

## Assessment of the upper airway as an indicator of prognosis and treatment of odontogenic infections

Avaliação da via aérea superior como indicador de prognóstico e tratamento de infecções odontogênicas

Evaluación de la vía aérea superior como indicador de pronóstico y tratamiento de infecciones odontogénicas

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### Abstract

Odontogenic infections can directly impact the airways. The present study aimed to evaluate the upper airway as a prognostic factor and its influence on treating odontogenic infections via computed tomography. Data were obtained from 28 patients with odontogenic infections who required hospitalization between September 2018 and November 2019. The collected variables included medical history, vital signs, infection history, previous antibiotic therapy, and hospital stay. The laboratory test results were analyzed upon admission and 48 hours after the surgical procedure, and the laboratory risk indicator for necrotizing fasciitis (LRINEC) index was calculated. The airway was assessed via calculations of volume and the shortest retroglossal distance. Spearman's statistical test was used to study the data. The CRP value at admission was correlated with the airway volume at +0.107 and the AP/LT index at +0.352, with a significance level of 0.066. The LHS showed a correlation coefficient for airway volume of +0.066 and a correlation for the AP/LT index of +0.248, with a significance level of 0.203. The LRINEC index was correlated with the airway volume at -0.027 and with the AP/LT index at +0.332, with a significance level of 0.084. The airway is altered in patients with odontogenic infection; this phenomenon must be better defined, considering that the compression of the airway and the location in which it is most constricted can indicate severity.

**Keywords:** Tomography, X-ray computed; Airway obstruction; Periapical abscess; Retropharyngeal abscess.

### Resumo

As infecções odontogênicas podem impactar diretamente as vias aéreas. O presente estudo teve como objetivo avaliar a via aérea superior como fator prognóstico e sua influência no tratamento de infecções odontogênicas por meio de tomografia computadorizada. Os dados foram obtidos de 28 pacientes com infecções odontogênicas que necessitaram de hospitalização entre setembro de 2018 e novembro de 2019. As variáveis coletadas incluíram histórico médico, sinais vitais, histórico de infecção, antibioticoterapia prévia e internação hospitalar. Os resultados dos exames laboratoriais foram analisados na admissão e 48 horas após o procedimento cirúrgico, e o índice de risco laboratorial para fascíte necrosante (LRINEC) foi calculado. As vias aéreas foram avaliadas por meio de cálculos de volume e da menor distância retroglossal. O teste estatístico de Spearman foi utilizado para estudar os dados. O valor da PCR na admissão correlacionou-se com o volume da via aérea em +0,107 e com o índice AP/LT em +0,352, com nível de significância de 0,066. O LHS apresentou coeficiente de correlação para o volume da via aérea de +0,066 e correlação

para o índice AP/LT de +0,248, com nível de significância de 0,203. O índice LRINEC correlacionou-se com o volume da via aérea em -0,027 e com o índice AP/LT em +0,332, com nível de significância de 0,084. A via aérea está alterada em pacientes com infecção odontogênica; esse fenômeno deve ser melhor definido, considerando que a compressão da via aérea e o local em que ela está mais constricta podem indicar gravidade.

**Palavras-chave:** Tomografia computadorizada por raios X; Obstrução das vias respiratórias; Abscesso periapical; Abscesso retrofaríngeo.

### Resumen

Las infecciones odontogénicas pueden afectar directamente a las vías respiratorias. El presente estudio tuvo como objetivo evaluar la vía aérea superior como factor pronóstico y su influencia en el tratamiento de infecciones odontogénicas mediante tomografía computarizada. Los datos se obtuvieron de 28 pacientes con infecciones odontogénicas que requirieron hospitalización entre septiembre de 2018 y noviembre de 2019. Las variables recopiladas incluyeron antecedentes médicos, signos vitales, antecedentes de infección, terapia antibiótica previa y estadía hospitalaria. Los resultados de las pruebas de laboratorio se analizaron al ingreso y 48 horas después del procedimiento quirúrgico, y se calculó el índice indicador de riesgo de laboratorio para fascitis necrosante (LRINEC). La vía aérea se evaluó mediante cálculos de volumen y la distancia retroglosa más corta. Para el estudio de los datos se utilizó la prueba estadística de Spearman. El valor de PCR al ingreso se correlacionó con el volumen de la vía aérea en +0,107 y el índice AP/LT en +0,352, con un nivel de significancia de 0,066. El LHS mostró un coeficiente de correlación para el volumen de la vía aérea de +0,066 y una correlación para el índice AP/LT de +0,248, con un nivel de significancia de 0,203. El índice LRINEC se correlacionó con el volumen de la vía aérea en -0,027 y con el índice AP/LT en +0,332, con un nivel de significancia de 0,084. La vía aérea se encuentra alterada en pacientes con infección odontogénica, este fenómeno debe ser mejor definido, considerando que la compresión de la vía aérea y el lugar en el que se encuentra más constreñida pueden indicar gravedad.

**Palabras clave:** Tomografía computarizada por rayos X; Obstrucción de las vías respiratorias; Absceso periapical; Absceso retrofaríngeo.

## 1. Introduction

Infections that affect the fascial spaces of the head and neck are defined as disseminating processes throughout the facial spaces of this region and can be divided into superficial or deep infections (Cassagneau et al., 2011; Flynn et al., 2011; Sepanen et al., 2008); thus, they can be established as localized processes, or they can spread through primary and secondary fascial spaces (Opitz et al., 2015). Most of these infections are associated with odontogenic foci and are characterized by their polymicrobial nature, with aerobic and anaerobic bacteria being indicated (Taub et al., 2017; Velhonoja et al., 2020). In addition, odontogenic infections are a growing clinical challenge (Velhonoja et al., 2020).

Clinical features, laboratory tests, and imaging can provide a set of criteria to assess the severity of infection (Cassagneau et al., 2011; Alotaibi et al., 2015). Contrast-enhanced computed tomography of the neck is indicated when there is suspicion of this process in the deep cervical fascial spaces, thus allowing for the demonstration of airway obstruction and a determination of the anatomical spaces that are involved (Petitpas et al., 2012; Vytla & Gebauer, 2017).

When treating odontogenic infections, patients respond well to drainage of the involved spaces and intravenous antibiotic therapy. In more severe cases, it is necessary to ensure a safe airway (Alotaibi et al., 2015; Storoe & Haug, 2001; Taub et al., 2017). However, life-threatening complications associated with deep neck infections can arise, including airway obstructions (Caccamese & Coletti, 2008).

Imaging studies, particularly computed tomography, are frequently requested in emergency units to confirm the diagnosis, and some parameters are indicative of the severity of the infection, such as gas formation and the involvement of several fascial spaces (Caccamese et al., 2008; Silva et al., 2022). However, an incorrect diagnosis can lead to airway impairment, with more prognostic factors being important for diagnosis (Silva et al., 2022; Christensen et al., 2018; Gonzalez-Beicos & Nunez, 2012). Therefore, the present study aimed to evaluate the upper airway as a prognostic factor and its influence on treating odontogenic infections via computed tomography.

## 2. Methodology

Patients diagnosed with odontogenic infections who required hospitalization and who were admitted between September 2019 and November 2020 to the Oral and Maxillofacial Surgery Clinic were prospectively evaluated. All of the patients who participated in the study signed an informed consent form. This study received approval from the Human Research Ethics Committee of the Municipal Health Department of São Paulo (SMS/SP) (Jan 18, 2019; CAAE: 22418619.2.0000.0086). The present study was carried out through an epidemiologic study of a quantitative nature (Pereira et al., 2018; Toassi & Petry, 2021) using descriptive statistics classes, mean values, and standard deviations (Shitsuka et al., 2014) and statistical analysis (Vieira, 2021).

Patients over 18 years of age who were diagnosed with a cervical infection of dental origin, who underwent computed tomography of the neck with a contrast agent, and who underwent surgical treatment under general anesthesia were included in the study. Individuals with infections of dental origin involving the middle third of the face and patients who refused to participate were excluded from the study.

### 2.1 Data Collection

The following data were collected: medical history; vital signs (blood pressure, heart rate, respiratory rate, and body temperature); presence of dysphagia, odynophagia, dyspnea, and laryngeal crepitation; involvement of the sternal notch; palpation of the mandibular base; and measurements of mild (mouth opening greater than 20 mm), moderate (mouth opening between 10–20 mm) and severe (mouth opening less than 10 mm) trismus (Sainuddin et al., 2017).

Systemic blood pressure was measured via the Omron Automatic Wrist Blood Pressure Monitor (Omron Healthcare, Jundiaí, Brazil). A G-Tech OLED Pulse Oximeter was used to obtain heart and respiratory rates, and the temperature of each individual was measured via a G-Tech Noncontact Digital Forehead Thermometer (Accumed-Glicomed, Rio de Janeiro, Brazil).

Data on the infection history of each individual, such as the duration of disease progression in days until hospitalization, duration of antibiotic therapy before hospitalization, and length of hospital stay in days, were collected. The collected data were collated in a data collection form for future tabulation and analysis.

### 2.2 Assessment of Laboratory Test Values

The values obtained in the laboratory tests on admission and in the tests conducted 48 hours after the surgical procedure were collated in the data collection form. On admission, laboratory values such as hemoglobin, leukogram, sodium, potassium, urea, creatinine, blood glucose, and C-reactive protein (CRP) were collected. At 48 hours after the surgical procedure, the hemoglobin, leukogram, and CRP values were collected.

### 2.3 LRINEC Index Calculation

The LRINEC (laboratory risk indicator for necrotizing fasciitis) index is a numerical score ranging from 0 to 13. It is calculated via six laboratory indicators: the CRP level, leukocyte count, hemoglobin count, sodium level, creatinine level, and blood glucose level (Table 1) (Zemplenyi et al., 2017). With the use of this system, an index less than or equal to 5 indicates a risk of less than 50% for developing necrotizing fasciitis (NF), an index between 6–7 indicates a risk of 50–70% for NF, and an index greater than 8 indicates a risk greater than 75% for NF.

**Table 1 - LRINEC index calculation. \***

Laboratory parameters	LRINEC Index
CRP, mg/l	
<150	0
≥150	4
Leukocytes x10 <sup>9</sup> /l	
<15	0
15-25	1
>25	2
Hb, g/dl	
>13.5	0
11-13.5	1
<11	2
Sodium, mmol/l	
≥135	0
<135	2
Creatinine, mg/dl	
≤1.6	0
>1.6	2
Blood glucose, mg/dl	
≤180	0
>180	1

\* According to Zemplyeni et al. (2017).

## 2.4 Computed Tomography Assessment

Following the diagnostic protocol, images were obtained from the hospital database of individuals with cervical infection of dental origin who underwent contrast-enhanced neck computed tomography to visualize and determine the affected fascial spaces; determinations were made according to density differences using the Hounsfield scale.

## 2.5 Airway Assessment in Computed Tomography

A two-channel tomograph was used to perform the examination. The patients were placed in the supine position, and the operator standardized the head position, which was laterally supported by stabilizing equipment, to acquire the images.

The images were acquired via computed tomography in digital imaging and communications in medicine (DICOM) format and were imported into InVesalius 3.1 software and Meshmixer® software. The tomographic images were oriented according to the SN plane, which is determined between the sella and nasion points, the mid-sagittal plane which is oriented based on the crista galli, basion, anterior nasal spine, and posterior nasal spine, and the coronal plane which is perpendicular to the mid-sagittal plane and centered on the upper edges of the orbits. These planes were used as a reference for correction and standardization in the examination, which allowed for their complete visualization (Vinha et al., 2016). After the planes were corrected, a new series of DICOM images was saved and all of the measurements were obtained from this series.

The airway measurement was determined using the line passing through the posterior nasal spine as the upper limit, which corresponds to the airway formed just after the end of the maxilla; additionally, the lower limit was determined by using the lowest point of the C3 vertebral body (Susarla et al., 2011) (Figure 1). The smallest anteroposterior (AP) and laterolateral (LT) retroglottal distances were measured (Abramsom et al., 2011) (Figure 2). The software segmentation tool was used to determine the volume while accounting for the density of the standard image in all of the measurements because the software automatically selects the volume based on the image density (Figure 3). The collected data were collated in the data collection form for tabulation and analysis.

**Figure 1** - Measurement of the airway. The upper limit was indicated by the line passing through the posterior nasal spine. The lower limit was the lowest point of the C3 vertebral body, in the sagittal section.



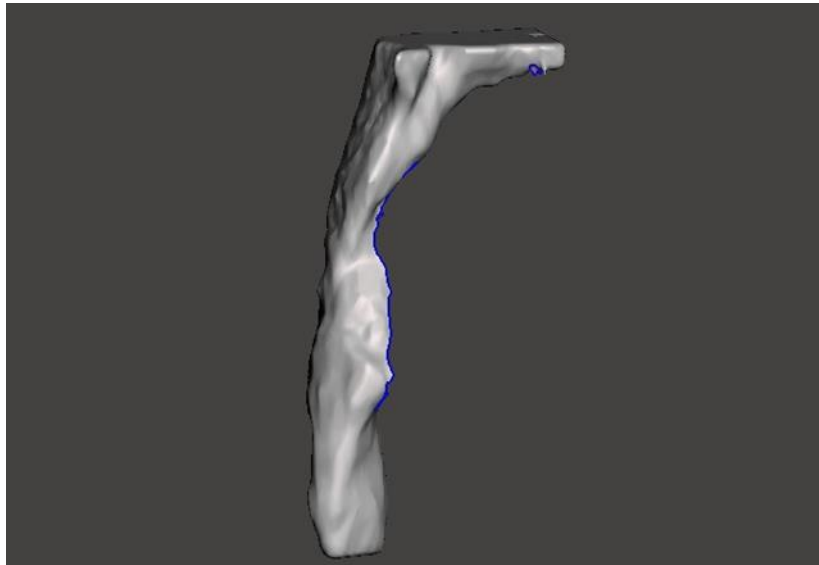
Source: Research data.

**Figure 2** - Measurement of the smallest retroglossal distance anteroposterior (AP) in red and laterolateral (LT) in green in the axial section.



Source: Research data.

**Figure 3** - Three-dimensional reconstruction of the upper airway.



Source: Research data.

## 2.6 Statistical Analysis

The obtained data were statistically analyzed via the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Software Group, Chicago, IL, USA). Spearman's correlation analysis was used to verify the degree of relationship between the following variables: airway volume value with LHS, airway volume with CRP and the LRINEC index, the AP/LT ratio index with LHS, and the AP/LT ratio index with CRP and the LRINEC index.

## 3. Results

A total of 90 patients were admitted with a diagnosis of odontogenic infection during the study period, 28 of whom met the inclusion criteria. The remaining sample (62 patients) was excluded because of the following factors: absence of a computed tomography scan of the neck, infections involving the fascial spaces of the middle third of the face, drainage under local anesthesia, or being under 18 years of age. The mean age of the sample was 38.9 years (18–65 years), with 16 male patients (57.1%) and 12 female patients (42.9%) being included. Concerning the presence of comorbidities, 6 patients (21.4%) had systemic arterial hypertension, 5 (17.9%) had diabetes mellitus, 3 (10.7%) had asthma, 2 (7.1%) had depression, 1 (3.6%) had liver failure, 1 (3.6%) had hepatitis B, and 1 had (3.6%) syphilis. For habits and addictions, 10 patients (35.7%) reported smoking, and 8 (28.6%) reported the use of illicit drugs.

The signs and symptoms that were obtained during the clinical examinations of the patients who were included in the study were nonpalpable mandibular bases in 27 patients (96.4%), dysphagia in 21 patients (75.0%), odynophagia in 24 patients (85.7%), and dyspnea in 20 patients (71.4%). Ten patients (35.7%) had no laryngeal crepitation, and 2 (7.1%) had involvement of the sternal notch on physical examination. Regarding the limitation of mouth opening, 14 patients (50.0%) had severe trismus, 13 (46.4%) had moderate trismus, and 1 (3.6%) had mild trismus.

On admission, the following mean values ( $\pm$  standard deviation) of vital signs were obtained: systolic blood pressure, 133.9 mmHg ( $\pm$  16.0); diastolic blood pressure, 85.7 mmHg ( $\pm$  6.5); heart rate, 77.1 beats per minute ( $\pm$  6.00); respiratory rate, 18.3 ( $\pm$  1.4); and body temperature, 36.7 °C ( $\pm$  0.6).

For the laboratory tests, significant changes in leukocyte, blood glucose, and CRP levels were observed. Furthermore, for the laboratory tests obtained 48 hours after surgery, there was an improvement in leukocyte and CRP levels. The mean

values ( $\pm$  standard deviations) of the laboratory test results at admission and at 48 hours after surgery are shown in Table 2. The LRINEC index had a mean value of 2.75 ( $\pm$ 2.37).

**Table 2** - Mean values of laboratory tests at admission and 48 hours after surgery.

Tests	Admission values (s.d.)	48h after surgery (s.d.)
Hb, g/dl	14.2 (1.7)	12.8 (2.0)
Leukocytes $\times 10^9/l$	13,946.4 (5,251.8)	12,778.3 (4,279.2)
Blood glucose, mg/dl	130.3 (91.3)	-
Sodium, mmol/l	138.5 (4.3)	-
Creatinine, mg/dl	0.7 (0.3)	-
CRP, mg/l	14.0 (11.4)	9.3 (6.9)

s.d.= standard deviation. Source: Research data.

Antibiotics were used before hospital admission by 13 (46.4%) patients. The disease progression until the time of hospital admission had a mean duration of 5.2 ( $\pm$ 2.7) days; additionally, the mean time in hours until surgical approach was 10.2 ( $\pm$ 4.7) hours, and the average total number of days of hospitalization was 7.7 ( $\pm$ 6.6) days.

In the tomographic analysis of the involved fascial spaces, 11 (39.3%) patients had involvement in the right buccal space, and 10 (35.7%) patients had involvement in the left buccal space. Eighteen (64.3%) patients had involvement in the right submandibular space, 14 (50.0%) patients had involvement in the left submandibular space, 12 (42.9%) patients had involvement in the right submental space, 14 (50.0%) in the left submental space, 13 (46.4%) of the right sublingual space and 12 (42.9%) patients had involvement in the left sublingual space. In the secondary spaces, 4 (14.3%) patients had involvement in the right superficial temporal space, and no patient had involvement in the left superficial temporal space. There was no involvement of the deep temporal spaces on either side. Nine (32.1%) patients had involvement in the right masseteric space, 4 (14.3%) patients had involvement in the left masseteric space, and 1 (3.6%) patient had involvement in the left pterygomandibular space. There was no involvement of the infratemporal spaces on either side. Regarding the cervical spaces involved, 5 patients (17.9%) had involvement in the right lateral pharyngeal space, 6 (21.4%) patients had involvement in the left lateral pharyngeal space, and 5 (17.9%) patients had involvement in the retropharyngeal space. There was no involvement of the prevertebral space.

For the tomographic evaluation of the upper airway volume, the mean A/P measurement was 9.89 mm ( $\pm$  3.77), and the L/T measurement was 15.94 mm ( $\pm$  7.18). The mean airway volume was 11.75 ml ( $\pm$  4.19). The mean AP/LT ratio was 0.89 ( $\pm$  0.97). The results of the tomographic evaluation of the upper airway are shown in Table 3.



**Table 3** - Values of tomographic evaluation of the upper airway according to the patient.

Patient	Volume (ml)	AP (mm)	LT (mm)	AP/LT
1	13.5	6.2	20.0	0.3
2	12.9	8.0	10.6	0.8
3	7.3	20.8	4.0	5.2
4	6.1	10.6	9.7	1.1
5	11.3	6.8	12.6	0.5
6	10.5	10.8	22.3	0.5
7	16.6	11.8	28.3	0.4
8	6.9	7.5	14.6	0.5
9	16.3	7.7	16.8	0.5
10	15.7	14.6	10.7	1.4
11	6.2	8.0	12.4	0.6
12	12.0	9.2	14.2	0.7
13	7.7	10.1	6.5	1.6
14	15.3	5.4	19.5	0.3
15	11.8	6.8	28.0	0.2
16	5.1	4.8	17.4	0.3
17	9.2	9.3	29.7	0.3
18	10.8	10.2	20.7	0.5
19	20.7	8.7	28.7	0.3
20	19.6	6.3	14.8	0.4
21	8.4	11.3	5.7	2.0
22	8.1	9.7	6.8	1.4
23	13.4	11.4	20.3	0.6
24	17.0	19.5	14.4	1.4
25	8.6	6.9	16.5	0.4
26	9.2	9.1	12.6	0.7
27	14.7	14.1	8.6	1.6
28	14.0	11.4	20.1	0.6

Source: Research data.

The CRP value at admission correlated with the airway volume (ml) at +0.107 and the AP/LT index at +0.352, with a significance level of 0.066. The CRP level at 48 hours after surgery was correlated with the airway volume (ml) at +0.028 and the AP/LT index at +0.354, with a significance level of 0.098. The length of hospital stay (LHS), measured in days, showed a correlation coefficient with the airway volume (ml) of +0.066 and a coefficient with the AP/LT index of +0.248, with a significance level of 0.203. The LRINEC index exhibited a correlation coefficient concerning airway volume (ml) of -0.027 and a coefficient regarding the AP/LT index of +0.332 with a significance level of 0.084. Spearman correlation analysis of the variables of interest, airway volume, and the AP/LT index is shown in Table 4.



**Table 4** - Spearman correlation analysis of the variables of interest, airway volume, and AP/LT index.

Variable	Statistic	Airway volume (ml)	AP/LT
CRP admission	Correlation coefficient ®	+0,107	+0,352
	Calculated significance (p)	0,587	0,066
	N	28	28
CRP 48 hours postoperatively	Correlation coefficient ®	+0,028	+0,354
	Calculated significance (p)	0,900	0,098
	N	23	23
LHS	Correlation coefficient ®	+0,066	+0,248
	Calculated significance (p)	0,738	0,203
	N	28	28
LRINEC index	Correlation coefficient ®	-0,027	+0,332
	Calculated significance (p)	0,891	0,084
	N	28	28

LHS = Length of hospital stay. Source: Research data.

#### 4. Discussion

With the advancement of new technologies, early diagnosis of various diseases is possible; thus, the investigation of the airway has become an important factor in the planning and prognosis of many aspects of the disease. However, its use as an indicator of the severity of odontogenic infections can still be discussed. This study aimed to evaluate computed tomography images and airway volume to determine the prognosis of patients with odontogenic infections. This study showed that there is an alteration of the airway in patients with odontogenic infection; however, this alteration must be better defined in consideration of the fact that the compression of the airway (as measured by using the AP/LT ratio) can be an indicator of severity and should be considered for patients who require intubation.

The lower airway values that were observed in our study may be due to greater airway compression resulting from edema caused by disseminated odontogenic infections. According to a survey that analyzed the airway by using computed tomography in patients with obstructive sleep apnea syndrome (OSAS) and a control group with asymptomatic patients, the following measurements were obtained in the control group: LT of  $22.3 \pm 7.7$  mm, AP of  $10.9 \pm 4.1$  mm, AP/LT ratio of  $2.4 \pm 1.4$  and volume of  $12.3 \pm 4.6$  ml (Abramson & Susarla, 2010). However, in our study, our patients had an LT of  $15.9 \pm 7.2$  mm, an AP of  $9.9 \pm 3.8$  mm, an AP/LT ratio of  $0.9 \pm 1.0$ , and a volume of  $11.75 \pm 4.19$  ml.

The combination of an elongated airway with decreased retroglossal AP length has been correlated with the severity of OSAS, thus resulting in increased airflow resistance, as described by the Poiseuille equation. In this context, in the present study, the shorter upper airway, with a larger diameter, was the airway observed in the control population (Abramson et al., 2010; Abramson et al., 2011). A low AP/LT ratio may be associated with a greater airway compression index and greater severity of odontogenic infection.

In this study, the LHS measured on hospital days exhibited a correlation coefficient for the AP/LT index, the AP/LT index for CRP, and the AP/LT index for the LRINEC index. Thus, compression and deformation of the airway may be among the factors that can be used for prognosis; however, due to the sample size and the fact that the group was standardized only for severe cases, this relationship was not significant.

CRP tests have worsened during admission in the last decade compared with those in the previous decade. In 2003, no

patient admitted to the emergency unit with odontogenic infection had a CRP level greater than 15 mg/l; however, ten years later, some patients exhibited CRP levels greater than 15 mg/l (Fu et al., 2018). Currently, some authors question the use of CRP as a prognostic factor for odontogenic infections. Thus, some authors do not consider CRP to be a good prognostic factor, which does not allow for presumptions concerning the length of hospital stay (Mirochnik et al., 2017). However, this type of study requires a larger sample and correlation analyses of other factors. Thus, by using associations of factors, a scale can be created that includes the airway together with other factors, such as several parameters: via this analysis, it has been demonstrated that CRP levels greater than 10 mg/l associated with cervical edema and respiratory difficulty had a positive correlation with severity (Wang et al., 2003). CRP levels 48 hours after surgery were significantly correlated with the airway volume and the AP/LT index. This result was expected because there was an improvement from the previous level. Laboratory tests at the time of admission and on the fourth day of hospitalization were performed as controls, and after the 4th day of hospitalization, the leukogram and CRP values were significantly lower (Kaman et al., 2018).

In the literature, we did not find studies that correlated airway volume with the severity of odontogenic infections. Furthermore, it is possible that the airway volume is not related to the greater severity of the cases, with the shape of the airway (as shown by the AP/LT index) being closer to representing a severity factor of these infections, due to the fact that the obtained airway volume correlated with the CRP at +0.107, with a significance level of 0.587. Moreover, the LHS correlated with the airway volume at +0.066, with a significance level of 0.738, and the LRINEC index correlated with the airway volume of -0.027 with a significance level of 0.891. However, the airway volume observed in our study was smaller than in the control groups of other studies (Susarla et al., 2011). Further studies are needed that divide the airway into portions, thus allowing for a better verification of the influence of airway volume on the prognosis of patients with odontogenic infections.

## 5. Conclusion

When considering the results that were obtained within the limitations of the study, it was concluded that there is an alteration of the airway in patients with odontogenic infections and that this alteration needs to be better defined, due to the fact that the compression of the airway (as measured via the AP/LT ratio) can be an indicator of severity, as well as an important factor to be considered during surgical planning for patient intubation. However, airway volume did not influence treatment efficacy and was not shown to be a prognostic factor.

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