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Research Article

Importance of Biomarkers in Determining Post-Implantation Syndrome Developing Due to Endovascular Aneurysm Repair

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Abstract

Objectives: In this study, we aimed to undertake a systematic review of the literature in order to investigate whether preoperative biomarkers have diagnostic significance in determining post-implantation syndrome PIS possibility after endovascular aneurysm repair (EVAR).

Methods: Literature review was carried out in PubMed electronic database without any limitations of date. Included were studies that recorded the preoperative levels of inflammatory biomarkers in which PIS develops following EVAR and that were published only in English. Results of the studies were evaluated based on either random or fixed effect model in accordance with the presence of heterogeneity (I2>25%). Statistical analysis were performed by Open meta Analyst® software.

Results: A total of 349 articles were found upon a database screening. After the article titles and abstracts were analysed, 6 articles were included in the meta-analysis that cover 891 patients and comply with inclusion criteria. It was observed in the studies that WBC, CRP, thrombocyte, IL-6, and fibrinogen levels were analysed. It was found from the conducted analysis that the preoperative levels of WBC (SMD: 0.70 95% CI: 0.55-0.86 and p<0.001), fibrinogen (SMD: 0.27 95% CI: 0.03-0.51 and p=0.02), IL-6 (SMD: 1.04 95% CI: 0.64-1.44 and p<0.001), and thrombocyte (SMD: 0.91 95% CI: 0.13-0.69 and p=0.02) were significant in determining the PIS development, however, CRP levels were not (SMD: 0.37 95% CI: -0.20-0.96 and p=0.20).

Conclusion: We concluded that WBC, thrombocyte, fibrinogen, and IL-6 levels were effective in predicting PIS developing after EVAR in preoperative period.

Keywords: Biomarker, endovascular aneurysm repair, meta-analysis, post-implantation syndrome

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Inflammation plays a role both in abdominal aortic aneurysm (AAA) pathogenesis and in the period following endovascular aortic repair (EVAR).[1] Although the Post-implantation Syndrome (PIS) defined as the systemic inflammatory response is frequently observed in EVAR patients, it generally does not get a diagnosis. At this point, not resorting to differential diagnosis of the fever observed following the application and the absence of an internationally agreed diagnostic criteria appear to be an important factor.

Among the diagnostic criteria of PIS that is observed at such a high rate as 60% following the EVAR and that is defined as an inflammatory process are increased leukocyte (WBC>12000μL), increased C-reactive protein (CRP>10 mg/mL), and fever (>38°C).[2, 3]

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In studies found in literature, numerous biomarkers such as CRP, Interleukin-6 (IL-6), fibrinogen, WBC, procalcitonin, etc. were investigated. However, our literature study revealed no information on whether the preoperative levels of biomarkers are significant in predicting PIS formation following EVAR.Therefore, we aimed in this compilation study to investigate which biomarkers are important in order to predict PIS development before the operation.

Methods

Database Search Plan

We carried out our database search according to guideline of Moher et al.[4] published in 2015 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement - PRISMA). We conducted our electronic database search in order to identify which biomarkers may be important in predicting the PIS development following EVAR procedure. Researchers scanned the database up until 01.10.2017. No limitations were imposed on article publication dates. Only PubMed was utilised as the electronic database. No searches were conducted other than the electronic database. However, articles found in the references section of articles that may be of interest were analysed.

As the English keywords or a combination of these, (endovascular aortic aneurysm repair, EVAR, TEVAR, inflammatory response, post-implantation syndrome) were used. While articles published in English were searched, other languages were not included.

Selection of Studies

All retrospective or prospective studies were included without focusing on sample (patient) numbers. As the inclusion criteria:(i) clinical study, (ii) Implementation of EVAR, (iii) language of the article as English. Exclusion criteria:(i) experimental studies, (ii) case studies or case series, (iii) articles in languages other than English, and (iv)surgical interventions. Studies that were relevant to our subject of study but that did not investigate biomarkers were not included in the analysis. In addition, articles in which relevant data were presented as figures or graphs were excluded from the analysis.

Determination of Data

Researchers recorded the data in the relevant articles (name of the first author, date of publication, sample number, research design) independently from each other. Disagreements between the data and articles were resolved via consensus. Data were entered the meta-analysis software as mean, standard deviation, and number of patients. Data obtained as median and range instead of mean and standard deviation were estimated as mean and standard deviation according to the formula by Hozo et al.[5]

We recorded it to the international prospective register of systematic reviews of the University of York. PROSPERO registration number: CRD 42017073380.

Statistical Analysis

For the statistical analysis, Open Meta Analysist® (Brown University, Rhode Island, USA) software was used. Standard mean differences (SMD) and 95% confidence interval (CI) were applied. Heterogeneity was evaluated by I2 statistics. If I2 ≥25%, then heterogeneity was accepted as significant, analysis of moderators was evaluated for the determination of the cause of heterogeneity. Meta-analysis was carried out by using fixed or random models. In the presence of heterogeneity (I2>25%) random effects model was used, and in its absence(I2<25%), fixed effect model was used. Publication bias was evaluated with Begg's test.

Result

Database search flow chart is given in Figure 1.

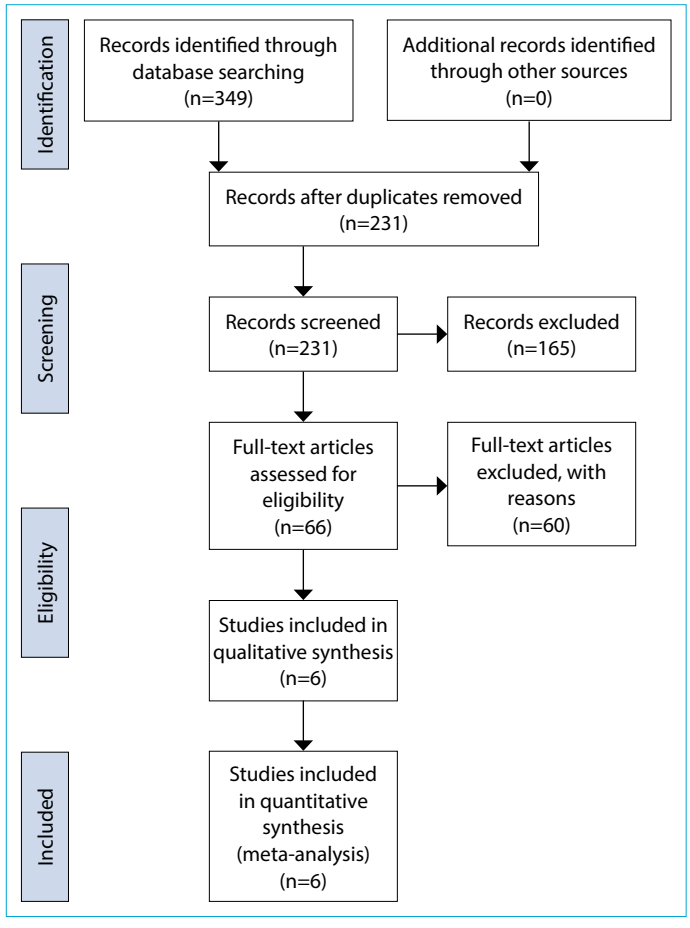

Figure 1. Database search flow chart.

Table 1. Features of studies included the analysis

	Year	PIS (n)	Total patients (n)	Design of study	LOS in hospital	LOS in ICU	Type of anesthesia	Mortality (PIS) n	Mortality (control) n
Arnatoglou et al. 2011[6]	2011	14	40	Prospective	Increased	?	General	?	?
Nano et al. 2014 [10]	2014	24	118	Retrospective	Increased	?	General (?) Spinal (?)	3	1
Arnatoglou et al. 2015[11]	2015	77	214	Prospective	Increased	Increased	General	?	?
Arnatoglou et al. 2016[7]	2016	65	182	Prospective	Increased	No difference	General	3	1
Gorla et al. 2016[8]	2016	21	133	Retrospective	?	?	?	0	7

PIS: Postimplantation syndrome; WBC: White blood cell; TEVAR: Thoracic endovascular aortic repair; CRP: C-reaktive protein.

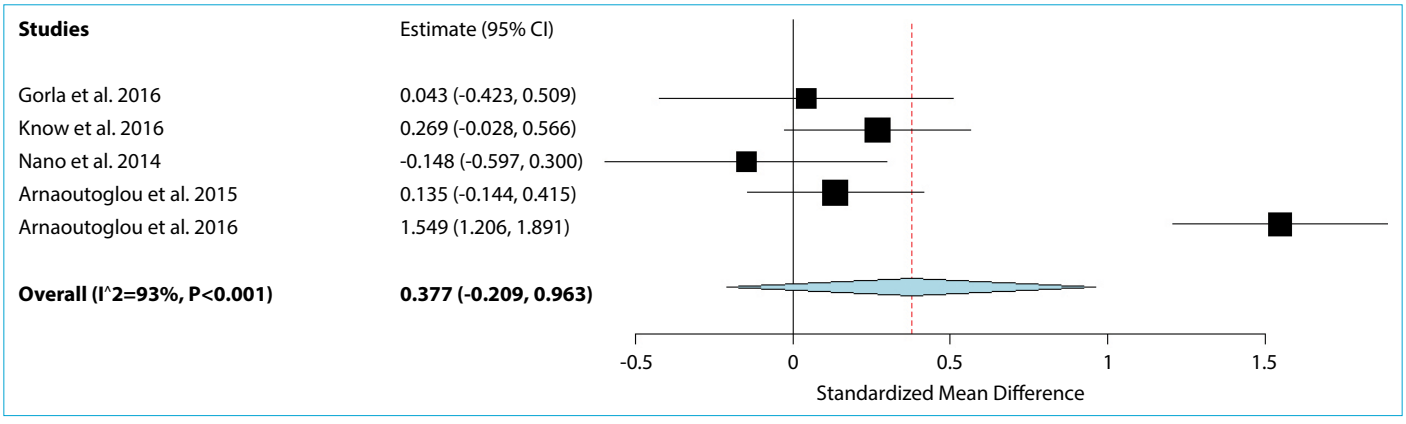

Figure 2. Results of analysis for CRP.

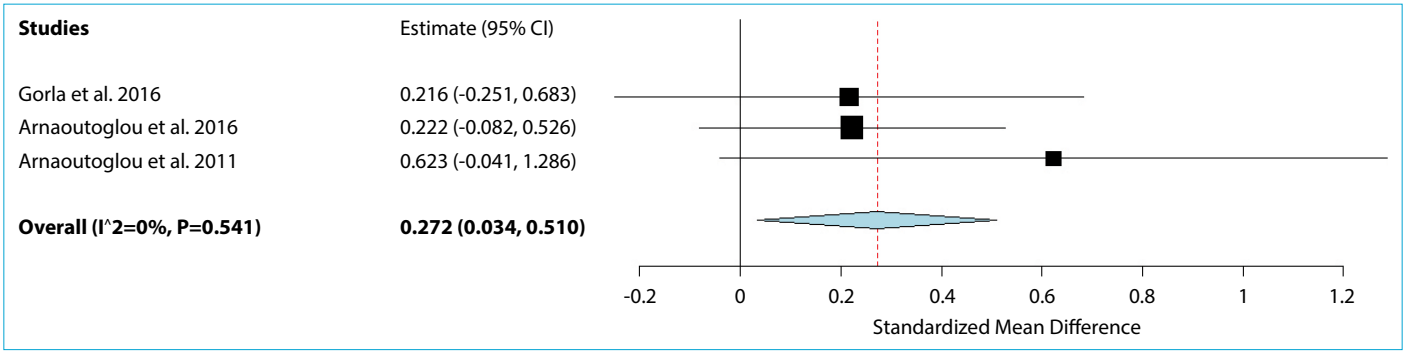

Figure 3. Results of analysis for fibrinogen.

Total number of articles obtained by electronic database search were 349. After the repeating articles were separated, the remaining number of articles were 231. Upon reviewing the abstracts and titles of the articles, 165 articles that were not relevant with the subject were excluded from the analysis. Of the 66 articles, the entire texts of which were analysed for compliance with the analysis, 60 were eliminated. A total of 6 research studies comprised of 891 patients were included in the quantitative synthesis.[6-11] Demographic data and characteristics of the articles are summarised in Table 1. PIS development rate in total were 29.7% (265 out of 891 cases).

Due to the fact that studies containing CRP, thrombocyte, and IL-6 being heterogeneous as a result of the analysis of articles that investigate the total 5 biomarkers, random effect model was used for CRP, thrombocyte, and IL-6, and fixed effect model was used for WBC and fibrinogen. It was observed that the characteristics of WBC (SMD: 0.70 95% CI: 0.55-0.86 and p<0.001), thrombocyte (SMD: 0.91 95% CI: 0.13-0.69 and p=0.02), fibrinogen (SMD: 0.27 95% CI: 0.03-0.51 and p=0.02), and IL-6 (SMD: 1.04 95% CI: 0.64-1.44 and p<0.001) in predicting post-EVAR PIS before the procedure were statistically significant (p<0.05), but that CRP (SMD: 0.37 95% CI: -0.20-0.96 and p=0.20) was not significant (p>0.05). The obtained results are given in Figure 2-6 and Table 2.

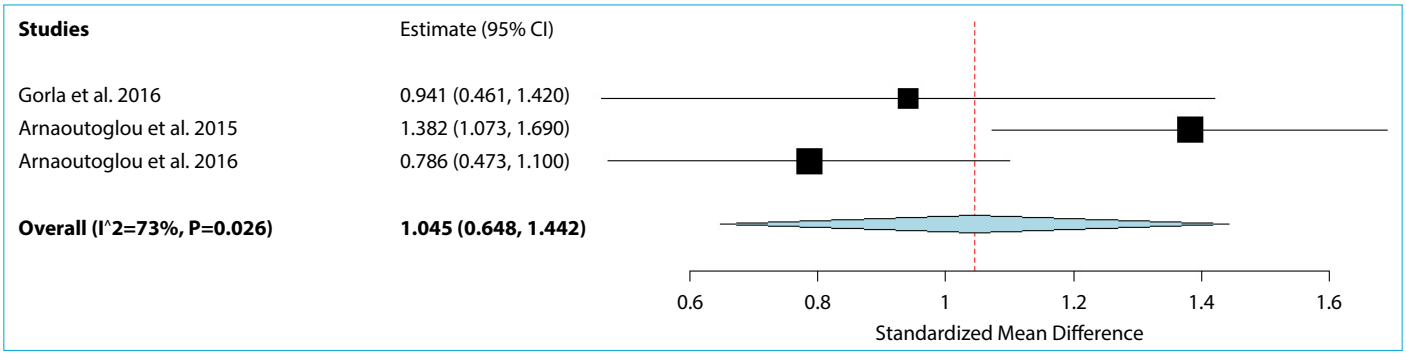

Figure 4. Results of analysis for IL-6.

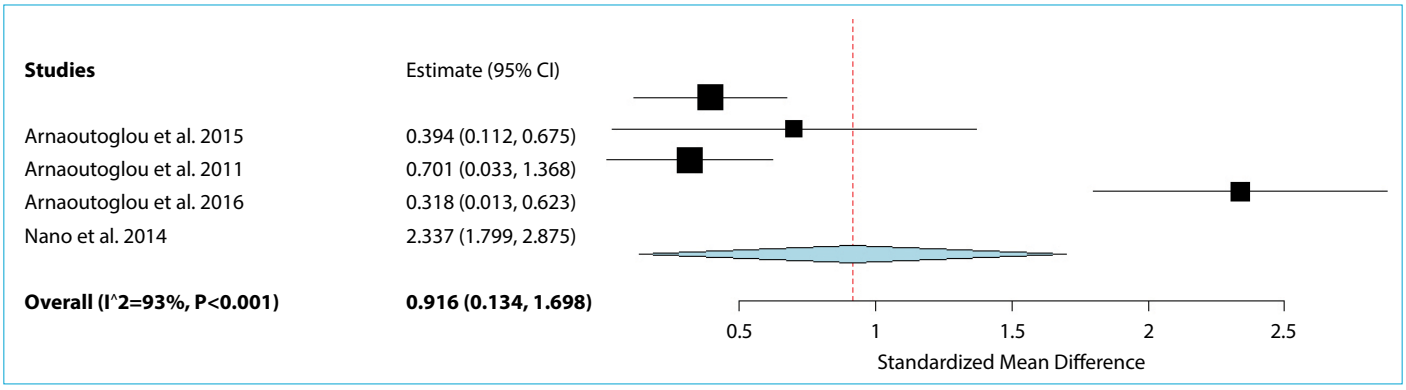

Figure 5. Results of analysis for thrombocyte.

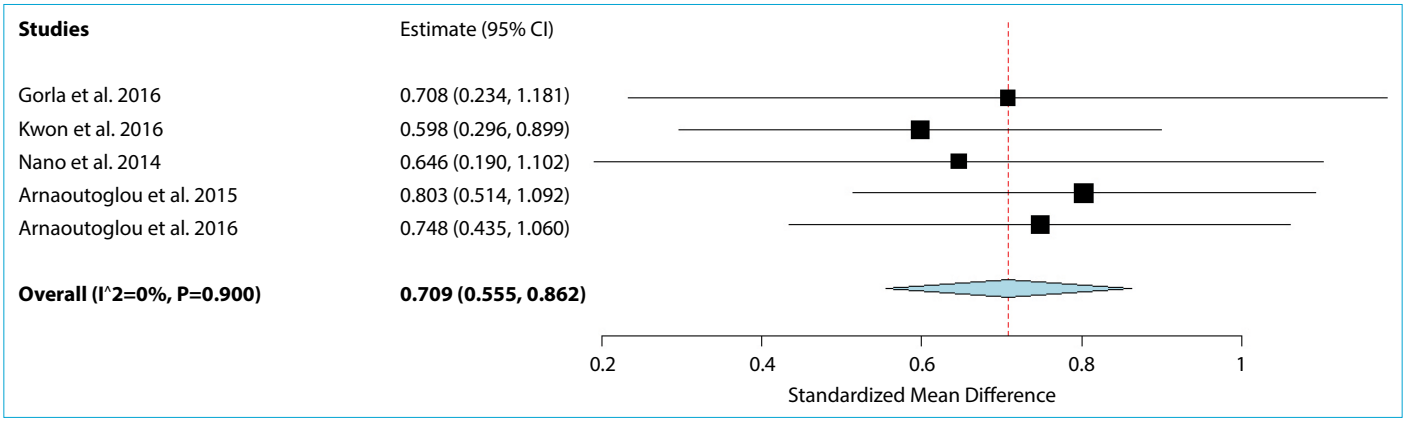

Figure 6. Results of analysis for WBC.

When analysed heterogeneity among the studies, heterogeneity was observed in articles containing CRP, thrombocyte, and IL-6 (I2>25%). When analysed the cause of heterogeneity, research design was observed to be a factor for CRP. While it was I2=18% in retrospective studies, it was found as I2=93% in prospective studies. However, since the number of studies containing IL-6 WAS 3 and that the number of articles covering a possible heterogeneity factor should be a minimum 2, cause of heterogeneity for IL-6 was not analysed. On the other hand, although the number of articles containing thrombocyte values was 4, when various factors were examined as moderator in the sub-group analysis, an analysis was not possible since the group distribution was constantly 1 against 3 articles. Results on the heterogeneity analysis are summarised in Table 2.

Possible publication bias evaluation results were not significant according to Begg's test(tau 2>0.05). Relative weights obtained from the researches were 10.49%-28.14% for WBC, 19.12%-20.60% for CRP, 27.69%-36.29% for IL-6, 22.86%-26.50% for thrombocyte, and 12.83%-61.19% for fibrinogen (Table 3).

Table 2. Results of analysis

Variables	Results of analysis				Heterogeinity				Bias
	SMD		%95 CI	p	Q	df	p	I^2	Tau^2
WBC	0.70	0.55	0.86	<0.001	1.06	4	0.9	0%	0.07
CRP	0.37	-0.20	0.96	0.20	55.36	4	<0.001	93%	0.41
IL – 6	1.04	0.64	1.44	<0.001	7.33	2	0.02	73%	0.08
Fibrinogen	0.27	0.03	0.51	0.02	1.22	2	0.54	0%	0.06
Thrombocyte	0.91	0.13	0.69	0.02	45.37	3	<0.001	93%	0.58

SMD: Standard mean differences; CI: Confidence interval; WBC: White blood cell; CRP: C-reactive protein; IL-6: Interleukin-6.

Table 3. Weights of studies in analysis

	WBC	CRP	IL -6	Fibrinojen	Thrombocyte
Arnatouglou et al. 2011[6]				12.83	22.86
Nano et al. 2014[10]	11.34	19.29			24.28
Arnatouglou et al. 2015[11]	28.14	20.72	36.29		26.50
Arnatouglou et al. 2016[7]	24.08	20.25	36.01	61.19	26.34
Gorla et al. 2016[8]	10.49	19.12	27.69	25.96	
Kwon et al. 2016[9]	25.93	20.60			

WBC: White blood cell; CRP: C-reactive protein; IL-6: Interleukin-6.

Discussion

As a result of our meta-analysis, we observed that preoperative WBC, fibrinogen, thrombocyte, and IL-6 levels were significant in predicting PIS development following EVAR. Preoperative levels of CRP that is regarded by certain authorities as one of the diagnostic criteria were observed to not have a PIS-predicting characteristics. However, due to the fact that the number of studies covering other biomarkers (d-dimer,haematocrit, creatinine, IL-1, tumour necrosis factor-α etc.) a quantitative analysis result was not obtained.

While, essentially, post-EVAR prevalence is considerable, only a limited number of articles that cover biomarkers are within reach due to the fact that PIS lacks an internationally agreed diagnostic criteria. PIS diagnosis was fundamentally derived from systemic inflammatory response syndrome. Velazquez et al.[12] who created the first definition noted that, in cases in which culture results are negative, WBC that is among inflammatory parameters would be above 11,000/mL and fever above 38.5°C. Such systemic inflammatory response syndrome criteria as leukopenia, fever below 36°C, pulse, and respiratory rate were excluded from this definition. However, despite the fact that it is not a complicated definition, not resorting to differential diagnosis of fever that is frequently observed in up-to-date studies manifests the reported PIS rate as lower than it actually is. For instance, Yazman et al.[13] in their studies in which they investigated 30-day early postoperative complications, they did not find infection and PIS differential diagnosis despite they established fever in 12.8% of the patients. We must also consider that the symptoms and findings such as fever and leukocytosis with negative blood cultures, may also be present in anaphylaxis.[14]

On the other hand, some authors count CRP level among diagnostic criteria. Among the studies that we included in the analysis, only Gorla et al.[8] used CRP among diagnostic criteria. This shows similarity with Blum et al.[15] and Voute et al.[16]

As a result of our literature analysis, we observed that five biomarkers (WBC, IL-6, CRP, fibrinogen, and thrombocyte) were investigated in more than one study. As distinct from these five biomarkers, Gorla et al.[8] studied d-dimer, Nano et al.[10] studied haematocrit and creatinine, and Arnaoutoglou et al.[6] studied interleukin-1, tumour necrosis factor-α (TNF-α). However, a significant difference was not observed among the preoperative values of all four markers other than Interleukin-1. Arnaoutoglou et al.[6] observed that preoperative interleukin-1 levels were higher in PIS group. Due to the fact that there is only one study each on these markers, statistical analysis was not possible.

When examined the studies separately, Arnaoutoglou et al.[11] observed significant difference for thrombocyte, Gorla et al.[8] observed this for fibrinogen, and Kwon et al.[9] observed the same for WBC and thrombocyte in terms of preoperative levels between patient groups that develop or did not develop PIS. For the results of studies excluding

studies that investigate these biomarkers and CRP, a significant difference was not observed between the groups that develop or did not develop PIS in terms of serum levels of biomarkers when these individual studies were examined separately. On the other hand, the result of our analysis coincides with findings that were obtained separately in studies covering CRP.

Inflammatory biomarkers were analysed both in terms of open surgery technique and EVAR. Odegard et al.[17] observed that postoperative IL-6, WBC, and CRP levels increased in both groups. On the other hand, while thrombocyte and fibrinogen levels dropped, TNF-α was left unchanged. Ikoma et al.[18] analysed WBC, CRP, thrombocyte, and fibrinogen from among inflammatory markers measured preoperatively and postoperatively in 88 patients that were implemented EVAR. In the wake of the study, while increases were observed in WBC and CRP levels depending on EVAR, thrombocyte levels were found to have decreased. Fibrinogen, on the other hand, followed a higher course on the postoperative first and tenth days.

In studies that analysed cases that developed PIS, it was observed that the preoperative levels of inflammatory markers within normal limits in both groups that did and did not develop PIS, however, that WBC increased only in PIS group in postoperative period, fibrinogen, IL-6, and CRP increased in both groups, and that thrombocyte levels dropped below the normal levels only in PIS group.[6, 8, 9] When examined the obtained results, increases in WBC, CRP, fibrinogen, and IL-6 were observed as natural depending on the process during the development of PIS that is an inflammatory process.

Arnaoutoglou et al.[19] showed a linear correlation between preoperative WBC increase manifesting within normal reference values and major negative events observed following EVAR in a recent study. This finding supports the results of our analysis.

Studies conducted in recent years show that thrombocytes also play an important role in inflammation in addition to hemostasis and coagulation. Thrombocytes manifest these characteristics by interacting with granulocytes, blood vessel wall, and pathogens and through their anti-inflammatory and proinflammatory mechanisms.[20] Thrombocytes are also the primary source of inflammatory proteins.[21]

On the other hand, the possibility of the finding we obtained on biomarkers as a result of the synthesis of studies included in the analysis which notes that biomarkers other than CRP are significant in predicting PIS development would be affected depending on properties belonging to patients (such as simultaneous systemic diseases) and to the implemented techniques (such as anaesthesia) and on variables were not investigated in this analysis.However, a significant difference was not observed between the groups in these studies in terms of systemic diseases.[6-8]

Another factor that needs to be investigate and that affects a possible PIS development was observed to be the implemented technique of anaesthesia. Zura et al.[22] concluded in their study that postoperative leukocyte increase in general anaesthesia was not significant compared to preoperative values, however, drop in thrombocyte level and increase in CRP level in both spinal and general anaesthesia were significant compared to preoperative levels. On the other hand, while a significant difference was not observed between general anaesthesia and spinal anaesthesia in terms ofIL-4, IL-6, IL-8, IL-10, IL-1α, IL-1β, tumour necrosis, factor-α, interferon-γ, vascular endothelial growth factor, and epidermal growth factor levels, IL-2 level was shown to increase more in general anaesthesia compared to spinal anaesthesia.

Despite all these findings, general anaesthesia was administered to patients in three of the studies that we included in the analysis.[6, 7, 11] In the remaining two studies, both general and regional anaesthesia were administered, however, detailed data were not presented as to which technique was implemented on which patients.[9, 10] In another study, no information was found on the technique of anaesthesia.[8]

Except the inflammatory biomarkers that we analysed, the neutrophil lymphocyte ratio, platelet-to-lymphocyte ratio and other biomarkers, which may be released due to stent/graph implantation, should be considered in future trials to assess the inflammatory response after endovascular procedures.[22]

Limitations

Our study had two significant several limitations. First one was the fact that the database search was conducted in only one (PubMed) electronic database, and the second was the choice of the language of articles as English only. As a third limitation, three of six studies were retrospective and none of them were randomised controlled trials.

In our opinion, routine preoperative analysis of WBC, IL-6, fibrinogen, and thrombocyte may help to predict PIS in clinical practice. On the other hand, the larger studies must be performed for predictor value of CRP.

Conclusion

As a result of the analysis, we obtained the finding that preoperative levels of WBC, IL-6, fibrinogen, and thrombocyte were beneficial in predicting PIS development following EVAR. However, we believe that the other remaining risk factors of PIS that is an inflammatory process should be established and that the interaction of these risk factors and biomarkers should be simultaneously addressed.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.O., I.O.; Design – S.O., I.O, U.K., K.K., M.E.E., M.A.K; Supervision – S.O. I.O., U.C.K; Materials – S.O., U.K., K.K., M.E.E., M.A.K., Y.K., S.M.S., I.O., U.C.K; Data collection &/or processing – S.O., U.K., K.K., M.E.E., M.A.K., Y.K., S.M.S., I.O., U.C.K; Analysis and/or interpretation – S.O., U.K., K.K. I.O.; Literature search – S.O., U.K., K.K., M.E.E., M.A.K., Y.K., S.M.S., I.O., U.C.K; Writing – S.O., U.K., K.K., M.E.E., M.A.K., I.O; Critical review – U.K., U.C.K.

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