Clinical related factors to neuroendocrine tumors in Ecuadorian patients: a logistic biplot approach.

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Abstract. Neuroendocrine tumors (NETs) are relative rare, affecting neuroendocrine cells throughout the body. Most tumors are diagnosed at advanced stages. NETs prevalence has increased in the last years but there is little data available in developing countries. The aim of this study was to describe symptoms associated with NETs in patients of the Society for the Fight Against Cancer (SOLCA) in Ecuador from 2005 to 2020; using logistic biplots, in a hospital database, generating binary responses (presence/absence) relevant to this study. The results showed that the mean age was 59 and the study showed no difference in prevalence between genders. NETs were mainly found in lungs (19%), followed by stomach (18%) and skin (9%). Most patients had pathological diagnosis G2 and G3 (30% and 70%, respectively). Symptoms as cough, dyspnea, weight loss, diarrhea, constipation, abdominal pain, dyspepsia, hypertensive crisis, distended abdomen and intestinal obstruction had p values <0.05. Additionally, the statistical analysis showed that cough and intestinal obstruction were also common, bearing in mind that patients had most frequent NETs in the lungs and skin. In summary, our results indicate that symptoms of NETs patients were positively associated with lung and skin. Further investigation is needed focusing on the type of NETs and their symptoms in order to establish an early marker for diagnosis.

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Factores clínicos asociados a tumores neuroendocrinos en pacientes ecuatorianos: un análisis biplot logístico.

Resumen. Los tumores neuroendocrinos (TNE) son relativamente raros y afectan a las células neuroendocrinas de todo el cuerpo. La mayoría de los tumores se diagnostican en etapas avanzadas. La prevalencia de los TNE ha aumentado en los últimos años, pero hay pocos datos en los países en desarrollo. El objetivo de este estudio fue determinar los síntomas asociados a los TNE en pacientes de la Sociedad de Lucha contra el Cáncer (SOLCA) en Ecuador entre 2005 y 2020, utilizando biplots logísticos en una base de datos hospitalaria, generando respuestas binarias (presencia / ausencia) relevantes para este estudio. Los resultados mostraron que la edad promedio era de 59 años y el estudio no encontró diferencias en la prevalencia entre géneros. Los TNE se encontraron con mayor frecuencia en los pulmones (19%), seguidos del estómago (18%) y piel (9%). La mayoría de los pacientes tenían diagnóstico patológico G2 y G3 (30% y 70% respectivamente). Los síntomas como tos, disnea, pérdida de peso, diarrea, estreñimiento, dolor abdominal, dispepsia, crisis hipertensiva, abdomen distendido y obstrucción intestinal tuvieron valores de p <0,05. Además, el análisis estadístico mostró que la tos y la obstrucción intestinal también eran comunes, teniendo en cuenta que los pacientes tenían TNE más frecuentes en los pulmones y la piel. En resumen, nuestros resultados indican que los síntomas de los pacientes con TNE se asociaron positivamente con los pulmones y la piel. Se necesitan más investigaciones que se centren en el tipo de TNE y sus síntomas a fin de establecer un marcador más temprano para el diagnóstico.

INTRODUCTION

Neuroendocrine tumors (NETs) are a group of malignant tumors appearing from neuroendocrine cells throughout the body that are defined as epithelial neoplasms with predominantly neuroendocrine differentiation [1]. NETs are commonly located in the pancreas, digestive tract, and the lungs although they can appear in any organ [2]. NETs grading is probably the most useful instrument for providing prognostic information for clinicians [3]. Currently, the classification recognizes that neuroendocrine cancer at any anatomical site is either well-differentiated defined as NETs, and poorly differentiated defined as neuroendocrine carcinoma [3]. Severity may be evaluated by grading the tumor between 1 and 3 and per proliferation fraction as measured by mitotic count by the Ki67-positive percentage [4,5]. Approximately one-third of the high-grade group are the most aggressive NETs fraction, predicting either a worst event-free

survival or overall survival compared with grade 2 NETs [6]. Unfortunately, most patients are diagnosed in late stage of NETs [7].

NETs symptoms vary depending on biological aggressiveness and the anatomical location of the tumor [8]. Vague and nonspecific symptoms may cause considerable delay and difficulty in diagnosis [9]. The clinical presentation of NETs is generally related to the secretion of hormones that may indicate carcinoid syndrome or hormonal symptoms [10]. Carcinoid syndrome commonly cause diarrhea, flushing, fatigue [9], abdominal pain and intermitted bowel obstruction [11]. It is worth mentioning that the number of bowel movements and flushing episodes significantly affect the quality of life of NETs patients [10]. The intensity of these symptoms can vary widely, depending primarily on the site of disease and grade of tumor. More studies are necessary for clinicians to become familiar with the natural history and patterns of disease progression, which are characteristic of NETs [7]. Therefore, the precocious diagnosis of tumor may increase survival and improve NETs patient's quality of life.

In Ecuador, the Cancer Fighting Society (SOLCA) Quito Nucleus and National Tumor Registry exists since 1984 (Minist Salud Pública) and cares for approximately 31% of the oncological cases of the country [12]. In Ecuador, the clinical management of NETs is significantly lower, compared to that of the United States and Europe and there are few specialized centers managing a multidisciplinary environment [13]. Despite the high prevalence and severity of NETs, this tumor has not been previously studied in people from Ecuador to the best of our knowledge. Consequently, the aim of this research was to investigate the presence of NETs patients in the hospital database over fifteen years. Based on the above, a logistic biplot is proposed as an alternative to identify the most frequent symptoms in patients with NET using binary variables (presence / absence) with binomial distribution [14]. This analysis allows us to obtain a graphic representation of the NETs types and the main associated symptoms. In this sense, the approach that provides a better interpretation to relate the type of tumor with its symptoms, taking into account the comparison with the classic classification / ordering techniques, is provided by the biplot methods [15, 16], where a simultaneous graph represents the columns (variables) and the rows (individuals) of the given data matrix.

MATERIAL AND METHODS

Collected database

The study was done using the hospital database of SOLCA Portoviejo, in the Province of Manabí, Ecuador, analyzing patients with NETs diagnosis between 2005 and 2020.

Statistical analysis

The main problem with our data is the very limited number of patients and the high number of variables (symptoms, types of tumor, locations, etc…) that prevents from using standard methods as logistic regression. An exploratory multivariate technique would be more adequate to explore possible patterns before trying to apply a more formal model using a relevant subset of symptoms obtained from it. This kind of techniques have also the advantage of showing the interrelations among all the variables.

For the exploratory analysis of our data, we used a multivariate technique called "logistic biplot" [14] that was specifically designed to treat binary data, as well as more traditional analyses. Although logistic biplots have not been extensively used with medical data, some authors [17] propose these kind of multivariate techniques as a mean to perform an exploratory analysis previous to a more formal analysis. Other authors [18] also propose the technique as an analysis of the residuals of a model, to check for the goodness of fit or the violation of some previous hypothesis about the data.

Because logistic biplots are less known, we include here a brief description. A biplot is a graphical representation of a data

matrix, containing the measures subjects on numerical variables [15], that jointly represents subjects and variables on the same plot. We have patients with different NETs and related symptoms (presence or absence) organized in a binary data matrix (0 for presence, 1 for absence).

The adequate method for binary data is the logistic biplot, originally proposed by Vicente-Villardón *et al* [14] and later extended by Demey *et al* [19] to binary matrices where the number of variables is high compared to the number of individuals. This extension was applied to the investigation of the single nucleotide polymorphisms related to different racial groups of people with data from the HAPMAP project [20]. The method has been applied in different fields as sustainability [21], dermatology [22] and lately it has also been extended to deal with nominal data [23].

Logistic biplots represent individuals as points on a Euclidean map (scattergram) and variables as directions (arrows) on the same map. Patients with similar combinations of symptoms tend to group together while distinct individuals tend to pull apart. The vectors for the variables on the plot are the directions more correlated to the presence of the symptom, so we can infer which symptoms are responsible for the grouping of the patients. To interpret the symptoms associated to the grouping of patients we project the points onto the direction of the vectors - the further (in the direction of the arrow) the point is projected, the higher is the probability of the symptom. The origin of the vector is the point predicting probability 0.5 and the arrow indicates the direction of increasing probabilities.

Angles among vectors can help with the identification of the relationships among the symptoms: small acute angles mean strong positive relations; plane angles (Formed by two right angles 180°), negative relations; and straight angles (formed by two perpendicular lines 90°), are not related. The position of the vectors can also help identifying the main gradients (or latent traits) summarizing the variation of the symptoms and

its relation to the different locations of the cancer. It is called logistic biplot because the relation of the symptoms and the traits (dimensions) is logistic, it is like a Principal Component Analysis (or biplot) for binary data in which the relation to the components is logistic rather than linear. When data are binary, like those obtained in the analysis of neuroendocrine tumors, Classical Linear Biplots and Principal Components Analysis (PCA) are not suitable because the response along the dimensions is linear. This is the same reason why linear regression is not appropriate for binary or categorical data [14, 21].

The MULTBIPLOT [24] and MultBiplotR [25] packages were used to perform the calculations and obtain the graphical representations. For this study, we first performed a Principal Coordinates Analysis (Classical Multidimensional Scaling), with the simple matching coefficient, and then fitting separated logistic regressions to represent the directions on the Euclidean map [19]. The interpretation of the relevance of the symptoms to classify the patients was evaluated by traditional indicators for logistic regressions as Wald tests, pseudo R-squared coefficients or percentages of accurate classification.

RESULTS

Population characteristics and NETs symptoms

A total of 94 adult patients (aged 19 to 95 years-old) were diagnosed with NETs between 2005 and 2020 and included in our research. The most frequent primary location was the lungs (19%), followed by stomach (18%), rectum (8%) and skin (8%). Unknown primary location represents 8% of the tumors studied. The set symptoms present in our patients with different types of NETs are shown in Table 1.

Table 2 represent sociodemographic characteristic, mortality, primary site and histologic grade of NETs patients. The mean age in this study was 59 years-old and the prevalence was higher in men (57% versus

Table 1
Represent total symptoms found in NETs patients among eleven years in SOLCA, Manabí.

Primary location	Patient	Porcentage
LUNG	18	19%
STOMACH	17	18%
RECTAL	8	9%
SKIN	8	9%
UNKNOWN PRIMARY	8	9%
PANCREAS	5	5%
GANGLIA	4	4%
LIVER	4	4%
DUODENUM	3	3%
APPENDIX	2	2%
CECAL APPENDIX	2	2%
CERVIX	2	2%
COLON	2	2%
RETROPERITONEUM	2	2%
RIGHT COLON	2	2%
COLEDOCO	1	1%
ENDOMETRIC	1	1%
ILEUM	1	1%
LEFT COLON	1	1%
SOFT TISSUES	1	1%
UTERINE NECK	1	1%
VESICAL TUMOR	1	1%
TOTAL	94	100%

Table 2
Represent sociodemographic characteristic, mortality, primary site and histologic grade of NETs patients.

Variable	Parameters	No. Patients (n)	Porcentage
Age	<40	11	12%
	40-54	22	23%
	55-70	30	32%
	> 70	31	33%
Sex	Man	54	57%
	Woman	40	43%
Mortality	Alive	38	40%
	Dead	56	60%
Histologic grade	Type 1 y 2	28	30%
	Type 3	66	70%

3). We observe that most patients having lungs as the primary location are on the top of the plot, while tumors related to the digestive system (rectum, stomach, right colon, ileum and pancreas) are on the bottom part and well separated from the "lung" group, so we can conclude that the analysis has some power to classify the tumors.

When projecting the patients' points onto the directions for the symptoms, we obtain the expected probability that the patient has the symptom. In order to predict the expected presence when the expected probability is higher than 0.5. For each arrow, we only represent the point predicting 0.5 and the direction of increasing probabilities. Thus, we can correctly predict 95.75% of the presences and absences. All the individual symptoms have percentages of correct predictions over 94%. The associated R-squared values are all over 70% and the information of each variable can be accurately interpreted. We can conclude that the representation is a good picture of our data matrix and can be used for exploration.

To search for the symptoms that characterize each group, we can look at the di-

43%). The most prevalent stage in NETs patients was G3 (70%) while G1 and G2 represent 30% of the patients.

Logistic Biplot in types of NETs and our symptoms in patients of SOLCA

Fig. 1 shows the result of applying the logistic biplot to the binary matrix of 94 patients and 37 symptoms. Each patient (points) has been labeled using the primary location of its tumor and each symptom (arrow) using the name of the symptom. Only the symptoms significantly related to the patient's configuration were retained on the plot (See Table
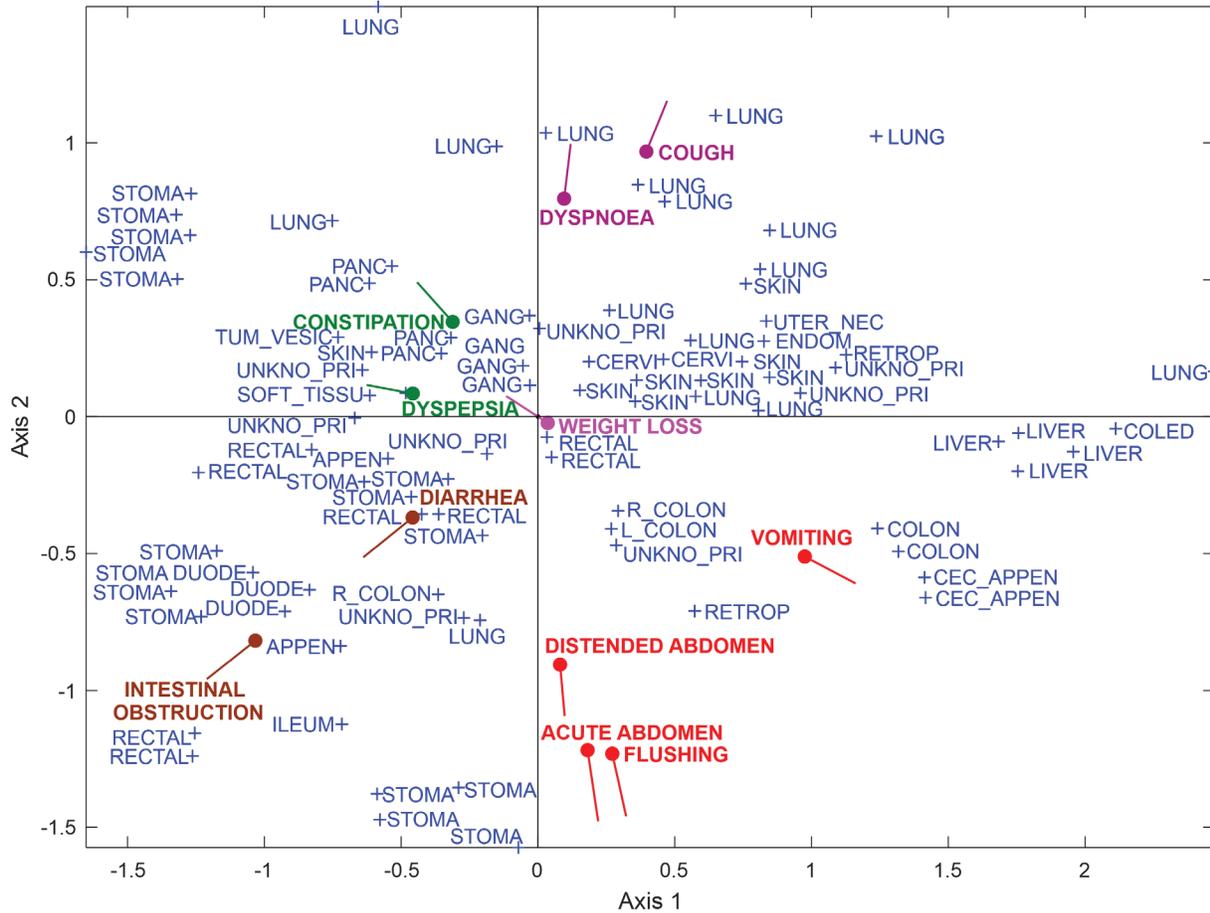
Fig. 1. Biplot representation of the relations among the type of disease and the symptom that determine the groups structure in the simulation. Small acute angles mean strong positive relations; plane angles (Formed by two right angles 180º), negative relations; and straight angles (Formed by two perpendicular lines 90º), are not related. Sign (+) represents each of the individuals. Segments (lines) represent each of the variables (symptoms). Point represents the value of 0.05. Direction of the vector predicts the increase in the probability. The colors: red, brown, green, purple represents group the variables with respect to the individuals.

rection they point. For example, *Dyspnea* and *Cough* are present in patients for which the primary location is *lungs*, while *Diarrhea, Stomach pains, Distended abdomen, Hypertensive Crisis* and *Intestinal obstruction* point to the direction of the tumors related to the digestive system. Both sets of symptoms point in opposite direction meaning that they are inversely related, that is, the symptoms present in one group are absent in the other. Together, they de-

fine the gradient that separate both types of tumors. *Dyspnea* and *Cough* point to the same direction, meaning that they are highly positively correlated and appear together in some patients. *Weight Loss* has a very good fit but is not clearly characterized in any of the groups. The same is true to *Dyspepsia* and *Constipation*. The three are closely related to the first dimension, but they are less important to separate between groups of tumors.

Table 3
Goodness of adjunct for the main symptoms in NETs patients.

Primary symptom	Deviance	p-value	R2	% Correct
Vomiting	5.326	2,22045E-14	0,9390	100
Dyspepsia	6.467	0	0,8622	91.489
Flushing	4.791	1,78129E-07	0,8474	100
Distended Abdomen	5.922	1,69207E-11	0,8167	97.872
Diarrhea	4.848	0	0,8136	94.681
Weight Loss	6.146	0	0,8129	94.681
Cough	5.591	8,95759E-10	0,7999	97.872
Intestinal Obstruction	4.953	1,40092E-09	0,7847	94.681
Dyspnoea	5.574	6,51029E-11	0,7410	94.681
Acute Abdomen	4.306	1,96949E-07	0,7350	98.936
Constipation	5.730	1,26565E-14	0,7266	92.553

DISCUSSION

Neuroendocrine cells have endocrine and neural properties and are widely distributed in the body [3]. Many organs contain this cell phenotype and may be affected by NETs. The tumor has a particular morphofunctional characteristic, such as the hormones production, and the immunohistochemical features staining pattern with chromogranin, synaptophysin, and neuron-specific enolase [26]. Moreover, the World Health Organization (WHO) advices characterizing NETs by proliferation fraction as measured by either mitotic count or (more easily) by the Ki67-positive percentage (Ki67 index) [6]. It is worth mentioning that, epidemiological studies indicate that the most frequent source of metastasis in NETs are the small intestine, lungs and colon [27]. In the present retrospective databased study, we found lungs and stomach as more frequent NETs followed by rectum, and skin. Here, the diagnosis was through synaptophysin, chromagranin or Ki67 by biopsy, and most patients had several pathological diagnostics. Despite the malignancies of the tumor, to the best of our knowledge, this is the first evidence about NETs in patients from the Ecuadorian coast.

An approach that facilitates the genetic interpretation, compared to the classic techniques of classification/ordination, is provided by the Biplot methods [28, 15, 16], that is, a simultaneous graphical representation of the rows (individuals) and the columns (variables) of a given data matrix. The main uses are exploratory, although it has also been used as a graphical representation for more formal models [29]. The biplot can be fitted by performing alternating regressions and interpolations [30-32]. However, when data are binary, like those obtained in the analysis of molecular information, Classical Linear Biplots and Principal Components Analysis (PCA) are not suitable because the response along the dimensions is linear. This is the same reason why linear regression is not appropriate for binary or categorical data.

There is a significant delay between the symptoms onset and diagnosis of NETs and, consequently, most patients are diagnosed at a late stage of the disease [7]. Our results demonstrated that most patients were diagnosed in histologic grade 3, metastatic or advanced NETs and do not survive. Previous works consider NETs as a low-grade, usually non-functioning, malignant cancer characterized by long survival of pa-

tients with prognosis depending on grade and stage [33]. In fact, WHO in 2017 classified NETs with a Ki67 >20% as either grade 3 NET (well-differentiated) or as grade 3 NEC (poorly differentiated) on the basis of morphological characteristics as necrosis and differentiation [34]. NETs account for about 0.5% of all currently diagnosed malignancies [35]. Given this scenario, our work presents most NETs cases registered in the advanced stage, which could explain, at least in part, the death rates from NETs found in the present data-based study. Furthermore, the retrospective characteristic of the study with a duration of fifteen years should be considered. Indeed, NETs origin and ranking grade can define patient survival if previously reported 103 months from disease originating in the small intestine and only 14 months for cancers originating in the colon [36]. A severity nation-wide multi-center study in Korea reported a high G1 percentage of 92.3% [37]. However, research in Kentucky found a population with 67% in G3 [38]. Reinforcing this notion, our study reports most patients in G3 - 70%. Nevertheless, of special importance is that lower grade NETs do not indicate a better outcome in terms of survival [38].

Given this background, retrospective studies in different populations are important as an alert for the early diagnosis of disease. In the present study, we decided to investigate NETs more frequently and its associated symptoms. Lungs were the most frequently NETs reported in our study and it was associated with the symptoms of cough and dyspnea. In line with our results, previous research as a nation-wide study from the Netherlands and SEER database reported pulmonary NETs as being the most prevalent [36]. The NETs are often misdiagnosed before the cause of the patient's symptoms is finally diagnosed and managed appropriately [9].

Our results demonstrated that after lung and stomach, the most incidence of NETs was in the rectum and skin. We found a significantly positive relationship between the most frequent symptoms and the NETs found during or study. Therefore, symptoms such as diarrhea, constipation, dyspepsia, and intestinal obstruction in addition to weight loss were more prevalent. We should note that our research found that NETs in the stomach and rectum were associated with syndromes such as carcinoid syndrome. It has been previously described that carcinoid syndrome occurs in 8% to 35% of NETs patients [39]. This event appears when vasoactive hormones secreted by metastases (i.e serotonin, histamine, or tachykinins), are no longer metabolized and inactivated by the liver and reach the general circulation [40]. The classic symptom of episodic diarrhea was previously described by more than 70% of patients as consequence of carcinoid syndrome [41]. This data point is similar with what we found in our study. Additionally, it is important to note that the clinical presence of diarrhea and/or abdominal pain can often lead to misdiagnosis, confusing carcinoid syndrome as small bowel obstructions or irritable bowel disease [42]. Unfortunately, there is a delay between the onset of symptoms and the diagnosis of carcinoid tumor; the median time reported range from 2 to 20 years [43]. It is well established that early diagnosis of any type of cancer can improve the quality of life and survival and patients with carcinoid syndrome have a significantly worse quality of life than patients with only NETs [44]. Supporting this fact, our findings underscore the need to further identify all symptoms associated with NETs in an effort to aid physicians to speed up the diagnosis.

Unsurprisingly, the lungs are the most frequently found NET during the fifteen years studied. Importantly, we demonstrated that skin was the fourth most frequently NETs discovered. Based on previous work, NETs in the skin or soft tissue delay late manifestations of disease when represent metastases from other organs [45]. However, notably, according to the World Health Organization

books on skin and soft tissue tumors stated that primary cutaneous and soft tissue NETs are extremely rare, except for Merkel cell carcinoma of the skin [46]. Therefore, only a few case studies of soft tissue NETs are available in the literature [47]. Our findings show that 8% of all cases in the fifteen years studied were skin NET, mostly in elderly men. Supporting this finding, previous studies showed that Merkel cell carcinoma are most commonly found in elderly and in sun-exposed skin [48, 49], patients typically have fair-skin and the median age of diagnosis of 65 years [49]. It is interesting to note that the most common symptom reported in our work is skin damage with unknown or asymptomatic causes. This evidence is corroborated by other studies. Despite the diversity of skin manifestations, the tumor is typically painless and develops as a small, less than 2 centimeters, violaceous papule, plaque, cyst, or infiltrative nodule [50]. The tumor has a multifactorial cause and the exact mechanism by which it acts in the organism it is not fully elucidated, but Merkel cell polyomavirus is thought to be a major contributor to the pathogenesis of this malignancy [51].

Altogether, the results provided suggest that the most frequent clinical symptoms (cough and intestinal obstruction) were positively related to the type of NETs. When looking at the prevalence of NETs, the lungs were the most frequent site, which reinforces the hypothesis of the vulnerability of this organ. Further research is needed and should focus on identifying symptoms of NETs with the objective of early diagnosis. Furthermore, the prevalence of NETs specific in each population must be underscored in future research.

The logistic biplot technique allows the generation of relevant information based on clinical antecedents, as it was for this study on the presence or absence of the disease, taking into account patients with different neuroendocrine tumors.

Declaration of competing interest

The authors declare that no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there is no personal financial holding that could be perceived as constituting a potential conflict of interest.

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Authors' contribution

- Interpretation of data, analysis and writing the manuscript (KME)
- Supervision and writing (JLVV)
- Data collected (DFAC)
- Writing the manuscript and prepared the final draft (AS).
- All authors have read and approved the final version of submitted manuscript.

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