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Neutrophil-to-lymphocyte ratio as a diagnostic and prognostic biomarker in pulmonary hypertension: A systematic review

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Abstract. *Background and aim:* The objective of this systematic review is to provide an overview of research that examined the relationship between pulmonary hypertension (PH) and the neutrophil-to-lymphocyte ratio (NLR). *Methods:* To identify the studies related to NLR, a search was done on PubMed, Scopus, and Web of Science with an end date of March 30th, 2023. A total of 25 studies were included in the review. These studies included a variety of pathologies that contribute to PH. We employed the Newcastle-Ottawa Scale to assess the quality of studies. For all studies, a significance level of $P<0.05$ was used. *Results:* In patients with sarcoidosis, chronic obstructive pulmonary disease, systemic sclerosis, chronic kidney disease, and congenital heart disease, NLR appears to be an independent predictor of PH. Also, it was frequently linked to the result, complications, and severity of the disease in PH patients. *Conclusions*: NLR may be utilized as a repeatable, inexpensive, and trustworthy proxy for the onset and severity of PH.

Key words: pulmonary hypertension, neutrophil-to-lymphocyte ratio, biomarkers, prognosis, diagnostic techniques

Introduction

Pulmonary hypertension (PH) has an abnormally high 5-year mortality rate (50%) and is an uncommon, crippling, and presumably incurable illness (1-3). The disease has classically been characterized as an increased mean pulmonary arterial pressure (MPAP) (>25 mmHg at rest), as determined by right heart catheterization (RHC) (4), while recent research suggests that the lower threshold for diagnosis should be dropped to 20 mmHg (5). The condition is marked by alterations in distal pulmonary arteries with hypertrophy of the pulmonary vascular wall, which increases pulmonary vascular resistance and elevates right heart pressure. These sequelae contribute to right ventricular (RV) dilatation and fibrosis, and eventually to decompensated right heart failure and death (6, 7). Using animal models of the disease has provided persuasive evidence for the significance of inflammation in PH development (8). Furthermore, clinical studies have shown that inflammatory biomarkers are higher in PH patients and can be used to predict overall prognosis (9). Biomarkers are

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considered critical, and they may be a useful noninvasive tool in clinical practice for improved diagnosis and management as well as precise risk assessment (9). The neutrophil-to-lymphocyte ratio (NLR) has been investigated in several fields, including cardiology, neurology, infectious diseases, and oncology (10). Researchers have recently become more interested in the involvement of NLR in PH as a predictive tool. In disorders like sarcoidosis, chronic obstructive pulmonary disease (COPD), systemic sclerosis (SSc), chronic kidney disease (CKD), and congenital heart disease (CHD), NLR has been shown to predict the development of PH reliably. Furthermore, various studies have suggested that this marker could predict outcomes for PH patients (11-35). The involvement of NLR in PH is the focus of this systematic review. The results of this study could have important clinical implications in predicting PH in patients with certain underlying diseases and determining prognosis in PH patients.

Methods

This research is a systematic review and meta-analysis and adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines.

Search strategy and study selection

We used the PubMed, Scopus, and Web of Science databases to find studies on the relationship between NLR and PH. The search method is provided in (Table S1). The search extended to a cut-off of March 30th, 2023.

Duplicate publications, experimental studies, commentaries, letters, reviews, case reports, and studies in which the connection of NLR and PH was not assessed were all excluded. We did not set any limitations on publication years or languages.

Data extraction and quality assessment

We used the Newcastle-Ottawa Scale (NOS) to rate the caliber of the studies (36). The following information was extracted: first author, publication year, PH etiology, PH diagnosis technique, and measured endpoints. In addition, we gathered information on the NLR value, such as the correlation coefficient, mean, standard deviation (SD), odds ratio (OR), or hazard ratio (HR). When there were enough articles (three or more), we used the meta-analysis to pool and quantify data; otherwise, we merely assessed the articles qualitatively.

Results

Search and selection of literature

Figure S1 depicts the process that was employed to find and select papers in this systematic review. After eliminating duplicate articles and reviewing the remaining articles, a total of 25 studies were included in the review.

Characteristics of the studies that were included

There were 25 studies in total, 22 of which were in English, 2 in Chinese, and 1 in Turkish. Table 1 lists the features of studies included in the review. Four studies were on the relationship between NLR and PH in acute exacerbation of COPD (AECOPD patients) (15, 33-35). Two focused on the involvement of NLR in sarcoidosis-associated PH (21, 23). Five examined the involvement of NLR in SSc-associated PH (13, 26-28, 30). Four studied the relationship between NLR and chronic thromboembolic pulmonary hypertension (CTEPH) (11, 14, 20, 29). One study examined the relationship between NLR and CKD-associated PH (32). Finally, three focused on the NLR value in congenital heart defect-associated pulmonary arterial hypertension (CHD-PAH) (17, 19, 31). In addition, six studies included data of patients with different PTH etiologies in the single analysis; We could not include these studies in the categories mentioned previously and reviewed them separately (12, 16, 18, 22, 24, 25). Table 1 shows the quality of included studies assessed using NOS.

NLR and PAH risk in AECOPD

COPD is characterized by a partially reversible restriction in airflow and is a systemic chronic inflammatory illness that also affects the airways. It is a significant public health hazard and a strain on the world's healthcare system (1). A prolonged (>48 h) worsening of a patient's clinical respiratory status that calls for additional medication or hospitalization is known as an acute exacerbation of COPD (AECOPD) (4, 5). With a poor median lifespan of

Table 1. Quality assessment based on NOS questionnaire

	Definition of cases	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	NOS score	PH diagnostic criteria
Feng (15)	+	+	+	+	− +	−	+	+	7	according to ESC 2015 guideline (37); MPAP ≥ 25 mmHg
Yong (35)	+	+	+	+	− −	−	+	+	6	Not exactly mentioned in the study. (abstract)
Yun (34)	+	+	+	+	+ +	−	+	+	8	Not exactly mentioned in the study. (abstract)
Zuo (33)	−	+	+	+	+ +	−	+	+	7	according to ESC/ERS 2015 guideline.
Mirsaeidi (23)	+	+	+	+	− −	−	+	+	6	PASP > 25 mmHg
Korkmaz (21)	−	+	+	+	− −	−	+	+	5	PASP > 25 mmHg
Esheba (13)	−	+	+	+	− +	−	+	+	6	Not exactly mentioned in the study.
Senturk (27)	+	+	+	+	+ +	−	+	+	8	MPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, PVR > 3Wood units (ESC/ERS 2015 guideline)
Sakr (26)	−	+	+	+	− +	−	+	+	6	Not exactly mentioned in the study.
Tezcan (28)	+	+	+	+	+ +	−	+	+	8	PCWP < 15 mm Hg and MPAP > 25 mm Hg in RHC (ESC/ERS 2015 guideline) after measuring systolic PAP ≥ 40 mm Hg on Doppler echocardiography.
Yayla (30)	+	+	+	+	+	−	+	+	7	MPAP > 25 mmHg and PCWP < 15 mmHg on RHC (ESC/ERS 2015 guideline).
Yanartas (29)	+	+	+	+	+	−	+	+	8	MPAP > 25 mmHg on RHC (ESC/ERS 2015 guideline).

Table 1 (*Continued*)

	Definition of cases	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	NOS score	PH diagnostic criteria
Fallah (14)	+	+	+	+	− +	−	+	+	7	MPAP > 25 mmHg and PCWP < 15 mmHg on RHC (ESC/ERS 2015 guideline).
Ataam (11)	+	+	+	+	− −	−	+	+	6	MPAP ≥25 mm Hg.
Kivrak(20)	−	+	+	+	− +	−	+	+	6	Not exactly mentioned in the study.
Zhang (32)	−	+	+	+	− −	−	+	+	5	PASP ≥35 mmHg on echocardiography
Gursoy(17)	−	+	+	+	− +	−	+	+	6	Not exactly mentioned in the study.
Herlambang (19)	−	+	+	+	− +	−	+	+	6	PASP >35 mmHg and estimated TR pressure > 20 mmHg
Yin (31)	+	+	+	+	− −	−	+	+	6	PASP > 40 mmHg on echocardiography
Yildiz (12)	+	+		+	+ +	−	+	+	7	MPAP > 25 mmHg and PCWP < 15 mmHg on RHC (ESC/ERS 2015 guideline).
Ozpelit (24)	+	+	+	+	+ +	−	+	+	8	MPAP > 25 mmHg and PCWP < 15, PVR > 3Wood units mmHg on RHC (ESC/ERS 2015 guideline).
Foris (16)	+	+	−	+	− −	−	+	+	5	Not exactly mentioned in the study. (abstract)
Harbaum (18)	+	+	+	+	+ +	−	+	+	8	MPAP > 25 mmHg and PCWP < 15, PVR > 3Wood units mmHg on RHC. (ESC/ERS 2015 guideline)
MacKenzie (22)	−	+	+	+	− −	−	+	+	5	Not exactly mentioned in the study. (abstract)
Pooder (25)	+	+	+	+	− −	−	+	+	6	Not exactly mentioned in the study. (abstract)

Abbreviations: ESC/ERS: European Society of Cardiology and European Respiratory Society; MPAP: mean pulmonary arterial pressure; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RHC: right heart catheterization; TR: tricuspid regurgitation; TRV: tricuspid regurgitation velocity.

only two to five years after diagnosis, PH is a significant AECOPD consequence. After searching through large databases, four studies looking at the connection between NLR and the emergence of PH in AECOPD patients were found (15, 33-35). In research conducted by Feng et al. (15), patients with AECOPD were divided into low, middle, and high-risk groups, according to the current ESC/ERS 2015 criteria (38, 39). The median (IQR) of NLR was 3.22 (2.21-6.42) in the low-risk group and 3.86 (2.60-7.94) in the intermediate-high-risk group. Between the two groups, NLR did not differ (p=0.070). They claimed that there was no connection between NLR and the risk of PH. In another study, Yong et al. (35) analyzed clinical data from 200 patients to investigate the utility of NLR in predicting clinical outcomes in COPD-associated PH. NLR was significantly higher in deceased patients than in the survivors (p= 0.001). The optimum cutoff value of NLR for mortality prediction was 4.7, with a sensitivity of 74.2%, specificity of 72%, and area under the curve (AUC) of 0.720 (p< 0.01). The Kaplan-Meier survival curve revealed that those with greater NLR levels had a worse prognosis than those with lower NLR levels (HR=1.031, % CI=1.012-1.051, p=0.01). However, the multivariate Cox regression analysis found no evidence of its importance in predicting long-term death. In the other study, Yun et al. (34) examined 66 patients with AECOPD and classified them into two groups based on RHC findings: normal MPAP and PH. Median and IQR values for NLR in the PH group were lower than in the patients with normal PAP (14 p<0.05) However, multivariate analysis revealed no significant relationship. Moreover, Zuo et al. (33) conducted a retrospective research with 185 patients diagnosed with AECOPD. Based on echocardiographic evidence, 101 patients were diagnosed with PH. In comparison to AECOPD patients without PH, those with PH exhibited a significantly higher median NLR value (6.52 versus 4.08, p=0.001). A higher NLR in AECOPD patients was found to be an independent predictor of PH development. However, there was no significant relationship between NLR and PH severity (mild PH:36 ≤PASP≤50 mmHg; moderate PH: 51 ≤PASP≤70 mmHg; severe PH: PASP > 70 mmHg). The median (IQR) NLR was 6.07 (4.86-11.25) in the mild group, 6.29 (5.05-10.62) in the moderate group, and 7.73 (4.80-17.73) in the severe group (p= 0.372). Furthermore, there was no correlation between NLR and estimated PH (r=0.087, p=0.389). These results suggest that in patients with AECOPD, the NLR may act as a standalone predictor of PH. Also, it was linked to the severity of PH in these individuals and appears to predict death in patients with.To fully comprehend the connection between NLR and PH associated with AECOPD, additional research is required.

NLR and risk of PH in sarcoidosis

Sarcoidosis is an inflammatory disorder with an unknown etiology that forms granulomas in affected organs, primarily the lungs. Patients are at risk for pulmonary fibrosis and permanent organ damage. As PH is a significant risk factor for poor prognosis, these patients are given higher priority for orthotopic lung transplantation. Increased PAP in these patients can be caused by comorbidities, including cardiac sarcoidosis and sleep apnea, and a variety of other causes such as mechanical, vasculogenic, and parenchymal factors. The effects of NLR in sarcoidosis-associated PH were investigated in two trials (21, 23). Mirsaeidi et al. (23) hypothesis was that sarcoidosis patients with PH would have greater levels of systemic inflammation than those without PH and that this test would be helpful in primary care. They studied 107 individuals who had been diagnosed with sarcoidosis and found that 28 of them (26%) had PH confirmed by Echocardiography. They found that the rate of NLR > 3.5 was significantly higher in sarcoidosis patients with PH (50% vs. 24%, p=0.016). The cutoff value for NLR was found to be 3.5, which produced a sensitivity of 50%, specificity of 78%, PPV of 41.9%, NPV of 81.4%, and an AUC of 0.619 for separating sarcoidosis patients with PH from those without PE. NLR >3.5 was independently related to PH in the multivariate model (OR 3.254, 95% CI 1.094–9.678, p=0.034). Korkmaz et al. (21) reported that there was no significant relation between NLR and PH diagnosed by transthoracic echocardiography in patients with sarcoidosis. The disparity in results between these two studies could be attributable to differences in their PH diagnosing methods. Although echocardiography is a valuable method for assessing PH, RHC remains the gold standard for diagnosing the illness.

NLR and PH in SSc

SSc is a debilitating and chronic disease characterized by a wide range of symptoms, particularly

in collagen-dominated tissues such as the blood vessels, skin, and several internal organs. PAH, which is commonly detected by ECHO and confirmed during RHC, occurs at an 8–12% rate in SSc patients. It has been reported to be an independent indicator of mortality in these patients. Five studies investigated the involvement of NLR in SSc-associated PAH (13, 26-28, 30). Esheba et al. (13), studied 25 patients with SSc. According to echocardiographic data, three patients (12%) developed PH. In SSc patients with PH diagnosed by echocardiography, the NLR was significantly higher than in those without PH (3.9±0.56 vs. 2.15±0.42, p<0.001). Senturk et al. (27) published a study that included 107 patients with SSc. Based on RHC, 26 patients had a confirmed diagnosis of pre-capillary PH. Although NLR was higher in sarcoidosis patients with PAH (4.28 ± 3.21) than in those without PAH (3.29 ± 1.94). The difference was not statistically significant (p=0.147). In a study by Sakr et al.(26) consisting of 35 patients with SSc, of which 6 (17.1%) developed PH, SSc patients with PH had no differences in NLR levels than those without PH (median NLR: 2.4 and 2.3, respectively). A study by Tezcan et al. (28) assessed 129 patients with SSc, 17 of whom had PH verified by RHC. It was reported that NLR was significantly higher in the PH group than in the non-PH group (2.10±0.63 and 3.38±3.78, p < 0.001). The cut-off value for predicting PH in SSc patients was determined to be an NLR of 2.209 with an AUC of 0.703, a sensitivity of 76.5%, and a specificity of 54.5%. NLR was associated with the development of PH (OR=3.75, 95% CI=1.15-12.21, p=0.028). Yayla et al. (30) conducted a similar study but had different results. They gathered 69 SSc cases, and RHC revealed that 5 (7.4%) of the patients had PH. They found that the NLR values were comparable between SSc patients with PH and without (3.16±6.44 and 2.39±7.82 respectively, p=0.165). Our meta-analysis of the pooled data revealed that patients with PH had a trend toward greater levels of NLR than those without (Standardized mean difference (SMD)= 1.395, 95% CI =0.250-2.540). However, because the studies by Esheba et al. (13) and Sakr et al. (26) did not give mean± SD NLR values, they were excluded from the meta-analysis. Based on the findings of the studies stated above, we infer a strong association between NLR level and the development of PH in patients with SSc.

NLR and chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a significant chronic form of PH believed to be induced by vascular remodeling and fibrotic deposition after a pulmonary embolism (PE). As a result, a cascade of events involving inflammation and healing follows, resulting in an increase in PAP and RV failure. In observational studies, the prevalence of CTEPH has been reported to be as high as 9.1% and as low as 0.5%. Even though pulmonary endarterectomy improves survival by removing the luminal blockage, surgery is commonly linked to perioperative hemodynamic instability and death, primarily due to severe systemic vasodilation. Four publications have been published about the link between NLR and CTEPH (11, 14, 20, 29). In 2015, Yanartas et al. (29) investigated the function of NLR in predicting surgical mortality in CTEPH patients. In univariate analysis, patients in the deceased group had substantially greater NLR upon admission (6.1 ± 3.9 vs. 2.6 ± 1.3, p<0.001). According to multivariate logistic regression analysis (HR= 2.767; % CI: 1.432–5.347; p = 0.002), patients with a higher NLR at admission had a significantly higher death rate. NLR at admission predicts mortality with a sensitivity of 86%, specificity of 40%, and AUC of 0.825 with a 95% CI of 0.713-0.938 in ROC analysis using a cut-off value of 2.54. Moreover, a significant connection (r = 0.214, p = 0.027) between preoperative pulmonary vascular resistance and NLR was discovered. Fallah et al. (14) conducted a prospective study among acute PE survivors who had been treated with anticoagulants for at least three months. CTEPH was identified in 25 of the 290 PE patients (8.6%). They found no difference in median NLR between PE patients with CTEPH and those without CTEPH (2.46 and 2.78, respectively, p=0.39). Ataam et al. (11) used the national CTEPH registry in France to analyze 159 patients with CTEPH from 2009 to 2013 (derivation cohort) and 238 patients from 2015 to 2016 (validation cohort) in a study published in 2020. In the derivation cohort, NLR was unable to predict poor outcomes in CTEPH patients (early mortality, heart-lung transplant, or need for extracorporeal membrane oxygenation or prolonged inotropic/catecholamine support) (OR=1.26, 95% CI=0.81-1.96, p=0.31). However, we could not access the validation cohort results. CTEPH develops not only from vascular remodeling after a PE

but also as a result of vascular diseases, such as atherosclerosis. Accordingly, in 2017, Kivrak et al. (20) studied the link between NLR and pulmonary artery atherosclerosis in CTEPH patients. In their investigation, 56 patients with CTEPH were enrolled. The resected chronic thromboembolic material was subjected to a pathologic study for the presence of atherosclerosis. They observed that the NLR levels of atherosclerotic and non-atherosclerotic patients were similar (5.8 ± 3.8 and 6.6 ± 3.5, respectively, p= 0.97). Taken together, the NLR appears to be linked to both CTEPH severity and mortality. Based on the findings of the studies stated above, we may infer a strong link between chronic systemic inflammation and the development of CTEPH.

NLR and PH in patients with CKD

PH is common in CKD patients and might hurt their prognosis. Patients on continuous ambulatory peritoneal dialysis have a 12–36% chance of developing PH, while those on maintenance hemodialysis have a 35–38% chance of developing PH. For patients on maintenance hemodialysis, PH is well-proven as an independent risk factor for mortality. One study investigated the link between NLR and CKD-associated PH (32). Zhang et al. (32) published a retrospective cohort research that included 1092 pre-dialytic CKD patients. Based on echocardiographic results, 174 (15.93%) of them were diagnosed with PH. The NLR value in the PH group was significantly higher than that of the non-PH group (median (IQR) of 3.0 (2.1, 4.3) and 2.4 (1.7, 3.4), respectively, p= 0.001). In univariate logistic regression, NLR was found to increase the risk of PH in CKD patients (OR=1.08, % CI=1.02–1.15, p=0.008). However, in multivariate analysis, NLR data was not reported. Inflammatory mechanisms are thought to have a role in the etiopathogenesis of CKD-associated PH. However, there is little evidence in the literature about the role of NLR in this setting. As a result, we believe that large-scale, prospective investigations are required.

NLR and CHD-associated PH

The term "CHD-PAH" refers to the increase in PAP brought on by CHD with a shunt from the systemic circulation to the pulmonary circulation. We discovered three papers evaluating the NLR value in CHD-PAH after searching databases (17, 19, 31). Gursoy et al. (17) found that NLR was independently associated with peak and mean PAP (p< 0.01) in 201 individuals (mean age of 18.28± 16.84) with CHD-PAH. However, NLR was not associated with intubation time or ICU stay. NLR was also higher in patients that presented with PH crisis (p=0.047) and those who were deceased compared to those who did not (p=0.03). Herlambang et al. (19) performed a cross-sectional investigation on 30 children with cyanotic CHD, ranging in age from 1 month to 18 years. According to echocardiographic findings, 17 of them (56.6%) developed PAH. PAH patients had significantly higher NLR levels than non-PAH patients (3.56±1.07 vs. 2.04±0.34; p< 0.001). The NLR cut-off point was 2.355, with an AUC of 0.901, 84.2% sensitivity, and 84.6% specificity. Yin et al. (31) set out to investigate the association between the NLR and early clinical outcomes in children with CHD-PAH who underwent heart surgery. A retrospective observational study involving 190 children with CHD-PAH was conducted. They found that higher pre-operative NLR was linked to elevated levels of glutamic oxaloacetic transaminase (AST), total serum bilirubin, creatinine, and uric acid (p<0.05). In contrast, postoperative NLR was linked to glutamic pyruvic transaminase (ALT), AST, and blood urea nitrogen (BUN) (P<0.05). Furthermore, pre-operative NLR levels were significantly associated with a total length of stay, mechanical ventilation duration, and ICU length of stay (p< 0.05), whereas postoperative NLR levels were only significantly correlated with the former two variables (all p< 0.05). The ROC analysis revealed that AUC for predicting prolonged mechanical ventilation duration beyond 24 h, 48 h, and 72 h by NLR was statistically significant (p<0.05). We conclude that NLR may help predict the development of PAH in CHD patients based on the results of the aforementioned trials. The outcomes of CHD-PAH patients, including PH crises, time spent on mechanical ventilation, duration of stay in the ICU, the overall length of stay, and mortality, also appear to be predicted by NLR.

Additional research

Six studies included the data of patients with PH with different etiologies in the single analysis; so we could not include them in the categories mentioned before. Here we reviewed these six studies

(12, 16, 18, 22, 24, 25). Yildiz et al. (12) initiated the first major analyses and discussions of NLR in PH. They compared a study group of 25 PAH patients (who had their diagnosis verified by RHC) to a control group of 25 healthy volunteers. Idiopathic etiologies were found in 14 cases, while CHD was found in 11 others. When compared to healthy controls, NLR was significantly higher in PAH patients (2.44±1.06 vs. 1.55±0.38, p<0.05). They also used the Spearman test to analyze the relation between PAP and NLR and found that AP was linked with NLR (r=0.414, p=0.004). Ozpelit et al.(24) conducted prospective research in 101 adults PAH patients, measuring NLR during initial diagnostic RHC. The etiologies of PAH were not mentioned in their study. For 36.8± 23.6 months, the patients were followed up. They were then divided into three tertiles based on NLR: Tertile 1 had 33 cases with NLR≤ 2.2, Tertile 2 had 34 cases with NLR 2.3–3.5, and Tertile 3 had 34 cases with NLR≥3.6. As the NLR tertile increased, the prevalence of pericardial effusion increased (P<0.001) and the patients' New York Heart Association functional class (NYHA FC) increased significantly(p=0.001). Among the RV echocardiographic findings, only the tricuspid plane annular systolic excursion (TAPSE) differed significantly among the tertiles, with TAPSE decreasing with increasing NLR tertile (p = 0.002). The three NLR tertiles had similar RHC measures, such as systolic PAP, MPAP, pulmonary vascular resistance, and cardiac index. Brain natriuretic peptide (BNP) was significantly higher (p =0.001), and hemoglobin was significantly lower (p=0.027) with increasing NLR tertile. The level of C-reactive protein (CRP) also increased significantly as the NLR tertile increased (p=0.019). Spearman's rank correlation coefficient analysis showed a significant correlation between CRP and NLR (r = 0.702, p=0.001). During the study period, 32 people died. When patients were divided into two groups based on the occurrence of death, those who died had a significantly higher median NLR value than survivors (3.9 versus 2.7, respectively; p= 0.003). However, a multivariate Cox logistic regression analysis revealed that NLR was not an independent predictor of death (hazard ratio (HR)=0.639, 95 percent confidence interval (CI) = 0.379-1.075). Baseline NLR was significantly linked with NYHA FC (r=0.421, P<0.001), BNP (r=0.362, p=0.001), and TAPSE (r=0.275, p= 0.007), according to Spearman's rank correlation coefficient analysis. However, the baseline NLR was not associated with echocardiographic measures (other than TAPSE), or a 6-min walking distance (6MWD). Foris et al. (16) conducted a retrospective study and recruited 83 patients with newly diagnosed PAH and 71 patients had normal PAP as confirmed by RHC. They discovered that the NLR in the PAH group was modestly but significantly higher than that in the control group (3.8 ± 2.5 vs. 3.3 ± 2.7 p<0.008). An NLR ≥2.62 cut-off had a sensitivity of 69% and a specificity of 56% in identifying PAH patients, and it was linked to a poor overall 5-year survival in PAH patients (47% vs. 69%, p=0.038). Harbaum et al.(18) evaluated 77 patients who had PAH confirmed by RHC. In their study, the etiology of PAH was idiopathic in 54 patients (70%), congenital in two patients (3%), drug-induced in one patient (1%), and associated PAH (APAH) in 20 patients (26%). Connective tissue disease was the cause of APAH in 12 of the 20 APAH patients (60%), while Porto-pulmonary hypertension was found in 2 individuals (10%), and congenital heart disease was found in 3 patients (15%). In one patient, the diagnosis of idiopathic PAH at the time of RHC was later changed to HIV-associated PAH. They discovered that a higher NLR was related to a more severe World Health Organization FC and a shorter 6-MWD, as well as elevated right atrial pressure and a high BNP level. Two patients were referred to lung transplantation, and 23 patients died during a median follow-up time of 31 months (range 16-56). Patients who died or were referred for lung transplantation had a greater NLR. Elevated NLR was linked with shorter transplantation-free survival (HR=1.05, 95 % CI=1.01–1.08, p=0.006), independent of C-reactive protein (CRP) and hemodynamic parameters in Cox proportional hazards analysis. With a sensitivity of 40% and specificity of 71%, the NLR threshold calculated from ROC analysis was 4.14. This cut-off was also related to patients' functional and hemodynamic deterioration. MacKenzie (22) conducted a study to investigate the prevalence of metabolic dysfunction and its risk factors in PAH patients. Patients with higher C-peptide, which is used to assess insulin resistance and metabolic dysfunction, had higher NLR (p=0.016) than those with lower C-peptide. Finally, Pooder et al. (25) enrolled 200 patients with a diagnosis of PAH based on RHC in a study published in 2019. Their report made no mention of the etiology of PH in their study population. They found a link between a higher NLR and

the PH severity. Patients were separated into two groups based on the median NLR ratio. According to a Kaplan-Meier analysis of transplantation-free survival analysis, NLR was associated with shortened transplant-free survival. Based on findings from these studies, we hypothesize that NLR is linked to disease severity, complications, and outcome in PH patients.

Discussion

After literature review, our results indicated NLR can be considered as an independent predictor of PH in the patients with COPD (15, 33), CHD and its complication including PH crises, mechanical ventilation usage duration, ICU stay period, the overall length of stay in the hospital, and mortality (31), CTEPH severity and mortality, and systemic sclerosis development (11, 20, 29, 40). Also, some studies found a link between NLR and NYHA functional class, TAPSE, CRP level (24), 6-MWD, right atrial pressure, BNP level (18), C-peptide (22), lung transplantation-free survival, and 5-year survival (25) in PH patients with various etiologies. Generally, previous studies suggested a prediction potential for NLR in PH severity. However, the strength of the findings may be diminished by the small number of available studies. Inflammatory state is relatively common and related to worse clinical outcomes in many chronic diseases, notably in individuals who suffer from PH. The inflammatory status in PH can be attributable to various reasons, including an elevated level of pro-inflammatory cytokines, oxidative stress and acidosis, chronic and recurrent infections, and gut microbiota dysbiosis (41, 42). According to previous studies, inflammation plays a vital role in PH in the systemic arteries. Neutrophils are the major cell types of the innate immune system and the first barrier to protection against infection. Lymphocytes primarily participate in the adaptive immune response, serving both regulatory and protective functions during inflammation. The neutrophil count signifies inflammation, whereas the lymphocyte count denotes the condition of overall stress and nutrition. The response to various insults of pathogens usually shows an increase in neutrophils and a decrease in lymphocytes. Therefore, the NLR has been recommended as a consistent and extremely cost-effective indication for monitoring systemic inflammatory status, compared with other indicators of inflammation such as CRP, and interleukin-6 (26, 43).

The NLR has demonstrated the ability to predict mortality across diverse populations. In retrospective investigations including individuals with diverse cancers (breast, colorectal, esophageal, liver), the NLR effectively predicted survival outcomes in cases of melanoma, ovarian, pancreatic, and prostate cancers, as well as in individuals with lung illnesses such as chronic obstructive pulmonary disease (44, 45). Moreover, population-based studies indicated that an elevated NLR was an independent predictor of heart failure and cardiovascular mortality (46). The NLR was an independent predictor of right ventricular dysfunction in patients with inferior ST-segment elevation myocardial infarction. The findings indicate that an elevated NLR may signify a tendency towards right-ventricular dysfunction, particularly pertinent in PAH, where right-ventricular failure is the primary cause of mortality (26). Nevertheless, these concepts remain conjectural, necessitating additional research to examine the correlation between NLR and right ventricular function. NLR can be easily calculated from a normal blood test, which is accessible for a majority of patients, even those live in deprived areas, and can gives physicians helpful insights into PHT prognosis and progression. Our results are consistent with prior research, supporting the NLR's role as a predictor of disease severity and survival in PAH (20,33). However, there is still contracting evidence. In our review study, the study by Mirsaeidi (23) was conducted on USA population with EF>40 mmHg; while the study by Korkmaz (21) contained Turkey patients with higher stages of SSs (2,3, and 4). Different studies' population can give rise to conflicting results. The normal NLR values in a non-geriatric and otherwise healthy adult population range from 0.78 to 3.53. An NLR exceeding the normal upper limit (> 3.5) likely indicates a pathological condition characterized by heightened systemic inflammation and physiological stress. Additionally, age, gender, and ethnicity are recognized factors that affect the NLR. Genetic ancestry may elucidate these disparities, as previous studies indicating a higher NLR (> 3.5) predominantly involved Caucasians from Canada and Germany, while those with lower NLR values were derived from Turkey (44, 47, 48). Thus, variations in the reported NLR values for PAH patients may come from underlying patient characteristics. We should also notice that

various etiologies can cause various levels of PAH. For example, patients with sarcoidosis with persistent or unexplained dyspnea have higher prevalence of PH (> 50 %) (49). Similarly, patients with CHD might show higher percentage of PH, which can be due to a significant decrease in mean platelet volume values, which is attributable to PAH (50). Moreover, we reviewed 25 studies used RHC or echocardiography for PH diagnosis. Although RHC is the definite diagnostic tool for PH, echocardiography is a non-invasive imaging technique which is helpful in PH evaluation, facing difficulties in assessing right ventricular ejection fraction due to its distinct geometry. Previous studies investigated the correlation between echocardiography and RHC parameters and indicated moderate to good correlation for SPAP and MPAP (r=0.65, r=0.60, and r= 0.805) between them (51, 52). In contrast, the other study by Hegazy et al. found patients with higher MPAP values on transesophageal echocardiography did not correlate with MPAP ≥ 35 mmHg on RHC (40). Therefore, the tool for PH diagnosis is able to contribute to distinctive results. Moreover, we should consider that the included studies utilized various NLR threshold (Table 2); which can give rise to discrepancy. Also, some studies did not mention the exact criteria for PH diagnosis (Table 1); all of which indicates the necessity for future research.

Table 2. Studies of relationship between NLR and PH

First author	Participants	Year	Method of PH Diagnosis	Cutoff	Outcomes
Feng (15)	Patients with AECOPD	2021	RHC	–	NLR was not associated with the risk of PH.
Yong (35)	COPD-associated PH	2016	RHC	4.7	NLR was significantly higher in deceased patients than in survivors.
Yun (34)	Patients with AECOPD	2019	RHC	–	NLR could not predict PH in AECOPD patients in multivariate logistic regression.
Zuo (33)	Patients with AECOPD	2019	Echocardiography	4.65	Higher NLR in AECOPD patients was found to be an independent predictor of PAH development. There was no significant connection between NLR and PH severity; the calculated PAP was not linked with NLR.
Mirsaeidi (23)	Patients with sarcoidosis	2015	Echocardiography	3.5	NLR was associated with PH in sarcoidosis patients.
Korkmaz (21)	Patients with sarcoidosis	2020	Echocardiography	2.07	There was no significant difference in NLR between sarcoidosis cases with PH and those without PH.
Esheba (13)	patients with SSc	2016	Echocardiography	–	In SSc patients with PH, the NLR was significantly greater than in those without PH.
Senturk (27)	patients with SSc	2019	RHC	–	NLR was similar in sarcoidosis patients with PAH and those without PAH.
Sakr (26)	patients with SSc	2020	–	–	SSc patients with PH had no differences in NLR levels compared to those without PH.
Tezcan (28)	patients with SSc	2020	RHC	2.209	In SSc patients with PH, the NLR was significantly greater than in those without PH.
Yayla (30)	patients with SSc	2020	RHC	–	SSc patients with PH had no differences in NLR levels compared to those without PH.

First author	Participants	Year	Method of PH Diagnosis	Cutoff	Outcomes
Yanartas (29)	patients with CTEPH	2015	RHC	2.54	Patients with a greater NLR in admission have a significantly higher death rate. A strong association between preoperative pulmonary vascular resistance and NLR was also found.
Fallah (14)	acute PE survivors	2020	echocardiography, ventilation/ perfusion scan, or RHC	–	No difference in NLR level was found between PE patients with CTEPH and those without CTEPH.
Ataam (11)	patients with CTEPH	2020	multidetector CT angiography and/ or pulmonary angiography	–	NLR was found to be unable to predict poor outcomes in CTEPH patients (early mortality, heart-lung transplant, or need for extracorporeal membrane oxygenation or prolonged inotropic/ catecholamine support)
Kivrak (20)	patients with CTEPH	2017	—	–	Among patients with CTEPH, the NLR levels of atherosclerotic and non-atherosclerotic patients were similar.
Zhang (32)	pre-dialytic CKD patients	2020	Echocardiography	–	NLR was found to be an independent predictor of PH in CKD patients.
Gursoy (17)	CHD-PAH	2015	—	–	NLR was independently linked with peak and mean PAP. It was higher in patients with a pulmonary hypertension crisis and who died. It was not, however, linked to intubation time or ICU stay.
Herlambang (19)	children with acyanotic CHD	2019	Echocardiography	2.355	PAH patients had significantly higher NLR levels than non-PAH patients.
Yin (31)	children with CHD-PAH who had had heart surgery	2021	RHC	–	Pre-operative NLR levels were significantly associated with total length of stay, mechanical ventilation duration, and ICU stay, whereas postoperative NLR levels were only significantly correlated with the first two.
Yildiz (12)	PAH patients	2013	RHC	1.65	When compared to healthy controls, NLR was considerably higher in PAH patients. Also, NLR was linked with PAP.
Ozpelit (24)	adult PAH patients	2015	RHC	–	As the NLR increased, the prevalence of pericardial effusion increased. NLR was not an independent predictor of death among PAH patients.
Foris (16)	patients with newly diagnosed PAH	2016	RHC	2.62	NLR in PAH patients was significantly higher than in healthy controls.

Table 2 (*Continued*)

First author	Participants	Year	Method of PH Diagnosis	Cutoff	Outcomes
Harbaum (18)	PAH patients	2017	RHC	4.14	PAH patients who died or were referred for lung transplantation had a greater NLR. Elevated NLR was linked with poor transplantation-free survival.
MacKenzie (22)	PAH patients	2018	—	–	Among PAH patients, those with higher C-peptide, which is used to assess insulin resistance and metabolic dysfunction, had higher a NLR than those with lower C-peptide.
Pooder (25)	PAH patients	2019	baseline pulmonary function testing, six minute walk tests, RHC	–	A link between NLR and the severity of the PH was found. PAH patients with higher NLR levels had worse outcomes (median transplant-free survival) than those with lower ratios.

Abbreviations: PH: Pulmonary hypertension; NLR: neutrophil to lymphocyte ratio; PAH: Pulmonary arterial hypertension; PAP: pulmonary arterial pressure; RHC: right heart catheterization; COPD: chronic obstructive pulmonary disease; SSc: systemic sclerosis; CKD: chronic kidney disease; CHD: congenital heart disease: CT: computed tomography.

Conclusion

In this systematic review, we have provided a summary of the literature concerning the relationship of NLR with PH. Although few definitive studies are present with different types of PH, heterogeneous endpoints, and not fully explained causal links to the pathophysiology, which are the primary limitations of the review, some strong inferences can be made. We assert that the development of PH is linked to abnormal systemic inflammation, which NLR can help as a biomarker. NLR appears to be a simple, repeatable, inexpensive, and reliable laboratory biomarker for predicting disease severity, complications, and outcome in PH patients. Further larger prospective randomized studies investigating the association between NLR and the development of PH may also provide crucial information in elucidating the mechanism of PH.

Limitation

Our study has some limitations. Firstly, the low number of included studies in each section prevents us from reaching a definite conclusion. Also, the baseline characteristics of the studies participants, such as gender, genetics, and their underlying conditions including diabetes, can affect the results. Moreover, different studies design including cohort and trials can significantly impact the results. Therefore, we need additional randomized co-founders-controlled studies in the future.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article. RG has been a consultant/ speaker for Kinevant, Mallinckrodt, ANI and United Therapeutics.

Authors' Contribution: The study's design was influenced by all of the writers. Initial searches were conducted by ShKh and BL, and articles were then selected for inclusion by AR and PJ RP. The first draft of the work was written by FR and CK. The initial draft was edited by FC, ShKh and MG, and the final manuscript was approved by all writers.

List of abbreviations:

Neutrophil To Lymphocyte Ratio (NLR)
Pulmonary Hypertension (PH)
Right Heart Catheterization (RHC)
Right Ventricular (RV)
Chronic Obstructive Pulmonary Disease (COPD)
Systemic Sclerosis (Ssc)
Chronic Kidney Disease (CKD)
Congenital Heart Disease (CHD)
Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)
Standard Deviation (SD)
Odds Ratio (OR)

Hazard Ratio (HR)
Acute Exacerbation of COPD (AECOPD)
Congenital Heart Defect-Associated Pulmonary Arterial Hypertension (CHD-PAH)
The Area Under the Curve (AUC)
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
Pulmonary Embolism (PE)
Glutamic Oxaloacetic Transaminase (AST)
Glutamic Pyruvic Transaminase (ALT)
Blood Urea Nitrogen (BUN)
New York Heart Association Functional Class (NYHA FC)
Brain Natriuretic Peptide (BNP)
C-Reactive Protein (CRP)
6-Min Walking Distance (6MWD)
Tricuspid Plane Annular Systolic Excursion (TAPSE)
Associated PAH (APAH)
Pulmonary Arterial Pressure (PAP)
Systolic Pulmonary Artery Pressures (SPAP)
Mean Pulmonary Artery Pressures (MPAP)

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ANNEX

Table S1. Search strategy

Database	Search terms	Number of articles
PubMed	"Pulmonary"[All Fields] AND "hypertension"[All Fields] AND ("neutrophil"[All Fields] AND "lymphocyte"[All Fields] AND "ratio"[All Fields]) OR "NLR"[All Fields])	59
Scopus	(TITLE-ABS-KEY (pulmonary AND hypertension)) AND (ALL (neutrophil AND to AND lymphocyte AND ratio) OR NLR))	314
Web of Science	(All=(neutrophil AND lymphocyte AND ratio) OR NLR)) AND (All=(Pulmonary AND hypertension))	63

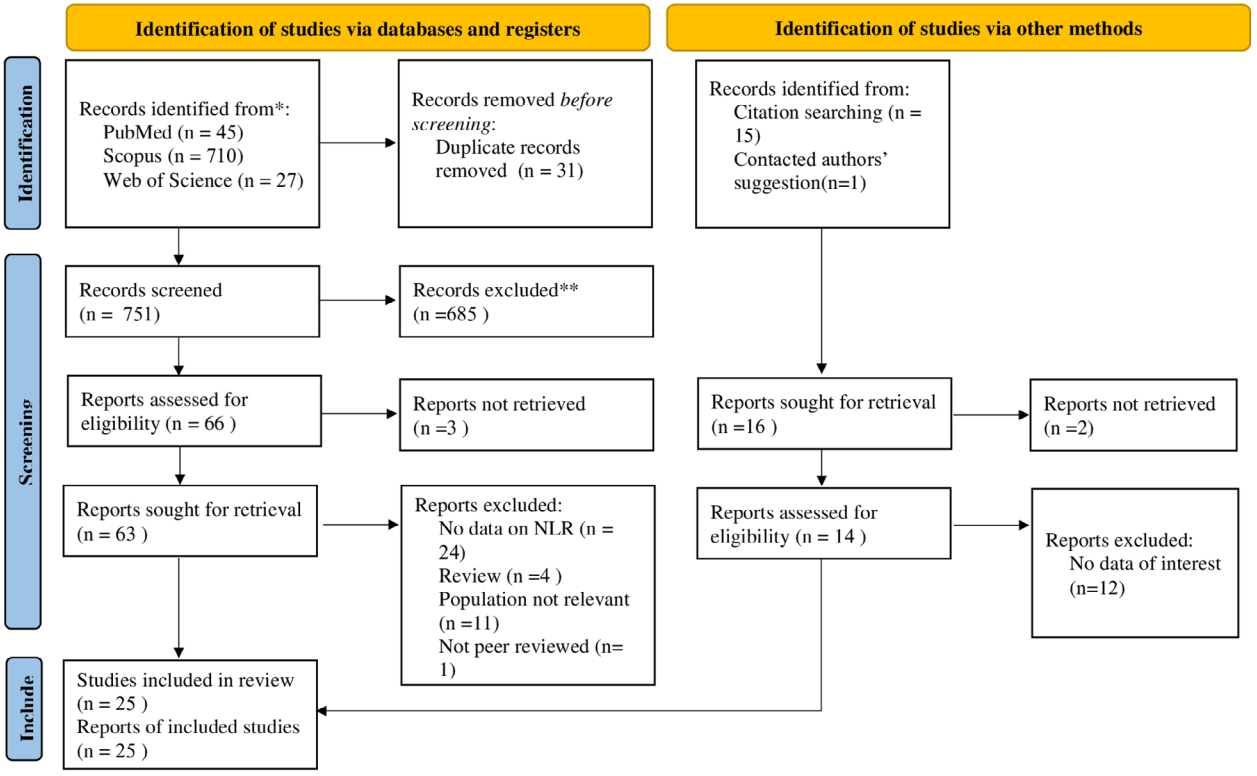

Figure S1. Flow chart of search and study selection.