Laboratory Profiles of Nasopharyngeal Carcinoma Patients

Nur Akbar Aroeman*, Ifiq Budiyan Nazar, and Yussy Afriani Dewi

Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Universitas Padjadjaran/ Hasan Sadikin Hospital, Bandung, Indonesia
**Corresponding author. Email: aroeman_ent@yahoo.com*

ABSTRACT
Nasopharyngeal Carcinoma (NPC) is one of the most common head and neck malignant neoplasms worldwide. Laboratory profile is rarely evaluated in Indonesia as a prognostic consideration. The aim of this research is to describe the laboratory profile of NPC patients. This is descriptive research using a total sampling method from 2016-to 2020. The general characteristics and laboratory profiles are collected from Nasopharyngeal Cancer Registry. The data collected will be presented in tables as frequency and percentages. More than half of the participants were male (68.27%), aged more than 45 years old (65.38%). The majority of the subjects reported a KPS of more than 80 (84.94%). Most of the participants showed WHO type III (47.57%). Bone (42.22%) was the most common metastases site. Normal hemoglobin (57.14%), leukocyte (57.99%), thrombocyte (91.36%), ALP (81.82%), AST (89.66%), ALT (61.26%), direct bilirubin (76.00%), indirect bilirubin (63.30%), total bilirubin (86.60%) and urea (84.10%) levels were found in most of our subjects. Calcium <8.6 mg/dL (92.21%) and creatinine >1.5 mg/dL (69.2%) were observed in most cases. This study indicated a worse prognosis by anemia, leukocytosis, and a high De Ritis ratio. In comparison, a better prognosis is predicted by low ALP levels, high calcium, direct bilirubin, and total bilirubin. In addition, pretreatment laboratory profiles should be assessed to predict the prognosis of patients with NPC.

Keywords: *Nasopharyngeal Carcinoma, Laboratory Profiles, Prognosis, Predictors.*

1. INTRODUCTION

Nasopharyngeal Carcinoma (NPC) is one of the most common head and neck malignant neoplasms worldwide, with an incidence of 6.2/100,000 populations per year [1]. This malignancy is commonly seen in Southeast Asia, including Indonesia [2]. Previous studies reported a prevalence of 41.7% of NPC in our center. Even though endemic in Indonesia, the diagnosis of NPC is often delayed due to its unspecific symptoms. The late diagnosis of NPC results in higher mortality and morbidity. A study in the UK showed a declining pattern of 5-year survival rate in stage I, stage II, stage III, and Stage IV (0%, 65%, 60%, and 50%). A similar pattern is shown in America (72%, 64%, 62%, and 38%). In our center, the five-year survival rate is 30.9%, with a much lower survival rate in stage I (44.6%) [3].

Every approach should be assessed to improve the survival of patients with NPC. However, as one of the factors predicting prognosis, laboratory profile is rarely evaluated in Indonesia as a prognostic consideration. Therefore, our study aims to shows the laboratory profile of NPC patients.

2. METHODS

This is descriptive research using a total sampling method conducted in Dr. Hasan Sadikin General Hospital during 2016-2020. The data collected were taken from Nasopharyngeal Cancer Registry. All subjects were diagnosed with nasopharyngeal carcinoma based on history taking, imaging, and histopathological examination. Patients with other malignancies or incomplete data were excluded.

General characteristics obtained include gender, age, Karnofsky Performance Score (KPS), histopathological type based on WHO classification, and the presence of metastases to bone, liver, lung, or distal nodal metastases. In addition, laboratory examinations were performed at the initial diagnosis. The profile includes hemoglobin,

leukocyte, thrombocyte, Alkali Phosphatase (ALP), calcium, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), direct bilirubin, indirect bilirubin, total bilirubin urea, and creatinine. The data collected will be presented in tables as frequency and percentages.

3. RESULTS

From 2016 to 2020, there were 588 data of patients with NPC. However, 34 subjects were excluded. The characteristics are presented in Table 1. More than half of the participants were males (68.27%) aged over 45 years old (65.38%). The majority of the subjects can carry out normal activities with a KPS of more than 80 (84.94%). Most participants showed WHO type III (47.57%) based on histopathology examination. Based on TNM staging, T3 (36.07%) and N3 (42.18%) were the most common stage found in this study. Metastases were reported 8.12% subjects, consisting of bone (3.43%), liver (2.35%), lung (1.62%) and distant nodal metastases (0.72%). Stage IV (73.01%) was mostly seen based on the clinical stage.

Table 1. Characteristics of NPC Patients

Characteristics	N=554	%
Gender		
Male	378	68.27
Female	176	31.73
Age		
<45 years old	192	34.62
≥45 years old	362	65.38
Mean, years old	48.62	
Karnofsky performance score		
<80	83	15.06
≥80	471	84.94
Histopathology (WHO)		
Type I	32	5.83
Type II	258	46.6
Type III	264	47.57
T Stage		
T1	111	20.09
T2	175	31.51
T3	200	36.07
T4	68	12.33
N Stage		
N0	109	19.73
N1	90	16.33
N2	121	21.77
N3	234	42.18
M Stage		
M1	45	8.12
Bone	19	3.43
Liver	13	2.35
Lung	9	1.62
Distant Nodal	4	0.72
M0	509	91.88
Clinical Stage		
I	12	2.08
II	59	10.73
III	79	14.19
IV	404	73.01

The laboratory examinations were conducted before the administration of any intervention. Normal hemoglobin (57.14%), leukocyte (57.99%), thrombocyte (91.36%), ALP (81.82%), AST (89.66%), ALT (61.26%), direct bilirubin (76.00%), indirect bilirubin (63.30%), total bilirubin (86.60%) and urea (84.10%) levels were found in most of our subjects. Calcium <8.6 mg/dL (92.21%) and creatinine >1.5 mg/dL (69.2%) were observed in most cases.

Table 2. Laboratories Profile of Patients with NPC

Laboratory Profiles	N=554	%
Hemoglobin (g/L)		
<11.5	223	40.18
11.5-15.5	317	57.14
>15.5	14	2.68
Mean	11.84	
Leukocyte (x109/L)		
<4.4	61	10.96
4.4-11.3	321	57.99
>11.3	172	31.05
Mean	93.09	
Thrombocyte (x109/L)		
<150	25	4.55
150-450	508	91.36
>450	23	4.09
Mean	341.14	
Alkali phosphatase (IU/L)		
<46	76	13.64
46-116	453	81.82
>116	25	4.54
Mean	83.48	
Calcium (mg/dL)		
<8.6	504	90.91
8.6-10.3	43	7.79
>10.3	0	0.00
Mean	10.53	
AST (U/L)		
5-37	497	89.66
>37	57	10.34
Mean	25.13	
ALT (U/L)		
<16	120	21.62
16-63	339	61.26
>63	95	17.12
Mean	26.13	
De Ritis ratio (AST/ALT)		
<1.65	76	13.76
³1.65	478	86.24
Mean	1.13	
Direct Bilirubin (mmol/L)		

Laboratory Profiles	N=554	%
≤5.13	133	24.00
>5.13	421	76.00
Mean	8.52	
Indirect Bilirubin (mmol/L)		
<3.42	106	19.20
3.42-13.68	351	63.30
>13.68	97	17.50
Mean	8.28	
Total Bilirubin (mmol/L)		
<1.71	17	3.10
1.71-17.1	480	86.60
>17.1	57	10.30
Mean	10.12	
Ureum (mg/dL)		
<15	7	1.30
15-39	466	84.10
>39	81	14.60
Mean	23.49	
Creatinine (mg/dL)		
<0.6	8	1.40
0.6-1.5	163	29.40
>1.5	383	69.20
Mean	1.21	

4. DISCUSSION

Nasopharyngeal carcinoma is the 4th most common malignancy with an incidence of 6.2/100,000 populations per year.[1] It is an endemic malignancy mainly found in Southern China, North Africa, the Arctic, and Southeast Asia, including Indonesia [2]. In Indonesia, the incidence of NPC is higher in males (8.3/100.000 vs. 3.0/100.000) with a ratio of 2-3:1 [4]. This was in line with our study that reported that male is the most prevalent with a ratio of 2.2:1. The predominance of males in this malignancy may be related to the more prevalent carcinogenic exposure in males, such as tobacco smoking and occupational exposure to formaldehyde and dust [1,5]. Internal factor such as androgen induces the proliferation of tumor cells. In comparison, estrogen suppresses tumor cell growth. Estrogen Receptors (ERs) and NAG7, the inhibitor of ERs, were observed in NPC tissue, suggesting estrogen's protective role in NPC development in women, especially before menopause [5].

Although NPC is also reported in children and adolescents, this malignancy is more frequently observed in 40-50 years old populations. In this study, 65.38% of participants were older than 45 years old, and 29.49% were aged 40-50 years old [1]. Salehiniya et al. reported that the growth of NPC due to carcinogenic exposure has been progressing for several decades before inducing significant signs and symptoms [6]. Therefore, primarily found in older age.

Kurniawati et al. reported that KPS is declining parallelly with the advancing age and stage of the tumor [7]. In this study, most participants reported a KPS of more than 80. The decrease in the quality of life is associated with the slow finding of NPC in Indonesia. Hutajulu et al. stated that the late diagnosis might be related to the poor diagnosis of general practitioners resulting in delayed referral and the lack of visibility of nasopharyngeal [8]. NPC symptoms frequently mimic other chronic diseases such as chronic rhinitis, hearing loss, and headache. Hence, delaying the diagnosis furthermore. The denial of illness and the economic burden of NPC may also delay the intervention. The high KPS in this study may be related to the short waiting time for diagnosis, 26.92 days, ranging from 1-12 weeks, compared with 34.2 days in another cancer center in Jakarta [9].

In 2005, WHO classified NPC as type I (Squamous Cell Carcinoma/SCC), type II (non-keratinizing carcinoma), and type III (undifferentiated carcinoma). Kimura and WHO reported that WHO type III is the most common type of NPC, as seen in our study.[10,11] WHO type I is primarily found in a low-risk population and is related to carcinogenic substances. WHO type II is commonly observed in young adults with a familial predisposition? While WHO type III is commonly seen in high-risk populations such as individuals with genetic polymorphisms and dietary exposure to a nitrosamine [11]. Nitrosamine is a substance formed by the interaction of nitrates added in preserved goods and the heat of the Sun [12].

Based on TNM staging, T3 and N3 were mainly seen in this study, classified as a locally advanced stage of NPC (stage III and IV) [13]. The result we yielded was in line with another study in Palembang reporting stage III was found in 12.73% and stage IV in 77.27% patients. This late NPC discovery may be caused by the lack of knowledge leading to delay in diagnosis and treatments in health facilities. The unspecific symptoms of NPC are also associated with the treatment delay. The symptoms are directly correlated with the location of the primary tumor, infiltration of a tumor to surrounding tissue, and the presence of metastases. A nasopharyngeal mass may appear as nasal congestion and runny nose. Epistaxis is observed in NPC with ulceration. While unilateral conductive hearing loss, otalgia, tinnitus, and serous otitis media are commonly seen in mass surrounding the eustachian tube. A previous study in our center reported that most patients with NPC mainly seek professional help due to neck lymph node metastases. The advanced stage contributes to the high mortality rate of NPC, stage III 15.4%, stage IVA 13.8%, and stage IVB 1.5% [3,14].

The factor prognosis of NPC can be affected by patient, disease, and treatment. Patient-related factors include age, gender, and ethnicity. Disease-related factors include histology-type, TNM classification, and

staging, which represent the extent of the disease [15]. Several laboratory parameters can be used to predict prognosis in NPC. Hemoglobin of less than 14 mg/dL was found in 86.61% of the participants. This result was consistent with a prior study conducted by Susilawati that 87.5% of patients with NPC had anemia [16]. A study in China reported that hemoglobin level less than 11g/dL significantly lowers the Overall Survival (OS) in NPC (70% vs. 78%).

The presence of anemia also significantly lowers the response rate to radiation. The complete and partial response rate was 69.8% and 30.2% in individuals with anemia. While in the non-anemic group, the complete and partial response rate was 85.7% and 14.3% [17]. Malignancy anemia is caused by several factors such as malnutrition, malabsorption, acute/chronic bleeding, inflammation, metastatic infiltration to bone marrow, and myelosuppression due to cancer therapy [18]. Susilawati also reported that hypochromic microcytic anemia is the most common type in NPC patients, associated with iron deficiency anemia [16]. In patients with malignancy, tumor cells induce the secretion of serotonin and bombesin, resulting in appetite suppression. Inflammation of oral and digestive tract mucosa in NPC patients results in pain and psychological distress during food ingestion is associated with malnutrition [17]. Blood loss due to epistaxis may also exacerbate anemia [16]. While polycythemia may be related to dehydration in NPC cases resulting in volume depletion rather than the actual increase of RBC mass [19].

Leukocytosis is commonly found in solid tumors, including NPC. Su et al. reported that leukocytosis occurs in 8.7% of NPC patients and impacts mortality (HR 1.4, 95% CI 1.15-1.70, p=0.001), progression (HR 1.25, 95% CI 1.06-1.47, p=0.007) and metastases (HR 1.21, 95% CI 0.97-1.52, p=0.088) of NPC. Initial leukocytosis is associated with TNM classification, clinical-stage suggesting more advanced disease stage and worse survival. Qiu et al. reported a higher prevalence of 25.6%. In this study, leukocytosis was observed in 31.05% of all subjects and 23.53% of patients with metastases. Cvitkovic stated that leukocytosis is a new symptom of NPC. The appearance of leukocytosis is considered the first sign of malignancy, and the reappearance is considered the sign of NPC relapse. This sign is affected by several conditions, including infections, corticosteroid administration, bone marrow metastases, paraneoplastic leukemoid syndrome, and the usage of granulocyte-colony stimulating factors (G-CSF). NPC is known to upregulate the hematopoietic growth factor such as G-CSF. These growth factors increase the expression of β1-integrin which worsen the adhesion and invasiveness of NPC cells, promoting metasastases [20].

Inflammation is commonly seen in cancer, promoting cancer growth, host immunity, and tumor response to treatment. In NPC, IL-6 that is overly expressed contributes to platelet generation or thrombocytosis. These cells protect cancer cells by interfering with the activity of natural killer cells and secreting numerous growth factors, including Platelet-Derived Growth Factor (PDGF), Tumor Growth Factor- β (TGF-β), and Vascular Endothelial Growth Factors (VEGF), remoting neovascularization, progression of tumor cells and metastases [21]. Chen et al. reported that thrombocytosis of >300x10^9/L was found in 15.3% of patients, especially in females and advanced stage of NPC (stage III-IV). In our study, thrombocytosis was observed in 4.09% of participants. This difference may be related to the higher cutoff value in our study.

The presence of thrombocytopenia in NPC is considered rare. This condition is classified into three categories based on the mechanisms as platelet underproduction, platelet destruction, and platelet sequestration. In NPC, thrombocytopenia may be caused by diffuse tumor penetration to bone marrow and bone marrow suppression after radiotherapy or chemotherapy, causing platelet underproduction, metastases to the spleen, and immune-mediated as part of paraneoplastic syndrome resulting in platelet destruction [22].

Indrasari et al. reported that bone (40.54%) is the most common metastases site in NPC. This result was similar to another study by Bensouda stated that 70-80% distant metastases were commonly seen in the bone. In our study, bone metastases were found in 42.22% of all metastases. Bone metastases occur in two interrelated processes, osteoblastic and osteolytic types. Huang et al. reported a decrease in calcium level in 53% of patients. In our study, low serum calcium level was observed in almost all patients (90.91%). Calcium ions are messengers regulating cellular functions such as cell proliferation, death, migration, and invasion. This ion is mainly regulated by the parathyroid hormone, intestine, and kidney. In osteoblastic metastases, the deposition of calcium and phosphate occurs, causing a decrease in serum calcium. This process stimulates the release of parathyroid hormone and enhances the mobilization of calcium ions to the serum. Hence, inducing bone invasion in bony metastases. A study in China reported significantly worse 5-year OS (96.6% vs 84.0%, p=0.011), 5-year Disease-Free Survival/DFS (79.5% vs 95.9% p=0.012), Distant Metastases-Free Survival/DMFS (88.4% vs 84.9% p=0.004) in individuals with lower serum calcium level [1,23]. On the other hand, hypercalcemia is also commonly seen in NPC, accounting for 47% of all participants. A study in 2020 reported that lower calcium levels are related to worse prognosis than those with high calcium levels [23]. The mechanism of hypercalcemia in NPC includes humoral hypercalcemia due to the secretion of Parathyroid Hormone Related Peptide (PTHrP), osteolytic bone metastases, and the activation of 1-α-hydrolase leading to the increase of calcitriol [24].

ALP is an enzyme involved in the removal of phosphate groups called dephosphorylation. ALP is mainly seen in bone, liver, bile duct, kidney, and placenta. In a pathological process such as bile duct obstruction, kidney disease, hepatocellular carcinoma, and bone metastases, ALP may be released into the bloodstream. Therefore, this enzyme is used to predict bony metastases in NPC. In addition, serum ALP is also significantly correlated with liver metastases. Consequently, higher ALP (>110 IU/L) is observed in subjects with bone and liver metastases than in one metastatic site. In this study, 25 participants were recorded with ALP of >110 IU/L, and 24 participants were recorded with ALP of >147 IU/L. This may be related to this study's lower rate of metastases (8.12%). Pretreatment ALP is not significantly associated with treatment response. A study by Jin et al. stated that this parameter declined post-treatment in 59.5% of participants. The response rate was significantly higher in participants with normal ALP after treatment [25].

AST is widely distributed in various tissues. In contrast, ALT is enriched in the liver. Consequently, a single measurement of ALT and ALT is not a reliable predictor of prognosis since it is also related to non-tumor factors. High De Ritis ratio (serum AST/ALT) is associated with increased anaerobic glycolysis. In malignancy, tumor progression is affected by glucose metabolism. Cells with anaerobic glycolysis processes are prone to hypoxia and cellular damage. In this condition, AST is found higher than ALT. Wu et al. reported that De Ritis ratio of ≥1.65 is associated with unfavorable survival outcomes [26]. However, normal AST and ALT were mainly found in this study with an average De Ritis ratio of 1.13, 86.24% reported ratio of <1.65, and 13.76% with a ratio of ≥1.65.

Bilirubin is a major product of heme catabolism, produced by the oxidation of heme during biliverdin production. The reduction of biliverdin generates indirect bilirubin. This waste product will be conjugated with glucuronic acid, forming direct bilirubin, and excreted by the small intestine as a component of bile. Previously, bilirubin had been recognized as only a waste product. However, several studies currently reported the antioxidant activity of bilirubin. Free radicals and Reactive Oxygen Species (ROS) induce oxidative stress in cells. This mechanism contributes to transformation, survival, proliferation, the resistance of therapies, angiogenesis, and metastases of NPC by activating many molecules, including Ras, PI3K/Akt, ERK1/2, p38 MAPK, and JNK1/2. The activation of these molecules is associated with the upregulation of Matrix Metalloproteinase (MMP), which is important in invasion and metastases of NPC.[27] Yao et al. found that indirect bilirubin of more than 7.15 mmol/L is associated with better Progression-Free Survival/PFS (HR 0.51, 95% CI 0.36-0.72, p<0.001), OS (HR 0.60, 95% CI 0.39-0.90, p=0.012) and DMFS (HR 0.54, 95% CI 0.35-0.85, p=0.006). While direct bilirubin >2.76 mmol/L is associated with superior PFS (HR 0.60 95% CI 0.43-0.83, p=0.002) [28]. In our study, the majority of all bilirubin indexes were shown within normal limits. The averages of the three indexes showed higher than 7.15 mmol/L (indirect bilirubin), 2.67 mmol/L (direct bilirubin), and 9.8 mmol/L (total bilirubin), suggesting a superior prognosis.

Urea and creatinine are the markers of kidney function. Therefore, both parameters are frequently used in evaluating the kidneys after chemoradiation. Urea is the end catabolism product of protein and amino acid produced by the liver. High serum urea can be caused by declining kidney function and dehydration. In contrast, low serum urea is associated with a deficiency of protein intake.

In contrast, serum creatinine is the end metabolism product of creatinine in muscle and phosphocreatine excreted in kidneys. The elevation of serum creatinine in NPC is mainly related to dehydration due to oral and digestive tract mucosa inflammation [29]. In this study, 14.60% presented with high urea levels, and 69.20% presented with high creatinine levels. The limitation of this study was that it didn't evaluate the significance of each variable and only included the pretreatment laboratory profiles. Further analysis should be conducted to evaluate the alteration of the profiles.

5. CONCLUSION

This study indicated a worse prognosis by anemia, leukocytosis, and a high De Ritis ratio. In contrast, a better prognosis is predicted by low ALP levels, high calcium, direct bilirubin, and total bilirubin. In addition, pretreatment laboratory profiles can be assessed to predict the prognosis of patients with NPC.

REFERENCES

[1] Indrasari S, Sudarman K, Fedriani J. The Primary Tumor and Regional Lymph Node Clinical Status of Distant Metastasis in Nasopharyngeal Carcinoma. J Otorhinolaryngol Hear Balance Med. 2018;1(2):9.

[2] Wu L, Li C, Pan L. Nasopharyngeal carcinoma: A review of current updates. Exp Ther Med. 2018;15(4):3687–92.

[3] Adriana R, Dewi YA, Samiadi D, Candra EW. Survival Analysis of Nasopharyngeal Carcinoma in Hassan Sadikin Hospital. Int J Nasopharyngeal Carcinoma. 2019;1(1):03–6.

[4] Utama DS. The Characteristics of Nasopharyngeal Carcinoma Patients in Mohammad Hoesin General Hospital Palembang

January 2013 - December 2017. Int J Nasopharyngeal Carcinoma. 2019;1(1):30–2.

[5] Xie SH, Yu ITS, Tse LA, Mang OWK, Yue L. Sex difference in the incidence of nasopharyngeal carcinoma in Hong Kong 1983-2008: Suggestion of a potential protective role of estrogen. Eur J Cancer. 2013;49(1):150–5.

[6] Salehiniya H, Mohammadian M, Mohammadian-Hafshejani A, Mahdavifar N. Nasopharyngeal Cancer in the World: Epidemiology, Incidence, Mortality and Risk Factors. World Cancer Res J. 2018;5(1):1–8.

[7] Dewi Kurniawati, F.G. Kuhuwael AQP. Penilaian Kualitas Hidup Penderita Karsinoma Nasofaring Berdasarkan Karnofsky Performance Scale, Eortc Qlq-C30 Dan Eortc Qlq-H & N35 Di Makassar Quality of Life Assessment in Nasopharyngeal Carcinoma Patients With Karnofsky Performance Scale, Eortc Qlq-. Orli. 2013;

[8] Hutajulu SH, Howdon D, Taroeno-Hariadi KW, Hardianti MS, Purwanto I, Indrasari SR, et al. Survival outcome and prognostic factors of patients with nasopharyngeal cancer in Yogyakarta, Indonesia: A hospital-based retrospective study. PLoS One. 2021;16(2):1–20.

[9] Dwijayanti F, Samosir N, Herawati C. Association of Waiting Time for Diagnosis with Quality of Life (QoL) in Nasopharyngeal Carcinoma : A Survey in Dharmais Cancer Hospital. 2020;2(4):124–9.

[10] WHO. 2014 Review of Cancer Medicines on the WHO List of Essential Medicines Nasopharyngeal Carcinoma. Union Int Cancer Control. 2014;1–9.

[11] Kanno M, Narita N, Fujimoto Y, Wakisaka N, Yoshizaki T, Kodaira T, et al. Third epidemiological analysis of nasopharyngeal carcinoma in the central region of Japan from 2006 to 2015. Cancers (Basel). 2019;11(8).

[12] Hardianti RA, Dewi YA, Utami RD. Risk Factor of Nasopharyngeal Carcinoma Dr. Hasan Sadikin General Hospital Bandung. Int J Nasopharyngeal Carcinoma. 2019;1(03):110–1.

[13] Komite Penanggulangan Kanker Nasional Kemenkes RI. Panduan Penatalaksanaan Kanker Nasofaring. Kementeri Kesehat Republik Indones Kom Penanggulangan Kanker Nasional. 2015;1–56.

[14] Kuswandi A, Kuswandi NH, Kasim M, Tan'im T, Wulandari M. Karakteristik Histopatologi dan Stadium Klinis Kanker Nasofaring. J Ilm Kesehat Sandi Husada. 2020;11(1):243–51.

[15] Siti-Azrin AH, Norsa'adah B, Naing NN. Prognostic factors of nasopharyngeal carcinoma patients in a tertiary referral hospital: a retrospective cohort study. BMC Res Notes. 2017;10(1):705.

[16] Susilawati NK, Kadriyan H. Incidence of Anemia in Patient With Nasopharyngeal Carcinoma At Ent-Hns Department West Nusa Tenggara. Int J Nasopharyngeal Carcinoma. 2019;1(1):33–5.

[17] Kadriyan H, Sulaksana MA, Lestarini IA, Susilawati NK, Punagi AQ, Pieter NAL, et al. Incidence and characteristics of anemia among patients with nasopharyngeal carcinoma in Lombok, Indonesia. AIP Conf Proc. 2019;2199(12).

[18] Busti F, Marchi G, Ugolini S, Castagna A, Girelli D. Anemia and iron deficiency in cancer patients: Role of iron replacement therapy. Pharmaceuticals. 2018;11(4):1–14.

[19] Pillai AA, Fazal Sa, Babiker HM. Polycythemia. StatPearls. 2021.

[20] Su Z, Mao YP, OuYang PY, Tang J, Xie FY. Initial hyperleukocytosis and neutrophilia in nasopharyngeal carcinoma: Incidence and prognostic impact. PLoS One. 2015;10(9):1–14.

[21] Lin YH, Chang KP, Lin YS, Chang TS. Pretreatment combination of platelet counts and neutrophil-lymphocyte ratio predicts survival of nasopharyngeal cancer patients receiving intensity-modulated radiotherapy. Onco Targets Ther. 2017;10:2751–60.

[22] Yang K, Zhang T, Chen J, Fan L, Yin Z, Hu Y, et al. Immune Thrombocytopenia As a Paraneoplastic Syndrome in Patients With Nasopharyngeal Cancer. Head Neck. 2012;36(10):127–30.

[23] Huang SY, Chen Y, Tan XR, Gong S, Yang XJ, He QM, et al. Serum calcium levels before antitumor therapy predict clinical outcomes in patients with nasopharyngeal carcinoma. Onco Targets Ther. 2020;13:13111–9.

[24] Chaudhary S, Sah JP. Hypercalcemia due to nasopharyngeal carcinoma. J Nepal Med Assoc. 2017;56(205):182–5.

[25] Jin Y, Yuan MQ, Chen JQ, Zhang YP. Serum alkaline phosphatase predicts survival outcomes in patients with skeletal metastatic

nasopharyngeal carcinoma. Clinics. 2015;70(4):264–72.

[26] Wu J, Li S, Wang Y, Hu L. Pretreatment aspartate aminotransferase-to-alanine aminotransferase (De ritis) ratio predicts the prognosis of nonmetastatic nasopharyngeal carcinoma. Onco Targets Ther. 2019;12:10077–87.

[27] Deng CC, Xu M, Li J, Luo XL, Zhu YJ, Jiang R, et al. Unconjugated bilirubin is a novel prognostic biomarker for nasopharyngeal carcinoma and inhibits its metastasis via antioxidation activity. Cancer Prev Res. 2016;9(2):180–8.

[28] Yao JJ, Kou J, Peng QH, Dong J, Zhang WJ, Lawrence WR, et al. Prognostic value of serum bilirubin in southern Chinese patients with advanced nasopharyngeal carcinoma. Clin Chim Acta [Internet]. 2018;484(March):314–9.

[29] Iqhbal RM, Ningrum FH, Prihharsanti CN. Pengaruh Kemoradiasi Kanker Kepala Leher Terhadap Kadar Ureum dan Kreatinin Serum. 2018;7(2):813–25.