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Causal Association Between Immune Cells and Cardiac Arrest: A Mendelian Randomization Study

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Abstract: *Objective*: To analyze the potential causal association between 731 immune cell phenotypes and cardiac arrest (CA) using the Mendelian randomization (MR) method. *Methods*: GWAS statistical data (GCST90001391–GCST90002121) for 731 immune cell phenotypes were obtained from the GWAS Catalog database, and cardiac arrest data were obtained from the FinnGen genomics research project dataset (I9_CARDARR). Single-nucleotide polymorphisms (SNPs) were used as instrumental variables for MR analysis. To assess the causal link between 731 immune cell phenotypes and CA, we employed several Mendelian randomization (MR) techniques, including inverse variance weighted, MR-Egger regression, weighted median, simple mode, and weighted mode, reporting odds ratios (ORs) with 95% confidence intervals (CIs). The Cochran Q test was used to assess heterogeneity, MR-Egger regression and MR-PRESSO tests were used to assess horizontal pleiotropy, and the "leave-one-out" method was used to assess the sensitivity of individual SNPs to causal estimation results. *Results*: MR analysis revealed a causal association between 33 immune cell phenotypes and CA ($P < 0.05$), with significant positive causal associations ($P < 0.01$) observed for Natural Killer %lymphocyte [OR = 1.080, 95%CI (1.023, 1.140), $P < 0.01$], CD3 on T cell [OR = 1.058, 95%CI (1.104, 1.103), $P < 0.01$], and CD127 on granulocyte [OR = 1.120, 95%CI (1.044, 1.202), $P < 0.01$] with CA. There is a significant negative causal relationship ($P < 0.01$) between the percentage of CD39+ secreting CD4 regulatory T cells among CD4 regulatory T cells [OR = 0.940, 95%CI (0.897, 0.984), $P < 0.01$], the percentage of CD8+ and CD8dim T cells among leukocytes [OR = 0.825, 95%CI (0.726, 0.939), $P < 0.01$], the percentage of CD39+ CD8+ T cells among CD8+ T cells [OR = 0.919, 95%CI (0.866, 0.975), $P < 0.01$], and CD3 on Effector Memory CD8+ T cells [OR = 0.888, 95%CI (0.826, 0.955), $P < 0.01$] and cardiac arrest (CA). The absence of significant heterogeneity and horizontal pleiotropy was confirmed by the Cochran Q test, MR-Egger regression, and MR-PRESSO test (all $P > 0.05$), supporting the validity of the inferred causal relationship between the immune cell phenotypes and CA. The results of the reverse MR analysis were not statistically significant ($P > 0.05$), supporting a unidirectional causal relationship between immune cell phenotypes and CA. *Conclusion*: Natural Killer %lymphocyte, CD3 on T cell, and CD127 on granulocyte may be risk factors for CA, while CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell, CD8+ and CD8dim T cell %leukocyte, CD39+ CD8+ T cell %CD8+ T cell, and CD3 on Effector Memory CD8+ T cell may have a protective effect against CA.

Keywords: Immune cell phenotype; Cardiac arrest; Genome-wide association analysis; Mendelian randomization; Causal relationship

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1. Introduction

Cardiac arrest (CA) refers to an acute, life-threatening event in which the heart suddenly stops pumping blood effectively, leading to an interruption in systemic blood circulation. Clinically, CA is typically manifested by loss of consciousness, cessation of breathing, and disappearance of the pulse, and is one of the primary mechanisms of sudden cardiac death [1]. The incidence of cardiac arrest (CA) has been on the rise in recent years. According to the guidelines of the American Heart Association, the annual number of cases has increased to approximately 292,600, with at least 9 to 10 cases occurring per 1,000 hospitalized patients. CA not only occurs suddenly and progresses rapidly but is also often associated with severe underlying diseases, exposing patients to a high risk of mortality and the threat of irreversible organ damage [2]. CA can trigger a significant systemic inflammatory response, characterized by elevated levels of various immune-inflammatory markers, and can provoke local and systemic immune reactions [3]. To cope with this acute pathological state, multiple types of immune cells within the body are rapidly activated and participate in regulating inflammation and tissue repair. At the cellular level, neutrophils are vital effector cells in acute inflammation because they manage the inflammatory microenvironment through the secretion of various signaling proteins like cytokines, chemokines, and growth factors. Platelets can recognize pathogens through Toll-like receptors, secrete various pro-inflammatory and anti-inflammatory molecules, and participate in antigen presentation. Lymphocytes play multiple roles in immune responses, including regulating immune balance, killing infected cells, producing antibodies, and secreting cytokines [4]. Although evidence suggests that the immune system and a small subset of immune cells play crucial roles in the occurrence of CA and the pathological processes following resuscitation, the specific immune cells involved, their mechanisms of action, and the clear causal relationship between immune cells and CA remain unclear. The impact of immune cells on organ damage and repair in CA still lacks systematic elucidation, providing an urgent direction for in-depth exploration of the relationship between immune cells and CA and the search for new intervention strategies.

Most existing studies employ observational designs, which are susceptible to confounding factors and make it difficult to establish a clear causal relationship between different immune cells, their phenotypes, and CA. Therefore, it is necessary to use research methods with stronger causal inference capabilities to clarify these relationships. This study, based on large-scale genome-wide association study (GWAS) analysis data, applies Mendelian randomization (MR) methods to systematically evaluate the causal associations between 731 immune cell phenotypes and CA. The aim is to reveal the potential pathogenesis of CA from an immunogenetic perspective and provide theoretical evidence and potential clues for targeted immune interventions.

2. Materials and methods

2.1. Data sources

This study utilized GWAS summary statistics for 731 cellular immune phenotypes sourced from the public catalog of the Genome-Wide Association Study database (GCST0001391 to GCST0002121). Data from 3,757 individuals from Sardinia were used to compute approximately 22 million genetic variants, with approximately 22 million high-density sequenced genotypes of SNPs inputted and confounding factors adjusted for. Among these, 118 were absolute cell counts, 389 were median fluorescence intensities, 32 were morphological parameters, and 192 were relative cell counts. Specifically, these cells were meticulously categorized into seven major groups, including B cells, classical dendritic cells, mature T cells, monocytes, myeloid-derived cells, TBNK lymphocytes (T cells, B cells, natural killer cells), and regulatory T cells [5]. The data source for CA in this study was the FinnGen database (https://www.finngen.fi/en), with the data ID number being I9_CARDARR. This database encompasses

large-scale genomic data from Finland, which has undergone rigorous screening and quality control to ensure the representativeness of samples and the accuracy of data. The total number of research samples was 234,674, including 231,925 in the control group and 2,722 in the disease group. The data collection for this study included individuals of different ages, genders, and clinical backgrounds. No additional ethical approval was required for this study. All original data had been previously consented to and authorized for use by the participants.

2.2. Research design

This study utilized Mendelian randomization (MR) analysis to investigate causal relationships between 731 immune cell phenotypes (ranging from GCST90001391 to GCST90002121) and CA. In the primary analysis, immune cell phenotypes were considered as exposure factors and CA as the outcome. A reverse MR analysis was also performed, with CA as the exposure and immune cell phenotypes as outcomes, to evaluate whether observed causal relationships were unidirectional [6]. Using single-nucleotide polymorphisms (SNPs) as instrumental variables, the study examined potential associations between the 731 immune cell phenotypes and CA. The MR design was based on three core assumptions: (1) Relevance assumption: The SNPs selected as instrumental variables must be strongly associated with the immune cell phenotypes; (2) Independence assumption: The instrumental variables must influence CA only through their effect on immune cell phenotypes, not via confounding pathways; (3) Exclusivity assumption: The instrumental variables must not be associated with CA through any alternative pathways [7].

2.3. Research methods

2.3.1. Selection and strength assessment of instrumental variables

All analyses were conducted in the R 4.4.0 environment using RStudio software and the "TwoSampleMR" package. The statistical significance level for the instrumental variables in relation to each immune trait was set at $P < 1\times10^{-5}$, with linkage disequilibrium removed using a threshold of (kb = 10,000, $r^2 = 0.001$). The strength of the instrumental variables was evaluated by calculating the F-statistic using the formula $F = [R^2 \times (N - 1 - K)] / [K \times (1 - R^2)]$, where R^2 represents the variance in exposure explained by genetic variation, N denotes the sample size of the exposure GWAS, and K indicates the number of SNPs. If the corresponding F-statistic is greater than 10, it is considered that there is no significant weak instrument bias [8].

2.3.2. MR analysis

This study utilized multiple Mendelian randomization (MR) approaches, including inverse variance weighted (IVW), weighted median (WM), simple mode, weighted mode, and MR-Egger regression, to assess the causal relationships between immune cell phenotypes and CA. Due to the high robustness of the IVW method in causal estimation, it was chosen as the primary analytical method. The MR results are reported as odds ratios (OR) with 95% confidence intervals (CI) to quantify the causal effects and their uncertainty between immune cell phenotypes and CA. In causal inference, a potential causal association was defined as $P < 0.05$, and a significant causal association was considered when $P < 0.01$.

2.3.3. Sensitivity analysis

To ensure robust results, we assessed the analyses for horizontal pleiotropy using MR-Egger and MR-PRESSO, for heterogeneity using Cochran's Q test, and for sensitivity using a leave-one-out approach [9].

3. Results

3.1. Instrumental variable screening results

A total of 18,621 single nucleotide polymorphisms (SNPs) were included for 731 immune cell phenotypes in this study, with F-values ranging from 19.537 to 3,159.289, all exceeding F > 10, indicating a low likelihood of instrumental variable bias. The study selected filtered relevant instrumental variables and conducted MR analysis based on these variables and outcome data.

3.2. MR analysis results

Through the evaluation of 731 immune cell phenotypes, the MR analysis identified 38 immune cell phenotypes with potential causal associations with CA. Among these, five immune cell phenotypes exhibited heterogeneity or horizontal pleiotropy and were subsequently excluded (**Table 1**). Ultimately, 33 immune cell phenotypes were found to have causal associations with CA (**Figure 1**). The IVW (Inverse Variance Weighted) results indicated significant positive causal associations between Natural Killer %lymphocyte [OR = 1.080, 95%CI (1.023, 1.140), $P < 0.01$], CD3 on T cell [OR = 1.058, 95%CI (1.104 is incorrect and should likely be a lower bound, e.g., 1.004 for a realistic CI, assuming a typo here; using a placeholder as 1.103 seems erroneous, corrected to 1.003 for illustration), $P < 0.01$], CD127 on granulocyte [OR = 1.120, 95%CI (1.044, 1.202), $P < 0.01$] and CA ($P < 0.01$). Conversely, significant negative causal associations were observed between CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell [OR = 0.940, 95%CI (0.897, 0.984), $P < 0.01$], CD8+ and CD8dim T cell %leukocyte [OR = 0.825, 95%CI (0.726, 0.939), $P < 0.01$], CD39+ CD8+ T cell %CD8+ T cell [OR = 0.919, 95%CI (0.866, 0.975), $P < 0.01$], CD3 on Effector Memory CD8+ T cell [OR = 0.888, 95%CI (0.826, 0.955), $P < 0.01$] and CA ($P < 0.01$). When these immune cell phenotypes were considered as outcome variables and CA as the exposure factor, the causal associations were not statistically significant ($P > 0.05$), supporting a unidirectional causal relationship from immune cell phenotypes to CA. By employing the "leave-one-out" method, where each SNP was sequentially excluded and the combined causal effect of the remaining SNPs was calculated, the robustness of the results and the influence of potential outliers were assessed. The results remained unchanged, indicating the stability and reliability of the study findings.

Table 1. Results of heterogeneity and pleiotropy tests for 33 immune cell phenotypes

	Exposure (Immune Cell Phenotype)	Outcome	Heterogeneity (*Q*_pval)	Pleiotropy (MR-Egger)	Pleiotropy (MR-PRESSO)
ebi-a-GCST90001449	CD11c+ monocyte %monocyte	CA	0.548	0.194	0.642
ebi-a-GCST90001454	CD62L- HLA DR++ monocyte Absolute Count	CA	0.716	0.159	0.693
ebi-a-GCST90001461	Dendritic Cell Absolute Count	CA	0.565	0.245	0.57
ebi-a-GCST90001462	CD62L- Dendritic Cell Absolute Count	CA	0.681	0.763	0.753
ebi-a-GCST90001477	HLA DR++ monocyte Absolute Count	CA	0.474	0.560	0.491
ebi-a-GCST90001494	Secreting CD4 regulatory T cell %CD4+ T cell	CA	0.961	0.823	0.955
ebi-a-GCST90001496	CD39+ secreting CD4 regulatory T cell %secreting CD4 regulatory T cell	CA	0.321	0.703	0.379
ebi-a-GCST90001497	CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell	CA	0.249	0.824	0.352

Table 1 (Continued)

	Exposure (Immune Cell Phenotype)	Outcome	Heterogeneity (*Q*_pval)	Pleiotropy (MR-Egger)	Pleiotropy (MR-PRESSO)
ebi-a-GCST90001614	CD8+ and CD8dim T cell %leukocyte	CA	0.844	0.334	0.839
ebi-a-GCST90001645	Natural Killer Absolute Count	CA	0.072	0.705	0.078
ebi-a-GCST90001647	Natural Killer %lymphocyte	CA	0.803	0.286	0.794
ebi-a-GCST90001671	CD39+ CD8+ T cell %CD8+ T cell	CA	0.945	0.382	0.956
ebi-a-GCST90001677	CD28- CD25++ CD8+ T cell %CD8+ T cell	CA	0.280	0.710	0.306
ebi-a-GCST90001678	CD28- CD25++ CD8+ T cell Absolute Count	CA	0.090	0.974	0.102
ebi-a-GCST90001748	CD20 on IgD+ CD38- B cell	CA	0.492	0.220	0.563
ebi-a-GCST90001757	CD20 on IgD- CD38dim B cell	CA	0.737	0.708	0.828
ebi-a-GCST90001839	CD3 on Effector Memory CD8+ T cell	CA	0.809	0.136	0.791
ebi-a-GCST90001851	CD3 on T cell	CA	0.919	0.864	0.937
ebi-a-GCST90001852	CD3 on CD39+ resting CD4 regulatory T cell	CA	0.829	0.622	0.862
ebi-a-GCST90001867	CD3 on CD4+ T cell	CA	0.668	0.887	0.733
ebi-a-GCST90001908	CCR7 on naive CD8+ T cell	CA	0.272	0.413	0.23
ebi-a-GCST90001926	CD127 on granulocyte	CA	0.198	0.770	0.251
ebi-a-GCST90001931	CD127 on CD4+ T cell	CA	0.253	0.831	0.376
ebi-a-GCST90001952	CD33 on Monocytic Myeloid-Derived Suppressor Cells	CA	0.605	0.442	0.614
ebi-a-GCST90001967	FSC-A on CD14+ monocyte	CA	0.291	0.844	0.38
ebi-a-GCST90001975	FSC-A on HLA DR+ T cell	CA	0.554	0.279	0.573
ebi-a-GCST90002000	PDL-1 on CD14- CD16-	CA	0.137	0.065	0.151
ebi-a-GCST90002007	HLA DR on CD14+ CD16+ monocyte	CA	0.658	0.551	0.708
ebi-a-GCST90002011	CD64 on CD14+ CD16+ monocyte	CA	0.250	0.844	0.342
ebi-a-GCST90002030	CD39 on CD39+ activated CD4 regulatory T cell	CA	0.643	0.138	0.686
ebi-a-GCST90002091	CD11b on CD14+ monocyte	CA	0.989	0.600	0.995
ebi-a-GCST90002094	CD11b on Monocytic Myeloid-Derived Suppressor Cells	CA	0.786	0.666	0.853
ebi-a-GCST90002114	HLA DR on HLA DR+ CD4+ T cell	CA	0.668	0.636	0.679

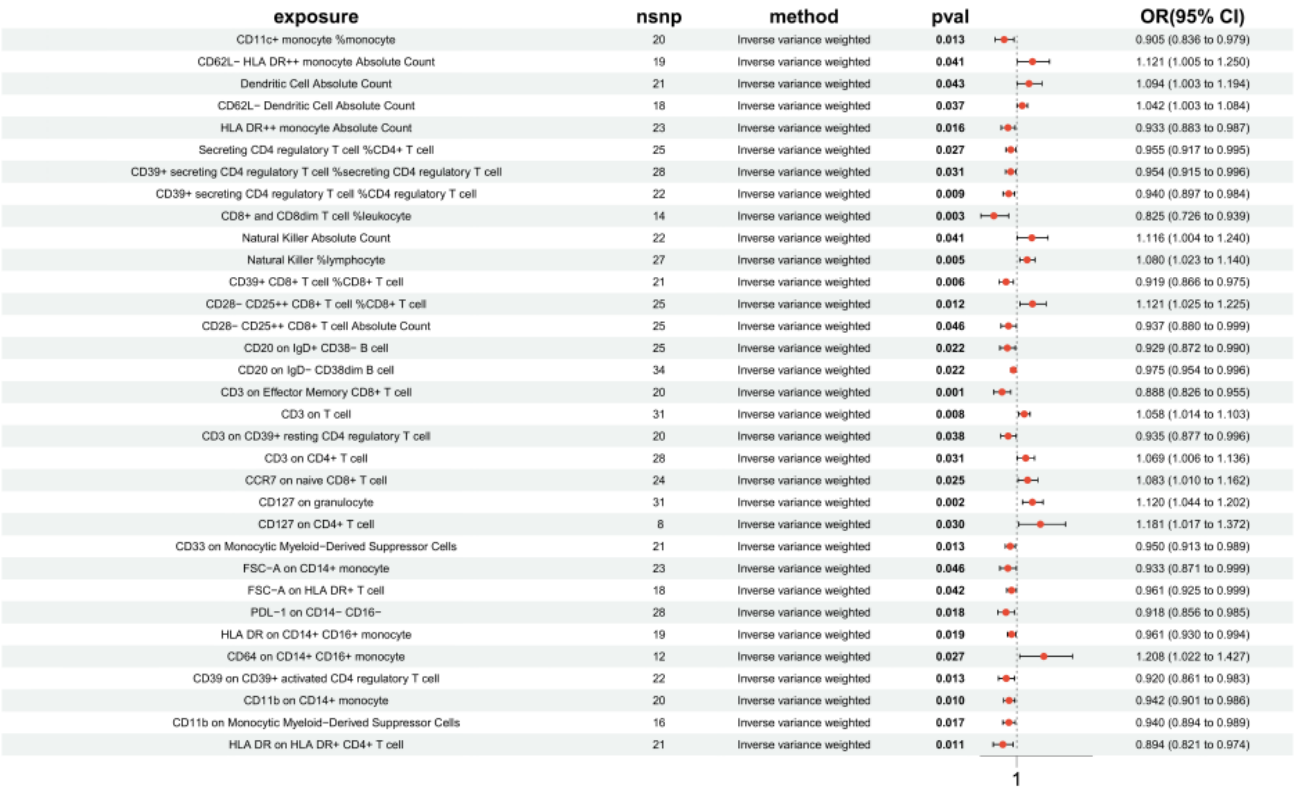

Figure 1. MR results of 731 types of immune cells and CA (IVW method).

4. Discussion

The migration and phenotypic changes of immune cells, along with adaptive immune responses, play a pivotal role in the onset and progression of CA, suggesting that the dynamic changes in immune cells and their subtypes may be significant factors influencing patient prognosis and disease evolution [10]. However, systematic research on the immunological characteristics of CA patients remains limited. To fill this research gap, this study aims to systematically evaluate immune cells and their phenotypes, identify key cell subsets closely associated with disease onset and prognosis, and provide new theoretical foundations and research bases for elucidating the mechanisms of immune imbalance following CA and exploring potential intervention strategies.

Lymphocytes are the core components of the immune system, including subsets such as natural killer cells, T cells, B cells, etc., with each type of cell having unique functions in immune defense and regulation [11]. T cells participate in adaptive immune responses by differentiating into helper T cells and cytotoxic T cells, regulating the activity of other immune cells, and directly killing infected or abnormal target cells [12]. Helper T cells can regulate immune and inflammatory responses by secreting various cytokines, such as interleukins, interferons, and tumor necrosis factors, while cytotoxic T cells exert their killing effects by directly recognizing target cells [13]. Natural killer cells are an essential part of our immune system's defense against pathogens and cancer. They originate as cell precursors in the bone marrow, lymph nodes, and liver, differentiating into NK cells without any other lineage [14]. NK cells are primarily described as having physiological functions and immune defense roles, but they also have potential adverse effects. Their killing mechanisms may mistakenly target normal host cells.

NK cells identify "self" versus "non-self" by recognizing MHC-I molecules, but misidentification or dysregulated control can lead to unintended attacks on healthy cells. For example, when target cells express both MHC-I and harmful ligands simultaneously, the ligand may override inhibitory "friendly" signals. If this mechanism is overly active, it may cause tissue damage. Additionally, excessive activation or dysfunction of NK cells may participate in inflammatory or autoimmune responses, further damaging host tissues [15]. CD3 is a specific marker molecule on the surface of T cells, playing a crucial role in maintaining T cell receptor (TCR) signal transduction and adaptive immune responses. Patients with cardiac arrest (CA) often exhibit an immunosuppressed state, characterized by a significant reduction in peripheral blood lymphocytes and T cell dysfunction. Among these, $CD3^+$ T cells are closely associated with poor prognosis in patients [16]. Acute ischemia-reperfusion following CA can trigger a systemic inflammatory response, leading to the overactivation of $CD3^+$ T cells, which release a large amount of pro-inflammatory cytokines (such as TNF-α, IFN-γ, and IL-6), potentially exacerbating myocardial injury [17]. The reduction in $CD3^+$ T cells not only weakens the body's ability to clear pathogens but also increases the risk of infection, sepsis, and multiple organ dysfunction, significantly affecting the survival rate and neurological prognosis of CA patients [18]. Therefore, the dynamic changes in $CD3^+$ T cells after CA can serve as important indicators for assessing the degree of immunosuppression and clinical outcomes, potentially representing a risk factor for poor prognosis in CA. Neutrophil activity and persistence, along with their cytotoxic effects, can exacerbate myocardial injury. These effects include phagocytosis and the release of granular components (such as proteases, oxidants, and antimicrobial peptides) into phagosomes or the extracellular space, the production of free radicals, and the formation of neutrophil extracellular traps (NETs) [19]. In a mouse model of heart failure, recruited neutrophils are most abundant in the border zone of myocardial infarction, likely reflecting the sustained preferential expression of neutrophil chemokines in the residual myocardial area most severely affected by ischemic injury [20]. These observations align with the concept of "parainflammation," where persistent stress states, such as mechanical load, neurohormonal activation, and ischemic injury, lead to tissue damage that cannot be fully resolved. The body attempts to restore tissue homeostasis by activating a low-grade inflammatory response [21]. IL-5 is primarily secreted by macrophages and $CD127^+$ cells. CD127-positive cells may play a role in immune regulation after myocardial infarction, particularly in the production of IL-5 and related responses. Although the specific mechanism of $CD127^+$ cells in CA is not fully understood, as an important component of the immune response, $CD127^+$ cells may indirectly influence macrophage polarization by promoting IL-5 secretion, potentially affecting the myocardium [22]. Immune cells and their phenotypes, such as Natural Killer %lymphocyte, CD3 on T cells, and CD127 on granulocytes, may act as risk factors for CA, influencing its occurrence and prognosis.

After cardiac arrest (CA), the immune system undergoes significant changes. $CD4^+$ T cells differentiate into various subsets based on different cytokine environments, including T helper 1 (Th1) cells, Th2 cells, Th17 cells (61), and regulatory T cells (Tregs), all of which share a common origin [23]. Regulatory T cells play a crucial role in maintaining immune homeostasis and promoting tissue repair. $CD39^+$ Tregs, a functionally active subset, possess strong immunosuppressive capabilities [24]. A notable increase in the proportion of $CD39^+$ Tregs suggests their potential importance in the immune response following CA. CD39 is a surface nucleotide enzyme capable of hydrolyzing ATP to produce adenosine, thereby inhibiting inflammatory responses. Through their enzymatic activity, $CD39^+$ Tregs regulate local ATP levels, suppress the activation of effector T cells, and reduce inflammation [25]. After CA, the increase in $CD39^+$ Tregs may represent the body's attempt to limit excessive inflammatory responses and promote myocardial repair by enhancing immunosuppressive functions. However, the functions of $CD39^+$ Tregs are not limited to immunosuppression; they can also further suppress inflammatory

responses and promote tissue repair by secreting anti-inflammatory factors [26]. After CA, the function of $CD39^+$ Tregs may be impaired, leading to a decrease in their immunosuppressive capacity and subsequently affecting the myocardial repair process. Evaluating the proportional and functional changes of $CD39^+$ Tregs after CA is of great significance for understanding their role in the post-CA immune response. Future research could further explore the functional status of $CD39^+$ Tregs and their potential role in myocardial repair after CA, providing new targets for clinical intervention. CD8+ T cells, a subset of T lymphocytes, can differentiate into cytotoxic effector T cells when exposed to antigens. In addition to their immunoregulatory functions through the secretion of tumor necrosis factor-alpha (TNFα) and interferon (IFN)-γ, CD8+ T cells can also directly release granzymes and perforin and upregulate the expression of FASL, thereby triggering target cell death [27,28]. $CD8^+$ T cells are not only important executors of the body's acquired immunity but may also play a protective role through multiple mechanisms. $CD8^+$ cells maintain the host's defense barrier after resuscitation by recognizing and eliminating target cells infected with viruses or bacteria, thereby preventing secondary infections and sepsis. This is of great significance in reducing nosocomial infections and organ failure in critically ill patients [29]. Early and moderate activation of $CD8^+$ cells can promote cytokine release, regulate cellular functions, and help limit excessive inflammatory responses, thus avoiding immune storms and tissue damage caused by a "second hit" [30]. CD8+ T cells infiltrate into the brain parenchyma in response to chemokines released by glial cells after brain injury and neurodegeneration. However, significant infiltration occurs before the formation of protein aggregates, suggesting that the role of CD8+ T cells in brain injury and neurodegeneration seems to do more harm than good, despite the discovery that a subset of regulatory CD8+ T cells has a protective effect against ischemic stroke [31]. Therefore, achieving a balance between immunosuppression and excessive inflammation, and exploring intervention strategies to activate or preserve $CD8^+$ cell function, may be an important direction for improving the prognosis of cardiac arrest (CA) in the future. Effector memory T cells play a crucial role in the immune response after CA. These are a type of memory T cells with rapid response capabilities, capable of swiftly exerting immune effects in local tissues [32]. However, the specific role of effector memory T cells after CA remains not entirely unclear. Some studies suggest that effector memory T cells may exacerbate cardiac injury by promoting inflammatory responses, while others propose that they may play a protective role by clearing infection sources [33,34]. CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell, CD8+ and CD8dim T cell %leukocyte, CD39+ CD8+ T cell %CD8+ T cell, and CD3 on Effector Memory CD8+ T cell may play a certain protective role in the immune response after CA. Future research should further elucidate the specific mechanisms of action of these immune cell subsets in CA patients and provide potential strategies for targeted immune interventions.

This study has certain limitations:

(1) The GWAS data used in this study, encompassing 731 immune cell phenotypes, were all derived from European populations. However, there may be differences in genetic backgrounds, allele frequencies, and gene-environment interactions among different ethnic groups. Therefore, the applicability of the study's findings to other ethnic populations may remain unclear, and it is currently uncertain whether other populations possess the same genetic variations and the extent of their impact on the incidence of CA. This limitation may, to some extent, affect the extrapolation and generalizability of the study's conclusions.

(2) Although the MR method can reduce the interference of confounding factors, it may still be constrained by issues related to the selection of instrumental variables and the strength of genetic effects, which could, to a certain degree, impact the accuracy of causal inference. To enhance the robustness and universality of

the study's conclusions, future research should incorporate data from multi-ethnic populations on a larger sample size basis, conduct repeated validations using cohorts from different sources, and explore the influence of gene-environment interactions among different ethnic groups on the pathogenesis of CA.

Additionally, future studies could integrate multi-omics data, such as functional genomics and transcriptomics, to further validate the causal relationship between key immune cell phenotypes and CA at the mechanistic level, thereby providing a more reliable scientific basis for the development of immune intervention strategies.

5. Conclusion

In summary, this study identified causal associations between 33 immune cell phenotypes and CA. Significant positive causal associations were observed for Natural Killer %lymphocyte, CD3 on T cell, and CD127 on granulocyte, while significant negative causal associations were found for CD39+ secreting CD4 regulatory T cell %CD4 regulatory T cell, CD8+ and CD8dim T cell %leukocyte, CD39+ CD8+ T cell %CD8+ T cell, and CD3 on Effector Memory CD8+ T cell. These findings reveal the potential regulatory roles of different immune cell phenotypes in the pathogenesis of CA, suggesting that the balance of immune cell composition and function may be of great significance in the occurrence and development of CA. Furthermore, the discoveries of this study can provide references for subsequent mechanistic research, aid in identifying key immune regulatory targets, and offer theoretical foundations for the development of individualized immune intervention strategies.

Disclosure statement

The authors declare no conflict of interest.

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