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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Haematological indices as predictors of atrial fibrillation following isolated coronary artery bypass grafting, valvular surgery, or combined procedures: a systematic review with meta-analysis

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Abstract

Background: New postoperative atrial fibrillation (POAF) is one of the most critical and common complications after cardiovascular surgery precipitating early and late morbidities. Complete blood count (CBC) is an imperative blood test in clinical practice, routinely used in the examination of cardiovascular diseases.

Aim: This systematic review with meta-analysis aimed to determine the strength of evidence for evaluating the association of haematological indices in CBC tests with atrial fibrillation following isolated coronary artery bypass graft (CABG), isolated valvular surgery, or a combination of these treatments.

Methods: We conducted a meta-analysis of studies evaluating pre- and postoperative haematological indices in patients with POAF. A comprehensive subgroup analysis was performed to explore potential sources of heterogeneity.

Results: A literature search of all major databases retrieved 732 studies. After screening, 22 studies were analysed including a total of 6098 patients. Pooled analysis showed preoperative platelet count (PC) (weighted mean difference [WMD] = -7.07×10^9/L and $p < 0.001$), preoperative mean platelet volume (MPV) (WMD = 0.53 FL and $p < 0.001$), preoperative white blood cell count (WBC) (WMD = 0.130×10^9/L and $p < 0.001$), preoperative neutrophil-to-lymphocyte ratio (NLR) (WMD = 0.33 and $p < 0.001$), preoperative red blood cell distribution width (RDW) (WMD = 0.36% and $p < 0.001$), postoperative WBC (WMD = 1.36×10^9/L and $p < 0.001$), and postoperative NLR (WMD = 0.74 and $p < 0.001$) as associated factors with POAF.

Conclusions: Haematological indices may predict the risk of POAF before surgery. These easily-performed tests should definitely be taken into account in patients undergoing isolated CABG, valvular surgery, or combined procedures.

Key words: atrial fibrillation, complete blood count, coronary artery bypass, cardiac surgical procedure, review, meta-analysis

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INTRODUCTION

New postoperative atrial fibrillation (POAF) is one of the most critical and common complications after cardiovascular surgery, precipitating early and late morbidities such as cardiovascular events, thromboembolism, cerebrovascular events, prolonged hospital stay and readmissions to the intensive care unit (ICU) and hospital, organ failure, as well as increased health care costs and mortality [1–3]. Atrial fibrillation (AF) is a hazardous and widespread complication following coronary artery bypass graft (CABG), with an incidence of 20% to 50%, and with incidence peaks occurring two to three days after surgery [1–3]. The pathophysiological mechanism of AF is highly complex and is affected by diverse factors, and a variety of diagnostic modalities have been shown to be useful in predicting or diagnosis of POAF [4, 5].

Conventionally, diagnosis and management of AF have been focused on the patient's medical history, examination, and detection of AF through cardiac monitoring [6, 7]. Complete blood count (CBC) is an imperative blood test in clinical practice routinely used in the examination of cardiovascular diseases [8, 9]. The association of CBC test with the occurrence and recurrence of paroxysmal, persistent, and permanent AF in patients not undergoing cardiac surgery has been well reported and documented [8]. However, the diagnostic performance of haematological indices for AF after cardiac surgery has remained unexplored.

Various studies have been recently published focusing on the association of haematological indices with the occurrence of POAF. However, so far the data from the studies have been largely inconclusive. This comprehensive meta-analysis sought to determine the strength of evidence for evaluating the association of platelet count, mean platelet volume (MPV), platelet distribution width (PDW), white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), red blood cell (RBC) count, red blood cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), haematocrit (HCT), and haemoglobin (Hb) with the occurrence of POAF.

METHODS

Literature search

A comprehensive literature search was carried out by three investigators independently in medical databases (Medline/PubMed, Web of Science, Embase, Ovid, Science Direct, and Google Scholar) from their inception until 5th May 2017 in order to identify relevant studies on the association of primary haematological indices such as platelet count, MPV, PDW, WBC count, NLR, RBC count, RDW or secondary haematological indices including MCV, HCT, and Hb, with the occurrence of POAF. Predefined keywords for searching were as follows: "platelet count", "mean platelet volume", "MPV", "platelet distribution width" "PDW", "white blood cell count", "leucocyte", "WBC", "neutrophil to lymphocyte ratio", "NLR", "red blood cell count", "RBC count", "red blood cell distribution width", "RDW", and "atrial fibrillation" or "supraventricular arrhythmia" and "cardiac surgery", "coronary artery bypass surgery", "CABG", "valvular surgery", "surgery". The sample sizes of the studies, time and language of publications were not restricted. Abstracts without peer-review or those only published as

congress presentations, as well as grey literature, were not included in the study. Studies were excluded also if they had the report of non-matched data as mean ± standard deviation (SD) or median [minimum–maximum] or they had not reported demographic details in AF and SR group separately. All retrieved references of the enrolled studies, recently published review articles, and meta-analyses were checked to find additional studies not indexed in common databases.

Study selection

Inclusion criteria to be enrolled in the analysis were as follows: 1) human subjects; 2) case-control or cohort studies; 3) patients undergoing either CABG or heart valve surgery, or a combination of both; and 4) studies comparing patients with POAF and postoperative sinus rhythm (POSR) in terms of haematological indices.

Data extraction and outcome measures

Five investigators (S.A-H-S, A.S, S.Y, M-P.S, and S.J.M) independently searched and extracted the data. To resolve the discrepancies a consensus standardised abstraction checklist was used for recording data in each included study. Subgroup analyses of disparities in the patients' characteristics were performed for exploration of heterogeneity among the studies examining the following items: (1) the time of publication (before 2000 vs. after 2000); (2) geographical zone (Africa, Asia, Europe, North-America, Oceania, South-America); (3) study design (case-control vs. cohort); (4) sample size (≤ 200 vs. > 200); (5) mean age (≤ 60 vs. > 60 years); (6) percentage of men (≤ 70% vs. > 70%); (7) history of diabetes (≤ 30% vs. > 30%); (8) history of hypertension (≤ 70% vs. > 70%); (9) cigarette smoking (≤ 30% vs. > 30%); (10) history of myocardial infarction (≤ 20% vs. > 20%); (11) preoperative left ventricular ejection fraction (≤ 50% vs. > 50%); (12) preoperative use of drugs such as beta-blockers, statins, diuretics, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers (for each: ≤ 70% vs. > 70%); (13) type of surgery (isolated CABG, isolated valvular surgery, combined procedures); (14) method of surgery (on-pump, off-pump); (15) status of surgery (elective, non-elective), (16) cross-clamp time (≤ 60 min vs. > 60 min); and (17) cardiopulmonary bypass time (≤ 100 min vs. > 100 min).

Homogenisation of extracted data

Continuous data were presented as mean ± SD. When interquartile ranges were reported, the mean was calculated as (minimum+maximum+2[median])/4 and SD as (maximum–minimum)/4 for groups with sample sizes of n ≤ 70, and (maximum–minimum)/6 for n > 70 [10].

Quality assessment and statistical analysis

Three investigators (T.L, L.M, and M.G) independently evaluated the Newcastle-Ottawa Scale and design of the studies to assess the quality of the studies [11]. Total scores ranged between 0 (worst) and 9 (best quality) for case-control or cohort studies. For non-categorical data, pooled effect size was expressed as weighted mean difference (WMD) with 95% confidence interval (CI). Significant heterogeneity was observed among the studies considering p value < 0.1 for Q test or I^2 > 50%. Heterogeneity among the trials was tested by applying a random effect model when indicated. Publication biases were evaluated using the Begg's test, which examines the presence of association among the effect estimates and their variances. Statistical significance level was considered as p value < 0.05. Data analysis was conducted by STATA (version 11.0, Stata Corporation, College Station, Texas) using METAN and METABIAS commands.

RESULTS

Literature search strategy and included studies

A total of 732 studies were extracted from the literature search and screened databases, of which 710 (96.9%) were excluded after detailed evaluation through the first review for either unnecessary information (n = 384), insufficient report of endpoints of interest (*n* = 312), or report of non-matched data as mean ± SD or median [minimum–maximum] (*n* = 14). Finally, 22 studies were analysed through meta-analysis [12––33]; including a total of 6098 patients (details about excluded and included studies were presented in **Supplemental Table 1 — see journal website**).

Association of preoperative haematological indices with the occurrence of POAF

Platelet count

A total of 1417 cases were selected from seven studies, of which 392 were assigned to the POAF and 1025 to the POSR (Table 1). The population of the studies ranged from 94 to 662 patients, 79.34% males (mean age: 64.23 years) (Table 1). Mean platelet count was 235.53 × 10^9/L in the POAF group and 241.67 × 10^9/L in the POSR group (Table 2). Pooled analysis indicated that the mean platelet count was statistically lower in patients with POAF (negative predictor) than POSR cases with WMD of –7.07 × 10^9/L (95% CI –11.75 to –2.39; p < 0.001) by utilising a random effect model (Fig. 1). There was a significant heterogeneity among the studies (I^2 = 57.1%; heterogeneity p = 0.03), indicating a random effect.

MPV

A total of 1744 patients were enrolled from six studies, of whom 476 were allocated to the POAF group and 1268 to the POSR group (Table 1). The populations of the studies ranged from 94 to 1138 patients, 73.82% males (mean age, 63.5 years) (Table 1). Mean level of MPV was 9.35 FL in the POAF and 9.05 FL in the POSR group (Table 2). Pooled analysis showed that MPV was significantly greater in patients with POAF (positive predictor) compared to POSR with WMD

Table 1. Characteristics of included studies for meta-analysis of association of pre- and postoperative haematological indices with postoperative atrial fibrillation

First author, year of publication	Country	Design	N-AF	N-SR	Age-AF	Age-SR	Male-AF	Male-SR	TOS	On or off pump	ES or NES	NOS
Jacob [12], 2017	Netherland	Cohort	277	380	68	62.9	69	71.1	CABG and/or valve	On	Elective	7
Saskin [13], 2017	Turkey	Cohort	153	509	62	61	77.8	82.9	Alone CABG	On	Elective	7
Saskin [14], 2016	Turkey	Cohort	294	844	60.5	60	25.1	74.9	Alone CABG	On	Elective	7
Cerit [15], 2016	Turkey	Cohort	36	70	67.3	63.2	83.3	92.9	Alone CABG	On	Elective	7
Anatolevna [16], 2016	Russia	Case-control	22	59	67.7	65.8	90.9	74.6	Alone CABG	On and off	No data	7
Gecmen [17], 2016	Turkey	Cohort	31	63	66	59	87	71	Alone CABG	On	Elective	8
Korantzopoulos [18], 2015	Greece	Cohort	44	65	65.4	67.7	70	74	CABG and/or valve	On and off	Elective	8
Narducci [19], 2014	Italy	Case-control	14	24	71	69	64	75	Alone CABG	On	Elective	8
Limite [20], 2014	Italy	Cohort	173	271	66.2	56.4	74	73.4	CABG and/or valve	On	No data	9
Erdem [21], 2014	Turkey	Cohort	38	127	67	64.9	81.57	77.16	Alone CABG	On	Elective	8
Ertas [22], 2013	Turkey	Cohort	33	99	60.2	60.9	75	74	Alone CABG	On	Elective	7
Durukan [23], 2013	Turkey	Cohort	91	432	65.44	60.76	75.82	75.92	Alone CABG	On	Elective	7
Sabol [24], 2012	Slovakia	Case-control	30	15	62.5	61.9	76.7	66.7	Alone CABG	No data	No data	7
Garcia [25], 2012	Chile	Cohort	38	142	73.5	62.4	76.3	81	Alone CABG	On	Elective	8
Gungor [26], 2011	Turkey	Cohort	10	30	68.5	56.1	ND	ND	Alone CABG	On	Elective	8
Kaireviciute [27], 2010	Lithuania	Cohort	30	70	67	63.2	93.3	82.9	Alone CABG	On	Elective	8
Gibson [28], 2010	UK	Cohort	107	168	68	63	87.9	81	Alone CABG	On and off	Elective	9
Sood [29], 2009	USA	Cohort	173	377	70.3	66.8	72.8	68.5	CABG and/or valve	On	No data	7
Choi [30], 2009	South Korea	Cohort	66	249	67.1	64.6	74.24	70.68	Alone CABG	Off	Elective	7
Fontes [31], 2009	USA	Cohort	17	43	71.8	70.3	94.1	74.4	Alone CABG	On	Elective	8
Lamm [32], 2006	Austria	Cohort	99	154	67.5	63.7	55.5	63	CABG and/or valve	On	Elective	9
Abdelhadi [33], 2004	USA	Cohort	60	121	66	59.6	75	62	CABG and/or valve	On	Elective	9

AF — atrial fibrillation; CABG — coronary artery bypass graft; ES — elective surgery; N — number; NES — non-elective surgery; NOS — Newcastle Ottawa Scale; SR — sinus rhythm; TOS — type of surgery

Table 2. Information about haematological indices and these levels in each study

First author	Markers	Levels
Measurement of hematologic indices		
Jacob [12]	WBC, NLR	Preoperative: WBC [AF: 7.8 ± 2.6 vs. SR: 7.7 ± 1.9] NLR [AF: 2.72 ± 0.26 vs. SR: 2.48 ± 0.27]
Saskin [13]	PC, WBC, HCT, Hb	Preoperative: PC [AF: 264 ± 42.3 vs. SR: 279 ± 49.6] WBC [AF: 7.75 ± 0.93 vs. SR: 7.52 ± 1.05] HCT [AF: 40.9 ± 3.43 vs. SR: 41.1 ± 3.40] Hb [AF: 13.3 ± 0.93 vs. SR: 13.85 ± 1.16]
Saskin [14]	MPV, HCT, Hb	Preoperative: MPV [AF: 9.03 ± 0.74 vs. SR: 8.32 ± 0.6] HCT [AF: 40.7 ± 4 vs. SR: 40.6 ± 4.1] Hb [AF: 13.3 ± 1.4 vs. SR: 13.4 ± 1.5] Postoperative: MPV [AF: 9.9 ± 0.9 vs. SR: 8.8 ± 0.6] HCT [AF: 28.7 ± 3.2 vs. SR: 29.1 ± 3.1] Hb [AF: 9.1 ± 1.2 vs. SR: 9.2 ± 1.1]
Cerit [15]	PC, MPV, WBC, NLR, Hb	Preoperative: PC [AF: 214.9 ± 61.1 vs. SR: 238.2 ± 64.1] MPV [AF: 10.5 ± 1.1 vs. SR: 10.3 ± 0.9] WBC [AF: 7.7 ± 2.4 vs. SR: 7.5 ± 1.8] NLR [AF: 2.9 ± 2 vs. SR: 2.1 ± 0.8] Hb [AF: 13.4 ± 1.9 vs. SR: 13.7 ± 1.6]
Anatolevna [16]	WBC	Preoperative: WBC [AF: 6.7 ± 2 vs. SR: 7 ± 1.8] Postoperative: WBC [AF: 13.5 ± 3.4 vs. SR: 13.4 ± 3.3]
Gecmen [17]	PC, MPV, WBC, RDW, Hb	Preoperative: PC [AF: 253 ± 68 vs. SR: 231 ± 57] MPV [AF: 7.5 ± 0.9 vs. SR: 7.4 ± 0.9] WBC [AF: 8.1 ± 2.2 vs. SR: 8.3 ± 2.2] RDW [AF: 15 ± 1.4 vs. SR: 15 ± 1.2] Hb [AF: 13.1 ± 1.5 vs. SR: 13.5 ± 1.5]
Korantzopoulos [18]	PC, MPV, WBC, RDW, Hb	Preoperative: PC [AF: 212.52 ± 18.87 vs. SR: 213.2 ± 17.2] MPV [AF: 10.97 ± 0.47 vs. SR: 10.90 ± 0.4] WBC [AF: 8.18 ± 1 vs. SR: 7.88 ± 0.85] RDW [AF: 14.25 ± 0.5 vs. SR: 13.3 ± 0.4] Hb [AF: 13.27 ± 0.47 vs. SR: 13.52 ± 0.47]
Narducci [19]	WBC	Preoperative: WBC [AF: 7.24 ± 0.7 vs. SR: 8.27 ± 1.03] Postoperative: WBC [AF: 10.79 ± 1.58 vs. SR: 12.51 ± 1.43]
Limite [20]	WBC	Preoperative: WBC [AF: 6.5 ± 0.36 vs. SR: 6.4 ± 0.4] Postoperative: WBC [AF: 12.07 ± 0.88 vs. SR: 10.72 ± 0.75]
Erdem [21]	PC, MPV, WBC, NLR, RDW, MCV, Hb	Preoperative: PC [AF: 252.6 ± 61.5 vs. SR: 265.1 ± 59] MPV [AF: 8.9 ± 1.4 vs. SR: 7.9 ± 1.2] WBC [AF: 7.5 ± 4.3 vs. SR: 7 ± 3.5] NLR [AF: 3.2 ± 1.9 vs. SR: 2.6 ± 1.2] RDW [AF: 17 ± 0.3 vs. SR: 16.9 ± 0.4] MCV [AF: 80.9 ± 8.3 vs. SR: 79.8 ± 8.8] Hb [AF: 12.5 ± 1.8 vs. SR: 13 ± 1.5]

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Table 2 (cont). Information about haematological indices and these levels in each study

First author	Markers	Levels
Ertas [22]	MPV, WBC, RDW, Hb	Preoperative: MPV [AF: 9.2 ± 1.4 vs. SR: 9.5 ± 1.9] WBC [AF: 8.9 ± 4.6 vs. SR: 8.5 ± 2.5] RDW [AF: 13.9 ± 1.4 vs. SR: 13.3 ± 1.2] Hb [AF: 15.4 ± 8.1 vs. SR: 14.1 ± 6.6]
Durukan [23]	WBC, NLR	Preoperative: WBC [AF: 8.14 ± 2.11 vs. SR: 8.39 ± 2.36] NLR [AF: 3.02 ± 2.3 vs. SR: 2.9 ± 2.1] Postoperative: WBC [AF: 15.11 ± 4.08 vs. SR: 15.16 ± 4.22] NLR [AF: 9.34 ± 6.73 vs. SR: 10.07 ± 21.97]
Sabol [24]	WBC	Preoperative: WBC [AF: 13.6 ± 3.6 vs. SR: 11.3 ± 3.6] Postoperative: WBC [AF: 13.7 ± 4.1 vs. SR: 11.4 ± 13.7]
Garcia [25]	WBC	Preoperative: WBC [AF: 6.9 ± 1.7 vs. SR: 7.4 ± 1.8]
Gungor [26]	WBC, HCT, Hb	Preoperative: WBC [AF: 8.54 ± 3.8 vs. SR: 7.66 ± 2.03] HCT [AF: 40.2 ± 6.3 vs. SR: 41.2 ± 3.6] Hb [AF: 13.4 ± 2.2 vs. SR: 13.7 ± 1.5]
Kaireviciute [27]	PC, WBC, Hb	Preoperative: PC [AF: 236.7 ± 57.8 vs. SR: 236.2 ± 58.8] WBC [AF: 7.3 ± 1.6 vs. SR: 6.8 ± 1.6] Hb [AF: 14.02 ± 1.49 vs. SR: 14.4 ± 1.3]
Gibson [28]	WBC, NLR, Hb	Preoperative: WBC [AF: 7.95 ± 0.4 vs. SR: 7.75 ± 0.4] NLR [AF: 3.03 ± 0.25 vs. SR: 2.5 ± 0.21] Hb [AF: 14.52 ± 0.31 vs. SR: 14.32 ± 0.25] Postoperative: WBC [AF: 13.72 ± 0.88 vs. SR: 12.17 ± 0.71] NLR [AF: 9.19 ± 0.95 vs. SR: 7.4 ± 0.75] Hb [AF: 10 ± 0.3 vs. SR: 9.95 ± 0.3]
Sood [29]	WBC	Postoperative: WBC [AF: 12.25 ± 4.7 vs. SR: 10.91 ± 3.55]
Choi [30]	WBC, HCT	Preoperative: WBC [AF: 7.1 ± 2.1 vs. SR: 7.3 ± 2] HCT [AF: 39.3 ± 5.7 vs. SR: 39 ± 4.8] Postoperative: WBC [AF: 12.2 ± 4.3 vs. SR: 11.1 ± 3.2] HCT [AF: 26.1 ± 3.3 vs. SR: 26.7 ± 3.3]
Fontes [31]	WBC	Preoperative: WBC [AF: 9.2 ± 3.6 vs. SR: 6.8 ± 1.8] Postoperative: WBC [AF: 12.9 ± 3.4 vs. SR: 11.7 ± 3.4]
Lamm [32]	WBC, Hb	Preoperative: WBC [AF: 6.8 ± 1.9 vs. SR: 6.8 ± 2.2] Hb [AF: 13.4 ± 1.6 vs. SR: 13.7 ± 1.2] Postoperative: WBC [AF: 16.3 ± 6.5 vs. SR: 15 ± 4.2]
Abdelhadi [33]	PC, WBC, Hb	Preoperative: PC [AF: 215 ± 62 vs. SR: 229 ± 59] WBC [AF: 7.58 ± 2.2 vs. SR: 7.01 ± 1.83] Hb [AF: 13.74 ± 1.72 vs. SR: 13.65 ± 1.81] Postoperative: WBC [AF: 13.7 ± 5.6 vs. SR: 9.8 ± 3.1]

AF — atrial fibrillation; Hb — haemoglobin; HCT — haematocrit; MCV — mean corpuscular volume; MPV — mean platelet volume; NLR — neutrophil-to-lymphocyte ratio; PC — platelet count; RBC — red blood cell; RDW — red blood cell distribution width; SR — sinus rhythm; WBC — white blood cell

of 0.53 FL (95% CI 0.45 to 0.60; $p < 0.001$, Fig. 2) with considerable heterogeneity among the studies ($I^2 = 91.7\%$; heterogeneity $p < 0.001$).

WBC

A total of 4460 cases were included from 20 studies, of whom 1369 were recruited in the POAF group and 3091 in the POSR group (Table 1). The populations of the studies ranged from 38 to 662 patients, 72.62% males (mean age, 64.86 years) (Table 1). Mean WBC count was 7.97×10^9/L in cases with the occurrence of POAF and 7.66×10^9/L in POSR (Table 2). Pooled analysis reported that the count of WBCs was higher in the POAF group (positive predictor) compared to the POSR group with WMD of 0.130×10^9/L (95% CI 0.08 to 0.18; $p < 0.001$) (Fig. 3). Significant heterogeneity was observed among the studies ($I^2 = 57.2\%$; heterogeneity $p = 0.001$).

NLR

A total of 1726 patients were included from five studies, of them 549 were enrolled in the POAF group and 1177 in the POSR group (Table 1). The populations of the studies ranged from 106 to 657 patients, 79.56% males (mean age: 65.05 years) (Table 1). Mean NLR was 2.97 in the POAF and 2.51 in the POSR group (Table 2). Using a random effect model, pooled analysis indicated that the NLR was significantly higher in patients with POAF (positive predictor) compared to POSR with WMD of 0.33 (95% CI 0.30 to 0.37; $p < 0.001$, Fig. 4), with considerable heterogeneity among the studies ($I^2 = 94.2\%$; heterogeneity $p < 0.001$).

RDW

A total of 500 patients were selected from four studies, of which 146 were allocated to the POAF group and 354 to the POSR group (Table 1). The populations of the studies ranged from 94 to 165 patients, 76.21% males (mean age, 63.88 years) (Table 1). Mean of RDW was 15.03% in the POAF group and 14.62% in the POSR group (Table 2). Pooled analysis showed that RDW was significantly higher in the POAF group (positive predictor) than in the POSR group with WMD of 0.36% (95% CI 0.26 to 0.45; $p < 0.001$, Fig. 5). There was remarkable heterogeneity between the studies ($I^2 = 95.3\%$; heterogeneity $p < 0.001$).

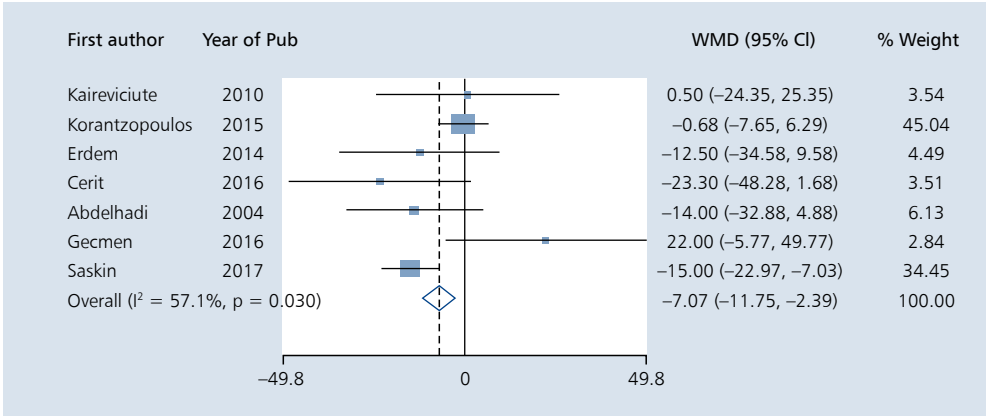

Figure 1. Forest plot of weighted mean difference (WMD) for association between preoperative platelet count and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

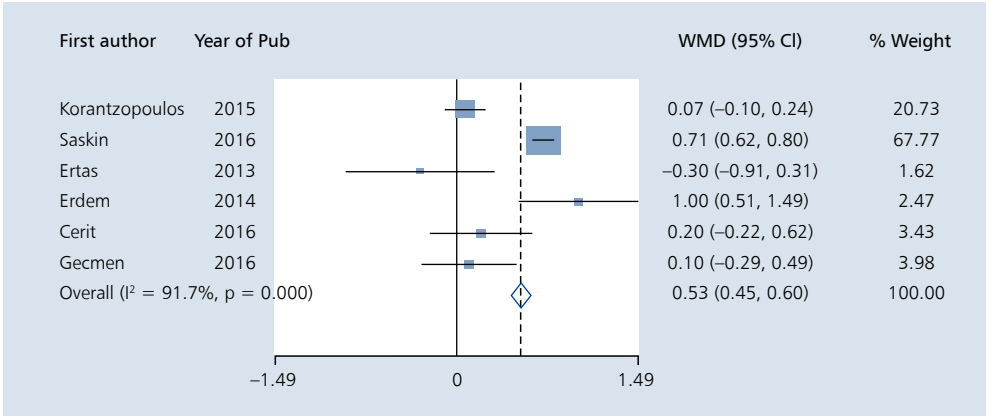

Figure 2. Forest plot of weighted mean difference (WMD) for association between level of preoperative mean platelet volume and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

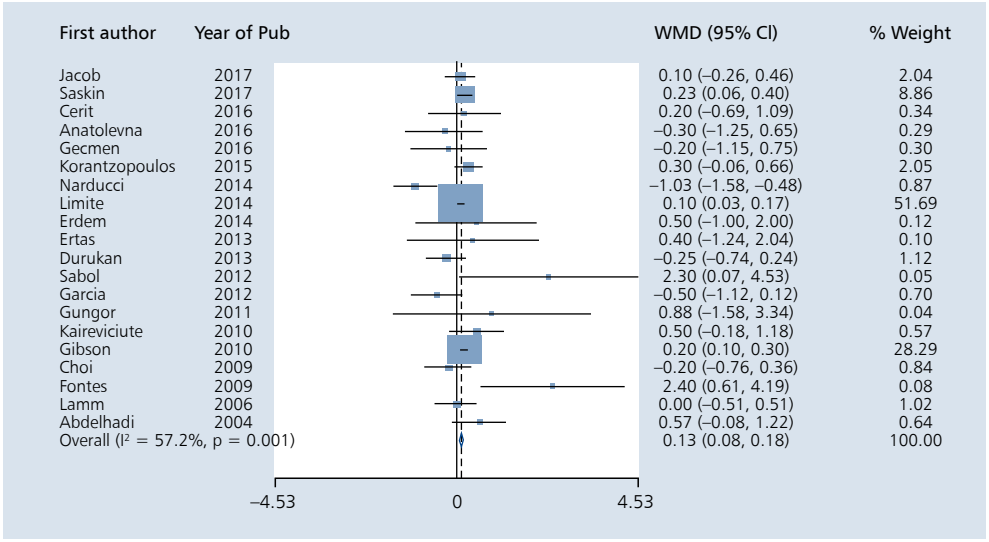

Figure 3. Forest plot of weighted mean difference (WMD) for association between preoperative white blood cell count and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub: publication

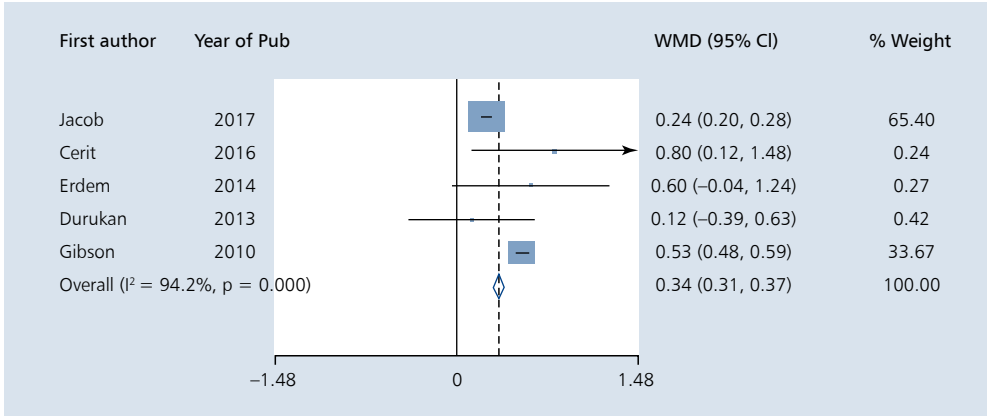

Figure 4. Forest plot of weighted mean difference (WMD) for association between preoperative neutrophil-to-lymphocyte ratio and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

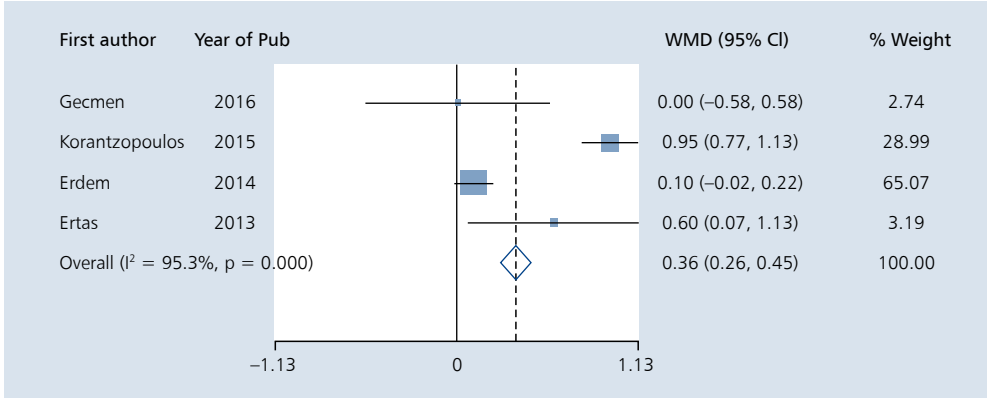

Figure 5. Forest plot of weighted mean difference (WMD) for association between preoperative red blood cell distribution width and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

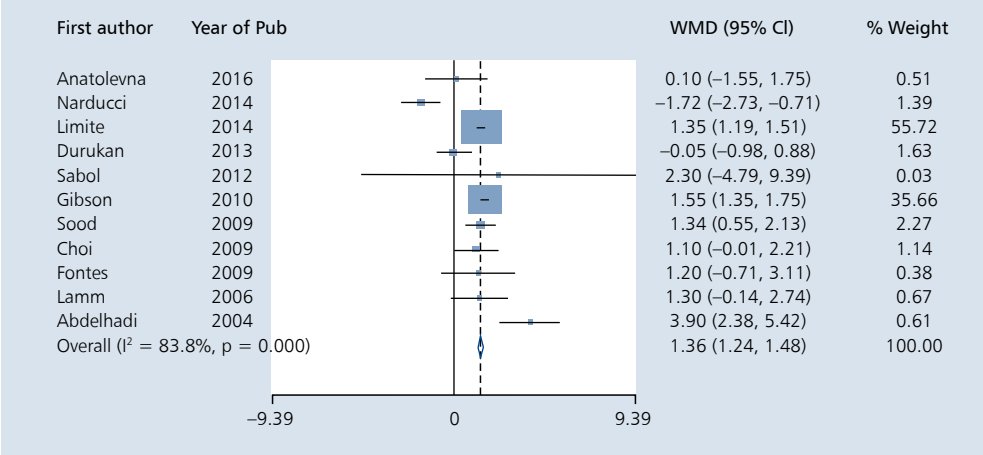

Figure 6. Forest plot of weighted mean difference (WMD) for association between postoperative white blood cell count and recurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

Preoperative secondary haematological indices

Regarding pooled assessment analysis, both groups were similar regarding the level of HCT (number of studies = 4, WMD of –0.015 FL, 95% CI –0.40 to 0.37; p = 0.94 and I^2 = 0.0%; heterogeneity p = 0.8) and Hb (number of studies = 12, WMD of 0.024 g/dL, 95% CI –0.033 to 0.08; p = 0.4 and I^2 = 87.1%; heterogeneity p < 0.001).

Association of postoperative haematological indices with the occurrence of POAF

Mean WBC count was 13.29 × 10^9/L in the POAF group and 12.17 × 10^9/L in the POSR group (Table 2). Postoperative mean WBC count (number of studies = 11, WMD of 1.36 × 10^9/L, 95% CI 1.24 to 1.48; p < 0.001; Fig. 6; I^2 = 83.6%; heterogeneity p < 0.001) and the level of NLR (number of studies = 2, WMD of 0.74, 95% CI 0.56 to 0.92; p < 0.001 and I^2 = 99.2%; heterogeneity p < 0.001) were considerably higher in patients with POAF (positive predictors) compared to POSR cases.

Postoperative secondary haematological indices

HCT and Hb levels were examined in at least two studies included in the meta-analysis. The level of HCT (number of studies = 2, WMD of –0.43, 95% CI –0.81 to 0.05; p = 0.02 and I^2 = 0.0%; heterogeneity p = 0.69) was lower in the POAF group (negative predictor) compared to the POSR group. The level of Hb (number of studies = 2, WMD of 0.023 g/dL, 95% CI –0.04 to 0.08; p = 0.49 and I^2 = 65.7%; heterogeneity p = 0.08) was similar in both groups.

Other parameters

Regarding the association of the occurrence of POAF with preoperative haematological indices such as PDW, RBC count, MCV, and postoperative haematological parameters such as platelet count, PDW, MPV, RBC count, RDW, and MCV, the number of studies were insufficient for analysis.

Publication bias and subgroup analysis

Begg's tests revealed that all results were without publication bias except for the relationship between preoperative Hb levels and the occurrence of POAF (**Supplemental Figures 1–11 — see journal website**). Classification according to probable heterogeneity agents and subgroup analyses are reported in detail in **Supplemental Tables 2 and 3, respectively, see journal website**.

DISCUSSION

Atrial fibrillation is a hazardous and widespread complication following CABG, with an incidence rate of 20% to 50% in patients undergoing CABG, with incidence peaks two to three days after surgery [34–36]. Administration of antiarrhythmic agents for prevention or treatment of AF can reduce its incidence and recurrence rate. Nevertheless, the use of these drugs is not free of complications. Several surgical approaches during cardiothoracic surgeries such as posterior pericardiotomy are considered simple surgical methods that reduce the risk of postoperative AF [34–36]. Reports have suggested that performing CABG and valve surgery at the same time using cardiopulmonary bypass particularly with prolonged duration of surgery could significantly increase the incidence of POAF [35, 36]. POAF can precipitate postoperative morbidity and mortality, thus it is critical to initiate prophylactic measures based on risk stratification for the patients prone to POAF before its occurrence [4, 5]. An appropriate diagnostic modality should, on the one hand, facilitate preventive and therapeutic measures by timely diagnosis, and on the other hand, should not burden patients with exorbitant healthcare costs and be applicable in the majority of health centres throughout the world [9].

While using patient's history, such as the history of cardiac arrhythmia, clinical workups, electrocardiogram, and Holter monitoring, can help in terms of diagnosis and control of AF, it should be noted that in clinical practice some diagnostic modalities routinely performed in all in-patients might be of

more clinical value than previously thought [4–6]. CBC test is one of the most common tests performed in patients hospitalised in cardiac care unit, ICU, and cardiac surgery wards, with multiple examinations before and after surgery [5–8]. It was recently reported that haematological parameters in CBC test, as well as coagulation and endothelial markers, may be reliable predictors of paroxysmal, persistent, and permanent AF in patients receiving pharmacotherapy, cardioversion, and catheter ablation [9]. Varasteh-Ravan et al. [8] reported that haematological indices in patients with ST-segment elevation myocardial infarction, who received streptokinase therapy, may predict clinical outcomes after treatment. Therefore, since CBC is sensitive to haemodynamic conditions, it can have a significant predictive power.

In the present study, we attempted to investigate the association of haematological indices in CBC test with the occurrence of AF in patients undergoing cardiac surgery. Our findings indicated that preoperative platelet count in patients with POAF was significantly lower than POSR patients; therefore, we reject the popular belief among physicians that patients with thrombocytosis are at higher risk of AF. Our previous findings showed an inverse relationship between platelet count and the risk of the occurrence of AF in patients with a history of paroxysmal, persistent, or permanent AF [9]. As a result, a decrease in platelet count might be associated with AF in patients undergoing cardiac surgery or those receiving pharmacotherapy or undergoing catheter ablation. A subgroup analysis also indicated an inverse relationship between platelet count and POAF in patients undergoing isolated CABG, while this relationship was not found in patients undergoing simultaneous CABG and valve surgery. Differences in type of surgery, comorbidities, such as diabetes and arterial hypertension, and the use of statins are proposed as factors of heterogeneity.

Mean platelet volume is an important biomarker of platelet function. Many significant mediators of blood coagulation, inflammation, thrombosis, and atherosclerosis are secreted by large platelets [37]. MPV is also closely associated with coronary artery disease [37]. Patients with coronary artery disease and slow coronary blood flow were shown to have higher MPV compared to the control group [38, 39]. The current study demonstrated that MPV was considerably greater in patients with POAF compared to the control group, thus being a potential predictive marker for POAF. A subgroup analysis revealed diabetes and arterial hypertension as the factors of heterogeneity. Platelet characteristics were strongly associated with cardiovascular risk factors of hypertension and diabetes mellitus [9]. Weymann et al. [4] suggested that MPV, as a valuable haematological parameter in CBC test, could strongly predict the occurrence of paroxysmal, persistent, or permanent AF; therefore, MPV was confirmed to be added to the risk stratification of AF [4]. In the present study, we also emphasise that MPV not only predicts AF in patients receiving-antiarrhythmic therapy or undergoing catheter ablation, but also firmly predicts the occurrence of POAF. Therefore, we recommend adding this haematological index to diagnostic criteria of AF.

Atrial fibrillation is associated with the infiltration of immune cells and proteins mediating the inflammatory response in cardiac tissue [40]. Moreover, inflammation in the heart or systemic circulation can predict the occurrence of AF and recurrence in the general population and in patients after cardiac surgery, cardioversion, and catheter ablation [40]. Investigators have claimed that anti-inflammatory drugs played a considerable role in prevention of POAF by regulating inflammatory mediators; by inhibition of one of the mechanisms of AF, they not only reduced postoperative arrhythmia, but also strongly decreased consequent complications of AF [41]. They believed that inflammation and oxidative stress were the most important mechanisms of AF [41].

Our findings indicated that pre- and postoperative WBC were directly related to the occurrence of POAF because WBC count was significantly higher in patients with POAF compared to those with sinus rhythm. A subgroup analysis found diabetes and arterial hypertension, statin and angiotensin converting enzyme inhibitor therapy, cross-clamp time, and cardiopulmonary bypass time as the factors of heterogeneity. Our previous findings indicate that WBC count was remarkably higher in patients with a history of AF undergoing cardioversion and catheter ablation, who developed recurrent AF, as compared to patients who had successful treatment, thus confirming the association of WBC count with the recurrence of AF [9]. Our new findings showed that regular WBC check before and after surgery may be of major importance in terms of detecting the inflammatory state and onset of infection, as well as making timely diagnosis of cardiovascular events, such as arrhythmias, within a short period of time. NLR is another haematological marker related to the inflammation-based pathogenesis of AF [42]. We confirm that the NLR level before and after surgery has a significant association with the occurrence of POAF. Summarising, WBC count and NLR may have a potential predictive power, particularly when used together.

Red blood cell distribution width is known as a parameter measuring variability in circulatory red cell size obtained in CBC tests [43]. Higher RDW represents the presence of anisocytosis, which is related to impaired erythropoiesis and RBC degradation and appears as chronic inflammation and increased oxidative stress [43]. In the present study, we found that the preoperative RDW level was considerably higher in patients with POAF as compared with the control group, confirming the fact that increased RDW in CBC test before surgery warns of the risk of AF. Several reports have recently emphasised the predictive role of RDW for clinical outcomes and haemodynamic status in patients suffering from heart failure, myocardial infarction, and acute coronary syndrome [44, 45], whereas no reports have been published regarding the difference in postoperative RDW between POAF and POSR groups. We recently pointed out that RDW has a re-

markable predictive power for the occurrence and recurrence of paroxysmal, persistent, or permanent AF [9].

Anaemia is considered an independent predictor for morbidity and mortality in a number of cardiovascular diseases, such as heart failure and myocardial infarction [46]. Sharma et al. [46] defined anaemia as an important predictor for hospitalisation and mortality in elderly patients with AF. It should be noted that anaemia caused by peri- and postoperative bleeding, along with blood transfusion as a therapeutic strategy, can lead to an increased risk of AF by changing physiological set points and reduced proinflammatory state [46]. Alameddine et al. [47] reported that an increase in blood transfusion requirements was notably associated with an increased risk of the incidence of POAF. Our findings showed that there was no difference in the levels of Hb and HCT before surgery and also Hb level after surgery between POAF and POSR groups. It is noteworthy that the level of these haematological indices was not significantly different between the two groups, probably due to homogeneity of patients enrolled in the studies, the small number of studies, the elective nature of surgical procedures performed, and the lack of significant bleeding events in the included studies. Considering these findings, we cannot accept or reject the present hypotheses about the association of anaemia with the occurrence of atrial fibrillation.

Limitations of the study

This meta-analysis has several limitations. It is a study-level meta-analysis with an inherent lack of available data on end-points assessed in studies included in the meta-analysis. Also, there are different definitions of arrhythmia and sinus rhythm between studies, and there is no data on various types of cardiothoracic surgeries.

CONCLUSIONS

Haematological indices may predict the risk of POAF before surgery. These readily performed tests should definitely be taken into account in patients undergoing isolated CABG, valvular surgery, or combined procedures.

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