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The Relationship between Severe Stage Chronic Kidney Disease and Iron Deficiency Anemia in Children

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ABSTRACT

Chronic kidney disease (CKD) is a serious health problem in children with increasing prevalence and mortality rate. One of the most common complications in CKD is anaemia. When the kidneys fail to function, erythropoietin (EPO) production decreases significantly and reduces red blood cells production in the bone marrow. There have been no studies looking for a link between severe CKD and iron deficiency anaemia in Indonesia. This study assessed the relationship between severe stage CKD and the prevalence of iron deficiency anaemia in children. This research was an observational analytic study with a cross-sectional design involving thirty children at progressed stage of CKD. Research was carried out at Haji Adam Malik hospital, Medan, Indonesia from January to March 2022. Iron status examination was carried out. The relationship between severe CKD and iron deficiency anaemia was analysed using Kruskal Wallis test. There were four (4/10, 40%) children with iron deficiency anaemia at stage 3A. Two (2/4, 50%) children at stage 3B had iron deficiency anaemia. One third of children at stage 4 had iron deficiency anaemia (1/3, 33.3%). Eight (8/13, 61.5%) children at stage 5 had iron deficiency anaemia. Kruskal Wallis analysis test did not show any relationship between CKD stage and iron deficiency anaemia ($p = 0.711$). Iron deficiency anaemia was more common in progressed stages of CKD, where stage 5 had the highest incidence of iron deficiency anaemia. However, this study showed no significant relationship between severe CKD and iron deficiency anaemia.

1. Introduction

Chronic kidney disease (CKD) is an abnormal condition of the functions and structures of the kidneys that last more than three months with the presence of one or more kidney damage symptoms [1]. It is a serious health problem in children, where the prevalence and mortality rate are increasing from year to year. The prevalence of CKD in the world is 800 cases per one million population, while the incidence of end-stage renal disease (ESRD) is at 150 – 200 cases per one million population [2], [3]. The causes of CKD in

children can come from various aetiologies, such as congenital, acquired, or inherited kidney diseases, including metabolic kidney disease. Congenital abnormalities, such as hypoplasia, renal dysplasia, and obstructive uropathy, are the most common causes of CKD in children under the age of five. Meanwhile, CKD in children over the age of five is frequently brought on by genetic conditions like Alport's syndrome or acquired condition like glomerulonephritis [4].

Patients at stage one to three of chronic kidney disease with glomerular filtration rate (GFR) of 30 – 60 ml/min usually do not show symptoms. Clinical symptoms only appear in later stages. Progressive kidney damages can result in an increase in blood pressure from fluid overload and the production of vasoactive hormones, i.e. hypertension, pulmonary oedema, and congestive heart failure. Moreover, the condition may also lead to uraemia (lethargy, pericarditis, and encephalopathy), potassium build-up with symptoms of malaise to fatal conditions, such as arrhythmias, anaemia from decreased erythropoietin synthesis, hyperphosphatemia and hypocalcaemia from vitamin D3 deficiency, and metabolic acidosis from the accumulation of sulphate, phosphate, and uric acid [5]. In general, complication from CKD are brought on by the diminishing functions of the kidney to excrete excess substances, like urea, potassium, and phosphate, in the body [6].

One of the most common complications in children with CKD is anaemia. The data from the North American Paediatric Renal Trials and Collaborative Studies (NAPRTCS) revealed that the prevalence of anaemia in children with CKD ranging from 73% to 93%, depending on the stage of CKD [6]. When the kidneys fail to function, the amount of erythropoietin (EPO) produced decreases significantly and reduces the number of red blood cells produced in the bone marrow. Consequently, anaemia is developed and the red blood cells carry less oxygen than what the body needs [7].

In addition to the decrease in red blood cell productions, the causes of iron deficiency anaemia in CKD patients are blood loss due to blood retention in the tubes and equipment during haemodialysis, malnutrition, and inflammatory conditions, including lupus, arthritis, inflammatory bowel disease, and diabetic ulcers, including other issues involving the bone marrow [8]. There have been no studies looking for a link between severe CKD and iron deficiency anaemia in Indonesia. Therefore, this study was carried out to observe the relationship between severe stage CKD and the prevalence of iron deficiency anaemia in children.

2. Materials and Methods

This research was an observational analytic study with a cross-sectional design study to assess the relationship between severe stage chronic kidney disease, stage 3 to 5, and iron deficiency anaemia in children. This research was carried out at the Paediatric Nephrology Polyclinic and Paediatric Ward Haji Adam Malik hospital Medan, Indonesia from January to March 2022.

2.1 Research Subjects

Research subjects were children over two years old and under 18 years old with chronic kidney disease stage 3 to 5 (GFR < 60 ml/min/1.73 m^2). Child patients were excluded from the research subjects if they had digestive tract disorders, such as gastric and stomach resection, oesophageal varices, gastrointestinal bleeding, and ileus, as well as history of tumours and malignancies, such as leukaemia or other severe blood diseases.

Sampling technique used was consecutive sampling. Sample size was calculated using the following formula for unpaired categorical analysis test:

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$$n = \left(\frac{\mathbf{Z\alpha}\sqrt{\boldsymbol{Po(1-PO)}} + \boldsymbol{Z\beta}\sqrt{\boldsymbol{Pa\ (1-Pa)}}}{\boldsymbol{Pa-Po}} \right)^2$$

Where Zα was alpha standard deviation set at 0.05 (Zα = 1.96), Zβ was beta standard deviation set at 0.2 (Zβ = 0.84), po was the prevalence of severe CKD (based on past research) at 28.2% equivalent to 0.282 (8), pa-po was the proportion difference that was considered significant, such as 25%, equivalent to 0.25, pa was po + 0.25, which was equivalent to 0.282 + 0.25 equalled to 0.532.

$$n = \left(\frac{1.96\sqrt{0.282(0.718)} + 0{,}84\sqrt{0{,}532(0.468)}}{0.25} \right)^2 = 27$$

Therefore, the minimum number of research subjects needed in this research was 27.

2.2 Procedure

Basic data of the research subjects were gathered through interviews and anamnesis. Anthropometric measurements were taken to evaluate nutritional status using the World Health Organization (WHO) curve for subjects under the age of five and the Waterlow criteria for subjects above the age of five based on weight-for-height/length percentage (W/H %) [9], [10]. All the research subjects also had their kidney function, iron status, and GFR evaluated.

2.3 Kidney Function Examination

Serum urea and creatinine were examined for kidney function assessment. Serum urea was examined using an enzymatic method, where the urease enzyme hydrolysed urea in the blood sample to produce ammonium ions. Ammonium ions were measured. Creatinine was examined using a colorimetric method, such as Jaffe's reaction method. Creatinine in alkali formed a reddish-orange colour complex when reacted with picric acid, where the formation of this complex was directly proportional to the concentration of creatinine in the sample.

2.4 Iron Status Examination

Iron status examination involving serum iron, total iron binding capacity (TIBC), and serum ferritin level tests. Iron deficiency anaemia was categorised into absolute and functional iron deficiency anaemia based on the haemoglobin (Hb) level in the blood. Absolute iron deficiency anaemia is the condition when Hb level is below normal and iron reserves in the body decreases (serum ferritin <100 µg/L PD, peritoneal dialysis). Functional iron deficiency anaemia occurs when total body stores are adequate, but the gradual release of iron into the bloodstream is insufficient (serum ferritin <200 µg/L HD, haemodialysis).

Serum iron examination was carried out using the colorimetric-ferrozine method. The method principle is to break the bond between ferric (Fe^{3+}) and transferrin by guanidine in 4.8 pH condition, followed by the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) with the presence of ascorbic acid and the formation of coloured complex with the presence of ferrozine. Normal serum iron was <30 µg/dl.

Total iron binding capacity (TIBC) was assessed using the saturation method. TIBC was evaluated after transferrin is saturated by iron solution and the excess iron is absorbed by magnesium hydroxide carbonate, where the iron concentration in the supernatant is measured. Transferrin saturation was 20% and normal TIBC range was >400 µg/dl.

Serum ferritin was examine using electrochemiluminescence immunoassay (ECLIA) principle. The first incubation was a sandwich complex made up of 10 µl sample, biotinylated monoclonal ferritin-specific antibody tagged with ruthenium complexes. In the second incubation, biotin and streptavidin combined to produce a complex that bound to the solid phase after the addition of streptavidin-coated microparticles. The mixture was aspirated into a measuring cell where the microparticles were magnetically attracted to the surface of the electrodes. Unbound substances were eliminated using the wash and buffer solution (Procell). The photomultiplier measured the chemiluminescent emission that occurred when voltage was applied to the electrodes. Serum ferritin was determined by a calibration curve, which was generated using a 2-point calibration and the master curve in an instrument.

2.5 Glomerular Filtration Rate Examination

Chronic kidney disease (CKD) is defined as kidney failure that lasts for three months or longer due to structural or functional abnormalities of the kidneys, with or without the decrease in glomerular filtration rate (GFR) or GFR less than 60 mL/min/1.73 m^2 for three months or longer. This research calculated GFR based on the creatinine value, followed by the determination of the stage of CKD, such as stage 3 (3a GFR 45 – 59 mL/min/1.73 m^2, 3b GFR 30 – 44 mL/min/1.73 m^2), stage 4 (GFR 15 – 29 mL/min/1.73 m^2), and stage 5 (GFR <15 mL/min/1.73 m^2).

2.6 Data Analysis

The collected data were analysed using the statistical package for the social sciences (SPSS) software version 20.0 with a significance level of $p < 0.05$. Iron deficiency anaemia was the independent variable and stage of chronic kidney disease was the dependent variable. Both variables were analysed using Kruskal Wallis statistical analysis test. In the research subject characteristic data, various tests, such as Chi-square, T-independent, Kruskal Wallis, Mann-Whitney, and One-way ANOVA, were used to assess the difference between the group with and without iron deficiency anaemia.

2.7 Ethical Consideration

All research subjects were asked for parental consent after a prior explanation of the objective of the research. This research has been approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara and Haji Adam Malik hospital, Medan, Indonesia (Reference No. 1353/KEP/USU/2021).

3. Results

3.1 Research Subjects Demographic Characteristic

Thirty children under the age of eighteen with severe chronic kidney disease were involved in this research. Table 1 provides a complete breakdown of subject characteristics. There were five (45.5%) among eleven male children and ten (52.6%) among nineteen female children developing iron deficiency anaemia. The analysis result using the Chi-square test showed no relationship between gender and iron deficiency anaemia ($p = 0.705$).

The mean age of child patients with iron deficiency anaemia was 14.47 years old, while the mean age of children without iron deficiency anaemia was 12.18 years old. The T-independent test showed no relationship between age and the incidence of iron deficiency anaemia in children with severe CKD ($p = 0.061$).

Regarding parent's education, there were ten children whose parents were elementary school graduate and

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four (40%) of then had iron deficiency anaemia. There were six children whose parents were secondary school graduate and half (50%) of them developed iron deficiency anaemia. Meanwhile, there were fourteen parents who were high school graduate and eight (57.1%) children had iron deficiency anaemia. Using the Kruskal Wallis test, the correlation analysis between parents' education and iron deficiency anaemia showed no relationship (p = 0.718). Similarly, parents' occupation also had no relationship with the incidence of iron deficiency anaemia (p = 0.520).

Body weight and height also did not show any relationship with iron deficiency anaemia incidence (p > 0.05). As for nutritional status, among eleven malnourished children, six (54.5%) children developed iron deficiency anaemia. There were five under nourished children, where three (60%) children had iron deficiency anaemia. A total of twelve children had good nutritional status and half of them (50%) had iron deficiency anaemia. Only two children were obese and they did not have iron deficiency anaemia. The analysis test using Kruskal Wallis test showed no relationship between iron anaemia deficiency and nutritional status (p = 0529).

The length of CKD diagnosis was also recorded. There were thirteen children who had been diagnosed for more than twelve months and eight (61.5%) of them had iron deficiency anaemia. Twelve children had been diagnosed for six to twelve months and five (41.7%) of them had iron anaemia deficiency. Meanwhile, among five children with length of diagnosis below six months, two (40%) children had iron deficiency anaemia. Using Kruskal Wallis test, there was no relationship between length of CKD diagnosis and iron deficiency anaemia (p = 0.553).

Table 1. Research subject characteristic data

Characteristic	Iron deficiency anaemia		p
	Yes (n=15)	No (n=15)	
Gender, n (%)			
Male	5 (45.5)	6 (54.5)	0.705[a]
Female	10 (52.6)	9 (47.4)	
Age, years old			
Mean (SD)	14.47 (2.49)	12.18 (3.79)	0.061[b]
Median (Min – Max)	14.83 (10.08-17.92)	12.5 (5-17)	
Parents' education, n (%)			
Elementary school	4 (40)	6 (60)	0.718[c]
Secondary school	3 (50)	3 (50)	
High school	8 (57.1)	6 (42.9)	
Parents' occupation, n (%)			
Civil servant	6 (54.5)	5 (45.5)	0.520[c]
Employees of state-owned enterprises	1 (100)	0	
Gardener	1 (100)	0	
Farmer	0	1 (100)	
Entrepreneur	7 (43.8)	9 (56.2)	
Body weight, kg			
Mean (SD)	39.3 (11.58)	36.53 (18.55)	0.628[b]
Median (Min – Max)	40 (20-55)	32 (13-75)	
Body height, cm			
Mean (SD)	145.67 (18.99)	133.87 (22.71)	0.129[d]
Median (Min – Max)	151 (97-173)	141 (88-158)	
Nutritional status, n (%)			
Malnourished	6 (54.5)	5 (45.5)	0.529[c]
Under-nourished	3 (60)	2 (40)	
Good nutrition	6 (50)	6 (50)	
Obese	0	2 (100)	

Haemodialysis, n (%)			
Yes	8 (61.5)	5 (38.5)	0.269[a]
No	7 (41.2)	10 (58.8)	
GFR, mL/min/1.73m^2			
Mean (SD)	25 (19.68)	30.27 (20.93)	0.560[d]
Median (Min – Max)	14 (2-53)	40 (3-54)	
Length of diagnosis, n (%)			
> 12 months	8 (61.5)	5 (38.5)	0.553[c]
6 – 12 months	5 (41.7)	7 (58.3)	
< 6 months	2 (40)	3 (60)	

[a]*Chi Square,* [b]*T Independent,* [c]*Kruskal Wallis,* [d]*Mann Whitney*

3.2 Blood Test Results of Subjects with and without Chronic Kidney Disease

Table 2 shows the blood work results, such as urea, creatinine, haemoglobin (Hb), serum iron, total iron binding capacity (TIBC), and serum ferritin, of all CKD research subjects with and without iron deficiency anaemia. Almost all of the parameters showed no significant relationship with iron deficiency anaemia. Serum iron, however, showed a significant relationship between children with and without iron deficiency anaemia ($p < 0.001$), where children with iron deficiency anaemia had a mean serum iron value of 21.27 µg/dL (SD = 18.07 µg/dL) and children without iron deficiency anaemia had a much higher mean level at 63.13 µg/dL (SD = 18.95 µg/dL).

Table 2. Blood work analysis in research subjects based on iron deficiency anaemia status

Blood work parameter	Iron deficiency anaemia		p
	Yes (n=15)	No (n=15)	
Urea, mg/dL			
Mean (SD)	116 (55.39)	120.13 (69.56)	0.879[a]
Median (Min – Max)	122 (30-225)	86 (45-268)	
Creatinine, mg/dL			
Mean (SD)	5.06 (3.73)	5.4 (6.31)	0.561[b]
Median (Min – Max)	5.75 (1.41-12.99)	1.94 (1.4-19.3)	
Haemoglobin, g/dL			
Mean (SD)	6.77 (1.55)	7.37 (1.83)	0.219[b]
Median (Min – Max)	6.6 (4.1-9)	7.5 (3.8-9)	
Serum Iron, µg/dL			
Mean (SD)	21.27 (18.07)	63.13 (18.95)	<0.001[b]
Median (Min – Max)	18 (5-82)	63 (35-88)	
TIBC, µg/dL			
Mean (SD)	135.2 (52.67)	127.6 (41.86)	0.819[b]
Median (Min – Max)	119 (75-277)	133 (48-196)	
Ferritin, mcg/L			
Mean (SD)	1250.36 (1101.21)	646.9 (282.55)	0.057[a]
Median (Min – Max)	988 (35.38-4073.76)	689.3 (220.9-1222.65)	

[a]*T Independent,* [b]*Mann Whitney*

3.3 Relationship between Stage of Chronic Kidney Disease and Iron Deficiency Anaemia

The relationship between the stage of CKD and the incidence of iron deficiency anaemia is presented in Table 3. Among ten children at stage 3A CKD, there were four (40%) children with iron deficiency anaemia. There were four children at stage 3B CKD, half of them (50%) had iron deficiency anaemia. There were three children at stage 4 CKD and one (33.3%) of them had iron deficiency anaemia. Meanwhile, there were thirteen children at stage 5 CKD and eight (61.5%) children had iron deficiency anaemia. Kruskal Wallis analysis test did not show any relationship between the stage of CKD and iron deficiency anaemia ($p = 0.711$).

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Table 3. Relationship between the stage of CKD and iron deficiency anaemia

CKD Stage	Iron deficiency anaemia		p
	Yes (n=15)	No (n=15)	
Stage 3 A	4 (40)	6 (60)	0.711*
Stage 3 B	2 (50)	2 (50)	
Stage 4	1 (33.3)	2 (66.7)	
Stage 5	8 (61.5)	5 (38.5)	

*Kruskal Wallis

3.4 Iron Status Level based on the Stage of Chronic Kidney Disease

The highest haemoglobin level – at a mean value of 9 gr/dL was observed in children at stage 4 CKD. Whereas, the lowest haemoglobin level was found in patients at stage 5 CKD, such as at a mean level of 6.44 gr/dL (SD = 1.45). The Kruskal Wallis analysis test showed a relationship between haemoglobin level and the severity stage of CKD ($p = 0.020$). Other parameters, such as serum iron, TIBC, serum ferritin, and transferrin, were not significantly correlated to the stage of CKD ($p > 0.05$). Table 4 shows the examination results for haemoglobin, serum iron, TIBC, serum ferritin, and transferrin according to the stage of CKD.

Table 4. Iron profile status based on CKD severity

Iron Status	CKD stage			p
	Stage 3 (n=14)	Stage 4 (n=3)	Stage 5 (n=13)	
Haemoglobin, g/dL				
Mean (SD)	7.24 (1.78)	9 (0)	6.44 (1.45)	0.020[a]
Median (Min – Max)	7.85 (3.8-9)	9 (9-9)	6.6 (4.1-9)	
Serum Iron, µg/dL				
Mean (SD)	48.71 (30.1)	37.67 (11.24)	36.23 (28.28)	0.526[a]
Median (Min – Max)	48.5 (5-88)	35 (28-50)	23 (10-86)	
TIBC, µg/dL				
Mean (SD)	124.71 (40.36)	160 (106.11)	132 (37.66)	0.512[b]
Median (Min – Max)	126 (48-183)	133 (70-277)	133 (75-196)	
Ferritin, mcg/L				
Mean (SD)	1012.06 (1022.33)	532.71 (265.31)	976.3 (736.73)	0.302[a]
Median (Min – Max)	831.87 (35.38-4037.76)	552.63 (258-787.49)	689.3 (119.81-2575.89)	

[a]*Kruskal Wallis*, [b]*Oneway Anova*

4. Discussion

In chronic kidney disease (CKD), gender is one of the risk factors for the disease. The incidence of CKD is higher in males than in females due to the higher prevalence of congenital kidney and urinary tract disorders in men [11]. Men also have larger and wider kidneys than women, even though the overall renal volume seems to be equivalent. A number of studies involving animal subjects reported differences between sexes in the structures of kidneys, including the volume of glomeruli [12]. In this research, there were more female subjects than male (2: 1 ratio). The relationship between gender and chronic kidney disease was not assessed in this study. The gender demographic data in this research may not serve as a proper reference due to the small sample size in this research.

This research gathered parent's education and occupation status data and assessed their relationship with iron deficiency anaemia in CKD patients. [13] concluded that parents with resources and proper support can help parents to deal and adapt better with their child's condition. Parents with good financial ability will provide them confidence to continue caring for their children, despite the high medical costs. Moreover, factors like healthy parent-child relationship, emotional support from the spouse, and child's academic and social success encourage parents to help and lead their children and family to successfully adaptation. In

this research, we found no significant relationship between parents' education and iron deficiency anaemia incidence. Neither was there relationship between parents' occupation and iron deficiency anaemia. Since the samples were small in size, we found low proportion of parents with low education level and low-income job.

The Guidelines for Paediatric Nephrology noted in 2021 that nutritional deficiency in random CKD cases frequently manifested as protein energy wasting (PEW). There are many factors contributing to malnutrition in children with CKD, including uraemia, metabolic acidosis, and gastrointestinal disorders [14]. A study in Brazil focusing on children on dialysis demonstrated that over 40% of children receiving chronic dialysis had mild nutrition [15]. Paediatric populations with CKD are also becoming more prone to overweight and obesity. Therefore, it is important to balance energy and protein intake with the risks of overweight and obesity in relation to cardiovascular, psychosocial, and transplant outcomes. While preserving nutritional sufficiency, interventions to lower the risk of excessive energy intake in this condition needs to be considered [14]. In this research, almost half our research subjects had good nutritional status, and the remaining half were undernourished. There were no overweight or obese CKD patients with or without iron deficiency anaemia. This study did not assess the relationship between nutritional status and CKD. The relationship between nutritional status and iron deficiency anaemia was not significant.

Among all of the parameters of iron status examination showed non-significant relationships, except for serum iron. The study by [16] reported a different result, where serum iron did not have a statistically significant relationship with anaemia. In contrast, their study reported a significant relationship between serum ferritin and anaemia with $p < 0.0001$. Serum ferritin increases as CKD stage progressed [17]. Serum ferritin may function as an inflammatory marker. The serum has a positive correlation with hepcidin, where hepcidin and C-reactive protein increase with the progressing stage of CKD [18]. This correlation shows that serum ferritin can indicate inflammation in patients with CKD. Although iron is present in adequate amounts, proven by the increase in serum ferritin level and normal serum iron, erythropoietic tissues cannot access iron. CKD patients with anaemia usually have normal or increasing iron stores, but the iron mobilisation in the body is impaired, which was caused by the deficiency [19]. Iron deficiency and anaemia are risk factors for CKD. The results of this study showed the significance of using erythropoietin (EPO)-stimulating medications and iron supplements simultaneously as an effective therapeutic strategy in preventing anaemia in patients with CKD.

Iron is mainly absorbed in the duodenum, and it is also a regeneration of the old red blood cells. Iron circulates in plasma with transferrin attached. In the body, iron is primarily attached to the haemoglobin, reticuloendothelial system, and hepatocytes. Small amounts are also stored in muscles and other tissues. Iron-containing transferrin attaches to erythroid cells and endocytosed by the red blood cells to produce heme. Non-iron containing red blood cells are stored as ferritin or hemosiderin. Iron metabolic pathways are disturbed in patients with CKD. Transferrin levels also decrease to half or one-third from the normal level. As a result, the transport of iron to the bone marrow for the production of red blood cells decrease in patients with CKD. Patients with kidney failure also experience impaired release of stored iron from macrophages and hepatocytes to transferrin. Clinically, this condition manifests as high ferritin level as a result of the impeded release of stored iron. This is what causes iron deficiency anaemia to occur in CKD patients [17].

The results of this study can clarify the significance of screening for iron deficiency in CKD patients at the time of initial diagnosis. However, to obtain a more precise and significant result, further study needs to

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conduct a more thorough blood analysis, such as the addition of haemoglobin reticulocyte examination. Cohort studies can also be carried out in future research to remove any bias, where the fact that iron deficiency anaemia truly occurs from CKD by looking at the iron profile prior to the onset of severe CKD.

5. Conclusion

This research found that serum iron was the only component in the iron profile that was significantly correlated with iron deficiency anaemia in patients with stage 3 – stage 5 CKD. Iron deficiency anaemia was more common in progressed stages of CKD, where stage 5 had the highest incidence of iron deficiency anaemia. However, this study showed no significant relationship between severe CKD and iron deficiency anaemia.

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