Predictors of Quality of Life in People with Hemophilia Affiliated Hospital Entity, a Review of Literature

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Abstract

To describe the evidence on predictors of quality of life (QoL) in hemophiliacs in a hospital. Narrative and documentary literature review. Five research studies were obtained from the Scopus database. The variable Quality of life in people with hemophilia was evaluated during the period 2018-2024. Predictors of poor QoL are the absence of early prophylaxis, the lack of more effective and better treatments, the presence of low self-esteem, anxiety and depression, poor coping resources, and the appearance of inhibitors. Hemophilia, as an orphan, chronic and complex disease, requires the observation of all aspects that involve the health and well-being of people with hemophilia (PWH), and that these be estimated by multidisciplinary teams and through instruments that evaluate their QoL.

Keywords: Quality Of Life, Hemophilia, Predictors, Treatments, Review.

INTRODUCTION

Hemophilia and treatments

Hemophilia, also known as the "disease of kings," according to Albert (2014). It is a rare or orphan disease due to its low prevalence. (Soucie et al. 2020), affecting some 400,000 people in the world. (Stoffman et al. 2019). This hemorrhagic disease is a congenital, recessive, chromosome-linked disease X Von Mackensen et al. (2012) in hemophilia A and B, there are other types of hemophilia such as hemophilia C, which is not related to the X chromosome. This condition causes a deficiency in blood coagulation due to the absence or deficiency of factor XI, factor VIII in type A, and factor IX in type B. (Strike et al. 2016).

There is approximately one case for every 5000 to 10000 people with hemophilia (PWH) type A in the world, being one case with hemophilia B between 30,000 to 40,000 people, Brazil being recognized as the fourth country with the largest population of PWH (Ministério da Saúde (MS), 2018; Sayago & Lorenzo, 2020). The prevalence in men and women in Colombia is 3.8 cases per 100,000 inhabitants (World Federation of Hemophilia, 2014).

The form of manifestation of this disease is hemorrhage, which can appear in any part of the body, and can be visible in muscles and joints causing pain, significantly decreasing the movement of the body Molina A. et al. (2014) producing functional alterations in the target joints, which can cause disability, where 80% are articular (Rodriguez-Merchán, 1996). The area of the body that suffers most hemorrhages in early childhood is the ankle (33%), with the knee (33%) presenting arthropathy during adolescence (Rodriguez-Merchán, 2006), while, elbow, shoulder and hip (33%), which has a significant negative impact on physical, mental and social health in PWH (Fuenmayor Castaño et al. 2017; Zuñiga C. 2008).

Early detection of PWH, i.e., from birth to three years of age, is of vital importance and will directly contribute to improve the quality and perspective of life of these people, since at this age it is possible to implement an adequate prophylaxis for severe cases, before the appearance of the first hemorrhosis (Ministério da Saúde (MS) 2014). This prevents serious and irreversible damage to the target joints, thus avoiding compromising the physical health of PWH (Ministério da Saúde (MS) 2014, 2015).

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Given the vertiginous advances in science, with respect to the disease, there is a wide range of treatments with greater efficacy and safety, contributing to the increase in the well-being and health of PWH, achieving the availability of safer and more effective products, as mentioned by the Institute for the Evaluation of Health Technologies and Research (IETSI), in its preliminary opinion of health technology assessment No. 028-DETS-IETSI-2023, in which it approves the prophylactic use of emicizumab (Hemlibrar) in adult patients with hemophilia A, with the presence of inhibitor antibodies, providing other possibilities such as treatment at home, as well as comprehensive patient care by multidisciplinary teams that join forces for the good of the patient, such as hematologists, gastroenterologists, orthopedic surgeons, nurses, psychologists, dentists, physiotherapists and social workers (IETSI - EsSALUD, 2021).

The choice of better treatment schemes has produced a substantial change, with an increase in life expectancy, a decrease in hospital visits and therefore in absenteeism from work and school, an improvement in academic performance, a decrease in hemophilic arthropathy and better control of infectious diseases (Aledort et al. 1994; Aznar et al. 2000; Fuenmayor Castaño et al. 2017; Liesner et al. 1996; Rodriguez-Merchán et al. 2008; Rosendal et al. 1989; Solovieva et al. 2004; Triemstra et al. 1995).

These positive changes brought about by the advances in the integral-multidisciplinary treatment of the disease, have repercussions in positive changes, finding the possibility of leading a life as normal as possible in a PWH.

Quality of Life

When referring to quality of life, it is possible to describe two approaches, one that mentions it as the individual's perception of his/her position in life, contextualized to his/her own culture and value system, in addition to its relation to his/her goals and expectations, or to his/her standards and interests (“The World Health Organization Quality of Life Assessment (WHOQOL): Position Paper from the World Health Organization,” 1995) and, another approach is health-related quality of life (HRQoL), which is the subjective perception, influenced by the person's health status, of his or her ability to perform those activities that are important to him or her. (Fuenmayor Castaño et al., 2017; MJ Naughton, 1996).

The chronic disease condition causes negative emotional reactions in PWH, such as stress, low self-esteem, anxiety and depression, cognitive problems, including sexual problems, which affect HRQoL. (Fuenmayor Castaño et al. 2017; Guzmán et al. 2020; Mancuso et al. 2020; Martínez Sánchez et al. 2017; Osorio-Guzmán et al. 2017; Williams et al. 2016). In this regard, the care of PWH, from a spiritual and compassionate approach, by the multidisciplinary team, would help them to develop resilience, which would allow them to face difficult situations with greater strength and emotional support (Kieffer et al. 2024).

Early pharmacological prophylaxis to prevent bleeding in moderate to severe PWH, thus preventing or minimizing damage; participation in physical and occupational rehabilitation programs through exercise, use of orthotics, and orthopedic surgery, in the search to control bleeding through synovectomy, and correct joint deformities by performing osteotomies, tendon lengthening or arthroplasty, would be essential in improving HRQoL (Chen et al. 2015; Lindvall et al. 2012).

METHODOLOGY

This research was a review of narrative literature. Making an approach, in which a theory can be discussed, which in turn clarifies paradigms and offers new approaches for future research (Gonçalves, 2019).

The PRISMA model was used for the document selection procedure (Page et al. 2021).

The information obtained from the exhaustive search of articles was extracted (Arias Cardona & Alvarado Salgado, 2015). A systematic review of the literature available in the Scopus database was carried out, in which studies in Spanish, English and Portuguese language were chosen, during the (2018-2024). As part of the search strategy, descriptors were used for quality of life, hemophilia, predictors, treatments, using searches with field adjustments of title, abstract, keywords, according to researchers' criteria.

Inclusion criteria included original articles, those with access to the full text, and those that were published in Spanish or English. As part of the exclusion criteria, duplicate articles, book chapters, clinical cases, narratives,
The scientific literature search was conducted from April 2018 to August 2024, included terms and descriptors for QoL, hemophilia, predictors and treatments, being reviewed by an expert in bibliometrics and performed by 5 independent reviewers, finding 8 results in Scopus. The title, abstract, methodology, results and conclusions were reviewed, including studies that aimed to describe the evidence on predictors of QoL on PWH of a hospital entity.

Original articles, short original articles and short communications were selected. After eliminating duplicate items and under inclusion and exclusion criteria, 4 studies, all cross-sectional, were chosen. The aim of the study was to review the scientific evidence on the predictors of QoL on PWH of a hospital entity (see table 1 and appendix).

The selected studies used different instruments to measure QoL in PWH, one of which, in two of the studies, could be considered the most important for Latin America, the Haem-A-Qol, having been translated and back-translated into 21 languages and validated cross-culturally. It is composed of 46 items distributed in the domains: physical health, self-perception, feelings, leisure and sports, school and work, future, treatment, sexuality, family planning and relationships (Arteaga-Rubiano & García-Valencia, 2021; Mackensen & Gringeri, 2004; Trindade et al. 2019; Vieira Nobre et al. 2022; von Mackensen et al. 2013). These take a score ranging from 0 to 100, with the highest scores indicating a deteriorating QoL. (Remor, 2005; Limperg et al. 2017).

The instrument Short Form-36 (SF-36), composed of 36 questions, for 8 health dimensions that measure social function, physical function, emotional performance, physical performance, mental health, vitality, general health and bodily pain. It is scored as 0 for the worst health status, and 100 for a good health status; it has been validated in Colombia.

The instrument also validated for Colombia, to evaluate QOL in relation to health (HRQoL) for the child population, is the KIDSCREEN 27, a generic instrument whose 5 dimensions are: physical activity and health, mood and feelings, family life and free time, social support and friends, and school environment. Its scores per dimension are transformed into values with a mean of 50 and a standard deviation of 10, with higher scores indicating better QoL and well-being. (Quintero et al. 2011).

Another generic instrument designed by the World Health Organization, the WHO-DAS II, provides as a measure of disability, whose 6 dimensions are: comprehension and communication, self-care, ability to move around, relationships with others, participation in society and activities of daily living. It ranges from 0 to 100, from best to worst (WHO Disability Assessment Schedule (WHODAS) 2.0, 2010).

It was found that PWH in a specialized clinic in Medellín, Colombia obtained a total Hemolatin-QoL score of 81.5, in a total of 48 adults, with a mean age of 32 years (RI: 23,2-40,7), In terms of severity, 16.7% were found...
to be mild, 12.5% moderate and 70.8% severe, with regard to treatment 75% for prophylaxis, 22.9% for demand and 2.1% for immunotolerance, 37.5% had reduced mobility, while 16.7% had hemophilia due to comorbidity. Advanced age, the number of comorbidities, low socioeconomic level, the presence of arthropathies and reduced mobility are the factors associated with lower quality of life. Longitudinal studies in a larger sample would be useful to establish causal associations (Arteaga-Rubiano & García-Valencia, 2021).

The greatest comorbidity in a sample of 59 PWH was hemophilic arthropathy, which was observed in 42 patients (71%). There were 89 affected joints, knee 48.3%, ankle 24.7%, elbow 19.1%, hip 4.5% and shoulder 3.3%, among these only one patient with hip joint replacement. A large percentage of the population, 86.4% participated in a program of aerobics, stretching and strengthening led by a physiotherapist, at a rate of 4 times per week, also 84% of the population said they walked, cycled or swam. It was observed that their HRQoL is as high as that of the general Colombian population, a finding similar to other studies of QoL in PWH (Lindvall et al., 2012; Scalone et al., 2006).

One aspect of consideration to note regarding the high QoL scores is that 96.6% of patients were receiving prophylaxis, which is associated with less joint damage, and also that very few patients had the presence of inhibitors. (Brown et al., 2009; Tagliaferri et al., 2015).

Minimal or mild depression is another very important aspect of influence for good QoL scores (Kim et al., 2013). The scores obtained on the QoL with the KIDSCREEN-27, were higher than those observed in other pathologies such as mental illness, congenital diaphragmatic hernia and long-term survivors of hemophilia (Michel et al., 2013; Weitkamp et al., 2013). The WHO DAS II assessment shows that PWH have less disability than other chronic musculoskeletal diseases, such as ankylosing spondylitis (van Tubergen, 2003). The affected domains were the ability to move around and participation in society, and pain was also found to be a significant causal factor of functional limitation and impairment in QoL (Elander et al. 2009; Van Genderen et al. 2006). Multiple cardiovascular risk factors may be predictors of lower QoL, as may the presence of inhibitors and the severity of hemophilia (Franchini & Mannucci, 2010). This study reported a QoL comparable to that of the general Colombian population without hemophilia, reiterating the importance of prophylactic pharmacological treatment by involving hemophilia patients in a rehabilitation program that promotes functional independence and a healthy lifestyle (Fuenmayor Castaño et al., 2017).

The HRQoL scale yielded higher average scores in the dimensions: Feelings and Relationships and Couple, while the lowest corresponded to the dimensions: Sport and Free time and Future. The self-esteem variable shows that the Intellectual work dimension obtained a higher average and the dimensions: Emotional Affective and Failure resulted in low scores. In coping with chronic pain, the Catharsis dimension had the highest average, while the Distraction dimension had the lowest. Psychological support is essential for those suffering from this disease, promoting emotional intelligence, vision of the future with respect to their health care and self-esteem, since self-esteem is a predictor variable of HRQoL in participants with hemophilia (Aguir & Palacios et al., 2022).

In this study only 13 PWH participated, in whose social profile 69.2%, equivalent to 9, stopped studying and working. In the clinical aspects, 53.8% (n=7) correspond to type A hemophilia, 69.2% (n=9) severe, diagnosed before the age of 3 years only 7.7%, that is 1 of 13 patients. The existence of hemarthrosis, in 84.6% where 11 of them claimed to have had previous symptoms. Their perception of health, 92.3%, i.e. 12 of them understand the disease and 76.9%, i.e. 10 of them consider themselves healthy. The Haem-A-Qol questionnaire evidenced a total average of 30.94 with a standard deviation of 12.23; indicating a low average corresponding to a low general deterioration of QoL, that is, the closer to 100, the worse the QoL. The minimum value reached was 16.85 and the maximum value was 53.72. Early detection of the disease, from birth to three years of age, contributes directly to the QoL and life expectancy of these individuals, since at this age it is already possible to implement prophylaxis for severe cases, before the appearance of the first hemorrhoses Ministério da Saúde (MS) (2015).

This prevents serious and irreversible damage to the joints (Mercan et al., 2010; Ministério da Saúde (MS), 2015). Hemarthroses were the most frequent and important clinical manifestations of hemophilia (Feijó et al., 2018; Ministério da Saúde (MS), 2015). The most affected aspect in hemophilia is physical health, in which frequent and successive hemorrhages affect locomotion and cause sequelae that make the patient’s mobility
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impossible, in addition to intense pain (Baek et al. 2020).

Adequate and well-performed physical activity optimizes the psychosocial conditions of the person with hemophilia, increasing strength and avoiding muscle atrophy, improving mobility and joint stability, flexibility, balance and functionality, these aspects show a clear performance of activities of daily living in people with hemophilia. (Jorge et al., 2016).

It is important to mention that the Hematology and Hemotherapy Center of the Research Center has neither a multidisciplinary team nor a physiotherapist to monitor the locomotor system. Coping is related to body care, the identification of hemorrhages and their management, and is also related to the hemophilia patient's ability to assume self-care and control his or her treatment (Rambod et al., 2018; Varaklioti et al., 2018). Evidence that makes HRQoL unsatisfactory is frequent pain, movement restrictions and difficulty in identifying and managing signs and symptoms of the disease from the onset (Vieira Nobre et al. 2022).

Table 1: Characteristics of predictors of the quality of life of hemophiliacs in a hospital entity.

<table>
<thead>
<tr>
<th>Nro</th>
<th>Design</th>
<th>Objective</th>
<th>Instrument</th>
<th>Sample</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>[1]</td>
<td>Transversal</td>
<td>To determine health-related QoL in adults with hemophilia enrolled in a coagulopathy program and explore its association with clinical and demographic factors.</td>
<td>Hemolatin QoL</td>
<td>n=48 clinic Medellín, Colombia</td>
<td>The population varied in hemophilia severity (mild 16.7 %, moderate 12.5 % and severe 70.8 %) and treatment (75.0 % prophylaxis, 22.9 % demand and 2.1 % immunotolerance). 37.5 % had reduced mobility and 16.7 % had comorbidity. The total Hemolatin QoL score was 81.5. Factors associated with lower QoL were older age, number of comorbidities, low socioeconomic status, presence of arthropathy and reduced mobility.</td>
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<tr>
<td>[2]</td>
<td>Transversal</td>
<td>To evaluate health-related QoL in people with hemophilia, in Medellín during 2014.</td>
<td>Functional test mobility arches Gait test HQoL SF-36 KIDSSCREEN-27 WHODAS II, EVA PHQ-9.</td>
<td>n=59 Medellín, Colombia.</td>
<td>Fifty-nine patients agreed to participate in the study, mean age 28 (SD ± 14.8) years, mild hemophilia 5%, moderate 20.3% and severe 74.5%. A total of 96.6% were being treated with prophylaxis and 84% of the patients attended physical therapy. The major comorbidity was hemophilic arthropathy in 71% of the patients, followed by dyslipidemia (27%), overweight (20%) and smoking (11.8%). The gait test reported an average distance of 584.2 meters and SF-36 scores were similar to those of the general population.</td>
</tr>
<tr>
<td>[3]</td>
<td>Transversal</td>
<td>To analyze the predictive effect of self-esteem and coping strategies toward HRQoL in people with hemophilia.</td>
<td>Hemophilia-Specific QoL, Self-Esteem and Coping with Chronic Pain</td>
<td>n=59</td>
<td>The level of HRQoL was mostly moderate. Low levels were observed in the dimensions Sport and leisure time and Future. The Success dimension of the self-esteem scale correlated positively with the Sport and leisure time (r(60)=0.59), Physical health (r(60)=0.54) and Self-perception (r(60)=0.48) dimensions of the HRQoL scale; in addition to having shown a high level of prediction of QoL (R2= 0.35, p= 0.00)</td>
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<tr>
<td>[4]</td>
<td>Transversal</td>
<td>Evaluating the QoL of people with hemophilia.</td>
<td>Questionnaire Haem-A-Qol</td>
<td>n=13 Blood Bank in northeastern Brazil</td>
<td>A total average of 30.94 in relation to the ten domains evaluated. The domains with the highest averages were &quot;physical health&quot; with 49.23 and &quot;coping&quot; with 35.89 and with the lowest average was &quot;family planning&quot;. have an unsatisfactory QoL in relation to physical health and coping and, satisfactory in relation to relationships and sexuality.</td>
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</table>

DISCUSSION

Better quality of life in PWH is a predictor of disease.

Hemarthrosis, and severe and irreversible joint damage as the most frequent and most important complication in PWH as mentioned by different studies (Feijó et al. 2018; Ministério da Saúde (MS) 2014, 2015), could be prevented by early detection of the disease, i.e. from birth to three years of age, which would
contribute to a higher and better QoL, improving their life prospects with an optimal prophylaxis, not only for severe cases (Ministério da Saúde (MS) 2015). The physical aspects of PWH are the most affected by hemorrhages that directly affect the locomotor system and cause sequelae that impair their mobility, reduce their range of motion, and add to their pain (Back et al. 2020). Similar statements are found in the study published by Chen et al., who found that limitation in hip and knee arcs of mobility are predictors of QoL in PWH. (Chen et al. 2015), the results showed that this group did not receive treatment with prophylaxis at an early age and developed hemophilic arthropathy due to bleeding, mainly in the knees and ankles. However, it should be noted that these treatments are not always available to all those diagnosed with hemophilia. (Wellington Criollo, 2018).

One study reported such a high HRQoL, similar to that of the Colombian population (Fuenmayor Castaño et al. 2017) which can be corroborated with other authors in which their sample in PWH where their QoL is high, corroborated with the highest data in physical function, bodily pain and general health of the SF-36 (Lindvall et al. 2012; Scalone et al. 2006)

The presence of inhibitors, the difference in the severity of hemophilia, their employment situation, the different forms or cultural manifestations of the different public health policies of each country, supports mixed results in the SF-36, on the other hand, the prophylaxis received in 96% of patients means that few have inhibitors, which is associated with less joint damage due to hemarthrosis (Brown et al. 2009; Tagliaferri et al. 2015). The minimal presence of inhibitors has an influence on the evaluated results of physical function, but this is not observed in other studies in which only patients with inhibitors are evaluated (Scalone et al. 2006).

In the clinical profile of PWH it was found that hemophilia A is observed more frequently than hemophilia B, corresponding to 80% of cases (Feijó et al. 2018; Ferreira et al. 2021; Santos et al. 2018; Trindade et al. 2019) which is seen in other studies that also showed severe hemophilia to be predominant (Santos et al. 2018; Trindade et al. 2019). There was evidence of multiple cardiovascular risk factors that would be predictors of lower QoL, as well as the presence of inhibitors and the severity of hemophilia (Franchini & Mannucci, 2010).

The multidisciplinary approach to PWH care encourages the participation not only of a health care team with different specialties, but also promotes family and community participation in self-care, health education and guidelines for improving QoL (Sayago & Lorenzo, 2020). Similarly, other studies showed high scores in emotional performance and mental health (Gringeri et al. 2003; Plug et al. 2008), showing that scores of minimal or mild depression have a positive impact on their QoL (Kim et al. 2013). Patients who were participating in physiotherapy programs are highlighted, which contributes to their emotional and physical well-being, resulting in a better QoL. (Negrier et al. 2013; Niu et al. 2014).

These data bring us closer to a different vision, which goes beyond the application of coagulation factors, directing attention to a chain of continuous care from a multidisciplinary team (Sayago & Lorenzo, 2020). The perception of well-being of the patient included in a comprehensive care program that allows him/her uninterrupted access to his/her prophylactic treatment, as mentioned by Elander et al. (2009). Colombian regulations require them to provide timely care to diagnosed patients and in accordance with their updated guidelines (Elander et al. 2009). This has been demonstrated in other studies (Franchini & Mannucci 2010; Hartl et al. 2008).

The levels of self-esteem and security are diminished in people with this disease (Reinicke et al. 2019). It has been observed that close contact in social networks gives them the opportunity to experience closeness, contact and understanding, raising their self-esteem (Sheeran et al. 2016). The importance of the psychologist in this group of patients, to provide emotional support, promote emotional intelligence, their vision of the future regarding their health care and their self-esteem, turns out to be a predictor of HRQoL in PWH (Aguilar-Palacios et al., 2022).

Self-care is related to coping resources, in areas such as body care, early identification of bleeding and how to manage it, and is associated with their capacity for self-care and control of their treatment, being found at...
very high levels (Rambod et al. 2018; Varaklioti et al. 2018).

The comparison of QoL with the Colombian population, a lower average score in social function, indicating a strong interference with social activities, motivated by physical or emotional problems, usually due to the frequency of attending medical treatments and the difficulties encountered in obtaining a job, also observed slightly higher levels of depression and is the group where there were more patients with hepatitis C infections, which have been associated with lower QoL (Lindvall et al. 2012).

The KIDSCREEN-27 QoL score was superior to those observed in other pathologies such as mental illness, congenital diaphragmatic hernia and long-term survivors of hemophilia. (Weitkamp et al. 2013). This finding could be explained by the use of prophylactic treatment from an early age in 84% of patients, as early prevention of arthropathies, attendance to a physical therapy program and additional home exercises, reporting a QoL comparable to the general population of Colombia, without hemophilia. This evidence reiterates that pharmacological prophylaxis and a rehabilitation program promoting healthy lifestyles and functional independence are imperative (Arteaga-Rubiano & García-Valencia, 2021).

The low results in sport and leisure and future, could be due to the difficulties that PWH present in the performance of activities that require physical effort, reflecting a moderate HRQoL (van Os et al. 2017). The lowest HRQoL is observed in elderly people, which is explained by the absence of treatment for decades, with the known complications, dysfunctions and pain (Von Mackensen et al. 2012) the sequelae increase restrictions in daily tasks, movement and participation in social, sporting, recreational and leisure activities (Solovieva et al. 2004). The presence of arthropathies and reduced mobility is associated with lower QoL (Chen et al. 2015; Kempton et al. 2018; Poon et al. 2012).

**CONCLUSIONS**

Early prophylaxis and participation in rehabilitation programs are predictors of QoL, thus avoiding limitation of hip and knee mobility arcs in PWH, as well as preventing the appearance of inhibitors, together with health promotion and healthy lifestyles. Multidisciplinary care would ensure that few PWH present inhibitors, and this result would be associated with less joint damage due to hemarthrosis. Multiple risk factors are predictors of QoL, including the severity of hemophilia, the presence of inhibitors and cardiovascular aspects.

The relevance of self-esteem, coping styles and emotional aspects are predictors of QoL, the inclusion of other aspects such as anxiety and depression are necessary, in PWH, in which they could be present, since the variable QoL is multicausal, this would help to shed more light for its explanation. The spiritual and compassionate approach, by the multidisciplinary team, would help to develop resilience in PWH. Hemophilia, as an orphan,
chronic and complex disease, requires the observation of all aspects that involve the health and well-being of PWH, and that these be estimated through multidisciplinary teams and instruments that assess their QoL.

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APPENDIX


