A SYSTEMATIC REVIEW OF THE ASSOCIATION BETWEEN ERYTHROCYTE INDICES AND STAGES OF CHRONIC KIDNEY DISEASE

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ABSTRACT

Objective: *To obtain the association between the erythrocyte indices and the stages of CKD.* ***Material & Methods:*** *This is a systematic review study conducted by searching for articles through PubMed, Proquest, and Google Scholar. Publication year are from 2010 to 2020.* ***Results:*** *There are 10 articles analyzed. There were 3 articles that showed a significant association and 2 articles that showed no significant association between erythrocyte indices and stages of CKD. Other article that used anemia morphology to represent the erythrocyte indices showed the normocytic normochromic as the largest percentage. 4 out of 5 articles with CKD patients who were known to be undergoing hemodialysis showed a significant difference in erythrocyte indices.* ***Conclusion:*** *There is association between the erythrocyte indices and stages of CKD.*

Keywords: *Erythrocyte indices, RBC indices, MCV, MCH, MCHC, chronic kidney disease.*

ABSTRAK

Tujuan: *Mendapatkan hubungan antara nilai indeks eritrosit dengan derajat keparahan PGK.* ***Bahan & Cara:*** *Penelitian ini merupakan penelitian systematic review dengan pencarian artikel melalui database PubMed, Proquest, dan Google Scholar. Tahun publikasi artikel dari tahun 2010 sampai 2020.* ***Hasil:*** *Terdapat 10 artikel yang dianalisis. Terdapat 3 artikel yang menunjukkan terdapat hubungan yang signifikan dan 2 artikel yang menunjukkan tidak terdapat hubungan yang signifikan antara indeks eritrosit dengan derajat PGK. Artikel lainnya yang menggunakan morfologi anemia untuk merepresentasikan indeks eritrosit menunjukkan gambaran normositik normokrom sebagai persentase terbanyak. Sebanyak 4 dari 5 artikel dengan pasien PGK yang diketahui sedang menjalani hemodialisis menunjukkan adanya perbedaan signifikan pada indeks eritrosit.* ***Simpulan:*** *Terdapat hubungan antara nilai indeks eritrosit dengan derajat keparahan PGK.*

Kata Kunci: *Indeks eritrosit, MCV, MCH, MCHC, penyakit ginjal kronik.*

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INTRODUCTION

Chronic kidney disease (CKD) is one of the world's health problems with a high burden of health costs.[1] According to WHO's data, 1.2 million people worldwide died due to kidney failure in 2015.[2] Riskesdas (2013) states that CKD occupies 2% of the total noncommunicable disease percentage in Indonesia.[3] CKD is a disease that encompasses a spectrum of pathophysiological processes with various etiologies, associated with abnormal renal function and decreased glomerular filtration rate (GFR).[4-5] Usually, CKD ends up being renal failure characterized by decreased renal function which is irreversible and requires renal replacement therapy. CKD is classified into stage 1 to 5.[4]

Kidney disease is associated with changes in several hematological parameters, one of which is anemia.6 Anemia occurs in 80-90% of patients with chronic kidney disease. This is related to the failure of the kidneys to produce erythropoietin (EPO) which is the hormone controlling the erythropoiesis process.[4,7]

Erythrocyte indices which consist of Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH), and Mean Cell Hemoglobin Concentration (MCHC) can be used to determine the morphology of anemia.[8] Anemia in chronic diseases, including

CKD usually indicates normocytic normochromic anemia.[7] The dominant normocytic normochromic appearance is due to absolute deficiency of EPO. The severity of anemia increases with the increasing degree of kidney damage in CKD. CKD patients receiving hemodialysis treatment are more anemic than non-hemodialysis patients and are usually at an advanced stage (stage 4 or 5). Hemoglobin values and erythrocyte indices are lower in CKD patients that receiving hemodialysis treatment.[9]

OBJECTIVE

This study aims to obtain the association between the erythrocyte indices and the stages of CKD, and obtain a description of the erythrocyte indices in CKD patients.

MATERIAL & METHODS

This is a systematic review. The research was conducted from August 2020 to January 2021. The search for literature used three databases, namely PubMed, ProQuest, and Google Scholar.
The inclusion criteria of this study were:

1. All studies examined the association between the erythrocyte indices and the stages of CKD.
2. Obtained from predetermined databases
3. Full text available
4. Obtained by using predetermined keywords
5. Publication year are from 2010 to 2020.
6. In Indonesian or English
7. Cohort study, case control, and cross sectional
8. The study sample was ≥ 15 years old and ≤ 75 years old

The exclusion criteria of this study were:

1. Publication with abstract / title only
2. In languages other than Indonesian and English
3. Review or case report
4. Not enough data to process
5. The study sample was < 15 years old and > 75 years old

The exposure in this study were the stages of CKD. The outcome in this study were the erythrocyte indices. The keywords used for literature search can be seen in table 1.

Study quality and risk of bias in each literature were reviewed using The Joanna Briggs Institute (JBI) Critical Appraisal.

Table 1. Keywords.

Database	Keywords
PubMed	("Erythrocyte Indices"[Mesh] OR "Red Cell Indices"[Title/Abstract]) AND ("Renal Insufficiency, Chronic"[Mesh] OR "Chronic Kidney Disease"[Title/Abstract])
ProQuest	("Erythrocyte Indices" OR "Red Cell Indices") AND ("Chronic Kidney Disease" OR "Chronic Renal Insufficiency")
Google Scholar	("Erythrocyte Indices" OR "Red Cell Indices") AND ("Chronic Kidney Disease" OR "Chronic Renal Insufficiency") "Indeks Eritrosit" DAN "Penyakit Ginjal Kronik"

RESULTS

The literature search used PRISMA flow diagrams and can be seen in figure 1. The study results can be seen in table 2.

In the study by Salman et al, out of 615 CKD patients, there were 260 (42.3%) in stage 3; 240 (39%) in stage 4; 115 (18.7%) in stage 5. There was a significant association between MCH and MCHC with the stages of CKD.[10] In the study by Devi et al, out of 250 CKD patients there were: 161 (64.4%) in stage 1; 75 (30%) stage 2; 13 (5.2%) in stage 3; 1 (0.4%) in stage 4. There was no significant association between MCV, MCH, and MCHC with the stages of CKD.[11]

The study by Poudel et al stated that there was a significant association between MCV, MCH, and MCHC with the stages of CKD.12 In the study by Loutradis et al, out of 368 CKD patients (184 diabetic and 184 non-diabetic) there were each in each group: 26 (14.1%) in stage 2 ; 127 (69%) in stage 3; 31 (16.8%) in stage 4. There was no significant difference between the diabetic and non-diabetic groups ($p = 0.739$; $p = 0.748$; $p = 0.523$).[13] In the study by Vikrant, out of 584 CKD patients, there were: 72 (12.3%) in stage 3; 193 (33%) in stage 4; 319 (54.6%) in stage 5. Vikrant also compared the erythrocyte indices between diabetic and non-diabetic patients, which did not show a significant difference ($p = 0.391$).[14]

In the study by Shastry and Belurkar, out of 300 CKD patients there were: 1 (0.3%) in stage 2; 26

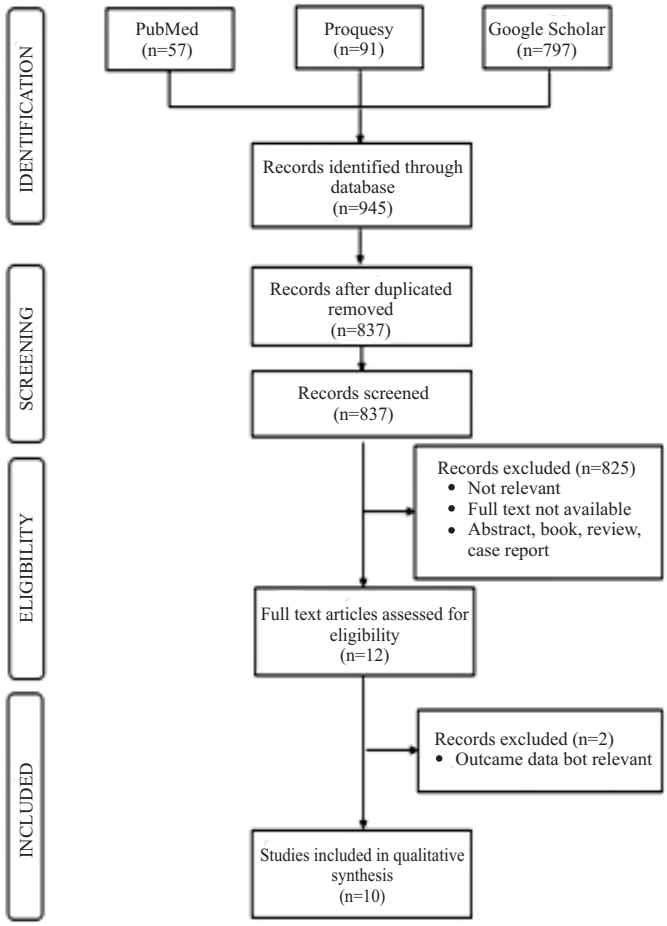

Figure 1. Literature search method.

(8.7%) in stage 3; 67 (22.3%) in stage 4; 206 (68.7%) in stage 5. There was no significant association between MCV, MCH, and MCHC with the stages of CKD.[12] In the study by Gromadzinski et al, out of 73 CKD patients there were: 21 (28.7%) in stage 2; 31 (42.5%) in stage 3; 14 (19.2%) in stage 4; 7 (9.6%) in stage 5. There was significant difference between MCV at stage 3 and 4, MCH at stage 2 and 3, and MCHC at stage 2 and 4 & 5.[16] In a study by Sundhir et al, out of 100 CKD patients there were: 2 in stage 1; 4 in stage 2; 8 in stage 3; 23 in stage 4; 63 in stage 5. MCV, MCH, and MCHC were significantly lower in patients undergoing hemodialysis.[9]

The study by Chowdhury et al compared the erythrocyte indices in pre-hemodialysis and post-hemodialysis patients and found a significant difference in MCV and MCHC before and after hemodialysis.[17] Study by Wantini and Hidayati compared the erythrocyte indices in pre-hemodialysis and post-hemodialysis patients and found significant differences in MCV, MCH, and MCHC before and after hemodialysis.[18]

DISCUSSION

Almost all the studies reviewed showed all three erythrocyte indices within normal limits. This is in accordance with the theory that the main factor of anemia in CKD is an absolute deficiency of erythropoietin due to renal dysfunction and uremic syndrome which causes inactivation of erythropoietin and inhibits the proliferation of progenitor cells to form red blood cells. Deficiency in the production of red blood cells without iron deficiency causes the shape and color of erythrocytes in normal conditions.[9,19] The theory also supports 2 studies which stated that there was no significant association between MCV, MCH, and MCHC with the stages of CKD.[11,15]

Table 2. Study Results Summary.

No.	Authors and Year	Study Design	Sample	Results
1	(Salman M, *et al,* 2016).	*Cross sectional* (retrospective)	615 pre-dialysis CKD patients at Hospital Universiti Sains Malaysia	*Mean Value*: **MCV** = 84.9 ± 7.4 fL (p = 0.33) **MCH** = 28.3 ± 2.7 pg (p = 0.047) **MCHC** = 33.2 ± 1.6 g/dL (p = 0.046)
2	(Devi KR, *et al.,* 2018)	*Cross sectional* (prospective)	250 patients with newly diagnosed type 2 diabetes who visited Diabetes OPD at JNIMS	*Mean Value*: **MCV** = 84.61 ± 6.358 fL (p = 0.84) **MCH** = 28.22 ± 2.65 pg (p = 0.756) **MCHC** = 32.92 ± 2.413 g/dL (p = 0.71)
3	(Poudel B, *et al*., 2013)	*Cross sectional* (prospective)	163 CKD patients who visited the OPD and TUTH Nepalese nephrology unit	**MCV** = p = 0.012 **MCH** = p = <0.001 **MCHC** = p = <0.001
4	(Loutradis C, *et al., 2016)*	*Nested case control*	368 CKD patients who visited the General Hospital in Grevena for the first time	*Mean Value*: **MCV** = diabetic 87.62 ± 6.99; non diabetic 87.9 ± 6.99 **MCH** = diabetic 29.91 ± 5.08, non diabetic 29.78 ± 2.64 **MCHC** = diabetic 323.8 ± 17.6, non diabetic 322.6 ± 20.1 g/L
5	(Vikrant S, 2019) 2019)	*Cross sectional* (retrospective)	584 non-dialysis CKD patients in India	Normochromic normocytic 227 (38.9%); hypochromic normocytic 155 (26.5%); hypochromic microcytic 83 (14.2%); hypochromic macrocytic 63 (10.8%); normochromic macrocytic 56 (9.6%)
6	(Shastry and Belurkar, 2019)	*Cross sectional* (ambispective)	300 CKD patients at Kasturba Hospital India	*Mean value*: **MCV** = 86 ± 7.07 fL (p = 0.576) **MCH** = 28.4 ± 2.59 pg (p = 0.392) **MCHC** = 32.8 ± 1.71 g/dL (p = 0.267)
7	(Gromadzinski L, *et al*., 2014)	*Cross sectional* (prospective)	73 ambulatory CKD patients in Polandia	**MCV** Grade 4 < 3 (p = <0.05) **MCH** Grade 2 > 3 (p = <0.05) **MCHC** Grade 2 > 4 & 5 (p = <0.05)
8	(Sundhir N, *et al*., 2018)	*Cross sectional* (prospective)	100 ambulatory CKD patients at Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research	**MCV** (non-HD) = 81.33 ± 1.98 **MCV** (HD) = 79.66 ± 2.29 (p = 0.001) **MCH** (non-HD) = 26.67 ± 0.99 **MCH** (HD) = 25.91 ± 1.36 (p = 0.003) **MCHC** (non-HD) = 31.04 ± 1.65 **MCHC** (HD) = 30.23 ± 1.71
9	(Chowdhury MNU, et al., 2017)	*Cross sectional* (prospective)	40 CKD patients undergoing maintenance hemodialysis at the Department of Nephrology, Chittagong Medical College Hospital, Chittagong	(p = 0.019) **MCV** (pre) = 96.20 ± 11.57 **MCV** (post) = 92.80 ± 10.75 (p = 0.001) **MCH** (pre) = 29.10 ± 3.62 **MCH** (post) = 28.79 ± 3.77 (p = 0.236) **MCHC** (pre) = 29.25 ± 3.69 **MCHC** (post) = 30.25 ± 3.57 (p = 0.003)
10	(Wantini S & Hidayati A, 2018)	*Cross sectional* (retrospective)	280 chronic renal failure patients undergoing hemodialysis therapy at RSUD Dr. H. Abdul Muluk Lampung	**MCV** (pre) = 88.2267 **MCV** (post) = 87.1467 (p = 0.019) **MCH** (pre) = 30.6733 **MCH** (post) = 29.5733 (p = 0.000) **MCHC** (pre) = 34.7733 **MCHC** (post) = 33.9133 (p = 0.002)

On the other hand, there were 3 studies which stated that there was a significant association between the erythrocyte indices and the stages of CKD. The study by Salman et al stated that MCH and MCHC significantly decreased as kidney function deteriorated. The percentage of patients with stage 5 CKD with moderate and severe anemia was significantly higher than those with other stages of CKD. These findings reflect that the severity of anemia increases with decreased kidney function, which could be due to various factors associated with the development of anemia in CKD, such as erythropoietin insufficiency, iron and vitamin deficiency, malnutrition, inflammation, platelet dysfunction, decreased red blood cell survival, and hemolysis.[10]

The study by Poudel et al, stated that MCV, MCH, and MCHC were significantly decreased in CKD patients as well due to anemia of chronic diseases other than erythropoietin deficiency.[12] Study by Gromadzinski et al showed a significant decrease in MCV values at degrees 3 with 4, MCH at degrees 2 with 3, and MCHC at degrees 2 with 4 and 5.[16]

Medical manipulations such as hemo-dialysis can affect the erythrocyte indices. Out of the 10 studies reviewed, there were 5 studies whose samples were patients undergoing hemodialysis. 4 out of 5 studies showed a significant difference in the erythrocyte indices. The study by Sundhir et al stated that MCV, MCH, and MCHC were significantly lower in patients undergoing hemodialysis compared to those not undergoing hemodialysis. This is because patients with maintenance hemodialysis are usually in an advanced stage (grade 4 or 5) with marked decreases in erythropoietin production and increased nutritional deficiencies (iron and vitamin B12).[9]

The study by Chowdhury et al stated that there were significant differences in MCV and MCHC before and after hemodialysis. The significantly decreased MCV may be due to the correction of intracellular fluid volume during hemodialysis. The significantly increased MCHC may be due to the correction of intracellular fluid volume (RBC) with a consequent decrease in MCV.[17] The results of this study show similarity to a article by Muhammad et al which stated that a decrease in MCV is likely due to loss of erythrocyte membranes during hemodialysis and the increase in MCHC is probably due to the removal of extra waste fluid after ultrafiltration technique in hypervolumic patients.[20]

The study by Wantini and Hidayati stated that there were significant differences in MCV, MCH, and MCHC before and after hemodialysis. Significantly decreased MCV is because patients undergoing long-term hemodialysis will lose blood to the dialyser so they can have iron deficiency.[18] So, it is important for CKD patients undergoing hemodialysis to receive optimal therapeutic interventions such as ESA therapy and adequate intake of iron, folate, and vitamin B12.[9,18]

In the study by Vikrant, the erythrocyte indices was represented by peripheral blood morphology in which normochromic normocytic anemia accounted for the largest percentage (38.9%).[14] Studies by Shastry and Belurkar, Salman et al, and Devi et al, also stated that the most peripheral blood morphology was normocytic normochromic. This peripheral blood morphology can support the erythrocyte indices data. Morphology of normocytic anemia normochrome means MCV and MCH within normal limits.[21] which is also supported by the theory of absolute erythropoietin deficiency.

There were 2 studies by Shastry & Belurkar and Loutradis et al. which showed the use of erythropoiesis stimulating agents (ESA) in the CKD patients studied. Both study results showed that the erythrocyte indices value was within normal limits. ESAs work by increasing the production of red blood cells and thus may play a role in optimizing red blood cell mass. Thus, it can be concluded that the use of ESA by CKD patients in these 2 studies can maintain the erythrocyte indices so that it is still within normal limits.[22]

There are a number of limitations to this systematic review. First, although many journal articles discuss the relationship between erythrocyte indices and CKD, few specifically discuss the relationship between erythrocyte indices values and the stages of CKD, making it difficult for researchers to find studies that can be used in this systematic review. Second, study characteristics such as samples and GFR calculation methods, could not be homogenized due to limited number of studies. Researchers can offer a remedy by maximizing the similarity of inclusion and exclusion criteria and learning more about GFR conversion from various measuring methods.

However, perhaps, this new research, which is presented as a systematic review, will add to our understanding of the association between the erythrocyte indices and the severity of CKD and may be used as a predictor of the type of anemia in each degree of CKD and aid in the selection of the appropriate treatment strategy for each type of anemia.

CONCLUSION

This systematic review study shows that there is a association between the erythrocyte indices and the stages of chronic kidney disease. Erythrocyte indices decreases with increasing stages of CKD. This is due to many factors related to the development of anemia along with decreased kidney function and the processes that occur during hemodialysis. The majority of CKD patient's erythrocyte indices showed values within normal limits with normocytic normochromic morphology.

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