Abstract
Hemophilia is a coagulation disease, generally hereditary, in which the patient’s coagulation cascade is variably compromised, either by mutations in the proteins of this cascade, or by the presence of antibodies that affect the coagulation process. Its severity depends on the altered protein, and in the most severe cases can trigger life-threatening hemorrhagic events. Three types of hemophilia have been described (A, B, C), and their classification depends on the specific protein affected or mutated in the patient. In this review of the literature in our region, we will be reviewing the pathophysiology of this disease, its effect on the quality of life of patients, and the tools available for its assessment.

INTRODUCTION
Hemophilia is a hematological disease that affects the individual’s ability to initiate the clotting process [1]. Its classification can be congenital or acquired. Within congenital hemophilia there are 3 subtypes [1,2], while within acquired hemophilia we have that associated with antibodies that inhibit coagulation factors [3]. In cases of severe hemophilia, the signs and symptoms of patients can be disabling and life-threatening due to the risk of bleeding [4]. However, in mild hemophilia, spontaneous bleeding is very rare. In general, patients with hemophilia have a good quality of life. However, the occurrence of pain is frequent and affects their mood, thus decreasing their quality of life [4]. This is why the follow-up of these patients and good therapeutic adherence is of great importance. [5].

The patients’ condition is not restricted only to coagulation status, but they may suffer from multiple mental health complications and reduced quality of life that is usually ignored. Although treatment of the disease can improve the patient’s condition, it can also lead to psychological changes such as depression, anxiety and distress, thus generating fear of the treatment and their condition and avoidance of coping [6]. It is important to mention that the genesis of these problems is due to the early onset in the patient’s life, which forces him to have a relationship with the health service from an early age and that to a lesser or greater degree this young patient requires the support of third parties to carry out their daily activities.

Another limitation for these patients is the difficulty in accessing specialized medical services for their disease. Since it is a hematological disease, whether hereditary or autoimmune, specialist evaluation is required to ensure the best possible quality of care. This is not possible in some settings outside of large cities, where there are health posts.
with scarce resources. Patients in these cases are given infrequent appointments, and must travel long distances to receive specialized care [7].

There is a questionnaire called Hemolatin-QoL which was developed by authors simultaneously in several countries such as: Argentina, Brazil, Chile, Colombia, Cuba, Nicaragua, Uruguay and Venezuela, and it is useful to classify the HRQOL of people with hemophilia [8].

Hemophilia is a rare coagulopathy. In Latin America, we see an incidence of 1:10,000 in Colombia, while in countries such as Panama, the incidence can be as high as double, 1:5,000 [8].

**Congenital or hereditary hemophilia**

Congenital hemophilia is characterized by a deficiency in the production or formation of clotting factors (VIII, IX and XI). Its most obvious clinical manifestations are bleeding such as hemarthroses [9]. Severe cases can be recognized at birth with spontaneous bleeding in the central nervous system or cephalo-hematomas. In less severe cases, in the first year of life, hematomas or musculoskeletal hematomas may be seen at sites of fall trauma. Wound bleeding is seen in mild hemophilia, usually due to circumcision. In adolescence, it is frequently detected with difficult to manage metrorrhagia. Depending on the clotting factor affected, there are 3 different types of hereditary hemophilia, which vary in frequency and severity. For hemophilia A and B, the factors (VIII and IX) are on chromosome X, while factor XI for hemophilia C is located on chromosome 4 (see Table 1).

Congenital factor XI deficiency (formerly called hemophilia C or Rosenthal disease) is characterized by a mutation of the F11 gene (4q35.2), located on chromosome X [2]. Most people have two sex chromosomes, one from each parent. In the male, having only one X chromosome (XY), if he has the mutation, he will develop the disease because his other chromosome, the Y, does not have the capacity to produce factor VIII or factor IX. In the female, there are two XX chromosomes. In this case, even if one of the two chromosomes carries a mutation in either factor, the factor will be produced by the second X chromosome present in the female. Interestingly, the bleeding caused in this deficiency is variable, meaning that some patients with factor levels below 20% do not bleed; in contrast, patients with higher levels (50%) may be found to bleed in invasive procedures [10].

The pathophysiology of this deficiency affects the amplification process of the coagulation cascade. In this scenario, there is already initial thrombin produced from the interaction between tissue factor and factor VII. However, there will also be some involvement of the Tenase Complex [11], which is also responsible for the transformation of prothrombin to additional thrombin, partially coagulation. For this reason, the involvement of the coagulation cascade will be less in this deficiency. With further understanding through research, a new model of the coagulation cascade has been developed called the "Cellular Model of the Coagulation Cascade" which is presented in Figure 1.

In summary, the main problem lies in the fact that amplification of fibrin production cannot be performed because activation of the factors is required. In any case, all three types of hemophilia have an affected factor located in the intrinsic coagulation pathway, where coagulation factors are required. If there is a deficiency in the production of these factors (VIII, IX and XI), the patient will have a variable decrease in the production of fibrin, because he/she needs thrombin to

<table>
<thead>
<tr>
<th>Type</th>
<th>Inheritance</th>
<th>Factor</th>
<th>Chr.</th>
<th>Gene</th>
<th>Freq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>X-linked, recessive</td>
<td>VIII</td>
<td>X</td>
<td>F8</td>
<td>+++</td>
</tr>
<tr>
<td>B</td>
<td>X-linked, recessive</td>
<td>IX</td>
<td>X</td>
<td>F9</td>
<td>++</td>
</tr>
<tr>
<td>C</td>
<td>Autosomal dominant – variable penetrance</td>
<td>XI</td>
<td>4</td>
<td>F11</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: Chr: chromosome; Freq: relative frequency.

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**Table 1. Types of hemophilia and their differences.**
convert fibrinogen to fibrin. This occurs despite the production of Thrombin through tissue factor and factor VIII, also known as the extrinsic pathway in the classical model of coagulation. The direct result will be that fibrin will be produced in lower proportion giving a bleeding effect [12].

Acquired hemophilia

It is an entity that develops due to the presence of autoantibodies that inhibit the function of factor 8 [2]. The manifestations observed are similar to those of inherited hemophilia, with large bleeds, involvement of skin tissue or subcutaneous tissue. It is frequently detected in the elderly and in pregnant or immunocompromised women [2].

METHODS

A literature review was performed in the following databases: Fedhemo, Scielo, Pubmed, National Library of Medicine, RareDiseaseAdvisor and Elsevier, using keywords such as hemophilia, quality of life, Latin America. The articles found in these sources were filtered using criteria such as: hemophilia article in the Latin American region, quality of life component, quality of life measurement instruments. articles [13,14]. Twenty-five articles were selected in which the latest updates about the information under investigation were taken into account. Articles that did not meet the criteria were not included.

RESULTS

During our literature review we found estimates of patients with hemophilia in Latin America (see Table 2).

Table 2 presents the number of patients with hemophilia A and B, showing a predominance of hemophilia A cases in all

Table 2. People suffering from hemophilia in Latin America (2017).

<table>
<thead>
<tr>
<th>País</th>
<th>Population</th>
<th>Persons with Hemophilia</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
<th>Unknown Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>213,993,441</td>
<td>13,337</td>
<td>11,141</td>
<td>2,196</td>
<td>--</td>
</tr>
<tr>
<td>Mexico</td>
<td>130,262,220</td>
<td>5,892</td>
<td>4,867</td>
<td>728</td>
<td>297</td>
</tr>
<tr>
<td>Colombia</td>
<td>51,265,841</td>
<td>3,931</td>
<td>3,220</td>
<td>711</td>
<td>0</td>
</tr>
<tr>
<td>Argentina</td>
<td>45,808,747</td>
<td>2,843</td>
<td>2,448</td>
<td>392</td>
<td>3</td>
</tr>
<tr>
<td>Venezuela</td>
<td>28,704,947</td>
<td>2,905</td>
<td>2,289</td>
<td>616</td>
<td>--</td>
</tr>
<tr>
<td>Chile</td>
<td>19,212,362</td>
<td>1,909</td>
<td>1,670</td>
<td>186</td>
<td>53</td>
</tr>
<tr>
<td>Bolivia</td>
<td>11,832,936</td>
<td>150</td>
<td>122</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Cuba</td>
<td>11,317,498</td>
<td>498</td>
<td>414</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>10,953,714</td>
<td>526</td>
<td>470</td>
<td>42</td>
<td>14</td>
</tr>
<tr>
<td>Honduras</td>
<td>10,062,994</td>
<td>385</td>
<td>324</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>Paraguay</td>
<td>7,219,641</td>
<td>436</td>
<td>397</td>
<td>39</td>
<td>--</td>
</tr>
<tr>
<td>El Salvador</td>
<td>6,518,500</td>
<td>203</td>
<td>180</td>
<td>23</td>
<td>--</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>5,139,053</td>
<td>227</td>
<td>182</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Panama</td>
<td>4,381,583</td>
<td>319</td>
<td>284</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Uruguay</td>
<td>3,495,152</td>
<td>281</td>
<td>235</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>560,158,829</td>
<td>33,842</td>
<td>28,243</td>
<td>5,197</td>
<td>402</td>
</tr>
</tbody>
</table>

countries. The three countries with the highest number of patients with hemophilia are Brazil, Mexico, Colombia, Argentina and Venezuela. On the other hand, Costa Rica, Panama and Uruguay have the lowest number of cases in the region. Based on the data in Table 2, we calculated the prevalence for each country, per 100,000 inhabitants. Likewise, the overall incidence for the region was calculated to establish a benchmark for Latin America. The table shows that Venezuela, Chile, Uruguay, Colombia, Panama, Brazil and Argentina have the highest rates of hemophilia in Latin America, above 6.0 x 100,000 inhabitants (Figure 2). The countries with the lowest incidences are Honduras, El Salvador and Bolivia, with incidences below 4.0 x 100,000 inhabitants.

The severity of cases can also vary significantly. We have found that patients with hemophilia frequently present comorbidities such as hemophilic arthropathy (71%), followed by dyslipidemia (27%), overweight (20%) and finally smoking (11.8%). On the other hand, we see difficulties in accessing treatment, limitations in physical activities, and problems such as depression and anxiety. For this reason, an integrated, holistic management has been proposed that allows the assessment, follow-up and comprehensive treatment of these patients [8].

**Health-related quality of life (HRQoL)**

The assessment of health-related quality of life (HRQL) has been applied to patients with hemophilia in multiple countries. Among these we have Mexico, Colombia, Brazil, among others, applying the concepts of holistic assessment that takes into account multiple factors. Among these factors are physical function, physical performance, bodily pain, general health, vitality, social function, emotional performance and mental health [15,16].

In some Latin American studies in adults, it was observed that the Hemolatin-QoL, a specific instrument for measuring quality of life in hemophilia patients, is used [17]. This has 27 items

**Figure 2.** Incidence of hemophilia in Latin America.

Source: Generated from data obtained from the article World Federation of Hemophilia. "Annual Survey 2021." (See Table 1)
with adjectival options to answer between 0 and 4. The score can be determined in two ways: a total score that can range from 0 to 108 and another is a score by domains, physical functioning (6 items), social functioning (4 items), mental health (5 items) and environmental conditions (3 items). These cut-off points are given by percentile, where a value below 25 indicates low HRQoL, 25-50 medium low, 50 medium, 50-75 medium high and above 75 indicates a high HRQoL. The score indicates that the higher this percentile the better the health-related quality of life.

Management of comorbidities
Hemophilia may be accompanied by other diseases that can cause physical and emotional involvement, demonstrating the importance of comprehensive care [18]. Pain management is an important factor described where it was reported that 39% of patients in their study were taking analogs and 9% were taking treatment for depression and anxiety [19]. Other important factors that have been reported as considerably low are sport, leisure time, and uncertainty in the future within the HRQoL aspects. Another aspect described in the literature is the social support groups that share with people with hemophilia through social networks and hemophilia centers, which positively impact patients’ quality of life [20].

Treatment Availability
According to the Aguilar-Palacios study in Cuba, availability of treatment received an average score of 30.73, the highest on the HRQL scale. However, in areas such as Rio de Janeiro, great advances have been made in the treatment of people with hemophilia, since they have supplies of coagulation factors which are provided to them free of charge [21]. Likewise, in countries such as Mexico, half of the patients are treated by a certified institution such as the World Federation of Hemophilia or the Mexican Institute of Social Security. While the other half were reported to be treated with obsolete techniques such as plasma or cryoprecipitates, leaving in evidence the high risk in the quality of life in these patients, making them a target for hospitalizations and other complications with the disease [22]. However, we have not found HRQoL evaluation to assess the impact of these interventions on the quality of life of these patients.

A cross-sectional study in patients with hemophilia conducted in Medellin - Colombia, showed that hemophilia is usually treated with prophylaxis and some also have to attend physical therapy, thus conditioning the treatment to a more comprehensive management [15]. In this case, the HRQoL assessment places physical function, with a score of 77.3, in patients with moderate and severe hemophilia comparing them with the indices of the general population. This is followed by bodily pain with a score of 73.6, and general health, with a score of 72.7.

Physical therapy
The importance of physical fitness, in relation to the prevention and treatment of musculoskeletal injuries in the hemophilic patient, was also analyzed. Some institutions such as the World Federation of Hemophilia (WFH) explain that the physical condition of the hemophilic patient, instrumented through clotting factor replacement therapy, is fundamental and requires physiotherapy, physical exercise and sport [23].

Self-esteem
Self-esteem is another factor studied in this population. In a cohort of 60 patients, the degree of self-esteem was evaluated by means of forms, taking into account sports activities, leisure time, the future [19]. Low levels of self-esteem were observed in patients and this aspect was defined as predictive for quality of life.

There are psychological and clinical sequelae that are rooted to performance in various areas such as functionality at home, social integration and work productivity, of which the highest scores obtained in the SF-36 tests refer to the domains of the physical area: “pain and physical functioning”, which can affect to a greater or lesser extent in the countries shown as an example [15,16,19,24].

DISCUSSION
In our Latin American countries, there is an important incidence of hemophilia cases. Cases of hemophilia can be classified as mild, moderate or severe according to the amount of active plasma residues of the deficient factor found, each of which can affect the patient’s performance to a greater or lesser extent [1,2]. The data found reveal that although Brazil, Mexico and Venezuela have the majority of cases, there is a
higher incidence in Chile, Venezuela, Uruguay, and Panama. It is worth noting that Venezuela appears with both a large number of cases and a significant incidence (see Table 1 and 2).

The predominant type of hemophilia in the Americas is type A. Some studies show that moderate hemophilia is the most frequent, manifesting in patients with high-frequency bleeding, although it is normal that in several circumstances they may refer to the severe type due to its clinical evolution over time [1,8]. It should be noted that, although spontaneous bleeds are much more frequent in severe hemophiliacs. However, the percentage of the factor should not be the only criterion for patient classification, since the individual clinical expression of the disease, its complications and the sequelae that could contribute to bleeding at certain sites should also be taken into account and vary significantly among patients [4,6].

Quality of life is also an aspect that should be taken into account when managing a patient with hemophilia. The quality of life of individuals is compromised due to the discomfort and complications that can occur during life, especially in children, adolescents and adults [3]. Studies have been conducted in various regions to analyze how much the disease can affect them in their daily lives. It should be noted that current regional efforts are focused on improving the impact on the quality of life of patients in recent decades and not only on symptomatic management [15,22].

The importance of health-related quality of life (HRQL) assessment tools should be highlighted as they are necessary to implement the assessment in more countries. Some of the tools identified in the studies were: SF-36 and PedsQLTM [8,15,16].

The psycho-social aspects are very relevant. This is observed in the scores of the psychological aspects which include emotional functioning and mental health, both obtained medians close to the maximum scores of each subscale studied [19]. This coincides with the results of a Brazilian and a Greek study using the HaemA-Qol scale, which can be explained by the holistic patient management that decreases stigma and symptoms of anxiety and depression [18,23].

This suggests the need for psychological support and moderate care that allows reducing the discomfort presented by these patients, as a way of control and restoring in some way the quality of life of a healthy person, although differences can be noted in the results between countries such as Sweden and Brazil with Latin American countries. The experience of countries such as Sweden and Brazil can be taken as a model to be implemented in our Latin American countries, by investing in resources for the comprehensive and effective management of patients with hemophilia [14,17,25].

Studies have also revealed that school age groups have a greater sensitivity to the reduction of HRQOL, which may be related to the availability of resources and the degree of awareness of the disease from an early age (both parents and patients) [15,22]. As an example we can use Iran as a reference, where low HRQoL is observed due to deficiencies in access to a specialized medical and educational system. This can also be observed even in developed and developing countries [16].

The HRQoL score is also affected by the sequelae of the disease, which affect the patient’s daily tasks and normal movement. Their participation in social, sports and recreational activities are limited, thus reducing their quality of life [23].

As additional data, if we add older patients we can find HRQOL behaviors even more deteriorated than compared to children and adults of recent decades, as it could be explained because they were without treatment for a long time, which led to dysfunctions, complications and pain due to sequelae [23,24].

The number of bibliographic sources available today associated with the quality of life of hemophilia patients demonstrates a global effort to improve the care of these patients in a holistic manner. We hope that this trend will continue in our Latin American countries to provide care that includes aspects of quality of life, both psychological and physical, over time [17,19,24].

**CONCLUSIONS**

As a final point of this work, it can be concluded that hemophilia can be presented in two ways: congenital, due to an alteration in coagulation factors VIII, IX or XI; or acquired,
due to the presence of antibodies in case of neoplasia or as an autoimmune disease.

Although sometimes hemophilia can affect the quality of life of people and their interpersonal relationships, every day we work to try that people with this condition have a normal life based on new techniques and treatment as mentioned above, and giving importance to physical therapies, taking into account that physical condition is important to prevent this condition. Our final message is that it is of utmost importance that clinical protocols are developed that allow the comprehensive assessment of these patients that includes hematological aspects, but also psycho-social aspects that positively impact their quality of life.

Acknowledgement

We thank Dr. Ignacio Véliz, Dr. Gabriel Chichilla, and Dr. Enrique D. Austin for critical review, and recommendations to improve this literature review; likewise we thank Dr. Jorge D. Méndez-Ríos, for guiding us in the process of elaboration of this manuscript and support in the writing.

REFERENCES


