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Impact of the Covid19 pandemic on health-related quality of life in patients with Fabry disease - implications for future care of patients with rare diseases

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ABSTRACT

Background: The worldwide Covid19 pandemic caused by the rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represented a unique challenge for patients and healthcare professionals. Patients with chronic rare diseases had to face novel burdens, like the inability to perform regular on-site visits or even difficulties in the supply of medication. Patients with Fabry disease (FD) are affected by a variety of organ manifestations leading to physical but also psychological burden and limitations, which are usually presented in low health-related quality of life (HR-QoL). We sought to examine the impact of the Covid19 pandemic on HR-QoL in patients with FD and their implications for the future care of patients with rare diseases.

Methods: This single-center study included patients seen shortly prior to and after the peak of the Covid19 pandemic in 2020 at our study site. All patients had a confirmed genetic diagnosis of FD. Subjects with presumed apathogenic to benigne genetic variants in the GLA gene were excluded. The Short Form (36) Health Survey (SF-36) was used to obtain patients‘self-reported outcome. Clinical data and SF-36 scores were collected and analysed for the time period prior to and after the peak of the pandemic.

Results: In total, 60 patients (mean age 47.9 ± 15 years, 53.3 % male) were included. The majority presented with a pathogenic gene variant (63.3 %) associated with classic phenotype. At baseline, 66.7 % were on enzyme replacement therapy (ERT), and 21.7 % on chaperone therapy. Predominant organ manifestations were cardiac (42/60, 70.0 %) and neurological (39/60, 65.0 %). After paired comparison prior and post peak of the pandemic in 2020, all eight items of the SF-36 score showed a numeric decline. Three items presented with a intergroup difference: social functioning (72.5 ± 29.3 vs. 64.8 ± 29.3, $p = 0.012$), energy/fatigue (56.8 ± 21.7 vs. 48.3 ± 23.9, $p < 0.001$), and role limitations due to physical health (64.2 ± 42.0 vs. 51.1 ± 45.5, $p = 0.007$). Subgroup analysis (regarding gender, age, and treatment) revealed that especially male and older ($\geq$50 years) patients with FD showed reductions in multiple categories of HR-QoL. The item "energy/fatigue" presented significant declines among all subgroups.

Conclusions: The worldwide Covid19 pandemic had a persistent negative affect on self-reported HR-QoL in patients with FD, including both mental and physical aspects. It remains unclear to what extend the disease itself and accompanying circumstances including local and governmental actions and restrictions contributed to these deteriorations. Our findings stress the importance for meticulous and constant interdisciplinary care including psychosocial aspects in patients with chronic progressive diseases as well as the need for a change in mindset concerning future medical care including further progress in digitalisation and a strengthening of the remote health care sector by authorities.

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1. Introduction

After the first detection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Germany (January 27, 2020), various personal restrictions by national federal law were enacted to confine further spread. These regulations affected everyday life not only of those directly concerned by the disease, but the whole population. Calls for general social distancing, quarantine measures, compulsory wearing of face masks and "lock downs"(March 22, 2020) followed quickly after the WHO declared Covid19 as a worldwide pandemic on March 12th, 2020 [1]. The never-before-seen personal limitations and the fear of a new contagious virus affected everyday life and caused deep concerns and worries on multiple levels among individuals. In addition to physical health, the Covid19 pandemic was also a threat for mental health [2], and affected health-related quality of life (HR-QoL) in a negative way [3]. Especially patients with chronic (rare) diseases had to face novel additional burdens, including not only a higher risk of a severe disease course, but at the same time appointments with medical health care professionals got cancelled, and even difficulties in the supply of medication arised [4].

Fabry disease (FD, OMIM 301500) is an X-linked lysosomal storage disorder causing multiple organ manifestations due to deficient enzyme α-galactosidase A (EC 3.2.1.22). As a result of reduced or missing enzyme activity, the substrate globotriaosylceramide (Gb3) is not sufficiently degraded and causes cell damage and further pathological cascades, like inflammation, fibrosis, endothelial dysfunction etc. [5] Many patients present with chronic progressive organ impairment and related complications such as renal and heart failure, cerebral stroke, small fiber neuropathy, and FD-associated pain [6]. A distinction is made between a severe "classical" phenotype, which typically presents the above-mentioned symptoms, and a "late-onset" phenotype, causing milder symptoms or being limited to certain organs [7]. Severely affected patients report their first symptoms in childhood - especially pain (crises), unusual sweating behaviour, gastrointestinal involvement. Major systemic complications such as severe kidney injury and cerebrovascular events may affect those patients already as young adults in their second or third decade and lead to end-stage disease earlier than in general population [8].

In addition to physical symptoms, patients with FD are often also confronted with neuropsychological issues. Depression is herein particularly prevalent and assumed to be still under-diagnosed [9]. It is currently discussed whether a deposition of Gb3 is directly responsible for neuropsychological symptoms or mainly a dysfunctional processing and coping with physical limitations and/or pain [10]. As the assessment and monitoring of depression depend on many different factors and life circumstances, it is currently not clear what specific affect can be attributed to FD, so that further research is definitely needed [11]. Nevertheless, it is clear that both physical and psychiatric manifestations have a strong impact on patients' quality of life.

Due to above mentioned considerations, patients with FD present with substantially lower scores for HR-QoL compared to the general population [12]. The additional impact of the Covid19 pandemic has not been investigated. While patients with chronic diseases were generally considered being "at higher risk"of adverse impact of the pandemic (both widespread diseases such as diabetes [13] and rare diseases such as Fabry or Pompe [14]), actual data in rare diseases is very limited. We therefore sought to examine the impact of the Covid19 pandemic on HR-QoL in patients with FD, exemplary for other chronic and/or rare diseases. Finally, we analysed the consequences that we should draw from those findings for the future care of patients with rare diseases.

2. Material and methods

2.1. Study population

In this single center study, patients participating in the prospective HEAL-FABRY study (prospective cohort study to evaluate predictors of heart failure and sudden cardiac death in patients with FD) were included presenting prior to and immediately after the peak of the Covid19 pandemic in 2020 at our hospital. All patients have a confirmed genetic diagnosis of FD. Subjects with presumed apathogenic to benign genetic variants in the GLA gene (D313Y/c.937G>T[15], A143T/c.427G>A, S126G/c.376A>G[16,17]) were excluded. During every visit, patients not only receive extensive clinical investigations but also filled in SF-36 questionnaires to report their current subjective health state.

For assessing the impact of the Covid19 pandemic, we divided the scores from the SF-36 in following groups: "one to two years prior to the pandemic" ($n = 15$ in 2018 and $n = 45$ in 2019) and "one to two years post pandemic" ($n = 39$ in 2021 and $n = 21$ in 2022).

The investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the Local Ethics Committee at the University of Würzburg. Written informed consent was obtained from all patients or their guardians prior to study start.

2.2. Outcome measurement

The Short Form (36) Health Survey (SF-36) was used to obtain patients'self-reported outcomes. This questionnaire consists of 36 questions regarding eight different categories: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. The scores are then calculated by converting the answers into relevant point scales. The best possible score is 100 and the worst possible score is 0.

2.3. Statistical analysis

Data analysis was performed using SPSS Statistics Version 29 (IBM, New York, USA). SF-36 scores are expressed as mean ± standard deviation (SD); categorical variables as count and percentage. To compare the scores before and after the pandemic paired Student's *t*-tests were carried out. A two-tailed probability value <0.05 was considered significant.

3. Results

3.1. Clinical characteristics at baseline

In total, 60 patients completed SF-36 questionnaires and were included in our analysis. The mean age was 48 ± 15 years with a balanced gender ratio (53.3 % male and 46.7 % female). At baseline, the majority received FD-specific therapy (66.7 % were on enzyme replacement therapy, 21.7 % on chaperone therapy) and presented with a pathogenic GLA gene variant (63.3 %) associated with a classic phenotype. Regarding organ involvement, especially cardiac (70.0 %) and neurological (65.0 %) manifestations were highly prevalent, follwed by renal manifestation (55.0 %). Detailed patient demographics are given in Table 1.

3.2. Effect of the Covid19 pandemic

Reviewing the number of patients presenting at our study center for regular follow-up care, we detected a decline with the lowest level reached in 2020, Fig. 1. A total of 14 patients (23.3 %) included in this study, reported a symptomatic Covid19 infection during this time period; none of them experienced a severe infection requiring mechanical ventilation.

By paired comparison, we found a numeric decline in all eight items of HR-QoL. Three items presented with a significant difference: role limitations due to physical health (64.2 ± 42.0 vs. 51.1 ± 45.5, $p = 0.007$), energy/fatigue (56.8 ± 21.7 vs. 48.3 ± 23.9, $p < 0.001$) and

Table 1
Baseline clinical characteristics. ERT: enzyme replacement therapy, N = total number.

Clinical demographics	$N = 60$
Age at baseline (mean years ± SD)	47.9 ± 15
Age at diagnosis (mean years ± SD)	39.1 ± 16
Sex (n /%)	
Male	32 /53.3
Female	28 /46.7
Current therapy (n /%)	
None	7 /11.7
Chaperone	13 /21.7
ERT	
Agalsidase beta	26 /43.3
Agalsidase alfa	14 /23.3
Years of treatment (mean years ± SD)	8.2 ± 6
Mutation (n /%)	
Classic	38 /63.3
Late-onset	22 /36.7
Organ manifestation (n /%)	
Cardiac	42 /70.0
Neurological	39 /65.0
Renal	33 /55.0
Otolaryngologic	25 /41.7
Ophthalmologic	19 /31.7
Gastrointestinal	15 /25.0
Covid 19 infection (n /%)	14 /23.3

social functioning (72.5 ± 29.3 vs. 64.8 ± 29.3, $p = 0.012$), Fig. 2.

3.3. Subgroup analysis

Subgroup analyses for gender, age and treatment are shown in Table 2. Especially male and older (≥50 years) patients with FD showed reductions in multiple categories across the entire spectrum of HR-QoL.

Strikingly, the item "energy/fatigue" presented significant declines in all subgroups independent of gender (male: 54.5 ±23.4 vs. 48.8 ±24.5, p=0.025; female: 59.3 ± 19.7 vs. 47.7 ± 23.5, p<0.001), age (<50 years: 59.6 ± 22.7 vs. 52.2 ±24.2, p=0.020; ≥50 years: 54.4 ±20.8 vs. 45.0 ±23.5, p<0.001) and treatment (ERT: 49.6 ±19.2 vs. 41.3 ±20.7, p=0.002; chaperone: 68.8 ±18.2 vs. 62.3 ± 22.8, p=0.037). Meanwhile, "pain" and "general health" remained without significant differences in all subgroup analyses.

4. Discussion

Analysing the SF-36 scores of patients with FD prior to and after the peak of the Covid19 pandemic in 2020 led to the main finding that the pandemic with its accompanying circumstances had a substantial additional negative impact on patients‘ self-perceived and self-reported HR-QoL. Although slow attenuation of the pandemic and all accompanying circumstances appeared since 2022 and also federal restrictions loosened gradually, there appear to be long-lasting consequences. We found a decline in three domaines of the HR-QoL representing broad facets of everyday life: social, mental and physical.

4.1. Impact of the Covid19 pandemic

Socially, patients suffered mainly from lockdowns and concomitant isolation [3]. Personal precaution and federal restrictions meant patients could not follow their routines and meet family and friends, interact with colleagues or directly communicate with other patients. With all patient meetings cancelled, the feeling of being left alone with a rare disease and its complications represents a specific problem in FD. For patients with rare chronic progressive diseases, regular options to exchange with other affected patients and their relatives and pursuing everyday activities like everyone else might be a particularly important part of emotional stability. The importance of stable social relationships was also presented by Pieh et al. showing that a good relationship quality is even a protective factor for mental health during Covid19 pandemic [18]. Furthermore, contacts with treating physicians and study centers were reduced to a minimum, worrying one could get infected in hospital by other patients or health care employees. This is also reflected in the number of patients presenting at your study site. We assume that regular follow up visits and direct communication between health care professionals and patients contribute to stabilized emotional well-being as well.

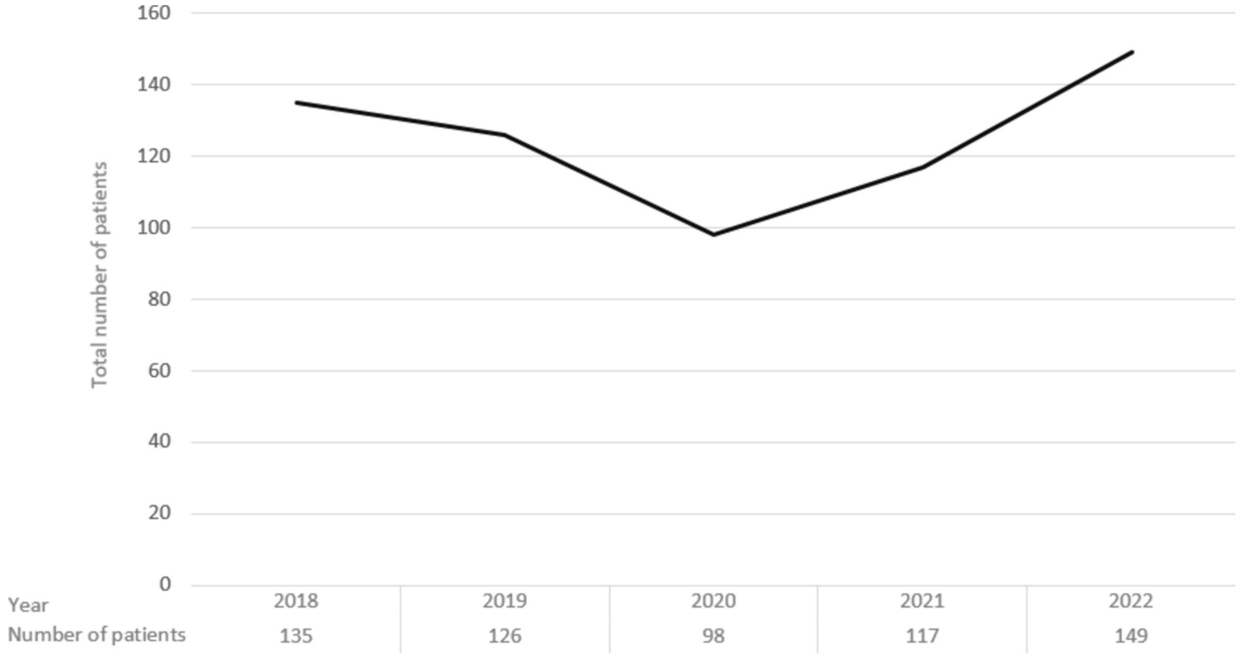

Fig. 1. Number of patients presenting at our study site before and after the peak of the pandemic.

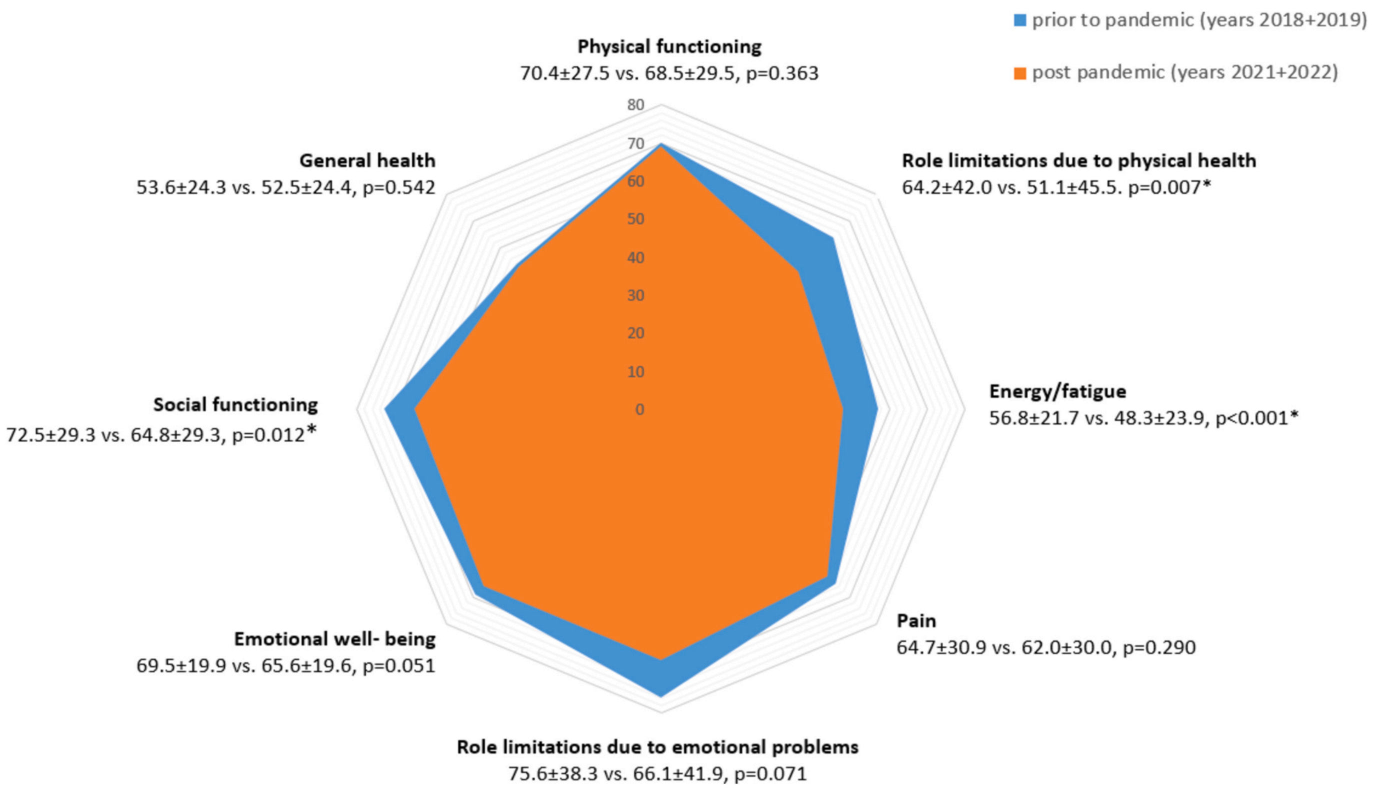

Fig. 2. Changes in the eight items of the SF-36 score prior to and post peak of the Covid19 pandemic in 2020, * significant difference.

Another consequence of voluntary safety measures and federal restrictions including repeated lockdowns was a substantial reduction in physical activity. As patients with FD often suffer from a decreased physical performance due to FD-associated pain, cardiac involvement, or cerebral strokes [6]. Regular moderate physical exercise is considered of great importance to counteract a further deterioration of their physical constitution. During Covid19 pandemic, all sport clubs, fitness centers and even physiotherapy practices were closed. This might have contributed to the finding that also in our cohort patients reported worse role limitations due to physical health after the pandemic. Physical activity has a proven positive effect on mental health – especially in periods of crisis [19]. Therefore, it is reasonable to encourage patients with FD to resume physical activity on a regular basis as far as possible.

Regarding the domain “energy/fatigue“, it has to be acknowledged that both aforementioned items potentially show interaction. The item “energy“ indeed represents a specific combination of physical and mental aspects. Potential reasons for the lower scores achieved here are diverse: additionally to the aforementioned governmental restrictions in many aspects of personal development opportunities, hard-to-measure specific features like reduced income due to short-time work, fear of worsening of organ damages due to cancelled on-site visits, FD-related complications, issues concerning the biweekly administration of ERT, sorrows for a severe Covid19 infection and even death may be possible factors influencing the mental well-being of FD patients. In a prior prospective study focusing on patient-reported outcomes, Müntze et al. detected a specific decrease of emotional SF-36 scores in patients on migalastat therapy during the pandemic [20]. Interestingly, this study also showed that various items of the SF-36 not necessarily decline over time in FD, but there can also be significant improvements as a potential effect of therapy. Additionally, the item “emotional well-being“ has not shown any significant reduction, although it focuses mainly on emotional aspects. An important factor for emotional stability is the capacity for resilience, namely the mental ability to cope well with disasters and adapt to current circumstances. Manchia et al. demonstrated that during the Covid19 pandemic subgroups of the general population showed a prolonged capability of resilience resulting in possibly unaffected well-being [21]. Therefore, we assume the same positive effects of resilience in our study cohort.

4.2. Lessons learnt from the pandemic and their implications for the future care of patients with rare diseases

Looking back at the course of the pandemic and consecutive actions taken by individuals and authorities, analyses should focus on what lessons can be learned for the future. In a report released by the European Centre for Disease Prevention and Control (ecdc) several areas have been identified, which mainly cover health policy aspects [22]. The most important lesson in this report with regard to patients is the need for more investment in the area of mental health. This includes both the budget and the personal, who must be well trained and resilient, especially in times of crisis. In addition to a subliminal offer of psychological counselling (e.g. via anonymous telephone or online counselling), each contact between physician and patient should include questioning and assessing the current mental well-being.

Furthermore, one aspect of future health policies is integrating and strengthening structures of psychological health. The establishment of public health units is a promising example. In their study COMPASS, 2018–2022 Benny et al. could demonstrate that mental health programms in cooperation with public health units diminished anxiety in students during the Covid19 pandemic [23]. Such approaches are considered also useful for other “persons at risk“ (elderly, home residents, pregnant women, single parents, patients with life-threatening diseases etc) by e.g. supporting self-help groups or patient communities, which play an important role in networking and communication between patients.

Another important lesson which should be drawn from the pandemic is the importance of sufficient flexibility in the care of chronically ill patients, often opposed by bureaucracy. Naturally, legal hurdles often counter straightforward patient treatment by means of high costs of treatments, fear of wrong application, insufficient documentation and

Table 2
Subgroup analysis regarding changes in HR-QoL during Covid19 pandemic. ERT: enzyme replacement therapy, N = total number.

Gender	Prior to pandemic	Post pandemic	*p*-value
Male (*N* = 32)			
physical functioning	73.3 ± 23.7	70.9 ± 26.9	0.524
role limitations due to physical health	67.2 ± 38.9	52.8 ± 46.3	0.025
role limitations due to emotional problems	80.2 ± 33.7	70.8 ± 39.5	0.203
energy/fatigue	54.5 ± 23.4	48.8 ± 24.5	0.025
emotional well being	70.6 ± 21.1	67.0 ± 20.9	0.224
social functioning	74.2 ± 28.6	66.8 ± 30.3	0.025
pain	64.6 ± 28.7	62.2 ± 28.8	0.456
general health	53.8 ± 25.9	51.4 ± 25.5	0.401
Female (*N* = 28)			
physical functioning	67.1 ± 31.3	65.7 ± 32.5	0.429
role limitations due to physical health	60.7 ± 45.9	49.1 ± 45.4	0.131
role limitations due to emotional problems	70.2 ± 42.9	60.7 ± 44.5	0.211
energy/fatigue	59.3 ± 19.7	47.7 ± 23.5	< 0.001
emotional well being	68.1 ± 18.7	64.0 ± 18.3	0.112
social functioning	70.6 ± 30.4	62.5 ± 28.5	0.142
pain	64.7 ± 33.8	61.9 ± 31.9	0.464
general health	53.4 ± 22.8	53.8 ± 23.4	0.868

Age	Prior to pandemic	Post pandemic	p-value
<50 years (*N* = 27)			
physical functioning	77.9 ± 27.3	82.2 ± 22.7	0.053
role limitations due to physical health	69.4 ± 41.2	68.3 ± 43.8	0.833
role limitations due to emotional problems	70.4 ± 40.7	69.1 ± 41.3	0.839
energy/fatigue	59.6 ± 22.7	52.2 ± 24.2	0.020
emotional well being	69.8 ± 22.4	69.0 ± 21.7	0.779
social functioning	75.3 ± 31.0	74.1 ± 27.1	0.707
pain	72.7 ± 32.9	66.9 ± 32.2	0.111
general health	59.4 ± 27.7	59.6 ± 24.5	0.947
≥50 years (*N* = 33)			
physical functioning	64.2 ± 26.4	57.3 ± 29.9	0.035
role limitations due to physical health	59.8 ± 42.8	36.9 ± 42.5	0.003
role limitations due to emotional problems	79.8 ± 36.3	63.6 ± 42.8	0.047
energy/fatigue	54.4 ± 20.8	45.0 ± 23.5	<0.001
emotional well being	69.2 ± 17.9	62.8 ± 17.6	0.026
social functioning	70.3 ± 28.0	57.2 ± 29.2	0.008
pain	58.1 ± 27.9	58.0 ± 28.0	0.983
general health	48.8 ± 20.3	46.7 ± 23.0	0.364

Treatment	Prior to pandemic	Post pandemic	p-value
ERT (*N* = 40)			
physical functioning	62.5 ± 28.3	61.6 ± 30.2	0.760
role limitations due to physical health	52.5 ± 43.0	54.0 ± 45.4	0.195
role limitations due to emotional problems	68.3 ± 41.3	58.3 ± 44.5	0.129
energy/fatigue	49.6 ± 19.2	41.3 ± 20.7	0.002
emotional well being	65.8 ± 20.5	61.3 ± 19.6	0.081
social functioning	65.8 ± 30.5	57.5 ± 29.7	0.037
pain	57.7 ± 32.1	56.4 ± 31.0	0.675
general health	47.6 ± 24.1	44.6 ± 22.9	0.201
Chaperone (*N* = 13)			
physical functioning	83.5 ± 16.9	80.4 ± 22.7	0.446
role limitations due to physical health	80.8 ± 34.1	56.9 ± 45.6	0.024
role limitations due to emotional problems	89.7 ± 28.5	84.6 ± 25.9	0.656
energy/fatigue	68.8 ± 18.2	62.3 ± 22.8	0.037
emotional well being	74.8 ± 15.9	75.4 ± 14.9	0.856
social functioning	86.5 ± 19.4	82.7 ± 17.3	0.392
pain	72.9 ± 23.0	72.1 ± 24.4	0.796
general health	64.6 ± 20.2	68.5 ± 18.5	0.268

others. An impressive example is home infusions for patients with lysosomal disorders requiring enzyme replacement therapy. During the Covid19 pandemic, implementing this form of care as opposed to the patient vice versa having to visit a HCP – private practice or clinic - for bimonthly infusions proved to be even easier in Germany due to the lack of alternatives and special licenses approved by governmental bodies. Home infusion ERT has been shown well accepted among patients and their relatives and associated with many positive emotions and reduction of stressors; for example, the fear of a serious infection due to possible contacts in hospitals could be diminished [24].

A further aspect that potentially requires more flexibility, but also a new mindset, is digitalisation in medicine. During the pandemic, new ways of contacting patients had to be established very quickly. Herein, remote visits in particular have proven to be a useful alternative to face-to-face contacts, especially for patients with chronic rare diseases, who have to travel far to the next reference centre or are no longer physically able to do so. Further, as described by Ali et al. telecounseling in patients with FD and mental health issues may as well be as beneficial as in person counselling [25]. This also highlights that in times when personal contact is not possible, digital alternatives for assessing and monitoring patients‘ mental health statuses should thoroughly be considered [26]. Nevertheless, new guidelines are needed focusing on ethical, social and political aspects of telehealth as discussion continues [27].

Our findings stand in line with previous studies emphasizing the usefulness of currently monitoring the psychological health status more closely since distress - as induced during the pandemic - can cause permanent mental issues [28]. Even cases of Covid19-related post-traumatic stress disorder (PTSD) have been described [29]. As patients with FD and similar chronic diseases have to deal with the burden of lifelong usually multi-organ health issues, the need for interdisciplinary care is now higher than ever. We therefore recommend to specifically aim at addressing these issues in patients with (rare) chronic diseases by offering professional support for all facets of life. Furthermore, it is important to draw increasing public attention and interest to the field of mental health and the supportive impact of HCP in this regard, especially among vulnerable patient groups with a higher risk of mental health issues.

5. Limitations

A relevant limitation of our analysis is the missing structured assessment of symptomatic Covid19 infections in our FD patient cohort, mostly due to spatial distance of many patients to the center, but also the specific travel and quarantine stipulations during the pandemic. Deteriorations experienced in HR-QoL might be influenced by severe infections and their physical longterm complications, even if not causing the need for in-hospital stay. Of note, especially the item “energy/fatigue” has been linked with Post-Covid19 Syndrome [30]. As patients with chronic diseases generally face specific challenges in times of crisis, it is not possible to determine whether patients with FD are specifically more impacted by this syndrome, as overlap occurs.

Furthermore, we investigated the impact of the pandemic for a relatively short period of time (1–2 years post its peak). Whether the pandemic caused long-lasting changes in HR-QoL in patients with FD needs to be further monitored in the coming years.

6. Conclusion

Our data imply a negative impact of the worldwide Covid19 pandemic on HR-QoL in patients with FD. Whereas the tendency for decline could be detected in all eight items of the SF36-score, social functioning, energy/fatigue, and role limitations due to physical health remained significant. As patients with FD face specific issues and hurdles inherent in the burden of chronic disease usually requiring lifelong therapy, regular meticulous interdisciplinary care including physiological and social-emotional aspects might be of particular importance. The pandemic has also shown us that a change in mindset concerning future medical care is needed, allowing for improved flexibility in the health care system by means of further progress in digitalisation and strengthening the sector of remote patient care, still under-developed in many countries including Germany.

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Ethical approval and information

Patients represent a subgroup of the prospective HEAL-FABRY cohort study (AZ#157/17-me).

Consent statement

The author has obtained written informed consent from all patients.

CRediT authorship contribution statement

Victoria Sokalski: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Kolja Lau:** Writing – review & editing, Data curation. **Tereza Cairns:** Writing – review & editing, Data curation. **Claudia Sommer:** Writing – review & editing. **Nurcan Üçeyler:** Writing – review & editing. **Peter Nordbeck:** Writing – review & editing, Conceptualization.

Declaration of competing interest

CS received consulting fees from Kedrion, Nevro, Agiax, Takeda, Grifols, Bayer, Roche, Merz, Omega, LFB; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Kedrion, TEVA, CSL Behring, Takeda, Pfizer, Grifols, Amicus, Alnylam. She is IASP past president, member of the Board of the Peripheral Nerve Society and deputy editor of the European Journal of Neurology. VS received speaker honoraria from Takeda Pharmaceuticals and support for attending meetings from Amicus Therapeutics and Sanofi Genzyme. TC received speaker honoraria from Amicus Therapeutics and support for attending meetings from Sanofi Genzyme. PN received consulting and speaker fees from Abbott, Abiomed, Amicus, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Cardiac Dimensions, Chiesi, Idorsia, Novartis, Sangamo, Sanofi-Genzyme, Takeda.

The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

[1] M. Yüce, E. Filiztekin, K.G. Özkaya, COVID-19 diagnosis -a review of current methods, Biosens. Bioelectron. 172 (2021) 112752.
[2] S. Agha, Mental well-being and association of the four factors coping structure model: a perspective of people living in lockdown during COVID-19, Ethics Med Public Health. 16 (2021) 100605.
[3] K. Sayin Kasar, E. Karaman, Life in lockdown: social isolation, loneliness and quality of life in the elderly during the COVID-19 pandemic: a scoping review, Geriatr. Nurs. 42 (5) (2021) 1222–1229.
[4] M. Gorordo, R. Rojas-Cortés, J. Carino, J. Vahos Zambrano, J.L. Castro, Health alerts for substandard, falsified, and unregistered medical products at the onset of the COVID-19 pandemic in the AmericasAlertas de saúde Para produtos médicos abaixo do padrão, falsificados e não registrados no início da pandemia de COVID-19 nas Américas, Rev. Panam. Salud Publica 48 (2024) e7.
[5] R. El-Abassi, D. Singhal, J.D. England, Fabry's disease, J. Neurol. Sci. 344 (1–2) (2014) 5–19.
[6] C. Wanner, M. Arad, R. Baron, et al., European expert consensus statement on therapeutic goals in Fabry disease, Mol. Genet. Metab. 124 (3) (2018) 189–203.
[7] M. Arends, C. Wanner, D. Hughes, et al., Characterization of classical and nonclassical Fabry disease: a multicenter study, J. Am. Soc. Nephrol. 28 (5) (2017) 1631–1641.
[8] A. Ortiz, D.P. Germain, R.J. Desnick, et al., Fabry disease revisited: management and treatment recommendations for adult patients, Mol. Genet. Metab. 123 (4) (2018) 416–427.
[9] A.L. Cole, P.J. Lee, D.A. Hughes, P.B. Deegan, S. Waldek, R.H. Lachmann, Depression in adults with Fabry disease: a common and under-diagnosed problem, J. Inherit. Metab. Dis. 30 (6) (2007) 943–951.
[10] S. Körver, G.J. Geurtsen, C.E.M. Hollak, et al., Depressive symptoms in Fabry disease: the importance of coping, subjective health perception and pain, Orphanet J. Rare Dis. 15 (1) (2020) 28.
[11] F.E. Bolsover, E. Murphy, L. Cipolotti, D.J. Werring, R.H. Lachmann, Cognitive dysfunction and depression in Fabry disease: a systematic review, J. Inherit. Metab. Dis. 37 (2) (2014) 177–187.
[12] M. Arends, C.E. Hollak, M. Biegstraaten, Quality of life in patients with Fabry disease: a systematic review of the literature, Orphanet J. Rare Dis. 10 (2015) 77.
[13] M.S. Nagpal, N. Jalali, D. Sherifali, P.P. Morita, J.A. Cafazzo, Managing type 2 diabetes during the COVID-19 pandemic: scoping review and qualitative study using systematic literature review and Reddit, Interact J Med Res. 13 (2024) e49073.
[14] M.T.M. Theunissen, R.M. van den Elsen, T.L. House, et al., The impact of COVID-19 infection, the pandemic and its associated control measures on patients with Pompe disease, J. Neurol. 271 (1) (2024) 32–45.
[15] D. Oder, N. Üçeyler, D. Liu, et al., Organ manifestations and long-term outcome of Fabry disease in patients with the GLA haplotype D313Y, BMJ Open 6 (4) (2016) e010422.
[16] K. Lau, N. Üçeyler, T. Cairns, et al., Gene variants of unknown significance in Fabry disease: clinical characteristics of c.376A>G (p.Ser126Gly), Mol. Genet. Genomic Med. 10 (5) (2022) e1912.
[17] M. Breyer, et al., In vitro characterization of cells derived from a patient with the GLA variant c.376A>G (p.S126G) highlights a non-pathogenic role in Fabry disease, Molecular Genetics and Metabolism Reports 38 (2024).
[18] C. Pieh, T OR, Budimir S, Probst T., Relationship quality and mental health during COVID-19 lockdown, PLoS One 15 (9) (2020) e0238906.
[19] C. Pieh, S. Budimir, T. Probst, The effect of age, gender, income, work, and physical activity on mental health during coronavirus disease (COVID-19) lockdown in Austria, J. Psychosom. Res. 136 (2020) 110186.
[20] J. Müntze, K. Lau, M. Cybulla, et al., Patient reported quality of life and medication adherence in Fabry disease patients treated with migalastat: a prospective, multicenter study, Mol. Genet. Metab. 138 (2) (2023) 106981.
[21] M. Manchia, A.W. Gathier, H. Yapici-Eser, et al., The impact of the prolonged COVID-19 pandemic on stress resilience and mental health: a critical review across waves, Eur. Neuropsychopharmacol. 55 (2022) 22–83.
[22] Theocharopoulos. ABDCOCGSaG, European Centre for Disease Prevention and Control. Lessons from the COVID-19 Pandemic, ECDC, Stockholm, 2023, p. 2023.
[23] C. Benny, B.T. Smith, K.A. Patte, S.T. Leatherdale, R. Pabayo, Public health unit engagement in school mental health programs and adolescent mental health during the COVID-19 pandemic: COMPASS, 2018-2022, J. Public Health (Oxf.) (2024).
[24] A. Fiumara, G. Lanzafame, A. Sapuppo, A. Arena, L. Cirnigliaro, R. Barone, Positive impact of home ERT for Mucopolysaccharidoses and Pompe disease: the lesson learnt from the COVID-19 pandemic, Healthcare (Basel) 11 (8) (2023).
[25] N. Ali, S. Gillespie, D. Laney, Treatment of depression in adults with Fabry disease, JIMD Rep. 38 (2018) 13–21.
[26] E.G. Lattie, E.C. Adkins, N. Winquist, C. Stiles-Shields, Q.E. Wafford, A.K. Graham, Digital mental health interventions for depression, anxiety, and enhancement of psychological well-being among college students: systematic review, J. Med. Internet Res. 21 (7) (2019) e12869.

[27] B. Kaplan, Revisiting Health Information Technology Ethical, Legal, and Social Issues and Evaluation: Telehealth/Telemedicine and COVID-19, Int. J. Med. Inform. 143 (2020) 104239.

[28] F.S. Lee, C.S. Ang, Positive vibes are not always easy: examining the association between Covid-19 stress and mental well-being, Psychol. Rep. 332941221149179 (2023).

[29] H.Z. MacDonald, Risk and resilience factors associated with college students' psychological distress and PTSD symptoms during the COVID-19 pandemic, J. Am. Coll. Heal. 1-15 (2023).

[30] F. Ceban, S. Ling, L.M.W. Lui, et al., Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis, Brain Behav. Immun. 101 (2022) 93–135.