to unhealed infections and/or inflammation, with UGI malignancies accounting for a substantial part of the disease burden [13]. Despite these instances of the immune system contributing to tumorigenesis and progression, there is also a wealth of data supporting the protective role of immunity in tumor suppression. While numerous cross-sectional and cohort studies have investigated the relationship between immune cells and UGI outcomes [14-15], their observational nature limits them to establishing a correlation rather than a causation [15]. Although randomized controlled trials (RCTs) have the potential to infer causation, interventions to manipulate immune cells are neither feasible nor ethical, limiting our ability to draw causal inferences. Given the limited evidence from both observational and interventional studies, the Mendelian randomization (MR) approach in human genetics presents a unique opportunity to robustly explore the potential causal links between increased immune cells and UGI cancers [16]. This approach leverages the random allocation of genetic variation at conception, well before the onset of disease, making MR a valuable tool for establishing causality and mitigating the risk of reverse causality, independent of confounders typically present in study designs [17-19]. Here, MR was utilized to investigate the histophysiology and pathophysiological involvement of the immune cells in the development of UPI cancers, based on a recent statistical summary from a genome-wide association study (GWAS) focused on immune cells [20]. Our study was dedicated to exploring the causal relationship between 731 immune cells and UGI cancers, with a special focus on their involvement in tumor initiation, progression, and treatment resistance. This paper proposed an extensive MR study that could not only identify specific immune cells associated with UGI cancers but also address the constraints in current research. The objective of this research was to provide valuable insights that could refine future immune cells methodologies and advance etiological research. Collectively, this research was designed to provide certain support for precision prevention, control, and the development of innovative therapeutic approaches.

2 Materials and Methods

2.1 Study Design

The cause-and-effect relationship between 731 immune cells and UGI cancers was assessed using two-sample MR analyses. MR leveraged genetic variations as proxies for risk factors. To ensure reliable causal inference, the instrumental variables (IVs) used in MR needed to satisfy following three key assumptions: (1) The genetic variation must be associated with the exposure directly; (2) The genetic variant was not linked with potential confounding factors between the exposure and outcome; (3) The genetic variation influenced the outcome exclusively through the

exposure, not via alternative pathways **Figure 1**.

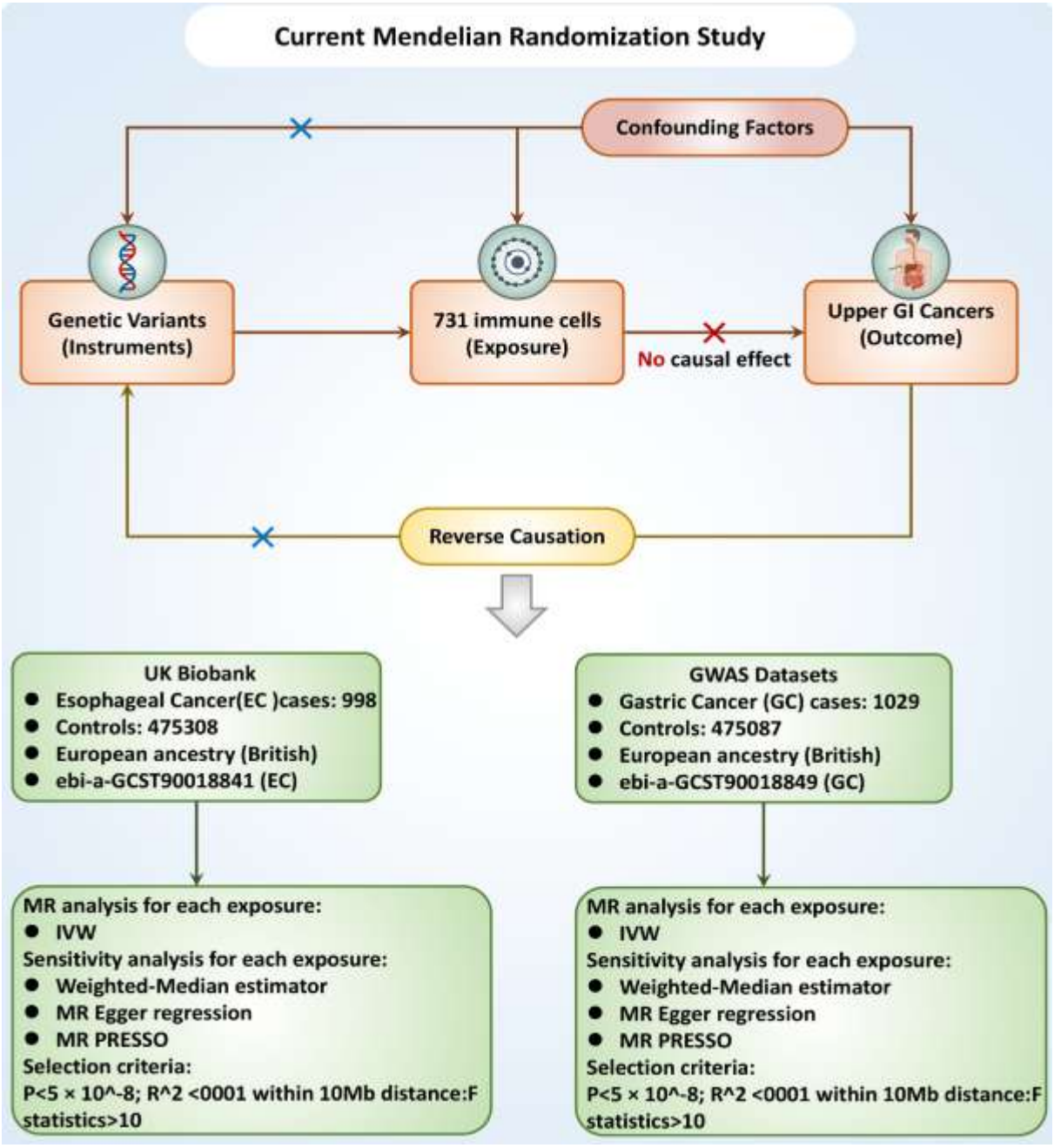

Figure 1 The flowchart of the study design

2.2 Data Sources for Exposure and Outcome

A summary of GWAS statistics for each immune trait is publicly accessible from the GWAS catalog (accession numbers: GCST0001391 to GCST0002121) [21]. The immune traits were searched based on the keywords of each cancer (https://gwas.mrcieu.ac.uk/). The immune traits included: ebi-a-GCST90018841 (EC), ebi-a-GCST90018849 (GC). A total of 731 immune phenotypes were included, including absolute cell (AC) counts, median fluorescence intensities (MFI, which reflected surface antigen levels), morphological parameters (MP) and relative cell (RC) counts. The MFI, AC, and RC features contained B cells, classical dendritic cells (DCs), mature T cells, monocytes, myeloid cells, TBNK (T cells, B cells, natural killer cells) cells, and Treg panels, while the MP feature contained classical DC and TBNK panels. The GWAS database is a comprehensive collection of genetic variation and its association with various traits or diseases, which provides a valuable resource for researchers and clinicians interested in

understanding the genetic basis of complex traits and diseases. Based on the ID of each cancer, online data from GWAS, including 476,306 European individuals (n = 998 case patients and 475,308 control participants) for EC and (n = 1,029 case patients and 475,087 control participants) for GC were extracted to analyze the relationship between immune cells and each cancer (immune traits) (https://www.ebi.ac.uk/gwas/).

2.3 Instrument Selection

Considering the single nucleotide polymorphism (SNP) number demonstrating extensive genome-wide significance ($p < 5 \times 10^{-8}$) for immune cells traits, more stringent correlation thresholds ($p < 5 \times 10^{-9}$) were recruited for Genetic IVs selection [21]. These IVs were identified by grouping them according to the reference panel of the Linkage Disequilibrium (LD) from the 1000 Genomes Project, with a threshold of $R^2 < 0.001$ at a distance of 1,000 kilobases (kb). Given the relatively limited size of the GWAS data for immune cells, we employed a p-value cutoff of 5×10^{-5} and a less significant clustering threshold ($R2 < 0.001$ at a distance of 1000 kb) [22]. To ensure the reliability of our tools, IVs with F-statistics exceeding 10 were selected and identified as strong instruments for subsequent analyses. Then, We then extracted these IVs from the summary statistics pertaining to UGI cancer outcomes, excluding any that showed potential pleiotropic effects ($p < 10^{-5}$) on UGI cancer, in line with methodologies from previous studies [23]. For maintaining consistency in our analysis, the SNPs between the exposure and outcome datasets were synchronized, ensuring uniform effect estimates for the same effect allele. Any alleles with mid-range effect allele frequencies (EAFs > 0.42) or SNPs incompatible with the allele were excluded from our analysis [22].

2.4 Statistical Analysis

In our study, a range of genetic variants were employed as IVs, rather than relying solely on an allele score. This approach was chosen to thoroughly examine key assumptions, uncover potential pleiotropy, and facilitate more effective sensitivity and multivariable MR analyses [24]. To assess the consistency of our findings under different assumptions about heterogeneity and pleiotropy, we utilized four distinct MR methodologies: the inverse variance weighted (IVW; random-effects model) method, weighted medians, MR-Egger, and MR pleiotropy residual sum and outlier (MR-PRESSO). The IVW method, employing a random-effects model, served as the primary analysis framework for all four sets of IVs. Besides, the heterogeneity was quantified using Cochran's Q statistic.

Our study also included analyses with more stringent conditions. The IVW method, under the assumption that all genetic variants are valid, can be biased if many SNPs are influenced by horizontal pleiotropy [25]. Conversely, the weighted median approach, effective when less than 50% of variants exhibit horizontal pleiotropy, presumes most genetic variants are valid [26]. In cases where over 50% of variants are affected by horizontal pleiotropy, we evaluated the strength of our genetic instruments through F statistics, considering a mean F-statistic of less than 10 indicative of weak IVs [27].

Furthermore, the MR-Egger method was applied to check for potential directional pleiotropy. Here, a significant intercept indicated a violation of IV assumptions, suggesting directional pleiotropy [28]. Also, the MR-PRESSO method was applied to minimize heterogeneity in causal effect estimates by excluding disproportionately influential SNPs (NbDistribution = 1,500) [29]. Additionally, Steiger-filtering analyses were conducted to detect and eliminate genetic variants more significantly associated with the outcome than the exposure, indicating possible reverse causality [30].

All statistical analyses were performed using R version 4.3.1 (R Foundation) and specific R packages ("TwoSampleMR" and "MR") tailored for MR analysis [31-32]. The TwoSampleMR package provided causal estimates from the four MR models (IVW, weighted median, MR-Egger, and MR-PRESSO), and the Mendelian Randomization package was utilized for multivariable MR. Detailed methodologies were further provided in the online Supporting Information Methods.

3 Results

3.1 Causal Estimates between Immune Cells and Upper Gastrointestinal Cancers

3.1.1 Causal Estimates between Immune Cells and Esophageal Cancer

To investigate the causal effect of EC on immune phenotyping, we conducted a two-sample MR analysis and utilized IVW as the primary analysis method. Our results showed the association between 20 immune cells and EC **Figure 2**, highlighting some of the strongest associations.

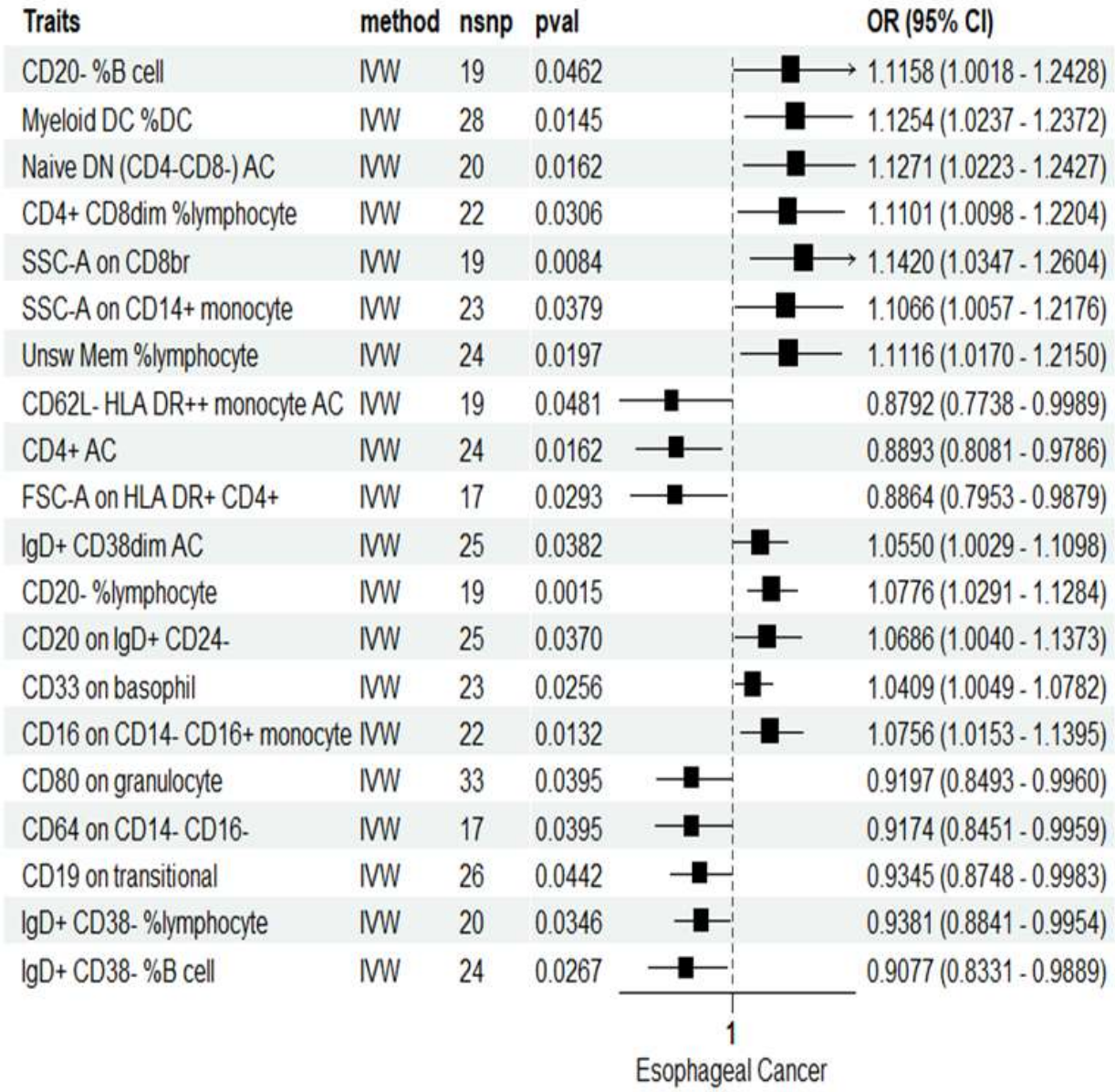

Figure 2 Causal estimates between immune cells and esophageal cancer

Briefly, higher CD20− B cell counts [odds ratio (OR) = 1.1158 , 95% confidence interval (CI) = 1.0018–1.2428, p = 0.0462], Myeloid DC counts (OR = 1.1254, 95% CI = 1.0237–1.2372, p = 0.0145), Naive double negative (DN) (CD4−CD8−) AC counts (OR = 1.1271, 95% CI = 1.0223–1.2427, 0.0162), CD4+ CD8+ dim % lymphocyte counts (OR = 1.1101, 95% CI = 1.0098–1.2204, 0.0306), SSC−A on CD+ cell counts (OR = 1.1420, 95% CI = 1.0347–1.2604, 0.0084), SSC−A on CD14+ monocyte counts (OR = 1.1066, 95% CI = 1.0057–1.2176, 0.0379), and Unsw Mem % lymphocyte counts (OR= 1.1116, 95% CI = 1.0170 − 1.2150, 0.0197) predicted a higher risk of EC. Conversely, lower CD62L− HLA-DR++ monocyte AC counts (OR = 0.8792, 95% CI = 0.7738–0.9989, p = 0.0481), CD4+ AC counts (OR = 0.8893, 95% CI = (0.8081–0.9786, p = 0.0162), and FSC−A on HLA-DR+ CD4+ counts (OR = 0.8864, 95% CI = 0.7953–0.9879, p = 0.0293) predicted a lower risk of EC. Besides, neither the MR-Egger intercept test nor Cochran's Q test revealed pleiotropy or heterogeneity. **(Suppl. Table 1A, B)**.

Suppl. Table 1A The pleiotropy of causal relationship between immune cells and esophageal cancer. The p-values for the MR-Egger intercept were above 0.05, suggesting that no significant pleiotropy effects were found

Traits	egger_intercept	se	pval
IgD+ CD38dim AC	0.001213381	0.015490924	0.938244235
IgD+ CD38- %B cell	-0.014699951	0.014919407	0.335194216
CD20- %B cell	0.017834713	0.023623781	0.460612357
IgD+ CD38- %lymphocyte	-0.004642157	0.0159342	0.774127312
Unsw Mem %lymphocyte	0.031192289	0.018618169	0.10801893
CD20- %lymphocyte	0.012065994	0.013793241	0.393887173
CD62L- HLA DR++ monocyte AC	0.016522708	0.028047227	0.563539307
Myeloid DC %DC	-0.022298078	0.0187793	0.245814716
DN (CD4-CD8-) AC	0.005716259	0.021328542	0.791738925
CD4+ AC	0.005580903	0.015777772	0.726916534
CD4+ CD8dim %lymphocyte	-0.001930529	0.021218693	0.928411615
CD19 on transitional	0.003105353	0.014142956	0.828063696
CD20 on IgD+ CD24-	-0.016936125	0.012371129	0.184220246
CD33 on basophil	0.00629893	0.014721573	0.673101169
FSC-A on HLA DR+ CD4+	-0.01478548	0.020841359	0.488939422
CD16 on CD14- CD16+ monocyte	-0.003870674	0.016658578	0.818624795
CD64 on CD14- CD16-	0.008298051	0.01803828	0.652096267
CD80 on granulocyte	-0.011643772	0.017366203	0.507513612
SSC-A on CD14+ monocyte	0.006790738	0.020351846	0.741939704
SSC-A on CD8br	-0.004160618	0.01801836	0.820140928

Suppl.Table 1B The heterogeneity of causal relationship between immune cells and esophageal cancer. The p-values for the Cochran's Q yielded were above 0.05, suggesting that no significant heterogeneity effects were found.

Traits	method	Q	Q_df	Q_pval
	MR Egger	29.64930426	23	0.159735987
IgD+ CD38dim AC	Inverse variance weighted	29.65721334	24	0.196373818
	MR Egger	18.6612494	22	0.66614263
IgD+ CD38- %B cell	Inverse variance weighted	19.63204689	23	0.663993711
	MR Egger	25.92023301	17	0.075926113
CD20- %B cell	Inverse variance weighted	26.78924034	18	0.083034285
	MR Egger	12.50682955	18	0.819998295
IgD+ CD38- %lymphocyte	Inverse variance weighted	12.59170443	19	0.858801515
	MR Egger	20.32577874	22	0.562669591
Unsw Mem %lymphocyte	Inverse variance weighted	23.13263751	23	0.453048097
	MR Egger	16.27708665	17	0.504283852
CD20- %lymphocyte	Inverse variance weighted	17.04231939	18	0.520197253
	MR Egger	16.39743541	17	0.495855573
CD62L- HLA DR++ monocyte AC	Inverse variance weighted	16.74447784	18	0.540734028
	MR Egger	17.46657439	26	0.894310786

Myeloid DC %DC	**Inverse variance weighted**	**18.87643461**	**27**	**0.87446019**
	MR Egger	**21.92779426**	**18**	**0.235206624**
DN (CD4-CD8-) AC	**Inverse variance weighted**	**22.01529744**	**19**	**0.283495588**
	MR Egger	**21.10572381**	**22**	**0.514212596**
CD4+ AC	**Inverse variance weighted**	**21.23084119**	**23**	**0.566992627**
	MR Egger	**14.45160737**	**20**	**0.806880491**
CD4+ CD8dim %lymphocyte	**Inverse variance weighted**	**14.45988518**	**21**	**0.849046851**
	MR Egger	**17.06946401**	**24**	**0.845684311**
CD19 on transitional	**Inverse variance weighted**	**17.1176745**	**25**	**0.877481341**
	MR Egger	**15.7633659**	**23**	**0.865209959**
CD20 on IgD+ CD24-	**Inverse variance weighted**	**17.63753799**	**24**	**0.820229263**
	MR Egger	**21.30102227**	**21**	**0.440697288**
CD33 on basophil	**Inverse variance weighted**	**21.48671987**	**22**	**0.490857491**
	MR Egger	**9.133230852**	**15**	**0.870448745**
FSC-A on HLA DR+ CD4+	**Inverse variance weighted**	**9.636521401**	**16**	**0.884908355**
	MR Egger	**18.01031825**	**20**	**0.586728501**
CD16 on CD14- CD16+ monocyte	**Inverse variance weighted**	**18.06430627**	**21**	**0.644931181**
	MR Egger	**12.48651239**	**15**	**0.641893042**
CD64 on CD14- CD16-	**Inverse variance weighted**	**12.69813494**	**16**	**0.694687721**
	MR Egger	**36.75458099**	**31**	**0.219608595**
CD80 on granulocyte	**Inverse variance weighted**	**37.28758129**	**32**	**0.238832384**
	MR Egger	**25.17413887**	**21**	**0.239700787**

3.1.2 Causal Estimates between Immune Cells and Gastric Cancer

According to the IVW model **Figure 3**, there were 25 immune cells causally associated with GC, of which the strongest associations were highlighted. In brief, the risk of GC was strongly correlated with DN (CD4−CD8−) AC count (OR = 1.1483, 95% CI = 1.0607–1.2432, $p < 0.001$), HLA-DR++ monocyte %leukocyte count (OR = 1.1089, 95% CI = 1.0274–1.1969, $p = 0.0080$), CD62L− HLA-DR++ monocyte AC count (OR = 1.1350, 95% CI = 1.0522–1.2243, $p = 0.0011$), and IgD+ CD24− % lymphocyte count (OR = 0.8938, 95% CI = 0.8323–0.9598, $p = 0.0020$). This article summarized the results of the sensitivity analysis. Despite noting heterogeneity in some immune cells (CD28+ CD45RA+ CD8dim %CD8dim and Naive CD4+ AC), Cochran's Q test produced a p-value below 0.05. However, the causality estimates were still satisfactory when applying a random-effects IVW method. In addition, p-values for the MR-Egger intercept were above 0.05, suggesting the absence of significant pleiotropy effects. (**Suppl. Table 2A, B**).

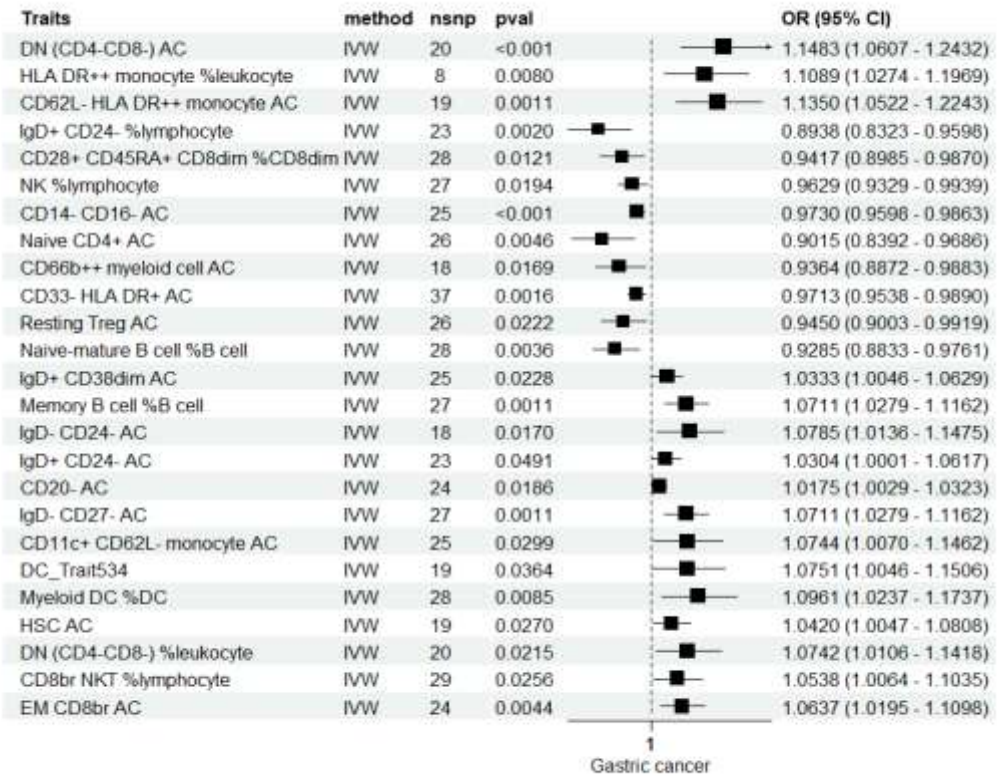

Figure 3 Causal estimates between immune cells and GC

Suppl.Table 2A The pleiotropy of causal relationship between immune cells and gastric cancer. The p-values for the MR-Egger intercept were above 0.05, suggesting that no significant pleiotropy effects were found.

traits	egger_intercept	se	pval
IgD+ CD38dim AC	-0.013046051	0.00828052	0.128794847
IgD- CD27- AC	-0.000114027	0.009842898	0.99084894
Memory B cell %B cell	0.011788581	0.010125803	0.254910234
Naive-mature B cell %B cell	-0.009191733	0.009061388	0.319746548
IgD- CD24- AC	0.000314663	0.016060234	0.984610556
IgD+ CD24- AC	-0.008997389	0.009946212	0.375936258
CD20- AC	0.005133053	0.005471933	0.358394075
IgD+ CD24- %lymphocyte	0.008171315	0.020852662	0.699110309
CD11c+ CD62L- monocyte AC	0.018618218	0.012028457	0.135309809
CD62L- HLA DR++ monocyte AC	0.007827319	0.01908592	0.68684752
CD11c+ HLA DR++ monocyte AC	-0.004747133	0.014364823	0.745083291
Myeloid DC %DC	-0.009123217	0.014797652	0.542904988
HLA DR++ monocyte %leukocyte	-0.00825421	0.021434646	0.713453836
Resting Treg AC	-0.001155987	0.011786603	0.922686189
HSC AC	0.001680388	0.009978489	0.868255085
CD33- HLA DR+ AC	-8.01E-05	0.008055809	0.992125825
CD66b++ myeloid cell AC	0.0024717	0.015301284	0.873693905

CD4+ AC	-0.008738167	0.016938263	0.610656177
EM CD8br AC	0.005329018	0.008239505	0.524475546
CD14- CD16- AC	-0.003847496	0.006703313	0.57155952
DN (CD4-CD8-) AC	-0.018772887	0.015813575	0.250604698
DN (CD4-CD8-) %leukocyte	0.006864017	0.010601835	0.525521399
CD8br NKT %lymphocyte	0.002247356	0.009703802	0.818598509
NK %lymphocyte	-0.004346587	0.007110496	0.546525291
CD28+ CD45RA+ CD8dim % CD8dim	-0.010097526	0.00889813	0.266816468

Suppl.Table 2B The heterogeneity of causal relationship between immune cells and gastric cancer. The p-values for the Cochran's Q yielded were above 0.05, suggesting that no significant heterogeneity effects were found.

traits	method	Q	Q_df	Q_pval
	MR Egger	25.33325142	23	0.33333491
IgD+ CD38dim AC	Inverse variance weighted	28.06729837	24	0.25721156
	MR Egger	24.00567546	25	0.519045648
IgD- CD27- AC	Inverse variance weighted	24.00580966	26	0.575633029
	MR Egger	27.19433023	26	0.399198354
Memory B cell %B cell	Inverse variance weighted	28.61198055	27	0.379961637
	MR Egger	25.7011317	26	0.479623893
Naive-mature B cell %B cell	Inverse variance weighted	26.73010791	27	0.478426837
	MR Egger	17.04523473	16	0.382675837
IgD- CD24- AC	Inverse variance weighted	17.04564368	17	0.451277891
	MR Egger	25.8332429	21	0.212878978
IgD+ CD24- AC	Inverse variance weighted	26.83989006	22	0.217370834
	MR Egger	17.22315669	22	0.750926537
CD20- AC	Inverse variance weighted	18.10313069	23	0.751871474
	MR Egger	23.65323379	21	0.31016182
IgD+ CD24- % lymphocyte	Inverse variance weighted	23.82618838	22	0.356405879
	MR Egger	27.34883805	23	0.241410234
CD11c+ CD62L- monocyte AC	Inverse variance weighted	30.19767394	24	0.17828625
	MR Egger	14.12734915	17	0.658067751
CD62L- HLA DR++ monocyte AC	Inverse variance weighted	14.29553904	18	0.709632171
	MR Egger	15.73436785	17	0.542737817
CD11c+ HLA DR++ monocyte AC	Inverse variance weighted	15.8435778	18	0.60346316
	MR Egger	29.30774941	26	0.297274177
Myeloid DC %DC	Inverse variance	29.73621854	27	0.32613545

	weighted			
	MR Egger	**6.849322924**	**6**	**0.335006908**
HLA DR++ monocyte %leukocyte	**Inverse variance weighted**	**7.018606502**	**7**	**0.426945131**
	MR Egger	**21.31582448**	**24**	**0.620031099**
Resting Treg AC	**Inverse variance weighted**	**21.32544345**	**25**	**0.674329627**
	MR Egger	**13.49184947**	**17**	**0.702688229**
HSC AC	**Inverse variance weighted**	**13.52020838**	**18**	**0.759789892**
	MR Egger	**38.51805883**	**35**	**0.313371097**
CD33- HLA DR+ AC	**Inverse variance weighted**	**38.51816755**	**36**	**0.356308843**
	MR Egger	**16.42019843**	**16**	**0.424038362**

4. Discussion

MR analysis has been frequently employed to illustrate possible causality between risk factors and diseases. In the present study, MR was applied to generate proof of an inverse causal relationship between immune cells and UGI cancers, with some of the strongest associations highlighted in the following discussion sections.

Myeloid DC % DC represents the percentage of myeloid DCs within a given sample or population of immune cells. Myeloid DCs, as a subpopulation of DCs, are important antigen-presenting cells involved in activating immune responses. Endogenous myeloid cells are enlisted by tumors, turn into tumor-associated macrophages, DCs, myeloid-derived suppressor cells, and/or neutrophils, and are regulated to maintain immunosuppressive settings. Cancer cell-driven overexpression of immune mediators, including granulocyte-macrophage colony-stimulating factor and vascular endothelial growth factor, leads to myeloid hematopoiesis in the bone marrow [33]. Recent studies [34] have shown that Myeloid DC is correlated with a high risk of EC, consistent with our findings.

CD20− % B cell represents the percentage of B cells within a given sample that do not express the CD20 surface marker. CD20 is a type of surface antigen that is exhibited at particular stages of B cell maturation. One effective strategy for treating hematologic malignancies such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia is targeting CD20-positive B cells with therapeutic monoclonal antibodies, and its absence (CD20−) indicates a subset of B cells that do not express it [35]. Our study suggested that CD20− % B cell was strongly correlated with EC risk, consistent with prior work [36].

CD4+ CD8dim % lymphocyte represents the percentage of lymphocytes within a given sample that are CD4+ (expressing the CD4 co-receptor) and CD8dim (having a lower level of CD8 expression). This notation describes lymphocyte subpopulations that have both CD4 and a diminished level of CD8 on their cell surfaces. CD4+CD8dim+ (TC5) has specifically primary hemohistocompatibility complex category I-restricted cytotoxic effect on Cou-LB autonomous tumor cell lines. TC5-mediated killing has been demonstrated in Cou-LB lymphoma and leukemia [37]. Neoplastic cell lines exhibit permanent expression of MHC class I histocompatibility elements, but do not express MHC class II. B-cell-derived cutaneous lymphomas are usually MHC class II+, but cutaneous T-cell lymphomas do not always exhibit MHC class II gene products. Hence, the present study is the first to demonstrate the presence of CD4+ and CD4+CD8dim+ cytotoxic tumor-specific T-cell clones within the skin infiltration zone [38]. Previous studies have reported that the CD4+ CD8dim phenotype was associated with cutaneous T-cell lymphomas, but not with any other cancer. Interestingly, we found that this phenotype was strongly associated with EC risk. However, the role of CD4+ CD8dim % lymphocytes in EC still remains unclear, and further exploration is needed.

Naive DN (CD4- CD8-) T cells account for a small proportion of circulating T lymphocytes, with phenotypic features such as loss of CD4 and CD8 co-receptors and γδ or αβ. Given the

complicated roles of T cell receptors, excluding skin and cardiac allotransplantation by exclusively suppressing anti-transplant-specific CD8+ T cell functions may lead to detrimental consequences [39]. Inhibiting DN (CD4- CD8-) T cell activation can reduce interferon-gamma-mediated inflammatory responses. However, a previous study revealed an increase in the proportion of DN DN (CD4- CD8-) T cells in thyroid cancer, indicating that tumor growth may be related to DN (CD4 CD8 −) T cell infiltration. On the one hand, perforin and granzymes expressed by DN T cells can target and kill natural killer cells within the tumor microenvironment [40]. On the other hand, DN T cells may also block natural killer cell-mediated pro-inflammatory immune environments, thereby promoting cancer cell survival [41]. Interestingly, recent studies have shown that DN (CD4- CD8-) tumor-infiltrating lymphocytes derived from solid tumor tissue inhibit tumor cell proliferation in an MHC-independent manner after expansion in vitro. Our study showed that DN (CD4-CD8-) T cell activation was a risk factor for both EC and GC.

CD4+ AC typically represents a distinct subpopulation of immune cells characterized by the presence of CD4 co-receptors. CD4, a co-receptor predominantly expressed on helper T cells, plays a crucial role in the interaction between T cells and antigen-presenting cells. Analysis of CD4+ cells may be important for both research and clinical purposes. CD4+T cells are key coordinators of the immune system, as they produce several cytokines after activation and differentiation. CD4+ T helper cell subtypes (including T helper 1, T helper 2, T helper 17, T helper 9, and regulatory -T cells) have different immune functions after differentiation from naïve T cells. Different types of CD4+ T cells require different cytokines and master transcription factors for activation [42]. Previous research has demonstrated that CD4+ T cells can be found in the tumor microenvironments of lung cancer, melanoma, colorectal cancer (CRC), lymphomas, cervical cancer, and ovarian cancer. However, the role of CD4+ T cells in EC is relatively understudied [43-48]. Interestingly, our findings indicated that CD4+ T cells served as a protective factor in EC and GC. More functional research is needed to confirm these findings.

SSC−A on CD14+ monocyte involves an analysis or measurement performed using flow cytometry to assess a specific characteristic of monocytes with CD14+ expression in relation to the scatter parameter SSC-A (Side Scatter Area). CD14+ is a type of pattern recognition receptor that potentiates immune responses in innate immunity. CD14+ was originally classified as a monocyte marker that triggered intracellular responses upon encountering bacteria. Due to the lack of an endocytic tail, CD14+ was suspected to possess signaling capabilities. CD14+ was subsequently demonstrated to be a TLR co-receptor which functioned to identify pathogen-related molecular patterns. CD14 is now understood to be a versatile receptor, however, as it has recently been found to activate nuclear factor of activated T cells, modulate myeloid cell life cycle in a TLR4-dependent manner, and transit inflamed lipids and induce phagocyte hyper-activation. The effects of CD14+ on a variety of related diseases have also been investigated [49]. CD14+ has been shown to be related to tumor relapse, proliferation, metastasis, and chemoresistance, all of which are features of cancer stem cells. Therefore, it was hypothesized that esophageal hematopoietic stem cells (EC) may also display CD14+. In a recent study, human EC sections were paraffin-embedded, and the co-expression of CD14 and the EC marker aldehyde dehydrogenase 1 was measured using immunofluorescence. CD14+ cells were then separated using immunomagnetic separation for stemness assays, which included the assessment of proliferation, migration, invasion, and tumorigenicity. Proliferative abilities were detected using the Cell Counting Kit-8, EdU, and colony formation assays; metastatic abilities were detected using Transwell and wound healing assays; and tumorigenic abilities were detected with xenograft assays. The experimental results showed that aldehyde dehydrogenase 1-labeled EC expressed CD14, and primary CD14+ cells were identified as cancer stem cells. Therefore, this study suggested that CD14+ could also serve as a cellular surface marker for EC [50]. Our present results were consistent with these findings.

HLA-DR is a cell surface protein used to recognize antigen-presenting cells, such as monocytes. Monocytes express HLA-DR, which account for antigen presentation to T cells, thereby delivering antigens to adaptive immune system cells [51]. HLA-DR expression can reflect

the activation status of monocytes. In chimeric antigen receptor T-cell therapy for diffuse large B-cell lymphoma, patients with low HLA-DR expression on monocytes had worse prognoses than those with high HLA-DR expression; and downregulation of HLA-DR reduced plasma interferon-gamma and IL-2 levels, which may inhibit inflammation and tumor immune environments [52]. In addition, some studies have reported that HLA-DR antigens on antigen-presenting cells are identified by activated CD4-positive T-lymphocytes. HLA-DR antigen loss may be related to a decrease in the host's immune defense ability, which may lead to the immune escape of GC and CRC tumor cells. High HLA-DR antigen expression is usually associated with better prognosis in GC and CRC patients [53-54]. Our research results showed that HLA-DR++monocyte% leukocyte was correlated with a higher risk for GC, inconsistent with these prior findings. Therefore, further experimental research on the function of HLA-DR++monocyte% leukocytes in GI cancers is needed.

CD24, also known as heat-stable antigen (HSA), is a highly glycosylated glycosylphosphatidylinositol-anchored membrane protein expressed on mature granulocytes and B-lymphocytes and regulates developmental and polarization signals in these cells. CD24 is also highly expressed in certain tumor cells. Through binding the inhibitory receptor Sialic acid binding Ig-like lectin 10 (Siglec-10), CD24 promotes tumor immune evasion by blocking phagocytosis [55]. Furthermore, CD24 is also associated with tumor growth, proliferation, and metastasis [56-58]. Notably, monoclonal antibodies can block the interaction between CD24 Siglec-10, thereby effectively inhibiting the anti-phagocytic effects of CD24. In this paper, IgD+CD24 −% lymphocyte was a protective factor in GC, consistent with previous research results. As the proportion of lymphocytes that do not express CD24 increases, the prognosis of GC has been improved.

Our research revealed that CD62L− HLA-DR++monocyte infiltration was closely related to GC and PC, and was a negative factor for PC prognosis. These monocytes express HLA-DR strongly but do not express CD62L. HLA-DR is an MHC class II cell surface marker regulated by the HLA complex located on chromosome 6 (region 6P21). Generally, HLA-DR, mainly expressed on antigen-presenting cells, contains two subunits with molecular weights of 36 kD and 27 kD, respectively (α Subunit and β Subunits). Previous research has suggested that tumor-specific MHC-II expression is associated with good outcomes. For example, upregulated HLA-DR/MHC-II genes in tumors serve as predictive factors for neoadjuvant chemotherapy responses and good clinical outcomes in locally advanced rectal cancer [59]. In addition, increased MHC-II expression in tumor cells is associated with improved melanoma treatment responses, progression-free survival, and overall survival [60]. It can also be used as a positive predictor of good outcomes in Hodgkin lymphoma after PD-1 blockade [61]. Interestingly, HLA-DR expression in non-tumor cells cannot predict treatment responses. Moreover, we found that the overexpression of HLA-DR in monocytes was a risk factor for EC, GC, and pancreatic cancer [62]. CD62L is a gene encoding L-selectin protein, which belongs to the selectin family. Selectin is a cellular adhesion molecule related to leukocyte adhesion and migration, and the expression level of tumor cell surface selectin increases significantly in some tumors. Furthermore, the growth-promoting effect of increased tumor-infiltrating CD62L+ T cells on melanoma indicates that CD62L is linked to poor prognosis, consistent with our present findings. In our research, increased CD62L− HLA-DR++monocyte infiltration were a protective factor for the development of EC but a risk factor for GC.

5. Limitations

Our two-sample MR analysis was designed to analyze the causality between immune cells and UGI cancers based on large-sample GWAS data. This design reduced the limitations of traditional observational studies by eliminating the influence of confounding factors and reverse causality. In addition, MR mitigated the representativeness and feasibility issues inherent to RCTs. However, there are several limitations in this study. Firstly, this research depended on publicly accessible GWAS data, which prevented further exploration of the impact of other relevant factors on UGI cancers, such as gender, age, and body mass index [63]. Secondly, these findings can only be generalized to European populations, as that was

the sample present in the original GWAS, so further study is needed in different ethnic subgroups [64]. Thirdly, even with multi-sensitivity analysis, horizontal pleiotropy could not be comprehensively evaluated. Finally, we adopted a wider threshold to assess the results, which may have increased false positives but also allowed for a more integrated evaluation of the associations between circulating immune profiles and UGI cancers.

6. Conclusions

In summary, our MR analysis for the role of immune cells in UGI cancers provides a framework for understanding of circulating immune status. Systematic assays of infiltrating immune cells in UGI cancers can help dissect the immune status of UGI cancers, assess the current use of checkpoint blockers, and, most importantly, aid in the development of innovative immunotherapies.

Author Contribution: Pengkhun Nov acquisition of data, analyzing,interpretation of data, Nan Luo drafting the article; Juanli Xu, and Jiqiang Li designing, revising, and guiding the study. The authors read and approved.

Declarations

Ethics approval Not applicable

Consent for publication All the authors of the article agreed to be published in the journal.

Availablity of data and material: All the data for this article can be found on GWAS database **Competing interests** The authors declare no competing interests.

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