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The Serological Examination of Immunoglobulin A Anti-Early Antigen of Epstein–Barr Virus (Anti-EA EBV IgA) in the Nias Tribe Nasopharyngeal Cancer Patients

Hana Isal Salina Ginting[1]*, Farhat Farhat[2], Mutiara Indah Sari[3]

[1]Master Program in Tropical Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [2]Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [3]Department of Biochemistry, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

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***Correspondence:** Hana Isal Salina Ginting, Master Program in Tropical Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia. E-mail: hanasalsalina@gmail.com
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Abstract

BACKGROUND: Nasopharyngeal cancer (NPC) is a health problem associated with malignancies of the ear, nose, and throat. The main pathogenesis of NPC is Epstein–Barr virus (EBV) infection. The signs and symptoms of NPC are non-specific, causing the occurrence of delay in diagnosis leading to treatment failure. The early detection based on the NPC profile using immunoglobulin A (IgA) antibodies against the early antigen (EA) can be done, but many factors affect anti-EA EBV IgA levels, one of which is ethnicity.

AIM: This study aimed to compare levels of anti-EA EBV IgA in NPC patients and non-NPC in the Nias tribe.

MATERIALS AND METHODS: This study was cross-sectional involving 29 NPC patients and 29 non-NPC in the Nias tribe. The subjects of the study were blood tests to measure the levels of anti-EA EBV IgA by a serological test. Data were analyzed by Chi-square test.

RESULTS: The results showed that the mean value of anti-EA EBV IgA levels is 246.22 ± 320.05 U/mL and the proportion of positive serology tests is 55.2% in NPC patients. The mean value of anti-EA EBV IgA levels is 51.79 ± 1.55 U/mL and the proportion of positive serology tests is 10.3% in non-NPC. The comparison of mean anti-EA EBV IgA between NPC patients and non-NPC was significant ($p < 0.001$). The comparison of positive and negative serology tests of anti-EA EBV IgA between NPC patients and non-NPC was significant ($p < 0.05$).

CONCLUSION: The serology tests of anti-EA EBV IgA play a role in differentiating NPC patients from non-NPC, so it can be useful as a screening tool for NPC in the Nias tribe.

Introduction

Nasopharyngeal cancer (NPC) is one of the health problems associated with malignancies of the ear, nose, and throat (ENT). NPC is a throat cancer that occurs in the outer layer of the nasopharynx with a predilection for Rossenmuller fossa in the nasopharynx which is a transitional area, where the cuboidal epithelium changes to squamous epithelium [1], [2]. Globally, NPC is uncommon cancer and the incidence of NPC is around 80,000 new cases reported per year, which is 0.7% of all cancers that occur globally in 2014 [3]. In 2018, the highest incidence of NPC occurred in Southeast China at 40–50 cases per 100,000 population [1]. The incidence of NPC ranks eighth of the types of cancer that occurs in Indonesia, namely, 6.6 cases per 100,000 population in 2018. In Indonesia, NPC occurred as many as 17,992 new cases, namely, 5.2% in 2018. Over 5 years, lastly, the incidence of NPC was 48,401 cases [4].

Risk factors of NPC are genetic, environmental, and lifestyle [5], [6]. One of the environmental factors is EBV infection [7], [8]. EBV infection is a significant factor involved in the pathogenesis of NPC, especially in undifferentiated nasopharyngeal carcinoma [9]. The increased risk of NPC that occurs due to EBV infection indicates an increased frequency of viral reactivation. Aberrant EBV reactivation was demonstrated by the detection of serum EBV immunoglobulin A (IgA). The results of different EBV antibody profile between healthy individuals and individuals with NPC so that EBV IgA in blood samples (dry) can be a measure of detection of NPC patients. Individuals suffering from NPC have a higher level of IgA EBV seroactivity than normal individuals [10].

Non-specific signs and symptoms of NPC and lack of awareness of NPC symptoms make NPC diagnosis late or fail. Delay in diagnosis causes treatment failure, the cure rate is low, and the recurrence rate is high. This condition makes the need for prevention and early detection efforts based on the NPC profile [11]. Therefore, it is necessary to develop a non-invasive NPC diagnostic tool so that the tool can be developed into an early detection tool for NPC.

So far, one of the NPC diagnostic tools that have been developed is the detection of IgA antibodies against EA extract antigens, but antigens in the form of extracts have limited stability. It still uses induced cell lines so that the quality consistency cannot be ensured for each production. The other alternative to these antigens is synthetic peptides which are considered more stable. Until now, no synthetic peptide has been proven to have sufficient diagnostic significance for clinical use [12].

Detecting IgA antibodies against EA antigen and EBV virus in NPC patients can be a tool for early detection in NPC patients to facilitate the management of NPC patients and prevent the severity and increase the success of therapy. The previous studies reported that IgA anti-EA EBV was significantly different between NPCs and controls [13], but other studies reported different results, where IgA anti-EA EBV was significantly different between NPCs and controls [14]. In addition, EBV anti-EA IgA was reported to differ by ethnicity [15]. Inconsistency of results required similar studies to confirm results. The study was only conducted in the Nias tribe to ignore the effect of ethnic differences and to observe the relationship only in the Nias tribe which had never been studied before. Therefore, this study aimed to determine the difference in levels of IgA anti-early antigen (EA) Epstein–Barr virus in patients with NPC and in individuals who are not patients with nasopharyngeal carcinoma in the Nias tribe. This result can able to obtain a screening method for early detection of NPC through the detection of IgA anti-EA EBV values that can be applied to the Nias tribe.

Materials and Methods

The study was conducted at the Integrated Laboratory of the Faculty of Medicine, University of North Sumatra, Medan in 2020. It was a prospective cross-sectional study involving 29 NPC patients and 29 non-NPC who met the inclusion and exclusion criteria. The inclusion criteria for the NPC group were patients diagnosed with NPC, Nias ethnic patients, willing to sign the informed consent. The inclusion criteria for the control (non-NPC) group were individuals from the Nias tribe, had good physical or psychological conditions and awareness, and were willing to sign an informed consent. The exclusion criteria had other malignancies and pregnant and lactating women.

The study has received approval from the Health Research Ethics Commission, Faculty of Medicine, University of North Sumatra/H. Adam Malik Hospital Medan (No. 221/TGL/KEPK FK USU-RSUP HAM/2020). The study was conducted by taking blood samples and IgA anti-EA EBV measured by serological test using an enzyme-linked immunosorbent assay kit. Positive and negative serology were based on the criteria, namely, negative serology <cut off and positive serology cut off. The cutoff value is 0.10 + the average negative control absorbance if the negative control absorbance is <0.05. The cutoff value is the average negative control if the absorbance of the negative control is 0.05.

All data were collected and recorded using the Statistical Product and Service Solution (SPSS) version 23 program. Values are expressed as mean ± SD or the appropriate percentage. Comparative analysis of IgA anti-EA EBV between NPC patients and non-NPC patients was calculated statistically using the Chi-square test for categorical data and using the independent sample t-test for normal data and using the Mann–Whitney U-test for abnormal data. A difference was considered significant at $p < 0.05$.

Results

The research subjects consisted of 58 patients consisting of 29 NPC patients and 29 non-NPC individuals. Most of the study subjects were <60 years old in both groups. Subjects aged more than or equal to 60 years were found in the group of NPC patients (6.9%). The subjects of this study, both in the group of NPC patients and non-NPC, were mostly male.

Hypothesis test results in Table 1 showed that there is no significant difference in the age between NPC patients and non-NPC with p = 0.491 (>0.05). The results of the hypothesis test showed that the sex did not differ significantly between the Nias ethnic group between NPC patients and non-NPC with p = 1,000 (> 0.05).

Table 1: Characteristics of research subjects

Characteristics	NPC n = 29		Non-NPC n = 29	Total n = 58		p-value
	F	%		F	%	
Age (Mean SD) years	44.86	12.70	37.39-1-8.76			0491'
<60	27	93.1	29 100	56	96.6	
≥60	2	6.9	0 0	2	3.4	
Sex						
Male	17	58.6	17 58.6	34	58.6	1,000[f]
Female	12	41.4	12 41.4	24	41.4	

'Fischer's Exact Test, €Chi-square Test, *p-value < 0.05 were considered as statistically significant.

Table 2 showed that the mean level of IgA anti-EA EBV in NPC patients was greater (246.22 ± 320.05 U/mL) than in non-NPC (51.79 ± 1.55 U/mL). Comparison of the mean levels of IgA anti-EA EBV between NPC patients and non-NPC is shown in Figure 1. The results of the Shapiro–Wilk normality test obtained p = 0.000 (<0.05) for data on anti-EA EBV IgA levels in the NPC patients, which showed that the data were not normally distributed. The results of the Shapiro–Wilk normality test obtained p = 0.845 (>0.05) for data on IgA levels of anti-EA EBV in the control group, which showed that the data were normally distributed. Hence, the test of the difference in the mean of anti-EA EBV IgA levels of the two groups was carried out using

the Mann–Whitney U-test. The test results showed that there was a significant difference in the mean of anti-EA EBV IgA levels between NPC patients and non-NPC with p = 0.000 (<0.05).

Table 2: Differences in IgA levels of anti-EA EBV in NPC patients and non-NPC

Group	IgA anti-EA EBV (U/mL)				p-value[ñ]	p-value¥
	n	Min	Max	Mean ± SD		
NPC	29	51.00	1214.00	246.22 ± 320.05	0.000	0.000**
Non-NPC	29	48.00	55.00	51.79 ± 1.55	0.845	

[ñ]Normality, Mann Whitney, **p-value < 0.001 were considered as statistically significant.

Table 3 showed that the IgA anti-EA EBV serology test obtained positive results in 16 55.2%) in NPC patients, and 3 (10.3%) in non-NPC. The results of the Chi-square test showed that there was a significant difference of IgA anti-EA EBV serological tests between NPC patients and non-NPC with p = 0.001 (<0.05). The positive results of IgA anti-EA EBV serology were more commonly found in NPC patients than in non-NPC.

Table 3: Comparison of IgA anti-EA EBV serology tests between NPC patients and ncri-NPC in the Nias tribe

IgA anti-EA	NPC		Non-NPC		Total		p-value
EBV	F	%	F	%	F	%	
Positive	16	55.2	3	10.3	19	32.8	
Negative	13	44.8	26	89.7	39	67.2	0.001[¤ſ]
Total	29	100	29	100	58	100	

Contemn>, Correction [ſ]p-value < 0.001 were considered as statistically significant.

Table 4 showed that based on age, the IgA anti-EA EBV serology test results were positive, that mostly at the age of fewer than 60 years. The same results for the serological negative. The Chi-square test results showed that the age is not significantly associated with IgA anti-EA EBV serological test results in NPC patients with p = 1.000 (>0.05). Based on sex, the results of the IgA anti-EA EBV serology test were positive, mostly in the male (56.3%). The same results for negative results 61.5%). The Chi-square test results showed that sex is not significantly associated with IgA anti-EA EBV serological test results in NPC patients with p = 1.000 (>0.05).

Discussion

Nias tribe NPC patients in this study was 44.86 ± 12.70 years old. Most NPC patients were <60 years old (93.1%) and most of them were male (58.6%). In line with this study, Rahman *et al*. reported that NPC patients in Padang were found at an average age of 44.6 years and mostly occurred in men (60%) [13]. The results are in line with research in Denpasar Bali that the incidence of NPC is mostly found in patients aged more than 50 years [16]. Research in North Sumatra also reported that 58.6% of NPC patients were male and most of them occurred at the age of fewer than 60 years (93.1%), especially at the age of 41–60 years (55.2%) [17]. The age distribution of patients with NPC is different. In areas with a low incidence of NPC, the incidence of NPC increases with increasing age, in areas with a high incidence of NPC that increases after 30 years old [18].

Serological results obtained Ig A anti-EA EBV levels in NPC Nias patients with a mean of 246.22 ± 320.05 U/mL. This result is higher than the level of IgA anti-EA EBV in NPC patients in the hospital Hasan Sadikin of 52.18 ± 8.93 U/mL and in NPC patients at Dr. M. Djamil Padang of 114.705 ± 136.524 U/mL [13], [19].

Serology tests of anti-EA EBV IgA in Nias tribal NPC patients found positive in 16 (55.2%). This result is smaller than previous studies that were found in 10 NPC patients in North Sumatra (66.7%) and 212 NPC patients in Yogyakarta (41.7%) [13], [15]. Serology tests Ig A anti-EA EBV of non-NPC Nias tribe found positive in 3 (10.3%). The results differ in individuals in Padang, there were no positive results [13].

Serological results showed that there was a significant difference in IgA anti-EA EBV levels in NPC patients compared to non-NPC individuals with p < 0.05. The mean levels of IgA anti-EA EBV in NPC patients (246.22 ± 320.05 U/mL) were greater than in non-NPC (51.79 ± 1.55 U/mL) in the Nias tribe. These results are in line with Rahman *et al*. that NPC patients had higher levels of EA-IgA (114.705 ± 136.524 U/mL) compared to healthy controls (1.749 ± 0.498 U/mL) with p < 0.05 [13]. Anugrahani *et al*. also reported an increase in the levels of IgA anti-EA EBV in NPC patients compared to non-Hodgkin lymphoma [19].

These results showed that there had a significant difference in the serological tests of IgA anti-EA EBV between NPC patients and non-NPC with p = 0.002 (<0.05). Positive results of IgA anti-EA EBV serology were more commonly found in NPC patients than non-NPC. Thus, the serological tests of IgA anti-EA EBV play a role in screening of NPC patients of the Nias tribe. Positive results serological tests of IgA anti-EA EBV in patients with NPC Nias tribe is 16 (55.2%). Thus, serological tests can be used to distinguish NPC patients from non-NPC based on IgA anti-EA EBV values. A serological test by measuring IgA anti-EA EBV can serve as a diagnostic tool for NPC patients of the Nias tribe.

In line with this research, Rahman *et al*. reported that NPC patients had higher levels of EA-IgA compared to healthy controls. Antibody levels of IgA anti-EA EBV increased in NPC patients and were more common in NPC patients than in control [13]. Sun *et al*. also reported similar results in a study in Shandong, China, that there was an increase in serum IgA anti-EA EBV in NPC patients [20].

EBV infects two sites in the human body, including lymphocytes and salivary gland epithelial cells. The incoming virus replicates in epithelial cells which, then, become latent in B lymphocytes. This viral infection occurs by binding to complement C3d (CD21 or CR2). Several mechanisms of EBV infection

may result from direct contact between infected lymphocytes and cells in the apical membrane, through the interaction of integrins 1 or 5B1 with EBV on the basolateral membrane, and through the direct effect of viral infection on the lateral membrane [21], [22].

The surface of B lymphocytes consists of the CD21 protein which is a target for EBV infection, because this protein can bind to the membrane glycoprotein receptor gp 350/220 on the EBV capsule. EBV enters the host cell cytoplasm after 1–2 h of binding. Terminal repeat fuse to form a circle of the epitope. EBV particles decompose and latent EBV infection occurs after the EBV genome enters the nucleus. The latent infection is characterized by EBV activation in B lymphocyte cells as a result of cell proliferation and activation processes [21], [22].

Differences between normal and malignant EBV infection have been described. In normal conditions, a few B cells are infected, because the EBV infection can be controlled. In malignant conditions, a latent epitome is formed as a result of the presence of the EBV genome in each tumor cell. During cell division, genome replication occurs. The DNA expression in EBV in the latent episomal form was identified, so it was useful as a marker of the development of NPC [23].

The occurrence of NPC is closely related to Epstein–Barr virus (EBV) infection. EBV antibodies are widely used as markers in NPC screening. Several studies have shown that screening for NPC using EBV antibodies is an effective measure to increase the survival rate of NPC patients [24].

Positive results of the IgA anti-EA EBV serology test were mostly found at the age of fewer than 60 years and in males. The age was not significantly related to the IgA anti-EA EBV serological test results with p = 1.000 (>0.05). Sex was not significantly related to the IgA anti-EA EBV serological test results with p = 1.000 (>0.05). These results are in line with research by Zhou *et al*. that no significant association was observed between sex, education, BMI, and family history of tumors or NPC and IgA anti-EA EBV [25].

However, several studies report different results. The age was found to be linearly correlated with antibody levels IgA anti-EA EBV [25]. Older age and females increase positive results of IgA anti-EA EBV. This is assuming that older patients have more exposure to EBV triggers along with a weakened immune response that could facilitate EBV reactivation, leading to increased anti-EBV IgA [26]. Seroreactivity to EBV in females is stronger than in men, probably due to hormonal effects on the immunologic response [15].

The others studies have reported various factors associated with antibody level IgA anti-EA EBV in NPC patients. Januardi *et al*. reported that there was an association between increased titration of IgA anti-EA EBV in type III NPC with risk factors for salted fish and preserved food, smoking, and the use of smoked mosquito coils [27]. Serology IgA VCA/IgA EA as a tumor marker (tumor marker) does not play a role in establishing the diagnosis but is used as screening and basic data for treatment evaluation. This serological examination is performed before a series of diagnostic tests for NPC [1].

Table 4: Relationship between age and sex with IgA anti-EA EBV serology test in NPC patients

Characteristics	Positive ri = 16		Negative sr 13		Total		p-value
	F	%	f	%	f	%	
Age							
<60 years old	15	92.3	12	93.8	27	93.1	1,000'
60 years	1	7.7	1	6.3	2	6.9	
Sex							
Male	9	56.3	8	61.5	17	58.6	1,000'
Female	7	43.8	5	38.5	12	41.4	

€Continuity Correction, £Fi shet's Ex act Test

Conclusion

Serology results antibody IgA anti-EA EBV plays a role in differentiating NPC patients from healthy individuals with the result that there was a significant difference in serological results antibody IgA anti-EA EBV between NPC patients and non-NPC in the Nias tribe. Thus, serology antibody IgA anti-EA EBV can be useful as a biomarker for screening NPC in the Nias tribe. This study implies that serological tests can be applied in clinical practice in screening and early diagnosing NPC. Age and sex were not significantly associated with IgA anti-EA EBV so that screening tests with serological tests could be applied with the same cutoff between overall age and sex. Research only studies differences of IgA anti-EA EBV between NPC patients and non-NPC with small sample size and homogenous, only in the Nias tribe. The study also did not measure EBV anti-EA IgA levels before and after the diagnosis of NPC and only after NPC and not NPC. This research can be carried out by involving various tribes and ethnicities in Indonesia to examine the influence of tribes and ethnicities on levels of IgA anti-EA EBV in NPC patients supports these results so that they can be practiced clinically for various ethnic groups. The results of this study only imply IgA anti-EA EBV use as a screening of NPC. Its use as a diagnostic tool needs further research.

References

1. Kementrian Kesehatan Republik Indonesia. Panduan Penatalaksanaan Kanker Nasofaring Kementerian Kesehatan Komite Penanggulangan Kanker Nasional. Indonesia: Kementrian Kesehatan Republik Indonesia; 2019.
2. Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, *et al*. Nasopharyngeal carcinoma in Indonesia: Epidemiology, incidence, signs, and symptoms at

presentation. Chin J Cancer. 2012;31(4):185-96. https://doi.org/10.5732/cjc.011.10328

PMid:22313595

3. World Health Organization. Comprehensive Cervical Cancer Control. 2nded. A Guide to Essential Practice. Geneva: World Health Organization Press; 2014.
4. Globacan. Indonesia. The Global Cancer Observatory; 2019. Available from: https://www.gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf [Last accessed on 2021 Apr 27].
5. Hashim NA, Ramzi NH, Velapasamy S, Alex L, Chahil JK, Lye SH, *et al*. Identification of genetic and non-genetic risk factors for nasopharyngeal carcinoma in a southeast Asian population. Asian Pac J Cancer Prev. 2012;13(12):6005-10. https://doi.org/10.7314/apjcp.2012.13.12.6005

PMid:23464394

6. Zhang X, Sjöblom T. Targeting loss of heterozygosity: A novel paradigm for cancer therapy. Pharmaceuticals (Basel). 2021;14(1):57. https://doi.org/10.3390/ph14010057

PMid:33450833

7. Wu L, Li C, Pan L. Nasopharyngeal carcinoma: A review of current updates. Exp Ther Med. 2018;15(4):3687-92. https://doi.org/10.3892/etm.2018.5878

PMid:29556258

8. Okekpa SI, Mydin RB, Mangantig E, Azmi NS, Zahari SN, Kaur G, *et al*. Nasopharyngeal carcinoma (NPC) risk factors: A systematic review and meta-analysis of the association with lifestyle, diets, socioeconomic and sociodemographic in Asian region. Asian Pac J Cancer Prev. 2019;20(11):3505-14. https://doi.org/10.31557/APJCP.2019.20.11.3505

PMid:31759378

9. Banko A, Lazarevic IB, Folic MM, Djukic VB, Cirkovic AM, Karalic DZ, *et al*. Characterization of the variability of Epstein-Barr virus genes in nasopharyngeal biopsies: Potential predictors for carcinoma progression. PLoS One. 2016;11(4):e0153498. https://doi.org/10.1371/journal.pone.0153498

PMid:27071030

10. Hutajulu SH, Ng N, Jati BR, Fachiroh J, Herdini C, Hariwiyanto B, *et al*. Seroreactivity against Epstein–Barr virus (EBV) among first-degree relatives of sporadic. EBV-associated nasopharyngeal carcinoma in Indonesia. J Med Virol. 2012;84(5):768-76. https://doi.org/10.1002/jmv.23263

PMid:22431025

11. Jayalie V, Paramitha MS, Jessica J, Liu CA, Ramadianto AS, Trimartani T, *et al*. Profile of Nasopharyngeal Carcinoma in Dr. Cipto Mangunkusumo National Hospital 2010. J Kedokteran Indones. 2016;4(3):156-62.
12. Sihotang T, Paramita D. Identifikasi Peptida Early Antigen Virus Epstein-Barr (EA-EBV) Sebagai Kandidat Penanda Diagnosis Karsinoma Nasofaring. Indonesia: Universitas Gadjah Mada; 2014.
13. Rahman S, Kurniawan H, Budiman BJ, Yerizel E, Bachtiar H. Evaluation of serum IgA antibodies to Epstein-Barr virus early and viral capsid antigens in nasopharyngeal carcinoma. KnE Eng. 2019;1:275.
14. Nikakhlagh S, Rahim F, Khodadi A, Saki N. The association between Epstein-Barr virus with nasopharyngeal carcinoma in patients from southwestern region of Iran. Int J Cancer Res. 2010;6:89-94.
15. Hutajulu SH, Fachiroh J, Argy G, Indrasari SR, Jati TB, Paramita DK, *et al*. Seroprevalence of IgA anti Epstein-Barr virus is high among family members of nasopharyngeal cancer patients and individuals presenting with chronic complaints in head and neck area. PLoS One. 2017;12(8):e0180683. https://doi.org/10.1371/journal.pone.0180683

PMid:28800616

16. Raditya IG, Suanda IK, Asthuta AR. Differences of mean platelet volume (MPV) value among clinical stage of undifferentiated type nasopharyngeal carcinoma patient at ORL-HNS outpatient, Sanglah general hospital denpasar. Int J Nasopharyngeal Carcinoma. 2021;3(1):10-3. https://doi.org/10.32734/ijnpc.v3i01.5726
17. Farhat F, Sari MI, Chrestella J, Syari RP. The genetic variant of GSTP1 and immune response of immunoglobulin A (IgA) on nasopharyngeal carcinoma patients. IOP Conf Ser Earth Environ Sci. 2021;713:6-13.
18. RS Kanker Dharmais. Kanker Nasofaring, Kasus Keganasan Baru? RS Kanker Dharmais; 2019. Available from: https://www.dharmais.co.id/news/489/Kanker-Nasofaring,-Kasus-Keganasan-Baru [Last accessed on 2021 Apr 27]
19. Anugrahani A, Soeseno B, Dewi YA, Aroean NK. The comparison of elevated levels of Ebv immunoglobulin a early antigen between nasopharyngeal carcinoma who Type 3 with malignant non-hodgkin Lymphoma. Int J Nasopharyngeal Carcinoma. 2019;1(2):41-4. https://doi.org/10.32734/ijnpc.v1i2.1137
20. Sun Y, Sun C, Zhang E. Expression of serum sialic acid, early antigen-Ig A, and viral capsid antigen-Ig A in nasopharynx cancer patients: The diagnostic implication of combined assays. Med Sci Monit. 2015;28:4068-73. https://doi.org/10.12659/msm.894951

PMid:26709095

21. Jassim MM, Mahmood MM, Hussein MH. Human Herpetic Viruses and Immune. IntechOpen: Innate Immunity in Health and Disease; 2021.
22. Perez EM, Foley J, Tison T, Silva R, Ogembo JG. Novel Epstein-Barr virus-like particles incorporating gH/gLEBNA1 or gB-LMP2 induce high neutralizing antibody titers and EBV-specific T-cell responses in immunized mice. Oncotarget. 2017;8(12):19255-73. https://doi.org/10.18632/oncotarget.13770

PMid:27926486

23. Coghill A, Hildesheim A. Epstein-Barr virus antibodies and the risk of associated malignancies: Review of the literature. Am J Epidemiol. 2014;180(7):687-95. https://doi.org/10.1093/aje/kwu176

PMid:25167864

24. Rao D, Fu M, Chen Y, Liu Q, Xiao L, Zhang X, *et al*. A combination of two ELISA tests for nasopharyngeal carcinoma screening in endemic areas based on a case-control study. PeerJ. 2020;8:e10254. https://doi.org/10.7717/peerj.10254

PMid:33240616

25. Zhou T, Yang D, He Y, Xue WQ, Liao Y, Zheng MQ, *et al*. Associations between environmental factors and serological Epstein-Barr virus antibodies in patients with nasopharyngeal carcinoma in South China. Cancer Med. 2019;8(10):4852-66. https://doi.org/10.1002/cam4.2348

PMid:31241250

26. Du JL, Chen SH, Huang QH, Xie SH, Ye YF, Gao R, *et al*. Subtype distribution and long-term titer fluctuation patterns of serum anti-Epstein-Barr virus antibodies in a non-nasopharyngeal carcinoma population from an endemic area in South China: A cohort study. Chin J Cancer. 2016;35(1):78. https://doi.org/10.1186/s40880-016-0130-2

PMid:27527073

27. Januardi R, Dewi YA, Basriyadi T. Correlation of IgA-EA Epstein Barr virus with risk factors on nasopharyngeal carcinoma Type III. Int J Nasopharyngeal Carcinoma. 2020;2(3):71-3. https://doi.org/10.32734/ijnpc.v2i03.4507