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Research article

# Report of joint hypermobility in malignant hyperthermia susceptible patients: Observational study with a case-control descriptive design

Rita CCS. Santos [a], Larissa FCDMS. Lima [a], Pâmela V. Andrade [a], Joilson M. Santos [a], Leonardo Galleni [c], Antonio FR. Junior [c], Lucas S. Souza [c], Beny Schmidt [d], Acary SB. Oliveira [b], José LG. Amaral [a], Mariz Vainzof [c], Helga CA. Silva [a,*]

[a] *MH Diagnosis and Investigation Study Centre (CEDHIMA: Centro de Estudo, Diagnóstico e Investigação de Hipertermia Maligna) - Anesthesiology, Pain and Intensive Therapy Department - Universidade Federal de São Paulo, São Paulo, SP, Brazil*
[b] *Department of Neurology, Universidade Federal de São Paulo, São Paulo, SP, Brazil*
[c] *Bioscience Institute, Human Genome and Stem Cells Research Center - University of São Paulo, São Paulo, SP, Brazil*
[d] *Department of Pathology, Universidade Federal de São Paulo, São Paulo, SP, Brazil*

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ABSTRACT

*Background:* Hypermobility is the capacity to perform joint movements in amplitudes greater than normal. Hypermobility is present in nearly 100 % of congenital myopathy central core disease (CCD) patients but is sporadically described in the allelic disease malignant hyperthermia (MH). Our objective was to investigate the frequency/characteristics of hypermobility in MH susceptible patients as compared to a control group, aiming the identification of correlations between hypermobility and demographic/clinical findings in MH patients.
*Methods:* We recruited 26 MH patients (MH history, positive *in vitro* contracture test (IVCT), no muscle weakness, no cores in muscle biopsy) and 23 controls (no MH/myopathy history). Patients/medical records were evaluated for obtaining demographic/clinical data. Hypermobility was assessed in all patients and controls with Bulbena score. Goniometry was performed in a subset of 11 patients and 11 controls.
*Results:* Bulbena score indicative of hypermobility was significantly more frequent in MH than in the control group (50 % versus 13 %, relative risk 2.06 (95%CI 1.27–3.35), chi-square test, $p < .01$). Goniometric assessment revealed significantly greater range of motion of mostly proximal movements in MH versus control groups. In the MH group, there was no correlation of the Bulbena score with age, sex, clinical complaints of myalgia/cramps, CK levels, IVCT result, or degree of contracture after caffeine or halothane.
*Conclusions:* It is possible that predominantly proximal hypermobility is part of a clinical spectrum associated with *RYR1* gene variants, as it was present even when associated muscle weakness was

*Abbreviations:* central core disease, (CCD); malignant hyperthermia, (MH); *in vitro* contracture test, (IVCT); caffeine-halothane contracture test, CHCT; ryanodine-receptor-type-1 gene, (*RYR1)*; calcium-voltage-gated-channel α1S-subunit gene, (*CACNA1S*); SH3 and cysteine-rich domain 3, (*STAC3)* gene; range of motion, (ROM); Medical Research Council, (MRC); creatine kinase, (CK); standard deviation, (SD); contracture after halothane and after caffeine, (MHShc); contracture only after halothane, (MHSh); contracture only after caffeine, (MHSc).

* Corresponding author. Brazilian Malignant Hyperthermia Center. University Federal São Paulo, Rua Pedro Toledo, 781, SP, 04039-032, Brazil.
*E-mail address:* hsilva@unifesp.br (H.CA. Silva).

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not present. More studies are necessary to measure evolution and long-term impact of hypermobility in MH patients.

## 1. Introduction

Hypermobility, the capacity to perform joint movements in amplitudes greater than normal, is the main characteristic of inherited connective tissue diseases [1]. Additionally, hypermobility can occur with some myopathies, such as congenital myopathy central core disease (CCD) [1]. CCD causes stable/gradually progressive symmetrical proximal muscle weakness/atrophy, hypotonus/hyporeflexia, delayed motor development, and areas without oxidative activity (cores) on muscle biopsies [2,3]. CCD is allelic with malignant hyperthermia (MH), a rare and potentially lethal autosomal dominant pharmacogenetic disorder [3].

MH is characterized by a hypermetabolic crisis triggered by halogenated inhalational anesthetics and/or the neuromuscular blocker succinylcholine. An *in vitro* contracture test (IVCT) in response to halothane/caffeine (or the caffeine-halothane contracture test: CHCT) is the gold standard criterion for diagnosing MH susceptibility and is also frequently positive in CCD individuals [2,3]. MH primarily results from ryanodine-receptor-type-1 gene *(RYR1)* variants and rarely from variants in the calcium-voltage-gated-channel α1S-subunit *(CACNA1S*) or SH3 and cysteine-rich domain 3 (*STAC3)* genes [2,3].

Despite the lack of clear phenotypical abnormalities in the majority of MH patients, sometimes they can present variable characteristics, such as ptosis, strabismus, hiatal/inguinal/umbilical hernia, kyphoscoliosis, cryptorchidism, clubbed foot, muscle weakness, increased/decreased muscle tone, and hypermobility [4–6]. Hypermobility has been described occasionally in MH patients, despite being present in up to 100 % of CCD patients [6–8]. However, hypermobility has not been systematically investigated in MH individuals or quantified with specific instruments that measure joint range of motion (ROM). Our objectives here were 1. to investigate and compare the frequency/characteristics of hypermobility between an MH and a control group, and 2. to search for correlations between hypermobility and demographic/clinical findings in MH patients.

## 2. Materials and methods

### 2.1. Study design

An observational study with a case-control descriptive design was used to compare the frequency/characteristics/relationships of hypermobility among MH susceptible patients and control subjects.

### 2.2. Participants

This research was conducted in accordance with international ethical standards (1964 Declaration of Helsinki and its later amendments) and was approved by the Institutional Research Ethics Committee (195.807/2013, 0804/2016, 0979/2017). All participants provided their written informed consent. This manuscript adheres to the applicable STROBE guidelines.

For this study, we invited all 154 patients who had been investigated in an MH center from 1997 to 2019 due to the possibility of MH susceptibility and presented a positive IVCT (Supplementary Fig. 1). The investigation performed in the MH center included *vastus lateralis* muscle biopsy with histochemistry [9], IVCT [9], and molecular analysis. We excluded individuals under 18 years old, without personal or family history of MH, patients with muscle weakness or cores in the muscle biopsy, and those who had undergone osteoarticular surgery in the evaluated joints up to one year before the study.

Twenty-six patients from 15 unrelated families were eligible and agreed to participate. Two MH patients survived an anesthetic crisis, and 24 were relatives. We included a second group of 23 controls who were university/community members and did not have a personal/family history of anesthetic-induced MH or core myopathy; this group did not undergo an IVCT/anatomopathological study. The 23 controls were paired with 23 of the 26 MH individuals by decade of age and sex assigned at birth. We included a third group of 19 non-MH susceptible relatives of MH susceptible patients, all of them with negative IVCT, normal serum creatine kinase (CK) levels, and normal muscle biopsy with histochemistry.

### 2.3. Procedures

All 26 patients were evaluated by the same neurologist to obtain demographic data (age, sex assigned at birth), clinical histories (including evaluations of previous medical records and joint problems), and physical/neurological examination (muscle strength was assessed with the Medical Research Council (MRC) grading system). Osteoarticular problems, such as joint dislocations (luxations), kyphoscoliosis, lordosis, and club foot, were assessed by the neurologist in the physical examination and confirmed by orthopedic evaluations and/or radiological exams. CK levels were obtained for all patients.

All participants (26 patients, 19 non-MH susceptible relatives, and 23 controls) underwent a hypermobility assessment performed by two physical therapists who received the same orientation and were unaware of both the clinical diagnosis and IVCT/anatomopathological/molecular analysis results. Hypermobility was assessed with the Bulbena score in all patients, relatives and controls and with the goniometry in a subset of 11 MH patients and 11 controls paired by sex and age, in order to determine the pattern of distribution of the hypermobility across the joints [10–13]. Hypermobility was diagnosed by the Bulbena score with values $\geq 5$ in females

or ≥4 in males; these cutoffs have been validated in normal/hypermobile groups [11,12]. Goniometry was used to measure the maximal joint angle (total joint ROM). ROM was assessed in both ankles, knees, hips, elbows, shoulders, thumbs, and fifth metacarpophalangeal joints [13]. For goniometry assessments, a V-shaped instrument (goniometer) was placed over the joint and along the proximal and distal bones. The assessments were performed passively with two universal goniometers (CARCI Universal): the first for hallux dorsiflexion (measuring 0–15 cm, 0–110°) and the second for the other joints (0–35 cm, 0–350°) [13].

### 2.4. Data analysis

Data were analyzed with the GraphPad Prism statistical package for Windows. Data distributions were calculated and descriptive analyses were performed. Absolute (n) and relative (%) frequencies were used to describe sex, clinical complaints, presence of increased CK levels, result of the IVCT, and absence/presence of hypermobility by the Bulbena score. Age and intensity of contractures in the IVCT were expressed as the mean/standard deviation (SD). The ROM was expressed as the median/25–75 % percentiles. Independent groups were compared by using Chi-square tests (sex, clinical complaints, presence of increased CK levels, result of the IVCT, and absence/presence of hypermobility by Bulbena score), unpaired t-tests (age, intensity of contractures in IVCT), and Mann Whitney test (ROM). A *P* value of $<0.05$ was considered statistically significant.

The sample size was calculated a priori with a hypermobility frequency of 20 % for the general population and a frequency of 100 % for the *RYR1*-associated CCD myopathy [8,10]. Considering those available frequencies, for detecting a difference of at least 80 % in the frequency of hypermobility between the MH and control groups, with a detection power of 80 % and an alpha level of 0.05, at least 7 MH patients and 7 control subjects would be needed.

## 3. Results

There was no difference between the MH and control groups regarding the age (41.96 ± 14.58 versus 38.61 ± 12.2, unpaired *t*-test, p non-significant (ns)) or sex (13 females/13 males versus 13 females/10 males, chi-square, p: ns) (Supplementary Tables 1 and 2). Hypermobility, assessed by the Bulbena score, was significantly more frequent in the MH than in the control groups (13/26 (50 %) versus 3/23 (13 %), chi-square, p 0,005). MH patients had a 2.06 times higher estimated risk of hypermobility than controls (95%CI 1, 27-3,35; odds ratio 6.67, 95%CI 1.58–28.05).

There was no difference between the MH patients and non-MH susceptible relatives groups regarding the age (41.96 ± 14.58 versus 38.58 ± 11.65, unpaired *t*-test, p non-significant (ns)) but there were more females in the second group (13 females/13 males versus 16 females/3males, chi-square, p: 0.0179) (Supplementary Tables 1 and 3). Hypermobility, assessed by the Bulbena score, was significantly more frequent in the MH than in the non-MH susceptible groups (13/26 (50 %) versus 3/19 (15.7 %), chi-square, p 0,0179). MH patients had a 1.813 times higher estimated risk of hypermobility than controls (95%CI 1.13–2.89; odds ratio 5.33, 95%CI 1.24–22.82).

In the MH group (Table 1, Supplementary Table 1), there was no significant difference between the groups with and without hypermobility, assessed by the Bulbena score, regarding the age, sex, clinical complaints of myalgia/cramps, osteoarticular problems/dysmorphisms (scoliosis, kyphosis, ptosis/strabismus, high-arched palate, club-foot, pectus carinatum), abnormal CK levels, IVCT result, or intensity of muscle contractures after exposure to caffeine or halothane during the IVCT. Three MH patients presented increased levels of CK of 1.2, 2.2, and 3 times the normal limit. The result of the IVCT classified the patients in MHShc (n = 6, contracture after halothane and after caffeine, MHSh (n = 17, contracture only after halothane), and MHSc (n = 3, contracture only after caffeine). One MH patient with hypermobility presented a chronic dislocation of the first metatarsophalangeal joint. The patients from this specific sample had no history of undergoing orthopedic surgeries.

There was no difference between the subset of 11 MH patients and 11 controls regarding age (42 ± 16.85 versus 43 ± 12.48,

**Table 1**
Characteristics of MH patients with and without hypermobility.

| | MH with hypermobility (n = 13) | MH without hypermobility (n = 13) | p |
|---|---|---|---|
| Age | 40.54 ± 16.928 | 43.38 ± 12.33 | ns* |
| Sex (female/male) | 8/5 | 5/8 | ns† |
| Myalgia/cramps | 6 | 3 | ns† |
| Increased CK | 2 | 1 | ns† |
| Scoliosis/kyphosis | 2 | 3 | ns† |
| Pectus carinatum | 0 | 1 | ns† |
| Ptosis/strabismus | 4 | 3 | ns† |
| High-arched palate | 3 | 6 | ns† |
| Club-foot | 2 | 1 | ns† |
| IVCT: | | | ns† |
| MHShc | 2 | 4 | |
| MHSh | 8 | 9 | |
| MHSc | 3 | 0 | |
| Muscle contractures after caffeine | 0.17 ± 0.29 g | 0.08 ± 0.14 g | ns* |
| Muscle contractures after halothane | 0.36 ± 0.64 g | 0.31 ± 0.15 g | ns* |

Legend: CK: creatine kinase, IVCT: *in vitro* contracture test, MH: malignant hyperthermia, ns: non significant, *: unpaired *t*-test, †: chi-square test.

unpaired *t*-test, p ns) and sex (5 females/6 males in both groups). The goniometry in this subset of 11 MH patients and 11 controls demonstrated that the ROM was significantly larger in mostly proximal joints of the MH compared with the control group (Table 2, Supplementary Tables 4 and 5).

Among the 15 unrelated MH families, the molecular study already disclosed *RYR1* gene variants related to 7 families (encompassing 16 MH patients), and the other 8 families are still under study (Supplementary Table 6). Seven different variants were identified in the *RYR1* gene (4 pathogenic, 1 probably pathogenic, and 2 variants of unknown significance) and one in the *CACNA1S* gene (probably pathogenic). Four of the *RYR1* gene variants were already listed as diagnostic variants by the European Malignant Hyperthermia Group (www.emhg.org): three were previously reported with MH and associated myopathy (exon 6:c.C487T:p.Arg163Cys, exon17:c.C1840T:p.Arg614Cys, exon 45:c.G7304A:p.Arg2435His) and one with MH but not associated myopathy (exon 2:c.G131A:p.Arg44His) [14,15]. One *RYR1* gene variant was not previously reported with MH, but only with associated myopathy (exon2:c.122T > C:p.Phe41Ser) [16]. The *CACNA1S* gene variant (exon 26:c.3256C > T:p:Arg1086Cys) was previously reported in association with MH [17] and our patient harboring this variant never presented hypokalemic periodic paralysis, one of the phenotypes related to the *CACNA1S* gene variants. Considering the seven families with identified variants in the *RYR1* gene, in five of them patients presented hypermobility (Supplementary Table 6).

## 4. Discussion

This study showed higher hypermobility frequency in MH patients than in controls and non-MH susceptible relatives. Hypermobility presence was not affected in our sample by age or sex, in contrast with what is reported in normal samples. In an unselected population, hypermobility was more frequent in females [18]. Additionally, hypermobility incidence normally decreases with age: the incidence of joints affected by hypermobility decreases from 34 % (20–30 years) to 18.4 % (up to 60 years) [18].

Goniometry showed increased ROM in almost all proximal joints of our MH patients. An increased ROM in all joints occurs in normal school-aged children but with smaller values than those found in our MH group [18,19]. Moreover, we excluded patients under 18 years old from our study.

The proximal predominance of hypermobility in our sample resembles the pattern of muscle weakness in core myopathy. But patients with muscle weakness were a priori excluded from our sample, to avoid this confounding factor, as muscle weakness in both flexor/extensor muscle groups may lead to hypermobility [7,20]. Moreover, clinically evident and generalized or predominantly distal hypermobility has been described with core myopathies and hypermobility syndromes [7,21]. Despite that, there are previous descriptions of indicators of proximal joint hypermobility in CCD patients, such as hip dislocation/subluxation and recurrent patellar dislocation [8]. It is possible that proximal joint hypermobility could be difficult to detect with clinical assessments without the Bulbena score/goniometry. This possibility would explain the underdiagnosis and consequently the underreporting of this proximal hypermobility in MH patients.

To the best of our knowledge, no study has systematically quantified hypermobility with goniometry in exclusively anesthetic-induced MH patients compared to controls and non-MH susceptible relatives. However, hypermobility, patellar instability, and patella luxation have been described in some MH families [9,22]. Hypermobility and recurrent joint luxation have also been described in the King-Denborough syndrome, a disease characterized by MH susceptibility, osteomuscular anomalies, and dimorphisms, caused by *RYR1 gene* variants in some families [23]. Here, five of the seven families (71 %) that completed the molecular study presented hypermobility, suggesting that this characteristic could be in fact associated with some *RYR1* gene variants causing MH.

**Table 2**
Goniometry in a subset of MH and control patients.

| Joint hypermobility Assessment (normal range in degress) | MH (n = 11) median (25–75%percetiles) | control (n = 11) median (25–75%percetiles) | p (Mann Whitney) |
|---|---|---|---|
| **R 5th Metacarpophalangeal Passive Dorsiflexion (0–110)** | 90 (90–93) | 90 (90–90) | ns |
| **R Elbow Hyperextension (0–10)** | 12 (10–13.5) | 0 (0–0) | **0.001** |
| **R Knee Hyperextension (0–10)** | 13 (11–17) | 0 (0–0) | **0.0004** |
| **R Shoulder ER (0–90)** | 100 (89–110) | 90 (90–90) | ns |
| **R Hip Abduction (0–45)** | 90 (90–110) | 45 (45–45) | **<0.0001** |
| **R Ankle Dorsiflexion (0–20)** | 20 (20–25) | 20 (20–20) | ns |
| **R Ankle Eversion (0–20)** | 23 (20–25) | 20 (20–20) | **0.045** |
| **R 1st Metatarsophalangeal Dorsiflexion (0–90)** | 90 (90–91.5) | 90 (90–90) | ns |
| **R Knee Flexion (0–140)** | 145 (145–150) | 140 (140–140) | **0.004** |
| **L 5th Metacarpophalangeal Passive Dorsiflexion (0–110)** | 90 (79–95) | 90 (90–90) | ns |
| **L Elbow Hyperextension (0–10)** | 12 (10–19) | 0 (0–0) | **0.001** |
| **L Knee Hyperextension (0–10)** | 14 (11.5–17) | 0 (0–0) | **0.001** |
| **L Shoulder ER (0–90)** | 108 (100–115) | 90 (90–90) | **0.004** |
| **L Hip Abduction (0–45)** | 100 (88–115) | 45 (45–45) | **<0.0001** |
| **L Ankle Dorsiflexion (0–20)** | 20 (20–25.5) | 20 (20–20) | ns |
| **L Ankle Eversion (0–20)** | 20 (20–29) | 20 (20–20) | ns |
| **L 1st Metatarsophalangeal Dorsiflexion (0–90)** | 90 (90–97.5) | 90 (00–90) | ns |
| **L Knee Flexion (0–140)** | 145 (140–149) | 140 (140–140) | **0.04** |

Legend: n: number, MH: personal/familiar anesthetic crisis with a positive IVCT result, R: right side of the body, L: left side of the body, ER: external rotation.

The mechanism underlying hypermobility in MH patients may be multifactorial. Hypermobility may theoretically result from two different mechanisms: dynamic joint alterations associated with muscle weakness/myopathy or changes in cells from tendons/ligaments due to an *RYR1* variant [7]. The absence of muscle weakness in our MH patients supports the second mechanism. It has been shown that mechanical load increases the intracellular calcium concentrations of normal fibroblasts from tendons/ligaments [24]. Fibroblast function could theoretically be affected by calcium dysregulation related to *RYR1* gene variants, thus affecting collagen production and causing hypermobility [7,24].

Hypermobility predisposes patients to recurrent musculoskeletal lesions, such as ankle sprains and knee ligament injuries, mostly occurring in sports/military training [25]. Additionally, hypermobility increases the frequency of fractures, fatigue, pain, and psychological distress [26,27]. MH patients with hypermobility from our study did not report muscle pain/cramps or fractures more frequently than MH patients without hypermobility did. Nevertheless, it would be necessary to continue this study with a longitudinal evaluation of MH patients in order to detect the evolution of hypermobility, as well as the occurrence of complaints and complications related to the increase in the ROM of the affected joints. Additionally, preventive measures could be recommended for increasing joint mechanical support/proprioception, such as exercises for peri-articular muscles and the use of straps/guards [25]. It is important that the anesthetist be aware of the possibility of joint hypermobility in MHS patients. Specifically during general anesthesia, patients with MH and hypermobility could present a greater risk of joint injury during patient positioning and would deserve special attention in order to minimize the stretching of a hypermobile joint.

Silva et al., 2013 reported a patient with recurrent patellar dislocations between ages 11 and 23 - her father, paternal aunt, and grandmother presented the same problem [9]. Similar reports suggest that, sporadically, patients with a personal/family history of hypermobility may also be susceptible to MH [9,22]. However, since 20 % of the population has hypermobility and MH susceptibility occurs at a maximum rate of 1:300, isolated hypermobility *per se* would not indicate MH in the general population [28].

### *4.1. Study limitations*

Given the rarity of MH, the limited sample size is an inherent limitation of this study. Another limitation of all clinical studies of MH patients is the genetic heterogeneity of MH. Moreover, *RYR1* gene variants can be expressed in two ways: loss-of-function (core patients with negative IVCT) and gain-of-function. This gain-of-function, expressed as muscular enhanced calcium release at functional studies and a positive IVCT result, occurs under anesthesia alone (MH patients) or under both anesthesia and resting (Core myopathy patients with positive IVCT).[2,5,29,30] Despite patients with cores in the muscle biopsy have been excluded a priori from our sample, it is impossible to exclude the presence of cores in other muscles not biopsied. Nevertheless, none of the MH patients from this sample presented muscle weakness.

*RYR1* gene homepage (https://databases.lovd.nl/shared/genes/RYR1) lists hundreds of variants and it is estimated that less than 10 % have been characterized with functional studies of enhanced calcium release.[31] Until all *RYR1* gene variants are characterized, studies of the clinical expression and correlation of phenotype/genotype are necessary to increase our knowledge about MH.[31] Additionally, It is necessary to compare our data on hypermobility frequency in Brazilian patients with those of MH patients from different centers and genetic backgrounds. Despite the fact that Figueroa et al. proposed that the MHSh group would be functionally different from the MHShc group due to a higher elevated resting cytosolic calcium, these subgroups had not any difference regarding hypermobility in our sample.[32]

## 5. Conclusion

This study found more frequent hypermobility in MH patients than in controls. It is possible that hypermobility is part of a clinical spectrum associated with *RYR1* gene variants, as it was present even when associated muscle weakness was not present.

## CRediT authorship contribution statement

**Rita CCS. Santos:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Larissa FCDMS. Lima:** Writing – review & editing, Formal analysis, Data curation. **Pâmela V. Andrade:** Writing – review & editing, Formal analysis, Data curation. **Joilson M. Santos:** Writing – review & editing, Formal analysis, Data curation. **Leonardo Galleni:** Writing – review & editing, Formal analysis, Data curation. **Antonio FR. Junior:** Writing – review & editing, Formal analysis, Data curation. **Lucas S. Souza:** Writing – review & editing, Formal analysis, Data curation. **Beny Schmidt:** Writing – review & editing, Formal analysis, Data curation. **Acary SB. Oliveira:** Writing – review & editing, Formal analysis, Data curation. **José LG. Amaral:** Writing – review & editing, Formal analysis. **Mariz Vainzof:** Writing – review & editing, Formal analysis, Data curation. **Helga CA. Silva:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Ethical statement

Ethical approval statement: This research was approved by the Universidade Federal de São Paulo Institutional Research Ethics Committee (195.807/2013, 0804/2016, 0979/2017) and all participants provided their written informed consent.

## Data availability statement

Data supporting reported results can be found in the Supplementary information section.

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## Declaration of competing interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41776.

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