

Head and neck manual lymphatic drainage for self-reported neurocognitive symptoms in post-COVID condition: a proof-of-concept cohort study

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Short Report

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Abstract

Objective

Neurocognitive symptoms, such as brain fog, difficulty concentration, sleep disturbances, and headaches, are among the most common and hardest-to-treat symptoms of post-COVID syndrome (PCC) and have been linked to blood-brain barrier disruption and impaired glymphatic clearance. Cerebrospinal fluid drains into cervical lymph nodes, an efflux enhanced by head and neck lymphatic manipulation. This proof-of-concept study investigated whether manual lymphatic drainage (MLD) of the head and neck region is associated with a change in neurocognitive symptom burden in 49 patients with PCC. Headache, brain fog, concentration, and sleep were assessed before and after treatment on a 100-mm visual analog scale, life satisfaction (primary endpoint), fatigue, and a subjective efficacy rating were additional endpoints.

Results

Life satisfaction remained unchanged (SWLS – 0.2, $P = 0.738$). All four symptoms decreased significantly (brain fog – 15.6 mm; concentration – 13.5 mm; headache – 11.3 mm; sleep – 8.2 mm; all $P \leq 0.014$), as did fatigue (FSS – 0.6, $P = 0.006$). In this uncontrolled, single-arm design, these changes cannot be distinguished from spontaneous remission, regression to the mean, or expectation effects. Nevertheless, MLD of the head and neck region was associated with an improvement in self-reported neurocognitive symptoms, the findings generate new hypotheses and warrant randomized controlled trials

Introduction

Post-COVID condition (PCC) comprises symptoms that persist for more than twelve weeks after SARS-CoV-2 infection, last for at least two months and cannot be explained by an alternative diagnosis [1]. Up to 7% of adults develop PCC [2]. The pathogenesis is considered multifactorial, and viral persistence, chronic inflammation, autoimmunity, microthrombosis and endothelial dysfunction have all been proposed [3]. Frequent symptoms include headache, autonomic dysfunction, cognitive deficits ("brain fog"), post-exertional malaise and sleep disorders [2, 3]. Cognitive complaints primarily affect attention, working memory, processing speed and verbal fluency [2]. A motor and cognitive fatigue resembling that of myalgic encephalomyelitis/chronic fatigue syndrome has been described in up to 82% of patients with PCC, [2] pointing to possible shared pathomechanisms across post-acute infection syndromes [4]. Proposed mechanisms of neurocognitive symptoms include dysregulated microcirculation, reduced cerebral perfusion and impaired oxidative capacity [5].

Impaired blood-brain barrier permeability has been demonstrated as a correlate of neurocognitive complaints in PCC, allowing increased passage of serum constituents and cytokines into the central nervous system (CNS) [6]. This brings the efficiency of cerebral waste clearance into focus. As the brain parenchyma lacks conventional lymphatic vessels, the CNS depends on paravascular drainage routes

collectively described as the glymphatic (glial-lymphatic) system, which drains metabolic waste into the cerebrospinal fluid (CSF) [7–11]. Transport out of the CNS is provided, among other routes, by the meningeal lymphatic vessels. They take up CSF together with dissolved metabolites, particularly at the skull base along the cribriform plate, and convey it into the peripheral lymphatic system, mainly the deep cervical lymphatics [12–16]. The lymphatic nature of the cerebrospinal spaces was recognised early: in 1869 Schwalbe described the subarachnoid space as a lymphatic compartment, [17] and its macroscopic lymphatic connections had been mapped even earlier, a history recently retraced from Mascagni onward [18]. Földi later postulated that impaired cervical outflow is accompanied by neuropsychiatric and cognitive symptoms ("lymphostatic encephalopathy") and described improvement after MLD [19, 20]. Modern anatomical work has since confirmed the meningeal-lymphatic efflux route [12–14].

This efflux is an actively modifiable system, and at our centre MLD of the head and neck has long been used clinically for symptoms of the CNS. Given the large number of patients with neurocognitive symptoms in PCC and the absence of established therapeutic options, we asked whether targeted modulation of cranial clearance might have a therapeutic effect. Building on this treatment tradition and on recent insights into the modifiability of meningeal-lymphatic efflux, we investigated MLD of the head and neck in patients with PCC.

Material and Methods

Study design and setting

This is an a priori defined proof-of-concept subgroup analysis of a monocentric, prospective, non-randomized, single-arm observational cohort study on the effects of physical therapies in PCC, conducted at a university outpatient clinic for physical and rehabilitation medicine (ReCoVer study). Reporting follows the STROBE recommendations for observational studies [21]. The study was conducted in accordance with the Declaration of Helsinki, approved by the institutional ethics committee (EA1/345/21) and registered in the German Clinical Trials Register (DRKS00027821). All participants gave written informed consent. Recruitment and data collection took place from 1 February 2022 to 30 April 2023.

Participants

Consecutively presenting patients were included if they met the following criteria:

- Age ≥ 18 years
- Post-COVID condition (compatible symptoms and a positive SARS-CoV-2 test at least three months before assessment)

- Self-reported impairment of neurocognitive performance (brain fog, impaired concentration, fatigue) and/or headache

Patients were excluded if there was no indication for treatment and/or a contraindication to MLD. Criteria for discontinuation were the patient's own wish and a medically indicated termination of therapy. Given the exploratory setting, no objective neuropsychological testing was performed. Overall disease severity was graded with the Post-COVID-19 Functional Status (PCFS) scale and summarized as mild, moderate or severe/relevant [22].

Intervention

MLD of the head and neck was prescribed within a semi-structured, individualized physical therapy programme and delivered by physiotherapists certified in MLD. A treatment series comprised, on average, two 30-minute sessions per week over six weeks (up to twelve sessions). MLD is a gentle, rhythmic, low-pressure manual technique that follows the anatomy of the lymphatic system. Each session began proximally, at the venous angle and the deep cervical lymph nodes, to raise lymphangiomotor activity before the more distal head and neck regions were treated, so that congested territories drained into previously cleared ones. Standardized strokes were applied in the direction of physiological lymph flow toward the deep cervical chain. Treatments were delivered within routine outpatient care, no pharmacological or device-based co-interventions were mandated.

Outcomes

The primary outcome was life satisfaction, assessed with the Satisfaction with Life Scale (SWLS).[23] Secondary outcomes were neurocognitive symptom intensity, sleep disturbance, fatigue and a subjective treatment-effect rating. At first presentation (t0) and after completion of the treatment series (t1), headache, brain fog, concentration difficulties and sleep disturbance were each rated on a 100-mm VAS (0 = no symptoms, 100 = maximum intensity), and fatigue was assessed with the Fatigue Severity Scale (FSS).[24] In addition, at t1 patients rated the subjective effect of treatment on a bidirectional 100-mm VAS (50 mm = no change; below 50 mm = improvement, 0 mm = maximum improvement; above 50 mm = deterioration, 100 mm = maximum deterioration), for the program overall, for MLD as a whole, and separately for headache, brain fog and concentration difficulties.

Statistical analysis

Because the values were not normally distributed, within-group pre-post comparisons used the Wilcoxon signed-rank test for paired samples. Data are reported as mean $\pm$ standard deviation (SD) and, where appropriate, as median and interquartile range (IQR). Mean changes are reported with 95% confidence intervals (CI), with the lower and upper limits separated by a semicolon. The significance level was $P = 0.05$ (two-sided). P values are exploratory, no adjustment was made for multiple testing or for potential

confounders, and only unadjusted estimates are reported. Complete cases with VAS data at both time points were analysed, without imputation. The sample size was pragmatic, comprising all eligible patients available during the recruitment period, no a priori sample-size calculation was performed. Demographic and clinical baseline data were analyzed descriptively. Analyses were performed with IBM SPSS Statistics 29.

Results

Study population

A flow chart of the parent study (ReCoVer) together with this subgroup analysis is shown in Figure a. Of 64 patients who received MLD of the head and neck, complete VAS data at both time points were available for 49, who formed the analysis population. Patients had a mean age of 40.9 ± 8.6 years and were predominantly female (81.6%). Severe or clinically relevant PCC was present in 73.5%. Demographic and clinical baseline data are presented in Table 1.

Figure a. Flow of participants through the study. PCC = post-COVID condition, MLD = manual lymphatic drainage, SWLS = Satisfaction with Life Scale, VAS = visual analogue scale, t0 = baseline, t1 = follow-up.

Table I. Demographic and clinical baseline characteristics of the analysis population (n = 49).

Characteristic	Total (n = 49)
Demographics	
Age, years – mean $\pm$ SD	40.9 $\pm$ 8.6
Age, years – median (range)	39 (22–64)
Female sex, n (%)	40 (81.6)
Disease severity (PCFS-graded) a	
Mild, n (%)	3 (6.1)
Moderate, n (%)	10 (20.4)
Severe/relevant, n (%)	36 (73.5)
Disease course	
Inpatient acute treatment, n (%)	4 (8.2)
Previous rehabilitation, n (%)	8 (16.3)
Current inability to work, n (%)	28 (57.1)
SARS-CoV-2 vaccination, n (%)	46 (93.9)
Baseline symptom intensity (VAS, 0–100 mm; mean $\pm$ SD)	
Brain fog	46.9 $\pm$ 26.7
Concentration	54.3 $\pm$ 22.1
Headache	27.8 $\pm$ 22.0
Sleep disturbance	53.1 $\pm$ 31.0
Comorbidities, n (%)	
Asthma / chronic bronchitis	12 (24.5)
Thyroid dysfunction	7 (14.3)
Arterial hypertension	4 (8.2)
Obesity	3 (6.1)
Autoimmune disease	3 (6.1)
Infectious disease	2 (4.1)
Diabetes mellitus	1 (2.0)
Cancer	1 (2.0)
Lymphoedema	0 (0.0)

Characteristic	Total (n = 49)
Demographics	
Current smoking	7 (14.3)

SD = standard deviation, PCC = post-COVID condition, PCFS = Post-COVID-19 Functional Status, VAS = visual analogue scale.

Primary outcome

Life satisfaction, the primary outcome, showed no significant change from t0 to t1 (SWLS t0: 22.6 ± 7.1 ; t1: 22.5 ± 6.5 ; mean difference -0.2 ; 95% CI -1.7 ; 1.4 ; $P = 0.738$). At the individual level, life satisfaction increased in 44.9% of patients ($n = 22/49$), was unchanged in 4.1% and decreased in 51.0%.

Secondary outcomes

All four VAS symptom scores decreased significantly from t0 to t1 (Figure b, Table 2, negative values indicate improvement). The largest change was for brain fog (mean difference -15.6 mm; 95% CI -23.5 ; -7.9 ; $P < 0.001$), followed by concentration difficulties (-13.5 mm; 95% CI -21.3 ; -5.8 ; $P = 0.002$) and headache (-11.3 mm; 95% CI -18.3 ; -4.4 ; $P = 0.003$). Sleep disturbance also decreased significantly (-8.2 mm; 95% CI -15.4 ; -0.5 ; $P = 0.014$), as did fatigue severity (FSS t0: 5.5 ± 1.4 ; t1: 4.9 ± 1.6 ; mean difference -0.6 ; 95% CI -1.0 ; -0.2 ; $P = 0.006$). Considering any improvement from baseline, regardless of magnitude, improvement was seen in 69.4% of patients for brain fog, 67.3% for concentration difficulties, 68.8% for headache and 63.3% for sleep disturbance, fatigue (FSS) improved in 63.6%.

Table 2
Symptom intensity on the 100-mm VAS before (t0) and after (t1) manual lymphatic drainage.

Symptom	t0 (mean $\pm$ SD)	t1 (mean $\pm$ SD)	Δ mm (95% CI)	P
Headache	27.8 ± 22.0	16.5 ± 17.9	-11.3 (-18.3 ; -4.4)	0.003
Brain fog	46.9 ± 26.7	31.4 ± 25.5	-15.6 (-23.5 ; -7.9)	< 0.001
Concentration	54.3 ± 22.1	40.8 ± 24.6	-13.5 (-21.3 ; -5.8)	0.002
Sleep disturbance	53.1 ± 31.0	44.9 ± 30.0	-8.2 (-15.4 ; -0.5)	0.014
SD = standard deviation, CI = confidence interval, Δ = mean difference t1 – t0 (negative = improvement)				

Figure b. Neurocognitive symptom intensity on the 100-mm VAS before (t0) and after (t1) manual lymphatic drainage ($n = 49$). Bars show mean $\pm$ SD. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Subjective treatment effect

On the bidirectional VAS (50 mm = no change; below 50 mm = improvement), all rated dimensions lay below the indifference value, indicating a perceived improvement, although individual patients reported deterioration (above 50 mm). Median ratings were 29 mm for the programme overall (IQR 20–43; mean 32.5 ± 19.7), 37 mm for MLD as a whole (IQR 22–45; mean 33.3 ± 17.7), 35 mm for headache (mean 31.9 ± 19.2), 41 mm for brain fog (mean 34.9 ± 17.8) and 44 mm for concentration difficulties (mean 38.3 ± 16.9). Expressed as the distance below the indifference value, this corresponds to a median perceived improvement of 21 mm for the programme overall, 13 mm for MLD overall, and between 6 and 15 mm for the individual symptoms (Figure c).

Figure c. Subjective treatment effect on the bidirectional 100-mm VAS. The dashed line marks the indifference value (50 mm = no change), values to the left indicate improvement, values to the right deterioration. Boxes show median and interquartile range.

Discussion

In this exploratory single-arm proof-of-concept study, life satisfaction, the pre-specified primary outcome, remained unchanged ($P = 0.738$). This contrasts with rehabilitation trials reporting improved health-related quality of life after structured exercise [25–27], but those used multidimensional instruments (SF-36, SF-12, EQ-5D), whereas the five-item SWLS is a unidimensional measure of cognitive-evaluative life satisfaction that is comparatively insensitive to short-term symptomatic change.

Self-reported neurocognitive symptoms and fatigue decreased over the treatment period. However, because the study had no control group, these within-group changes cannot be distinguished from spontaneous recovery, regression to the mean, attention or expectancy. For fatigue, the point estimate (FSS – 0.6) exceeds the minimally important difference of approximately 0.45 points established for the FSS in multiple sclerosis [28] and applied to post-COVID rehabilitation cohorts, [29] however, the confidence interval (-1.0 ; -0.2) includes changes below this threshold.

To date, evidence on lymphatic drainage in PCC has been limited to two case reports and one preliminary report, each describing a positive association [30, 31]. Heald et al. reported, in 20 patients after about ten weekly sessions of MLD, a reduction in fatigue-related symptoms of approximately 50% across subscales, with improvements in concentration, post-exertional malaise and restorative sleep [31]. Overall et al. described, in two case reports, improvements in cough, exertional dyspnoea and fatigue as well as better sleep after MLD (Vodder method) [30]. The underlying hypothesis of an impaired central-nervous lymphatic or cerebrospinal outflow after COVID-19 as a rationale for lymphatic drainage was formulated early [32]. Our results extend these observations by a differentiated, symptom-specific assessment in a larger cohort.

MLD is thought to increase lymphangiomotor activity and decongest the cervical lymphatics. Efflux of gadolinium-based tracer from the CSF into the deep cervical lymph nodes has been shown in animal models and, for intrathecal contrast, by MRI in humans [14, 16]. In a pilot study, a reduction of intracranial pressure was observed during MLD of the head and neck, [33] presumably reflecting improved CSF efflux

via the deep cervical lymphatic system. Recent high-impact work supports the modifiability of this route. Jin et al. showed that non-invasive mechanical stimulation of the superficial cervical lymphatics increased CSF drainage in murine and non-human primate models, [34] and MLD of the head and neck adapted to mice improved cognition and reduced neurodegeneration markers in an Alzheimer model [35]. Glymphatic modulation is increasingly discussed as a therapeutic option in ME/CFS and related post-infectious syndromes [36]. Improved clearance of cytokines and metabolic waste is a plausible but untested explanatory framework for the observed changes in brain fog, headache and concentration. The direction of any causal relationship cannot be inferred from our data, and part of the headache change could also reflect MLD-related myofascial relaxation and treatment of cervical trigger points.

Sleep is physiologically linked to glymphatic clearance, which is most effective during sleep, [37] whereas sleep deprivation promotes accumulation of metabolites such as amyloid-beta.[38] Improved sleep was also reported in the case reports of MLD in PCC [30, 31]. These parallels are hypothesis-generating and were not tested mechanistically here.

Limitations

The results must be interpreted with several limitations in mind. This is an exploratory subgroup analysis of a non-randomized, single-arm proof-of-concept study without a control group; a causal relationship between MLD and symptom change cannot be established, and non-specific effects (spontaneous recovery, attention, expectancy) cannot be excluded for any outcome. Because of the multimodal therapy concept, treatment modalities overlapped, hampering the isolated assessment of MLD. Neurocognitive symptoms were assessed exclusively by self-report (VAS), without objective neuropsychological testing, and no minimally important difference has been established for these VAS ratings in PCC, so clinical relevance could not be quantified against a validated threshold. Fifteen eligible patients were excluded because of missing baseline VAS documentation, although they attended follow-up, documentation-related selection cannot be fully excluded. MLD could not be fully standardized, reflecting real-world care, as some patients were treated near their homes rather than at the study centre, and the exact number of sessions and the t0–t1 interval were not centrally recorded. Recruitment at a specialized university outpatient clinic may have introduced selection bias.

Conclusions

MLD of the head and neck could be a potential treatment option for neurocognitive symptoms in post-COVID condition. The data are hypothesis-generating and should be tested in randomized controlled trials with a control group, a standardized intervention, stratification for PCC severity and objective endpoints. Beyond post-acute infection syndromes, this approach may also prove relevant to other neurocognitive disorders, and we consider its systematic investigation a promising scientific field

Abbreviations

CI, confidence interval, CNS, central nervous system, CSF, cerebrospinal fluid, FSS, Fatigue Severity Scale, HRQoL, health-related quality of life, IQR, interquartile range, MLD, manual lymphatic drainage, PCC, post-COVID condition, PCFS, Post-COVID-19 Functional Status, SD, standard deviation, SWLS, Satisfaction with Life Scale, VAS, visual analogue scale.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Charité – Universitätsmedizin Berlin (EA1/345/21) and registered in the German Clinical Trials Register (DRKS00027821). It was conducted in accordance with the Declaration of Helsinki. Written informed consent to participate was obtained from all participants.

Consent for publication.

Not applicable. the manuscript contains no individual person's identifying data, images or videos.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because of data-protection restrictions but are available from the corresponding author (NE) on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The authors received no external funding for this study, it was supported by institutional resources. The funder had no role in study design, data collection, analysis, interpretation or writing.

Authors' contributions

NE and MEL conceived and designed the study. CS and AR contributed to the acquisition, analysis and interpretation of the data. NE and MEL drafted the manuscript, and all authors revised it critically for important intellectual content. All authors read and approved the final version of the manuscript.

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Figures

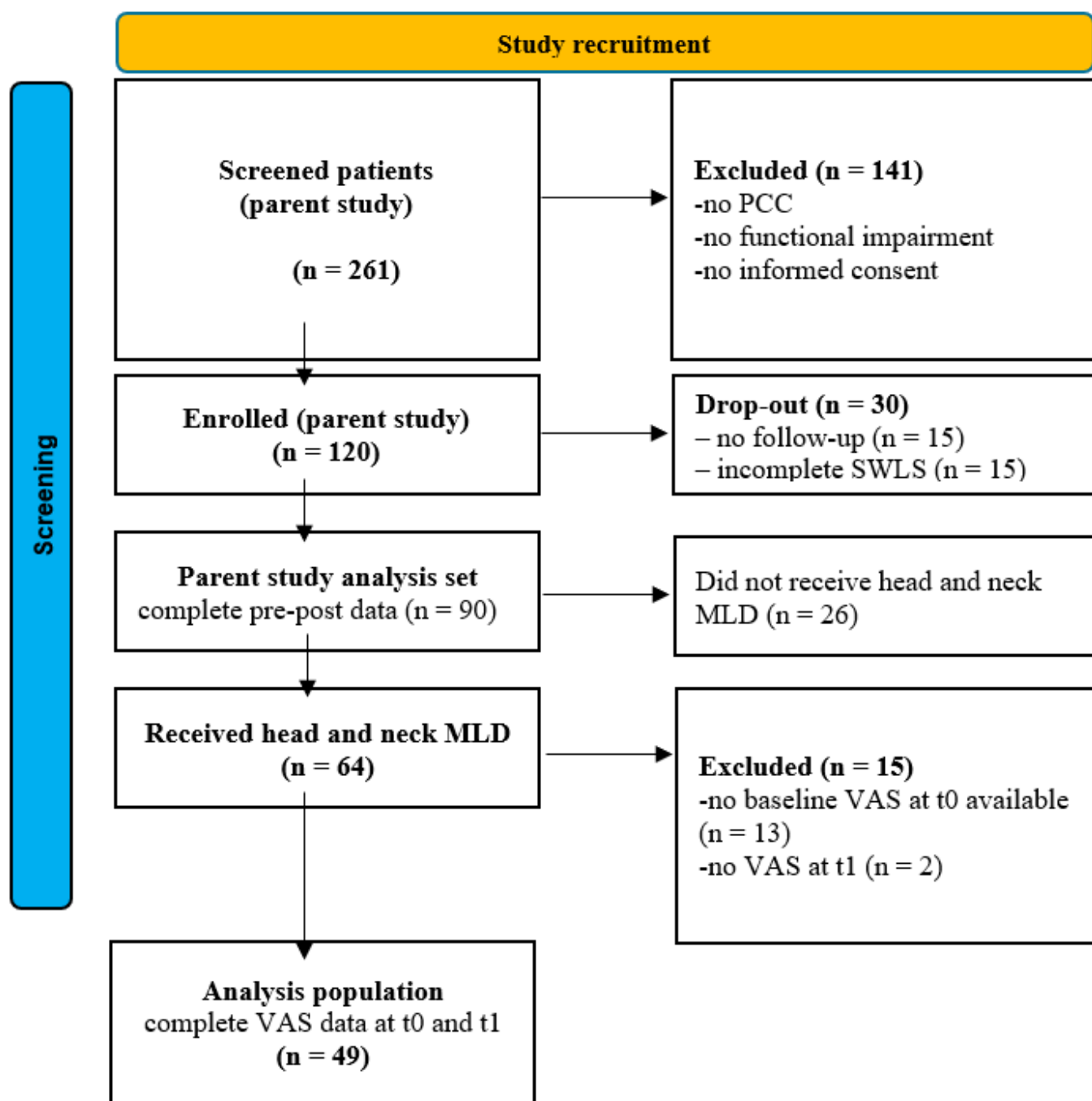


Figure 1

Figure a. Flow of participants through the study. PCC = post-COVID condition, MLD = manual lymphatic drainage, SWLS = Satisfaction with Life Scale, VAS = visual analogue scale, t0 = baseline, t1 = follow-up.

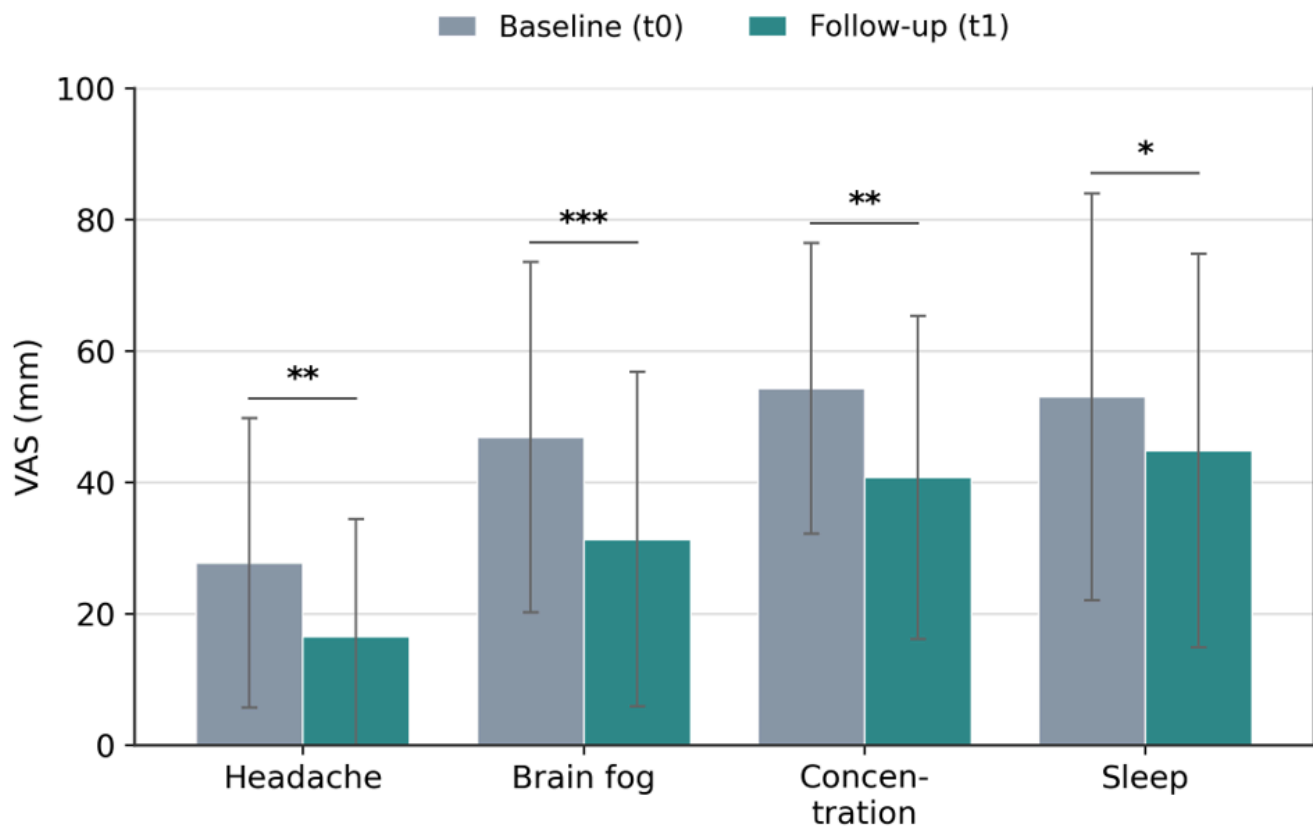


Figure 2

Figure b. Neurocognitive symptom intensity on the 100-mm VAS before (t0) and after (t1) manual lymphatic drainage (n = 49). Bars show mean $\pm$ SD. *P < 0.05; **P < 0.01; ***P < 0.001

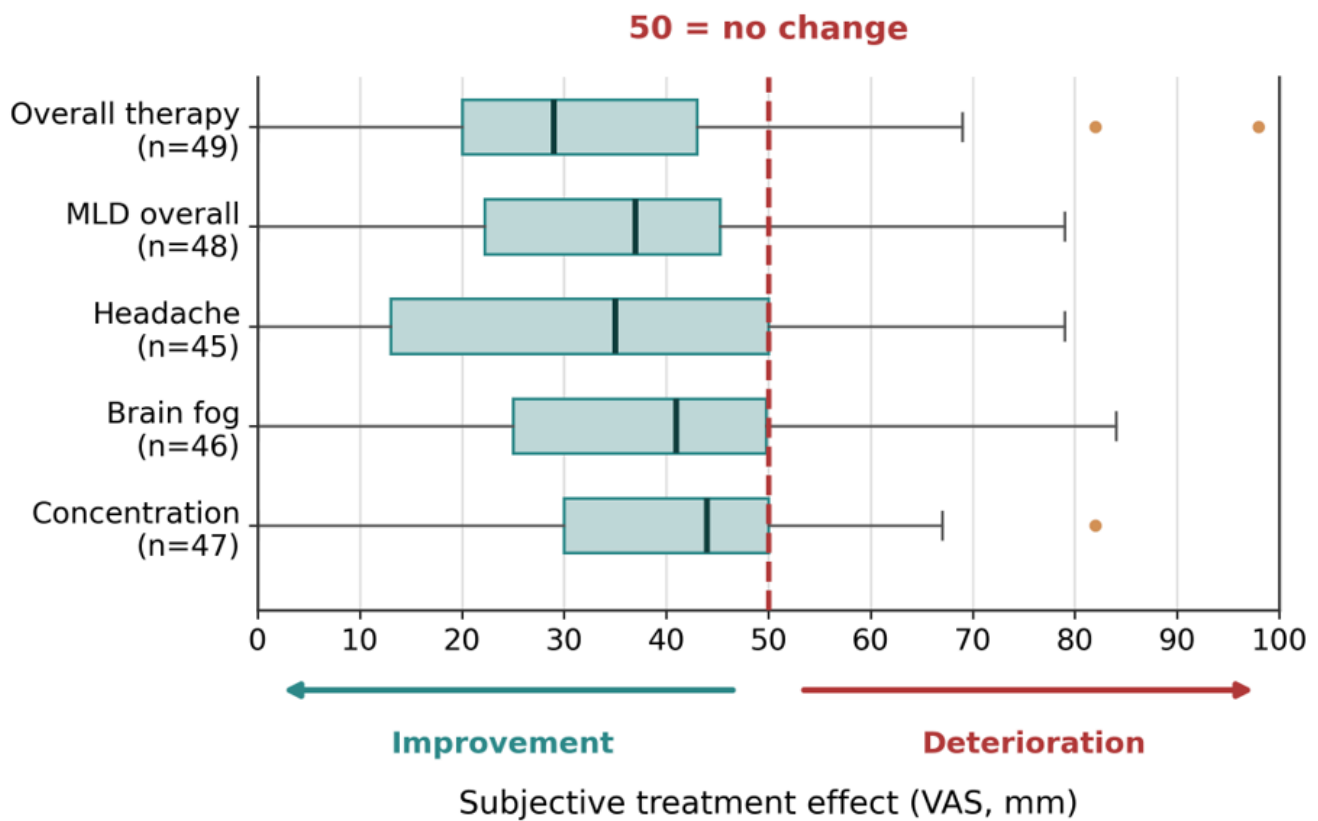


Figure 3

Figure c. Subjective treatment effect on the bidirectional 100-mm VAS. The dashed line marks the indifference value (50 mm = no change), values to the left indicate improvement, values to the right deterioration. Boxes show median and interquartile range.