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Neutrophil to Lymphocyte Ratio as a Prognostic Biomarker for Morbidity and Mortality in Patients Undergoing Benign Surgery: A Systematic Review

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Abstract

Background: Neutrophil to lymphocyte ratio (NLR) reflects the degree of systemic inflammation. Several clinical trials have shown that a high preoperative NLR predicts morbidity and mortality after surgery for malignant disease. Whether preoperative NLR predicts morbidity and mortality after benign surgery is uncertain. The aim of this systematic review was to investigate whether preoperative NLR predicts postoperative morbidity and mortality after benign surgery.

Method: A systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses. The population was limited to adults undergoing benign surgery. The search was performed in PubMed, Scopus, Embase and the Cochrane Library. Risk of bias was evaluated with ACROBAT-NRSI.

Results: 25 clinical observational studies with a total of 10,015 patients were included. Types of surgery were cardiac surgery (N = 11), vascular surgery (N = 6) and non-cardiac non-vascular surgery (N = 8). The studies in cardiac and vascular surgery showed associations between preoperative NLR and postoperative mortality. 11 out of 13 studies in cardiac and vascular surgery showed a significant association between NLR and postoperative morbidity. In orthopaedic surgery, NLR predicted troponin elevation after hip surgery and postoperative infections after knee surgery, while no association was shown between preoperative NLR and postoperative complications in patients amputated due to diabetic foot ulcers. NLR predicted postoperative complications after prosthesis implantation and bowel resection. NLR did not predict the risk of postoperative complications after abdominal and miscellaneous non-cardiac surgery.

Conclusion: In cardiac and vascular surgery, a high preoperative NLR was significantly associated with postoperative morbidity and mortality. The predictive value of NLR in non-cardiac non-vascular surgery was unclear and should be investigated in larger clinical studies.

Introduction

In recent years, the role of the neutrophil to lymphocyte ratio (NLR) has gained significant attention in a variety of malignant diseases including colorectal cancer, hepatocellular cancer, advanced pancreatic cancer, ovarian cancer and oesophageal cancer, as an independent predictor of morbidity and mortality[1-5]. A systematic review including 40,559 patients showed that a high pre-operative NLR was associated with overall survival and disease-free survival in solid tumours[6]. Likewise, a clinical study including 404 patients with gastric cancer undergoing curative gastrectomy showed that a high pre-operative NLR (NLR > 3) independently predicted the development of postoperative infectious complications and NLR > 3 was independently associated with overall- and cancer-specific survival[7]. A cohort study including 418 patients reported that NLR was the most efficient biomarker to predict recurrence-free survival, cancer-specific survival and overall survival in patients undergoing radical cystectomy for bladder cancer compared to platelet-lymphocyte ratio and absolute platelet counts[8]. Moreover, NLR has been studied in a range of clinical non-surgical settings and has e.g. been shown to be a better indicator than total white blood cell count in the staging of acute pancreatitis[9]. Whether preoperative NLR predicts morbidity and mortality after benign surgery is unclear. The purpose of this systematic review was to investigate whether a pre-operative NLR is a predictor of postoperative morbidity and mortality after benign surgery.

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Method

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA)[10]. A version of the review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42016050756).

The population was limited to patients ≥18 years who underwent benign surgery. Studies including patients who underwent transplantation or patients with cancer were excluded. Only studies with a pre-operative NLR were included. Outcomes were postoperative morbidity and mortality. We excluded non-English publications and unpublished studies including proceeding abstracts. Date of publication was not restricted. A literature search was conducted in November 2017 in PubMed, Scopus, Embase and the Cochrane Library. In PubMed the following search terms were used: Humans, adults, surgical specialties, surgery, operation, surgical procedures - operative, resection, incision, neutrophils, lymphocytes, neutrophil, lymphocyte, neutrophil/lymphocyte, neutrophil-to-lymphocyte ratio, NLR, survival, mortality, mortalities, death, morbidity, mortalities, morbidities. The PubMed MesH terms were modified to corresponding terms in the other databases. Reference lists from included articles were manually searched for additional publications of relevance. Two reviewers independently screened all articles on title and abstract and resolved disagreement through discussion.

Two reviewers extracted data on; author, study design, number of participants, characteristics of the population, type of surgery and priority, lengths of follow-up, pre-operative NLR and clinical outcomes. Disagreements were resolved through discussion.

Methodological quality assessment

A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) was used to assess the methodological quality of the individual studies[11]. The quality assessment evaluated the potential risk of introducing bias or limit applicability of the studies. ACROBAT-NRSI assesses the studies across seven specified domains of bias distributed in two types of pre-intervention bias, one kind of intervention bias and four types of post-intervention bias. All studies were rated on the risk of pre-intervention bias, intervention bias and post-intervention bias. The rating was divided into 'low', 'moderate', 'serious', 'high' or 'non relevant'. For each study, the overall risk of bias was determined by the highest rated risk of bias in any of the domains.

Results

A total of 4,663 articles were identified in the PubMed database, Scopus, EMBASE and Cochrane clinical trials. After manual removal of 534 duplicates, 4,129 articles were left for screening on title and abstract. 4,012 articles were excluded after screening on title and abstract. After full-text review, 94 articles were excluded and 23 articles were included in the systematic review. Furthermore, a manual search of reference lists led to inclusion of 2 additional articles, figure 1.

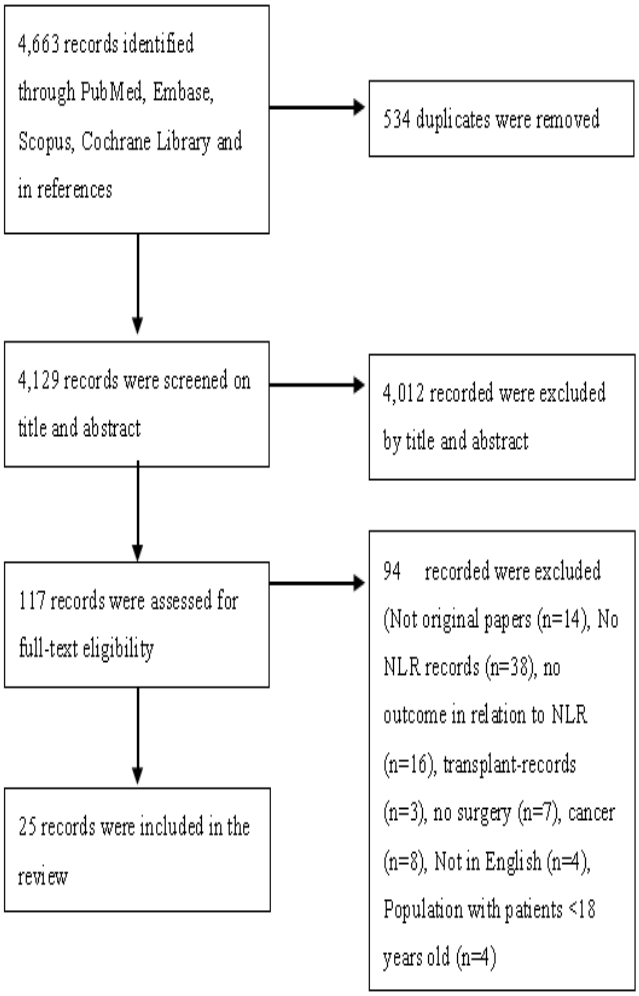

Figure 1: Flowchart of included articles and the screening process. The violation of any inclusion criterion resulted in the exclusion of the article.

Study characteristics

25 clinical studies with a total of 10,015 patients were included[12-36]. The studies consisted of 10 prospective cohort studies[12-14,18,19,22,25-28] retrospective cohort studies[15-17,20,21,23,29-36] and two case-control study[24,31]. Lengths of follow-up ranged from one day to108 months after surgery.

The mean age ranged from 37.6 ± 13.1 years[36] to 82 ± 8years[28], table1.

The studies were divided into three categories according to the type of surgery: cardiac surgery (N = 11)[12-17,28,30-32,37], vascular surgery (N = 6)[1-23,33] and non-cardiac non-vascular surgery (N = 8)[24-27,29,34-36] including four studies in orthopaedic surgery[24,25,29,35], two studies in abdominal surgery[26,36], one study in urology[34] and one study in miscellaneous types of non-cardiac non-vascular surgery[27].

Table 1: Clinical studies assessing Neutrophile to Lymphocyte Ratio prior to benign surgery.

Author	N	Design	Priority	Type of surgery	Age, years	Population NLR	Population Morbidity	Population Mortality	Follow up after surgery
Cardiac surgery									
Azab B et al (2013) [12]	1,126	Prospective cohort study	Elective	CABG	Tertile 1: Sternotomy 62.5 ± 10.2 MICS: 60.7 ± 10.9 Tertile 2: Sternotomy 64.3 ± 11.0 MICS: 62.6 ± 10.7 Tertile 3: Sternotomy 67.5 ± 11.0 MICS: 65.6 ± 10.7	-	-	-	49 ± 15.2 months
Gibson P et al (2007)[13]	1,938	Prospective cohort study	-	CABG	65±9	2.43 (1.86-3.36)	-	177/1,938 (9.1%)	3.6 (1.4-4.7) year (median, q1-q3)
Gibson P et al (2010)[14]	275	Prospective cohort study	Elective	CABG	65 (58-70) (median (q1-q3))	-	Atrial fibrillation 107/275 patients (38.9%)	-	7 days or until discharge
Tasoglu I et al (2013)[15]	444	Retrospective cohort study	Elective	CABG	61.9±10.6	-	SVGF: 258/444 patients (58.1%)	-	Tertile 1: 41.7 ± 4.2 months Tertile 2: 37.5 ± 6.2 months Tertile 3: 43.5 ± 5.4 months
Aydınlı Bet al (2016)[29]	1500	Retrospective cohort study	Elective	CABG, isolated single cardiac valve surgery, combined surgery	60±11.7	3.2 ± 2.3	CAE 296/1500 patients (19.8%)	-	-
Sevuk U et al (2016)[31]	172	Retrospective case-control study	Elective	CABG	Post-pericardiotomy syndrome 60.5 (52.25-66) No post-pericardiotomy syndrome 61 (54-67) (median (q1-q3))	-	Post-pericardiotomy syndrome 72/172 patients (41.8%)	-	15 ± 1 day
Saskin H et al (2015)[32]	916	Retrospective cohort study	Elective	CABG	60 ± 8.3	-	-	-	30 days

Kim W et al (2015) [16]	590	Retrospective cohort study		Open cardiac or thoracic aorta surgery with cardiopulmonary bypass	Quartile 1: 66 (55-73) Quartile 2: 64 (56-74) Quartile 3: 68 (55-74) Quartile 4: 66 (56-73) (median (q1-q3))	-	Acute kidney injury 166/590 patients (28.1%)	-	1 year
Yost GL et al (2015)[17]	273	Retrospective cohort study	Acute	Implantation of left ventricular assist devices	59.85 ± 12.95	-	Right ventricular failure: 84/273 patients (30.8%)	30-days mortality 9/273 patients (3.3%) 1-year mortality 117/273 patients (42.9%) 2-years mortality 174/273 patients (63.7%)	2 years
Lafci G et al (2014) [21]	104	Retrospective cohort study	Acute	Type I aorta dissection	55.2 ± 14	-	-	In-hospital mortality 33/104 patients (31.7%)	-
Kalkan ME et al (2017)[30]	184	Retrospective cohort study	Acute	Type I aorta dissection	53.1 ± 11.4	-	Re-operative surgery 9/184 patients (4.8%) Multi-organ dysfunction 23/184 patients (12.5%) Major bleeding 22/184 patients (11.9%) AKI 26/184 patients (14.1%) Stroke 12/184 patients (6.5%) Extremity embolism 1/184 patients (0.5%) Hospital-related infection 36/184 patients (19.5%)	In-hospital cardiovascular mortality 38/184 patients (20.7%)	-
Vascular surgery									
Appleton ND et al (2014)[18]	350	Prospective cohort study	Elective, acute	Repair of abdominal aortic aneurysms	72.9 ± 7.9	-	-	30 days mortality 32/350 patients (9.4%) 1-year mortality: 136/350 (38.8%)	-
Halazun H et al (2014)[19]	432	Prospective cohort study	Elective	CEA for high-grade carotid artery stenosis	-	3.4 ± 2.9	Postoperative cognitive dysfunction 70/432 patients (16.4%)	-	1 day
Kordzadeh A et al (2015)[20]	80	Retrospective cohort study	Acute	Ruptured abdominal aortic aneurysms	75 (51-92) (median (q1-q3))	9.40 (4.14-13.69) (median (q1-q3))	30 days morbidity (Clavien-Dindo ≥ 3) 41/80 patients (51.2%)	30-days mortality 11/80 patients (13.8%)	30 days

Kullar P et al (2012)[22]	126	Prospective cohort study	Elective, acute	Lower limb revascularisation	Patients with graft patency 73 (64-78) Patients witn no graft patency 77 (71-81) (median (q1-q3))		Graft patency 79/126 patients (62.7%)		1 year
Tasoglu I et al (2014)[23]	245	Retrospective cohort study	Acute	Embolectomy (open) for acute limb ischemia	66.0 ± 13.3	-	-	30-days mortality 25/245 patients (10%) Long-term mortality 49/245 patients (20.0%)	26 months (mean)
Wang Q et al (2017) [33]	270	Retrospective cohort study	Acute, elective	Major amputation (above and below knee) or minor amputation (toe and foot) due to ischaemia	71 ± 6	7.9 ± 8.0	Myocardial infarction or stroke: 9/270 patients (3.3%)	30-days mortality 22/270 patients (8.1)	30 days
Non-cardiac non-vascular surgery									
Gölge UH et al (2016)[24]	133	Retrospective case-control study	Elective	Total knee arthroplasty	Patients with prosthetic joint infection: 64.3 ± 9.3 (48-82) Control group: 66.2 ± 7.4 (45-85)				30.5±4.01 weeks
Fisher A et al (2016)[28]	294	Prospective cohort study	Acute	Hip fracture surgery	82.1 ± 8.0	-	Troponin rise: 75/294 patients (18.1%)	In-hospital mortality 10/294 patients (2.4%)	
Sedlár M et al (2015)[25]	104	Prospective cohort study	Acute	Hip fracture surgery	80 ± 9	10.0 ± 7.7		5-years mortality 64/104 patients (61.5%)	60 months (48-84) (median (q1-q3))
Forget P et al (2015)[26]	82	Prospective cohort study	-	Major abdominal surgery	62 (27-80) (median (q1-q3))	4.0±4.91	Postoperative complications: 45/82 patients (54.9)	-	30 days
Alkhamis T et al (2014)[27]	60	Prospective cohort study	Elective	Surgery due to intestinal organ diseases, expansive process of central nervous system, or degenerative hip disease	62.5 (56-72.5) (median (q1-q3))	-	-	-	5 days

Bolat D et al (2017) [34]	153	Retrospective kohort study	Elective	Penile prosthesis implantation	56.4 ± 8.0	-	Postoperative infectious complications: 18/153 patients (11.8%)	-	56 ± 30.4 months
Metinereen H et al (2017)[35]	56	Retrospective cohort study	-	Limb amputation as a result of diabetic foot ulcer	72.73 ± 10.53	8.25 (1.3-70) (median (min-max))	-	2-weeks mortality due to sepsis 24/56 patients (42%)	2 weeks
Kang W-M et al (2017)[36]	108	Retrospective cohort study	-	Abdominal surgery (bowel resection) due to Crohn's disease	37.6 ± 13.1	5.9±12.1	Postoperative complications: 30/108 patients (27.8%)	1/108 (0.9%)	17 days

*clavien-dindo ≥ 3

Continuous data were expressed as mean +/- standard deviation unless indicated otherwise
95% CI: 95% confidence interval; q1: 1st quartile; q3: 3th quartile

AF: Atrial Fibrillation; AKI: Acute Kidney Injury; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area Under the Curve (i.e., ROC curve); CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CAE: Combined Adverse Events (myocardial infarction, cardiac reoperation, prolonged mechanical ventilation (> 48h), prolonged hospital stay, rehospitalization or mortality); CCS: Canadian Cardiovascular Society; CEA: Carotid Endarterectomy; DBP: Diastolic Blood Pressure; HB: Hemoglobin; HTN: Hypertensive; HR: Hazard Ratio; LOS: Length of hospital stay; LVEF: Left Ventricular Ejection Fraction; MCV: Mean Corpuscular Volume; MI: Myocardial infarction; MICS: Minimally Invasive Cardiac Surgery; MPV: Mean Platelet Volume; NLR: Neutrophil-Lymphocyte Ratio; OR: Odds Ratio; PCI: Percutaneous Coronary Intervention; PLR: Platelet:Lymphocyte Ratio; PPS: Post –Pericadiotomy Syndrome; PTH: Parathyroid Hormone; rAAA: ruptured Abdominal Aortic Aneurysm; RDW: Red Cell Distribution Width; ROC: Receiver Operating Characteristic; RV: Right Ventricular; SBP: Systolic Blood Pressure; SVGF: Saphenous Vein Graft Patency

Cardiac surgery

Six studies included patients undergoing coronary artery bypass grafting (CABG)(n = 4,771)[12-15,31,32] and one study included patients undergoing CABG, isolated single cardiac valve surgery and combined surgery (n = 1500)[29]. An eighth study included patients undergoing different types of open cardiac or thoracic aortic surgery with cardio-pulmonary bypass (n = 590)[19]. A ninth study included patients with advanced heart failure who received left ventricular assist devices (n = 273)[17]. Two studies included patients who underwent surgery for acute type I aorta dissection (n = 288)[21,30] table 1.

In one study patients who underwent CABG with a high preoperative NLR (NLR > 3.00 (2.30-3.85)) had a significantly higher risk of developing atrial fibrillation compared with patients with a low NLR[14]. Another study found no association between high NLR and atrial fibrillation[38], table 2.

NLR was independently associated with the risk of saphenous vein graft failure[15], adjusted OR = 1,39 (1,19-1,61), and was an independent predictor for combined adverse events[29], OR = 0.21 (0.2-0.3), table 2. NLR was independently associated with sternum revision[38], adjusted OR = 2.95 (1.32-6.63), but no association was found between NLR and post-pericardiotomy syndrome[31] or neurologic events[38] in patients who underwent CABG, table 2.

NLR was also independently associated with right ventricular failure[17] in patients with advanced heart failure implanted with left ventricular assist devices OR = 1.12, CI = 1.04-1.20, p = 0.003), table 2.

Likewise, patients with an NLR ≥ 2 had a significantly higher risk of developing acute kidney injury[16], table 2.

NLR was independently associated with multi-organ dysfunction, major bleeding and hospital-related infection[30], in patients with aorta dissection, table 2.

Six studies evaluated the association between preoperative NLR and postoperative mortality[12,13,30,37,39,40]. All but one study[39] reported a high pre-operative NLR to be associated with overall postoperative mortality[12,13,32,36,40], table 2.

Table 2:

Cardiac Surgery						
Author	**NLR and Morbidity**		**NLR and Mortality**		**ROC**	**Variables in the adjusted analysis**
	Categorical	**Continuous**	**Categorical**	**Continuous**		
Azab B et al (2013) [12]	-	-	30-days, 6-months, 1- and 5-years mortality rates: NLR < 2.3: 0.5%, 1.6%, 2.4% and 8% 2.3 ≤ NLR ≤ 3.4: 1.3%, 4.3%, 5.1% and 13% NLR > 3.4: 2.7% 7.7%, 9.9% and 20%) p < 0.0001	uHR 1.09 per unit NLR (1.06-1.13), p < 0.001 aHR 1.06 per unit NLR (1.01-1.10), p = 0.008	-	Mortality, continuous: Age, gender, family history of coronary artery disease, smoking, dialysis, COPD, ACE-I, statin, aspirin, post-operative sepsis, preoperative glucose
Gibson P et al (2007) [13]	-	-	All-cause mortality: uHR NLR quartile 1 (low): 1 NLR quartile 2: 0.89 (0.56-1.42) NLR quartile 3: 0.89 (0.56-1.43) NLR quartile 4 (high): 2.06 (1.39-3.06), p < 0.001 aHR NLR quartile 1 (low): 1 NLR quartile 2: 0.81 (0.51-1.30) NLR quartile 3: 0.77 (0.48-1.23) NLR quartile 4 (high): 1.42 (0.95-2.15), p = 0.09	All-cause mortality: Survived: NLR=2.39 (1.84-3.27) Deceased: NLR=2.79 (2.00-4.22) uHR: 1.13 per unit NLR (95% CI 1.08-1.18) p < 0.001 aHR: 1.08 per unit NLR (95% CI 1.02-1.15), p = 0.008 Cardiovascular mortality: uHR: 1.12 per unit NLR (95% CI 1.06-1.18) p < 0.001 aHR: 1.08 per unit NLR (95% CI 1.00-1.16) p = 0.046	-	All-cause mortality, categorical: Euroscore All-cause mortality, continuous: Preoperative total WCC, preoperative monocyte count, Euroscore. Cardiovascular mortality, continuous: Preoperative total WCC, preoperative monocyte count, Euroscore.
Gibson P et al (2010) [14]	Risk of atrial fibrillation NLR quartile 1 (low): 20/68 patients (29%) NLR quartile 2: 20/69 patients (29%) NLR quartile 3: 31/69 patients (45%) NLR quartile 4 (high): 36/69 patients (52%) P = 0.001 NLR > 2.63: uOR 2.23 (1.36-3.67) p = 0.002 aOR 1.76 (1.04-2.97), p = 0.03	No atrial fibrillation: NLR = 2.42 (1.94-3.23) Atrial fibrillation: NLR = 3.00 (2.30-3.85), p = 0.001 Risk of atrial fibrillation uOR 1.29 per unit NLR, p = 0.007 aOR 1.29 (1.07-1.55), p = 0.007	-	-	Atrial fibrillation NLR cut-off 2.63 sensitivity 63% specificity 68% AUC 0.61 (0.55-0.68), P = 0.001.	Morbidity, categorical: age, sex, BMI, previous myocardial infarction, ejection fraction, diabetes mellitus, current smoker, hypertension, Euroscore, parsonnet score, New York Heart Association functional class III/IV, Canadian Cardiovascular Society angina class III/IV, estimated glomerular filtration rate, aspirin/clopidogrel, Beta-blocker, statin, ACE inhibitor/angiotensin receptor blocker, preoperative haemoglobin, preoperative total white blood cell count, high sensitivity C-reactive protein, off-pump procedure, preoperative intra-aortic balloon pump, no. of bypass grafts, internal mammary artery used, bypass time, cross-clamp time, perioperative inotropes, postoperative total WBC count, postoperative C-reactive protein, postoperative troponin I at 48 hours, postoperative AF Morbidity, continuous: Euroscore

Tasoglu I et al (2013) [15]		Risk of SVGF: uOR1.42 per unit NLR (1.22-1.74) P < 0.001 aOR1.39 per unit NLR (1.19-1.61) P < 0.001				Morbidity, continuous: Creatinine > 1.2, target artery diameter < 1.5 mm, smoking, diabetes, interval between operation and angiogram
Aydınlı Bet al (2016) [29]		Combined adverse events NLR = 5.1 ± 3.7 No CAE: NLR = 2.7 ± 1.4 P = < 0.001 Risk of CAE aOR 4.76, (-3.39-6.67), p < 0.001				Morbidity, continuous: Euroscore, hemoglobin, red cell distribution width, mean platelet volume, platelet:lymphocyte ratio
Sevuk U et al (2016) [31]	-	PPS: NLR = 2.39 (1.8-3.15) No PPS: NLR = 2.6 (1.9-3.3), p = 0.35 Median (q1-q3)				
Saskin H et al (2015) [32]		Sternum revision: uOR 3.38 per unit NLR (95% CI 1.93-5.91), p = 0.0001 aOR 2.95 per unit NLR (95% CI 1.32-6-63), p = 0.009 Neurologic events: uOR 1.52 per unit NLR (95% CI 0.88-2.63), p = 0.14 Atrial fibrillation: uOR 1.81 per unit NLR (95% CI 1.49-2.19), p = 0.0001 aOR 1.17 per unit NLR (95% CI 0.92-1.50), p = 0.20				Morbidity, continuous: sex, age, ejection fraction, diabetes mellitus, hypertension, hyperlipidemia, smoking, fasting blood glucose, preoperative LDL, preoperative platelet, preoperative lymphocyte, PLR, preoperative neutrophil, preoperative CRP, preoperative hematocrit, preoperative hemoglobin, aortic cross clamp time, use of blood products, use of inotropic support, amount of drainage
Kim W et al (2015) [16]	NLR<1.5: AKI: 29/166 patients (17.6%) uOR = 1 1.5 ≤ NLR < 2: AKI: 34 (20.6%) uOR= 1.40 (95% CI 0.80-2.46) P = 0.237 2 ≤ NLR < 3: AKI: 50 (30.3%) uOR: 2.08 (95% CI 1.23-3.53) p = 0.006 NLR ≥ 3: AKI: 52 (31.5%) uOR: 2.19 (95% CI 1.29-3.70) p = 0.004	No AKI: NLR =1.93 (1.43-2.83) AKI: NLR = 2.30 (1.67-3.29) uOR: 1.07 (95% CI 0.99-1.12Al) P = 0.086	Unadjusted 1-year survival stratified by NLR-quartiles, Log-rank test, P = 0.314			

Yost GL et al (2015) [17]	RV failure: Tertile 1 (NLR = 2.21 ± 0.66): 19/91 patients (20.9%) Tertile 2 (NLR = 4.01 ± 0.59): 25/91 patients (27.5%) Tertile 3 (NLR = 9.15 ± 6.05): 40/91 patients (44.0%), p < 0.001	Risk of RV failure: uOR 1.117 per unit NLR (95% CI 1.039-1.201), P = 0.003	30-days survival: NLR tertile 1 (low): 91/91 patients (100%) NLR tertile 2: 89/91 patients (97.8%) NLR tertile 3 (high): 84/91 patients (92.3%), p = 0.011 1-year survival: NLR tertile 1 (low): 58/91 patients (87.9%) NLR tertile 2: 53/91 patients (82.8%) NLR tertile 3: 45/91 patients (69.2%), p = 0.022	2-years all-cause mortality: aOR 1.159 per unit NLR (95% CI 1.022-1.314), p = 0.021		Mortality, continuous: Age, serum sodium, BUN, creatinine, BNP, AST, bilirubin, WBC counts, blood pressure, mitral regurgitation, previous stroke, chronic kidney disease
Lafci G et al (2014) [21]	-	-	-	Deceased in-hospital: NLR = 12.3 ± 7.4 Survived: NLR 9.0 ± 6.3 p = 0.025 uHR 1.07 per unit NLR (95% CI 1.02-1.13), p = 0.03 aHR 1.05 per unit NLR (95% CI 1.01-1.10), p = 0.03	Mortality: NLR cut-off 8.0, sensitivity 70% specificity 53% AUC: 0.634 (95% CI 0.516-0.753)	Mortality, continuous: cross-clamp time, cardiopulmonary bypass time, intensive care unit duration, ventilation time, hemorrhage amount, aspartate aminotransferase level, platelet count
Kalkan ME et al (2017) [30]	Reoperation NLR > 6: 7/91 patients (8%) NLR ≤ 6: 2/93 patients (2%) p = 0.079 Multi-organ dysfunction: NLR > 6: 16/91 patients (17%) NLR ≤ 6: 7/93 patients (8%) p = 0.032 Major bleeding: NLR > 6: 17/91 patients (19%) NLR ≤ 6: 5/93 patients (5%) p = 0.005 Acute renal failure: NLR > 6: 15/91 patients (16%) NLR ≤ 6: 11/93 patients (12%) p = 0.112 Stroke: NLR > 6: 9/91 patients (10%) NLR ≤ 6: 3/93 patients (3%) p = 0.06 Extremity emboli: NLR > 6: 0/91 patients (0%) NLR ≤ 6: 1/93 patients (1%) p = 0.505 Hospital-related infection: NLR > 6: 23/91 patients (25%) NLR ≤ 6: 13/93 patients (14%) p = 0.041		In-hospital mortality NLR > 6: 28/91 patients (30%) NLR ≤ 6 10/93 patients (10%) p = 0.001	In-hospital cardiovascular mortality: uOR 1.182 per unit NLR (95% CI 1.077-1.298), p < 0.001 aOR 1.147 per unit NLR (95% CI 1.030-1.276), p = 0.012	In-hospital cardiovascular mortality cut-off: NLR > 6.5 Sensitivity 71% Sensibility 63%	AUC: 0.71 (95% CI 0.631-0.789), p < 0.001 Mortality, continuous: WBC, Operation duration, NLR

aOR: Adjusted odds ratio

COPD: Chronic obstructive pulmonary disease
uOR: unadjusted odds ratio
WCC: White cell count

Vascular surgery

Two studies included patients undergoing surgery for aortic aneurysms (n = 782)[18,20]. A high preoperative NLR was shown to be a predictor of postoperative short- and long-term mortality[18,20] and postoperative morbidity[20], table 3. Morbidity was defined according to the Clavien-Dindo classification ≥ 3[20].

In patients who underwent elective carotid endarterectomy[19] or embolectomy for acute limb ischemia[23], a high pre-operative NLR (NLR ≥ 5[19] and NLR ≥ 5.2[23]) predicted postoperative cognitive dysfunction[19] and poor limb survival[23], table 3.

NLR was an independent predictor of myocardial infarction, stroke and death, in patients with critical limb ischemia, who underwent major amputation[33], table 3.

In patients who underwent lower limb revascularization, no association was shown between preoperative NLR and postoperative graft patency in the multivariate analysis[22].

Table 3:

Vascular surgery						
Author	**NLR and Morbidity**		**NLR and Mortality**		**ROC**	**Variables in the adjusted analysis**
	Categorical	**Continuous**	**Categorical**	**Continuous**		
Appleton ND et al (2014)[18]			30 days mortality: NLR > 5: 12/ 52 patients (23%)NLR < 5 20/298 patients (6.7%), uOR 4.17 (95% CI 1.90-9.18), p = 0.0007 1-year mortality NLR < 5: 102/298 patients (34.3%) NLR > 5: 26/52 patients (50%), uOR 1.92 (1.06-3.48), p = 0.043	Deceased within 30 days: NLR = 4.2 (2.6-7.5) Survived: NLR = 2.8 (2.1-3.8), p = 0.0001 Deceased within 1 year: NLR = 3.2 (2.5-4.6) Survived: NLR = 2.6 (2.0-3.6), p = 0.00004 median (q1-q3)		
Halazun H et al (2014) [19]	Cognetive dysfunction: NLR<5: 46/360 patients (12.8%) NLR ≥ 5: 25/72 patients (34.7%) p < 0.001 Risk of cognetive dysfunction: NLR ≥ 5: aOR 3.38 (95% CI 1.81-6.27), p < 0.001	"Cognetive dysfunction: NLR = 4.5 ± 4.0 No cognitive dysfunction: NLR 3.2 ± 2.6 p < 0.001 "				Morbidity, categorical: sex, education, statin use, diabetes mellitus
Kordzadeh A et al (2015)[20]	"30-days morbidity (Clavien-Dindo ≥ 3): NLR < 5: 6/25 patients (24%) NLR > 5: 35/55 patients (63.6%) uOR = 5.54 (95% CI 1.9-10.15), p = 0.02 aOR = 4.28 (95% CI 1.27-14.42), p = 0.02 "		"30-days mortality: NLR < 5: 2/25 patients (8%) NLR > 5: 9/55 patients (16.4%) uOR 2.25; 95%, CI 0.45-11.28, p = 0.32 "			Morbidity, categorical: hypertension
Kullar P et al (2012)[22]		"Risk of graft patency: uOR 0.87 per unit NLR (0.74-1.03), p = 0.09 aOR 0.9 per unit NLR (0.75-1.08), p = 0.27"				Morbidity, continuous: postoperative NLR, smoking, vein graft, age

Tasoglu I et al (2014)[23]	"Amputation within 30 days: NLR ≥ 5.2: uOR 7.9 (95% CI 2.2-28), p = 0.001 aOR 10.2 (95% CI 2.3-44.7), p = 0.002 Amputation at follow-up (26 months): NLR ≥ 5.2: uOR 3.2 (95% CI 1.5-6.9), p = 0.001 aOR 3.1 (95% CI 1.2-7.7), p = 0.01 "	"Non-amputated: NLR = 6.1 ± 3.12 Amputated: NLR = 9.7 ± 3.95, p=0.04 Amputation within 30 days: uOR 1.1 per NLR unit ≥ 5.2 (95% CI 1.04-1.1), p = 0.001 aOR 1.1 per NLR unit ≥ 5.2 (95% CI 1.04-1.2), p = 0.002 Amputation at follow-up (26 months): uOR 1.1 per NLR unit ≥ 5.2 (95% CI 1.01-1.1), p = 0.008 aOR 1.06 per NLR unit ≥ 5.2 (95% CI 1.01-1.1), p = 0.01"	"30 days mortality: NLR < 5.2: 9/142 patients (6%) NLR ≥ 5.2: 14/103 patients (14%), uOR 2.32 (95% CI 0.96-5.60), p = 0.06 Mortality during follow-up (26 months): NLR < 5.2: 23/142 patients (16%) NLR ≥ 5.2: 26/103 patients (25%) uOR 1.75 (95% CI 0.93-3.28), p = 0.08"		"Amputation within 30 days cut-off: NLR ≥ 5.2 Sensitivity: 83% Specificity: 64% AUC: 0.8 (95% CI 0.71-0.87) Amputation at follow-up (26 months) cut-off: NLR ≥ 5.2 Sensitivity: 63% Specificity: 63% AUC: 0.7 (95% CI 0.58-0.79) "	Morbidity, categorical and continuous: COPD, diabetes mellitus, no arterial back bleeding
Wang Q et al (2017)[33]	Clinical complications (myocardial infarction, stroke, death): NLR ≥ 8.08 aOR 26.23 (95% CI 5.80-118.58), p < 0.001	"Clinical complications (myocardial infarction, stroke, death): NLR = 20.12 ± 16.29 No clinical complications: NLR = 6.30 ± 4.12, p < 0.001"	-	-	"Clinical complications cut-off: NLR ≥ 8.08 Sensitivity 93.5% Specificity 75.7% AUC 0.898"	Morbidity, categorical: gender, age, progress classification, smoking history, hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, cerebral apoplexy, PLR, MCV, RDW

aOR: Adjusted odds ratio
PLR: Platelet Lymphocyte Count
RDW: Red Cell Distribution Witdt
uOR: Unadjusted Odds Ratio

Non-cardiac non-vascular surgery

A study including 1,087 patients examined whether preoperative NLR predicted the risk of infection in patients undergoing total knee arthroplasty[24]. Non-infected patients had a significantly lower NLR than infected patients after surgery[24], table 4. A second study included 294 patients aged 60 years and over undergoing hip-fracture surgery[28]. NLR predicted both postoperative myocardial injury (NLR > 5.1)[28] and in-hospital mortality (NLR > 8.5)[28], table 4. A third study included 56 patients who underwent limb amputation as a result of diabetic foot ulcer[35] and a fourth study included 104 patients with hip fractures undergoing surgery[25]. NLR did not predict mortality after surgery[25,35].

A fifth study on 108 patients examined the risk of postoperative complications in patients with Crohn's disease who underwent abdominal surgery[36]. NLR predicted postoperative complications, a OR = 2.78 (1.04-7.43)[36], table 4. Another study on 82 patients examined the risk of postoperative complications within 30 days of major abdominal surgery[26]. There was no significant difference in preoperative NLR for patients with or without medical- or surgical complications[26], table 4.

A study examined NLR as a predictor of early penile prosthesis implant infection[34]. A preoperative NLR ≥ 6.2 was associated with postoperative infectious events[34], table 4.

Finally, a study included 60 patients who underwent elective surgery due to intestinal disease, expansive process of the central nervous system or degenerated hip disease[27]. Preoperative NLR did not predict the risk of postoperative sepsis within day 5 of surgery[27].

Table 4:

Non-cardiac non-vascular surgery						
Author	**NLR and Morbidity**		**NLR and Mortality**		**ROC**	**Variables in the adjusted analysis**
	Categorical	**Continuous**	**Categorical**	**Continuous**		
Gölge U et al (2016)[24]		"No infection NLR = 2.1 ± 0.7 Infection: NLR = 3.2 ± 0.7 p < 0.001"			Infection NLR cut-off: 2.45 Sensitivity 90% Specificity 72%	
Fisher A et al (2016)[28]	"Risk of troponin elevation Tertile 1 (NLR < 5.1): uOR 1 Tertile 2 (NLR 5.1-8.5): uOR 2.60 (95% CI 1.12-6.14), p = 0.014 Tertile 3 (NLR > 8.5): uOR 5.87 (95% CI 2.67-13.20), p = 0.000 Troponin elevation, NLR > 5.1 aOR 2.40 (95% CI 1.11-5.22), p = 0.026"	"No troponin elevation NLR = 7.12 ± 4.60 Troponin elevation: NLR = 13.18 ± 10.68 p = 0.0000 Risk of troponin elevation: uOR 1.136 per unit NLR (95% CI 1.088-1.185), p = 0.000 aOR 1.086 per unit NLR, (95% CI 1.032-1.142), p = 0.001"	"In-hospital mortality NLR > 8.5 aOR 16.63 (95% CI 1.70-163.09), p = 0.016 "	"Deceased in-hospital death: NLR = 18.35±7.88 Survived: NLR = 8.00 ± 6.37, p = 0.0000 uOR 1.097 per unit NLR (95% CI 1.044-1.152), p = 0.000 aOR 1.106 per unit NLR (95% CI 1.002-1.221) p = 0.045"	"In-hospital mortality NLR cut-off: NLR > 8.5 sensitivity 86.7%, specificity 38.5% AUC = 0.847, p = 0.000 Post-operative troponin elevationNLR cut-off: NLR > 5.1 Sensitivity 86.7% Specificity 38.5% AUC = 0.738, p = 0.000"	"Morbidity and mortality, continuous: Age, sex, presence of any fractures or HF, history of coronary artery disease, chronic kidney disease, hemoglobin, albumin, D-vitamin, PTH, smoking status and alcohol overuse Morbidity and mortality, categorical: Age, sex, dementia, AF "
Sedlár M et al (2015)[25]				"Deceased, NLR = 9.8 ± 8.4 Survived, NLR = 10.4 ± 6.3 p > 0.05"		
Forget P et al (2015)[26]		"No postoperative complications: NLR = 4.13 ± 4.43 With postoperative complications NLR = 3.89 ± 5.35 p > 0.05 Risk of complications uOR 0.97 per unit NLR (95% CI 0.87-1.08), p = 0.59"				
Alkhamis T et al (2014)[27]					"Postoperative sepsis NLR cut-off: NLR > 7.18 Sensitivity: 50% Specificity: 96.6% AUC = 0.664, (95% CI 0.530-0.781), p = 0.445"	
Bolat D et al (2017)[34]		"No postoperative complication (infection) NLR = 2.2 ± 1.4 Postoperative complication NLR = 7.2 ± 3.9, P < 0.001"			"Postoperative infection NLR cut-off: NLR ≥ 6.2 Sensitivity 67% Specificity 99% AUC 0.91 (95%, CI 0.83-0.98), p < 0.001"	

Metineren H et al (2017)[35]				"Deceased within 2 weeks: NLR = 8.65 (1.5-47.9) Survived: NLR = 7.15 (1.3-70), p = 0.369 Median(min-max)"		
Kang W-M et al (2017) [36]	"Risk of postoperative complications, NLR < 4.1: 9/53 patients (17.0%) NLR > 4.1: 21/55 patients (36.4%) uOR 3.02 (95% CI 1.23-7.43), p = 0.0161 "	"Postoperative complications, aOR 2.78 per NLR unit (95% CI 1.04-7.43), p = 0.041 "			"Postoperative complications NLR cut-off: NLR ≥ 4.1 Sensitivity 70% Specificity 56.4% AUC: 0.675 "	Morbidity, continuous: gender, age, smoking history, history of appendectomy, emergency operation, blood type, extraintestinal manifestations, perianal lesions, preoperative BMI, Onodera prognostic nutrition index, primary lesions, disease type, preoperative duration, preoperative neutrophil count, preoperative lymphocyte count, preoperative haemoglobin, preoperative albumin, preoperative enteral nutrition

Risk of bias within the studies

The methodological assessment is summarized in table 5.

In 23 out of 25 studies, risk of bias was scored to moderate. Two studies were scored to serious risk of bias, since there was no adjustment for confounding[18,24]. The populations examined were generally representative with patients of all ages in both genders. The quality of definitions according to diagnosis was specific in general. Objectives and cut-offs were in the majority of studies decided in advance and definitions of postoperative outcomes were clear. The studies differed in clinical diagnostic methods but followed clinical standards.

Table 5: Risk of bias within studies.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall risk of bias
Azab B et al (2013)[12]	Moderate	Low	Low	Non relevant	Low	Low	Moderate	Moderate
Gibson P et al (2007) [13]	Moderate	Low	Low	Non relevant	Moderate	Low	Moderate	Moderate
Gibson P et al (2010) [14]	Moderate	Moderate	Low	Non relevant	Moderate	Low	Moderate	Moderate
Tasoglu I et al (2013) [15]	Moderate	Low	Low	Non relevant	Low	Low	Low	Moderate
Kim W et al (2015)[16]	Moderate	Moderate	Low	Non relevant	Low	Low	Low	Moderate
Yost GL et al (2015) [17]	Moderate	Low	Low	Non relevant	Low	Moderate	Moderate	Moderate
Lafci G et al (2014)[21]	Moderate	Low	Moderate	Non relevant	Low	Low	Moderate	Moderate
Kalkan ME et al (2017)	Low	Moderate	Moderate	Non relevant	Low	Low	Moderate	Moderate
Sevuk U et al (2016)	Moderate	Moderate	Low	Non relevant	Low	Moderate	Moderate	Moderate
Saskın H MD et al (2015)	Low	Moderate	Low	Non relevant	Low	Low	Low	Moderate
Appleton ND et al (2014) [1]	Moderate	Low	Moderate	Non relevant	Moderate	Low	Serious	Serious
Halazun H et al (2014) [19]	Low	Low	Low	Non relevant	Moderate	Low	Low	Moderate
Kordzadeh A et al (2015) [20]	Moderate	Low	Moderate	Non relevant	Low	Low	Moderate	Moderate
Kullar P et al (2012) [22]	Moderate	Low	Low	Non relevant	Low	Moderate	Moderate	Moderate
Tasoglu I et al (2014) [23]	Moderate	Low	Low	Non relevant	Low	Moderate	Moderate	Moderate
Wang Q et al (2017)	Moderate	Moderate	Moderate	Non relevant	Low	Low	Moderate	Moderate
Gölge G et al (2016) [24]	Serious	Moderate	Moderate	Non relevant	Moderate	Moderate	Moderate	Serious

Sedlár M et al (2015) [25]	Moderate	Low	Low	Non relevant	Moderate	Low	Moderate	Moderate
Forget P et al (2015) [26]	Moderate	Moderate	Moderate	Non relevant	Moderate	Moderate	Moderate	Moderate
Alkhamis T et al (2014) [30]	Moderate	Low	Moderate	Non relevant	Moderate	Moderate	Moderate	Moderate
Fisher A et al (2016) [2]	Moderate	Moderate	Low	Non relevant	Moderate	Moderate	Moderate	Moderate
Aydınlı B et al (2016) [29]	Moderate	Low	Low	Non relevant	Low	Moderate	Low	Moderate
Bolat D et al (2017)	Moderate	Moderate	Moderate	Non relevant	Moderate	Moderate	Moderate	Moderate
Metineren H et al (2017)	Moderate	Moderate	Moderate	Non relevant	Moderate	Low	Moderate	Moderate
Kang W-M et al (2017)	Low	Low	Moderate	Non relevant	Moderate	Low	Low	Moderate

Discussion

A total of 25 clinical observational studies with 10,015 surgical patients were included. All but two studies in cardiac- and vascular surgery showed a significant association between preoperative NLR and postoperative mortality while 11out of 13 studies reported that high NLR predicted postoperative cardiovascular morbidity. In orthopaedic surgery, NLR predicted troponin elevation after hip surgery and postoperative infections after knee surgery, while no association was shown between preoperative NLR and postoperative complications in patients amputated due to diabetic foot ulcers. NLR predicted postoperative complications after prosthesis implantation[34] and bowel resection[36].
NLR did not predict the risk of postoperative complications after abdominal and miscellaneous non-cardiac surgery.

NLR reflects a systemic inflammatory state[24]. This association between the inflammatory response and the clinical outcome after surgery is complex. In studies investigating NLR in relation to cancer surgery, it has been reported that neutrophils secrete factors favourable for growth of malignant solid tumours e.g. tumour growth promoting factors[6,41,42]. However, the pathophysiological link between preoperative NLR and clinical outcomes after benign surgery is unclear. Neutrophils release inflammatory mediators, proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals that may promote rupture of coronary plaques and cause further tissue injury[13]. NLR could reflect an imbalance in the acute immunological response. The antibacterial response of natural killer cells and activated T-cells may be supressed by an increased number of neutrophils[47]. The high NLR may then reflect an increased neutrophil-dependent inflammatory response and a decreased lymphocyte-mediated antibacterial immune response[47]. This may weaken the lymphocyte-mediated antibacterial immune response contributing to an increased bacterial invasion and growth[47]. Moreover, a low lymphocyte count indicates a state of immunosuppression and physiological stress that have adverse effects on the overall clinical outcome after surgery[20].

A clinical study with 211 patients[43] showed that relative lymphopenia is significantly associated with survival of patients with known or suspected stable coronary artery disease. A low relative lymphocyte count may reflect the cortisol-induced stress response[43]. Therefore, the relative lymphocyte count could be a marker of the systemic stress induced by the adrenal axis[43]. Furthermore, a study including 309 patients diagnosed with acute heart failure[49] showed, that a low absolute lymphocyte count was associated with greater in-hospital mortality[49] and that a low absolute lymphocyte count was an independent predictor of all-cause mortality[49].

The prognostic value of NLR has been compared with other inflammatory biomarkers. In prosthetic joint surgery, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were used to predict prosthetic joint infections. A study including 1087 patients[49] concluded that NLR together with C-reactive protein (CRP)and ESR would increase the accuracy of the diagnosis and prediction of prosthetic joint infection after total knee arthroplasty[49].

WBC count is included in scoring systems of systemic inflammatory response syndrome[50]. Like WBC, NLR has been shown to predict the risk of sepsis in critically ill patients[50]. A study including 3,227 patients with acute myocardial infarction reported that WBC count was an independent predictor of death or myocardial infarction within 7 years[51]. The best predictive values in the study were a high neutrophil count or a low lymphocyte count resulting in a high NLR[51].

Moreover, the NLR was shown to be a better predictor of bacteraemia than the currently used inflammatory markers (CRP, WBC and ESR), which had a poor prognostic value compared with the NLR[51]. These results were confirmed in a clinical study including 395 patients[52] diagnosed with community acquired pneumonia. NLR had a higher prognostic accuracy compared with neutrophil count, WBC count, lymphocyte count and CRP[52].

Additionally, a study[53] including 92 patients with suspected community-acquired bacteraemia showed NLR to be a superior predictor of bacteraemia compared to CRP, WBC and ESR[53]. Hence, NLR is an easy available and inexpensive method whose predictive value has great potential.

Strengths and limitations

The systematic review was performed according to the PRISMA guidelines. The systematic literature search was performed in four major medical databases. Registration on PROSPERO secured transparency of the study. We excluded studies on patients undergoing transplantation due to the potential confounding of immunosuppressive medicine. The studies reported a variety of predictive NLR cut-off values. In heart surgery, the predictive NLR cut-off value was around 3, while the cut-off value in vascular surgery was around 4.5. In a majority of studies, NLR > 5 was considered to be predictive of clinical outcomes after cancer- surgery[54,55]. The predictive NLR cut-off value seems to depend on the population and type of surgery. With regard to non-cardiac non-vascular surgery, further studies are needed to come closer to a NLR cut-off. Even though a larger number of studies were included in the systematic review a meta analysis was not performed due to heterogeneous clinical outcomes and a heterogeneous reporting of short- and long-term postopera-

tive mortality. The studies in non-cardiac non-vascular surgery were minor studies. The non-significant findings could be due to a lack of power. Therefore, to corroborate or invalidate NLR as a prognostic biomarker in patients undergoing non-cardiac non-vascular surgery further studies with larger populations are needed.

Conclusion

NLR predicted short-term mortality after cardiac- and vascular surgery. In 11 out of 13 studies, a high NLR predicted postoperative cardiovascular morbidity. In orthopaedic surgery, a high NLR predicted postoperative myocardial injury and mortality after hip surgery and postoperative infections after knee surgery. In general surgery, NLR predicted postoperative complications in patients with Crohn's disease undergoing bowel resection and postoperative infectious complications. NLR has potential as a prognostic biomarker in patients undergoing benign surgery, however, the prognostic impact of NLR should be further explored in patients undergoing non-cardiac non-vascular surgery.

Conflict of interest: none

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