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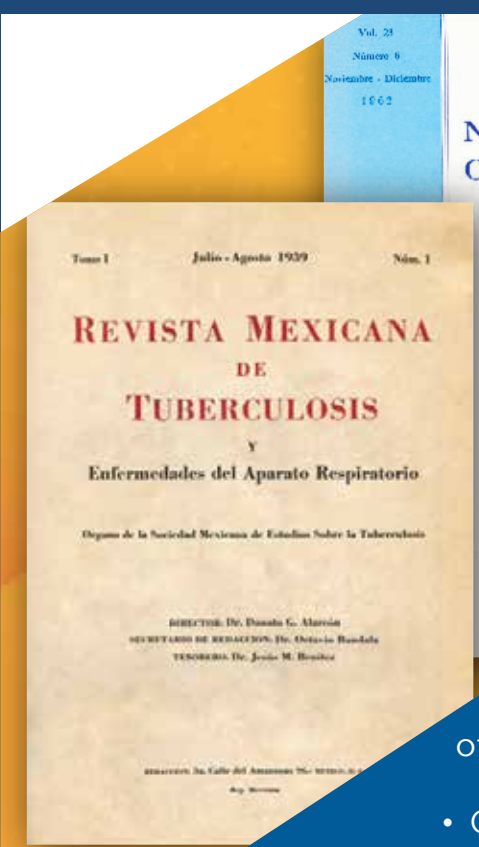
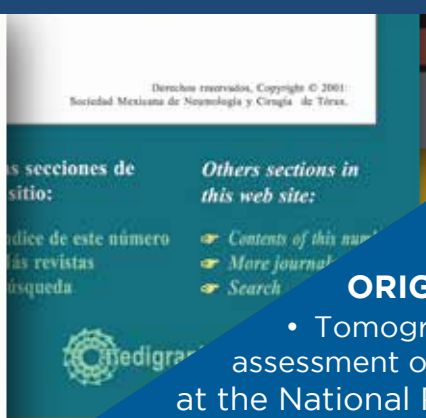
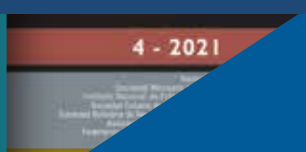
NCT

Neumología y Cirugía de Tórax

NCT new generation







ORIGINAL RESEARCH

- Tomographic scale for the assessment of COVID-19 severity at the National Respiratory Diseases Institute
- Implications of the body weight of older adults hospitalized for community-acquired pneumonia in the capacity to expectorate, severity on admission and lethality
- Relationship between maxillary disjunction and level of asthma control in school-aged patients
- Outpatient follow-up of patients with broncopulmonary dysplasia

RESPIRATORY WORLD

Tribute to Dr. Jaime Villalba Caloca.
At one year after his departure

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Editorial

NCT new generation

NCT nueva generación

Juan Carlos Vázquez-García*

*Editor in Chief of *Neumología y Cirugía de Tórax* (NCT).

On March 15, 1939, the Mexican Society of Studies on Tuberculosis and Respiratory Diseases was founded at the Sanatorium of Tuberculosis Patients in Huipilco, now *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas* (INER).[1,2] On Thursday, May 4, 1939, in the Miguel Jiménez classroom of the former School of Medicine, the second scientific session of the nascent association was held; in this session, Dr. Donato G Alarcón, first president of the Society, requested authorization for the publication of the first issue of a scientific journal, the official organ of the Society. In the scientific session of July 6 of the same year, Dr. Alarcón presented a budget of $500.00 for the printing of 1,000 copies of the journal, a cost that should be covered with the fees of the members of Mexico City. At the regulatory session held on August 10, 1939, Dr. Alarcón reported that Dr. Gustavo Baz, Rector of the *Universidad Nacional Autónoma de México* (UNAM), authorized the printing of the journal in the university's printing press with the costs covered by the Society. Finally, in the session of October 5, 1939, Dr. Alarcón officially presented the first issue of the Mexican Journal of Tuberculosis and Respiratory Diseases (*Revista Mexicana de Tuberculosis y Enfermedades del Aparato Respiratorio*). This issue covered the period from July to August of 1939, Dr. Alarcón himself served as director of the journal and in his first editorial wrote:[3]

The creation of the Mexican Society of Tuberculosis Studies immediately imposed the need for a national publication to make our class aware of the work of the group of Mexican specialists who strive to place the country in one of the first places in this branch of medical science.

By approval of its General Assembly, on August 16, 1962, during the presidency of Dr. José Ramírez Gama, our association became the *Sociedad Mexicana de Neumología y Cirugía de Tórax A. C.* (SMNyCT). Since the first issue of that year, the journal has been called Pulmonology and Thoracic Surgery (*Neumología y Cirugía de Tórax*, NCT). In the year 2010, under the chairmanship of Dr. Andrés Palomar Lever, the general direction of INER by Dr. Rogelio Pérez Padilla and with the prior approval of the General Assembly of the Society, it was decided to merge the journal of Pulmonology and Thoracic Surgery with the journal of INER, which was published since July of 1988. Since the first issue of the year 2010 (volume 69), under the editorial direction of Dr. Patricio Santillán Doherty, the journal has been identified only as NCT. This strategic merge made it possible to join forces for greater financial, administrative, editorial and scientific support; at the same time, unfavorable competition between both was avoided and within the same scientific and professional community of our country.

After almost 83 years of existence and with this first issue of the volume 81, a new generation of NCT begins; it seeks to reach its final positioning in the national and international scientific community of the matter. This project includes a more rigorous editorial and scientific work system under international standards, as well as

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Table 1: Editors of the journal *Neumología y Cirugía de Tórax.*

Period	Editors
1939-1945	Donato G. Alarcón
1945-1950	Alejandro Celis Salazar
1950-1951	Ismael Cosío Villegas
1951-1953	Aradio Lozano Rocha
1953-1957	Enrique Staines
1958	Manuel de la Llata
1959-1960	Guillermo Solórzano Gutiérrez
1961-1970	Miguel Schulz Contreras
1971-1972	Juan Del Río Huidobro
1973-1977	Andrés Ramos Rodríguez
1977-1978	Sotero Valdez Ochoa
1979-1981	Carlos Ibarra Pérez
1981-1983	Héctor M. Ponce de León
1983-1986	Emilio García Procel
1987-1991	Javier Castillo Nava
1992-1995	Rogelio Pérez Padilla
1995-1997	Mario H. Vargas Becerra
	Juan Urueta Robledo
1997-1999	Héctor M. Ponce de León (1997-1999)
	Francisco Navarro Reynoso (1997-2000)
2000-2002	Mario H. Vargas Becerra
2003-2005	Andrés Palomar Lever
2005-2007	Jaime Eduardo Morales Blanhir
2007-2009	José Javier Elizalde González
2009-2021	Patricio Santillán Doherty
2021-	Juan Carlos Vázquez García
Editors of the INER Journal	
1988-2003	Celso García Espinosa
2003-2004	Eugenia M. de Lizalde
2005-2008	Carlos Ibarra Pérez
2008-2009	Raúl H. Sansores M.
	Ma. Elena Yuriko Furuya Meguro
	Mario Vargas Becerra

INER = National Institute of Respiratory Diseases (*Instituto Nacional de Enfermedades Respiratorias*).

a more modern and user-friendly print edition and website. For the first time, a simultaneous digital version appears, completely in English; it seeks to bring NCT and its scientific contents, mainly of Mexican and Latin American respiratory medicine, to more international readers. All our appreciation to our medical specialities and the soundness attained by its highest institutions: SMNyCT and INER, of whom represents as the official organ. Likewise, to all its historical legacy product of the work carried out by its 28 editors *(Table 1)*, its editorial teams and, of course, to all the authors who over more than eight decades have entrusted and shared their scientific contributions.

To express our wishes for this new generation of NCT, perhaps there are no better words than those written by Dr. Alarcón in the first issue of the journal:

At the beginning of the publication of this journal, we are full of optimism. This journal will be successful because it is needed in the country, because it has the backing of a large original publishable material and because the medical environment is conducive to its appearance. Our efforts will not be developed on sterile ground, but on the fertile soil already fertilized by the interest towards the years of past effort.

Congratulations to SMNyCT, INER and especially to its official organ: NCT.

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NCT
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Original

Tomographic scale for the assessment of COVID-19 severity at the National Respiratory Diseases Institute

Escala tomográfica para evaluar la gravedad de COVID-19 en el Instituto Nacional de Enfermedades Respiratorias

Fortunato Juárez-Hernández,*‡ Marina Patricia García-Benítez,*§ Juan Pablo Farías-Contreras,* Randall Rojas-Varela,* Alda Marcela Hurtado-Duarte,* Roberto Sotelo-Robledo,* Lya Edith Pensado-Piedra,* Aloisia Paloma Hernández-Morales,* Julio César Gómez-Penagos,* Ana Karen Barocio-Ramírez,¶ María Luisa Vázquez-Villegas¶,||

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico, City, Mexico; ‡Unidad de Detección y Diagnóstico Clínica de Mama No. 1, Mexico, City, Mexico, Instituto Mexicano del Seguro Social, Mexico; §Hospital General Regional No. 46, Jalisco, Instituto Mexicano del Seguro Social, Mexico; ¶Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara; Guadalajara, Mexico; ||Unidad de Medicina Familiar No. 4, Jalisco, Instituto Mexicano del Seguro Social, Mexico.

ABSTRACT. Introduction: The pandemic of SARS-CoV-2 (COVID-19) has caused high rates of morbidity and mortality. The use of adequate diagnostic methods to identify the evolution of this disease is necessary; computerized tomography (CT) is of the main tools by image, with sensitivity of 96-99%. Different studies have created scales to evaluate the extent and severity of lung disease from COVID-19, with a variability in the results. **Objective:** To evaluate the use of a tomographic scale (TS) to determine the severity of lung affectation in COVID-19. **Material and methods:** Analytical cross-sectional study including patients with confirmed diagnosis of COVID-19 and initial CT. ATS was used to evaluate the lung affectation, to identify pulmonary pattern and to establish the state of the disease. Statistical analysis consisted in descriptive and analytical statistics (ROC curve). **Results:** 151 patients, mean age 50 years. The predominant pulmonary pattern was «crazy paving» (46%), identified in the phase of progression. The area under the ROC curve was 0.831 (95% CI: 0.764-0.898), with a cut-off value of 16.5 to discriminate the severe from non-severe affectation, with sensitivity 84% and specificity 74%. **Conclusion:** The use of TS in initial CT showed an acceptable sensitivity to identify the severity of the disease.

Keywords: Severity, tomographic scale, lung, COVID-19, respiratory disease.

RESUMEN. Introducción: La pandemia por SARS-CoV-2 (COVID-19) provocó altas tasas de morbimortalidad. Es necesario el uso de métodos diagnósticos para la identificación o evolución de este padecimiento; la tomografía computarizada (TC) es una de las principales herramientas por imagen con sensibilidad de 96-99%. Diferentes estudios han elaborado escalas para evaluar la extensión y gravedad de la enfermedad pulmonar por COVID-19 con variabilidad en sus resultados. **Objetivo:** Evaluar la utilidad de una escala tomográfica (ET) para determinar la gravedad de la afectación pulmonar en COVID-19. **Material y métodos:** Estudio transversal analítico; se incluyeron pacientes con diagnóstico confirmado de COVID-19 con TC inicial en la cual se aplicó la ET para evaluar la afectación pulmonar, identificar el patrón pulmonar y establecer el estadío. El análisis estadístico fue descriptivo y analítico, con cálculo de curva ROC. **Resultados:** 151 pacientes con edad media de 50 años. El patrón pulmonar predominante fue el «empedrado» (46%) identificado en fase de progresión; el área bajo la curva fue 0.831 (IC95%: 0.764-0.898) con punto de corte 16.5 para discriminar la afectación grave, con sensibilidad de 84% y especificidad de 74%. **Conclusión:** El uso de la ET en TC inicial mostró una sensibilidad aceptable para identificar la gravedad de la enfermedad.

Palabras clave: Gravedad, escala tomográfica, pulmón, COVID-19, enfermedad respiratoria.

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INTRODUCTION

The SARS-CoV-2 virus is responsible for the COVID-19 disease, causing the current pandemic and a global public health emergency; the clinical manifestations of this condition can progress from mild symptoms to acute respiratory distress syndrome.[1-3] High morbidity and mortality rates have placed Mexico as one of the countries with the greatest affectation;[4] this could be due to different risk factors[5] and comorbidities (obesity, hypertension and

diabetes *mellitus*) that affect our population,[6] because they have an important role in the progression and evolution of COVID-19 diseases.[7-9]

Among the diagnosis methods used, chest CT has emerged as the main diagnosis tool, with a sensitivity between 96 and 98%.[10-12] There is controversy about the usefulness of CT as a standard method, experts point out that it is useful for assessing the severity of the disease.[13-15] Typical tomographic lung patterns (TLP) associated with COVID-19 are: ground glass opacity (GGO), «crazy-paving» pattern and consolidation, these are associated with disease progression;[16] these TLP have also been identified in the Mexican population.[17] In the evolution of the disease, the pattern of organizing pneumonia (OP) has been described,[18] characterized by the presence of different TLP such as consolidation, GGO, bronchiectasis, bronchioloectasis, nodules, halo sign, pulmonary parenchymal bands, and perilobular consolidation.[19]

Several studies have proposed semi-quantitative staging methods such as the creation of scales to assess the extent and severity of the damage to the lung tissue. The scales proposed by Chang, *et al*. evaluated the tomographic changes in the recovered population of severe acute respiratory syndrome (SARS), it was found that the CT score was correlated with clinical and laboratory parameters.[20] Likewise, Yang, *et al*. developed a CT scale to determine the severity, they evaluated 20 pulmonary segments to identify the status of parenchyma in severe COVID-19, using the amount of tomographic affectation as a substitute of the load of COVID-19 disease;[21] however, these scales require a domain of pulmonary segmental anatomy that in daily practice are a limitation due to the complexity it represents, since more time in the analysis and interpretation of the findings is needed, it is not compatible with the high demand for care in the health system.

The objective of this study is to develop and evaluate a tomographic scale to determine the severity of COVID-19, that allows us to know the predominant TLP and the stage of disease evolution; the proposal of this scale is characterized by an evaluation by lobes of the lungs, simplifying the interpretation of the imaging study.

MATERIAL AND METHODS

This work was approved by the Ethic Committee of the National Institute of Respiratory Diseases (INER), approval code: C37-20. Cross-sectional study carried out from March to June of 2020; patients who went to the emergency service of INER with a diagnosis of COVID-19, > 18 years, both sexes and confirmed positive result with polymerase chain reaction in real time (RT-PCR) (GeneFinder™ COVID-19 Plus RealAmp Kit) were selected. Imaging studies were selected consequently during the indicated period and only patients who had a chest CT scan at admission or within the first 24 hours after hospitalization were included. The outcome variable to carry out the cut-off point of the scale in the statistical analysis (ROC curve) it was the presence of severe disease defined by the need for intubation and/or death.

Imaging technique

It was used a multidetector scanner SIEMENS brand (SOMATON Sensations model, 64 detectors); A Siemens-branded multidetector tomograph (SOMATON sensations model, 64 detectors) was used; the studies were performed with volumetric acquisition in supine decubitus during maximum inspiration in pulmonary and mediastinal window. All images were reconstructed with high spatial resolution algorithm and B70 lung filter with window amplitude of -600/1,200; for the mediastinum, B30 filter with window width of 50/350 was used.

The images were blinded in random order and independently evaluated by two thoracic radiologists with more than 17 years of experience, obtaining a Cronbach's alpha of 0.912 in the interobserver evaluation. The final decision was reached by consensus with adjudication if there were disagreements in the interpretation.

Table 1: Description of sociodemographic, clinical and tomographic characteristics in patients with COVID-19. N = 151.

Variables	n (%)
Age (years)	50 ± 14
Male	94 (62)
Duration of the disease	9 ± 5
Oxygen saturation percentage	77 ± 14
Presence of comorbidities • Diabetes • Hypertension • Obesity	95 (63) 42 (28) 34 (23) 43 (29)
Score on tomographic scale	18 ± 6
Category • Non-severe (< 16.5 points) • Severe (≥ 16.5 points)	 53 (35) 98 (65)
Tomographic pattern • Ground glass opacity • «Crazy-paving» pattern • Consolidation	 64 (42) 69 (46) 18 (12)
Organizing pneumonia Intubation Death	136 (90) 84 (56) 54 (36)

Qualitative variables were expressed in frequencies (%); quantitative variables were expressed in means ± standard deviation (SD).

Table 2: Comparison of clinical aspects between three groups according to tomographic patterns.

Variables	Tomographic patterns			p
	Ground glass opacity	«Crazy-paving» pattern	Consolidation	
	N = 64 n (%)	N = 69 n (%)	N = 18 n (%)	
Age (years)	49 ± 14	52 ± 13	44 ± 17	0.061
Male	38 (60)	45 (65)	11 (61)	0.787
Duration of the disease (days)	8 ± 5	9 ± 4	8 ± 4	0.531
Oxygen saturation percentage	80 ± 12	76 ± 14	67 ± 17	**0.001**
Presence of comorbidities	39 (63)	44 (65)	12 (71)	0.842
Score on tomographic scale	15 ± 6	19 ± 4	20 ± 5	**< 0.001**
Organizing pneumonia	53 (39)	66 (48)	17 (13)	**0.038**
Intubation	26 (41)	44 (64)	14 (78)	**0.004**
Death	20 (31)	27 (39)	7 (39)	0.616

Qualitative variables were expressed in frequencies (%); quantitative variables were expressed in means ± standard deviation (SD). For the comparison of proportions, the χ^2 and ANOVA tests were used for analysis of variance.

Determination of tomographic scale (TE) score

To assess lung involvement using the scale, the percentage of affected tissue in each lobe was determined. The TLP were defined based on what is stablished in the Glossary of the Fleischner Society.[22]

Severity scale description

The proposed TE is an adaptation of the scale developed by Chang *et al.* for patients with SARS, in which findings such as GGO, consolidation and air entrapment are identified and correlated with clinical and laboratory parameters.[20] The present scale evaluated the extent of structural changes in each lobe, resulting in a score of zero to five points for each lobe. Based on the score, a value of zero indicates no involvement, one indicates involvement of less than 5% of the lobe, two indicates > 5-25%, three indicates > 25-50%, four indicates > 50-75% and five indicates > 75%. The total sum of the score obtained for each lobe varies from zero to 25 points. The scores are divided into two groups according to the cut-off values obtained with the ROC curve, where a cut-off point of 16.5 points indicates severe disease.

For the qualitative evaluation of the TLP, the main findings in viral pneumonia are GGO (category A, initial stage of involvement), «crazy-paving» pattern (category B, stage of progression) and consolidation (category C, advanced stage).[16,23]

Statistical analysis. A descriptive analysis was performed as well as a χ^2 test for differences between proportions, and a Student's t test for mean comparisons. ANOVA was used for comparisons between TLP. ROC curve analysis was developed to determine the usefulness of the scale among patients with severe and non-severe COVID-19. Logistic regression was performed to determine variables associated with the scale score. A value $p \leq 0.05$ was considered significant.

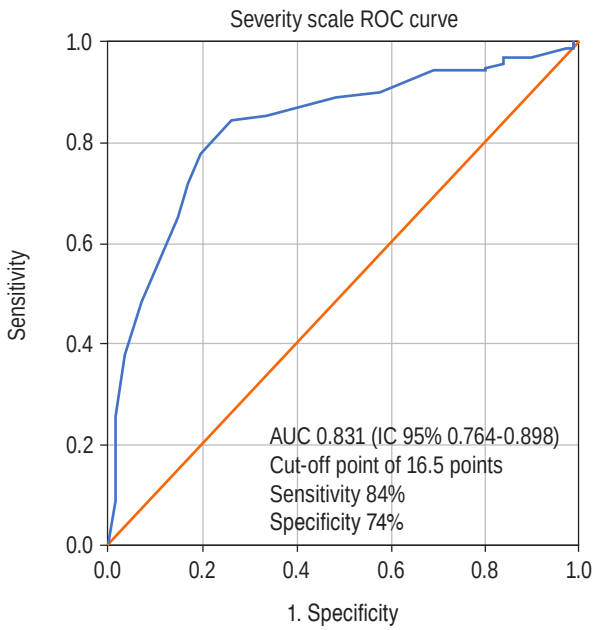

Figure 1: ROC curve cut-off on the tomographic scale to assess its utility in discriminating between severe and non-severe COVID-19 patients.

RESULTS

151 patients with COVID-19 pneumonia were included. *Table 1* describes the sociodemographic, clinical and tomographic characteristics; 62% were men, with a mean age of 50 years and a mean disease duration of nine days. The total score obtained in the TE was 18 points, therefore, 65% had severe disease and 35% non-severe disease. The observed TLP were: 46% «crazy-paving» pattern, 42% GGO and 12% consolidation; 90% had a NO pattern. Overall, 56% of patients required intubation and 36% died.

In data not shown in tables, the comparison of clinical characteristics between patients with severe and non-severe COVID-19, severe patients were older (52 years of age vs. 45 years of age, p = 0.008). Oxygen saturation was significantly lower in patients with severe disease (71 vs 87%, p < 0.001), the same patients obtained a higher punctuation in the TE (21 points vs 11 points, p < 0.001). Finally, the presence of NO was higher in severe patients (97 vs 77%, p < 0.001).

Table 2 compares the clinical characteristics among the three groups stratified by TLP. The groups were age, duration of disease, distribution of comorbidities, and mortality rates similar. Patients with consolidation had a lower mean percentage of oxygen saturation (67 vs 76% in patients with the «crazy-paving» pattern and 80% in those with GGO, p = 0.001). The score on the scale was significantly higher in patients with consolidation than in patients with other patterns (mean of 20 points vs. 19 points in patients with the «crazy-paving» pattern and 15 points in those with GGO, p < 0.001). The presence of NO was higher in patients with a «crazy-paving» pattern compared to the other TLP (p = 0.038). There was a need of intubation in patients with consolidation findings (p = 0.004).

Figure 1 shows the results of the analysis to determine the cut-off point in the tomographic scale base on the ROC curve to identify severe and non-severe disease in patients with COVID-19. The area under ROC curve was 0.831 (IC de 95%: 0.764-0.898) for the cut-off value of 16.5 (sensitivity, 84%; specificity, 74%).

Table 3 shows the results of the linear regression analysis that was performed to determine the clinical variables associated with severe disease, according to the scale score; the selection of the variables was included by biological plausibility. After adjusting for age, it was observed that the longer the duration of the disease (p = 0.02) the lower the oxygen saturation (p < 0.001) and the need for intubation or death (p < 0.001); a higher score result will be obtained in the TE.

The different TLP identified in the study: a) GGO pattern, b) «crazy-paving» pattern, and c) mixed pattern are shown in the *Figure 2*. According to the qualitative assessment of

Table 3: Linear regression to evaluate the association of clinical variables with the tomographic scale. N = 151.

Patients with COVID-19	Method: Enter		Method: Stepwise	
	β	p	β	p
Age	0.01	0.651	–	–
Duration of the disease	0.17	**0.027**	0.17	**0.027**
Oxygen saturation percentage	-0.18	**< 0.001**	-0.18	**< 0.001**
Severity (intubation/death)	2.88	**0.001**	2.93	**0.001**

Dependent variable: scale score. The covariates included this analysis were the qualitative and quantitative variables with biological plausibility that explain severity.

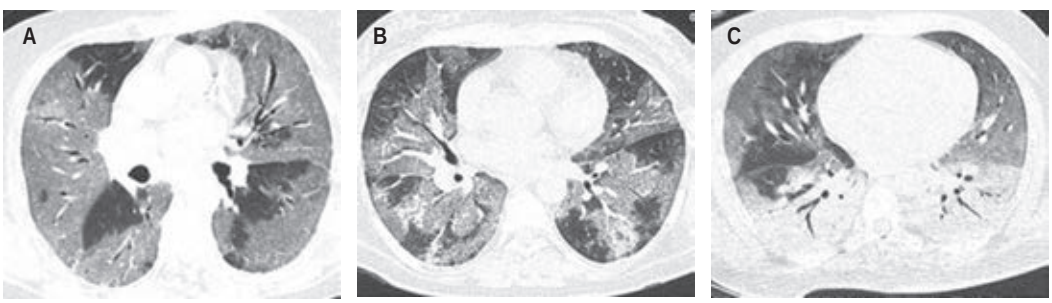

Figure 2: Axial chest tomography images with window for lung parenchyma in three different patients to demonstrate the different patterns. **A)** Ground glass opacity pattern, diffuse distribution, bilateral with subpleural predominance. **B)** Predominantly central-peribronchial «crazy-paving» pattern. **C)** Mixed pattern, mid-lobeglass ground glass opacity pattern and lingula associated with a consolidation pattern in lower lobes.

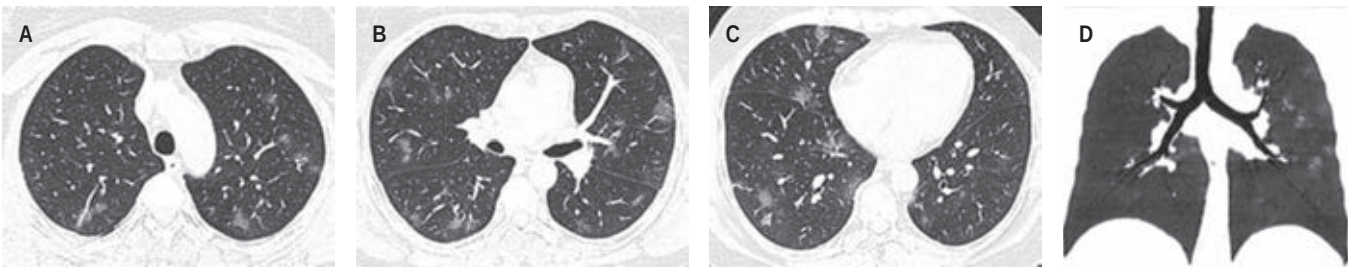

Figure 3: A-C) Thoracic axial tomography images with window for pulmonary parenchyma. **D)** MiniP coronal reconstruction. Ground glass with random distribution in patches, score of 5/25 points, category A, non-severe disease.

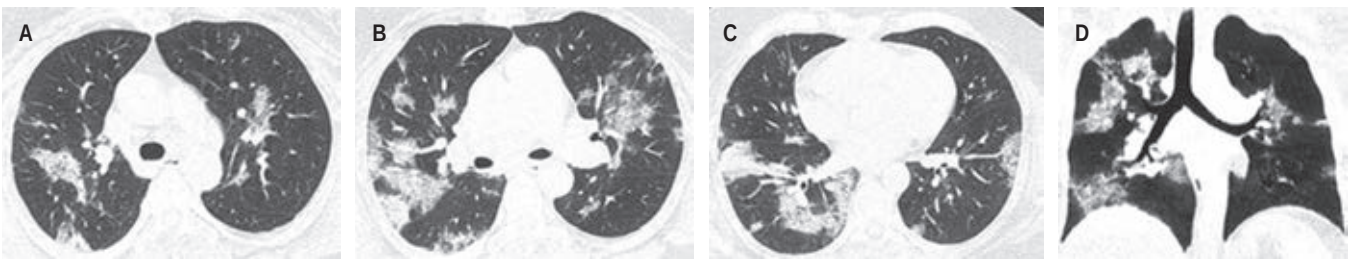

Figure 4: A-C) Thoracic axial tomography images, with window for pulmonary parenchyma. **D)** MiniP coronal reconstruction. Predominant «crazy-paving» pattern with consolidation focal areas with subpleural and peribronchial distribution, score of 13/25 points, category B, non-severe disease.

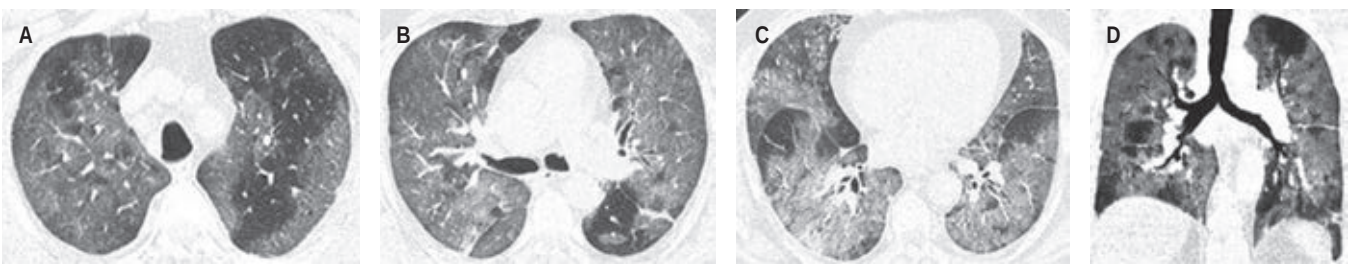

Figure 5: A-C) Thoracic axial tomography images with pulmonary parenchyma window. **D)** MiniP coronal reconstruction. Predominant pattern of bilateral, diffuse ground glass with areas of «crazy-paving» pattern in posterior and inferior segments, score of 24/25 points, category A, severe disease.

the predominant TLP of the disease it was given category A (initial stage of involvement) identifying a mean score in the TE of 15 points, with 48% of severe disease *(Figure 3)*; category B (stage of progression) showed a mean score on the scale of 19 points, with a severe disease at 77% *(Figure 4)*; and category C obtained a mean score of 20 points, with 78% of severe disease (advanced stage). However, we found a higher frequency of severe disease according to the score obtained in the TE *(Figure 5)*, regardless the stage of disease progression.

DISCUSSION

This paper proposes the adaptation of a semi-quantitative TE for the evaluation of pulmonary involvement in patients with COVID-19. The analysis of the ROC curve, the area under the curve was of 0.831 (95% CI: 0.764-0.898), with a sensitivity of 84% and specificity of 74%, using a cut-off point of 16.5, for the prediction of serious disease.

Yang, *et al.* applied a semi-quantitative TE to evaluate 20 segments, with a total score between zero and 40, with a cut-off point of 19.5, the scale could identify a serious disease with a sensitivity of 83.3% and specificity of 94%.[21] Compared to the scales used in the present study, the scale described above had higher cut-off and diagnostic value; however, the reproducibility of the assessment with a lung segment scale is reduced in staff with less experience in the thoracic area.

Francone *et al.* in a longitudinal study evaluated a TE in patients with COVID-19 through the assessment of the initial

CT, with the aim to predict mortality by obtaining a score on the scale equal to or greater than 18 points. In this study we did not follow up patients but a regression analysis was proposed to identify clinical variables that were associated as predictors of severity of severe disease based on the proposed TE score.[15]

Pan *et al.* identified the TLP and described the stage of disease assessment.[16] In this study, the «crazy-paving» pattern was the most common corresponding to the stage of disease progression, attributable to the date of acquisition of the tomography, which on average was performed on the ninth day of set of symptoms. In addition, individuals with consolidation were observed to have higher initial severity scores and lower oxygen saturation ($p = 0.01$), a figure that is consistent with that reported in the study by Pan *et al.*[16] y Sabri *et al.*[24] in which they identified the greatest severity of the disease is observed with the consolidation pattern. According to the TLP identified in the present study, a pattern similar to those described in patients with SARS and MERS is evident.[23,25]

The mortality rate identified was similar between patients with a «crazy-paving» patterned those with consolidation; a higher risk of mortality has been observed in patients with comorbidities, initially described in China; this association was not significant in our study.[26] The mortality rate in our study was 36%, similar to that reported by Yuan M. *et al* 37%,[9] however, these authors related elderly age and underlying diseases (hypertension, diabetes and heart disease), with the presence of this event; despite the high percentage of patients with comorbidities in our population, this finding was not significant ($p > 0.05$).

CONCLUSION

The application of TE in the initial CT as a diagnostic test demonstrated a good sensitivity to identify the severity of the disease in the population served in the institute; it is useful to know the predominant TLP and the stage of the evolution of the disease, therefore, it is proposed to implement the use of this scale in the evaluation of initial TC of patients with COVID-19.

The limitations of this research include the lack of follow up, which does not allow the scale to be applied to other CT scans performed at different stages of the disease; therefore it is necessary to carry out longitudinal studies to evaluate the effectiveness of the scale and its contribution in clinical decision-making.

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Original

Implications of the body weight of older adults hospitalized for community-acquired pneumonia in the capacity to expectorate, severity on admission and lethality

Implicaciones del peso corporal de adultos mayores hospitalizados por neumonía adquirida en la comunidad en la capacidad para expectorar, gravedad al ingreso y letalidad

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ABSTRACT. Introduction: One of the diseases whose course can be altered as a consequence of the nutritional status of the patient is community-acquired pneumonia. **Objective:** To determine the implications of different states of the body weight of patients hospitalized for pneumonia in the capacity to expectorate, in the state of severity at the time of admission and in the lethality due to the disease, taking into account the age of the patients. **Material and methods:** Descriptive study, with 967 patients hospitalized for community-acquired pneumonia between April 2016 and December 2019, whose body mass index was calculated. Bivariate and multivariate analysis (logistic regression) was performed; The ratio of crossed products (*odds ratio*) and its 95% confidence interval were used as the statistician. **Results:** A slightly significant association was observed between being overweight and age under 60 years (OR 1.3 [1.02;1.8]), and more evident between underweight and older adults (OR 2.3 [1.4,3.7]). Low weight was significantly associated with the inability to expectorate (OR 1.5 [1.1;2.1]), the state of severity at the time of admission (OR 2.1 [1.5;3]) and death of the patient (OR 2 [1.4,2.8]), specifically in older adults. **Conclusions:** Low body weight in older adults with pneumonia determines the inability to expectorate, a state of severity at the time of admission and a higher risk of death, which is why it constitutes an adverse prognostic factor.

Keywords: Community-acquired pneumonia, severity, malnutrition, older adult.

RESUMEN. Introducción: Una de las enfermedades cuyo curso puede alterarse como consecuencia del estado nutricional del paciente es la neumonía adquirida en la comunidad. **Objetivo:** Evaluar las implicaciones de diferentes estados del peso corporal de pacientes hospitalizados por neumonía en la capacidad para expectorar, en el estado de gravedad al momento del ingreso y en la letalidad por la enfermedad, teniendo en cuenta la edad de los pacientes. **Material y métodos:** Se realizó un estudio descriptivo que incluyó 967 pacientes hospitalizados por neumonía entre abril de 2016 y diciembre de 2019, en quienes se evaluó el peso mediante el índice de masa corporal. Para evaluar la asociación del peso corporal con la capacidad para expectorar, el estado de gravedad y la letalidad se realizó análisis bivariante y multivariado (regresión logística); como estadígrafo fue utilizada la razón de productos cruzados (*odds ratio*) y su intervalo de confianza de 95%. **Resultados:** Se observó una asociación significativa entre el exceso de peso y la edad por debajo de 60 años (OR 1.3 [1.02;1.8]), y más evidente entre el bajo peso y los adultos mayores (OR 2.3 [1.4;3.7]). El bajo peso estuvo significativamente asociado a la incapacidad para expectorar (OR 1.5 [1.1;2.1]), al estado de gravedad al momento del ingreso (OR 2.1 [1.5;3]) y al fallecimiento del paciente (OR 2 [1.4;2.8]), específicamente en los adultos mayores. **Conclusiones:** El bajo peso corporal en los adultos mayores con neumonía condiciona incapacidad para expectorar, estado de gravedad al momento del ingreso y mayor riesgo de muerte, por lo que afecta adversamente el pronóstico.

Palabras clave: Neumonía adquirida en la comunidad, gravedad, malnutrición, adulto mayor.

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INTRODUCTION

The association between the nutritional state and the increase of morbidity and mortality in older adults has determined that a major attention is given to the aspects related to the malnutrition in this population. In this sense, it is recognized that in certain populations called «third and fourth age» the overweight and obesity are not rare,[1,2] the malnutrition is considered as a problem of great incidence in such a stage of life, which could influence in the life quality of the person and in the prognosis of various pathological processes.[3-7]

One of those processes which course can be altered as a consequence of the nutritional state it is the community-acquired pneumonia (CAP). Named by Sir William Osler, ironically, as «the friend of old people» due to its high frequency after 60 years of age, CAP constitutes currently an important problem of public health due to its well known association with death.[8-13] In our country specifically, the infections of the respiratory system have represented the fourth cause of death during the last years, being the first among the causes of infectious nature.[14]

In the Hospital «Dr. Gustavo Aldereguía Lima» of Cienfuegos, Cuba studies have been carried out, directed to the identification, in the local context, of associated factors with death of patients assisted by CAP, which includes the nutritional state in general, and the corporal weight in specific, but without significant statistical results about it.[15] Moreover, the daily assisted practice of the authors has allowed us to observe the affectation to the ability to expectorate from patients whose body weight is diminished; affectation that at the same time interferes in the correct evolution of these sick people.

The objective of the study consisted of assessing the implications of different weight loss state of hospitalized patients by CAP in the capacity to expectorate, in the state of severity at the time of admission and in the lethality due to the disease, taking into account in the analysis their age.

MATERIAL AND METHODS

An observational study was carried out, with a descriptive design, covering a population of 967 patients (221 between 18 and 59 years of age and 746 elderly adults) with a coinciding diagnosis admission-discharge of CAP, hospitalized in the institution in the period between April 2016 and December 2019. The research subjects represented 87.5% of the total CAP admissions in the studied period (1,105 cases), constituting a sample for convenience determined by the quality of the information presented in the clinical history. The diagnosis of pneumonia and its community origin, confirmed by the authors, was based on the clinical, radiological and necropsy criteria (in the diseased, if any) established.[16-19]

Techniques and procedures: The authors reviewed the medical records of each patient to obtain the necessary information: age, weight, size, capacity to expectorate, state of severity at the time of admission and state at discharge; in the cases that required it, clarifications were made directly with the patient or their relatives.

Anthropometric evaluation was performed by calculating the body mass index (BMI) or the index of Quetelet, using the formula «weight (in kg) divided by size (in meters) squared».[20-22] The patient was considered «normal or normal weight» when the BMI was between 18.5 and 24.9, according to the criteria of the World Health Organization (WHO);[23] above and below these values were considered «excess weight» and «low weight», respectively. Low weight in turn, specifically for older adults, was classified as mild (BMI between 17 and 18.4), moderate (BMI between 16 and 16.9) and severe (BMI less than 16).[23]

The patient with «capacity to expectorate» was considered when they presented expectoration during any evolutionary moment of the condition; the condition of «inability to expectorate» was reserved for the absence of cough or the existence of dry or wet cough but not productive. Severity status at admission was assessed using the «Instrument for Stratification of Patients with Out-of-hospital Pneumonia» (IENAC).

The IENAC is based on the use by the attending physician of clinical information supplemented with radiological information to frame the patient in one of three classes, according to the severity of the process: mild, moderate or severe pneumonia.

Each class in turn is subdivided into two categories (A or B), determined by specific criteria for each class. In patients with mild pneumonia, the existence or absence of any factor, of any nature, that limits or affects the possibility of outpatient treatment is used as a criterion. In patients with moderate pneumonia, the criterion is related to the existence of some particularity that increases the probability that the patient presents an unfavorable course, even without being serious at the time of its initial assessment; in the case of patients with severe or serious pneumonia, the criterion used is related to the analysis of the probabilities of recovery of the patient.[24-26]

The data obtained was processed on computer using the SPSS version 15.0 for Windows. Bivariate and multivariate analysis was performed, the latter using logistic regression techniques, as a statistician, given the character of a cross-sectional-study, the Odds Prevalence Ratio (ORP) and its 95% confidence interval were used. The results are presented in text, tables and figures, expressed in numbers and percentages.

Ethical considerations: given characteristics of the study, it was not necessary to carry out particular bioethical considerations. However, a strictly scientific use of the results obtained and judgments emanating has been ensured. The study was evaluated and approved by the institution's ethical committee.

RESULTS

Table 1 shows the general behavior of the variables studied. The inability to expectorate was present in almost half of the cases, while in almost one third, a state of severity was observed at the time of hospitalization; the lethality of the series was of 27%. The three variables mentioned were more frequent and statistically significant in patients 60 years of age or older (ORP of inability to expectorate in older adults versus adults not older equal to 1.7 [1.2;2.3]; ORP of presence of severity at admission in order adults versus adults not older equal to 1.8 [1.2;2.5]; ORP of death in older adults versus adults not older equal to 8.8 [4.8;16.1]).

As for body weight, only 37% of the patients were evaluated as normal; the largest number of patients had excess weight (43%), while 191 cases (20%) were classified as «low weight». In the distribution of patients in the different categories of BMI, differences were also found between the population under 60 years of age and older adults. Although the frequency of patients with adequate weight was similar between both subgroups and patients with BMI predominated above normal in both subgroups, excess weight was significantly more frequent in subjects younger than 60 years of age (ORP of excess weight in patients younger than 60 years of age vs older adults equal to 1.3 [1.02;1.8]), while low weight was significantly more

Table 1: Frequency of variables studied according to age group.

	Less that 60 years (N = 221) n (%)	60 years or more (N = 746) n (%)	Total (N = 967) n (%)
Female	99 (45)	395 (53)	494 (51)
Inability to expectorate	85 (38)	391 (52)	476 (49)
Severity at admission	50 (23)	260 (35)	310 (32)
Deaths	12 (5)	251 (34)	263 (27)
Body weight • Excess of weight • Normo weight • Low weight	 110 (50) 86 (39) 25 (11)	 312 (42) 268 (36) 166 (22)	 422 (43) 354 (37) 191 (20)

Table 2: Frequency of inability to expectorate, severity at admission and lethality according to body weight.

	Inability to expectorate (%)	Severity status at admission (%)	Lethality (%)
Excess of weight (N = 422)	45	28	22
Normo weight (N = 354)	48	29	27
Low weight (N = 191)	58	47	40

frequent in patients 60 years of age or older (ORP of low weight in older adults vs patients younger than 60 years of age equal to 2.3 [1.4;3.7]).

the total study population *(Table 2)*, both inability to expectorate and severity status at admission and death were significantly more frequent in patients with low body weight (ORP of inability to expectorate in subjects with low body weight versus subjects without low body weight equal to 2.1 [1.5;3]; ORP of severity status at admission in patients with low body weight versus patients without low body weight equal to 2 [1.4;2.8]).

The behavior described above for the total subjects showed some differences depending on the age of the patients *(Figures 1 to 3)*. For example, in patients under 60 years of age, there were no obvious differences in the frequency of inability to expectorate, the state of severity at admission and lethality, between the different categories of body weight.

In contrast, in the elderly population of the study, the frequency of the inability to expectorate was significantly higher in cases with low body weight (ORP of inability to expectorate in patients with low body weight versus subjects without low body weight equal to 1.5 [1.08;2.1]); also the severity status at admission and the occurrence of death were significantly more frequent in patients with low body weight (ORP of severity status at admission in patients with low weight versus without lower weight equal to 2.2 [1.6;3.2]; ORP of death in patients with low weight versus patients without low weight equal to 1.7 [1.2;2.5]).

Additionally, when particularizing in the subgroup of elderly with low weight, a progressive (not statistically significant) increase in lethality was observed in correspondence with the decrease in body weight: 42% (of 146 patients) in those of the «low light weight» category and 60% (of 20 patients) in the «low moderate weight» (ORP of death in patients with low moderate weight versus subjects with low light weight equal to 2 [0.8;5.4]). The only case with «low severe weight» died.

In the multivariate analysis y logistic regression, the frequency of death by CAP was significantly higher in all

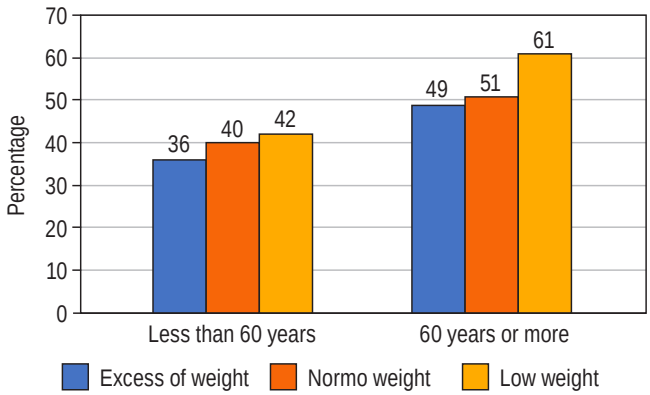

Figure 1: Percentage frequency of the inability to expectorate according to body weight and age.

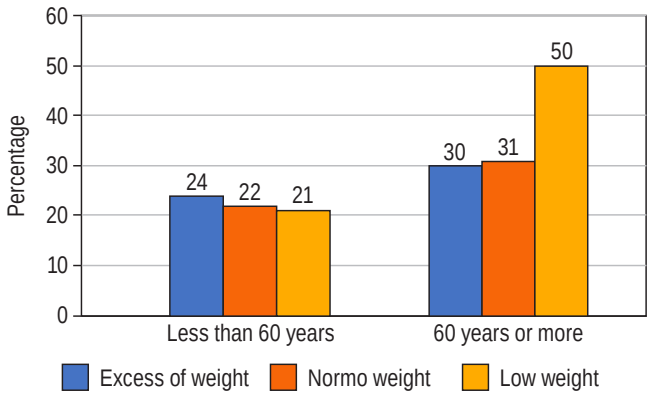

Figure 2: Percentage frequency of the severity status at admission according to body weight and age.

the conditions incorporated into the evaluated model (ORP of death in patients 60 years of age or older versus patients under 60 years of age equal to 8.4 [4.4;15.9]; ORP of death in patients with severity status at admission versus patients without severity status at admission equal to 2.9 [2.1;4]; ORP of death in patients with inability to expectorate versus patients without inability to expectorate equal to 1.4 [1.02;1.9]; ORP of death in patients with low body weight status versus patients without low body weight status equal to 1.4 [1.009;2]).

DISCUSSION

The carried out study found a significantly higher frequency of inability to expectorate, severity at admission and deaths in older adults with CAP, compared to patients under 60 years of age. Similarly, low-body weight status was more frequent (significantly) in this same age group. In these patients with CAP, the elderly, the three variables initially mentioned were significantly associated with low body weight, a situation that did not occur in cases of younger age. For this reason, the analysis of these results focuses on the theoretical elements and implications of the findings particularly in the elderly population.

In human beings there are age-related anatomical-physiological changes. Among the most visible changes, there is the decrease in the subcutaneous fat content, but also a decrease in body water, muscle mass (phenomenon known as sarcopenia) and bone mass.[20,27]

To these physiological changes that affect body weight, are added the decrease in food intake, anorexia associated with psychosocial factors, masticatory and swallowing problems, physiological changes in gastrointestinal function, chronic oncological and non-oncological diseases, polypharmacy and depression, among others, which makes older adults at a great risk of malnutrition.[28-31] All these elements are decisive in the association identified in this study between older adults and the condition of low body weight.

Unfortunately, and despite the recognized situations that lead to a decrease in body weight in people aged 60 years and over, malnutrition by default in older adults is often a long and overlooked process by the staff in charge of caring for these patients.

The elements analyzed in this study are closely related to each other. Low body weight, usually associated with muscular mass loss and the consequent muscular strength decrease, is one of the factors that limit the capacity to achieve a useful cough for the expulsion of secretions resulting from the inflammatory process of the lung parenchyma. Thus factor (low weight) is added to certain changes in the thorax and respiratory system of the older adult including loss of elastic properties of lung tissue, thorax stiffness due to calcification of the rib cartilage and kyphosis, weakness of the respiratory muscles and less effective cough reflex.[20]

Additionally, if the low weight is due to a malnutrition by default, then the risk of infection and poor defense against it

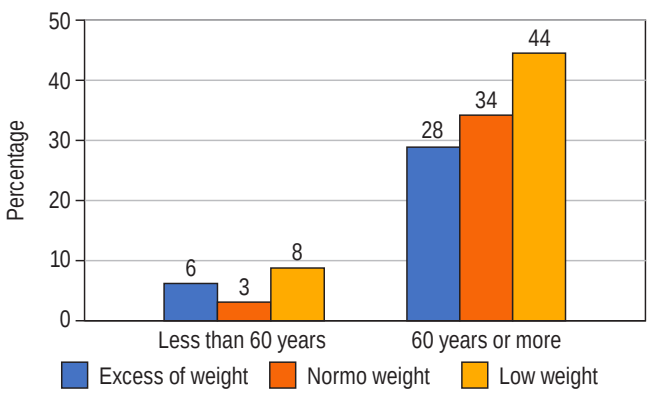

Figure 3: Percentage of lethality according to body weight and age.

(due to deterioration of cellular immune function) is added to the previous elements to condition not only higher risk of pneumonia, but of a more unfavorable prognosis.[20,32] In this sense, the study has shown the early torpid evolution of elderly patients with low body weight, in whom a high percentage already showed signs of severity at hospital admission. It is true that there is a diversity of nutritional assessment scales.

Mini-Nutritional Assessment, Nutrition Screening Initiative, Nutrition Risk Assessment Scale, Global Subjective Assessment (GSA) and Malnutrition Universal Screening Tool.[21] But within the anthropometric evaluation as a dimension of nutritional evaluation, and although it is not devoid of controversy,[20] some authors consider BMI as the most important of all anthropometric parameters, since it is a good prognostic marker in the elderly (higher mortality with a low BMI). The desirable range established by the WHO in people over 65 years of age is 24-30 kg/m^2, because values outside this range increase morbidity and mortality. According to the SENECA study *(Survey in Europe on Nutrition and the Elderly),* for example, it is the BMI of 27.1 (confidence interval [CI] of 95% 24.1-29.3) that confers the lowest risk of mortality. For its part, an excess mortality has been described in an inverse linear relationship with BMI, which begins when it is less than 23.5 in men and 22 in women.[21] In this study, an increase in lethality was observed in patients with CAP as body weight decreased, within the «low weight» condition itself.

Unfortunately, there are not many recent studies that analyze with specificity the associations addressed here, although we already mentioned a previous investigation by the authors where the status of body weight below normal was not associated with higher mortality in patients with pneumonia. However, this study did not take into account in the analysis a distinction of patients according to age, so the analysis was carried out from the results of the total set of subjects.

CONCLUSIONS

It has been considered, by way of conclusion, that in the series of patients with acquired pneumonia in the studied community, the state of low body weight was not only more frequently observed in older adults than in younger ones, but also that in the former, unlike in the latter, it also conditioned the inability to expectorate, the state of severity at admission and higher risk of death, so it has an adverse impact on the prognosis in this subgroup of patients.

The authors recognize as a limitation of the research the difficulties for the extrapolation of their results to subjects with CAP assisted in the community environment, who may not be reflected in the characterization carried out.

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Original

Relationship between maxillary disjunction and level of asthma control in school-aged patients

Relación entre disyunción maxilar y nivel de control del asma en pacientes de edad escolar

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ABSTRACT. Introduction: Dentofacial disorders in children are associated significantly to respiratory disorders, particularly asthma and allergic rhinitis, and although not pinpointed the mechanism by which impact these pathologies craniofacial development, it is suggested that obstruction upper airway difficult nasal breathing forcing the patient to compensate such obstruction by mouth breathing, this condition being the origin of malocclusion. **Objetive:** The present study was conducted to determine whether treatment of malocclusion, specifically the correction of transverse compression maxillary positively influences asthma control assessed by clinical evidence of asthma control (Asthma Control Test) and as spirometry (FEV_1, FEV_1/FVC) at baseline and response tests bronchodilator addition of drug treatment. **Material and methods:** The study just took a group of 15 patients between seven and 12 years of age diagnosed with asthma and allergic rhinitis which were under pharmacological medical treatment for a minimum of six months. **Results:** Among the main results it was observed that there is a significant correlation between the maxillary disjunction and clinical asthma control and lung function in children with asthma and allergic rhinitis, mainly from the third month of orthopedic treatment. **Conclusion:** The use of maxillary circuit breakers, represents an alternative for an adequate management of respiratory disorders manipulating the conditions in the generation processes making the proposed system more efficient.

Keywords: Asthma, rhinitis, maxillary disjunction.

RESUMEN. Introducción: Las alteraciones dentofaciales en la edad pediátrica se encuentran asociadas de manera importante a trastornos respiratorios, principalmente al asma y la rinitis alérgica, y aunque no está claramente establecido el mecanismo por el cual impactan dichas patologías del desarrollo craneofacial, se sugiere que la obstrucción de la vía aérea superior dificulta la respiración nasal obligando al paciente a compensar dicha obstrucción por medio de una respiración bucal, siendo esta última el origen de la maloclusión. **Objetivo:** El presente estudio tuvo como objetivo determinar si el tratamiento de la maloclusión, específicamente la corrección de la compresión transversal del maxilar superior, influye positivamente en el control del asma evaluado por la prueba clínica de control del asma (*Asthma Control Test*), así como por espirometría (FEV_1, FEV_1/FVC) en pruebas basales y respuesta a broncodilatador, además del tratamiento farmacológico. **Material y métodos:** El estudio se llevó a cabo en un grupo de 15 pacientes entre los siete y 12 años de edad con diagnóstico de asma y rinitis alérgica, los cuales se encontraban bajo tratamiento médico farmacológico por un tiempo mínimo de seis meses. **Resultados:** Se observó una correlación significativa entre la disyunción maxilar y el control clínico del asma y la rinitis alérgica, mejorando de manera importante la función pulmonar a partir del tercer mes del tratamiento de ortopedia dentomaxilar. **Conclusión:** El uso de disyuntores maxilares representa una alternativa para un adecuado manejo de desórdenes respiratorios, manipulando las condiciones en los procesos de generación haciendo el sistema propuesto más eficiente.

Palabras clave: Asma, rinitis, disyunción maxilar.

INTRODUCTION

In order to understand the close relationship between respiratory function and the development of the stomatognathic apparatus, we must remember that the function is closely related to growth and development, in such a way that through nasal breathing multiple nerve endings are stimulated that generate diverse responses such as the amplitude of thoracic movement, three-dimensional development of the nostrils, ventilation and the size of

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the maxillary sinuses, but which also induce the growth and remodeling of the adjacent orofacial structures, as well as the transverse development of the maxilla and the direction of facial growth.[1] Some researchers claim that nasal obstruction is associated with chronic mouth breathing, constituting the main etiological factor of anomalous craniofacial development, manifesting clinically as vertical facial growth or long face syndrome with subsequent dentomaxillary deformities.[2] Among the main stomatological manifestations, deep and narrow palates characterized by inverted V-shaped arches and an increase in palatal depth are reported, with a consequent maxillary protrusion, developing in most cases a class II subdivision 2 malocclusion, also known as distal dysgnathia, associated with mandibular retrusion.[3,4] In addition, mechanical obstructions of congenital origin have been found, such as choanal atresia, alterations in Waldeyer's ring and other endonasal obstructions, as well as physiological alterations of the airways, which if not resolved in time may cause dentocraniofacial deformities.[4] The prevalence of asthmatic problems has been increasing during the last years, rising from 3.2 to 25%, being considered the most frequent chronic respiratory disease.[5] In Mexico, asthma affects from 5 to 8% of the population, with variations among the different regions of the country.[6] The prevalence of asthmatic problems has been on the rise in recent years, increasing from 3.2 to 25%, being considered the most frequent chronic respiratory disease.[5] In Mexico, asthma affects 5 to 8% of the population, with variations among the different regions of the country.[6] Thus, the states of Colima, Tabasco, Chihuahua, Yucatán and Mexico City are those with the highest incidence figures of bronchial asthma.[7,8] Multiple epidemiological, pathophysiological and therapeutic studies have demonstrated the association between allergic rhinitis and asthma; 90% of patients diagnosed with asthma have allergic rhinitis,[9] making it the most frequent chronic disease[10] and the most common childhood allergic disease.[11] It is clinically defined as a symptomatic disorder of the nose induced by immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose following exposure to an allergen.[10] Asthma and allergic rhinitis are chronic respiratory diseases that obstruct the upper airways,[12] inducing an alternative mode of breathing and contributing to breathing through the mouth,[7-9] resulting in orofacial developmental disorders, with dental malocclusion being the most frequent manifestation and of greatest interest to the pediatric stomatologist.[13] The development of the craniofacial mass and specifically the components of the stomatognathic apparatus may be altered in the presence of a nasorespiratory obstruction, since if nasal breathing is compromised, it is compensated by oral breathing,[14] which causes an imbalance between the lips, buccinator muscles and tongue, exerting an abnormal force on the vestibular and lingual faces of the teeth, resulting in dental malpositions, mainly in the transversal direction.[15]

However, the severity of asthma can change over time and depends not only on the severity of the underlying disease but also on its response to treatment.[16] Asthma and allergic rhinitis have been defined as chronic inflammatory airway diseases, which are closely related, especially in childhood, and are manifested by both upper and lower airway obstruction, emphasizing that for good asthma control it is important to adequately control allergic rhinitis, as lack of control of the latter leads to a suboptimal level of asthma control.[17] In the most recent revision of the global initiative for the treatment of asthma GINA 2021, it is established that asthma should be evaluated periodically to verify the level of control of the disease and it is classified as: completely controlled, partially controlled or not controlled at all, as well as to perform pulmonary function measurements by means of spirometry or flowmetry, which allows determining the risk of possible later complications. Likewise, in cases where good control is not achieved, it is recommended to investigate adherence to treatment and the correct technique for the use of inhaled medications, as well as adverse environmental factors, comorbidities such as allergic rhinitis, rhinosinusitis, obesity, among others.

The objective of this research work was to establish how pediatric patients with a diagnosis of asthma and with strict pharmacological control of asthma, who present long face syndrome due to being chronic mouth breathers, can improve their pulmonary function by receiving a dentofacial orthopedic treatment, specifically, rapid maxillary expansion.

MATERIAL AND METHODS

The sample consisted of 15 patients who attended the Pediatric Pneumology Service of the Hospital Infantil de Especialidades del Estado de Chihuahua, aged between 7 and 12 years, all of whom had a baseline diagnosis of asthma and allergic rhinitis. These patients were under strict pharmacological control; However, when they were checked by the pediatric stomatologist, long face syndrome and maxillary compression in a transversal sense were observed, which we consider to be a factor that can interfere in the maximum results that can be obtained with the pharmacological medical treatment, for which reason, with previous authorization of the parents, each one of them was given a stomatological file that included diagnostic aids such as panoramic X-rays and study models, as part of the treatment and follow-up by the Pneumology Service, the patients were evaluated on four occasions, with a time interval of 30 days between one evaluation and another. The first intervention consisted in the evaluation

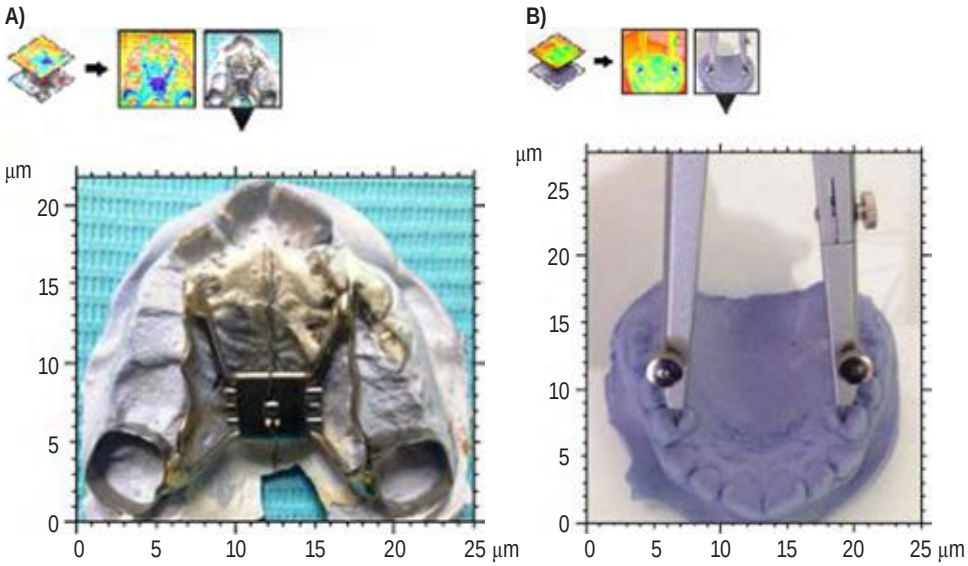

Figure 1:

A) A Hyrax® type rapid maxillary expansion screw is shown. **B)** It can be seen how the transverse width of the maxilla is calculated with the intention of obtaining the dentomaxillary discrepancy.

of asthma control by the treating pulmonologist, applying the Asthma Control Test (ACT), with the presence of the pediatric stomatologist to determine if despite being well controlled the patient presented long face syndrome and transverse compression of the maxilla.

The following protocol was followed during the four visits: first the ACT test was performed, then spirometry was performed with an EasyOne® ultrasonic spirometer to determine the values of forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), as well as the FEV1/FVC ratio, and finally a bronchodilator was applied, and after 20 minutes the spirometry was repeated in a comparative manner.

- Pharmacological treatment. All patients who participated in the study were under the following pharmacological scheme for asthma: an inhaled steroid was used in combination with a long-acting β2 agonist (salmeterol/fluticasone) in metered-dose aerosol, at a low dose of fluticasone, that is, a bottle containing a concentration of 25/50 µg, to receive in total 100/200, the total dose being 50/100 µg every 12 hours of salmeterol/fluticasone. As for the treatment of allergic rhinitis, this consisted of the application of a nasal spray of mometasone fuorate 0.05%, with 50 µg per dose every 24 hours in both nostrils.
- Dentomaxillary orthopedic treatment. The orthopedic treatment consisted of placing an 11 mm Hyrax® type fixed palatal disjunctor, adjusting universal steel Dentaurum® orthodontic bands in upper first permanent molars and impressions were taken with Kromopan® alginate, impressions were taken with Kromopan® alginate, which were cut in high resistance stone plaster type III Magnum®, thus obtaining a working model, on which the fast maxillary disjunction appliance was made, to finally be cemented in the patient's oral cavity with a reinforced glass ionomer AquaCem®. The amount of activation was indicated to each patient according to the degree of maxillary compression estimated by means of the space analysis proposed by Pont, which consists of estimating the arch perimeter necessary for dental eruption based on the mesiodistal width of the upper permanent incisors and upper permanent lateral incisors *(Figure 1)*. Once the expansion was completed, the appliance was left for three months without activation, acting as a retainer, thus allowing the ossification of the palatal suture at the site of disjunction, reducing the possibility of recurrences. Once the ossification of this area was corroborated by taking an occlusal radiograph, the appliance was removed. The data obtained were analyzed using SPSS version 2021 statistical software. The present work was carried out in accordance with the codes of ethics of the world medical association for experiments, including human experiments.

RESULTS

ACT test. Of the patients who attended the pulmonology office of the Hospital Infantil de Especialidades de Chihuahua, 15 participated in this research protocol, who were under strict pharmacological control, with a minimum treatment time of six months, such treatment was focused on the control of asthma and allergic rhinitis, the sample consisted of 10 male patients and five female patients, between the age ranges of seven to 12 years, with a mean of 8.46 and a SD of 1.50 years. The age at which patients were diagnosed as asthmatic ranged from five to 96 months, with a mean age at diagnosis of

39.53 months (3.2 years) and a SD of 24.60 months (2.05 years). All patients underwent a space analysis, obtaining the degree of transverse maxillary compression, where a mean compression in the anterior segment of 4.6 mm was observed, and in the posterior segment of 5.2 mm, with a SD of 1.5 and 2.4 mm, respectively. It is important to mention that when there is a transverse compression of the maxilla, the palate becomes deeper at the expense of the floor of the nostrils. An anterior maxillary compression standard deviation of 1.5 mm and a posterior maxillary compression standard deviation of 2.4 mm was obtained.

Based on the results obtained in the ACT test, it was observed that all the patients in the sample had good or acceptable control of their clinical condition, since their score was equal to or greater than 20 points as an effect of the continuous pharmacological treatment they had at least six months before entering the study. However, the patients clinically manifested adenoid facies and long face syndrome, a sign that the patient is a mouth breather, which almost always causes maxillary compression, a manifestation corroborated by the pediatric stomatologist at the first visit, as previously mentioned. Spirometry studies were also performed in all visits to each of the cases as part of the objective evaluation of asthma control by measuring pulmonary function according to age, weight and height and thus FEV_1 and its predicted percentage, FVC and its predicted percentage and the FEV_1/FVC ratio were obtained. It should be noted that spirometry provides an objective measurement to determine airway obstruction in patients with asthma and to measure the level of severity of airway obstruction. The FEV_1/FVC ratio allows determining the presence of airway obstruction, since normally this index should be greater than 0.8. When it is less than 0.8, an obstructive pattern is defined in the spirometry and to classify the degree of obstruction the FEV_1 result is used compared to its predicted value, leaving this classification of obstruction as described in *Table 1*.

Table 1: Classification of the degree of obstruction obtained by spirometry.

FEV_1 % of predicted value	Obstruction
70-80	Mild
60-69	Moderate
50-59	Moderately severe
35-49	Severe
< 35	Very severe

The FEV_1 values obtained were equal to or greater than 85% of the predicted value from the first visit or visit zero *(Table 2)*, indicating good asthma control due to strict adherence to pharmacological treatment; however, it can be observed that at visit three there was a significant increase in the same reaching values of 89.6% of the predicted FEV_1, here the variable included was the rapid decompression of the maxilla in a transverse direction. This allows us to suggest that such decompression favors pulmonary function. The above data were verified with a Pearson correlation where we found that the highest correlation was between the percentage predicted at visit two and visit three. There is a statistically significant increase from visit one, increasing and lasting the effect until visit three *(Table 3)*.

As part of the protocol, spirometry with application of a bronchodilator was performed 20 minutes after the baseline

Table 2: Predicted percentage values for baseline spirometry at each visit for all patients.

FEV_1 % predicted	Media ± standard deviation	Minimum	Maximum
Visit 0	86.108 ± 15.92256	63.79	110.89
Visit 1	85.97467 ± 14.07274	62.76	110.89
Visit 2	85.85067 ± 17.9075	51.44	111.83
Visit 3	89.608 ± 14.53569	65.33	113.10

Table 3: Correlation between variables with post BD FEV_1 and baseline FEV_1 values (Pearson correlation).

FEV_1	%PRED/0	%PRED/1	%PRED/2	%PRED/3
%PRED/0	1.0000			
%PRED/1	0.6983	1.0000		
%PRED/2	0.7791	0.9096	1.0000	
%PRED/3	0.7096	0.8445	0.9163	1.0000

spirometry, for comparative purposes, by obtaining the average percentage change using the following formula:

$$(FEV_1 \text{ post BD} - FEV_1 \text{ baseline})$$

$$\text{Baseline } FEV_1 = \% \text{ change}$$

When the percentage change is greater than 12% there is a significant change and thus the volume measured in milliliters was using the following formula: FEV_1 post BD - FEV_1 basal, when it is more than 150 mL (200 mL), we have a significant change.

The mean percentage change was less than 12%, which indicates that there is no significant change after the application of the bronchodilator, which means that most patients were well controlled pharmacologically, although between visits zero and one some cases showed an increase of more than 12%, which indicates that despite the pharmacological treatment at the time of maxillary expansion, an additional improvement in pulmonary function was obtained, as shown in cases 6 and 14 of *Table 4*.

Table 4: Average percent change per patient post BD.

Patient	Visit 1	Visit 2	Visit 3	Visit 4
1	5.83	1.77	1.76	3.42
2	0.79	1.43	6.95	1.43
3	0.47	7.92	11.48	4.43
4	2.76	8.19	1.78	0.56
5	6.17	4.50	2.48	6.43
6	8.13	11.85	2.96	19.85
7	11.66	11.40	4.54	5.09
8	5.9	7.93	8.71	7.93
9	1.27	1.29	2.56	1.94
10	4.25	8.69	4.66	6.21
11	3.91	3.16	1.25	5.30
12	3.75	17.70	4.70	8.69
13	3.31	2.44	3.33	2.44
14	26.05	21.81	15.05	13.97
15	3.40	0.33	5.26	2.30

A Pearson correlation was made between the percentages of change and maxillary compression and the following was found: there is a statistically significant and positive correlation between anterior and posterior compression (0.77), which means that as the anterior maxillary compression increases, so does the posterior maxillary compression. The percentage of change between visit zero and visit one is also positive (as the percentage of change between visit zero increases in this sample so does that of visit one (0.70), that is, as maxillary expansion increases the percentage of change, this effect was also observed in visit two (0.59) although to a lesser degree and visit three (0.67) *(Table 5)*.

Due to the great demographic variability in the country on the prevalence of asthma and rhinitis in children and adolescents, the results shown in this research are conclusive to represent a statistical behavior with positive bias, since it is more common to find values above the value of zero and not below zero, which would show the total absence of such clinical manifestations.

DISCUSSION

In the present study, the ratio of asthmatic patients corresponds to a ratio of 2:1 with respect to gender, that is, it is more frequent in the male gender in pediatric age. Most orthopedic treatments in asthmatic patients are aimed at increasing nasal airflow by disjunction of the maxilla, decreasing airflow resistance from 45 to 53%.[17] When the mid-palatal suture is expanded, nasal airflow capacity is increased when measured at maximal effort.[18] Other authors have evaluated the changes in nasal airflow after rapid maxillary expansion, with a significant increase in airflow through the nasal passage.[19] It is important to mention that

Table 5: Pearson's correlation between percent change and maxillary compression post BD.

		Compression		% of change			
		Anterior	Posterior	Visita 0	Visita 1	Visita 2	Visita 3
Compression	Anterior	1.000					
	Posterior	0.7788	1.000				
% of change	Visit 0	-0.0996	-0.2330	1.000			
	Visit 1	0.2792	0.1928	0.7029	1.00		
	Visit 2	-0.1160	-0.2868	0.5308	0.5327	1.000	
	Visit 3	0.2049	-0.1017	0.5915	0.6795	0.2897	1.000

none of the studies found in the literature review performed a measurement like this, being that spirometry is a useful, reliable and accessible tool in tertiary hospitals such as the Hospital Infantil de Especialidades de Chihuahua. It is worth mentioning that the maximum improvement in pulmonary function measured by spirometry was observed three months after maxillary expansion, which had not been previously reported by other authors. In this study it is observed that the implementation of the maxillary expansion treatment significantly improved the level of clinical control of asthma as measured by the ACT questionnaire. To show the involvement of the disjunctor during expansion, we propose the following mechanism: due to the fact that disjuncture allows bone separation and this in turn exerts a tension on the palatal suture, a stimulation of osteoblastic activity is generated for bone formation function through the generation of mechanical stress between the sections of the maxillary bone with the consequent production of mediators such as prostaglandins, nitric oxide and growth factors that are able to overcome the resorption process.

CONCLUSIONS

It is essential to perform a multidimensional evaluation of the patient's asthma control, since the ACT test alone should not be considered reliable because it is a subjective test, since it depends on the patient's responses; however, when correlated with pulmonary function it acquires a greater value, since it is expected to have a normal ACT test with a good pulmonary function, the latter measured with baseline spirometry. Now, in this study, maxillary expansion was added as a therapeutic strategy with the intention of improving nasal breathing, annulling mouth breathing, so that once the expansion was performed, it could be observed that there was no longer a positive bronchodilator response, which was observed at visit zero, suggesting that prior to the expansion the patient could still improve his lung function, which at visits two and three approached optimal values.

According to the results obtained, maxillary expansion had a negative correlation with FEV1, that is, the greater the maxillary compression, the lower the FEV1 value. These data are important because they show that patients with greater upper airway obstruction have decreased lung function, as measured by spirometry.

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Original

Outpatient follow-up of patients with broncopulmonary dysplasia

Seguimiento ambulatorio de pacientes con displasia broncopulmonar

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ABSTRACT. Introduction: Bronchopulmonary dysplasia (BPD), a chronic lung disease, it is frequent in premature infants who require mechanical ventilation and/or prolonged oxygen therapy. **Objective:** To retrospectively describe demographic characteristics, associated factors and comorbidities in patients with BPD from the Pediatric Pneumology Service of the Hospital Infantil de México Federico Gómez. **Material and methods:** Retrospective observational study. 386 patients with BPD treated between 2014 and 2018 were evaluated. Neonatal, maternal and care variables were analyzed using STATA v.14 software. **Results:** 57.51% were male, with a gestational age of 31 weeks (range: 28 to 35), birth weight of 1,305 g (range 1,160 to 2,870 g); 73.83% were born before week 34. 95.34% were hospitalized between 1 and 3 times; 89.38% had between 1 and 10 visits with Pneumologist in the first two years of life and 26.94% used oxygen in the first visit. Patients with severe BDP used oxygen > 54.2 days (95% CI: 49.23 to 53.33; p = 0.0000). The most frequent comorbidity was neurological alteration (19.69%, p = 0.034) and the basic treatment was inhaled corticosteroids (p = 0.015) and salbutamol (p = 0.014). **Conclusion:** The characteristic of patients with moderate-severe BPD was the prolonged use of mechanical ventilation and supplemental oxygen, where inhaled corticosteroids can be useful for outpatient management.

Keywords: Bronchopulmonary dysplasia, lung diseases, infant premature, premature birth, premature diseases.

RESUMEN. Introducción: La displasia broncopulmonar (DBP) es una enfermedad pulmonar crónica, frecuente en prematuros que requieren ventilación mecánica y/o oxigenoterapia prolongada. **Objetivo:** Describir retrospectivamente características demográficas, factores asociados y comorbilidades en pacientes con DBP del Servicio de Neumología Pediátrica del Hospital Infantil de México «Federico Gómez». **Material y métodos:** Estudio observacional retrospectivo. Evaluó 386 pacientes con DBP atendidos entre 2014 y 2018. Analizó variables neonatales, maternas y de atención, mediante el software STATA v.14. **Resultados:** El 57,51% fue de sexo masculino, con edad gestacional de 31 semanas (rango: 28 a 35), peso al nacer de 1.305 g (rango 1.160 a 2.870 g). 73,83% nació antes de la semana 34. El 95,34% se hospitalizaron entre una y tres veces; 89,38% tuvo en los dos primeros años de vida entre una y 10 consultas con Neumología y 26,94% usaba oxígeno en la primera consulta. Pacientes con DPB grave usaron oxígeno > a 54,2 días (IC95%: 49,23 a 53,33; p = 0,0000). La comorbilidad más frecuente fue la alteración neurológica (19,69%, p = 0,034) y el tratamiento de base fueron corticoides inhalados (p = 0,015) y salbutamol (p = 0,014). **Conclusión:** La característica de pacientes con DBP moderada-grave fue el uso prolongado de ventilación mecánica y oxígeno suplementario, donde los corticoides inhalados pueden ser útiles para manejo ambulatorio.

Palabras clave: Displasia broncopulmonar, enfermedad pulmonar, recién nacido prematuro, prematuro, enfermedades del prematuro.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) was described by Northway, Rosen and Porter (1967) as a lung disease in preterm infants requiring prolonged mechanical ventilation and high levels of supplemental oxygen[1,2] and is defined by total duration of supplemental oxygen use, positive pressure requirement and gestational age, as well as oxygen dependence at 36 weeks postnatal age.[3,4]

The incidence in care centers varies between 20 and 75%.[5] Cohort studies such as ELGAN, Canadian Neonatal Network, Korean Neonatal Network, Vermont-Oxford

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Network and Swiss Neonatal Network, and studies conducted in China, Taiwan and India, show prevalences between 11 and 50%, due to differences related to gestational age or birth weight criteria associated with the diagnosis.[6]

The variation in neonatal outcomes identified in multicenter and multinational cohorts may result from differences in coverage, population characteristics, structure of perinatal health care, case definitions, quality and processes of care in different countries.[1]

Risk factors include intrauterine growth restriction, male sex, chorioamnioitis, race, smoking,[1] and even genetic risk.[7-10]

Since 2005, the prevalence of BPD from the Vermont Oxford Network has decreased from 31 to 28%. Globally, BPD rates ranged from 13 to 32% in the iNEO (International Network for Evaluation Outcomes in Neonates) between 2007-2010.[6,11-15]

Recent evaluations in the USA indicate that BPD develops in approximately 10% of preterm infants born between 28 and 31 weeks, and in 40% of preterm infants younger than 28 weeks.[16] In Europe, 10 to 20% of preterm infants between 23 and 31 weeks developed BPD.[16] In Mexico the prevalence of preterm infants is 10%, of which 8 to 12% are less than 1,200 g or less than 32 weeks, being this the population susceptible to develop BPD.[17]

Although BPD continues to be the most frequent complication in children under 30 weeks and low birth weight, in the last 50 years management has evolved through the use of prenatal corticosteroids, advanced techniques in neonatal care and the use of surfactant, allowing newborns with BPD to have better survival and a lower risk of mortality, although this favors an increase in prevalence.[1,18,19]

Despite all efforts to prevent lung injury, it remains the most prevalent chronic lung disease in the preterm infant,[20] characterized by uniform inflammation, low-grade fibrosis, absence of airway epithelial metaplasia, smooth muscle hypertrophy, larger alveoli, and pulmonary vascular dysfunction.[21]

Care of the extremely premature infant requires hospitalization for approximately 60 days, and in some cases rehospitalization after discharge.[5] During their first year of life, 49% require readmission.[22,23] Follow-up studies are important because they allow visualization of pulmonary involvement, asthma-like symptoms, pulmonary hypertension and exercise intolerance with altered response to hypoxia.[24]

In this work, our aim was to retrospectively describe the demographic characteristics, associated factors and comorbidities in patients with BPD who attended pediatric Pneumology outpatient clinic between 2014 to 2018.

MATERIAL AND METHODS

An observational, descriptive, retrospective study was conducted in 386 patients with a diagnosis of BPD who met the definition according to Bancalari *(Table 1)*, and were seen in the outpatient Pneumology department of the Hospital Infantil de México «Federico Gómez» between 2014 and 2018. Patients with cyanosinging congenital heart disease or incomplete clinical history were not included.

Data for this study were taken from medical records and information on care received in the first two years of life was evaluated. Qualitative variables were reported as absolute and relative frequencies and quantitative variables as medians and ranges, after verification of the normality assumption with the Shapiro-Wilk test.

Table 1: Classification of bronchopulmonary dysplasia.

Gestational age at birth	< 32 weeks	> 32 weeks
Time of evaluation	36 weeks postconceptional age or hospital discharge (whichever comes first)	More than 28 days but less than 56 days postnatal age or hospital discharge (whichever occurs first)
Oxygen treatment	More than 21% during 28 days or more	
Mild BPD	Breathes room air at 36 weeks postconceptional age or at discharge (whichever comes first)	Breathing room air at postnatal day 56 or discharge (whichever comes first)
Moderate BPD	Receives supplemental oxygen with FiO_2 2 < 30% at 36 weeks postconceptional age or at discharge (whichever occurs first)	Receives supplemental oxygen with FiO_2 < 30% at postnatal day 56 or at discharge (whichever occurs first)
Severe BPD	Receives supplemental oxygen with $FiO_2 \geq 30\%$ and/or CPAP or MV at 36 weeks postconceptional age or at discharge (whichever occurs first)	Receives supplemental oxygen with $FiO_2 \geq 30\%$ and/or CPAP or MV at postnatal day 56 or at discharge (whichever occurs first)

CPAP = continuous positive airway pressure, BPD = bronchopulmonary dysplasia, FiO_2 = fractional inspired oxygen, MV = mechanical ventilation.
Adapted from: Jobe A, *et al*.[3]

Comparison between groups according to the severity of BPD was performed using the χ^2 test and Fisher's exact test for qualitative variables and the Kruskal-Wallis test for quantitative variables; a p value < 0.050 was considered significant. Statistical analyses were performed in STATA v.14.

This project was approved by the Institutional Ethics Committee and was carried out in accordance with the guidelines established in the Declaration of Helsinki and local regulations.[25]

RESULTS

We retrospectively analyzed 386 clinical histories of patients with a diagnosis of BPD who met the inclusion criteria and attended a Pneumology consultation. Three patients were not included in the analysis, one because of cyanotic congenital heart disease and two because of incomplete clinical history. 57.51% (n = 222) were male, with a median gestational age of 31 weeks (range: 28 to 35 weeks), 73.83% (n = 282) of the patients were born before 34 weeks of gestation and had a median birth weight of 1,305 g (range: 1,016 to 2,087 g) *(Table 2)*.

Patients were classified according to the severity of BPD into mild, moderate and severe according to the time of supplemental oxygen use and use of positive airway pressure, 47.15% (n = 182) of the cases were classified as moderate BPD, 33.68% (n = 130) as severe BPD and 18.39% (n = 71) as mild BPD *(Table 2)*.

In all three BPD categories, the most affected were male patients (p = 0.153); median gestational age ranged from 31 to 31.4 weeks, p = 0.450 *(Figure 1A)*; and median birth weight was 1,500 g (range: 1,030 to 2,200 g) in mild BPD group; 1,300 g (range: 1,000 to 2,100 g) in moderate BPD group and 1,305 (range: 1,050 to 2,050 g) in severe BPD group (p = 0.775) *(Figure 1B)*.

The main characteristics of the study population are shown in *Table 2*. The number of days of oxygen use was higher in the severe BPD group (180 days; range: 96 to 370 days), compared with the mild BPD group (40 days; range: 30 to 57 days), p = 0.001. In the mild and moderate BPD groups, most patients (92.96 and 42.31%, respectively) used oxygen for a shorter period of time (less than three months); while in the severe BPD group, 46.15% used it for periods longer than six months.

Mechanical ventilation was used in the mild and moderate BPD groups for a period of less than one month, compared to the severe BPD group, where 71.54% used it for a period close to two months. Specifically, the use of mechanical ventilation was 12 days (range: 6 to 22) for the mild group, 20 days (range: 10 to 30 days) for the moderate and 54.2 days (95% CI: 49.23 to 59.33 days) for the severe, p = 0.000.

The use of surfactant was established in only 28.45% (n = 109) of the population, and its administration was higher in the severe BPD group (33.08%). On the other hand, at hospital discharge from the newborn unit, a high number of patients with moderate (64.84%) and severe BPD (71.54%) used oxygen, compared to the mild BPD group (25.35%), p = 0.000.

The analysis of variables related to newborn history showed that low birth weight (9.97%), perinatal asphyxia (25.39%), intraventricular hemorrhage (19.69%) and patent ductus arteriosus (PDA) (19.69%) were the most prevalent, being more frequent in the severe BPD group, with no differences found between BPD groups.

The mothers of patients with BPD were mostly (79.27%) between 20 and 39 years of age with a grade of schooling mainly primary education (47.41%); only 3.37% (n = 13) had multiple pregnancies, 26.68% (n = 103) had early rupture of membranes and 15.54% (n = 60) suffered gestational hypertension. 73.63% (n = 282) had cesarean delivery, but no difference was found between BPD groups with respect to vaginal delivery (p = 0.876).

Family history of atopy (familial asthma) and environmental history (exposure to passive smoking, wood smoke and zoonosis) were also evaluated, but none of them showed differences between BPD severity groups *(Table 2)*.

The most frequent comorbidities were: neurological alteration (19.69%) basically due to neurodevelopmental delay, cerebral palsy and central nervous system malformation, among others; cardiac alteration (9.33%), diagnosed by echocardiogram, included mainly PDA, atrial septal defect, ventricular septal defect and pulmonary hypertension (5.18%). Neurological disturbance and pulmonary hypertension were more frequent in the severe BPD group, and showed differences between BPD groups (p = 0.034 and p = 0.037 respectively); recurrent wheezing was present in only 0.78% of the population.

Information on other comorbidities found is detailed in *Table 2*. None of the patients evaluated (n = 383) were found to have diaphragmatic hernia. Analysis by BPD severity subgroups showed no differences.

The number of hospitalizations and medical care received in the first two years of life documented within the study period was evaluated, as well as signs and symptoms presented at the first Pneumology consultation. 95.34% of the patients had no or a maximum of three hospitalizations, while 4.66% had between four and seven hospital admissions. Regarding the number of consultations, 89.38% of the patients had between one and 10 Pneumology consultations (median: 4 consultations; range: 2 to 7 consultations), 8.81% between 11 and 20 consultations and 1.81% between 21 and 30 consultations and no differences were observed between

Table 2: Main characteristics of the study population.

	BPD Severity				
	SD	Mild n (%)	Moderate n (%)	Severe n (%)	p
Variables	**3**	**71 (18.39)**	**182 (47.15)**	**130 (33.68)**	**NA**
Maternal variables					
Sex Female Male	1	 26 (36.62) 44 (61.97)	 79 (43.41) 103 (56.59)	 55 (42.31) 75 (57.69)	 0.153
Gestational age Median and range (weeks) Range		 31.0 29-35	 31.4 28-34	 31.2 28-34	 0.861
Birth weight Median (g) Range		 1,500 1,030-2,200	 1,300 1,000-2,100	 1,305 1,050-2,050	 0.597
Days with O_2 Median (days) Range		 40 30-57	 107 63-210	 180 96-370	 0.001*
Mechanical ventilation days Median (days) Range	36	 12 6-22	 20 10-30	 54 49-59	 0.001*
Surfactant Yes		 17 (23.94)	 49 (26.92)	 43 (33.08)	 NC
Egress with O_2 Yes		 18 (25.35)	 118 (64.84)	 93 (71.54)	 0.000*
Prenatal history					
Chorioamnioitis Yes		 0 (0)	 3 (1.65)	 2 (1.54)	 0.717
Intraventricular hemorrhage Yes		 9 (12.68)	 31 (17.03)	 27 (20.77)	 0.344
Persistent ductus arteriosus Yes		 10 (14.08)	 33 (18.13)	 33 (25.38)	 0.115
Enterocolitis Yes		 4 (5.63)	 20 (10.99)	 13 (10.00)	 0.466
Perinatal asphyxia Yes		 17 (23.94)	 44 (24.18)	 37 (28.46)	 0.577
Malnutrition at birth Yes		 66 (92.96)	 165 (90.66)	 122 (93.85)	 0.285
Maternal background					
Maternal age (years) < 20 20-39 > 40		 10 (14.08) 58 (81.69) 3 (4.23)	 28 (15.38) 141 (77.47) 13 (7.14)	 13 (10.00) 106 (81.54) 11 (8.46)	 0.574
Maternal schooling Primary High school Technical University Does not read or write		 31 (43.66) 28 (39.44) 2 (3) 7 (10) 3 (4)	 94 (51.65) 68 (37.36) 4 (2) 16 (9) 0.00 (0.00)	 57 (43.85) 52 (40.00) 4 (3.08) 14 (10.8) 3 (2.31)	 0.39

Table 2 continues: Main characteristics of the study population.

	BPD Severity				
	SD	Mild n (%)	Moderate n (%)	Severe n (%)	p
Variables	**3**	**71 (18.39)**	**182 (47.15)**	**130 (33.68)**	**NA**
Maternal background					
Cesarean section Yes		54 (76.06)	133 (73.08)	95 (73.08)	0.876
Multiple pregnancy Yes		3 (4.23)	5 (2.75)	5 (3.85)	0.807
Premature rupture of membranes Yes		19 (26.76)	44 (24.18)	40 (30.77)	0.432
Gestational hypertension Yes		12 (16.9)	29 (15.93)	19 (14.62)	0.905
Family and environmental background					
Passive smoking Yes		10 (14.08)	26 (14.29)	12 (9.23)	0.493
Zoonoses Yes		22 (30.99)	48 (26.37)	26 (20.00)	0.338
Wood smoke Yes		4 (5.63)	4 (2.2)	4 (3.08)	0.393
Family history of asthma Yes		5 (7.04)	7 (3.85)	9 (6.92)	0.462

* Statistically significant. BPD = bronchopulmonary dysplasia.

BPD groups (p = 0.707), the details by severity groups can be seen in *Table 3*.

The mean age of the first consultation with Pneumology was 6.69 months (range: 3.78 to 15.51 months), and there was no significant difference in relation to the severity of BPD (p = 0.141).

Of the patients, 69.17% were symptomatic at the first consultation *(Table 3)* and 26.94% used oxygen, with the frequency of use being higher the greater the severity of BPD (p = 0.000). Chest X-ray was ordered in all patients in their first outpatient control, and analyzed in conjunction with the Radiology Service, finding results compatible with BPD such as linear interstitial infiltrates, reticular and hyperinflation in a total of 143 patients 37.05%; no differences were evident between severity groups (p = 0.353).

The use of medicines such as prenatal corticosteroid (18.60%), postnatal inhaled corticosteroid (80.31%), diuretics (58.29%) and salbutamol (39.90%) were part of the therapeutic scheme received by these patients. All medications had frequencies of use that increased gradually according to the severity of BPD, but only inhaled corticosteroid (p = 0.015) and salbutamol (p = 0.014) showed differences between groups.

DISCUSSION

The present study, based on information from a pediatric population of patients referred from early neonatal care in our institution and from patients referred from external hospitals, generates a great diversity in the population group attended, becoming a good option to describe factors associated with the risk of suffering BPD, as well as comorbidities characteristic of children with this disease.

Moderate and severe forms of BPD were frequent in the study population, especially in patients born around week 31 and with low birth weight (1,500 g), coinciding with that reported in the study by D'Angio *et al.*[26] who demonstrated that premature, small for gestational age or intrauterine growth restricted infants have a higher risk of adverse pulmonary effects and worse complications.

Lum *et al.*[27] report that children with a history of BPD are at increased risk of childhood respiratory symptoms or disease and chronic hypoxemia, due to decreased airway caliber, decreased expiratory flows and volumes, and reduced diffusing capacity reflecting disrupted alveolar development, decreased surface area for gas exchange,

and disrupted angiogenesis. This work found that the requirement for mechanical ventilation, the number of days of prolonged supplemental oxygen use, as well as the use of oxygen at hospital discharge are factors that in our population fit the diagnostic criteria for BPD, which are usually necessary interventions in the most critical stages of neonates and are clearly related to the pathogenesis of the disease, as described in the study by Tapia *et al.*[28]

BPD was more prevalent in male patients and in those who presented risk factors such as intraventricular hemorrhage, PDA and enterocolitis in the neonatal stage, showing an increase related to the severity of BPD, although it was not statistically significant. There are some factors that have been frequently identified in the development of BPD, among which are gestational age, male sex, and PDA.

In contrast to the study by Cunha *et al.*[29] regarding the characteristics of mothers of BPD patients, preeclampsia was not found to be a variable of interest, while premature rupture of membranes was, as was the study by Cokyaman *et al.*[30] The high frequency of cesarean section observed in our investigation agrees with that reported by Cunha *et al.*[29] and allows us to infer that these women probably had an early diagnosis of maternal and fetal complications that could have led them to a more rigorous control of pregnancy and delivery, despite their low schooling. Maternal age, unlike that reported by Klinger *et al.* was not related to the presence or severity of BPD in newborns with low birth weight.[31]

According to Cherian *et al*,[32] oxygen is the most commonly used therapy during the stay of cases in neonatal units and plays an important role, since hypoxia can lead to pulmonary vasoconstriction and pulmonary hypertension, while hyperoxia can lead to the development of BPD, retinopathy of prematurity or injury to the cerebral white matter; the latter injury may be associated with neurodevelopmental delay (characteristic of these patients), referred to in our publication as neurological impairment.

The long-term repercussions commonly present are chronic pulmonary alterations that lead to frequent hospitalizations, generating up to 49% of readmissions during the first year of life.[33] In our study, during the first two years of life, the vast majority of cases required at least three hospitalizations, between one and 10 consultations by Pneumology and first attention by our service at around six months of age.

Other alterations that have been frequently identified in the development of BPD are persistent anomalies in the development of pulmonary function with the presence of chronic cough, wheezing and the use of bronchodilator medicines, with a high incidence of asthma at five years of age.[33-35] In our study, although cough and wheezing were documented, we did not find a high frequency in the patients seen in consultation, but the use of bronchodilators did have an important frequency, their formulation being significant in patients with BPD.

In our study, inhaled corticosteroids were used with a high frequency and we were able to demonstrate that their use in the management of BPD is very useful. The above is aligned with that reported by the neurosis study, a double-blind, placebo-controlled trial conducted in 40 centers in nine European countries that measured the long-term effect of inhaled corticosteroids in 863 preterm infants aged 23 to 27 weeks, finding that the incidence of BPD was 27, 8% compared to 38% in those who did not receive this therapy, and also showed that in the long term there was no neurodevelopmental disability, deafness or blindness,[36,37] and therefore they recommend its use, given its anti-inflammatory activity and fewer side effects than systemic steroids.[36]

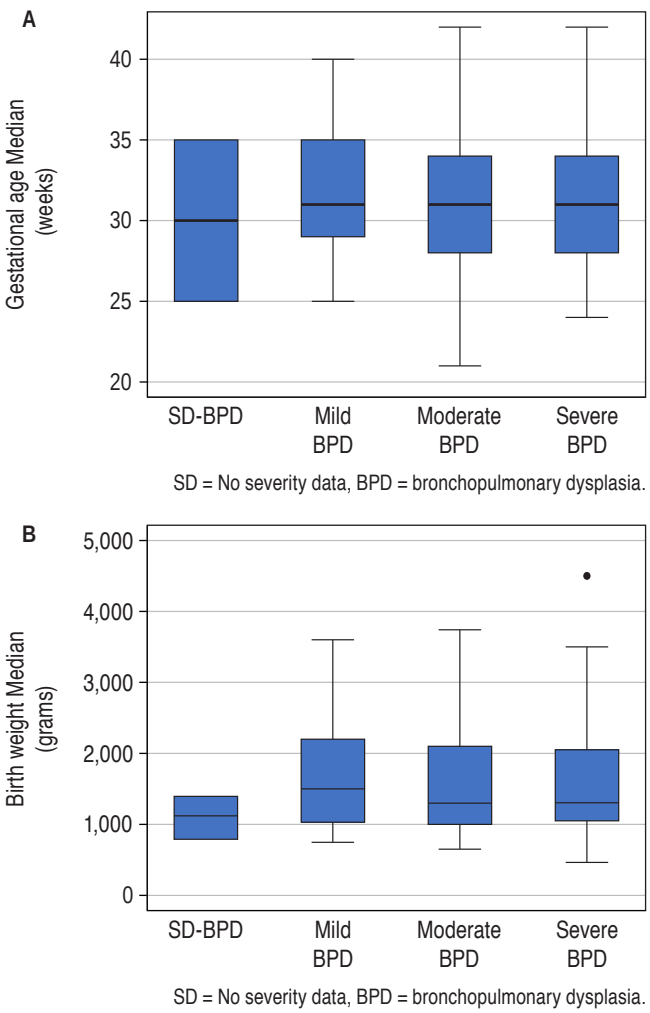

Figure 1: Median gestational age and birth weight in the study population.

Table 3: Characteristics of medical care.

			BPD Severity		
	SD	Mild n (%)	Moderate n (%)	Severe n (%)	
Variables	**3**	**71 (18.39)**	**182 (47.15)**	**130 (33.68)**	**p**
Medical care received					
Hospitalizations due to respiratory causes 0 to 3 4 to 7		 68 (95.77) 3 (4.23)	 177 (97.25) 5 (2.75)	 120 (92.31) 10 (7.69)	 0.140
Number of pulmonology consultations					
Median and range Range 0 to 10 11 to 20 21 to 30		5 (2 to 7) 61 (85.92) 8 (11.27) 2 (2.82)	4 (2 to 7) 164 (90.11) 16 (8.79) 2 (1.10)	5 (2 to 7) 118 (90.77) 10 (7.69) 2 (1.54)	0.489 0.707
Characteristics of the first pulmonology consultation					
Age Median (months) Range	26	 5.95 2.84 to 12.72	 6.27 3.22 to 15.35	 6.88 4.60 to 15.61	 0.141
Weight Median (kg) Range	19	 5.0 3.5 to 8.0	 4.8 3.5 to 7.2	 4.7 3.29 to 7.1	 0.446
Size Medium (cm) Range	20	 60 53 to 71	 59 52 to 72	 57 51 to 70	 0.590
Nasal obstruction Yes		 3 (4.23)	 10 (5.49)	 4 (3.08)	 0.641
O_2 saturation Median (%) Range	19	 94 93 to 95	 93 91 to 95	 93 92 to 96	 0.269
Rhinorrhea Yes		 3 (4.23)	 15 (8.24)	 9 (6.92)	 0.604
Wheezing Yes		 3 (4.23)	 5 (2.75)	 8 (6.15)	 0.305
Pulling Yes		 1 (1.41)	 5 (2.75)	 7 (5.38)	 0.315
Cough Yes		 14 (19.72)	 32 (17.58)	 30 (23.08)	 0.493
Uses O_2 Yes		 9 (12.68)	 45 (24.73)	 49 (37.69)	 0.000*
Cyanosis Yes		 2 (2.82)	 4 (2.20)	 5 (3.85)	 0.668
Crypts Yes		 4 (5.63)	 7 (3.85)	 10 (7.69)	 0.330
Dyspnea Yes		 4 (5.63)	 3 (1.65)	 7 (5.38)	 0.115

* Statistically significant. BPD = bronchopulmonary dysplasia.

In general, the data obtained show similar frequencies in the maternal and newborn variables reported in the study by Maya-Barrios *et al.*[33] conducted in the Mexican neonatal population.

One of the limitations of the study, given its retrospective nature, was the inability to perform reliable statistical estimation of important variables in patients with BPD, such as the use of surfactant and the presence of gastrointestinal comorbidity. This was due to the fact that it was not possible to establish with certainty in the entire population the use of surfactant and the performance of tests to confirm the presence of gastroesophageal reflux and/or alterations in swallowing mechanics, which are part of the gastrointestinal alterations. This may be due to underreporting in the medical records.

The goal with these patients has been to achieve increasingly faster discharges so that they are incorporated as soon as possible to an adequate outpatient follow-up that includes management by a multidisciplinary team that leads to the prevention of respiratory diseases, to achieve an early withdrawal of home oxygen and to an adequate nutritional, cardiovascular and neurodevelopmental follow-up, for which we have been working institutionally in the constitution of the BPD clinic with the support of different services.

CONCLUSIONS

The population of patients with BPD that was part of this study was characterized by having mainly severe and moderate disease requiring prolonged use of mechanical ventilation and oxygen therapy. No maternal, newborn history, or environmental factors were found to be statistically associated with the severity of BPD. Neurological alterations and pulmonary hypertension were significant complications in our population. Despite the severity of BPD, there was no high requirement for hospitalization, achieving outpatient follow-up through outpatient consultation in the Pneumology Service, where the use of inhaled corticosteroid proved to be very useful.

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Review

Associated psychological factors to chronic obstructive pulmonary disease: a narrative review

Factores psicológicos asociados a la enfermedad pulmonar obstructiva crónica: una revisión narrativa

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ABSTRACT. Chronic obstructive pulmonary disease (COPD) is the third leading cause of global death, and the disease burden is further increased by multiple comorbidities, including some psychological disorders, like anxiety and depression, among others. This interplay between mental health and COPD has become a subject of intense study in recent years. Our objective was to describe the psychological factors associated with COPD, the interplay of factors leading to psychological impacts, and to analyze the effective treatment and intervention alternatives available. A narrative literature search was performed in PubMed and Cochrane Library, by using a snow-ball search technique to identify papers published on the subject. A search was conducted for relevant original articles with emphasis on years 2015-2021. Relevant was the emphasis of a multidisciplinary team to support patients with COPD, experts on psychological factors associated with the disease, especially on anxiety and depression. Treatments available, including psychological interventions demonstrated an improvement in quality of life, adherence to treatments, reduced hospitalizations, symptomatology and exacerbations.

Keywords: COPD, mental health, anxiety, depression, psychiatric disorder, risk factors.

RESUMEN. La enfermedad pulmonar obstructiva crónica (EPOC) es la tercera causa principal de muerte a nivel mundial, y la carga de la enfermedad aumenta por múltiples comorbilidades, incluidos algunos trastornos psicológicos, como ansiedad y depresión, entre otros. Esta interacción entre la salud mental y la EPOC se ha convertido en un tema de intenso estudio en los últimos años. Nuestro objetivo fue describir los factores psicológicos asociados con la EPOC, la interacción de factores que conducen a un impacto en la enfermedad y analizar las alternativas de tratamiento e intervención efectivas disponibles. Se realizó una búsqueda de literatura narrativa en PubMed y Cochrane Library, utilizando una técnica de búsqueda de bola de nieve para identificar artículos publicados sobre el tema. Se realizó una búsqueda de artículos originales relevantes con énfasis en los años 2015-2021. Fue relevante el énfasis de un equipo multidisciplinario de apoyo a los pacientes con EPOC, resulta relevante la evaluación de factores psicológicos asociados a la enfermedad, especialmente ansiedad y depresión. Los tratamientos disponibles, incluidas las intervenciones psicológicas, demostraron una mejora en la calidad de vida, adherencia a los tratamientos, reducción de hospitalizaciones, sintomatología y exacerbaciones.

Palabras clave: EPOC, salud mental, ansiedad, depresión, trastorno psiquiátrico, factores de riesgo.

INTRODUCTION

Currently, chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death across the globe, while the World Health Organization (WHO) predicts that COPD will become the third leading cause of death by 2030.[1] Similarly as other chronic conditions, COPD negatively affects quality of life and the disease burden is further increased by multiple comorbidities, including cardiovascular disease and cerebrovascular disease. Additionally, patients with COPD are two to three times more likely to have problems of mental health that the general population.[2] Patients with comorbid physical and mental ill health are less likely to be identified, diagnosed, and treated.[3]

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Among patients with COPD, various psychological aspects of functioning have been investigated but so far with little consequence for clinical practice.[4] In the most recent Clinical Practice Guidelines, anxiety and depression are included as frequent comorbidities in COPD and are associated with poor health status and prognosis. Importantly, comorbidities with symptoms also associated with COPD may be overlooked e.g., heart failure and lung cancer (breathlessness) or depression (fatigue and reduced physical activity).[5]

The objective of the present review was to integrate the psychological factors associated with COPD and analyze the effective treatment alternatives available. A search was conducted in January and February 2021 with no language restrictions under the following criteria: [COPD OR chronic obstructive pulmonary disease] [COPD-mental health], [psychopathology-COPD], [depression-depressive disorder COPD], and [anxiety- anxiety disorders COPD] to identify manuscripts related to the objective. Inclusion criteria were the diagnosis of COPD and at least one psychological factor with a clearly indicated assessment. We searched for other potentially relevant studies by screening the reference lists and citations of included studies. Finally, all authors reviewed, analyzed using the GRADE system, and discussed the articles to provide recommendations. We present the following article in accordance with the narrative review reporting checklist.[6]

Anxiety

The morbidity rate of anxiety in non-hospitalized settings of COPD patients has varied from 13 to 46%, and in hospitalized settings from 10 to 55%.[7]

The coexistence of anxiety disorders and COPD has been shown in a worsening of symptoms, especially the shortness of breath or cough, but also leads to a higher rate of hospital care and increased doses of drugs such as bronchodilators, inhaled corticosteroids, and antibiotics. As an additional result, it causes a higher incidence and severity of adverse effects, accompanied by a worse overall prognosis.[8,9]

According to the retrospective analysis of a randomized controlled trial found that more than half of trial participants (of a total 1200 responses) reported mood disturbance during the study, participants reported symptoms of anxiety and low mood at least once during the previous 12 months.[10]

The available evidence suggests that less than one-third of COPD patients with anxiety are receiving appropriate treatment. Untreated comorbid anxiety and depression in patients with COPD have devastating consequences, as they tend to overwhelm the coping strategies of COPD patients and their caregivers, and may increase healthcare utilisation.[11]

Table 1: Summary of publications regarding the association between psychological factors and pulmonary obstructive chronic disease.

Outcome measures/Reference	Odds ratio - risk ratio - adjusted odds ratio - hazard ratio	Other factors found
Depression and emergency hospital admissions[12] Depression and attendances at emergency departments	OR = 2.63; 95% CI (1.48-4.66) OR = 2.78; 95% CI (1.55-4.99)	Even mild symptoms and moderate to severe symptoms of depression increase the risk of use of urgent care, these findings are independent of severity of disease and comorbidity of other chronic physical conditions
COPD and the likelihood of suicide[13]	OR = 1.90; 95% CI (1.27-2.48)	Similarly, risk factors associated with suicide, such as mental disorders, are underdiagnosed and undertreated
Comorbid depression and risk of mortality[14]	RR = 1.83; 95% CI (1.00-3.36).	COPD increases the risk of developing depression (RR = 1.69; 95% CI 1.45-1.96)
Bipolar disorder and COPD[15] Schizophrenia and COPD[16]	OR 1.55; 95% CI (1.45-1.65) OR 1.57; 95% CI (1.43-1.72)	The most important confounding factor the contribution of which must be evaluated to clarify the nature of the association between COPD and major mental illness is the smoking
Stress with acute care use in COPD	AOR = 2.51; 95% CI (1.06-5.98)	The high stress group had a 2.5-fold increased adjusted odds of acute care use compared to the low stress group
Physical activity-depression in COPD[17] PA-anxiety in COPD	HR = 0.85; 95% CI (0.75-0.95) HR = 0.89; 95% CI (0.79-1.00)	The study found more physically active patients [with higher PA levels equivalent to 2.5 metabolic equivalent tasks (METs), e.g., those who report walking outside vs. those who do not] had 15% and 11% lower risks of developing depression and anxiety, respectively, compared to physically inactive patients

OR = Odds ratio, RR = risk ratio, AOR = adjusted odds ratio, HR = hazard ratio, COPD = pulmonary obstructive chronic disease, PA = physical activity, CI = confidence intervals.

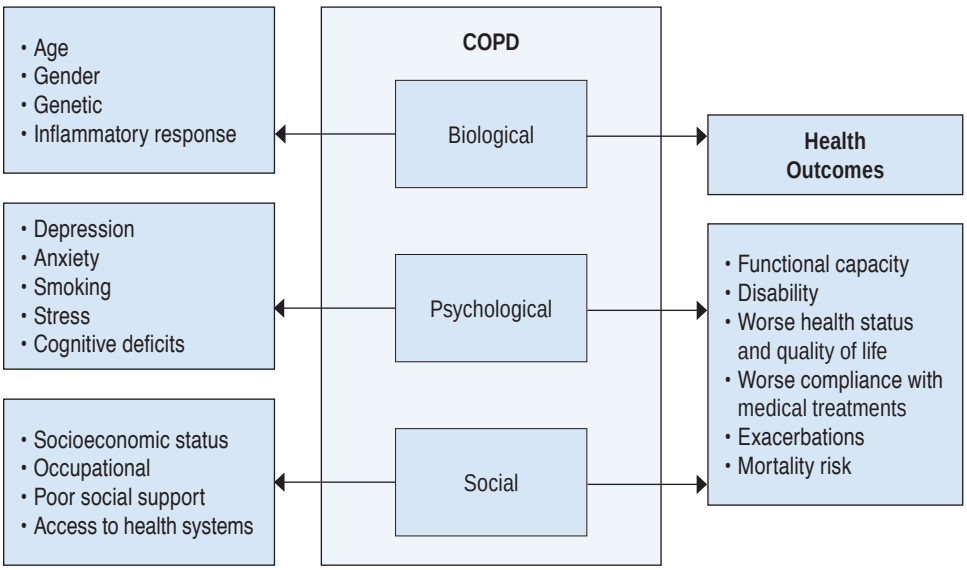

Figure 1:

Illustrative model of biopsychosocial factors that interact in pulmonary obstructive chronic disease and its adverse health outcomes. Modified from Latent Health Risk Classes Associated with pulmonary obstructive chronic disease.[22]
COPD = pulmonary obstructive chronic disease.

Depression

In a prospective longitudinal study of 355 patients with COPD it was found that depression was a predictor of emergency care in COPD, independent of severity of disease or physical comorbidity. Even mild symptoms of depression increase the risk of care by more than twofold, and moderate to severe symptoms of depression increase the risk by nearly five times *(Table 1)*.[12]

A systematic review has shown that COPD patients are 1.9 times more likely to commit suicide than people without COPD *(Table 1)*.[13] However, it is well known that the association between clinically relevant depression and COPD is bidirectional: a meta-analysis demonstrated that not only COPD increases the risk of developing depression (relative risk RR, 1.69; 95% CI, 1.45-1.96) but also, depression increases the risk of COPD adverse outcomes and mortality (RR, 1.43; 95% CI, 1.20-1.71) *(Table 1)*.[14] In a similar manner, an association between COPD, schizophrenia and bipolar disorder has been described. A systematic review found that patients suffering from schizophrenia were significantly more likely to have comorbid COPD as were patients suffering from bipolar disorder.[15] It has also been described that acute care use and stress are associated in COPD. These associations are more pronounced in the low-income more high stress population who disproportionately contribute to health care utilization.[16] It has been reported as a protective factor to physical activity, in COPD patients, those who perform a great physical activity are less likely to develop symptoms of depression or anxiety in the long term *(Table 1)*.[17]

Moreover, as a risk factor, the evidence shows that treatment adherence in patients with COPD has a significant negative correlation with depression. In a study about medication adherence among patients with COPD treated in a primary general hospital during the COVID-19 pandemic showed that COPD with possible depression represented 31% of all cases (191 patients), and possible depression was an independent risk factor for poor treatment adherence over the past two months.[18]

These research data highlight the importance of the proper assessment of the screening tools when measuring depression-anxiety and its appropriate intervention in COPD patients.

Other psychiatric disorders

In addition to mood disorders, patients with COPD are more susceptible to other psychiatric disorders.

One third of patients with COPD reported post-traumatic stress disorder (PTSD) symptoms and met criteria for PTSD. In a study with multivariable analysis model, the presence of two or more exacerbations led to a near twofold increase in the prevalence of post-traumatic stress symptoms related to PTSD (PR, 1.71; $p = 0.015$) specially in those requiring hospitalization (PR, 1.13; $p = 0.030$). Overall, these findings suggest that psychological domains should be addressed along with exacerbations in COPD patients.[19]

Moreover, a study demonstrated a reduced survival in COPD if psychiatric comorbidity was present including substance addiction, schizophrenia, bipolar affective disorder, depressive episode, depressive disorder, anxiety episode, behavioral syndromes associated with physiological disturbances and disorders of personality.[20]

An high score on the type A personality scale, and an increase in risk propensity were associated with dyspnea,

and a decrease in empathy score was predictor of number of infections in men with COPD.[21]

The biopsychosocial factors associated with COPD and their associated adverse health outcomes are illustrated in *Figure 1*, modified from latent health risk classes associated with COPD.[22] *Figure 2* shows some of the most common symptoms in COPD with their associated psychological factors, based on comorbidities of chronic obstructive pulmonary disease.

Psychological interventions for patients with COPD

The first-line treatment recommended in the COPD clinical practice guidelines is cognitive behavioral therapy (CBT). The CBT has recollected scientific evidence related to its effectiveness and has proven to be a cost-effective alternative. A meta-analysis and systematic review which analyzed randomized controlled trials to evaluate the effect of CBT on anxiety and depression in patients with COPD, showed that CBT can effectively improve anxiety and depression, CBT can change patients' wrong cognitive ideas through communication and emotional management, eliminate patients' negative emotions such as negative pessimism and low self-esteem, help patients form a healthy lifestyle and improve their quality of life.[23]

According to a meta-analysis CBT can serve as a complementary therapy to improve anxiety, depression, visits to emergency departments and quality of life in COPD patients and deserves more widespread application in clinical practice.[24]

A Cochrane review analyzing the benefits of psychological therapies for the treatment of anxiety disorders in patients with COPD pointed out that studies were heterogeneous, treatment efficacy was inconclusive, and overall quality of evidence was low.[25] Therefore, well-controlled randomized trials are needed. In another more recent Cochrane review indicated that psychological therapies (using a CBT-based approach) may be effective for treating COPD-related depression; the patients improved more in the intervention (CBT) groups compared to: 1) no intervention (attention placebo or standard care), 2) educational interventions, and 3) a co-intervention (pulmonary rehabilitation). However, the effect sizes were small and quality of the evidence very low due to clinical heterogeneity and risk of bias.[26]

Group psychological treatments, aimed at improving functional social support, have been found to promote expansion in peer networks, since social comparison and interaction with other people with COPD offer learning opportunities, a sense of validation of the lived experience and an opportunity to make new friends, promoting the sense of belonging and identity to a group.[27]

In a randomized controlled trial conducted by Farver-Vestergaard *et al.*,[28] on a group intervention that integrates mindfulness meditation with elements of cognitive-behavioral therapy, called mindfulness-based cognitive therapy for patients with COPD; was shown to be capable of achieving a statistically significant and lasting effect on psychological distress, indicating that it may be an effective complement to standard programs for patients with COPD.

The National Institute for Clinical Excellence (NICE) advises clinicians to 'ask people with COPD if they experience breathlessness, as they find it frightening. If they do, consider including a cognitive behavioral component in their self-management plan to help them manage anxiety.[29]

On the other hand, a meta-analysis examined the efficacy of digital interventions on the outcomes of psychological comorbidities (depression and anxiety) related to a specific group of chronic diseases in adult populations (cardiovascular disease, stroke, diabetes, and COPD) revealing an overall moderate and significant effect on the depression outcome. However the effect on anxiety was small and non-significant.[30]

A survey eliciting clinician and patient perspectives on what is appropriate for ongoing health crisis, involved clinicians (n = 55) and patients with COPD (n = 19) and respondents agreed that there are activities appropriate for remote provision such as: planned activities (gathering patient information on COPD and health status, providing counseling on smoking cessation, and providing education

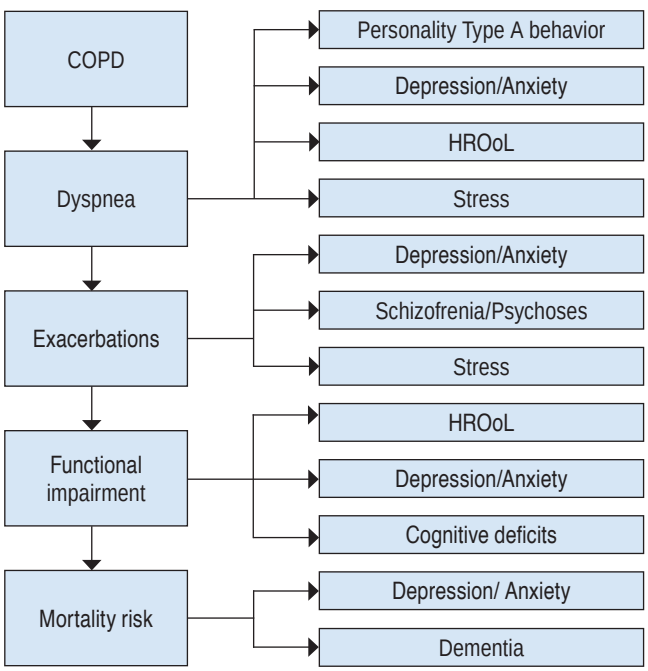

Figure 2: A proposed mapping of pulmonary obstructive chronic disease symptomatology and psychological factors associated (based on comorbidities of chronic obstructive pulmonary disease).
COPD = pulmonary obstructive chronic disease.

on COPD or developing a self-management plan) and urgent care activities (triaging patients for face-to-face care and initiating use of rescue packs).[31]

CONCLUSIONS

Psychological comorbidities are very common in COPD, and adversely affect well-being, and quality of life. Multidisciplinary interventions including nurses, psychologists, rehabilitators, occupational therapists, home care services especially working as a team are effective in improving the condition of patients and the prognosis of evolution.

Still to be defined is to measure the impact of comprehensive care of patients with COPD, in quality of life, in prevention of exacerbations, reduction of dyspnea, adherence to treatment and survival. Thus, awareness of the importance of timely screening for these conditions should be promoted among clinicians and heightened attention should be paid to modifiable risk factors.

Psychosocial factors related to COPD should be considered for comprehensive care. Clinicians should strengthen patient supervision and monitoring; encourage integrated medical teams including pharmacists, nurses, and psychologists; and improve disease management, as well consider humane and empathetic care with patients, further studies are needed and should be focused on enhancement of adjustment to illness, preserving mental health and quality of life related to health.

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Review

Polyunsaturated fatty acids and their derivatives regulate respiratory infections

Los ácidos grasos poliinsaturados y sus derivados regulan infecciones respiratorias

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ABSTRACT. The regulation of inflammation is a complex pathophysiological process that depends on the production of oxygenated lipid derivatives essential polyunsaturated fatty acids, like omega-3 and omega-6, among which are the lipoxins resolvins and protectins, called specialized pro-resolving lipid mediators (SPM). Their activity is associated with the control of respiratory infection processes to modulate the production of proinflammatory cytokines, avoiding damage due to inflammation-associated necrosis, reducing microbial loads, and promoting tissue remodeling. Therefore, we review some of the biochemical, physiological and immunological aspects of SPM in the regulation of inflammation in respiratory infections.

Keywords: Eicosapentaenoic acid, docosahexaenoic acid, inflammation, respiratory infections, specialized pro-resolving lipid mediators.

RESUMEN. La regulación de la inflamación es un proceso fisiopatológico complejo que depende de la producción de lípidos oxigenados derivados de los ácidos grasos poliinsaturados esenciales, como el omega-3 y el omega-6, entre los que se encuentran las lipoxinas, resolvinas y protectinas, denominados mediadores lipídicos pro-resolvedores de la inflamación (SPM, del inglés *specialized pro-resolving lipid mediators*). La actividad de éstos se asocia con el control de procesos respiratorios infecciosos al modular la producción de citocinas proinflamatorias, evitar el daño por necrosis asociado a la inflamación, disminuir cargas microbianas y promover la regeneración de los tejidos. En este trabajo revisamos los aspectos bioquímicos, inmunológicos y fisiopatológicos de los SPM en la regulación de la inflamación en infecciones respiratorias.

Palabras clave: Ácido eicosapentaenoico, ácido docosahexaenoico, inflamación, infecciones respiratorias, mediadores lipídicos pro-resolvedores de la inflamación.

INTRODUCTION

Polyunsaturated fatty acids (PUFA), such as omega-3, are obtained from rich sources of fish, salmon, walnuts and flaxseeds, while rich sources of omega-6 include vegetable oils from corn, safflower, sunflower, soybean and some animal products.[1-3]

PUFA have been increasingly studied for their involvement in the regulation of inflammatory responses, such as the production of specialized pro-resolving lipid mediators (SPMs). PUFA-derived SPMs such as linoleic acid (C18: Δ2, n-6), arachidonic acid (AA, C20: Δ4, n-6), eicosapentaenoic acid (EPA, 20:55,8,11,14,17) and docosahexaenoic acid (DHA, 22: 64,7,10,13,16,19) are generated from enzymatic reactions mediated by lipooxygenases (LOX) and/or cyclooxygenases (COX), which include DHA-derived protectins and D-series resolvins, EPA-derived E-series resolvins, and AA-derived lipoxins, as shown in *Figure 1*.[4-9]

In both *in vitro* and *in vivo* models, SPMs promote bacterial clearance by stimulating the production of antimicrobial peptides,[7,10] increase the phagocytic activity of macrophages[11-13] and decrease the production of proinflammatory cytokines. In addition, they aid in tissue repair, increase host defenses and improve survival.[14,15]

There is evidence that respiratory infections are affected by the patient's nutritional status, metabolic status, medication, complications and the course of the pulmonary disease itself,[16-22] so achieving a balance between the protective and detrimental effects of the immune

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response may help to reduce morbidity and mortality and complications in respiratory infections. Therefore, investigating the biochemical, immunological and pathophysiological aspects of PUFA and their derivatives will help to envision routes, routes of administration and nutritional formulations that will help to select strategies to eradicate respiratory tract pathogens.

PHYSIOLOGICAL ROLE OF PMS

The biological actions of SPMs are mediated by the activation of cognate receptors. Signaling is initiated locally by specific G protein-coupled receptors (GPCRs) that are expressed in different cell types (polymorphonuclear cells [PMN], dendritic cells, monocytes, macrophages, epithelial cells, fibroblasts, adipocytes, etc.) and promote tissue selectivity, exerting their action against extracellular responses. *Table 1* shows some of the SPM receptors found to date, as well as their agonists, antagonists and regulatory genes.[23-30]

ALX was the first receptor identified, it is activated by cognate endogenous ligands, including lipoxin A4 (LXA4) and resolvins D1 and D3 (RvD1 and RvD3), as well as those triggered by aspirin (AT-LXA4, AT-RvD1). RvD1 activates the GPR32 receptor that leads to the regulation of several micro-RNAs (miRNAs) involved in the orchestration of acute inflammation, including miR-(miRNA)146b, miR-208a and miR-219. This receptor also mediates the biological actions of RvD5 in the context of bacterial infections, whereby its activation by RvD5 leads to enhanced bacterial phagocytosis in human macrophages and downregulation of several proinflammatory genes, including NF-κB (nuclear factor enhancer of activated B-cell kappa light chains) and TNF-α (tumor necrosis factor alpha).[31,32]

The biological effect of resolvins is mediated by ALX, FPR2, DRV1, GPCR32, DRV2, GPCR18, ChemR23 or ERV1 receptors. RvD1 has been shown to inhibit canonical NF-κB (p65/p50) and activation of the non-canonical NF-κB pathway (p50/p50), leading to inhibition of apoptosis and blockade in the production of proinflammatory cytokines, reducing PMN transendothelial migration, increasing macrophage activity, resulting in clearance of apoptotic cells.[33] Moreover, RvD1 is able to activate PPARγ

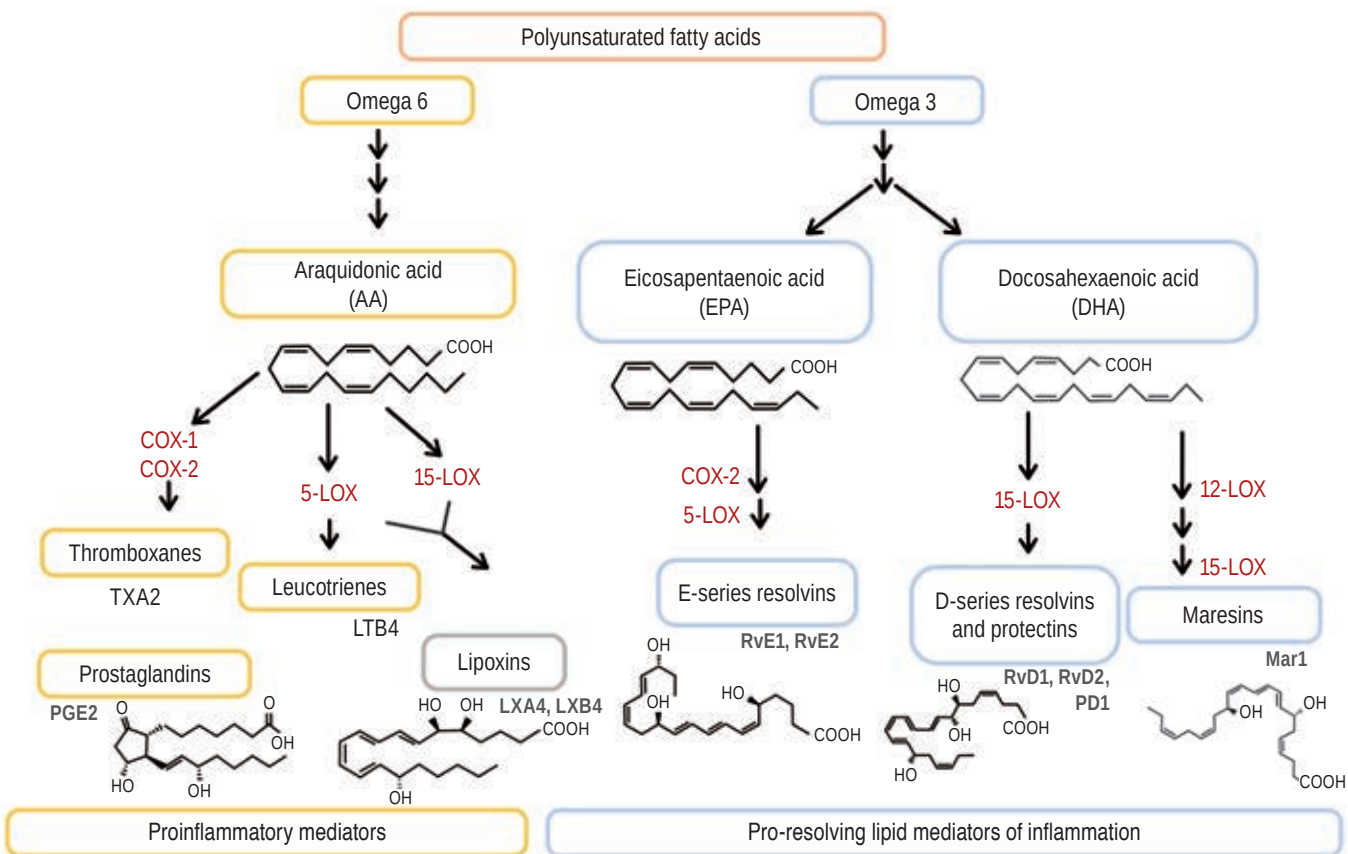

Figure 1: Biosynthesis of proinflammatory and pro-resolving lipid mediators of inflammation.

Table 1: Receptors, genes and agonists of specialized pro-resolving lipid mediators in various cells.

SPM	GPCR Receptors	Gen	Antagonist	Cells
RvD1	ALX, ALX/FPR2, FPR2, DRV1, GPCR32/ ALX	GPCR32	–	PMN, DC, monocytes, macrophages, macrophages, epithelial cells, fibroblasts
RvD2	DRV2, DRV/GPCR2, DRV2/GPCR18, GPCR18	–	–	NKs, PMNs, lymphocytes, monocytes, macrophages, epithelial cells
RvD3	ALX, DRV1	–	–	Lymphocytes, PMNs, monocytes, macrophages
RvD5	DRV1, DRV1/GPCR32	GPCR32	–	PMN
AT-RvD1	ALX/FPR2	–	–	NKs, PMNs, lymphocytes, monocytes, macrophages, epithelial cells
RvE1	ChemR23, ERV	CMKLR1	BLT1	PMN, monocytes, macrophages
RvE2	ERV1/ChemR23	CMKLR1	BLT1	Monocytes, macrophages
LXA4	ALX, FPR2	FPR2	CB1	NKs, PMNs, lymphocytes, monocytes, macrophages, epithelial cells
AT-LXA4	ALX, DRV1/GPCR32	GPCR32	–	NKs, PMNs, lymphocytes, monocytes, macrophages, epithelial cells
Mar1	–	–	BLT1	PMNs, lymphocytes, macrophages

SPM = specialized pro-resolving lipid mediators; GPCR = G protein-coupled receptors; RvD1 = resolvin D1; ALX = lipoxin receptor; FPR2 = N-formyl peptide receptor 2; PMN = polymorphonuclear cells; GPCR32 = G protein-coupled receptor 32; DC = dendritic cells; RvD2 = resolvin D2; DRV2 = resolvin D2 receptor; DRV = resolvin D-series resolvin receptor; GPCR2 = G protein-coupled receptor 2; GPCR18 = G protein-coupled receptor 18; NK = natural killer cells; RvD3 = resolvin D3; DRV1 = resolvin D1 receptor; RvD5 = resolvin D5; AT-RvD1 = aspirin-triggered resolvin D1; RvE1 = resolvin E1; ERV = E-series resolvin receptor; CMKLR1: chemerin chemokine-like receptor 1; RvE2 = resolvin E2; ERV1 = resolvin E1 receptor; LXA4 = lipoxin A4; CB1 = cannabinoid receptor type 1; AT-LXA4 = aspirin-triggered lipoxin A4; Mar1 = maresin 1.

(peroxisome proliferator-activated receptor gamma) and suppress NF-κB degradation via p65.[34]

Some studies have shown that RvD2 activates the DRV2/GPCR18 receptor controlling phagocyte functions in both humans and mice for these receptors, where bacterial infections were controlled, improving survival in murine and providing organ protection, while these actions were diminished in DRV2 knockout (KO) transgenic mice.[35]

In the case of RvE1, it has been shown to function as an agonist for ChemR23/ERV and an antagonist for the LTB4 receptor (BLT1) in PMN. Being able to inhibit PMN superoxide anion in response to TNF-α or bacterial peptide N-formyl-methionyl-leucyl-phenylalanine (f-MetLeuPhe), it also stimulates phagocytosis of apoptotic PMN by macrophages. While in a rabbit model of periodontitis, administration of RvE1 resulted in regeneration of damaged tissues, including bone, compared to the use of aspirin or steroids such as dexamethasone, it selectively inhibited thromboxane, demonstrating its ability to exert anti-inflammatory effects.[26]

Evaluations of SPM concentrations in the body are performed using high structural resolution techniques such as liquid chromatography-mass spectrometry (LC-MS), metabololipidomics and UV spectroscopy. Data reported to date suggest that the basal levels of SPMs are in the submicromolar and nanomolar ranges.[23,29,30,34,36,37] Shivakoti *et al*.[38] conducted a comparative study of the concentrations of some SPMs, where they determined that Australian diabetic (DM) patients had higher serum concentrations of RvD1, RvD2, RvE1, RvE2 and Mar1 compared to patients with tuberculosis (TB) and patients with TB and diabetes (TB-DM), indicating that infection promotes an imbalance between these lipid mediators, giving rise to the consideration of SPM levels as biomarkers of disease.

PMS IN RESPIRATORY DISEASES INFECTIOUS AND NON-INFECTIOUS

The human respiratory system is usually divided into upper and lower respiratory tract. The upper airways include nasal cavities, oral cavity, paranasal sinuses, nasopharynx and larynx (which play an important role in particle clearance). The lower airways include the trachea, main bronchi, terminal bronchi, and respiratory bronchi, as well as the alveoli.[39,40] Infections can affect both airways, the most common being acute rhinopharyngitis (common cold, caused by rhinovirus, coronavirus and respiratory syncytial virus [RSV], and more rarely by enterovirus, influenza and parainfluenza).[41-47] In murine models, it has been shown that infection by H5N1 influenza virus causes a deregulation in

the expression and signaling of PMS, such as lipoxins,[48] while exogenous administration of PD1 inhibits infection by this virus, improving survival and lung function.[49] On the other hand, Ramón *et al.*[50] demonstrated a coadjuvant effect with the administration of 17(S)-hydroxydocosahexaenoic acid (17-HDHA) after vaccination against influenza, by significantly increasing the levels of anti-H1N1 antibodies in serum, as well as the number of B cells in murine bone marrow.

Other frequent infections are pharyngotonsillitis (inflammation of the oropharyngeal membranes and palatine tonsils, commonly caused by adenovirus, parainfluenza, Epstein-Barr virus, Coxsackievirus and group A β-hemolytic Streptococcus),[43,44,51-53] and rhinosinusitis (inflammation of the mucosa lining the paranasal sinuses, caused by *Haemophilus influenzae*, *Staphylococcus aureus*, *Staphylococcus pyogenes*, Bacteroides sp. and *Fusobacterium sp.*).[51,54,55] In a model of infection with *H. influenzae*, administration of AT-RvD1 has been found to regulate leukocyte transport to the lung, increasing phagocytosis of neutrophils by macrophages and reducing levels of interleukin 6 (IL-6) and TNF-α.[56]

On the other hand, the permeability of the alveolar epithelium can trigger an inflammatory response by the entry of different exogenous and endogenous agents that can persistently stimulate the organism, which implies a challenge for the maintenance of homeostasis and the resolution of inflammation.

Some microorganisms have the capacity to become chronically established, such as *Mycobacterium tuberculosis*, the cause of TB, which has the highest number of deaths due to infectious disease in the world after the human immunodeficiency virus (HIV).[57-59] In an experimental model of mice deficient in 5-lipooxygenase (5-LO, an enzyme responsible for the production of lipoxins), it appears to have better control of *M. tuberculosis* infection compared to wild-type mice infected with *M. tuberculosis* treated with a 5-LO inhibitor, where the latter had higher mortality and higher bacterial load. These results suggest that infection control is related to leukotriene production (proinflammatory pathway) rather than lipoxin production (anti-inflammatory pathway).[60] While in another *in vitro* model of human macrophages infected with the virulent Mtb H37Rv strain treated exogenously with RvD1 and Mar1 induced the expression of antimicrobial peptides such as BPI (bactericidal permeability-increasing protein) and the human cathelicidin LL37, regulating the production of TNF-α and controlling the intracellular growth of Mtb.[10] These investigations show us strategies that may eventually be used to support current TB treatment, either by supplementation of PMS precursors such as DHA/EPA or by exogenous administration of the PMS themselves.

Other external agents that can cause respiratory conditions include allergens (e.g., Derp2 proteins present in dust mite feces), non-degradable particles (such as asbestos) and even endogenous particulate crystals (e.g., cholesterol),[61-63] not to mention cigarette smoke, which is associated with chronic respiratory, cardiovascular and tumor diseases, affecting the phagocytic capacity of macrophages.[39,64-68] Some research has shown that prostaglandin analogues and lipoxins have physicochemical properties that improve the use of glucocorticoids, since a decrease in the latter improves the adverse effects, as well as resistance to steroids in asthma.[69-71] In addition, in a model of allergic asthma, it was determined that the administration of some activators such as TLR7 (toll like receptor 7) increased DHA-derived SPMs such as PD-1, 17-HDHA and 14-HDHA, helping to control the eosinophilia characterized in this animal model, as well as in another model by intraperitoneal administration of RvE1.[72,73]

Chronic obstructive pulmonary disease (COPD), neonatal respiratory distress syndrome (NRDS), acute respiratory distress syndrome (ARDS), acute lung injury (ALI) and asthma are respiratory system conditions with high incidence, morbidity and mortality. COPD is characterized by airflow limitation and is associated with an abnormal inflammatory response of the lungs to noxious particles or gasses. Tobacco smoke is the main risk factor,[74-76] followed by air pollution,[77,78] occupational exposure to dust and chemicals, recurrence of respiratory infections during childhood or genetic predisposition. Some studies in murine models have focused on the exogenous administration of LXA4, since this SPM competes with serum amyloid A (SAA, Serum amyloid A) proteins for the GPCR FPRR/ALX, SAA increases considerably in infections and is related to excessive neutrophil recruitment in COPD, therefore, both act as antagonists, which may help prevent chronic inflammation and pulmonary emphysema.[75,76,79]

On the other hand, NRDS, ARDS and ALI are diseases related to the pulmonary surfactant system, but also occur more frequently in the context of pneumonia, sepsis, aspiration of gastric contents or severe trauma, unlike asthma, which is considered a highly prevalent heterogeneous inflammatory disorder of the airways due to inflammation caused by various allergens.[80-82] Eickmeier *et al.*[83] found that administration of AT-RvD1 in a murine model of ALI decreased the amount of bronchoalveolar lavage fluid neutrophils, improved epithelial and endothelial barrier integrity, significantly decreased levels of proinflammatory cytokines such as interleukin 1β (IL-1β), IL-6 and TNF-α, as well as nuclear translocation of p65 phosphorylated by NF-κB, so this SPM could also work for NRDS and ARDS.

Currently, COVID-19 disease caused by the SARS-CoV-2 coronavirus has prompted the search for new

Table 2: Action of specialized pro-resolving lipid mediators in different experimental models.

SPM	Cell or study model	Action	References
Mar1	Bronchial epithelial cells	Reduced IL-6, TNF-α and IL-8, decreased neutrophil accumulation	13
	Human macrophages	Induces BPI expression, regulates TNF-α production and induces intracellular growth control of *Mycobacterium tuberculosis*	10
AT-RvD1	Bronchial epithelial cells	Modulates LPS-induced bronchoalveolar lavage cell activation and the immune response of *Dermatophagoides pteronyssinus* mites	95
RvE1	Murine models of pneumonia	Reduces IL-1β, IL-6, PMN infiltration, improves survival and decreases bacterial loads	11
	Murine models of critical illness	Inhibits translocation and activation of NF-κB (p65)	96
RvD1	Murine model	In *Escherichia coli* and *Staphylococcus aureus* infections, it limits PMN infiltration, aids bacterial clearance and enhances	97
	Murine model	PMN infiltration, helps bacterial clearance and increases the resolution of the infection	12
	Human alveolar macrophages	In mice exposed long-term to cigarette smoke, it reduced emphysema and airspace enlargement, as well as and airspace enlargement as well as inflammation, oxidative stress and cell death	68,98
	Human macrophages	In human alveolar macrophages from COPD and non-COPD patients decreased IL-6 and TNF-α levels, while increased phagocytosis and promoted an M2 macrophage phenotype	10
		Induces BPI and LL37 expression, upregulates TNF-α production and induces intracellular growth control of *Mycobacterium tuberculosis*	
PD1	Human eosinophils	Patients with PD1 impairment contribute to severe asthmatic persistence and severity of the disease, decreased adhesion molecules (CD11b and L-selectin), decreased chemotaxis	96
LXA4	Serum and murine models	Negatively regulate protective Th1 lymphocyte responses against *Mycobacterium tuberculosis* infection	14
DHA, EPA and ALA	Human pulmonary fibroblasts and bronchial cell line (BEAS-2B)	They cause an amplification of inflammatory responses to viral and bacterial components, with production of IL-6 and CXCL8.	15

SPM = specialized pro-resolving lipid mediators of inflammation; Mar1 = maresin 1; IL-6 = interleukin 6; v TNF-α = tumor necrosis factor alpha; IL-8 = interleukin 8; BP1 = bactericidal/permeability-increasing protein; AT-RvD1 = aspirin-triggered resolvin D1; LPS = lipopolysaccharide; RvE1 = resolvin E1; IL-1β = interleukin 1β; PMN = polymorphonuclear cells; NF-κB = nuclear factor enhancer of activated B cell kappa light chains (nuclear factor-κB); RvD1 = resolvin D1; COPD = chronic obstructive pulmonary disease; LL37 = cathelicidin; PD1 = protectin D1; LXA4 = lipoxin A4; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ALA = α-linolenic acid; CXCL8 = chemokine [C-X-X motif] ligand 8.

therapeutic strategies to combat the severity of the disease, focusing on the elimination of responses exacerbated by the production of proinflammatory cytokines,[84] where some groups focused on SPM precursors, such as omega-3 PUFA supplementation, finding improvements in some parameters of respiratory and renal function in critically ill patients with COVID-19 evaluated for one month, compared to patients without supplementation.[85] Evaluation of the levels of some PMS in patients diagnosed with COVID-19 showed that critically ill patients had lower concentrations of PMS than those who were discharged.[86,87] Recchiuti *et al*.[88] found in an *in vitro* model of macrophages with or without cystic fibrosis exposed to SARS-CoV-2 virion glycoprotein S (Spike 1) that both RvD1 and RvD2 were able to regulate inflammatory functions by modulating miR-16, miR-29a and miR-103, and simultaneously selectively increased miR-223 and miR-125a, involved in NF-κB activation and macrophage inflammatory polarization. However, it remains to be elucidated whether different disease-associated risk factors including advanced age, hypertension, diabetes, obesity, or other comorbidities have any association with PMS.

As has been seen throughout the text, the analysis of the biological effects of PMS in respiratory infections may lead to new proposals for therapeutic immunomodulation.

Recently, De Toledo *et al*.[64] demonstrated that fraction 39 of the mucus of the slug *Phyllocaulis* boraceiensis contains PUFA with potent antiviral activity against measles virus and influenza virus. Cell viability and toxicity of the mucus were evaluated in Madin-Darby canine kidney cells (MDCK) by the 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazole bromide (MTT) assay, where they demonstrated that hydroxylated PUFA interfered with influenza virus binding to the host cell receptor, causing reduction in viral titers.

Moreover, in an *in vitro* model of human neutrophils, aspirin-triggered administration of lipoxin (15-epi-LXA4) abrogates the suppression of myeloperoxidase (MPO, an enzyme with microbicidal activity) neutrophil apoptosis by blocking integrin β_2-mediated signaling, improving the resolution of MPO-sustained lung injury.[89-91] Meanwhile, in a murine model, acute lung injury by intraperitoneal injection of *Escherichia coli* was evaluated in mice and it was found that subsequent treatment with 15-epi-LXA4 promoted neutrophil apoptosis and improved the resolution of inflammation in lung injury, comparable to mice treated with RvD1 prior to ALI by LPS, where RvD1 improved the survival rate of mice exposed to ALI with inhibition of TNF-α, IL-6 and decreased COX-2 expression.[92] Similar results have been found with the administration of RvE1 in a murine model of pneumonia, with exposure to *E. coli*, where there was a reduction in the production of proinflammatory cytokines, a decrease in PMN and a reduction in *E. coli* bacterial loads, improving murine survival.[11]

On the other hand, Raposo *et al*.[93] evaluated the nutritional intake of vitamin C, vitamin E, DHA, AA, selenium and zinc in a cohort of more than 1,500 individuals aged 25 to 64 years who were followed for nine months, found an association in the susceptibility to upper respiratory tract infection in women than in men due to a decrease in the intake of DHA, AA and vitamins C and E. In contrast, in human lung fibroblasts and bronchial cell line (BEAS-2B) it has been shown that PUFA such as DHA, EPA and ALA (α-linolenic) elicit an amplification of inflammatory responses to viral and bacterial components, with production of IL-6 and CXCL8, suggesting that polyunsaturated fatty acids have no anti-inflammatory effects in these lung cells.[94] A brief summary of the action of SPMs are shown in *Table 2*.

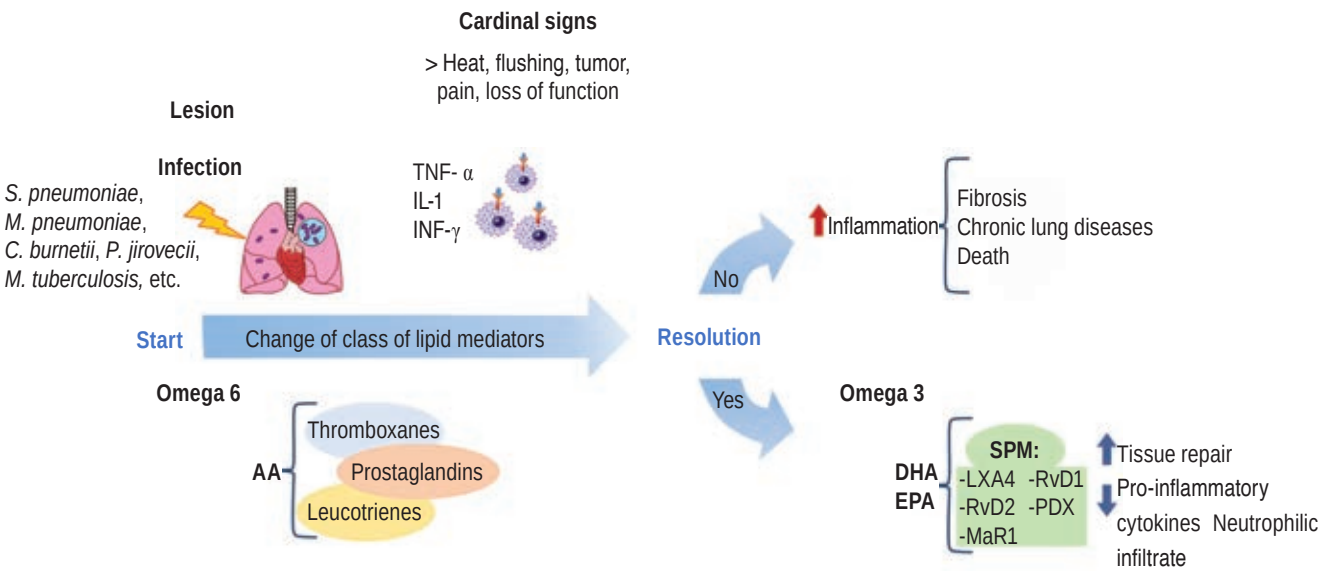

Figure 2: Inflammatory response and its resolution. After damage or infection by some microorganism an acute inflammatory response is initiated, which activates cardinal signs (heat, flushing, tumor, pain or loss of function) with production of proinflammatory cytokines (TNF-α, IL-1, IFN-γ, etc.) and neutrophilic infiltrate. This process also involves prostaglandins, leukotrienes and thromboxanes that come from the synthesis of arachidonic acid in an attempt to eliminate pathogens or noxious agents. This proinflammatory response shifts to an anti-inflammatory phenotype with the participation of pro-inflammatory lipid mediators. These lipid mediators come from the synthesis of eicosapentaenoic acid and docosahexaenoic acid ingested in the diet as omega-3 and omega-6 fatty acids. Resolution of the inflammatory response comes with tissue repair and restoration of homeostasis, but if there is no class switch from the proinflammatory lipid mediators to the anti-inflammatory phenotype, it can shift to chronic inflammation, with systemic and deleterious repercussions for the host.

TNF-α = tumor necrosis factor α; IL-1 = interleukin 1; AA = arachidonic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; SPM = pro-inflammatory lipid mediators; LXA4 = lipoxin A4; RvD1 = resolvin D1; Mar1 = maresin 1; RvD2 = resolvin D2; PDX = protectin DX; *Streptococcus pneumoniae*; *Mycoplasma pneumoniae*; *Coxiella burnetii*; *Pneumocystis jirovecii*; *Mycobacterium tuberculosis*.

INVOLVEMENT OF SPM IN THE RESOLUTION OF INFLAMMATION

Inflammation is a response of an organism's immune system to damage caused by pathogens or substances of a biological, chemical, physical or mechanical nature and, depending on the duration, can be classified as acute or chronic.

Acute inflammation involves significant changes in plasma levels of histamine, bradykinin, prostaglandins, leukotrienes, thromboxanes and proinflammatory cytokines (TNF-α, IL-1, IL-1β, IL-2 and IL-6), crucial for controlling and eliminating harmful agents,[99-104] but if acute inflammation is sustained, it leads to chronic inflammation with systemic and deleterious repercussions for the host, such as tissue infiltration by leukocyte aggregates (granuloma formation), uncontrolled collagen biosynthesis, leading to fibrosis or cirrhosis, permanent loss of normal tissue function (functio laesa) or oxidative damage to deoxyribonucleic acid (DNA), leading to degenerative diseases such as autoimmune diseases, cardiovascular disorders, osteoporosis, rheumatoid arthritis, Alzheimer's disease, certain types of cancer and even death.[103]

Thus, the involvement of SPMs in the maintenance and response of inflammation is peremptory, performing the switch from a proinflammatory to an anti-inflammatory phenotype, thus aiding in tissue repair and the restoration of homeostasis,[105] as shown in *Figure 2*.[104]

CONCLUSIONS

PUFA and their derivatives, SPM, have a protective and controlling effect on the elimination of pathogenic microorganisms, inflammation and tissue repair, which makes them important candidates for the search for new therapeutic strategies, as well as possible biomarkers. Further knowledge of their signaling mechanisms, synthesis pathways, production of their epimers, and research evaluating PUFA consumption and SPM levels in healthy subjects versus patients with respiratory diseases is needed to better understand the relationship between overall dietary PUFA profiles and their impact on future nutritional or pharmacological interventions as strategies to eradicate pathogens from various respiratory conditions.

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Clinical case

COVID-19 with a prolonged course associated with a state of immunosuppression. Response to treatment with remdesivir

COVID-19 de curso prolongado asociado con estado de inmunosupresión. Respuesta al tratamiento con remdesivir

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ABSTRACT. The pandemic due to the coronavirus disease 2019 (COVID-19) has had a variable presentation in the population, from mild to severe cases where large hospital supplies are required for its care. In the case of immunosuppressed patients this disease has had an uncertain behavior in terms of its presentation as well as its prognosis. This clinical case shows a presentation of a prolonged course of COVID-19 associated with a state of immunosuppression due to maintenance treatment with rituximab due to the diagnosis of follicular lymphoma, where a course of migratory pneumonia without the development of acute respiratory distress syndrome is observed (ARDS) being that unlike what has been published in the literature a control and maintenance of the disease is shown only with the use of remdesivir, however the prognosis of the patient is conclusively unknown.

Keywords: Coronavirus disease 2019, remdesivir, follicular lymphoma, rituximab, immunocompromised.

RESUMEN. La pandemia por la enfermedad por coronavirus 2019 (COVID-19) ha tenido una presentación variable en la población, desde casos leves hasta graves donde se requieren grandes insumos hospitalarios para su atención. En el caso de los pacientes inmunosuprimidos, dicha enfermedad ha tenido un comportamiento incierto en cuanto a la presentación de la misma, así como del pronóstico. En este caso se muestra una presentación de curso prolongado de la COVID-19 asociado a un estado de inmunosupresión debido al tratamiento de mantenimiento con rituximab como manejo de un linfoma folicular, donde se observa un curso de neumonías migratorias sin desarrollar síndrome de insuficiencia respiratoria aguda (SIRA) mostrando un control y mantenimiento de la enfermedad en relación al tratamiento con remdesivir, correlacionado con lo publicado por algunos autores donde se ha visto que los pacientes inmunodeprimidos son propensos a cursos prolongados de la enfermedad (recurrencia de COVID-19) pero al mismo tiempo pueden estar protegidos de una enfermedad de curso grave posiblemente al evitar el estado de hiperinflamación (tormenta de citoquinas); sin embargo, el pronóstico así como el impacto de la inmunosupresión en esta infección en estos pacientes se desconoce de manera concluyente.

Palabras clave: Enfermedad por coronavirus 2019, remdesivir, linfoma folicular, rituximab, inmunosupresión.

INTRODUCTION

Most patients with COVID-19 present with mild to moderate symptoms, while a minority develop a more severe course of illness that may include complications such as ARDS, septic shock, cardiac injury, and thrombosis.[1,2] Immunosuppressed patients with hematologic malignancies have historically been more susceptible to viral respiratory illnesses, including less virulent strains of coronaviruses.[3] In general, immunosuppressed patients have been found to be prone to prolonged courses of disease (COVID-19 recurrence), but at the same time may be protected from severe course disease possibly by avoiding the hyperinflammatory state (cytokine storm); however, further

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information on the component of immunosuppression in this setting is lacking to date.[4-6]

The elimination of CD20-positive mature B lymphocytes committed to differentiate into autoantibody-producing plasma cells is considered the main effect of rituximab; hypogammaglobulinemia has been reported after rituximab treatment in patients with lymphoma and rheumatoid arthritis; low immunoglobulin G (IgG) has attracted the most attention because of its significant role in protective immunity; however, the incidence and clinical implications of low immunoglobulin M (IgM) have not been studied in detail (the dose, frequency, and number of drug infusions appear to be important variables in this regard). In patients treated with rituximab, B-cell recovery begins at six months of treatment and normal levels are generally recovered within 12 months after the end of treatment, although in some patients it may take longer (up to a median recovery time of 23 months after induction therapy).[7,8] The nucleotide analog remdesivir is an antiviral agent approved for the treatment of COVID-19, helping to improve the clinical outcome of patients hospitalized on a five-day regimen.[9,10]

Here, we report a prolonged course of COVID-19 with SARS-CoV-2 viremia in a patient who received CD20+ lymphocyte depletion therapy via rituximab as maintenance management for follicular lymphoma prior to viral infection, after subsequent remdesivir therapy for five days this patient now shows sustained virologic control of COVID-19.

CASE DESCRIPTION

This is a 61-year-old man who presented with the diagnosis of follicular non-Hodgkin's lymphoma immunophenotype B (CD20 positive) in 2017, receiving rituximab-cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) treatment being refractory to said scheme, Therefore, he received lenalidomine as well as 18 sessions of radiotherapy with adequate response to such treatment, while rituximab was administered bimonthly (as maintenance) since the end of the R-CHOP scheme (a total of 18 infusions).

COVID-19 started mildly in January 2021, with improvement only with symptomatic treatment. However, two weeks later the patient begins with febrile peaks without showing hypoxemia by pulse oximetry, and serum labs show lymphopenia and elevated inflammatory markers *(Table 1)*, so a chest CT scan is indicated, which showed areas of ground glass in the right upper lobe and left lower lobe *(Figure 1)*, and symptomatic treatment was started again, but this time adding azithromycin and high doses of inhaled steroids without the need for supplemental oxygen; The patient showed clinical improvement with stabilization of temperature and significant improvement of the areas of ground glass mentioned above *(Figure 1)*, decreasing inflammation at biochemical level and without lymphopenia *(Table 1)* and with a new negative PCR test for SARS-CoV-2.

One week later, the patient began to have new febrile peaks above 38 °C, as well as a dry cough while maintaining adequate oxygenation, so we proceeded to perform a new chest CT scan that showed a new increase in ground glass and the presence of an alveolar consolidation zone in the left lower lobe *(Figure 1)*, In this context, a new PCR for SARS-CoV-2 was considered, which was positive again, accompanied by elevation of inflammatory markers *(Table 1)*, and the possibility of a reinfection or persistence due to COVID-19 was considered, ruling out other infectious etiologies. In view of the above, the patient was managed without the need for supplemental

Table 1: Evolution at the serum laboratory level. The behavior of the main inflammatory markers for COVID-19 is shown, with ferritin being the most clinically useful. Evolution is shown as the number of days after initial symptoms.

	Day 14	Day 18	Day 26	Day 39	Day 49	Day 56	Day 83
LHD (U/L)	337	304	287	327	266	307	318
ESR (mm/h)	45	42	48	53	72	60	20
CRP (mg/dL)	39.5	48.4	14.5	13	2.96	2.14	0.1
Ferritin (ng/mL)	240	613	319	831	1,369	712	468
D-dimer (µg/mL)	250*	0.57	508.4*	0.27	0.38	0.3	0.17
Fibrinogen (mg/dL)	---	675	202	488	---	---	---
Leukocytes (µL)	6,400	5,430	4,700	5,240	5,300	6,040	4,060
Lymphocytes (µL), [%]	1,408 [22]	850 [15.7]	1,175 [25]	650 [12.4]	940 [17.7]	860 [14.2]	990 [24.4]

* (ng UEF/mL)
LHD = lactate dehydrogenase, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein.

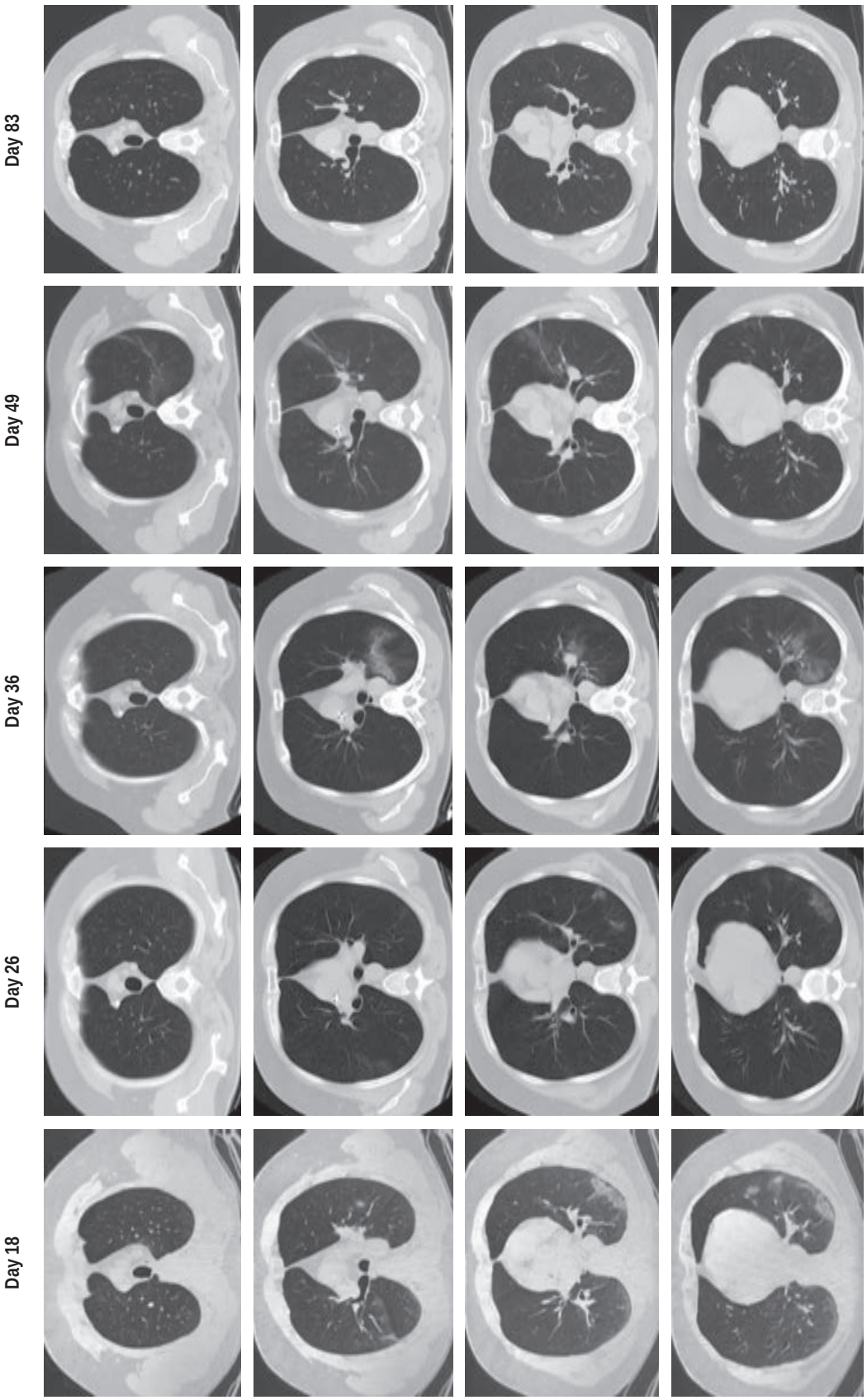

Figure 1: Transition of the pulmonary lesions due to COVID-19 pneumonia in the case presented on computed tomography. The migratory behavior of the COVID-19 lung lesions is evident. The evolution is shown as the number of days after the initial symptoms.

oxygen with prophylactic anticoagulation (apixaban) and the use of systemic steroids (prednisone), with the empirical addition of levofloxacin and fluconazole; The immunological profile was evaluated, showing decreased total IgM immunoglobulin in serum, as well as lymphocyte subpopulations without detecting CD19+ B lymphocytes by flow cytometry; a quantitative test of specific antibodies for SARS-CoV-2 was also performed, showing an IgG index of 4. 33 (positive) and IgM with 0.74 (negative). Taking into account this immunosuppression status together with the absence of hypoxemia in the patient, it was decided to suspend systemic steroid on the third day of its initiation and remdesivir was started with a scheme suggested in the context of the patient without hypoxemia with 200 mg on the first day, followed by 100 mg once a day for four days intravenously, with which significant clinical improvement was obtained with stabilization of fever and cough 24 hours after starting the medication. The patient remained stable with follow-up at one week with a new PCR test for SARS-CoV-2, which was negative, and also continued with reduction of inflammation at the biochemical level *(Table 1)*.

Finally, the patient remained without new febrile peaks and with improvement of cough, in the follow-up at one month he was practically asymptomatic with control chest CT scan showing almost total improvement of the areas of pulmonary involvement described above *(Figure 1)*, negative PCR test for SARS-CoV-2 and with improvement of inflammation in control laboratories *(Table 1)*.

DISCUSSION

SARS-CoV-2 infection has been shown to trigger an immune response; cases diagnosed with follicular lymphoma have had complete remission of follicular lymphoma following SARS-CoV-2 infection.[11] Unfortunately, in other patients with follicular lymphoma with SARS-CoV-2 infection who have previously received chemotherapy treatment, mainly in those who have had controlled disease with maintenance B-cell depletion therapy (anti-CD20 therapy), uncertainty persists about the strength of viral control, the degree of immunity, and the risk of reinfection and/or persistence (reactivation) of viral disease.[4,12] The case presented shows a behavior of persistence or reactivation of the viral load manifesting itself with moderate to severe clinical condition (even presenting pneumonia), it is important to mention that at no time had the need for supplemental oxygen, this may speak of a possible protective factor to severe disease by the same immunosuppression that the patient presents but that it does not allow eliminating the viral load.[5,13] Contradictorily to the above, there are other studies that mention greater severity and susceptibility of the disease in this population.[14]

On the other hand, during the evolution of the disease the patient had remained in strict home isolation, so the possibility of a reinfection was considered very unlikely and it was considered as persistent or prolonged course COVID-19, similar to that published in the literature.[8] We should also comment on the atypical migratory character of the ground glass lesions that the patient presented at tomographic level (crescentic-menguing effect), ruling out other bacterial, tuberculous and/or fungal etiologies *(Figure 1)*, data similar to that shown in previous publications.[4]

Regarding the treatment that can be offered for this type of cases, there are few publications and with a low level of evidence, only supported by case reports where plasma from COVID-19 convalescents has been used alone or combined with the use of remdesivir.[8,13] In this case, viral control was achieved only with the use of remdesivir, unfortunately regarding this treatment it is unknown whether a sustained viral response can be produced and at what time it can be achieved after the elimination of the virus.

In the PRIMA study, both viral and general infections were found to be increased in patients with follicular lymphoma undergoing rituximab maintenance therapy, the association of increased infections and rituximab therapy is a well-established concept.[15]

CONCLUSION

To date, the impact of immunosuppression due to treatment with CD20+ lymphocyte depletion therapy in hematologic malignancies during SARS-CoV-2 disease is unclear, and the extent to which these patients are protected from reinfection by their immune system is unknown. Therefore, the presentation of COVID-19 in this population requires further research to know the prognosis, as well as the best treatment in these patients, pointing out the importance of initiating and/or continuing with the use of such anti-CD20+ therapy in this population with COVID-19 based on the risk-benefit of the same.

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Clinical case

Cytomegalovirus and COVID-19 co-infection: case report

Coinfección por citomegalovirus y COVID-19: caso clínico

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ABSTRACT. 5% of patients with severe acute respiratory syndrome (SARS-CoV-2) by coronavirus 2 disease (COVID-19) develop acute respiratory distress syndrome (ARDS) resulting in a high mortality rate. A 36-year-old male patient with a history of renal transplant from a related living donor presented with fever of 39 °C, asthenia, adynamia, myalgias and arthralgias. Polymerase chain reaction (PCR) for (COVID-19) was performed, as well as computerized axial tomography (CAT) of the thorax with a finding of CO-RADS 5, he developed greater respiratory insufficiency requiring invasive mechanical ventilation, cultures were obtained with the result of quantitative PCR/DNAc cytomegalovirus (CMV): 554 copies/mL, valganciclovir 900 mg was started, with the patient presenting adequate evolution until mechanical ventilation was withdrawn. Co-infection by CMV and SARS-CoV-2 at pulmonary level should be clinically suspected in the context of pneumonia in the immucompromised patient, favoring the correct and timely treatment that allows complete recovery of the patient.

Keywords: Kidney transplantation, cytomegalovirus, COVID-19.

RESUMEN. De los pacientes con síndrome respiratorio agudo severo (SARS-CoV-2) por enfermedad por coronavirus 2 (COVID-19), 5% desarrollan síndrome de insuficiencia respiratoria aguda (SIRA) que resulta en una alta tasa de mortalidad. Paciente masculino de 36 años de edad, el cual tiene antecedente de trasplante renal de donador vivo relacionado, mostró cuadro clínico de fiebre de 39 °C, astenia, adinamia, posteriormente presentó mialgias, artralgias. Se realizó reacción en cadena de la polimerasa (PCR) para (COVID-19) así como tomografía axial computarizada (TAC) de tórax con hallazgo de CO-RADS 5, desarrolló mayor insuficiencia respiratoria requiriendo ventilación mecánica invasiva; se obtienen cultivos con resultado de PCR/ADNc citomegalovirus (CMV) cuantitativa: 554 copias/mL, se inició valganciclovir 900 mg, el paciente presentó adecuada evolución hasta lograr retiro de ventilación mecánica. La coinfección por CMV y SARS-CoV-2 a nivel pulmonar se debe sospechar clínicamente en el contexto de neumonía del paciente inmucomprometido, lo que favorece el tratamiento correcto y oportuno que permite la recuperación total del paciente.

Palabras clave: Trasplante de riñón, citomegalovirus, COVID-19.

INTRODUCTION

Over the past year it has been reported that 40-50% of severe acute respiratory syndrome type 2 coronavirus (SARS-CoV-2) infections are asymptomatic;[1,2] those who develop symptoms usually have mild to moderate disease, about 15% develop severe pneumonia requiring hospitalization, and approximately 5% develop septic shock and multiorgan failure resulting in a high mortality rate.[3,4]

Several studies suggest that the course of coronavirus disease 2019 (COVID-19) may be less favorable in immunosuppressed patients. A highly vulnerable group appears to be those with renal transplantation, in whom a mortality rate ranging from 20-28% has been reported,[5-9] it has also been proposed that some immunosuppressive therapies such as rituximab are associated with severe COVID-19 when compared with other therapies.

We present the clinical case of a man with a renal transplant who, after showing humoral rejection, was treated with rituximab, in whom, in addition to identifying the SARS-CoV-2 virus, co-infection with cytomegalovirus (CMV) was confirmed, one of the most frequent opportunistic viral pathogens in kidney transplantation. We consider that the success in the treatment of this case lies in the clinical suspicion and identification of the second agent in bronchioloalveolar lavage.

CLINICAL CASE

A 36-year-old man with a history of related living donor renal transplantation (2003) for bilateral renal hypoplasia presented humoral rejection in November

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2021 and required immunosuppressive management with rituximab, to later receive mycophenolate, prednisone and tacrolimus, conditioning hematologic toxicity and severe immunosuppression. He also suffers from secondary systemic arterial hypertension, in treatment with calcium antagonist and angiotensin II converting enzyme inhibitor. He was admitted for a clinical picture of four days of evolution characterized by fever of 39 °C, dysgeusia, anosmia, cough, myalgias and arthralgias, accompanied by progressive dyspnea up to modified Medical Research Council (mMRC) 4 and pulse oximetry saturation (SpO_2) of 88%. On admission to the emergency room he had blood pressure: 105/65 mmHg, heart rate: 85 bpm, respiratory rate: 29 rpm, temperature: 36.7 °C, SpO_2: 87%, arterial blood gas (ABG) arterial oxygen pressure (PaO_2): 57.6 mmHg, arterial carbon dioxide pressure ($PaCO_2$): 36.6 mmHg, pH: 7.43, arterial oxygen pressure/inspired oxygen fraction index (PaO_2/FiO_2): 274 mmHg. Chest computed tomography scan confirmed the presence of ground glass areas of random distribution both peripherally and centrally affecting more than 60% of the lung parenchyma *(Figure 1A and 1B)*, and also revealed pancytopenia. Polymerase chain reaction retrotranscriptase (PCR-RT) test for SARS-CoV-2 in nasopharyngeal exudate was positive. Supportive treatment, dexamethasone 6 mg every 24 hours and prophylactic anticoagulation with enoxaparin was initiated. However, 24 hours after hospital admission he developed severe acute respiratory failure syndrome (PaO_2/FiO_2: 49.4 mmHg) and septic shock. A second simple chest computed tomography scan was performed, which showed significant extension of the pneumonia *(Figures 1C, 1D and 2)*, so he was admitted to the intensive care unit (ICU) for advanced airway management and assisted mechanical ventilation. Due to clinical and radiological deterioration and because he was a patient with hematologic toxicity due to immunosuppressants, bronchioloalveolar lavage was performed and CMV was identified by polymerase chain reaction/ complementary deoxyribonucleic acid (PCR/cDNA) for cytomegalovirus: 554 copies/mL. The patient's clinical course was torpid, requiring vasoactive amines and renal function replacement therapy. However, after the administration of valganciclovir 900 mg every 24 hours for 21 days, together with the rest of the treatment, the evolution was favorable. Percutaneous tracheostomy was performed due to muscle weakness and prolonged mechanical ventilation; mechanical ventilation was withdrawn after 26 days of stay in ICU, and renal function was recovered, which allowed suspending renal function replacement therapy. The patient was discharged from the hospital five days later with supplemental oxygen 2 L/minute and physical and respiratory rehabilitation. Swallowing test and endoscopic revision of the airway were performed 10 days after discharge, in which malacia and stenosis were ruled out, and the tracheostomy tube was removed.

DISCUSSION

Cytomegalovirus (CMV) is a human virus of the family Herpesviridae, a β-Herpesvirus (HHV) like HHV-6 and

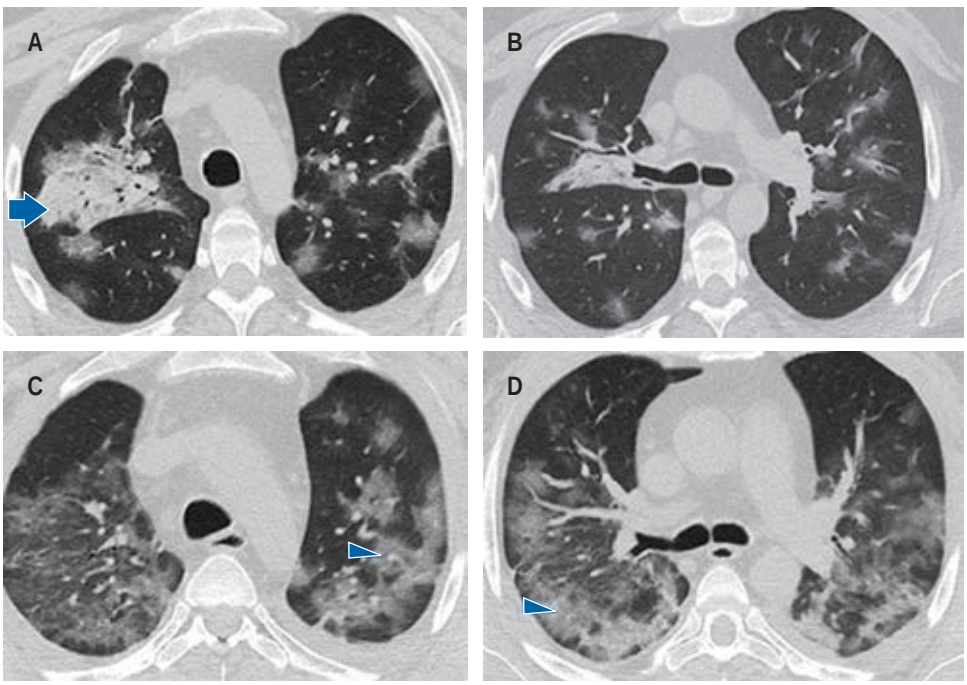

Figure 1:

A) Chest plain tomography, pulmonary window showing areas of attenuation in ground glass predominantly peribronchovascular and subpleural. Consolidation in the right upper lobe (arrow). **B)** Bilateral ground glass images are observed. **C)** Progression of frosted glass lesions, ground glass images and consolidation in left lung parenchyma (arrow head). **D)** Frosted glass images with consolidation in right lung parenchyma (arrow head).

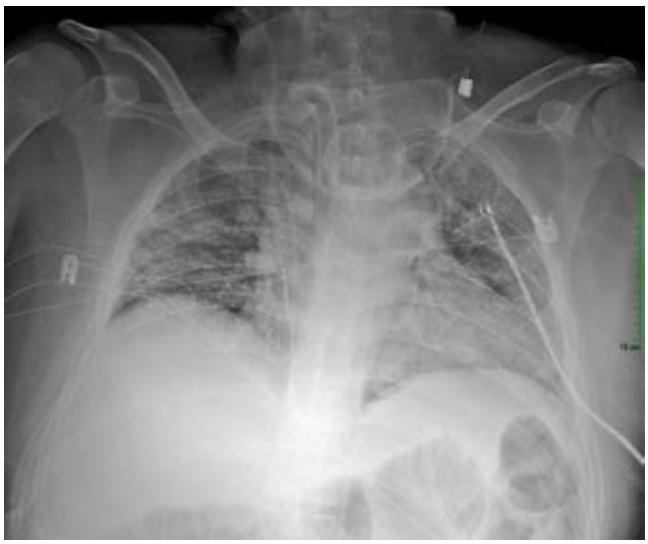

Figure 2: Portable chest X-ray, progression of disseminated bilateral pulmonary infiltrates is observed.

HHV-7.[10] First infection occurs in childhood and the seroprevalence is 70-90% of the adult population.[11] After the first infection, the presence of the virus can be identified in subpopulations of CD34+ myeloid progenitors as well as in CD14+ monocytes, dendritic cells and megakaryocytes.[12,13] In situations of immunosuppression, such as solid organ transplantation, CMV infection can occur as a primoinfection or as a reactivation after a long latency period.[13,14]

In the case presented, diagnosis and follow-up of cytomegalovirus infection was performed with PCR/cDNA testing of bronchioloalveolar lavage specimen, which is the gold standard, and treatment with 900 mg of valganciclovir every 24 hours (O) prophylactically was decided. At present, there is little information on CMV and SARS-CoV-2 coinfection. Amaral *et al* reported a case of SARS-CoV-2 infection and invasive CMV colitis successfully treated.[15]

CMV co-infection in patients with COVID-19 increases morbidity and mortality, as CMV reactivation can occur at any time, but is much more likely in the context of graft rejection, severe immunosuppression secondary to graft treatment, with special interest in the use of rituximab, in addition to the patient's critical condition already established by SARS-CoV-2 infection.

CONCLUSION

To our knowledge, this is the second described case of this co-infection at pulmonary level, so we report our experience, where the co-infection by CMV and SARS-CoV-2 at pulmonary level could be performed thanks to the high clinical suspicion in the context of pneumonia of the immucompromised patient with a history of humoral rejection, in whom the decision to perform bronchioloalveolar lavage allowed a complete etiological diagnosis, facilitating the correct and timely treatment that made possible the complete recovery of the patient.

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Clinical case

Hyper IgE syndrome and eosinophilic ulcer

Síndrome de hiper-IgE y úlcera eosinofílica en mucosa oral

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ABSTRACT. Hyper-IgE syndrome is a rare disorder characterized by elevated serum IgE, with skin manifestations (abscessed, eczema and infections) and recurrent pulmonary infections. This disorder occurs in two genetic patterns: Autosomal dominant (AD-HIES) and Autosomal recessive (AR-HIES). Eosinophilic ulcer of the oral mucosa is described as a benign, self-limited lesion with high predilection for the ventral mucosa of the tongue. Its diagnosis is established by histopathological study. We report the case of a 10-year-old male patient diagnosed with Hyper IgE Syndrome, with presence of Eosinophilic Ulcer in the oral mucosa, with approximately two months of evolution.

Keywords: Hyper IgE syndrome, eosinophilic ulcer, oral mucosa.

RESUMEN. El síndrome de hiper-IgE (SHIE) es una inmunodeficiencia primaria y trastorno poco frecuente, se caracteriza por un elevado nivel de IgE sérica, con manifestaciones cutáneas (eccema, abscesos o infecciones) e infecciones pulmonares recurrentes. Dicho trastorno se presenta en dos patrones genéticos: autosómica dominante (AD-SHIE) y autosómica recesiva (AR-SHIE). La úlcera eosinofílica (UE) de la mucosa oral se describe como una lesión benigna, autolimitada con alta predilección por la mucosa ventral de la lengua. Su diagnóstico se establece a partir del estudio histopatológico. Presentamos el caso de paciente masculino de 10 años de edad, diagnosticado con síndrome de hiper-IgE, con presencia de úlcera eosinofílica en la mucosa oral de dos meses de evolución.

Palabras clave: Síndrome hiperinmunoglobulina E, úlcera eosinofílica, mucosa oral.

INTRODUCTION

Hyper-IgE syndrome (HIES) is a multisystem disorder exhibiting immunologic and nonimmunologic features; the clinical triad that characterizes it is as follows: extreme elevations of serum IgE (higher than 2,000 IU/mL), cutaneous manifestations (eczema, abscesses or staphylococcal infections), and recurrent pulmonary infections. Staphylococcal skin abscesses may appear without signs of inflammation (cold) but are usually filled with pus; eczema may present as a newborn rash and is usually caused by *Staphylococcus aureus*; candidiasis may also manifest. Cases of pneumonia are complicated by parenchymal abnormalities of the lung (bronchiectasis and pneumatoceles).[1,2]

HIES was first described in 1966 by Davis SE *et al.*[3] as «Job's syndrome», reporting that two girls showed severe eczema, pulmonary infections, and cold abscesses related to *Staphylococcus aureus*. In 1972, the syndrome was redefined by Buckley HR *et al.*,[4] reporting two cases that also had similar infectious problems and a distinctive facial phenotype along with highly elevated serum IgE levels.

HIES is rare, with an annual incidence of 1:1'000,000 displaying no gender or racial differences. It's a genetic disease that can present two patterns:

1. Autosomal dominant (AD-HIES).
2. Autosomal recessive (AR-HIES).[5,6]

The pathophysiology of the syndrome is still unknown; however, the etiology of the autosomal dominant form (AD-HIES) has been described as an error in the DNA binding domains and SH2 essential for the differentiation of Th17 cells, whose function involves the elimination of fungi and extracellular bacteria through the production of cytosines

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(IL-17, IL-22). The autosomal recessive form (AR-HIES) is probably due to a mutation present in the TYK2 gene, which emerges through B- and T-cell immunodeficiency.[1,6]

The diagnosis should be determined based on clinical and laboratory manifestations, mainly by identifying a genetic defect (STAT3 gene mutation); furthermore, the diagnosis can be established through the Grimbacher criteria (scoring system by the US Institutes of Health in patients with a family history of HIES). A score ≤ 30 has a sensitivity of 87.5% and specificity of 80.6% if less than 20 points are obtained: Dx unlikely; 20-40 points: Dx doubtful; and > 40 points: Dx probable. Differential diagnosis includes allergic bronchopulmonary aspergillosis, chronic granulomatous disease, T-cell lymphoma, and atopic dermatitis.[7,8] In most patients with HIES, there are a series of oral manifestations; among them, there are anomalies in the process of exfoliation of the primary dentition in 64% approximately. This alteration results in the ectopic eruption of permanent teeth and the development of malocclusion. In more than 75% of people enduring this pathology, the oral mucosa and gingiva lesions have been identified, markedly affecting the dorsum of the tongue, palate, labial and buccal mucosae.[2] In appearance, lesions on the palate are usually fibrous; abnormalities on the tongue appear in the form of grooves on the surface; lesions that develop at the mucosal level consist of shallow fissures and striae, patches, or plaques covered by a keratin layer, all of which are asymptomatic.[2]

Eosinophilic ulcer of the oral mucosa (EU), also known as traumatic ulcerative granuloma with stromal eosinophilia (TUGSE),[9] is described as a rare, self-resolving, benign clinical-evolving ulcerative lesion, histologically composed of abundant eosinophils among the cells of the inflammatory infiltrate found in the dermis; its incidence is slightly more frequent in women.[10,11]

Clinically, it presents as an ulcer of 1 to 2 cm in diameter with indurated borders, asymptomatic, or extremely painful.[12] Histologically, the ulcerated area of the mucosa appears covered by fibrinoid exudate with cellular detritus. At the base of the ulcer, there is granulation tissue and hyperplastic epithelial margins; the submucosa is occupied by a diffuse infiltrate composed of abundant eosinophils, lymphocytes, plasmacytes, and histiocytes.[13,14]

This article aims to present the case of a patient diagnosed with hyper-IgE syndrome and eosinophilic ulcer in the oral mucosa since we consider it relevant for pulmonologists to be aware of the possible oral manifestations of this condition, as well as for dentists to know about the hyper-IgE syndrome and its repercussions in the stomatognathic apparatus.

CLINICAL CASE

Here is the case of a ten-year-old male patient diagnosed with HIES, community-acquired pneumonia (CAP), and infectious exacerbation of bronchiectasis. A relative reported that the child had been admitted to the Pediatric Hospital two months before, seeking treatment for pneumonia and «a lesion in the mouth». Later, he was hospitalized at the *Instituto Nacional de Enfermedades Respiratorias* (INER), due to developing a productive cough having green, viscous, regular, non-cyanotizing, rubicundizing expectoration, frontal headache, preceded by nausea and dizziness for three days. The initial evaluation showed a Glasgow of 15,

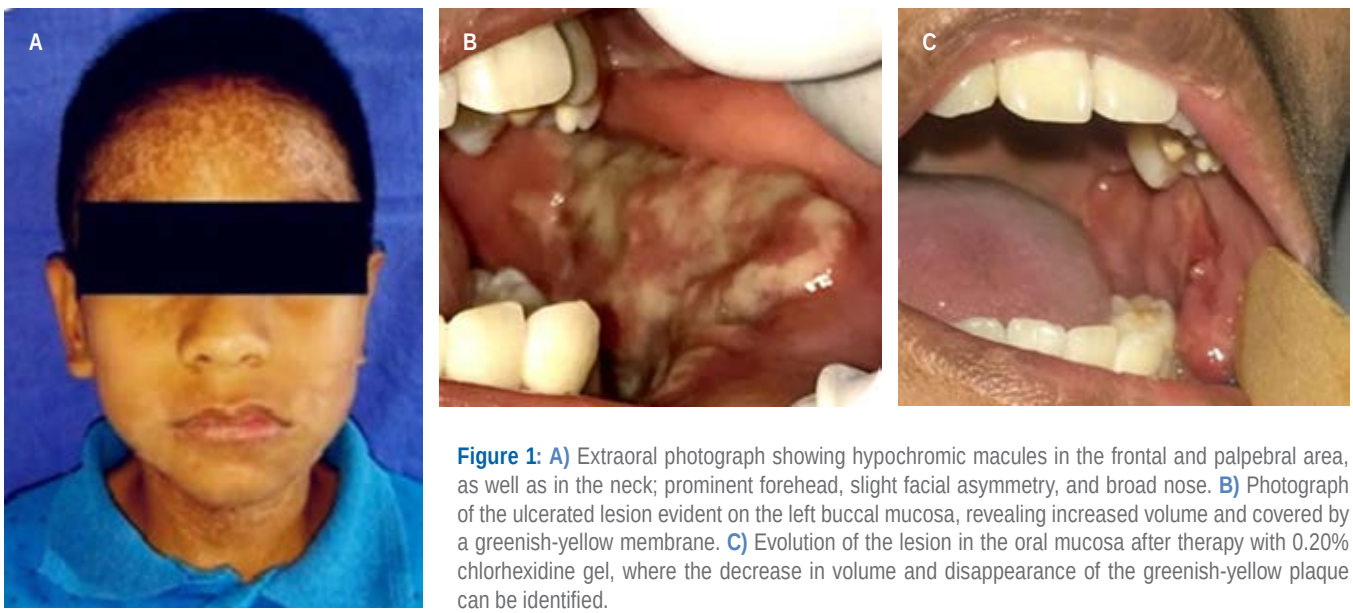

Figure 1: A) Extraoral photograph showing hypochromic macules in the frontal and palpebral area, as well as in the neck; prominent forehead, slight facial asymmetry, and broad nose. **B)** Photograph of the ulcerated lesion evident on the left buccal mucosa, revealing increased volume and covered by a greenish-yellow membrane. **C)** Evolution of the lesion in the oral mucosa after therapy with 0.20% chlorhexidine gel, where the decrease in volume and disappearance of the greenish-yellow plaque can be identified.

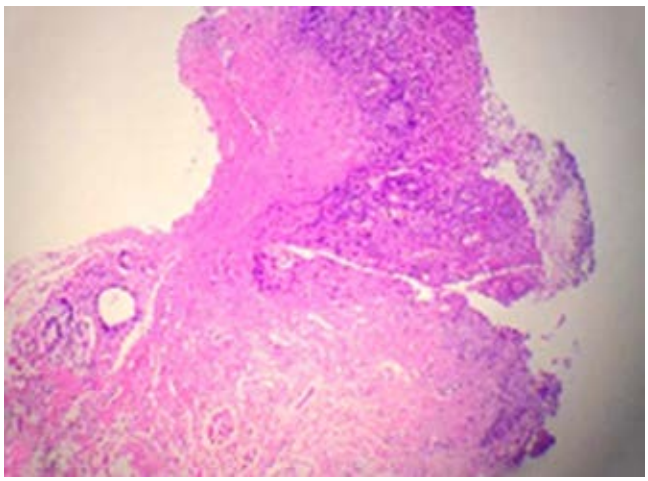

Figure 2: Microscopic image at 10× magnification, using hematoxylin-eosin stain; stratified parakeratinized squamous epithelium with intra- and intercellular edema, fibrin, and diffuse severe mixed inflammatory infiltrate, eosinophils, vascular neoformation and endothelial proliferation in a well-vascularized dense fibrous connective tissue.

fever of 38.1 °C, RR: 38 rpm, HR: 154 bpm, BP: 110/60 mmHg, O_2 saturation of 83% at room conditions, and serum IgE level of 4,570 IU/mL, general dehydration, referring pain at the abdominal level. A clinical-radiological diagnosis of pneumonia was made, and treatment with ceftriaxone and fluconazole was started empirically due to eosinophilia in peripheral blood.

Facial examination shows lips and mucous membranes dehydrated, asymmetric auricular pavilions, hypochromic macules in the frontal and palpebral areas of the face, neck, and arms, and isochoric pupils. He also manifests the typical facial phenotype of the syndrome: broad nose, prominent forehead, facial asymmetry, and retention of some primary teeth *(Figure 1A)*.

Intraoral examination reveals the presence of mixed dentition, multiple carious lesions, posterior open bite, and generalized gingivitis. In the left buccal mucosa, there was an ulcerated increase in volume extending from the labial mucosa to the cheek, of indurated consistency, covered by a greenish-yellow membrane and sessile base, for which the maxillofacial surgery department approached the patient *(Figure 1B)*. An incisional biopsy was performed, evidencing an eosinophilic ulcer *(Figure 2)*. The use of 0.20% chlorhexidine gel was indicated. Seven days after treatment, there was a notable improvement and decrease in the size and discomfort of the lesion *(Figure 1C)*.

DISCUSSION

Several authors have published texts on the oral implications associated with HIES, such as anomalies in the change of dentition, alterations in facial growth, and high susceptibility to oral infections; however, no cases reported in the literature were found in which EU is related to oral mucosa manifestations in patients having HIES. In this case, the patient demonstrated the main clinical and immunological characteristics of the syndrome. The physical features were coarse, prominent forehead, broad nose, dental retentions, a history of eczema, recurrent respiratory diseases (pneumonia and bronchiectasis), atopic dermatitis, oral herpes, generalized gingivitis, ulcers in the oral mucosa, and presence of vulgar flat warts. It was of fundamental importance to take a biopsy due to the appearance of the lesion to rule out the possibility of a malignant neoplasm.

Grimbacher B *et al.*[14] suspected that the process of late rhizolysis of the primary dentition could be a manifestation of the same defect resulting in an ineffective inflammatory response. Bencini AC *et al.*[13] describe that EU consists of a benign inflammatory process, characterized by a single ulceration with clear borders, and the causes that produce it in the oral mucosa are multiple: chemical, physical and thermal trauma; infectious agents (bacteria, viruses, fungi, parasites…); allergic reactions, systemic diseases; and lymphoproliferative disorders. In the case of our patient, we consider that the development of this type of non-neoplastic lesion is directly related to the high susceptibility to viral, bacterial, and fungal infections, among others; as a result of the error in the DNA binding domains and SH2 in the STAT3 gene, there is a defective inflammatory response against pathogens.

It was decided to perform conservative treatment with the application of 0.20% chlorhexidine gel, in addition to the placement and indication of the use of an occlusal guard; favorable results were obtained, without requiring any other therapeutic alternative, as indicated by Ficarra G *et al.*,[15] who propose the use of antibiotics, cryosurgery, surgery, corticosteroids or surgery combined with intralesional corticosteroid therapy.

An accurate diagnosis of this pathology is of significant importance due to its multiple manifestations and clinical similarity with other entities that respond to different treatments and evolution. From the stomatological approach, the dentist's role in diagnosing and treating these lesions is highly relevant. The pulmonologist should be familiar with the oral implications that patients enduring HIES may present and refer them promptly to the dentist for evaluation and treatment.

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Tribute to Dr. Jaime Villalba Caloca. At one year after his departure

Homenaje al Dr. Jaime Villalba Caloca. A un año de su partida

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Whoever doesn't know
Molecular Biology, is doomed
Dr. Jaime Villalba Caloca
Thoracic Surgeon. Doctor in Science

Dr. Jaime Villalba Caloca passed away on November 18, 2020 in the middle of the respiratory pandemic, a week later a tribute to this great master of Pneumology and Thoracic Surgery in the country was held at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, I was invited by the General Direction to participate in this event, where I expressed the following speech:

The present year 2020 will be remembered in our Institute as that of the impact of the COVID-19 pandemic and in which Dr. Jaime Villalba Caloca departed.

I arrived as a resident of Pneumology to our Institute at the beginning of this century, in the General Direction was the Doctor, who also assumed the position of Titular Professor of the course; he was in the final stretch of his administrative responsibility.

When by chance we met, we received his greeting and courtesy, always direct and frontal; he enjoyed the respect, affection and admiration of the vast majority of health personnel, regardless of hierarchy.

He was a pioneer in thoracic surgery and lung transplantation in Latin America; in the last third of his life he had a particular interest in research, achieving a PhD from the Instituto Politécnico Nacional, in addition to his incorporation to the National System of Researchers.

My relationship with him became closer the day he invited me to give a talk at the Hospital Bioethics Committee that he chaired, I spoke on a sensitive subject from the thanatological point of view as euthanasia, then I joined the committee and for 10 years we had a regular monthly session, and when the extraordinary one was needed we formed a Cineclub with themes of Medical Ethics, we gave conferences on this subject in several places of the Institute, I always had their sympathy in spite of the fact that sometimes there were subjects that forced us to discuss our personal points of view, in the end concord and respect prevailed. He reached what is called the old age and always maintained an enviable vitality.

He had a superior affection for our Institute, which is difficult for us to instill nowadays, but it's very necessary that it be so.

We were companions in the struggle when the vagaries of fate forced us to do so.

Every end of the year he organized a breakfast with our dear Lulu, his faithful squire, he was always cheerful, I think we were an extension of his family, which we proudly accepted.

It was interesting to hear his anecdotes; he had an incomparable sense of humor, combined with seriousness.

It's difficult to say goodbye to a teacher, friend and companion, despite having several decades of age difference with the Doctor, it was very pleasant to talk with him.

Dr. Jaime Villalba Caloca
https://www.medigraphic.com/pdfs/neumo/nt-2017/nt172i.pdf

I remember when he supported me in paying a well-deserved tribute to Dr. Ismael Cosío Villegas, founder of our Institute, in a general session, the way he talked about his experiences with the Master made it a memorable conference, at the end his humility was reflected when he approached me and asked me, "did I do well?"

We were able to achieve one of his dreams, to publish the book of Institutional Bioethics, to which he had dedicated many years of work, but the publishers did not comply with the agreement, in an agile way and with the support of the industry we fulfilled that desire, having it currently in paper version and in electronic form for free distribution since a year before his death.

When life forces us to answer "how would I like to grow old?", the quick answer would undoubtedly be "like Dr. Villalba"; the other question would be "will I have the temper, character and disposition of the Master?", I hope that time will clarify the answer.

The memory of Dr. Villalba Caloca will not be extinguished, tributes like this one and those to come will keep the flame of this great man and his light will show us the way in times of darkness.

We must remember that he arrived at our Hospital when there was another pandemic: tuberculosis. The so-called «white plague» seemed to be an incurable disease, but with work, dedication and service, even risking their lives, they were able to face it and come out ahead.

This example should be and is the current guide, we will do what is necessary and if the situation demands it, more than what is necessary.
Forever Dr. Jaime Villalba Caloca!
Forever INER!
Thank you very much.

Speech read on November 25, 2020 at the general session of the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas in honor of Dr. Jaime Villalba Caloca.

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Importance of a patent upper airway, prior to the use of a high-flow nasal cannula in obese patients with COVID-19

Importancia de una vía aérea superior permeable, previo al uso de cánula nasal de alto flujo en pacientes obesos con COVID-19

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Mr. Editor, we carefully read the article: COVID-19 disease in hospitalized young Mexican adults.[1] The authors point out that obesity is a predictor of hospitalization and poor prognosis in young patients with COVID-19. While hypertension and type II diabetes mellitus are the main comorbidities associated with a torpid presentation, obesity, which is increasing, is also an important factor to consider in the management of oxygenation in hospitalized patients with COVID-19. One of the oxygenation management strategies in patients with SARS-CoV-2 hypoxemia is the use of high-flow nasal cannula (HFNC), proposed as a safe and effective alternative.

The use of oxygen therapy with HFNC has increased from 12 to 49% in hospital centers during the first and third waves of the pandemic, respectively;[2] decreasing the use of mechanical ventilation and its complications.[3] Likewise, its correct use significantly decreases aerosol production, making it a great alternative for oxygen therapy during COVID-19. However, the increased use of HFNC is not accompanied by knowledge of the type of patients who may have success or failure during its application; likewise, there is no solid information to know whether its application in obese patients would have the same results as in non-obese patients.[2]

Obesity is perhaps one of the comorbidities that could alter airflow patency in the upper airway on its way to the lower airway, producing inadequate oxygenation in the face of the use of HFNC. The reported treatment failure with HFNC, mainly in male and obese patients, rates of 60.9 and 52.2% respectively, suggest the presence of other additional factors in obese patients that may justify the cautious use of HFNC. This begs the question: is it necessary to assess upper airway patency prior to the use of HFNC in obese patients with COVID-19?

In obese patients with COVID-19 using HFNC, possible causes of failure related to inadequate airflow passage in the upper airway could be: 1) higher resistance to airflow throughout the upper airway in obese compared to non-obese, which could alter airflow passage to the lower airway; 2) higher nasal resistance in patients, mainly obese males; where retrolingual air collapse and lower pharyngeal patency at the level of the soft palate could decrease transnasal oxygenation of the hfnc; 3) association between obesity, obstructive sleep apnea and hypertension, considering that inadequate oxygenation in obese patients with obstructive sleep apnea could worsen hypertension,[4] and increase the risk as comorbidity in patients with COVID-19; and 4) the presence of the association of obesity, age and male gender (greater number of male COVID-19 patients with greater complications,[3] directly associated with nasal obstruction).

These possible causes of failure reinforce the need to ensure a patent upper airway through the evaluation of the entire upper airway in obese patients with COVID-19 prior to the use of HFNC. We propose that such evaluation of the upper airway should allow the identification of possible anatomical or functional factors that alter adequate airflow to the lower airway. An alternative would be the endoscopic evaluation of the entire upper airway, which can be performed in a simple and ambulatory manner by means of a flexible nasolaryngoscopy procedure; which, when performed through a posterior approach to the patient, decreases the possibility of infection by COVID-19.[5] The performance of such a procedure in the different hospital settings (admission unit, inpatient unit, intensive care unit) in all obese COVID-19 patients would contribute to a better decision on the use of HFNC, would allow early use (within the first 24 hours), indicated as a factor associated with the reduction of intubation and mortality,[5] or directly decide on mechanical ventilation.

Finally, future large-scale studies are needed to identify and protocolize the evaluation of the upper airway in obese patients prior to the initiation of HFNC, which would help to ensure a patent upper airway, strengthening the early and safe application of HFNC in obese patients with COVID-19.

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Reply

Respuesta

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Dear Dr. Esteban Vergara de la Rosa *et al*:

I would like to comment on your letter to the editor as follows.

As national reference centers in Mexico for the care of patients with severe and critical COVID-19, at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City and at the Centro Médico del Instituto de Seguridad Social del Estado de México y Municipios (ISSEMyM) Toluca, State of Mexico, we were pioneers in the use of high-flow devices for the management of hypoxemic acute respiratory failure (ARF) in COVID-19 patients. It should be noted that although at the beginning there was a great lack of knowledge about the behavior of the virus transmissibility and the mechanism of the potential increase in the risk of nosocomial contagion by aerosol generation, as scientific evidence progressed we joined the unanimous recommendations regarding its use by the World Health Organization (WHO), the Pan American Health Organization (PAHO), the Italian Thoracic Society, the Respiratory Care Committee of the Chinese Thoracic Society, the Intensive Care Society of Australia and New Zealand, and joint statements from the German Societies of Intensive Care, Anesthesia and Emergency Medicine, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine.

When the recruitment of the patients in our study began, there was no scientific evidence fully in favor of the use of the high-flow nasal cannula (HFNC), nor the described profile of the COVID-19 subgroup of patients who would benefit the most. In both centers there was a need to expand the workforce due to the demand for critical patient care, which, added to the temporary lack of training of new staff with little or no experience in the use of high-flow devices, favored intrainstitutional advocacy for early orotracheal intubation in patients with acute respiratory distress syndrome (ARDS) by COVID-19, as an advantage over other oxygen therapy devices (other than HFNC) that do not provide positive pressure effect and respiratory comfort over invasive mechanical ventilation (IMV) was the decreased risk of hindering lung damage by tachypnea-induced lung injury itself.

In our cohort, obesity in young people became one of the main comorbidities known to the patient prior to admission, associated with deterioration and severity of SARS-CoV-2 infection and, although patients in our cohort did not benefit from this therapy, in both hospitals young people with ARDS avoided intubation with the use of HFNC and awake prone, the evidence of which over the months was compelling in favor of its use.

We believe that the need for rapid evaluations of upper airway patency is real, necessary, feasible and useful, so we support this recommendation in order to continue positioning HFNC as a contemplated therapeutic alternative for this spectrum of patients COVID-19 and others, for as time goes by, we are sure that we will continue to face people with ARDS due to different causes who concomitantly present obesity and mechanical partial airway occlusion, whose management without IMV and with HFNC could improve their prognosis.

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