Research article

Deciphering the circulating immunological landscape of thoracic aortic aneurysm: Insights from a two-sample Mendelian randomization study

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ABSTRACT

Background: Thoracic Aortic Aneurysm (TAA) poses significant health risks due to aortic dilation. Recent evidence suggests a pivotal role for the immune-inflammatory response in the mechanism of aortic aneurysm formation. In this study, we aim to investigate the causal relationship between circulating immune cells and TAA.

Methods: This study employs a two-sample Mendelian Randomization (MR) approach, utilizing genome-wide association study (GWAS) summary statistics for 731 immune cell types and two TAA data from large-scale studies. Causal effects of both peripheral immune cells on TAA and TAA on peripheral immune cells are explored. To ensure more accurate results, we intersected the findings from two TAA data from large-scale studies, excluding results where the direction of the odds ratio (OR) was inconsistent.

Findings: The study identifies specific immune cells associated with TAA. Notably, CD45^{+} NKT cell (OR: 0.95, 95CI%: 0.90–0.99 in FinnGen study; OR: 0.91, 95CI%: 0.84–0.99 in CHIP + MGI study) and CD45^{+} HLA-DR + CD8^{+} T cells (OR: 0.95, 95CI%: 0.90–0.99 in FinnGen study; OR: 0.90, 95CI%: 0.82–0.99 in CHIP + MGI study) demonstrate a protective role against TAA. In addition, CD28^{+} CD45RA- CD8^{+} T cells (relative cell counts and absolute cell counts) and HVEM + CM + CD8^{+} T cells are adversely affected by TAA.

Interpretation: The findings indicate that the potential protective influence exerted by specific subsets of peripheral NKT cells and CD8^{+} T cells in mitigating the development of TAA, while simultaneously highlighting the reciprocal effects of TAA on peripheral Treg cells subsets and T cell subsets. The complex interaction between immune cells and TAA could provide valuable clues for earlier detection and more efficacious treatment strategies for TAA.

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Research in context. Evidence before this study

Thoracic Aortic Aneurysms (TAA) pose a significant public health concern, necessitating innovative therapeutic interventions. Recent evidence suggests a pivotal role for the immune-inflammatory response in the mechanism of aortic aneurysm formation. In this study, we aim to investigate the causal relationship between circulating immune cells and TAA.

Added value of this study

In the current study, we conducted a two-sample Mendelian Randomization (MR) approach, utilizing genome-wide association study (GWAS) summary statistics for 731 immune cell types and two TAA data from large-scale studies. Causal effects of both peripheral immune cells on TAA and TAA on peripheral immune cells are explored. To ensure more accurate results, we intersected the findings from two TAA data from large-scale studies, excluding results where the direction of the odds ratio (OR) was inconsistent.

Implications of all the available evidence

The findings indicate that the potential protective influence exerted by specific subsets of peripheral NKT cells and CD8$^+$ T cells in mitigating the development of TAA, while simultaneously highlighting the reciprocal effects of TAA on peripheral Treg cells subsets and T cell subsets. The complex interaction between immune cells and TAA could provide valuable clues for earlier detection and more efficacious treatment strategies for TAA.

1. Introduction

Thoracic aortic aneurysm (TAA) is a life-threatening disease that manifests as dilatation of the ascending aorta, aortic arch, or descending aorta. As the diameter of the aorta continues to increase, it can compress the surrounding organs, aortic dissection or rupture may occur, and in severe cases, it can lead to patient death. The incidence rate of TAA is approximately 5–10 per 100,000 person-years [1]. Among all TAA, ascending aortic aneurysms and aortic root aneurysms account for about 60 %, descending aortic aneurysms account for approximately 30 %, and aortic arch aneurysms account for less than 10 % [1]. Currently, surgical treatments, including both traditional surgery and interventional procedures, are the most effective means for TAA. However, these approaches still carry a high risk and a notable incidence of complications. The primary objective of conventional drug therapy is to control risk factors, slow down disease progression, but it cannot reverse an already dilated aorta. Therefore, the exploration of a safe and effective novel treatment for the management of TAA is urgently needed.

An increasing body of evidence indicates that the immune-inflammatory response plays a pivotal role in the mechanism of aortic aneurysm formation. Single-cell sequencing analysis indicates that in thoracic aortic aneurysm tissues, there is an increased infiltration of immune cells compared to normal tissues, with a predominant increase in T lymphocytes [2]. Macrophages, especially M1 macrophages, have been shown to play a crucial role in the development of aortic aneurysms in previous studies [3,4]. Another study suggests that natural killer T cells (NKT) can promote the formation of aortic aneurysms. Controlling the activation state of NKT cells might be a potential strategy for treating aneurysms [5]. In addition, the involvement of immune cell-secreted inflammatory cytokines has been implicated in the pathogenesis of aortic aneurysms. A clinical comparative study measured the circulating levels of inflammatory cytokines in patients with aortic aneurysms compared to healthy individuals, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). The results indicate an elevation in the circulating levels of inflammatory cytokines in patients with aortic aneurysms, potentially correlating with the growth rate of the aneurysm [6]. However, previous studies have been conducted on a small scale, either in human or animal populations, and there is yet to be a large-scale investigation and validation of the relationship between immune inflammatory response and thoracic aortic aneurysms in a broader population.

Mendelian randomization (MR) utilizes genetic variation as an instrumental variable, providing robust evidence for causal relationships between exposure and outcomes [7,8]. According to Mendel's laws of inheritance, genetic variations are randomly allocated at conception, specifically before the onset of disease. Therefore, Mendelian randomization can mitigate confounding factors and reverse causation, making it an effective tool for causal inference. In this study, we performed a two-sample MR analysis to explore causal relationships between 731 circulating immune cell types and TAA. This approach allows for a comprehensive and accurate analysis of the association between immunoinflammatory mechanisms and TAA. The findings from our investigation aim to provide valuable insights and avenues for precision treatment strategies for TAA in the future.

2. Methods

2.1. Study design

This study employed a two-sample MR analysis to assess the causal relationship between immune cells in peripheral blood and TAA. According to the principles of MR, valid instrumental variables (IVs) in causal inference must satisfy three key assumptions: (1) genetic variation is directly associated with exposure; (2) genetic variation should be independent of potential confounders; (3) genetic variation does not affect the outcome through pathways other than exposure [8]. The design overview of this study was shown in Fig. 1.

2.2. Data sources

For the data of immune cells in peripheral blood, we used genome-wide association study (GWAS) summary statistics for each immune trait from the GWAS Catalog. There are 731 immune cell signatures with accession numbers from GCST0001391 to GCST0002121. A total of 731 immune phenotypes comprised median fluorescence intensity (MFI) reflecting surface antigen levels (n = 389), relative cell (RC) counts (n = 192), absolute cell (AC) counts (n = 118), and morphological parameters [MP] (n = 32). The immune features were extracted from the data of 3,757 Europeans without overlapping cohorts.

The data sources for TAA were taken from two independent large-scale case–control GWAS summary statistics. One was from summary-level data on TAA from the R9 data release of the FinnGen study, which included 353,049 Finnish adult subjects and consisted of 3,510 patients with TAA and 349,539 controls. The other data was from Cardiovascular Health Improvement Project (CHIP) and Michigan Genomics Initiative (MGI), which included 1,351 TAA individuals and 18,295 control individuals (European ancestry) [9].

2.3. Instrument selection

IVs were required to be in linkage equilibrium, physically separated (r2<0.001, distance = 10,000 kb), and associated with significance (p < 5E-08). Furthermore, to avoid biases introduced by weak instruments, IVs with an F-statistic greater than 10 as strong instruments were included for subsequent analyses.

2.4. Statistical analysis

All analyses were conducted using R software (4.3.1). MR analysis was performed using the "TwoSampleMR" package [10], employing methods such as inverse variance weighting (IVW), MR Egger, simple mode, weighted median, and weighted mode methods. The determination of significant P values was primarily based on the IVW method. To ensure more accurate results, we intersected the findings from the FinnGen study with the CHIP + MGI study, excluding results where the direction of the odds ratio (OR) was inconsistent. The final results were tested for heterogeneity and horizontal pleiotropy, and outliers were identified using the
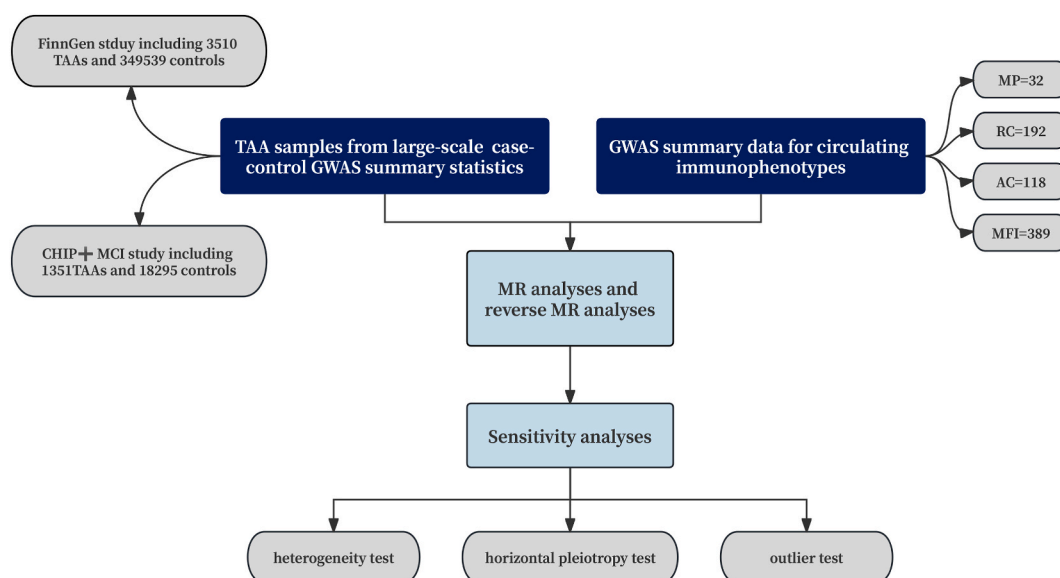

Fig. 1. Study design overview. TAA, thoracic aortic aneurysm; GWAS, genome-wide association study; MR, Mendelian randomization; MFI, median fluorescence intensity, RC, relative cell, AC, absolute cell counts, MP, morphological parameters.

leave-one-out method. Additionally, funnel plots demonstrated the robustness of the correlation and the absence of heterogeneity.

3. Results

3.1. Causal effect of peripheral immune cells on TAA

When TAA data from the FinnGen study was considered as outcome data, based on the P value of the IVW method being less than 0.05, 33 types of immune cells were identified as being related to TAA (Supplementary Table 1). In the CHIP + MGI study, 28 types of immune cells showed a significant causal relationship with TAA (IVW method: P < 0.05) (Supplementary Table 2). Intersecting the results from both cohorts, 5 types of immune cells were significantly associated with TAA (Supplementary Table 3). After excluding the results where the OR values were inconsistent in both cohorts, 2 types of immune cells were identified to have a significant causal relationship with TAA and were protective factors against TAA. Both of these cell types are in the TBNK panel, one is CD45 on the NKT cell (OR: 0.95, 95CI%: 0.90–0.99 in the FinnGen study; OR: 0.91, 95CI%: 0.84–0.99 in the CHIP + MGI study), and the other is CD45 on the HLA-DR + CD8br cell (OR: 0.95, 95CI%: 0.90–0.99 in the FinnGen study; OR: 0.90, 95CI%: 0.82–0.99 in the CHIP + MGI study). These results are shown in a forest plot (Fig. 2). Finally, we tested these two cell types in each of the two cohorts for heterogeneity and horizontal pleiotropy, with all P values of the tests being greater than 0.5, indicating no significant heterogeneity or horizontal pleiotropy. Leave-one-out analysis did not reveal any significant outliers (Supplementary Figs. 1–12).

3.2. Causal effect of TAA on peripheral immune cells

To ascertain the absence of inverse causality between CD45-positive NKT cells and CD45-positive HLA DR + CD8br cells with TAA and, concurrently, to delve deeper into the intricate dynamics between TAA and immunological mechanisms, we embarked on a comprehensive investigation. This involved a meticulous examination of potential reverse causal linkages, ensuring the rigor of our findings in delineating the intricate interplay between TAA and the immune system's cellular constituents. In this analysis, TAA was posited as the exposure variable, and 731 types of peripheral immune cells were considered as the outcomes. Confronted with the absence of significant intersections between the results of two study cohorts at the conventional p-value threshold of 0.05, we strategically recalibrated the significance criterion for the IVW metric in our reverse MR approach to 0.1. Within the ambit of the FinnGen study, 85 cellular phenotypes were identified with a p-value <0.1 in the IVW analysis (Supplementary Table 4); similarly, in the CHIP + MGI cohort, 61 cell types met this threshold (Supplementary Table 5). A cross-cohort comparison revealed an overlap of 10 cell types (Supplementary Table 6). However, a rigorous exclusion of cells with discordant OR directions across cohorts distilled this number to
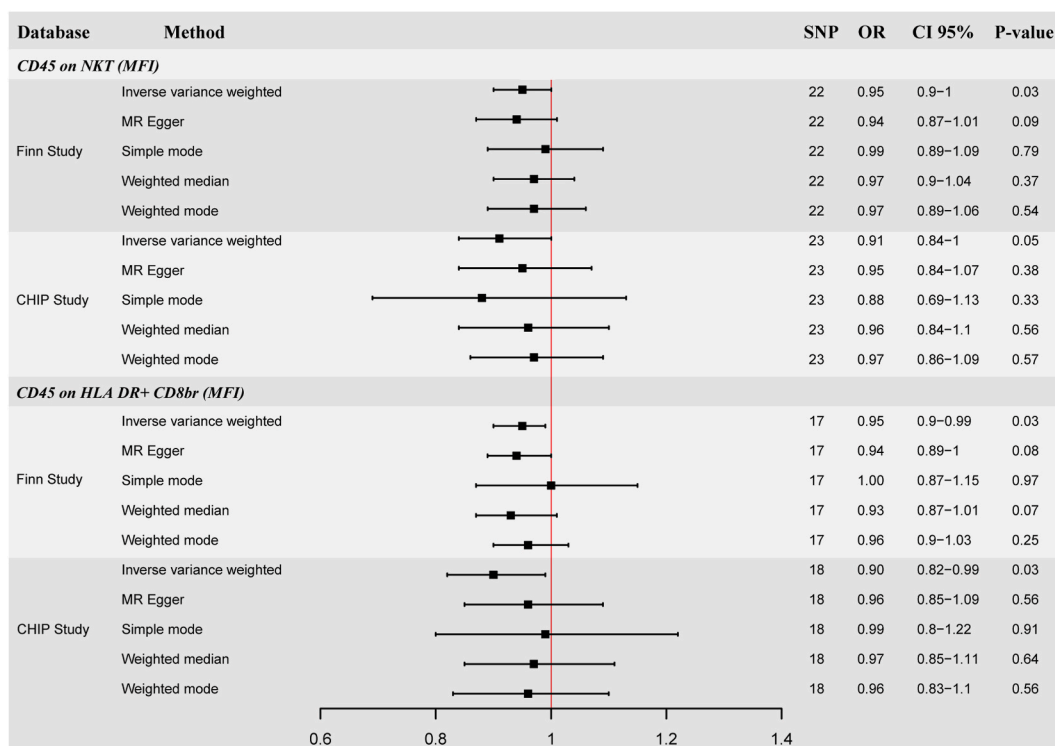
Database	Method		SNP	OR	CI 95%	P-value
CD45 on NKT (MFI)						
	Inverse variance weighted		22	0.95	0.9–1	0.03
	MR Egger		22	0.94	0.87–1.01	0.09
Finn Study	Simple mode		22	0.99	0.89–1.09	0.79
	Weighted median		22	0.97	0.9–1.04	0.37
	Weighted mode		22	0.97	0.89–1.06	0.54
	Inverse variance weighted		23	0.91	0.84–1	0.05
	MR Egger		23	0.95	0.84–1.07	0.38
CHIP Study	Simple mode		23	0.88	0.69–1.13	0.33
	Weighted median		23	0.96	0.84–1.1	0.56
	Weighted mode		23	0.97	0.86–1.09	0.57
CD45 on HLA DR+ CD8br (MFI)						
	Inverse variance weighted		17	0.95	0.9–0.99	0.03
	MR Egger		17	0.94	0.89–1	0.08
Finn Study	Simple mode		17	1.00	0.87–1.15	0.97
	Weighted median		17	0.93	0.87–1.01	0.07
	Weighted mode		17	0.96	0.9–1.03	0.25
	Inverse variance weighted		18	0.90	0.82–0.99	0.03
	MR Egger		18	0.96	0.85–1.09	0.56
CHIP Study	Simple mode		18	0.99	0.8–1.22	0.91
	Weighted median		18	0.97	0.85–1.11	0.64
	Weighted mode		18	0.96	0.83–1.1	0.56

Fig. 2. Forest plot for the causal effect of peripheral immune cells on TAA. OR, odds ratio; CI, confidence interval; TAA, thoracic aortic aneurysm; SNP, single nucleotide polymorphism; MFI, median fluorescence intensity.

three cell types of substantive relevance to TAA. Among this, two belong to the T regulatory (Treg) cell panel, representing distinct investigative approaches (relative count and absolute count) of the same cell type, specifically encompassing CD28$^+$ CD45RA- CD8br %CD8br (OR: 0.88, 95CI%: 0.81–0.96 in FinnGen study; OR: 0.97, 95CI%: 0.93–1.00 in CHIP + MGI study) and CD28$^+$ CD45RA-CD8br AC (OR: 0.90, 95CI%: 0.82–0.98 in FinnGen study; OR: 0.97, 95CI%: 0.93–1.00 in CHIP + MGI study). The third cell type falls within the maturation stages of the T cell panel, characterized as the HVEM CM CD8br cells (OR: 1.16, 95CI%: 1.01–1.34 in the FinnGen study; OR: 1.06, 95CI%: 1.00–1.13 in the CHIP + MGI study). These results are shown in Fig. 3. Further analytical rigor was applied through heterogeneity and horizontal pleiotropy assessments, which affirmed the uniformity and absence of pleiotropy across both cohorts. This was corroborated by funnel plot and scatter plot analyses, underscoring the methodological soundness of our findings. Additionally, a leave-one-out sensitivity analysis was employed, which substantiated the absence of notable outliers (Supplementary Figs. 13–30).

4. Discussion

We explored the causal relationships between 731 types of peripheral immune cells and TAA with a two-sample MR analysis. In this study, we utilized two distinct TAA cohorts for the investigation of causal interactions with immune cells. By integrating the findings from these cohorts, we were able to derive outcomes that were both more precise and robust. Our study identified that immune cells within the TBNK panel, particularly CD45$^+$ NKT cells and CD45$^+$ HLA-DR + CD8$^+$ T cells, demonstrate a protective role against TAA. Furthermore, we conducted an analysis on the effects of TAAs on peripheral immune cells. Utilizing reverse MR analysis, the results indicate that TAA provides a protective influence on CD28$^+$ CD45RA- CD8$^+$ T cells, in terms of both relative and absolute counts. Conversely, TAA was found to be detrimental to HVEM + CM + CD8$^+$ T cells.

The current diagnosis of TAA mainly relies on computed tomographic angiography (CTA). However, as an invasive examination, CTA is not suitable for routine screening in the general population. Yet, TAAs often have a covert onset, and when the aortic diameter enlarges to a certain extent, it may threaten life. Moreover, the current main treatment for TAA is surgical. However, traditional surgery is difficult and risky; endovascular intervention is expensive and not applicable for complex TAAs. Therefore, exploring
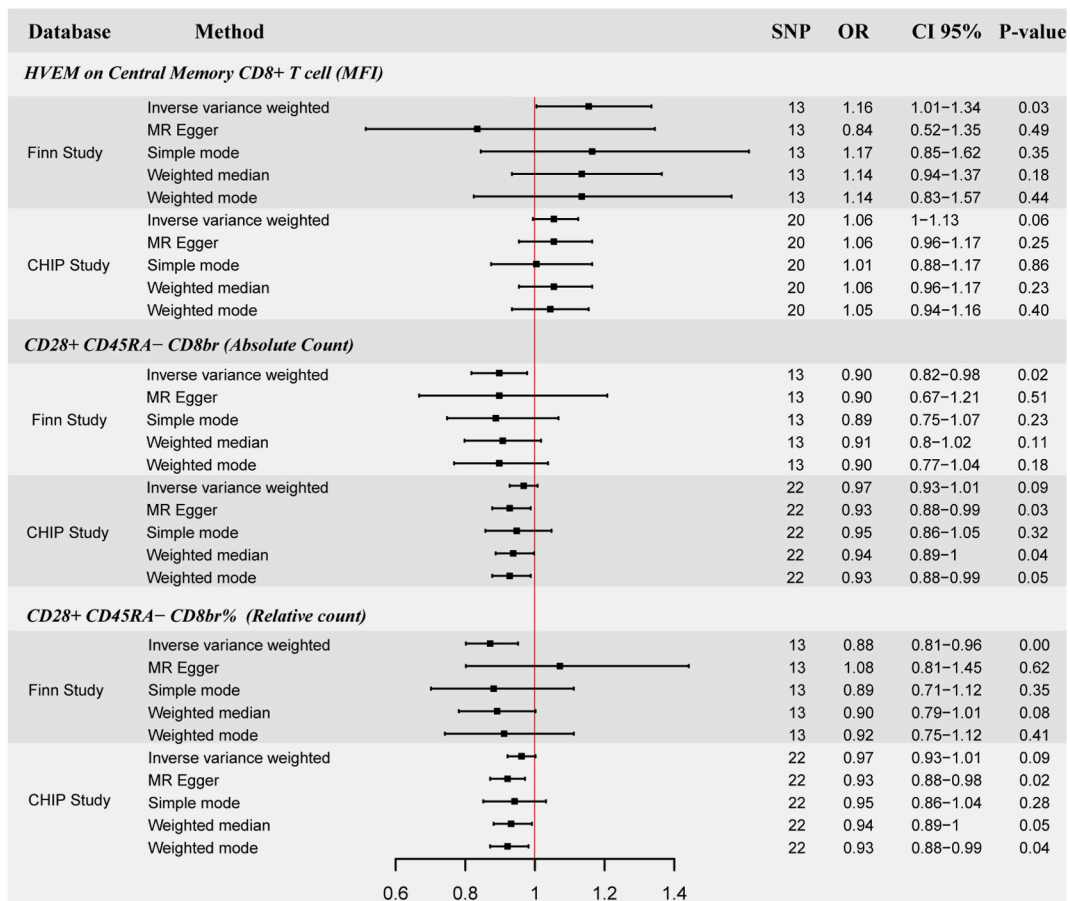
Database	Method	SNP	OR	CI 95%	P-value
HVEM on Central Memory CD8+ T cell (MFI)					
Finn Study	Inverse variance weighted	13	1.16	1.01–1.34	0.03
	MR Egger	13	0.84	0.52–1.35	0.49
	Simple mode	13	1.17	0.85–1.62	0.35
	Weighted median	13	1.14	0.94–1.37	0.18
	Weighted mode	13	1.14	0.83–1.57	0.44
CHIP Study	Inverse variance weighted	20	1.06	1–1.13	0.06
	MR Egger	20	1.06	0.96–1.17	0.25
	Simple mode	20	1.01	0.88–1.17	0.86
	Weighted median	20	1.06	0.96–1.17	0.23
	Weighted mode	20	1.05	0.94–1.16	0.40
CD28+ CD45RA− CD8br (Absolute Count)					
Finn Study	Inverse variance weighted	13	0.90	0.82–0.98	0.02
	MR Egger	13	0.90	0.67–1.21	0.51
	Simple mode	13	0.89	0.75–1.07	0.23
	Weighted median	13	0.91	0.8–1.02	0.11
	Weighted mode	13	0.90	0.77–1.04	0.18
CHIP Study	Inverse variance weighted	22	0.97	0.93–1.01	0.09
	MR Egger	22	0.93	0.88–0.99	0.03
	Simple mode	22	0.95	0.86–1.05	0.32
	Weighted median	22	0.94	0.89–1	0.04
	Weighted mode	22	0.93	0.88–0.99	0.05
CD28+ CD45RA− CD8br% (Relative count)					
Finn Study	Inverse variance weighted	13	0.88	0.81–0.96	0.00
	MR Egger	13	1.08	0.81–1.45	0.62
	Simple mode	13	0.89	0.71–1.12	0.35
	Weighted median	13	0.90	0.79–1.01	0.08
	Weighted mode	13	0.92	0.75–1.12	0.41
CHIP Study	Inverse variance weighted	22	0.97	0.93–1.01	0.09
	MR Egger	22	0.93	0.88–0.98	0.02
	Simple mode	22	0.95	0.86–1.04	0.28
	Weighted median	22	0.94	0.89–1	0.05
	Weighted mode	22	0.93	0.88–0.99	0.04

0.6   0.8   1   1.2   1.4

Fig. 3. Forest plot for the causal effect of TAA on peripheral immune cells. OR, odds ratio; CI, confidence interval; TAA, thoracic aortic aneurysm; SNP, single nucleotide polymorphism; MFI, median fluorescence intensity.

convenient and rapid strategies for early diagnosis of TAA and safe and effective treatment strategies has significant clinical importance.

Current research indicates that leukocyte subgroups are correlated with aortic aneurysms, including TAA and abdominal aortic aneurysm (AAA), suggesting that specific leukocyte subgroups may serve as clinical biomarkers for AAA screening [11,12]. Our study shows that TAA is related to the quantity of different subtypes of T lymphocytes in circulation. Although no related clinical studies have been conducted yet, this undoubtedly provides a new thought for the early diagnosis of TAA, by screening the large population for TAA through measuring the proportion of specific lymphocyte subgroups in peripheral blood. Additionally, current research has explored new treatment methods for aortic aneurysms [13]. Existing studies have shown that inhibiting immune checkpoints can slow down the growth of AAA [14]. Furthermore, our research also indicates that circulating immune cells can inhibit TAA, such as the TBNK panel, which provides new targets for the immunotherapy of TAA. Additionally, cellular therapies, such as chimeric antigen receptor T cells (CAR-T), have also achieved promising preclinical results in the treatment of cardiovascular diseases [15,16]. Based on the results of this study, designing cell therapies targeting specific subsets of lymphocytes is a potential strategy for treating TAA. Certainly, the study primarily investigates the interaction between immune cells and TAA to uncover pathological mechanisms, aiming to elucidate the link between immune responses and TAA. Applying these insights to clinical practice requires further exploration.

NKT cells, unique T cell subsets, combine TCR specificity for certain lipids and NK cell markers like NK1.1, Ly49, CD16 and CD122. Presented antigens via CD1d molecules on APCs, these cells exhibit variant TCRs in humans and semi-invariant ones in mice [17,18]. They're activated by CD1d-dependent/independent pathways, including cytokine signaling. NKT cells secrete both pro- and anti-inflammatory cytokines, contributing to the immune response and cytolytic activity [19,20]. Their dysregulation links to diseases like autoimmune diseases, infectious disease and cancer [21–25].

$CD45^+$ HLA-DR + $CD8^+$ T cells indicate a population of $CD8^+$ T cells that are highly active, as the presence of HLA-DR, a marker not typically found on resting $CD8^+$ T cells. Previous studies have demonstrated that a subset of partially activated T cells exhibit CD248 expression. Concurrently, there is an observed upregulation of the anti-inflammatory cytokine IL-10, coupled with a downregulation of pro-inflammatory cytokines, specifically IL-1β and INF-γ. This modulation in cytokine expression contributes to a decrease in pathological vascular remodeling, thereby attenuating the progression of TAAs [26]. Conversely, the findings in studies focusing on AAAs, present a contrasting perspective. A study that collects peripheral serum from patients with AAAs indicates that the levels of $CD8^+$ T cells in the serum of AAAs patients are higher compared to healthy individuals. Notably, patients with larger aneurysms exhibit higher levels of $CD8^+$ T cells than those with smaller aneurysms [27]. Furthermore, Zhou et al. indicate that CD43 on the surface of $CD8^+$ T cells can induce the production of IFN-γ and participate in the inflammatory cascade, thereby promoting the development of aneurysms [28]. A previous study reveals that NKT cells, particularly IL-4 producing types, may exacerbate plaque growth in apoE-/- mice [29]. Subsequent studies identified CD1d expression on dendritic cells and macrophages within human atherosclerotic lesions, suggesting a role in lesion development [30]. In the tissue of AAAs, activated NKT cells primarily produce IFN-γ, leading to an upregulation of Fas expression and an increase in vascular smooth muscle cells (VSMCs) apoptosis [31]. Additionally, NKT cells can upregulate the expression of matrix metalloproteinase in macrophages and endothelial cells, thereby promoting the formation of AAAs [32].

Several factors may contribute to the observed differences. Firstly, the pathogenesis of AAA and TAA differs. AAAs primarily originate from atherosclerotic lesions leading to endothelial damage and subsequent structural and functional changes in the aortic wall [33,34]. NKT cells express adhesion molecules common in the hematopoietic system, bind to endothelial cells, respond to chemotactic stimuli, and exacerbate local inflammation. Conversely, TAAs are often caused by genetic mutations, such as TGF-beta signaling-related genes, affecting aortic wall strength, leading to dilation under hypertension, with endothelial function generally remaining intact [35,36]. Secondly, this study's findings on TBNK cell spatial distribution differ from previous research. Studies on AAAs mainly explore local NKT cell impacts and mechanisms on the aortic wall, whereas our study investigates the relationship between circulating NKT cells and TAAs. Research indicates that NKT cells exhibit different phenotypes and functions between tissues and peripheral blood, indirectly explaining these differences [37,38]. However, further exploration is needed to understand the functional differences of immune cells in TAA peripheral blood and aortic tissue. Lastly, with advancements in molecular biology enabling finer classification of immune cells, different subtypes exhibit varied functions. Our study categorized immune cells into 731 subtypes, not entirely aligning with previous research, potentially leading to functional discrepancies. Certainly, further exploration is needed to understand the functional differences of immune cells in TAA peripheral blood and aortic tissue.

Moreover, our study further investigated the effects of TAA on the peripheral immune cell profile. The findings reveal that TAA results in a decrease in both the relative and absolute counts of the $CD28^+$ CD45RA- $CD8^+$ T cells subset within peripheral Tregs. Tregs have been demonstrated to regulate the function of VSMCs within aortic aneurysm tissues by expressing trefoil factor 1 (Tff1). This regulation promotes tissue repair, thereby inhibiting the formation of TAA [39]. In a study focusing on aortic aneurysms in HIV patients, there is a negative correlation between the circulating Tregs in HIV patients and the diameter of the aortic aneurysm, which is consistent with the results of our study [40]. Additionally, CD28 can interact with $CD8^+$ T cells through the activation of phosphatidylinositol 3-kinase (PI3K) during the internalization of the immunological synapse, facilitated by its interaction with the B7 ligand [41]. Recent research has elucidated that CD28 can be deactivated via PD-1 signaling pathways, resulting in the inhibition of T cell functionality [42]. This finding underscores the pivotal role of co-stimulatory pathways in the modulation of effector T cell activities and points towards novel strategies in immunotherapy, specifically targeting Tregs for the treatment of TAA.

HVEM, also known as herpesvirus entry mediator, is a member of the tumor necrosis factor receptor (TNFR) family. It engages in interactions with ligands from the TNF family, such as LIGHT and lymphotoxin-α, as well as with members of the immunoglobulin family, including B and T lymphocyte attenuators (BTLA) and CD160 [43,44]. These interactions are crucial in promoting the survival of T cells and the formation of memory cells, playing a significant role in immune responses against viral infections and tumors. In

specific pathological conditions, such as during viral infections or in the presence of tumors, the bidirectional co-stimulatory interaction between HVEM and BTLA is essential for antiviral defense and the differentiation of memory CD8 T cells [45]. HVEM engagement via BTLA recruits type 2 tyrosine phosphatases-1/-2 to BTLA to transmit inhibitory signals [46]. Conversely, HVEM engagement via BTLA recruits TRAF2 to HVEM, transmitting pro-inflammatory signals and thereby activating NF-κB [47]. Therefore, HVEM serves as a crucial immunoregulatory factor and plays a significant role in the immunotherapy of tumors and in the management of autoimmune diseases [48,49]. At present, the research landscape detailing the association between HVEM-positive immune cells and TAA remains largely uncharted. This gap presents a valuable and compelling prospect for advancing our understanding of the complex interplay between TAA and the intricacies of immune function.

Although further research is required to fully understand the relationship between HVEM + immune cells and TAA, HVEM plays a crucial role during viral infections. This study raises questions about the relationship between viral infections and aortic diseases. Cytomegalovirus (CMV), a significant human pathogen, infects most people at some point in their lives. In immunocompetent individuals, CMV usually remains latent without clinical symptoms. However, in immunocompromised states, CMV can reactivate, triggering an immune-inflammatory response. Studies have reported that CMV can lie dormant within the aortic wall, and its reactivation may induce an inflammatory response in the aorta, potentially leading to aneurysm formation [50]. Reactivation of latent CMV infection could promote the formation of atherosclerosis in humans [51]. Serological studies have found that high levels of CMV antibodies are associated with clinically apparent atherosclerosis [52]. CMV can induce VSMCs migration, affect lipid metabolism, induce adhesion molecule expression, control cytokine and chemokine production, and exacerbate inflammatory responses by inducing COX-2 and 5-lipoxygenase expression, thereby activating macrophages [53]. Previous research also highlighted the significant role of macrophages in the inflammatory response of aortic aneurysms. CMV can infect VSMCs, promoting the expression of matrix metalloproteinases, which degrade collagen and elastin fibers [54]. Therefore, the reactivation of CMV is associated with the formation of aortic aneurysms, though it may not be the decisive factor [55]. Targeting HVEM + T cells could potentially inhibit the aortic wall's inflammatory response caused by viral reactivation.

CMV-encoded microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) play significant roles in the virus's life cycle, especially during latency and reactivation. CMV-encoded miRNAs regulate the virus's latency and reactivation. For example, miR-UL112-3p, one of the most studied CMV-encoded miRNAs, binds to the 3′UTR of the host cell's MICB, suppressing its expression to help CMV evade immune detection mediated by NKG2D, possibly a mechanism for maintaining latent infection [56]. Moreover, miR-UL112-3p can diminish the cytotoxicity of natural killer cells by reducing type I interferon signaling, further facilitating the virus's latency and immune evasion [57,58]. CMV-encoded lncRNAs also play vital roles in the virus's lifecycle. Notably, lncRNA4.9 regulates viral DNA replication. Studies have shown that RNA4.9, by forming R-loop structures, regulates viral DNA replication, affecting the levels of the viral single-stranded DNA binding protein, potentially establishing a connection between the activity regulation at the viral DNA replication origin and the modulation of ssDBP levels [59]. This indicates that lncRNA4.9, through a conserved mechanism in beta-herpesviruses, regulates viral DNA replication and may play a key role in viral latency and reactivation. Therefore, in-depth research into these non-coding RNAs' functions and mechanisms is vital for understanding CMV's pathophysiology and developing new therapeutic strategies against CMV-induced aortic wall inflammation.

In this study, we conducted a meticulous and robust analysis of the relationship between TAA and the immune system, intersecting MR analysis from two large GWAS cohorts of TAA with 731 types of peripheral immune cells. This approach has yielded new insights into the immunological underpinnings of TAA pathogenesis, providing a novel insight for future explorations in immunotherapy and cellular treatment modalities. However, this study has some limitations. Firstly, the absence of individual-level data precluded the possibility of more nuanced, stratified population analysis. Secondly, the research, being rooted in a European demographic, may not extend its applicability to other ethnic groups, thus potentially limiting the global applicability of our findings. Lastly, the adoption of a relatively lenient threshold in reverse MR analysis might have introduced a higher probability of false-positive results.

5. Conclusion

Our study elucidates the potential protective influence exerted by specific subsets of peripheral NKT cells and CD8$^+$ T cells in mitigating the development of TAA, while simultaneously highlighting the reciprocal effects of TAA on peripheral Treg cells subsets and T cell subsets. This underscores the complex and dynamic interplay between the immune system and TAA. Moreover, our findings propose that particular immune cell types and genetic predispositions may act as biomarkers for assessing TAA risk, offering novel avenues for targeted therapeutic interventions. This could provide valuable clues for earlier detection and more efficacious treatment strategies for TAA.

Data sharing statement

All data analysed in this study can be obtained by a reasonable request to corresponding authors.

CRediT authorship contribution statement

Haoyu Gao: Writing – review & editing, Writing – original draft, Validation, Resources, Funding acquisition, Formal analysis, Conceptualization. **Xin Wang:** Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Hanghang Gan:** Software. **Ming Li:** Software. **Jun Shi:** Visualization, Supervision, Project administration. **Yingqiang Guo:** Visualization, Supervision, Project administration.

Declaration of competing interest

Acknowledgments

Appendix A. Supplementary data

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