Prevalence and severity of symptoms and signs in patients with advanced cancer in the last days of life: the East Asian collaborative cross-cultural study to elucidate the dying process (EASED)

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Abstract
Purpose Few large-scale studies have focused on the prevalence of symptoms and signs during the last days of patients diagnosed with advanced cancer. Identifying the patterns of specific symptoms according to cancer type is helpful to provide end-of-life care for patients with advanced cancer. We investigated the prevalence and severity of symptoms and signs associated with impending death in patients with advanced cancer.

Methods In this secondary analysis of an international multicenter cohort study conducted in three East Asian countries, we compared the severity of symptoms and signs among dying patients in the last 3 days of life according to the type of primary cancer using one-way analysis of variance (ANOVA). Post hoc analysis was conducted for multiple comparisons of each symptom according to the type of primary cancer.

Results We analyzed 2131 patients from Japan, Korea, and Taiwan. The prevalence of most symptoms and signs were relatively stable from 1 week after admission to the last 3 days of life. According to cancer type, edema of the lower extremities was the most common symptom and fatigue/ascites were the most severe symptoms in digestive tract cancer. For lung cancer, respiratory secretion was the most prevalent and dyspnea/respiratory secretion were the most severe symptoms.

Conclusion We demonstrated the prevalence and severity of symptoms and signs associated with the impending death of patients with advanced cancer in East Asia. Our study can enable clinicians to recognize the specific symptoms and signs at the very end of life.

Keywords Palliative care · Advanced cancer · End of life · Signs and symptoms · East Asia

Introduction

Patients experience a variety of physical and psychological symptoms as they approach the last days of their lives [1]. A better understanding of various symptoms associated with impending death can enable clinicians improve the diagnostic performance of palliative patients [2]. However, few studies have focused on the prevalence of symptoms during the last days of patients on a large scale [1, 3–8]. These studies focused on the specific symptoms recognized in actively dying patients. Therefore, the frequency of common clinical symptoms such as fatigue and dyspnea in the last days has yet to be systematically analyzed. In a systematic review that included both cancer patients and non-cancer patients, dyspnea, pain, respiratory secretions/death rattle, and confusion were the most prevalent symptoms in the last 2 weeks of life [2]. A recent study involving East Asian countries has reported the prevalence of leg edema and ascites in patients with pancreaticobiliary cancer and myoclonus and respiratory secretions in patients with gastroesophageal cancer 3 days before death [9].

Identification of the pattern of specific symptoms and signs according to cancer type facilitates our understanding of the characteristics of patients with specific cancer
type and provide end-of-life care. Thus, we investigated the prevalence and severity of symptoms and signs associated with impending death in patients with advanced cancer in three East Asian countries.

Methods

Study participants

This is a secondary analysis of an international multicenter cohort study conducted in three East Asian countries including Japan, Korea, and Taiwan. The original study was the East Asian collaborative cross-cultural study to elucidate the dying process (EASED), which investigated the dying process and end-of-life care of inpatients with far advanced cancer in palliative care units (PCUs) in three East Asian countries. Eligible, newly admitted inpatients in the participating PCUs during the study period were consecutively enrolled in the study. All observations were performed in the course of routine clinical practice. The inclusion criteria were as follows: (1) adults (age > 18 years in Japan and Korea and > = 20 years in Taiwan), (2) suffering from locally extensive or metastatic cancer, and (3) admitted to a participating PCU. The exclusion criteria were (1) scheduled discharge within 1 week and (2) refusal by patients or their families to participate in the study.

Data collection

The attending palliative care physicians and nurses recorded all demographic data on admission and symptoms in the last 3 days of life based on the structured questionnaire. The questionnaire was developed through discussions among EASED investigators and the results of both western and eastern studies analyzing “impending death” and “good communication practices” involving dying patients and their families in PCUs [8, 10–14].

We obtained and analyzed the following data: patient demographics and clinical characteristics on admission and symptoms and signs at 1 week after admission and in the last 3 days of life. Symptoms were defined as observations based on subjective experiences or descriptions of patients based on validated measurements by medical professionals. However, signs were defined as objective outcomes. Symptoms included fatigue, dry mouth, drowsiness, dyspnea, delirium, and hallucination. Signs included respiratory secretion, leg edema, ascites, and myoclonus. We selected one or more items from validated instruments to reduce variability among raters. We used the Integrated Palliative Outcome Scale (IPOS) to objectively measure patients’ symptoms including fatigue, dry mouth, and drowsiness: 0, not at all; 1, slightly; 2, moderately; 3, severely; 4, overwhelmingly; 5, cannot assess because of unconsciousness. The Japanese version of IPOS is a valid and reliable tool for assessing physical, psychological, social, and spiritual symptoms and measuring the outcomes of adult cancer patients in Japan [15]. The IPOS is currently undergoing validation in Korea. Taiwanese investigators have completed the validation of the IPOS and reported the results at an international symposium (Tohoku Forum for Creativity 2020). Dyspnea was scored as follows: 0, normal; 1, exertional only; and 2, at rest. We assessed delirium using the 10-item Memorial Delirium Assessment Scale (MDAS), based on item #9 (psychomotor activity): 0, normal or psychomotor hypoactivity; 1, mild; 2, moderate; and 3, severe [16]. Hallucination was evaluated using the Delirium Rating Scale-revised-98 (DRS-R-98), with respect to item #2 (perceptual disturbances and hallucinations): 0, not present; 1, mild perceptual disturbance; 2, illusions present; and 3, hallucinations present [17]. MDAS item #7 can serve to assess perceptual disturbance. However, we used DRS-R-98 for hallucination evaluation to separate it from illusion. Respiratory secretion was scored as follows: 0, not audible; 1, only audible at the head of the bed; 2, clearly audible at the foot of the bed; and 3, clearly audible 6 m away from the foot of the bed [18]. The severity of leg edema was determined by measuring the depth upon pressing the skin for a sufficient amount of time in the area between the upper and the lower joints and was categorized as follows: 0, none; 1, mild (< 5 mm); 2, moderate (5–10 mm); and 3, severe (> 10 mm) [19, 20]. Ascites was scored as follows: 0, physically undetectable; 1, physically detectable but asymptomatic; or 2, symptomatic based on physician examination. We evaluated myoclonus based on five levels of jerking frequency per 10 s at rest: 0, none; 1, ≤ 1 jerk; 2, 2–3 jerks; 3, 4–9 jerks; and 4, ≥ 10 jerks.

Statistical analysis

All analyses were performed using JMP version 14 for Windows (SAS, Cary, NC, USA).

First, we classified study participants into 3 groups according to the type of primary cancer prevailing in East Asia: digestive tract, lung, and others. Digestive tract cancer includes gastroesophageal, colorectal, hepatobiliary, and pancreatic cancer. Lung cancer includes small-cell and non-small cell types. Other cancers include breast, gynecological, urological, head and neck, bone and soft tissue, skin, brain cancer, and hematological malignancies.

Second, we performed descriptive analyses to summarize baseline characteristics of study participants according to the type of primary cancer.

Third, descriptive analyses were summarized as the prevalence of physical and psychological symptoms and signs.
according to the type of primary cancer in patients at admission, 1 week after admission and in the last 3 days of life. We defined “present symptoms” as having more than one point of the score of the response scale.

Fourth, we compared the severity of physical and psychological symptoms and signs in the last 3 days of life according to the type of primary cancer using one-way analysis of variance (ANOVA) for comparison of means. Additionally, the Kruskal–Wallis tests were performed to compare medians of each symptom according to the type of primary cancer. Post hoc analysis was conducted using the Steel–Dwass test.

Ethics

In accordance with the ethical guidelines for human research of Japan’s Ministry of Health, Labor, and Welfare, informed patient consent was waived in Japan because of the completely observational nature of the study. However, Japanese patients and their families accessed study information online. If they decided not to participate in the study, they had the right to express their wills of refusal. In Korea and Taiwan, informed consent was obtained from the patients or their families (if the patient lacked the capacity to make decisions). The study was approved by the local Institutional Review Boards of all participating institutions. Also, the independent ethics committee of Tohoku University School of Medicine (approval no. 2016–1-689) approved this study.

Results

Patient characteristics

A total of 2638 patients were enrolled across 38 palliative care units (23 in Japan, 11 in South Korea, and 4 in Taiwan). The patients were enrolled from January 2017 to September 2018. We excluded 500 ineligible patients (digestive tract: 213, lung: 72, others: 215) because they were discharged alive. Among 2138 eligible patients, 7 patients (digestive tract: 2, lung: 5, others: 0) were excluded for missing values of all symptoms in the last 3 days of life. Thus, a total of 2131 patients (digestive tract: 1042, lung: 368, others: 721) were evaluated (Fig. 1) including 1107 men (digestive tract: 575 (55.2%), lung: 239 (65.0%), others: 293 (52.6%)). Japanese patients who participated in the study were as follows: digestive tract group; 76.9%, lung group; 79.2%, others. Korean patients who participated in the study were divided into the following groups: digestive tract group; 76.9%, lung group; 79.2%, others. Korean patients who participated in the study were divided into the following groups: digestive tract group (14.5%), lung group (10.9%), and others (8.6%). Taiwanese patients who participated in the study were categorized into the...
following groups: digestive tract group (10.9%), lung group (12.2%), and others (12.2%). The median survival time was 15 days (95% confidence interval [CI], 2.0–71.0) in the digestive tract group, 15 days (95% CI, 2.0–90.2) in the lung group, and 15 days (95% CI, 2.0–79.0) in the others group. The characteristics of the patients are listed in Table 1.

Table 1 Baseline characteristics of study participants according to the type of primary cancer (n = 2131)

| Characteristics | Digestive tract | Lung | Others |
|-----------------|-----------------|------|--------|
| n (%)           | 1042 (48.9)     | 368 (17.3) | 721 (33.8) |
| Age (years)*    | 71.3 ± 13.0     | 72.8 ± 10.9 | 70.0 ± 14.3 |
| Survival time (days, median [95% CI])** | 15 [2.0–71.0] | 15 [2.0–90.2] | 15 [2.0–79.0] |
| Sex             | Male 467 (44.8) | 129 (35.1) | 428 (59.4) |
|                 | Female 575 (55.2) | 239 (65.0) | 293 (40.6) |
| Country         | Taiwan 777 (74.6) | 283 (76.9) | 571 (79.2) |
|                 | Japan 151 (14.5) | 40 (10.9) | 62 (8.6) |
|                 | Korea 114 (10.9) | 45 (12.2) | 88 (12.2) |
| Metastasis      | None 365 (35.2) | 64 (17.5) | 227 (31.5) |
|                 | Liver 499 (47.9) | 92 (25.1) | 221 (30.7) |
|                 | Lung 316 (30.4) | 168 (45.7) | 286 (39.7) |
|                 | Bone 142 (13.6) | 164 (44.7) | 268 (37.2) |
|                 | Brain 43 (4.1)  | 159 (43.3) | 97 (13.5) |
|                 | ≥ 2 organs 252 (24.3) | 181 (49.5) | 262 (36.3) |
| Charlson Comorbidity Index | 604 (58.0) | 206 (56.0) | 471 (65.3) |
|                 | 0 258 (24.8) | 94 (25.5) | 156 (21.6) |
|                 | 1 75 (7.2) | 49 (13.3) | 56 (7.8) |
|                 | 2 105 (10.1) | 19 (5.2) | 38 (5.3) |
| ECOG PS         | 0–1 16 (1.5) | 3 (0.8) | 8 (1.1) |
|                 | 2 87 (8.4) | 24 (6.5) | 45 (6.2) |
|                 | 3 428 (41.1) | 146 (39.7) | 277 (38.4) |
|                 | 4 511 (49.0) | 195 (53.0) | 391 (54.2) |
| KPS*            | 10–40 752 (72.2) | 285 (77.5) | 549 (76.3) |
|                 | 50–70 280 (26.9) | 81 (22.0) | 168 (23.3) |
|                 | 80–90 10 (1.0) | 2 (0.5) | 3 (0.4) |

Data are presented as mean ± standard deviation or number (percentage). Digestive tract cancer includes gastroesophageal, colorectal, hepatobiliary, and pancreatic cancers. Lung cancer includes small-cell and non-small cell types. Others include breast, gynecological, urological, head and neck, bone and soft tissue, skin, brain, and hematological malignancies.

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky Performance Scale

*Missing value (n = 1)
**Missing value (n = 2)

Prevalence of symptoms and signs

The prevalence of physical and psychological symptoms and signs according to the type of primary cancer in patients in the last 3 days of life is presented in Table 2. The changes in the prevalence of symptoms and signs are shown in Fig. 2. Fatigue, dry mouth, drowsiness, and dyspnea were the most frequent symptoms detected in nearly half of all patients (41.1–56.9%), and edema of the lower extremities was the most common sign (62.4%). For digestive tract cancer, edema of the lower extremities was the most common sign (68.1%) in the last 3 days of life. Respiratory secretion was the most prevalent sign (56.1%) associated with lung cancer in the last 3 days of life. As for other types of cancer, edema of the lower extremities was the most predominant sign (62.6%) in the last 3 days of life. The proportion of unconsciousness was up to 35.8–36.8%.

Severity of symptoms and signs

The severity of physical and psychological symptoms and signs in the last 3 days of life according to the type of primary cancer is presented in Table 3. The severities of six symptoms and signs varied significantly according to the type of primary cancer after ANOVA tests: fatigue (p < 0.01), dry mouth (p = 0.03), dyspnea (p < 0.01), respiratory secretion (p < 0.01), edema of the lower extremities (p < 0.01), and ascites (p < 0.01). Post hoc analysis revealed that fatigue and ascites were significantly more severe in patients with digestive tract cancer, while dyspnea and respiratory secretion were significantly more severe in lung cancer. The severities of six symptoms and signs differed significantly also according to the type of primary cancer after Kruskal–Wallis tests for comparison of medians (Fig. 3).

Results of Kruskal–Wallis tests and post hoc analysis were the same to those of ANOVA in Table 3. Additionally, we categorized others group into hematological malignancies, head and neck cancer, brain cancer, and others. The severity of physical and psychological symptoms and signs in the last 3 days of life were compared according to the newly categorized type of primary cancer using ANOVA and post hoc analysis. There were some significant differences among those cancers (Supplementary Table S1).

Discussion

The aim of this study was to investigate the prevalence and severity of symptoms and signs associated with impending death in patients with advanced cancer in three East Asian countries. The prevalence of most symptoms and signs was relatively stable from 1 week after admission to the last 3 days of life. According to cancer type, edema of the lower
Fatigue was the most common symptom and fatigue/ascites were the most severe symptoms in digestive tract cancer. For lung cancer, respiratory secretion was the most prevalent and dyspnea/respiratory secretion were the most severe symptoms.

Notably, dyspnea, edema of the lower extremities, and respiratory secretions increased markedly in the last 3 days of life (Fig. 2). Dyspnea and edema of the lower extremities are well-known prognostic indicators of a poor outcome. Respiratory secretion in the last days of life (“death rattle”) is a sign of impending death [14]. The awareness of symptom changes was useful for clinicians to predict final days [21]. Therefore, in general, clinicians can focus increasingly on the preparation of families for patients in their final days using indicators of worsening of dyspnea, edema, and respiratory secretions. In general, fatigue and drowsiness were present in nearly half of all patients. Also, unconsciousness reached 36 to 37% in the last 3 days. Clinicians can help patients and families to understand the natural course of death using this information.

Based on the severity of symptoms, fatigue was the most severe symptom in patients with digestive tract cancer. In a Canadian study [22], similar to ours, fatigue was the most severe symptom in patients with gastrointestinal cancer. Respiratory secretion was the most frequent and severe sign of lung cancer. It is not surprising considering the pathophysiology which is associated with obstructive pneumonia [23,24] and the higher prevalence of brain metastasis which may

| Symptoms and signs             | Digestive tract | Lung     | Others | Total |
|-------------------------------|----------------|----------|--------|-------|
| Fatigue                       | 637 (61.1)     | 190 (51.6) | 386 (53.5) | 1213 (56.9) |
| Present                       | 54 (5.2)       | 35 (9.5)  | 44 (6.1)  | 133 (6.2)  |
| Absent                         | 351 (33.7)     | 143 (38.9) | 291 (40.4) | 785 (36.8)  |
| Unconscious                    |                |          |        |       |
| Dry mouth                     | 549 (52.7)     | 176 (47.8) | 318 (44.1) | 1043 (48.9) |
| Present                       | 153 (14.7)     | 55 (15.0)  | 116 (16.1) | 324 (15.2)  |
| Absent                         | 340 (32.6)     | 137 (37.2) | 287 (39.8) | 764 (35.8)  |
| Unconscious                    |                |          |        |       |
| Drowsiness                     | 559 (53.7)     | 185 (50.3) | 339 (47.0) | 1083 (50.8) |
| Present                       | 129 (12.4)     | 44 (12.0)  | 92 (12.8)  | 265 (12.4)  |
| Absent                         | 354 (34.0)     | 139 (37.8) | 290 (40.2) | 783 (36.7)  |
| Unconscious                    |                |          |        |       |
| Dyspnea                       | 363 (34.8)     | 206 (56.0) | 308 (42.7) | 877 (41.1)  |
| Present                       | 633 (60.8)     | 143 (38.9) | 393 (54.5) | 1169 (54.9) |
| Absent                         | 46 (4.4)       | 19 (5.2)   | 20 (2.8)   | 85 (4.0)    |
| Unconscious                    |                |          |        |       |
| Delirium*                     | 292 (28.1)     | 107 (29.1) | 186 (25.8) | 585 (27.4)  |
| Present                       | 749 (72.0)     | 261 (70.9) | 535 (74.2) | 1545 (72.5) |
| Absent                         |                |          |        |       |
| Hallucination                  | 316 (30.3)     | 106 (28.8) | 191 (26.5) | 613 (28.8)  |
| Present                       | 726 (69.7)     | 262 (71.2) | 530 (73.5) | 1518 (71.2) |
| Absent                         |                |          |        |       |
| Respiratory secretion*         | 401 (38.5)     | 206 (56.1) | 321 (44.5) | 928 (43.6)  |
| Present                       | 641 (61.5)     | 161 (43.9) | 400 (55.5) | 1202 (56.4) |
| Absent                         |                |          |        |       |
| Edema of the lower extremities**| 709 (68.1)     | 170 (46.2) | 451 (62.6) | 1330 (62.4) |
| Present                       | 332 (31.9)     | 198 (53.8) | 269 (37.4) | 799 (37.5)  |
| Absent                         |                |          |        |       |
| Ascites*                      | 479 (46.0)     | 20 (5.4)   | 157 (21.8) | 656 (30.8)  |
| Present                       | 562 (54.0)     | 348 (94.6) | 564 (78.2) | 1474 (69.2) |
| Absent                         |                |          |        |       |
| Myoclonus                     | 75 (7.2)       | 23 (6.3)   | 58 (8.0)   | 156 (7.3)   |
| Present                       | 967 (92.8)     | 345 (93.8) | 663 (92.0) | 1975 (92.7) |
| Absent                         |                |          |        |       |

*Missing value (n = 1)
**Missing value (n = 2)

Data are presented as number (percentage). Digestive tract cancer includes gastroesophageal, colorectal, hepatobiliary, and pancreas cancers. Lung cancer includes small-cell and non-small cell types. Others include breast, gynecological, urological, head and neck, bone and soft tissue, skin, brain, and hematological malignancies.
be related to frequent respiratory secretion [25, 26]. Dyspnea was the most severe symptom in lung cancer than in other types of cancer. The intensity of dyspnea in primary and metastatic lung cancer is higher [27, 28] than that of any type of cancer [29, 30]. These figures are the highest at the end of life [31, 32], as our findings. Thus, clinicians should pay more attention to dyspnea and respiratory secretion in patients with lung cancer in the final days. It can lead to proactive coping such as prophylactic application of scopolamine patch [33].

The strengths of our study are as follows. This was the first large-scale study reporting the prevalence and severity of symptoms and signs associated with impending death in patients with advanced cancer in East Asian countries. Our findings reflect the cross-cultural demands in the last days of life. For instance, the recognition can be helpful for survival prediction and preparation of medical professionals and families, the unmet business of Japanese families [34]. Korean palliative care professionals should decide when to move to a private room before 96 h of death, which is covered by national health insurance in Korea. Taiwanese regard “returning to home when death comes very nearer” as an important component of good death [35]. Another strength is that we predefined the assessment of severities and the timing of symptoms and signs based on consensus among the international investigators.

We recognize that this study has some limitations. First, we used IPOS for the assessment of symptoms. It was previously reported that the inter-class correlation coefficients (ICCs) of fatigue, drowsiness, and dry mouth for IPOS-patient and IPOS-staff were 0.646 (which meant substantial relationship), 0.593 (moderate), and 0.576 (moderate), respectively, in Japan [36]. In Taiwan, ICCs between patients and staff were 0.611 (substantial) for fatigue, 0.867 (good) for drowsiness, and 0.785 (good) for dry mouth. Therefore, we regarded IPOS-staff as an acceptable tool for our study. Second, there was a possible recall bias involved in symptom assessment. We evaluated the symptoms after patients’ death by recalling their symptoms in the last 3 days of life. Additionally, we were unable to assess symptoms in the last 3 days of life of 35.8–36.8% of patients because of their unconsciousness. As a result, unconscious patients were excluded from analysis in the current study. Therefore, selection bias might be considered in the current study. Third, there was a small overlap between assessed data during the 1 week after admission and the last 3 days of life in the patients who died from day 8 to day 10 were checked twice based on measurements at 1 week and the last 3 days of life. However, a 10.7% (228/2131 patients) duplication did not...
Fig. 3 The severity of symptoms and signs in the last 3 days of life according to the type of primary cancer (n=2131). Y-axis represents the severity of symptom or sign scores. The blue line shows the overall average of symptom or sign scores. Data are presented as medians and ranges from first to third quartile in boxplots. P values are based on Kruskal–Wallis tests. Differing superscripts in two cells (e.g., a versus b) indicates that the values in those two cells are significantly different. The absence of superscripts indicates that there are no significant differences among values. Digestive tract cancers include gastroesophageal, colorectal, hepatobiliary, and pancreatic cancers. Lung cancer includes small-cell and non-small cell types. Others includes breast, gynecological, urological, head and neck, bone and soft tissue, skin, brain, and hematological malignancies.
have a significant effect on our results. Fourth, our categorization of types of cancer may need further subdivision. For instance, the “others” group can be divided into hematological malignancies, head and neck cancers, and other cancers according to the research objectives in the future. Fifth, our findings did not include significant symptoms such as pain. Evidently, pain is one of the key components of palliative care. However, we assumed that a substantial number of patients became noncommunicable in their final days. Thus, the pain scores were excluded from this study. Lastly, we evaluated symptom burden based on the three groups of cancer. We believe that it is useful for clinicians to recognize indicators of imminent death based on each patient’s cancer type. However, it may be insufficient for individualized care, and thus, further studies should elucidate key symptoms from a patient’s perspective.

**Conclusion**

We demonstrated the prevalence and severity of symptoms associated with the impending death of patients with advanced cancer in East Asia. Due to the large scale and regional diversity, our study can enable clinicians to recognize the very end-of-life patterns of specific symptoms and signs. Timely awareness of such patterns will lead to enhanced quality of end-of-life care for patients. Furthermore, it can facilitate the preparation of medical professionals, patients, and their families. Further studies are needed to extend patients’ understanding and wishes about symptoms of impending death in palliative care [37].

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00520-022-06969-9.

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**Author contribution** Yusuke Hiratsuka: conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing – original draft, writing – review and editing.

Sang-Yeon Suh: conceptualization, investigation, methodology, project implementation, supervision, writing – review and editing.

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**Data availability** The data that support the findings of this study are available from the corresponding author, Sang-Yeon Suh, upon reasonable request. All authors agree to provide data to the journal for review if needed.

**Code availability** Not applicable.

**Declarations**

**Ethics approval** This study was approved by the local Institutional Review Boards of all participating institutions. The independent ethics committee of Tohoku University School of Medicine (approval no. 2016–1–689) approved this study.

**Consent to participate** In accordance with the ethical guidelines for human research issued by the Ministry of Health, Labor, and Welfare in Japan, patients’ informed consent was waived because of the completely observational nature of the study. Patients were provided with the opportunity to opt out. In Korea and Taiwan, informed consent was obtained from the patients or their families (in case the patient lacked the capacity to decide).

**Consent for publication** The authors affirm that human research participants provided informed consent for the publication of the article.

**Conflict of interest** The authors declare no competing interests.

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