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**Research**

# The correlation between IL-10 expression and histopathological type in nasopharynx carcinoma patients

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## ABSTRACT

**Background:** Nasopharyngeal carcinoma (NPC) is a malignancy originated from nasopharyngeal epithelial cells. NPC therapy response could be predicted from histopathological type, but some patients with the same histopathological type, showed a different therapy response. Interleukin (IL)-10 expression is expected to be able to predict a better response of therapy in NPC patients. **Purpose**: To find out the correlation between IL-10 expression and histopathological type in NPC patients. **Method**: An analytic observational study with cross sectional approach towards 33 samples taken from the Oncology Polyclinic of Outpatient Unit of Otorhinolaryngology Head and Neck Surgery Department, Dr. Soetomo General Hospital. Formalin-fixed paraffin-embedded biopsy specimens were obtained. The IL-10 expression was studied with immunohistochemistry using rabbit polyclonal antibody Anti IL-10. Assessment of the staining used Allred scale. The Fisher exact test was utilized to determine the correlation of IL-10 expression and histopathological type of NPC, with p value = 0.05. **Result**: The result of IL-10 expression in NPC patients with histopathological WHO type I NPC obtained 1 sample (8.3%) with strong positive expression and 2 samples (9.5%) with weak positive expression. In patients with histopathological WHO type II NPC obtained 2 samples (16.7%) with strong positive expression and 12 samples (57.1%) with weak positive expression. In patients with histopathological WHO type III NPC obtained 9 samples (75%) with strong expression and 7 samples (33.3%) with weak positive expression. **Conclusion**: There was moderate positive correlation between IL-10 expression and histopathological type in NPC patients.

**Keywords:** nasopharyngeal carcinoma, IL-10 expression, histopathological type

## *ABSTRAK*

***Latar belakang:*** *Karsinoma nasofaring (KNF) adalah suatu keganasan yang berasal dari epitel nasofaring. Respon terapi KNF selama ini dapat dinilai berdasarkan tipe histopatologi, namun pada kenyataannya penderita KNF dengan tipe histopatologi sama dapat menunjukkan respon terapi berbeda. Pemeriksaan ekspresi interleukin (IL)-10 diharapkan dapat memberikan prediksi lebih baik mengenai respon terapi pada penderita KNF.* ***Tujuan:*** *Mengetahui hubungan antara ekspresi IL-10 dengan tipe histopatologi pada penderita KNF.* ***Metode:*** *Penelitian observasional analitik dengan pendekatan* cross sectional *pada 33 sampel yang diperoleh dari Poliklinik Onkologi Unit Rawat Jalan, Departemen THT-Bedah Kepala Leher, RSUD Dr Soetomo. Ekspresi IL-10 diperiksa dari blok parafin dengan teknik pemulasan imunohistokimia menggunakan* rabbit polyclonal antibody Anti IL-10*. Ekspresi IL-10 dinilai dengan menggunakan skala Allred. Uji* Fisher exact *digunakan untuk menentukan korelasi antara ekspresi IL-10 dan tipe histopatologi KNF, dengan p = 0,05.* ***Hasil:*** *Ekspresi IL-10 pada KNF WHO tipe I didapatkan ekspresi positif kuat 1 penderita (8,3%) dan ekspresi positif lemah 2 penderita (9,5%). Hasil ekspresi IL-10 pada KNF WHO tipe II didapatkan ekspresi positif kuat 2 penderita (16,7%) dan ekspresi positif lemah 12 penderita (57,1%). Hasil ekspresi IL-10 pada KNF WHO tipe III 9 penderita (75%) dengan ekspresi positif kuat dan 7 penderita (33,3%) dengan ekspresi positif lemah.* ***Kesimpulan:*** *Didapatkan korelasi positif sedang antara ekspresi IL-10 dan tipe histopatologi pada penderita KNF.*

***Kata kunci :*** *karsinoma nasofaring, ekspresi IL-10, tipe histopatologi*

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## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy originated from lymphoepithelial tissue and nasopharyngeal epithelial cells. All this time, the therapy response of NPC was considered could be predicted from the histopathological type, but some patients with the same histopathological type, might show different therapy responses.[1] Evidently, this proves that histopathological type was not accurate enough to predict the therapy response in NPC patients.

Budiani et al.[2] had proven that IL-10 level and expression increased significantly in WHO type III NPC patients compared to WHO type II. This statement was supported by a research in Dr. Moewardi General Hospital, Surakarta, which had shown that IL-10 expression increased in WHO type III NPC patients.[3]

The examination of IL-10 expression and the histopathological type were expected to be able to make a better prediction of therapy response for NPC patients. The correlation between IL-10 expression and histopathological type in NPC patients who visited the Oncology Polyclinic at the Outpatient Unit of Otorhinolaryngology Head and Neck Surgery Department, Dr. Soetomo General Hospital, Surabaya, until to date has never been investigated.

The histopathological WHO type II and III NPC were recognized to have better therapy response, nevertheless, not all WHO type II and III NPC patients brought forth complete therapy response.[4,5] According to Bergonie and Tribondeau law, the cell sensitivity towards radiation is in inverse proportion with cell differentiation. Meaning, the worse cell differentiation, the better therapy response will be. WHO type II NPC has a good-moderate differentiation degree, and WHO type III has no differentiation.[1] A study by Fibrian,[1] (2010) had almost the same therapy response in all three histopathological types of NPC patients, particularly in stadium III and IV.

IL-10 is produced by Epstein-Barr Virus (EBV)-encoded RNAs (EBER) in situ in NPC cell nucleus.[2,6] Human tissues which contained EBER is radiosensitive by nature, therefore it has a better prognosis to radiotherapy.[5] Several studies reported the role of IL-10 in NPC development.[7] These data were supported by a study of Farzin et al.[8] (2012) which revealed that IL-10 level was high in advanced stage of head and neck squamous cell carcinoma.

According to Tan et al.[9] (2006), there was a significant correlation between Epstein-Barr Virus (EBV) Load and IL-10, so that it could be used as a marker to evaluate NPC therapy response. Fujieda et al.[6] (1999) found out that IL-10 expression could be a factor for evaluating therapy response and prognosis of NPC patients.

IL-10 has a major role in NPC cell development through various means, among others by increasing cell differentiation, suppressing local immune response, stimulating proliferation, inducing angiogenesis, and inhibiting apoptosis.[10,11]

Epstein Barr Virus encoded EBV RNAs (EBER) is responsible for the production of viral Interleukin (vIL)-10 or BCRF1 in the NPC cell nucleus. The vIL-10 protein has homologous amino acid with IL-10

produced by human body, and plays a role as an autocrine growth factor for NPC cells. The activation of Latent Membrane Protein-1 (LMP-1) in NPC is stimulating the production of vIL-10 with the aid of Cluster of Differentiation 4 (CD4).[2] Latent membrane protein (LMP) 1 could activate IL-10 through Cytokines Tumor Necrosis factor Activating Receptor1,2 (CTAR1,2), Tumor Necrosis factor Receptor-Associated factors (TRAFs), Tumor Necrosis Factor Receptor-Associated Death Domain (TRADD) routes, furthermore effecting Jun N kinase (JNK), Janus Kinase (JAK), and Activating Protein (AP)-1, and Tyrosine kinase (TYK)-2 routes.[12] IL-10 stimulates activation of Signal Transducer and Activator of Transcription (STAT)-3 effecting cell differentiation and causing invasive growth of independent nasopharyngeal epithelial cells that would eventually become carcinoma cells.[5,13-15]

Based on the above description, it is necessary to do a research to find out the correlation between IL-10 expression and histopathological type in NPC patients who came for treatment at the Oncology Polyclinic of Otorhinolaryngology Head and Neck Surgery Department, Dr. Soetomo General Hospital.

## METHOD

This was an analytic observational study with cross sectional approach using secondary (retrospective) data. Research subjects were WHO type I, II, III NPC patients who came to Oncology Polyclinic of the Outpatient Unit of Otorhinolaryngology Head and Neck Department, Dr.Soetomo General Hospital, Surabaya, and fitted the inclusion and exclusion criteria.

Thirty three samples were taken by nasopharyngeal biopsy through consecutive sampling method, during the period of October until December 2016. Paraffin blocks were cut and IL-10 expression was studied with immunohistochemistry using rabbit polyclonal antibody Anti IL-10. The IL-10 assessment was conducted by one Anatomical Pathology senior specialist from the Anatomical Pathology Department of Dr. Sardjito General Hospital, Yogyakarta, and the reports were sent to the researcher.

Statistical analysis was using Fisher exact test with p=0.05 to find out the correlation between IL-10 expression and histopathological type of NPC patients.

## RESULT

As many as 33 WHO type I, II, III NPC patients participated in this study.

**Table 2. Patient distribution based on age group**

| Age (years) | Number | % |
|---|---|---|
| 20 – 29 | 3 | 9.10 |
| 30 – 39 | 2 | 6.06 |
| 40 – 49 | 11 | 33.33 |
| 50 – 59 | 12 | 36.36 |
| 60 – 69 | 5 | 15.15 |
| Total | 33 | 100.00 |

The highest number of NPC patients was the 50-59 age-group as many as 12 patients (36.36%), followed by the 40-49 age-group as many as 11 patients (33.33%), and 5 patients of 60-69 age-group (15.15%). The youngest age was 20 and the oldest was 67 years old.

The number of male patients was 24 (72.73%) and female patients was 9 (27.27%). The ratio of male and female was 2.7 : 1.

Based on race ethnicity, the highest number of NPC patients was Javanese with 25 patients (75.76%), Madurese was 7 patients (21.21%), and Manadonese was 1 patient (3.03%).

NPC patient distribution based on occupation was shown in Table 2.

The highest occupation number was farmer as many as 10 patients (30.30%) followed by street vendor as many as 7 patients (21.21%).

**Table 2. Patient distribution based on occupation**

| Occupation | Total | % |
|---|---|---|
| Farmer | 10 | 30.30 |
| Driver | 4 | 12.13 |
| Factory worker | 2 | 6.06 |
| Civil servant | 1 | 3.03 |
| Street vendors | 7 | 21.21 |
| Mechanic | 2 | 6.06 |
| Bricklayer | 2 | 6.06 |
| Teacher | 2 | 6.06 |
| Housewife | 2 | 6.06 |
| Police | 1 | 3.03 |
| Total | 33 | 100.00 |

NPC patient distribution based on histopathological type was shown in Table 3.

The highest number of histopathological type was WHO type III with 16 patients (48.48%) followed by WHO type II with 14 patients (42.42%).

**Table 3. Distribution of histopathological type**

| Histopathology | Number | % |
|---|---|---|
| WHO type I | 3 | 9.10 |
| WHO type II | 14 | 42.42 |
| WHO type III | 16 | 48.48 |
| Total | 33 | 100.00 |

The result of IL-10 expression in various histopathological type of NPC patients was shown in Table 4.

**Table 4. The result of IL-10 expression in NPC various histopathological type**

| | | | Histo.PA | | | |
|---|---|---|---|---|---|---|
| | | | WHO Tipe 1 | WHO Tipe 2 | WHO Tipe 3 | Total |
| IL.10.Allred | Weak | Count | 2 | 12 | 7 | 21 |
| | | % within IL10.Allred | 9.5% | 57.1% | 33.3% | 100.0% |
| | Strong | Count | 1 | 2 | 9 | 12 |
| | | % within IL10.Allred | 8.3% | 16.7% | 75.0% | 100.0% |
| Total | | Count | 3 | 14 | 16 | 33 |
| | | % within IL10.Allred | 9.1% | 42.4% | 48.5% | 100.00% |

Note:

Assessment of IL-10 expression (Allred scale):

a. Weak expression, final score ≤ 100
b. Strong expression, final score >100

The research obtained WHO type I NPC with IL-10 strong expression in 1 patient, and weak expression in 2 patients; WHO type II NPC with IL-10 strong expression in 2 patients, and weak expression in 12 patients; and WHO type III NPC with IL-10 strong expression in 9 patients, and weak expression in 7 patients.

From all patients, IL-10 strong intracell expression was 36.36%. From all patients, IL-10 weak intracell expression was 63.64%, and there was increased cell numbers which gave strong expression in WHO type III NPC patients.

## DISCUSSION

The result of this study had shown that the highest number of NPC patients was the 50-59 age-group, as many as 12 patients

(36.36%), followed by the 40-49 age-group with 11 patients (33.33%), and the 60-69 age-group with 5 patients (15.15%). The NPC youngest age was 20 and the oldest was 67 years old.

Predisposing factor of NPC in productive age was assumed to be exposure of carcinogenic substance or pollution, latent EBV infection, and decreased immunity factor. This was the cause of high incidence in people 40-60 years of age.[16]

A previous study at the same place by Indra[17] (2017) obtained a similar result with this study, out of 40 NPC patients, the highest incidence was in the 50-59 age-group as many as 15 patients (35.71%), followed by 40-49 age-group 14 patients (33.33%), and 60-69 age-group 6 patients (14.29%).[17]

Kentjono[18] also found the highest NPC incidence was in the productive age ranged 30-59 years (80%), with peak age at 40-49, and the highest incidence was in range age 40-60 years old.

Based on gender, in this study there were 24 male (72.73%) and 9 female (27.27%) patients, with the ratio 2.7:1. It was assumed that the higher NPC incidence was in male, due to the different life style and occupation, where men were more in contact with carcinogenic substances, such as smoking, fumes exposure, dust smoke, and chemical hazards found at working place, which could increase the NPC risk by 2-6 times. Formaldehyde in work place will increase the risk of NPC 2-4 times. Using firewood, exposure to industrial pollution, and burning products will also double the NPC risk.[19]

This result was similar with an earlier study by Sabilarrusydi[20] (2016), where there were 14 (66.67%) male and 7 (33.33%) female patients, with the ratio 2:1. Research in United States revealed that the ratio was 3:1. The distribution of NPC patients based on gender found the majority cases was male (70%), with ratio 3:1 for male and female.[18] This was in accord with our study result.

NPC patients distribution based on race ethnicity found that the highest race was Javanese 25 patients (75.76%), followed by Madurese 7 patients (21.21%), and Manadonese 1 patient (3.03%). The higher NPC patients in Javanese race was due to fact that the research was held in Surabaya which had a majority of Javanese population.

An immunogenic study in Jakarta in 1997 had found HLA-A24 and HLA-B63 to be suspected as the causal factor for the vulnerability of pure Indonesian origin to acquire NPC.[18]

The study result of the distribution of NPC patients based on occupation showed the highest was farmers as many as 10 patients (30.30%), followed by street vendor 7 patients (21.21%). The correlation of farmers and NPC incidence was assumed due to prolonged exposure to pesticide, while in workers were the exposure to dust or to medium sized particles (5-10 mm). These particles were easily absorbed by nasopharynx mucosa.[21]

This result was the same with an earlier study at the same place by Indra[17] (2017), where the highest number of NPC sufferers was farmers 16 patients (38.09%) and street vendor 6 patients (14.29%).[17]

Several epidemiologic studies had revealed that there was an increased risk factor of acquiring NPC to those workers who were exposed to firewood dust for a certain period and dose. Other studies found increased risk factor to NPC for those who were in contact with burnt materials (coal, ashes). This exposure could increase NPC risk factor to farmers, although epidemiologically the result could vary based on the length and duration of exposure, the dose and the endemic area.[21]

The highest number of histopathological type in this study was WHO type III NPC 16 patients (48.48%), followed by WHO type II 14 patients (42.42%), and 3 patients (9.10%) WHO type I NPC. In Indonesia, the

most frequent found histopathological type was WHO type III. It was assumed due to exposure of EBV infection in endemic areas. EBV incidence in developing country is high around 80-90% in adults, and seropositive 90% in children above 2 years old.[22]

A study by Hoesin and Santoso in 1992, quoted by Kentjono[23] at the Anatomical Pathology Department of Faculty of Medicine Universitas Airlangga, Surabaya, found patients WHO type I, II and III NPC consecutively as 17.91%, 10.45%, and 71.64%. A study by Kentjono[23] (2003) at the Outpatient Unit of the Otorhinolaryngology Head and Neck Surgery, Dr.Soetomo General Hospital, obtained NPC patients WHO type I, II and III in sequence as 5.59%, 8.04% and 85.66%.[23] The most frequent histopathological type found in Indonesia was WHO tipe III NPC.[24]

Our study found that in WHO type I NPC, there was IL-10 strong expression in 1 patient, weak expression in 2 patients. In WHO type II NPC, there was IL-10 strong expression in 2 patients, and weak expression in 12 patients. In WHO type III NPC, there was IL-10 strong expression in 9 patients and 7 patients with weak expression, and also found increased cell number which gave strong expression in NPC patients WHO type III NPC patients. The outcome of statistical analysis showed a correlation between IL-10 expression and histopatological type (WHO type I, II, and III NPC), $p=0.040$ and contingency coefficient (C)=0.384. This outcome showed a significant correlation ($p<0.05$). Contingency coefficient (C)=0.384 meant there was a positive correlation between IL-10 expression and histopatological type (WHO type I, II, and III NPC).

This result was in accordance with the hypothesis of this research, based on theory that IL-10 had a role in increasing NPC cell differentiation (WHO type I, II, and III) through the activation of STAT3. The activation of STAT3 in epithelial cell infected by EBV had involve Janus Kiknase-1 (JAK1), Activating Protein-1 (AP1), Jun N kinase (JNK), and Tyrosine Kinase-2 (TYK2) routes.[25,26]

The binding of IL-10 with its receptor was related with the activation of Janus tyrosine Kinases and downstream signaling stimulation. The activation of JAK1, TYK2 and STAT3 involved in signaling cascade. IL-10 stimulated the activation of STAT3 resulting in the invasive growth of independent nasopharyngeal epithelial cell layers, which eventually will become carcinoma cells. The high activation of STAT3 could increase NPC cell differentiation. Numerous evidence had shown that the activation of STAT3 played a role in forming and developing tumor.[5,13-15]

Latent membrane protein (LMP)1 inhibits the terminal differentiation of human stratified squamous epithelial cells. Although some signal routes had a role in the process, both AP1 and NF-κB were assumed to have a role in regulating cell differentiation. In stratified squamous epithelial, it was assumed that the cell differentiation depended on AP1, but the process was still unclear. LMP1 also regulates tumor micro environment and induces inflammation causing tumor forming through the activation of nuclear factor kappa-light-chain-enhancer of activated B cells NF-κB route. In normal epidermis, NF-κB is activated as migrant cells from basal layer, thus, it showed that NF-κB route had a role in epithelial cell differentiation. Inhibition of NF-κB function by dominant expression of NF-κB protein inhibitor in the form of IκBs had resulted an inhibition in differentiation and promoting epithelial hyperplasia. In gel culture, LMP2A engenders the phenotype change including independent growth, inducing b catenin signal of epithelial cell, inhibiting cellular differentiation, and stimulating cell growth through phosphatidylinositol 3-kinase and Akt PI3K-Akt.[27,28]

Histological studies have indicated that the different histological types of NPC are

variants of a homogenous group of neoplasms. Histogenetically, all type of NPC is squamous in origin, and this essential squamous nature of both NKC (WHO type II NPC) and UC (WHO type III has been confirmed by electron microscopy and immunohistochemistry. Dedifferentiation in tumors is known to occur in sarcomas. This phenomenon is well recognized in NPC, and it is not unusual for lesions that recur, or tumors metastatic to lymphnodes to demonstrate histological features that differ from those observed at the time of initial diagnosis.

Shanmugaratnam quoted by Pathmanathan et al.[29], found that 8% of undifferentiated carcinoma (UC) or WHO type III NPC, and 26% of nonkeratinizing carcinoma (NKC) or WHO type II NPC, could be presented as squamous cell carcinoma (SCC) or WHO type I NPC when the lesion recurred or metastasized. Similarly 50% of tumors initially diagnosed as SCC recurred as either NKC or UC and afterwards had relapsed could be diagnosed as WHO type II or III NPC. From the morphological point of view, the existence of mixed histological types of the NPC and the phenomenon of the dedifferentiation in the clinical course and biological evolution of NPC could explain histogenetically the relatedness of all three WHO types of NPC.

This result was similar with the study conducted by Budiani et al.[2] (2002) which had proven that IL-10 expression and level significantly increased in WHO type III NPC compared to WHO type II. The study found that LMP-1 activation in NPC also stimulates IL-10 production assisted by CD4. Latent membrane protein (LMP) 1 could trigger the IL-10 activation through Cytokines Tumor Necrosis factor Activating Receptor1,2 (CTAR1,2), Tumor Necrosis Factor Receptor Associated Factor (TRAF), TNF Receptor-Associated Death Domain (TRADD), henceforth, had an impact on Jun N kinase (JNK), JAK, and Activating Protein 1 (AP1) routes.[12] This route would stimulate the activation of STAT3 which will influence NPC cell differentiation.[5,13-15]

This result was also in accordance with a study performed in Dr. Moewardi General Hospital in Surakarta, which had shown that IL-10 expression escalated in WHO type III NPC patients.[3] The stroma inflammation and cytokine routes played a role in stimulating the growth and the expression of EBV genes, both latent or lytic in NPC epithelial cells. Cytokine which was produced by inflammation cells had activated NF-kB dan STAT3 signal route in the EBV infected epithelial cells. Chronic inflammation of EBV infected epithelial cell had a role in the pathogenesis of WHO type III NPC.[28]

In our study the examination of IL-10 expression in WHO type I NPC obtained 1 patient with strong expression, and 2 patients with weak expression. This result showed the role of EBV on WHO type I NPC because intracell IL-10 was produced by EBER. A study by Pathmanathan et al.[29], (1995) found that from all 4 WHO type I NPC patients, there was EBV clonal episomal forms without detectable linear viral DNA, also with non-increasing IgA VCA antigen titer in the patient. The combined result of the reverse transcriptase polymerase chain reaction (PCR) analyses and the LMP1 immunohistochemistry indicate that EBNA1, LMP1, LMP2, and BamHI A are consistently transcribed in SCC (WHO type 1 NPC). EBV gene transcription in latently infected lymphoid and epithelial cells is complex, although there are clearly specific viral/ epithelial cells interactions.

The viral infection is unique in EBV pathogenesis in that the infection is permissive with the production of linear viral DNA and expression of LMP1 and replicative antigens in the absence of EBER expression. However, despite the apparent differences in the morphological appearances of the three types of NPC, the identity of their histogenetic origin

and squamous nature, the frequent admixture of varying histological types of NPC within a single tumor, and the demonstration of dedifferentiation suggest that there are greater similarities than differences between the forms of NPC. The overall conclusion on the basis of epidemiological, pathological, and molecular biological grounds, is that all types of NPC are variants of an EBV-associated malignancy.

Mocellin et al.[7] (2005) had shown that IL-10 expression was a predictor for therapy response and prognosis of NPC, and had proven to select valuably NPC patients as candidates for aggressive therapy. IL-10 expression became the parameter to evaluate/ predict NPC therapy response related to EBV infection. The same statement was disclosed by Yao et al.[30] (1997) dan Fujieda et al.[6] (1999) in their studies, that IL-10 expression could be a marker of therapy response and prognosis of NPC patients.[6,30]

The study result showed there was different IL-10 expression in the same histological type, even weak expression (zero) in some histopathological types. This outcome was assumed due to other factors influencing cell differentiation. There were many factors which could increase NPC cell differentiations, among others were p63 expression and NF-κB. The interaction of LMP1 and EBNA-2 would escalate p63 expression, while LMP2A would activate NF-κB. The NF-κB signal was also activated by Toll-like Receptor 3 (TLR3) which was a censor to detect EBER by activating signal cascade through Toll reseptor IL-1 (TIR) *domain containing adaptor inducing* IFN-β (TRIF). The inhibition towards NPC cell differentiation was induced by LMP1 and LMP2A activation through b catenin activation.[26,28]

All this time, NPC therapy response was predicted from histopathological type, but some patients with the same histopathological type, showed a different therapy response. Thus, additional supporting examinations were needed to be able to predict more accurately a better therapy response.

Interleukin-10 expression and histopathological type are expected to be able to predict a better response of therapy in NPC patients. A good comprehension on the correlation between IL-10 expression and histopathological type (WHO type I, II, and III NPC) is required, so that it was necessary to do this research. This study was in accord with the hypothesis, meaning IL-10 expression and histopathological type could be used to more accurately predict the therapy response in NPC patients.

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