Prevalence of Angle Closure Glaucoma in Vogt-Koyanagi-Harada Disease

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Abstract

Background: This study aims to determine the prevalence, clinical characteristics, and mechanisms of secondary glaucoma in Vogt-Koyanagi-Harada (VKH) disease. We performed a retrospective, observational, and longitudinal study in VKH patients seen from 2001 to 2019. Demographic data, disease stage, glaucoma development, visual outcome, and management were analyzed.

Results: A total of 305 eyes from 155 VKH patients, including 114 (74.4%) females and 39 (25.6%) males with a mean age of 38.8± 12.8 years, were analyzed. The median follow-up time was 22 months (range 7-60 months). Secondary glaucoma developed in 67 (22.0%) eyes, most of which had chronic recurrent VKH disease at presentation 43 eyes (62.4 %). Angle-closure was the most observed mechanism of glaucoma in 55 (82.1%) eyes, as shown by the development of peripheral anterior synechiae in 58 (86.6%) eyes and posterior synechiae in 51 eyes (76.1%). The combination of pupillary block and posterior synechiae resulted in iris bombé in 17 (25.4%) eyes with glaucoma. Forty-one (61.2%) eyes with glaucoma required either a laser or surgical procedure to control the intraocular pressure. At the last visit, visual acuity was significantly worse in eyes with glaucoma ($p<0.001$).

Conclusions: As evidenced by the development of anterior and posterior synechiae, the angle-closure disease is a significant cause of secondary glaucoma in eyes with VKH. Eyes with glaucoma are more likely to present in the chronic recurrent stage of the disease. Most of the eyes with glaucoma required a surgical procedure to control intraocular pressure.

Background

Vogt-Koyanagi-Harada (VKH) is an autoimmune disease that affects the skin, auditory system, nervous system (meninges), and eyes [1, 2]. VKH is characterized by a sudden onset bilateral granulomatous panuveitis during the acute stage of the disease, accompanied by diffuse choroidal stroma inflammation, and exudative retinal detachment [2, 3]. Secondary glaucoma is a common and potentially blinding complication of VKH. The combination of open and closed angle mechanisms in the pathogenesis of glaucoma contributes to the development of ocular hypertension and characteristic optic disc neuropathy [4]. The compromised outflow of the trabecular meshwork by inflammatory cells and steroid-induced ocular hypertension are described as two of the most common open-angle glaucoma mechanisms in VKH eyes [5]. However, there is growing evidence that secondary angle-closure disease, characterized by the development of peripheral anterior and posterior synechiae with secondary iris bombé, plays a major role in the development of glaucoma [6]. Few authors have addressed angle-closure disease as a significant contributor to glaucoma development in VKH eyes [4, 6–9].

This study aims to determine the prevalence, clinical characteristics, and mechanisms of secondary glaucoma in a Mexican-mestizo population of VKH patients.

Methods

We conducted a retrospective, observational, and longitudinal single-center case series analysis of Vogt-Koyanagi-Harada (VKH) patients recruited from the Uveitis and Inflammatory Eye Disease Service at Fundación de Asistencia Privada Conde de Valenciana, Mexico City, Mexico, between January 2001 and February 2019. Patients included in the study previously read and signed informed consent on using their clinical records data for research purposes. The study was approved by the Institutional Review Board and Ethics Committee following the tenets of the Declaration of Helsinki.

All patients included for analysis fulfilled the revised diagnostic criteria for VKH disease and were followed for at least three months [10]. Other forms of uveitis were excluded based on history, laboratory investigation for infectious disease, and clinical examination. The patients´ medical records were entirely reviewed, and clinical information was collected from the first and last visit, including demographics, stage of VKH disease at the first visit, best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp biomicroscopic evaluation, lens status, optic nerve assessment, gonioscopy, and medical and surgical management. The mean change in BCVA, IOP, and optic nerve cup-to disk-ratio was recorded at the first and last visit also.

The clinical features were used to categorize the stage of VKH disease. Initial-onset acute phase was defined by the presence of the first episode of bilateral granulomatous uveitis associated with areas of subretinal fluid or serous retinal detachment and optic disc hyperemia and swelling. Patients with recurrent acute anterior uveitis or a distinctive depigmented “sunset glow fundus” with peripheral chorioretinal atrophic scars, loss of retinal pigment epithelium, or subretinal fibrosis were classified as having features of chronic recurrent disease. If no episodes of reactivation of anterior uveitis were documented, patients were classified in the convalescent phase.

Ocular hypertension (OHT) was defined as an IOP elevation of more than 22 mmHg in two consecutive visits at least two weeks apart without characteristic glaucomatous optic disc neuropathy. Glaucoma was diagnosed when the cup-to-disc ratio was greater than 0.7, there was an asymmetry between the two eyes greater than 0.2, or a nerve fiber layer defect was clinically observed. The iridocorneal angle was classified as closed if more than 180 degrees of posterior trabecular meshwork were not visible at gonioscopy without indentation. The presence of anterior peripheral or posterior synechia of more than 3 clock hours was documented. VKH eyes were divided into with or without glaucoma, and their demographic and clinical characteristics were compared in between.

Data were entered into an Excel spreadsheet (version 365, 2020, Microsoft Corporation, Redmond, WA) and analyzed using IBM Statistical Package for Social Sciences (SPSS) v.21 (IBM Inc., Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were described with means and standard deviations, while non-normally distributed variables were described with medians and interquartile ranges (IQR). For the comparative analysis, normally distributed data will be examined with the parametric T-student test. The Mann-Whitney and Wilcoxon tests were used for the non-normally distributed data. The Pearson chi-square test was applied to analyze significance between variables. A p-value < 0.05 was considered statistically significant. BCVA was measured with the Snellen

chart under standardized conditions, and it was converted into Logarithm of the Minimum Angle of Resolution (LogMAR) acuity for statistical purposes.

Results

A total of 305 eyes from 155 VKH patients, including 114 (74.4%) women and 39 (25.6%) men with a mean age of 38.8± 12.8 years were analyzed. The median follow-up period was 22 months (range: 7–60). Secondary glaucoma was found in 37 (23.9%) patients with bilateral involvement in 29 (78.4%) of them.

Clinical characteristics of VKH eyes with and without glaucoma

Of the 305 eyes included, 67 (22%) developed secondary glaucoma during the follow-up time. We found no difference in age, gender, or follow-up time between groups. OHT developed in 63 (94%) and 62 (26.1%) of the eyes with and without glaucoma, respectively ($p < 0.001$). Four eyes with glaucoma developed hypotony after trabeculectomy. Glaucomatous eyes were more likely to present in the chronic recurrent stage at the initial visit, 64.2% (n = 43) of eyes compared to only 28.2% (n = 67) of eyes without glaucoma. The acute uveitic phase was more prevalent in the group without glaucoma, with 122 (51.3%) eyes presenting at this stage of disease.

Anterior chamber signs of prior intraocular inflammation were present in most eyes with glaucoma, where the development of anterior (n = 58, 86.6%) and posterior (n = 51, 76.1%) synechiae was associated with a high prevalence (n = 55, 82.1%) of angle-closure disease compared to only 50 (21%) eyes in the non-glaucoma group ($p < 0.001$). Furthermore, iris bombé configuration was found in 17 (25.4%) *vs.* 13 (5.5%) eyes with and without glaucoma, respectively. Acute angle-closure presenting as iris bombé was found in 8 (47.1%) of the 17 eyes that developed glaucoma. Interestingly, papillitis at presentation was more prevalent in eyes without glaucoma (n = 54, 22.7%) compared to only 3 (4.5%) eyes with glaucoma. Regarding the lens status, cataract development was more common (n = 36, 53.7%) in glaucomatous eyes, and only 9 (13.4%) eyes remained with a clear lens at the last visit (Table 1).

Table 1
Demographic data and clinical features of Vogt-Koyanagi-Harada eyes with and without glaucoma included in the study

Variables	Total eyes (*n* = 305)		Eyes with glaucoma (*n* = 67)		Eyes without glaucoma (*n* = 238)		*P*
	n	(%)	*n*	(%)	*n*	(%)	
Gender							**0.784**
Female	**227**	**74.4**	**49**	**73.1**	**178**	**74.8**	
Male	**78**	**25.6**	**18**	**26.9**	**60**	**25.2**	
Mean age (years)	38.8 ± 12.8		38.7 ± 12.3		38.9 ± 13.1		0.942
Follow-up (months)	22 (7–60)		15 (5–53)		23.5 (7–60)		0.339
Ocular hypertension[a]	125	41.0	63	94.0	62	26.1	< 0.001
Stage presentation of VKH							
Acute	146	47.9	24	35.8	122	51.3	< 0.001
Chronic recurrent	110	36.1	43	64.2	67	28.2	
Convalescent	49	16.1	0	0	49	20.6	
PAS on gonioscopy	123	40.3	58	86.6	65	27.3	< 0.001
Posterior synechiae	153	50.2	51	76.1	102	42.9	< 0.001
Iris bombé	30	9.8	17	25.4	13	5.5	< 0.001
Iridocorneal angle							< 0.001
Open[b]	200	65.6	12	17.9	188	79.0	
Closed[c]	105	34.4	55	82.1	50	21.0	
Lens status							< 0.001
Clear	145	47.5	9	13.4	136	57.1	
Cataract[d]	115	37.7	36	53.7	79	33.2	
Pseudophakia	38	12.5	19	28.4	19	8.0	
Aphakia	7	2.3	3	4.5	4	1.7	

Variables	Total eyes (*n* = 305)		Eyes with glaucoma (*n* = 67)		Eyes without glaucoma (*n* = 238)		*P*
	n	(%)	*n*	(%)	*n*	(%)	
Gender							**0.784**
Female	**227**	**74.4**	**49**	**73.1**	**178**	**74.8**	
Male	**78**	**25.6**	**18**	**26.9**	**60**	**25.2**	
Papillitis	57	18.7	3	4.5	54	22.7	< 0.001

VKH Vogt-Koyanagi-Harada, *PAS* peripheral anterior synechiae

[a]Intraocular pressure ≥ 22mm Hg in two or more consecutive visits separated by two weeks.

[b]Defined as ≤ 180 degrees of iridotrabecular contact.

[c]Defined as > 180 degrees of iridotrabecular contact.

[d]Defined as trace or greater posterior subcapsular cataract, or a 1 + or greater cortical or nuclear cataract.

The mean change in IOP, BCVA, and cup-to-disk ratio from the first to last visit was compared between groups. (Table 2). In the glaucoma group, the median BCVA remained stable during the follow-up (1.8 LogMAR). There was, however, a significant change in the median IOP between the first (17 mmHg, IQR 13–32) and last (14mmHg, IQR 10–21) evaluation. As expected, in eyes with secondary glaucoma, the mean cup-to-disk ratio (C/D) had a 0.4 increase from the first (C/D = 0.3, IQR 0.3–0.6) to last visit (C/D = 0.7, IQR 0.5–0.9). However, in the non-glaucoma group, the median IOP and C/D remained unchanged, but there was a 0.3 LogMAR improvement in mean BCVA ($p < 0.001$).

Table 2
Main outcomes of Vogt-Koyanagi-Harada eyes with and without glaucoma included in the study

Variable	Eyes with glaucoma (*n* = 67)		*P*	Eyes without glaucoma (*n* = 238)		*P*	Comparison between groups (*P*)
	Initial	Final		Initial	Final		
IOP (mm Hg)	17 (13–32)	14 (10–21)	0.002	13 (12–15)	14 (12–15)	0.683	< 0.001
BCVA (LogMAR)	1.8 (0.4–2.3)	1.8 (0.7–2.8)	0.019	0.5 (0.2–1.3)	0.2 (0.0–0.6)	< 0.001	< 0.001
Cup-to-disc ratio	0.3 (0.3–0.6)	0.7 (0.5–0.9)	0.001	0.3 (0.3–0.3)	0.3 (0.3–0.4)	< 0.001[a]	0.024

IOP intraocular pressure, *BCVA* best corrected visual acuity

[a]Although statistically significant, such value is not clinically significant

Anti-inflammatory management of VKH disease

Nearly half of the glaucoma eyes (49.3%) continued to use topical corticosteroids at their last visit, and they were more likely to have been exposed to intravenous methylprednisolone 22 (32.8%). In contrast to the glaucoma group, only 62 (25.6%) of eyes without glaucoma were using topical corticosteroids at the time of the last evaluation and required less intravenous steroid therapy (n = 20, 8.4%). Both groups did not show a difference in the use of intravitreal (p = 0.388) or periocular (p = 0.968) corticosteroids during their follow-up time. The use of nonsteroidal immunosuppressive drugs during the disease course was not significantly different between groups (p = 0.668) (Table 3).

Table 3
Medical management of Vogt-Koyanagi-Harada disease in eyes with and without glaucoma

Variables	Total eyes (n = 305)		Eyes with glaucoma (n = 67)		Eyes without glaucoma (n = 238)		P
	n	(%)	n	(%)	n	(%)	
Corticosteroids[ab]							
Topical[a]	94	30.8	33	49.3	61	25.6	< 0.001
Systemic oral (prednisone)[a]	81	26.6	19	28.4	62	26.1	0.706
Systemic IV (methylprednisolone)[c]	42	13.8	22	32.8	20	8.4	< 0.001
Intravitreal (triamcinolone injection)[c]	19	6.2	6	9.0	13	5.5	0.388
Periocular (triamcinolone injection)[c]	259	84.9	57	85.1	202	84.9	0.968
Immunosuppressive therapy	212	69.5	48	71.6	164	68.9	0.668

IV intravenous, *IOP* intraocular pressure

[a]At last visit.

[b]At last visit. Numbers include eyes exposed to each approach either alone or in combination with other modalities.

[c]During follow-up.

Management of secondary glaucoma

Topical hypotensive drugs, either alone or in combination with glaucoma surgery, were the mainstay of treatment for OHT. Regarding medical treatment, a significant proportion of eyes (n = 48, 71.6%) required at least three medications to achieve a successful IOP control between 6–18 mmHg (Table 4). In 18 (7.6%) eyes without glaucoma, a period of transient OHT related to steroids and inflammatory relapses was detected and treated with either temporary IOP-lowering medication and laser or surgical peripheral iridotomy when necessary. Forty-one (61.2%) eyes with glaucoma required an IOP-lowering procedure. The most common surgical treatments were Ahmed glaucoma valve implant in 17 eyes (25.4%), surgical iridectomy in 11 (16.4%), and both procedures in 6 eyes (9.0%). Mitomycin-C assisted trabeculectomy was required in 7 (10.4%) eyes. In contrast, only 23 (9.7%) eyes without glaucoma required surgical intervention due to acute IOP elevation caused by iris bombé, with laser peripheral iridotomy performed in

15 (6.3%), selective laser trabeculoplasty in 2 (0.9%), and surgical iridectomy performed in 6 (2.5%) eyes (Table 4).

Table 4
Medical and surgical management of ocular hypertension and glaucoma

Variables	Total eyes (*n* = 305)		Eyes with glaucoma (*n* = 67)		Eyes without glaucoma (*n* = 238)		*P*
	n	(%)	*n*	(%)	*n*	(%)	
Hypotensive drugs[a]							
1–3	**72**	**23.6**	**54**	**80.6**	**18**	**7.6**	< 0.001
> 3	66	91.7	48	71.6	18	7.6	
	6	8.3	6	9.0	0	0	
Laser procedures alone							
LPI	**17**	**5.6**	**0**	**0**	**17**	**7.1**	< 0.001
SLT	15	88.2	0	0	15	88.2	
	2	11.8	0	0	2	11.8	
Surgical procedures	**47**	**15.4**	**41**	**61.2**	**6**	**2.5**	< 0.001
SPI	17	36.2	11	26.8	6	100	
Trabeculectomy	7	14.9	7[d]	17.1	0	0	
AV placement[b]	17	36.2	17[d]	41.5	0	0	
AV + SPI	6	12.8	6	14.6	0	0	
IOP-lowering procedures[c]	**64**	**21.0**	**41**	**61.2**	**23**	**9.7**	< 0.001

LPI laser peripheral iridotomy *SPI* surgical peripheral iridectomy, *SLT* selective laser trabeculoplasty, *AV* Ahmed valve

[a] At last visit

[b] Ahmed valve (New World Medical, Inc., Rancho Cucamonga, CA)

[c] Includes laser and surgical therapies

[d] Two eyes in each group were also managed with laser peripheral iridotomy

Discussion

Multiple mechanisms have been implicated in secondary glaucoma development in eyes with VKH disease. According to our findings, the angle-closure disease appears to be a significant contributor in combination with open-angle mechanisms for the development of OHT/glaucoma. We found a significantly higher prevalence of anterior (86.6%) and posterior (76.1%) synechiae in eyes with glaucoma during the follow-up period. Our findings are consistent with recent studies that found posterior and anterior synechiae in 64% of glaucoma eyes in a smaller population (n = 28) of VKH patients [6]. However, earlier studies report a lower prevalence, with only 25% (34/136) of VKH eyes exhibiting this iris complication [14]. The value of posterior synechiae as a predictor of VKH-related ocular complications, including glaucoma, was reported in a retrospective analysis of 87 VKH patients treated with high-dose systemic corticosteroids [11]. The relatively high prevalence of anterior and posterior synechiae in our population suggests that VKH recurrent episodes of anterior segment inflammation may be a key mechanism in the development of glaucoma. This condition is supported by the fact that 64.2% of the eyes with glaucoma had chronic disease at presentation, probably due to a late diagnosis or inadequate control of inflammation. Our findings emphasize the importance of performing gonioscopy during routine evaluations to detect early signs of angle-closure disease.

The prevalence of glaucoma in our study (n = 67 eyes, 22%) is consistent with previous studies that have reported a rate of glaucoma in VKH eyes ranging from 2.6–45%, depending on the year and population studied [4, 8, 12–14]. However, compared to other studies, the prevalence of angle-closure glaucoma (82.1%) was higher. In a large series of 448 eyes of 224 VKH patients of India, Pandey et al. reported that angle-closure mechanisms were responsible for glaucoma development in only 29.6% of cases [4]. This finding is similar to one of the first studies of secondary glaucoma in VKH, which found angle-closure, mainly due to pupillary block in 43.7% of the eyes in a Hispanic population [8]. Both studies failed to provide a clear definition of angle-closure disease. Since we defined angle-closure as more than 180 degrees of irido-trabecular contact on gonioscopy, we probably found a higher prevalence of secondary angle closure in our study. Our findings are consistent with Yang et al., who discovered the angle-closure disease in 50.6% of OHT/glaucoma cases in a large study of 695 VKH eyes from China. Among the mechanisms described by these authors were pupillary-block arising from complete iris posterior synechiae (28.9%), extensive peripheral anterior synechiae (10.8%), and acute angle-closure glaucoma at onset (10.9%) [15].

Other inflammatory mechanisms, such as ciliary body swelling and effusion, have been implicated in uveitic glaucoma, in addition to a pupillary block from posterior synechiae, as demonstrated by ultrabiomicroscopic findings [16, 17]. In our study, 8 of the 17 glaucoma-affected eyes had acute angle-closure and an iris bombé configuration, requiring immediate iridectomy. It is likely that besides pupillary block, ciliary body edema with anterior rotation of the ciliary processes resulted in a shallow anterior chamber and acute angle-closure due to poorly controlled inflammation [16–18]. However, in the acute angle-closure, no ultrabiomicroscopy was performed.

At the time of presentation, 35.8% of eyes had acute VKH disease, and 64.2% had chronic recurrent VKH disease ($p < 0.001$). When considering eyes that had angle-closure glaucoma, 69.1% had the chronic VKH

disease associated with recurring episodes of anterior segment inflammation. The chronic recurrent form is significantly associated with secondary glaucoma [6, 12, 14, 16, 19, 20]. Arevalo et al. reported that 58.4% and 20.7% of the eyes that developed glaucoma had the chronic recurrent and acute form of VKH disease, respectively ($p \leq 0.0001$) [12]. Abu El-Asrar et al. also reported a statistically significant association between glaucoma, cataract, or subretinal neovascular formation with the chronic recurrent form of VKH [11].

In our study, baseline IOP was significantly higher in glaucoma eyes ($p < 0.001$). Sixty-three of the eyes (94%) with glaucoma developed OHT, compared to only 26.1% in the non-glaucoma group. In VKH eyes, IOP elevation may result mainly from two mechanisms. First, topical corticosteroid use is a well-known risk factor for IOP elevation. Studies report that 13%-62% of eyes with acute and chronic uveitis of any etiology are steroid-responders [21–23]. During the acute stage of VKH, eyes usually have a low IOP secondary to low aqueous production by the ciliary body, which may protect from OHT development. However, anterior segment inflammation may damage the trabecular meshwork either by accumulation of inflammatory cells, posterior synechiae formation, and/or appositional closure [5]. After the inflammation subsides and aqueous production restores, the damaged angle leads to a compromised aqueous outflow with subsequent IOP elevation [4].

Regarding treatment for VKH disease, 33 eyes (49.3%) and 61 eyes (25.6%) of glaucoma and non-glaucoma group, respectively, were on topical corticosteroids at the last visit ($p < 0.001$). This difference might be explained by the fact that most eyes in the glaucoma group also have the chronic recurrent form of VKH disease. In such a form, sustained inflammatory control is harder to achieve [6]. Statistical significance was also reached in the increased use of intravenous corticosteroids in the glaucoma group (32.8% *vs.* 8.4%). In our study, 212 eyes (69.5%) from both groups required management with IMT to control intraocular inflammation, with no statistically significant difference between groups. The use of IMT has been widely recognized as effective in improving visual outcomes and reducing complications arising from VKH disease, such as cataracts, glaucoma, and/or subretinal neovascular membranes [11, 24, 25]. Despite the latter, prospective controlled studies are required to determine the role of IMT in glaucoma development in eyes with VKH.

Although most eyes with and without glaucoma (64.2% *vs.* 96.6%, $p < 0.001$) met our definition of IOP control, most eyes in the glaucoma group required laser and/or surgical management (61.2% *vs.* 9.7%, $p < 0.001$). Ahmed valve placement was the surgery of choice for glaucoma treatment in 17 eyes (36.2%). Previous evidence supported this finding that both Ahmed valve and trabeculectomy with mitomycin-C achieved adequate IOP control in patients with uveitic glaucoma; however, the cumulative success rate at 1-year favored significantly the Ahmed valve group [26]. Regarding other tube implants, a study performed by Chow et al. reported no difference in IOP reduction between trabeculectomy, Ahmed, and Baerveldt implant; however, postoperative hypotony was significantly higher in the trabeculectomy group [27]. In our study, hypotony was reported in 5 (71.4%) of the trabeculectomy eyes, with persistent choroidal detachment resulting in two eyes with no light perception. There were no cases of hypotony identified in the Ahmed valve group.

Limitations of our study include its retrospective design. Also, since many patients were referred and previously managed, data of their initial presentation and the exact moment of glaucoma development could not be obtained. Our clinical service is a tertiary referral center, and the referral bias poses some limitations on the extrapolation of the results. The relatively large sample size provides a more accurate assessment of glaucoma prevalence and mechanisms in a population of Mexican VKH patients over 18 years.

Conclusion

Secondary glaucoma is a common and sight-threatening complication in the eyes with VKH disease. Our findings suggest that angle-closure disease, as evidenced by the high prevalence of peripheral anterior and posterior synechiae, is a common mechanism of IOP elevation and glaucoma development in VKH eyes. The chronic recurrent form of VKH disease is significantly associated with glaucoma. The clinical observations highlight the importance of adequate inflammatory control and early detection of angle-closure disease with gonioscopy as an aid in the prevention of secondary glaucoma in VKH disease.

Abbreviations

BCVA: best-corrected visual acuity; C/D: cup-to-disk ratio; IMT: immunosuppressive therapy; IOP: intraocular pressure; IQR: interquartile ranges; LogMAR: Logarithm of the Minimum Angle of Resolution; OHT: ocular hypertension; VKH: Vogt-Koyanagi-Harada.

Declarations

Ethics approval and consent to participate:

The study was approved, prior to initiation, by the Institutional Review Board and Ethics Committee following the tenets of the Declaration of Helsinki. Written informed consent was obtained from each study participant, and from the guardian of underage (< 18 years) particpants prior to clinical examination and data collection. Information was kept confidential throughout the study.

Consent for publication:

Not applicable

Availability of data and materials:

Results obtained in this study were generated from data collected and analyzed based on the stated methods section. Since all data is already found in the manuscript, there are no supplementary files.

Competing interests:

The authors report no conflicts of interest nor financial disclosure.

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Authors' contributions:

CAG, MPS, and CHM participated in the study design. CAG and CFNV collected the data. CAG, MPS and MPS participated in the analysis of data. CAG, MPS, CFNV, and MPS participated in the clinical management of the patients enrolled in the study. RERL wrote the main manuscript text and created the tables. ARG and JEGV edited the manuscript. CHM, MPS, ARG, and JEVG supervised the work. All authors read and approved the final manuscript.

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