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The Latin-American Experience in POEMS Syndrome: A Study of the GELAMM (Grupo de Estudios Latinoamericanos de Mieloma Múltiple)

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Keywords
POEMS · Latin-America · GELAMM

Abstract
Introduction: POEMS syndrome is a rare paraneoplastic syndrome caused by an underlying plasma cell disorder. The acronym refers to the following features: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal paraproteinemia, and skin changes. ***Methods:***

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The study was conducted at 24 hematological centers across 8 Latin-American countries. The study included a total of 46 patients {median age was 52 years (interquartile range [IQR]: 42–61.5), 30 males and 16 females} fulfilling the POEMS syndrome criteria diagnosed over a period of 12 years (January 1, 2011, through July 31, 2023). Epidemiological and clinical data were collected in an ad hoc database sent to the members of GELAMM, as well as the Kolmogorov-Smirnov test and Kaplan-Meier estimates. ***Results:*** All patients had polyneuropathy and monoclonal gammopathy; 89% had bone marrow plasma cell infiltration, 33% had sclerotic bone lesions. Only 10 patients underwent vascular endothelial growth factor (VEGF) testing in plasma samples. The paraproteinemia was IgG λ in 32% and IgA λ in 30%. 59% patients presented with cutaneous changes, mainly hyperpigmentation, 54% had organomegaly, and 74% endocrinopathy. The median interval from symptom onset to diagnosis was 7.7 months (IQR: 4.0–12.6). 69% of patients received a single line of treatment. The median follow-up period was 25 months (IQR: 9.37–52.0) and the 2-year overall survival rate was 100%. All patients who underwent transplantation (43%) are alive, with a median follow-up of 45.62 months (IQR: 15.46–70). ***Conclusion:*** This study investigates POEMS syndrome in Latin America and presents an initial overview of the disease in the region. VEGF usage is recommended for accurate diagnosis, but only 7 hematology centers in the region used it. Survival rate in Latin America is comparable with those observed internationally.

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Introduction

POEMS syndrome is a rare paraneoplastic syndrome caused by an underlying plasma cell disorder (PCD). The acronym refers to the following features: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal paraproteinemia, and skin changes. The estimated incidence of POEMS syndrome is approximately 0.3 cases per 100,000 individuals [1], with a peak incidence in the fifth-sixth decades of life [2]. Over the years, different countries have reported cohort series with similar prevalence [3–7].

Until now, the cause of the clonal proliferation remains unclear; however, vascular endothelial growth factor (VEGF) seems to play a significant role in its pathogenesis [8, 9]. VEGF is expressed by osteoblasts, macrophages, and tumor cells plays an important role in angiogenesis [10]. It increases vascular permeability, provoking arterial obliteration and allowing serum components to damage nerves. Other elements that have been linked to the disease activity are elevated levels of matrix metalloproteinases and tissue inhibitor metalloproteinases, and high levels of interleukins (ILs): IL-1β, TNF-α, IL-6, and IL-12 [2, 10]. These events may underlie the presence of edema, organomegaly, and skin lesions [2]. Current criteria for diagnosis require [10] the presence of polyneuropathy and a monoclonal protein (lambda light chain plasma cells in 95% of all patients), plus at least one major and one minor criteria (Table 1).

Early diagnosis becomes challenging because of the nonspecificity of symptoms, mimicking other more frequent entities such as chronic inflammatory demyelinating neuropathy (CIDP), monoclonal gammopathy of undetermined significance-associated neuropathy, amyloidosis, and cryoglobulinemia. In one study, the time from the onset of symptoms to diagnosis was 2–24 months [11]. Raising awareness of the disease is the best way to increase suspicion and avoid unnecessary delays.

The recommended treatment depends on the extent of plasma cell infiltration. In those with localized disease, without bone marrow involvement, radiation is the recommended therapy [12], which can improve symptoms over the course of 3–36 months and, in some cases, be curative [10]. On the other hand, for those with diffuse disease, systemic therapy is recommended [12]. The most common used therapy is alkylator-based therapy in low or high doses with autologous peripheral blood stem cell transplant [10]. Other drugs that can be used include lenalidomide, thalidomide, and bortezomib, due to their anti-VEGF and anti-TNF effects. In a study using lenalidomide and dexamethasone a response rate of 46% was found, with a neurological response rate of 95%, and a VEGF response rate of 83% [10]. Adequate supportive care improves patient outcomes. The use of physical therapy, orthosis, and continuous positive airway pressure improves quality of life [10]. The aim of this study was to analyze the clinical, diagnostic, and epidemiological characteristics of patients with POEMS syndrome in Latin America.

Methods

Study Design and Population

This is a cross-sectional, international study. An ad hoc database was sent to the participating Latin-American centers. Ethical Committees' consents were obtained. Only patients fulfilling the POEMS criteria diagnosed over a period of 12 years (January 1, 2011, through July 31, 2023) were included. Patients with Castleman's

Table 1. Criteria for the diagnosis of POEMS syndrome [10]

Mandatory major criteria	1. Polyneuropathy
	2. Monoclonal plasma cell-proliferative disorder
Other major criteria (one required)	3. Castleman disease
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values

disease were excluded since there is a Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal PCD.

Outcome Measures

Clinical and laboratory data were recorded (e.g., polyneuropathy, monoclonal plasma cell proliferation, sclerotic bone lesions). We also evaluated the long-term outcomes: overall survival (OS) and relapse-free survival (RFS) in all patients. OS was calculated from the date of treatment initiation until the date of death from any cause or until data censoring at the last day at which the patient was known to be alive. RFS was calculated from the date of treatment initiation until the date of disease relapse or until data censoring at the last day on which the patient was stable. Follow-up time was calculated as the time from the first assessment date until an event (death or incident) or the censoring date, whichever came first.

Statistical Analysis

Data are presented as median and interquartile range. χ^2 and Student's t tests were used to compare the data. The Kaplan-Meier method was used to estimate OS and RFS. Statistical analysis was performed using the SPSS 25 software (IBM Corp. Published 2017. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) and GraphPad Prism 9 (GraphPad Prism version 9 for Windows; GraphPad Software, San Diego, CA, USA, www.graphpad.com).

Results

Baseline Characteristics

Forty-six patients from 24 hematological centers from eight Latin-American countries were included: 30 (65%) were males and 16 (35%) were females (Table 2). The median age at diagnosis was 52 years (interquartile range [IQR]: 42–61.5). The frequencies of the presence of IgG λ and IgA λ were 41% and 30%, the remaining 29% showed IgG kappa (20%) and only light chain λ (9%). 89% had monoclonal plasma cell proliferation in the bone marrow. Only 11 patients (24%) were tested for VEGF, the median VEGF was 580.3 pg/mL (IQR: 302–830). Volume overload was observed in 15 (33%) patients. None of the patients had a kappa monoclonal protein and none of the patients had clonal kappa plasma cells in the marrow. All 11 patients who were tested for VEGF met the simplified criteria for POEMS syndrome proposed by Suichi et al. [5].

Clinical Characteristics

All patients had polyneuropathy. Only 4 patients (9%) were previously diagnosed with CIDP and 2 (4%) patients were treated with intravenous Immunoglobulin. Twenty-seven (59%) patients presented with the following cutaneous changes: hyperpigmentation (n = 15, 32%), white nails (n = 4, 9%), hemangiomas (n = 5, 11%), acrocyanosis (n = 1, 2%), Raynaud's phenomenon (n = 1, 2%), and lichenoid dermatitis (n = 1, 2%).

Table 2. Clinical characteristics with POEMS syndrome (n = 46)

Clinical characteristics of persons with POEMS syndrome	
Age at diagnosis (median [IQR])	52 years (IQR: 42–61.5)
Polyneuropathy, *n* (%)	46 (100)
Cutaneous changes, *n* (%)	27 (59)
Organomegaly, *n* (%)	25 (54)
Endocrinopathy, *n* (%)	34 (74)
Volume overload, *n* (%)	15 (33)
IgG λ, *n* (%)	**19 (41)**
IgA λ, *n* (%)	**14 (30)**
IgG kappa, *n* (%)	**9 (20)**
Only light chain λ, *n* (%)	**4 (9)**
Bone marrow plasma cell infiltration, *n* (%)	**41 (89)**
Plasma levels VEGF pg/mL (median [IQR]) *n* = 11	580.3 (IQR: 302–830)
Treatment, *n* (%)	
CyBorD	13 (28)
Lenalidomide and dexamethasone	10 (21)
Melphalan and prednisone	6 (13)
Autologous hematopoietic cell transplantation	20 (43)
Country of origin	
Chile	16
Argentina	15
Colombia	1
Cuba	1
México	5
Paraguay	2
Perú	4
Uruguay	2
Survival	
Interval from symptom onset to diagnosis (median, IQR)	7.7 (4.0–12.6) months
Follow-up (median, IQR)	25 (9.28–53.0) months
2-year OS, %	**100**
2-year RFS, %	**95**

IQR, interquartile range; VEGF, vascular endothelial growth factor; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; IQR, interquartile range; OS, overall survival; RFS, relapse-free survival.

Organomegaly was observed in 25 (54%) patients: adenopathies (n = 9, 20%), splenomegaly (n = 8, 17%), and hepatosplenomegaly (n = 8, 17%). Thirty-four patients (74%) had endocrinopathy: hypothyroidism (n = 21, 46%), diabetes (n = 4, 9%), dyslipidemia (n = 1, 2%), gynecomastia (n = 1, 2%), hyperprolactinemia (n = 3, 7%), hypogonadism (n = 3, 7%), and adrenal insufficiency (n = 1, 2%). Volume overload was observed in 15 (33%) patients. Sclerotic bone lesions were seen in 15 patients (33%): 9 (20%) patients had sclerotic lesions in pelvis and/or lower limbs, 4 (9%) in spinal column, 1 (2%) patient in sternum, and 1 (2%) in scapula.

The median interval from symptom onset to diagnosis was 7.7 months (IQR: 4.0–12.6). The monoclonal component was IgG λ and IgA λ in 41% and 30%, respectively. 89% of patients had a median of 5% (IQR 5–11%) of monoclonal plasma cell infiltration in the bone marrow, all lambda. Ten patients (22%) were tested for VEGF, median VEGF was 580.3 pg/mL (IQR: 302–830), reference normal values VEGF <100 pg/mL.

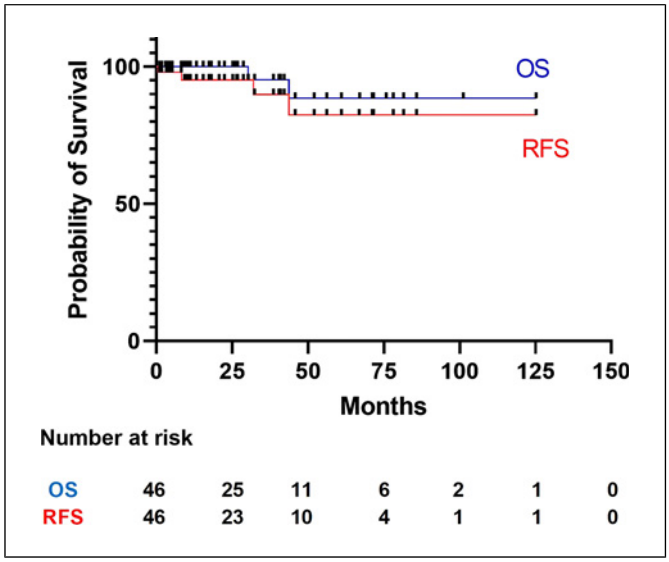

Fig. 1. OS and RFS in patients with POEMS syndrome in Latin America.

Treatment

Thirty-two patients received one line of treatment, 12 received two lines of treatment, and only 2 patients received a third line; 34 patients were initially treated with corticosteroids + chemotherapy, 3 patients were treated with radiation therapy for solitary plasmacytoma. The three most used schemes were cyclophosphamide, bortezomib, and dexamethasone (CyBorD) (13 patients), lenalidomide plus dexamethasone (10 patients); and melphalan plus prednisone (6 patients). Only 2 patients were initially treated with corticosteroids only. Twenty patients underwent autologous stem cell transplantation (ASCT) as a second line of treatment.

Outcomes

Twenty-three patients showed hematologic complete remission (50%), of which 10 (22%) showed neurologic complete remission, 6 (13%) showed partial remission, and 7 (15%) had persistent neuropathy. The median follow-up period was 25 months (IQR: 9.37–52.0). As observed in Figure 1, the 2-year OS was 100%, and the RFS was 95% (81.6–98.6%). Death was reported in only 2 patients (4%), one was a man of 62 years who presented liver failure and the other patient was a woman of 61 years who died because of pneumonia, both were under treatment with melphalan plus prednisone.

All patients who received transplantation are alive, with a median follow-up of 45.62 months (IQR: 15.46–70), Table 3 shows the comparison of clinical characteristics between patients treated with auto HSCT and chemotherapy. Table 4 shows the OS in our study and other countries around the world.

Discussion

In this study, we have described the current epidemiological, clinical profiles, and treatment POEMS syndrome in Latin America. The average age at diagnosis in our cohort (52.2 ± 13.7 years) was similar to information reported in studies conducted in different populations. According to Dispenzieri, for the diagnosis, there are two mandatory criteria – polyradiculoneuropathy and PCD – and three additional major criteria, one of which must be present, and six minor criteria, one of which must be present [2]. In our data, at least 5 patients did not strictly have all the criteria required from Dispenzieri; this may be explained in part by the retrospective design of this study, or there may be nonsecretory plasma cells in POEMS syndrome as occasionally present in multiple myeloma. Atypical cases of POEMS syndrome have been described in the literature, some of them with the absence of polyneuropathy as reported by Morizane et al. [13] described a case of atypical POEMS syndrome without polyneuropathy [13], in contrast in a Japanese nationwide survey from 167 patients all showed polyneuropathy; however, 89% had monoclonal plasma cell proliferation [5] and Dispenzieri [14] indicate that among 67 patients with POEMS syndrome, 12% had normal iliac crest bone marrow biopsies, showing absence of clonal plasma cells, plasma cell rimmed lymphoid aggregates, and megakaryocyte hyperplasia. In addition, we should consider that current diagnostic criteria are more complicated than necessary. Suichi et al. [15] proposed a simplified list of criteria, in which several parameters were removed from existing criteria. They proposed three major criteria instead of two (polyneuropathy, monoclonal plasma cell-proliferative disorder and VEGF elevation) and four minor criteria instead of six (extravascular volume overload, skin changes, organomegaly, and sclerotic bone lesions). For the diagnosis of POEMS using the simplified list of criteria, all major criteria and at least two of the four minor criteria are required. Their analysis showed that the accuracy of the simplified diagnostic criteria was equivalent to Dispenzieri criteria [15].

The symptoms observed in our population are consistent with those reported in other studies. Twenty-six (60%) patients presented with various types of skin lesions, most commonly acrocyanosis. According to a study

Table 3. Clinical characteristics of patients treated with auto HSCT and chemotherapy

Clinical characteristics of persons with POEMS syndrome	Chemotherapy (*n* = 26)	Auto HSCT (*n* = 20)	*p* value
Age at diagnosis (median [IQR])	58 years (IQR: 46–67)	45 years (IQR: 38.5–55.25)	0.002[a]
Polyneuropathy, *n* (%)	26 (100)	20 (100)	–
Cutaneous changes, *n* (%)	16 (62)	11(55)	0.200[b]
Organomegaly, *n* (%)	12 (46)	13 (65)	0.203[b]
Endocrinopathy, *n* (%)	18 (69)	16 (80)	0.509[c]
Volume overload, *n* (%)	10 (38)	5 (25)	0.364[c]
IgG λ, *n* (%)	11 (42)	8 (40)	0.874[b]
IgA λ, *n* (%)	7 (27)	7 (35)	0.555[b]
IgG kappa, *n* (%)	7 (27)	2 (10)	0.262[c]
Only light chain λ, *n* (%)	1 (4)	3 (15)	0.303[c]
Bone marrow plasma cell infiltration, *n* (%)	23 (88)	18 (90)	1.000[c]
VEGF pg/mL (median, IQR)	*n* = 7	*n* = 4	0.730[a]
	658 (323.5–843.2)	490.2 (253–864.6)	
Interval from symptom onset to diagnosis (median, IQR)	8.6 (6.0–13.2) months	6.5 (2.312.5) months	0.228[a]

IQR, interquartile range; VEGF, vascular endothelial growth factor. [a]Mann-Whitney test. [b]χ^2 test. [c]Exact fisher.

Table 4. OS among patients with POEMS syndrome in our study and other regions of the world

Country/region	Patients, *n*	OS	Reference
Latin America	41	**2 years, 100%**	Our data
USA	59	5 years, 94%	D'Souza et al. [4] (2012)
China	347	3 years, 90.4%	Zhao et al. [3] (2019)
Japan	167	10 years, 93%	Suichi et al. [5] (2019)
China	362	5 years, 84%	Wang et al. [6] (2017)
China	41	3 years, 90%	Li et al. [7] (2018)

conducted by Miest et al. [16], 90% of their patients had cutaneous manifestations, with acrocyanosis in 34% of all patients, with hyperpigmentation and hemangioma being the most common manifestations (47%). Furthermore, they also identified a strong association between the skin lesions and an abnormal pulmonary function test, indicating potential respiratory involvement, which should be further studied [16]. In our cohort, endocrinopathy was found in 74% of patients, and the most common was hypothyroidism. In a cohort from UK, the endocrinopathy was found in 63% of patients at diagnosis and in 92% of patients during follow-up. The most common deficiencies found were hypogonadism and hypothyroidism [17]. According to a report from the Mayo Clinic, 69% of patients with POEMS syndrome from 1960 to 2006 had a recognized endocrinopathy [18]. In addition, 30% of our cohort had sclerotic bone lesions, which were observed in 2 patients by radiography, in 5 by CT, in 1 by MRI and in 5 by PET. As stated by He et al. [19], 9 of their 13 patients presented with bone lesions, of which 6 had sclerotic bone lesions, 2 had lytic lesions, and 1 had mix sclerotic and lytic lesions at the moment of diagnosis. Another study conducted by Wang et al. [6] where 362 patients where studied, 199 of them (55%) had osteosclerosis, which gives us an insight into the importance of evaluating bone lesions at the moment of diagnosis.

Although the difficulty in diagnosing POEMS syndrome is well recognized, in our population, we found a

median delay in diagnosis from symptom onset of 7.7 months. This contrasts with reports from other studies that report diagnostic delays of 12–18 months and up to 24 months [20–23]. It is undeniable that neuropathy serves as the prevailing characteristic in POEMS syndrome. It is crucial to determine the nature and scope of the neuropathy, which is peripheral, ascending, symmetrical, and affects both sensory and motor functions. The need for a thorough physical examination to identify neurological and dermatological signs suggestive of the diagnosis is of great importance. During physical examination, one can observe objective manifestations of the aforementioned neurological symptoms, as well as nonbulky adenopathy, gynecomastia, darkened areolae, diminished breath sounds, hepatosplenomegaly, areflexia, and a steppage gait, often accompanied by a positive Romberg sign [10]. The finding of a lambda monoclonal protein is an important clue.

CIDP is a treatable neuropathy in which an abnormal immune response causes peripheral nerve demyelination and axonal damage, is characterized by symmetrical paresthesia, progressive weakness, sensory dysfunction in extremities, areflexia, and fatigue [24, 25]. The use of VEGF has been suggested to be used for the differential diagnosis between CIDP and POEMS syndrome [26, 27]. In our data, VEGF levels were analyzed in only 10 patients: 2 patients from Perú, 3 from Chile, 3 from Argentina, and 2 from Uruguay. In our region, VEGF testing is not available in all countries, whereas in others, it is not officially approved as a diagnostic test for POEMS syndrome.

According to our results, the most used treatment in our region is CyBorD, in contrast to other populations; however, OS at 3 and 10 years in this study was 95% and 87%, respectively, similar to results reported in other studies performed worldwide. A Japanese study evaluated 167 patients with POEMS syndrome for a median follow-up of 71 months, treated predominantly with thalidomide as first-line therapy, and only 5% received an ASCT as first-line therapy, obtaining a 10-year survival of 93% [5]. Furthermore, a study from the Mayo Clinic analyzed 59 patients with POEMS syndrome for a median follow-up of 45 months, using conditioning chemotherapy with melphalan and ASCT (54%); the 5-year survival was 94% and the PFS was 75% [4]. Another study conducted in China reported 41 patients with POEMS syndrome with a median age at diagnosis of 49 years and a median time of follow-up of 34 months, treated with lenalidomide + dexamethasone obtaining a 3-year survival and PFS of 90% and 75%, respectively [7]. In a larger study with 362 patients with POEMS syndrome, the median age at diagnosis was 47 years and 5- and 10-year survival rates were 84% and 77%, respectively, most of whom were treated with lenalidomide, ASCT, and melphalan-based regimens [6].

It should be noted that, although all patients in our cohort had polyneuropathy, a large proportion of patients were treated with bortezomib, with its potential for chemotherapy induced polyneuropathy. However, several studies have reported that patients treated with this proteasome inhibitor have shown significant clinical improvement after this treatment and have considered that therapy related polyneuropathy could be avoided using reduced doses of bortezomib [28–31].

The main limitation of our study has to do with the size of the sample analyzed; although this is a GELAMM multicenter study in Latin America, we do not have data from centers that do not belong to GELAMM and from all Latin-American countries, so there are probably a greater number of patients with POEMS syndrome in our region than we report in this study. Because this is a retrospective analysis, there are incomplete data or data that were not clearly provided by patients or physicians. In addition, as the analysis covers a long period of time, treatment or diagnostic options have been updated, and these results may not accurately reflect the current management of patients with POEMS syndrome in our region.

Conclusion

This multi-institutional study examines the presence of POEMS syndrome in Latin America and serves as an initial report on the status of this disease in our region. Although the use of VEGF is recommended for an accurate diagnosis of POEMS syndrome, in our region only 7 hematology centers evaluated it. It is also noteworthy that a low number of patients had kappa-restricted light chain. According to our results, the survival rate in Latin America is comparable to that observed in other regions of the world; however, more studies are needed to estimate the prevalence of POEMS syndrome and to have a better understanding of diagnosis and treatment in Latin America.

Statement of Ethics

Written informed consent was obtained from all the patients for publication of the details of their medical case and any accompanying images prior to their passing away. The study was

conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Centro de Hematología y Medicina Interna, Clínica Ruiz, Approval No. 06/2022-2.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Moisés Manuel Gallardo-Pérez: data curation, methodology, formal analysis, and writing – review and editing; Paola Negrete-Rodríguez: investigation and writing – original draft preparation; Morie A. Gertz: writing – review and editing; Camila Peña and Eloisa Riva: conceptualization, data curation, investigation, and writing – original draft preparation; Virginia Gilli, Gloritza Rodríguez, César Samanez, Joaquín Ferreira, Sergio Portiño, Jacqueline Montaña, Pilar León, Yaima Gutiérrez, Caroline Del Castanhel, Cristian Seehaus, Maria Eugenia Funes, Rodrigo Meneces Bustillo, Patricio Duarte, Claudia Shanley, Giannini Elvira, Paola Ochoa, Hernan López-Vidal, Humberto Martinez-Cordero, Jule Vasquez, Alana von Glasenapp, Javiera Donoso, José Luis Viñuela, and Guillermo José Ruiz-Delgado, : investigation; Guillermo Jose Ruiz-Arguelles: supervision and writing – review and editing.

Data Availability Statement

The data supporting the conclusions of this study are not publicly available because they contain information that could compromise the privacy of research participants but are available from the corresponding author, G.J.R.A., upon reasonable request.

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