Review Article

Non-nutritional and disease-related anemia in Indonesia: A systematic review

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Non-nutritional anemia, the second most common type of anemia worldwide after nutritional anemia, includes the anemia of inflammation (AI) and that due to helminthiasis. In this review, we examine the contribution that non-nutritional anemia makes to incidence in Indonesia. Anemia due to helminthiasis is a common problem in Indonesia and contributes to prevalence, particularly in children under 5 years. We conducted a systematic literature review based on Google Scholar and Pubmed for non-nutritional anemia. We supplemented this with hemoglobin and chronic disease data in Makassar where prevalence and type of anemia were available. To effectively reduce anemia prevalence in Indonesia, interventions should address both nutritional and non-nutritional contributing factors, including infection and genetic predisposition.

Key Words: anemia of inflammation, helminthiasis, non-nutritional anemia, chronic disease, iatrogenic anemia

BACKGROUND

Anemia is a major public health problem in Indonesia.[1-3] Despite the various efforts of the Indonesian government, such as providing iron and folic acid supplements to pregnant women and food fortification, anemia prevalence has remained high.[4] Anemia typically presents as a symptom of a disease caused by various factors, including that that are nutritional and non-nutritional.[5] The primary causes of nutritional anemia include low nutrient intake but may also be nutritionally responsive and secondary.[6] The secondary causes include impaired absorption, blood transport, metabolism, and storage of nutrients. Because genetic factors underlie the secondary causes, their pathomechanisms are increasingly being delineated through nutrigenomics. For instance, gene polymorphisms affect nutrient metabolism, causing variations in the nutritional requirements for erythrocyte formation. Therefore, to prevent anemia, individuals with such gene variants are required to consume certain nutrients at levels higher than the recommended daily allowance.

Anemia of inflammation (AI) and iron deficiency (ID) anemia (IDA), the two most common forms of anemia worldwide, often coexist in developing countries where the prevalence of malnutrition and infectious disease is typically high.[7] AI is a frequently reported anemia in hospitalized patients and those with ***chronic, metabolic, or infectious disease***. AI prevalence typically increases along with that of its associated diseases including diabetes mellitus (DM), CVD, cancer, tuberculosis (TB), malaria[8] and HIV infection in Indonesia. Obesity, the metabolic syndrome, type 2 DM (T2DM) and CVD are also associated with anemia. In addition, Anemia is also a key feature of ***chronic kidney disease (CKD)***, itself a serious complication of T2DM and hypertension.

Helminthiasis is endemic disease in Indonesia (particularly in <5-year-old children), and contributes to anemia. Therefore, for comprehensive anemia management, the health authorities, systems and workers must identify and mitigate the underlying non-nutritional factors. Intersectoral and eco-nutritional approaches are needed to resolve persistent anemia in Indonesia.[1]

This systematic review discusses AI pathomechanisms and prevalence in Indonesia and globally. Several Indonesian studies, not only of anemia in infectious, chronic, and metabolic disease, but also in helminthiasis are considered. The genetic variations contributory to nutrient absorption, transport, metabolism, and storage and to erythropoiesis are considered.

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METHODS

We searched the PubMed databases as well as Google Scholar and Google search engines for relevant literature using the following keywords: "anemia," "hemoglobin," "inflammation," "kidney," "obesity," "chronic disease," "heart failure," "helminthiasis," "tuberculosis," "HIV," and "Indonesia." Original articles published in both international and Indonesian journals, unpublished theses, and registry data were selected. In total, 39 Indonesian studies from Indonesian journals (35 studies) and university theses (4 studies) were finally included. Internationally published articles on AI in Indonesia were scant. The studies were typically cross-sectional or descriptive, with some o only reporting the proportions or mean hemoglobin levels without describing anemia type. Anemia in helminthiasis data were mostly observational, conducted in Indonesia and published variously in international and Indonesian journals. The definitions of anemia varied with different cutoff points for hemoglobin.

We also obtained data for Makassar from patients of the Clinical Nutrition Department, Universitas Hasanuddin affiliated to the Dr. Wahidin Sudirohusodo Hospital, in Makassar, Indonesia from July 2019 to September 2020.

INFLAMMATION

AI most commonly presents as a mild-to-moderate ***normocytic normochromic anemia,*** which is caused by systemic inflammation that inhibits erythrocyte formation and survival. In AI, hemoglobin rarely drops below 8 g/dL. In contrast to IDA, which is characterized by low serum iron and ferritin, AI exhibits low serum iron but normal or high serum ferritin levels. This phenomenon may be due to the iron redistribution in AI shifting from the location of utilization to that of storage, particularly in the hepatic and splenic mononuclear phagocyte system.[9]

AI is commonly found in patients with chronic systemic inflammatory conditions including both infectious and noninfectious diseases. Thus, AI is typically associated with chronic systemic inflammatory diseases including TB, malaria HIV, acquired immunodeficiency syndrome (AIDS), immune-mediated diseases (e.g., systemic lupus erythematosus), cancerous and hematological malignancies, obesity, T2DM, anemia in elderly persons, anemia in critical illness, congestive heart failure, CKD, and chronic pulmonary diseases.[10]

Tropical infectious diseases, which are typically acute (e.g., typhoid fever), are highly prevalent infectious diseases in Indonesia. The prevalence of other acute infectious diseases, such as diphtheria, pertussis, and morbilli, is extremely low due to successful vaccination by the Indonesian government. However, the prevalence of chronic infectious diseases such as TB and chronic hepatitis remains high, both in children and adults. In Indonesia, the highest prevalence of infectious diseases is seem with upper respiratory tract infection, diarrhea, and pneumonia (4.4%–9.3%, 6.8%–8%, and 2%–4%, respectively), followed by filariasis, pulmonary TB, hepatitis, and malaria (0.8%, 0.42%, 0.39%, and 0.37%, respectively (Indonesian Basic Health Research Data, 2018).[4]

Pathophysiology

Inflammation that occurs in both infectious and noninfectious diseases can lead to increased levels of cytokines, particularly tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, and IL-6. IFN-γ elicits leucocyte proliferation, thus activating macrophages to phagocytose erythrocytes and shortening the erythrocyte life; TNF-α inhibits erythroid precursor proliferation; and IL-6 promotes liver hepcidin synthesis.[11,12] Moreover, proinflammatory cytokines suppress erythropoietin production; this natural mechanism reduces iron availability in the blood to inhibit the survival and reproduction of microorganisms that use iron. Although this adaptative mechanism is beneficial in mitigating acute infections, its chronic continuation in chronic infections can lead to AI and disrupt metabolism.[11]

In plasma, iron binds to transferrin, which carries it to the bone marrow for hemoglobin synthesis. Hepcidin is an iron-regulating hormone that binds to ferroportin to block the iron transfer from duodenal enterocyte cells, macrophages, and liver cells to blood plasma. Under normal conditions, hepcidin synthesis is regulated by the number of iron stores and serum iron levels. However, in low-grade chronic inflammatory conditions such as those in obesity and anemia, increased hepcidin levels have been reported worldwide, including in Indonesia.[13] Hepcidin also worsens impaired renal function and is associated with inflammation.[14]

AI is typically normocytic and normochromic, which means that AI exhibits normal erythrocyte size and normal hemoglobin content (Table 1). In some cases, particularly those of chronic inflammation, AI may be microcytic (small erythrocyte size) and hypochromic (low hemoglobin content).[7]

CHRONIC AND METABOLIC DISEASE

Noncommunicable diseases (NCDs) or chronic diseases result from a combination of factors including those that are genetic, behavioral, and environmental. In Indonesia, hypertension and T2DM incidence is 84 and 20 per 1000 population, respectively.[4] The prevalence of anemia in some chronic diseases among the patients from our department is illustrated in Figure 1.

The prevalence of obesity, a major risk factor for metabolic syndrome, has also increased considerably in Indonesia (Table 2A). In adults, central obesity prevalence

Table 1. Differences in IDA and AI biomarkers

Biomarker	Iron deficiency anemia (IDA)	Anemia of inflammation (AI)
Mean corpuscular volume	Low	Normal
Mean hemoglobin volume	Low	Normal
Reticulocyte hemoglobin content	Low	Normal
Serum transferrin	High	Low
Serum transferrin receptor	High	Normal
Serum ferritin	Low	High
Serum hepcidin	Low	High

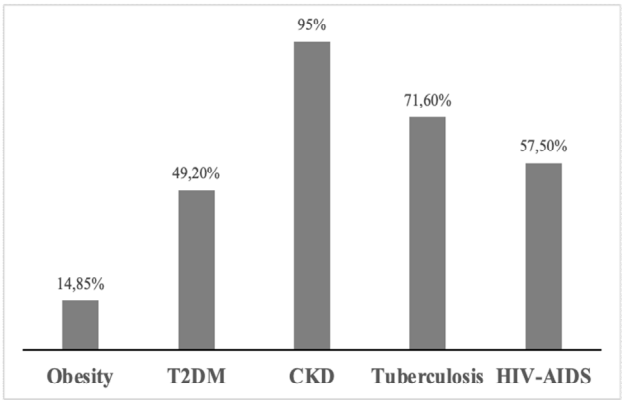

Figure 1. AI prevalance in patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia.

has reached 31%—exceeding the global obesity and overweight prevalence (13% and 39%, respectively).[15] This means that 1 in 3 Indonesian adults has central obesity and thus has an increased metabolic syndrome risk compared with general population.[4]

Corresponding to the increasing national prevalence of obesity reported in Indonesian Basic Health Research (Riskesdas) 2018,[4] Herningtyas et al also found a high metabolic syndrome prevalence (21.7%) among 8573 individuals from 20 provinces and of 27 ethnicities in Indonesia—with the most common metabolic syndrome components being a low HDL concentration and hypertension.[16]

The obesity–ID association has been discussed previously.[17,18] Obesity induces inflammation, thereby increasing the cytokine and hepcidin levels and thus promoting the sequestration of iron in the mononuclear phagocytes system, particularly in the liver and spleen, and reducing iron absorption in the gut.[13]

In four extracted studies including obese individuals,[19-22] the average anemia incidence was 14.85% (range: 6.9%–30%), but not all studies mentioned the anemia type (Table 2B): Wijayanti et al[19] found 12% (4.3% men and 23.8% women) of the included 50 obese individuals to have anemia, but they neither detailed the type of anemia observed nor included nonobese controls in their study. Although obesity is associated with ID, anemia prevalence was lower in obese individuals than in their normal-weight counterparts.[20,21,23] In some conditions, micronutrient deficiency, such as vitamin B-12 or folate deficiency, inflammation, sickle cell disease, bone marrow disorders, thalassemia, and other hemolysis types, might contribute to total anemia.[23,24]

In a Taiwanese study, Huang et al[25] reported BMI to be positively associated with hemoglobin levels, meaning that the BMI the lower is, the higher is the risk of anemia. Moreover, BMI is correlated positively with serum ferritin levels but inversely with serum iron levels. Hence, the BMI–IDA association can be defined to be similar to the definition of IDA.

Moreover, in two Indonesian studies, the anemia prevalence was higher in nonobese individuals than in obese

Table 2A. Obesity by BMI for age groups in Indonesia[1]

No	Age group	Prevalence (%)	CI 95%
1	Children 5–12 years old†	9.2	9.0–9.5
2	Adolescent 13–15 years old†	4.8	4.6–5.1
3	Adolescent 16–18 years old†	4	3.8–4.3
4	Adult >18 years old	21.8	21.7–22.0
5	Adult with Central Obesity	31	30.8–31.2

†Body mass index for age obesity Z score was used.

Table 2B. Anemia in obesity in Indonesia

No	Author	Population	Study design	Anemia prevalence (%)
1	Wijayanti et al., 2018[19]	50 obesity patients. No nonobesity controls	Cross-sectional study	12%
2	Heryati et al., 2014[20]	38 elementary school students with overweight and obesity and 62 students with normal nutritional status	Cross-sectional study	10.5% of obese students 21% in normal nutritional status students
3	Sukarno, Marunduh, Pangemanan, 2016[21]	29 subjects with BMI >25 kg/m^2 31 subjects with BMI <25 kg/m^2	Cross-sectional study	6.9% in obese subjects 15.78% in BMI <18.5 8.33% in BMI 18.5–24.9
4	Nisa, Nissa, Probosari, 2019[22]	30 obesity and 30 non-obesity (based on BMI over age) patients age 15–18 years old	Cross-sectional study	30% in obese subjects and 30% in nonobese subjects

Table 3. Anemia in T2DM in Indonesia

No	Author	Population	Study design	Anemia prevalence (%)
1	Wijaya et al., 2015[26]	46 patients with T2DM with mildly to severely impaired renal GFR (Data from the medical records)	Cross-sectional study	80.4% total anemia, 26.1%, 39.1, 15.2% in mildly, moderately, and severely impaired GFR, respectively
2	Wijaya et al., 2014[27]	192 T2DM patients in RSUP Sanglah Hospital, Bali (Data from the medical record)	Cross-sectional study	Total anemia 41.67%, mild anemia 76.25%, moderate anemia 21.25%, severe anemia 2.5%
3	Balela, Arifin, Noor, 2014[28]	78 T2DM patients	Cross-sectional study	57% in patients with T2DM <5 years 86% in patients with T2DM ≥5 years

GRF: glomerular filtration rate; T2DM: type 2 diabetes mellitus.

individuals: Heryati et al[20] found that among elementary students (aged 10–12 years), anemia was present in 21% of those with normal nutritional status and in only 10.5% of those overweight and obese. Among adults, Sukarno et al. found that nonobese participants with a BMI of <18.5 and 18.5–24.9 kg/m^2 had an anemia prevalence of 15.78% and 8.33%, respectively, whereas obese participants with a BMI of >25 kg/m^2 had an anemia prevalence of only 6.9%.[21] However, none of these studies performed any serum iron assessments. Hence, future studies investigating the iron status–obesity association in Indonesia are warranted.

Type 2 diabetes mellitus

In the Indonesian Basic Health Research in 2018, T2DM prevalence in individuals aged >15 years was 2%[4] based on diagnoses made by a physician—higher than the 2019 global T2DM prevalence (estimated to be 9.3% [i.e., 463 million persons]).[29]

Moreover, the prevalence of AI in T2DM was high in Indonesia: 27.9% and 33.4% in well-controlled and poorly controlled T2DM, respectively.[30] This trend accords with that found by another study: 50 (34%) of 146 patients with T2DM had anemia.[31]

Both obesity and T2DM are associated with low-grade chronic inflammation.[32] In addition, hyperglycemia in T2DM can lead to increased free radical production and worsened inflammation.[33] Hyperglycemia is directly associated with the development of inflammation, as shown by increased levels of proinflammatory cytokines such as IL-6, TNF-α, and nuclear factor κB.[31] Increased IL-6 concentration can lead to a reduction in the sensitivity of the erythrocyte progenitor to erythropoietin and induce apoptosis in immature erythrocytes, in turn reducing the hemoglobin concentration.[34,35]

Studies on anemia in T2DM in Indonesia have generally focused on patients who have experienced complications in the kidney such that the cause of anemia is a combination of inflammation and impaired erythropoietin production.[26-28] The anemia incidence can increase up to 80% with increases in disease duration and kidney disorder severity.[26,28] Based on the Indonesian studies (Table 3), the average prevalence of anemia in T2DM is 49.2%.

In the data on anemia in T2DM obtained from our department patients (Table 4), the prevalence of anemia in T2DM was 79.6%—higher than the prevalence indicated by the national data. The reason for this phenomenon may be the following: as a referral hospital, our hospital receives patients with high-severity T2DM. According to our data, of 93 patients with T2DM, 74 (62.8%) patients had anemia. Of these, 58 (78.3%) had normocytic normochromic anemia, 8 (10.8%) had microcytic hypochromic anemia, 7 (9.5%) had microcytic normochromic anemia, and 1 (1.4%) had macrocytic hypochromic anemia. Our study were was in line with the 2019 study of Saraswati et al[30] in Indonesia: even when the HbA1c levels indicated severe T2DM, the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were normal; moreover, the mean hemoglobin concentration was 13.5 (range: 8.3–17.7) g/dL.

Normocytic normochromic anemia is a common type of anemia in chronic diseases due to the erythrocyte lifecycle being shortened to 80 days in these diseases; moreover, the circulating erythrocyte removal process is related to inflammatory processes.[31]

Chronic kidney disease

Anemia in CKD was initially considered to be associated with impaired erythropoietin production, and thus, it was not considered to be AI. However, recently, inflammation was found to be involved in anemia in CKD. Inflammation increases hepcidin synthesis, promotes erythrophagocytosis, suppresses erythropoiesis in the bone marrow, and reduces erythropoietin production in the kidney. According to the 11th Report of the Indonesian Renal Registry, 78% of patients with CKD had hemoglobin concentrations <10 g/dL.[39] Patients with CKD have the highest rate of anemia, among other chronic metabolic diseases, particularly at the advanced CKD stage, reaching up to 95% (Table 5).[36-40] Minhajat et al[38] found that 95.38% of patients with CKD had anemia, most (88.56%) of whom were at CKD stage 5. Normocytic normochromic anemia was the predominant (66.13%) type of anemia in CKD, consistent with a characteristic of AI. However, microcytic hypochromic anemia was noted only in 13.71% of the patients.

Cardiovascular disease

According to the 2018 Indonesian Basic Health Research (Riskesdas),[4] CVD prevalence in Indonesia is 15 per 1000 population. In their 2018 Indonesian study, Dzakiyah et al[41] found the prevalence of anemia in chronic heart failure to be 37.5%, with most (78.1%) of the participants having NYHA Functional Class III heart failure. The

Table 4. Prevalence of anemia in various diseases in patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia

Disease	n	Mean hemoglobin (g/dL)	Prevalence of anemia (%)	Type of anemia
Malignancy	92	8.1	88	70.4% Normocytic normochromic 12.4% Microcytic hypochromic 3.7% Normocytic hypochromic 1.2% Macrocytic hypochromic 12.3% Microcytic normochromic
Tuberculosis	28	11.1	67.8	57.9% Normocytic normochromic 10.5% Microcytic hypochromic 21% Normocytic hypochromic 5.2% Macrocytic hypochromic 5.2% Microcytic normochromic
HIV	58	10.4	89.6	80.7% Normocytic normochromic 9.6% Microcytic hypochromic 1.9% Normocytic hypochromic 3.8% Macrocytic hypochromic 3.8% Microcytic normochromic
Cardiovascular disease	105	11.7	62	67.9% Normocytic normochromic 29.3% Microcytic hypochromic 3% Normocytic hypochromic
T2DM	93	11.1	79.6	78.4% Normocytic normochromic 10.8% Microcytic hypochromic 9.4% Microcytic normochromic 1.3% Macrocytic hypochromic

T2DM: type 2 diabetes mellitus.

prevalence of anemia in heart failure regardless of the ejection fraction is up to 30% in outpatients and up to 50% in hospitalized patients. Anemia is associated with mortality in heart failure, with a crude mortality risk of up to 1.96. Moreover, in heart failure, anemia might be caused by several neurohormonal activations, which increase inflammatory cytokine levels, resulting in functional ID. Moreover, heart failure can cause renal dysfunction and thus eventually affect erythrocyte production. Loss of appetite in heart failure is also a common finding that leads to absolute ID. Finally, fluid retention can cause hemodilution, which in turn results in reduced hemoglobin concentrations.[42,43]

In our collected patient data, the prevalence of anemia in CVD (including heart failure and myocardial infarction) was 62% (Table 4). Of the 105 patients admitted to the cardiovascular ward, 65 (62%) patients had anemia, of whom 44 (67.7%) had normocytic normochromic anemia, 19 (29.2%) had microcytic hypochromic anemia, and 2 (3%) had normocytic hypochromic anemia. Therefore, in CVD, the predominant type of anemia was normocytic and normochromic—consistent with the characteristics of AI.

Because ID prevalence potentially contributes to ane-

Table 5. Anemia in CKD in Indonesia

No	Author	Population	Study design	Prevalence
1	Adiatma DC et al., 2014[36]	35 CKD patients with hemodialysis. stage 1-4 CKD 29%, stage 5 CKD 71%	Cross-sectional study	Total anemia: 86%, anemia of chronic disease 80%, IDA 10%, hemolytic anemia 3.3%, posthemorrhagic anemia 6.7%
2	Aisara S, Azmi S, Yanni M. 2018[37]	104 CKD patients with HD	Observational-descriptive study	Hb <7: 6.7% Hb 7-10: 68.3% Hb >10: 25%
3	Minhajat, 2016[38]	130 CKD patients stage 3b (2 pts), stage 4 (8 pts) stage 5 (120 pts), 43% with HD in RSUP dr. Wahidin Sudirohusodo Makassar	Cross-sectional study	Total anemia: 95.38% (88.56% in stage 5) Normocytic normochrom: 66.13% Microcytic hypochromic: 13.71%
4	PERNEFRI. 11th Report of Indonesian Renal Registry, 2018[39]	87,710 chronic kidney disease patients	Registry	Hb <10: 78% Hb >10: 22%
5	Suega K, Bakta M, Dharmayudha TG et al. 2005[40]	26 CKD-dialytic patients 26 CKD-predialysis patients	Cross-sectional study	96.2% in dialytic group 30.8% in the predialysis group

CKD: Chronic Kidney Disease; IDA: Iron Deficiency Anemia; HD: Hemodialysis; RSUP: Rumah Sakit Umum Pusat (Central General Hospital); PERNEFRI: Perhimpunan Nefrologi Indonesia (Indonesian Nephrology Association); Hb: Hemoglobin.

mia in heart failure, further relevant studies are recommended.

CANCER

In cancer, anemia can occur independently due to chemotherapy, typically as a consequence of chronic inflammation, and its features can resemble those of anemia in chronic inflammatory diseases. In most cases, anemia in cancer is normochromic and normocytic, with normal-to-low serum iron levels, low total iron-binding capacity,[44] and possibly, normal-to-high serum ferritin levels.

In an Indonesian study,[45] 50% of the four hematology and lymphoma malignancy cases had anemia; moreover, 47.8% of patients with solid cancer had anemia, and the factor that significantly influenced the hemoglobin concentration was radiotherapy dose: when the dose was <60 and >60 Gy, anemia prevalence was 29.4% and 57.6%, respectively. However, in 2002, Harrison et al[46] found that 41% of patients with cancer has anemia before radiotherapy initiation, and this number increased as radiotherapy progressed. Moreover, anemia prevalence was the highest in patients with uterine or cervical cancer both before and after radiotherapy (75% and 79%, respectively), and patients with head and neck cancer had the lowest mean hemoglobin concentrations during radiotherapy (1.8 g/dL).

According to our data on department patients with malignancies such as colon cancer, head and neck cancer, and ovarian cancer, the prevalence of anemia in cancer was 88% (Table 4). Of 92 patients with malignancy, 81 (88.1%) had anemia, of whom 57 (70.4%) had normocytic normochromic anemia, 10 (12.3%) had microcytic hypochromic anemia, 3 (3.7%) had normocytic hypochromic anemia, 10 (12.3%) had microcytic normochromic anemia, and 1 (1.2%) had macrocytic hypochromic anemia. Thus, our data indicated that the most common type of anemia in cancer was normocytic and normochromic—the typical AI.

TUBERCULOSIS

The highest TB burden in the world is in India, followed by China and Indonesia.[47] Indonesia has a pulmonary TB prevalence of 0.4%.[4] As a disease involving chronic inflammation, the incidence of anemia in TB is high. Pulmonary TB can be characterized by several inflammatory markers, such as C-reactive protein (CRP) and other cytokines (i.e. IFN-γ, IL-6 and TNF-α). Hence, in patients with pulmonary TB, anemia may be caused by AI, blood loss, hemoptysis, malnutrition, and pyridoxin deficiency (a side effect of isoniazid).[48]

Of all studies found in our literature search, most (n=13) were discussed anemia in patients with pulmonary TB (Table 6). The average prevalence of anemia in pulmonary TB was 50%–70%, including that of normocytic normochromic and microcytic hypochromic anemia being 5.8%–54.8% and 47%–81.48%, respectively (Table 6).[48-60] In Indonesia, in addition to inflammation, a combination of many factors such as low protein and micronutrient intake can contribute to anemia.

In one study,[61] the use of antimicrobial agents in patients with anemia in pulmonary TB completely alleviated the anemia in nearly one-third of the patients after 1 month of treatment and in approximately half of the patients after 2 months of treatment.

In the extracted Indonesian studies, the average prevalence of anemia in TB was 71.6%. In our department patients with pulmonary TB, anemia prevalence was 67.9%. Of 28 patients with pulmonary TB, 19 (67.9%) had anemia, of whom 11 (39.2%) had normocytic normochromic anemia, 4 (14.2%) had normocytic hypochromic anemia, 2 (7.2%) had microcytic hypochromic anemia, 1 (3.6%) had macrocytic hypochromic anemia, and 1 (3.6%) had microcytic normochromic anemia. In 2019, Mukherjee et al[63] also found normocytic normochromic anemia to be the predominant type of anemia in pulmonary TB, with a prevalence of 56.9%.

HIV/AIDS

In 2018, Indonesia had 640 000 individuals living with HIV, and it had an HIV infection prevalence of 0.17% among all age groups and of 0.4% among adults.[62] In 2017, the number of new HIV cases was 1.94 million globally. Although the number of new cases has decreased recently, the increased use of antiretroviral therapy has increased patient survival and in turn increased HIV prevalence (with 35.8 million individuals living with HIV).[63]

Being an infectious disease, HIV/AIDS also leads to AI in many patients (prevalence reaching 76%; Table 7).[64-67] In the Indonesian studies, the average prevalence of anemia in HIV/AIDS was 57.5%. In our department patients (Table 4), the prevalence of anemia in HIV/AIDS was 89.6% (the relatively high prevalence might be due to the generally high disease severity among our referral hospital's patients). Of all 58 patients with HIV/AIDS, 52 (80%) had anemia, of whom 42 (80.7%) had normocytic normochromic anemia, 5 (9.6%) had microcytic hypochromic anemia, 2 (3.8%) had macrocytic hypochromic anemia, 2 (3.8%) had microcytic normochromic anemia, and 1 (1.9%) had normocytic hypochromic anemia. Consistent with other worldwide reports, we also found normocytic normochromic anemia to be the predominant type of AI.

PREGNANCY

Anemia in pregnancy is common worldwide, particularly in developing countries.[5] In Indonesia, the prevalence of anemia in pregnancy (at age >15 years) was 45.1% in 1997; it then increased to 46.5% in 2000, decreased to 37.5% in 2008,[68] and finally, increased again to 48.9% in 2018.[4] The etiology of anemia in pregnancy is multifactorial. However, in general, ID is assumed to be the major cause[69,70] because anemia diagnosis is generally based on hemoglobin measurement alone. Other possible etiologies of anemia include erythrocyte disorders (e.g., thalassemia), malaria, inflammatory diseases, hookworm infestation, and other micronutrient deficiencies, which may be significant factors depending on the geographic setting and population type.[70]

More detailed laboratory examinations are required to distinguish the underlying etiologies. In their study on 399 women in the first trimester of pregnancy, Siridamrongvattana et al[71] found an unexpectedly low prevalence of anemia (19.3%), ID (20.1%), and IDA (6%); of the 77

Table 6. Anemia in pulmonary TB in Indonesia

No	Author	Population	Study design	Anemia prevalence
1	Kalma et al., 2019[49]	21 samples, including seven patients with treatment of 2 months, seven patients with treatment of 4 months, and seven patients with treatment of 6 months at Maccini Sawah Public Health Centre Makassar	Cross-sectional study	Normal hemoglobin level (42.86%) and anemia (57.14%).
2	Sundari et al., 2017[54]	74 pulmonary TB-infected patients: 61% men, 39% women; ages ranged from 18 to 63 (32.6 + 12.2) years; 24 (32%) with the Beijing strain, and 50 (68%) with non-Beijing strain infections.	Cross-sectional study	Hemoglobin level ranged from 8.6 to 14.8 (11.8) g/dL and 8.1 to 16.5 (12.0) g/dL for the Beijing strain and non-Beijing strain, respectively, with more anemia found in Beijing strain patients (71%) than non-Beijing strain (62%) patients.
3	Adzani, Dalimoenthe, Wijaya, 2016[48]	49 pulmonary TB patients	Cross-sectional study	Total: 63.26% of patients with anemia. In men: mild anemia 57.14%, moderate anemia 42.86%; in women: mild anemia 58.82%, moderate anemia 41.18%. In men: 42.86% normochromic normocytic, 42.86% hypochromic microcytic, 7.14% normochromic microcytic, and 7.14% hypochromic normocytic; in women: 5.88% normochromic normocytic, 47.06% hypochromic microcytic, 17.65% normochromic microcytic, 29.41% hypochromic normocytic.
4	Sadewo et al., 2014[55]	692 pulmonary TB patients in West Borneo (2010–2012)	Cross-sectional study	76.4% anemia -59.1% mild anemia -54.8% normocytic normochromic anemia
5	Lasut et al., 2014[56]	67 patients with pulmonary TB at Prof. Dr. R. D. Kandou Manado General Hospital (January 2014–December 2014)	Cross-sectional study	Among 67 patients, 45 patients had hemoglobin levels below the normal value or anemia (65.67%)
6	Fauziah et al., 2013[57]	30 patients with pulmonary TB, 15 men and 15 women (Haji Abdul Halim Hasan Public Health Centre Binjai)	Cross-sectional study	Hemoglobin level before treatment: men: 15.4±0.68, women: 12.94±0.33. After 3 months of treatment, men: 11.88±0.52, women: 10.42±0.44.
7	Fathan et al., 2013[58]	61 pulmonary TB patients in West Nusa Tenggara Barat Province Hospital	Case–control study	Total anemia: 78.7%; normocytic normochromic: 19.52%; microcytic hypochromic: 81.48%
8	Lokollo et al. 2010[59]	22 pulmonary TB patients aged 1–14 years in Kariadi Hospital Semarang	Case–control study	40.9% with anemia
9	Purnasari et al., 2011[60]	30 pulmonary TB child patients at Community Pulmonary Health Center (BKPM) Semarang in Jun–Jul 2011. Patients aged 1–11 years	Cross-sectional study	43.3% of pulmonary TB pediatric patients were anemic. Anemia of chronic disease was found at 61.5%, and iron deficiency anemia at 38.5%.
10	Pramono & Meida, 2003[50]	66 pulmonary TB patients; 43 men, 23 women, PKU Muhammadyah Hospital, Yogyakarta	Cross-sectional study, retrospective from medical records (2000)	65.15% anemia: 100% men, 0% women
11	Karyadi, 2000[51]	41 active TB patients (25 men, 16 women) in Cipto Mangunkusumo Hospital and 41 healthy participant (25 men, 16 women)	Case–control study	58.5% TB patients had anemia; 21.9% healthy controls had anemia. TB patients had mean hemoglobin concentrations 13% lower than healthy controls and 11% lower median hematocrit.
12	Karyadi, 2002[52]	110 TB patients before antituberculosis treatment	Double-blind, placebo-controlled trial	57% TT patients before antituberculosis treatment

TB: Tuberculosis; BKPM: Balai Kesehatan Paru Masyarakat (Community Pulmonary Health Center).

Table 7. Anemia in HIV/AIDS in Indonesia

No	Author	Population	Study design	Anemia prevalence
1	Wisaksana et al., 2011[66]	611 HIV/AIDS patients – ART naïve	Cross-sectional study	Total anemia: 49.6% of 611 ART-naïve patients. Mild anemia: 62%, mod–severe anemia: 38% 67.36% with a high ferritin level
2	Yolanda, 2016[67]	201 HIV/AIDS patients who underwent voluntary counseling and testing	Cross-sectional	76% anemia 5.5% pancytopenia
3	Massang, Edward, Purwanto, 2018[68]	68 HIV/AIDS patients, 34 with Antiretroviral agents and 34 without Antiretroviral agent; nutritional anemia was excluded	Cross-Sectional	Total Median Hb: 11.7 g/dL Median Hb in ARV group: 10.60 Median Hb in non-ARV group 12.63
4	Defiaroza, 2018[69]	10 HIV/AIDS patients	Descriptive	Mean: 13 gr%, SD: 2.26 gr%

ART: Antiretroviral Therapy; ARV: Antiretroviral.

women with anemia, 24 (31.2%) had ID, 20 (26.0%) had thalassemia-related genes, and 33 (42.9%) had unknown underlying factors.

Pregnant women have been reported to have systemic low-grade inflammation,[72] which is correlated with AI.[9] However, Finkelstein et al reported a relatively low prevalence of inflammation (CRP >5 mg/L: 17%; ambulatory glucose >1.0 g/L: 11%) and AI (hemoglobin <11.0 g/dL and serum ferritin >15.0 µg/L plus CRP>5 mg/L or ambulatory glucose >1.0 g/L: 2%) in pregnant women.[73] Nevertheless, AI risk in pregnant women with chronic infectious or metabolic diseases may still be high.[9]

In 2018, Judistiani et al[74] found that 7.5% (201) of pregnant women had anemia, with 24.9% of them noted to have hyperferritinemia. Moreover, proinflammatory cytokine levels increased in women with late pregnancy.

However, the authors did not report any inflammatory markers and reported a positive correlation between ferritin status and anemia only in the first trimester. In addition, they reported that pregnant women with low cholecalciferol levels tended to have anemia, particularly in the third trimester (relative risk: 2.96; 95% CI: 0.36–24.53). Nevertheless, vitamin D deficiency is associated with inflammatory status, and supplementation can alleviate the inflammatory status in some diseases.[75]

HELMINTHIASIS

Infection by soil-transmitted helminths (STH; i.e., helminthiasis), including *Necator americanus* (hookworm), *Ascaris lumbricoides*, and *Trichuris trichiura*, represents a major community health concern in regions worldwide.[76] The pathological process underlying the host response for helminthiasis may lead to inflammatory conditions.[77] In helminthiasis, altered intestinal iron uptake and iron metabolism and intestinal bleeding can lead to ID.[78,79] Moreover, the destruction of the intestinal mucosa impedes the absorption of nutrients, including micronutrients such as iron, negatively affecting the host's nutritional status and immune system.[80]

Globally, a main cause of IDA is infection by parasites such as hookworms, whipworms, and roundworms, which results in intestinal bleeding in the stool.[81] Hookworm infection leads to anemia by inducing chronic intestinal blood loss: infection by *Ancylostoma duodenale* and *N. americanus* can cause blood loss of 0.15–0.2 mL per day. These hookworms release anticlotting factors such as coagulase to prevent blood clots and ensure continuous blood flow.[82]

Disruption of iron absorption can also be due to damage to the intestinal integrity caused by the inflammatory process. Helminthic infection can increase inflammation: in a host, the existence of helminths is detected by the epithelial or immune cells in response to worm products; these cells then release cytokines (e.g., IL-25) from the enterocytes, promote Th2 cell proliferation, and upregulate effector mechanisms (e.g., evocation of eosinophils by IL-5), all to destroy the parasite. However, the helminths manipulate the host immune system by releasing molecules to facilitate the formation of a leaky epithelial barrier.[83] In general, this damage to intestinal integrity can reduce intestinal iron uptake and induce anemia: in children with such parasitic infections, malnutrition may occur due to a lack of essential nutrients, resulting in nutritional anemia.[84]

Prevalence of anemia due to helminthiasis in Indonesia

Approximately 42% of global STH infections occur in Southeast Asia. Of children with STH infections in Southeast Asia, 64% are from India, 15% from Indonesia, and 13% from Bangladesh. In Indonesia, 17 million preschool-age children and 42 million school-age children have an STH infection.[85] STH infection is thus one of Indonesia's leading public health issues, with a high prevalence in the range of 45%–65%. In Indonesia, the highest STH infection prevalence is 80%, mainly in areas with poor sanitation.[86] In a cross-sectional survey in Semarang, Central Java, STH infection prevalence was approximately 34% in 6466 individuals aged 2–93 years.[87] Pegelow et al[88] reported that soil-transmitted nematode infection was predominant in 8–10-year-old children in the rural area of Sukaraja, West Java: based on the testing of 348 stool samples, *T. trichiura* infection was the most prevalent (76%), followed by *A. lumbricoides* (44%) and hookworm (9%) infections. Among 365 blood samples, anemia prevalence was 13%. Moreover, the prevalence of low nutritional status was 51% in general. Table 8 lists the prevalence of anemia in helminthiasis in Indonesia from several studies.[88-98]

In several districts of North Sumatra, helminthiasis prevalence differed considerably between suburban and rural areas. A report from Medan, North Sumatra, reported a high STH infection prevalence in school-age chil-

Table 8. Anemia in Helminthiasis in Indonesia

No	Population/Location	Lab examination	Prevalence (%)					
			Any†	HK	AL	TT	SS	Anemia
1	60 students from five grade 3 and 4 elementary schools in North Pontianak, West Kalimantan[91]	Kato–Katz thick smear Blood tests	16.7					55
2	140 stools of school-age children, Makassar Sulsel[93]	Katokatz method	33.6		24.3	27.9		
3	A total of 331 individuals, aged 1 month to 44 years, Mimika Papua[94]	A single stool sample, using Real Time-Polymerase Chain Reaction for SS		17.2	23.9	18.4	32	
4	132 students, aged 8–12 years, Medan and Deli Serdang Sumut[89]	Direct examination and Kato–Katz method Cobas e601 in the hematology laboratory	7.6					11.4 (serum iron)
5	3 to 70 years Controls: n=244; intervention: n=283 Two villages, Central Java, Indonesia[95]	Microscopically, according to the Willis-Mollay flotation technique	STH: 21.7% in controls and 25.8% in the interventional group					
6	629 children aged 1–59 months from 800 households Mimika Papua[92]	Katokatz method Hb by electronc coulter counter (HB <10 gr/dL = anemia)	37.9 (105/269)	13	27.9	20.8		24.5 (122/497)
7	99 children (3–13 years old) in two villages (intervention and control) south of Semarang City[96]	Microscopic method	20					
8	418 boys and girls aged 0 to 12 years at recruitment[97]	Katokatz method Hb		-	30.6	23.4		22.4
9	8 to 10-year-old students from 10 schools located in the rural district of Sukaraja, West Java, Indonesia[88]	348 stools 365 blood samples		9	44	76		13
10	Two elementary schools in Makassar, the capital city of South Sulawesi[98]	340 stools from individuals of high socioeconomic status 271 stools from individuals of low socioeconomic status Katokatz method	22.4 vs 90.4		5.9 vs 76.8	19.1 vs 87.1		
11	1982 people assigned to albendazole treatment and 2022 to a placebo Ende, East Nusa Tenggara[90]	Polymerase Chain Reaction for HW and AL, microscopic for TT	Baseline Placebo vs Albendazole Any helm 87.2 (571/655) vs 87.7 (533/609) HK 74.5 (509/683) vs 77.3 (486/629) AL 34.9 (238/683) vs 33.2 (209/629) TT 27.1 (258/953) vs 27.8 (237/852)					

†Any: any helminthiasis. HK: hookworm; AL: *Ascaris lumbricoides*; TT: *Trichuris trichiura*; SS: *Strongyloides stercoralis.*

dren (40.3%).[89] Nasution et al[99] reported that STH infection prevalence was 76.8% in Singkuang (56 children) and 87.2% in Sikapas (242 children) primary schools: the prevalence of *A. lumbricoides* infection was 58.9% in Singkuang and 69.8% in Sikapas, that of *T. trichiura* infection was 57.1% in Singkuang and 78.1% in Sikapas, and that of hookworm infection was 1.8% in Singkuang and 19.4% in Sikapas. A consecutive fecal analysis of 132 8–12-year-old students during May–October 2016 in Public Primary School 060925 Amplas, Medan, and 101747 Hamparan Perak, Deli Serdang, indicated that the prevalence of helminthiasis was 7.6%, with that of low serum iron levels being 11.4%.[89]

In North Pontianak, West Kalimantan, helminthiasis was noted in 16.7% of 60 elementary school students, with an anemia prevalence of 55%.[91] In Mimika, Papua, helminthiasis was present in 105 (43%) of 269 children. Anemia (defined as hemoglobin <10 g/dL) was noted in 122 (24.5%) of 497 included children and was associated with hookworm carriage (OR: 2.6, p=0.026) and *Plasmodium*–helminth coinfection (OR: 4.0, 95% CI: 1.4–11.3, p=0.008).[92]

A cohort study[100] on 442 pregnant women in Purworejo District, Central Java, reported that the anemia prevalence was the highest in the second trimester (approximately 37.1%). Moreover, low iron stores were noted in approximately 49.5% women in the third trimester. Most of the included pregnant women (69.7%) were infected with at least one species of intestinal helminths; *T. trichiura* was the most common, followed by hookworm and *A. lumbricoides*.

OTHER CAUSES OF NON-NUTRITIONAL ANAEMIA

Genetic factors

Genetic disorders can also lead to non-nutritional anemia. Iron absorption may be impaired due to genetic abnormalities in the metal divalent transporter-1 gene (*MDT1*). Mutations in *MDT1* have been noted in patients with microcytic anemia, low serum ferritin levels, and liver iron overload.[101] After the iron is absorbed, it is carried by transferrin (TF) in the blood to the liver storage areas, spleen, red bone marrow, and tissues with demand for iron.[102,103] Genetic abnormalities in the TF gene can cause

atransferrinemia and IDA.[104] Moreover, iron carried by TF enters the tissue after being captured by the TF receptor (TFR). Thus, genetic abnormalities in the TFR gene can also cause anemia.

Hepcidin, a regulator of iron levels in the body, inhibits iron absorption by binding to MDT-1. Hepcidin can also attach to ferroportin and block the release of iron from the macrophages to be carried to the site of erythrocyte synthesis. *TMPRSS6* encodes the enzyme maptriptase-2, which controls hepcidin levels and thus plays a role in the development of anemia. The G allele of rs4820268 is associated with low serum iron levels.[104]

Vitamin B-12 deficiency has been linked to many complications, including increased macrocytic anemia risk. In total, 16 studies have identified single-nucleotide polymorphisms (SNPs) that exhibit significant associations with vitamin B-12 concentrations; of these SNPs, 59 are vitamin B-12-related gene polymorphisms, which are thus associated with vitamin B-12 status. However, most of the genes that could explain variations in vitamin B-12 concentrations have been identified in Caucasian populations.[105]

Megaloblastic anemia involves disturbed DNA synthesis, which results in morphologic and functional changes in erythrocytes, leukocytes, platelets, and their precursors in the blood and bone marrow. This type of anemia is characterized by the presence of large, immature, abnormal erythrocyte progenitors in the bone marrow, and 95% of megaloblastic anemia cases are attributable to folic acid or vitamin B-12 deficiency.[106]

Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) are two important folate-metabolizing enzymes involved in the remethylation of homocysteine into methionine as well as in the synthesis of DNA.[107] The common polymorphisms in *MTHFR* (C677T and A1298C) and *MTRR* (A66G) result in reduced in vivo MTHFR and MTRR activity and thus in folate metabolism impairment. Zhang et al[108] found that *MTHFR* (C677T) is strongly correlated with megaloblastic anemia and might participate in its pathogenesis.

The risk of low iron status has been assessed based on a combination of rs3811647 in the TF gene, rs7385804 in the TRF gene, and rs4820268 in *TMPRSS6*; that of low folate status was assessed using the two common *MTHFR* polymorphisms, C677T and A1298C;[108] and that of low vitamin B-12 status was evaluated using rs1801131, rs2298585, rs41281112, and rs3760776. Citrate lyase beta-like (*CLYBL*) encodes a human mitochondrial enzyme. The risk allele A of rs41281112 terminates the translation of *CLYBL*, resulting in the disruption of protein–metal ion binding and leading to vitamin B-12 malabsorption. The rs2298585 in *MS4A3* might disrupt intestinal and gastric epithelial cells rejuvenation as well as vitamin B-12 absorption.

Gastric pathogens reduce vitamin B-12 absorption in the gut. *FUT6* encodes fucosyl-transferase 6, which is involved in forming Lewis-associated antigens, which inhibit the adherence of gastric pathogens to the gastric mucosa. A study showed that rs3760775 in *FUT6* was associated with elevated vitamin B-12 levels.[105]

Iatrogenic anemia

Drugs can induce anemia via several pathways: immunohemolytic anemia, nonimmune hemolytic anemia, methemoglobinemia, megaloblastic anemia, sideroblastic anemia, aplastic anemia, and pure red cell aplasia. Immuno-hemolytic anemia due to the destruction caused by the reaction between antibodies and antigens in the erythrocyte membrane (e.g., penicillins and cephalosporins). Non-immune hemolytic anemia is hemolytic anemia that is typically caused by side effects of drugs such as primaquine and nitrofurantoin; in these cases, glucose-6-phosphate dehydrogenase deficiency is common. Methemoglobinemia, which is anemia due to excessive methemoglobin production, can be induced by several drugs that oxidize hemoglobin (e.g., phenazopyridine, dapsone, primaquine, local anesthetics, isobutyl nitrite). Acquired megaloblastic anemia can be caused by vitamin B-12 with or without folic acid deficiencies induced by drugs such as trimethoprim, pyrimethamine, sulfasalazine, phenytoin, and antiretrovirals. Drugs such as isoniazid, chloramphenicol, and linezolid can cause sideroblastic anemia by interfering with heme biosynthesis. Aplastic anemia—the failure to produce blood cells (hemoglobin, leukocyte, and platelet)—can be induced by chloramphenicol, sulfonamide, trimethoprim/sulfamethoxazole, and other drugs that can suppress bone marrow function. Pure red cell aplasia can be caused by azathioprine and other immunosuppressants, linezolid, isoniazid, rifampin, IFN-α, chloroquine, allopurinol, and other drugs.[109]

Iatrogenic anemia or hospital-acquired anemia occurs after blood loss due to medical procedures such as surgery, hemodilution due to excessive intravenous fluid administration, and phlebotomy. Surgery can cause blood loss in >20% cases, particularly in high-risk surgical procedures. Phlebotomy also contributes to hospital-acquired anemia.[110,111] Thavendiranathan et al[112] showed that every milliliter of blood drawn can reduce hemoglobin by 0.07±0.011 g/L.

CONCLUSIONS

Despite the many governmental measures, anemia remains a major public health problem in Indonesia. A possible reason for the failure of anemia intervention to reduce anemia prevalence is that the causes underlying anemia are not only nutritional but also non-nutritional. AI, the most common type of non-nutritional anemia, is associated with chronic infectious diseases and NCDs. IDA can also coexist in patients with chronic AI. Anemia in helminthiasis is another type of non-nutritional anemia. For comprehensive and successful mitigation of anemia prevalence in Indonesia, the causes of nutritional and non-nutritional anemia, including genetic and iatrogenic factors must be acknowledged and addressed.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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