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Spatial distribution and identifying biochemical factors affecting haemoglobin levels among women of reproductive age for each province in Indonesia: A geospatial analysis

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Abstract

Anaemia is still a public health problem in Indonesia. The iron supplement program, known as *Tablet Tambah Darah* (Blood Add Tablet) has not yet produced optimal results. This study aimed to identify the cause of anaemia and the factors that influence it. Biochemical indicator data are haemoglobin (Hb), C-reactive protein (CRP), ferritin and serum transferrin receptor (sTfR) from 9,463 women of reproduction age. Data from the Basic Health Research (Riskesdas) project of 2013 were used for the study. ANOVA as well as global and local regression approaches (classical regression and geo-weighted regression) were used to compare the mean Hb and CRP values between provinces and to determine the factors that influence Hb concentrations. The results showed that the distribution of anaemia in Indonesia is uneven and not always caused by iron deficiency. The lowest Hb mean coupled with the highest iron deficiency was found in Papua, where there are high rates of parasitic infections. In contrast, the highest mean Hb coupled with low iron deficiency, and also low infection rates, was found in North Sulawesi. The Hb concentrations were significantly associated by ferritin, CRP and sTfR and there were varying magnitudes between provinces. Although anaemia is mainly influenced by the iron concentration, CRP, ferritin and sTfR can also affect it through their association with inflammatory reactions. Identification of all causes of anaemia in each province needs to be done in the future, while blanket iron supplementation should be reviewed.

Introduction

Anaemia is a condition in which the haemoglobin (Hb) level and/or the number of red blood cell (RBC) are lower than normal and insufficient to meet an individual's physiological needs. According to the World Health Organization (WHO), the factors that cause anaemia can be broadly divided into four main types: disease (infection and inflammation); social, behavioral and environmental; biological; and genetic (WHO, 2017). A person is considered anaemic if the Hb level is <110 g/L for children aged 6 - 59 months; 115 g/L in children aged 5 - 11 years; 120 g/L in children aged 12 -14 years and non-pregnant women aged ≥15 years; 110 g/L in pregnant women; and 130 g/L in males ≥15 years of age (WHO, 2011). WHO, in collaboration with other United Nation (UN) organizations, recommend that the cyanmethemoglobin method with the HemoCue® system should be the reference laboratory method for determining Hb levels (WHO/UNICEF/UNU, 2001).

In Indonesia, anaemia is still a public health problem, especially in women of reproductive age (WRA). The results of the Indonesian Basic Health Research (Riskesdas) project show that prevalence of anaemia in WRA was 22.7% in 2013 (Ministry of Health, 2013) and 21.3% in 2018 (Ministry of Health, 2018a). Although decreasing, the prevalence of anaemia is still more than 20%, which indicates that it is still a public health problem (WHO, 2011). Long term-anaemia in WRA leads to higher case numbers of anaemia in pregnant women, many of whom are subsequently at risk of giving birth to babies with low birth weight (LBW) that can lead to maternal and infant mortality (Rahman *et al.*, 2016). Health of WRA is thus increasingly important and the goal is to achieve 50% reduction in the global prevalence of anaemia in WRA in 2025 (WHO, 2012).

Iron deficiency is still estimated to be the most common cause of anaemia and contributes to >14.0% of all anaemia cases (Andriastuti *et al.*, 2020). Iron deficiency anaemia (IDA) arises due to reduced iron supply for erythropoiesis due to empty iron stores that in turn affects the formation of Hb in the body. Prevention and treatment of anaemia in Indonesia is done through iron supplementation known as *Tablet Tambah Darah* or Blood Add Tablet (BAT), which is given to adolescent girls and WRA (Ministry of Health, 2018b) as well as to pregnant women (Ministry of Health, 2020). All target groups will receive BAT without exception (blanket approach). However, anaemia is not only caused by iron deficiency (ID), some nutrients (such as folate, vitamin B12 and vitamin A), inflammatory conditions (particularly parasitic infections as they are often chronic) and disorders affecting Hb synthesis and the red blood cell count (WHO, 2011b). Although the Hb level alone cannot diagnose IDA, it is a basic test that should always be carried out.

The serum level of ferritin is the most recommended measurement to determine the presence of ID in both anaemic and non-anaemic patients. It can be used as an indicator to assess iron storage and even replace bone marrow examination which otherwise is the gold standard for ID diagnosis. A reduced serum ferritin level is the earliest indicator of decreasing iron stores (WHO, 2020). Thus, tests for Hb and ferritin are routinely applied for IDA detection. However, ferritin is an acute-phase protein, the level of which can be confounded by infection and inflammation. Therefore the serum ferritin test are not helpful when dealing with populations at high risk for various infections, e.g, various endemic parasite infections (Chaparro and Suchdev, 2019). For this reason, it is necessary to test for the C-reactive protein (CRP), another acute phase protein that serves as an early marker of inflammation or infection and also leads to reduced Hb levels in the body (WHO, 2014a). This protein is synthesized in the liver and is usually found at level less than 10 mg/L in the blood. During infectious or inflammatory disease states, CRP level rise rapidly in the first 6 to 8 hours and peak at level up to 350-400 mg/L after 48 hours.

When inflammation or tissue damage resolves, CRP levels drop making it a useful marker for monitoring disease activity (Pattola *et al.*, 2020). There is a strong association between the elevated level of CRP "a sensitive biomarker" and prediction of premature uterine contractions. Measurement of the level of CRP during pregnancy can be used as a predictive screening biomarker for detection of subclinical infections that cause preterm uterine contraction and hence early intervention and intensive antenatal care to reduce the peri-natal morbidity and mortality (Nakishbandy and Barawi, 2014). Another way to determine the presence of ID and IDA is to measure the serum level of transferrin receptor (sTfR), which is present on the erythroblasts in bone marrow and many other cells. Measurement of sTfR is a novel marker of iron metabolism reflecting iron stores and total erythropoiesis in the body (WHO, 2014b). Thus, to determine evidence-based anaemia in Indonesia, tests for all four parameters need to be carried out. In general, the effect of CRP, ferritin and sTfR on Hb can be done by constructing a global linear regression model with Hb as the dependent variable and CRP, ferritin and sTfR as the independent variables.

Based on data from the Population Administration (Adminduk) as of June 2021, the total population of Indonesia is 272,229,372, 137,521,557 of whom are males and 134,707,815 females (Directorate General of Population and Civil Registration, 2021). Indonesia covers a large area (1,916,906.77 km^2) and the number of islands amount to 16,056 (Central Agency for Statistics, 2019). Because the large numbers and the geographical variability, the number of anaemia cases in each region varies considerably. It has been suggested that the proportion of IDA in Indonesia depends on the different population groups and the variable prevalence of infectious diseases that can cause anaemia (Chaparro and Suchdev, 2019). So far, neither has research on the potential effects on the number of anaemia cases been carried out, nor has their probable association of Hb, CRP, ferritin and sTfR been studied. This study aimed to identify the cause of anaemia, the distribution of infectious diseases and the associated serum factors on WRA in the different provinces, which all have relatively unique cultural characteristics that may influence consumption patterns and behaviour. The overall aim would be to decrease the anaemia problem in Indonesia, so that future interventions will be better and more targeted.

Examination of the serum levels of Hb, CRP, ferritin and sTfR in the Indonesian population is important as the three latter factors greatly affect the Hb level. The purpose of this research was: a). to compare the average Hb, CRP, ferritin and sTfR levels between the provinces, b). to develop a global linear regression model with Hb as the dependent variable and CRP, ferritin and sTfR as the independent variables, and c). to use geographically weighted regression (GWR) for comparison of the the intensity of the effects of CRP, ferritin and sTfR on Hb levels in people living in the different provinces in Indonesia.

Materials and Methods

We used a combination of secondary data and primary data, with the former being 15,947 Hb level data from the Riskesdas 2013 report as biomedical blocks covering WRA belonging to the 25-45 years age group (obtained by *Application for the Use of National Data* from the Health Research Agency, no. 06091601). The primary data were serological information concerning ferritin, CRP and sTfR from the same WRA individuals (n = 9,463) for whom we had acess to secondary data. This information was part of a previous study *National Profile of the Nutritional Status of Iron (Fe) and Vitamin A (VA) in Indonesia* involving 17,117 individuals and conducted by the Center for Public Health Efforts, Health Research and Development Agency in 2016. The ferritin, CRP abd sTfR data were obtained from the Riskesdas 2013 stored biological material by permission obtained through a

Letter of Request for the Use of Riskesdas Specimens 2013 (no. TU- 02-03 /1/10436/2016). There was no specific sampling for WRA as samples were representative of households. Blood samples (biomedical samples) were sub-samples of selected census blocks (BS) from the Provincial Census Blocks (CBs) including a total of 1,000 CBs originating from 33 provinces. We sampled 25 households per CBs. All WRA blood samples collected in each province became research samples automatically.

Analysis of Hb, CRP, ferritin and sTfR levels

The analysis of the CRP, ferritin and sTfR serum samples was carried out by the enzyme-linked immunosorbent assay (ELISA) using a semi-automatic ELISA reader (Chromote 4300) and a microplate washer (Star Fax@2600) following the protocol contained in the instruction manuals for the ELISA kits. The ferritin kits came from NovaTec Immundiacnostica GMBH, Dietzenbach, Germany; the CRP kits were from Cortez Diagnostics Inc., Calabasas, CA, USA; and the sTfR from PT Indec Diagnostics, East Jakarta City and West Java Indonesia. Known standard samples were included for the preparation of calibration curves. Quality control (QC) by testing serum samples with low and high analyte contents and internal calibration were carried out on a daily basis to ensure data accuracy. Every laboratory activity, both methods, materials, tools and personnel carrying out the analyses were periodically validated by including certified reference materials (CRMs) as one of the samples. To compare the levels of Hb, CRP, Ferritin, Stfr of WRA between provinces, we calculated the average levels of Hb, CRP, Ferritin, Stfr of the WRA for each province.

Factors affecting the Hb level

We used i) global regression to find factors that influence the Hb level linearly for all of Indonesia, and ii) local regression to find out factors influencing the Hb level linearly for each province. In the former model, we used 9,463 WRA data with the Hb level as the dependent variabel and ferritin, CRP and sTfR as the independents variables. For the local approach, we used GWR applying a dataset referring to the average level of the four varables per province (n=33). The multiple equation for the linear global regression model for the population according to Uyanik and Guler (2013) was the following:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k + \varepsilon \quad (1)$$

where Y is the Hb serum level; X_1 the ferritin level; X_2 the CRP level; and X_3 the sTfR level.

Simultaneous testing with the F test either shows that the regression of all parameters is equal to zero (H_0) or at least one parameter is equal zero (H_1) (Walpole *et al.*, 2012), while testing each multiple regression coefficient using the t-test for H_0 the i^{th} parameter of the regression is equal to zero versus H_1 where the i^{th} parameter is not equal to zero (Alexopoulos, 2010; Rawlings *et al.*, 1998).

Meanwhile, to find the multiple regression equation for each province, GWR was used based on the following equation:

$$y_i = \hat{\beta}_0 (u_i, v_i) + \sum_k^p \hat{\beta}_k (u_i, v_i)\, x_{ik} + \varepsilon_i \quad (2)$$

where i = 1,2,3,…,33 (since n=33) and consequently is the observed value of the response variable for the i^{th} location; $\hat{\beta}_0 (u_i, v_i)$ the estimated intercept; $\hat{\beta}_k (u_i, v_i)$ the estimated regression coefficients for the k^{th} independent variable at the i^{th} location; x_{ik} the observed value of the k^{th} independent variable at the i^{th} location; the number of independent variables (CRP, ferritin, sTfR) in the model; and ε_i the i^{th} residual (Edayu and Syerinna, 2018; Fotheringham *et al.*, 2002). A spatial weighting matrix, the Gaussian kernel (Bullmann *et al.*, 2018; Ruzgas and Drulytė, 2013; Tigani *et al.*, 2019) and the bi-square kernel function (Mohammadinia *et al.*, 2017; Nugroho and Slamet, 2018), was used to find the regression coefficient for each location. The optimum bandwidth, *i.e.* the coefficient of variation (CV) is expressed by the equation:

$$CV = \sum_{i=1}^{n} [y_i - y_{\neq i}(b)]^2 \quad (3)$$

where $y_{\neq i}(b)$ is the estimated value of y_i with observations at the i^{th} location removed from the estimation process. An iterative process obtains the optimum bandwidth when the minimum CV value is reached (Jung and Hu, 2015). The QQ plot was used to test the normality assumption (Loy *et al.*, 2016; Yap and Sim, 2011). Assumptions were analyzed by plotting the error with the estimated value (Klein *et al.*, 2016; Su and Berenson, 2017; Zhou *et al.*, 2015) as well as the Breusch-Pagan value (Breusch and Pagan, 1979; Halunga *et al.*, 2016). The multicollinearity between independent variables was measured by the variance inflation factor (VIF) greater than 10 (Daoud, 2017; Shrestha, 2020).

Results

Distribution of the average variable levels

The 9,463 WRA of the 15-45 years age group had an average age of 32.2 years. The average levels of Hb, CRP, ferritin and sTfR for each of year in the 33 provinces are presented in Table 1. Based on distribution according to WHO recommendations (2011), there are four groups of pregnancy conditions with respect to Hb levels (not the physiological conditions of pregnancy): normal (Hb ≥ 12 mg/dL), mild (Hb=11.0-11.9 mg/dL), moderate (Hb=8-10.9 mg /dL) and severe (Hb <8 mg/dL) (WHO, 2011b). As seen in Table 1, the populations in the two provinces Papua and West Papua showed mild anaemic condition (Hb =11.0-11.9 mg/dL). The other provinces had normal Hb averages.

An overview of the grouping of Hb levels between provinces is presented in Table 1 and Figure 1. The average Hb levels per province were ordered from small to large and divided into three groups: low (11.82 <= Hb <=12.36), medium (12.36 <= Hb<=12.95) and high (12.95 <= Hb <= 13.61). As seen in Figure 1, the three Hb groups were found to be spatially clustered at the regional level, a fact that emphasizes that the average Hb levels are geographically associated with the populations in the country. Based on the distribution of the CRP levels, most of the WRA in Indonesia are infected (possibly because most of them were in endemic areas for various parasitic diseases) since 26 provinces had an average of CRP level ≥ 3 mg/L (Table 1). Thus, the presumed, non-infectious conditions of WRA were only seen in seven provinces as shown by their low average CRP levels (<3 mg/L) (Table 1).

Factors affecting Hb levels

The regression analysis carried out to get information about which factors affect the Hb level nationally showed that VIF was 1.226876 for ferritin, 1.092325 for CRP and 1.202059 for sTfR. With VIF values <10, there is no violation of the multicollinearity assumption. As the QQ results plot the quantile points following and approaching the diagonal line it can be concluded that the regression model meets the normality assumption. The plot between residuals with the fitted value forming a certain pattern such as a curved graph indicates that the assumption of homoscedasticity was not met. In other words, the data used contains spatial heterogeneity.

The estimation model with the average Hb level as the dependent variable (Y) and ferritin (X1), CRP (X2), sTfR (X3) as the tree independent variables is the following:

$$\hat{Y} = 13.667 + (0.0032)X_1 + (0.0030)X_2 - (0.0425)X_3 \quad (4)$$

with the following p values: 2 x 10^{-16} (intercept), 2 x 10^{-16} (slope for ferritin), 0.205 (slope for CRP) and 2 x 10^{-16} (slope for sTfR). Thus, according to the global regression, the levels of ferritin and sTfR affect the Hb level, but not the CRP level (at p=0.05).

For the GWR, the Breusch-Pagan test value obtained was 232.75, df=3 and p <2.6 x10^{-16} (*i.e.* considerably less than α=5%), so the decision would be to reject H_0. It can then be concluded that the diversity between regions varies at the 5% level of significance and can be analyzed by GWR with the weighted matrix kernel Gaussian function optimum bandwidth obtained from the iteration results that produced the minimum CV value. The bandwidth was 1,471,035 km with CV = 4,492,289, which means that the distance between provinces with values <1471,035 km would have a measurable influence, which larger distances would not.

A global test using ANOVA identified that the GWR model provides a better explanation than the global regression model for the relationship between the response and explanatory variables

Table 1. Aggregate data on the average level of haemoglobin and C-reactive protein by province.

Province no.	Province name	*n*	Hb (mg/dL)	CRP (mg/L)
1	Aceh Special Region	115	12.57	2.92[a]
2	North Sumatera	425	12.81	3.13
3	West Sumatera	197	13.00	5.62
4	Riau	120	13.18	3.20
5	Jambi	122	13.08	3.34
6	South Sumatera	373	12.73	3.89
7	Bengkulu	50	12.36	4.30
8	Lampung	346	13.10	4.82
9	Bangka Belitung	19	12.11	4.87
10	Riau Island	79	12.95	2.55[b]
11	Jakarta Capital Special Region	73	12.80	4.87
12	West Java	1,623	12.85	5.48
13	Central Java	1,468	13.02	3.18
14	Special Region of Yogyakarta	218	12.68	3.14
15	East Java	1,311	13.03	3.50
16	Banten	668	12.61	5.84
17	Bali	190	12.85	2.95[c]
18	West Nusa Tenggara	397	12.84	3.25
19	East Nusa Tenggara	171	13.09	1.13[d]
20	West Kalimantan	156	12,34	3,96
21	Central Kalimantan	34	12.63	4.29
22	South Kalimantan	158	12.80	4.89
23	East Kalimantan	157	12.91	8.24
24	North Sulawesi	109	13.61	2.99[e]
25	Central Sulawesi	152	12.90	4.46
26	South Sulawesi	301	13.18	3.73
27	Southeast Sulawesi	20	12.81	1.70[f]
28	Gorontalo	41	12.88	6.29[g]
29	West Sulawesi	53	12.84	1.88
30	Maluku	83	12.71	3.35
31	North Maluku	47	12.86	5.99
32	West Papua	68	11.851	3.65
33	Papua	119	11.822	6.83

Source: Measurement of 9,463 females, 2013 & 2016. [1,2] are mild anemia. [a,b,c,d,e,f,g] are CRP levels <3 mg/L (non Infection).

[either there is no significant difference between the global regression model and GWR (H_0) or there is a significant difference between the two regression models (H_1)]. The middle total GWR improvement of 1.5052 (p= 0.1446) showed that there was no significant difference between the global regression model and the Gaussian fixed kernel GWR model in explaining the functional relationship between the response variable and the explanatory variables. The bandwidth obtained with GWR using the bisquare kernel weighting matrix was 3,710,409 km with a CV of 4,479787, indicating that the distance between provinces withvalues less than 3,710,409 km would havea greater influence than the distance between districts/cities whose value was more than 3,710,409 km. The results of the bi-square fixed kernel GWR ANOVA obtained a *p*-value of 0.1716 so it does not reject the null hypothesis. This means that at the 5% level of significance, there is no significant difference between the global regression model and the bi-square fixed kernel GWR model in explaining the functional relationship between the response variables and the explanatory variables.

When calculating the Akaike information criterion (AIC) to find the best model, the global regression obtained an AIC of 29.84800, the Gaussian fixed kernel GWR an AIC of 12,41599, and the bisquare fixed kernel GWR an AIC of 13.54958. Even though H_0 was accepted in the ANOVA test between the global regression model and GWR, there was no difference between the two regression models and as the AIC value in the GWR with a fixed Gaussian kernel weighting had the lowest AIC, this model was taken as the best, which suited the purpose of this study, namely to obtain differences in the intensity of the effect of CRP, ferritin and STFR levels with respect to Hb levels between the provinces.

From the best model obtained, a spatial pattern can be made that shows the range of coefficients for each explanatory variable by region. The list of regression coefficient estimators for each province using the GWR with a fixed Gaussian kernel weight based on Eq 4 is shown in Table 2 (where each province has its own GWR model).The spatial pattern for the coefficient of ferritin content (X1) is presented in Figure 2. In this figure, it can be seen

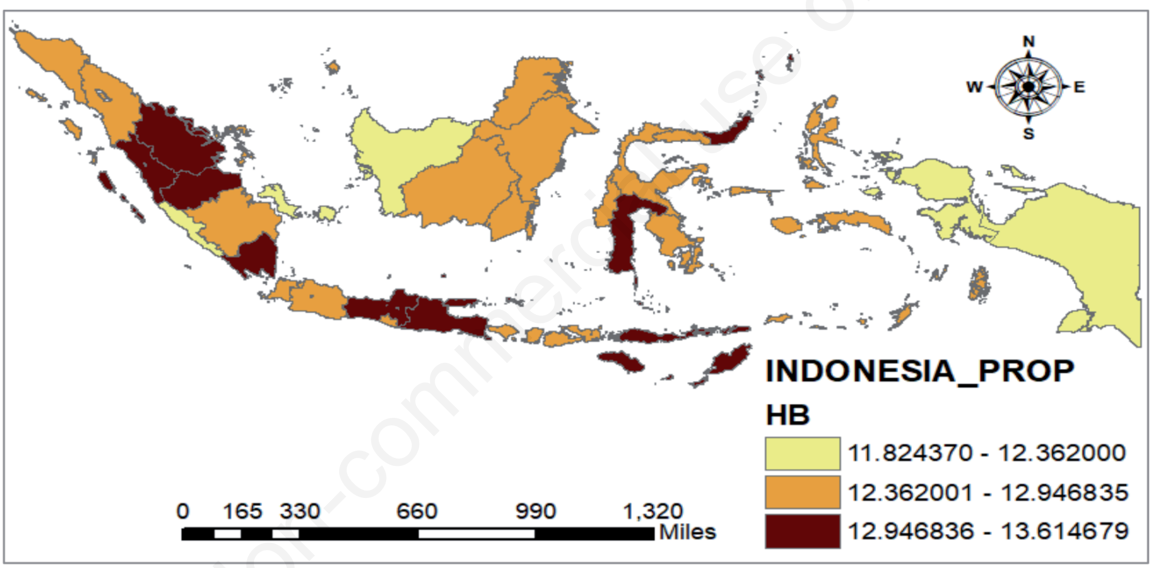

Figure 1. Regional distribution of the average Hb levels in Indonesia.

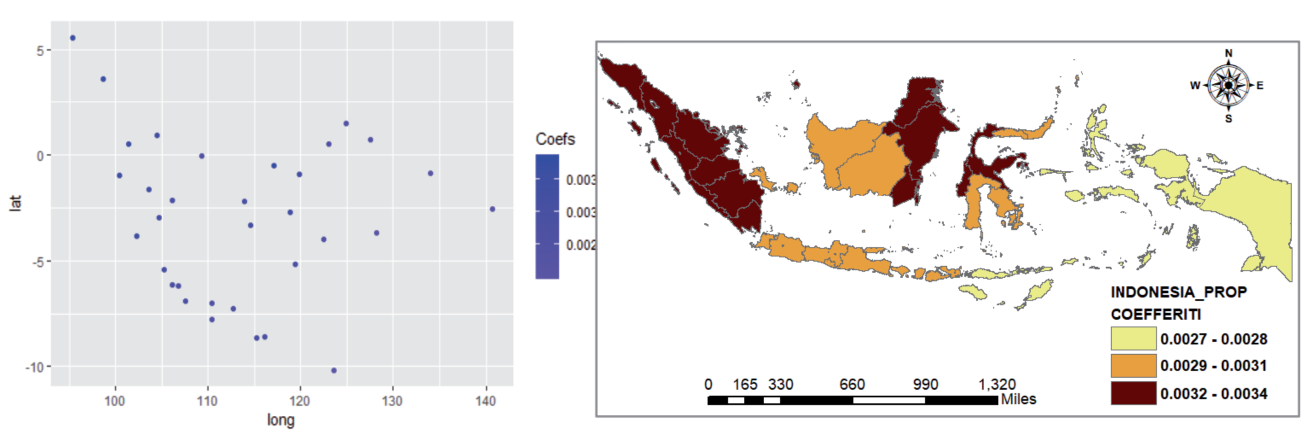

Figure 2. Spatial pattern of coefficient for the ferritin variable (X1).

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that the regression coefficient with ferritin content tends to be positive for all regions. The higher the ferritin level, the higher the Hb level in the body.

The spatial pattern for the CRP coefficient (X2) is presented in Figure 3, where it can be seen that the CRP coefficient tends to be negative for the entire region. This indicates that the relationship between the Hb level and the CRP is negative, *i.e.* the higher the CRP level in the body, the lower the Hb level. Finally, the spatial pattern for the sTfR coefficient (X3) is presented in Figure 4, which shows that the sTfR coefficient varies between regions, with some negative and others positive. For the western part of Indonesia, the sTfR coefficient was generally positive, which indicates a higher Hb level, while for the central and eastern parts of Indonesia, the it tended to be negative. Thus, the higher the sTfR for an area, the higher the Hb in that area.

Discussion

Infectious diseases such as malaria, human immunodeficiency virus (HIV), hookworm infection and schistosomiasis are the main disease that cause anaemia (WHO, 2017). As seen in Tables 1, 2 and Figure 1, the average Hb values of WRA of 25-45 years in each province were normal, though slightly below for the provinces of Papua and West Papua. For WRA of 15-45 years it was found to be >12 mg/dL, except in the two provinces mentioned. Conversely, the highest Hb levels were found in South Sulawesi and North Sulawesi, with low infection and high iron levels. One of the causes of the low Hb in these two provinces is probably due to malaria, HIV and filariasis. Indonesia's 2020 health profile report states that the provinces of Papua and West Papua are the provinces with the highest annual parasitic incidence, while these provinces and West Nusa Tenggara have high malaria endemicity (Ministry of Health, 2021; Ali *et al*., 2022).

Table 2. Parameter Estimator of Gaussian kernel GWR model for each province.

No	Province	b_0	b_1	b_2	b_3
1	Aceh Special Region	12.45663	0.003887	-0.06783	0.018117
2	North Sumatera	12.48996	0.003736	-0.06266	0.016094
3	West Sumatera	12.51027	0.003665	-0.05999	0.014912
4	Riau	12.52378	0.003630	-0.05841	0.014128
5	Jambi	12.55488	0.003565	-0.05535	0.012408
6	South Sumatera	12.57313	0.003539	-0.05388	0.011438
7	Bengkulu	12.53543	0.003599	-0.05721	0.013496
8	Lampung	12.58158	0.003526	-0.05332	0.011018
9	Bangka Belitung	12.59684	0.003519	-0.05218	0.010183
10	Riau Island	12.56783	0.003551	-0.05420	0.011683
11	Jakarta Capital Special Region	12.61000	0.003503	-0.05153	0.009564
12	West Java	12.62516	0.003494	-0.05074	0.008815
13	Central Java	12.68846	0.003490	-0.04820	0.005760
14	Special Region of Yogyakarta	12.68669	0.003487	-0.04831	0.005862
15	East Java	12.75136	0.003506	-0.04666	0.002886
16	Banten	12.59733	0.003511	-0.05229	0.010209
17	Bali	12.82941	0.003519	-0.04575	-0.000460
18	West Nusa Tenggara	12.86194	0.003525	-0.04550	-0.001830
19	East Nusa Tenggara	13.21848	0.003320	-0.04678	-0.015360
20	West Kalimantan	12.66204	0.003513	-0.04871	0.006871
21	Central Kalimantan	12.78753	0.003556	-0.04552	0.001104
22	South Kalimantan	12.80988	0.003558	-0.04532	0.000165
23	East Kalimantan	12.90194	0.003619	-0.04406	-0.003880
24	North Sulawesi	13.29520	0.003464	-0.04373	-0.019080
25	Central Sulawesi	13.02228	0.003616	-0.04372	-0.008710
26	South Sulawesi	13.00354	0.003560	-0.04457	-0.00771
27	Southeast Sulawesi	13.16331	0.003490	-0.04471	-0.01385
28	Gorontalo	13.18918	0.003551	-0.04360	-0.01515
29	West Sulawesi	12.97795	0.003598	-0.04412	-0.00685
30	Maluku	13.53110	0.002995	-0.04736	-0.02671
31	North Maluku	13.47946	0.003190	-0.04513	-0.02543
32	West Papua	13.97379	0.002182	-0.05159	-0.04128
33	Papua	14.46180	0.001088	-0.06288	-0.05572

The 2013 Health Profile also reported that HIV cases in Papua were also high and ranked second after Jakarta Capital Special Region. In addition to malaria and HIV, Papua is also a province with a high number of filariasis cases (Ministry of Health, 2014a). This information may explain the low Hb levels in these provinces.

In addition to infectious and genetic diseases, anaemia can also be caused by social, behavioral and environmental factors. One such factor is the prevailing consumption patterns that can indirectly influence anaemia in an area. It is estimated that most of the anaemia in Indonesia is due to iron deficiency. Lack of intake of iron-rich food results in low Hb levels that leads to IDA. This consumption pattern in West Papua and Papua (Ministry of Health, 2014b, 2018b) may contribute to the particularly low value of Hb values in the people there. Economic parameters, especially poverty, are strong risk factors for the incidence of anaemia (Hakizimana *et al.*, 2019; Kibret *et al.*, 2019). Research on the WRA in Rwanda (Hakizimana *et al.*, 2019) showed that when compared to WRA with poor economic status, well-off WRA were only 0.74 times at risk of anaemia and those with moderate economic status only mariginally more at risk (0.83 times). In 2012, Papua Province was recorded as a province of particularly poor state economically and with many deprived people (966.59 thousand or 31.1%) (Central Agency on Statistic, 2013). Poverty affects the purchasing power of the population and affects access to adequate food. In addition, natural disasters that occurred throughout 2012 had an impact on the 2,331 residents in Papua Province. Indeed, increase in household wealth, educational attainment and access to better sanitation can contribute significantly to the reduction of WRA anaemia (Owais *et al.*, 2021).

Table 1 and Figure 1 show three other provinces, Bangka Belitung, West Kalimantan and Bengkulu characterized by low average Hb levels in their poulations. Although these three provinces have fairly low average Hb levels, they are not classified as provinces with anaemia since their Hb levels are above the cut-off value. However, the factors that may cause the low levels of Hb of people in these three provinces should receive attention, so thery do not slip into anaemia. Although the highest type of anaemia in Indonesia is due to IDA but, this does not apply to the people of Papua and West Papua (Table 1). The average ferritin level of the people there was found to be quite high, 45.58882 and 47.95951 μg/L, respectively, indicating that people there have sufficient iron reserves in the body, so they are not classified as people with iron deficiency. The cut-off for ferritin is 15 μg/L, which means that people below this value are considered suffering from iron deficiency (WHO, 2017). This explains why iron supplements are ineffective in Papua and West Papua. Figure 2 shows that the regression coefficient for ferritin with respect to Hb is relatively small, so the effect of ferritin does not increase Hb. Most likely, the anaemia in Papua and West Papua is haemolytic mediated by malaria (Weatherall *et al.*, 2002), so the ferritin values are not low in these patients and the liver's iron content should be sufficient.

Inflammation as indicated by a CRP values >3 mg/L (WHO, 2014a) is common in people in almost all provinces of Indonesia. Of its 33 provinces, there are only six with an average CRP value <3 mg/L (Table 1). Infections and inflammations in these six provinces are rare in contrast to Papua and West Papua and their higher CRP values Increased ferritin levels increase the Hb levels (Table 2 and Figure 2). These results are in line with the results of previous studies which also showed this positive correlation (Franchini *et al.*, 2007). In healthy adults serum, ferritin is proportional to the level of iron stored in the body (Jacob *et al.*, 1972). This is supported by other studies stating that serum ferritin level is a useful parameter in determining the status of iron stored in the body (Alper *et al.*, 2000; Byg *et al.*, 2000). A study in pregnant women showed a substantial difference between serum ferritin and Hb in women who were not given iron supplements (positive correlation) and those who were given iron supplements (no correlation) (Milman *et al.*, 2000). Research on pregnant women shows that Hb level show large variations in pregnancy conditions according to the level of haemodilution, therefore Hb is a marker of poor iron status. Hb levels <105 g/L (Milman *et al.*, 2000) may be associated with iron deficiency, but only if stored iron is depleted, i.e. if serum ferritin level were <12 μg/L (Milman *et al.*, 1999).

Figure 2 shows that the provinces are Papua, West Papua, Maluku, North Maluku and East Nusa Tenggara (yellow shade in the figure) show a relatively small regression coefficient of ferritin on Hb, which indicates that the effect of ferritin on increasing Hb is relatively weak. This shows that the iron tablet supplementation program in the province is less effective. There may be other factors that have a greater influence on Hb, one of which is infection or inflammation. This is reinforced by the association of CRP on the relatively large decrease in Hb (Figure 3 and Table 2). To overcome the anaemia in the province, the problem of chronic inflammations must be first be controlled. Many provinces in Java, Bali and West Nusa Tenggara (light brown shade in Figure 2) showed a relatively moderate regression coefficient of ferritin with regard toHb indicating that ferritin has a relatively large positive effect on the Hb level (Table 2, Figure 2). The iron supplementation program in the province is quite effective, but the parasitic infections in these provinces must also be controlled. Provinces on the islands of Sumatra (shaded in dark brown in Figure 2) showed a relatively large regression coefficient of ferritin on Hb indicating that the effect of ferritin on increasing Hb is relatively strong (Table 2 and Figure 2), an indication that the iron supplementation program in the province is very effective. In general, these provinces have an average normal Hb level (WHO, 2011). However, treatment of chronic infections must be carried out, especially for all provinces on the islands of Sumatra, Banten, Jakarta Capital Special Region and West Java, because these provinces still have moderate levels of inflammation/infection (Table 2 and Figure 3).

The provinces Papua, West Papua, Maluku and East Nusa Tenggara (shaded yellow in Figure 3), show that the CRP regression coefficient on Hb is large and negative indicating a strong effect of CRP resulting in a decrease in Hb levels. This suggests that the region's level of infection or inflammation is considerable. Figure 2 shows a similar correlation that other factors other than serum ferritin in the region can also affect Hb values. Provinces shaded light brown in Figure 3 are all provinces on the island of Sumatra, Banten, Jakarta Capital Special Region, West Java, North Sulawesi, Southeast Sulawesi and North Maluku, show that the CRP regression coefficient on Hb is moderately negative, which can be related to the moderate to large levels of infections or inflammation in the area. All provinces on the islands of Kalimantan, West Java, Central Java, East Java, Bali, West Nusa Tenggara, West Sulawesi, South Sulawesi and Central Sulawesi Provinces (shaded in dark brown in Figure 3) show that the CRP regression coefficient with repect to Hb is small and negative. This situation indicates that there is an effect of CRP leading to decreasing Hb levels,but it is relatively small, and so is the rate of infection or inflammation in the area.

For the western part of Indonesia, the sTfR coefficient was generally positive, while the central and eastern parts tended to be negative in this regard. This indicates that the higher the sTfR level in this region reflect a decreasing Hb level in the body. sTfR is not substantially affected by the acute phase response but may be affected by malaria, age, ethnicity and gestational conditions. Research in India on iron supplementation in pregnant women has shown that supplementation in non-anemic pregnant women decreased Hb, increased iron stores but did not change the sTfR levels (Nair *et al.*, 2004). This effect may be due to the adequacy of iron in the tissues, which is reflected in lower sTfR levels in non-anaemic women. The sTfR level is not sensitive enough to detect iron supplementation, so the effect on sTfR was only seen in pregnant women with anaemia. There was no increase in sTfR level during pregnancy without iron deficiency, suggesting that the sTfR level during pregnancy only reflects the iron status and that changes in this sTfR biomarker occurs only in the presence of depleted iron stores and anaemia. Thus, high sTfR levels indicate the presence of iron deficient tissue, so it is necessary to pay attention to increase Hb (Nair *et al.*, 2004).

Papua, West Papua, Maluku, North Maluku, East Nusa Tenggara, Southeast Sulawesi, Central Sulawesi and Gorontalo (shaded in yellow in Figure 4) were shown to have large negative sTfR regression coefficients with regard to Hb indicating that the effect of sTfR on Hb reduction is relatively large. This is similar to that seen with CRP. A similar study was reported by Engle-Stone *et al.* (2013), wherer the sTfR levels were positively correlated with CRP and 1-acid glycoprotein. This may be related to malaria, which is endemic many Indonesian provinces, especially Papua and West Papua. When inflammation is present, sTfR is considered a more sensitive indicator than ferritin (Tomkins, 2003). Malaria is likely to cause changes in sTfR level, certain cytokines and body iron content, as haemolysis is known to increase sTfR levels by stimulating the erythropoiesis (Mockenhaupt *et al.*, 1999; Verhoef *et al.*, 2001). The Special Region of Aceh, North Kalimantan, East

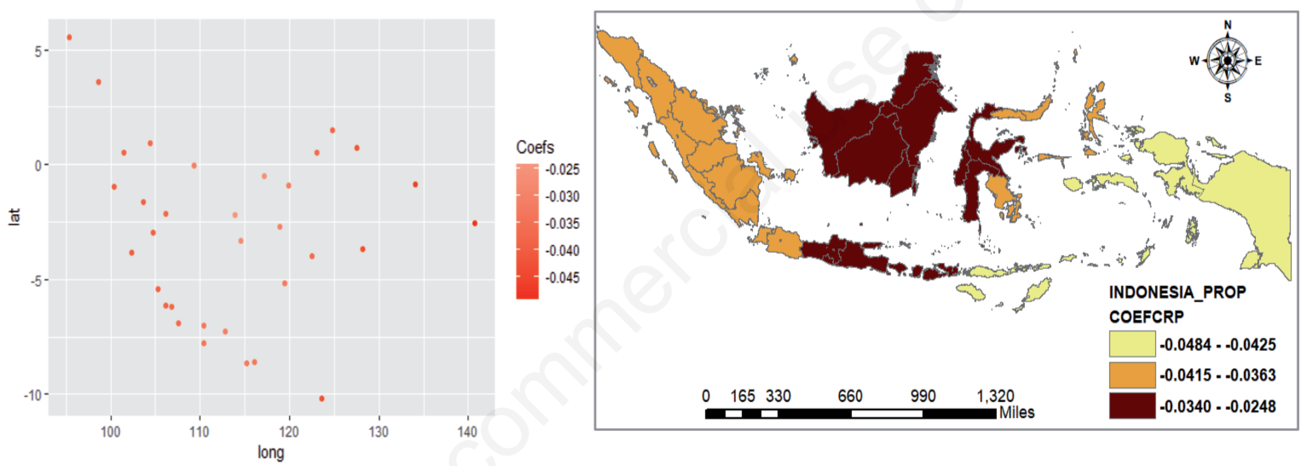

Figure 3. Spatial pattern of CRP variable coefficient (X2).

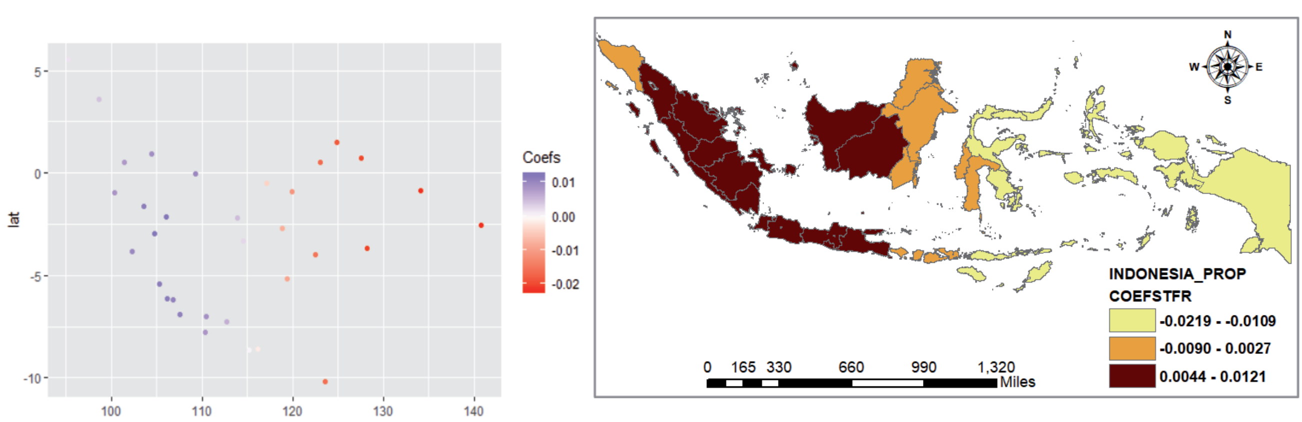

Figure 4. Spatial pattern of variable coefficient sTfR (X3).

Kalimantan, South Kalimantan, West Sulawesi, South Sulawesi, Bali and East Nusa Tenggara (shaded light brown in Figure 4) showed a small negative sTfR regression coefficient with regard to Hb levels indicating that the effect of sTfR on Hb reduction is relatively small. Meanwhile, other provinces (shaded dark brown in the Figure) are all Sumatra provinces except Aceh Special Region. All provinces on the islands of Java, West Kalimantan and Central Kalimantan showed a small positive sTfR regression coefficient with respect to Hb levels, indicating that the increasing effect of sTfR on Hb levels must be relatively small.

The evidence from the above findings suggests that the proportion of anaemia, both caused by iron deficiency and due to infection, is different in each region (and province). This is in accordance with the findings of Chaparro and Parminder (2019), who state that the proportion of IDA is influenced by geography, the influence of differences in population groups, the burden of infectious diseases and the prevalence of other causes of anaemia. Similar findings were put forward in the study by Hakizimana *et al.* (2019) and Kibret *et al.* (2019). Geographical variation is thus a factor associated with the high risk of anaemia in addition to underweight, marital status and intrauterine device use (Hakizimana *et al.*, 2019). The results of research on the identification of risk factors in WRA in Rwanda recommend the importance of new public health interventions that take into account geographical variations in the risk of anaemia, improvement of women's economic status, strengthening iron supplementation programs, especially for intrauterine device users and increased malaria prevention interventions for the alleviation of anaemia in the country (Hakizimana *et al.*, 2019).

Iron supplementation for WRA is a major part of the recommended strategies for controlling and preventing iron deficiency and treating mild to moderate IDA (Nagata *et al*., 2012; WHO, 2017). This strategy is most commonly used to control iron deficiency and iron-deficiency anaemia in developing countries (WHO/UNICEF/UNU, 2001). Figures 2,3 and 4 show that the Government's program for anaemia intervention through blanket approach of iron tablet supplementation needs to be reviewed (Ministry of Health, 2018b), especially in areas with high infection or high rates of chronic disease. In these areas, anaemia interventions should focus on infection/disease control. Other interventions to treat anaemia can be done through several nutrition-specific and nutrition-sensitive solutions as well as control of parasitic infections (malaria, soil-transmitted helminth infections and schistosomiasis) through various approaches (Pena-Rosas and Viteri, 2006; WHO, 2017).

Some limitation were encounteredby this study. For example, the estimation model of factors influencing Hb level s based on global regression shows that an increase of 1 unit of ferritin will increase Hb level by 0.0032 units; and an increase of 1 unit of sTfR will decrease the level of Hb by 0.0425 units. The Hb value shows a value of 13.667 when ferritin, CRP and sTfR = 0. This means that other factors affect Hb level that were not examined in this study. Table 2 also shows that Hb levels in each province are significantly influenced by CRP, ferritin and sTfR with varying regression coefficients or magnitudes of influence. The Hb value shows a high value with a diversity of values between 14.4618 – 12.45663 at the time of ferritin, CRP and STfR = 0 with the highest intercept value of -2nd owned by Papua and West Papua. This suggests that the Hb level in all provinces is more influenced by other factors (socio-characteristics demography, health status, home life, etc.) outside the biochemical indikators, so further research is needed to identify these factors in each province. Hb is influenced by various factors are genetic, disease, biological, social behavior and environment. Biological factors include race, age, gender, physiological conditions (pregnancy and breastfeeding), nutritional status and nutritional deficiencies. Social, behavioral and environmental include income, education, smoking behavior and consumption of alcoholic beverages, hygienic behavior, geographical location and sanitation (WHO, 2017).

Conclusions

This study shows that the geographical disparities in Hb levels in Indonesia are significantly influenced by ferritin, CRP and sTfR with varying influences between provinces. An increase in ferritin levels results in increased Hb levels in the body, while increased CRP levels results in the opposite. However, the effect of sTfR level on Hb level varies between provinces because sTfR is only sensitive in relation to IDA. In addition to these biochemical indicators, Hb levels in all provinces are also influenced by other factors (at the community level) so more research is needed to identify these factors. The administration of iron supplementation for the management of anaemia cannot be the same for the whole province, so blanket approaches must be replaced for treatment schedules and approaches adopted for smaller geographical areas (district or community). Anaemia management needs to pay attention to the need for mapping all causes of anaemia and infection throughout the region so that supplementation can be correctly targeted and better contribute to accelerating the decline of anaemia in Indonesia.

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