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Neutrophil-Lymphocyte Ratio for Predicting Mortality among Adult Patients with Acute Pancreatitis: A Meta-Analysis

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Abstract: **Acute pancreatitis (AP) is one of the most common gastrointestinal diseases in hospitalized patients. Numerous severity indicators have been described till date, most of which require reassessment after admission and resuscitation. Neutrophil-to-lymphocyte ratio (NLR) is a biological marker that has been shown to predict the mortality of Acute Pancreatitis. Current scoring systems for AP diagnosis are complicated, whereas NLR is a simple, practical, and effective marker.**

Objectives: To evaluate NLR as an independent prognostic factor for mortality among adults with AP

Methods: We screened cohort studies through Cochrane, Embase, Medline, PubMed in investigating the association between NLR and mortality in AP adult patients up to June, 2020. The primary outcome was mortality. Pooled risk ratio, sensitivity, specificity, and an area under the receiver operating characteristic curve (AUC) was performed by a statistician

Results: Out of the 151 studies searched, there were 5 studies (N= 1999) which met the inclusion criteria for this meta-analysis. Forrest plot analysis showed that elevated NLR (> 12) is associated with 11.5 times increased risk of dying among adult patients with AP (p-value<0.0001, 95%CI: 6.86 to 19.54). NLR has a pooled high sensitivity of 86 %; (p value 0.85, 95%, CI: 78-92%) and a specificity of 73%; (p value 0, 95%CI: 64 to 80%). The pooled accuracy was also high 88% (95%CI=85 to 91%)

Conclusions: In patients with AP, NLR is an independent prognostic factor for mortality among adults with AP. A NLR (>12), is associated with higher risk of mortality.

Keywords: **Acute Pancreatitis; Mortality; Neutrophil to lymphocyte ratio. NLR.**

I. INTRODUCTION

AP is characterized by acute inflammation of the pancreas in patients with upper abdominal pain. AP may present as abdominal pain located at the epigastric or left upper-quadrant and may radiate to the back.[,] The diagnosis is established by two of the following three criteria (1) typical abdominal pain in the epigastrium that may radiate to the back, (2)

threefold or greater elevation in serum lipase and/or amylase, and (3) confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging.[6]

The Philippine Health Statistics reported an incidence of 1,754 per 100,000 population and a mortality rate of 1.8 per 98,011,951 population of AP. [2] The overall mortality rate of AP was 21.1%. Only 2.22% of the patients with a mild disease died, as opposed to 45.63% of the patients with severe pancreatitis. Several parameters and scoring systems using imaging, diagnostics and clinical presentation among patients are available and widely used to predict the clinical course of AP. [8]

NLR has been frequently reported as a significant indicator of systemic inflammation in various medical conditions. The NLR is an easily calculated, systemic inflammation-based parameter. In a number of studies, NLR has been suggested as a marker of AP prognosis. Normal NLR values in an adult, non-geriatric, population in good health are between 0.78 and 3.53. [5]

Among patients with AP who have SIRS and hypoxemia at presentation, there was evidence of severe systemic inflammation as assessed by NLR, D-Dimer and CRP. [4] NLR was found superior than total WBC in predicting adverse outcomes of AP. A NLR is a cut-off value of > 4.7, which is considered a simple indicator of severity in patients presenting with AP.[3] Current data shows increased NLR as an independent risk factor for persistent organ failure, longer ICU stay, and in-hospital mortality in AP.-Quick diagnosis is essential in AP. Current scoring systems for AP diagnosis are complicated, whereas NLR is a simple, practical, and effective marker.[1]

II. OBJECTIVE

To evaluate NLR as an independent prognostic factor for mortality among adult with AP

III. METHODS

1. Search Strategy

This analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An electronic search of the following databases was undertaken: PubMed, Medline, Cochrane Database of Systematic Reviews, EMBASE, and Google Scholar; Search terms included “NLR,” “Mortality”, “Acute pancreatitis,” and “Adults”, “Cohort”. All databases were searched from January 1, 2000-June 30, 2020. Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. A total of 150 studies were searched and screened. 142 of those were excluded due to not related to search strategy. 8 studies were subjected to eligibility criteria and 3 studies were excluded. A total of 5 studies were included in the study. The full search strategy is described in ***Appendix A***.

2. Study Selection

In order to reduce clinical heterogeneity, included in this study are Adult Patients (>18y/o), Diagnosis of AP is confirmed if at least two of the following three features present: 1. abdominal pain characteristic of AP. 2. serum amylase and/or lipase greater than 3 times the upper limit of normal. 3. radiographically demonstrated AP on CT scan or abdominal ultrasound, 4. Cohort Study with mortality outcome. Excluded in this study are 1. Patients do not meet the criteria for AP 2. Patients who are under the age of 19. 3. Patients with chronic pancreatitis. 4. Patients with recurrent AP, 5. Studies without NLR data for Mortality, Case-control or cross sectional studies. Duplicate publications were excluded. Two reviewers (J. Tabanda, A. Quirit) evaluated independently all of the titles identified by the search strategy. The results were then pooled, and all potentially relevant publications were retrieved in full. The same two reviewers then assessed the full articles for eligibility.

3. Data extraction and Validity Assessment

The literature search, data extraction, and quality assessment were independently undertaken by 2 authors (J. Tabanda and A. Quirit)) using a standardized approach. Any inconsistencies were settled by 3rd person (B. Castro) until a consensus was reached. The following details were extracted from included studies using predesigned data abstraction forms: name of first author, year of publication, number of patients included in analysis and mortality of study, cutoff value used to define high NLR, sensitivity and specificity. In the case of any discrepancy during the process of data extraction and evaluation, a cross-check was performed by a biostatistician.

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4. Risk of bias assessment

Validity of included studies was assessed by two independent reviewers (J. Tabanda and A. Quirit) using the Quality in Prognostic Studies (QUIPS) tool. The QUIPS tool comprises 30 questions categorized into six domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). Studies were rated according to each domain as being at low, moderate, or high risk of bias, based on the likelihood that they might alter the relationship between the NLR and Mortality.

IV. STATISTICAL ANALYSES

Extracted data were pooled using RevMan 5.3 analysis software and STATA 14 (Pooled Sensitivity and specificity) by a statistician (R. Salonga) (see Appendix C). Data was analyzed using Area under the Curve (AUC), pooled sensitivity and specificity, and a Forest Plot was created to compare the risk ratio of each study. Estimates for Risk Ratio were pooled and weighted by Mantel Haenszel Model and were computed by fixed-effects. Heterogeneity was assessed using Chi-square and I squared statistics. If significant heterogeneity was present (I 2 > 50% or p-value >0.1 %), a random-effects model was used.

V. RESULTS

Five studies comprising of 1999 patients were included. All studies collected date retrospectively, and all were published in 2000 or later. **Table 1** shows a summarized studies showed different NLR Cut off of 8 to 16, O'Connel (2018) had the highest sensitivity of 100% and Zhou (2019) had the highest Specificity of 84 and highest risk ratio of 26.92.

Table 1. General features of the included studies

Study	Year	Design	Total Patient	Mortality	NLR Cut- Off Value	Sensitivity	Specificity	Risk Ratio
Zhang	2016	Cohort	974	58	11	88	61	9.41
Li	2017	Cohort	359	31	16.64	84	74	11.77
O'Connel	2018	Cohort	185	2	8.01	100	64	2.92
Zhou	2019	Cohort	406	14	12.195	86	84	26.92
Silva-Vaz	2020	Cohort	75	5	14.64	83	76	49.50

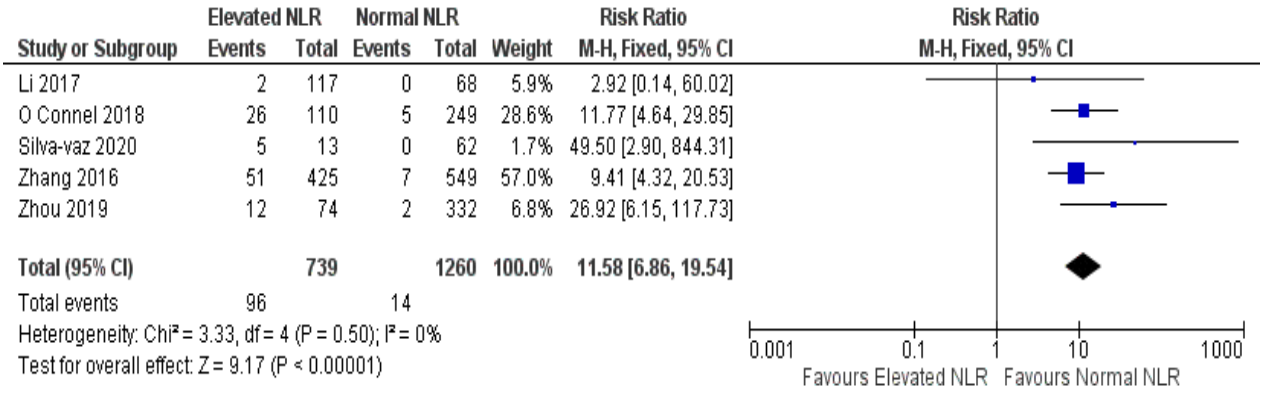

Figure 1. Forest Plot of Risk Ratios

Figure 1 shows a Forest Plot of AP patients with elevated NLR was significantly associated with 11.58 times higher risk of dying compared to those with normal NLR (p-value<0.0001, 95%CI: 6.86 to 19.54). The five included studies were homogenous, I^2 of 0% showed a low to minimal heterogeneity present in the study[18].

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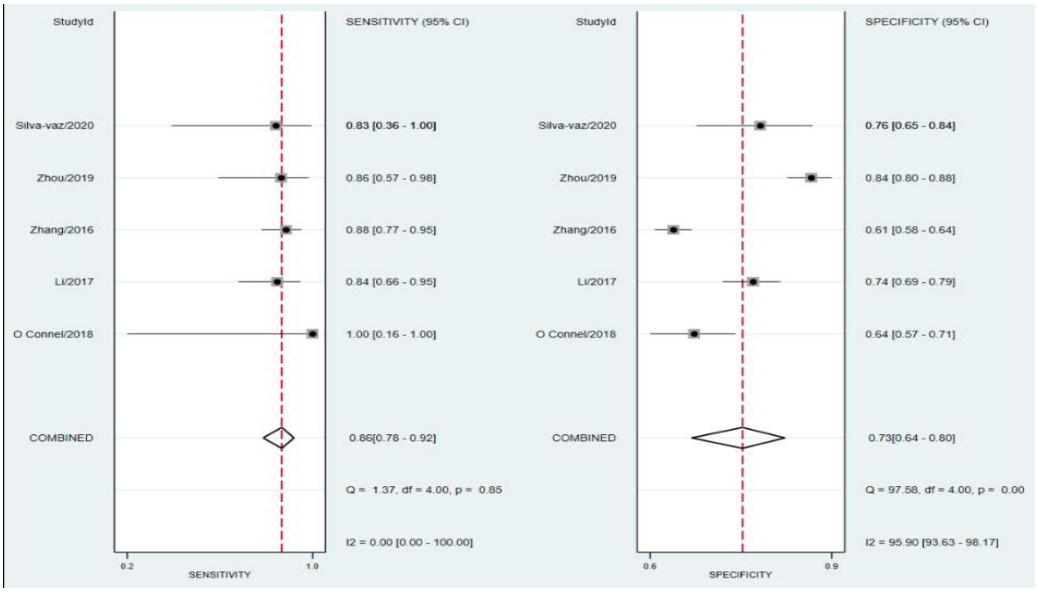

Figure 2. Pooled Sensitivity and Specificity

Figure 2 showed the pooled high sensitivity of 86 %; (p value 0.85, 95%, CI: 78-92%) which means that among those with high NLR, 86% were correctly predicted to die and specificity of 73%; (p value 0, 95%CI=64 to 80%) was acceptable which means that among those with low NLR, 73% were correctly predicted to survive. The pooled accuracy was also high 88% (95%CI: 85 to 91%) as shown in the AUC (Figure 3).

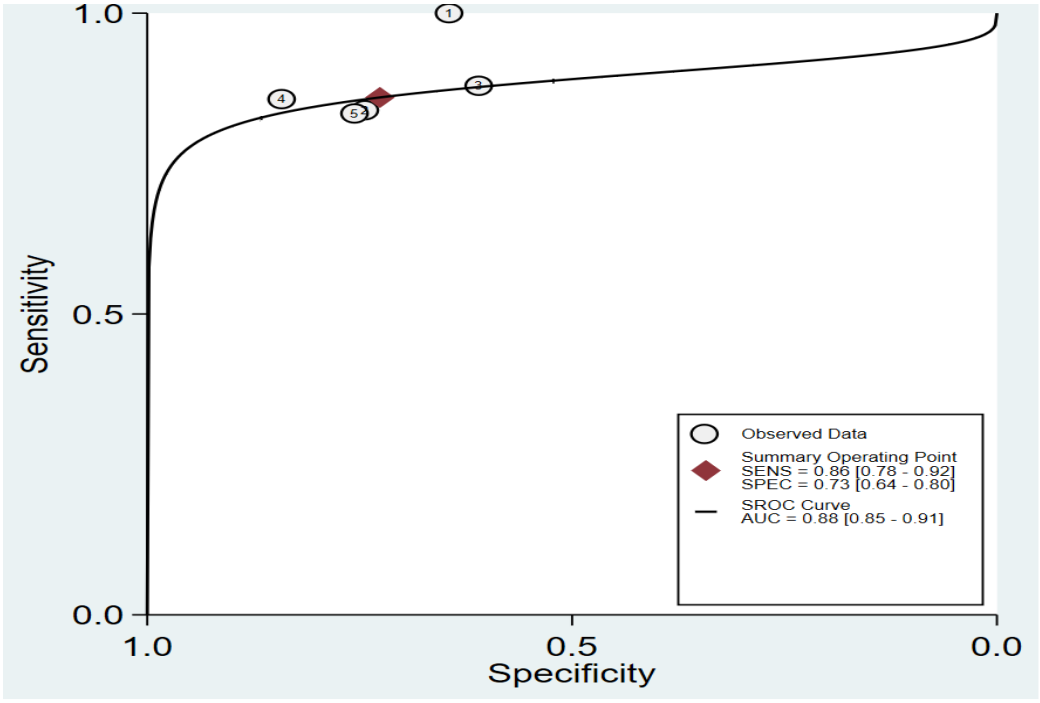

Figure 3. Combined Sensitivity and Specificity

VI. DISCUSSION

AP is an inflammatory disease, with mortality arising mainly from organ failure or infected pancreatic necrosis. The study estimated the prognostic value of NLR for predicting mortality of AP. AP causes imbalance of proteolytic enzymes and protease inhibitors, thus triggering enzyme activation, autodigestion and cell destruction. Once AP has been initiated, the

appearance of interstitial edema and inflammatory infiltration are the basic features of acute pancreatitis. The accumulation of polymorphonuclear granulocytes in pancreatic and extrapancreatic tissue, and the release of leukocyte enzymes play an essential role in the further progression of the disease and in the development of systemic complications[19].

NLR shows various different levels on several factors. First, Women before age 50 had significantly higher NLR than women of 51-70 years of age and higher NLR than men. whereas in age groups of >51 years, it was the reverse[21]. Second, NLR is particularly low in Non-Hispanic Black subjects, from 2.24 observed in Whites to 1.76 in Blacks, Third, NLR is associated with several self-reported chronic conditions, such as diabetes and heart disease, with being a smoker, with high BMI, and with increasing age, all conditions that are known to increase the body inflammatory milieu. Lastly, an index of socioeconomic status, the income to poverty ratio, is inversely associated with NLR, it may due to poor dietary habits, low in nutrients and antioxidants, or lack of physical exercise, or occupational exposures to chemicals and carcinogens[20].

The classification of AUC showed the ability of the NLR to predict mortality was excellent (88 percent)[11]. NLR is an inexpensive and readily available in every hospital or clinic. The study shows a 11.58 times higher risk of dying compared to those patients with low NLR compared to their cut off upon admission. We recommend a NLR cut off of more than 12 based on the study done by Zhou (2019) with the highest specificity among the included studies of 84%. The meta analysis showed a pooled sensitivity of 86 % which means that among those with high NLR, 86% were expected to die and a pooled specificity of 72% which means that among those with low NLR, 72% were correctly expected to survive. The study was accurate enough to predict the mortality in patient with high NLR.

VII. CONCLUSION

In patients with AP, NLR is an independent prognostic factor for mortality among adults with AP. A NLR (>12), is associated with higher risk of mortality

VIII. RECOMMENDATION

A simple, feasible and reproducible laboratory parameter, using NLR (cut off value >12) can be used to predict poor outcome among adult patients with AP. This is the first study to analyze the relationship of NLR and AP, additional randomized controlled trials may be done to strengthen the value of NLR among adult patients with AP.

IX. LIMITATION OF THE STUDY

The number of studies included were limited and patient baseline characteristics were not enumerated from the studies included.

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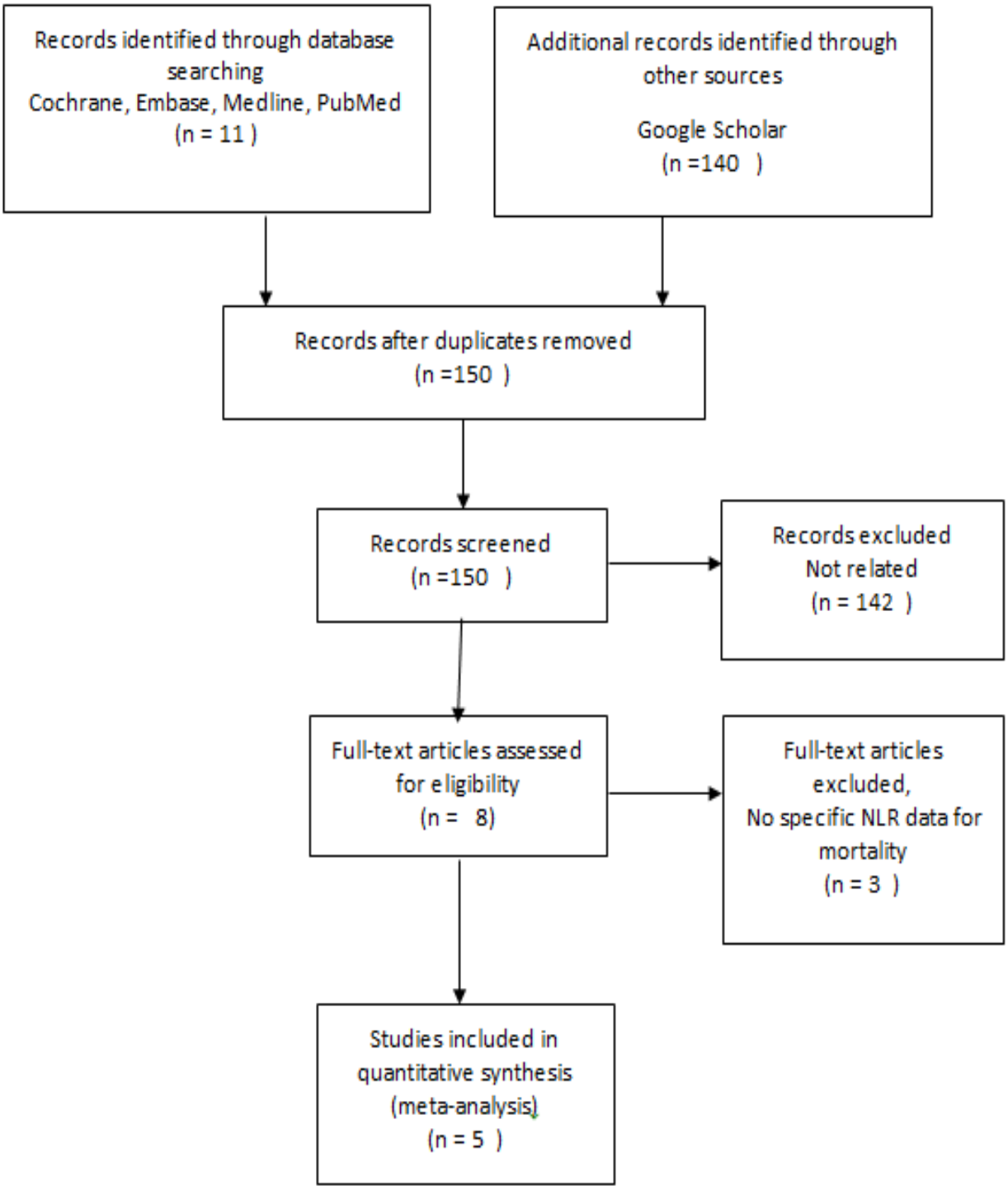
Appendix A



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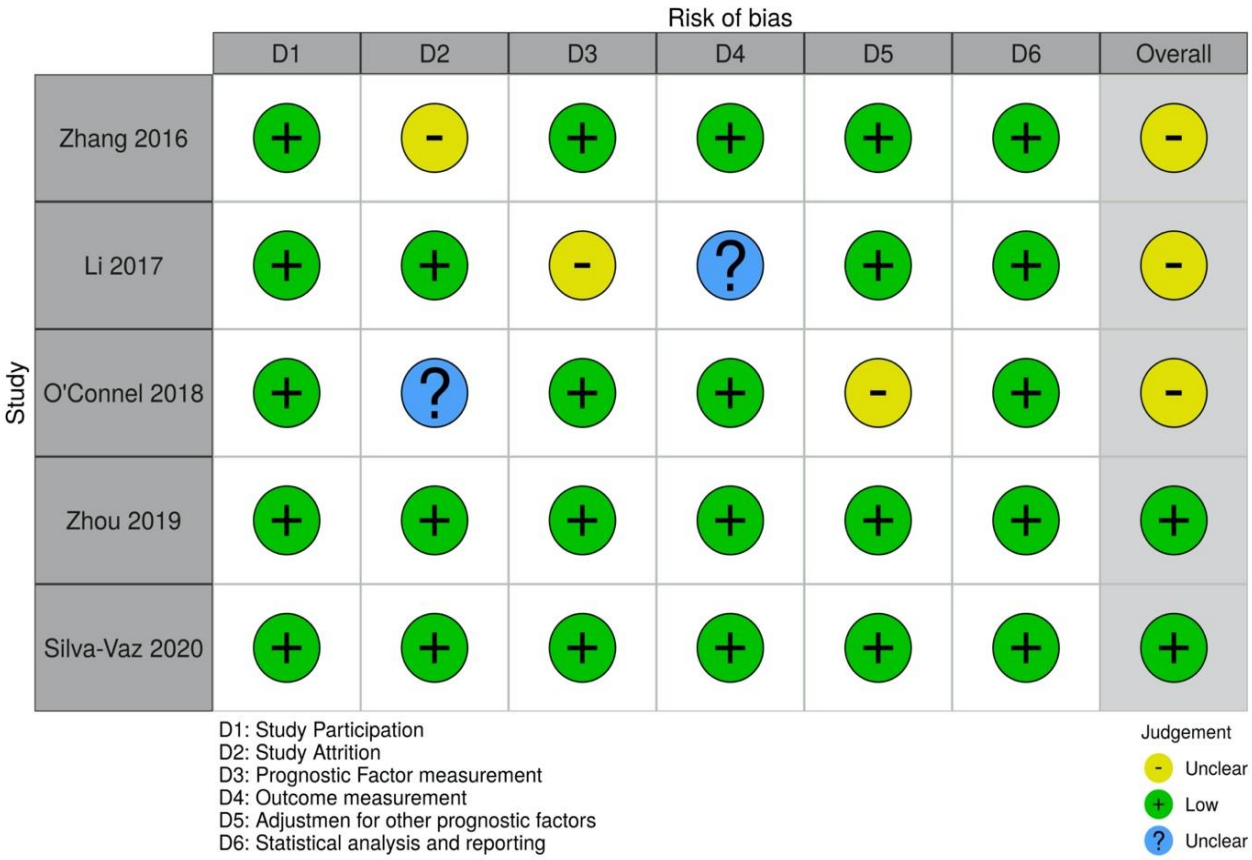

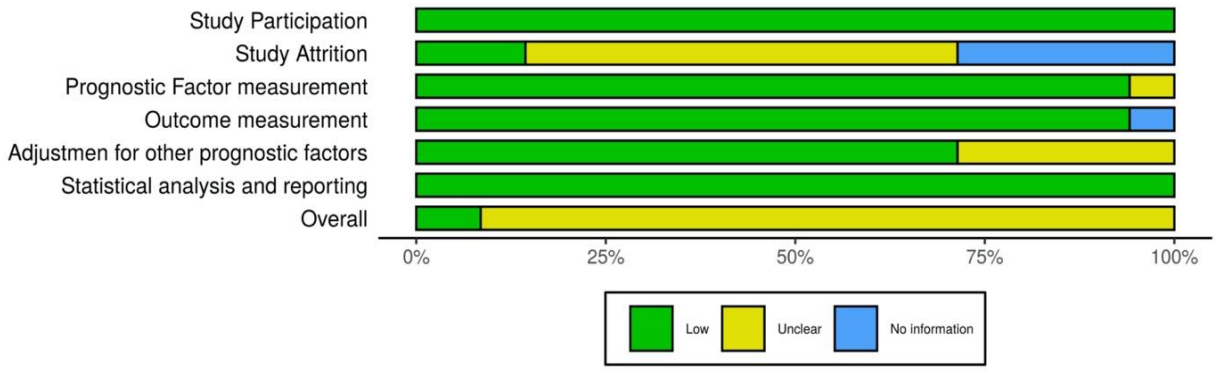

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