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REVIEW ARTICLE

The objective assessment of sleep in cluster headache: State of the art and future directions

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Summary

Several lines of evidence suggest that cluster headache is related to chronobiology and sleep. Nevertheless, the nature of such a relationship is unclear. In this view, the objective evaluation of sleep in cluster headache has strong theoretical and clinical relevance. Here, we provide an in-depth narrative review of the literature on objective sleep assessment in cluster headache. We found that only a small number of studies ($N = 12$) focused on this topic. The key research aims were directed to assess: (a) the relationship between cluster headache and sleep breathing disorders; (b) the temporal relationship between sleep stages/events and cluster headache attacks; (c) sleep macrostructure in patients with cluster headache. No studies considered sleep microstructure. The reviewed studies are heterogeneous, conducted by a few research groups, and often characterised by relevant methodological flaws. Results are substantially inconclusive considering the main hypothesis. We outline several methodological points that should be considered for future research, and suggest that evaluating sleep microstructure, local sleep electrophysiology and actigraphic measures may strongly increase knowledge on the relationship between sleep and cluster headache.

KEYWORDS

actigraphy, arousal, cluster headache, polysomnography, rapid eye movement sleep, sleep, sleep breathing disorders, sleep macrostructure

1 | INTRODUCTION

Cluster headache (CH) is the most common trigeminal autonomic cephalalgia, affecting up to 0.1% of the population (Fischera et al., 2008). This primary headache is characterised by recurrent attacks (15–180 min) of severe unilateral pain in the orbito-temporal area associated with ipsilateral autonomic symptoms. Attacks occur most frequently at specific times of the year, occurring in "cluster" or "bouts" that last weeks or months; their frequency can vary from once every 2 days to eight times per day. The International Classification of Headache Disorders, 3rd edition (ICHD-3), discriminates an episodic form of the disorder (eCH), with bouts from 7 days to 1 year separated by pain-free periods ≥ 3 months, and a chronic form (cCH), with bouts lasting 1 year or longer without remission or with out-of-bout periods lasting less than 3 months (Olesen, 2018). Such disorder represents a heavy burden for patients (Jensen et al., 2007) with relevant socio-economic costs (Gaul et al., 2011; Hoffmann & May, 2018; Olesen et al., 2012; Petersen et al., 2022).

The CH attacks occur regularly with circadian and seasonal rhythmicity (Barloese, Lund, et al., 2015; Rozen & Fishman, 2012), pointing to the existence of a link between chronobiological processes and CH. The relevance of the hypothalamus (where the main biological clock of the brain

is located) in CH pathophysiology is suggested by clinical, neuroendocrinological and neuroimaging evidence (Ferraro et al., 2019; Silvestro et al., 2022). Crucially, sleep seems to have a role in CH (Barloese, 2021; Pergolizzi Jr et al., 2020; Pilati et al., 2023): up to 80% of patients report nocturnal sleep as a trigger for CH attacks (Barloese, Lund, et al., 2015), and nocturnal attacks are more severe than daytime ones (Hagedorn et al., 2019). Moreover, patients exhibit reduced subjective sleep quality both during and outside the bout (Barloese, Lund, et al., 2015), and frequent insomnia (Ofte et al., 2013; Sahota & Dexter, 1993). Nevertheless, the specific nature of the relationship between sleep and CH is unclear. First, starting from the observation that CH attacks are more frequent during sleep, it is essential to understand if specific sleep-related processes or events represent predictors and/or triggers for CH attacks. Second, a clear description of sleep features in different conditions (e.g. nights with and without headache) and phases of the disorder (e.g. in bout and in remission) can help to determine if altered sleep represents a "stable" feature of patients with CH or a specific correlate of in-bout periods. Finally, it is important to clarify if sleep in CH is characterised by specific disorders or alterations, and whether they are merely correlates/consequences of CH or have a role in its pathophysiology. Until now, several hypotheses have been proposed concerning: (a) a possible role of rapid eye movement (REM) sleep as a trigger of CH attacks; (b) an association between sleep disorder breathing and CH; (c) reduced arousal in CH as a marker of altered sleep in patients with CH (Barloese, 2021; Pergolizzi Jr et al., 2020; Pilati et al., 2023). Clearly, the objective evaluation of sleep in CH is necessary to answer these questions, but only a few studies provided this kind of assessment.

The present paper is aimed to provide a comprehensive narrative review of the state of the art on the objective evaluation of sleep in CH. Specifically, we will assess in depth the questions that guided research in this field, highlighting the methodological features and limitations of the available studies and the main results obtained. We will discuss the actual support of the present results to the proposed theories on the relationship between sleep and CH, also considering methodological facets. Finally, we will outline future directions for the research in this field, considering a theoretical and methodological framework provided by the current knowledge on sleep regulation processes and functions.

2 | METHODS

2.1 | Search method

We performed a literature search through PubMed, Scopus, and Web of Science, considering the available studies up to March 2023. Search terms included: "sleep", "microstructure", "macrostructure", "polysomnography", "PSG", "EEG", "electroencephalography", "actigraphy", "actigraph", "NREM", "REM", "slow wave sleep", "sleep disorders", "sleep disturbances", "sleep apnea", "OSAS", "insomnia", "headache", "cluster headache", "chronic headache", "episodic headache". Search terms had to be included in the title, abstract or keywords.

2.2 | Inclusion/exclusion criteria

Two authors (MG, GG) screened titles, abstracts and keywords independently to meet the following criteria: (a) English language; (b) peer-reviewed paper; (c) empirical study; (d) objective assessment of sleep features; (e) focus on patients with CH. Considering the relatively small literature on this topic, we included in the review also uncontrolled descriptive studies. Books, abstracts, comments, reviews, meta-analyses, pre-prints, letters to editor, and single case studies were excluded. Instances and disagreements concerning study eligibility were resolved through careful consultation and discussion. The reference lists of the selected articles were further reviewed for other potential papers. If a reference included some of the search terms in the title, it was considered as a potential paper of interest and checked for the inclusion/exclusion criteria.

3 | RESULTS

The main features and results of the reviewed studies are reported in Table 1. Overall, 12 studies published between 1984 and 2019 met the inclusion criteria, and were considered in the present review (see flowchart in Figure 1). Of these, 11 studies performed polysomnographic (PSG) recordings to assess sleep, while only one study used actigraphy (Lund, Snoer, Jennum, et al., 2019). Among PSG evaluations, one study (Evers et al., 2014) used MESAM, a device designed to provide a polygraphic screening for sleep apnea. Four studies had a substantially descriptive nature (Graff-Radford & Newman, 2004; Kudrow et al., 1984; Pfaffenrath et al., 1986; Terzaghi et al., 2010), and only six studies provided a comparison with a healthy control (HC) group (Barloese, Jennum, et al., 2015; Evers et al., 2014; Lund, Snoer, Jennum, et al., 2019; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003, 2005). The study sample sizes ranged from five subjects (all patients with CH; Zaremba et al., 2012) to 80 participants (32 eCH in bout, 23 eCH in remission, and 25 HC; Lund, Snoer, Petersen, et al., 2019) for PSG studies, while the actigraphy study was performed on 23 patients with eCH compared with 15 HC (Lund, Snoer, Jennum, et al., 2019). Almost all PSG studies performed a single-night recording, except Pfaffenrath et al. (1986) who performed two consecutive sleep recordings, Zaremba et al. (2012) who performed four consecutive PSG recordings, and Evers et al. (2014) who performed the MESAM recordings twice: in-bout and symptom-free period. In the actigraphic study, participants wore the actigraph for 2 weeks (Lund, Snoer, Jennum, et al., 2019).

Four studies did not provide information about medications management during the experimental protocol (Chervin et al., 2000; Evers et al., 2014; Graff-Radford & Newman, 2004; Nobre et al., 2005). In three studies, all medications were withdrawn 1 week prior to sleep recording (Nobre et al., 2003; Pfaffenrath et al., 1986; Zaremba et al., 2012). One study reported that six out of seven patients were not under treatment for headache attacks, while one was on daily verapamil (Terzaghi et al., 2010). Finally, two studies report that medications were kept stable 1 week before (Barloese, Jennum, et al., 2015) and during the study period (Lund, Snoer, Jennum, et al., 2019). Five studies specified that patients had the possibility to

TABLE 1 Studies focused on objective sleep assessment in CH.

Authors	Sample size	Mean age (range)	Medication	Study design	Inclusion and exclusion criteria	Sleep recording setting	Key findings
PSG studies							
1. Kudrow et al. (1984)	5 eCH (5 M) 5 cCH (4 M)	eCH: 54.8 ± 10.9 years cCH: 40.4 ± 11.9 years	Patients were allowed to self-administer oxygen inhalation at 71/min for up to 15 min in the event of cluster attacks occurring during the sleep study	One night PSG in laboratory Unspecified if patients were recorded during the active cycle of the headache disorder	Unspecified	Two EEG channels (C3 and P4) Left and right EOG chin EMG; left and right anterior tibialis EMG EKG; nasal and buccal thermistors; abdominal and thoracic strain gauges; ear oximeter	Six out of 10 patients with CH had sleep apnea Attack onset occurred with greater frequency in cCH during later hours; while in eCH, onset was equally distributed throughout the night. Of 19 attacks experienced by both groups, 42% occurred during the last 2 h of sleep
2. Pfaffenrath et al. (1986)	9 cCH (4 M)	58.8 ± 19.8 years (27–81 years)	All medication was withdrawn 1 week prior to the sleep recording Attacks were treated with oxygen inhalation	Two consecutive PSG recordings in sleep laboratory	Diagnosis of CH was based upon the criteria of the World Federation of Neurology and those of Ekbom All patients have experienced CH attacks with regular nocturnal onset during the past 2 years	EEG (channels not specified) EOG EMG; microphone	In 12 out of 17 nights recorded, eight patients had a total of 25 CH attacks Three patients awoke during REM sleep with a CH attack Except for two patients, all had attacks in stage 2 sleep Two patients had additional arousals in stage 3 sleep Five CH attacks occurred in REM sleep, 11 in stage 2, four in stage 1, and two in stage 3 One patient exhibited three attacks during wakefulness Headache nights had reduced frequency and length of REM periods, reduced SE, and higher number of awakenings and sleep stage shifts
3. Chervin et al. (2000)	25 CH (22 M) • 23 eCH • 2 cCH	43 ± 14 years	Unspecified	24-hr continuous ambulatory PSG Only 8 subjects out of 25 were recorded during the cluster period	CH criteria of the IHS No diagnosis of SDB	Four EEG channels (C3-A2, C4-A1, O1-A2, and O2-A1) Two EOG leads (right and left outer canthi) Chin and bilateral anterior tibialis surface EMG Two EKG leads Nasal and oral airflow (thermistors) Thoracic and abdominal excursion (piezoelectric strain gauges) Finger oximetry	Frequent SDB among individuals with CH (80%) Patients with active CH showed higher maximum end-tidal carbon dioxide levels than those with inactive CH

(Continues)

TABLE 1 (Continued)

Authors	Sample size	Mean age (range)	Medication	Study design	Inclusion and exclusion criteria	Sleep recording setting	Key findings
4. Nobre et al. (2003)	16 eCH (14 M) 29 HC (26 M)	eCH: 40 years (26–55 years) HC: 37 years (19–59 years)	Patients were seen during cluster periods, while using prophylactic medication on a regular basis The medication was discontinued 1 week before the PSG	Nocturnal PSG eCH were recorded during the cluster period	Patients with concomitant heart disease, pulmonary disease or haematological disease were excluded The presence of significant brain computerised tomography abnormalities was established as exclusion criterion	EEG (channels not specified) Right and left EOG Submental EMG EKG Nasal and oral thermistors Thoracic and abdominal excursion Finger oximetry	Five out of 16 (31.3%) patients with eCH and two out of 29 HC (10.3%) presented sleep apnea Increased stage 1 NREM sleep in patients with eCH Two patients with sleep apnea had two CH attacks during the study period that followed episodes of oxygen desaturation and were associated with REM sleep In two patients with sleep apnea and CH, treatment with continuous positive airway pressure abolished their oxygen desaturation, sleep apneas and headaches
5. Graff-Radford & Newman (2004)	31 eCH (M 23)	51 years (33–78 years)	Unspecified	PSG in sleep laboratory Unspecified if patients with eCH were recorded during the active cluster cycle	IHS diagnosis for CH	Unspecified	80.64% of patients had sleep apnea Average respiratory depression index was 19.0 Oxygen saturation decreased on average to 88.4% SE was 76.2%
6. Nobre et al. (2005)	37 eCH (31 M) 35 HC (31 M)	Not reported	Unspecified	Nocturnal PSG Unspecified if patients with eCH were recorded during the active cluster cycle	Patients with associated heart, lung and haematological diseases were excluded Absence of chronic headache or any complaint of health problem in HC	Four EEG derivations (C3-A2, C4-A1, O1-A2, and O2-A1) Two EOG Chin and bilateral anterior tibialis surface EMGs Two EKG leads Nasal and oral airflow Thoracic and abdominal excursion Finger oximetry	Greater apnea–hypopnea index in patients with CH Patients with CH had 8.8 times more chance of OSA than HC The risk increases to 26 in patients with BMI > 25 kg m^{-2}, and increases to 14.25 in patients > 40 years old The risk diminishes sharply in patients with BMI < 25 kg m^{-2} and < 40 years old
7. Terzaghi et al. (2010)	7 eCH (all M)	38.4 ± 9.2 years (range: 29–54 years)	Six patients were not under treatment for their nocturnal headache attacks One patient was on verapamil 360 mg daily	24-hr continuous ambulatory PSG All patients were in active cluster cycle	ICHD-II criteria for a diagnosis of eCH No subject Reported symptoms suggestive of sleep apnea The patients were instructed not to change their usual sleep–wake cycle and scheduled activities	Eight EEG electrodes (Fp2; Fp1; C4; C3; T4; T3; O1; O2) referred to Fz Horizontal bipolar EOG montage Chin EMG Heart rate	Five CH attacks reported during sleep: four during NREM sleep, one during REM sleep Three NREM sleep-related episodes arose during stable stage 2 sleep, and the other one, towards morning, during a mixed state of unstable stage 2 sleep and wakefulness
8. Zaremba et al. (2012)	5 CH (all M) • 2 eCH • 3 cCH	54.4 ± 4.39 years (50–60 years)	No prophylactic medication before/during study (one patient stopped lithium/verapamil 1 week before) Two patients: triptans/other: O2	PSG during four consecutive nights	Participants reported nocturnal CH attacks during similar times almost every night before study inclusion	Two-channel EEG EKG	20 CH attacks: 7 from wakefulness, 13 from NREM sleep (without significant differences between NREM stages) Higher percentage of total wake time and lower stage 1 NREM

TABLE 1 (Continued)

Authors	Sample size	Mean age (range)	Medication	Study design	Inclusion and exclusion criteria	Sleep recording setting	Key findings
							sleep and SE in nights without headache compared with those with headache in all patients
						EOG	Higher total wake time and NREM stage 3 amount and lower SE during nights without headache than nights with headache in patients with cCH
						Chin EMG	Higher total wake time, TST, NREM stage 2 percentage, and lower NREM stage 1 sleep percentage, arousal index and SE during nights without headache than nights with headache in eCH
						Thoracic and abdominal respiratory efforts (impedance plethysmography)	Total wake time and arousal index were lower and SE was higher in cCH compared with eCH during nights without headache SL was lower in cCH during nights with headache
						Body position (position sensor) Oxygen saturation (pulse oximetry) Surface EMG of tibialis muscles Oronasal airflow (nasal cannula)	Overall, total wake time and NREM stage 4 sleep percentage were lower in cCH compared with eCH
9. Evers et al. (2014)	42 CH (40 M) • 26 eCH • 16 cCH	CH: 45 ± 9 years	Unspecified	MESAM recordings	CH diagnosis according to IHS criteria, 2nd edition	Flow at mouth and nose	Patients with CH had a significantly higher respiratory distress index compared with HC, with higher desaturation index More patients than HC fulfilled the criteria for OSAS
		HC: 47 ± 8 years		In patients with eCH, recording was made twice, once in cluster period and once in a symptom-free interval		Oxygen saturation	eCH showed a significantly higher respiratory distress index, OSAS, central apneas, desaturation index during the cluster period than outside the episode
	28 HC (25 M)			Ten patients used the device in the hospital as inpatients The remaining patients and all control subjects used the device at home		Thoracic and abdominal expansion Heart rate EKG Movements/body position Pressure of continuous positive airway pressure (if applicable)	No difference in PSG parameters between nights with and without headache clusters
10. Barloese, Lund, et al. (2015)	40 CH (29 M) → 21 eCH → 19 cCH	CH: 44.2 ± 11.2 years	If patients were on prophylactic medication, this was kept stable for at least 7 days prior to the investigation	Two PSG recordings for patients and one for HC	CH diagnosis according to ICHD-2 criteria	Six EEG channels (F3, C3, O1-A2, F4, C4, O2-A1)	Lower REM density and latency in patients with CH compared with HC

(Continues)

TABLE 1 (Continued)

Authors	Sample size	Mean age (range)	Medication	Study design	Inclusion and exclusion criteria	Sleep recording setting	Key findings
		HC: 47.6 ± 12.1 years	Patients would attempt to treat their attacks using oxygen but were allowed to use other medication such as injectable or nasal triptans, as a rescue	Patients were recorded during the active cycle of the headache disorder and at least 2 weeks in the bout	Exclusion criteria were other chronic primary or secondary headaches, and serious somatic or psychiatric illness	Vertical and horizontal EOG	Lower SE and longer SL in patients with CH compared with HC
	25 HC (16 M)				HC did not suffer from chronic headaches, sleep disorders or any other health problem	Submentalis and tibialis anterior muscle EMG	No temporal association between REM sleep, any other sleep stage or particular sleep-related events, including apneas and desaturations, and observed, spontaneous nocturnal CH attacks
						EKG	Fewer arousals in patients with CH
						Nasal airflow	No difference in prevalence of sleep apnea between patients with CH and HC
						Abdominal and thoracic respiratory effort	
						Oxygen saturation	
						Video	
11. Lund, Snoer, Jennum, et al. (2019)	32 eCH in bout (81.3% M)	eCH in bout: 45.4 years	Attacks during admission were preferably treated with oxygen, but triptans were accepted	PSG recording →15 eCH participated both in disease phases	-eCH: Previous bouts > 2 weeks; 1–8 attacks per day	Six EEG derivation (F3, C3, O1, F4, C4, O2) referenced to the contralateral mastoid	No difference for patients with CH in bout and remission for TST, SE, SL, REM sleep latency, distribution of sleep stages and PLMs, LMs, arousal per hr and apnea–hypopnea index
		eCH in remission: 43.7 years			CH attacks clearly distinguishable from other headache attacks	Vertical and horizontal EOG	Compared with HC, patients in bout exhibited longer SL and REM sleep latency, lower SE and lower REM sleep density
	23 eCH in remission (73.9% M)	HC: 48.0 years			Preventive therapy stable for > 1 week; O2 prefer but also triptans	Submentalis and tibialis anterior muscles EMG	Compared with HC, patients in remission had longer SL
	25 HC (68.0% M)				Exclusion: chronic primary headache disorder; secondary headache disorder; serious somatic/psychiatric illness; alcohol abuse; psychopharmacological drug different from lithium; pregnancy/breast feeding; transitional therapy (GON)	EKG Nasal air flow	43.8% of patients suffered from at least one CH attack Attacks were unrelated to sleep stage, apnea episodes, PLMs, LMs and arousals However, they were preceded by fragmented sleep, with rapid shifts between different sleep stages, arousals and wake in four patients
					HC were excluded if they suffered from chronic headache, sleep disorders or any other health problems	Abdominal and thoracic respiratory effort Oxygen saturation Video	No differences were observed between nights with and without attacks in patients in bout
Actigraphic study							
12. Lund, Snoer, Jennum, et al. (2019)	23 eCH (78.3% M)	eCH: 43.6 years	Alterations in headache preventive treatment within the last week prior to	Controlled actigraphy study with sleep log for 2 weeks	eCH Age: 18–66 years; steady attack pattern; CH attacks	Participants wore the actigraph on the non-dominant wrist	Compared with HC, patients with CH in bouts spent more time in bed and TST was longer, while

TABLE 1 (Continued)

Authors	Sample size	Mean age (range)	Medication	Study design	Inclusion and exclusion criteria	Sleep recording setting	Key findings
			participation were not permitted Patients were asked to keep their medication stable during the study period		clearly distinguishable from other headache attacks Exclusion: chronic primary headache disorder; secondary headache disorder; psychopharmacological drug different from lithium		actigraphic measures were comparable
	15 HC (73.3% M)	HC: 43.0 years		17 eCH actograms recorded in bout; 11 eCH actograms in remission Five patients participated in both disease phases		Epoch length: 30 s Activity count ≥ 80 per epoch was detected as wake; 10 min of immobility marked as sleep onset	No differences observed between HC and patients in remission No difference between patients with eCH in two disease phases
					HC Age: 18–66 years; excluded if they suffered from primary headache disorders for more than 1 day per month on average or any secondary headaches Common exclusion criteria: mild to moderate depression; pregnancy or breastfeeding; severe somatic or psychiatric diseases; moderate to severe chronic obstructive lung disease; moderate to severe cardiovascular disease; cardiac rhythm disorders; known sleep apnea (treated or untreated); treatment with sleep medication within the last week and during the study period; reported alcohol consumption higher than 168 and 84 grams of alcohol per week for men and women, respectively; shift work; holiday lasting longer than the normal weekend All participants had to be able to speak and read Danish		No differences between in-bout patients with and without night attacks In five out of the 10 patients that suffered from nocturnal attacks, CH attacks/awakenings occurred around the same hour several nights in a row The time was individual for each patient, but did not seem to be related to the sleep duration preceding the attacks/awakenings Awakenings at the same hour several nights in a row were not observed in patients in remission or in controls

Note: Main methodological features and key findings are reported.

Abbreviations: BMI, body mass index; cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; EEG, electroencephalography; EKG, electrocardiography; EMG, electromyography; EOG, electrooculography; HC, healthy controls; ICHD-II, International Classification of Headache Disorders, 2nd edition; IHS, International Headache Society; LMs, limb movements; M, males; min, minutes; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; OSAS, obstructive sleep apnea syndrome; PLMs, periodic limb movements; PSG, polysomnography; REM, rapid eye movement; SDB, sleep-disordered breathing; SE, sleep efficiency; SL, sleep latency; TST, total sleep time.

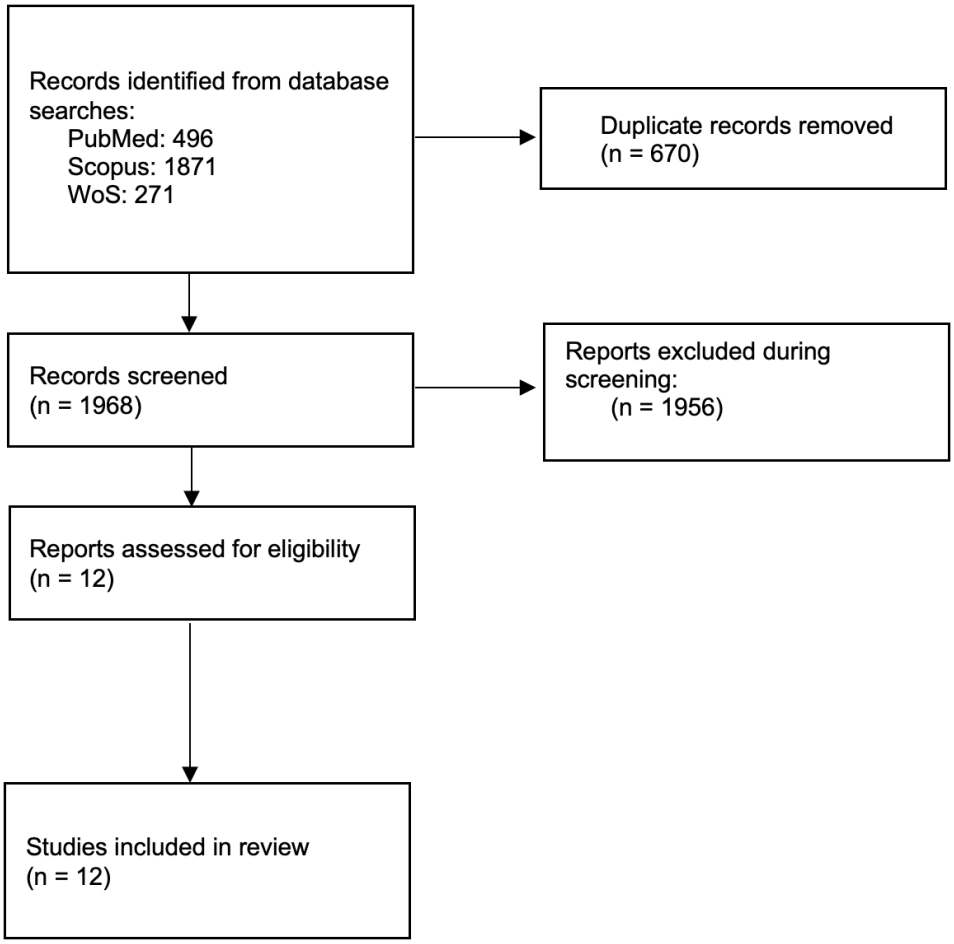

FIGURE 1 Flowchart of the literature search and study selection.

treat headache attacks during the study using oxygen inhalation (Barloese, Jennum, et al., 2015; Kudrow et al., 1984; Lund, Snoer, Petersen, et al., 2019; Pfaffenrath et al., 1986; Zaremba et al., 2012) and triptans (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019; Zaremba et al., 2012). The reviewed literature is characterised by large variability in inclusion and exclusion criteria. Moreover, while several studies included only patients with cCH (Pfaffenrath et al., 1986) or eCH (Graff-Radford & Newman, 2004; Lund, Snoer, Jennum, et al., 2019; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003, 2005; Terzaghi et al., 2010), others included both CH subtypes (Barloese, Jennum, et al., 2015; Chervin et al., 2000; Evers et al., 2014;Kudrow et al., 1984; Zaremba et al., 2012).

Considering the phase of the pathology in which patients were recorded, two studies did not clarify if recordings were performed during or outside the active cycle of the headache disorder (Kudrow et al., 1984; Nobre et al., 2005). In the study from Chervin et al. (2000), only eight subjects out of 25 were recorded during the cluster period. Lund, Snoer, Petersen, et al. (2019) compared patients with CH in bout with patients with CH in remission and HC. Only the MESAM study compared PSG measures collected during and outside the episode in the same patients with eCH (Evers et al., 2014). In the actigraphic study, 17 eCH actograms were collected in bout and 11 in remission (Lund, Snoer, Jennum, et al., 2019).

All PSG studies described the sensors used for the recordings with only one exception (Graff-Radford & Newman, 2004). Concerning the electroencephalogram (EEG) montage, the scalp derivation goes from 2 (Kudrow et al., 1984; Zaremba et al., 2012) to 8 (Terzaghi et al., 2010), but one study did not perform EEG monitoring (Evers et al., 2014) and another one did not specify the EEG montage (Nobre et al., 2003).

The reviewed studies had different specific research aims. In particular, we can classify the following for PSG studies: (a) assessment of the relationship between CH and sleep breathing disorders (Barloese, Jennum, et al., 2015; Chervin et al., 2000; Evers et al., 2014; Graff-Radford & Newman, 2004; Kudrow et al., 1984; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003, 2005); (b) assessment of the temporal relationship between sleep stages/events and the emergence of CH attacks (Barloese, Jennum, et al., 2015; Lund, Snoer, Jennum, et al., 2019; Pfaffenrath et al., 1986; Terzaghi et al., 2010; Zaremba et al., 2012); and (c) assessment of sleep macrostructure in patients with CH (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003; Pfaffenrath et al., 1986; Zaremba et al., 2012). No PSG study performed an evaluation on sleep microstructure and local EEG measures. The actigraphic study aimed to assess time in bed, total sleep time (TST), sleep latency, sleep efficiency and wake after sleep onset in patients with eCH in bout and in remission, and in HC (Lund, Snoer, Jennum, et al., 2019).

3.1 | Relationship between CH and sleep breathing disorders

Several observational studies suggested that sleep apnea was common in eCH attacks. In particular, an early uncontrolled work conducted on a small sample found that six out of 10 patients with eCH had sleep apnea, and most recorded nocturnal attacks were preceded by oxyhaemoglobin desaturation (Kudrow et al., 1984). Similarly, Chervin et al. (2000) found a high frequency (80%) of obstructive sleep apnea (OSA) in their sample of 25 patients with CH. Moreover, patients with active CH had greater maximum ends-tidal carbon dioxide levels compared with inactive CH, and more severe oxygen desaturation was related to a typical occurrence of attacks reported in the first half of the nocturnal sleep period (Chervin et al., 2000). In their uncontrolled observational study, Graff-Radford and Newman (2004) also found a high percentage of OSA (80.64%) among 31 patients with CH.

Only five PSG studies investigated the relationship between CH and sleep breathing disorders providing a comparison with HC. Nobre et al. (2003) found that sleep apneas were present in five out of 16 patients with eCH (31.3%), and only two out of 29 HC (6.9%). On a descriptive level, the authors also observed two CH attacks during the study period in two patients with sleep apnea, both following episodes of oxygen desaturation associated with REM sleep. Moreover, treatment with continuous positive airway pressure abolished oxygen desaturation, sleep apnea and headaches in two patients. In a larger group of patients with eCH, the authors found a significantly higher percentage of OSA diagnosis (59.5%) compared with HC (14.3%; Nobre et al., 2005). Examining the apnea–hypopnea index in relation to body mass index (BMI) and age, patients with CH had 8.8 times more chance of OSA than HC. The risk increases to 26 in patients with BMI > 25 kg m^{-2} and 14.25 in patients > 40 years old (Nobre et al., 2005). Nevertheless, it should be considered that information about the age of the participants was not reported in this study. More recently, using the MESAM device, Evers et al. (2014) found in the larger sample of CH assessed in this field a significantly higher respiratory distress index in patients with active CH than HC, with a greater desaturation index. Moreover, more patients with CH (29%) than HC (7%) fulfilled the obstructive sleep apnea syndrome (OSAS) criteria, and only patients had central apneas. No changes in PSG breathing parameters were found between nights with and without CH. However, full PSG was not recorded in this study, and no exclusion criteria were reported. On the other hand, in a large sample recorded during two PSG nights, Barloese, Jennum, et al. (2015) found no difference in the prevalence of sleep apnea between patients with CH and HC. Moreover, the authors report the absence of a temporal association between apneas/desaturation events and spontaneous nocturnal attacks recorded during the study. Similarly, Lund, Snoer, Petersen, et al. (2019) found no difference in breathing parameters between patients with CH in bout, in remission, and HC, and detected CH attacks were unrelated to apnea episodes.

Overall, the results about the relationship between sleep breathing disorders and CH appear conflicting. Albeit several studies suggest the existence of such a relationship, many of them were uncontrolled, performed on small samples, or characterised by several methodological flaws (i.e. absence of information about age; absence of exclusion criteria). The studies with the higher quality level found no relationship between sleep apnea and CH (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019), but they were performed by a single Danish research group and need replication.

3.2 | Temporal relationship between CH attacks and sleep stages and events

In their descriptive observational study, Kudrow et al. (1984) found that, among 14 CH attacks recorded in 6 patients with eCH with sleep apnea, eight (57%) arose from REM sleep. Another early observational study described 25 CH attacks during sleep in a small group ($N = 9$) of patients with cCH, showing that 20% of the attacks occurred during REM sleep, 44% during stage 2, 16% in stage 1%, and 8% in Stage 3 (Pfaffenrath et al., 1986). More recently, Terzaghi et al. (2010) recorded eight CH attacks in four out of seven patients with eCH: four out of five attacks that occurred during sleep arose from stage 2 sleep, and one from REM sleep. Zaremba et al. (2012) collected 20 CH attacks in five patients undergoing four consecutive PSG recordings: seven attacks arose from wakefulness and 13 from non-rapid eye movement (NREM) sleep, without significant difference between NREM sleep stages. More recent controlled studies were conducted on a larger number of PSG recordings. In 45 CH attacks recorded during 74 nights of PSG in 40 patients, Barloese, Jennum, et al. (2015) found no temporal association between spontaneous attacks and specific sleep stages or events. Similarly, Lund, Snoer, Petersen, et al. (2019) described CH attacks in 14 out of 32 patients in bout, showing the absence of a relationship between CH attacks and sleep stages, albeit attacks were preceded by sleep fragmentation, with rapid shifts between different stages, arousals and wake in four patients.

In summary, the present literature does not support the existence of a temporal relationship between specific sleep stages/events and the emergence of CH attacks.

3.3 | Sleep macrostructure in patients with CH

A first description of sleep macrostructure in patients with CH showed that headache nights were characterised by reduced frequency and length of REM periods, reduced sleep efficiency, and a higher number of awakenings and sleep stage shifts (Pfaffenrath et al., 1986).

Zaremba et al. (2012) recorded four consecutive PSG nights in a small group of patients with CH ($N = 5$; 2 eCH and 3 cCH), showing that nights with headache were characterised by lower total wake time and higher stage 1 sleep and sleep efficiency compared with nights without headache. Considering only cCH, nights with headache showed lower total wake time and Stage 3 sleep amount and higher

sleep efficiency compared with nights without headache. Moreover, eCH showed lower total wake time, TST, stage 2 sleep percentage, and higher stage 1 sleep percentage, arousal index and sleep efficiency during nights with headache. Compared with eCH, cCH showed lower total wake time and arousal index and higher sleep efficiency during nights without headache, lower sleep latency in nights with headache, and overall lower total wake time and stage 4 sleep percentage (Zaremba et al., 2012). Nevertheless, these results have been not replicated.

In a first attempt to compare sleep architecture in patients with CH and HC, the authors found increased stage 1 sleep in patients with CH (Nobre et al., 2003). In a larger group, Barloese, Jennum, et al. (2015) showed that, compared with HC, patients with CH were characterised by lower REM density and latency, reduced sleep efficiency, longer sleep latency, and fewer arousals. Finally, a recent study from the same group compared for the first time sleep macrostructure in CH in bout, in remission, and HC (Lund, Snoer, Petersen, et al., 2019). No difference in sleep macrostructure and sleep events was found between PSG nights of patients in bout and in remission. Compared with HC, patients in bout showed longer sleep latency and REM sleep latency, lower sleep efficiency and lower REM sleep density, while patients in remission exhibited only longer sleep latency. Among patients in bout, the authors found no difference between nights with and without attacks (Lund, Snoer, Petersen, et al., 2019).

Taken together, the literature on sleep macrostructure in patients with CH is quite heterogeneous. Only five studies assessed this topic, with different specific aims: comparison between nights with and without headache (Pfaffenrath et al., 1986; Zaremba et al., 2012); comparison between patients with eCH and cCH (Zaremba et al., 2012); comparison between patients with CH and HC (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003); and comparison between patients in bout and in remission (Lund, Snoer, Petersen, et al., 2019). The most consistent findings provided by a couple of studies from a single research group point to longer sleep latency, reduced sleep efficiency and lower REM density in CH compared with HC (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019).

3.4 | Actigraphic findings

Only one study collected actigraphic sleep measures in eCH and HC during a continuative period (Lund, Snoer, Jennum, et al., 2019). The authors recorded actigraphic measures for 2 weeks in 23 patients with eCH and 15 HC. Among eCH, 17 eCH actograms were recorded in bout and 11 eCH actograms in remission. Five patients participated in both disease phases. Results showed that patients with eCH in bout had a longer time in bed and TST compared with HC, while actigraphic measures were comparable. On the other hand, no difference was observed between HC and patients in remission, between eCH in the two disease phases, and between nights with and without attacks. The authors also described that, in five out of the 10 patients that exhibited nocturnal attacks during the study, CH attacks/awakenings were detected around the same hour several nights in a row. The time was individual for each patient and appeared unrelated to previous sleep duration. Patients in remission and HC did not exhibit awakenings at the same hour several nights in a row.

4 | DISCUSSION

The number of studies focused on the objective sleep assessment in CH is small, including 12 papers in a period of 33 years (1986–2019) if we exclude single case reports. Despite the scientific interest on this topic (Barloese, 2021; Pergolizzi Jr et al., 2020; Pilati et al., 2023), no studies have been performed during the last 3 years. The reviewed literature is heterogeneous, characterised by several methodological issues, and conducted by a few research groups. Taken together, these points most likely highlight the intrinsic difficulties of performing research studies on objective sleep measures in a rare condition like CH (Barloese, 2021). Consistently, the main hypotheses proposed until now to describe the relationship between sleep and CH are not supported by striking evidence at present.

One frequently discussed hypothesis in this field concerns the existence of a causal relationship between OSAS and CH. Indeed, early (mainly uncontrolled) studies found a large prevalence of OSAS in patients with CH (Chervin et al., 2000; Graff-Radford & Newman, 2004; Kudrow et al., 1984). More recent studies that compared patients with CH with HC found conflicting results about the prevalence of sleep breathing disorders in this population (Barloese, Jennum, et al., 2015; Evers et al., 2014; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003, 2005). Two well-conducted Danish studies found no temporal relationship between CH attacks and apnea episodes or desaturation events (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019). Therefore, the literature on this issue is inconclusive. It has been proposed that sleep apnea and CH are not causally associated, but may represent parallel hypothalamus-related processes (Graff-Radford & Teruel, 2009).

Another theory claims a role of REM sleep as a trigger of CH attacks, suggested by the observed trend of arising attacks about 90 min after sleep onset (Barloese, Lund, et al., 2015; Manzoni et al., 1981, 1983), which should coincide with the first REM episode of the night. However, the reviewed literature does not support the notion of a specific temporal relationship between REM sleep (or any other sleep stages/events) and CH attacks. Sleep fragmentation has been recently reported before the attacks (Lund, Snoer, Petersen, et al., 2019), but it has been interpreted as a secondary phenomenon caused by pain instead of an attack trigger. An intriguing observation came by the recent 2-week assessment performed by the only actigraphic study reviewed (Lund, Snoer, Jennum, et al., 2019): in half of the patients in which nocturnal attacks were recorded, CH attacks and awakenings were detected around the same hour several nights in a row, with an individual timing for each patient not related to previous sleep duration. On the other hand, this pattern of stable timing for nocturnal awakening has not been observed in patients in remission and HC

(Lund, Snoer, Jennum, et al., 2019). If confirmed, this finding may suggest that nocturnal CH attacks are not triggered by specific sleep macrostructural features per se but can be explained by involvement of the circadian system. In particular, the possibility that the nocturnal recurrence of CH is due to an intrinsic circadian rhythm independent of the sleep–wake cycle cannot be excluded. Further studies, and actigraphic studies in particular, are needed to clarify this point.

Concerning the description of sleep macrostructure in patients with CH, the literature is small and dissimilar concerning the difference between nights with and without headache (Pfaffenrath et al., 1986; Zaremba et al., 2012), while single studies compared eCH and cCH (Zaremba et al., 2012) and patients in bout and in remission (Lund, Snoer, Petersen, et al., 2019). Only three studies compared sleep macrostructure between HC and CH (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019; Nobre et al., 2003). The most consistent findings have been recently reported by two studies from a Danish group, and pointed to signs of disrupted sleep in patients with CH in bout compared with HC, including longer sleep latency, reduced sleep efficiency and lower REM density (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019), with lower differences between HC and patients in remission and no differences between patients in bout and in remission (Lund, Snoer, Petersen, et al., 2019). At present, no conclusion can be drawn as these results need adequate replication.

Starting from these findings, it is clear that further effort is needed to elucidate the relationship between sleep and CH. Beyond increasing the number of studies in this field providing the necessary replication, several methodological and theoretical points should be considered. As previously observed, some early uncontrolled studies have been performed on small and heterogenous samples without a control group. On the other hand, the most recent studies provided evidence on larger samples with narrower exclusion criteria and a comparable HC group (Barloese, Jennum, et al., 2015; Lund, Snoer, Petersen, et al., 2019). Albeit the recruitment of patients with rare disorders like CH for objective sleep studies is challenging, the research in this field should continue in this last direction. On one hand, the exclusion of patients with medical, neurological and psychiatric conditions that may affect sleep is crucial to understand the actual relationship between sleep and CH. On the other hand, the possible interplay between CH, sleep problems and the frequently associated psychiatric disorders (Robbins, 2013) should be directly investigated. Severe disability due to CH attacks makes it essential to use acute and prophylactic therapies during the study protocol: in this view, a clear definition of the pharmacological treatment management during the study protocol should always be provided, and its possible influence on findings should be considered. Studies in this field should always clarify if patients' sleep was recorded during or outside the bout, and longitudinal assessment of sleep measures in different phases of the disorder are necessary to understand the nature of sleep alterations in CH. It is worth noting that many reviewed studies were characterised by a very large age range, including in the same sample young and older adults. It is well-known that aging strongly impacts on sleep quantity and quality, influencing its macro- and microstructure (Mander et al., 2017). In this view, the effects of age in future studies on the relationship between sleep and CH should be carefully controlled.

Interestingly, none of the reviewed PSG studies assessed sleep EEG measures. Nevertheless, the main electrophysiological sleep hallmarks are strongly involved in sleep maintenance and environmental disconnection, modulation of the arousal level, sleep homeostasis, and regulation of neural plasticity (Gorgoni et al., 2023). In this view, there are strong theoretical reasons to promote their assessment in the research field on CH. Several studies found alterations of the cyclic alternating pattern (CAP), a microstructural measure of sleep instability (Parrino et al., 2012), in patients with different migraine disorders (Della Marca, Vollono, Rubino, Di Trapani, et al., 2006; Nayak et al., 2016; Zhou et al., 2023). The assessment of CAP in CH may help to understand the relationship between nocturnal attacks and the arousal modulation system in these patients. Moreover, according to a growing body of in vitro, animal and human studies in the theoretical framework of the local sleep theory (Krueger et al., 2019), sleep should be considered a fundamental property of local neural networks in diverse brain areas. Many sleep EEG features represent local "use-dependent" phenomena: sleep oscillations have specific regional expressions and are strictly associated with local diurnal activity (Ferrara & De Gennaro, 2011). Local sleep EEG peculiarities have been observed in several neurological, psychiatric and sleep disorders (Castelnovo et al., 2018; D'Rozario et al., 2017; Gibbs et al., 2016; Gorgoni et al., 2020; Gorgoni & Galbiati, 2022; Kaskie & Ferrarelli, 2020; Mander, 2020; Poryazova et al., 2015). Moreover, the role of local sleep electrophysiology in rehabilitation and functional recovery has been highlighted (Gorgoni et al., 2013), and regional sleep features are under evaluation as possible therapeutic targets for neurodegenerative processes (Cordone et al., 2021). Starting from these notions, the assessment of local sleep in CH could represent a relevant scientific and clinical research field. Considering the role of regional electrophysiology in sleep protection, arousal and homeostasis, a specific local EEG pattern may trigger, or at least be predictive, of the CH attacks. Moreover, bearing in mind the fingerprint-like nature of the topographic EEG distribution during sleep (De Gennaro et al., 2005) and the genetic regulation of many electrophysiological sleep features (Adamczyk et al., 2015; Ambrosius et al., 2008; De Gennaro et al., 2008; Gorgoni et al., 2019; Markovic et al., 2018), it would be interesting to understand if patients with CH, and specifically those with prevalent nocturnal attacks, are characterised by a distinctive sleep EEG profile. Also, the assessment of the main sleep EEG hallmarks may allow a more in-depth understanding of the sleep modulation between different phases of the pathology, helping to determine if sleep alterations in this population are stable features (e.g. observable in both bout and remission periods) or strictly link to cluster periods and/or headache nights.

Actigraphy may also represent a useful tool to better understand the role of sleep in CH. Indeed, it allows a continuative, ecological, non-invasive and cost-effective evaluation of sleep and circadian rhythms for long periods. Actigraphic recordings have been performed to assess the relationship between sleep and several types of headaches (Bruni et al., 2004; Bursztein et al., 2006; Kikuchi et al., 2007, 2011; Smitherman

et al., 2016). At present, with the exception of a single case report (Della Marca, Vollono, Rubino, Capuano, et al., 2006), only one recent study used actigraphic recordings to assess sleep in CH (Lund, Snoer, Jennum, et al., 2019), showing longer time in bed and TST in patients with eCH in bout compared with HC, interpreted as the effect of greater tiredness in patients, and absence of differences between HC and patients in remission, between eCH in bout and in remission, and between nights with and without attacks. Results are promising, but they clearly need replication. Moreover, the observation that the recorded CH attacks and awakenings were often observed around the same hour several nights in a row without a relationship to previous sleep duration suggests the need of a systematic assessment of this phenomenon through continuative actigraphic recordings. Indeed, as previously observed, it may point to an intrinsic circadian rhythm underlying the nocturnal CH recurrence, without a specific role of the sleep–wake cycle. A longitudinal evaluation of in bout and remission periods should be provided, and the possible relationship between sleep alterations and the so-called "ghost attacks" should be clarified (Giuliani et al., 2023). Finally, to better characterise the specific sleep and circadian rhythms features in CH, a comparison with other types of primary headache disorders should be considered.

Overall, the objective sleep assessment in CH is challenging: the reviewed literature is limited and characterised by several methodological issues. Nevertheless, a better understanding of the role of sleep in CH has strong scientific and clinical relevance (Barloese, 2021; Pilati et al., 2023; Pergolizzi Jr et al., 2020). We suggest that the assessment of sleep microstructure, local sleep electrophysiology and actigraphic measures have the potential to strongly increase our knowledge on the relationship between sleep and CH.

AUTHOR CONTRIBUTIONS

Maurizio Gorgoni: Conceptualization; writing – original draft; writing – review and editing; investigation; validation; visualization; supervision. **Giada Giuliani:** Conceptualization; investigation; writing – review and editing; visualization; validation. **Mariangela Fratino:** Validation; visualization; writing – review and editing. **Vittorio Di Piero:** Validation; visualization; writing – review and editing; conceptualization.

CONFLICT OF INTEREST STATEMENT

None of the authors has potential conflicts of interest to be disclosed.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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