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The Relationship between Epstein-Barr Virus Infections with Papillary Thyroid Cancer: A Review of Studies in Iran

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Abstract--

Background and aim: *Papillary thyroid cancer (PTC), It is the most common thyroid cancer and one of the most common cancers of the glands. The causes of this cancer are varied but more recently, the role of viral infections has been suggested. EBV is one of the most important viruses that it is related to different types of malignancies. In this review article, The Relationship between EBV and Papillary Thyroid Cancer in studies conducted in Iran has been investigated.*

Methods: *This review study was performed in the period of last 10 years (2010-2020). All related articles with Keywords: EBV, EPSTEIN-BARR VIRUS, Papillary thyroid cancer, PTC, follicular thyroid cancer AND FTC searched in research engines: Google Scholar, science Direct, PubMed and Sid (for article in Persian) Entered the study. Search results showed that in this time period of 10 years, 3 related studies conducted in Iran. In this article we have summarized the results of these three studies.*

Result: *All three studies reviewed, emphasized that Epstein-Barr virus is associated with papillary thyroid cancer and it can be considered a risk factor for this cancer. So monitoring patients with latent EBV, for papillary thyroid cancer can be very important.*

Conclusion: *We found correlation between EBV and thyroid cancer in based on the current evidence. But more studies are needed to demonstrate the relationship between the virus and Papillary thyroid cancer. Future studies are warranted to reveal the significance of EBV in thyroid tumor developments.*

Key words--*Papillary thyroid cancer, Epstein-Barr virus, EBV, PTC.*

I. INTRODUCTION

EBV infects 2 to 60 lymphocytes per million lymphocytes in the blood and results in hidden infections (1). If the virus is controlled by the host's immune response, the latent virus infection persists and healthy people carry the viral genome in their B cells (2). Latent infection of B cells is mainly transmitted through saliva and possibly

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also can be spread through sex (3). Most EBV infections appear to occur during infancy or early childhood (4). Cancer is a complex multifactorial disease after cardiovascular disease and accidents; it is the third leading cause of death in Iran. Nowadays, Cancer has been one of the hottest topics in the field of cellular and molecular biology and annual more than 30,000 Iranians from cancer, lose their lives. It is estimated More than 70,000 new cancer cases occur in the country each year. With increasing life expectancy and an increasing percentage of the population in the country, Cancer cases are expected in the next two decades Double the current amount, increase (5).

One of the common endocrine malignancies is thyroid cancer which increased rapidly in recent decades. Thyroid cancer exists in several histological forms, including follicular, papillary, medullary, and undifferentiated anaplastic thyroid carcinoma(5). Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are the two most common thyroid cancers. They account for 90–95% of all thyroid malignancies and are most often seen in patients over forty years of age(6). The tumor usually presents as an asymptomatic solitary intra-thyroid nodule. In patients with FTC, distant metastases at the time of diagnosis are reported in 11–20% of patients(7).

Microenvironment changes in thyroid tissue such as inflammation and ionizing radiation possibly involve in tumor progression(8). Human carcinogenic viruses account for approximately 10 to 15 percent of all cancers worldwide (9). EPSTEIN-BARR VIRUS (EBV) is a gamma herpesvirus that infects >90% of adults worldwide(10). Direct oral exposure and contamination through saliva are the most important EBV transmission routes, although contamination through blood transfusion, organ transplantation and placenta is also possible, in western societies and young adults, the virus is often transmitted by kissing. In developing societies, transmission of the virus usually occurs through fingers, toys and other saliva-contaminated devices (11). EBV is the causative agent of infectious mononucleosis and is associated with the development of epithelial and lymphoid malignancies, including nasopharyngeal carcinoma, gastric cancer, Burkitt's lymphoma, and Hodgkin lymphoma. Although EBV infects primarily B lymphocytes, it has also been shown to infect T lymphocytes, myocytes, and epithelial cells of the oropharynx and stomach(10). Whether EBV infects the thyroid gland is not known. In recent years, a handful of studies have found evidence of EBV infection of thyroid tissue using PCR, in situ hybridization, and immunohistochemistry, but to the best of our knowledge, no study has examined the effect of EBV on cellular signaling or proliferation in thyroid cancer cell lines (12-14).

Chronic inflammation induced by EBV infection may play a significant role in the progression of cancer(15). From a handful of available publications from 2001 to 2015, Stamatiou at al. summarized the EBV detection rate in thyroid cancer specimens(5). Epstein-Barr virus (EBV) is a well-known human tumor virus with a very high prevalence in the population, especially for children and youth. EBV serum (IgG) is positive in an estimated 95% of the world's population(16). EBV infection is associated with epithelial and lymphoid malignancies, including nasopharyngeal carcinoma (NPC), gastric cancer, Hodgkin's lymphoma and Burkitt's lymphoma(17, 18) . Although EBV has B-lymphocyte tropism, it can also infect T lymphocytes, myocytes, and

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epithelial cells in the oropharynx and stomach(15). Once EBV infects a host cell, it starts to induce a lytic or latent infection with diverse genes expressed. EBV nuclear antigens (EBNA 1, 2, 3A, 3B, 3C, and LP), the latent membrane proteins (LMP 1, 2A, and 2B) and two small noncoding RNAs (EBVcoded small RNA, EBER-1, and EBER-2) are expressed during the infection(18) . These genes collaborate to induce tumorigenesis by causing systematic inflammation, suppressing the antitumoral immune system, and preventing anoikis. Whether EBV infects the thyroid gland remains controversial. To date, only a handful of reports on the association between EBV and thyroid tumorigenesis have been investigated. Stamatiou et al(5). summarized publications regarding the EBV detection rate in thyroid cancer specimens from 2001 to 2015. The conclusion was inconclusive because the results were highly contradictory, ranging from negative to 100% positive for EBV infection.

Previous studies in EBV-infected B cells have demonstrated that EBNA2 activates the NOTCH responsive HES1 (hairy/enhancer of split) promoter(19). Similarly, EBNA2 mimics the effect of an activated NOTCH receptor on proliferation in a myogenic cell line, most likely through induction of HES1(20). EBNA2 is expressed during EBV infection of normal tongue epithelial cells as well as in a subset of nasopharyngeal carcinomas(21, 22); however, the effect of EBNA2 on NOTCH-responsive genes in epithelial cells is unknown. In epithelial thyroid cells, the NOTCH1 isomer is believed to function as a tumor suppressor. NOTCH1 signaling is absent or decreased in thyroid cancer cell lines, and the relative quiescence of NOTCH1 signaling correlates with tumor severity(23). Likewise, overexpression of NOTCH1 decreases cellular proliferation and promotes differentiation in in vitro and murine models(23). While NOTCH requires activation through binding of extracellular ligands before engaging RBP-jk, EBNA2 is constitutively active. Given the ability of both NOTCH and EBNA2 to interact with limiting amounts of RBP-jk, we hypothesized that EBNA2 could potentially either mimic or inhibit transcription of NOTCH1 targets in thyroid cancer cell lines. Here we show that only a subset of NOTCH1 targets are activated by EBNA2 in thyroid cancer cells.

The purpose of the present study was to investigate the relationship between Epstein-Barr virus infections with papillary thyroid cancer: a review of studies in Iran. We conducted this review study to determine does Epstein-Barr virus cause papillary thyroid cancer Whether or not it plays a role in Iranian patients. If the results are positive based on that be able to produce vaccines and supportive care Prevention and treatment can begin.

II. METHODS

In this review study in the period of last 10 years (2010-2020) All related articles with Keywords: EBV, EPSTEIN-BARR VIRUS, Papillary thyroid cancer, PTC, follicular thyroid cancer and FTC searched in research engines: Google Scholar, science Direct, PubMed and Sid (for article in Persian). Search results showed that in this time period of 10 years 3 related studies conducted in Iran. In this article we have summarized the results of these studies.

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III. RESULTS AND DISCUSSION

3 related studies Were reviewed. One article was published in Persian and two in English. other studies have been conducted in Iran in connection with Relationship between Epstein-Barr virus with gastric cancer(24), esophageal cancer(25), breast cancer(26-28), and Hodgkin's lymphoma(29-31). All of these studies have emphasized the link between Epstein-Barr virus and cancer.

Review of The first study was published by Homayounia et al in 2017. In this study the presence of Epstein-Barr Nuclear Antigen 1 (EBNA1) gene in papillary thyroid carcinoma tissues were examined by nested-PCR method. Paraffin-embedded tissues (N = 41) blocks of thyroid cancer were used. DNA was extracted from all samples and then samples were evaluated for the presence of EBV gene. In 41 samples, EBNA1 was detected in 65.8% of patients with papillary thyroid carcinoma which was significantly higher in younger ages. The researchers concluded that the significant presence of EBV genome in papillary thyroid carcinoma suggests that this virus may play a role in this cancer especially in younger ages. As a result, monitoring of patients with EBV latent infection for PTC can be very important(32). So the researchers confirmed that Epstein-Barr virus is linked to papillary thyroid cancer. Due to the Study of the genome of this virus by nested-PCR their results can be greatly trusted, but it shouldn't was unaware of Another Role of Papillary Thyroid Risk Factors and their relationship and impact on each other.

Review of The second study was published by Moghoofei et al in 2017. The aim of this study was to determine the presence of the Epstein–Barr virus (EBV) and the association between viral gene products and thyroid tumor development. In this study, Fifty-seven thyroid cancer specimens were collected from the same number of patients as well as 18 samples from healthy controls. The presence of the EBV genome and the genotyping was examined by polymerase chain reaction (PCR). Also, an enzyme-linked immunosorbent assay and real-time PCR were used to measure the expression levels of viral and cellular genes. Result of Their study showed that The EBV DNA was detected in 71.9% of the samples, and it was also found that the presence of the EBV was associated with increasing development of thyroid tumor. The researchers concluded that results demonstrated that EBV infection may play a role in the development of thyroid tumor(33).

In this study also Study of the virus genome with real-time PCR technique done .So, their results are also reliable. Other things to keep in mind are that small sample sizes cannot be definitively generalized to the whole community. The role of ethnicity and geographical location will also be considered.

Review of Third was published by Mokhtari et al in 2016(article in Persian). in this study Epstein-Barr virus core antigen expression in a group of patients Patients with Papillary Thyroid Carcinoma in Isfahan Was studied. This study was conducted On 43 samples of papillary thyroid carcinoma Approved by the pathologist. By using paraffin-embedded block of formalin-fixed tissue, by qualitative Polymerase chain reaction (PCR), EBNA

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expression was evaluated in tumor tissue. The findings of this study showed that EBNA expression was detected in 5 cases (4.9%) of the samples. Investigation of the relationship of EBNA expression with various factors showed that there was a significant relationship between age and gene expression. Other factors had no significant relationship with EBNA expression the researchers concluded that considering that about 4% of EBNA patients expressed, it is possible that there is a link between the disease and the expression of this gene, but for a closer look, it is suggested that in designing other studies, the control group should also be considered (34). This article as in the previous two articles used the PCR technique to confirm the presence of the virus with its genome so it has reliable results Simultaneous existence of Epstein-Barr virus and papillary thyroid cancer, conforms that Theory of its effect on thyroid cells and increased chance of cancer.

All three studies reviewed emphasized that Epstein-Barr virus is associated with papillary thyroid cancer and it can be considered a risk factor for this cancer. However, the relationship between thyroid tumorigeneses and EBV has not been fully elucidated with conflicting results. The preliminary investigation of EBV in thyroid lymphoma was inspired by EBV persistently infecting B lymphocytes, contributing to lymphoma formation. In 2003, Shimakage et al. first reported EBV infection in other types of thyroid malignancies with a Japanese cohort Shimakage et al (14). Bychkov et al reported that 1 of 20 thyroid cancer tissues contained single EBER-positive inflammatory cells. Cancer cells and normal thyroid tissues were consistently negative for ISH(35). Additionally, Tsai et al reported a negative association between benign tumors and EBV infection using ISH or PCR or Southern hybridization in a Taiwanese population(36). EBV is highly prevalent in southern China. Additionally, NPC, which has a closer relationship with EBV infection, is more endemic than in any part of the world, especially in Guangdong Province and Hong Kon g (37). VCA/IgA and EA/IgA antibodies could reflect the status of recent viral infection and, therefore, are widely used biomarkers for screening NPC in the southern China population(38). In the current study, the positivity rate of serological antibody analysis was 10.9%, which is similar to that in previous national population-based studies conducted in the 1970s (38, 39). EPSTEIN-BARR VIRUS (EBV) is a gamma herpesvirus that infects >90% of adults worldwide. EBV is the causative agent of infectious mononucleosis and is associated with the development of epithelial and lymphoid malignancies, including nasopharyngeal carcinoma, gastric cancer, Burkitt's lymphoma, and Hodgkin lymphoma. Although EBV infects primarily B lymphocytes, it has also been shown to infect T lymphocytes, myocytes, and epithelial cells of the oropharynx and stomach(40). Whether EBV infects the thyroid gland is not known. In recent years, a handful of studies have found evidence of EBV infection of thyroid tissue using PCR, in situ hybridization, and immunohistochemistry (12-14), but to the best of our knowledge, no study has examined the effect of EBV on cellular signaling or proliferation in thyroid cancer cell lines. EBV encodes a transcription factor called EBV nuclear antigen 2 (EBNA2) that is essential to Bcell immortalization(20). Interestingly, EBNA2 can be considered a functional homologue of an activated NOTCH receptor. NOTCH genes encode a family of transmembrane signaling proteins that function as tumor suppressors in

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thyroid cells(23). Both EBNA2 and activated (cleaved) NOTCH receptors bind to a cellular protein called RBP-jk (also known as CBF1, RBP-J, KBF2, and CSL) to modulate expression of other genes. Through this common interaction with RBP-jk, EBNA2 and NOTCH activate a set of promoters that is overlapping, yet not identical, in lymphocytes(20).

IV. CONCLUSION

In these 3 studies that we reviewed, we found correlation between EBV and thyroid cancer in based on the current evidence. These findings may support a potential role for EBV infection in the development of thyroid cancers. Given the immunogenicity of EBV proteins, the EBV genome may be lost during later stages of thyroid cancer progression once cellular transformation is complete and no longer requires the presence of EBV-encoded proteins. Although it seems that EBV plays an important role in the etiology of papillary thyroid cancer but definitely more studies are needed in connection with the role of this virus involve in papillary thyroid cancer. To clarify its mechanism in the pathogenesis process. It is, therefore, suggested that Investigate the relationship between the virus and cancer in different communities and ethnicities unless approved can be with vaccine production and supportive care and treatment prevented papillary thyroid cancer that a large population of people of Iran and the world are affected by it. And prevent other diseases associated with the virus.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. 2016;66(1):7-30.
2. Glaser SL, Hsu JL, Gulley ML. Epstein-Barr virus and breast cancer: state of the evidence for viral carcinogenesis. Cancer Epidemiology and Prevention Biomarkers. 2004;13(5):688-97.
3. Joshi D, Buehring GC. Are viruses associated with human breast cancer? Scrutinizing the molecular evidence. Breast cancer research and treatment. 2012;135(1):1-15.
4. Lawson JS, Heng B. Viruses and breast cancer. Cancers. 2010;2(2):752-72.
5. Stamatiou DP, Derdas SP, Zoras OL, Spandidos DA. Herpes and polyoma family viruses in thyroid cancer. Oncology letters. 2016;11(3):1635-44.
6. Mazzaferri E. Papillary and follicular thyroid cancer: a selective approach to diagnosis and treatment. Annual review of medicine. 1981;32(1):73-91.
7. MARTIN S, MAURICE T, VATHAIRE FD, CATHERINE H, GARDET P, TRAVAGLI J-P, et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. The Journal of Clinical Endocrinology & Metabolism. 1986;63(4):960-7.
8. Xing M. Molecular pathogenesis and mechanisms of thyroid cancer. Nature Reviews Cancer. 2013;13(3):184.
9. Al-Haddad S, El-Zimaity H, Hafezi-Bakhtiari S, Rajendra S, Streutker CJ, Vajpeyi R, et al. Infection and esophageal cancer. Annals of the New York Academy of Sciences. 2014;1325(1):187-96.

DOI: 10.37200/IJPR/V24I8/PR280847
Received: 21 Jan 2020 | Revised: 08 Feb 2020 | Accepted: 14 Mar 2020

10. Knipe D, Howley P, Griffin D, Lamb R, Martin M, Roizman B, et al. Fields Virology, Volumes 1 and 2. 2007.
11. TAYEBI D, MOKHTARI M, SALEHI S, MOHAMMADI B, EBRAHIMPOUR M. SEROPIDEMIOLOGY OF EPSTEIN–BARR VIRUS INFECTION AMONG ASYMPTOMATIC STUDENTS OF ISLAMIC AZAD UNIVERSITY OF KAZEROON, SOUTHWEST OF IRAN. 2006.
12. Janegova A, Janega P, Rychly B, Kuracinova K, Babal P. The role of Epstein-Barr virus infection in the development of autoimmune thyroid diseases. Endokrynologia Polska. 2015;66(2):132-6.
13. Stamatiou D, Derdas SP, Symvoulakis EK, Sakorafas GH, Zoras O, Spandidos DA. Investigation of BK virus, Epstein-Barr virus and human papillomavirus sequences in postoperative thyroid gland specimens. The International journal of biological markers. 2015;30(1):104-10.
14. Shimakage M, Kawahara K, Sasagawa T, Inoue H, Yutsudo M, Yoshida A, et al. Expression of Epstein-Barr virus in thyroid carcinoma correlates with tumor progression. Human pathology. 2003;34(11):1170-7.
15. Thorley-Lawson DA, Hawkins JB, Tracy SI, Shapiro M. The pathogenesis of Epstein–Barr virus persistent infection. Current opinion in virology. 2013;3(3):227-32.
16. Morrison BJ, Labo N, Miley WJ, Whitby D, editors. Serodiagnosis for tumor viruses. Seminars in oncology; 2015: Elsevier.
17. Tsai M-H, Raykova A, Klinke O, Bernhardt K, Gärtner K, Leung CS, et al. Spontaneous lytic replication and epitheliotropism define an Epstein-Barr virus strain found in carcinomas. Cell reports. 2013;5(2):458-70.
18. Tsao SW, Tsang CM, To KF, Lo KW. The role of Epstein–Barr virus in epithelial malignancies. The Journal of pathology. 2015;235(2):323-33.
19. Callahan J, Aster J, Sklar J, Kieff E, Robertson E. Intracellular forms of human NOTCH1 interact at distinctly different levels with RBP-jkappa in human B and T cells. Leukemia. 2000;14(1):84.
20. Zimber-Strobl U, Strobl LJ, editors. EBNA2 and Notch signalling in Epstein–Barr virus mediated immortalization of B lymphocytes. Seminars in cancer biology; 2001: Elsevier.
21. Webster-Cyriaque J, Raab-Traub N. Transcription of Epstein–Barr virus latent cycle genes in oral hairy leukoplakia. Virology. 1998;248(1):53-65.
22. Banko AV, 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.
23. Ferretti E, Tosi E, Po A, Scipioni A, Morisi R, Espinola M, et al. Notch signaling is involved in expression of thyrocyte differentiation markers and is down-regulated in thyroid tumors. The Journal of Clinical Endocrinology & Metabolism. 2008;93(10):4080-7.
24. Ghasemi M, Abedian Kenari S, Torabizadeh Z, Iri N, Marjani J, Mirabi AM. The Relationship between Epstein-Barr Virus (EBV) and Virus-Encoded BARF-1 Gene in Gastric Adenocarcinoma. Journal of Mazandaran University of Medical Sciences. 2011;21(82):10-6.
25. Mr H, A. R, F. Z, F N. Frequency of Epstein Barr Virus in esophageal squamous cell carcinoma biopsies in Mazandaran and Golestan provinces in 2008. Iranian Journal of Medical Microbiology. 2009;3(1):43-.
26. Akbari A, Razzaghi Z, Homaee F, Khayamzadeh M, Movahedi M, Akbari ME. Parity and breastfeeding are preventive measures against breast cancer in Iranian women. Breast cancer. 2011;18(1):51-5.
27. Hejazi H, Hejazi H. Study on the association of Epstein-Barr virus with breast cancer in Khorramabad breast cancer patients, Iran. Yafteh. 2019;21(1).
28. SALAHSHOURNIA Z, HEJAZI H, HADI F, SAEEDI Z. THE STUDY OF RELATIONSHIP BETWEEN EPSTEIN-BARR VIRUS AND BREAST CANCER IN ISFAHAN PROVINCE. 2018.
29. Mozafari L, Najafipour S, Meshkibaf MH, Moravej A. Expression of Epstein-Barr virus in Hodgkin lymphoma Specimens in IRAN. Journal of Fasa University of Medical Sciences. 2013;3(2):143-8.
30. MOZAFARI L, NAJAFIPOUR S, MESHKIBAF MH, MORAVEJ A. Analysis of the presence of Epstein-Barr virus in Hodgkin's lymphoma in Iranian children by EBER in situ hybridization. 2014.
31. SAR N. Detection of Epstein-Barr virus infection in lymphoma: ELISA and PCR method. Tehran University Medical Journal TUMS Publications. 2010;67(11):787-92.

DOI: 10.37200/IJPR/V24I8/PR280847
Received: 21 Jan 2020 | Revised: 08 Feb 2020 | Accepted: 14 Mar 2020

32. Homayouni M, Arabzadeh SAM, Nili F, Razi F, Amoli MM. Evaluation of the presence of Epstein-Barr virus (EBV) in Iranian patients with thyroid papillary carcinoma. Pathology-Research and Practice. 2017;213(7):854-6.
33. Moghoofei M, Mostafaei S, Nesaei A, Etemadi A, Sadri Nahand J, Mirzaei H, et al. Epstein–Barr virus and thyroid cancer: The role of viral expressed proteins. Journal of cellular physiology. 2019;234(4):3790-9.
34. Mokhtari M, Bahreini M, Isfahani, Naji F, Safaei A. Expression of Epstein-Barr Virus Nuclear Antigen (EBNA) in Papillary Thyroid Carcinoma in a Population of Patients in Isfahan City, Iran. Journal Of Isfahan Medical School. 2017;34(415):1648-52.
35. Bychkov A, Keelawat S. Epstein–Barr virus and thyroid cancer: the controversy remains. Journal of endocrinological investigation. 2017;40(8):891-2.
36. Tsai JH, Tsai CH, Cheng MH, Lin SJ, Xu FL, Yang CC. Association of viral factors with non-familial breast cancer in Taiwan by comparison with non-cancerous, fibroadenoma, and thyroid tumor tissues. Journal of medical virology. 2005;75(2):276-81.
37. Chang ET, Adami H-O. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiology and Prevention Biomarkers. 2006;15(10):1765-77.
38. Cao S-M, Liu Z, Jia W-H, Huang Q-H, Liu Q, Guo X, et al. Fluctuations of epstein-barr virus serological antibodies and risk for nasopharyngeal carcinoma: a prospective screening study with a 20-year follow-up. PloS one. 2011;6(4):e19100.
39. Liu Y, Huang Q, Liu W, Liu Q, Jia W, Chang E, et al. Establishment of VCA and EBNA1 IgA-based combination by enzyme-linked immunosorbent assay as preferred screening method for nasopharyngeal carcinoma: a two-stage design with a preliminary performance study and a mass screening in southern China. International journal of cancer. 2012;131(2):406-16.
40. Richman DD, Whitley RJ, Hayden FG. Clinical virology: John Wiley & Sons; 2016.

DOI: 10.37200/IJPR/V24I8/PR280847
Received: 21 Jan 2020 | Revised: 08 Feb 2020 | Accepted: 14 Mar 2020