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THE ASSOCIATION OF NEUTROPHIL LYMPHOCYTE RATIO AND IN-HOSPITAL MORTALITY IN ACUTE CORONARY SYNDROME PATIENTS: META ANALYSIS

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ABSTRACT

Coronary artery disease, including acute coronary syndrome (ACS), is a major cause of mortality and morbidity worldwide. The neutrophil lymphocyte ratio (NLR) is a nonspecific marker of inflammation and previous studies have shown that increased NLR is associated with mortality in acute coronary syndrome patients and may act as a prognostic marker. The aim of this study was to assess the association of NLR and in-hospital mortality in ACS patients. The method used in this study was, Literature search was carried out using the Ebsco, Embasse, Nature, Proquest, PubMed, Science Direct and Scopus databases until March 2022 to find an observational cohort study that assessed the association of NLR and in-hospital mortality in ACS patients. A systematic review of published studies following the preferred reporting items for systematic review and guideline meta-analysis (PRISMA) was conducted. Study quality was assessed with the Newcastle Ottawa Scale (NOS) and only high quality studies were included in this meta-analysis. The primary outcome was in-hospital mortality and the effect was measured in Risk Ratio (RR) and 95% CI. Conclusion: A high NLR increases the risk of in-hospital death in acute coronary syndrome patients. Further studies in large settings are needed to assess the NLR

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	threshold values that can predict in-hospital mortality in acute coronary syndrome patients
KEYWORDS	*NLR, in Hospital Mortality, Acute Coronary Syndrome*
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INTRODUCTION

Acute coronary syndrome (ACS) is a life-threatening condition that attacks the coronary arteries and is an acute manifestation of CHD characterized by acute chest pain (angina pectoris) due to myocardial ischemia (Antman & Loscalzo, 2018; Hijazi et al., 2021) . CHD is the most common cardiovascular disease, with a prevalence in the world in 2017 of 1,655/100,000 or around 125 million people with CHD in 2017 (Khan et al., 2020; Roth et al., 2020) .

Neutrophil lymphocyte ratio (RNL) is a non-specific inflammatory marker that has the potential to be a prognostic marker in ACS patients (Dentali et al., 2018; Li et al., 2020; Zhang et al., 2018) . Previous studies have shown an association between increased RNL with mortality and *major adverse cardiovascular events* (Akpek et al., 2012; Azab et al., 2010; Dentali et al., 2018; Ergelen et al., 2014; Gazi et al., 2015; Gul et al., 2017; Han et al., 2013; He et al., 2014; Kaya et al., 2013; Li et al., 2020; Machado et al., 2018; Misumida et al., 2015; Pan et al., 2015; Sen et al., 2013; Shen et al., 2010; Tamhane et al., 2008; Tavares et al., 2022) . However, the results of various studies still show varying results and the value of the RNL cut-off point. Therefore, the aim of this systematic literature review and meta- analysis was to identify and summarize studies that assessed the association of RNL with *in-hospital mortality in* ACS patients and analyzed the data pool.

RESEARCH METHOD

1. Study Identification

A systematic literature search was conducted using the *preferred reporting items for systematic reviews and meta-analysis* (PRISMA) guidelines to search for observational studies looking at the association between RNL and short-term mortality in acute coronary syndrome patients published through March 2022. The search was conducted using the Ebsco database. , Embasse, Nature, Proquest, PubMed. Science Direc and Scopus using the keywords ("Neutrophil to Lymphocyte Ratio" OR "Neutrophil Lymphocyte Ratio" OR "Neutrophil-Lymphocyte Ratio" OR "NLR") AND ("Mortality") AND ("Acute Coronary Syndrome" OR "ACS " OR "ST-segment Elevation Myocardial Infarction" OR "ST segment Elevation Myocardial Infarction" OR "ST-segment Myocardial Infarction" OR "ST elevation Myocardial Infarction" OR "STEMI" OR "Non ST-

segment Myocardial Infarction" OR "Non ST segment Myocardial Infarction" OR "Non ST-elevation Myocardial Infarction" OR "Non ST elevation Myocardial Infarction" OR "NSTEMI" OR "Unstable Angina Pectoris" OR "STEAM") AND ("Observational" OR "Observational study" OR "Observational studies" "). A manual search was carried out for identification of additional studies through references from related articles.

2. Inclusion and Exclusion Criteria

Studies were included in this meta-analysis if they met the following inclusion criteria: (1) acute coronary syndrome patients with a diagnosis of either UA, NSTEMI or STEMI according to existing guidelines such as guidelines from the American Heart Association (AHA) or the European Society of Cardiology (ESC).), (2) RNL was calculated at the time of admission (*on admission*) (3) was a prospective or retrospective cohort study, (4) included data on the number of subjects experiencing short-term mortality or included measures of association of RNL with short-term mortality. The study was excluded if: (1) the study was in the form of a literature review, (2) a pre-clinical study, (3) seminar abstracts, (4) not published in English, (5) did not divide research subjects based on RNL scores.

3. Data Extraction and Quality Assessment

Study search and data extraction were carried out independently by two *reviewers* (NF, RF). Study quality was assessed using the *Newcastle Ottawa Scale* (NOS) and only studies with scores above 6 stars were included in this meta- analysis.

4. Data analysis

The main outcome in this meta- analysis was short-term mortality, i.e. mortality occurring within <90 days, including mortality during treatment or intra-hospital mortality. Data analysis was carried out using the *Review Manager* version 5.3 application. Heterogeneity between studies was assessed by the I^2 statistic . I^2 50% indicates that there is heterogeneity between the studies and the analysis will use the *random effects model* . *Fixed effect* model would be used if there was no heterogeneity between studies. Subgroup analysis will be used to examine the relationship between RNL and short-term mortality in STEMI and NSTE-ACS patients and to minimize heterogeneity. *Outcome was* measured by the association measure *Risk Ratio* (RR) and 95% CI. P *value* <0.05 was used to describe statistical significance.

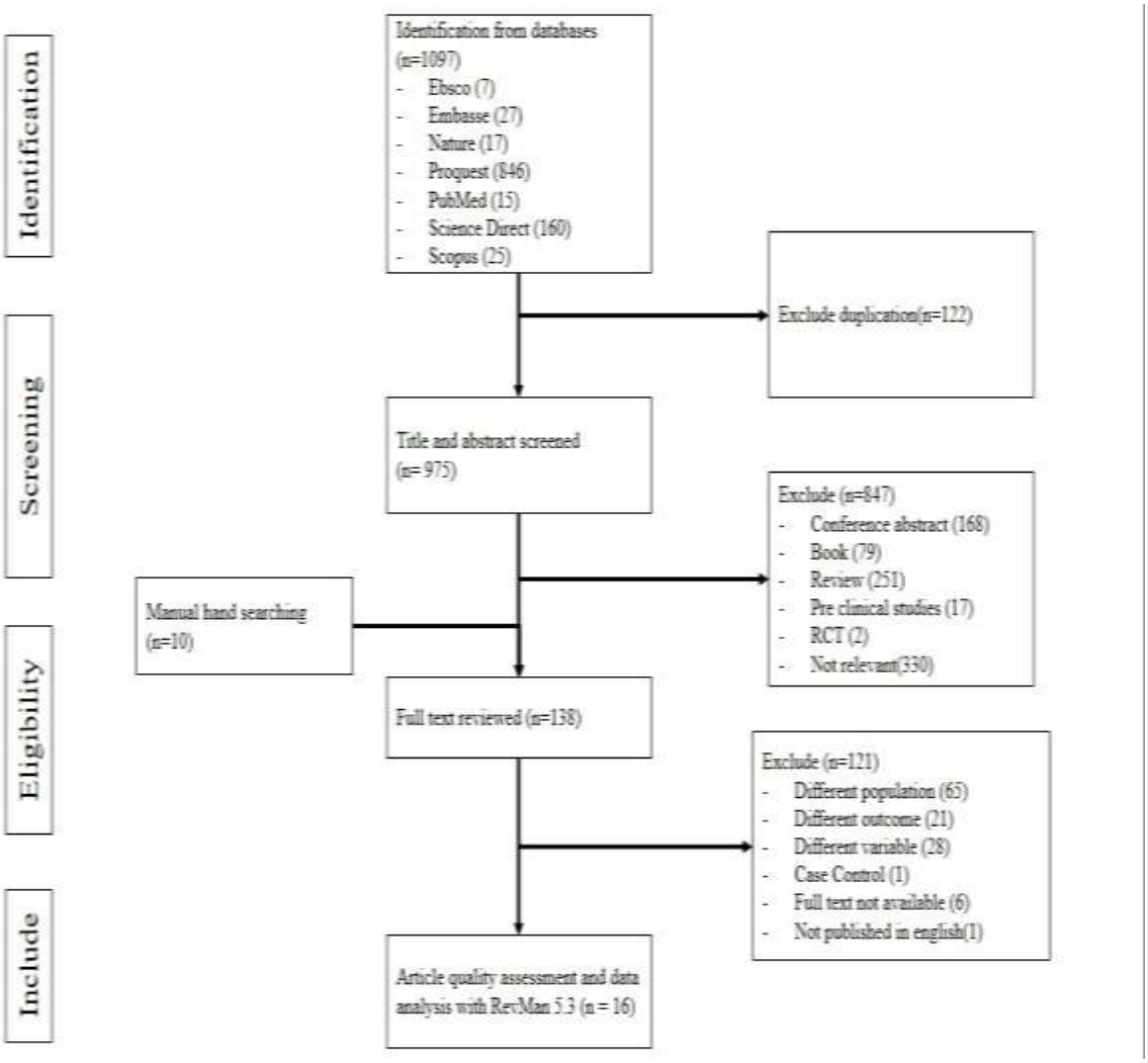

Figure 1. Flowchart of PRISMA

RESULTS AND DISCUSSION

5. Study Identification

Literature search results from Ebsco, Embasse, Nature, Proquest, PubMed databases. Science Direct and Scopus obtained 1,097 studies. The literature review was carried out systematically with the stages as listed in Figure 1. After excluding studies that contained duplication, a literature review through titles and abstracts was carried out and as many as 847 studies were excluded at the title and abstract screening stage. Additional manual searches were performed through study identification from related articles or similar studies. A total of 10 studies were obtained through additional manual searches for full manuscript evaluation. In the next stage in the form of evaluation of the full text, 122 studies were excluded because there were differences in population, differences in outcomes assessed, differences in independent variables assessed, case control studies, not

in English and the full text could not be obtained. The final results of 16 studies that will be included in the analysis and study quality assessment are carried out with the study characteristics listed in Table 1. The results of the study quality assessment with NOS show that all studies have good study quality.

Table 1. Study characteristics in the meta- analysis

No	Writer	Year	Number of Samples	Inclusion Criteria	RNL Potong Intersection	Intersection Method
1	Akpek M, et al (Akpek et al., 2012)	2012	418	STEMI	> 3.3	ROC
2	Azab B, et al (Azab et al., 2010)	2010	619	NSTEMI	> 4.7	IV quartile
3	Ergelen M, et al (Ergelen et al., 2014)	2014	2410	STEMI	> 6.97	IV quartile
4	Gazi E, et al (Gazi et al., 2015)	2015	522	STEMI	>5.77	IV quartile
5	Gul U, et al (Gul et al., 2017)	2017	320	STEMI	> 4.50	Previous research average
6	Han YC, et al (Han et al., 2013)	2013	326	STEMI	> 6.53	IV quartile
7	He J, et al (He et al., 2014)	2014	692	STEMI	> 4.75	IV quartile
8	Kaya MG, et al (Kaya et al., 2013)	2013	682	STEMI	> 4.4	IV quartile
9	Li CKH, et al (Li et al., 2020)	2020	1361	NSTEMI	> 9.51	IV quartile
10	Machado GP, et al (Machado et al., 2018)	2021	625	STEMI	> 9.41	Tertil III
11	Misumida N,	2015	396	NSTEMI	> 2.8	ROC

	et al (Misumida et al., 2015)					
12	Pan W, et al (Pan et al., 2015)	2015	636	STEMI	> 6.40	Tertil III
13	Sen N, et al (Sen et al., 2013)	2013	204	STEMI	> 6.0	Tertil III
14	Shen X, et al (Shen et al., 2010)	2010	551	STEMI	> 6.46	IV quartile
15	Tamhane UU, et al (Tamhane et al., 2008)	2008	2831	STEMI, NSTEMI, UA	N/A	Tertil III
16	Tavares F, et al (Tavares et al., 2022)	2021	1860	STEMI	> 7.3	Tertil III

RNL and Short-Term Mortality

A total of 16 studies with a total of 14,453 research subjects were included in this meta-analysis (Akpek et al., 2012; Azab et al., 2010; Ergelen et al., 2014; Gazi et al., 2015; Gul et al., 2017; Han et al., 2013; He et al., 2014; Kaya et al., 2013; Li et al., 2020; Machado et al., 2018; Misumida et al., 2015; Pan et al., 2015; Sen et al., al., 2013; Shen et al., 2010; Tamhane et al., 2008; Tavares et al., 2022) . A total of 3 studies looked at the association of RNL with short-term mortality in patients with *non -ST-elevation myocardial* infarction (NSTEMI), 12 studies in patients with *ST-elevation myocardial infarction* (STEMI) and 1 study looked at patients with *unstable angina* (UA), NSTEMI and STEMI. The values for determining the RNL cut-off point in all studies are different and the methods for determining the RNL cut-off point vary widely, including using *receiver operating characteristics* (ROC), quartiles, tertiles and averages from previous studies as listed in Table 1.

In all studies using quartiles and tertiles (Azab et al., 2010; Han et al., 2013; He et al., 2014; Kaya et al., 2013; Li et al., 2020; Machado et al., 2018 ; Pan et al., 2015; Sen et al., 2013; Shen et al., 2010; Tamhane et al., 2008; Tavares et al., 2022) , significant differences in RNL were found in the top quartile or tertile. Therefore, the top quartile or tertile RNL value was used as the cut-off point in this meta- analysis study.

The results of the data pool analysis showed that high RNL was significantly associated with short-term mortality with an RR of 2.79 (95% CI, 2.05 – 3.80) and *p value* < 0.00001 (Figure 2). In this analysis, heterogeneity between studies is quite high with I2 ^{85} % so that the analytical model used is the *random effect model* .

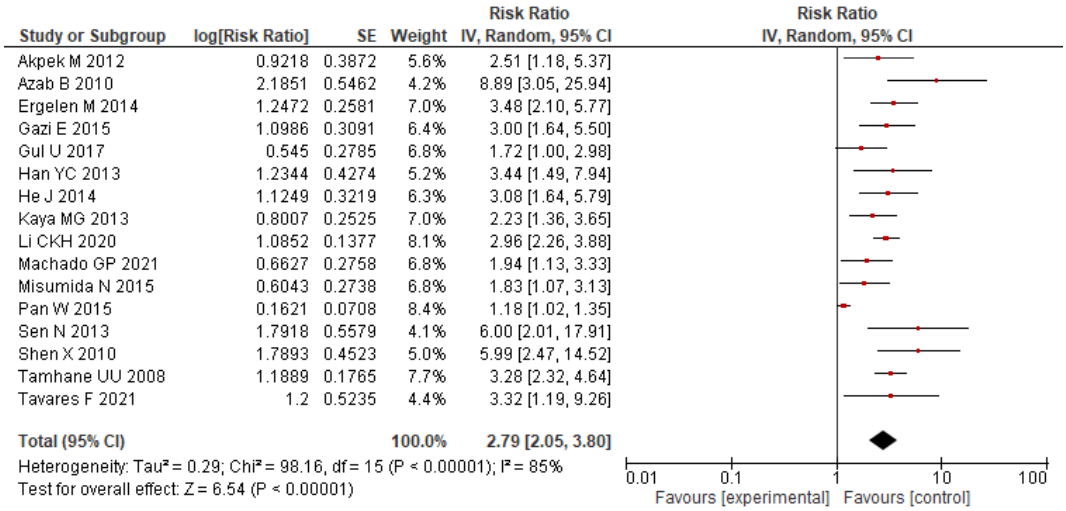

Figure 2. Forrest plot of the relationship of high RNL with mortality during treatment (*in hospital*)

Subgroup analysis was performed to see the size of the association in the NSTEMI and STEMI groups separately (Figure 3). There were 15 studies conducted by the analysis subgroup. This is because 1 study (Tamhane et al., 2008) did not include data on the number of deaths based on RNL in each of the STEMI, NSTEMI and UA groups so that a separate subgroup analysis could not be performed. Heterogeneity between studies in each subgroup was still high with I^2 = 72% for NSTEMI and I^2 = 81% for STEMI. Data pool analysis showed that a high RNL was associated with a risk of short-term mortality in NSTEMI patients with an RR of 3.08 (95% CI, 1.69 – 5.62, p < 0.00001) and in STEMI patients with an RR of 2.65 (95% CI, 1.85 – 3.81, p < 0.00001) (Figure 3).

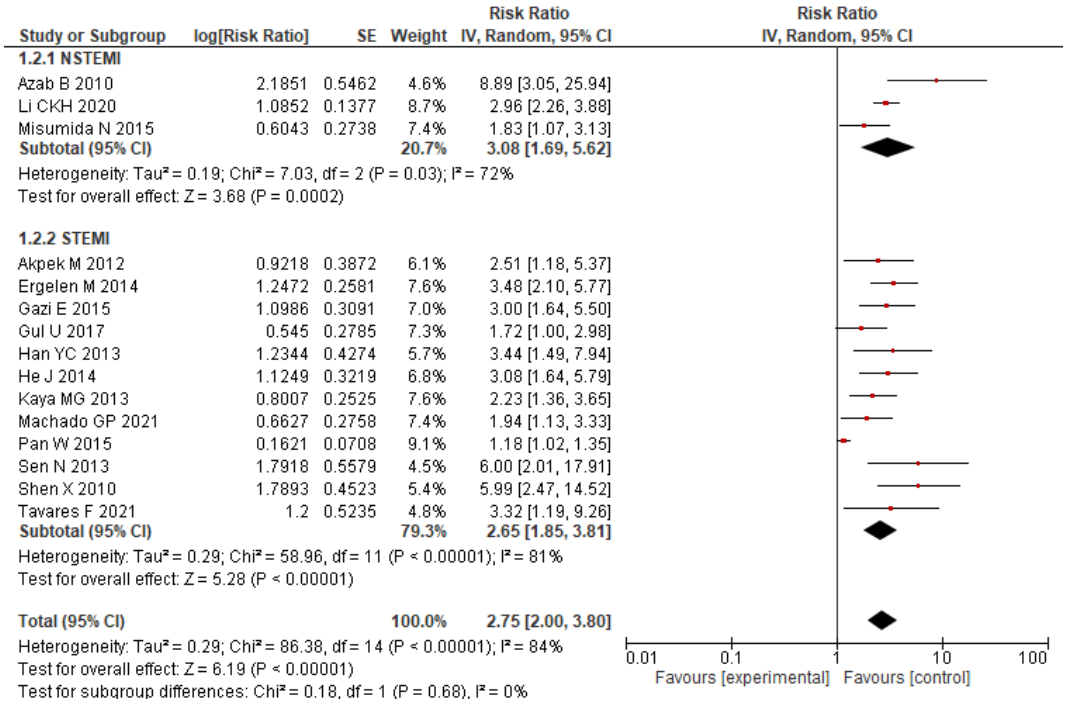

Figure 3. Forrest plot analysis of the relationship between RNL and mortality during treatment (*in hospital*) with NSTEMI and STEMI subgroups

DISCUSSION

Coronary heart disease, including acute coronary syndrome , is the leading cause of mortality in the world. Previous meta-analysis studies have shown that an increase in RNL is associated with mortality in ACS patients and *major adverse cardiovascular events* (MACE) (Dentali et al., 2018) . Therefore, this meta-analysis study was conducted to assess the association between increased RNL and short-term mortality in ACS patients.

In this research study, *16 studies with 14453 participants were* included in a meta-analysis to see the relationship between increased RNL and short-term mortality of ACS patients (Akpek et al., 2012; Azab et al., 2010; Ergelen et al., 2014; Gazi et al., 2014). ., 2015; Gul et al., 2017; Han et al., 2013; He et al., 2014; Kaya et al., 2013; Li et al., 2020; Machado et al., 2018; Misumida et al. , 2015; Pan et al., 2015; Sen et al., 2013; Shen et al., 2010; Tamhane et al., 2008; Tavares et al., 2022) . The results of this systematic literature review and meta-analysis showed an association between increased RNL and short-term mortality in patients with acute coronary syndromes with an RR of 2.79 (95% CI, 2.05 – 3.80, $p < 0.00001$) in line with previous meta-analyses that looked at the relationship between increased RNL with *in-hospital mortality in* STEMI patients (Dong et al., 2018; Mikhael et al., 2020) and a meta-analysis study that looked at the association of increased RNL with *major adverse cardiovascular events* (MACE) (Dentali et al., 2018) .

The heterogeneity between studies in this meta- analysis is quite high with I^2 = 85%, this could be due to the RNL cut-off value used varies between studies and is determined by various methods. The existence of differences in diagnosis between NSTEMI and STEMI is also suspected to cause high heterogeneity so that a subgroup analysis was carried out by dividing the groups based on the diagnosis of NSTEMI and STEMI. However, the results of the subgroup analysis still have high study heterogeneity in both groups, with I^2 = 72% for NSTEMI and I^2 = 84% for STEMI, so there are other factors that can affect the heterogeneity of the study such as the mean age of patients who have differences, comorbid factors that accompany the condition at the time of the patient's admission to the hospital and other factors. This result is in line with previous meta-analyses which also had high heterogeneity (Dentali et al., 2018; Dong et al., 2018; Mikhael et al., 2020) .

Neutrophils are one of the first leukocytes to be found at the site of myocardial damage after monocytes. Activated neutrophils exacerbate the inflammatory response through the secretion of inflammatory mediators such as myeloperoxidase, elastase, oxygen free radicals and arachidonic acid derivatives. The inflammatory process that occurs in ischemia and infarction conditions further triggers the migration of pro-inflammatory cells, including neutrophils, and increases the severity of myocardial tissue damage, plaque damage, activation of the coagulation cascade and thrombosis, microvascular occlusion, tissue necrosis and expansion of infarct size (Yalcinkaya et al. ., 2014) .

RNL is a combination of two non-specific markers of inflammation, namely neutrophils and lymphocytes (Yalcinkaya et al., 2014) . RNL describes the balance of neutrophil and lymphocyte levels in the body and is an indicator of systemic inflammation (Celik et al., 2017) . RNL can act as a marker describing the combination of an acute inflammatory reaction and activation of the neurohormonal system (Park et al., 2018) .

meta- analysis study has several weaknesses, including the studies included in the meta-analysis that have some differences in both the inclusion and exclusion criteria, the method used to determine the RNL cut-off point, the RNL cut-off point and other comorbid factors present in the patient. Therefore, the heterogeneity in this study is quite large and it is questionable whether it can be combined into an analysis pool. However, considering that all studies showed significant results and the pool analysis was carried out using *random effects* , namely the analysis method that took into account variance, the heterogeneity did not affect the validity of the study.

CONCLUSION

The results of this meta- analysis indicate that RNL has the potential to predict the prognosis of ACS patients. RNL is a test that is available in all types of hospitals, easy to do with low cost. However, further studies with large sample sizes are

needed to determine an RNL cut-off point that can be used as a parameter to assess prognosis, especially mortality during treatment, in ACS patients.

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