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*by* Hamsu Kadriyan 20

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Hamsu Kadriyan, Mochammad Alfian Sulaksana, Ima Arum Lestarini, Ni Ketut Susilawati, Abdul Qadar Punagi, Nova Audry L. Pieter, and Masyita Gaffar



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## Incidence and Characteristics of Anemia Among Patients with Nasopharyngeal Carcinoma in Lombok, Indonesia

Hamsu Kadriyan<sup>1,a)</sup>, Mochammad Alfian Sulaksana<sup>1</sup>, Ima Arum Lestari<sup>2</sup>, Ni Ketut Susilawati<sup>3</sup>, Abdul Qadar Punagi<sup>4</sup>, Nova Audry L Pieter<sup>4</sup>, Masyita Gaffar<sup>4</sup>

<sup>1</sup>Department of ENT-HNS, Medical Faculty Mataram University/ RSUD Propinsi NTB, Indonesia

<sup>2</sup>Department of Pathology Clinic, Faculty of Medicine Mataram University, Indonesia

<sup>3</sup>Department of ENT-HNS, Praya Hospital West Nusa Tenggara, Indonesia

<sup>4</sup>Department of ENT-HNS, Medical Faculty Hasanuddin University, Indonesia

<sup>a)</sup>Corresponding author: hamsukadriyan@yahoo.co.id

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**Abstract.** Since the anemia and nasopharyngeal cancer (NPC) are a major problem in Indonesia and anemia has become one of the prognostic factors for the treatment of NPC, it is important to analyse the incidence and its characteristics in NPC patients especially in rural areas in Indonesia, such as Lombok. The purpose of this study is to analyse the incidence and the characteristics of anemia in NPC patients in a secondary referral hospital, Lombok, Indonesia. This research was carried out by analytic descriptive study using medical record data from secondary referral hospitals, Lombok, Indonesia. The data were obtained between April 2017 to March 2018. Nasopharyngeal cancer was established through physical examination, imaging, and histopathological examination. The stage of disease was defined according to AJCC 2017. Anemia was defined as Haemoglobin level less than 11 g/dl and the severity level according to WHO criteria. Classification of anemia based on MCV and MCHC are divided into normocytic, microcytic and macrocytic as well as normochromic, hypochromic, and hyperchromic according to the criteria of Chinese Clinical Oncology guideline 2012. There were 40 cases of patient with anemia who fulfil the study criteria, which consist of 30 male and 10 female, with the ratio 3:1. According to the age, patients were distributed from 13 to 67 years old with the mean age for males was 46 (SD± 11.04) years old while the mean age for female was 50,9 (SD± 12,37) years old. Patients were found in stage II-IV, however, most of them were stage IV (68.75%). There were 87.5% of patients with anemia in different severity levels. However, the highest number was found in mild anemia level (57.5%). Based on the erythrocyte index, the majority types of anemia were hypochromic microcytic and normocytic normochromic (39,3%). The incidence of anemia in a patient with nasopharyngeal carcinoma at secondary referral hospitals in Lombok was 87,5%. Most of them were mild and hypochromic microcytic as well as normocytic normochromic type.

### INTRODUCTION

Anemia remains a major health problem in Indonesia. A study on farmers in Indonesia found that 62.6% of them suffered from anemia [1]. Another study reported that the incidence of anemia in non-pregnant women >15 years old, pregnant women >15 years old and men >15 years old were consecutively 26,6%, 37.3%, and 15.4% [2]. WHO (2011) reported that the prevalence of anemia among Asian countries was 31,9% while in Europe only 20% [3]. On the other hand, Southeast Asian countries, including Indonesia is known as a region with a medium incidence of nasopharyngeal cancer. The incidence of nasopharyngeal cancer in Indonesia was reported about 5.66/100.000 population and mostly found in advance stage [4].

Anemia in cancer can occur as a result of absolute iron deficiency due to a decreased of hepcidin and ferritin level less than 100 ng/dl. Anemia can also occur because of functional iron deficiency due to an increase of hepcidin and ferritin level more than 100 ng/dl. Both conditions will make the transferrin saturation decreased to less than 20% and finally will fall to anemia. In advanced, anemia in cancer is caused by several factors, including chronic bleeding and low nutrition intake [5].

Anemia is recognized as one of the prognostic factors that affect several indicators for life expectancy among patients with nasopharyngeal carcinoma. A research in China found the overall survival between patient with Hb less than 11 g/dl and more than 11 g/dl was significantly different, with the value of 70% and 78% respectively [6]. Another study in China found a significant difference of response rate to intensity-modulated radiation therapy between the patient with and without anemia. The complete response and partial response in the group of anemia were 69.8% and 30,2% whereas in the non-anemia group consecutively 85,7% and 14,3%. This response was significantly different (p=0.02) [7]. The researchers researcher found that pre-treatment anemia was significantly associated with adverse disease-specific survival (hazard ratio 2.15, 95% CI: 1.62-2.85, p<0,001) and distant metastasis-free survival (hazard ratio 1,53, 95% CI: 1.08-2.17, p=0.018) compared to patients with normal haemoglobin level [8].

A study on colorectal cancer found that 78 (10%) patients suffered from microcytic anemia and 108 (23%) patients had normocytic anemia. They also found a significant correlation between normocytic anemia with cancer-specific survival rate whereas microcytic was not significantly correlated. In other words, microcytic anemia has a better prognosis in those cases [9]. The publication about anemia on NPC is limited, especially the characteristic based on the red blood cells index. Furthermore, if the data about anemia is available, several treatments could be done to increase the prognosis of NPC.

## METHODS

Descriptive analytic study using medical record data was conducted in a secondary referral hospital, Lombok, Indonesia from April 2017 to March 2018. The samples were taken from patients data who was diagnosed with nasopharyngeal carcinoma and treated at the ENT-HNS department, West Nusa Tenggara Hospital. Diagnosis of nasopharyngeal cancer was established with histopathologic examination according to WHO criteria. The stage of nasopharyngeal cancer based on AJCC 2017 which is divided into stage I-IV based on the TNM system.

The classification of anemia according to World Health Organization (WHO) was divided into 5 levels. First level (level 0) if Hb more than 11 g/dl or within normal limit. Level 1 (mild) if Hb between 9.5-10.9 g/dl, level 2 (moderate) if Hb between 8.0-9.4 g/dl. Level 3 (severe) if Hb between 6.5-7.9 g/dl and the last level (extremely severe) if Hb was less than 6.5 g/dl.

Several data including patients identity, diagnosis, the haemoglobin concentration and index erythrocyte consist of mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) from laboratory results will be collected at the first diagnosis of NPC. Classification of anemia based on MCV and MCHC are divided into normocytic, microcytic, and macrocytic as well as normochromic, hypochromic and hyperchromic according to the criteria of the Chinese Clinical Oncology guideline 2012 [10]. All the collected data were then analysed with the SPSS program.

## RESULTS

During the study period, 40 NPC patients were included in this study. The subjects consists of 75% male and 25% female. According to the age category, patients were divided into several groups. The majority patients were found in the older age category (more than 41 years old) with a frequency of 26 or 67.5%, followed by young adults (21-41 years old) with the frequency of 11 or 27.5%. The mean age for males was 48.8 (SD± 11,04) years old while for females was 51.8 (SD± 12.37). Based on gender, the cases were mostly found in males, with male and female ratio 3:1.

Patients generally come at an advanced stage, most of them were found at stage IV (67.5%) and followed by patients with stage III and II that was found 27.5% and 5% sequentially. None of them was in the first stage.

TABLE 1. Distribution of patients with nasopharyngeal carcinoma based on age and stage by gender

Age (year)	Male		Female		Total	
	Frequency	%	Frequency	%	Frequency	%
<21	2	5.0	0	0	2	5.0
21-40	9	22.5	2	5.0	11	27.5
41-61	13	32.5	6	15.0	19	47.5
>61	6	15.0	2	5.0	8	20.0
Stage						
I	0	0.0	0	0.0	0	0.0
II	2	5.0	0	0.0	2	5.0
III	9	22.5	2	5.0	11	27.5
IV A	11	27.5	2	5.0	13	32.5
IV B	7	17.5	6	15.0	13	32.5
IV C	1	2.5	0	0.0	1	2.5
Total	30	75,00	10	25	40	100

Based on table 2, patients with normal haemoglobin level were found in 7 (17.5%) patients. On the other hand, 33 (82.5%) patients suffered from anemia. The mean haemoglobin level was 10.99 (SD±1.4) mg/dl. Most patients had mild anemia with the frequency of 23 patients (57.5%). All women in this study suffered from anemia while 69.7% of the male patients had anemia.

**TABLE 2.** Distribution of patients according to anemia status (WHO)

Anemia	Male		Female		Total	
	Frequency	%	Frequency	%	Frequency	%
Normal	7	17.5	0	0	7	17.5
Mild	18	45.0	5	12.5	23	57.5
Moderate	4	10.0	4	10.0	8	20.0
Severe	1	2.5	1	2.5	2	5.0
Very severe	0	0.0	0	0.0	0	0.0
Total	30	75	10	25	40	100

According to the stage, patients with anemia were found in almost all stage of NPC. The severity of anemia follows the severity stage of NPC. Table 3 shows the detailed distribution of anemia based on the stage.

**TABLE 3.** Distribution of anemia based on the stage of NPC

Stage	Anemia Severity (Frequency (%))				
	Normal	Mild	Moderate	Severe	Very Severe
I	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
II	1 (2.5)	1 (2.5)	0 (0)	0 (0)	0 (0)
III	3 (7.5)	7 (17.5)	1 (2.5)	0 (0)	0 (0)
IVA	2 (5.0)	8 (20.0)	3 (7.5)	1 (2.5)	0 (0)
IVB	1 (2.5)	6 (15.0)	4 (10.0)	1 (2.5)	0 (0)
IVC	0 (0)	1 (2.5)	0 (0)	0 (0)	0 (0)
Total	7 (17.5)	23 (57.5)	8 (20.0)	2 (5.0)	0 (0)

According to the size of the red blood cell and concentration of haemoglobin, most patients had normocytic normochromic anemia and microcytic hypochromic anemia with the frequency of 39.3%. Microcytic hypochromic anemia were mostly found in patient with a mild anemia (30.2%) and normocytic normochromic anemia were mostly found in patient with moderate anemia (24.2%). Severe anemia were only found in 2 (6.1%) patients. Based on the erythrocyte index, 1 patient (3%) had severe anemia with microcytic normochromic type anemia and 1 patients (3%) had severe anemia with microcytic hypochromic type anemia (Table 4).

**TABLE 4.** Type of anemia based on MCV and MCHC with the severity of anemia

Anemia	Mild	Moderate	Severe	Total
	N (%)	N (%)	N (%)	
Normocytic Normochromic	8 (24.2)	5 (15.1)	0 (0)	13 (39.3)
Normocytic Hipocromic	2 (6.1)	1 (3.0)	0 (0)	3 (9.1)
Microcytic Normochromic	2 (6.1)	0 (0)	1 (3.0)	3 (9.1)
Micrositic Hipocromic	10 (30.2)	2 (6.1)	1 (3.0)	13 (39.3)
Micrositic Hiperchromic	1 (3.0)	0 (0)	0 (0)	1(3.0)
Total	23 (69.7)	8 (24.2)	2 (6.1)	33 (100)

## DISCUSSION

In Indonesia, NPC is the 4th most malignancy found in males [4]. Previous study reported 129,079 new cases of nasopharyngeal cancer with 72,984 deaths annually because of this cancer [9]. This report was higher than Globocan report [1] 2012. New cases were increasing 1.4 times and had a similar pattern on death cases [10].

NPC is mainly found in productive age men (the ratio of male and female is 2.18: 1) and 60% of patients were aged between 25 and 60 years. The highest incidence in the world is in the province of Southeast China, with 40 - 50 cases among 100,000 residents. On the other hand, nasopharyngeal cancer is very rare in areas of Europe and North America with an incidence of <1 / 100,000 population [11].

The causes of malnutrition in cancer patients are very complex and multifactorial. Serotonin and bombesin hormones that are secreted by tumour cells can suppress the appetite and lead to anorexia. Nasopharyngeal cancer can also induce the inflammation of the oral mucosa and mucous membranes of the digestive tract, decreased salivary gland secretion, psychologic distress and tooth disorder. Decreased of oral intake can cause a decrease in endurance, infection and weight loss. The tumour on NPC is fragile and neovascularization is increased, furthermore, it is prone to bleeding. The persistent bleeding may also cause anemia. Therapy for cancer also affects the nutritional status of patients. A study found that more than 40% of cancer patients who were treated were malnourished [12]

Chemotherapy is one of the management of advanced nasopharyngeal cancer. The drugs used in cancer therapy work by one of the mechanism such as damaging, suppressing and preventing the spread of cancer cells that grows rapidly. However, chemotherapy agents not only affect cancer cells but also normal cells, and in certain amounts may cause side effects on the oral and gastrointestinal mucosa, hair follicles, reproductive system and hemopoietic system [13].

One of the effects of chemotherapy is the formation of free radicals from cisplatin administration. A high free radicals levels are toxic, which may damage normal cells in the body including bone marrow, which results in the suppression of formation of the blood cell. The blood cell formation system has a role in producing haemoglobin [14].

Anemia is a common problem in patients who receive chemotherapy because it can occur as a result of cancer itself or as a complication of chemotherapy. Anemia occurs in 67-81% of patients who received chemotherapy. The occurrence of anemia in chemotherapy and radiotherapy administration can cause the treatment to be less effective. The response rate and the survival rate of patients with radiotherapy and or chemoradiotherapy can be decreased [13]. A study in Europa revealed that 39% of cancer patients were anemic in initial assessment. The percentage was increased after treatment with chemotherapy to 63%. In their study, anemia was defined as an Hb level of less than 12 g/dl [15].

The main causes of anemia are the lack of iron from oral intake or low levels of iron absorption and the presence of inhibitors in absorption of iron. It makes the iron absorption not optimal and leads to the iron level to be lower than body's requirement [10].

According to mean corpuscular volume and mean corpuscular haemoglobin concentration, anemia are divided into normochromic normocytic, normochromic macrocytic, and hypochromic microcytic. The types of anemia is divided into normochromic normocytic anemia if anemia occurs due to excessive blood loss, causing the bone marrow to work harder in erythropoiesis, furthermore, many young erythrocytes are seen on the peripheral circulation. Normochromic macrocytic anemia if anemia is due to vitamin B12 deficiency. Hypochromic microcytic anemia if anemia is due to iron deficiency [10].

Based on the result of our study, we found the comparison between males and female patients was 3: 1. The research in the United States has found a ratio of 2: 1. [9]. NPC is always found higher in men. The incidence of NPC often occurs with male and female ratios of 3:1. [4]. Males are more at risk of being exposed to carcinogens in their work environment than women, so they have higher risk of cancer. In this study, we obtained the highest age range of patients between 41-67 years, this result is similar to several kinds of literature which 60% of patients were distributed in the age group between 25 to 60 years old. The incidence of anemia in female is higher than male. This result was correlated with the report by Susanto et al., 2017 which states that women have a higher risk to anemia [1].

According to this study, 95% patients were found in advanced stages, which was 27.5% for stage III and 67.5% for stage IV respectively. On the other hand, patients found in early stages were only 0% and 5% on stage I and II respectively. This data proved that patients usually come at an advanced stage because of the low awareness of NPC patients in Lombok, Indonesia. The hidden location of the tumour in the nasopharynx may lead to the requirements of a special examination in a hospital that has complete facilities. Those factors also make the early detection of this cancer becoming more complicated. Knowledge of the signs and symptoms that often appear in patients such as nasal obstruction, epistaxis, headaches, and tinnitus which is often considered as common cold leads

to late detection of nasopharyngeal cancer. The delay in diagnosis is also related to the patient's unconsciousness to NPC as well as the tendency of patients to seek traditional medicine as the first modality treatment [16]. In addition, according to this study, there was a tendency that anemia was more severe in the more advanced cancer stage. This is logic because as the stage becomes more advanced, the more disturbances occur. Furthermore, the patients will be more susceptible to anemia.

In cases of malignancy, anemia often occurs. In this study, most of the patients suffered from mild anemia. The cases could mostly occur as a result of cancer itself or as a complication of chemotherapy agents and radiotherapy. According to the pathophysiology of cancer-related anemia, anemia can occur as a result of decreased production and increased destruction of blood cells, blood loss or combination of those factors. Chemotherapy can increase the destruction of blood cells [15].

In this research, authors found the most types of anemia are hypochromic microcytic and normocytic normochromic. Hypochromic microcytic refer to the number of red blood cells or haemoglobin (oxygen transport protein) in blood cells was below the normal standard. This problem may be caused by iron deficiency. The other causes of iron deficiency are low iron intake, absorption impairment, persistent blood loss, and neoplasms itself. The case of anemia due to iron deficiency usually occurs gradually. It starts by iron loss and reduced amount of iron reserves which leads to the increased requirement for the red blood cell production. The human body will adapt to this condition. The bone marrow will try to replace iron deficiency by increasing the cell division and producing the red blood cells in a very small size (microcytes). In case of iron deficiency and anemia is getting worse, the symptoms will occur such as fatigue, shortness of breath, and lack of energy [15].

## CONCLUSION

Anemia was found predominant in inpatient with nasopharyngeal cancer in West Nusa Tenggara Hospital with the incidence of 82.5%. Mild anemia and hypochromic microcytic as well as the normocytic normochromic were the major finding in this study. A further study is needed to deeply analyse the characteristic of anemia on NPC with a better design.

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