Literature Review

Neutrophil to Lymphocyte Ratio in Preeclampsia

Rasio Neutrofil terhadap Limfosit pada Preeklamsia

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Abstract

Objective: To determine the correlation between neutrophil to lymphocyte ratio and preeclampsia. To determine whether neutrophil to lymphocyte ratio can be used as a screening tool for preeclampsia.

Methods: This study was conducted with a systematic review method. Articles that had been gathered and filtered were reviewed by QUADAS-2 tool. Guidelines from the American Congress of Obstetricians and Gynecologists (ACOG) and Pedoman Nasional Pelayanan Kedokteran were used as a diagnostic criteria for determining preeclampsia.

Result: Studies conducted by Kirbas et al, Cakmak et al, Wang et al and Panwar et al stated that there is a correlation between neutrophil to lymphocyte ratio to preeclampsia (p-value < 0.05). Cut-off values are diverse between 3.5 - 5.6 with different sensitivity and specificity.

Conclusions: This systematic review shows that there is a relationship between neutrophil to lymphocyte ratio and preeclampsia. Neutrophil to lymphocyte ratio can be used as screening tools for preeclampsia in the first trimester.

Keywords: neutrophil to lymphocyte ratio, NLR, preeclampsia.

Abstrak

Tujuan: *Mengetahui apakah terdapat hubungan antara rasio neutrofil terhadap limfosit dengan preeklampsia. Mengetahui apakah rasio neutrofil terhadap limfosit dapat dijadikan sebagai alat bantu skrining preeklampsia.*

Metode: *Penelitian ini dilakukan dengan metode systematic review. Artikel yang disaring akan ditentukan kualitasnya menggunakan QUADAS-2. Kriteria diagnostik preeklampsia yang digunakan adalah American College of Obstetricians and Gynecologists (ACOG) untuk penelitian luar negeri dan Pedoman Nasional Pelayanan Kedokteran untuk penelitian dalam negeri.*

Hasil: *Penelitian yang dilakukan oleh Kirbas et al, Cakmak et al, Wang et al, dan Panwar et al menyatakan bahwa terdapat hubungan antara rasio neutrofil terhadap limfosit dengan preeklampsia (p-value < 0.05). Nilai cutoff dari rasio neutrofil terhadap preeklampsia beragam mulai dari 3.5 - 5.6 dengan sensitivitas dan spesifisitas yang berbeda-beda.*

Kesimpulan: *Penelitian systematic review ini menunjukan bahwa rasio neutrofil terhadap limfosit memiliki hubungan dengan penyakit preeklampsia. Rasio neutrofil terhadap limfosit dapat dijadikan sebagai alat bantu skrining untuk preeklampsia pada trimester pertama.*

Kata kunci: *rasio neutrofil terhadap Limfosit, NLR, preeklamsia.*

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INTRODUCTION

Maternal mortality rate is still an issue in many countries. At least 830 women die every day caused by pregnancy and labour. World Health Organization (WHO) claimed 99% death comes from developing countries. In 2015, WHO claimed 303.000 women died during and after pregnancy or giving labour. In the same year, Indonesia sets the target for maternal mortality rate to 102 deaths per 100,000 births. Indonesia in 2015, recorded 305 deaths per 100,000 births and hypertension is the second caused of maternal death.[1-3]

Hypertension in pregnancy is a concerning condition because it can increase morbidity or mortality of the mother or the fetus. This condition also one of the criteria to diagnose preeclampsia. Preeclampsia is a condition marked by high blood pressure and proteinuria and begins after

20 weeks of pregnancy. It is often affected other organs of the pregnant woman. Ten million women suffer preeclampsia every year around the world and up to 76,000 pregnant women die caused by preeclampsia or other hypertension causes.[4-5]

The aetiology of preeclampsia remains unknown. A theory stated that there is an endothelial leakage caused by endothelial dysfunction. When a woman suffers preeclampsia, there will be a secretion of inflammatory cytokines and it will cause endothelial dysfunction which leads to endothelial leakage. When endothelial dysfunction occurs, it is presumed there will be a neutrophil activation that leads to a further endothelial dysfunction.[6]

The neutrophil to lymphocyte ratio can be used to predict preeclampsia and stated that both variables correspond to each other. A study states that the ratio of neutrophils to lymphocytes can be used to detect preeclampsia. However, there are other studies that suggest that the ratio of neutrophils to lymphocytes is not compatible with preeclampsia.[7-9]

Preeclampsia remains a big problem in Indonesia and still donates a significant amount of maternal mortality rate. The aetiology of preeclampsia remains unclear, but there is a theory that stated that there is a correlation between preeclampsia and neutrophils which is supported by the studies above. Considering the urgency of preeclampsia, and to learn further about the correlation between preeclampsia and neutrophil to leukocyte ratio, we are interested in doing this study.

METHODS

This was a systematic review study. Subjects were pregnant women with preeclampsia or severe preeclampsia that had been diagnosed based on ACOG or PNPK criteria. The total population included in this systematic review is 1977 women. Studies from Pubmed, Proquest and EBSCO were included in this study.

The inclusion criteria were every study that is related with neutrophil to lymphocyte ratio and preeclampsia along with p-value, sensitivity and specificity. Studies conducted over the last 5 years and use ACOG or PNPK criteria. The exclusion criteria were studies with only title nor abstract studies using other than English or Bahasa.

The studies that had been gathered will be sorted and filtered based on the inclusion and exclusion criteria. Studies that were included will be reviewed using QUADAS-2 tools to appraise its study.

RESULTS

Studies Quality

Table 1. Risk of Bias QUADAS-2

Studi	Patient Selection	Index Test	Reference Standard	Flow and Timing
Kirbas, 2015	Low	Low	Low	High
Cakmak, 2017	Low	Low	Low	Low
Wang, 2019	Unclear	Low	Low	Low
Panwar, 2019	High	Low	High	Low

Interpretation: there were few high and unclear risk of the studies conducted in this study.[8,10-12]

Table 2. Applicability Concerns QUADAS-2

Studi	Patient Selection	Index Test	Reference Standard
Kirbas, 2015	High	Index	Low
Cakmak, 2017	Low	Low	Low
Wang, 2019	Low	Low	Low
Panwar, 2019	Low	Low	Low

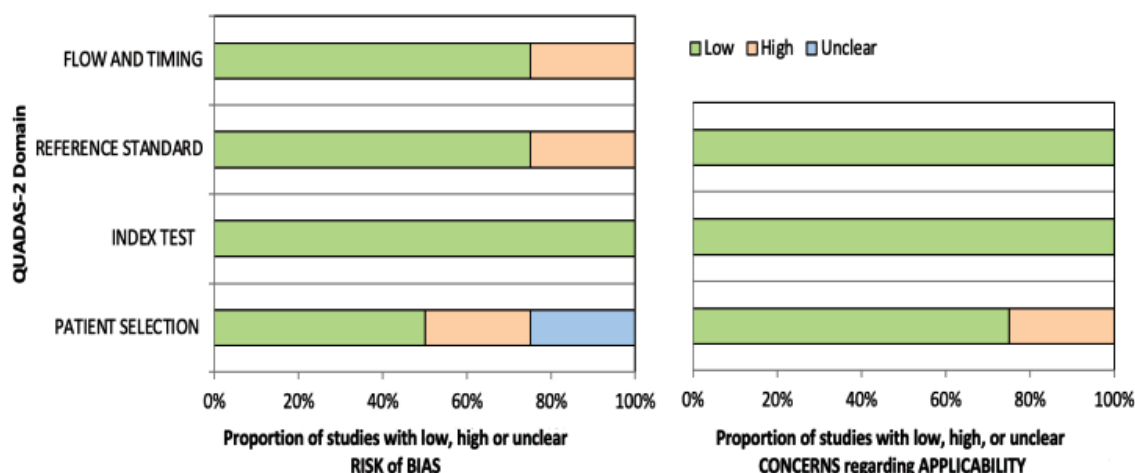*Interpretation: most studies applicable to the study.*

Figure 1. QUADAS-2 Risk of Bias and Applicability Concern.
A stacked bar graphs of studies that were being appraised by QUADAS-2.

Table 3. Studies characteristics

Studi	Year	Country	Age	No. P/K	Criteria	Cut off	*P-value*
Kirbas	2015	Turkey	PE: 29.3 ± 14.3 SPE: 27.9 ± 4.9	614/ 320	ACOG	4.01	
Cakmak	2017	Turkey			ACOG		p < 0.001
			PE: 27 ± 6 SPE: 27 ± 5	100/40		3.5	p < 0.001
Wang	2019	China	PE: 27.7 ± 4.14 SPE: 28.2 ± 4.62	302/161	ACOG	4.19	p < 0.01
Panwar	2019	India	-	64/376	ACOG	5.6	p < 0.001

No. P/C = Number of Patient/ Control, PE = Preeclampsia, SPE = Severe Preeclampsia
Interpretation: p-value of all studies are significant.

Neutrophil to Lymphocyte Ratio

All of the studies taken showed a significant correlation between NLR and preeclampsia (p-value < 0.05). There are studies conducted in Turkey, China and India. Every study has its own subjects characteristic and the population taken is diverse between each study. Each study has its own sensitivity and specificity of NLR cutoff taken and preeclampsia.

DISCUSSION

Preeclampsia is part of hypertension in pregnancy and it is one of the most prominent because of its impact on maternal mortality and perinatal mortality around the world. Preeclampsia is a condition marked by high blood pressure and proteinuria and begins after 20 weeks of pregnancy. Preeclampsia can be accompanied by headache, temporary vision loss, blurred vision, abdominal pain, nausea or vomiting, oliguria, thrombocytopenia, liver dysfunction and shortness of breath.[13]

There are few theories about the pathogenesis of preeclampsia, one theory stated that preeclampsia is caused by the failure of spiral artery remodelling which results in endothelial dysfunction. The syncytiotrophoblast that starved of nutrients and oxygen, reacts by releasing highly inflammatory microparticles into the maternal circulation. These particles have been proposed to contribute to endothelial dysfunction. The endothelial dysfunction will activate neutrophil to make further damage.[14-15]

Based on the results above, all the studies

concluded that there is a correlation between NLR and preeclampsia. One study showed that the NLR correlate with the development of the preeclampsia. The same results can be seen concluded that higher value of NLR in the first trimester can be a predictor for preeclampsia. High NLR can be used to become a diagnostic tool for preeclampsia.[16-17]

This shows that preeclampsia has a relation with the neutrophil and lymphocyte. The increasing NLR value shows that systemic inflammation and endothelial dysfunction are present. This occurs via an interaction of endothelial adhesion molecules and surface receptors on the neutrophil. When the neutrophil activates, granules will be released, and it can mediate vascular damage. Leukotriene will also be synthesized, and superoxide will be generated. Both of these will provoke vascular damage. The mechanism of neutrophil activation remains unknown, but there is a potential mechanism of neutrophil activation has been identified.[18]

The studies also showed various cutoff ranging from 3.5 - 5.6 which every study has its own sensitivity and specificity. This is caused by the differences between each study. The diverse of the population taken from each study is different and the place that the study takes also differs from one another. The studies shows that the specificity of NLR to preeclampsia is over 80% which indicates that it can be used as a screening tool for preeclampsia in the early pregnancy.

CONCLUSIONS

In conclusion, this study shows that there is a correlation between neutrophil to lymphocyte ratio and preeclampsia. Every study that was taken shows that there is a significant p-value for NLR and preeclampsia. Neutrophil to lymphocyte ratio also can be used as a screening tool for defining preeclampsia.

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