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Warthin Tumour-Associated Synchronous Neoplasia and COVID-19: Does SARS-CoV-2 Infection Increase the Risk of Benign Tumours and Cancer?

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ABSTRACT

Purpose: This review determined the prevalence of Warthin tumour (WT)-associated synchronous neoplasia or tumours (STs) in a bid to identify high-risk anatomical sites of tumourigenesis. It also highlights hypothetical pathways of SARS-CoV-2-associated tumourigenesis. **Hypothesis:** It is hypothesized that SARS-COV-2-host angiotensin-converting enzyme 2 (ACE2) complex induces cytokine release syndrome and thrombocytopenia with concomitant stimulation of sialadenitis, fibrosis, hyperplasia, metaplasia and premalignant tumours. **Method:** Peer-reviewed articles published between 2002 and 2020 on databases such as Google Scholar, Scopus, PubMed Central, and EMBASE were selected using the PRISMA standard. Search keywords included WT, head and neck cancer, and WT-associated STs. T-test analysis was performed for ages. **Results:** There were 146 cases and 48 classified types of WT-associated STs. The male to female ratio of occurrence was 6.6:1. The mean age of males with STs (63.5± 2.42 years) was higher than that of their female counterparts (47.11± 6.2 years; p= 0.006). Subgroups of STs included head and neck tumours (55.4%), lymphoma (19.2%), lungs (13.0%), breast (3.4%), and prostate (2.1%) cancers, among others. Of the 81 cases of head and neck STs, 44.4% were malignant and 55.6% were benign. **Conclusion:** This review revealed that WT-associated STs are prevalent in males and the head and neck region. Due to high expression of ACE2 in normal tissues and tumour cells, this review suggests that severe and critical COVID-19 diseases could induce DNA damage and genetic instability which could increase the risk of cancer, especially in the head and neck region with pre-existing oncoviruses. Thus, patients with severe and critical COVID-19 should be followed-up.

Keywords: Warthin tumour, SARS-CoV-2, COVID-19, Neoplastic tumours, epithelial transformation
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INTRODUCTION

Salivary glands, which majorly include parotid, submandibular and sublingual regions, are affected by a variety of lesions ranging from inflammation (24.4%) to neoplasia (73.1%) (1). Salivary gland neoplasia (SGN) accounts for 5% of all head and neck neoplasms (2), and 0.5-2% of all tumours worldwide (3). They also account for 2–6.5 % and 2.8-10% of all the head and neck tumours in developed and developing countries, respectively (2,4,5). In Africa, SGN accounts for 0.32% of histological specimens and 5.1% of all head and neck tumours (6). Benign tumours of the salivary gland majorly include pleomorphic adenoma, Warthin tumour (WT), and oncocytoma while malignant tumours majorly include squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma (2,5). Warthin tumour, also known as adenolymphoma or papillary lymphomatous cystadenoma, is a slow-growing mass with epithelial, glandular and lymphoid histological characteristics (7-9). Warthin tumour (WT) is a benign salivary gland mass with an inflammatory origin which harbours and/or favours the development of synchronous neoplasia or tumours (STs) in its micro- and macro-environments. It is exclusively localized in parotid gland cauda and rarely in peri-parotid lymph nodes (8%) (10). It is the second most common benign neoplasm of the parotid gland, comprising 2-15% of the parotid epithelial tumors and approximately 5-6 % of epithelial salivary gland neoplasms (2). Evidence shows that SARS-CoV-2 (COVID-19), which was first reported in Wuhan China, is detected in about 92% of self-collected saliva (11,12). This suggests that the virus seeds into the salivary glands from the nasopharyngeal region and bind to abundant angiotensin-converting enzyme 2 (ACE2) receptors in the glands (12). The virus can also seed into other sites with ACE2 expression such as the tongue and epithelial cells of the oral cavity (13). The potential of the virus to induce epithelial disruption through tumour-promoting cytokine and chemokines in organs with and without neoplasia precipitates some concerns (14). This review highlights hypothetical pathways of SARS-CoV-2-associated tumourigenesis. It also determined the prevalence of WT-associated STs in a bid to identify high-risk anatomical site of tumourigenesis in the event of severe or critical COVID-19 disease.

METHODS

In this systematic review, peer-reviewed articles published between 2002 and 2020 were screened and selected using the PRISMA standard (figure1) (15,16). Sources of articles include Google Scholar, Scopus, PubMed Central, and EMBASE. Search keywords included Warthin tumour, head and neck cancer, and Warthin tumour-associated synchronous neoplasia or tumours in males and females. Inclusion criteria included: Studies carried out between 2002 and 2020, studies with cases of Warthin tumour and synchronous neoplasia or tumours and must be full-length articles. Exclusion criteria: Articles not written in English, abstracts, and non-full-length article. T-test was performed to evaluate the difference between the ages of male and female (in GraphPad Prism, version 6.0), and significance was set at $p \leq 0.05$).

RESULTS

The mean age of males with STs (n= 119; 63.51 ± 2.42 years) was significantly higher than that of their female counterparts (47.11 ±6.17 years) at p= 0.006. The ratio of males to females diagnosed with STs was 6.6:1 (n= 119 vs 27). The maximum, median, and minimum ages of STs occurrence in males were 102, 64, and 30 years while that of their female counterparts is 68, 48, and 16 years, respectively. Globally, there were (N) 146 cases of classified and unclassified STs.

In order of ranking, the subgroups of STs were head and neck tumours (55.4%), lymphoma (19.2%), lungs cancer (13.0%), breast cancer (3.4%), thyroid and urinary tract carcinoma (2.7% each), prostate cancer (2.1%), liver and cervix cancers (0.7% each; tables 1a and 1b).

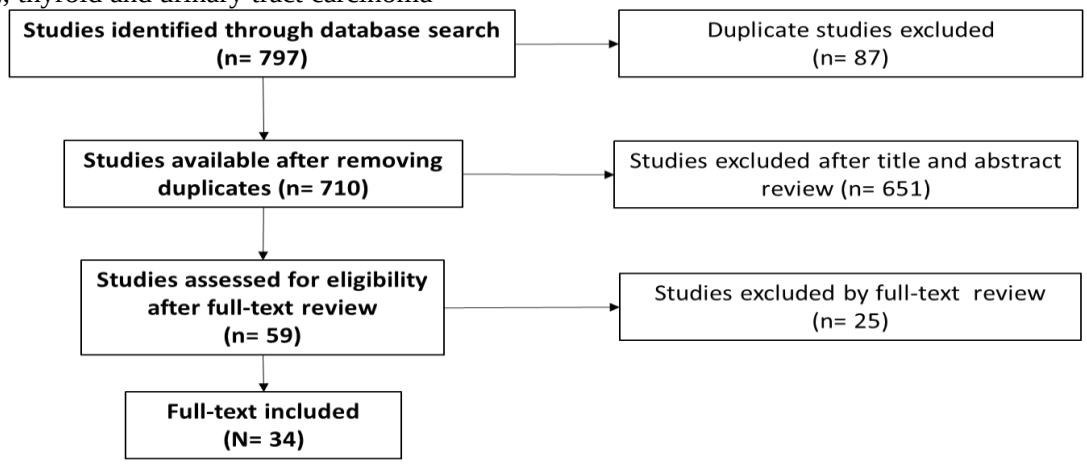

Figure 1: PRISMA flow diagram of database search for studies on WT-associated STs

Table 1a: Head and neck neoplastic tumours occurring synchronously with Warthin tumour

Location of tumour	N= 146 (%)	References
Non-SCC Head and Neck neoplasia	**45 (30.8)**	
Pleomorphic adenoma	11 (7.5)	(7,17-19)
Basal cell carcinoma (Cervical/ facial skin)	9 (6.1)	(20-22)
Mucoepidermoid carcinoma	10 (6.7)	(23-28)
Basal cell adenoma and cystadenoma oncocyticum	3 (2.1)	(29)
Melanoma	2 (1.4)	(22)
Oncocytoma	2 (1.4)	(18)
Oncocytic Papillary Cystadenoma	2 (1.4)	(29,30)
Oligoastrocytoma	1 (0.7)	(22)
Basal cell adenoma	1 (0.7)	(29)
Myoepithelial carcinoma	1 (0.7)	(18)
Papilloma of the Pharynx	1 (0.7)	(31)
Carcino ex Pleomorphic adenoma	1 (0.7)	(32)
Adenocarcinoma (High grade-ductal type; parotid)	1 (0.7)	(33)
Epidermoid carcinoma (parotid)	1 (0.7)	(34)
SCC of Head and Neck Neoplasia	**36 (24.7)**	
Tongue	7 (4.8)	(22,35)
Larynx	6 (4.1)	(20,31)
Head and neck (unclassified)	5 (3.4)	(36)
Oropharynx	5 (3.4)	(31,35)
Parotid	5 (3.4)	(37-39)
Buccal	4 (2.7)	(35)
Adenocarcinoma (parotid)	1 (0.7)	(40)
Ear	1 (0.7)	(22)
Nostrils	1 (0.7)	(22)
SCC (unknown)	1 (0.7)	(22)

There were twenty-two classified types of WT-associated STs found in the head and neck regions (cases, n= 81). Of the 81 cases, 44.4% were malignant and 55.6% were

benign. Overall, the prevalent types of head and neck ST were pleomorphic adenoma (13.6%), mucoepidermoid carcinoma (12.3%), basal cell carcinoma (11.1%), and squamous cell carcinoma of the tongue (8.6%) and larynx (7.4%; Table 1a).

Table 1b: Other neoplastic tumours occurring synchronously with Warthin tumour

Location of tumour	N= 146 (%)	References
Lymphoma	**28 (19.2)**	
Follicular Lymphoma	12 (8.2)	(41,42)
Non-Hodgkin's lymphoma	3 (2.1)	(22,20,35)
Small Lymphocytic Lymphoma/ Chronic Lymphocytic Leukemia	3 (2.1)	(41,43)
MALT lymphoma	3 (2.1)	(44,45)
Diffuse large B-cell lymphoma	1 (0.7)	(8)
Hodgkin Lymphoma	1 (0.7)	(41)
T-Lymphoblastic Lymphoma	1 (0.7)	(41)
Mantle cell lymphoma	1 (0.7)	(41)
Peripheral T-cell lymphoma/leukemia	1 (0.7)	(22)
Nodular Lymphocyte-Predominant Hodgkin Lymphoma	1 (0.7)	(46)
Lymphocyte-rich classical Hodgkin's lymphoma	1 (0.7)	(47)
Lung cancer	**19 (13.0)**	
Lung adenocarcinoma/cancer	10 (6.8)	(22,48-50)
SCC of the lungs	6 (4.1)	(20,22)
Small cell carcinoma of the lungs	2 (1.4)	(49)
Non-small cell lung carcinoma	1 (0.7)	(51)
Breast Neoplasia	**5 (3.4)**	
Breast carcinoma	3 (2.1)	(20,22)
Breast lipoma	1 (0.7)	(31)
Metastatic breast carcinoma	1 (0.7)	(31)
Thyroid Cancer	**4 (2.7)**	
Thyroid carcinoma	3 (2.1)	(31)
Papillary thyroid carcinoma	1 (0.7)	(22)
Urinary tract cancers	**4 (2.7)**	
Renal cell carcinoma	3 (2.1)	(20,22)
Urothelial cell carcinoma (bladder)	1 (0.7)	(20)
Prostate Cancer	**3 (2.1)**	
Prostate Carcinoma	2 (1.4)	(31)
Prostate adenocarcinoma	1 (0.7)	(22)
Cholangiocarcinoma (Liver)	**1 (0.7)**	(22)
Uterine cervical carcinoma	**1 (0.7)**	(31)

DISCUSSION

Risk and co-morbidities of WT and COVID-19 disease

The causes of WT are yet to be fully understood and elucidated however, studies have shown a strong positive relationship between the malefactor and WT (7,52). The relationship may largely be accrued to the higher rate of smoking among males than among females. The prevalence of smoking among patients with WT range from 79-100% (7,53). Over the past three decades, the male to female ratio of WT distribution gradually changed from 5.3:1 to 2.1:1 (54). The shift is believed to be associated with increasing female smokers (55). Interestingly, the mean age of females with WT is significantly higher than their male counterparts (60.9 vs 57.9 years; $p< 0.001$) (56). In this review, STs occur frequently in males than in females. This pattern of distribution is also found among male and female patients diagnosed with COVID-19 disease; with a ratio of 4.6:1, respectively (57). Apart from tobacco consumption, about 33% and 22% of WT are associated with oncogenic viruses such as Epstein-Barr virus (EBV) and human papillomavirus (HPV), respectively (58). Just like in WT, current smokers are at higher risk of contracting SAR-CoV-2 than former smokers (12.6% vs 1.9%) (59). Of note, the comorbidities of WT and severe COVID-19 are also similar given the fact that the prevalence of hypertension, diabetes mellitus type 2 (DM2), coronary heart disease (CRD), and chronic obstructive pulmonary disease (COPD) among patients diagnosed with WT is 31%, 14%, 10%, and 8%, respectively (7). In severe COVID-19 diseases, the prevalence of hypertension, DM2, CRD, COPD, and malignancy is approximately 24-49%, 16-17%, 6-18%, 4% and 2-6%, respectively (57). Thus, it is hypothesized that patients with COVID-19 disease and aforementioned comorbidities are more likely to develop WT and WT-associated STs.

Synchronous and metachronous tumours associated with WT

Despite the benign nature of WT, patients with WT are at a higher risk of developing other primary malignancies than individuals without WT, especially when the tumour harbours EBV and HPV DNA (20). In the absence of EBV, HPV and Cytomegalovirus (CMV) activities, malignant transformation of WT is rare (1%) and when it does occur, it results in mucoepidermoid carcinoma (21). Studies have shown that WT can synchronously develop (19.2% to 37%) (18,22,31), while malignant tumours can metachronously exist with WT (7.7 to 14.8%) (10,18,22,48,60,61). Additionally, Zaccarini and Khurana reported that about 70% of WT diagnosed with malignant tumours developed metachronously (22), and about 5-10% of this tumour reoccur after resection (62). Thus, screening for WT while investigating for SARS-CoV-2 may facilitate early diagnosis of pre-existing neoplastic tumours in smokers, and monitoring COVID-19 patients diagnosed of WT may lead to early detection of synchronous and metachronous malignant tumours (51,63).

Hypothetical pathways of SAR2-CoV-2 associated neoplasia

It is being predicted that there will be an explosion of salivary gland neoplastic cases including WT-associated STs based on two hypotheses: i) treatment of benign tumours is being postponed due to the high-risk of SARS-Cov-2 transmission to either the patient or the clinician (64), ii) the inflammation caused by SARS-CoV-2 triggers cascades of events that are likely to yield neoplastic tumours. The virus-host cell (ACE2) receptor complex in salivary glands

upregulate pro-inflammatory cytokines with concomitant induction of fibrosis, hyperplasia, and sialadenitis (65). A similar pattern of fibrotic and inflammatory processes have also been reported in infarcted WT (66). According to Soldatova *et al*. (67), patients with non-neoplastic tumour (NNT) have 10% risk of developing malignancy. Malignant tumours may occur due to DNA damage and genetic instability caused by reactive nitrogen intermediates (RNI) and reactive oxygen species (ROS). The activities of ROS and RNI promote tumourigenesis by favouring the entry of EBV, CMV, and HPV into the microenvironment of WT or metaplastic epithelium with subsequent dysregulation of mismatch genes and enzymes (14,68). This suggests that SARS-CoV-2 infected patients are at a high risk of developing WT, given the fact that WT formation requires an inflammatory background which COVID-19 disease conveniently provides through sialadenitis (65,69,70). The tendency of sialadenitis transforming to benign or malignant tumour following the invasion of oncoviruses might explain why sialadenitis sometime coexist with other malignant or metastatic tumours (71). Gan *et al*. (72) revealed that the risk of squamous cell carcinoma (SCC) is higher among HPV infected smoker than HPV infected non-smokers. Since WT majorly occurs in smokers, the presence of EBV or HPV in its microenvironment may increase the risk of malignant transformation following SARS-CoV-2 induced cytokine storm (figure 2). However, the pathogenicity of the oncoviruses may depend on the thrombopoietic potential of the infected individual and the continual production of pro-inflammatory and tumour-promoting cytokines (IL-6/CCL2 and NF-kB/AP-1, respectively). The latter need is met by severe COVID-19 disease which causes sustained FN-γ-mediated-M1 macrophage production of not only interleukin 6 (IL-6) but also tumour necrosis factor-alpha (TNF-α) with minimal involvement of CD8+ T cells (14,73,74). The interaction between NF-kB, AP-1, and EBV latent membrane protein 1 in tissues may bring about epithelial transformation (75). The immune response induced by COVID-19 also promotes the angiogenic activity of CCL2 and CXCL8 which ensures the survival and/or metastasis of neoplastic cells (74).

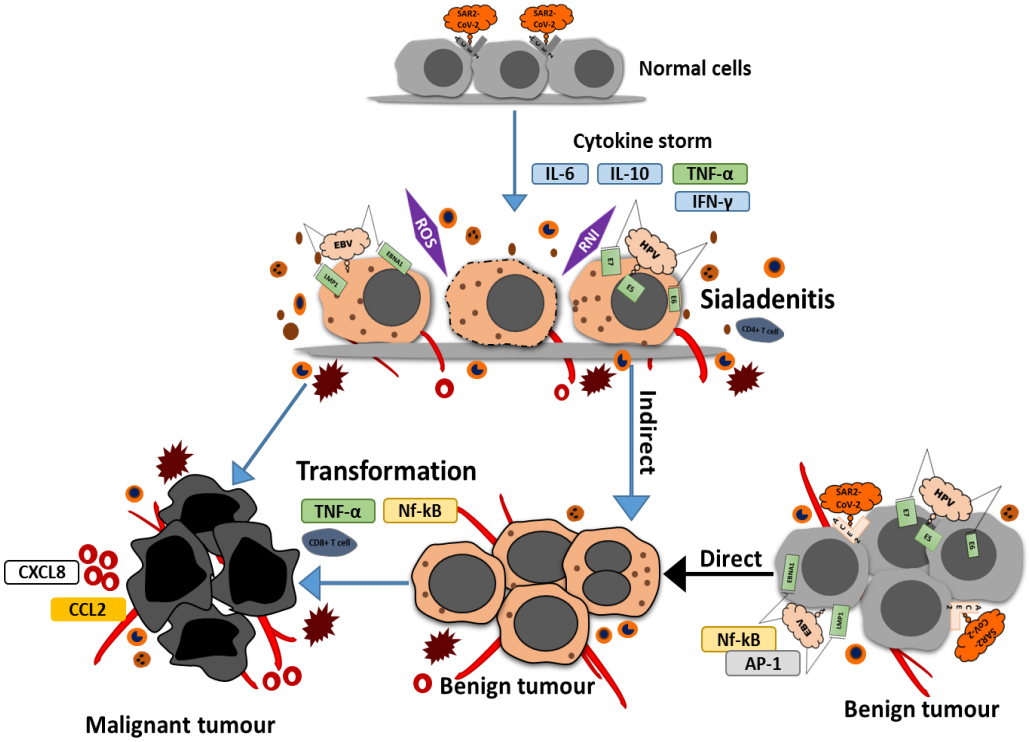

Figure 2: Diagrammatic representation of the hypothetical pathway of SARS-CoV-2-associated neoplastic events (Source: authors)

Figure 2 shows that when normal cells are infected by SARS-CoV-2 it results in the induction of cytokine storm which leads to inflammation of salivary glands (sialadenitis) and thrombocytopenia. The ROS and RNI mediated inflammation induces DNA damage in originally normal cells which may permit the invasion of oncoviruses such as HPV and EBV. With continuous bouts of cytokine storm, the immune evasion and persistence of oncoviruses may trigger the formation of benign tumour which could progress to malignant tumour (indirect pathway). When the virus seeds, it also causes inflammation in organs with high expression of ACE2 receptors, especially WT-associated ST sites. In the direct pathway, the presence of high expression of ACE2 in pre-existing benign tumours, especially undiagnosed tumours, promotes the symbiotic relationship between tumour and SARS-CoV-2. The SARS-CoV-2-ACE2 complex, thrombocytopenia, and angiogenesis in tumour micro-environment could facilitate malignant transformation of the pre-existing tumours (12-14,66-79).

Risk of cancer and incidental diagnosis of SARS-CoV-2 in of cancer

According to Chang *et al.* (16), approximately 73% of SARS-CoV-2 infected patients develop thrombocytopenia following SARS-CoV-2-ACE2 complex in the bone marrow. Thrombocytopenia and decrease in platelet ACE2 expression occurs following initial increase in mean platelet volume and platelet hyperactivity with concomitant secretion of inflammatory factors and the formation of leukocyte–platelet aggregates (76). These events occur early in patients prior to the manifestation of symptoms (77). Zhang *et al.* and Lippi *et al.* (76,78) opined that SARS-CoV-2-associated thrombocytopenia increases the risk of severe disease by 5 fold. This severe event is prevalent in patients with cancer who are constantly plagued by thrombocytopenia (79). Thus, it hypothesized that the double

impact of thrombocytopenia from both malignant disease and SARS-CoV-2 aggravates tumourigenesis through the cytokine release syndrome. This is underscored by the fact that Guerini-Rocco *et al*. (80), made an incidental diagnosis of SARS-CoV-2 RNA in a non-smoker and non-drinker who presented with poorly differentiated squamous cell carcinoma (SCC) of the tongue. In an Italian study, 5 out of 7 (71%) patients who presented with cancer had an incidental diagnosis of SAR2-CoV-2 infection (81). Of note, these patients were asymptomatic to COVID-19 at the time of cancer presentation. Although, the stage of malignancy at the time of infection is unknown, it is believed that the coexistence of the virus and malignancy may have shortened the time of cancer presentation.

Due to the presence of ACE2 in other organs, the relationship between SARS-CoV-2 and ACE2 goes beyond the nasopharyngeal region (12,13). Xu *et al*. (82) observed that the expression of ACE2 was higher in tumour cells (of the lungs, oral cavity, esophagus, stomach, and colon) than in healthy tissues, and its expression increases from chronic inflammation, metaplasia to early cancer. This suggests that ACE2 serves not only as a receptor for SARS-CoV-2 in the nasopharyngeal region but also as a biomarker of epithelial transformation following chronic inflammation. In other words, there is a symbiotic association between SARS-CoV-2 and tumour cells through ACE2. SARS-CoV-2 infection and its persistence has been associated with lower CD3+ T cells, CD4+ T cells, CD8+ T cells, and B cells (83). This suggests that SARS-CoV-2 infection compromises the immune status of the affected patients. This reduces the ability of the body to clear damaged, premalignant cells or oncoviruses. The progressive increase of pro-inflammatory cytokines (IFNγ and IL10) from mild, severe to critical COVID-19 disease (84), reduced immune status (82), and persistence of oncoviruses in tissues of patients with COVID-19 disease may trigger malignant transformation (85,86). This is underscored by the findings of Wei *et al*. (84) which shows a significant positive relationship between C-reactive protein (CRP; a marker of inflammation) and serum cancer biomarkers which includes carbohydrate antigens 125 (CA125), CA153, carcinoembryonic antigen (CEA), cytokeratin-19 fragment (CYFRA21-1) and squamous cell carcinoma antigen (SCCA) at $p< 0.001$. This suggests that the risk of malignant transformation increases with the duration and extent of inflammation. Interestingly, Wei *et al*. (84) also reported a progressive increase in serum levels of CRP and serum cancer biomarkers (CA125, CA153, CEA, and CYFRA21-1) from mild, severe to critical COVID-19 disease when compared with healthy individuals ($p< 0.01$). Wei and colleagues (84) also observed a significant increase in levels of CA199 and SCCA only in critical COVID-19 cases as compared with healthy patients, patients with mild and severe cases of COVID-19 disease ($p< 0.05$ and $p< 0.01$, respectively). This suggests that there is a link between the pathogenesis of COVID-19 and cancer, and ACE2 serves a mordant between the two entities. More studies are needed in order to identify the link and understand the pathogenesis behind the elevated levels of cancer biomarkers in patients with COVID-19 disease. They may lead to the discovery of a dual-purpose therapy, both for cancer and COVID-19 disease. Taken together, it is hypothesized that in the advent of SARS-CoV-2 infection tumourigenesis occurs due to bouts of cytokine storm, hence the progressive increase in serum cancer biomarker levels. If that is the case, patients with pre-malignant or benign tumour may be at risk of malignant transformation or developing cancer. Since the levels of cancer

biomarkers in patients who have had severe and critical COVID-19 disease is significantly elevated, this group of patients should be follow-up in order to detect pre-malignant and malignant tumours early.

CONCLUSION

This review revealed that head and neck tumours were the prevalent WT-associated STs, possibly due to proximity to the salivary glands which have abundant ACE2 in its microenvironment. This review suggests that the higher expression of ACE2 in tumour cells constitutes cancer risk and that the progressive increase of cancer biomarkers from mild, severe to critical COVID-19 diseases also suggests that SARS-CoV-2 plays a direct or indirect role in tumourigenesis. Due to the recent emergence of SARS-CoV-2, it is difficult to confirm our hypothesis at the moment. However, since a link between SARS-CoV-2, inflammation, and tumour has been proposed, an inspection of the head and neck region of patients with severe and critical COVID-19 disease should be carried out during sample collection for COVID-19 testing, especially among smokers. This will increase the chances of identifying neoplastic tumours at their early stages thereby reducing the mortality rate among COVID-19 survivors post-hospitalization.

Competing Interest

The authors declare that they have no competing interests.

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REFERENCES

1. Gnepp RD, Simpson RH, Eveson J. Salivary and Lacrimal gland. In: Gnepp RD, editor. Diagnostic surgical pathology of the Head and Neck, 2nd ed. Saunders, Philadelphia. 2012, p 413-438
2. Bussu F, Parrilla C, Rizzo D, Almadori G, Paludetti G, Galli J. Clinical approach and treatment of benign and malignant parotid masses, personal experience. Acta Otorhinolaryngol Italica, 2011; 31(3): 135-143.
3. Auclair PL, Ellis GL, Gnepp DR, Wenig BM, Janney CG. Salivary gland neoplasm: General consideration. In: Ellis GL, Auclair PL, Gnepp DR, editors. Surgical pathology of the salivary glands: Major problems in Pathology. WB Saunders. Philadelphia. 1991, p 135-164
4. Yaor MA. The pattern of presentation of salivary gland tumors in Africa: A review of published reports. ENT: Ear, Nose, Throat J, 2010; 89(2): 17
5. Atri SK, Bhagat S, Rana VM, Bhagat S, Rana MV, Singh K *et al*. Role of fine needle aspiration cytology in diagnosis of salivary gland lesions. J Evol Med Dental Sci, 2019; 8(14): 1111-1116.
6. Ladeji A, Adebiyi K, Komolafe A, Soyele O, Adesina O. A clinicopathologic study of neoplastic epithelial salivary gland tumour seen over 15 years at a Nigerian tertiary centre. Afr J Oral Maxillofac Path Med, 2018; 4(2): 11-21.
7. Teymoortash A, Krasnewicz Y, Werner JA. Clinical features of cystadenolymphoma (Warthin's tumor) of the parotid gland: a retrospective comparative study of 96 cases. Oral Oncol, 2006; 42(6): 569-573.
8. Gorai S, Numata T, Kawada S, Nakano M, Tamaru J, Kobayashi T. Malignant Lymphoma arising from heterotopic Warthin's tumour in the

neck: Case report and review of the literature. Tohoku J Exp Med, 2007; 212(2): 199-205.
9. Cope W, Naugler C, Taylor SM, Trites J, Hart RD, Bullock MJ. The Association of Warthin Tumor with Salivary Ductal Inclusions in Intra and Periparotid Lymph Nodes. Head Neck Pathol, 2014; 8(1): 73-76.
10. Kızıl Y, Aydil U, Ekinci Ö, Dilci A, Köybaşıoğlu A, Düzlü M, *et al*. Salivary gland tumors in Turkey: demographic features and histopathological distribution of 510 patients. Indian J Otolaryngol Head Neck Surg, 2013; 65(1): 112-120.
11. To KK, Tsang OTY, Yip CC, Chan KH, Wu TC, Chan JMC *et al*. Consistent Detection of 2019 Novel Coronavirus in Saliva. Clin Infect Dis, 2020. doi: 10.1093/cid/ciaa149
12. Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary Glands: Potential Reservoirs for COVID-19 Asymptomatic Infection. J Dent Res, 2020. doi: 10.1177/0022034520918518.
13. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, *et al*. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci, 2020; 12(1): 2-5
14. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. Cell, 2010; 140(6): 883-899.
15. Liberati A, Altman DG, Tetzlaff J, Mulrov C, Gotzsche PC, Loannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med, 2009; 62(10): e1-34.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7): e1000097. doi: 10.1371/journal.pmed.1000097
17. Franzen AM, Franzen CK, Guenzel T, Lieder A. Increasing incidence of Warthin tumours of the parotid gland: a 42-year evaluation. Euro Archives of Oto-Rhino-Laryngol, 2018; 275(10): 2593-2598.
18. Bello IB, Salo T, Dayan D. Epithelial Salivary Gland Tumors in Two Distant Geographical Locations, Finland (Helsinki and Oulu) and Israel (Tel Aviv): A 10-Year Retrospective Comparative Study of 2,218 Cases. Head Neck Pathol, 2012; 6(2): 224-231.
19. Horisk N, Stephenson E, Sayers C, Reid J. Incidental finding of synchronous pleomorphic salivary adenoma and Warthin's tumour within a parotid gland. BMJ Case Rep, 2019; 12(4): e228675. doi: 10.4103/1742-6413.105119
20. Maiorano E, Lo Muzio L, Favia G, Piattelli A. Warthin's tumour: a study of 78 cases with emphasis on bilaterality, multifocality and association with other malignancies. Oral Oncol, 2002; 38(8): 35-40.
21. Hellquist H, Paiva-Correia A, Poorten VV, Quer M, Hernandez-Prepa JC, Andreasen S *et al*. Analysis of the Clinical Relevance of Histological Classification of Benign Epithelial Salivary Gland Tumours. Adv Ther, 2019; 36(8): 1950-74.
22. Zaccarini, DJ, Khurana KK. Incidence of Non-Salivary Gland Neoplasms in Patients with Warthin Tumour: A study of 73 cases. Head Neck Pathol, 2020; 14(2): 412-418.
23. Yamada S, Matsuo T, Fujita S, Suyama K, Yamaguchi A, Mizuno A. Mucoepidermoid carcinoma arising in Warthin's tumor of the parotid

gland. Pathol Int, 2002; 52(10): 653-656.
24. Mardi K, Sharma J. Mucoepidermoid carcinoma arising in Warthin's tumor: A case report. Indian J Pathol Microbiol, 2007; 50(2): 331-333.
25. Srivastava S, Nadelman C. Synchronous Ipsilateral Warthin Tumor Encased by a Separate Mucoepidermoid carcinoma of the Parotid Gland: A case report and review of the literature. Diag Cytopathol, 2010; 389(7): 533-537.
26. Kaur J, Mannan R, Duggal P, Bhasin TS, Manjari M, SGRDIMSR AP. Fine needle aspiration diagnosis of ipsilateral synchronous neoplasm-mucoepidermoid carcinoma with Warthin tumor in parotid gland. Gulf J Oncol, 2012; 1(11): 75-78.
27. Mohapatra M, Satyanarayana S. Low grade mucoepidermoid carcinoma in a setting of Warthin's tumor. Indian J Pathol Microbiol, 2012; 55(3): 392.
28. Yu C, Song Z, Xiao Z, Lin Q, Dong X. Mucoepidermoid carcinoma arising in Warthin's tumour of the parotid gland: Clinicopathological characteristics and immunophenotypes. Scientific Rep, 2016; 6(1): 30149-30157.
29. Stryjewska-Makuch G, Kolebacz B, Janik MA, Wolnik A. Increase in the incidence of parotid gland tumors in the years 2005–2014. Otolaryngol Pol, 2017; 71(2): 1-6.
30. Kakkar A, Zubair A, Sharma N, Monga R, Sharma SC. Synchronous oncocytic papillary cystadenoma and Warthin tumor of the parotid gland. Int J Surg Pathol, 2020; 28(3): 296-301.
31. Cardoso SV, do Nascimento Souza KC, de Faria PR, Lima RA, Nascimento MF, Eisenberg AL. Warthin's tumor at the Brazilian National Cancer Institute: additional evidence of homogeneous sex prevalence and association with other neoplasms. ORL J Otorhinolaryngol Relat Spec, 2008; 70(6): 339-343.
32. Ochai-Choinska A, Bruzgielewicz A, Osuch-Wojcikiewicz E. Synchronous multiple unilateral parotid gland tumours of benign and malignant histological types: Case reports and Literature review. Braz J Otorhinolaryngol, 2019; 85(3): 388-392
33. Deodhar KK Shah M, Chaturvedi P. High-grade adenocarcinoma, (ductal type) arising in unilateral Warthin tumour of the parotid gland. Indian J Pathol Microbiol, 2011; 54(3): 574-577.
34. Bolat F, Kayaselcuk F, Erkan AN, Cagici CA, Bal N, Tuncer I. Epidermoid carcinoma arising in Warthin's tumor. Pathol Oncol Res, 2004; 10(4): 240-242.
35. Xu W, Lu H, Zhu Y, Ruan M, Zhang C, Yang W, et al. Warthin's tumour in oral and maxillofacial regions: an 18-year retrospective study of 1084 cases in an eastern-Chinese population. Int J Oral Maxillofac Surg, 2018; 47(7): 913–917.
36. Naumaan A, Ghai R, Gattuso P. Warthin's tumor of the parotid gland: a simple lesion with complex clinical implications; a clinical pathologic review. Lab Investig, 2017; 97: 330A
37. Sharma M, Saxena S, Agrawal U. Squamous cell carcinoma arising in unilateral Warthin's tumour of paratid gland. J Oral Maxillofacial Pathol, 2008; 12(2): 82-84.
38. Yaranal PJ, Umashankar T. Squamous cell carcinoma arising in Warthin's tumour: a case report. J Clin Diag Res, 2013; 7(1): 163-165.

39. Kim J-E, Kim TG. Squamous cell carcinoma arising from Warthin's tumor in the parotid gland. BJR Case Rep, 2019; 5(4): 20190032. doi: 10.1259/bjrcr.20190032
40. Sayar' H, Öztarakcp H, Sayar C, Agirba C. Adenocarcinoma Arising in Warthin Tumor of the Parotid Gland. Turk Patoloji Derg, 2012; 28(2): 278-281.
41. Arcega RS, Feinstein AJ, Bhuta S, Blackwell KE, Rao NP, Pullarkat ST. An unusual initial presentation of mantle cell lymphoma arising from the lymphoid stroma of Warthin tumor. Diag Pathol, 2015; 10(1): 209-215.
42. Alnoor F, Gandhi JS, Stein MK, Gradowski JF. Follicular lymphoma diagnosed in Warthin tumor: A case report and review of the literature. Head Neck Pathol, 2020; 14(2): 386-391.
43. Jawad H, McCarthy P, O'Leary G, Heffron CC. Presentation of chronic lymphocytic leukemia/small lymphocytic lymphoma in a Warthin tumor: case report and literature review. Int J Surgl Pathol, 2018; 26(3): 256-260.
44. Marioni G. MALT-type lymphoma and Warthin's tumour presenting in the same parotid gland. Acta Otolaryngol, 2004; 124(3): 318-323.
45. Chen Y-A, Wu C-Y, Yang C-S. Application of the Milan system for reporting salivary gland cytopathology: A retrospective study in a tertiary institute. Diag Cytopathol, 2019; 47(11): 1160-7.
46. Di Napoli A, Mallel G, Bartolazzi A, Cavalieri E, Becelli R, Cippitelli C, et al. Nodular Lymphocyte-Predominant Hodgkin Lymphoma in a Warthin Tumor of the Parotid Gland: A Case Report and Literature Review. Int J Surg Pathol, 2015; 23(5): 419-423.
47. Liu, LQ, Tang QI. Concomitant lymphocyte-rich classical Hodgkin's lymphoma and Warthin tumour. Oral Maxillofacial Pathol, 2013; 116(2): e177-e120.
48. Dua S, Purandare N, Shah S, Rangarajan V. Bilateral synchronous and multifocal Warthin's tumor mimicking metastases from lung cancer: A rare cause of false positive flourodeoxy glucose positron emission tomography/computed tomography. Indian J Nuclear Med, 2012; 27(2): 139-140.
49. Naumaan A, Ghai R, Gattuso P. Warthin's tumor of the parotid gland: a simple lesion with complex clinical implications; a clinical pathologic review. Lab Investig, 2017; 97: 330A
50. Zorlu E, Atasoy P, Gunal N, Dural K, Ozpolat B. Lung cancer and Warthin's tumour: a case report and review of the literature. Curr Thoracic Surg, 2018; 3(1): 13-16.
51. Haberal MA, Akar E, Dikis OS. Metastatic lung cancer associated with Warthin's tumour. Nig J Clin Prac, 2019; 22(4): 585-587.
52. Radoï L, Barulc C, Menvielled G, Cartone M, Matratf M, Sancheza M *et al*. Risk factors for salivary gland cancers in France: Results from a case-control study, the ICARE study. Oral Oncol, 2018; 80(2018): 56–63.
53. Chang D, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS *et al*. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA, 2020; 323(11): 1092-1093.
54. Franzen AM, Franzen CK, Guenzel T, Lieder A. Increasing incidence of Warthin tumours of the parotid gland: a 42-year evaluation. Euro Archives

of Oto-Rhino-Laryngol, 2018; 275(10): 2593-2598.
55. Cardoso SV, do Nascimento Souza KC, de Faria PR, Lima RA, Nascimento MF, Eisenberg AL. Warthin's tumor at the Brazilian National Cancer Institute: additional evidence of homogeneous sex prevalence and association with other neoplasms. ORL J Otorhinolaryngol Relat Spec, 2008; 70(6): 339-343.
56. Luers JC, Guntinas-Lichius O, Klussmann JP, Küsgen C, Beutner D, Grosheva M. The incidence of Warthin Tumors and Pleomorphic Adenomas in the Parotid Gland over a 25 year period. Clin Otolaryngol, 2016; 41(6): 793-797.
57. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA, 2020; 323(16): 1574-1581
58. Lin FCF, Chen PL, Tsao TY, Li CR, Jeng KC, Tsai SCS. Prevalence of human papillomavirus and Epstein–Barr virus in salivary gland diseases. J Int Med Res, 2014; 42(5): 1093–1101
59. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J *et al*. Clinical Characteristics of Coronavirus Disease 2019 in China. New Eng J Med, 2020; 382(18): 1708-1720
60. Thomas R, Sharma N, Burke C, Maxwell D, Howlett DC. Parotid incidentaloma detected during thoracic PET imaging: how should these lesions be managed? Br J Hospital Med, 2010; 71(5): 292-293.
61. White CK, Williams KA, Rodriguez-Figueroa J, Langer CJ. Warthin's tumors and their relationship to lung cancer. Cancer Investig, 2015; 33(1): 1-5.
62. Klussmann JP, Wittekindt C, Preuss SF, Al Attab A, Schroeder U, Guntinas-Lichius O. High risk for bilateral Warthin tumor in heavy smokers-review of 185 cases. Acta Otolaryngol, 2006; 126(11): 1213-1217.
63. Kuzenko YV, Romanuk AM, Dyachenko OO, Hudymenko O. Pathogenesis of Warthin's tumors. Int Med Applied Sci, 2016; 8(2): 41–48
64. Givi B, Schiff BA, Chinn SB, Clayburgh D, Iyer NG, Jalisi S, et al. Safety recommendations for evaluation and surgery of the head and neck during the COVID-19 pandemic. JAMA Otolaryngol Neck Surg, 2020; 146(6):579-584
65. Wang C, Wu H, Ding X, Ji H, Jiao P, Song H *et al*. Does infection of 2019 novel coronavirus cause acute and/or chronic sialadenitis? Med Hypotheses, 2020; 140, 109789.
66. Di Palma S, Simpson RH, Skalova A, Michal M. Metaplastic (infarcted) Warthin's tumour of the parotid gland: a possible consequence of fine needle aspiration biopsy. Histopathol, 1999; 35(5): 432–438.
67. Soldatova L, Rassekh CH, Baloch ZW, Jalaly JB, Sedora-Roman NI, Loevner LL *et al*. Salivary gland disease in the era of COVID-19 pandemic. Head Neck, 2020; 42(6): 1339-1343.
68. Inchingolo F, Santacroce L, Ballini A, Topi S, Dipalma G, Haxhirexha K *et al*. Oral Cancer: A Historical Review. Int J Environ Res Public Health, 2020; 17(9): 3168.
69. Sava A, Nemţoi A, Stan CI, Dumitrescu GF, Haba D, Budacu CC *et al*. Clinical–pathological correlations in Warthin tumors of

parotid gland: a series of 10 cases. Rom J Morphol Embryol, 2019; 60(2): 445–453.
70. Köybaşioğlu FF, Önal B, Han U, Adabağ A, Şahpaz A. Cytomorphological findings in diagnosis of Warthin tumor. Turk J Med Sci. 2020; 50(1): 148-154.
71. Witt RL. Major salivary gland cancer. Surg Oncol Clin N Am, 2004; 13(1): 113-127.
72. Gan LL, Zhang H, Guo JH, Fan MW. Prevalence of Human Papillomavirus Infection in Oral Squamous Cell Carcinoma: A Case-Control Study in Wuhan, China. Asian Pac J Cancer Prev, 2014; 15(14): 5861-5865.
73. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nature Rev Immunol, 2020; 20(4): 363-374.
74. Santosh TS, Parmar R, Anand H, Srikanth K, Saritha M. A Review of Salivary Diagnostics and Its Potential Implication in Detection of Covid-19. Cureus, 2020; 12(4): e7708. doi: 10.7759/cureus.7708
75. Guidry JT, Birdwell CE, Scott RS. Epstein-Barr virus in the Pathogenesis of Oral Cancers. Oral Dis, 2018; 24(4): 497–508.
76. Zhang S, Liu Y, Wang X, Yang L, Li H et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol, 2020; 13(1):1-22.
77. Zhao X, Wang K, Zuo P, Liu Y, Zhang M, Xie S *et al*. Early decrease in blood platelet count is associated with poor prognosis in COVID-19 patients—indications for predictive, preventive, and personalized medical approach. EPMA J. 2020; 11: 139-145
78. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clinica Chimica Acta, 2020; 506: 145-148.
79. Liebman HA. Thrombocytopenia in cancer patients. Thrombosis Res, 2014; 133 (Suppl 2), S63-69.
80. Guerini- Rocco E, Taormina SV, Vacirca D, Ranghiero A, Rappa A, Fumagalli C *et al*. SARS- CoV-2 detection in formalin- fixed paraffin-embedded tissue specimens from surgical resection of tongue squamous cell carcinoma. J Clin Pathol, 2020; 73(11): 754-757.
81. Albano D, Bertagna F, Bertolia M, Bosio G, Lucchini S, Motta F *et al*. Incidental findings suggestive ofcovid-19 in asymptomatic patients undergoing nuclear medicine procedures in a high prevalence region. J Nucl Med, 2020; 61(5): 632-636.
82. Xu J, Chu M, Zhong F, Tan X, Tang G, Mai J *et al*. Digestive symptoms of COVID-19 and expression of ACE2 in digestive tract organs. Cell Death Discovery, 2020; 6:76. doi: 10.1038/s41420-020-00307-w
83. Liu B, Han J, Cheng X, Yu L, Zhang L, Wang W *et al*. Reduced numbers of T cells and B cells correlates with persistent SARS-CoV-2 presence in non-severe COVID-19 patients. Sci Rep, 2020; 10(1): 1-9
84. Wei X, Su J, Yang K, Wei J, Wan H, Cao X *et al*. Elevations of serum cancer biomarkers correlate with severity of COVID-19. J Med Virol, 2020. doi: 10.1002/jmv.25957. Online ahead of print.

85. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and uninfected adolescent girls: risk factors and differenced, by phylogenetic type. J Infect Dis, 2004; 190(1): 37-45.
86. Omar T, Schwartz S, Hanrahan C, Modisenyane T, Tshabangu N, Golub JE *et al*. Progression and regression of premaligant cervical lesions in HIV-infected women from Soweto: a prospective cohort. AIDS, 2010; 25(1): 87-94.