

# Quality of Life in the Management of Home Parenteral Nutrition

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## Keywords

Quality of life · Parenteral nutrition · Home parenteral nutrition · Patient-reported outcomes · SF-36v2

## Abstract

**Introduction:** Home parenteral nutrition (HPN) is a rare but challenging therapy for patients with mostly severe underlying diseases. We aimed to investigate patient-reported health-related quality of life (QOL) of patients receiving HPN and its development over time in particular. **Methods:** We assessed QOL of HPN patients in a prospective multicenter observational study (SWISSHPN II study). We designed a questionnaire to record symptoms and negative impacts of HPN and completed the validated Optum® SF-36v2® Health Survey with the patients. **Results:** Seventy patients (50% women) on HPN were included. HPN commonly affected feelings of dependency ( $n = 49$ , 70%), traveling/leaving home ( $n = 37$ , 53%), attending cultural and social events ( $n = 25$ , 36%), and sleep ( $n = 22$ , 31%). Most frequently reported symptoms were diarrhea ( $n = 30$ , 43%), polyuria ( $n = 28$ , 40%), nausea/emesis ( $n = 27$ , 39%), dysgeusia ( $n = 23$ , 33%), and cramps ( $n = 20$ , 29%). At baseline, mean (standard deviation) SF-36v2® physical and mental health component

summary scores (PCS and MCS) were 45 (20) and 57 (19), respectively, and there was a trend toward improvement in PCS over the study period, while MCS remained stable. Satisfaction with health care professionals involved in HPN care was high. **Conclusion:** QOL is a crucial and decisive aspect of HPN patient care. Symptoms related to the underlying disease and PN are frequent. Impaired social life and an ambivalent attitude toward the life-saving therapy are major concerns for these patients and should be addressed in their care.

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## Introduction

For patients unable to meet their nutritional needs via the oral or enteral feeding route, nutrients may be infused intravenously as parenteral nutrition (PN). If long-term PN is required and patients are metabolically stable, it

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may be administered outside the hospital as home parenteral nutrition (HPN) [1].

Despite advances in PN handling and care, HPN is time-consuming and can impair everyday life by restricting social interactions, disturbing sleep, and hindering patients from leaving their home [2]. In addition, infusing a complex meta-stable emulsion through a central venous catheter bears the risk of serious and potentially life-threatening complications. This may include bloodstream infections, catheter occlusions, thromboses, and metabolic dysfunctions. Part of the responsibility to prevent such complications lies with the person administering PN, as they are required to strictly follow aseptic techniques when preparing and infusing PN [3]. Therefore, continuous training and measures to avoid such medication errors are mandatory and have to be implemented, ideally through a nutrition support team [4]. In addition to these concerns, patients on HPN often suffer seriously because of their underlying disease [2].

This double burden of life-saving but challenging HPN and severe underlying diseases affects patients' quality of life (QOL) [5]. As QOL is a major outcome indicator of quality of HPN care [6, 7], the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends that QOL should be part of nutrition therapy monitoring [8].

QOL is assessed with patient-reported outcome tools, which may be either HPN specific [9–12] or more general. The latter has the advantage that results are comparable to other clinical conditions and treatments. A widely used generic tool is the Optum<sup>®</sup> SF-36v2<sup>®</sup> Health Survey, which assesses patient-reported QOL related to physical and mental health based on eleven questions.

On behalf of ESPEN, an international study investigated the impact of HPN on QOL in fourteen European, North American, and Australian countries [13]. However, Switzerland was not among these countries, and data on QOL of Swiss HPN patients are limited [14, 15]. Therefore, this study aimed at investigating patient-reported health-related QOL in patients receiving HPN and its changes over time.

## Materials and Methods

### *Study Design and Data Collection*

We collected the data as part of the multicentric, prospective, longitudinal SWISSHPN II study [16], which assessed complications and survival of adult patients on HPN over 24 months, from January 2017 to January 2019. The methodology and design of the SWISSHPN II study have been described elsewhere [16]. In short, we interviewed patients at baseline and in 6-month intervals

thereafter up to January 2019. This secondary analysis focuses on symptoms and negative impacts of HPN and the Optum<sup>®</sup> SF-36v2<sup>®</sup> Health Survey questionnaire.

### *Sample*

Seventy adult patients (50% women) on HPN were included. Overall, 47% of patients ( $n = 33$ ) were weaned off HPN during the study, in which case no more follow-ups were performed. The most common underlying conditions were cancer (23%), bariatric surgery (11%), and Crohn's disease (10%). The most common indication was short bowel syndrome (30%) [16].

### *Questionnaires*

We designed a questionnaire which covered satisfaction with the personnel involved in HPN care, negative impacts of HPN, and symptoms (questionnaires are available as supplementary material; for all online suppl. material, see <https://doi.org/10.1159/000530082>). We asked patients which areas of life were impacted by PN: dependency, attendance of cultural and social events, traveling/leaving home (and whether patients go on vacation with PN), marriage/partnership/family life, sleep disorders (and whether patients take sleep medication), and other. In addition, patients rated the occurrence (once per week, 2–3 times per week, daily) of the following symptoms: fever, constipation, dysgeusia, edema, diarrhea, polyuria, reflux, nausea/emesis, cramps, and other.

Furthermore, patients completed the German or French version of the non-disease-specific Optum<sup>®</sup> SF-36v2<sup>®</sup> Health Survey questionnaires at baseline and at follow-up every 6 months. QOL is assessed with 36 items divided into eight domains, including physical functioning, role-functioning physical, body pain, general health, vitality, social functioning, role-functioning emotional, and mental health. Each domain is scored from 0% (worst QOL) to 100% (best QOL). A summary score of physical health (physical component summary score [PCS]) and mental health (mental component summary score [MCS]) can be calculated from the eight described domains.

### *Statistics*

Categorical variables are presented as number ( $n$ ) and percentage (%) and continuous variables as mean and standard deviation (SD). After assessment of the distribution of baseline MCS and PCS using quantile-quantile plots, we analyzed differences between underlying disease (benign vs. malign) and stoma with unpaired two-sided  $t$  tests. We assessed if age, PN duration, underlying disease (benign vs. malign), and stoma predicted MCS or PCS with univariate multiple linear regressions. The model for MCS was adjusted for antidepressant use. We evaluated the course of MCS and PCS throughout the study period with repeated measures linear mixed-effects models. Missing values were excluded, and no data were imputed. A  $p$  value  $< 0.05$  was considered statistically significant. We conducted statistical analysis using R version 4.2.2 [17] with packages tidyverse version 1.3.2 [18], lme4 version 1.1.31 [19], lmerTest version 3.1.3 [20].

### *Ethical Statement*

The SWISSHPN II study was conducted in accordance with the ethical guidelines of the 1957 Declaration of Helsinki and the current national laws. The Ethics Committee of the Canton of Bern approved the SWISSHPN II study (reference number 2016-00669).

**Table 1.** Baseline characteristics

| Baseline characteristic       | Overall<br>(N = 70) |
|-------------------------------|---------------------|
| Female, n (%)                 | 35 (50)             |
| Age, years, mean (SD)         | 57.8 (14.5)         |
| PN duration, years, mean (SD) | 2.59 (5.77)         |
| PN, parenteral nutrition.     |                     |

## Results

We included 70 patients on HPN. Table 1 briefly presents baseline characteristics of study participants; further socioeconomic parameters have been reported in the primary publication of the SWISSHPN II study [16]. Figure 1 shows patient-reported symptoms. The most frequently reported symptoms were diarrhea ( $n = 30$ , 43%), polyuria ( $n = 28$ , 40%), nausea/emesis ( $n = 27$ , 39%), dysgeusia ( $n = 23$ , 33%), and cramps ( $n = 20$ , 29%). As shown in Figure 2, common negative impacts of HPN were feelings of dependency ( $n = 49$ , 70%) and difficulties traveling or leaving home ( $n = 37$ , 53%) or attending cultural and social events ( $n = 25$ , 36%). Going on vacation with PN was possible for 23 patients (33%). HPN negatively affected marriage, partnership, or family life of 17 patients (24%). Sleep disturbances occurred in 22 patients (31%), of whom 8 (36%) took sedative hypnotics on a regular basis (4 [50%] benzodiazepines and 4 [50%] zolpidem). In total, 30 patients (43%) took analgesics and 11 (16%) antidepressants. Figure 3 shows the patients' satisfaction with the HPN care team.

Figure 4 shows baseline scores of the SF-36v2<sup>®</sup> health domains. The domains most impacted were role-physical, bodily pain, vitality, and general health. Baseline MCS and PCS did not differ between patients with benign ( $n = 50$ , 74%) and malignant ( $n = 18$ , 26%) underlying disease (mean [SD] MCS: 56 [19] vs. 54 [17],  $p = 0.68$ ; mean [SD] PCS: 42 [19] vs. 46 [18],  $p = 0.44$ ). There were no significant differences in MCS and PCS between patients with ( $n = 24$ , 36%) and without ( $n = 45$ , 64%) stoma (mean [SD] MCS: 58 [20] vs. 56 [19],  $p = 0.59$ ; mean [SD] PCS: 49 [18] vs. 42 [20],  $p = 0.13$ ).

Figure 5 shows the changes in MCS and PCS during the follow-up period. The repeated measures linear mixed-effects models for MCS and PCS were not significant ( $p = 0.38$  and  $p = 0.84$ , respectively). The overall univariate multiple linear regression was not statistically significant for MCS (adjusted  $R^2 = 0.06$ ,  $F[5, 62] = 1.85$ ,  $p = 0.12$ ) but statistically significant for PCS (adjusted

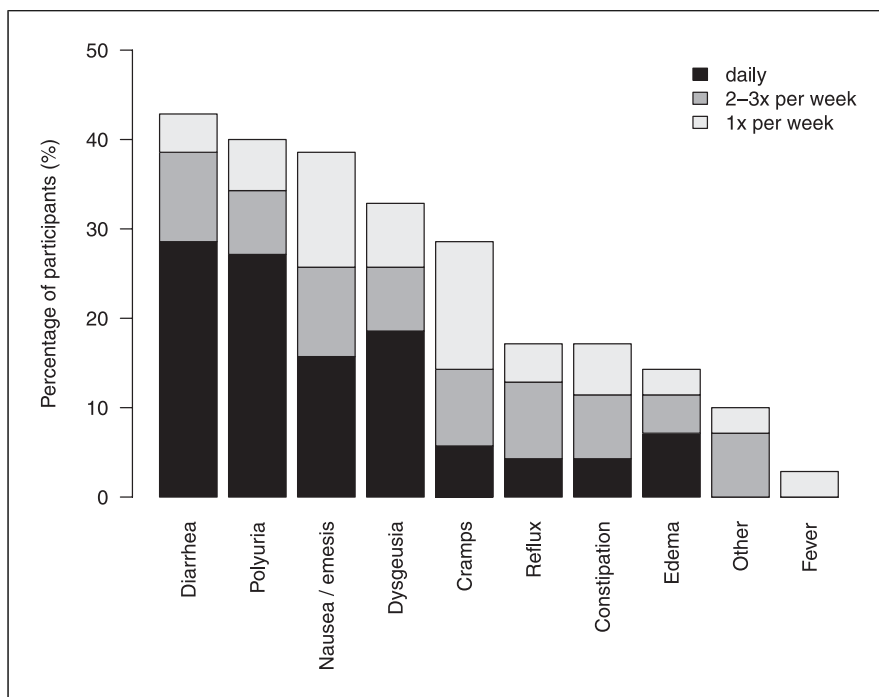
$R^2 = 0.10$ ,  $F[4, 63] = 2.95$ ,  $p = 0.03$ ). Age significantly predicted PCS (estimate [95% CI] = 0.36 [0.05, 0.68],  $p = 0.03$ ).

## Discussion

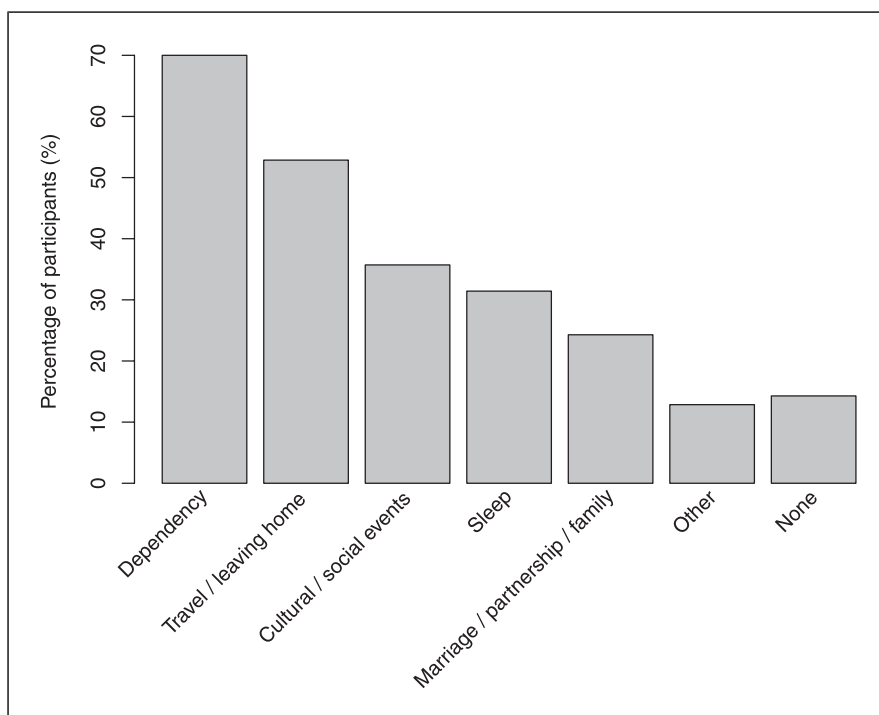
Patients on HPN reported decreased physical and mental health compared to the general population [21]. HPN led to dependency and restricted traveling/leaving home. Common symptoms related to HPN were diarrhea, polyuria, nausea/emesis, and dysgeusia.

QOL varied greatly between HPN patients, as conveyed by the wide range of SF-36v2<sup>®</sup> scores. HPN patients are a heterogeneous group, including patients of different age groups and social environments, with a wide range of prognostic forecasts and varying disease burden. Therefore, we could not identify specific factors that relevantly predicted MCS or PCS. A recent Cochrane review concluded that there is very limited certainty of evidence for QOL in patients on PN with inoperable malignant bowel obstruction [22]. However, Howard and Ashley reported anecdotal evidence that the response to HPN is likely to be positive if intestinal failure develops slowly, whereas it is often negative if intestinal failure develops acutely [23]. Finally, by disregarding the underlying disease, the ESPEN guideline on HPN states a benefit of HPN on health-related QOL [1].

Overall, the MCS remained stable over time, which is satisfactory considering the chronic or malignant underlying diseases, and there was a trend toward improvement in the PCS over the study period. Blüthner et al. [24] conducted a study in patients with intestinal failure receiving PN for less than 3 months at enrollment. In general, the SF-36 scores of these German patients were in a similar range as in our study, except for role-emotional and PCS, which were higher in our study. They observed a significant improvement in PCS within the first 6 months of PN, whereas only 22 (31%) of the patients in our study were on PN for less than 3 months at baseline. As in our study, they observed merely insignificant trends for PCS after 6 months and MCS. While we found no significant effect of PN duration on QOL, Winkler et al. [25] found in a qualitative, semi-structured interview that patients who had PN for less than 2 years expected HPN to be temporary and described their QOL as good. In contrast, patients receiving HPN for 2–10 years reported impaired QOL, while patients receiving HPN for more than 10 years reported reduced QOL due to the underlying disease.



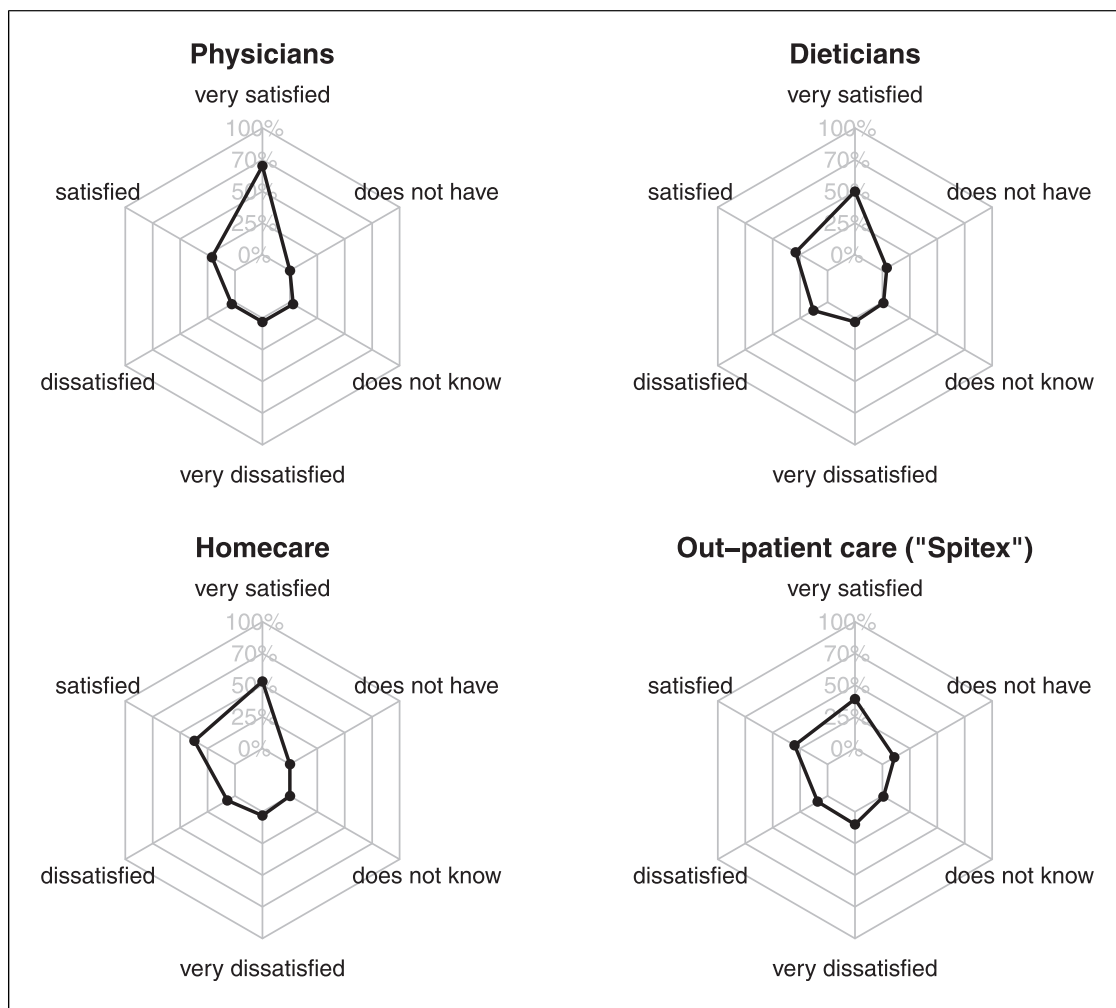
**Fig. 1.** Symptoms of patients receiving HPN.



**Fig. 2.** Areas of life affected by HPN.

The use of analgesics and antidepressants in our study was similar to the rates reported in a previous large multicentric study [26]. A recent study suggests that the

infusion volume affects the use of antidepressants in patients with chronic intestinal failure. The authors hypothesize that this could be related to the overall disease



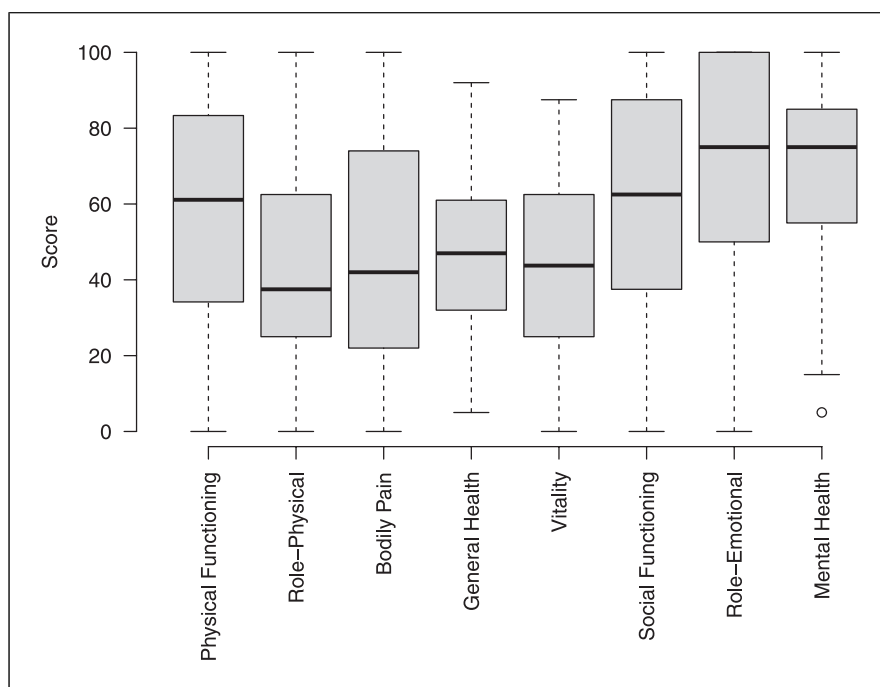
**Fig. 3.** Satisfaction of patients with personnel involved in HPN care.

burden and suggest to closely monitor patients with a high volume of intravenous supplementation, which is typically accompanied by a longer period of cycling PN [27].

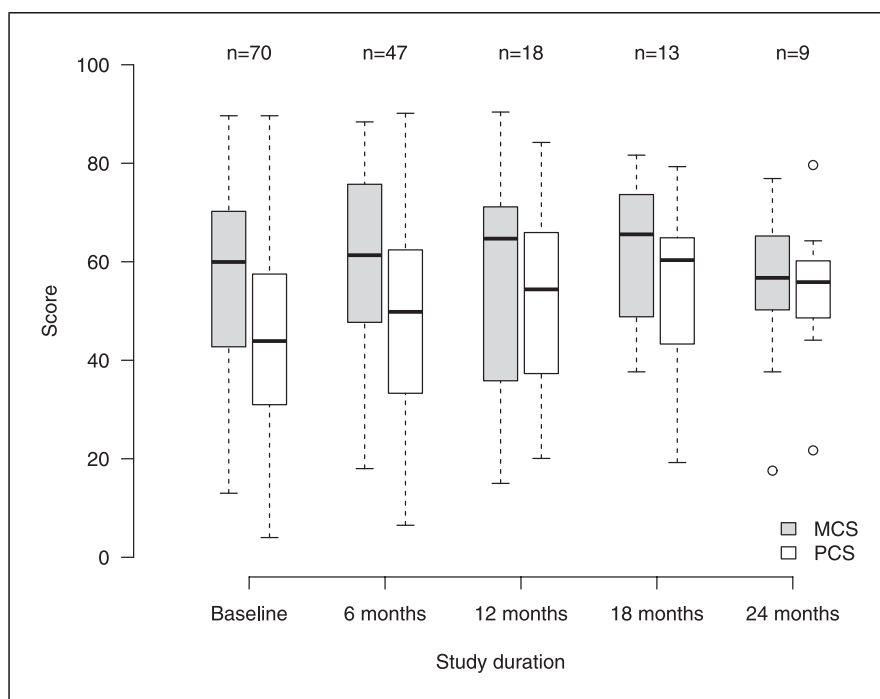
Most patients in our study felt dependent on PN, which did not diminish over the course of the study. This dependency also led to difficulties leaving home. It has been found that time-consuming procedures, carrying heavy backpacks as well as fears, worries, and a negative body image lead to difficulties keeping appointments and unwillingness to go out [28]. Furthermore, patients often feel overwhelmed by the large amount of material needed and their responsibilities in managing and coordinating home services [29]. Therefore, it is important to reduce infusion time as soon as possible and to provide additional free time and nights off PN whenever feasible [23, 30] but also taking into consideration the tolerance and complications of the HPN regimen [1, 4].

Although the latest data show that only 26% of HPN patients in Switzerland are interested in connecting with other patients [31], participants in the SWISSHPN II study often reported feeling alone in their situation and that they would like to meet other patients and have a network to talk and exchange information about their situation. HPN patient groups, which are also recommended by ESPEN but currently not systematically established in Switzerland, can empower patients by sharing experiences with others [32]. Additionally, substantial support and commitment for HPN are required from the family [29].

It was not possible to determine to which extent the reported symptoms are caused by PN or by the underlying disease. Patients reported fatigue due to sleep disturbances caused by the noise of the pump or nocturia as a result of the high intravenous volume load due to PN



**Fig. 4.** Boxplots of baseline scores of the SF-36v2<sup>®</sup> health domains.



**Fig. 5.** Boxplots of SF-36v2<sup>®</sup> summary scores over the course of the study period. MCS, mental component summary score; PCS, physical component summary score.

over night. Inappropriate medication timing may aggravate such symptoms like administration of furosemide just before bedtime in patients with high blood pressure or edema. Nocturia could be reduced if treatment is administered 2–4 hours before bedtime.

Our findings support those of Huisman-de Waal et al. [28], showing that patients have an ambivalent attitude toward HPN [25]. Although patients are aware of the vital importance of PN, they feel dependent on PN and homebound. We thus support the suggested importance

of interactive education, training on behavioral skills, and coping as well as resilience strategies (e.g., emotional support, stress management) for patients and their families as part of HPN programs from initiation of therapy [28]. Educational programs are important to prepare patients and their families for the challenge of living with HPN, to reduce anxiety, and to help gradually achieve a life as close to normal as possible [25]. Such programs should allow patients to regain autonomy and independence, thus improving QOL [30].

In conclusion, HPN is challenging for patients as well as their families and leads to dependency and restrictions in everyday life. However, it stabilizes mental health even in the case of severe underlying diseases. QOL is a crucial parameter in the care of HPN patients, influenced by a number of factors like restricted social life, anxiety related to HPN, sleep disturbances, quality of care, and physical health. All these factors depend not only on HPN but also on the underlying disease. Therefore, patients should be encouraged and supported, most importantly by the HPN care team, to foster independence and autonomy in order to enable a life as close to normal as possible. This can be further facilitated by patient support groups and training programs on behavioral coping strategies involving patients as well as their family members.

### Statement of Ethics

This study protocol was reviewed and approved by the Ethics Commission of the Canton of Bern, approval number 2016-00669. Written informed consent was obtained from all participants in the study.

### References

- 1 Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S, et al. ESPEN guideline on home parenteral nutrition. *Clin Nutr.* 2020;39(6):1645–66.
- 2 Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life—a review. *Clin Nutr.* 2007;26(3):275–88.
- 3 Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M; ESPEN. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr.* 2009;28(4):365–77.
- 4 Mühlebach S. Diets and diet therapy: parenteral nutrition. In: Ferranti P, Berry EM, Anderson JR, editors. *Encyclopedia of food security and sustainability*. 2. 1 ed. Amsterdam: Elsevier; 2019. p. 131–42.
- 5 Winkler MF. Quality of life in adult home parenteral nutrition patients. *JPEN J Parenter Enteral Nutr.* 2005;29(3):162–70.
- 6 Dreesen M, Foulon V, Hiele M, Vanhaecht K, De Pourcq L, Pironi L, et al. Quality of care for cancer patients on home parenteral nutrition: development of key interventions and outcome indicators using a two-round Delphi approach. *Support Care Cancer.* 2013;21(5):1373–81.
- 7 Dreesen M, Foulon V, Vanhaecht K, Hiele M, De Pourcq L, Pironi L, et al. Development of quality of care interventions for adult patients on home parenteral nutrition (HPN) with a benign underlying disease using a two-round Delphi approach. *Clin Nutr.* 2013;32(1):59–64.
- 8 Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr.* 2017;36(1):49–64.
- 9 Baxter JP, Fayers PM, McKinlay AW. The clinical and psychometric validation of a questionnaire to assess the quality of life of adult patients treated with long-term parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2010;34(2):131–42.
- 10 Theilla M, Kagan I, Chernov K, Cohen J, Kagan I, Singer P. Self-evaluation of quality of life among patients receiving home parenteral nutrition: a validation study. *JPEN J Parenter Enteral Nutr.* 2018;42(3):516–21.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Katja A. Schönenberger: methodology, formal analysis, writing – original draft, and visualization. Emilie Reber: conceptualization, methodology, formal analysis, investigation, writing – original draft, visualization, and project administration. Valentina V. Huwiler, Christa Dürig, and Raphaela Muri: writing – review and editing. Michèle Leuenberger: resources and writing – review and editing. Stefan Mühlebach: conceptualization, methodology, writing – review and editing, supervision, and funding acquisition. Zeno Stanga: conceptualization, methodology, resources, writing – review and editing, supervision, project administration, and funding acquisition.

### Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (K.A.S.) upon reasonable request.



- 11 Miller TL, Greene GW, Lofgren I, Greaney ML, Winkler MF. Content validation of a home parenteral nutrition-patient-reported outcome questionnaire. *Nutr Clin Pract*. 2017;32(6):806–13.
- 12 Berghöfer P, Fragkos KC, Baxter JP, Forbes A, Joly F, Heinze H, et al. Development and validation of the disease-specific short bowel syndrome-quality of life (SBS-QoL) scale. *Clin Nutr*. 2013;32(5):789–96.
- 13 Baxter JP, Fayers PM, Bozzetti F, Kelly D, Joly F, Wanten G, et al. An international study of the quality of life of adult patients treated with home parenteral nutrition. *Clin Nutr*. 2019;38(4):1788–96.
- 14 Aeberhard C, Leuenberger M, Joray M, Ballmer PE, Mühlebach S, Stanga Z. Management of home parenteral nutrition: a prospective multicenter observational study. *Ann Nutr Metab*. 2015;67(4):210–7.
- 15 Stanga Z, Aeberhard C, Scharer P, Kocher A, Adler S, Villiger PM. Home parenteral nutrition is beneficial in systemic sclerosis patients with gastrointestinal dysfunction. *Scand J Rheumatol*. 2016;45(1):32–5.
- 16 Reber E, Staub K, Schönenberger KA, Stanga A, Leuenberger M, Pichard C, et al. Management of home parenteral nutrition: complications and survival. *Ann Nutr Metab*. 2021;77(1):46–55.
- 17 R Core Team. *R. A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2022.
- 18 Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4(43):1686.
- 19 Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1).
- 20 Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. *J Stat Softw*. 2017;82(13).
- 21 Roser K, Mader L, Baenziger J, Sommer G, Kuehni CE, Michel G. Health-related quality of life in Switzerland: normative data for the SF-36v2 questionnaire. *Qual Life Res*. 2019;28(7):1963–77.
- 22 Sowerbutts AM, Lal S, Sremanakova J, Clamp A, Todd C, Jayson GC, et al. Home parenteral nutrition for people with inoperable malignant bowel obstruction. *Cochrane Database Syst Rev*. 2018;8:CD012812.
- 23 Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. *Gastroenterology*. 2003;124(6):1651–61.
- 24 Blüthner E, Pape UF, Stockmann M, Karber M, Maasberg S, Pevny S, et al. Assessing non-invasive liver function in patients with intestinal failure receiving total parenteral nutrition—results from the prospective PNLiver trial. *Nutrients*. 2020;12(5):1217.
- 25 Winkler MF, Hagan E, Wetle T, Smith C, Mailet JO, Touger-Decker R. An exploration of quality of life and the experience of living with home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2010;34(4):395–407.
- 26 Bakker H, Bozzetti F, Staun M, Leon-Sanz M, Hebuterne X, Pertkiewicz M, et al. Home parenteral nutrition in adults: a european multicentre survey in 1997. ESPEN-home artificial nutrition working group. *Clin Nutr*. 1999;18(3):135–40.
- 27 Cloutier A, Deutsch L, Miller B, Leahy G, Ablett J, Healey A, et al. Factors affecting antidepressant use by patients requiring home parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2022;46(1):153–9.
- 28 Huisman-de Waal G, Naber T, Schoonhoven L, Persoon A, Sauerwein H, van Achterberg T. Problems experienced by patients receiving parenteral nutrition at home: results of an open interview study. *JPEN J Parenter Enteral Nutr*. 2006;30(3):215–21.
- 29 Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. *JPEN J Parenter Enteral Nutr*. 2014;38(1 Suppl 1):32s–7s.
- 30 Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. *Aliment Pharmacol Ther*. 2013;37(6):587–603.
- 31 Schönenberger KA, Reber E, Vu DT, Krieger-Grübel C, Gerber PA, Muri R, et al. Attitudes and expectations of patients on home parenteral nutrition towards eHealth: a multicenter survey. *Clin Nutr ESPEN*. 2022;52:445–9.
- 32 Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr*. 2016;35(2):247–307.