Diagnostic value of the Neutrophil-to-Lymphocyte Ratio (NLR) In Predicting Mortality of Heart Failure

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Abstract

Introduction: The role of inflammatory processes in exacerbating fibrotic and atherosclerotic processes has been confirmed, such as increased neutrophil count. Some evidence identified the prognostic role of the neutrophil to the lymphocytic ratio (NLR) in predicting adverse outcomes of heart diseases. A review of the literature indicates controversial results about the role of this index in predicting mortality of heart failure (HF). In this comprehensive review, we aimed to evaluate the role of NLR in predicting mortality in patients with HF.

Methods: Initial search identified 67 studies from databases such as PubMed, Web of Knowledge, Google Scholar, SCOPUS, and Iranian databases, including SID and Magiran, and articles in non-English or non-Farsi languages case studies, review articles were excluded. At the final stage, 10 studies remained.

Results: Overall, 5 cases of acute heart failure and 5 cases of chronic heart failure were included. Totally, 5979 patients (3462 acute, and 2517 chronic) were studied. The mean follow-up time was 18 months (11.3 to 26 months). The mortality rate in patients with acute heart failure was 23.8% (22.4% to 25.2%), and in patients with chronic heart failure was 27.1% (24.9% to 29.5%), with a high heterogeneity among studies.

Conclusion: NLR was able to predict mortality among patients with acute and chronic heart failure, with a hazard ratio of 1.61 and 1.44, respectively. The NLR values above 4.4, have relatively good sensitivity and specificity to predict mortality in patients with acute heart failure.

Keywords: Heart failure; NLR; predictive value; mortality; myocardial infarction.

Introduction

Acute heart failure is a term used to describe the sudden onset or change in the signs and symptoms of heart failure [1]. The prevalence of this syndrome is increasing due to the increased incidence of coronary heart disease, particularly in older people. In addition, acute heart failure has a high mortality and morbidity [2]. Therefore, early and timely diagnosis and identification of patients at high risk is critical. Each year 5,000,000 people in the United States suffer from heart failure, and the prevalence of this disease worldwide is increasing, especially in developed countries [3]. Although the prevalence of heart failure with reduced ejection fraction is decreasing (due to increasing lifespans in developed societies and increased risk factors such as diabetes and hypertension) the proportion of patients with heart failure with maintained or near normal ejection fraction is increasing [4].

Many prognostic factors have been proposed for predicting mortality associated with acute heart failure [4-12]. Most of these factors were related to inflammation. Furthermore, the pathophysiological role of inflammatory factors in the progression of heart failure has been well established [13-15]. The ratio of neutrophil to lymphocyte or NLR in the peripheral circulatory system is one of the factors that is easily measured in the blood. Increased neutrophil counts have been suggested as a primary component in the activity of inflammatory

pathways, and lymphopenia is also known to be a predictor of physiological stress. Some evidence has been published that Neutrophil Lymphocyte Ratio (NLR) can predict cardiovascular disease risk [16-23]. However, the relationship between NLR and hospital mortality in patients with acute heart failure is a valuable question. This study aims to analyze and summarize studies on the role of NLR in predicting hospital mortality in patients with acute and chronic heart failure.

The role of neutrophils and lymphocytes in heart failure

Both types of heart failure - with reduced ejection fraction or ejection fraction close to normal- have also been associated with chronic inflammation [24, 25] . In this respect, some evidence suggests that neutrophils play a key role in the pathophysiology of heart failure [26, 27]. Neutrophils are leukocytes at the forefront of the host defense against pathogens and play as an important mediator in inflammatory processes caused by tissue damage [27]. Along with the proven role of neutrophils in counteracting microorganisms, neutrophils also play an essential role in triggering natural or acquired immune responses [26]. The importance of neutrophil involvement in inflammatory processes was obtained by assessing these cells' capacity to release neutrophilic extracellular ducts or NETs and their associated microparticles or MPs [28].

Physiologically, neutrophils play a major role in myocardial injury and are always infiltrated in the injured myocardium [26]. Due to natural and acquired immune responses, neutrophils can affect these responses and affect dendritic cell function and lymphocytes. Recent evidence suggests that neutrophils play a major role in the cardiac repair after myocardial infarction. Suppression of neutrophil function in animal models by inducing acute myocardial infarction has led to decreased cardiac function, the emergence of cardiac fibrosis, and a faster progression to HF [11]. Although the timing of neutrophil infiltration and following cardiac tissue repair after myocardial infarction has been evaluated and determined [29], the functional properties of neutrophils in heart failure remain unclear. Few studies have shown that neutrophils play an essential role in myocarditis [30, 31]. However, their role in the transition from inflammation to heart failure remains unclear. Several etiologies are involved in the incidence and development of myocarditis.

In some cases, for example in the myocarditis, giant cells plays a significant role in the induction of the myocarditis process [31, 32]. In most types of myocarditis, a natural immune response mediated by monocytes and macrophages and neutrophils plays a role in the autoimmune process. These cells can also play a role in promoting both injuries and repairing it [31]. In right ventricular failure due to transient pulmonary hypertension, increased expression of some interleukins, such as IL-1β, IL-6, and IL-10, along with infiltration of both neutrophil and macrophage cell lines, has strongly emphasized the role of myocardial inflammation in heart failure [33]. On the other hand, neutrophils and neutrophil-dependent oxidative stress are also involved in exacerbating the toxic cardiomyopathy process. In animal models, histological and staining evaluations for MPO activity have demonstrated high accu-

mulation of neutrophils in the infarcted and myocardial fibrotic area with decreased myocardial contractility [34]. Both high-risk patients and patients with heart failure have shown an increase in normal immune activity [35]. In some studies, neutrophil counts are significantly associated with severity of heart failure. They have been less related to peripheral vascular disease, cardiac death, abdominal aortic aneurysm, and non-lethal myocardial infarction [35]. Both neutrophil counts and neutrophil phenotype have been related to negative outcomes in patients with reduced EF heart failure [35]. Some reports reported an increase in the total leukocyte count and neutrophil count in expired patients, who had ventricular function abnormalities in heart failure [36]. Recent studies have also shown a significant relationship between increased neutrophil function, increased plasma CRP levels, and severity of heart failure [37, 38]. However, this relationship was only applicable to patients with heart failure with reduced EF.

When looking at inflammatory tissue, neutrophil counts may be far beyond other leukocytes, such as lymphocytes. Inflammation can occur in various time sequences and shapes of typical disorder. As a result, diagnostic biomarkers, clinical, pathological, and radiological, should be considered in a systematic way [39]. Given that increased neutrophil counts are an important factor in predicting the outcome of heart failure [40, 41], the ratio of neutrophils to lymphocytes is another factor in evaluating inflammation severity in patients with heart failure. Recent comprehensive data-based observations involving patients with heart failure, have shown that the neutrophil-to-lymphocyte ratio or NLR is associated with outcomes from some disorders, such as chronic kidney disease, major cardiovascular events, and readmissions due to heart failure [41]. This ratio is a prognostic factor in coronary heart disease and a significant predictor of mortality in patients with acute coronary syndrome [42]. This parameter has also been associated with an increased risk of ventricular arrhythmias and mortality in patients undergoing PCI [43]. Similarly, increased NLR was significantly correlated with increased mortality in patients with non-ST elevation MI (NSTEMI) [44]. It was also related to the outcome of the CRT procedure [44]. Finally, both NLR indices and platelet-to-lymphocyte count ratios correlated with mortality in patients undergoing heart transplantation [45].

Neutrophils are activated by hypoxia and a decrease in nitric oxide concentration along with the activity of prothrombotic and proatherogenic profiles [46]. Through the interaction between neutrophils and atherogenic cells such as monocytes, macrophages, and endothelial cells, neutrophils can influence the inflammatory response to atherosclerotic response, by maintaining and promoting proinflammatory and atherosclerotic processes [47].

Other evidence for the role of neutrophils has been related to the polarization of these cells after myocardial infarction. After myocardial injury, proinflammatory atherosclerotic processes will be observable [48]. Increased neutrophils after myocardial infarction lead to polarization of these cells, which coincides with the differentiation of M1 and M2 macrophages [49]. Numerous cytokines released by injured myocardial and

endothelial cells in HF can lead to rise in neutrophil counts. Overall, it's exciting that we can use ancient pathological biomarkers in new diagnostic criteria. For example, a previous markers of inflammation - Mast Cell Density- have link with inflammation Tumor Grade in Carcinoma [50]. Also, expression patterns of DNA repair proteins, such as microsatellite instability (MSI), have recently can be useful to predicting the prognosis of some tumor and inflammation [51]. In a clinical setting, these pathological correlations can be crucial. In patients with respiratory distress, for example, a good correlation was found between end-tidal carbon dioxide and partial arterial carbon dioxide pressure [52].

Routine analysis of blood biomarkers is very useful in evaluating patients with heart failure and determining their risk level. The role of inflammatory and proinflammatory factors has been well established [53-57]. Many of these markers and proteins have been identified as predictors of these patients' adverse risk and inappropriate outcomes. Therefore many of them are considered as therapeutic targeting factors [58]. Some biomarker in tumor and inflammation, in specific ages such as children, can changes the course of treatment [59]. Some of these inflammatory factors contribute to the progression and pathophysiology of heart failure and play a key role in the prognosis of the disease [5].

Project Results and Findings

Characteristics of the evaluated studies: A total of 10 studies about patients with heart failure (whether acute or chronic) were included in the project. According to the study population, 5 cases were about acute heart failure and 5 cases regarded chronic heart failure. Overall, 5979 patients (including 3462 cases with acute form and 2517 patients with chronic disease) were studied. The mean age of patients in acute form was 66.2 years and 69.4 years in chronic form. The mean follow-up time was 11.3 to 26 months, with an average of 18 months.

Mortality rate calculation based on studies

According to the meta-analytic analysis, the overall mortality rate for patients with heart failure was estimated to be 22.2% (18.1% to 23.3%) over the 18-month follow-up (**Table 2** and **Figure 1**). Further, the mortality rate among patients with
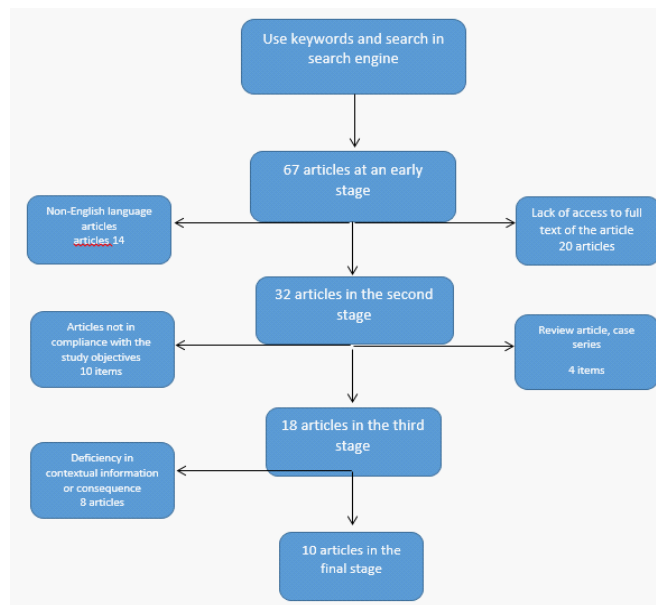

Figure 1: Pathway of literatures review.

Table 1: Details of the studies.

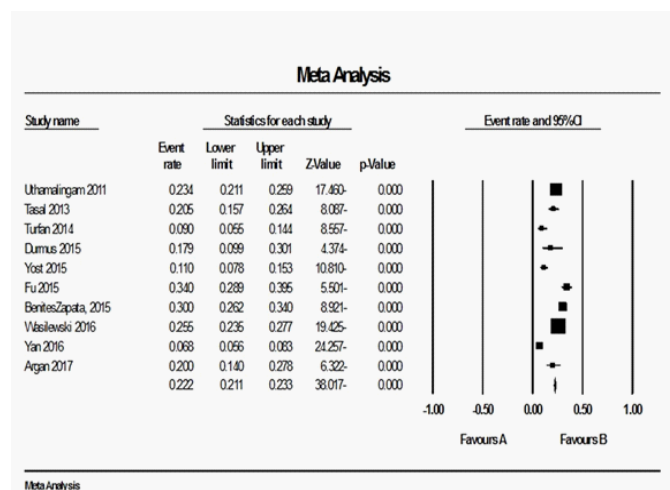| Author, year	Study design	Country	Type	Number	Mean age	Male	Follow-up (month)	Mortality
Uthamalingam 2011	Prospective	England	Acute	1212	73.9	50	26	284/1212
Tasal 2013	Retrospective	Turkey	Acute	219	63.4	66	NA	45/219
Turfan 2014	Retrospective	Turkey	Acute	167	67.7	59	NA	15/167
Durmus 2015	Prospective	Turkey	Chronic	56	73=.5	32	12.8	10/56,
Yost 2015	retrospective	USA	Chronic	273	59.9	78	24.3	30/273
Fu 2015	Prospective	China	Chronic	306	85	81	15.7	104/306
BenitesZapata, 2015	Prospective	USA	Chronic	527	56.3	72	11.3	158/527
Wasilewski 2016	Prospective	Poland	Acute	1734	61	20	22	443/1734
Yan 2016	Prospective	China	Chronic	1355	72.6	60	18	92/1355
Argan 2017	Prospective	Turkey	Acute	130	65.0	74	16	26/130

acute heart failure was 23.8% (from 22.4% to 25.2%) (**Table 3** and **Chart 2**) and among patients with chronic heart failure was 27.1% (24.9% to 29.5%) (**Table 4** and **Chart 3**). Overall, studies had high heterogeneity, in assessing both acute mortality rate (82.932% heterogeneity coefficient) and chronic mortality rate (91.02% heterogeneity coefficient). However, publication bias in mortality rate analysis in acute and chronic failure was not significant (**Charts 4** and **5**).

Relationship between NLR Ratio and Mortality due to Heart Failure

The mean NLR ratio in patients with acute heart failure in both groups with and without mortality was 5.9 and 3.5, respec-

tively. According to analysis, NLR was able to predict mortality among patients with acute and chornic heart failure with a hazard ratio of 1.61. Based on the results of three studies of five studies focusing on acute heart failure, NLR values were higher than 4.4 was able to predict 18-month mortality in patients with acute heart failure, with a sensitivity of 67.2% and a specificity of 67.1% (**Table 5**). Also, the mean NLR ratio in patients with chronic hear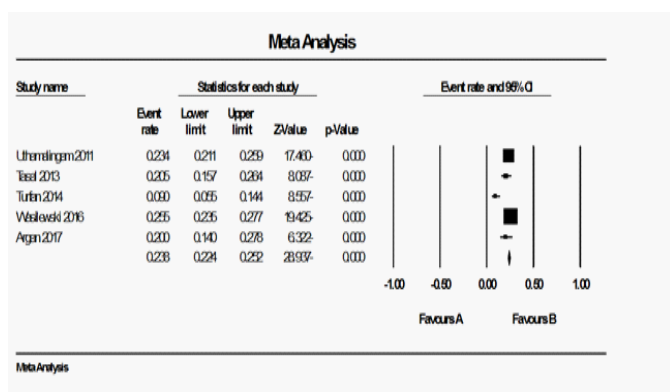t failure in both groups with and without mortality was estimated to be 4.7 and 2.3, respectively. Accordingly, NLR was able to predict mortality among patients with chronic heart failure, with a hazard ratio equal to 1.44 (**Table 5**).

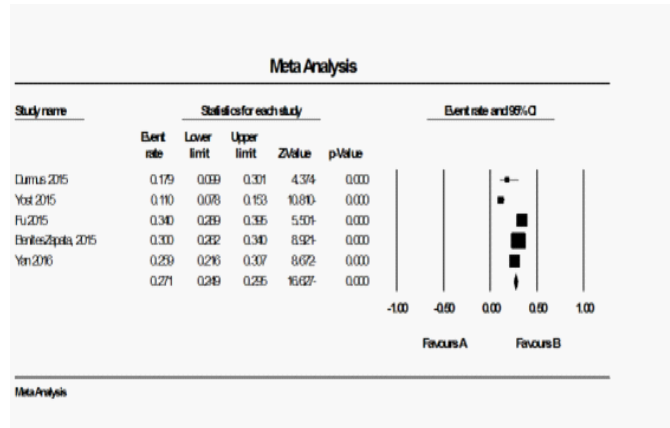*Table 2 and Chart 1: Total mortality rate in patients with heart failure.*

Meta Analysis

Study name	Statistics for each study					Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Z-Value	p-Value	
Uthamalingam 2011	0.234	0.211	0.259	17.460	0.000	
Tasal 2013	0.205	0.157	0.264	8.087	0.000	
Turfan 2014	0.090	0.055	0.144	8.557	0.000	
Durmus 2015	0.179	0.099	0.301	4.374	0.000	
Yost 2015	0.110	0.078	0.153	10.810	0.000	
Fu 2015	0.340	0.289	0.395	5.501	0.000	
BenitesZapata, 2015	0.300	0.262	0.340	8.921	0.000	
Wasilewski 2016	0.255	0.236	0.277	19.425	0.000	
Yan 2016	0.068	0.056	0.083	24.257	0.000	
Argan 2017	0.200	0.140	0.278	6.322	0.000	
	0.222	0.211	0.233	38.017	0.000	

Meta Analysis

$I^2 = 96.396$

Table 3 and Chart 2: Total mortality rate in patients with acute heart failure.

Meta Analysis

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Turfan 2014	0.090	0.055	0.144	8.557	0.000	
Wasilewski 2016	0.255	0.236	0.277	19.425	0.000	
Argan 2017	0.200	0.140	0.278	6.322	0.000	
	0.238	0.224	0.252	28.937	0.000	

Meta Analysis

82.932

Table 4 and Chart 3: Total mortality rate in patients with acute heart failure.

Meta Analysis

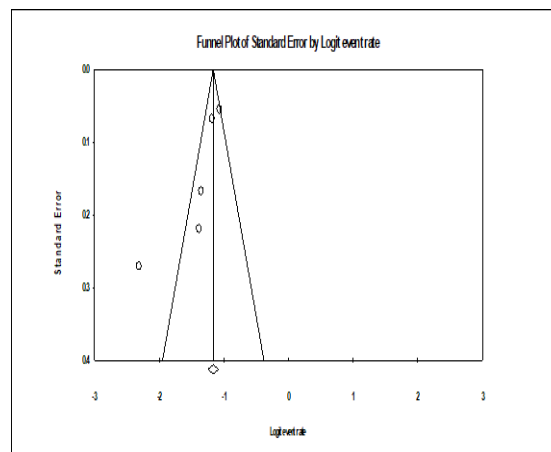| Study name	Statistics for each study					Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Z-Value	p-Value	
Durmus 2015	0.179	0.099	0.301	4.374	0.000	
Yost 2015	0.110	0.078	0.153	10.810	0.000	
Fu 2015	0.340	0.289	0.395	5.501	0.000	
BenitesZapata, 2015	0.300	0.262	0.340	8.921	0.000	
Yan 2016	0.259	0.216	0.307	8.672	0.000	
	0.271	0.249	0.295	16.627	0.000	

Meta Analysis

82.932

Figure 4: Publication bias in determining the mortality rate due to acute heart failure.
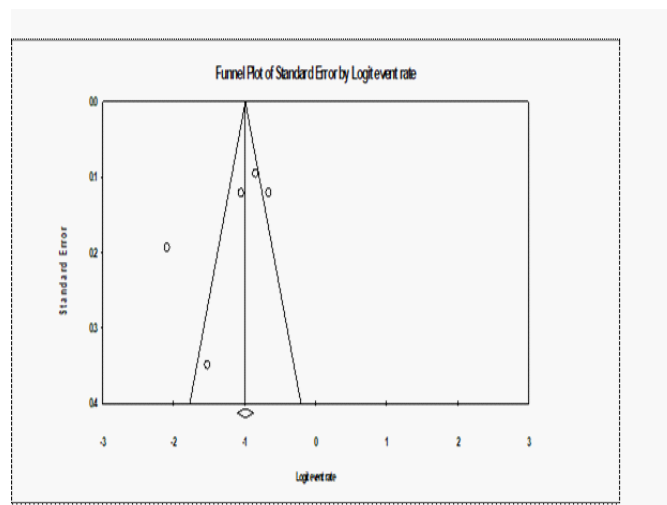

Figure 5: Publication bias in the determination of mortality rate due to acute heart failure.

Discussion

The role of inflammatory processes in exacerbating fibrotic and atherosclerotic processes in various studies has been confirmed. Increased neutrophil count as one of the immune and inflammatory systems mediators has also been emphasized. Some evidence has emphasized the prognostic role of the NLR ratio in predicting adverse outcomes in heart disease, including acute coronary syndrome and heart failure. However, a review of the literature indicates contradictory results regarding the role of this index in predicting medium- and long-term mortality.

In the 2017 study by Huang et al., 1923 patients with acute heart failure were investigated. The age of individuals in the study was 76 years (68% male). Consequently, 875 cases expired during a follow-up of 28.6 months. Through evaluation via regression modeling, NLR had a high value in predicting the mortality of these patients with a risk ratio of 1.166 [60]. In another study by Yu et al., the NLR ratio of 942 patients was divided into two groups: those experiencing heart failure and normal subjects. Patients were followed for 4.26 years. The study found that NLR was able to predict the risk of acute heart failure (risk ratio equal to 1.697). Additionally, NLR with a high-risk ratio of 4.26 was able to predict mortality in patients with heart failure [61].

Tasal et al. (2014), investigated 553 patients with a mean age

of 63.4 years (368 men) with heart failure. In this study, the NLR ratio was a mortality predictor with a probability ratio of 1.310. Using the area under the rock curve (AUC = 0.737), this ratio was still a predictor of mortality from heart failure [62]. Also, Uthamalingam et al. (2011) studied 1212 patients with heart failure who were monitored. During the 26-month follow-up period, 284 cases (23.4%) expired. Mortality rates in the three tertiles experienced NLR ratios of 32.8%, 23.2%, and 14.2%, respectively. Multivariate regression analysis showed that the NLR ratio with a risk ratio of 2.23 was able to predict mortality in these patients [63].

In this study, we aimed to evaluate and summarize the analytical results on the role of NLR in predicting mortality in patients with heart failure. Initially, the evaluation focused on two studies based on acute and chronic heart failure. First, our evaluation of mortality from acute and chronic heart failure over an 18-month follow-up showed a mortality rate of 23.8% and 27.1%, respectively. Of course, this mortality depends on many factors, such as duration of follow-up, patients' LVEF status (reduced or compensatory), and inclusion criteria such as the distribution of cardiac risk factors, sex distribution, age, and the acute or chronic manifestations of failure. These factors led to high heterogeneity between studies in the computation of total mortality. However, publication bias was favorably low. Publication bias in medical science journals refers to the publication of more articles that contain positive or statistically significant conclusions. This bias indicates that articles containing statistically negative or nonsignificant results are less likely to print. Based on our analysis, the journals we evaluated did not have such a bias (or tendency) among the editors of the various journals.

As a major finding, our study demonstrated the high role of NLR in predicting mortality in patients with acute and chronic heart failure. While all studies evaluated by our analysis have emphasized the role of the NLR in predicting mortality, the strengths and weaknesses of studies in this regard have varied. First, the NLR in the expired group was significantly higher than in living patients in all studies. Second, the relative mortality risk in patients with acute and chronic heart failure was estimated to be 1.6 and 1.4, respectively. In this regard, only three studies determined the best cutoff point for NLR to predict mortality (including in patients with acute heart failure). In summary, it was evident that NLR values above 4.4 with relatively good sensitivity and specificity were able to predict mortality in patients with acute heart failure. However, there have been no studies of the predictive value of NLR in predicting mortality in patients with chronic heart failure, and such studies based on analysis of the area under the ROC curve are essential.

Notably, the markers studied in the study, including neutrophils, lymphocytes, and even platelets, are affected by underlying conditions such as inflammation or infection. Evaluation of the relationship between markers and outcome of heart disease should be done with these confounding factors or exclusion of the patients under study, which was not mentioned in any of the studies studied, so this should be addressed in future studies.

Table 5: *Details of the relationship between NLR and mortality rate.*

Author, year	Type	NLR	Hazard Ratio	Cutoff for NLR	Sensitivity	Specificity
Uthamalingam 2011	Acute	Case: 5.1 Control: 2.8	2.80	-	-	-
Tasal 2013	Acute	Case: 10.2 Control: 6.1	1.31	>5.5	67.0%	66.0%
Turfan 2014	Acute	Case: 7.2 Control: 4.8	1.15	>4.78	66.7%	60.5%
Durmus 2015	Chronic	Case: 5.5 Control: 2.5	1.68	-	-	-
Yost 2015	Chronic	Case: 5.1 Control: 2.2	1.16	-	-	-
Fu 2015	Chronic	Case: 4.6 Control: 2.2	1.04	-	-	-
Benites Zapata, 2015	Chronic	Case: 3.9 Control: 2.2	2.16	-	-	-
Wasilewski 2016	Acute	Case: 4.4 Control: 2.4	1.43	-	-	-
Yan 2016	Chronic	Case: 4.8 Control: 2.4	1.17	-	-	-
Argan 2017	Acute	Case: 2.75 Control: 1.82	1.36	> 3.0	68.0%	75.0%

Conclusion

Overall, the incidence of mortality from acute and chronic heart failure during the 18-month follow-up was estimated to be 23.8% and 27.1%, respectively, with high heterogeneity among studies. The NLR values above 4.4 with relatively good sensitivity and specificity were able to predict mortality in patients with acute heart failure.

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