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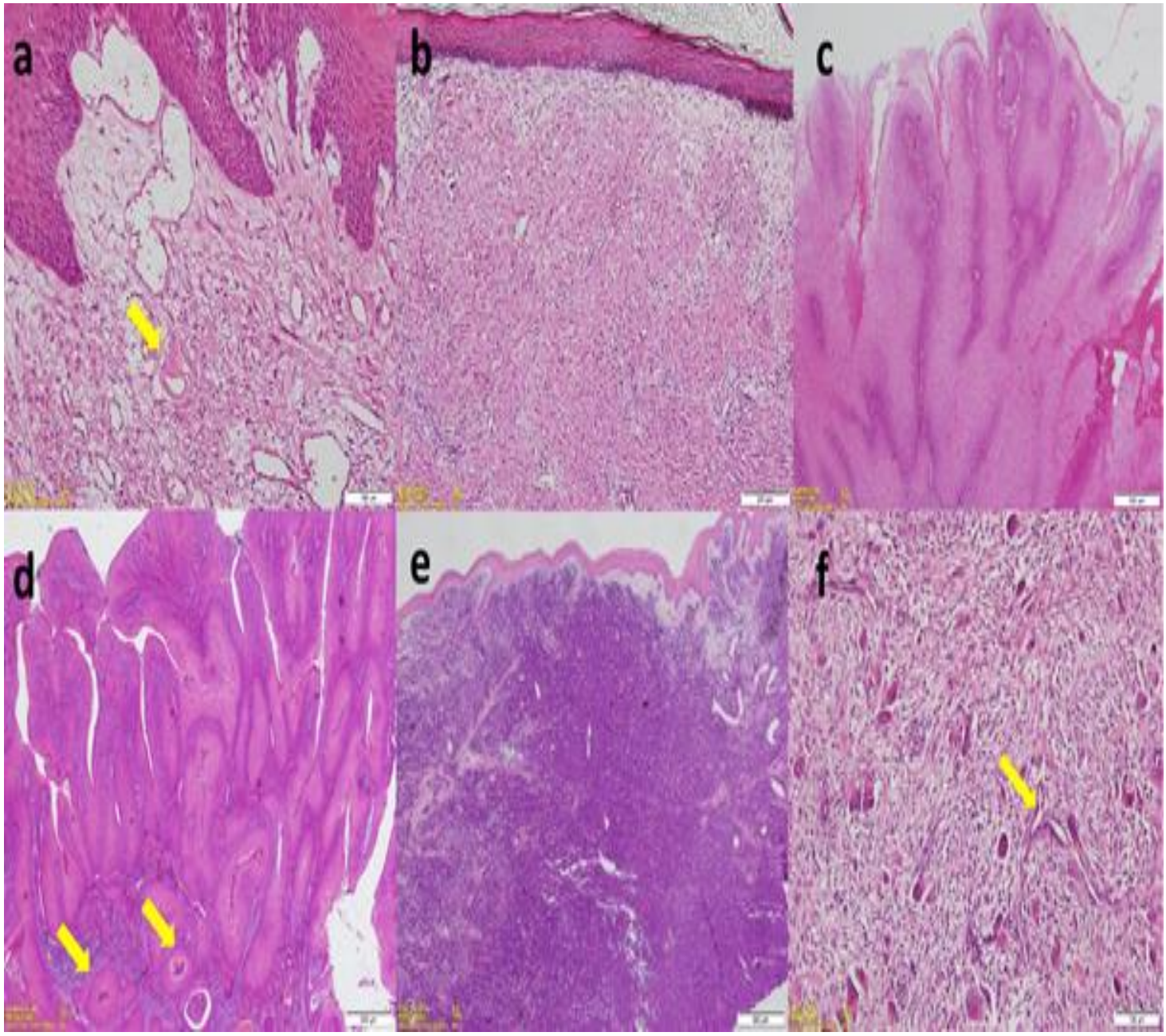

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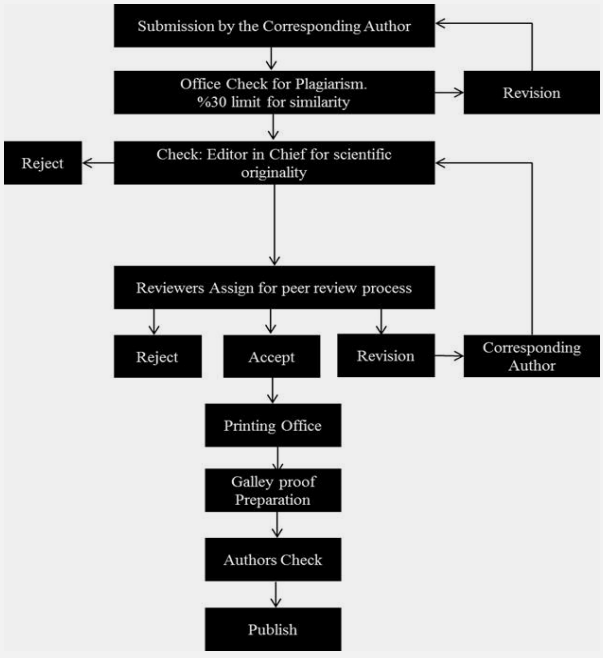

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Review Article Doi: 10.36472/msd.v7i9.421

Coronavirus and SARS-CoV-2 Pandemic Diseases

Ayhan Güler[1]*, Ceren Başkan[2] Belgin Sırıken[3]

Abstract

Coronaviruses which are a large family of viruses lead to upper-respiratory diseases in the especially respiratory system and enteric, hepatic and neurological systems with different severity in human as well as a wide variety of animals. Coronaviruses involved in four genera, and beta-CoVs are the most important group and the most highly pathogenic viruses against humans such as Severe Acute Respiratory Disease (SARS) -CoV-2. SARS-CoV-2 is the third quite pathogenic human coronavirus, and can pass through animals to human or human to human due to capable of cross the species barrier into the human populations. Up to 2 July, 2020, coronavirus cases are 10,720,755 and deaths number are 517,005. Many variety mammalians groups such as pigs, cows, chicken, dogs, cats and human are harbor for CoVs. Among them, especially bats are very important for harbor and enhance the change of interspecies transmission of the viruses. According to SARS-CoV-2 symptoms, it is change to asymptomatic forms to respiratory failure and systemic manifestations such as sepsis, septic shock and multiple organ dysfunctions syndrome. For SARS-CoV-2 inactivation way is by lipid solvents including 75% of ether, 80% of ethanol, 75% of isopropanol, chlorine containing disinfectant, peroxyacetic acid, and chloroform except for chlorhexidine, alkaline (pH> 12) or acidic (pH <3) conditions, formalin and glutaraldehyde treatments. It is taken community measures against SAR-CoV-2 to control the spread of infection and diseases. To SARS CoV-2, there has been no vaccine and specific anti-viral drugs so far. Therefore, public health measures are considered as an effective tool for community. For this aim, hand hygiene, use of mask, hospital environment, droplet, airborne and contact precautions, institutional safeguard and standard measures should be used.

Keywords: Coronavirus, SARS-CoV-2, structure, symptoms, preventive measure

Introduction

Viral diseases on going to emerge and cause serious disease in the world. The issue, therefore, a big challenge for public health. In the last two decades, severe acute respiratory coronavirus (SARS-CoV) and H1N1 influenza have been recorded in 2002-2003 and 2009, respectively. In addition, in 2012, Middle East Respiratory Diseases (MERS-CoV) was firstly identified (1). Then, in Wuhan, China, it was seen low respiratory infections detected in 2019 but the agent did not know. After, the etiology of this disease was identified as a novel virus and belonging to CoV family. The virus was called COVID-19 after soon SARS-CoV-2 (1)

Coronavirus: Generally, coronaviruses lead to diseases in the especially respiratory system and enteric, hepatic and neurological systems with different severity in human as well as a wide variety of animals. Severe Acute Respiratory Disease (SARS) -CoV-2 is the third quite pathogenic human coronavirus, and can pass through animals to human or human to human due to capable of cross the species barrier into the human populations.

The World Health Organization (WHO) reported that SARS-CoV-2 a pandemic and March (2,3,4) Up to 30 June, 2020, coronavirus cases are 10,435,321 and deaths number are 508,844 (5). Coronaviruses involved in four genera; Alfacoronavirus (alfa-CoVs), Betacoronavirus (beta-CoVs or ß-CoVs), Gammacoronavirus (gamma-CoVs) and Deltacoranavirus (delta-CoVs). Among four genera, beta-CoVs are the most important group and the most highly pathogenic viruses against humans such as SARS -CoV-2, Middle East respiratory Diseases (MERS)-CoV and SARS-CoV (6,7,8).

Structure: The CoVs has a single stranded and RNA positive polarity genome without segment. The CoVs's virions contain four main structural proteins; these are nucleocapsid (N) protein, which binding CoV's RNA genome and playing a role in the replication of viral RNA host's cellular response, the transmembrane (M) protein, playing a key role as it turns cellular membranes into factories for making new virus particles, the envelope (E) protein, playing three roles-interaction between cytoplasmic tail of M and E protein, releasing virions and the virus pathogenesis, and the last one is the spike (S) protein (9,10). (Figure 1).

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Betacoronaviruses are one of four of coronaviruses. It is in the subfamily Orthocoronavirinae in the family Coronaviridae, of the order Nidovirales. They are enveloped, positive-sense, single-stranded RNA, on average, 30 kilobases (Figure 2). The virus possesses zoonotic features. The coronavirus genera are each composed of varying viral lineages with the betacoronavirus genus containing four lineages: A, B, C and D (Table 1). In older literature, this genus is also known as group 2 coronaviruses (11).

Betacoranavirus (beta-CoVs or ß-CoVs)

Beta-CoVs was classified four subclassifications. The genera were reclassified in 2018 as Embecovirus, Sarbecovirus, Merbecovirus and Nobecovirus (12), previously called lineage A, B, C and D, respectively (13). After that, the new a fifth subgenus was also included named Hibecovirus (12, (Table 1).

The beta-CoVs of the greatest clinical importance concerning human are OC43 (which can cause the common cold) and HKU1 of the A lineage, SARS-CoV and SARSCoV-2 (which causes the disease COVID-19) of the B lineage (14), and MERS-CoV of the C lineage. MERS-CoV is the first betacoronavirus belonging to lineage C that is known to infect humans (Table 1) (15), 16).

The characteristic of CoVs can achieve rapid adaptation to new host or different environment conditions due to recombination tendency and inherently high mutation rate (17,18,20)..

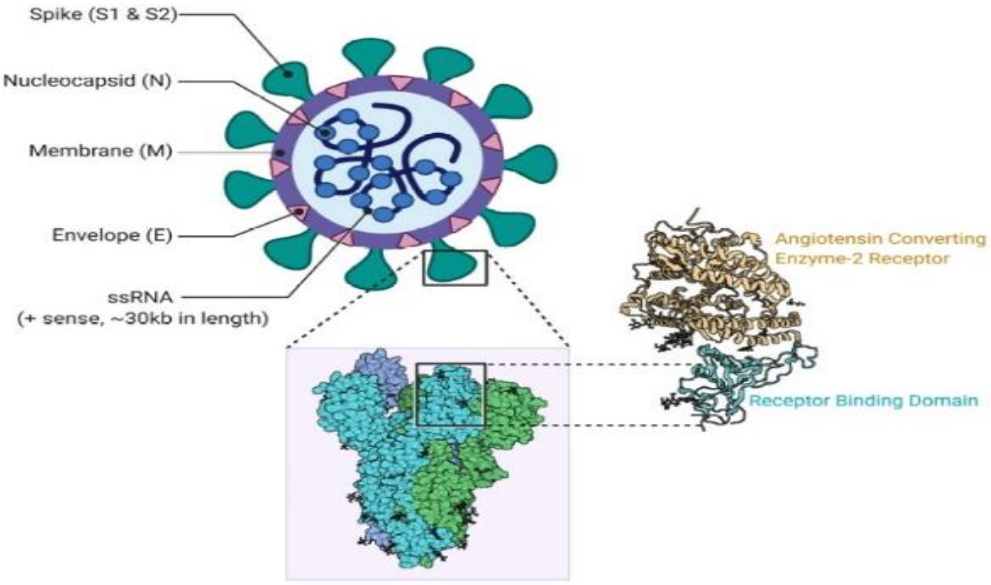

Figure 1. SARS- CoV 2 Structure (Rohan Bir Sing in (1).

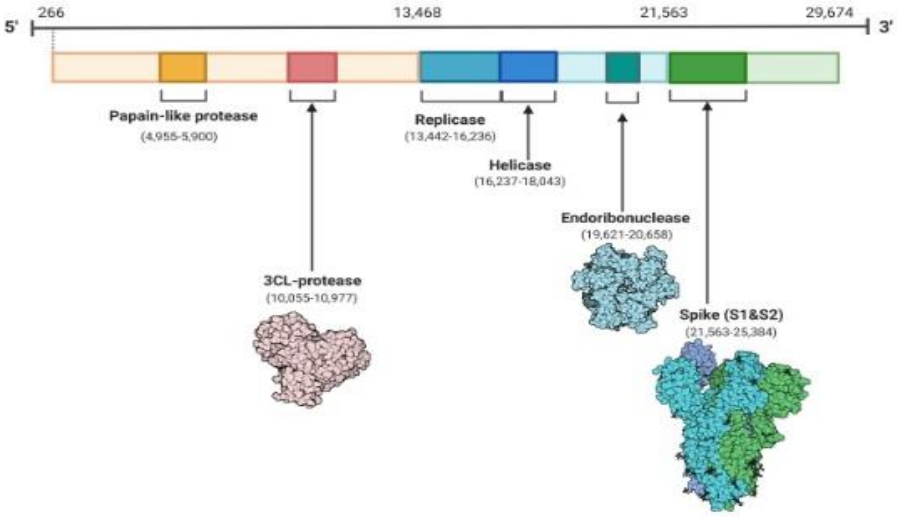

Figure 2. Single-stranded RNA genome of SARS-CoV2 ((Rohan Bir Sing in (1).

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Table 1. Betacoronavirus (11, 12,19)

Lineage	Lineage A	Lineage B	Lineage C	Lineage D	
Subgenus	*Embecovirus*	*Sarbecovirus*	*Merbecovirus*	*Nobecovirus*	*Hibecovirus*
Example	Human coronavirus (HCoV-OC43) HCoV-HKU1 (Various species)	SARSr-CoV (SARS-CoV-2, SARS-CoV-2 HKU4 (BtCoV-HKU4) Bat SL-CoV-W1V1	Tylonycteris bat coronavirus HKU4 (BtCoV-HKU4) Pipistrellus bat coronavirus HKU5 (BtCoV-HKU5)	Rousettus bat coronavirus HKU9 (BtCoV-HKU9)	Zaria bat coronavirus Bat Hp-betacoronavirus

Human coronaviruses

Firstly, three human coronaviruses were known to exist: human coronavirus 229E (HCoV-229E), HCoV-OC43 and severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV). Then, it was reported that the identification of a fourth human coronavirus, HCoV-NL63, using a new method of virus discovery (Table 1) (20). However, then, three CoVs have been identified. Nowadays, for human, at least seven coronavirus species are identified as pathogens. Four of these are represent above lines. In addition, the other three human coronaviruses are HCoV-HKU1, MERS-CoV (Middle East respiratory syndrome) and SARS-CoV-2 (CoVID-19). There is variation for pathogenesis among these 7 species. For instance, HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 lead to only mild upper respiratory disease. They seldom cause to disease for in infants, young children, and elderly people (21). Remaining three species are more dangerous and can cause lower respiratory tract and trigger a severe respiratory condition in humans. SARS-CoV caused outbreak in 2002 and 2003 (22, 2), and responsible for the Middle East respiratory syndrome (MERS-CoV), which emerged in 2012 and remained in the circulation in camels (23). SARS-CoV and MERS-CoV caused quite important concern because they crossed the species barrier and caused severe diseases. SARS-CoV emerged in Asia and spread rapidly to several countries across the world. MERS-CoV has largely been restricted to infections acquired in the Middle East. The two viruses are related to spread from human to human, and death rates are high (24).

Harbour of CoVs

Many variety mammalians groups such as pigs, cows, chicken, dogs, cats and human are harbor for CoVs. Among them, especially bats are very important for harbor and enhance the change of interspecies transmission of the viruses.

Before the SARS epidemic, bats were not known to be hosts for CoVs. But after the SARS epidemic, there are enhance, and bats have been found to be host of at least 30 CoVs (25).

Bats also recognized to be hosted some others (rabies and other lyssaviruses, Hendra, Nipah and Ebola virus) highly pathogenic viruses. Notable, horseshoe bats (high level) as well as palm civet cats (intermediate level) are considered to be reservoir of SARS-CoVs (26) (Figure 3). According to other subgenus Merbecovirus, which found to be closely related to the MERS-CoV in dromedary camels and humans (27,28).

For beta-CoVs subgenera, so far, Sarbocovirus (SARS-related CoVs), Merbecovirus (such as MERS-CoVs), Nobecovirus and Hibecovirus have been determined in bats (12, 27,29, 30).

As a result, in the last 125 years, it has witnessed a large number of novel CoVs, and bats are the largest number of CoVs harbor such as SARS-CoVs and MERS- CoVs (31). Beside beta-CoVs, bats are also harbor for alpha-CoVs. But birds are reservoir for gamma and delta-CoVs (32).

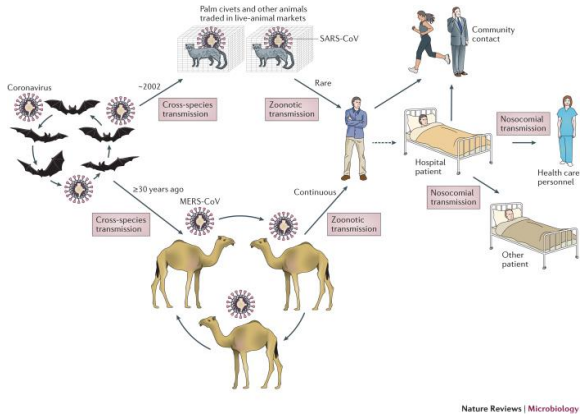

Figure 3. The emergence of SARS-CoV and MERS-CoV (33).

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Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2 or COVID-19)

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2 or COVID-19) is the one of coronavirus strain caused coronavirus disease 2019 (COVID-19). The agent is responsible of COVID-19 pandemic. The disease is a contagious and has been seen recently in worldwide. Although most people infected with the virus will experience mild or moderate respiratory illness and healing without requiring special treatment, older people and people with chronic diseases and immunosuppressive problems are more likely to develop quite serious diseases even resulting in death (4, 21).

Initially, the 2019-nCoV (Novel Coronavirus Pneumonia - NCP) called by the Chinese government causes severely lower respiratory tract diseases and also cause outbreak. The disease, then, was called COVID-19 by World health Organization (4.21) (Figure 4) (34). After that, 2019-nCoV was recalled Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) by the Coronaviridae Study Group of International Committee on Taxonomy of Viruses (35). The virus belongs to Pisuviricetes class, Nidovirales order and Coronaviridae familiy. The agent places the beta-coronavirus genus, Sarbecovirus subgenus and severe acute respiratory-related coronavirus species and severe acute respiratory syndrome coronavirus 2 strain (36).

The structure of the viruses has shown in Figure 5 A, B. A genomic structure of SARS-CoV-2 is typical of other betacoronaviruses. It contains 14 open reading frames (ORFs) encoding 27 proteins (37).

According to phylogenetic analysis of the SAES-CoV-2, the virus belongs to different clade from MERS-CoV, and it is highly related to Bat SARS-like coronavirus than SARS-CoV. It is known that Bat SARS like CoV isolated from Chine between 2015 and 2018, and main reservoir is bats (30,38). When genomic compression to SARS, SARS-CoV-2 has shown only 380 amino acid substitution, and 27 mutations are observed. Due to these mutation, pathogenicity of SARS-CoV-2 seem lower than SARS-CoV (30). The SARS-CoV and MERS-CoV structure and replication have also been showed in Figure 6. (33).

When compared to SARS (reproductive number (R0): 1.7-1.9), the R0 of the novel infection SARS CoV-2 is estimated by WHO to range between 2 and 2.5. The range is also higher than MERS (R0: <1). The higher R0 indicates that SARS-CoV-2 has a higher pandemic potential (Wu et al., 2020). However, fatality rate of SARS-CoV-2 (2.3%) is lower than SARS (9.5%) and MERS (34.4%) (CCDC).

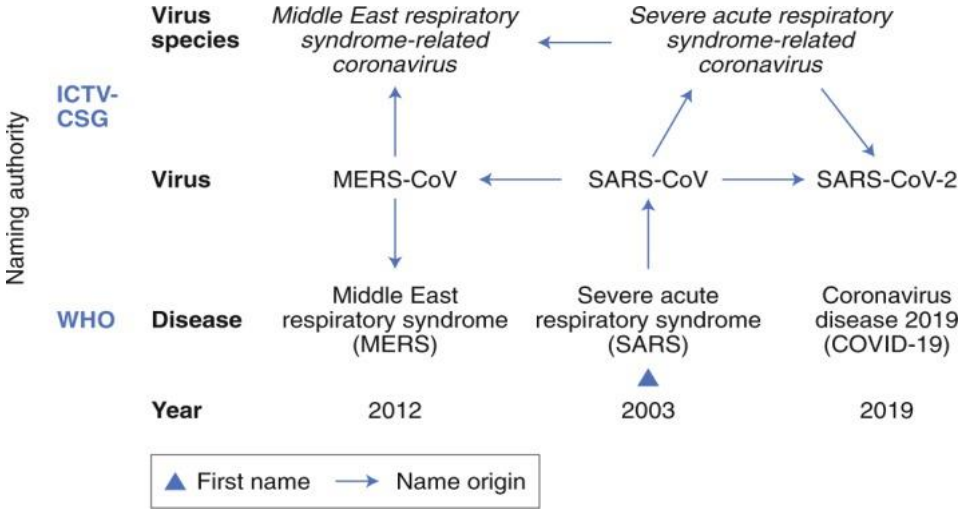
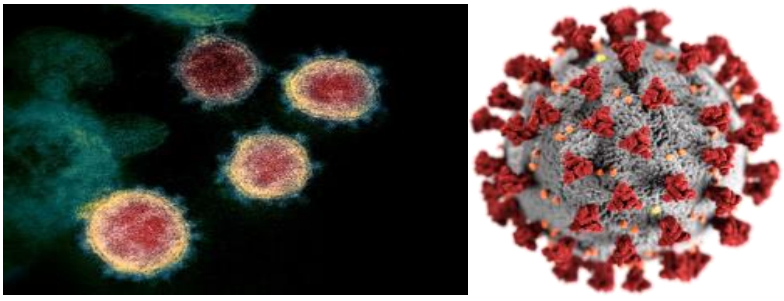


Figure 4. History of coronavirus naming during the three zoonotic outbreaks in relation to virus taxonomy and diseases caused by Coronaviruses (35).



A **B**

Figure 5. A-Electron microscope image of SARS-CoV-2 (Novel Coronavirus SARS-CoV-2- (39,40) B-Illustration of a SARS-CoV-2 virion

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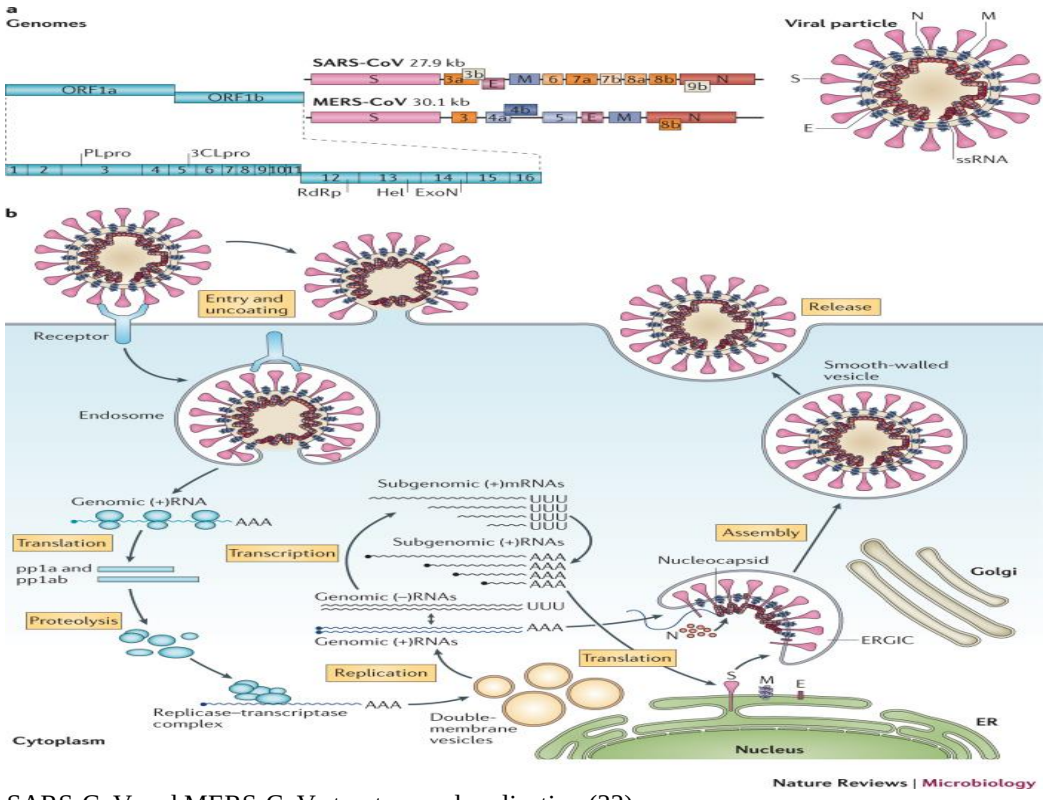

Figure 6. SARS-CoV and MERS-CoV structure and replication (33).

Symptoms

It is change to asymptomatic forms to respiratory failure and systemic manifestations such as sepsis, septic shock, and multiple organ dysfunctions syndrome. According to SARS-CoV2 symptoms, Huang et al. (2020) reported that fever, malaise, dry cough and dyspnea were seen patients. All cases have shown pneumonia. About third of those required intensive care unit and there were 6 (15%) fatal cases. Another reports, Chine CDC (41) stated that there were 62% confirmed cases of 72,314 cases , and 1% of whom was no symptoms, 49 of which with cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases, died (above 9 years old). According to (30), SARS-CoV-2 symptoms are divided three groups: mild, severe and critical diseases. Mild disease can occur 81% of cases. In the type, non- pneumonia or mild pneumonia are seen in the patients. The severe disease has shown 14% of cases. The symptoms are dyspnea, respiratory frequency (⩾30/minute) and needed ventilation with oxygen due to low blood oxygen saturation. Critical disease has seen 5% of cases. Respiratory failure, septic shock, and or multiple organ dysfunction or failure are seen in the cases with COVID-19.

According to (1), there are 3 types of symptoms may observe in patients with COVID-19 (1),.

These are;

1) Mild illness form: It is seen upper respiratory tract viral infections like mild fever, cough /dry form), sore throat, nasal congestion, malaise, headache and muscle pain, loss of smell taste, diarrhea, and vomiting. In more serious patient, it is also seen dyspnea.

2) Moderate pneumonia form: It is seen respiratory symptoms like cough and shortness of breath as symptoms.

3) Acute Respiratory Distress Syndrome (ARDS) form: It is seen failure of respiratory system or worsening of respiratory picture. It is seen also sepsis.

Inactivation of SARS CoV-2

The virus sensitive to ultraviolet light at 254 nm and heat treatment (65 °C or higher). Another inactivation way is by lipid solvents including 75% of ether, 80% of ethanol, 75% of isopropanol, chlorine containing disinfectant, peroxyacetic acid, and chloroform except for chlorhexidine, alkaline (pH> 12) or acidic (pH <3) conditions, formalin and glutaraldehyde treatments (42,43,44,45). According to (46), ethanol and 2-propanol of ⩾30% (vol/vol) concentration were efficient in inactivating the virus in 30 s. For virus inactivation, it needed biosafety 3 level (BSL 3) (47).

The number of Coronavirus cases and death in the some of the country

According to (5), up to 2 July, 2020, coronavirus cases are 10,720,755 and deaths number are 517,005. The number of cases according to country; In the United State, it has been seen 2,763,681 confirmed cases and 130,570 death, and the number is the highest number of confirmed coronavirus cases. Brazil is second range, and the number of SARS CoV-2 cases is 1,426,913 cases. A total COVID-19 number are 60,194 deaths, and China with 83, 534 cases and 4,634 death, England with 313,483 and 43,906 death, Germany with 196,296 and 9,059 deaths, Iran with 230,211 cases and 10,958 deaths, Spain with 296,739 cases and 28,363 deaths,

Italy with 240,760 cases and 34,788 death, Pakistan with 213,470 cases and 4,395 deaths, France with 165,719 cases and 29,861 deaths, Canada with 104,271 cases and 8,615 deaths, Sweden with 69,692 cases and 5,370 deaths, Netherlands with 50,273 cases and 6,113 deaths, . In Turkey, 5,150 death and 201,098 cases are seen.

Preventive measure of SARS CoV-2

It must be taken community measures against SAR-CoV-2 to control the spread of infection and diseases. To SARS CoV-2, there has been no vaccine and specific anti-viral drugs so far. Therefore, public health measures are considered as an effective tool for community. For this aim, it must use hand hygiene, use of mask, hospital environment, droplet, airborne and contact precautions, institutional safeguard and standard measures.

The most important measure to control the spread of COVID-19 infection is hand wash frequently with soap and water or with an alcohol-based hand sanitizer. If hands are not visibly dirty, they should preferably have washed with alcohol-based sanitizer for at least 20 to 30 seconds (48). But, if hand dirty, they should wash with soap and water for 40-60 seconds. It must be avoided to contracting person or other people, and hand must not contact eye or mount like that mucosa. Susceptible or infected surfaces and other surfaces must be clean with appropriate disinfection technique with 1.0% hypochlorite solution or 70.0% alcohol to limit the spread of infection To prevent of infection spread by aerosol or droplet infection, it must be mandatorily using mask. In the hospital, it is mandatory wear surgical mask. As air-droplet seldom crosses beyond 1 meter, within 1 meter between health and infected people, all health care workers must wear medical/ surgical mask along with face shield or goggles to protect eye from accidental spiting from patients. Personal protective equipment such as masks, gloves, gown, and goggles are necessary to prevent infection to health care workers. Dedicated instruments like stethoscope and thermometer) should be used for each patient however in case of sharing each instrument must be disinfected with alcohol or hypochlorite solution. Health care worker must avoid touching their mouth, nose or eye, frequent hand wash (21).

Conclusion

Severe Acute Respiratory Disease (SARS) -CoV-2 is the third quite pathogenic human coronavirus, and can pass through animals to human or human to human due to capable of cross the species barrier into the human populations. Up to 2 July, 2020, coronavirus cases are 10,720,755 and deaths number are 517,005. Many variety mammalians groups such as pigs, cows, chicken, dogs, cats and human are harbor for CoVs. Among them, especially bats are very important for harbor and enhance the change of interspecies transmission of the viruses. According to SARS-CoV-2 symptoms, it is change to asymptomatic forms to respiratory failure and systemic manifestations such as sepsis, septic shock and multiple organ dysfunctions syndrome. For SARS-CoV-2 inactivation way, it is treatment by using lipid solvent including 75% of ether, 80% of ethanol, 75% of isopropanol, chlorine containing disinfectant, peroxyacetic acid, and chloroform except for chlorhexidine, alkaline (pH> 12) or acidic (pH <3) conditions, formalin and glutaraldehyde treatments. It is taken community measures against SAR-CoV-2 to control the spread of infection and diseases. To SARS CoV-2, there has been no vaccine and specific anti-viral drugs so far. Therefore, public health measures are considered as an effective tool for community. For this aim, hand hygiene, use of mask, hospital environment, droplet, airborne and contact precautions, institutional safeguard and standard measures should be used.

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Author Contributions: AG, CB, BS: Review of the literature, data collection and analyzes **AG;** Writing and Revisions

Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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A single center study of oral mucosal lesions in a Turkish population during 12 years period

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Abstract

Objective: The prevalence of oral mucosal lesions, together with information on the risk habits associated with oral health, such as tobacco and alcohol use, can help in planning future oral health studies and screening programs.

Material and Methods: This study presents the findings of 805 oral mucosal biopsies from patients, received over twelve years period. The cases represent 0.6 per-cent of the total number of reports examined (130.680). The data were revised and compiled for diagnosis site, age, and sex. The patients were divided into nine age groups according to decades. The classification was modified and divided into eleven main groups

Results: Connective tissue lesions formed the largest group of diagnoses (24.4per cent) followed by white lesions (17.8 %per cent), verrucal-papillary lesions (15.4%per cent), red-blue lesions (14%per cent), ulcerous lesions (12.2%per cent), periodontal diseases (10%per cent), lymphoid tissue lesions (1.3%per cent), other tumors (2%per cent), pigmented lesions (0.6%per cent) only 1 metabolic disease (cherubism) (0.1per cent). Approximately 60 %per cent of the biopsies were from the second group patients with an almost equal distribution among sexes. The predominant site of the biopsies was gingiva (28%per cent) followed by lips (19.2%per cent).

Conclusion: The majority of the lesions were in the category of reactive and inflammatory lesions with most occurring in the thirty age group (31-40 age) that represents permanent dentition. These results suggest that the difficulties in maintaining oral hygiene or the presence of trauma may be the primary factor in mucosal lesions occurring in the permanent dentition period.

Keywords: Oral lesions, Maxillofacial lesions, Retrospective study, Turkish population

Introduction

More than 600 diseases of the oral mucosa are known. Most of these are benign lesions. Some of them are primary or secondary findings of systemic diseases. Malignant tumors are also the most dangerous among these diseases, but not the most common lesions in the oral cavity. Oral mucosal lesions are an important indicator of oral health and quality of life, especially in the elderly. The prevalence of oral mucosal lesions, as well as information on oral health-related risk habits such as tobacco and alcohol use, may help in the planning of future oral health studies and screening programs.

These lesions are classified in a variety of ways. The most common is the WHO Guideline. This study aims to determine the spectrum and the frequency of biopsied oral and maxillofacial mucosal lesions, hospital population, comprising patients of all ages and genders in Sivas / Central Anatolia / Turkey and comparing the results with other studies reported worldwide.

Material And Methods

The Human Research Ethics Committee of Sivas Cumhuriyet Univercity reviewed and approved the project (2018-03/01). Written informed consent was obtained from all participants.

It performed a retrospective, 12-year (2008–2020) descriptive analysis of oral and maxillofacial mucosal biopsies, at the Pathology Department of the University Hospital from the Clinics of Dentistry Faculty of Sivas Cumhuriyet University. This study presents the findings of 805 oral mucosal biopsies from patients, received ten years period. The cases represent 0.6% of the total number of reports examined (130.680). The data were anonymized before analysis information on gender, age, the site of the lesion, clinical diagnosis and the histopathological diagnosis were included in the analysis biopsies of normal tissue; repeated biopsies of lesions already diagnosed (e.g. the excisional removal of a lesion that was previously diagnosed with an incisional biopsy) and cases with unclear

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or missing data, or with an inconclusive diagnosis were the exclusion criteria.

It has based on the classification in the textbook of Oral Pathology of Regezi-Sciubba-Jordan, which are 1. Vesiculobullous diseases, 2. Ulcerative conditions, 3. White lesions, 4. Red-blue lesions, 5. Pigmented lesions, 6. Verrucal-papillary lesions, 7. Connective tissue lesions, 8. Salivary gland diseases 9. Lymphoid lesions 10. Metabolic and genetic diseases. 11. Cysts of the jaws and neck, 12. Odontogenic tumors, 13. Benign non-odontogenic tumors, 14. Inflammatory jaw lesions, 15. Malignancies of the jaws and 16. Abnormalities of teeth have been excluded (1). Instead of these, it has been included as 11. Other lesions inc. tumors. The study was performed in full accordance with the World Medical Association Declaration of Helsinki. Data regarding histopathological diagnosis and respective clinical information were retrieved from patient hospital records (Table.1)

Statistical analysis

The data obtained in this study were analyzed by SPSS 22.0 (IBM, Armonk, NY, USA). When parametric test assumptions were fulfilled (Kolmogorof-Simirnov), variance analysis was used, when the parametric test assumptions were not be fulfilled, Kruskal-Wallis test was used. The evaluation of the data obtained by counting Chi-square was used, when the assumptions were not fulfilled, Chi-square results were obtained from Monte Carlo model which is a Chi-square exact test. The data were expressed as mean±standard error of mean (SEM). Differences were considered as significant at $p<0.05$, when it was compare the distribution of oral cavity lesions by gender (Table 2) and the number of cases by type (Table 3).

Results

The most common lesions are connective tissue lesions consisting of 206 the all cases. Most of these lesions were traumatic fibroma making up 83 out of 206. The second most common lesions were reparative peripheral giant cell granulomas (epulis gigantocellularis).With 62 instances, the third most frequent lesions were peripheral ossifying fibroma with 33 cases. The rest of consists in 15 gingival fibrous hyperplasia, 4 lymphangioma, 3 neurofibroma (Fig. 1a), 2 granular cell tumors (Fig.1b), 1 fibromatosis, 1 nodular fasciitis, and 1 myxoma. White lesions consisted of 134 in the cases. 88 of these cases consist of oral lichen planus, 29 nodular leukoplakia, and 13 solar (actinic) cheilitis based on the color categorization of the lesions. The rest of the cases were geographic tongue, submucosal fibrosis, most commonly in the 6th decade. There were 124 cases of verrucal-papillary lesions with the distribution of 58 focal epithelial hyperplasias, 44 squamous papilloma/oral verruca vulgaris(Fig.1c), 13 inflammatory papillary hyperplasias, 4 keratoacanthoma (KA), 2 papillary hypertrophy of tongue, 2 verrucous carcinomas (Fig.1d) and 1 verruciform xanthoma. Most of the cases of the lesions in this category of etiology were due to viral infections. There were 108 cases of red-blue lesions with most commonly seen as pyogenic granulomas 74 out of 109 (67.9%.)

The second most common lesions were hemangioma from all subtypes as well as capillary, cavernous and verrucous capillary with 33 cases (30.2%). Ulcerous conditions are the fifth most common lesion type with 98 cases. The percentage of 63.2% (62/98) of these cases were squamous cell carcinoma, which is malignant ulceration. Traumatic granuloma is 10.2% (10/98) as well as ulcer, 9.2% (9/98) aphthous ulcer, 7.1% (7/98) eosinophilic ulcer, 5.1% (5/97) candidiasis. Pemphigus vulgaris were 11 of the 19 vesiculobullous lesions, 7 of those were bullous pemphigoid and one of those was confirmed by DIF (intraepithelial linear staining with IgG, IgA, IgM).

Six of the bullous pemphigoid cases were female and one was male. Female patients with pemphigus vulgaris were in the 4th, 6th, 5th and 7th, male patients in the 4th and 5th decades. Patients with bullous pemphigoid are in the 5th, 6th, 7th, 8th and 9th decades. Lymphoid hyperplasias are 10 and 2 are lymphomas of the 12 lesions in the lymphoid tissue diseases group.

One of the lymphoma cases is the gingiva involvement of Burkitt's lymphoma in the 3rd decade (Fig.1e), and the other is diffuse large B-cell lymphoma in the 8th decade. Both are male patients. There is one case only of cherubism (Fig.1f) is which is diagnosed in an 11-year-old girl in the metabolic diseases group.

In the group of “other lesions incL tumors” consist of 8 fibrolipomatous hamartomas, 3 metastatic tumors and 3 malignant mesenchymal tumors. One of the metastatic tumors is adenocarcinoma of unknown primary in an 83-year-old female patient, the second is a rectum ca metastasis in a 49-year-old male patient, and the third is a renal cell ca metastasis in a 64 years old male patient.

Malignant mesenchymal tumors are composed of 1) "embryonal rhabdomyosarcoma" in a 35-year-old male patient, 2) " adult-type pleomorphic rhabdomyosarcoma" which is seen in a 32-year-old female patient, and a “pleomorphic fusiform cell malignant tumor”, which is unknown primary.

According to its location in the oral cavity, connective tissue lesions, including all of the ossifying fibroma and all of the epulis, were mostly localized in the gingiva, as well as all of the squamous cell carcinomas in the tongue.

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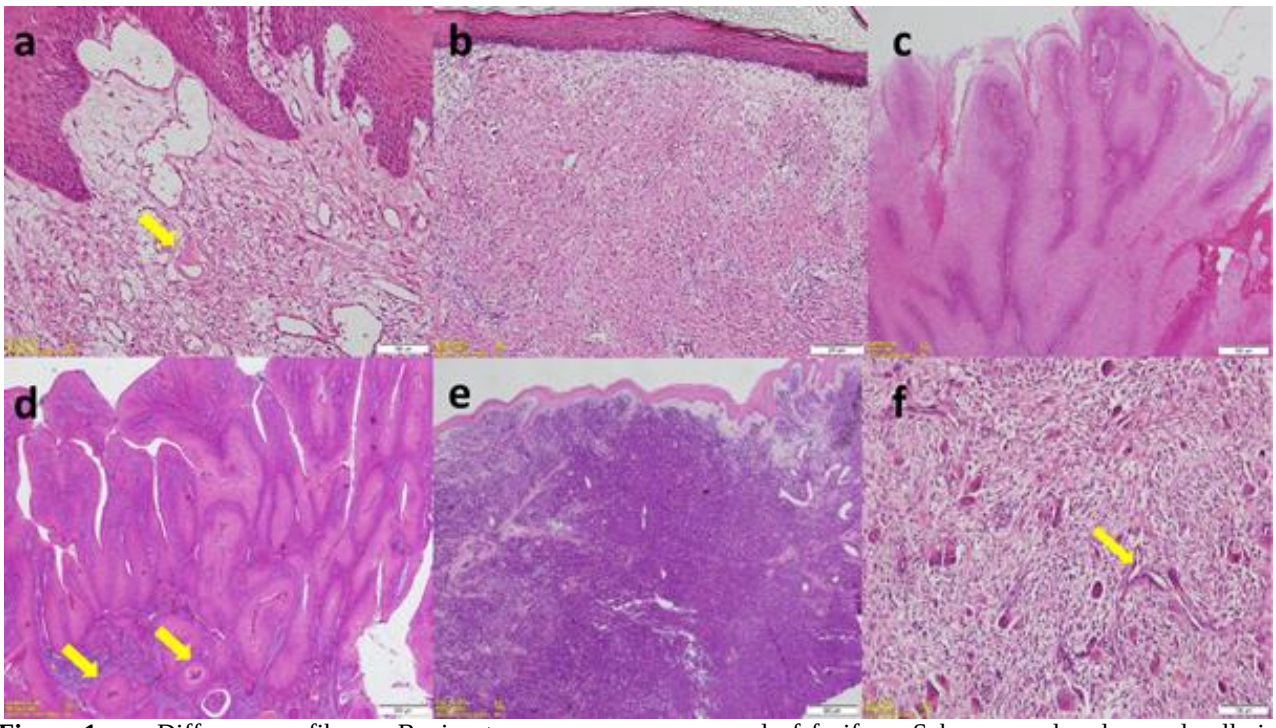

Figure 1. a : Diffuse neurofibrom: Benign tumor are seen composed of fusiform Schwann and endoneural cells in lamina propria. In addition, there are teleangiectasias and hyalinised vessels (marked with a yellow arrowhead) (HEX20). **b:** Granuler cell myoblastoma: Tumoral infiltration are seen beneath the surface epithelium, filling the entire lamina propria (HEX10). **c:** Squamous Papillom / Oral verruca vulgaris: Tumoral growth in the form of papillary-verrucal proliferations composed of cells with large clear cytoplasm so called koilocytes in the surface epithelium (HEX40) **d:** Verrucous carcinoma: Tumor characterized by exophytic-papillary proliferations are seen. There are microabscess in deep tumoral masses (marked with yellow arrowheads) (HEX40). **e:** Burkitt lymphoma: Immediately below the surface epithelium, lymphoid tumor infiltration is observed, characterized by a stary sky appearance that fills the entire stroma (HEX10) **f:** Cherubism: Lesion consisting of osteoclastic giant cells are seen among the fusiform cells. Perivascular hyalinization is also noticeable in this lesion (marked with a yellow arrowhead) (HEX20).

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	0-10		11-20		21-30		31-40		41-50		51-60		61-70		71-80		81>		TOTAL of gender		TOTAL of cases
Gender	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	805
I. VESICULOBULLOUS DISEASES																					
Pemphigus vulgaris							1	1	2	1	3		2		1				9	2	11
Bullous pemphigoid									1		1	1	2		1		1		6	1	7
Herpetic gingivostomatitis					1														1		1
Subtotal according to gender					1		1	1	3	1	4	1	4		2		1		16	3	19 (2.36%)
Subtotal according to decades			1	2	4	5	4	2	1			19									
II. ULCEROUS LESIONS																					
Squamous cell carcinoma	4	4	4	7	4	6	6	6	5	13	23	39	62								
Traumatic granulomas								1		4			3	1		1			3	7	10
Aphthous ulcers					1			2	2			2		2					3	6	9
Eosinophilic ulcers									1		2		1		1	1	1		6	1	7
Actinomycosis		1								2						2				5	5
Erythema multiforme													1						1		1
Drug reactions									1				1						2		2
Candidiasis								1							1				1	1	2
Subtotal according to gender		1			1			7	8	10	6	9	10	9	8	10	6	13	39	59	98 (12.2%)
Subtotal according to decades	1		1	7	18	15	19	18	19			98									
III. WHITE LESIONS																					
Lichen planus				1	4	3	7	7	10	5	13	10	11	4	8	5			53	35	88
Leukoplakia					1	1	1	2	2	4	2	4	3	6	1	1	1		11	18	29
Solar cheilitis										1	3			2				7	3	10	13
Geographic tongue			1						1		1								3		3
Submucous fibrosis											1								1		1
Subtotal according to gender			1	1	5	4	8	9	13	10	20	14	14	12	9	6	1	7	71	63	134 (16.6%)
Subtotal according to decades		2	9	17	23	34	26	15	8			134									
IV. RED-BLUE LESIONS																					
Pyogenic granuloma			6	3	8	7	10	6	1	5	7	8	6	3			3	1	41	33	74
Hemangioma	2	3	5	3	2		1	1		3		8	1	1		2		1	11	22	33
Thrombose venectasia/varix										1							1		1	1	2
Subtotal according to gender (FM)	2	3	11	6	10	7	11	7	1	9	7	16	7	4		2	4	2	53	56	109 (13.5%)
Subtotal according to decades	5	17	17	18	10	23	11	2	6			109									

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	0-10		11-20		21-30		31-40		41-50		51-60		61-70		71-80		81>		TOTAL of gender		TOTAL of cases
V. PIGMENTED LESIONS																					
Malignant melanoma												2						2		4	4
Compound nevus				1																1	1
Ephelis							1												1		1
Oral melanotic macul														1						1	1
Common Blue Nevus													1						1		1
Subtotal according to gender				1			1					2	1	1				2	2	6	8 (0.99%)
Subtotal according to decades		1		1		2	2		2			8									
VI. VERRUCAL-PAPILLARY LESIONS																					
Squamous papilloma /Oral verruca vulgaris	1		2	2	3	5	3	3	3	5	5	5	2		3	2			22	22	44
Focal epithelial hyperplasia			2		2	5	7	3	5	5	9	4	5	4	3	2	2		35	23	58
Inflammatory papillary hyperplasia				1		1			1	1	3	2	1	1.		2			5	8	13
Keratoacanthoma			1													3			1	3	4
Papillary hypertrophia of tongue									1		1								2		2
Verrucous carcinoma												1		1						2	2
Verruciform xanthoma	1																		1		1
Subtotal according to gender (FM)	2		5	3	5	11	10	6	10	11	18	12	8	6	6	9	2		66	58	124 (15.4%)
Subtotal according to decades	2	8	16	16	21	30	14	15	2			124									
VII. CONNECTIVE TISSUE LESIONS																					
Traumatic fibroma			5	2	2	4	8	9	8	6	12	5	13	5	4				52	31	83
Epulis	1	1	4	3	1	3	3	1	14	6	6	5	1	6	3	2	1	1	34	28	62
Peripheral ossifying fibroma	2		3	3	4	2	6	1	4	2	4		2						25	8	33
Gingival fibrous hyperplasia					1	2	1			3	3	1	2	1	1				8	7	15
Fibromatosis						1														1	1
Myxoma												1								1	1
Haemangioendothelioma									1										1		1
Neurofibroma							1				1	1							2	1	3
Lymphangioma		1				1				1		1								4	4
Granular cell tumor	1											1							1	1	2
Nodular fasciitis													1						1		1
Subtotal according to gender (FM)	4	2	12	8	8	13	19	11	27	18	26	15	19	12	8	2	1	1	124	82	206 (25.6%)
Subtotal according to decades	6	20	21	30	45	41	31	10	2			206									

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	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81>	TOTAL of gender		TOTAL of cases
VIII. LYMPHOID TISSUE LESIONS												
Lymphoid hyperplasia					1	2	1	4	1	1	1			7	4	11
Burkitt lymphoma				1											1	1
Diffuse large B-cell lymphoma									1						1	1
Subtotal according to gender (FM)				1	1	2	1	4	1	1	1		1	7	6	13 (1.6%)
Subtotal according to decades		1	1	3	5	2	1			13						
IX. PERIODONTAL DISEASES																
Nonspecific gingivitis		3		3	3	5	1	3	6	7	3	3	4	4	2	1	28	20	48
Inflammatory papillary hyperplasia		1	1		2	2		1	4	2	1		1		2		6	11	17
Amyloidosis								1			3		2	2	1		3	6	9
Subtotal according to gender (FM)		4	1	3	5	7	1	5	10	9	7	3	7	6	5	1	37	37	74 (9.2%)
Subtotal according to decades	5	8	8	15	16	10	11	1			74								
X. METABOLIC DISEASES																			
Cherubism		1															1		1
Subtotal according to gender																	1		1 (0.19%)
XI. OTHER LESIONS inc. TUMORS																			
Fibrolipomatous hamartomas				1	3	2	1					1					4	4	8
Metastatic tumors							1							1		1	2	1	3
Malignant mesenchymal tumors				1	1						1						1	2	3
Uranitis					1													1	1
Uvulitis													2					2	2
Inflammatory pseudocyst												1					1		1
Foreign body granuloma													1					1	1
Subtotal according to gender				2	5	2	2			1	2	3	1		1		8	11	19 (2.36%)
Subtotal according to decades			7	4	1	5	1	1			19								
Total according to decades	14 (1.7%)	54 (6.7%)		74 (9.2%)		107 (13.3%)		143 (17.8%)		169 (21%)		126 (15.7%)		76 (9.4%)		42 (5.2%)			805
Total according to gender																	424	381	805

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Table 2. Distribution of diagnosis types by gender

Types of diagnosis		Gender Female	Male	Total
1,00	S	16	3	19
	%	84,2%	15,8%	100,0%
2,00	S	39	59	98
	%	39.8%	60,2%	100,0%
3,00	S	71	63	134
	%		47,01%	100,0%
4,00	S	53	56	109
	%	48,6%	51,4%	100,0%
5,00	S	2	6	8
	%	25,0%	75,0%	100,0%
6,00	S	66	58	124
	%	53,2%	46,8%	100,0%
7,00	S	124	82	206
	%	60,2%	39,8%	100,0%
8,00	S	7	6	13
	%	53,8%	46,2%	100,0%
9,00	S	37	37	74
	%	50,0%	50,0%	100,0%
10,00	S	1	0	1
	%	100,0%	0%	100,0%
11,00	S	8	11	19
	%	42,1%	57.9%	100,0%
Total	S	424	381	805
	%	52,7%	47,3%	100,0%

X2=31,32 p=0,001 p<0,05 (significant). The difference was significant when the types of diagnosis were compared according to gender, (p<0,05).

Table 3. Distribution of types of diagnosis

Types of diagnosis	N	%
1	19	2,4
2	98	12,2
3	134	16,6
4	109	13,5
5	8	1,0
6	124	15,4
7	206	25,6
8	13	1,6
9	74	9,2
10	1	0,1
11	19	2,4
Total	805	100,0

X2=312,85 p=0,001 p<0,05 (significant). The difference was found significant when the distribution of diagnosis types was compared. (p<0,05).

Discussion

There are more than 600 different known diseases that are manifest in the oral cavity, apart from caries and periodontal disease (2). Oral-maxillofacial lesions (OMFLs) are so many and varied, but mostly from pre-school to young adolescents, such as pediatric (3-10), or geriatric (11-14) specific ages or risk groups (15-16), either pigmented lesions (17-18), or only on an organ base (19) such as the tongue. On the other hand, there are a few studies in the world that have at least some of the oral and maxillofacial lesions that are histologically based and included both oral lesions and patients of all ages in a comprehensive spectrum (20-27). A wide variety of lesions with different origins and heterogeneous features may develop in the oral cavity, including both benign and malignant lesions. The biopsy is one of the most important or may be the first research and diagnostic method of oral medicine and biopsy not only shows the morphological characterization of the tissue; it is also the gold standard for obtaining a definitive diagnosis in many lesions, especially malignant diseases. Everything is an estimate until the histological evaluation of the biopsy performing. Because of this, biopsy should be done in the following conditions:

The following biopsy indications were employed for soft tissue pathologies:

1. Persistent or widespread ulcerations that proved refractory to local therapy after a 3-week period;

2. Persistence of any lip or oral mucosal changes 3 weeks after removal of local irritants (e.g., traumatic or inflammatory);

3. Any new lesion noted on clinical examination;

4. Oral lesions with the recent change in size or symptoms;

5. Oral lesions with induration upon palpation;

6. New or enlarging pigmented lesions, especially those with an irregular border and non-homogenous coloration;

7. Lesions that are clinically suspected as mucocutaneous, immune- mediated or systemic disease or as potentially malignant lesions/disorders (PML/D) or malignancy (28).

The following biopsy indications were employed for hard tissue pathologies which are (i) Any new or rapid bone expansion; (ii) Bone lesions accompanied by pain, changes in sensation, or other symptoms; (iii) Rapid bone loss, spiking root resorption, tooth mobility, and irregular widening of the periodontal ligament, in the absence of trauma or an identifiable source of inflammation; (iv) Radiographic changes that are suspected as intraosseous cysts, tumors, or fibro-osseous lesions (28).

The purpose of the study was to evaluate the prevalence of oral mucosal lesions and conditions in a population in Ljubljana, capital of Slovenia. A total of 1609 subjects represented the study population in the survey about the periodontal treatment needs in a population in Ljubljana, conducted from 1983 to 1987. Ten years later the same 1609 subjects were invited to the second examination. Altogether, 555 (34.5%) of the invited subjects in the age range 25-75 years came for an interview and clinical examination at the Department of Oral Medicine and Periodontology of the Dental Clinic in Ljubljana. Oral mucosal lesions and conditions were evaluated according to the WHO Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases and Conditions. The results showed the presence of one or more mucosal lesions in 61.6% of the population. Fordyce's condition was observed the most frequently (49.7%) followed by: fissured tongue (21.1%), varices (16.2%), history of herpes labialis (16.0%), history of recurrent aphthae (9.7%), denture stomatitis (4.3%), leukoplakia (3.1%), cheek biting (2.7%), lichen planus

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(2.3%), frictional keratosis (2.2%), geographic tongue (2.2%), geographic and fissured tongue together (1.1%), mucocele (0.9%), smoker's palate (0.5%) and angular chelitis (0.4%). In the population examined, no oral malignancies were observed. Mucosal lesions like whitish lesions, denture-related lesions, fissured tongue, varices and mucocele were more prevalent with increasing age. Tobacco-related lesions (leukoplakia and smoker's palate together) were significantly more prevalent among men than among women ($p<0.05$), while lichen planus, denture stomatitis and herpes labialis occurred more frequently in the female population (20).

In an adult patient group of 500 cases, the overall incidence of oral mucosal changes or lesions was 15.5%. The lesions were classified as anatomic changes, ulcerated lesions, tongue lesions, white lesions, benign lesions, color alterations, and malignant lesions. Anatomic changes (7%), ulcerated lesions (6.6%), and tongue lesions (4.6%) were the most common lesions. White lesions were observed in 2.2% of all patients. Among the white lesions, leukoplakia was identified in men 4 times more frequently than it was in women. Benign lesions and color alterations were identified in 1.6% and 1.2% of all patients, respectively. Also, 3 patients (0.06%) were diagnosed as having squamous cell carcinoma, and 1 patient (0.02%) was diagnosed as having adenocarcinoma. There was a statistically significant relation between smoking and the occurrence of mucosal lesions whereas no relation was found between alcohol consumption and mucosal lesion occurrence. Besides, no relation was found between systemic diseases and oral mucosal lesion occurrence (21).

Data from 6,448 adult Swedish patients were collected by general dental practitioners using a standardized registration method. A total of 950 patients (14.7%) presented with some type of oral mucosal lesion and of these, 141 patients (14.8%) reported subjective symptoms. On a visual analogue scale (VAS), 43 patients (4.5%) scored their symptoms <30, 65 patients (6.8%) scored their symptoms ⩾30, and 28 patients (2.6%) scored their symptoms ⩾60. The most debilitating condition was aphthous stomatitis and the most common oral mucosal lesion was snuff dipper's lesion (4.8%), followed by lichenoid lesions (2.4%) and geographic tongue (2.2%). There was an agreement between the oral medicine specialists and the general practitioners over the diagnosis of oral mucosal lesions on the basis of a clinical photograph in 85% of the cases (n=803) (22).

A total of 3551 dentate adult Australians had complete data for this analysis. Over 20% of study participants presented with an OML on the day of examination. The prevalence of suspected malignancy was less than 1% and over 17% for non-ulcerated OMLs. Prevalence of non-ulcerated OMLs was associated with age, gender, residential location, household income, and smoking (23).

Overall 25.2% of the study participants presented with one or more white lesions. The most prevalent lesions were khat-induced white lesion (8.8%), leukoedema (5.1%), and frictional keratosis (3.9%). Potentially malignant lesions, such as lichen planus, leukoplakia, and smokeless tobacco-induced lesions, were seen in 2.4%, 1.2%, and 1.7% of participants, respectively (16).

According to Kilinc et al., under 709 benign tumors and tumor-like lesions supported by pathological diagnosis, in soft tissue related lesions, 220 of peripheral giant cell granulomas (PGCGs) were the most frequent lesions (37.4%), followed by epulis fissuratum (109: 709 = 18.5%), 50 pyogenic granulomas (50: 709 = 8.5%), 19 capillary haemangiomas (19: 709 = 3.9%), 4 cavernous haemangiomas (4: 709 = 3.4%), 3 verruca vulgaris (3: 709 = 0.5%), and 2 fibrolipomas (2: 709 = 0.3%). The ratio of males to females is approximately 3: 4 in all these lesions (24).

The analyses revealed that 1,520 (47.7%) patients were male and 1,666 (52.3%) were female. They had a mean age ± standard deviation of 47.8 ± 18.6 years. The site most frequently biopsied was the labial mucosa (17.5%). A non-neoplastic diagnosis was established in 2,162 (63.3%) cases, potentially malignant disorders in 163 (5.1%) and neoplasms in 886 (27.6%) (403 benign and 483 malignant). The most commonly reported diagnosis was fibroepithelial polyp (n = 186; 15.9%), followed by squamous cell carcinoma (SCC) (n = 158; 13.6%). SCC was the lesion most commonly found in male patients (n = 279; 18.4%) whilst fibroepithelial polyp was the lesion most commonly found in female patients (n = 268; 16.1%). The most common lesion was a follicular cyst (n = 25; 12.8%) in patients 0-17 years of age whereas in patients 18-64 years of age it was a fibroepithelial polyp (n = 299; 13%). SCC was the most common type of lesion found in patients ⩾ 65 years of age (n = 160; 24.6%) (25).

Kansky AA et al. from Slovenia, was conducted a survey upon oral mucosal lesions during the national project for oral cancer screening in spring 2017 in the Slovenia in which more than 50% of dentists participated and 2395 patients (904 men and 1491 women) were included. Results of Clinical examination, which was conducted according to the WHO standards revealed that 645 patients (27%) had oral mucosal lesions. The ten most common oral lesions detected were fibroma, gingivitis, Fordyce spots, white-coated tongue, cheek biting, linea alba, denture stomatitis, geographic tongue, recurrent aphthous ulcerations and lichen planus. Overall, these epidemiological data suggest need for specific health policies for the prevention, diagnosis and treatment of oral mucosal lesions (26).

Da Silva et al., get coverage a total of 29 studies from 1963 to 2018 in the systematic screening they collected all these epidemiological studies in 2019. The 10 of them from Asian countries, 2 of them also were of Turkey. The number of samples in these studies ranges from 255 to 39 206. The rules of the World Health Organization have been followed in terms of design, auditor training and data collection in most of the studies,-

However, approximately 25% of the studies have not determined reliability among observers. Moreover, almost half of the included studies did not report the response rate and presented the results with appropriate confidence intervals. The authors emphasized the importance of the studies, therefore, need to improve some important points

in population-based studies focusing on the prevalence of OMLs, in particular, these studies should be able to adequately report response rates and findings and, to a lesser extent, diagnostic criteria and training of auditors, to facilitate comparison of different findings (27).

Conclusion

In conclusion, the literature on the incidence and prevalence of oral and maxillofacial lesions not only raises awareness of disease patterns in populations, but is also important to emphasize the lesions most likely to be encountered by oral health professionals in their daily practice. However, the classification of oral mucosal lesions in a variety of complex forms leads to conflicts both in practice and in scientific studies, making it difficult to standardize the investigations. Therefore, OMLs should be classified according to their color and origin in terms of oral pathology and lesions of salivary glands and jaw-bones should be excluded.

We would like to emphasize the importance of standardized studies in epidemiological studies focusing on the prevalence of OMFLs and to facilitate the improvement of some key points and to compare different findings in this area.

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Author Contributions: AGS, ÖFG, HRE: project design and patient examinations, data collection and analyzes **Writing and Revisions:** AGS

Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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Prognostic value of baseline and posttreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in head and neck squamous cell carcinoma receiving chemoradiotherapy

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Abstract

Objective: The aim of this study was to evaluate the prognostic value of baseline and posttreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in head and neck squamous cell carcinoma (HNSCC) receiving chemoradiotherapy (CRT).

Material and methods: Ninety-two HNSCC patients who received adjuvant or primary radiotherapy (RT) between September 2014 and December 2019 were assessed retrospectively. Surgery was performed on 24 (26.1%) patients. Eight patients (8.7%) received induction chemotherapy (CT), 63 patients (68.5%) concomitant CT and 17 (19.5%) patients received adjuvant CT.

Results: The median follow-up time was 19 months (range 1-61 months). The median overall survival (OS) and progression-free survival (PFS) were 16 and 13 months, respectively. High baseline NLR level was found to be significantly associated with advanced T stage. Survival was significantly poor if baseline NLR cut-off was above 2.7. No significant correlation was revealed between post-RT NLR, baseline PLR and post-RT PLR and OS. Advanced T stage, presence of metastasis and high post-RT PLR were found to be significant factors that decrease PFS.

Conclusion: High baseline NLR level in HNSCC receiving CRT/RT was strongly associated with advanced T stage and poor prognosis. However, well designed, larger studies with longer follow-up are warranted.

Keywords: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), head and neck cancer, chemoradiotherapy, prognosis

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world (1). In its treatment, the cure is provided by surgery and /or adjuvant radiotherapy (RT) or primary chemoradiotherapy (CRT) (2,3). Despite this, 5-year survival rates are around 50% (4,5). Local recurrence and distant metastasis are the main causes of failure. TNM staging has been established with a certain role in determining the prognosis of the disease. The anatomic spread of tumor predicts prognosis (3-5).

Many factors such as genetic, viral infection status (HPV), hormonal and metabolic factors, autoimmunity and inflammation are blamed in the pathogenesis of head and neck cancers (HNC) (2,3). Inflammation plays an important role in tumorigenesis and tumor progression (6, 7).

The relationship between cancer and inflammation was first expressed by the German pathologist Rudolf Virchow in 1863 and has been more widely investigated for the last two decades (8, 9).

Many laboratory tests associated with the systemic inflammatory process, such as C-reactive protein, albumin, hemoglobin, white blood cell components have been investigated as prognostic and predictive markers in various cancer types. Peripheral inflammatory cells and their ratio, especially neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been demonstrated to be independent prognostic factors in some types of solid cancer (10-13). In recent years, many studies have suggested that high NLR, an increase in neutrophil level and/or a decrease in lymphocyte level, indicate a poor prognosis in HNCs (14-16).

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Based on the prediction that higher NLR and PLR are related to worse disease and poor survival, we retrospectively examined our series of HNC treated with CRT in our department. In this study, it was aimed to evaluate the independent predictor effect of NLR and PLR in patients with HNSCC receiving RT.

Material and methods

Patients Selection

Ninety-two HNSCC patients who received adjuvant or primary radiotherapy at Tokat Gaziosmanpasa University University Radiation Oncology Clinic between September 2014 and December 2019 were evaluated retrospectively. Patient interview information, patient files and electronic system data were used for the study. The demographic status, primary diagnoses, standard hemogram values, stage of the disease, treatment type, response to therapy and final status of the patients were noted.

Patients who had no bone marrow problem for any reason had normal biochemistry values and had complete file information and follow-up's were included in the study. Patients with secondary malignancy in the last five years, who have previously received RT in the head and neck region, and those under 18 years were excluded. In addition that, the patients with the use of drugs that have a direct effect on white blood cell (WBC), such as steroids, or infected patients were excluded from the study. Hemogram values within 7 days before RT were noted for baseline NLR.

Treatment Details

All patients were evaluated at the multidisciplinary treatment council before treatment. Patients were staged according to AJCC TNM staging classification (8th edition). With the Varian Clinac DHX Linac device, RT was delivered to the patients a total dose range 60-70 Gy in 30-35 fraction with IMRT technique. Cisplatin (40 mg/m2) weekly was administered to 68.5% of the patients simultaneously with RT. Patients were invited to the 3-month controls after treatment and their tests were performed.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)

According to the results of peripheral blood evaluation, NLR was calculated as absolute neutrophil/absolute lymphocyte count and PLR was calculated as absolute thrombocyte count/absolute lymphocyte count. ROC curve analysis was used for the cut-off value.

The primary endpoints

The primary endpoint of the study was whether NLR and PLR affect overall survival (OS) and progression-free survival (PFS). The endpoint for the OS was the exitus date for the dead patients and the last control date for the surviving patients. The endpoint for PFS was the progression date for patients progressing, the last control date for surviving patients, and the exitus date for the deceased.

The study was conducted in accordance with Helsinki declaration and this was approved by the Institutional Ethics Committee of Gaziosmanpaşa University.

Statistical Analysis

For the statistical analysis, SPSS 24 (IBM Corp., Armonk, NY) was used. The categorical demographic characteristics of the patients were calculated with Chi-square and Fisher's exact test. In the survey analysis, Kaplan Meier was utilized and compared with the log-rank test. Also, Cox proportional hazards model was employed in multivariate analyzes. A $p \leqslant 0.05$ was considered as statistically significant. The receiver operating characteristic (ROC) curve (AUC) test was used for the predictive value of PLR, NLR and other hematological parameters. Hazard ratio (HR) and 95% confidence interval (CI) values of statistically significant parameters were noted. If HR> 1, it is accepted that there is an increased relative risk according to the reference category.

Results

Patient characteristics

The median follow-up period of 92 patients with HNSCC who received RT was 19 months (range 1-61 months). The median age was 62 years (range, 25-88 years) and 75 (81.5%) patients were male. Surgery was performed on 24 (26.1%) patients. Eight patients (8.7%) received induction chemotherapy (CT), 63 patients (68.5%) concomitant CT and 17 (19.5%) patients received adjuvant CT. The patients with clinical T3 (cT3) tumors were the most frequently observed with 33 patients (35.9%); There were 43 (46.7%) patients with lymph-node negative and only 2 (2.2%) patients with metastatic disease. The patient and characteristics are shown in Table 1 in detail.

While 67 patients (72.8%) were alive during the follow-up period, 25 (27.2%) died. Local recurrence was observed in 11 (12%), distant metastasis in 5 (5.4%) and local recurrence + distant metastasis in 3 (3.3%) patients. The median OS was 16 months (1-61 months). The 1-year, 2-year and 3-year OS rates were 81.6%, 73.4% and 65.3%, respectively. The median PFS was 13 months (range 1-61 months). The 1-year, 2-year and 3-year PFS rates were 72.8%, 66% and 52.2%, respectively.

Overall survival and NLR/PLR relation

The relationship between OS and the variables was evaluated by COX regression analysis (Table 2). The relationship between OS and cT stage and baseline NLR was found to be significant. The median OS for cT1-2 patients was 24 months (range, 3-61 months), while for patients with cT3-4 was 11 months (range, 1-57 months) (p0.005) (Figure 1).

The median OS was 17 months (range,1-61 months) in the patients with baseline NLR cut off value $\leqslant 2.7$, whereas the median OS was 13 months (range,1-58 months) in the patients with baseline NLR cut off value >2.7 (p0.046) (Figure 1).

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As a result of ROC curve analysis, a significant correlation was detected between baseline NLR and OS. For the threshold value NLR 2.7, sensitivity was 66.7% and specificity was 42.6%. (p0.024; AUC 0.65; 95% Confidence Interval: 0.534-0.782) (Figure 2). As a result of the ROC curve analysis for post-RT NLR, baseline PLR and post-RT PLR, no significant correlation was observed between all these variables and OS (Table 3).

Progression-free survival (PFS) and NLR/PLR relation

The relationship between PFS and the variables was evaluated by COX regression analysis. PFS was found to be significantly associated with cT stage, metastasis status and post-RT PLR (Table 4).

The median PFS was 17 months (range, 2-61 months) in the patients with cT1-2, while 5 months (range, 1-53 months) in the patients with cT3-4 (p0.007) (Figure 3).

The PFS was 2 and 8 months in two patients who had metastasis and the median PFS was 16 months (range, 1-61 months) in the remaining patients without metastasis (p0.021) (Figure 3). The median PFS was 18 months (range, 1-58 months) in the patients with post-RT PLR ⩽ 326, whereas 5 months (range, 1-61 months) in the patients with post-RT PLR >326 (p 0.050) (Figure 3).

As a result of ROC curve analysis for PFS, there was no significant correlation between baseline NLR, post-RT NLR, baseline PLR, post-RT PLR and PFS (Table 5). In ROC curve analysis, there was no significant result between post-RT PLR and PFS. However, when cox analysis was performed, the result was close to the limit of significance (p0.42; AUC 0.55; 95%Confidence Interval: 0.424-0.682) (Figure 4). In order to clarify this situation, longer follow-up required and more patients should be included in the study.

Table 1. Patient characteristics

Age	**Median (range)** **65> N (%)** **65≤ N (%)**	**62 (aralık 25-88)** **56 (60.9%)** **36(39.1%)**
Gender, N (%)	Female Male	17(18.5%) 75(81.5%)
Oncological Surgery	No Yes	68(73.9%) 24(26.1%)
Induction CT	No Yes	84(91.3%) 8(8.7%)
Concurrent CT	No Yes	29(31.5%) 63(68.5%)
Adjuvant CT	No Yes	17 (19.5%) 75 (81.5%)
Site of primary tumor, N (%)	Nasopharynx Hypopharynx Larynx-Glottis Larynx-SupraGlottis Larynx-SubGlottis OralCavity Unknown Primary	22(24.4%) 1(1.1%) 23(25.6%) 22(24.4%) 4 (4.4%) 14(15.2%) 1(1.1%)
cT Stage	cT1 cT2 cT3 cT4	23(25%) 18(19.6%) 33(35.9%) 18(19.6%)
cN Stage	cN0 cN1 cN2 cN3 Missing	43 (46.7%) 8(8.7%) 33(35.9%) 2(2.2%) 6(6.5%)
Metastasis	No Yes	90(97.8%) 2(2.2%)
NLR	Baseline Post-RT	2.73(1.05-18.0) 5.2(1.6-13.75)
PLR	Baseline Post-RT	134(25-430) 326(35-771)

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Table 2. Cox regression analysis of OS

		HR (95% CI)	p
Age	65<, N (%)	1.71(0.77-3.97)	0.18
Gender	Male vs female	1.62(0.63-4.14)	0.30
Operation	Opereted vs non-opereted	0.20(0.013-3.37)	0.26
Clinic T Stage	cT1-2 vs cT3-4	3.80(1.49-9.72)	0.005*
Clinic N Stage	cN0 vs cN1-3	0.78(0.34-1.79)	0.57
Metastasis	Yes vs no	0.047(0.041-0.87)	0.58
Baseline NLR	2.7 lower vs higher	2.38(1.09-5.79)	0.046*
Post-RT NLR	5.2 lower vs higher	1.06(0.29-3.82)	0.92
Baseline PLR	134 lower vs higher	1.25(0.52-2.97)	0.60
Post-RT PLR	326 lower vs higher	1.97(0.84-4.63)	0.11

CI confidence interval, HR hazard ratio, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

Table 3. ROC analysis of PLR and NLR for overall survival

	Cut off	AUC	95% CI	p
Baseline NLR	2.7	0.65	0.534-0.782	0.024*
Post-RT NLR	5.2	0.61	0.487-0.745	0.16
Baseline PLR	134	0.52	0.394-0.657	0.71
Post-RT PLR	326	0.59	0.469-0.726	0.17

CI confidence interval, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

Table 4. Cox regression analysis of PFS

		HR (95% CI)	
Age	65<, N (%)	1.95(0.97-3.91)	0.059
Gender	Male vs female	1.54(0.69-3.54)	0.29
Operation	Opereted vs non-opereted	0.20(0.145-1.65)	0.96
Clinic T Stage	cT1-2 vs cT3-4	2.72(1.30-5.69)	0.007*
Clinic N Stage	cN0 vs cN1-3	0.83(0.41-1.69)	0.62
Metastasis	Yes vs no	5.58(1.291-24.144)	0.021*
Baseline NLR	2.7 lower vs higher	1.56(0.771-3.168)	0.21
Post-RT NLR	5.2 lower vs higher	1.62(0.79-3.34)	0.18
Baseline PLR	134 lower vs higher	1.37(0.68-2.76)	0.36
Post-RT PLR	326 lower vs higher	2.02(1.03-4.09)	0.050*

CI confidence interval, HR hazard ratio, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

Table 5. ROC analysis of PLR and NLR for progression-free survival

	Cutt off	AUC	95%Confidence Interval	p
Baseline NLR	2.7	0.60	0.480-0.728	0.10
Post-RT NLR	5.2	0.57	0.443-0.701	0.28
Baseline PLR	134	0.46	0.342-0.589	0.59
Post-RT PLR	326	0.55	0.424-0.682	0.42

CI confidence interval, RT radiotherapy, NLR neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *statistically significant

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Figure 1. The relation between OS and baseline NLR/ cT stage

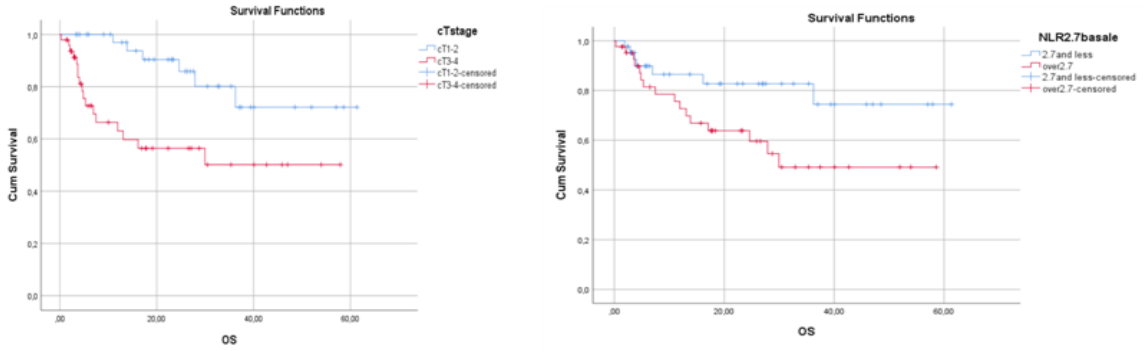


Figure 2. The relation between OS and baseline NLR in ROC analysis

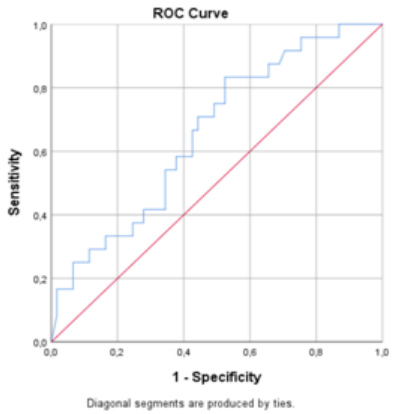


Figure 3. The relation between PFS and cT stage/ metastasis status/post-RT PLR

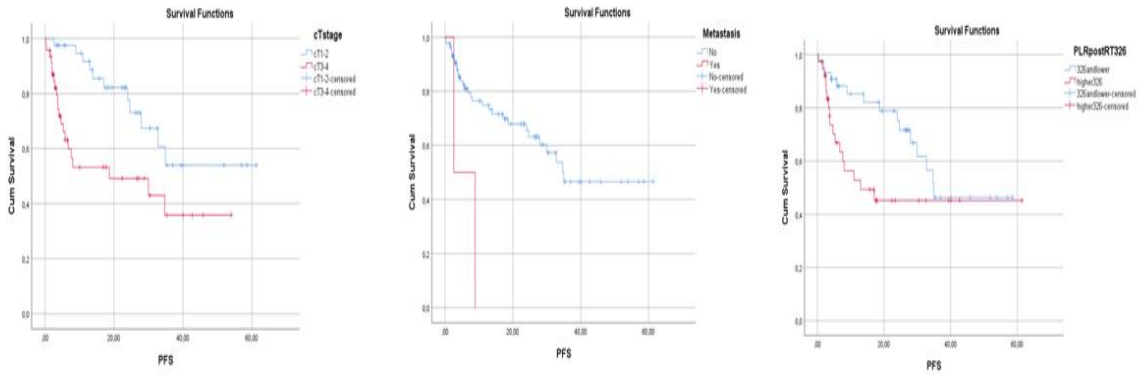
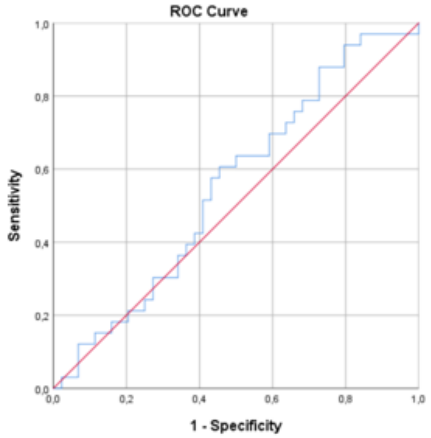


Figure 4. The relation between PFS and post-RT PLR in ROC analysis



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Discussion

The tumor microenvironment has an important role in tumor proliferation, invasion and metastasis. The two main factors associated with tumor microenvironment are tumor oxygenation and antitumoral immunity, which increase the sensitivity of the tumor to radiation. Immunity, inflammation and cancer are intertwined concepts (17,18). Based on this, many inflammatory markers have been investigated in terms of being prognostic and predictive recently. In particular, hematological parameters are valuable not only because they can be easily done in almost all centers, but also because they give an idea of tumor oxygenation and systemic inflammation. In the present study, we retrospectively analyzed the hematological markers of 92 patients with HNSCC before and after the RT or CRT. As a result of our study, high baseline NLR level was found to be significantly associated with advanced T stage. Survival was significantly poor if baseline NLR cut-off was above 2.7. No significant correlation was revealed between post-RT NLR, baseline PLR and post-RT PLR and OS. Advanced T stage, presence of metastasis and high post-RT PLR were found to be significant factors that decrease PFS. The median PFS was 18 and 5 months below and above post-RT PLR 326, respectively. According to the ROC curve analysis of our study, baseline NLR/PLR and post-RT NLR/PLR levels were not prognostic for PFS, whereas solely baseline NLR was displayed to be a significant prognostic marker for OS.

In the study of Haddad et al. they evaluated 46 advanced stage HNC patients treated with CRT, a significantly better 2-year OS was reported if NLR <5 (16). In the study on oral cavity tumors with 400 patients in which median follow-up time was 36 months, Malik et al found that NLR and PLR values are predictive for treatment results and survival (NLR cut off 2.5, PLR cut off 100) (19). In another study conducted with 153 patients with p16-negative squamous cell carcinoma of unknown primary in Head and Neck, the pre-operative NLR >6 was associated with poor prognosis (20). In the study of Lai et al, 126 local advanced HNC patients receiving induction CT was evaluated and NLR was reported to be prognostic for evaluating the response to induction CT (21). In their meta-analysis Yang et al. evaluated 6847 patients in 2019, NLR was reported to have a significant prognostic value for disease-free survival (DFS), cancer-specific survival (CSS) and PFS, but no significant effect for PLR (22). Similarly, in our retrospective series of 92 patients, we also demonstrated that baseline NLR was a prognostic marker, but PLR was not prognostic.

In the other study with 167 p16-positive oropharyngeal squamous-cell carcinoma patients treated with CRT, both NLR and anemia have been shown as prognostic (23). Significantly higher disease recurrence was observed in patients with NLR> 5 (23). In a retrospective study including 120 patients with hypopharyngeal cancer who received definitive CRT, the prognostic role of pretreatment serum NLR was investigated. The NLR has been shown as both independent prognostic and predictive of the CRT response, with a cut off 4. The high pretreatment NLR level was correlated with poor treatment response and reported to be prognostic for PFS (24). In the present study, the prognostic significance of both pretreatment and posttreatment NLR/PLR were examined. Similar to the many studies mentioned above, only pretreatment NLR (cut off 2.7) was found prognostic for OS. However, any correlation between OS and posttreatment NLR could not be demonstrated. Contrary to, Kim et al (25) reported that posttreatment NLR elevation was also associated with poor prognosis in their study with 104 HNSCC patients treated with CRT (25).

The study examining the prognostic significance of PLR was conducted with 247 patients with nasopharyngeal cancer who received CRT (26). Similar to our study, when NLR and PLR were analyzed with curve analysis, NLR was shown to be independent prognostic for OS and PFS but PLR was not prognostic (26).

The limitations of the study were that it was retrospective and performed with a heterogeneous group at a single-center. Furthermore, if the follow-up time was long, analysis of whether PLR is a prognostic marker could have been significant results.

Conclusion

High baseline NLR level in HNSCC receiving CRT/RT was strongly associated with advanced T stage and poor prognosis. Significantly worse PFS was also found at high post-RT PLR level. However, well designed, larger studies with longer follow-up are warranted.

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Author Contributions: **P**roject design, patient examination, biochemical analayzes, data collection and analyzes; GGA, IPA**, Writing and Revisions:** GGA

Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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Inflammatory biomarkers in the young stroke population

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Abstract

Objective: Studies showed that cerebral ischemia due to arterial occlusion is related to local inflammation. Neutrophil to Lymphocyte Ratio (N/L) and Monocyte to high density lipoprotein Cholesterol Ratio (M/H) are two biomarkers that are shown to be increased in inflammation. These biomarkers can be used to determine the risk for atherosclerotic ischemic stroke. Increased Homocysteinemia (Hcy) is also a risk factor for ischemic stroke, especially in the young population. There is insufficient data in the literature about the correlation of these biomarkers in young stroke patients.

We aimed to show if these biomarkers can be related to atherothrombotic cerebrovascular disease in the young population to provide information for young people to stroke risk.

Study design and method: This retrospective study included 43 atherosclerotic ischemic young stroke patients, age between 18- 55 years and age/ gender matched 42 healthy control group. Control group were enrolled from patients who were admitted to our outpatient clinics with headaches, having normal examinations and no other diseases.

Results: The ratios of N/L and M/H were both higher in the stroke group (p=0.008 and p=0.011 respectively), but the gender subanalysis showed there was no significance in the males. When the patients were sub-grouped as having hyper Hcy or not; these ratios did not show any significance.

Conclusion: Inflammatory biomarkers should be interpreted carefully by concerning the age and the gender of the patients. Further studies with large sample groups are necessary for the biomarkers of young stroke population.

Keywords: stroke, young adult, gender, inflammation, biomarkers

Introduction

Stroke is one of the leading causes of death and is also a major cause of disability(1). In the literature the upper age of “young stroke” is very variable and is accepted in the range of 45-60 years in various studies(2), (3).Hypertension, diabetes, hyperlipidemia, cardiac embolism, cervical arterial dissection and hyperhomocysteinaemia are some of the known risk factors of the young stroke patients and in 30% of the patients the etiology is unknown(3)–(5). Since the disability in young people has a greater effect on both the patients and their families as wellas on the economy it is important to provide primary protection by defining the risk factors.

Studies showed that cerebral ischemia due to arterial occlusion is related with local inflammation (6), (7). Neutrophil to Lymphocyte Ratio (N/LRatio) is a marker, which can be evaluated with a simple blood count, can show overall inflammatory status of the body (8).Celiktepe et al. found N/L Ratio higher in atherothrombotic acute cerebral ischemia and concluded that there is a positive association between N/L Ratio and clinical outcome in acute ischemic stroke (6).

Increased level of monocyte to high-density lipoprotein Cholesterol Ratio (M/HRatio) was also suggested to be a biomarker of inflammation(9), (10). However there is no defined universal normal ratio. Forget et al. studied the normal value of N/L Ratio and they suggested a mean N/L Ratio as 1.65(11).

Demethylation of methionine, an essential amino acid, is a form of the four-carbon aminoacid homocysteine (Hcy). Its normal range is between 5-15 µmol/L and above 15 µmol/L is accepted as hyperhomocysteinaemia, which may be due to deficiency of vitamin B12, B6, folate, smoking, impaired renal function, aging and C677T homozygote mutation of 5,10 methylenetetrahydrofolate reductase (MTHFR) (12). Atherosclerosis and atherothrombotic disease is associated with hyper Hyc. Increased Hcy is a risk factor for ischemic stroke and one study showed that it was an independent stroke risk factor in 30% of Malaysian Patients (13).

According to theliterature, N/L ratio, M/H ratio, and Hyper Hyc play role in the atherosclerotic cerebral ischemia and these biomarkers may be used to determine the risk of stroke .

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To our knowledge, there is insufficient data in the literature about the correlation of these biomarkersin young stroke patients. In this study, we aimed to show if these biomarkers can be related to atherothrombotic cerebrovascular disease in the young population in order to provide information to detect young people under-stroke risk by using simple blood tests andhelp clinicians to lead them for further evaluation for primary protection of stroke.

Material and Methods

This is a retrospective study that included patients between January 2019 and March 2020 at Prof Dr. Cemil Tascioglu City Hospital and Ozel Acibadem Taksim Hospital Neurology Clinics. A total of 43 young stroke patients, age between 18- 55 years and age and gender-matched 42 healthy group were enrolled. Stroke patients were consisted of atherosclerotic ischemic cerebral ischemia. The transient ischemic attack, cardioembolic stroke, venous ischemia, recurrent stroke, and hemorrhages were excluded. Stroke diagnosis was based on clinical evaluation (acute onset of neurological deficit) and acute infarct seen on diffusion Magnetic Resonance Imaging (MRI). Patients with underlying infectious diseases, rheumatoid diseases, malignancy, other neurological diseases, and renal insufficiency (glomerular filtration rate <90 ml/mn) were also excluded. All stroke patients were screened by biochemical analysis, cerebral MRI, carotid-vertebral arterial Doppler ultrasonography, 12-lead ECG (24 Hour ECG if necessary). Control group were enrolled from patients who admitted to our outpatient clinics with headache and had normal neurological examination and normal cranial MRI and had no other systemic diseases. Fasting blood samples were taken between 8-12 am. Patients were accepted as hypertensive if the blood pressure was over 140 mmHg systolic and/or over 90 mmHg diastolic. Positive story of diabetes was accepted if there was use of diabetic medicine or fasting blood glucose level is over 125 mg/dl or Hba1c level is greater than 6%. Hyper Hcy was defined as Hcy level greater than or equal to 13µmol/L, since this was the cut-off value of our laboratory. Cases with a body temperature over 37.5 degrees Celsius and/or high Sensitive C reactive protein (CRP) over 0.5 mg/dL were considered to have acute infection and they were not included to the study. All stroke patients were evaluated with electrocardiogram (ECG) and echocardiography in order to exclude a possible cardioembolic source. Carotid and vertebral arterial doppler evaluation were done to all stroke patients and so arterial dissection was also excluded.

Our study has the approval of the institutional ethical committee (315/14.7.2020).

Statistical Analysis: The statistical analysis has been performed with IBM SPSS for Windows version 22.0. Numerical variables were given as mean±standart deviation or as median (25.-75. Percent)values. Categorical variables were shown as numbers and percentages. Ki square test or Fisher's test were used to showing any difference between the categorical variables of the groups. Kolmogrov Smirnov test was used to see if the numerical variables showed a normal distribution and the homogeneity of the variants was tested with the Levene test. T-test was used to show any numerical difference between two independent groups, if the parametric test conjectures were provided and if the conjectures were not provided then Mann Whitney U test was used. Statistical significance was accepted as $p<0.05$.

Results

This study involved 43 young stroke patients and 42 headache patients with the normal neurological examination to form the control group.There was no statistical difference between the groups (p=1). Figure 1 shows the gender distribution of the groups.

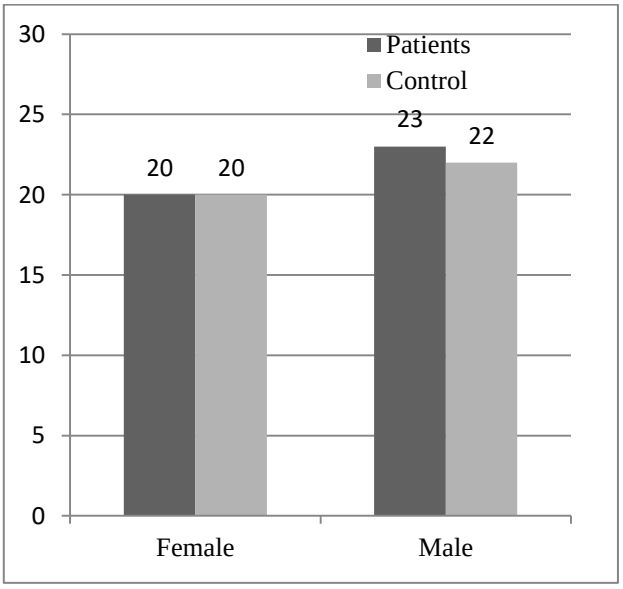

Figure1: Gender distribution of the groups

The ratios of Neutrophil to Lymphocyte (N/L) and monocyte to high-density lipoprotein Cholesterol (M/H) were both higher in the stroke group. This finding was statistically significant (p=0.008 and p=0.011 respectively). These differences of the N/L and M/H ratios between the groups were also analyzed according to the genders. There was no significance in the males but in the females, both ratios were higher in the stroke patients (Table 1 and 2).

Hyper Hcy was defined as a value equal to or greater than13µmol/L. When the patients were sub grouped as having hyper Hcy or not; the N/L and M/H ratios did not show any significance (Table 3). Also, there was no significance within the genders.

Metabolic factors (B12, folate, and GFR levels) that can affect Hcy level were investigated in the patients' group; between the cases who had Hcy< 13 µmol/L and⩾13 µmol/L. There were no significant differences of mean GFR and folate levels (Table 4), but the B12 level was significantly related to the higher Hcy level (Table 4).

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Table 1: N/L and M/H comparison of the groups

GROUP		N/L	M/H
PATIENTS	**N**	43	43
	Average	2.5 ± 1.17	16.65 ± 11.03
	Minimum	0.87	5.42
	Maximum	5.81	72.73
CONTROL	**N**	42	42
	Average	1.86 ± 0.68	12.33 ± 5.19
	Minimum	0.99	4.78
	Maximum	3.63	23.23
	p	**0.008**	**0.011**

Table 2: N/L and M/H comparison of the groups according to genders

	GENDER		N/L	M/H
FEMALE	PATIENTS	**N**	20	20
		Average	2.65 ± 1.05	18.40 ± 15.30
		Minimum	1.03	5.63
		Maximum	5.1	72.73
	CONTROL	**N**	20	20
		Average	1.93 ± 0.62	10.11 ± 4.74
		Minimum	0.99	4.78
		Maximum	2.98	21.16
		p	**0.013**	**0.001**
MALE	PATIENTS	**N**	23	23
		Average	2.36 ± 1.27	15.14 ± 5
		Minimum	0.87	5.42
		Maximum	5.81	29.00
	CONTROL	**N**	22	22
		Average	1.79 ± 0.74	14.35 ± 4.83
		Minimum	1.00	5.54
		Maximum	3.63	23.23
		p	**0.086**	**0.570**

Table 3: Comparison of N/L and M/H ratios according to Hcy levels.

	GENDER		N/L	M/H
FEMALE	Hcy < 13µmol/L	**N**	3	3
		Average	2.27 ± 0.13	35.62 ± 32.44
		Minimum	2.14	12.62
		Maximum	2.41	72.73
	Hcy ≥ 13µmol/L	**N**	17	17
		Average	2.71 ± 1.12	15.35 ± 9
		Minimum	1.03	5.63
		Maximum	5.10	47.69
		p	**0.616**	**0.118**
MALE	Hcy < 13µmol/L	**N**	11	11
		Average	2.55 ± 1.64	14.58 ± 5.13
		Minimum	0.87	5.42
		Maximum	5.81	21.94
	Hcy ≥ 13 µmol/L	**N**	12	12
		Average	2.17 ± 0.85	15.65 ± 5.05
		Minimum	1.18	10
		Maximum	4.33	29
		p	**0.786**	**0.976**

Table 4: Comparison of metabolic factors between the cases having Hcy< 13 µmol/L and ≥ 13 µmol/L

Metabolic Factor	Hcyµmol/L	N	Mean	Std. Deviation	p
GFR	< 13	14	105.37	12.13	0.47
	≥ 13	29	101.51	18.26	
Folate	< 13	14	7.86	2.35	0.21
	≥ 13	29	6.68	3.13	
B12	< 13	14	237.21	89.98	**0.01**
	≥ 13	29	172.17	71.94	

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Discussion

Atherosclerotic cerebral ischemia is related to local inflammation and it is shown that higher N/L ratio is associated with atherothrombotic acute cerebral ischemia(6). M/H ratio is also a biomarker ofinflammation and in a recent study M/H ratio showed an association with the odds of having ischemic stroke(9), (10),(14).

In this study it is found that both ratios were higher in the stroke patients when compared to the control group. This finding is in line with previous studies. When we compared the ratios in the gender subgroup we found that these ratios were significant in the female; but not in the male gender. The reason for this finding may be the difference of inflammatory reaction in opposite genders.

It is shown that, in some regions, healthy females may have higher N/L ratio, especially in the young population (age under 50 years)(15)–(17). Estrogen decreases during menopause and this hormonal change affects neutrophils and inflammatory response(18). In a study, which has investigated the gender difference in the inflammatory response in stomach cancer patients; preoperative blood tests showed similar N/L ratios between males and females, but postoperative tests showed a higher N/L ratio in the females, because of increased neutrophils and decreased lymphocytes. It is concluded in the paper that the females showed more immune-compromised pattern of immune cells after gastric surgery (19). To the best of our knowledge, there are no studies of N/L and M/H ratios, concerning only young stroke patients and subgrouping genders. We conclude that gender difference and age are two factors that must be considered while interpreting N/L ratio in stroke patients and more studies with larger sample groups are needed.

Inflammation and lipid abnormalities are two factors that are considered in the pathophysiology of atherosclerosis (20), (21). Since monocytes increase during inflammation and HDL decreases in atherosclerosis, it is expected that M/H ratio would increase and in a recent paper, this ratio is studied in stroke patients. It is found that M/H ratio is an independent predictor of ischemic stroke (14).

In this study, it is found that M/H ratio was increased only in the female gender. One of the explanations of this gender difference is the difference of inflammatory response, similar with the N/L ratio in the females, as discussed before. Another explanation may be the difference between the HDL levels of the healthy cases and patients, so we also compared the HDL levels between the groups. When bothgenders were included in the analysis, the mean HDL level of the patients was 38.74±8.16 and the controls' were 48.02±12.63 (p=0.0001). This difference was greater in the female gender (37.45±6.33 and 54.5±14.09; p=0.00001) and no significant difference was present in the male gender (39.86±9.46 and 42.13±7.44; p = 0.37). This significantly lower HDL level in the patient group, especially in the female gender, is preventing us to come to a definite conclusion of the increased inflammatory response in the young stroke patients.

Future studies must be planned with sample groups having similar HDL levels in order to see the relation of M/H ratio and ischemic stroke in the young population.

Strong association is shown in a recent study between young stroke patients and hyper Hcy especially in male patients between 36-45 years of age (22). There is still a controversy in the literature about which stroke subtype is related with the hyper Hyc, but studies support a relationship between large artery atherosclerosis and increased levels of Hyc (22), (23).

We tried to investigate any relation between hyper Hcy and inflammatory biomarkers, N/L and M/H ratios. During the literature research, we found only one study investigating the relation between hyper Hcy and N/L ratio in hypertensive patients (5). In the study, the authors found a correlation between hyper Hcy and N/L ratio. However,we were unable to find the same correlation in our study in both genders. Metabolic factors (B12, folate, and GFR levels) that can affect Hcy level were investigated in the patients group; between the cases who had Hcy< 13 µmol/L and⩾13 µmol/L. There were no significant differences of mean GFR and folate levels, but the B12 level was significantly related with the higher Hcy level (Table 4). The literature does not have enough studies to come to a conclusion about the relationship of Hcy and inflammatory biomarkers, especially for the young stroke patients. More studies with larger sample groups may provide more certain results.

Conclusion

This study has several limitations such as the number of the cases included is not enough for a definite conclusion for the whole young stroke population. We don't know the exact smoking histories of the patients and the control groups since this data was not available for the most of the cases and smoking is a separate risk factor for both ischemic stroke and hyper Hcy. On the other hand this study contributes to the literature in the perspective of concerning only young stroke patients. There is very limited data of the inflammatory biomarkers for the young population and again there are few studies investigating the biomarkers according to the genders. We can conclude that N/Lratio should be interpreted carefully by concerning the age and the gender of the patients. Hcy seems not to play a role in the inflammatory biomarkers and M/H ratio should also be evaluated carefully with significantly lower HDL levels. Finally, we think further studies with large sample groups are necessary for the biomarkers of young stroke population.

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Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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Leiomyosarcoma of the extremity deep soft tissues: analysis of factors predictive of survival and imaging features

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Abstract

Objective: This study aimed to report the visual outcomes of deeply located Leiomyosarcoma (LMS) in the extremities and treatment results.

Methods: The histological diagnosis of each case was confirmed by the pathology council and only cases with LMS localized in the deep soft tissue of the limb were included in this study. Treatment-related factors such as all the visual features of the tumor, type of therapy, local and distant recurrence, follow-up time, and outcome were analyzed. Overall survival time was determined.

Results: Evaluation was made of 17 patients, comprising 11 females and 6 males with a mean age of 64.35 years (range, 52-75 years). The localization of the primary lesion was the lower extremity in 14 patients (82.34%), and the upper extremity in 3 (17.34%). The average size of the lesions was 8.23 cm (range, 3-22 cm). All lesions were staged according to the TNM Classification of soft tissue sarcomas, as 3 (17.64%) patients in stage IIA, 9 (52.94%) in stage IIB, and 5 (29.41%) in stage IV. In the radiological features of the lesions, only two patients had scattered calcification and osseous pathology in the tumor tissue. The signal properties obtained in other soft tissue sarcomas on magnetic resonance images (MRI) were also present in these lesions. Neoadjuvant chemotherapy was applied to 5 of 17 patients, and surgical and adjuvant radiotherapy was applied to the remaining 12 patients. These patients were followed up for an average of 66 (23-111) months. Local recurrence occurred in 3 patients. The five-year disease-free survival rate was 58.8%, and the disease-survival rate was 64.7%.

Conclusion: The most important result of this study was that the only effective factor on overall survival is tumor size ($p < 0.001$). Neoadjuvant chemotherapy was not seen to have any significant effect on this disease.

Keywords: Leiomyosarcoma, deep soft tissues, cancer

Introduction

Leiomyosarcoma (LMS) is a malignant neoplasm characterized by histological differentiation of smooth muscle cells and is divided into three groups as cutaneous LMS, gastrointestinal and uterine LMS, and somatic LMS (1). These three groups should be considered as separate clinical entities due to different clinical behavior, different treatment, and different prognosis. Somatic LMS is often seen in the retroperitoneum, the soft tissue of the extremities, blood vessels, and occasionally in the bone. Although a rarely diagnosed tumor in the past, this sarcoma has started to be diagnosed more frequently with advances in histological diagnosis, especially in immunohistochemistry. Nevertheless, despite all these advances, histological diagnosis is still difficult because of the heterogeneity of soft tissue sarcomas, (2-4).

It is currently claimed that LMS constitutes 8-16% of non-visceral soft tissue sarcomas, but there is limited information about these tumors seen in deep soft tissues of the limbs (5,6). Although there is currently a relative increase in incidence, there are not enough data about the visual properties and treatments of these sarcomas localized in deep soft tissue, especially in the extremities. Wide resection has been specified as the gold standard for the treatment of these tumors, but there is no consensus on the treatment modality. In particular, controversy continues over the effects of adjuvant treatments and the way they are applied. This study aimed to present information about the visual properties, treatments and clinical outcomes of LMS with deep soft tissue location in a limb of 17 cases treated and followed up in our clinic.

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Material and Methods

The histological diagnosis of each case was taken into consideration by the pathology council and the LMS included in this study were histologically confirmed and localized in deep soft tissue that had not previously been exposed to radiotherapy. All tumors included in the study were confirmed based on positive immunohistochemical staining (IHCS) for smooth muscle actin and desmin, and morphology showing smooth muscle differentiation. Data were recorded of patient gender, age at the first visit, location of the primary tumour, tumor size, staging, and the presence of metastasis at the time of diagnosis. The analysis was also made of treatment-related factors, including all the visual features of the tumor, local therapy type, systemic chemotherapy, local and distant recurrence, follow-up time and outcome. Overall survival and disease-free survival time were determined.

The study was approved by the Local Ethics Committee and the procedures adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

Results

The evaluation was made of 17 patients with LMS located in limb deep soft tissue, diagnosed between 2002 and 2018. From the initial enrolment, 5 patients were excluded due to the lack of a final follow-up examination or specimens were determined as suspected diagnosis by the council, and 1 patient who started neoadjuvant chemotherapy but underwent amputation due to the progression of the tumor. The 17 patients comprised 11 females and 6 males with a mean age of 64.35 years (range, 52-75 years). On first presentation, all patients had complaints of swelling and pain. The primary lesion was localized in the lower extremity in 14 patients (82.34%), in the thigh region in 11 (64.70%), and the lower leg in 3 (17.34%). The primary lesion was located in the upper limb in the arm area in 3 (17.34%) patients. All lesions were staged according to the TNM Classification of soft tissue sarcomas, as 3 (17.64%) patients in stage IIA, 9 (52.94%) in stage IIB, and 5 (29.41%) in stage IV. Tumor size (in cm) was defined as the largest size of the tumor in the surgical sample reported by pathologists. The average size of the lesions was 8.23 cm (range, 3-22 cm).

Radiological properties

X-ray: Scattered calcification and severe destruction of the distal femur were detected in the tumor tissue of 2 patients. In one patient, new cortical bone formation was noted in the distal femur secondary to the large soft tissue mass. This patient had minimal cortical destruction and no medullary invasion. A pathological fracture was determined in one patient (Figure 1).

CT: Changes in bone tissue were determined in 2 patients. In addition to a very large soft tissue mass, one of these patients had new cortical bone formation and minimal cortical destruction in the distal femur, and no medullary invasion. The other patient had cortical destruction, medullary infiltration, and pathological fracture in addition to the large soft tissue mass. No appearance of calcification or ossification was observed in any of the other 15 patients.

MRI: MRI was obtained from all patients, including T1A, T2A, fat-suppressed sequences, and contrast images. The lesions were seen to have relatively regular borders and intramuscular localization. There were signals of medium to low on T1-weighted images and heterogeneous hyperintensity on T2-weighted images. Heterogeneous hyperintense signals were dominant on fatty images. Hyperintense signals were received, especially in the central area of the lesion. High contrast agent uptake was seen on the contrast images, with more evident contrast involvement in the periphery of the lesions, and minimal or absent involvement in the central regions (Figure 2,3).

Treatment type

Of the 17 patients included in the study, 5 received neoadjuvant therapy. RT was administered to these 5 patients in addition to chemotherapy. In total, 5 patients were using ifosfamide, doxorubicin, gemsutab, and docetaxel chemotherapeutic agents. In the remaining 12 patients, the only radiotherapy was applied as an adjuvant in their first treatment.

The surgical margin was defined according to the International Cancer Control Association (UICC) classification. Accordingly, resection was performed as R0 in 14 patients, R1 in 2 patients, and R2 in 1 patient. In 2 cases with secondary bone invasion of a soft-tissue leiomyosarcoma, tumor prosthesis was applied. The necrosis rate of patients receiving neoadjuvant therapy was 45% (40-60%) on average, histopathologically. No tumor necrosis rate was obtained over 90% in the resected specimen of any patient.

All 12 patients with localized disease had at least two operations. One of these patients went to amputation. All five patients with distant metastases at the time of admission did not receive secondary surgery due to advanced age and comorbidity.

Oncological results

These patients were followed up for an average of 66 (14-111) months. Local recurrence occurred in 3 patients, 2 of which had distant metastasis at the first presentation. All of these patients had both chemotherapy and radiotherapy. The surgical margins of patients with local recurrence were R0 in one and R1 in two. The five-year disease-free survival rate was 58.8%. The disease survival rate was 64.7%. All patients with metastasis died within an average of 18 (14-49) months from first admission.

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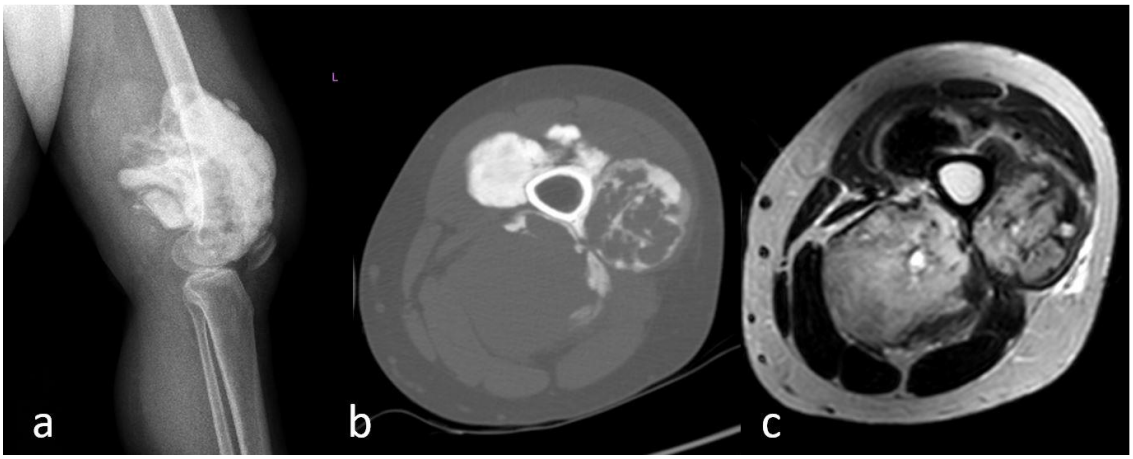

Figure 1. The x-ray and CT images of the mass showing calcification and new bone construction and not showing infiltration of the medulla in the distal metaphysioepiphysial region of the femur **(a-c)**.

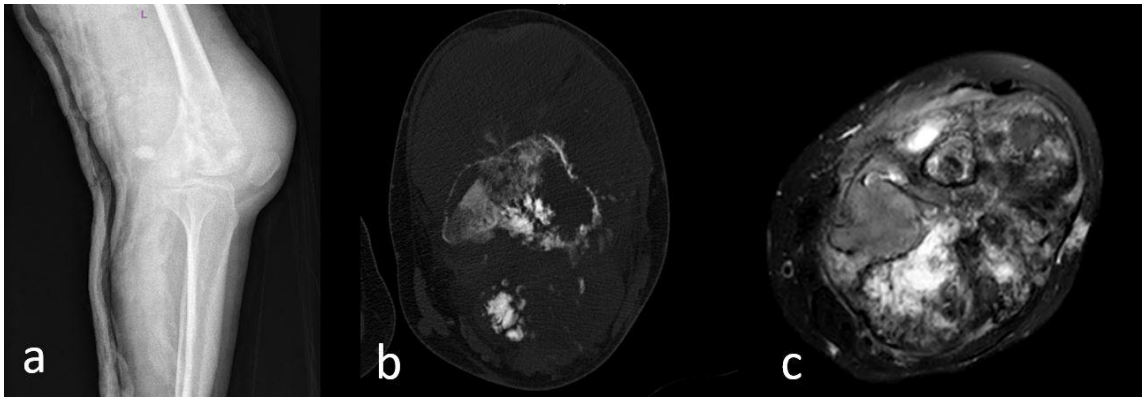

Figure 2. Another patient with a large soft tissue component causing cortical destruction and medullary infiltration in the distal femur **(a-b)**. A large mass with a heterogeneous signal in the axial T2W + FS image of the same patient **(c)**.

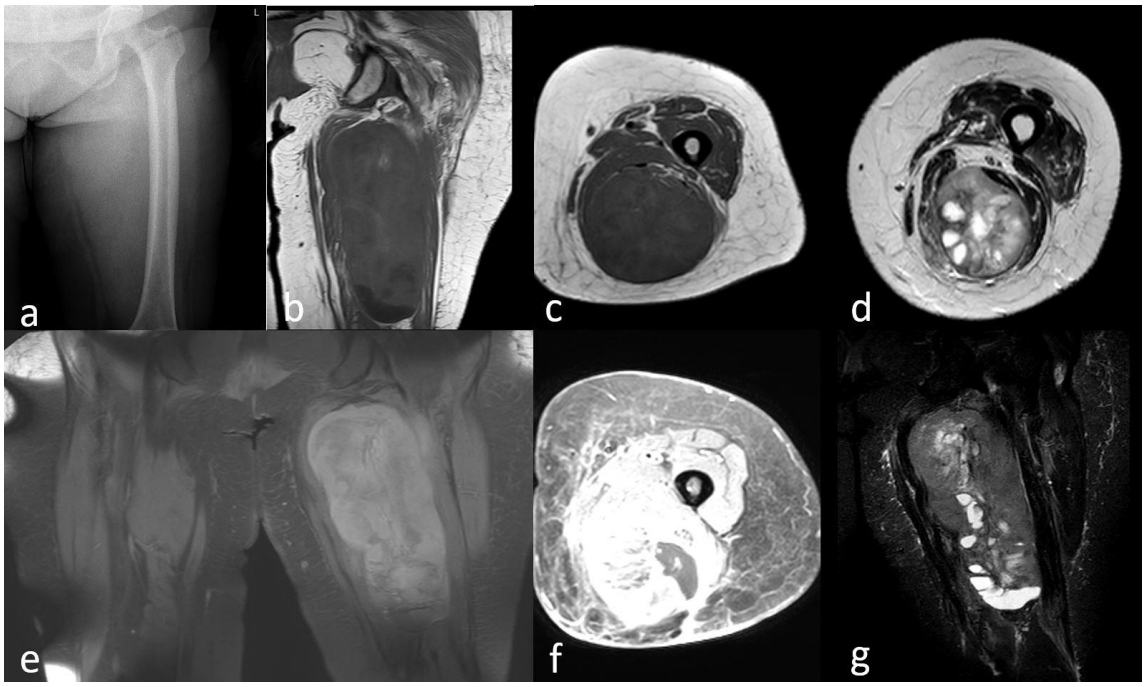

Figure 3. A 63-year old female patient presented with complaints of swelling in the posterior of the left thigh. **(a)** Increased soft tissue density in the thigh posterior region on the plain radiograph. There was no calcified or ossified lesion and no pathology in the bone tissue. **(b, c)** Heterogeneous hypointense lesion localized in a relatively well defined smooth muscle with deep location on MR, T1W images, **(d)** Heterogeneous appearance with a hyperintense signal especially in the central region, **(e, g)** Heterogeneous hyperintensity on STIR images, **(f)** contrast-enhanced central hypointense signal-dense lesion with intense contrast enhancement.

Discussion

LMS is defined as the most common soft tissue sarcoma that constitutes 10% of non-visceral soft tissue sarcomas, although this rate has not been determined with large series and meta-analytical studies. Current advances in both visual technologies and histopathological diagnostic tools have importance for the correct diagnosis and identification of this tumor. Therefore, new studies are needed on the frequency and rate of occurrence of this tumor.

However, the visual properties of deep-seated soft-tissue LMS of the limb have not been detailed as yet. Although the visual properties of primary osseous LMS have been partially defined, there are insufficient data about the visual properties of soft tissue LMS and the pathologies they create in bone tissue. The visual features of primary osseous leiomyosarcoma are defined as an aggressive osteolytic appearance, accompanied by endosteal erosion, and fine periosteal reaction. Soft tissue extension is very rare and if it is present, is minimal (7-9). Pathological fracture has only been reported rarely. Primary leiomyosarcoma is most common in the long bones of the lower extremities, especially the distal femur (8). Although internal calcification foci have been reported in these tumors in some studies (10), no internal calcification or ossification pathologies were encountered in the current study, except for the increase in soft tissue density. However, in two of the current study cases, in addition to the very large soft tissue mass, in one case there was noticeable cortical destruction and medullary invasion, while in the other case, minimal cortical destruction but not medullary invasion were detected on the images. In this last case, a wide periosteal serous bone formation was detected. It was not unusual for LMS, which originate from either soft tissue or bone, to display this type of image. To the best of our knowledge, there have been no previous reports of cases showing such a radiological feature. However, these two facts are controversial. These two cases were defined as LMS originating from soft tissue because they had a very large soft tissue component, and did not show radiological features resembling those of primary osseous LMS. In the MR images obtained in this study, the signals obtained were similar to those of general soft tissue sarcomas, with no different or specific visual data detected.

No consensus has been reached as yet on the treatment approaches for LMS, and there are insufficient data in the literature, especially regarding the effectiveness of chemotherapy. Studies conducted on heterogeneous groups with limited cases have provided different opinions. Some authors have reported that neoadjuvant chemotherapy has little effect on these tumors (11-13), while others have stated that the combination of trabectedin plus doxorubicin, and eribulin is effective (14-16). Unfortunately, many of those studies are related to visceral LMS. In the current study, adjuvant therapy was added to the surgical treatment of all 17 patients. Neoadjuvant chemotherapy was applied to 5 of 17 patients, and chemoradiotherapy was added after surgical treatment for these 5 patients, all of whom had lung metastasis on the first presentation. The surgical resection limits of these patients were evaluated as R0 in 4 patients and R1 in 1. The histopathological necrosis rate of the total resection specimens of these patients applied with neoadjuvant therapy was mean 45% (range, 40-60%). Satisfactory necrosis rates could not be obtained in any of these cases. The chemotherapy regimen was continued postoperatively due to the distant metastasis. Two of these patients developed local recurrence within the first year. A combination of surgery and adjuvant radiotherapy was applied to all 12 patients without distant metastasis. Surgical resection limits were obtained of R2 in 1 of these patients, R1 in 1, and R0 in 1. Local recurrence occurred in only one of these patients.,

In total local recurrence developed in 17.64% (3/17) of the patients. The surgical margin was R0 in two of these patients with local recurrence, and all had lung metastasis and chemoradiotherapy at the time of initial admission. In addition, the preoperative tumor size of two patients with local recurrence was 20 cm in one and 17 cm in the other. The other patient with local recurrence was the patient with the first surgical limit of R2. In that patient, local recurrence occurred in the re-resection despite a negative margin. The most prominent feature in patients with local recurrence was tumor size and patient age. All patients were in the geriatric age group and tumor size was >17 cm in all patients. Although a negative limit was obtained in 82.35% (14/17) of the current study patients, local recurrence occurred in 17.64%. The prominent feature of this study is that a negative limit was obtained, but recurrence developed in two cases where metastasis was present on admission. Some authors have stated that although positive margins adversely affected the local outcome, OS was not affected and thus, the quality of surgical margins only had an impact on local control (17,20,21). Due to the low number of cases in this study, it is not possible to make a definitive comment in this regard. However, the result obtained from the current study does not correspond to the above-mentioned view. Although the surgical margin is an important factor in local control, the degree of aggressiveness and size of the tumor also seem to be two important factors.

Soft tissue LMS with deep localization in the extremity are tumors with high metastatic potential. Distant metastasis rates have been reported as 23.3-44.7% in previous studies (17-20). In the current study, distant metastasis was determined in 5 patients on first admission, and later in another 2 (16.66%) of the other 12 patients. The time to development of metastasis was 32 months on average. All patients with distant metastasis died within an average of 18 months from first admission. Of the two patients who developed metastasis later, 1 died 55 months after treatment, and the other at 65 months.

In previous studies, histological grade, tumor size, and depth have been reported as important factors for disease-specific survival (DSS) (20). In the multivariate analysis of a study by Abraham et al. (21), histological grade and tumor depth were determined to be independent factors predicting OS. In a multi-institutional analysis by the Scandinavian Sarcoma Group (SSG), Svarvar et al. (17) evaluated the surgical outcomes of 225 patients with somatic LMS and found that tumour grade, size, and depth correlated significantly with OS in univariate analysis. It is

difficult to draw a conclusion about these parameters in the current study as all the tumors were high-grade with deep localization. However, the results of the study showed that tumor size was the most significant factor in overall survival. (p <0.001) Advanced age (p = 0.743) was not significant in overall survival.

Conclusion

In conclusion, although soft-tissue leiomyosarcomas are rare tumors in the extremities, they usually present as well-circumscribed or ill-defined, large, heterogenous soft tissue masses on CT and MRI. In 1 of the 17 patients in this study with biopsy-proven leiomyosarcoma, both cortical disruption and medullary invasion were apparent on CT and MRI. In another patient there was seen to be a feature that caused minimal cortical erosion and did not cause medullary invasion. However, in that tumor, there was a new peripheral bone formation in the distal femoral region. Therefore, it should be kept in mind that on CT and MRI, soft tissue leiomyosarcomas may simulate other malignant lesions such as osteosarcoma and metastases. To the best of our knowledge, gross cortical and medullary destruction has not been previously reported in extremity soft tissue leiomyosarcomas. When prognostic factors for local recurrence, distant metastasis, and overall survival were examined, overall survival was seen to be short, especially in all patients with distant metastasis and comorbidity. However, in the statistical analysis, it was determined that the only factor with an effect on overall survival was tumor size. Another important point of the study was the development of the opinion that chemotherapy has no significant effect on this disease. The patients with the longest overall survival were those with a tumor diameter <5 cm, regardless of age.

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Author Contributions: Project design, patient examination, biochemical analyzes, data collection and analyzes; **RK, OC,** Writing and Revisions**: OC**

Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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