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Association between white blood cell count and coronary artery bypass graft failure: an individual patient data analysis of clinical trials

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Abstract

Background Baseline systemic inflammation is associated with worse long-term outcomes after coronary artery bypass grafting [CABG], but the mechanisms of this association are unclear. This study aims to explore the association between pre-operative white blood cell [WBC] count and CABG graft failure.

Methods We pooled individual patient data from two randomized clinical trials with systematic CABG graft imaging. The primary analysis was the association between pre-operative WBC count and graft failure, as a continuous variable, at the time of imaging after CABG, using mixed-effects multivariable logistic regression models.

Results Overall, 910 patients and 2,036 grafts were included in the analysis [1,120 saphenous vein grafts, 828 left internal thoracic arteries, 76 right internal thoracic arteries, and 12 radial arteries]. The median time to imaging was 1.01 [interquartile range (IQR), 0.99;1.03] years and the median pre-operative WBC count was 7.1 [IQR, 6.0;8.4] x 10^9/L. There was no association between WBC count and graft failure at both the patient and the individual graft level [adjusted odds ratio (aOR) 1.07 (95% confidence interval (CI), 0.98;1.17), $p=0.11$ and aOR 1.09 (95% CI, 0.91;1.30), $p=0.37$], respectively. When evaluated as a dichotomous variable [≥ 11 vs. $< 11 \times 10^9$/L] and by quartile, WBC count was not associated with graft failure at the patient and individual graft levels.

Conclusion In this pooled analysis of individual patient data from two randomized clinical trials, WBC count was not associated with graft failure after CABG. The reported association between inflammation and CABG is likely mediated through other mechanisms, such as native coronary artery disease progression.

Impact on daily practice The lack of a clear association between WBC count and graft failure suggests that pre-operative WBC count should not be routinely used as a predictor of graft failure after CABG.

Classifications NSTEMI, Stable angina, Multiple vessel disease, Saphenous vein graft, Arterial graft, Clinical trials

Keywords Leukocyte count, Leukocytes, Saphenous vein graft, Arterial graft, Cardiac surgery, Perioperative

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Introduction

Preoperative subclinical inflammation markers have traditionally been associated with adverse post CABG outcomes, but the mechanisms of this association are unclear [1, 2]. Graft patency is the mechanism of the clinical benefits seen with coronary artery bypass grafting [CABG]; however, CABG graft failure has been reported to occur in 17% of grafts one year after surgery [3, 4]. Inflammation plays an important role in the development of intimal hyperplasia and atherosclerosis, both key mechanisms of graft failure [5–8]. It has also been suggested that leukocyte infiltration into endothelial cells may be an important mechanism of early CABG graft failure [9], but high quality evidence is limited [10].

On the other hand, systemic inflammatory markers, including white blood cell [WBC] count, C-reactive protein [CRP], neutrophil/lymphocyte ratio, interleukins, glycoprotein acetylation, and others have been associated with coronary disease development and progression [1, 2, 11] and recent randomized evidence has confirmed the beneficial effects of anti-inflammatory therapies on progression of coronary artery disease [12, 13].

It is unclear at present if the association between preoperative elevation of inflammatory makers and clinical outcomes after CABG is mediated through graft failure of native coronary disease progression. WBC count is a widely available and easily interpretable inflammatory marker which is already routinely used in clinical practice. To investigate this issue, we performed an individual patient data pooled analysis of two CABG randomized trials that used systematic imaging follow-up and collected preoperative WBC count.

Methods

The present study represents a sub-analysis of a previously reported individual patient data pooled analysis from CABG randomized clinical trials [RCTs] with systematic imaging follow-up [3]. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Individual Patient Data [PRISMA-IPD] checklist and flow diagram were utilized for this study (Fig. 1) [14]. As reported previously, a medical librarian searched Ovid MEDLINE, Ovid Embase, and the Cochrane Library [Wiley] to identify published randomized clinical trials that included patients with CABG with protocol-defined graft imaging at one or more years of follow-up from database inception to July 18, 2022. The reference lists of the selected articles were also searched for relevant publications. After removal of duplicate results, two independent reviewers [S.S. and L.H.] screened abstracts and full-text articles for inclusion or exclusion in the study based on predefined inclusion criteria and disagreements were resolved by consultation with a third reviewer [M.G.]. Individual patient data were requested for eligible trials and the full search strategy is presented (Table S1). Out of ten trials, two trials contained pre-operative WBC count data, and were included in this analysis: the DACAB [Different Anti-platelet Therapy Strategy After Coronary Artery Bypass Graft Surgery] and POPular CABG [The Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery] trials [15, 16]. The DACAB trial was a randomized, multicenter, open-label, clinical trial conducted at six tertiary hospitals in China, which enrolled 500 patients and was designed to compare the effects of dual antiplatelet versus single antiplatelet therapy on graft failure rates after CABG. The POPular CABG trial was a randomized, multicenter, double-blind, placebo-controlled trial conducted at six tertiary hospitals in the Netherlands, which enrolled 499 patients and was also designed to compare the effects of dual antiplatelet versus single antiplatelet therapy on graft failure rates after CABG. Ethics approval and informed patient consent from all participants were obtained by the study teams for the individual trials; the Weill Cornell Medicine Institutional Review Board waived the need for ethics approval and informed patient consent for the pooled analysis. The risk of bias for both trials was assessed using the Cochrane risk-of-bias tool 2 (Figure S1) [17]. Detailed information about the methods and sources for these trials have been reported previously [3].

Outcomes

The primary outcome was graft failure, defined at the patient level [patients with ≥ 1 failed graft] and at the graft level [per individual failed graft]. The determination of graft failure was defined as ≥ 50% stenosis or graft occlusion as assessed by either invasive coronary angiography or coronary computed tomography, which was a definition re-adjudicated and harmonized across the two trials included in the individual patient data pooled analysis (Table S2) [18]. Scheduled imaging occurred at one year in both trials, although imaging could occur earlier if driven by symptoms. The primary predictor of interest was pre-operative WBC count, which in both trials was collected once at the patient's pre-operative visit. Additional outcomes included myocardial infarction or repeat revascularization before per-protocol or unscheduled imaging. For unscheduled [clinically driven] imaging, myocardial infarction or repeat revascularization events occurring seven days after unscheduled imaging were also included.

Statistical analysis

The primary analysis was the association between preoperative WBC count, as a continuous variable, and graft failure. This association was also evaluated with WBC count as a categorical variable [≥ 11 vs. $< 11 \times 10^9$/L] and

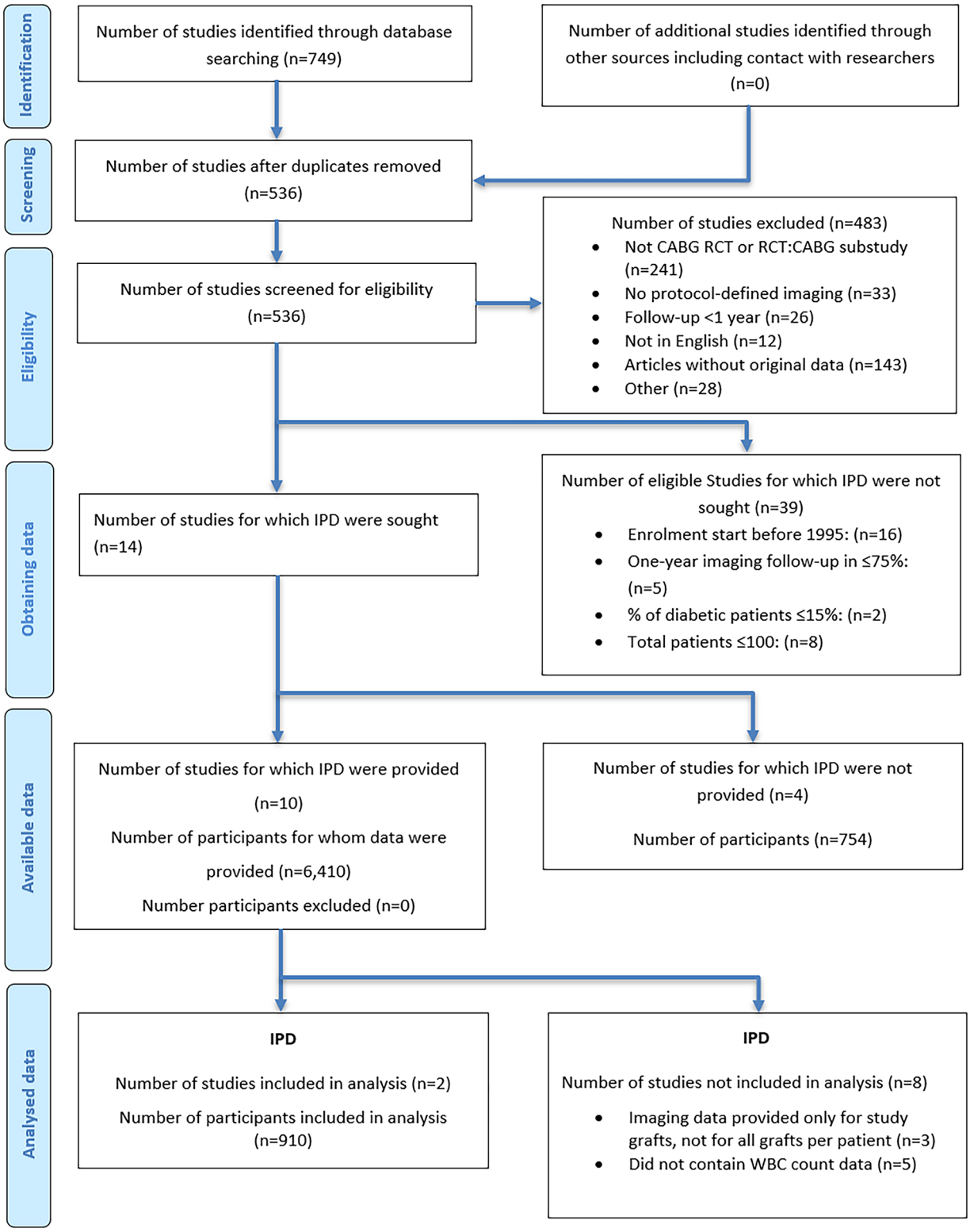

Fig. 1 Study flowchart. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for Individual Patient Data (IPD) flowchart

by quartiles. An additional analysis between pre-operative WBC count and myocardial infarction or repeat revascularization before imaging was performed.

At the patient level, multivariable analysis included adjustment for age, hypertension, smoking, diabetes, off-pump surgery, total number of grafts, total number of arterial grafts, statin use, dual antiplatelet therapy versus single antiplatelet therapy use, presence of graft to the LAD, and use of sequential grafting. At the individual graft level, multivariable analysis excluded adjustment for total number of grafts and total number of arterial grafts.

All patients in the pooled individual patient dataset with available per-protocol or unscheduled imaging were included in the analysis set. Categorical variables were reported as counts and percentages and were compared using the $\chi 2$ test, whereas continuous variables were reported as either mean [± standard deviation (± SD)] or median [interquartile range (IQR)] and compared using the *t* test. Mixed-effects multivariable logistic regression models were performed in order to account for the hierarchical nature of the data, where clustering of grafts within patients as well as patients within trials exists [19]. All analyses were based on the as-treated principle and treatment effects were reported as adjusted odds ratios [aOR] with 95% confidence interval [95% CI]. Statistical significance was set at 0.05 without multiplicity adjustment. Missing data by trial has been reported previously and was handled with complete case analysis [3]. Analyses were performed using the lme4, sjPlot, and tableone packages in R [version 4.3.1; R Project for Statistical Computing].

Results

In total 910 patients and 2,036 grafts were included in the analysis [1,120 saphenous vein grafts, 828 left internal thoracic arteries, 76 right internal thoracic arteries, and 12 radial arteries] (Fig. 2). The mean [± standard deviation (± SD)] age of patients was 65.40 [± 8.35] years and women comprised 15.5% of the cohort (Table 1). Patients with diabetes, previous myocardial infarction, and a history of heart failure comprised 34.4%, 23.0%, and 35.9% of the cohort respectively. Off-pump CABG was performed in 41.1% of patients and the mean number of grafts per patient was 2.24 [± 0.63]. The mean number of vein and arterial grafts were 1.23 [± 0.56] and 1.01 [± 0.43], respectively. Multiple arterial grafting was performed on 9.8% of patients and bilateral internal thoracic artery grafting was performed on 8.4% of patients. Baseline characteristics were well balanced between patients stratified by WBC count quartile and graft failure status (Table 1 and Table S3).

Post-operatively, antiplatelet and dual antiplatelet therapy was prescribed in 100% and 41.4% of patients respectively, with no significant differences when stratified by graft failure or WBC count quartile. Statin therapy was prescribed in 91.4% of patients, with no significant

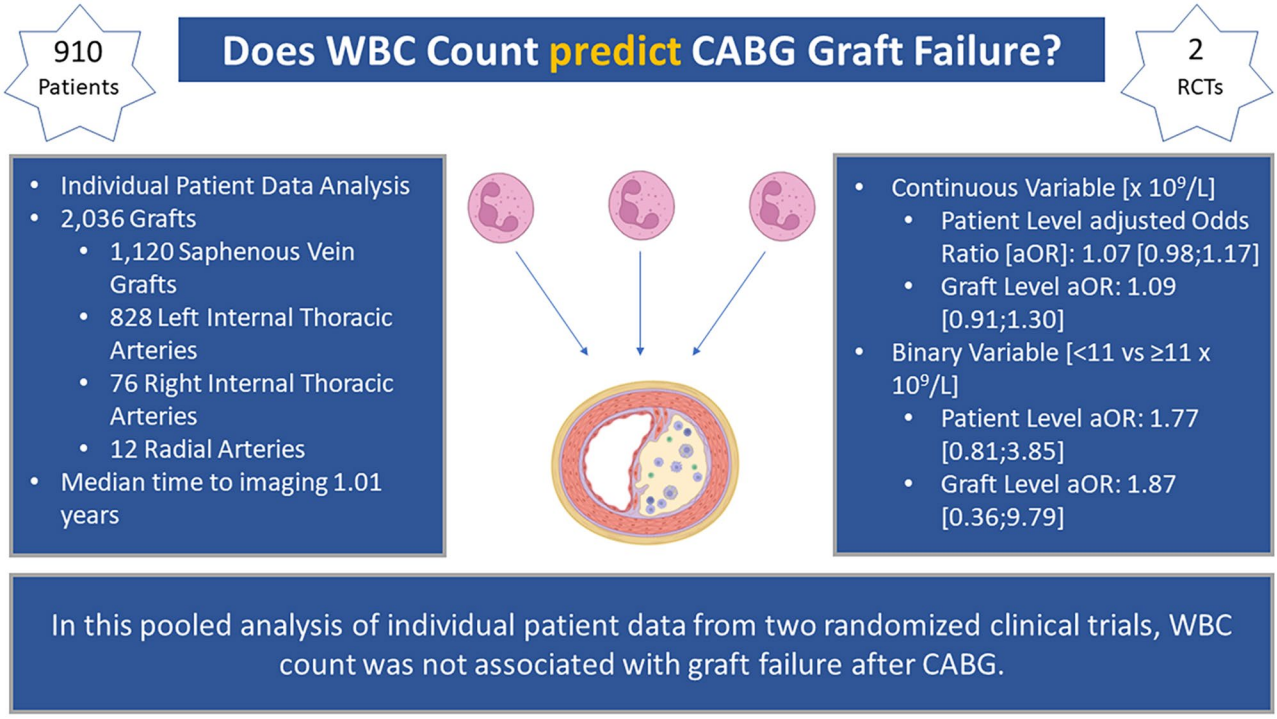

Fig. 2 Central illustration. Summary of the findings of the individual patient data pooled analysis evaluating the association between WBC count and CABG graft failure

Table 1 Baseline characteristics of the patients included in the analysis by white blood cell quartile

	Overall	WBC Quartile 1 [2.9-6.0 × 10^9/L]	WBC Quartile 2 [6.0-7.2 × 10^9/L]	WBC Quartile 3 [7.2–8.4 × 10^9/L]	WBC Quartile 4 [8.4–30.6 × 10^9/L]	*P*-value
	n = 910	*n* = 226	*n* = 221	*n* = 227	*n* = 221	
Age, years [± SD]	65.40 [8.35]	64.47 [8.76]	65.75 [7.64]	66.28 [7.53]	65.03 [9.38]	0.107
Female sex [%]	141 [15.5]	30 [13.3]	32 [14.5]	31 [13.7]	45 [20.4]	0.131
Hypertension [%]	622 [68.4]	152 [67.3]	161 [72.9]	154 [67.8]	145 [65.6]	0.393
Dyslipidemia [%]	581 [63.8]	143 [63.3]	154 [69.7]	139 [61.2]	133 [60.2]	0.157
Smoking [%]	273 [30.0]	74 [32.7]	65 [29.4]	59 [26.0]	70 [31.7]	0.410
Diabetes [%]	313 [34.4]	80 [35.4]	76 [34.4]	73 [32.2]	78 [35.3]	0.822
Previous stroke [%]	62 [6.8]	15 [6.6]	14 [6.3]	14 [6.2]	18 [8.1]	0.836
Previous MI [%]	209 [23.0]	60 [26.5]	56 [25.3]	46 [20.3]	42 [19.0]	0.154
Previous PCI [%]	126 [13.8]	31 [13.7]	34 [15.4]	27 [11.9]	31 [14.0]	0.760
Heart failure [%]	372 [35.9]	82 [36.3]	94 [42.5]	84 [37.0]	103 [46.6]	0.085
LVEF [± SD]	58.23 [9.59]	59.17 [9.42]	59.26 [8.94]	57.70 [10.11]	56.86 [9.86]	0.063
Peripheral vascular disease [%]	115 [12.6]	27 [11.9]	29 [13.1]	25 [11.0]	30 [13.6]	0.706
Chronic kidney disease [%]	44 [4.8]	7 [3.1]	9 [4.1]	14 [6.2]	14 [6.3]	0.302
Off-pump CABG [%]	374 [41.1]	122 [54.0]	98 [44.3]	81 [35.7]	69 [31.2]	< 0.001
Endoscopic vein harvesting [%]	41 [4.5]	6 [2.7]	15 [6.8]	8 [3.5]	11 [5.0]	0.182
No. of grafts [± SD]	2.24 [0.63]	2.20 [0.67]	2.24 [0.63]	2.22 [0.55]	2.25 [0.64]	0.803
No. of vein grafts [± SD]	1.23 [0.56]	1.25 [0.58]	1.25 [0.54]	1.19 [0.49]	1.20 [0.56]	0.504
No. of arterial grafts [± SD]	1.01 [0.43]	0.95 [0.44]	1.00 [0.39]	1.04 [0.41]	1.05 [0.49]	0.065
Multiple arterial grafting [%]	89 [9.8]	17 [7.5]	16 [7.2]	24 [10.6]	32 [14.5]	0.037
Bilateral internal thoracic artery graft [%]	76 [8.4]	14 [6.2]	12 [5.4]	22 [9.7]	28 [12.7]	0.022
Use of sequential graft [%]	768 [84.4]	198 [87.6]	186 [84.2]	197 [86.8]	177 [80.1]	0.116
Imaging: -Per-protocol [%]	909 [99.9]	226 [100.0]	220 [99.5]	227 [100.0]	221 [100.0]	0.383
-Clinically driven [%]	1 [0.1]	0 [0.0]	1 [0.1]	0 [0.0]	0 [0.0]	-
Use of statin therapy [%]	832 [91.4]	215 [95.1]	204 [92.3]	207 [91.2]	192 [86.9]	0.063
Use of antiplatelet therapy [%]	910 [100.0]	226 [100.0]	221 [100.0]	227 [100.0]	221 [100.0]	> 0.99
Dual antiplatelet therapy [%]	377 [41.4]	85 [37.6]	99 [44.8]	91 [40.1]	99 [44.8]	0.316

WBC, white blood count; SD, standard deviation; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting

Table 2 Post-operative outcomes of the patients included in the analysis by white blood cell quartile

	Overall	WBC Quartile 1 [2.9-6.0 × 10^9/L]	WBC Quartile 2 [6.0-7.2 × 10^9/L]	WBC Quartile 3 [7.2–8.4 × 10^9/L]	WBC Quartile 4 [8.4–30.6 × 10^9/L]	*P*-value
	n = 910	*n* = 226	*n* = 221	*n* = 227	*n* = 221	
Myocardial infarction or repeat revascularization before imaging [%]	22 [2.5]	6 [2.7]	5 [2.3]	7 [3.1]	4 [1.8]	0.84
Myocardial infarction before imaging [%]	14 [1.6]	2 [0.9]	4 [1.8]	5 [2.2]	3 [1.4]	0.70
Death after imaging [%]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	-

WBC, white blood count

differences when stratified by graft failure or WBC count quartile. The median time to imaging was 1.01 [interquartile range (IQR), 0.99;1.03] years and all patients except one received per-protocol scheduled imaging. The median pre-operative WBC count was 7.1 [IQR, 6.0;8.4] x 10^9/L. Post-operatively, myocardial infarction or repeat revascularization before imaging occurred in 22 (2.5%) of patients. Post-operative outcomes of patients did not significantly differ when stratified by WBC count quartile and graft failure status (Tables 2 and Table S4). There were no deaths from time of imaging until end of follow-up.

At multivariable analysis, there was no association between WBC count, as a continuous variable, and graft failure both at the patient and at the individual graft level [aOR 1.07 (95% CI, 0.98;1.17), $p = 0.11$ and aOR 1.09 (95% CI, 0.91;1.30), $p = 0.37$], respectively (Table 3). Patients with an elevated WBC count [≥ 11 × 10^9/L] at baseline had a similar risk of graft failure compared to patients with a normal WBC count [< 11 × 10^9/L] at baseline at

Table 3 Multivariable association of white blood cell count with graft failure

	Multivariable			
	Patient Level		Individual Graft Level	
	Graft Failure aOR [95% CI]*	*P*-value	Graft Failure aOR [95% CI]†	*P*-value
WBC count	1.07 [0.98;1.17]	0.12	1.09 [0.91;1.30]	0.37
Age [per 10 years]	1.04 [0.80;1.35]	0.78	1.01 [0.61;1.68]	0.97
Sex	0.91 [0.48;1.74]	0.79	0.98 [0.28;3.51]	0.98
Hypertension	0.80 [0.51;1.27]	0.34	0.83 [0.32;2.15]	0.71
Smoking	1.38 [0.84;2.25]	0.20	1.37 [0.51;3.72]	0.53
Diabetes	0.95 [0.60;1.51]	0.83	0.93 [0.36;2.39]	0.88
Off-pump CABG	1.35 [0.78;2.33]	0.28	1.23 [0.44;3.48]	0.69
Total no. of grafts	1.73 [1.15;2.62]	**0.01**	-	-
Total no. of arterial grafts	1.24 [0.68;2.24]	0.48	-	-
Statin use	0.72 [0.35;1.47]	0.37	0.71 [0.16;3.09]	0.65
DAPT vs. aspirin	0.68 [0.43;1.07]	0.09	0.66 [0.26;1.66]	0.38
Graft to LAD	1.10 [0.40;3.04]	0.86	1.07 [0.17;6.90]	0.95
Sequential graft	0.99 [0.53;1.84]	0.97	0.80 [0.25;2.56]	0.71

aOR, odds ratio; CI, confidence interval; WBC, white blood count; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; LAD, left anterior descending artery

*Adjusted for age, hypertension, smoking, diabetes, off-pump surgery, total number of grafts, total number of arterial grafts, statin use, dual antiplatelet therapy use, presence of graft to the LAD, and use of sequential grafting

†Adjusted for age, hypertension, smoking, diabetes, off-pump surgery, statin use, dual antiplatelet therapy use, presence of graft to the LAD, and use of sequential grafting

Table 4 Multivariable association of white blood cell count with graft failure as a continuous variable, binary variable, and by quartile

	Multivariable			
	Patient level		Individual Graft level	
	Graft failure aOR [95% CI]*	*P*-value	Graft failure aOR [95% CI]†	*P*-value
WBC count [$\times 10^9$/L]	1.07 [0.98;1.17]	0.11	1.09 [0.91;1.30]	0.37
WBC count [≥ 11 vs. $< 11 \times 10^9$/L]	1.77 [0.81;3.85]	0.15	1.87 [0.36;9.79]	0.46
WBC count by quartile				
1 [2.9-6.0 $\times 10^9$/L]	Ref		Ref	
2 [6.0-7.2 $\times 10^9$/L]	0.80 [0.41;1.56]	0.51	0.84 [0.22;3.24]	0.80
3 [7.2–8.4 $\times 10^9$/L]	1.53 [0.85;2.77]	0.16	1.67 [0.49;5.70]	0.41
4 [8.4–30.6 $\times 10^9$/L]	1.39 [0.76;2.54]	0.29	1.53 [0.44;5.33]	0.51

aOR, odds ratio; CI, confidence interval; WBC, white blood count; Ref, reference

*Adjusted for age, sex, hypertension, smoking, diabetes, off-pump surgery, total number of grafts, total number of arterial grafts, statin use, dual antiplatelet therapy versus single antiplatelet therapy use, presence of graft to the LAD, and use of sequential grafting

†Adjusted for age, sex, hypertension, smoking, diabetes, off-pump surgery, statin use, dual antiplatelet therapy versus single antiplatelet therapy use, presence of graft to the LAD, and use of sequential grafting

both the patient and individual graft levels [aOR 1.77 (95% CI, 0.81;3.85), $p = 0.15$ and aOR 1.87 (95% CI, 0.36;9.79), $p = 0.46$], respectively (Table 4). When evaluated by quartile, WBC count was not associated with graft failure at the patient and individual graft levels. At multivariable analysis, there was no association between WBC count and the composite of myocardial infarction or repeat revascularization before imaging both as a continuous variable [aOR 0.87 (95% CI, 0.69;1.10), $p = 0.24$] and by quartile [Q4 vs. Q1, aOR 0.58 (95% CI, 0.16;2.18), $p = 0.42$].

Discussion

There is substantial evidence in support of an association between preoperative inflammatory markers and long-term mortality after CABG [1, 2]. However, whether this association is mediated through graft failure remains unclear. In this pooled individual patient data analysis of two randomized CABG trials with systematic imaging follow-up including 910 patients and 2,036 grafts, pre-operative WBC count was not associated with graft failure at both the patient and the individual graft level, supporting the concept that the reported association between preoperative subclinical inflammation and adverse CABG outcomes is mediated through other mechanisms, such as native coronary artery disease progression.

Our findings are generally consistent with a sub-analysis of the Post CABG trial where WBC counts drawn a mean 4.9 years after CABG were not significantly associated with graft failure [OR 1.2 (95% CI, 0.9;1.7), $p = 0.32$]. [10] However, this study did not look at preoperative WBC count. The association between other surrogates for systemic inflammation, such as diabetes or obesity, and graft failure after CABG is debated, with many but not all studies showing increased graft failure in these patients. In a sub-analysis of the RAPS [Radial Artery Patency Study] trial, including 880 grafts, diabetes was a predictor of graft failure at 1 year [relative risk (RR) 1.45 (95% CI, 1.03;2.05), $p = 0.03$]. [20] However, in a sub-analysis of the PREVENT IV trial, among 1,539 patients, diabetes was not a risk factor for internal thoracic artery

graft failure [21]. Furthermore, in an analysis of 3,715 angiograms, diabetes was not a risk factor for graft failure after CABG [OR 1.12 (95% CI, 0.81;1.55), $p = 0.50$]. [22] In an individual patient data pooled analysis of six RCTs evaluating the association between obesity and graft failure, BMI was found to be slightly associated with reduced graft failure [OR 0.98 (95% CI, 0.97;0.99)] [23].

On the other hand, large population level studies consistently demonstrate an association between systemic inflammatory markers and extent and progression of native coronary artery disease. In a recent large observational and genetic study from the Copenhagen General Population Study, the UK Biobank, and the Blood Cell Consortium, inflammatory markers such as neutrophil counts were associated with several forms of cardiovascular disease, including ischemic heart disease and myocardial infarction [24]. Additionally, the benefits of several anti-inflammatory therapies in large RCTs have provided further evidence of the importance of targeting inflammation in coronary disease [12, 13].

Based on the available evidence and our findings, it is plausible that systemic inflammation could worsen outcomes after CABG through means other than graft failure, such as native coronary artery disease progression. This is consistent with a sub-analysis of the Post CABG trial that found that diabetics (a patients population with high baseline inflammatory burden) were no more likely than non-diabetics to develop late graft failure after CABG, but were more likely to experience 4-year MACCE [20.6% vs. 13.4%, $p = 0.03$]. [25, 26]

Some study limitations must be acknowledged. Out of ten RCTs, our study included only two RCTs which may introduce selection bias and limit the generalizability of our findings. Our data must also be read in the context of what is known on the natural history of CABG graft failure [7]. Early and late graft failure have distinctly different mechanisms, with early events [up to one year] mostly due to thrombosis and intimal hyperplasia, and late events due to atherosclerosis [27, 28]. With a median time to imaging of one year, our study addresses the potential contribution of systemic inflammation to early graft failure and suggests that it does not play a key role in this setting. However, as systemic inflammation is strongly associated with atherosclerosis, further research is needed on its possible role in determining late CABG grafts outcomes [7].

Conclusion

In this pooled analysis of individual patient data from two randomized clinical trials, WBC count was not associated with graft failure at 1 year after CABG, suggesting that the graft failure may not be the mechanism through which inflammation leads to worse outcomes after CABG.

Abbreviations

CABG	Coronary artery bypass grafting
WBC	White blood cell count
SD	Standard deviation
IQR	Interquartile range
aOR	Adjusted odds ratio
CI	Confidence interval
HR	Hazard ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-024-03330-5.

Supplementary Material 1

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None.

Author contributions
The authors confirm contribution to the paper as follows: study conception and design: An, KR. Gaudino, MFL. Verma, S.; data collection: Peper, J. Zhou, Y. ten Berg, JM. Harik, L. Zhu, Y. Willemsen, LM.; analysis and interpretation of results: An, KR. Sandner, S. Redfors, B. Gaudino, MFL.; draft manuscript preparation: An, KR. Sandner, S. Redfors, B. Gaudino, MFL. All authors reviewed the results and approved the final version of the manuscript.

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Data availability
The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s)).

Declarations

Ethics approval and consent to participate
Ethics approval was obtained by the study teams for the individual trials; the Weill Cornell Medicine Institutional Review Board waived the need for ethics approval for the pooled analysis.

Consent for publication
Informed patient consent was obtained by the study teams for the individual trials; the Weill Cornell Medicine Institutional Review Board waived the need for informed patient consent for the pooled analysis.

Competing interests
The authors declare no competing interests.

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