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ORIGINAL RESEARCH

Prolonged Inflammation Associates With Greater Infarct Size and Poor Outcome After ST-Segment Elevation Myocardial Infarction

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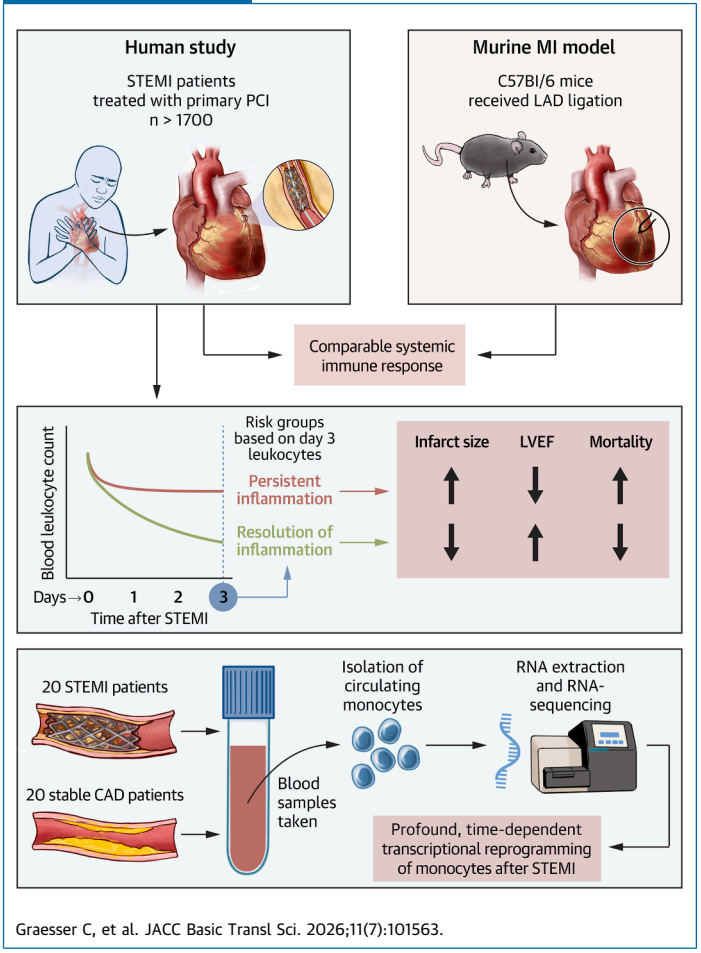
VISUAL ABSTRACT



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HIGHLIGHTS

- **STEMI triggers a rapid systemic inflammatory response, with leukocytes peaking at admission and typically normalizing by days 2 and 3, marking the transition toward inflammation resolution.**
- **A substantial fraction of patients shows nonresolving inflammation, reflected by persistently elevated leukocyte counts at 72 hours after STEMI.**
- **High leukocyte levels on day 3 are linked to larger infarct size by enzymatic markers (peak CK-MB, troponin T) and by 99mTc-sestamibi single-photon emission computed tomography perfusion defect, and to lower LVEF at baseline and follow-up.**
- **Persistent leukocytosis at day 3 identifies a high-risk phenotype with markedly higher 1- and 5-year all-cause mortality; day 3 leukocyte count remains an independent predictor of 1-year mortality in multivariable analysis.**
- **RNA sequencing of human inflammatory monocytes reveals profound, time-dependent transcriptional reprogramming after STEMI.**

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ABBREVIATIONS AND ACRONYMS

BW = body weight

CAD = coronary artery disease

CK-MB = creatine kinase-myocardial band

CMR = cardiac magnetic resonance

CRP = C-reactive protein

DEG = differentially expressed gene

FACS = fluorescence-activated cell sorting

LAD = left anterior descending artery

LVEF = left ventricular ejection fraction

MI = myocardial infarction

PBS = phosphate-buffered saline

PPCI = primary percutaneous coronary intervention

scintiT$_{\#d}$ = scintigraphic tertile at day #

SPECT = single-photon emission computed tomography

STEMI = ST-segment elevation myocardial infarction

T$_{\#d}$ = tertile at day #

T$_{ad}$ = tertile at admission

T$_{CRP}$ = tertile based on peak C-reactive protein

SUMMARY

AIMS Acute myocardial infarction (MI) induces a systemic inflammatory response that usually resolves within days, but the prognostic impact of persistent inflammation is uncertain. We assessed whether sustained leukocytosis after ST-segment elevation myocardial infarction (STEMI) relates to infarct size, left ventricular function, and clinical outcomes.

METHODS AND RESULTS In >1,700 STEMI patients treated with primary percutaneous coronary intervention, leukocytes peaked on admission and typically normalized by day 3. Patients were stratified by leukocyte tertiles at admission and day 3. High day 3 leukocyte counts were associated with larger infarct size (scintigraphy; peak creatine kinase-myocardial band and troponin T), worse left ventricular function in hospital and at 6 months, and higher 1- and 5-year mortality. Patients whose leukocyte counts declined had better recovery, whereas persistent leukocytosis marked the poorest outcomes. Monocyte RNA sequencing showed post-MI transcriptomic reprogramming, and murine MI models recapitulated a similar systemic immune response.

CONCLUSIONS Persistent inflammation, particularly elevated leukocyte counts at day 3 post-MI, is associated with adverse remodeling and increased mortality after STEMI, identifying unresolved inflammation as a negative prognostic marker and potential therapeutic target. (JACC Basic Transl Sci. 2026;11:101563)

Inflammation greatly contributes to development and progression of cardiovascular disease.[1-9] Leukocytes are the effector cells of the immune system and leukocyte levels are sensitive markers of systemic inflammation. Blood leukocytosis,[10,11] granulocytosis,[12,13] and monocytosis[14,15] are associated with adverse cardiovascular events. Myocardial infarction (MI)—one of the strongest contributors to worldwide mortality—triggers an immediate systemic inflammatory response. Cardiomyocytes become ischemic and necrotic and release damage-associated molecular patterns, which attract leukocytes from the circulation to the site of ischemia. Meanwhile, cardiac endothelial cells become activated and start to upregulate adhesion molecules and chemokines, which both further facilitate leukocyte accumulation at the injury site. Because leukocytes are recruited from the circulation to the ischemic myocardium at a high rate, continuous supply of the cells is needed. The bone marrow responds to MI with a transient increase in leukocyte production,[16,17] a process called emergency hematopoiesis. In this inflammatory phase of MI, neutrophils arrive first at the injury site and release proteolytic enzymes and reactive oxygen species. Thereafter, inflammatory monocytes invade the ischemic area and contribute to local inflammation and removal of debris and dead cells. Monocytes differentiate into macrophages, which further aid to clear necrotic tissue and secrete proinflammatory cytokines. The inflammatory phase is followed by the reparative phase in which inflammatory macrophages switch their phenotype and promote

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tissue repair, angiogenesis, and scar formation. While a timely resolution of inflammation is critical for sufficient tissue repair, a delayed and exacerbated inflammatory phase prevents proper healing and causes adverse remodeling and heart failure.

To this point, studies that specifically examined the impact of prolonged and nonresolving inflammation after ST-segment elevation myocardial infarction (STEMI) on infarct size and outcome are scarce. We sought to investigate the association of blood leukocyte levels on day 3 after MI, a time point that marks the transition from the inflammatory to the reparative phase after MI, with infarct size and outcome in patients with STEMI undergoing primary percutaneous coronary intervention (PPCI). Our study reveals a rapid induction of systemic inflammation early on after STEMI. Nonresolving and sustained inflammation, as indicated by prolonged leukocytosis (beyond day 3 post-MI), is associated with larger infarct sizes and poor prognosis.

METHODS

HUMAN STUDY: COHORTS. This study adopted a translational approach, incorporating experimental laboratory data derived from mouse models with prospective and retrospective analysis across two clinical cohorts of STEMI patients: 1) a cohort consisting of 1,781 STEMI patients enrolled between January 2002 and December 2022, recruited from two tertiary cardiac care centers: Deutsches Herzzentrum München and Klinikum rechts der Isar (both affiliated with the Technical University of Munich, Munich, Germany); and 2) a cohort of 20 STEMI patients and 20 age- and sex-matched stable coronary artery disease (CAD) patients for transcriptional phenotyping of blood inflammatory monocytes. The monocyte phenotyping cohort was established between September 2016 and February 2018.

In all cohorts, STEMI diagnosis was based on the standard European Society of Cardiology definition of acute MI with ST-segment elevation.[18] For the clinical cohorts, complete coronary angiography data were available. The culprit lesion in the infarct-related artery was identified by coronary angiography using established angiographic criteria, as previously described.[19] Significant CAD in non-infarct-related arteries was defined as a diameter stenosis of more than 50%.[19] Patients with acute MI due to other causes (non-type 1 MIs),[20] such as MI with nonobstructive CAD, were excluded from the study. All patients provided written informed consent for PPCI and imaging procedures.

HUMAN AND MOUSE STUDY: ETHICAL CONSIDERATIONS AND STUDY CONDUCT. The study protocol was approved by the institutional ethics committee (454/21 S-KH, 2023-414-S-SB, and 235/16 S for the clinical cohorts and 55.2-2532.Vet_02-17-179 for the murine experiments) and adhered to the principles outlined in the Declaration of Helsinki.

HUMAN STUDY: LABORATORY DATA, MEDICAL HISTORY, AND DEFINITIONS. In the clinical cohorts, laboratory measurements were routinely performed daily at the institute of laboratory medicine at the treatment site. Data were extracted from patients' charts for up to 10 days postadmission. To evaluate persistent inflammation, leukocyte counts measured 72 hours post-MI were analyzed. Serial leukocyte measurements were available for 1,450 (81.4%) of 1,781 patients. The cohort was stratified into tertiles according to the distribution of leukocyte levels at 72 hours, thereby enabling comparisons between low, intermediate, and high inflammatory responses following STEMI. A Sankey diagram was used to track transitioning between low, intermediate, and high leukocyte level tertiles from admission to day 3 post-STEMI. Additionally, in a subset of this cohort, complete differential blood counts (including leukocyte subsets such as neutrophils, lymphocytes, and monocytes) were available for 345 patients at admission and for 158, 146, 148, and 49 patients on days 2, 3, 4, and 5, respectively. In addition to leukocyte counts and phenotypes, we also investigated C-reactive protein (CRP) kinetics in response to MI. Of the 1,781 STEMI patients, serial CRP levels were available in 1,766 (99.2%). Renal function was assessed by calculating glomerular filtration rate using the Cockcroft-Gault formula 4-variable Modification of Diet in Renal Disease equation.[21] Peak levels were defined as the highest values recorded during hospitalization.

HUMAN STUDY: INFARCT SIZE AND LEFT VENTRICULAR FUNCTION. As biochemical markers of cardiomyocyte injury and surrogates of infarct size, peak serum levels of creatine kinase-myocardial band (CK-MB) and troponin T were utilized. In a subset of the clinical cohort with available serial leukocyte measurements (n = 1,450), 99mTc-sestamibi single-photon emission computed tomography imaging studies were additionally available in 976 patients and performed as described previously.[19] Briefly, infarct size was measured by injecting 99mTc-sestamibi (27 mCi [1,000 MBq]) intravenously between 7 and 14 days post-PPCI, followed by imaging 6 to 8 hours later. Perfusion defects were defined as areas with <50% uptake of 99mTc-sestamibi and expressed as a percentage of the left ventricle. All

measurements were performed by investigators blinded to the clinical or angiographic data of the patients. In the subset of patients with available scintigraphic data, left ventricular ejection fraction (LVEF) was obtained in 927 patients at admission (baseline) and in 376 patients at 6-month follow-up using left ventricular angiograms and the area-length method.

HUMAN STUDY: STUDY OUTCOMES AND FOLLOW-UP. The primary and secondary endpoints in the clinical cohort analysis were defined as 1- and 5-year all-cause mortality, respectively. Follow-up information was obtained by staff members who were unaware of the clinical data via phone calls 30 days post-percutaneous coronary intervention, 1-year post-percutaneous coronary intervention, and annually thereafter. Data on mortality were obtained from hospital records, death certificates, or phone contact with patients' relatives or referring physicians.

HUMAN STUDY: TRANSCRIPTIONAL PROFILING OF BLOOD INFLAMMATORY MONOCYTES. Characterization of blood leukocytes by flow cytometry. Blood leukocyte characterization was performed in patients (n = 20) at different time points after STEMI (<12, 24, 48, 72, 96, and 120 hours) and in age- and sex-matched patients with stable CAD. Peripheral blood was incubated in 1× red blood cell lysis buffer (BioLegend) for 5 minutes. Following lysis, cells were resuspended in fluorescence-activated cell sorting (FACS) buffer (phosphate-buffered saline [PBS] containing 0.5% bovine serum albumin; Sigma-Aldrich) and counted. Cell suspensions were stained with an antibody mix for 20 minutes at 4 °C in 300 μL of FACS buffer. The antibody mix included biotinylated lineage markers (CD3, CD19, CD20, CD56, CD66b; BioLegend: 300404, 302204, 302350, 362536, 305120), CD41 PerCP/Cyanine5.5 (303719), CD11b APC (301310), CD14 FITC (325604), and CD16 PE (302008). BV510-conjugated streptavidin (BioLegend; 405234) was used to detect the biotinylated lineage markers. Flow cytometry data were acquired using an LSRFortessa instrument (BD Biosciences) and analyzed using FlowJo software (version 10; BD Life Sciences). For statistical analysis of flow cytometry data, GraphPad Prism version 10 (GraphPad Software; RRID: SCR_002798) was used. Normal distribution was assessed using the D'Agostino-Pearson omnibus normality test. Comparisons of leukocyte counts between CAD patients and post-MI time points were performed using the Mann-Whitney *U* test. Changes over time within the MI cohort were analyzed using the Friedman test, followed by post hoc pairwise Wilcoxon signed rank tests with Holm correction for multiple comparisons. To identify statistical outliers, the 2-sided ROUT test was applied.

Isolation of $CD14^+$ monocytes from human blood. Circulating $CD14^+$ monocytes were isolated from the blood of stable CAD patients (single time point) and STEMI patients (two time points: within 12 hours of symptom onset and 3 days post-STEMI). Monocyte isolation was performed using magnetic-activated cell sorting following Ficoll-Paque density gradient centrifugation of peripheral blood mononuclear cells (PBMCs). Peripheral venous blood was collected in CPT tubes (BD Vacutainer CPT with sodium citrate) and centrifuged at 1,600 *g* for 30 minutes at room temperature. The resulting PBMC layer was resuspended in FACS buffer and incubated with CD14 MicroBeads (1:4 dilution; Miltenyi; 130-050-201) for 15 minutes on ice. After incubation, cells were washed, resuspended in FACS buffer, and applied to LS columns (Miltenyi). Magnetically labeled cells were eluted by flushing the column with FACS buffer using a plunger. To enhance purity, the separation process was repeated using a second LS column. Purity of the isolated $CD14^+$ monocytes was confirmed via flow cytometry. Cells were stained with the same antibody mix used for the characterization in 300 μL of FACS buffer for 20 minutes at 4 °C. After a wash, samples were analyzed by flow cytometry LSRFortessa. Flow cytometry data were analyzed using FlowJo software (version 10). For statistical analysis of flow cytometry data, GraphPad Prism version 10 was used (RRID: SCR_002798). Normal distribution was assessed using the D'Agostino-Pearson omnibus normality test. To identify statistical outliers, the 2-sided ROUT test was applied. The comparison of the purity of the sorted populations was performed using Kruskal-Wallis test followed by Dunn's multiple comparisons test. Following cell count and purity analysis, $CD14^+$ monocytes were resuspended in QIAzol reagent (Qiagen) and stored at −80 °C at a concentration of 1.5×10^6 cells per sample.

RNA sequencing. Total RNA was extracted from isolated $CD14^+$ monocytes using the RNeasy Mini Kit (Qiagen; 74104) following the manufacturer's protocol. Bulk RNA sequencing was performed by the DZHK Shared Expertise Platform (SE031) at the Heidelberg/Mannheim site. RNA quality and integrity were assessed using the Agilent Fragment Analyzer System with the Agilent DNF-471 RNA Kit. Library preparation was carried out using the Illumina TruSeq Total RNA Stranded Kit. RNA sequencing was performed on an Illumina HiSeq2000 platform, generating paired-end reads of 2 × 100 base pairs.

RNA sequencing data analysis. After standardized quality control of the raw RNA sequencing data using the FastQC software, the reads were trimmed using the Trimmomatic software.[22] This was followed by alignment to the human reference genome with the STAR aligner software and quality control of the alignment using the Qualimap software.[23] Subsequently, the deconvolution of the fragment data into gene data was performed using the featureCounts software.[24] Features with low counts (median <10) were removed using the edgeR package,[25] and the raw read data were normalized using the Trimmed Mean of M-values method.[26] A comparison of the normalized gene expression data of the 3 groups (chronic coronary syndrome patients, patients on the day of infarction, and patients on the third day after infarction) was carried out using LIMMA (linear models for microarray data) *t* test statistics with Benjamini-Hochberg correction for multiple testing problems (Benjamini-Hochberg or false discovery rate) to calculate differentially expressed genes (DEGs).[27] Genes were defined as differentially expressed if the relative gene expression (fold change) changed by at least a factor of 2, corresponding to a log2 gene expression change less than |log2 fold change| ≥1.0. A *P* value <0.05 with a false discovery rate <0.25% between the respective comparison groups was required. Visualization of the DEGs as a volcano plot was performed using the ggplot2 R package.[28] Functional enrichment analysis of the DEGs was performed using ToppFun from the ToppGene Suite, which detects functional enrichment in 24 annotation categories. Subsequently, significant functional enrichment of the DEGs in the Gene Ontology annotation categories molecular functions and biological processes was analyzed using the ToppFun software[29] from the ToppGene Suite website.

HUMAN STUDY: STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD for approximately normally distributed variables or median (Q1-Q3), depending on the normality of the distribution assessed using the Shapiro-Wilk test. For longitudinal comparisons of leukocyte values within the same patients across days, overall differences over time were tested using a 1-way repeated-measures analysis of variance restricted to complete cases. Post hoc comparisons were limited to adjacent (consecutive) days and were performed using paired *t* tests with Holm-adjusted *P* values to account for multiple testing. For comparisons among 3 independent groups (leukocyte tertiles), overall differences were assessed using the Kruskal-Wallis test. If the overall test was significant, post hoc pairwise comparisons between tertiles were performed using 2-sided Mann-Whitney *U* tests with Holm adjustment for multiple comparisons. Discrete variables are expressed as proportions (percentages) and were analyzed using the chi-square test. A 2-sided *P* value <0.05 was considered statistically significant. Univariable and multivariable analyses were performed in the STEMI cohort, including biologically plausible and clinically relevant variables. Univariable Cox regression analysis was used to identify factors contributing to 1-year all-cause mortality. Subsequently, a multivariable Cox proportional hazards model was utilized, incorporating only factors identified as significant in univariable analyses. Long-term clinical outcomes were assessed using the Kaplan-Meier method and log-rank test. The Cox proportional hazards model was used to assess the association between leukocyte tertiles and outcomes (ie, all-cause mortality). HRs are reported with 95% CIs. For statistical analysis and data visualization, Python version 3.9.16 (Python Software Foundation) and R Statistical Software version 4.1.2 (R Foundation for Statistical Computing) were used.

MOUSE STUDY: MODEL OF MI. All procedures were approved by the local committee for animal welfare (government of Bavaria, Germany) under the application 55-2-2535.Vet_02-17-179. To induce MI, mice were intubated under midazolam, medetomidine, and fentanyl (MMF) anesthesia (midazolam 5.0 mg/kg body weight [BW], medetomidine hydrochloride 1.0 mg/kg BW, fentanyl citrate 0.05 mg/kg BW; administered intraperitoneally), and thoracotomy was performed in the left intercostal space. The left anterior descending artery (LAD) was identified, and infarction was induced by permanently ligating the LAD using an 8-0 Prolene suture. Atipamezole hydrochloride (5 mg/kg BW) and flumazenil (0.1 mg/kg BW), administered subcutaneously, were used to reverse the effects of maxillomandibular fixation anesthesia. Mice received subcutaneous buprenorphine (0.3 mg/kg BW) as an analgesic every 8 hours for 3 days, beginning at the end of the surgical procedure.

MOUSE STUDY: TISSUE PROCESSING AND FLOW CYTOMETRY. To distinguish circulating leukocytes from resident leukocytes within cardiac tissue, an antibody against CD45 (BioLegend; 103140, BV605) (1:10 in 100 μL PBS; Gibco) was intravenously injected 5 minutes before euthanizing the animals. Peripheral blood was collected and incubated in 1× red blood cell lysis buffer for 5 minutes. Following lysis, the cells were resuspended in FACS buffer and counted. Hearts were flushed with PBS and isolated to obtain

the ischemic area and border zone. These cardiac regions were weighed, minced, and digested in an enzymatic solution (collagenase I, 450 U/mL; collagenase XI, 125 U/mL; DNase I, 60 U/mL; hyaluronidase, 60 U/mL; all from Sigma-Aldrich) at 37 °C and 750 rpm for 1 hour on a thermoshaker. The digested tissue was processed through a 40 μm cell strainer (Corning; 15360801) and resuspended in FACS buffer, and cells were counted. Cell suspensions from blood and heart were stained with an antibody mix for 20 minutes at 4 °C in 300 μL of FACS buffer. The antibody mix contained hematopoietic lineage markers (B220, CD90.2, CD49b, NK1.1, Ter-119, and Ly6G) in PE (103208, 108708, 116208, 127608, 108908, 140308), along with CD45.2 PerCP-Cy5.5 (109828), CD11b APC Cy7 (101226), CD115 BV711 (135515), F4/80 PE Cy7 (123114), and Ly6C FITC (128006) antibodies (all from BioLegend). For compensation, the antibodies mentioned previously were conjugated to OneComp eBeads (01-1111-42; Thermo Fisher Scientific). Flow cytometry data were acquired using an LSRFortessa. Recorded events were gated based on forward scatter and side scatter properties appropriate to the tissue type. Blood leukocytes and subsets were differentiated by expression of specific markers: circulating leukocytes ($CD45^{high}$, $CD45.2^{high}$), circulating monocytes ($CD45.2^{high}$, $CD11b^{high}$, $lineage^{low}$, $CD115^{high}$, $Ly6C^{high/low}$), and circulating neutrophils ($CD45.2^{high}$, $CD11b^{high}$, $lineage^{high}$, $CD115^{low}$, $Ly6C^{intermediate}$). Cardiac leukocytes and subsets were distinguished by their specific markers: cardiac leukocytes ($CD45^{neg}$, $CD45.2^{high}$), cardiac neutrophils ($CD45^{neg}$, $CD45.2^{high}$, $CD11b^{high}$, $lineage^{high}$), cardiac monocytes ($CD45^{neg}$, $CD45.2^{high}$, $CD11b^{high}$, $lineage^{low}$, $Ly6C^{high}$, $F4/80^{low}$), and cardiac macrophages ($CD45^{neg}$, $CD45.2^{high}$, $CD11b^{high}$, $lineage^{low}$, $Ly6C^{low}$, $F4/80^{high}$). Flow cytometry data were analyzed using FlowJo software (version 10). For statistical analysis of flow cytometry data, GraphPad Prism version 10 was used (RRID: SCR_002798). For sample sizes of $n > 8$, normal distribution was assessed using the D'Agostino-Pearson omnibus normality test. For smaller sample sizes ($n < 8$), the Shapiro-Wilk test was used. Comparisons of leukocyte counts at different time points and leukocyte purity after FACS sorting were performed using 1-way analysis of variance (ANOVA), and in particular, Kruskal-Wallis test followed by Dunn's multiple comparisons test. To identify statistical outliers, the 2-sided ROUT test was applied. Data are displayed as mean ± SD in the figures. The number of samples and the statistical tests performed are indicated in the figure legends.

RESULTS

BLOOD LEUKOCYTE KINETICS FOLLOWING MI. To examine the systemic immune response following MI, we analyzed blood leukocyte kinetics in a cohort of 1,781 STEMI patients treated with PPCI. Leukocyte levels were highest at the time of admission and subsequently showed a gradual decline (**Figure 1A**, Supplemental Table 1). By day 3 post-MI, leukocyte levels fell below the upper limit of the normal range, marking the onset of the inflammation resolution phase.

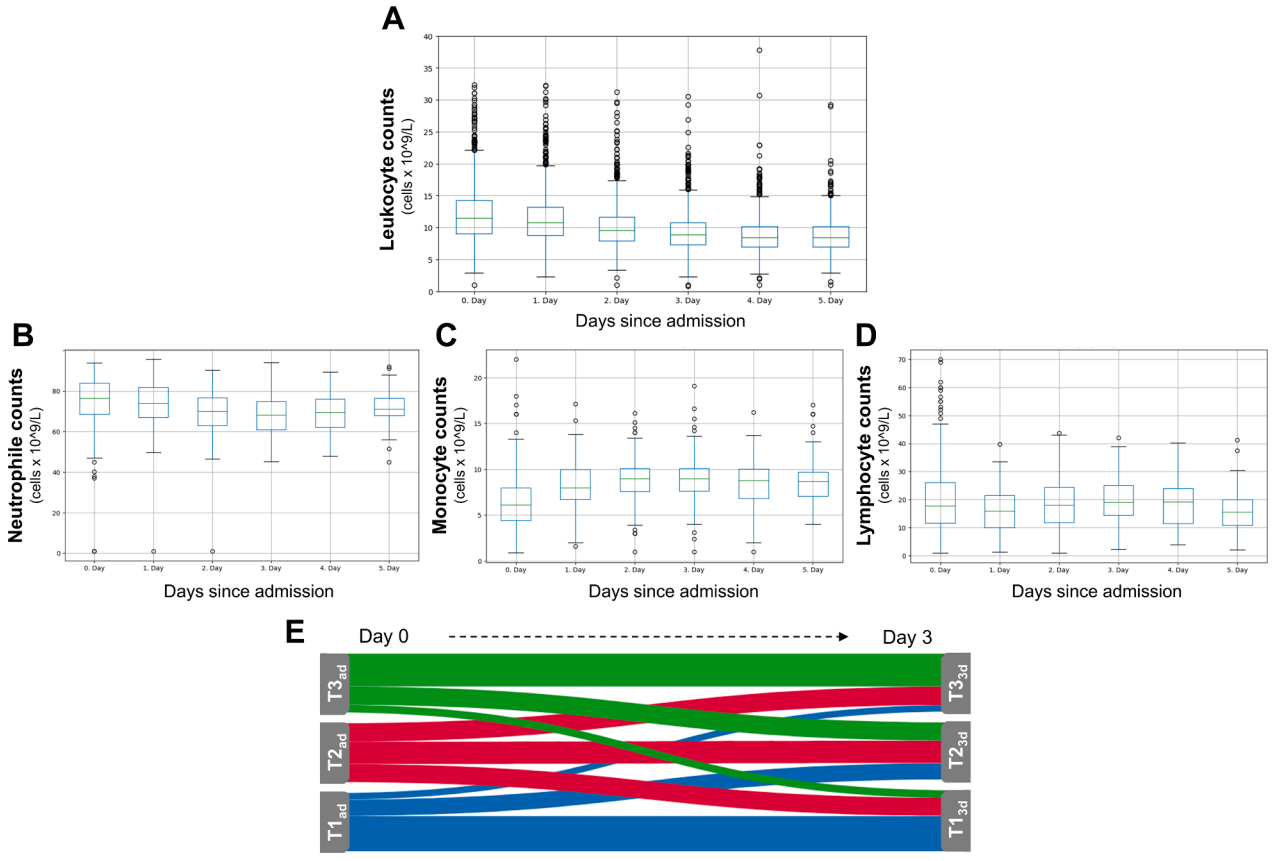
Analysis of leukocyte subsets revealed distinct temporal dynamics. Neutrophil levels (available in 345 patients) decreased from admission to day 2, stabilizing at lower levels thereafter (**Figure 1B**). In contrast, monocyte levels (available in 385 patients) increased from admission and plateaued by day 2 (**Figure 1C**). Lymphocyte counts (available in 387 patients) demonstrated a transient reduction on day 1 following STEMI (**Figure 1D**).

In summary, our data demonstrate a rapid systemic inflammatory response characterized by elevated inflammatory leukocyte levels. These levels normalized by days 2 to 3, signaling the resolution of the inflammatory phase.

To better understand the transition from the early inflammatory peak to the reparative phase and resolution of inflammation, we stratified patients with leukocyte values available at both admission and 72 hours post-MI ($n = 1{,}450$ of 1,781 patients [81.4%]) into tertiles based on their blood leukocyte counts at admission (tertile at admission [T_{ad}]) and on day 3 post-MI (tertile at day 3 [T_{3d}]). Baseline characteristics of this subcohort are detailed in Supplemental Table 2. The T_{ad}s were defined as follows: tertile 1 ($T1_{ad}$), $<9.8 \times 10^9$/L ($n = 480$); tertile 2 ($T2_{ad}$), 9.81 to 13.2×10^9/L ($n = 486$); and tertile 3 ($T3_{ad}$), $>13.21 \times 10^9$/L ($n = 484$). The T_{3d}s were defined as follows: tertile 1 ($T1_{3d}$), $<7.9 \times 10^9$/L ($n = 502$); tertile 2 ($T2_{3d}$), 7.91 to 10.1×10^9/L ($n = 470$); and tertile 3 ($T3_{3d}$), $>10.1 \times 10^9$/L ($n = 478$). Among patients exhibiting a pronounced initial inflammatory response (group $T3_{ad}$), a significant resolution of inflammation by day 3 (ie, a leukocyte decline) was observed in 213 (44.0%) individuals. In contrast, 271 (56.0%) patients demonstrated persistently elevated leukocyte counts, indicating sustained inflammation (**Figure 1E**).

LEUKOCYTE KINETICS AND IMPACT ON INFARCT SIZE AND LEFT VENTRICULAR FUNCTION. We next investigated whether a prolonged inflammatory phase beyond day 3 impacts infarct size. Baseline characteristics of T_{3d}s are presented in **Table 1**.

FIGURE 1 **Blood Leukocyte Kinetics Secondary to STEMI**



(A) Leukocyte counts at admission and during hospitalization over the course of 5 days in ST-segment elevation myocardial infarction (STEMI) patients in the total study population (N = 1,781). Leukocyte subset numbers derived from a subcohort of 345 patients, including (B) neutrophils, (C) monocytes, and (D) lymphocytes. (E) Transitioning between leukocyte tertiles at admission (T_{ad}) to tertiles at day 3 (T_{3d}) post-STEMI visualized using a Sankey diagram in a subcohort of 1,450 patients with leukocyte counts available at both admission and day 3. $T1_{ad}$ indicates low leukocyte levels, $T2_{ad}$ indicates intermediate leukocyte levels, and $T3_{ad}$ indicates high leukocyte levels. $T1_{3d}$ indicates low leukocyte levels, $T2_{3d}$ indicates intermediate leukocyte levels, and $T3_{3d}$ indicates high leukocyte levels. Data are presented as median with 25th to 75th percentiles (boxes), 10th to 90th percentiles (bars), and values outside the given percentiles (dots).

Notable differences among the groups were observed in body mass index, sex, glomerular filtration rate, hypertension, smoking status, and age. The leukocyte kinetics for individual tertiles are depicted in Supplemental Figure 1. Infarct size was largest in patients with highest leukocyte levels on day 3 (T_{3d}) as determined by enzymatic estimates (**Figures 2A and 2B**). Peak CK-MB levels were median 102 U/L (Q1-Q3: 51-210 U/L) in $T1_{3d}$, 122 U/L (Q1-Q3: 63-243 U/L) in $T2_{3d}$, and 173 U/L (Q1-Q3: 82-384 U/L) in $T3_{3d}$ (**Figure 2A**). Similarly, peak troponin T levels were median 2,940 ng/L (Q1-Q3: 1,240-5,565 ng/L) in $T1_{3d}$, 3,540 ng/L (Q1-Q3: 1,275-7,480 ng/L) in $T2_{3d}$, and 4,960 ng/L (Q1-Q3: 2,090-9,890 ng/L) in $T3_{3d}$ (**Figure 2B**).

In addition to biomarkers, scintigraphic data on infarct size were available in a subset of patients (n = 976 of 1,450). This subcohort was also categorized into tertiles based on blood leukocyte counts on day 3 after MI (scintigraphic tertiles 3 days post-MI [scintiT1-3_{3d}]). The scintiT_{3d}s were defined as follows: tertile 1 (scinti$T1_{3d}$), <7.7 × 10^9/L (n = 331); tertile 2 (scinti$T2_{3d}$), 7.71 to 9.7 × 10^9/L (n = 320); and tertile 3 (scinti$T3_{3d}$), >9.71 × 10^9/L (n = 325). Scintigraphy performed 7 to 14 days post-STEMI revealed median infarct sizes of 7.0% (Q1-Q3: 1.0%-17.0%) in scinti$T1_{3d}$, 12.0% (Q1-Q3: 3.0%-24.5%) in scinti$T2_{3d}$, and 13.0% (Q1-Q3: 5.0%-30.0%) in scinti$T3_{3d}$ of the left ventricle, with the scinti$T3_{3d}$ group displaying the largest infarct sizes (**Figure 2C**).

TABLE 1 Baseline and Procedural Characteristics of the Clinical Cohort With Serial Leukocyte Measurements Based on Leukocyte Tertiles on Day 3 Following Acute STEMI (N = 1,450)

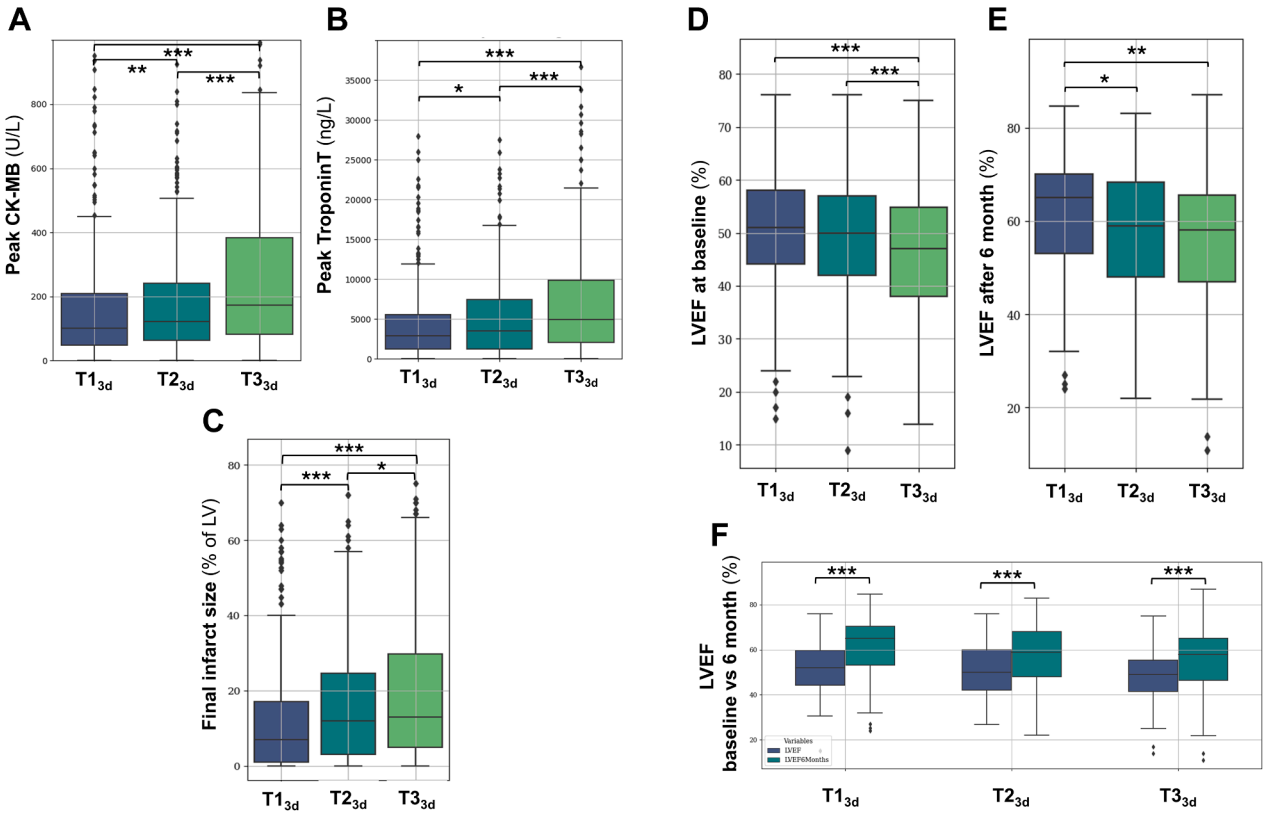
	Tertile 1 ($T1_{3d}$) (0.81-7.90 × 10^9/L)	Tertile 2 ($T2_{3d}$) (7.91-10.11 × 10^9/L)	Tertile 3 ($T3_{3d}$) (10.12-36.60 × 10^9/L)	*P* Value
Patients with leukocyte counts on day 3	502 (34.6)	470 (32.4)	478 (33.0)	
Leukocytes at admission (×10^9/L)	9.3 (4.91-17.3)	11.7 (6.82-19.40)	13.82 (7.31-27.1)	<0.001
Leukocytes after 72 h (×10^9/L)	6.8 (4.2-7.9)	9.0 (8.0-10.1)	11.7 (10.2-19.9)	<0.001
Age, y	63.7 ± 12.6	61.8 ± 12.8	63.7 ± 13.7	0.036
Female	136 (27.1)	93 (19.8)	117 (24.5)	<0.001
Diabetes	96 (19.1)	74 (15.7)	104 (21.8)	0.060
BMI, kg/m^2	26.3 ± 3.8	26.6 ± 3.7	26.9 ± 4.1	0.038
Hypercholesterolemia	273 (54.4)	275 (58.6)	245 (51.4)	0.078
Family history	184 (36.7)	162 (34.5)	132 (27.6)	0.008
Hypertension	340 (67.7)	285 (60.6)	318 (66.5)	0.048
Current smoking	162 (32.3)	203 (43.2)	197 (41.2)	<0.001
CrCl, mL/min	81.5 ± 30.0	86.1 ± 31.7	77.1 ± 31.7	<0.001
Affected vessels	2.1 ± 0.8	2.0 ± 0.8	2.1 ± 0.8	0.55
Previous MI	67 (13.3)	53 (11.3)	73 (15.3)	0.19
Previous CABG	19 (3.8)	9 (1.9)	14 (2.9)	0.22
Baseline TIMI flow	1.2 ± 1.5	1.1 ± 1.2	1.0 ± 1.1	0.27
LVEF, %	49.3 ± 11.3	48.0 ± 11.1	43.7 ± 12.0	<0.001
Anticoagulation on admission	10 (2.0)	14 (3.0)	26 (5.5)	0.009
Antiplatelet therapy on admission	12 (2.4)	9 (1.9)	11 (2.3)	0.87
ACE inhibitor on admission	104 (23.3)	76 (18.6)	82 (22.9)	0.20
Aldosterone antagonist on admission	6 (1.2)	3 (0.6)	9 (1.9)	0.22
ARB on admission	45 (10.1)	37 (9.1)	37 (10.3)	0.82
Beta-blocker on admission	130 (25.9)	99 (21.2)	88 (18.6)	0.019
Statin on admission	93 (18.6)	66 (14.1)	68 (14.4)	0.099
Anticoagulation at discharge	29 (5.8)	34 (7.3)	64 (13.5)	<0.001
Antiplatelet therapy at discharge	496 (99.0)	456 (97.4)	447 (94.5)	<0.001
ACE inhibitor at discharge	441 (88.0)	410 (87.8)	392 (83.4)	0.064
Aldosterone antagonist at discharge	24 (4.8)	35 (7.5)	53 (11.2)	0.001
ARB at discharge	46 (9.2)	40 (8.6)	38 (8.1)	0.83
Beta-blocker at discharge	482 (96.2)	454 (97.0)	439 (92.8)	0.005
Statin at discharge	489 (97.6)	455 (97.2)	427 (90.3)	<0.001

Values are n (%), median (Q1-Q3), or mean ± SD. $T1_{3d}$, $T2_{3d}$, and $T3_{3d}$ indicate low, intermediate, and high leukocyte numbers, respectively.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft surgery; CK-MB = creatine kinase-myocardial band; CrCl = creatinine clearance; LVEF = left ventricular ejection fraction; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction; $T1_{3d}$ = tertile 1 at day 3; $T2_{3d}$ = tertile 2 at day 3; $T3_{3d}$ = tertile 3 at day 3.

Angiographic assessment of LVEF during the index procedure was available for 927 (95.0%) of 976 patients in the scintigraphic data cohort: 314 patients in scintiT1_{3d}, 310 patients in scintiT2_{3d}, and 303 patients in scintiT3_{3d}. Median LVEF values were 51.0% (Q1-Q3: 44.0%-58.0%) in scintiT1_{3d}, 50.0% (Q1-Q3: 42.0%-57.0%) in scintiT2_{3d}, and 47.0% (Q1-Q3: 38.0%-47.8%) in scintiT3_{3d}, with the lowest LVEF observed in the scintiT3_{3d} group (Figure 2D). At the 6-month follow-up, LVEF measurements were available for 376 (41.6%) patients: 125 patients in scintiT1_{3d}, 131 patients in scintiT2_{3d}, and 120 patients in scintiT3_{3d}. Median LVEF values at 6 months were 65.0% (Q1-Q3: 53.0%-70.0%) in scintiT1_{3d}, 59.5% (Q1-Q3: 48.0%-68.3%) in scintiT2_{3d}, and 58.0% (Q1-Q3: 46.8%-65.3%) in scintiT3_{3d}, with the scintiT3_{3d} group continuing to demonstrate the lowest LVEF (Figure 2E). Data for LVEF at both baseline and 6-month follow-up were available for 357 (36.6%) patients: 117 patients in scintiT1_{3d}, 125 patients in scintiT2_{3d}, and 115 patients in scintiT3_{3d}. Significant recovery in LVEF was observed at 6 months across all groups, regardless of leukocyte counts on day 3 post-MI, indicating substantial improvement compared with baseline values (Figure 2F). Of note, patients without follow-up LVEF data (n = 619) were more often female (25.5% vs 19.6%; $P = 0.049$), were older (mean age 63.3 ± 13.7 years vs 60.9 ± 11.7 years; $P = 0.005$), had lower mean baseline LVEF (47.8% ± 11.7% vs 50.4% ± 11.8%; $P < 0.001$), and experienced

FIGURE 2 **Infarct Size and Left Ventricular Function in STEMI Patients Based on Leukocyte Counts on Day 3 (Tertile-Based Analysis)**



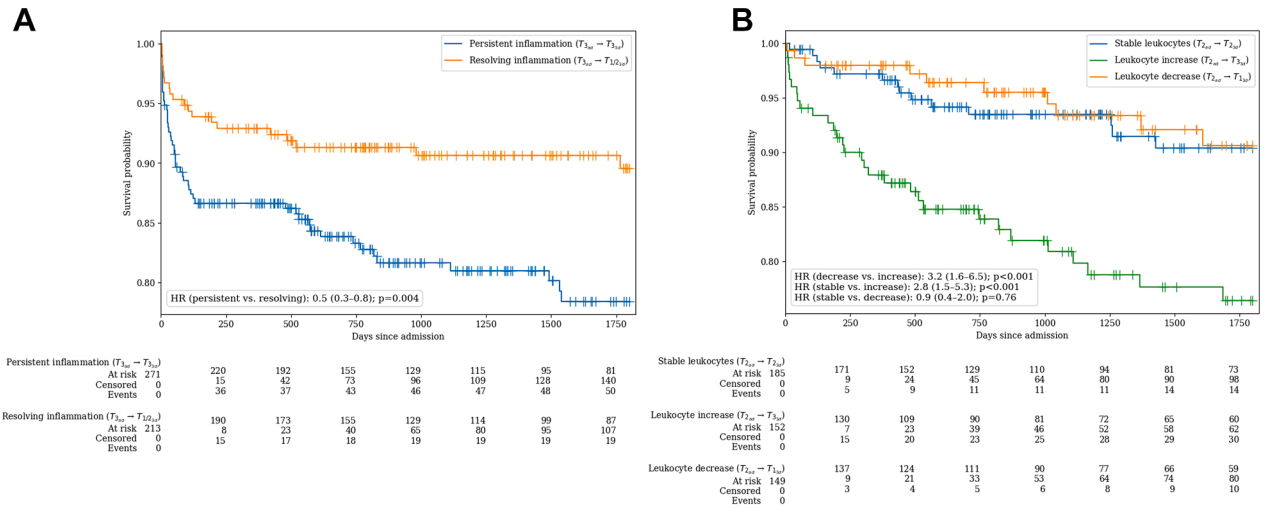
(A) Peak blood creatine kinase-myocardial band (CK-MB) values (U/L) and (B) peak troponin T values (ng/L) in patients with serial leukocyte measurement (n = 1,450). (C) Final infarct size assessed by scintigraphic imaging 7 to 14 days after primary percutaneous coronary intervention (% of the left ventricle [LV]) (n = 976 of 1,450). Left ventricular ejection fraction (LVEF) at (D) baseline, (E) 6 months after acute STEMI, and (F) comparison between baseline and 6 months (subgroup analysis of patients with scintigraphic data [n = 927 of 976]). Data are presented as median with 25th to 75th percentiles (boxes), 10th to 90th percentiles (bars), and values outside the given percentiles (dots). $T1_{3d}$ indicates low leukocyte levels, $T2_{3d}$ indicates intermediate leukocyte levels, and $T3_{3d}$ indicates high leukocyte levels. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. Abbreviations as in Figure 1.

higher crude 1-year mortality rates (34 of 619 [5.5%] vs 3 of 357 [0.8%]). These findings indicate that the absence of follow-up LVEF likely reflects real-world clinical constraints in a sicker patient cohort, rather than random missingness.

Next, we compared infarct sizes (based on CK-MB levels) in patients with a high initial inflammatory burden ($T3_{ad}$). Patients with persistent inflammation on day 3 (transition from $T3_{ad}$ to $T3_{3d}$) showed larger infarct sizes than patients with declining leukocyte levels (transition from $T3_{ad}$ to $T1{+}2_{3d}$). Median peak CK-MB levels were 250 U/L (Q1-Q3: 106-487 U/L) in $T3_{3d}$ and 160 U/L (Q1-Q3: 90-350 U/L) in $T1{+}2_{3d}$ ($P = 0.009$). These findings indicate that not every patient with an initial high inflammatory burden (high leukocyte counts at admission) developed a large MI. When inflammation subsided, infarct sizes were smaller than in patients with persistent inflammation.

IMPACT OF LEUKOCYTES KINETICS ON CLINICAL OUTCOME. We next examined the clinical implications of resolving inflammation (defined as a leukocyte transition from $T3_{ad}$ to $T2_{3d}$ or $T1_{3d}$ by day 3) vs sustained inflammation (absence of a leukocyte decline) (Figure 1E). Patients who transitioned from high leukocyte levels at admission ($T3_{ad}$) to intermediate or low levels by day 3 ($T2_{3d}$ or $T1_{3d}$) exhibited lower 5-year mortality rates (HR: 0.5; 95% CI: 0.3-0.8; $P = 0.004$) (Figure 3A). Moreover, patients with intermediate leukocyte levels at admission ($T2_{ad}$) that then showed a rise in leukocyte numbers (transition from $T2_{ad}$ at admission to $T3_{3d}$ by day 3) displayed worse outcomes than patients with sustained

FIGURE 3 Leukocyte Dynamics and Survival Outcomes in STEMI Patients With Serial Leukocyte Measurements



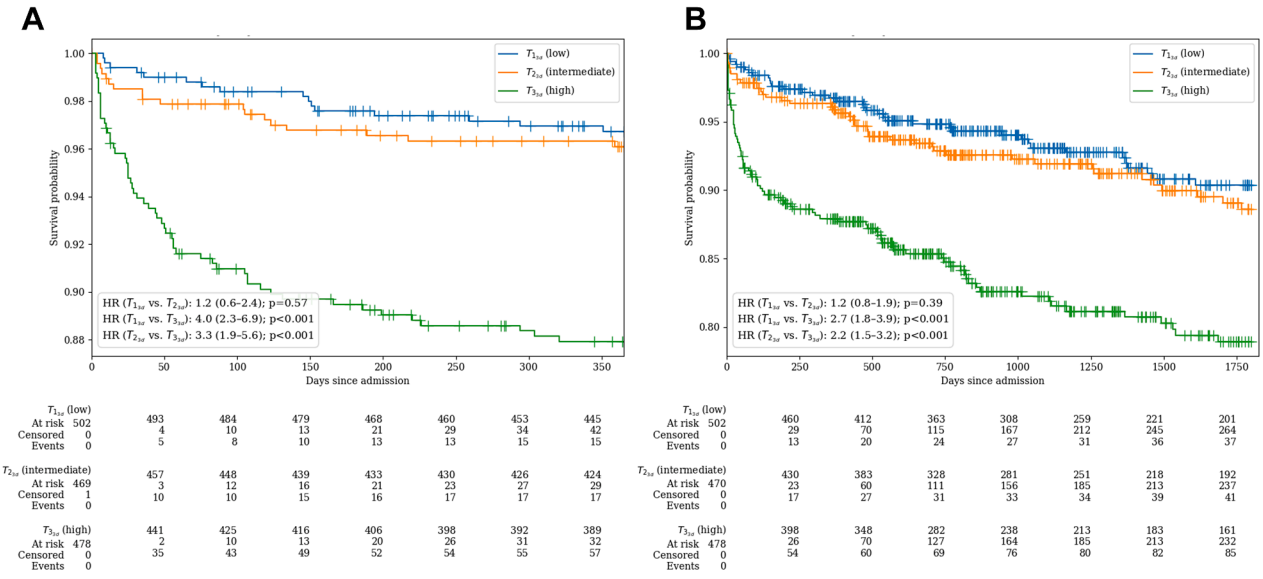
(A) Kaplan-Meier survival curves for patients with high leukocyte levels at admission ($T3_{ad}$). The blue curve represents patients with persistently high leukocyte levels from admission to day 3 ($T3_{ad}$ to $T3_{3d}$). The orange curve represents patients with resolving inflammation, indicated by a decline in leukocyte levels ($T3_{ad}$ to $T2_{3d}$ or $T1_{3d}$). (B) Kaplan-Meier survival curves for patients with intermediate leukocyte levels at admission ($T2_{ad}$). The blue curve represents patients with stable leukocyte levels from admission to day 3 ($T2_{ad}$ to $T2_{3d}$). The orange curve represents patients with resolving inflammation ($T2_{ad}$ to $T1_{3d}$), while the green curve represents those with increasing inflammation ($T2_{ad}$ to $T3_{3d}$). Abbreviations as in Figure 1.

(HR: 2.8; 95% CI: 1.5-5.3; $P < 0.001$) or declining leukocyte numbers (HR: 3.2; 95% CI: 1.6-6.5; $P < 0.001$) (Figure 3B). These findings again highlight the importance of leukocyte levels on day 3 after MI.

We next evaluated the impact of leukocyte counts on day 3 after STEMI on long-term outcomes with a median follow-up duration of 1,462 days (Q1-Q3: 732-1,800 days). One-year all-cause mortality (the primary endpoint) data were available for 1,347 (92.9%) patients, and 5-year mortality data were available for 717 (49.4%) patients. At 1 year, 89 patients had died: 15 in the $T1_{3d}$ group, 17 in the $T2_{3d}$ group, and 57 in the $T3_{3d}$ group. The Kaplan-Meier estimates for 1-year mortality were 3.3% (95% CI: 2.0%-5.3%), 3.9% (95% CI: 2.5%-6.1%), and 12.1% (95% CI: 9.5%-15.4%), respectively. Survival analysis revealed no significant difference in mortality between groups $T1_{3d}$ and $T2_{3d}$ ($P = 0.57$). However, group $T3_{3d}$ exhibited significantly higher mortality rates for $T1_{3d}$ vs $T3_{3d}$ (HR: 4.0; 95% CI: 2.3-6.9; $P < 0.001$), and for $T2_{3d}$ vs $T3_{3d}$ (HR: 3.3; 95% CI: 1.9-5.6; $P < 0.001$) (Figure 4A). At 5 years, there were 163 deaths: 37 in the $T1_{3d}$ group, 41 in the $T2_{3d}$ group, and 85 in the $T3_{3d}$ group. The Kaplan-Meier estimates for 5-year mortality were 9.6% (95% CI: 7.0%-13.2%), 11.4% (95% CI: 8.4%-15.3%), and 21.1% (95% CI: 17.2%-25.6%), respectively. Again, no significant difference was observed between groups $T1_{3d}$ and $T2_{3d}$ ($P = 0.39$), but mortality remained highest in the $T3_{3d}$ group. The HR for $T1_{3d}$ vs $T3_{3d}$ was 2.7 (95% CI: 1.8-3.9; $P < 0.001$), and for $T2_{3d}$ vs $T3_{3d}$, HR was 2.2 (95% CI: 1.5-3.2); $P < 0.001$) (Figure 4B).

A univariable regression analysis was conducted, including biologically plausible and clinically relevant variables such as age, sex, history of smoking, hypercholesterolemia, hypertension, diabetes, body mass index, estimated glomerular filtration rate, peak creatine kinase and CK-MB levels, peak troponin T, prior history of MI or coronary artery bypass grafting, and leukocyte counts on day 3 after STEMI (Table 2). Results identified age (HR: 1.05; 95% CI: 1.04-1.07; $P < 0.001$), estimated glomerular filtration rate (HR: 0.96; 95% CI: 0.95-0.97; $P < 0.001$), male sex (HR: 3.1; 95% CI: 2.0-4.9; $P < 0.001$), diabetes (HR: 1.93; 95% CI: 1.24-3.02; $P = 0.004$), hypercholesterolemia (HR: 0.6; 95% CI: 0.4-0.9; $P = 0.017$), history of smoking (HR: 0.5; 95% CI: 0.3-0.8; $P = 0.004$), previous MI (HR: 1.72; 95% CI: 1.04-2.85; $P = 0.035$), leukocyte counts on day 3 after STEMI (HR: 1.07; 95% CI: 1.05-1.08; $P < 0.001$), peak creatine kinase (per 100 units) (HR: 0.92; 95% CI: 0.89-0.95; $P < 0.001$), peak CK-MB (per 10 units) (HR: 1.02; 95% CI: 1.01-1.02; $P < 0.001$), peak troponin T (per 1000 units) (HR: 1.04; 95% CI: 1.01-1.06; $P = 0.003$), and LVEF (HR: 0.94; 95% CI: 0.92-0.96; $P < 0.001$) as predictors for 1-year mortality.

FIGURE 4 **Association of Leukocyte Count on Day 3 With Survival Outcomes in STEMI Patients**



Kaplan-Meier curves of (A) 1-year and (B) 5-year all-cause mortality according to leukocyte counts on day 3 (tertile-based analysis, T_{3d}) in STEMI patients with serial leukocyte measurements (n = 1,450). $T1_{3d}$ indicates low leukocyte levels, $T2_{3d}$ indicates intermediate leukocyte levels, and $T3_{3d}$ indicates high leukocyte levels. Abbreviations as in Figure 1.

These variables were then included in a multivariable analysis. Age (HR: 1.05; 95% CI: 1.02-1.07; $P = 0.001$), estimated glomerular filtration rate (HR: 0.98; 95% CI: 0.97-0.99; $P = 0.005$), LVEF (HR: 0.96; 95% CI: 0.94-0.98; $P = 0.002$), peak CK-MB (per 10 units) (HR: 1.01; 95% CI: 1.00-1.02; $P = 0.046$), and leukocyte counts on day 3 after STEMI (HR: 1.09; 95% CI: 1.03-1.17; $P = 0.006$) emerged as independent predictors for 1-year all-cause mortality (Table 2).

To separately analyze 5-year survival in patients with a high initial inflammatory burden ($T3_{ad}$), those with available leukocyte counts on admission were first stratified into large- and small-MI groups based on median CK-MB levels (large MIs: 273 U/L [Q1-Q3: 179-438 U/L], n = 666; small MIs: 64 U/L [Q1-Q3: 34-94 U/L], n = 677). There were 284 patients within the large MI group with a high initial inflammatory burden ($T3_{ad}$). Of these, 113 showed inflammatory resolution and 171 had persistent inflammatory burden until day 3 post STEMI. There were 9 deaths among patients with declining leukocyte counts and 35 deaths among those with persistently elevated leukocyte levels. Kaplan-Meier estimates for 5-year mortality were 8.1% (95% CI: 4.3%-15.0%) and 24.0% (95% CI: 17.5%-32.4%), respectively. Patients with large MIs who demonstrated a decline in leukocyte counts had better 5-year survival compared with those with persistent inflammation (HR: 2.81; 95% CI: 1.35-5.84; $P = 0.006$) (Supplemental Figure 2A). In the small MI group, there were 6 deaths among patients with declining leukocyte counts (n = 80) and 8 deaths among those with persistently high leukocyte levels (n = 78). Kaplan-Meier estimates for 5-year mortality were 10.3% (95% CI: 4.9%-20.8%) and 13.1% (95% CI: 6.6%-24.9%), respectively. In this group, 5-year survival was comparable between patients with and without persistent inflammation on day 3 (HR: 1.3; 95% CI: 0.5-3.6; $P = 0.62$) (Supplemental Figure 2B).

LEUKOCYTE PHENOTYPES FOLLOWING MI. Given these numeric and quantitative changes, we next explored whether inflammatory monocytes undergo phenotypic changes in response to MI. To that end, we isolated blood inflammatory monocytes ($CD14^+$ monocytes) from patients after STEMI (n = 20) and from age- and sex-matched patients with stable CAD (n = 20) (Supplemental Figures 3A and 3B) and subjected them to RNA sequencing. Baseline characteristics of the cohort are detailed in Supplemental Table 3. $CD14^+$ monocyte isolation achieved high purity (>95%) (Supplemental Figure 3C). Leukocyte subset kinetics are illustrated in Supplemental Figure 4. Monocytes undergo substantial transcriptional changes during the course of MI. Compared

TABLE 2 Cox Regression Analysis With 1-Year Mortality in STEMI Patients With Serial Leukocyte Measurements

	Univariable Analysis	*P* Value	Multivariable Analysis	*P* Value
Male	3.1 (2.0-4.9)	<0.001	1.36 (0.77-2.41)	0.29
Previous CABG	1.97 (0.80-4.86)	0.14	–	–
Previous MI	1.72 (1.04-2.85)	0.035	1.30 (0.64-2.64)	0.47
History of smoking	0.5 (0.3-0.8)	0.004	1.78 (0.93-3.41)	0.08
Hypercholesterolemia	0.6 (0.4-0.9)	0.017	0.81 (0.47-1.40)	0.46
Hypertension	1.09 (0.71-1.69)	0.69	–	–
Diabetes	1.93 (1.24-3.02)	0.004	1.34 (0.74-2.43)	0.34
Age	1.05 (1.04-1.07)	<0.001	1.05 (1.02-1.07)	0.001
CrCl	0.96 (0.95-0.97)	<0.001	0.98 (0.97-0.99)	0.005
Leukocytes after 3 d	1.07 (1.05-1.08)	<0.001	1.09 (1.03-1.17)	0.006
Peak CK-MB (per 10 units)	1.02 (1.01-1.02)	<0.001	1.01 (1.00-1.02)	0.046
Peak CK (per 100 units)	0.92 (0.89-0.95)	<0.001	1.01 (1.0-1.01)	0.19
Peak troponin T (per 1,000 units)	1.04 (1.01-1.06)	0.003	1.01 (0.97-1.05)	0.75
LVEF	0.94 (0.92-0.96)	<0.001	0.96 (0.94-0.98)	0.002
BMI	0.96 (0.91-1.02)	0.18	–	–

Values are HR (95% CI).
CK = creatine kinase; other abbreviations as in Table 1.

with stable CAD patients, monocytes from STEMI patients early after symptom onset (<12 hours) showed 1,708 DEGs (cutoff: |log2 fold change| ≥1.0 at a false discovery rate of 5%) out of 20,967 coding transcripts, of which 285 (16.7%) were up-regulated and 1,423 (83.3%) were down-regulated (Figure 5A). When compared with stable CAD, monocytes from STEMI patients 3 days after symptom onset exhibited 1,113 DEGs, of which 116 (10.4%) were up-regulated and 997 (89.6%) were down-regulated (Figure 5B). An intraindividual comparison between day 0 and day 3 after STEMI revealed 144 DEGs, of which 44 (30.6%) were up-regulated and 100 (69.4%) were down-regulated at day 3 (Figure 5C). A gene set enrichment analysis revealed the overrepresentation of these DEGs in distinct Gene Ontology pathways (Figures 5D to 5I).

Together, our data demonstrate both profound quantitative and qualitative alterations in the monocyte repertoire in response to STEMI.

CRP KINETICS FOLLOWING MYOCARDIAL INJURY AND IMPACT ON OUTCOME. Along with leukocyte numbers and phenotypes, we also explored CRP kinetics in response to MI. CRP is an acute phase protein secreted from hepatocytes as a result of activation of the NLRP3 infllammasome-interleukin-1β-interleukin-6 axis. CRP is known to reflect the inflammatory burden in both sterile and unsterile inflammation. Therefore, high-sensitivity CRP is an often used marker of inflammation in trials testing anti-inflammatory therapy (eg, the CANTOS [Canakinumab Antiinflammatory Thrombosis Outcome Study] and COLCOT [Colchicine Cardiovascular Outcomes Trial] trials).[30,31] However, CRP, unlike leukocytes, is not mechanistically involved in inflammatory processes, but rather is a marker of inflammation. CRP levels gradually rise after STEMI until levels reach a plateau, on day 3 or 4 after MI in our cohort. (Supplemental Figure 5). CRP kinetics differ largely from leukocyte kinetics after STEMI (Figure 1A), and CRP responds less rapidly as leukocytes.

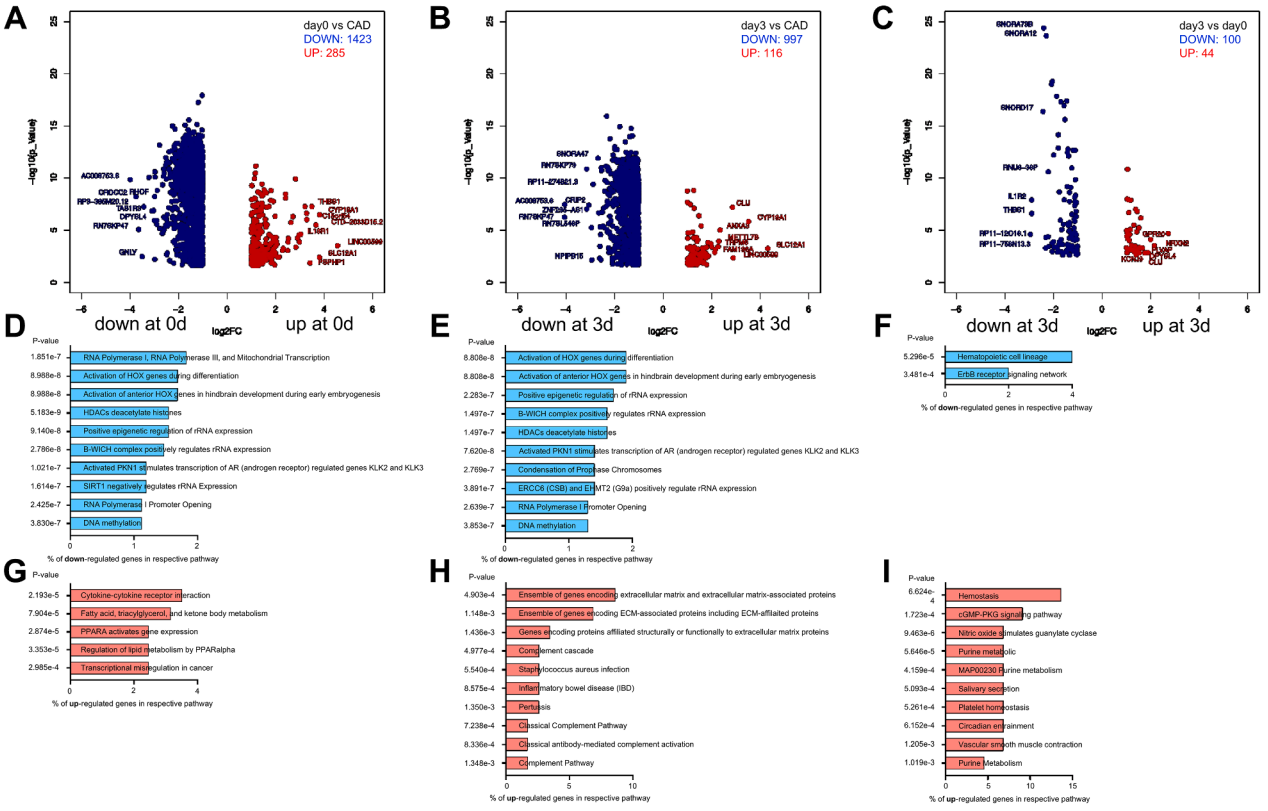
To investigate the impact of CRP levels on outcomes, we grouped patients into tertiles based on peak CRP levels. Of the 1,781 STEMI patients, 1,766 (99.2%) had CRP levels available. The tertiles (T_{CRP}) were defined as follows: tertile 1 ($T1_{CRP}$), <16.0 mg/L (n = 588); tertile 2 ($T2_{CRP}$), 16.1 to 58.0 mg/L (n = 590); and tertile 3 ($T3_{CRP}$), >58.0 mg/L (n = 588).

One- and 5-year follow-up for all-cause mortality was available for 1,638 (92.8%) patients and 859 (48.6%) patients, respectively. At 1 year, 121 patients were dead: 19 deaths in the $T1_{CRP}$ group, 22 deaths in the $T2_{CRP}$ group, and 80 deaths in the $T3_{CRP}$ group. Kaplan-Meier estimates of 1-year mortality were 3.3% (95% CI: 2.1%-5.1%), 3.8% (95% CI: 2.5%-5.7%), and 14.2% (95% CI: 11.6%-17.3%), respectively. Survival analysis revealed no significant difference between tertiles $T1_{CRP}$ and $T2_{CRP}$ (HR: 1.15; 95% CI: 0.62-2.12; $P = 0.66$). However, mortality was significantly higher in $T3_{CRP}$, with an HR of 4.5 (95% CI: 2.8-7.5; $P < 0.001$) for $T1_{CRP}$ vs $T3_{CRP}$ and 4.0 (95% CI: 2.5-6.4; $P < 0.001$) for $T2_{CRP}$ vs $T3_{CRP}$ (Supplemental Figure 6A).

At 5 years, 206 patients experienced all-cause mortality: 32 deaths in the $T1_{CRP}$ group, 49 deaths in the $T2_{CRP}$ group, and 125 deaths in the $T3_{CRP}$ group. Kaplan-Meier estimates of 5-year mortality were 7.2% (95% CI: 5.0%-10.3%), 10.9% (95% CI: 8.3%-14.3%), and 24.5% (95% CI: 20.9%-28.6%), respectively. Similar to the 1-year analysis, no significant differences were observed between tertiles $T1_{CRP}$ and $T2_{CRP}$ ($P = 0.11$). Mortality remained significantly higher in the $T3_{CRP}$ group, with an HR of 4.0 (95% CI: 2.7-5.8; $P < 0.001$) for $T1_{CRP}$ vs $T3_{CRP}$ and 2.8 (95% CI: 2.0-3.9; $P < 0.001$) for $T2_{CRP}$ vs $T3_{CRP}$ (Supplemental Figure 6B).

BLOOD AND HEART LEUKOCYTE KINETICS FOLLOWING MI IN MICE. Mouse models of MI are widely employed to emulate the clinical scenario of acute MI in humans and to investigate novel aspects of MI pathophysiology. However, differences in blood leukocyte composition between mice and humans (with granulocytes predominating in humans and lymphocytes in mice) raise questions

FIGURE 5 **Qualitative Alteration of Inflammatory Blood Monocytes Secondary to Acute ST-Segment Elevation Myocardial Infarction**



(A to C) Volcano plot displaying differentially expressed genes (|log2 fold change [FC]| ≥1.0 and adjusted $P < 0.05$) from inflammatory ($CD14^{+}$) blood monocytes isolated from stable coronary artery disease (CAD) patients and from patients 12 and 72 hours post-ST-segment elevation myocardial infarction (N = 20 per group, LIMMA (linear models for microarray data) *t* statistic approach with Benjamini-Hochberg multiple testing correction) as assessed by RNA sequencing. (D to I) Gene set enrichment analyses revealed overrepresentation of down- and up-regulated genes in distinct pathways. The percentage of down- and up-regulated genes per respective pathway and *P* values as assessed by Benjamini-Hochberg correction are shown for significant pathways.

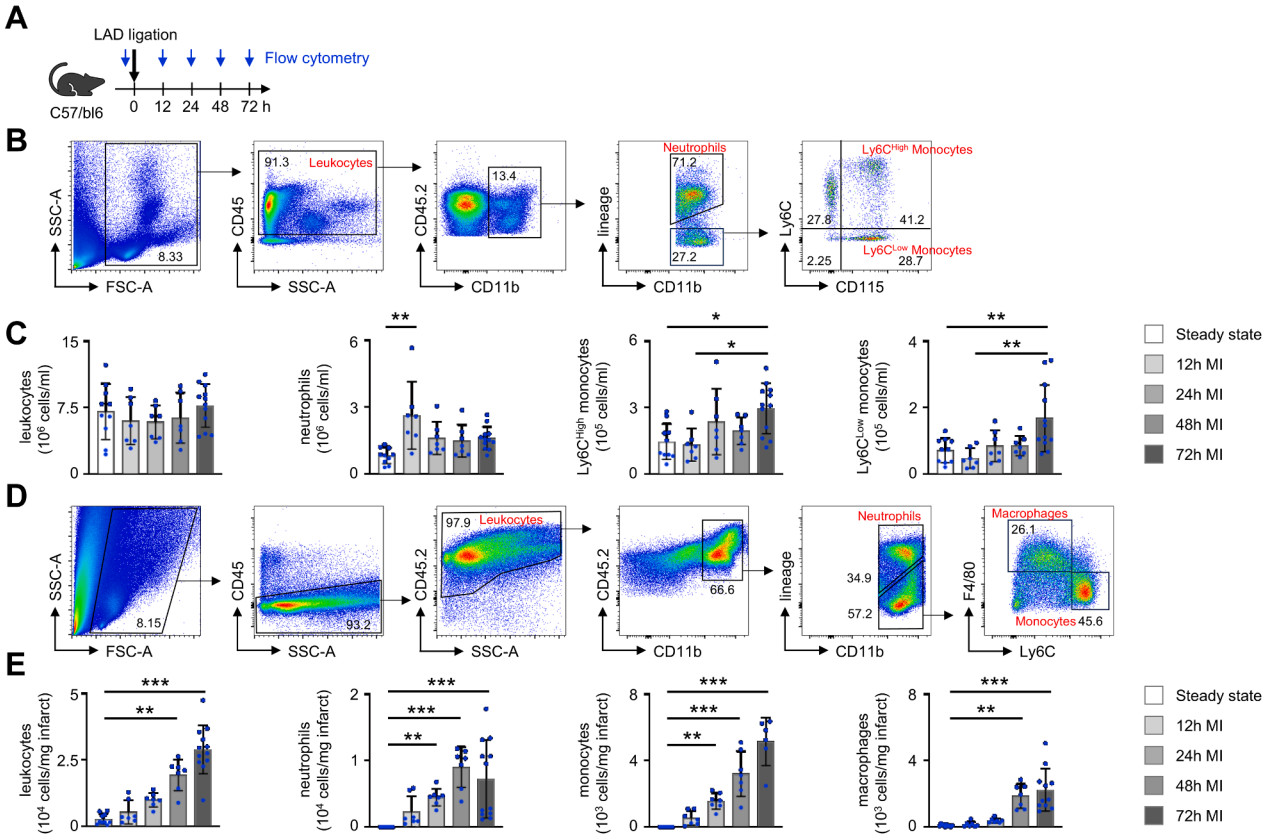
about the fidelity of these models in reflecting the human systemic immune response to MI. To address this, we induced acute anterior MI in healthy wild-type mice via permanent ligation of the mid-LAD (**Figure 6A**). Flow cytometry revealed an immediate increase in blood neutrophil numbers and a delayed rise in blood monocyte numbers compared with steady-state levels (**Figures 6B and 6C**), consistent with the myeloid cell kinetics observed in human MI. Similarly, neutrophils were the first to accumulate in the ischemic myocardium (as early as 12 hours post-MI), whereas monocyte and macrophage infiltration occurred later (**Figures 6D and 6E**).

Collectively, these findings indicate that mice exhibit a systemic immune response to MI that parallels the human condition, supporting the relevance of preclinical MI models for investigating inflammatory networks.

DISCUSSION

Inflammation plays a crucial role in the onset and progression of cardiovascular disease, particularly in acute MI, which triggers a robust systemic inflammatory response. Our data demonstrate that leukocyte levels are already elevated at the time of emergency room presentation, reflecting their early involvement in MI pathogenesis. These leukocytes are rapidly recruited from circulation and accumulate in the infarcted myocardium, where they phagocytose necrotic cells and tissue debris.[3] Neutrophils and monocytes exhibit distinct temporal patterns during this response. Neutrophil levels reach their peak early, notably at the time of admission, while monocyte levels peak on day 2. This temporal pattern indicates the culmination of the inflammatory phase following MI. Leukocytosis gradually declines

FIGURE 6 Leukocyte Kinetics in the Heart and Blood Following Experimental MI in Mice



(A) Experimental design. (B) Representative flow cytometry gating strategy (numbers next to gates indicate frequencies [%]) and quantification of (C) blood leukocyte subsets before and at different time points after myocardial infarction (MI). (D) Representative flow cytometry gating strategy and quantification of (E) cardiac leukocyte subsets pre- and post-MI (n = 7-12 mice per group, Kruskal-Wallis test followed by Dunn's multiple comparisons test). Data are presented as mean ± SD. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. FSC-A = forward scatter area; LAD = left anterior descending coronary artery; SSC-A = side scatter area.

thereafter, with leukocyte levels returning to normal by day 3 post-MI. This decline marks the transition from the inflammatory to the reparative phase, during which inflammation resolves. At this stage, leukocytes cease accumulating in the heart, and cardiac macrophages undergo a phenotypic shift towards a reparative role, limiting inflammation and promoting scar formation. This biphasic inflammatory response in MI led us to investigate the impact of prolonged or excessive inflammation beyond the initial peak, exploring its potential detrimental effects on healing and recovery.

Most previous studies have focused on the association between the peak of inflammation and clinical outcomes in acute MI. For instance, Tsujioka et al[14] reported that blood monocyte levels peak on day 3 in a heterogeneous cohort of acute MI patients (n = 36). This study also demonstrated that elevated levels of $CD14^{+}CD16^{-}$ monocytes (the proinflammatory subset) were negatively associated with myocardial salvage at 7 days post-MI, as measured by cardiac magnetic resonance (CMR). Similarly, van der Laan et al[32] showed that high levels of classical blood monocytes collected between days 4 and 6 after PPCI in STEMI patients (n = 58) correlated with reduced LVEF and increased infarct size, as assessed by CMR within 2 days post-MI. In a cohort of 975 acute MI patients treated with thrombolysis, leukocyte levels at admission were positively correlated with infarct size, estimated by peak creatine kinase levels, and with 30-day mortality.[33] Additionally, in 394 patients treated with fibrinolytic therapy for STEMI, neutrophil count at admission was positively associated with infarct size (as measured by peak creatine kinase levels).[34] Moreover, a study involving 4,621 acute MI patients treated with fibrinolytics and 3,027

patients with unstable angina reported that elevated white blood cell counts, assessed around the second day of hospitalization, were linked to increased 30-day and 10-month mortality.[35] Consistently, white blood cell count at admission was identified as an independent predictor of 30-day mortality in acute MI patients.[36] Furthermore, elevated leukocyte counts at admission predicted 1-year mortality in 4,329 patients with acute coronary syndrome treated with percutaneous coronary intervention.[37] In contrast to previous studies, we investigated whether persistent, nonresolving inflammation affects cardiac function after MI. Patients exhibiting elevated leukocyte levels through day 3 post-MI (group $T3_{3d}$) demonstrated the largest infarct sizes. This was associated with reduced left ventricular function, as well as increased mortality and morbidity during follow-up. Our findings underscore the critical role of inflammation resolution in infarct healing and in mitigating post-MI complications. Elevated leukocyte count on day 3 post-MI was identified as a negative prognostic marker for mortality. Specifically, our data suggest that unresolved inflammation may serve as a therapeutic target, potentially guiding future anti-inflammatory trials regarding optimal timing for intervention. Patients requiring suppression of ongoing inflammation could be readily identified by measuring blood leukocyte levels on day 3 post-MI.

Efforts to reduce inflammation in the context of acute MI have yielded mixed results. For instance, the administration of colchicine during STEMI was shown in 1 study to reduce surrogate markers of infarct size and improve LVEF.[38] However, another study involving STEMI patients found no significant reduction in infarct size, as assessed by CMR, following colchicine treatment.[39] More recently, a long-term outcome trial evaluated the efficacy of colchicine initiated early during MI and continued for a median of 3 years.[40] In this study, colchicine did not reduce the composite endpoint of cardiovascular death, MI, stroke, or unplanned ischemia-driven coronary revascularization. Interestingly, a single dose of the interleukin-6 receptor inhibitor tocilizumab administered to STEMI patients was associated with increased myocardial salvage, as determined by CMR.[41] Despite these findings, the efficacy of anti-inflammatory agents remains variable, likely due to differences in the dosages, timing of administration, and duration of treatment chosen in these studies. In the previously mentioned studies, anti-inflammatory agents were administered during the early phase of inflammation. Our findings suggest that targeting sustained inflammation may represent a more effective therapeutic approach. This perspective may guide future investigations toward optimizing the timing of anti-inflammatory interventions in MI management. Additionally, this personalized treatment strategy might enable the identification of patients who could particularly benefit from anti-inflammatory treatment, while sparing those without prolonged inflammation, in whom the side effects of anti-inflammatory therapy might outweigh its beneficial effects.

In addition to the quantitative alterations, our analyses revealed substantial phenotypic changes in monocytes during MI. Monocytes isolated immediately after infarction, compared with those from stable patients (day 0 vs stable CAD) (**Figures 5A, 5D and 5G**), up-regulate genes related to extracellular/cytokine signaling (*IL18RAP*, *IL18R1*, *TNFRSF21*, *IL1R2*, *IL1R1*, *IL1RAP*), indicating an increased ability to "sense" the inflammatory environment. Moreover, monocytes from early time points post-MI undergo a metabolic switch toward lipid metabolism. As shown by Fiorelli et al,[42] monocytes from acute MI patients display an altered ceramide composition, characterized by increased levels of lactosylceramide and phospholipids. In that study, Fiorelli et al reported a positive correlation between lactosylceramide levels and monocyte migration. It is well established that metabolic changes influence macrophage polarization; however, these changes may also play a role during monocyte recruitment to damaged tissue. Notably, when comparing monocytes derived from patients at day 3 post-MI with those from the stable CAD group (day 3 vs stable CAD) (**Figures 5B, 5E, and 5H**), genes involved in the complement cascade, such as *C1QB* and *C1QC*, were up-regulated. As previously described, activation of the complement cascade induces chemotaxis and amplifies inflammatory signaling.[43] In general, the transcriptomic analysis expectedly revealed that the major differences occurred between stable CAD and infarcted patients; in contrast, fewer genes were differentially expressed when comparing monocytes from day 0 and day 3 post-MI (day 3 vs day 0) (**Figures 5C, 5F, and 5I**). Interestingly, the "hematopoietic cell lineage" pathway was down-regulated in day 3 monocytes compared with day 0 monocytes. In particular, the down-regulation of FLT3 may indicate a reduced capacity of monocytes to differentiate into dendritic cells, instead favoring macrophage-oriented differentiation, as previously reported.[44]

Our study offers a comprehensive characterization of the systemic immune response after STEMI, detailing both quantitative and qualitative alterations in circulating leukocytes within a large,

well-characterized patient cohort. Additionally, we perform a cross-species comparison of the systemic immune response. While the composition of blood leukocytes varies significantly between mice and humans, murine models of MI are frequently employed to investigate cardiac inflammation. Our findings reveal that, despite these interspecies differences, the systemic response of blood myeloid cells (neutrophils and monocytes) in mice with surgically induced MI closely mirrors that of patients with STEMI. This highlights the value of such experimental models for advancing our understanding of the pathophysiology of cardiac ischemia.

STUDY LIMITATIONS. First, most data of our study rely on retrospective analyses of observational datasets and are not derived from prospective studies specifically designed to investigate the association between leukocyte counts and outcomes in patients with STEMI. As such, the findings should be interpreted as hypothesis-generating rather than definitive. Second, given that patient enrollment occurred over a period of 2 decades, therapeutic regimens (eg, antiplatelet therapy), stent technology, and interventional procedures have evolved substantially over time. Third, we did not have access to patient information regarding anti-inflammatory pretreatments (such as corticosteroids), hematological disorders, or chemotherapy, all of which may have influenced the systemic inflammatory response following MI. Fourth, we processed the blood immediately after sample collection. A positive selection approach using CD14 beads and subsequent magnetic purification was chosen. We cannot exclude the possibility that binding of magnetic beads to CD14 on monocytes may induce transcriptomic changes or monocyte activation. However, because this method was applied uniformly to all samples, any potential activation is expected to be consistent across the dataset and is therefore unlikely to account for a substantial number of DEGs. Fifth, blood samples were obtained at different times of the day: the first sample was collected immediately upon admission, followed by subsequent samples taken each morning between 7:00 and 9:00 AM. Therefore, circadian rhythms, which are known to influence blood leukocyte levels, may have affected our results. Sixth, only a single blood sample was collected on the day of admission, which may have led us to miss an acute further rise in total leukocytes or specific leukocyte subsets, as reported in another study.[45] Seventh, leukocyte subset data were available for only a small proportion of the overall cohort. Therefore, focusing primarily on total leukocyte levels may have obscured specific contributions from individual subsets. Eighth, although substantial similarities were observed, the immune response to MI in humans with atherosclerotic disease may differ from that in infarcted mice, which were otherwise healthy.

CONCLUSIONS

In patients with STEMI, persistent inflammation is associated with greater infarct size, as determined by scintigraphic and enzymatic measurements, and with increased 1-year mortality. Consequently, STEMI patients exhibiting persistent inflammation, as indicated by elevated leukocyte counts on day 3 following symptom onset, are at higher risk for adverse clinical outcomes. These findings underscore the pivotal role of timely inflammation resolution and provide insights into the optimal timing for initiating anti-inflammatory therapies to attenuate prolonged inflammatory responses post-STEMI.

DATA AVAILABILITY STATEMENT Materials used in this study are commercially available, with suppliers listed in the Methods. Upon request, samples or detailed descriptions for obtaining them can be provided. All relevant data are included in this paper and its supplemental materials.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: We explored the inflammatory response secondary to MI. In a study of 1,700 STEMI patients treated with percutaneous coronary intervention, we found that leukocyte counts peaked at admission and then declined by day 3. Patients with persistently high leukocyte levels had larger infarcts, worse left ventricular function, and higher mortality at 1 and 5 years. Apart from these quantitative changes, we also investigated the qualitative response to MI. Here, transcriptomic analysis of blood monocytes showed profound immune pathway reprogramming post-MI.

TRANSLATIONAL OUTLOOK: Persistent inflammation was linked to increased mortality, identifying leukocyte counts on day 3 post-MI as a key prognostic marker and suggesting unresolved inflammation as a potential therapeutic target for improving STEMI outcomes.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.