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ORIGINAL RESEARCH

Can the Assessment of the Circadian Rhythm of Pain Be Shortened? A Study of Community-Dwelling Participants with Chronic Pain

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Purpose: This study aimed to juxtapose the circadian rhythm of pain with the conventional 7-day assessment and ascertain the feasibility of condensing the evaluation of the circadian rhythm of pain into a 3-day timeframe.

Patients and Methods: Seventy-three patients with pain persisting for a minimum of 3 months and a numerical rating scale (NRS) score of ≥2 were recruited from three medical centers. The circadian patterns of pain were appraised over a 7-day period by quantifying the intensity of pain at six temporal junctures each day using a 10-cm visual analog scale (VAS). Cluster analysis was performed using six standardized variables derived from the VAS score of each participant at six designated time points to identify cohorts with analogous circadian rhythms of pain. The clusters were discerned for the 7- and 3-day assessments (Tuesday–Thursday, Friday–Sunday, and Sunday–Tuesday), according to the research objectives. Cohen's kappa coefficient was calculated to gauge the intra-observer variability to assess the consistency between the outcomes of the cluster analysis for the 7-day assessment and each of the 3-day assessments.

Results: The highest Cohen's kappa coefficient was observed for the 3-day evaluation spanning from Friday to Sunday, indicating a substantial concordance with the results of the 7-day assessment.

Conclusion: Our results suggest that it may be prudent to consider implementing a condensed 3-day evaluation of the circadian rhythm of pain that is tailored to individual characteristics. This approach will allow a better understanding of the diurnal rhythms of chronic pain in patients and implement more targeted and specific pain management strategies. Furthermore, it will contribute to increased patient satisfaction through early intervention.

Keywords: pain, chronic pain, physical activity, circadian rhythm

Introduction

Chronic pain, defined as "persistent or recurrent pain extending beyond a duration of 3 months",[1] can be attributed to central nervous system pathologies, exemplification of the aberrant dorsal horn of the spinal cord excitability,[2] or perturbation of pain-inhibitory mechanisms emanating from the cerebral cortex.[3–6] Psychosocial factors, in addition to these central quandaries, evince an intimate association with pain.[7–9] The management of chronic pain has proven to be an arduous endeavor in most cases.[10] Consequently, the therapeutic approach to chronic pain gravitates toward enhancing the quality of life and facilitating routine activities rather than the absolute alleviation of pain.[11] The pivotal role of pain management, which encompasses the engagement of pain during daily activities and physical exercise while considering unique pain patterns, has been underscored.[12] Previous studies have demonstrated that a comprehensive, multidisciplinary intervention integrating patient education for pain management could ameliorate self-management and self-efficacy in patients with chronic pain due to diverse etiologies.[13] Heightened physical activity levels correspond inversely with the occurrence of ancillary complications, such as fatigue and depression, in patients with chronic pain.[14] Thus, it is

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imperative to develop educational interventions tailored to patients with chronic pain to enable the optimization of their daily activities and physical exercise regimens in tandem with the effective management of pain. The incorporation of the circadian rhythm of pain experienced by patients with chronic pain into the assessment process may aid in refining the precision and efficacy of such educational endeavors.

Circadian rhythms of pain refer to fluctuations in pain sensitivity over a 24-hour period. These circadian rhythms of pain have been shown to exist even in pain-free healthy adults.[15] These rhythms are also influenced by the circadian clock, which regulates the processing of pain information.[16] Examination of the circadian rhythm of pain has been the primary focus of disease-related investigations, resulting in the documentation of diverse rhythmic patterns.[17–20] A cross-sectional study conducted by the authors on the circadian rhythm of pain in patients with chronic pain from the same community revealed three distinct forms of rhythmicity marked by distinct characteristics: rhythmicity characterized by the highest pain intensity upon awakening, rhythmicity displaying elevated pain during both awakening and sleep with diminished daytime discomfort, and rhythmicity typified by minimal pain upon waking, accompanied by progressive escalation of pain over time.[21] Owing to their susceptibility to external factors such as physical activity,[22] it has been hypothesized that evaluating the circadian rhythm of pain will aid in improving pain management by enabling specific consideration of treatment strategies grounded in the intricate interplay between pain and physical activity. Patient education aimed at pain management rooted in an understanding of the circadian rhythm of pain has led to a reduction in pain intensity and an increase in daytime physical activity levels.[23]

Thus, it is imperative to integrate the pain circadian rhythm into the evaluation of patients with chronic pain and contemplate treatment modalities accordingly. Nevertheless, the current landscape is characterized by reports on several treatment strategies that consider the circadian rhythm of pain, which makes it challenging to assert that the circadian rhythm of pain has firmly established itself as an evaluation criterion for chronic pain therapy. The requirement for a week-long evaluation, with multiple assessments within the same day,[20,21] places a substantial burden on patients. Consequently, the adoption of the circadian rhythm of pain as an assessment tool has been impeded. Condensing the assessment of pain circadian rhythms to a 3-day time frame may reduce patient burden and further solidify its role as an assessment tool for chronic pain management. Once the circadian rhythm of pain is established as an assessment tool, it has the potential for clinical application to better facilitate individualized educational interventions. Thus, this study aimed to ascertain the validity of a 3-day pain rhythmicity evaluation compared with that of the traditional 7-day assessment.

Materials and Methods

Ethics Approval and Informed Consent

The experimental protocol for this study was approved by the Kio University Ethics Committee (approval number: H30-38). The study protocol adhered to the Declaration of Helsinki (UMIN: 20141113–184337). Written informed consent to participate in the study was obtained from the participants after receiving an explanation of the procedure.

Participants

This study was conducted between April 2019 and December 2022. Seventy-three individuals residing within the community with pain persisting for a minimum of 3 months who had a numeric rating scale (NRS) score of ≥2 were recruited from three healthcare establishments in Japan: outpatient rehabilitation facilities, orthopedic clinics, and daycare facilities. Individuals who possessed greater than modified independence, individuals who were capable of moving indoors and outdoors, and those who did not require regular medical attention were included. Individuals diagnosed with dementia or mental illness were excluded from the study. All participants in this study resided in Japan, and data were collected in Japan. The sample size was determined based on previous studies in the field of pain that used cluster analysis, and their sample size was approximately 60.[24,25]

Procedure

Data regarding the sex, age, disease, major pain sites, duration of pain, medication use, and employment status, was obtained from each patient before commencing the study. Furthermore, the characteristics of pain were evaluated, and the circadian rhythm of pain was analyzed using questionnaires administered to the participants that were completed in real time.

Pain Circadian Rhythm

This study evaluated the circadian rhythm of pain over a period of 7 consecutive days based on the findings of a previous research.[20,21] The intensity of pain was assessed using a 10-cm paper-based visual analog scale (VAS) at six distinct time points throughout the day: upon awakening and at 9:00, 12:00, 15:00, 18:00, and 21:00. The participants were instructed to rate their pain at each time point. The patients were instructed to rate their pain within 1 hour before or after the scheduled time if the exact time could not be adhered to owing to work or personal commitments. The 7-day mean scores were used for the analysis, and participants with VAS ratings showing a variation of <1 cm across all six time points for all 7 days were excluded from the study (n=4), because they exhibited no circadian rhythm of pain.

Measures

The Neuropathic Pain Diagnostic Questionnaire (DN4) was used to identify neuropathic pain, whereas the Short-Form McGill Pain Questionnaire 2 (SFMPQ2) was used to comprehensively evaluate pain intensity. The Neuropathic Pain Symptom Inventory (NPSI) was used to determine the severity of neuropathic pain, and the Michigan Body Map (MBM) was used to identify the location of pain.

Neuropathic Pain Diagnostic Questionnaire

The DN4 rating scale, which comprises 10 questions, is used to distinguish between neuropathic and non-neuropathic pain.[26] The DN4 rating scale has questions regarding symptoms, such as burning sensations and electric shock-like pain, that specifically target neuropathic pain. The pain was classified as neuropathic if at least four of the items on the scale were applicable.

Short-Form McGill Pain Questionnaire 2

The SFMPQ2 questionnaire comprises 22 questions that can be categorized into four subdomains: continuous pain, intermittent pain, affective descriptors, and neuropathic pain. Each item is rated on an 11-point numerical scale, with higher scores indicating greater pain severity. The internal consistency of the SFMPQ2 was found to be good (Cronbach's alpha=0.86 for SFMPQ2 total).[27] Significant associations were observed between the total score of SFMPQ2 and other functional assessments (ρ=0.54 for VAS and ρ=0.79 for SFMPQ-total).[27]

Neuropathic Pain Symptom Inventory

The NPSI is a questionnaire comprising 10 questions that assess neuropathic pain, including the presence of spontaneous burning pain.[28] The questions were further divided into the following sub-items: pain attacks, provoked pain, and abnormal sensations. The severity of these symptoms was rated on an 11-point NRS based on the average pain experienced in the previous 24 hours, ranging from 0–10, with higher scores indicating greater pain severity. The total score on the NPSI questionnaire was used to determine the severity of neuropathic pain symptoms.

Michigan Body Map

The MBM is a self-reported measurement tool used to assess current pain in various body regions. The MBM is a visual representation comprising 35 boxes.[29] The severity of pain was directly proportional to the number of boxes marked on the image.

Data Analyses

Demographic variables, including sex, age, medical condition, primary location of pain, duration of pain, use of analgesics, and employment status, are presented as absolute numbers and percentages in all participants. A mixed distribution model cluster analysis was performed using standardized (z-score) VAS scores at six time points for individual participants to capture the circadian rhythm of pain. The purpose of this study was to classify pain rhythms into patterns based on their characteristics and examine the degree of agreement between assessment dates. Cluster analysis is a useful exploratory tool for analyzing small sample sizes and identifying such pain rhythm patterns. Clusters were extracted for each of the 7 days and 3-day intervals (Tuesday–Thursday, Friday–Sunday, and Sunday–Tuesday) in accordance with the objectives of the study. The level of physical activity that might influence the circadian rhythm of pain varies between weekdays and weekends; thus, separate analyses were performed in each of the three days of the week to identify a category of 3-day assessments that closely resembled those of the 7-day assessment. The Bayesian Information Criterion (BIC) value was used to determine the number of clusters, and the clusters with the lowest BIC values between two and seven were selected.[30] Cohen's kappa coefficient was computed to evaluate the intra-observer variability between the cluster analysis outcomes of the 7-day assessment and those of each 3-day evaluation. The efficacy of the kappa coefficients is mainly based on the following classification by Landis et al:[31] <0.01, poor agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, nearly impeccable agreement. All statistical analyses were performed using HAD 14.10 (132) with a significance level of 5%.

Results

Demographic Data

Seventy-three participants were enrolled in this study. Statistical analysis was performed using the data of 64 participants; 9 were excluded due to missing important assessment items (n=5) or missing circadian rhythm of pain (n=4). Table 1 summarizes the demographic characteristics of the participants. Primary pain sites accounted for just over 70% of the total and included upper and lower extremity pain. Approximately 34.3% of patients reported experiencing pain for more than 3 months but less than 1 year; 28.1% reported experiencing pain for more than 1 year but less than 5 years, and 37.5% reported experiencing pain for more than 5 years. Less than 50% of patients were receiving analgesics, and 37.5% were employed.

Cluster Analysis: 7-Day Evaluation

Cluster analysis yielded three clusters as the optimal grouping (Table 2). Subsequent descriptions were formulated for the three clusters identified in the 7-day evaluation to investigate disparities from the 3-day assessments. Cluster 1 (CL1): Pain intensity reached its nadir upon awakening, intensified as time progressed, and eventually surpassed the Z-score of zero after noon. Cluster 2 (CL2): Maintains values above Z-score 0 at the time of awakening and 21:00; however, the score remained consistently below Z-score 0 throughout daytime. Cluster 3 (CL3): The VAS scores peaked during the waking hours, gradually diminished over time, and ultimately fell below a Z-score of 0 post-noon (Figure 1). The clusters from each 3-day assessment were examined in accordance with these definitions.

Cluster Analysis: 3-Day Assessment from Tuesday to Thursday

Figure 2 depicts the outcomes of the cluster analysis for the 3-day assessment performed from Tuesday to Thursday. CL1 and CL3 conformed to the defined criteria and were determined to be identical to those observed in the 7-day assessment. CL2 demonstrated a comparable pattern between wakefulness and the 21:00 time point; however, the rhythmicity exceeded the Z-score threshold of 0 at 15:00. Consequently, CL2 was categorized as a distinct cluster that was not affiliated with any of the clusters observed in the 7-day evaluation.

Table 1 Characteristics of the Participants (n=64)

Characteristics, n (%)	
Sex (male)	27 (42.2)
Age (years), mean (SD)	64.3±17.6
Disease	
Spinal cord disease	23 (35.9)
Locomotor disorders	32 (50)
Stroke	2 (3.1)
Cause unknown	7 (10.9)
Main pain area	
Neck	1 (1.6)
Low back	16 (25)
Upper limb	19 (29.7)
Lower limb	28 (43.8)
Pain duration	
3 months to 1 year	22 (34.3)
1–5 years	18 (28.1)
>5 years	24 (37.5)
Analgesic use	29 (45.3)
Working	24 (37.5)
Outcome measures, mean (SD)	
Neuropathic pain diagnostic questionnaire, n (%)	23 (35.9)
Short-Form McGill Pain Questionnaire 2-total	38.2±34.1
NPSI-total	16.7±17.1
MBM	5.9±5.4

Notes: Spinal cord disease: spinal cord injury, spinal canal stenosis, cervical spondylosis. Locomotor disorders: osteoarthritis, after artificial joint replacement sequelae, fracture, lower back pain.
Abbreviations: SD, standard deviation; NPSI, neuropathic pain symptom inventory; MBM, Michigan body map.

Table 2 The Value of BIC in Each Cluster Number

	CL2	**CL3**	**CL4**	**CL5**	**CL6**	**CL7**
BIC of 7-day	943.67	937.52	947.59	954.20	975.90	1014.64

Abbreviations: CL, cluster; BIC, Bayesian information criterion.

Cluster Analysis: 3-Day Assessment from Friday to Sunday

Figure 3 depicts the outcomes of the cluster analysis for the 3-day assessment performed from Friday to Sunday. All clusters displayed a congruent rhythmic pattern with those observed in the 7-day evaluation; thus, they were categorized as similar clusters.

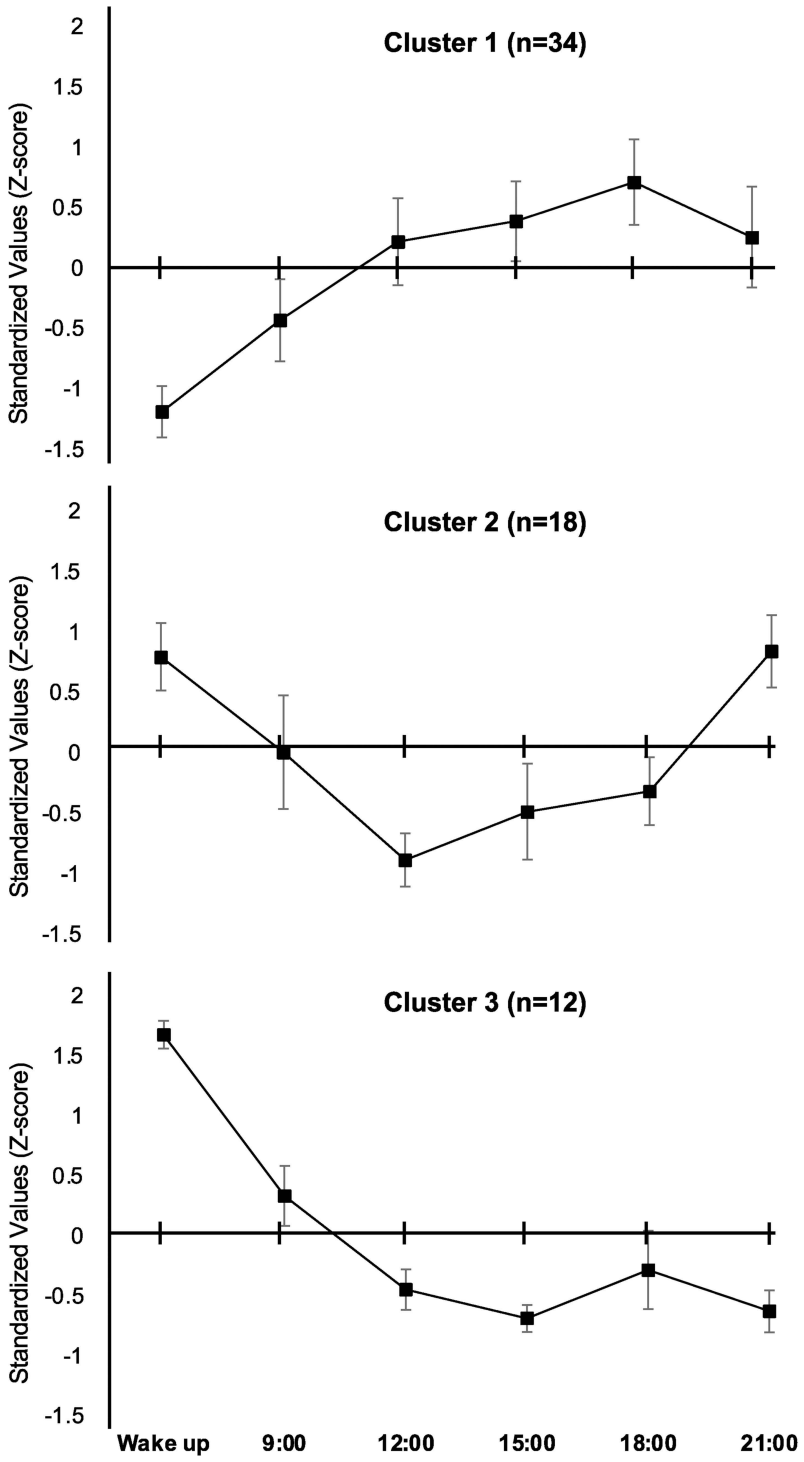

Figure 1 Categorization of the circadian rhythm of pain according to the 7-day assessment. The following criteria are applied to each cluster: CL1: The pain intensity is minimum at the time of awakening, but it increases subsequently and exceeds the Z-score 0 after noon. CL2: The pain intensity is above Z-score 0 at the time of awakening and at 21:00, but below Z-score 0 during the day. CL3: The VAS scores peaks during the waking hours and declined over time. The value is below Z-score 0 post-noon. Each data point is displayed with an error bar.
Abbreviations: CL, cluster; VAS, visual analog scale.

Cluster Analysis: 3-Day Assessment from Sunday to Tuesday

Figure 4 depicts the outcomes of the cluster analysis for the 3-day assessment performed from Sunday to Tuesday. CL1 and CL3 were determined to be identical to those in the 7-day evaluation according to the defined criteria. In contrast,

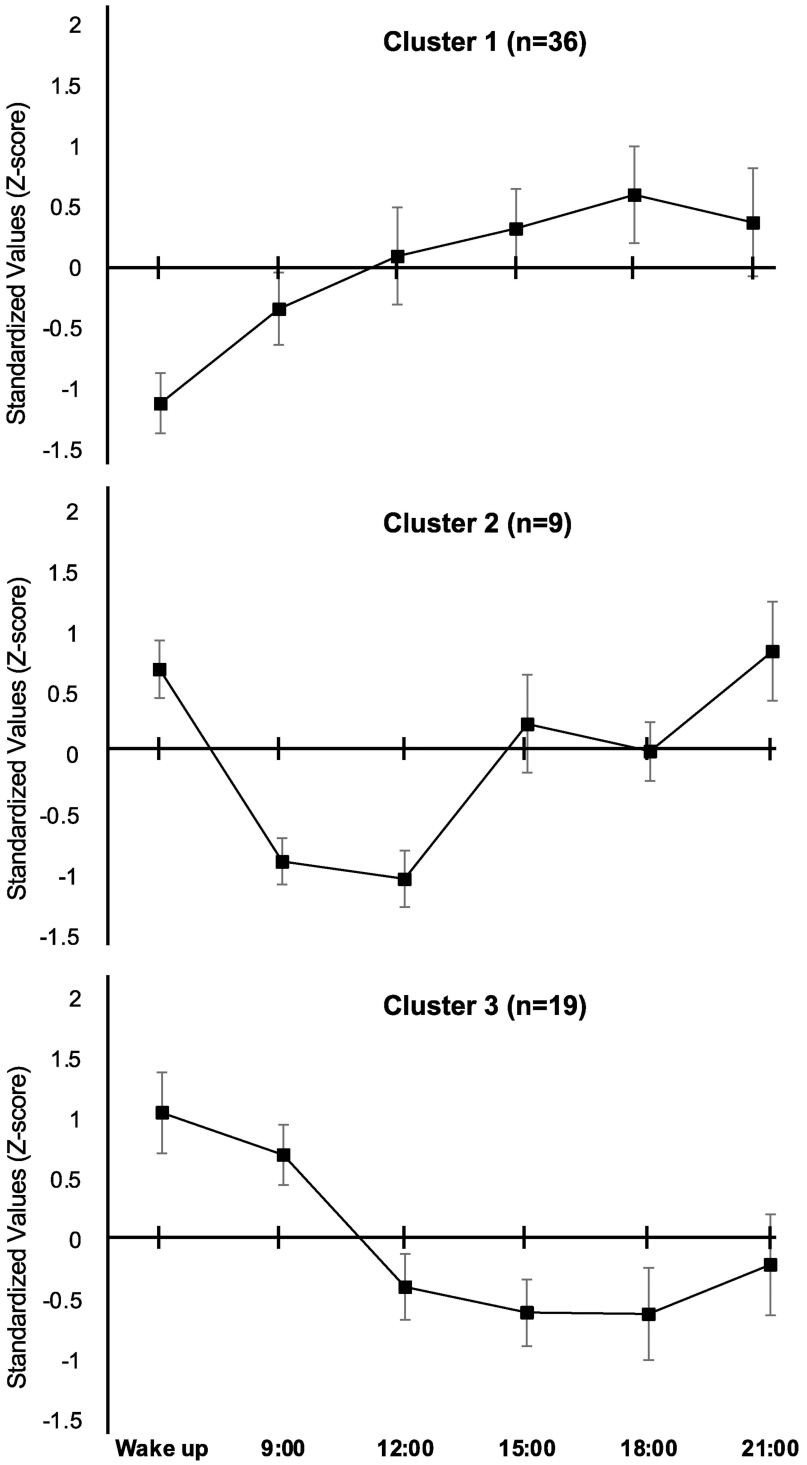

Figure 2 Categorization of the circadian rhythm of pain according to the 3-day evaluation (Tue–Thu). CL1 and CL3 adhere to the defined criteria, and mirroring clusters are observed during the 7-day assessment. A similar pattern emerges between wakefulness and 21:00 for CL2; however, the rhythmicity surpasses the Z-score threshold at 15:00, leading to its categorization as a separate cluster from the 7-day evaluation clusters. Each data point is displayed with an error bar.
Abbreviation: CL, cluster.

although the awakening VAS score of CL2 was similar to that of CL1, it failed to exhibit a progressive increase over time, with the Z-score falling below 0 at 15:00. Consequently, it was categorized as a distinct cluster that was not affiliated with any of the clusters observed in the 7-day evaluation.

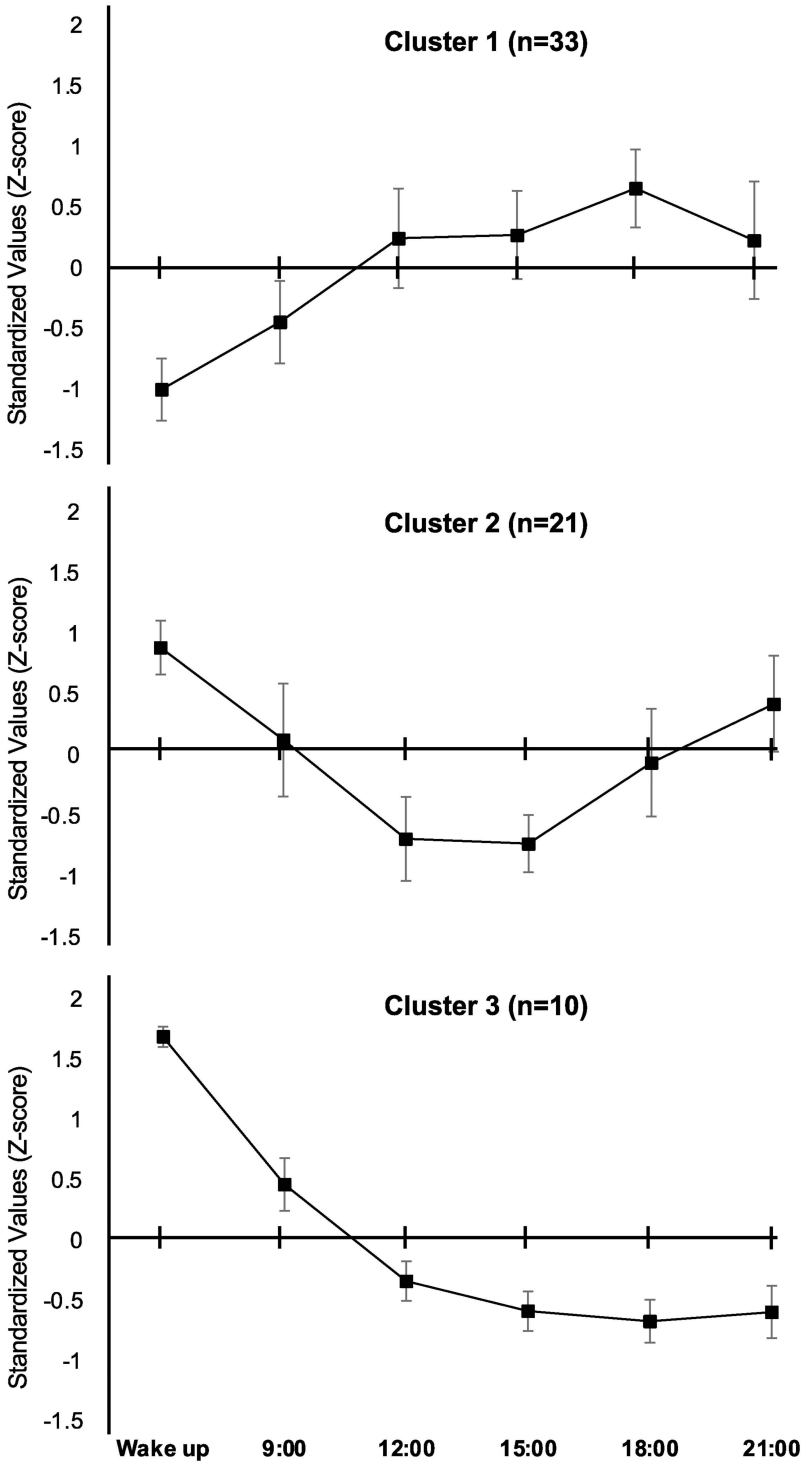

Figure 3 Categorization of the circadian rhythm of pain according to the 3-day evaluation (Fri–Sun). All clusters exhibit an analogous rhythmic pattern similar to that observed during the 7-day evaluation, resulting in their classification as akin clusters. Each data point is displayed with an error bar.

Assessment of Concordance Among Individual Clusters

Cohen's kappa coefficients, which indicate agreement levels among evaluation days, exhibited the following values: k=0.67 for the 3-day interval spanning from Tuesday to Thursday, k=0.77 for the 3-day interval spanning from Friday to Sunday, and k=0.34 for the 3-day interval spanning from Sunday to Tuesday. Notably, the analysis of agreement revealed that the highest Cohen's kappa coefficient was observed for the 3-day evaluation spanning from Friday to Sunday.

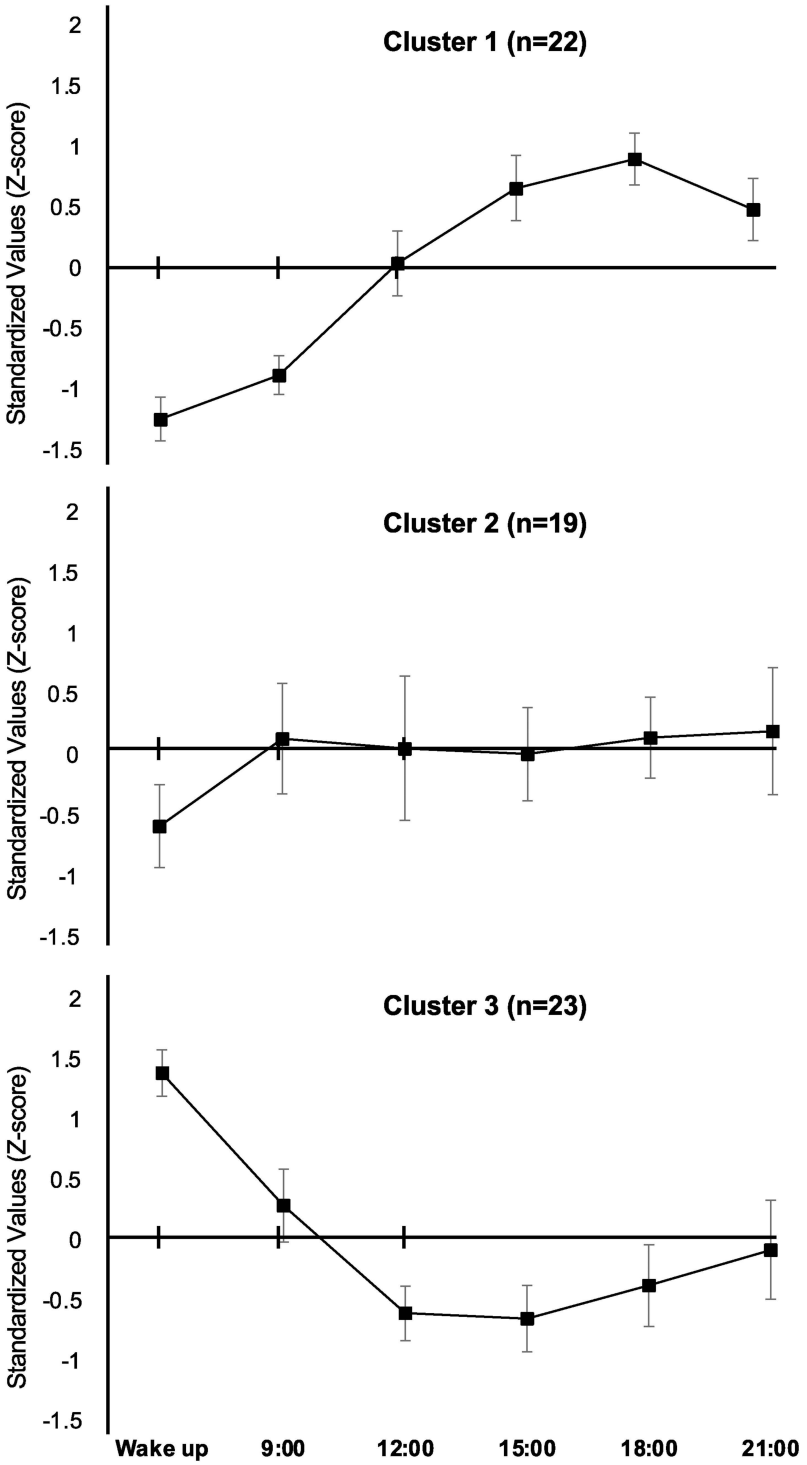

Figure 4 Categorization of the circadian rhythm of pain according to the 3-day evaluation (Sun–Tue). CL1 and CL3 match the 7-day evaluation clusters according to the predefined criteria. In contrast, CL2 does not show a progressive increase over time, with the Z-score falling below 0 at 15:00, despite having a similar awakening VAS value as CL1. As a result, it is classified as a separate cluster unrelated to the 7-day evaluation clusters. Each data point is displayed with an error bar.
Abbreviations: CL, cluster; VAS, visual analog scale.

Discussion

This study assessed the viability of reducing the period for evaluation of the circadian rhythm of pain from the customary duration of 7 days to a more concise timeframe of 3 days in patients with chronic pain within the same community. Pain localization was predominantly observed in the lower extremities in this study, which constituted the principal site of

pain in 43% of the patients. This collectively accounted for more than 70% of all cases when combined with those of upper extremity pain, and 23 participants displayed indicators of neuropathic pain. Furthermore, 45% of the participants reported receiving analgesics, and 37% were gainfully employed. An examination of the intra-observer variability in cluster outcomes derived from each of the three distinct 3-day assessments revealed the highest Cohen's kappa coefficient for the 3-day interval spanning from Friday to Sunday, in contrast to the outcomes of the cluster analysis for the 7-day assessments.

Circadian rhythms regulating the autonomic, endocrine, and hormonal systems are influenced by external behaviors, such as eating and physical activity, in addition to internal influence by the suprachiasmatic nucleus.[22] Physical activity is another factor that can alter the circadian rhythm of pain.[20,22] The amount of physical activity is not constant over all 7 days of the week, and it varies depending on the day of the week, such as weekdays and holidays.[32,33] Therefore, the 3-day evaluations were performed on three different days of the week in the present study to examine the agreement with the 7-day assessments.

The findings of the 3-day evaluation from Tuesday to Thursday (k=0.67) and that from Friday to Sunday (k=0.77) in this study showed values that were consistent with the Landis et al criteria.[31] Other reports on the validity of the kappa coefficient explicitly state that a kappa coefficient between 0.58 and 0.75 indicates a good agreement, while that greater than 0.75 indicates excellent agreement.[34] Byrt also reported that a kappa coefficient value between 0.61–0.80 denoted good agreement since it was unaffected by bias and prevalence.[35] Overall, the findings of the Tuesday–Thursday and Friday–Sunday 3-day ratings in the current survey are consistent with those of the 7-day overall ratings. However, the concordance level was deemed "fair" for the 3-day interval spanning from Sunday to Tuesday (k=0.34) according to the criterion delineated by Landis et al, indicating a diminished degree of agreement compared with those of other days of the week. Consequently, while the outcomes of the present study validated the efficacy of the 3-day evaluation, they concurrently underscored the variance in agreement levels contingent on the specific day of the week on which the evaluation was conducted. Therefore, if the circadian rhythm of pain assessment is shortened to 3 days, it may be necessary to consider the results of this study and make more careful decisions about the day of the week on which the assessment should be performed.

One of the rationales underpinning the variability in kappa coefficients across the 3-day assessments may be ascribed to the fluctuations in physical activity levels contingent on the day of the week. Among the patients included in this investigation, less than 40% of individuals were gainfully employed, indicating the possibility of divergent physical activity regimens between weekdays and weekends, notwithstanding work-related patterns. The availability of daycare services, facilitated by the insurance framework, was often suspended on Saturdays and Sundays even in the unemployed stratum, which may have resulted in potential disparities in physical activity levels between weekdays and holidays. Thus, based on the results of the present study and these points, the 3-day assessment performed on weekdays and holidays may be comparable with the results of pain rhythmicity over a 7-day period. The principal objective of this study was to investigate the feasibility of reducing the evaluation timeframe for the assessment of pain rhythmicity as the traditional 7-day assessment of pain rhythmicity could impose a substantial burden on patients and pose formidable challenges in its implementation as an evaluative metric. The findings of this study demonstrated that a 3-day assessment period, including holidays, yielded outcomes that were congruent with those of the conventional 7-day evaluation period, indicating the plausible viability of reducing the evaluation window in instances wherein the burden for the patients is anticipated to be onerous. The ability to shorten the assessment time will further establish the assessment of pain rhythmicity in clinical practice and may facilitate pain management that takes into account the pain rhythm at each time point. It is also believed that shorter assessment time will lead to earlier intervention and contribute to improved patient satisfaction. The status of patients with chronic pain must be solidified as an evaluative metric using diverse evaluation days to accommodate individual idiosyncrasies given the imperative nature of intricate pain assessment, exemplified by the scrutiny of pain circadian rhythms in the context of ameliorating the condition of patients with chronic pain and facilitating their reintegration into daily life activities.

Interpretation of the results of this study should be considered in light of several limitations. First, the sample size in this study was limited to 64 participants, and this should be considered when interpreting the results. Second, the diurnal oscillations of pain are intertwined with exogenous variables such as temperature, atmospheric pressure, and humidity;[20]

thus, it is imperative to acknowledge that the contribution of exogenous factors to the circadian rhythm of pain remains an unresolved facet owing to the non-standardized timing of data collection. Finally, the omission of a quantitative appraisal of physical activity affects the ability to definitively discern whether disparities in physical exertion transpired between weekdays and holidays or if the rhythmicity of pain was contingent upon varying levels of physical activity, as broached within the discourse. Future studies must endeavor to meticulously quantify physical activity concomitantly with the exploration of the circadian rhythm of pain to elucidate the intricate interplay between these two phenomena.

Conclusion

This study investigated the feasibility of condensing the assessment period of the circadian rhythm of pain in community-dwelling patients with chronic pain. The findings of the present study demonstrate the concordance of the results derived from the concise 3-day evaluation with those obtained through the traditional 7-day assessment. The ability to shorten the circadian rhythm of pain will further establish the assessment of pain rhythmicity in clinical practice and facilitate pain management that considers the rhythm of pain. In addition, it is believed that shorter evaluation time will lead to earlier intervention and contribute to improved patient satisfaction. Therefore, the results of this study suggest the need to establish a circadian rhythm pain assessment with a shorter 3-day assessment period to account for individual differences among patients.

Abbreviations

NRS, numeric rating scale; VAS, visual analog scale; DN4, Neuropathic Pain Diagnostic Questionnaire; SFMPQ2, Short-Form McGill Pain Questionnaire 2; NPSI, Neuropathic Pain Symptom Inventory; MBM, Michigan Body Map; BIC, Bayesian Information Criterion.

Data Sharing Statement

Data can be shared upon reasonable request.

Consent for Publication

There are no images, videos, recordings, etc. that require a publication consent form.

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Disclosure

The authors report no conflicts of interest in this work.

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