ORIGINAL ARTICLE

Prevalence, clinical characteristics and the burden of disease of the Croatian adult patients with HAE: nationwide survey analysis

Marko Barešić[1], Boris Karanović[1], Ljerka Čulav[2], Dijana Perković[3], Jasminka Milas-Ahić[4], Srđan Novak[5], Željka Kardum[4,6], Ana Marija Masle[4], Daniel Victor Šimac[5], Marijana Matijaš[3], Branimir Anić[1]

[1] Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University of Zagreb, School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia

[2] Department of Otorhinolaryngology, Šibenik General Hospital, Šibenik, Croatia

[3] Division of Rheumatology, Allergology and Clinical Immunology, Department of Internal Medicine, University of Split, School of Medicine, University Hospital Center Split, Split, Croatia

[4] Division of Rheumatology, Clinical Immunology and Allergology, Department of Internal Medicine, University of Osijek, School of Medicine, University Hospital Center Osijek, Osijek, Croatia

[5] Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, University of Rijeka, School of Medicine, University Hospital Center Rijeka, Rijeka, Croatia

[6] Department of Internal Medicine, General Hospital Zadar, Zadar, Croatia

Corresponding author:
Boris Karanović
Division of Clinical Immunology and Rheumatology
Department of Internal
Medicine, University of Zagreb
School of Medicine, University Hospital Center Zagreb
Kišpatićeva 12
Zagreb, Croatia
ORCID: 0000-0002-5884-1190
E-mail: boris.karanovic@gmail.com

Summary

Background. Hereditary angioedema (HAE) is a rare genetic disorder with variable prevalence, characterized by recurrent swelling in various parts of the body, including potential laryngeal attacks, significantly affecting patients' quality of life. **Methods**. A nationwide, cross-sectional survey study was conducted between December 2023 and June 2024, targeting adults (aged 18 and older). The patients filled out different HAE-related questionnaires. Descriptive statistics were used to analyze and summarize the data. **Results**. The prevalence of HAE in Croatia is estimated to be 3.10 per 100,000 people. The majority were females, patients with positive family history, and type 1 HAE. The median diagnostic delay was 13 years, with initial attacks typically occurring in adolescence, but diagnosis was often not established until young to middle adulthood. Regarding quality of life, approximately 51% reported a significant impact. Fatigue was prevalent, with 46.9% of patients experiencing mild to moderate levels, and 22.4% suffering from severe fatigue. Most patients reported minimal depression, and 37.7% presented with moderate to severe anxiety. Among employed individuals, a median presenteeism of 20% indicated productivity loss while at work, in contrast to generally minimal absenteeism. **Conclusions.** Recent more substantial diagnostic efforts and increased awareness are contributing factors to the higher observed prevalence of HAE in Croatia, mainly due to the sustained work of a dedicated patient organization and a well-developed network of national HAE experts. Patients still experience a high disease burden, impaired quality of life, and difficulties with daily activities, which trends also observed in other HAE cohorts worldwide.

Key words

Hereditary angioedema types I and II; surveys and questionnaires; patient reported outcome measures; prevalence; epidemiology.

IMPACT STATEMENT

This study offers valuable real-world insights into the epidemiological, demographic, and clinical features of Croatian HAE patients, thereby enhancing the limited existing data on HAE from Croatia and Southeast Europe.

Abbreviations

HAE = Hereditary angioedema
C1-INH = C1-inhibitor
pdC1-INH = Plasma derived C1-inhibitor
rC1-INH = Recombinant C1-inhibitor
HAE-nC1-INH = HAE with normal C1-INH levels
HAE-UNK = HAE with unknown mutation
SERPING1 = Serpin family G member 1
PROMs = Patient-reported outcome measures
AECT = Angioedema Control Test

AAS = Angioedema Activity Score
AE-QoL = Angioedema Quality of Life Questionnaire
HAE-AS = Hereditary Angioedema Activity Score
HAE-QoL = Hereditary Angioedema Quality of Life
FACIT = Functional Assessment of Chronic Illness Therapy
EQ-5D-5L = EuroQol – 5 dimensions – 5 levels
WPAI:GH = Work Productivity and Activity Impairment Questionnaire: General Health
ODT = On-demand treatment
STP = Short-term prophylaxis
LTP = Long-term prophylaxis
EU = European Union
IQR = Interquartile range

Introduction:

Hereditary angioedema (HAE) is an orphan disease characterized by recurrent swelling episodes, primarily linked to C1 inhibitor (C1-INH) deficiency or dysfunction resulting in excessive bradykinin production (1). HAE follows an autosomal dominant inheritance pattern, often affecting multiple members within the same family. The two most common forms, HAE types 1 and 2, account for approximately 90% of cases and are caused by mutations in the SERPING1 gene, which encodes the C1-INH protein. Nevertheless, approximately 20% of patients are diagnosed with *de novo* mutations (2). The most infrequent form is HAE with normal C1-INH levels (HAE-nC1-INH), which is linked to mutations in F12, PLG, ANGPT1, KNG1, MYOF, HS3ST6 and recently described genes CPN1 and DAB2IP (3). As with many other rare diseases, the precise global prevalence of HAE is unclear, and reported estimates vary, typically ranging from 1:50,000 to 1:150,000 according to different epidemiological studies (4,5). It is plausible that the observed variability in the reported prevalence of HAE is significantly influenced by differences in diagnostic resources and clinical awareness of medical professionals across regions, potentially contributing to both underestimation and occasional misclassification of cases (6). Founder effects, consanguinity and isolated gene pools can lead to higher frequencies of specific variants, as observed for mutations in F12, PLG and other genes (7). Beyond healthcare providers, non-medical subjects like patient advocacy groups and patient organizations are also instrumental in gathering essential data concerning individuals with HAE and their caregivers.

HAE is characterized by a high and multifaceted burden on patients, their families, and healthcare systems. This burden extends far beyond the physical symptoms of the attacks themselves (8). Patient-reported outcome measures (PROMs) are standardized, validated questionnaires that serve as tools that directly capture a patient's perception of their own health status, experiences, and burden of disease. PROMs can be generic and measure broad aspects of health-related quality of life that are applicable to a wide range of conditions and populations, and condition-specific, designed to measure outcomes relevant to a particular disease (9). Over time, angioedema and HAE-specific PROMs (HAE-PROMs) have been developed and put into use to monitor and manage patients with HAE (10). Most commonly used PROMs include: Angioedema Control Test (AECT) (11), Angioedema Activity Score (AAS) (12), Angioedema Quality of Life Questionnaire (AE-QoL) (13), Hereditary Angioedema Activity Score (HAE-AS) (14), and Hereditary Angioedema Quality of Life (HAE-QoL) (15). PROMs are valuable clinical tools for follow-up and can be of aid in the comprehensive assessment of patients, ultimately helping to develop improved therapeutic strategies. Due to intellectual property rights and the complexities of translation and cultural validation, not all HAE-specific PROMs are universally available or widely adopted in routine clinical practice outside of research settings, emphasizing the need for improved implementation strategies (10).

While data on HAE in Croatia appear limited, several significant medical publications have emerged over time. Notably, these include the national guidelines for the diagnosis and treatment of HAE, published in 2014 (16), and a 2019 national study that specifically identified Croatian pediatric HAE patients (17). In our current study, we are reporting results from a nationwide survey analysis conducted by Croatian HAE experts, aimed at elucidating up-to-date epidemiological data (primarily prevalence) and the comprehensive disease burden experienced by adult patients (18 years and older). The study did not include pediatric patients, as the PROMs used were not suitable and standardized for this age group's ability to self-report. The survey's data collection was performed before the first-line long-term prophylactic (LTP) treatments, lanadelumab and berotralstat, received regulatory approval and reimbursement in Croatia.

Methods:

Population of Croatia:

The population of Croatia is 3,871,833, as reported by the official Croatian Bureau of Statistics and the 2021 census (18), which positions the country among the smaller ones of the 27 EU member countries by population. Point prevalence was used to determine the proportion of individuals with HAE since this epidemiological measure captures both new and existing cases, and is typically expressed as 1:100,000 inhabitants.

Patients with HAE:

In our study cohort, all patients presented with typical recurrent angioedema. Patients with mast cell-mediated and medication-induced angioedema were excluded. Those with HAE types 1 and 2 exhibited low C4 and low functional C1-INH (with low/normal antigenic C1-INH levels), while patients with HAE-nC1-INH had normal C1-INH levels. Most HAE type 1 and 2 patients had a confirmed SERPING1 mutation. Among patients presenting with HAE-nC1-INH, none of the individuals analysed demonstrated a known non-SERPING1 mutation, some of them being negative for all known non-SERPING1 mutations, while others haven't been tested yet due to objective technical limitations. Therefore, a subset of our cohort remained genetically uncharacterized. As a result, they were collectively classified as HAE with unknown mutation (HAE-UNK). No patients with acquired angioedema were included although in everyday clinical practice we actively search for such patients by C1q testing. Croatian HAE patients receive diagnosis, treatment, and follow-up care at their respective regional medical centers, as centralization into a single medical center is not obligatory. A significant number of Croatian individuals affected by HAE, together with their caregivers, are affiliated with *HAE Hrvatska*, the Croatian patient organization, which is a constituent of the broader global non-profit organization, HAE International.

A cross-sectional, observational patient survey was conducted by leading Croatian HAE experts in partnership with *HAE Hrvatska*, from December 2023 to June 2024. This survey exclusively included adult patients (aged 18 years or older), who voluntarily completed the face-to-face survey after providing their written informed consent for participation. In a single point of time, the patients anonymously provided their demographics, general data about HAE history and treatment and filled out different questionnaires. In the study we used both angioedema and HAE specific questionnaires such as AECT and AE-QoL, in addition to standardized generic questionnaires not exclusively associated to HAE such as FACIT-FATIGUE, EQ-5D-5L, WPAI:GH, Beck's Depression and Anxiety Inventory (12,13,19–23). To facilitate participation, patients had the option to complete the surveys during their follow-up appointments or at home, submitting them afterwards or sending them to their treating physician. The survey targeted all adult HAE patients in Croatia. However, participation was limited to those who were members of the *HAE Hrvatska* organization or were in active follow-up at their hospital centers. A total of fifty-seven adult patients voluntarily completed the questionnaire.

Sufficient data security measures have been implemented. Subsequent processing and the application of descriptive statistics were carried out using Microsoft Office Excel. The study was approved by the Ethics committee of University Hospital Centre Croatia, Croatia (approval number: 8.1-24/86-2; 02/013 AG) and was carried out according to the principles of the Declaration of Helsinki.

Results:

Fifty-seven Croatian HAE patients took part in the study. The median age of the participants was 47, with half of the individuals falling between 36 and 54 years old, and their ages spanning from 19 to 78. Most patients were female (40; 70.2%), living in urban areas (44; 77.2%), and having a secondary level of education (41; 71.9%). Thirty-seven (64.9%) were diagnosed with HAE type 1, 8 (14%) with HAE type 2, and 12 (21%) with HAE-nC1-INH with unknown non-SERPING1 mutation (HAE-UNK). A positive family history was present in 44 (77.2%) of the patients, with a median of one child (range: 0-8) per patient. The median patient's age at their first HAE attack was 15 years (IQR 10-23; range: 1-47), while the median age at diagnosis was 26 years (IQR 19-39; range: 3-60). This indicates a median diagnostic delay of 13 years (IQR 6-20), with a range from 5 years before the first symptom to 43 years after the initial swelling. The most common localization of the first HAE symptom was the extremities, affecting 25 participants (43.9%), followed by face in 16 participants (28.1%), and abdomen in 14 participants (24.6%). Larynx was the first symptom localization for 2 participants (3.5%), while 7 participants (12.3%) experienced their first symptoms in other locations. It is worth noting that the percentages sum to more than 100%, indicating that some participants experienced their first symptoms in more than one localization. The most common localizations of HAE attacks were the extremities (33; 57.9%) and abdomen (30; 52.6%), followed by the face (19; 33.3%), larynx (12; 21.1%), and tongue (5; 8.8%). Again, some participants experienced their most common symptoms in multiple localizations. Stress was the most frequently reported trigger, affecting 37 participants (67.3%) followed by physical injury and menstrual cycle in 23 participants (40.4%) and 17 participants (29.8%), respectively. Medication was identified as a trigger in 5 participants (8.8%). Notably, 9 participants (15.8%) reported no specific trigger. Some participants identified more than one trigger for their HAE attacks. The median number of HAE attacks during the 3 months prior to participation was 2, with an IQR of 1-6 and a total range of none to 70 attacks. For ODT, most patients used icatibant (31; 54.4%) and intravenous C1-INH concentrates (21, 36.8%). Regarding the current LTP, it is essential to clarify that the study was conducted before the introduction of first-line LTP with lanadelumab and berotralstat in Croatia. Twenty-six patients (45.6%) were not treated by any LTP medication, while 19 patients (33.3%) were using danazol. For those on danazol, the median dose was 150 mg daily (IQR: 100-275 mg), with a range of 50-600 mg. Additionally, tranexamic acid and intravenous C1-INH concentrates were used in 5 (8.8%) and 12 patients (21.1%), respectively. In some patients, more than one drug was used concurrently. Baseline demographic characteristics, clinical features, and treatment data are shown in **Table I.**

AECT was used for assessing disease control, indicating poorly controlled disease with a median in both 4 week and 3 month AECT measuring 8, ranging from 1 to 16, IQR 5-15 for 4 week AECT and 0 to 16, IQR 5-12 for a median 3 month AECT, respectively. According to AE-QoL, 28 patients (51.0%) reported significant effect, 19 patients (34.5%) experienced no effect, and 8 patients (14.5%) reported a small to moderate impact on their quality of life.

When analyzing FACIT-fatigue, 15 patients (30.6%) reported very little to no fatigue, 23 patients (46.9%) experienced mild to moderate levels of fatigue, and 11 patients (22.4%) reported severe fatigue. Anxiety testing (BAI) reported 17 patients (32.1%) with minimal anxiety, 16 patients (30.2%) with mild anxiety, 6 patients (11.3%) with moderate anxiety and 14 patients (26.4%) severe anxiety. Depression testing (BDI) revealed minimal depression in 38 patients (76.0%) mild depression in seven patients (14.0%) moderate depression in four patients (8.0%) and severe depression in 1 patient (2.0%). Nineteen (33.9%) patients were employed with median absenteeism of 0%, and median presenteeism of 20%.

Results of the Croatian HAE patients PROMs are presented in **Table II**.

The health status, based on the EQ-5D-5L domains, is presented as follows: for Mobility, nearly half of the respondents (49.1%) reported no problems, while 29.1% experienced slight problems. Moderate, severe, and extreme problems accounted for 9.1%, 9.1%, and 3.6% respectively. In Self-care, an overwhelming majority (83.6%) reported no problems, with only small percentages experiencing slight (7.3%), moderate (7.3%), or severe (1.8%) problems. Usual activities show a more varied distribution. While 50.9% reported no problems, 21.8% had slight problems, 14.5% faced moderate problems, and 10.9% experienced severe problems. Pain is a significant issue, with only 32.7% reporting no problems. A nearly equal proportion (32.7%) experienced slight pain, while 27.3% reported moderate pain. Severe pain was reported by 5.5% and extreme pain by 1.8%. Finally, for Anxiety, 58.2% reported no problems, suggesting that a majority do not experience significant anxiety. However, a considerable portion did report some anxiety: 23.6% with slight problems, 10.9% with moderate problems, and 3.6% with severe problems. Extreme anxiety or being unable was reported by 3.6%, indicating that anxiety affects a notable segment of the population.

Results of assessment of participants health status according to EQ-5D-5L is shown in

Regarding patient perception of treatment success, the median satisfaction level is 9 out of 10, with an interquartile range (IQR) of 7-10 and a full range of 1-10. This suggests that while there's a broad spectrum of experiences, the majority of patients are highly satisfied with their treatment outcomes.

Patients' most frequently reported concern (50.9% of patients) is the fear of passing HAE to their children. This is followed by fear of failure to meet business responsibilities (42.1%) and neglecting social activities (35.1%). Fear of dying due to an HAE attack is a concern for 33.3% of patients, while a small percentage (15.8%) reported no concerns or fears. This highlights the significant impact HAE has on patients' personal, professional, and family lives.

In terms of suggestions for improving medical care, the overwhelming majority of patients (72.2%) emphasized the need for improved education and training of healthcare professionals. This indicates a perceived gap in the knowledge and skills of medical staff regarding HAE. Additionally, a substantial portion (46.3%) suggested improved education of the general population, which could potentially lead to greater awareness, understanding, and support for individuals with HAE. A smaller percentage (14.8%) recommended improved communication with their leading physician.

Patients' subjective personal perspectives and perceptions of HAE are summarized in **Table III.**

While specifying the exact number of HAE patients in Croatia is challenging, we utilized data that, to the best of the authors knowledge, is reliable and relevant. The Croatian patient organization *HAE Hrvatska*, the solely and the most important patient advocacy group in Croatia, reported 120 individuals with HAE, holding the up-to-date register of members/patients known to be associated with the organization. Among them, 98 are adults (aged 18 or older) and 22 are minors (aged 18 or younger). The majority of these individuals receive regular follow-up care at their regional medical centers.

The data provided by *HAE Hrvatska* offers the most accurate and consistent representation of real-world figures. Taking these estimates into account, and considering Croatia's total population of 3,871,833 reported by the 2021 census, the point prevalence is estimated at 3.10 per 100,000 people or 1.55 per 50,000 people.

Discussion and conclusions:

Recognizing the scarcity of recent epidemiological data, especially concerning prevalence, and the lack of comprehensive insights into the disease burden among adult HAE patients (≥18 years of age) from Croatia, the Croatian HAE experts undertook a nationwide survey analysis. The primary objective of this investigation was to assess the current status of HAE in Croatia, encompassing aspects such as diagnostic delays, treatment accessibility, and the overall patient-reported quality of life and disease burden. The study utilized a survey design. Survey research is a widely used quantitative research method involving the systematic collection of data from a sample of individuals through their responses to questions. As a versatile tool, it can provide insights into perceptions, measure behaviours, the severity of the disease, and identify trends within the observed group. While primarily quantitative, surveys can also incorporate qualitative elements through open-ended questions to gain a deeper understanding of the context. Surveys can take different forms, including face-to-face and web-based methods. Web surveys appear to be more practical for participants, but according to some authors, they have an 11% lower response rate compared to other modes, a finding that appears robust and not due to publication bias (24). Another study confirmed that the web survey had a significantly lower unit response rate (18.0%) compared to the face-to-face survey (43.1%), with differences most evident among older and less educated. Although the web survey was nearly three times more cost-effective per completed questionnaire, its lower and more selective response could introduce bias (25). Due to identified shortcomings, we opted for face-to-face surveys for our study, which the patients completed during their follow-up visits or at home, subsequently returning them to their leading physician.

Prevalence:

HAE is classified as an orphan disease, with global prevalence estimates ranging from 1:50,000 to 1:150,000 people. A recent systematic review and meta-analysis, encompassing 11,245 HAE cases from 24 studies between 2000 and 2024, reported a pooled worldwide prevalence of 1.22 cases per 100,000 people (95% CI: 0.91, 1.53). The review noted lower prevalence in Asia and Africa compared to Europe and North America, with HAE type 1 being the most common and a slight female predominance (4). Prevalence figures vary by countries and regions, often due to diagnostic and expert access and the methodology of the analysed data. Specific national studies further illustrate this variation. In the United States, HAE prevalence is estimated between 1.84 and 2.67 per 100,000 people, with claims-based data suggesting 2.43 to 2.67 per 100,000 and expert-reviewed records showing 1.84 to 2.13 per 100,000 (26). Mexican authors, using a mixed-methods approach, estimated a prevalence of 0.9 per 50,000 inhabitants (27). Similarly, a study in the Asia Pacific region reported a minimal prevalence of 0.02 per 100,000, attributing variability to limited access to diagnostic tests and therapies (28). South Australia identified 35 individuals, yielding a prevalence of 1 in 52,400 (29). Finland experienced a significant increase in HAE type 1 and 2 prevalence, rising from 0.8 to 2.6 per 100,000 persons by 2021, with 103 new diagnoses over a decade, and a mean incidence of 0.16 per 100,000. The higher Finnish prevalence, where patients were often diagnosed at a mean age of 39 years after misdiagnosis, may stem from a founder effect, genetic isolation, and improved diagnostic practices (6). In the United Kingdom, a survey identified 1152 patients, providing a minimum prevalence rate of 1:59,000 (30). Meanwhile, Latvia reported a point prevalence of 0.53 per 100,000 inhabitants from 10 diagnosed patients between 2006 and 2022 (31), while Belarus estimated a minimal prevalence of 1:148,000 for HAE due to C1-INH deficiency (32). The detected minimal prevalence of HAE in Spain is 1.09:100,000, a figure that is likely an underestimate due to the disease's rare nature and potential for patient misdiagnosis (33).

While primarily focused on genotype-phenotype association, novel SERPING1 mutations and drug prophylaxis, studies from Croatia's neighbouring countries, Slovenia, Serbia and Hungary, also provided estimated HAE prevalence rates of 0.95, 1.00 and 1.98:100,000, respectively (34,35).

National HAE experts, utilizing data from the Croatian HAE patient organization, estimated the point prevalence of HAE in pediatric and adult patients at 3.10 per 100,000 people (1.55 per 50,000). The prevalence of HAE in different countries and regions is shown in **Table IV**.

Variations in HAE prevalence across countries and populations are common and vary according to different sources and published papers. In all likelihood, reported differences result from the disease's rarity and the challenge of misdiagnosing, underdiagnosing, or overdiagnosing affected individuals. Delayed diagnosis increases the risk of life-threatening laryngeal attacks and unnecessary interventions. Disease is often underreported due to overlapping symptoms with other conditions. Insufficient disease awareness often leads to undetected cases, especially in patients who present with *de novo* mutation within their family. The emphasis should be put on the fact that accurate prevalence estimates are crucial for future planning of patient care, especially as new treatment options emerge. In Croatia, similar to the data from Finland, Hungary and the US, the elevated observed prevalence of HAE can be attributed to enhanced diagnostic initiatives and heightened national awareness, primarily facilitated by a dedicated patient organization and a well-established network of national HAE experts. However, further efforts are needed to elucidate and confirm our estimated prevalence, as the absence of an official HAE Registry in Croatia currently limits comprehensive data collection and validation.

Burden and quality of life:

PROMs are essential healthcare tools that directly capture a patient's perspective on their health, symptoms, functional abilities, disease burden, and quality of life. Despite their recognized benefits in clinical practice and research, PROMs have limitations. These include potential lack of comprehensiveness, as they may not capture all relevant aspects of a patient's experience. Furthermore, PROM scores can be influenced by various external factors unrelated to the assessed intervention, such as individual pain levels, psychological state, social circumstances, baseline functional status, age, sex, comorbidities, and personality traits. The reliability and validity of PROMs are also vulnerable to incomplete questionnaires or missing data. Nevertheless, their significant advantages in providing patient-centered insights typically outweigh these disadvantages, leading to their frequent use in daily clinical and research settings (9).

Reported patient demographics show some variation and represent only a portion of HAE patients, as not all individuals with HAE participated in published studies. The Croatian study reported a female predominance (70.2%) and HAE type 1 as most common (64.9%), followed by HAE-nC1-INH (21%) and HAE type 2 (14%). This differs slightly from the Canadian study where HAE type 1 was 46% and HAE-nl-C1-INH 43% (37), but is similar to another Canadian report with 57% HAE type 1 and 26% HAE type 2 (38). Portuguese reference center found a high prevalence of HAE type 2 (39).

By comparing the Croatian results with other published data, a significant diagnostic delay is a consistent theme across multiple studies. In Croatia, the median diagnostic delay for HAE was 13 years, mainly due to a lack of awareness among general medical practitioners. However, recent efforts by HAE experts and patient organization have significantly improved the diagnostic journey for patients, leading to more timely and accurate diagnosis. Similar delays are reported by Canadian (average 10-11 years) (38) and Indian authors (median 10 years) (40). German group reported an even longer mean diagnostic delay of 18.1 years (41), while Finnish colleagues noted a mean diagnostic age of 39 years due to misclassification (6). The Brazilian center also highlighted significant delays, particularly for those without a family history (42). Most Portuguese patients experienced initial symptoms before adulthood, around 12.6 years old (35), the Brazilian family study found a mean HAE diagnosis age of 16.7 years (36). These differences underscore a global lack of awareness among healthcare providers, leading to prolonged suffering and unnecessary treatments, as seen in cited published reports. Implementing targeted education for primary care physicians, conducting cascade testing in families, offering newborn screening to high-risk families, and running dedicated awareness campaigns are crucial steps to both shorten diagnostic delays and improve patient outcomes.

Attack localization and frequency also show similarities. In Croatia, extremities (57.9%) and abdomen (52.6%) were the most common attack sites, aligning with Canadian (38), Mexican (27), and German (41) findings where abdominal pain and cutaneous swelling were prevalent. Laryngeal involvement, a life-threatening symptom, was reported in 21.1% of Croatian patients as a common attack localization and 3.5% as the first symptom. This is consistent with Mexican data (27.5% severe laryngeal edema) (27) and Brazilian findings (significant laryngeal involvement in a quarter of respondents) (42). The high frequency of attacks is a recurring burden, with 35% of Canadian participants experiencing more than five attacks in six months (38), and acute episodes predominantly moderate to severe (77.0%) in Mexico (27). The Croatian data, indicated by a median AECT of 8, also suggests poorly controlled disease, as seen in the Dutch (36% poorly controlled by AECT) (43) and the Australian study emphasizing continued significant burden despite effective ODT (29).

Regarding healthcare utilization, Croatian patients reported median absenteeism of 0% and presenteeism of 20%, which reflects the impact of the disease on work, although less detailed than the general statement in the USA data about absenteeism and presenteeism for both patients and caregivers (44). Brazilian patients averaged 16.8 emergency visits annually (45), and Mexican patients averaged 7.6, pointing to the significant acute care burden (27). The median number of HAE attacks among Croatian patients in the 3 months preceding the survey was 2, with a range extending from 0 to 70 attacks. A significant portion of these patients were utilizing ODT such as icatibant and intravenous C1-INH concentrates.

The impact on quality of life is reported as an important issue in almost every published paper. Fifty-one percent of Croatian participants reported a significant effect on their quality of life (AE-QoL), with only 14.5% reporting small to moderate impact. This aligns with the Japanese study, which found significant impairment in health-related quality of life and a direct correlation between higher attack frequencies and increased impairment in daily life and work productivity (46). The USA data broadly states that HAE patients often experience reduced quality of life due to stress, anxiety, and depression (47). The Dutch study explicitly linked angioedema attacks to a significant drop in EQ-5D-5L utility values (43). While the South Australian study indicated generally satisfactory disease control with prophylactic therapies leading to high patient satisfaction, this is presented as a positive outcome of effective management, rather than a reflection of the inherent disease burden without adequate treatment (48). The overall picture indicates that HAE profoundly affects patients' quality of life across diverse geographical regions.

Psychological comorbidities according to Croatian participants are reported as a prominent problem, anxiety testing (BAI) showing 26.4% of patients experience severe anxiety, and 30.2% mild anxiety. Depression testing (BDI) revealed 8.0% with moderate depression and 2.0% with severe depression. This is similar to the USA data, which reported an increased prevalence of depression in female HAE-C1INH participants and generally stated that HAE patients often experience significant emotional impairment due to stress, anxiety, and depression (47). The German survey also highlighted the significant burden due to anxiety of unpredictable swelling attacks (49). The Japanese study explicitly linked elevated scores on AE-QoL domains (fatigue/mood and fears/shame) to higher anxiety levels (46). These consistent findings emphasize the critical need for psychological support as part of comprehensive HAE management.

Treatment approaches also vary, particularly concerning LTP. In Croatia, 54.4% participants were on LTP, with danazol being the most common (33.3%), compared to 45% of patients on LTP in the UK (predominantly danazol) (30) and 69% on C1-INH in Canada (38). The Croatian study was conducted before the introduction of modern first-line LTP, which explains the high proportion of patients on danazol, further emphasizing the disease burden in this cohort compared to regions with better access, where modern LTPs led to high patient satisfaction (29). The Croatian experience of self-administration of intravenous C1-INH at home proved to be an excellent way to reduce the pressure of Emergency room visits. Stress was the most frequently reported trigger in Croatia (67.3%), consistent with Portuguese findings, highlighting the psycho-social aspects of disease management (39). Modern LTP in comparison with older therapies (like attenuated androgens) has significantly improved efficacy, provided a favourable safety profile, and a better quality of life for patients. Recently conducted international survey among HAE experts concluded similar significant unmet needs and barriers to treatment, leading to a call for improved access to care, better education for physicians and patients, and increased collaboration among stakeholders (50).

In conclusion, global HAE studies consistently highlight delayed diagnoses, misdiagnosis, and the impact of the disease on quality of life, work productivity, and psycho-social aspects, a tendency also observed in Croatian data**.** The median 13-year diagnostic delay reported in Croatian patients, consistent with global trends, highlights the critical need for improved recognition and more efficient diagnostic patient pathways. With the recent approval and reimbursement of first-line long-term prophylactic therapies, such as lanadelumab and berotralstat, as well as other emerging treatments, significant improvements in quality of life and reductions in disease burden are expected in Croatia and worldwide.

Contributions:

MB – Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.
BK – Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing.
LČ – Methodology, Resources, Writing – review & editing.
DP – Validation, Visualization, Writing – review & editing.
JMA – Validation, Visualization, Writing – review & editing.
SN – Validation, Visualization, Writing – review & editing.
ŽK – Methodology, Resources, Writing – review & editing.
AMM – Investigation, Writing – review & editing.
DVŠ – Methodology, Resources, Writing – review & editing.
MM – Methodology, Resources, Writing – review & editing.
BA – Validation, Visualization, Writing – review & editing.

Conflict of interest: We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. It was presented as a poster during a poster session on the Global Angioedema Forum (GAF) held in Copenhagen, Denmark in October 2024. We declare that we have no conflicts of interest associated with this publication, and there has been no financial support for this work that could have influenced its outcome. As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors with subsequent modifications. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical statement: Informed consent was obtained from the patients included in the survey.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Data availability: The data from this study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors wish to express their sincere gratitude to all participating patients and their caregivers. Special thanks are also extended to the members of the patient organization *HAE Hrvatska*, and particularly to its president, Ms. Mihaela Šogorić, the driving force behind the entire Croatian HAE community.

References:

1. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. Allergy. 2022 July;77(7):1961–90.

2. Banday AZ, Kaur A, Jindal AK, Rawat A, Singh S. An update on the genetics and pathogenesis of hereditary angioedema. Genes Dis. 2020 Mar;7(1):75–83.

3. Loules G, Parsopoulou F, Zamanakou M, Csuka D, Bova M, González-Quevedo T, et al. Deciphering the Genetics of Primary Angioedema with Normal Levels of C1 Inhibitor. J Clin Med. 2020 Oct 23;9(11):3402.

4. Fisch SA, Rundle AG, Neugut AI, Freedberg DE. Worldwide Prevalence of Hereditary Angioedema: A Systematic Review and Meta-Analysis. Int Arch Allergy Immunol. 2025 Jan 17;1–9.

5. Tutunaru CV, Ică OM, Mitroi GG, Neagoe CD, Mitroi GF, Orzan OA, et al. Unveiling the Complexities of Hereditary Angioedema. Biomolecules. 2024 Oct 14;14(10):1298.

6. Sandberg A, Lassenius M, Vihervaara V, Toppila I, Huilaja L. Hereditary Angioedema Type 1 and 2 in Finland: Incidence, Prevalence, and Preceding Diagnoses. Acta Derm Venereol. 2024 May 6;104:adv24176.

7. Bork K, Wulff K, Steinmüller-Magin L, Braenne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. Allergy. 2018 Feb;73(2):442–50.

8. Banerji A, Davis KH, Brown TM, Hollis K, Hunter SM, Long J, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2020 June;124(6):600–7.

9. Churruca K, Pomare C, Ellis LA, Long JC, Henderson SB, Murphy LED, et al. Patient-reported outcome measures (PROMs): A review of generic and condition-specific measures and a discussion of trends and issues. Health Expect Int J Public Particip Health Care Health Policy. 2021 Aug;24(4):1015–24.

10. Brix ATH, Boysen HB, Weller K, Caballero T, Bygum A. Patient-reported Outcome Measures for Angioedema: A Literature Review. Acta Derm Venereol. 2021 May 19;101(5):adv00456.

11. Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Development of the Angioedema Control Test-A patient-reported outcome measure that assesses disease control in patients with recurrent angioedema. Allergy. 2020 May;75(5):1165–77.

12. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development, validation, and initial results of the Angioedema Activity Score. Allergy. 2013 Sept;68(9):1185–92.

13. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy. 2012 Oct;67(10):1289–98.

14. Forjaz MJ, Ayala A, Caminoa M, Prior N, Pérez-Fernández E, Caballero T, et al. HAE-AS: A Specific Disease Activity Scale for Hereditary Angioedema With C1-Inhibitor Deficiency. J Investig Allergol Clin Immunol. 2021 June 22;31(3):246–52.

15. Prior N, Remor E, Pérez-Fernández E, Caminoa M, Gómez-Traseira C, Gayá F, et al. Psychometric Field Study of Hereditary Angioedema Quality of Life Questionnaire for Adults: HAE-QoL. J Allergy Clin Immunol Pract. 2016;4(3):464-473.e4.

16. Marković AS, Rozmanić V, Anić B, Aberle N, Racić G, Novak S, et al. [Guidelines for the diagnosis and treatment of hereditary angioedema]. Lijec Vjesn. 2014;136(5–6):117–29.

17. Karadža-Lapić L, Barešić M, Vrsalović R, Ivković-Jureković I, Sršen S, Prkačin I, et al. HEREDITARY ANGIOEDEMA DUE TO C1-INHIBITOR DEFICIENCY IN PEDIATRIC PATIENTS IN CROATIA - FIRST NATIONAL STUDY, DIAGNOSTIC AND PROPHYLACTIC CHALLENGES. Acta Clin Croat. 2019 Mar;58(1):139–46.

18. Croatian Bureau of Statistics, Accessed on 30 June 2025 [Internet]. Available from: https://web.dzs.hr/hub24/stanovnistvo_en.html

19. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

20. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2011 Dec;20(10):1727–36.

21. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993 Nov;4(5):353–65.

22. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988 Dec;56(6):893–7.

23. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961 June;4:561–71.

24. Manfreda KL, Bosnjak M, Berzelak J, Haas I, Vehovar V. Web Surveys versus other Survey Modes: A Meta-Analysis Comparing Response Rates. Int J Mark Res. 2008 Jan;50(1):79–104.

25. Braekman E, Demarest S, Charafeddine R, Drieskens S, Berete F, Gisle L, et al. Unit Response and Costs in Web Versus Face-To-Face Data Collection: Comparison of Two Cross-sectional Health Surveys. J Med Internet Res. 2022 Jan 7;24(1):e26299.

26. Castaldo AJ, Wells KE, Khalid S, Rashidi E, Selva CN, Corcoran D, et al. Establishing a hereditary angioedema prevalence for the United States using a large administrative claims database. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2025 May 23;S1081-1206(25)00258-3.

27. Nieto S, Madrigal I, Contreras F, Vargas ME. Real-world experience of hereditary angioedema (HAE) in Mexico: A mixed-methods approach to describe epidemiology, diagnosis, and treatment patterns. World Allergy Organ J. 2023 Sept;16(9):100812.

28. Li PH, Pawankar R, Thong BYH, Fok JS, Chantaphakul H, Hide M, et al. Epidemiology, Management, and Treatment Access of Hereditary Angioedema in the Asia Pacific Region: Outcomes From an International Survey. J Allergy Clin Immunol Pract. 2023 Apr;11(4):1253–60.

29. Troelnikov A, Milburn K, Hissaria P, Thao Adriana Le T, Smith W. Hereditary angioedema prevalence and satisfaction with prophylaxis in South Australia. World Allergy Organ J. 2024 July;17(7):100918.

30. Yong PFK, Coulter T, El-Shanawany T, Garcez T, Hackett S, Jain R, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. J Allergy Clin Immunol Pract. 2023 Aug;11(8):2476–83.

31. Kanepa A, Nartisa I, Rots D, Gailite L, Farkas H, Kurjane N. National survey on clinical and genetic characteristics of patients with hereditary angioedema in Latvia. Allergy Asthma Clin Immunol Off J Can Soc Allergy Clin Immunol. 2023 Apr 8;19(1):28.

32. Guryanova I, Suffritti C, Parolin D, Zanichelli A, Ishchanka N, Polyakova E, et al. Hereditary angioedema due to C1 inhibitor deficiency in Belarus: epidemiology, access to diagnosis and seven novel mutations in SERPING1 gene. Clin Mol Allergy CMA. 2021 Apr 7;19(1):3.

33. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2005 Apr;94(4):498–503.

34. Rijavec M, Korošec P, Šilar M, Zidarn M, Miljković J, Košnik M. Hereditary angioedema nationwide study in Slovenia reveals four novel mutations in SERPING1 gene. PloS One. 2013;8(2):e56712.

35. Andrejević S, Korošec P, Šilar M, Košnik M, Mijanović R, Bonači-Nikolić B, et al. Hereditary Angioedema Due to C1 Inhibitor Deficiency in Serbia: Two Novel Mutations and Evidence of Genotype-Phenotype Association. PloS One. 2015;10(11):e0142174.

36. Horváth HR, Visy B, Kőhalmi KV, Balla Z, Andrási N, Czaller I, et al. A national survey of four decades of hereditary angioedema prophylaxis: Efficacy and safety of old and new drugs. Clin Immunol Orlando Fla. 2025 Oct;279:110542.

37. Boursiquot JN, Chapdelaine H, St-Pierre C, Hébert J. The Disease Burden of Hereditary Angioedema: Insights from a Survey in French-Canadians from Quebec. J Immunol Res. 2024;2024:3028617.

38. Lee EY, Hsieh J, Caballero T, McCusker C, Kanani A, Lacuesta G, et al. Demographic and clinical characteristics of patients with hereditary angioedema in Canada. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2022 Jan;128(1):89-94.e1.

39. Varandas C, Esteves Caldeira L, Silva SL, Costa C, Limão R, Silva MI, et al. Hereditary angioedema: 24 years of experience in a Portuguese reference center. Eur Ann Allergy Clin Immunol. 2024 Sept;56(5):210–8.

40. Perumalla S, Mathew L, Mathew J, Naina P, Joseph AJ, Prakash JAJ, et al. Clinical profile of hereditary angioedema from a tertiary care centre in India. Indian J Med Microbiol. 2021;39(4):509–12.

41. Magerl M, Gothe H, Krupka S, Lachmann A, Ohlmeier C. A Germany-wide survey study on the patient journey of patients with hereditary angioedema. Orphanet J Rare Dis. 2020 Aug 26;15(1):221.

42. Giavina-Bianchi P, Giavina-Bianchi M, Oliveira Martins R de, Cristina Fortunato M, Guersoni AC. Unmet needs in the management of hereditary angioedema from the perspective of Brazilian patients. World Allergy Organ J. 2024 Nov;17(11):100992.

43. Fijen LM, Klein PCG, Cohn DM, Kanters TA. The Disease Burden and Societal Costs of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2023 Aug;11(8):2468-2475.e2.

44. Anderson J, Soteres D, Mellor J, Connolly H, Wynne-Cattanach K, Earl L, et al. Physician- and patient-reported outcomes by hereditary angioedema type: Data from a real-world study. Allergy Asthma Proc. 2024 July 1;45(4):247–54.

45. Gehlen CT, Mazzeu JF, Veronez CL, Mendes AR, Bertoli AF, Grumach AS, et al. The Burden of Hereditary Angioedema in a Large Family in Brazil. Int Arch Allergy Immunol. 2024;185(12):1207–15.

46. Hide M, Kishimoto M, Kotera I, Oh A, Inoue Y, Yamamoto BA, et al. Analysis of disease burden in patients with hereditary angioedema from Japan by patient-reported outcomes. J Dermatol. 2025 Feb;52(2):256–69.

47. Christiansen SC, Wilmot J, Castaldo AJ, Zuraw BL. The US Hereditary Angioedema Association Scientific Registry: hereditary angioedema demographics, disease severity, and comorbidities. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2023 Dec;131(6):766-774.e8.

48. Katelaris CH, Boicos K, Button PH, McCloud PI, Burton PK, Perram FA, et al. Living With Hereditary Angioedema in Australia: Findings From a National Observational Study Using Short Message Service to Monitor the Burden of Disease. J Allergy Clin Immunol Pract. 2023 Aug;11(8):2457-2467.e1.

49. Magerl M, Martinez-Saguer I, Schauf L, Pohl S, Brendel K. The current situation of hereditary angioedema patients in Germany: results of an online survey. Front Med. 2023;10:1274397.

50. Buttgereit T, Aulenbacher F, Adatia A, Ayala CV, Al-Nesf MA, Altrichter S, et al. Unmet needs in hereditary angioedema: an international survey of physicians. Orphanet J Rare Dis. 2025 July 28;20(1):383.

Table I - Baseline demographic characteristics, clinical features and treatment of the Croatian HAE patients.

Variable		**Value**
Gender	Male, n (%)	17 (29.8)
	Female, n (%)	40 (70.2)
Age	median (IQR), (range)	47 (36-54), (19-78)
Place or residence	Rural, n (%)	13 (22.8)
	Urban, n (%)	44 (77.2)
Level of education	Primary education, n (%)	0
	Secondary education, n (%)	41 (71.9)
	Tertiary Education, n (%)	16 (28.1)
HAE type	HAE type 1, n (%)	37 (64.9)
	HAE type 2, n (%)	8 (14.0)
	HAE-nC1-INH (HAE-UNK), n (%)	12 (21.0)
Positive family history of HAE, n (%)		44 (77.2)
Number of children, median (IQR), (range)		1 (0-2), (0-8)
Age at the first attack in years, median (IQR), (range)		15 (10-23), (1-47)
Age at diagnosis in years, median (IQR), (range)		26 (19-39), (3-60)
Delay in diagnosis in years, median (IQR), (range)		13 (6-20), (-5-43)
Localization of the first symptoms of HAE	Extremities, n (%)	25 (43.9)
	Face, n (%)	16 (28.1)
	Abdomen, n (%)	14 (24.6)
	Larynx, n (%)	2 (3.5)
	Other, n (%)	7 (12.3)
	Extremities, n (%)	33 (57.9)

Most common localization of HAE attacks	Face, n (%)	19 (33.3)
	Abdomen, n (%)	30 (52.6)
	Tongue, n (%)	5 (8.8)
	Larynx, n (%)	12 (21.1)
Triggers of HAE attack	None, n (%)	9 (15.8)
	Stress, n (%)	37 (67.3)
	Menstrual cycle, n (%)	17 (29.8)
	Physical injury, n (%)	23 (40.4)
	Medication, n (%)	5 (8.8)
Number of HAE attacks during the past 3 months	Median (IQR), (range)	2 (1-6), (0-70)
Current ODT	Icatibant, n (%)	31 (54.4)
	intravenous C1-INH (pd + r), n (%)	21 (36.8)
Current LTP	None, n (%)	26 (45.6)
	Danazol, n (%)	19 (33.3)
	Danazol dose (mg), median (IQR), (range)	150 (100-275), (50-600)
	Tranexamic acid, n (%)	5 (8.8)
	intravenous C1-INH (pd + r), n (%)	12 (21.1)

Table II - Patient reported outcome measures (PROMs) of the Croatian HAE patients.

Variable		**Value**
AECT 4 week, median (IQR), (range)		8 (5-15), (1-16)
AECT 3 month, median (IQR), (range)		8 (5-12), (0-16)
AE-QoL	No effect on QoL, n (%)	19 (34.5)
	Small to moderate effect on QoL, n (%)	8 (14.5)
	Large effect on QoL, n (%)	28 (51.0)
FACIT-Fatigue	None or minimal fatigue: >40, n (%)	15 (30.6)
	Mild to moderate fatigue: >21 to ≤40, n (%)	23 (46.9)
	Severe fatigue: ≤21, n (%)	11 (22.4)
The Beck Anxiety Inventory (BAI)	Minimal anxiety (0-7), n (%)	17 (32.1)
	Mild anxiety (8-15), n (%)	16 (30.2)
	Moderate anxiety (16-25), n (%)	6 (11.3)
	Severe anxiety (26-63), n (%)	14 (26.4)
The Beck Depression Inventory (BDI)	Minimal depression (0-13), n (%)	38 (76.0)
	Mild depression (14-19), n (%)	7 (14.0)
	Moderate depression (20-28), n (%)	4 (8.0)
	Severe depression (29-63), n (%)	1 (2.0)
WPAI:GH	Worker / Employee, n (%)	19 (33.9)
	Absenteeism (%), median (IQR), (range)	0 (0-8), (0- 100)
	Presenteeism (%), median (IQR), (range)	20 (0-50), (0-100)

Table III - Patients' subjective personal perspectives and perceptions of HAE.

Variable		Value
Patient's subjective perception of treatment success (0 = highly dissatisfied; 10 = highly satisfied), median (IQR), (range)		9 (7-10), (1-10)
Patients' deepest concerns / fears	No concerns / fears, n (%)	9 (15.8)
	Neglecting social activities, n (%)	20 (35.1)
	Failure to meet business responsibilities, n (%)	24 (42.1)
	Fear of dying due to HAE attack, n (%)	19 (33.3)
	Fear of passing HAE to their children, n (%)	29 (50.9)
Patients' suggestions for improving medical care	Improved communication with leading physician, n (%)	8 (14.8)
	Improved education and training of healthcare professionals, n (%)	39 (72.2)
	Improved education of general population, n (%)	25 (46.3)

Table IV - Prevalence of HAE in different countries and regions.

Country / Region	Prevalence / per 100,000 people	Reference
Worldwide	1.22	(4)
USA	1.84 - 2.67	(26)
Mexico	1.8	(27)
Asia Pacific	0.02	(28)
South Australia	1.91	(29)
Finland	0.8 - 2.6	(6)
United Kingdom	1.69	(30)
Spain	1.09	(33)
Latvia	0.53	(31)
Belarus	0.68	(32)
Serbia	1.00	(35)
Slovenia	0.95	(34)
Hungary	1.98	(36)
Croatian (our study)	3.10	-

Figure 1 - Results of participants health status according to EQ-5D-5L.