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Technology guided assessment of vocalizations and their diagnostic value as pain indicators for people living with dementia

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Abstract

Background: During pain assessment in persons unable to self-report, such as people living with dementia, vocalizations are commonly used as pain indicators. However, there is a lack of evidence from clinical practice regarding their diagnostic value and relationship with pain. We aimed to explore vocalizations and pain in people with dementia undergoing pain assessments in clinical practice setting.

Methods: A total of 22,194 pain assessments were reviewed in people with dementia (n = 3,144) from 34 different Australian aged care homes and two national dementia-specific behavior support programs. Pain assessments were conducted by 389 purposely trained health care professionals and cares using PainChek® pain assessment tool. Vocalized expressions were determined based on nine vocalization features included in the tool. Linear mixed models were used to examine the relationship of pain scores with vocalization features. Using a single pain assessment for each of the 3,144 people with dementia, additional data analysis was conducted via Receiver Operator Characteristic (ROC) analysis and Principal Component Analysis.

Results: Vocalization scores increased with increasing pain intensity. High pain scores were more likely with the presence of sighing and screaming (eight times). The presence of vocalization features varied depending on the intensity of pain. The ROC optimal criterion for the voice domain yielded a cutoff score of ≥2.0 with a Youden index of 0.637. The corresponding sensitivity and specificity were 79.7% (*CI*: 76.8%-82.4%) and 84.0% (*CI*: 82.5%-85.5%), respectively.

Conclusion: We describe vocalization features during presence of different levels of pain in people with dementia unable to self-report, therefore providing evidence in regard to their diagnostic value in clinical practice.

Keywords: vocalization features, voice, pain assessment, pain levels, PainChek®, older people.

Keypoints:

- Vocalizations increase in higher pain intensities.
- This study provides evidence regarding the diagnostic value of vocalizations during assessment of pain.
- Our findings raise the possibility of digital phenotyping of vocalizations as a clinically-relevant biomarker.

Introduction

In population groups with communication difficulties such as those living with moderate and severe dementia, vocalized and verbal disruptive behaviors occur commonly and are an important source of patient distress and caregiver burden. (1) They can also be troublesome to family and caregivers as well as cause reactive vocalizations in other patients. (1,2) The American Geriatrics Society (AGS) suggests vocalizations are one of the key domains to consider when assessing pain in older adults with communication difficulties such as those living with dementia. (3) As a result, a number of vocalized expressions of pain have been proposed by a variety of observational pain assessment scales. (4)

Currently, vocalized features of people with dementia are rated subjectively in observational pain scales (5-7) and surprisingly, without a clear characterization in relation to the pain experience. As such, available scales vary in their content of vocalized expressions, ranging between nonverbal utterances, verbal utterances and breaths, and also vary in relation to differences between ordinal and binary assessment. (6-17) Additionally, the AGS domains have been developed based on consensus rather than empirical results, therefore leaving open the possibility that pain assessment could be further explored through a more specific subset of these domains. (18)

To date, no study has explored the relationship between vocalized expressions, pain and other non-vocalized pain indicators in adults with pain in large and clinical settings. In addition, less attention has been given to exploring vocalizations in the context of dementia, in comparison to other pain-related features such as facial expressions. Furthermore, whilst the literature suggests that voice parameters change in patients experiencing pain (19-21), there is a paucity of studies exploring more subtle characteristics of vocalization in patients with pain in general.

Here we aimed to explore vocalized expressions of people with moderate to severe dementia undergoing pain assessments in clinical practice settings with the view of providing empirical evidence related to a subset of reported pain-indicative vocalized expressions. In particular, we aimed to identify which vocalization features are present or absent during different levels of pain and the association of these features in relation to high pain scores. Additionally, we also aimed explore the discriminating power of vocalizations for categorizing pain. We leverage a unique large database of pain assessments collected using a technology guided pain assessment tool known as PainChek® in clinical practice. (22-24)

Methods

This was a 2-year retrospective study carried out in 34 Australian residential aged care homes (RACHs) and by two national dementia-specific behavior support programs over the period of September 2017 to March 2019. A total of 22,194 pain assessments conducted by trained clinical staff during this time were reviewed. Pain assessments were completed using the PainChek® pain assessment tool, a six-domain point-of-care (POC) medical device that uses facial recognition and analysis technology to identify facial action units (AUs; smallest building blocks of facial expressions) indicative of pain. (25-27) This is done in real time using artificial intelligence (AI) powered algorithms. Initially, the user assesses subject's face via the Face domain (Domain 1; 9 features) and then digitally combines the resultant scores with those of five other domains: Voice (9 features), Movement (7 features), Behavior (7 features), Activity (4 features), and Body (6 features). Each feature observed is given a score of one, with the maximum score being 42. A final total pain score and severity (which includes voice score) is calculated automatically by totaling features recorded in each of the six domains. The total calculated pain score and severity belongs to one of four categories: no pain (score: 0-6), mild pain (7-11), moderate pain (12-15) and severe pain (16-42).

The Voice domain assesses nine vocalization features: noisy pain sounds (e.g., 'ouch', 'ah', 'mm'), requesting help repeatedly, groaning, moaning, crying, screaming, loud talk, howling, and sighing. These features, as in other non-facial domains, are assessed by trained assessors and manually entered into a digital checklist in the PainChek® app at POC. Whilst completing the pain assessment, the PainChek user can click the information button adjacent to each vocal feature to find out a description of that feature. More information about the PainChek® tool can be accessed elsewhere. (28)

The study was approved (HR10/2014) by the Human Research Ethics Committee (HREC) of Curtin University (Bentley, WA, Australia). Permission was also granted by PainChek Ltd

(Sydney, NSW, Australia) to provide the dataset. The data comes from pain assessments conducted on POC smart devices which are automatically synchronized to a cloud repository database. This existing database is accessible via web administration portal (PainChek portal) allowing aggregation of deidentified data for the purposes of research and analysis as per the terms of the PainChek Application service agreement with the aged care provider.

Pain assessments and data collection

PainChek® pain assessments were completed by 389 trained users (i.e., consultants, nurses, allied health professionals and care support staff) working in 34 different Australian RACHs across various Australian states and territories (Australian Capital Territory, Victoria, New South Wales, Queensland, South Australia and Western Australia), and two national dementia-specific care programs. Pain assessments were completed as part of routine patient care procedures. Prior to using the PainChek® App, users received either face-to-face or online training which lasted between 1.5-2 hours. This training was essential to ensure that users were competent in using the tool and to meet the regulatory standards of quality and safety. Training received by PainChek users, in addition to ensuring competency in using the PainChek tool also included information on challenges of pain assessment in dementia, pain behaviors in people with dementia, compromised ability to self-report as well as pain triggers in people with dementia. This training guided PainChek users to first assess the capacity for self-report as means of assessing pain and only proceed with pain assessment using the PainChek tool if this ability to self-report is compromised in the person with dementia. The actual recording of completed pain assessments is a part of a workflow platform that includes the PainChek App (i.e., the pain assessment tool) and the

PainChek Portal. The PainChek Portal is a central web-based repository that allows the aggregation, storage and retrieval of electronic records of all pain assessment data from the PainChek App. The deidentified data which were provided by PainChek Ltd for the purposes of this study included: demographics of users and patients, chronological logs of pain assessments, pain scores, pain intensity categories, and the features recorded in each of the six PainChek domains for each assessment.

Data analysis

We used SPSS version 27 (IBM Corp. 2020) for the data analysis unless stated otherwise. For all statistical tests $p < 0.05$ was adopted to assess statistical significance, with confidence intervals (*CI*) reported as appropriate. Key demographics and proportion of total assessments conducted were described using frequency (*f*) and percent (%), mean (*M*) and standard deviation (*SD*).

A Voice domain score was computed by summing the Voice domain items and described (right skewed Kolmogorov-Smirnov) using *M*, *SD*, median (*Md*), and 25-75% interquartile range (*IQR*). Each Voice domain item was described using *f* and *%* for the total sample, four pain categories (none [pain score 0-6], mild, [7-11] moderate [12-15] and severe [16+]), and for the dichotomized pain category (low [none and mild], high [moderate and severe]).

Total pain score which includes the voice score (right skewed Kolmogorov-Smirnov) was described for each Voice domain item using *M*, *SD*, *Md*, and *IQR*. Cohen's *d* effect size with 95% confidence intervals and Common Language Effect Size (*CLES*) for non-parametric data was computed and interpreted as small (0.2), medium (0.5) and large (0.8). (28)

Linear mixed models (LMM) were used to examine the relationship of total pain score with Voice domain score and demographic patient items. LMM are flexible models that account for correlated errors associated with repeated, continuous and correlated observations and account for missing data. Two models were examined: one with Voice domain score (covariate) and the other with each Voice domain item (factor). The LMM examined pain score as a continuous outcome, with fixed effects age (covariate), sex and potential confounders aged care home and assessor role included (factors). Patient identifier was set as a random effect with a variance components covariance matrix. A restricted maximum likelihood method of estimation was selected. Model residuals were inspected and where violations were noted a log transformed dependent variable was used to resolve the violation. In addition, an interaction effect between age care home/program and assessor role was examined with model fit assessed by Akaike's Information Criterion (*AIC*), with lower AIC indicating an improved model fit. A separate comparison analysis was conducted with the outcome total pain score (minus voice score) and the results did not change.

The likelihood of a high pain category compared to low pain was examined using a binary logistic generalised estimated equation (GEE) with logit link function. Fixed effects included age (covariate), sex and voice domain items (factors), and patient identifier as the repeated subject. Similarly, a negative binomial with log link GEE was used to examine the four category pain score. The odds ratio (OR) and Wald CI are reported.

For the subset of 3,144 primary cases, a Receiver Operator Characteristic (*ROC*) analysis with sensitivity (true positive rate) and 100-specificity (false positive rate) for the Voice Domain score was conducted using NCSS (v21.0.1 2021). (29) Youden index was used to determine the diagnostic accuracy across potential cutoff points (sensitivity + specificity -1). Scores can range from 0 to 1, with higher scores representing the optimal cutoff point. Pain condition was determined based on Pain score categories of low pain (no pain or mild pain) and high pain (moderate or severe pain). Additionally, a Principal Component Analysis (*PCA*) for low and high pain was conducted for the Voice domain items using Eigenvalues >1 for extraction and the direct Oblimin rotation method. Both Kaiser-Meyer-Olkin measure of sampling adequacy (0.686) and Bartlett's test of sphericity (p <0.001) assumptions for factorability were met, with a Monte Carlo PCA for parallel analysis conducted (variables = 9, subjects = 2500, replications = 100) (30) to confirm factor structure.

Results

Sample demographics and user data

A total of 3,144 patients with dementia and cognitive impairment had 22,194 pain assessments conducted by trained users during various activities of daily living. Patients were aged 44-106 years (M_{age} 83.3 years [9.0]) with slightly more females (59.0%). Table 1 provides further demographic details. The average number of pain assessments completed per patient was 7.1 (SD = 35.7), with most (60.8%) assessments conducted for females. Total pain scores ranged from 0 to 35. Most assessments were conducted by nurses (44.5%) and care support staff (20.1%). Full demographic characteristics are described elsewhere. (31)

Table 1. Demographic data of study sample[31]

Characteristic	**Statistics**
Sample size, ***n*** (%)	3,144 (100)
Age, years	
Mean (***SD***)	83.3 (9.0)
Gender, ***n*** (%)	
Female, ***n*** (%)	1,856 (59.0)
Male, ***n*** (%)	1,288 (41.0)
Aged care homes, ***n*** (%)	34 (100)
Bed capacity, mean (range)	86.2 (22-176)

Ownership	
For profit,[a] ***n*** (%)	12 (35.3)
Not-for-profit,[b] ***n*** (%)	22 (64.7)
Location (remoteness)	
Major cities, ***n*** (%)	23 (67.6)
Regional, ***n*** (%)	9 (26.5)
Rural, ***n*** (%)	2 (5.9)

SD: standard deviation, *IQR*: interquartile range
Note: The sample was also drawn from two national dementia-specific behavior support programs.
[a]For-profit (private) providers, including both family-owned, and public companies.
[b]Not-for-profit, including religious, charitable, and community-based organizations.

Association between the presence/absence of vocalization features and pain scores/pain intensities

Pain scores for the presence or absence of Voice domain items and according to pain intensity are described at Table 2. For all Voice domain features, the presence of the vocalization was associated with a higher median pain score with large effect sizes (Table 2). Absent vocalization was associated with a median pain score of 4.0 for all nine pain related features of the Voice domain. Median pain scores when the vocalizations were present ranged from 9.0 to 13.0, with scores highest when screaming (*Md* = 13.0) and/or howling (*Md* = 12.0) were present. When comparing pain intensity, during severe pain (*n* = 580), noisy pain sounds were the most frequent vocalization (62.4%), followed by sighing (57.8%), groaning (52.8%) and moaning (52.4%). In lower pain intensities (i.e., mild pain episodes *n* = 3,865), sighing was the most common vocalization (28.2%) followed by noisy pain sounds (18.9%) and moaning (18.0%), whereas howling was the least common (2.5%). Noteworthy for high pain, emotive vocalizations, namely crying (19.4%), screaming (18.3%) and howling (9.1%) were least frequently reported.

Table 2. Voice Domain items 'present' described for total sample, pain score, four pain categories, and low/high pain.

Domain Item	Total	Pain Score		Effect Size			Pain Categories (Intensities)				*Pain Dichotomised	
	f (%)	*M (SD)* *[Md, IQR]*					*f* (%)				*f* (%)	
		Absent	**Present**	**CLES**	**Cohen's *d***		**None**	**Mild**	**Moderate**	**Severe**	**Low**	**High**
n	22,194				*d*	95%CI	16,617	3,865	1,132	580	20,482	1,712
Noisy pain sounds	1,843 (8.3)	4.4 (3.3)	11.5 (4.9)	0.93	2.05	2.00-2.10	272 (1.6)	730 (18.9)	479 (42.3)	362 (62.4)	1,002 (4.9)	841 (49.1)
		[4.0, 2.0-6.0]	[11.0, 8.0-15.0]									
Requesting help repeatedly	1,534 (6.9)	4.6 (3.6)	10.3 (4.9)	0.86	1.54	1.49-1.59	401 (2.4)	575 (14.9)	323 (28.5)	235 (40.5)	976 (4.8)	558 (32.6)
		[4.0, 2.0-6.0]	[9.0, 6.0-13.3]									
Groaning	1,551 (7.0)	4.5 (3.5)	11.3 (5.0)	0.91	1.88	1.82-1.93	265 (1.6)	590 (15.3)	390 (34.5)	306 (52.8)	855 (4.2)	696 (40.7)
		[4.0, 2.0-6.0]	[11.0, 8.0-14.0]									
Moaning	1,821 (8.2)	4.4 (3.5)	10.6 (5.1)	0.89	1.70	1.65-1.75	418 (2.5)	697 (18.0)	402 (35.5)	304 (52.4)	1,115 (5.4)	706 (41.2)
		[4.0, 2.0-6.0]	[10.0, 7.0-14.0]									
Crying	727 (3.3)	4.7 (3.8)	11.5 (5.3)	0.89	1.76	1.69-1.84	142 (0.9)	253 (6.5)	169 (14.9)	163 (28.1)	395 (1.9)	332 (19.4)
		[4.0, 2.0-6.0]	[11.0, 7.0-15.0]									
Screaming	524 (2.4)	4.8 (3.7)	13.2 (5.5)	0.94	2.24	2.15-2.33	55 (0.3)	155 (4.0)	139 (12.3)	175 (30.2)	210 (1.0)	314 (18.3)
		[4.0, 2.0-6.0]	[13.0, 9.0-17.0]									
Loudtalk	1,737 (7.8)	4.5 (3.6)	9.9 (5.2)	0.85	1.44	1.39-1.49	539 (3.2)	612 (15.8)	331 (29.2)	255 (44.0)	1,151 (5.6)	586 (34.2)
		[4.0, 2.0-6.0]	[9.0, 6.0-13.0]									
Howling	277 (1.2)	4.8 (3.9)	13.2 (5.5)	0.94	2.14	2.02-2.26	24 (0.1)	98 (2.5)	65 (5.7)	90 (15.5)	122 (0.6)	155 (9.1)
		[4.0, 2.0-6.0]	[12.0, 9.0-17.0]									
Sighing	2,883 (13.0)	4.3 (3.4)	9.5 (4.7)	0.85	1.45	1.41-1.49	902 (5.4)	1,089 (28.2)	557 (49.2)	335 (57.8)	1,991 (9.7)	892 (52.1)
		[4.0, 2.0-6.0]	[9.0, 6.0-12.0]									

Note. *f* frequency; % percent; M mean; SD standard deviation; Md median; CLES Common Language Effect Size; * Low = No or Mild pain, and High = Moderate or Severe pain

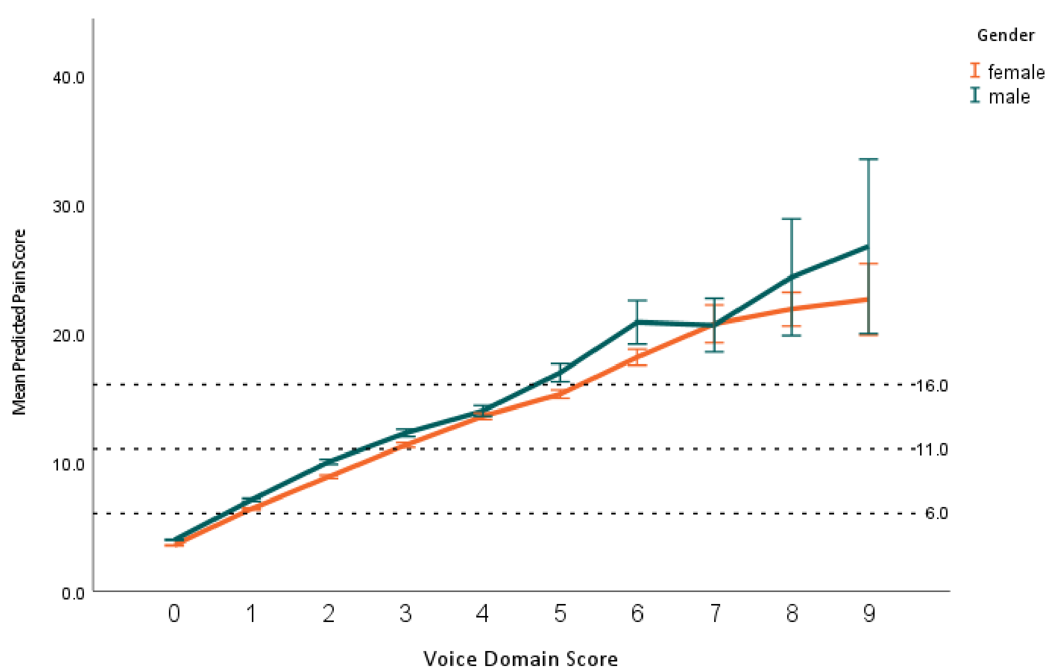
Gender and age

Gender was significantly associated with pain score (*p* <.001), with females recording slightly lower pain scores to males (β = -0.45, *SE* = 0.11, *CI*: -0.67 to -0.23). Age was not significantly associated with pain score (*p* = 0.494).

Assessor role and aged care home/program

LMM confirmed an adjustment for confounding by assessor role and aged care home/program was necessary. For assessor role, the 'consultant' category had the highest estimated marginal mean score (14.9, *SE* = 0.7, *CI*: 13.6-16.3) compared to other categories, with 'care support employee' category scoring the lowest (13.4, *SE* = 0.3, *CI*: 12.7-14.0). Likewise, the assessment of pain varied across the across the sample from a low estimated marginal mean of 12.5 (*SE* = 1.2, *CI*: 10.1-14.9) up to a high of 19.2 (SE = 3.1, *CI*: 13.1-25.3). Overall, the tests of fixed effects from the LMM showed that the number of Voice domain features was significantly associated with pain score (*p* <.001) (Figure 1).

Figure 1. Predicted pain scores for number of voice domain features present, separated for gender.



Presence of vocalization features and predictability of high pain scores

The binary logistic GEE odds of reporting a high pain score are reported in Table 3. The presence of sighing and screaming were associated with the highest odds of a high pain score (eight times), followed by noisy pain sounds and loudtalk (five times), then crying (four times). The remaining domain features increased the odds of a high pain score around three times. The likelihood of a high pain score was higher in males (almost two times), but no significant difference was noted for age (p = 0.414). Similarly, using a negative binomial with log link GEE model, all Voice domain features were significantly associated with the four-category pain intensity (Table 3), with sighing, loudtalk and noisy pain sounds having higher additive effects.

Table 3. Generalized estimating equation predictability of high pain scores when voice domain item was present.

Model	**Exp(β)**	**95% Confidence Interval Exp(β)**		***p*-value**
Pain: Low / High		Lower	Upper	
Intercept	0.0	0.0	0.2	*<.001
Gender (male)[1]	1.8	1.3	2.6	.001
Age	1.0	1.0	1.0	.414
Noisy pain sounds[2]	5.0	4.0	6.3	*<.001
Requesting help repeatedly[2]	3.3	2.3	4.9	*<.001
Groaning[2]	3.3	2.7	4.1	*<.001
Moaning[2]	2.8	2.2	3.7	*<.001
Crying[2]	4.1	2.6	6.4	*<.001
Screaming[2]	7.7	5.3	10.6	*<.001
Loudtalk[2]	5.0	3.6	7.1	*<.001
Howling[2]	2.9	1.8	4.5	*<.001
Sighing[2]	8.1	6.4	10.4	*<.001
Model	**β (*SE*)**	**95% Confidence Interval (β)**		***p*-value**
Pain: no, low, moderate, severe		Lower	Upper	
Intercept	-1.2 (0.4)	-2.1	-0.4	.005
Gender (male)[1]	0.3 (0.1)	0.1	0.4	.008
Age	-0.0 (0.0)	-0.0	0.0	.033
Noisy pain sounds[2]	0.8 (0.0)	0.8	0.9	*<.001
Requesting help repeatedly[2]	0.7 (0.1)	0.6	0.8	*<.001
Groaning[2]	0.6 (0.0)	0.5	0.8	*<.001
Moaning[2]	0.6 (0.1)	0.5	0.7	*<.001
Crying[2]	0.6 (0.1)	0.5	0.7	*<.001
Screaming[2]	0.7 (0.1)	0.6	0.8	*<.001
Loudtalk[2]	0.9 (0.1)	0.8	1.0	*<.001
Howling[2]	0.3 (0.1)	0.2	0.5	<.001
Sighing[2]	1.2 (0.1)	1.1	1.3	*<.001

Note. [1] compared to male, [2] compared to absent *statistically significant at $p < .000001$
Pain (low/high) model reports a binary logistic with odds ratio (Exp[β]) presented;
Pain (no, low, moderate, severe) reports a negative binomial with log link with beta estimate (β) and standard error (*SE*) presented.

Discriminating power of Voice domain score for categorizing low and high pain groups

Of the subset sample of 3,144 initial pain assessments for each patient analyzed a total of 827 (26.3%) had high pain and 2,317 (73.7%) had low pain episodes. The ROC area under the curve (0.884, *SE* = 0.007, 95% *CI*: 0.871-0.896, *z* = 58.7, *p* <.000001) indicated that the criterion variable Voice domain score was able to distinguish between the low and high pain groups. The optimal criterion Voice domain score was ≥2.0 with a Youden index of 0.637. Corresponding sensitivity was 79.7% (*CI*: 76.8%-82.4%), specificity was 84.0% (*CI*: 82.5%-85.5%). The ROC analysis, Youden Index, counts and classification proportions across cutoff values are presented in Table 4.

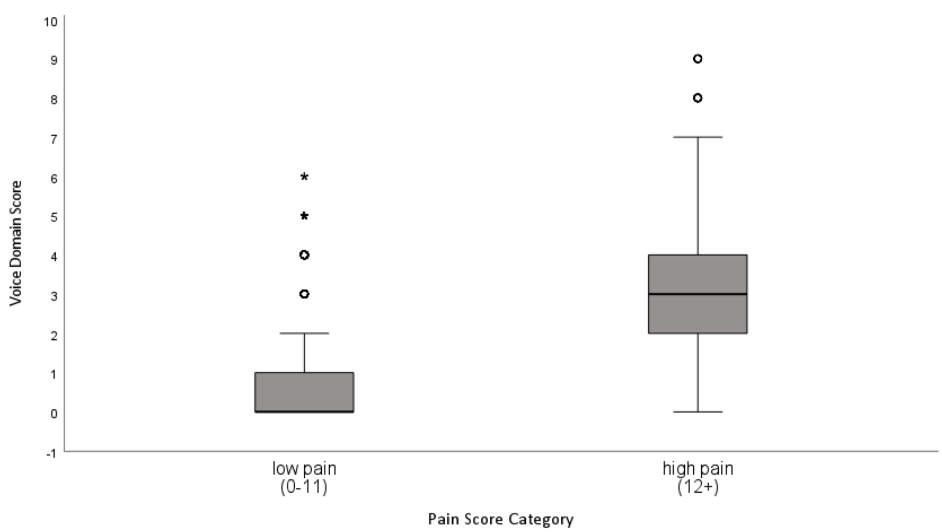
Table 4. Voice Domain Score ROC analysis summary of Youden index, counts, and classification proportions.

Cutoff Value	Youden Index	True Positive (n)	False Positive (n)	False Negative (n)	True Negative (n)	Correctly Classified Proportion	Correctly Classified 95% CI Lower	Correctly Classified 95% CI Upper	Incorrectly Classified Proportion	Incorrectly Classified 95% CI Lower	Incorrectly Classified 95% CI Upper
≥ 0.0	0.00	827	2,317	0	0	0.26	0.25	0.28	0.74	0.72	0.75
≥ 1.0	0.51	792	1,034	35	1,283	0.66	0.64	0.68	0.34	0.32	0.36
≥ 2.0	0.64	659	370	168	1,947	0.83	0.82	0.84	0.17	0.16	0.18
≥ 3.0	0.47	434	116	393	2,201	0.84	0.82	0.85	0.16	0.15	0.18
≥ 4.0	0.28	243	27	584	2,290	0.81	0.79	0.82	0.19	0.18	0.21
≥ 5.0	0.16	130	3	697	2,314	0.78	0.76	0.79	0.22	0.21	0.24
≥ 6.0	0.07	59	1	768	2,316	0.76	0.74	0.77	0.24	0.23	0.26
≥ 7.0	0.03	25	0	802	2,317	0.74	0.73	0.76	0.26	0.24	0.27
≥ 8.0	0.02	14	0	813	2,317	0.74	0.73	0.76	0.26	0.24	0.27
≥ 9.0	0.01	5	0	822	2,317	0.74	0.72	0.75	0.26	0.25	0.28

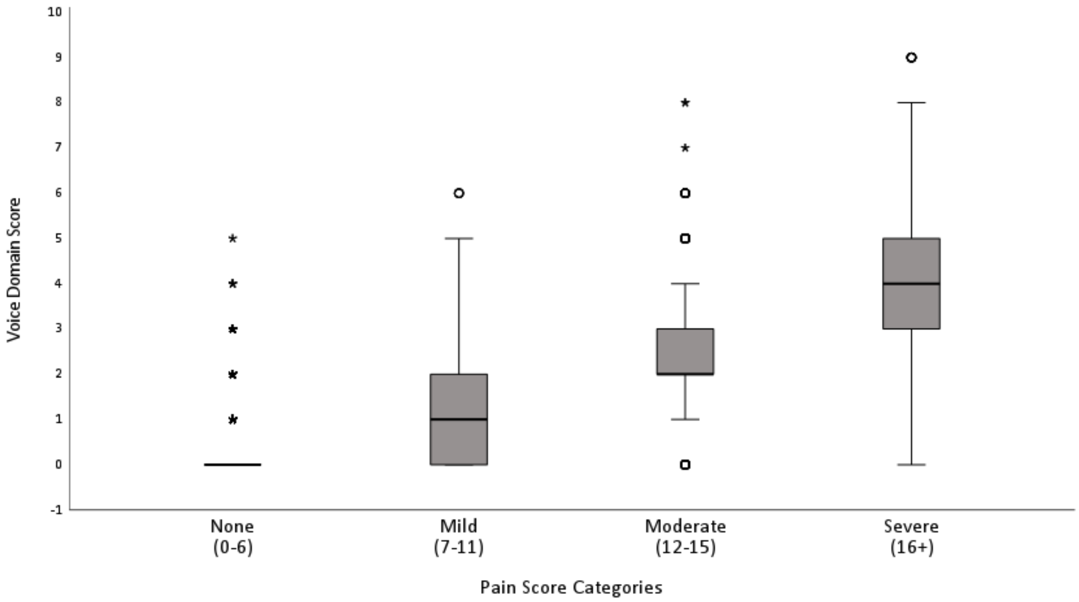
Note. Grey shaded row indicates the optimal criteria based on the highest Youden Index value of 0.637. CI confidence intervals

PCA revealed the presence of three components within the Voice domain with eigenvalues exceeding 1, explaining 23.8%, 15.6% and 11.1% of the variance, respectively. The scree plot and parallel analysis suggested an optimal two factor structure. For both the 3-factor and 2-factor PCA models, groaning (0.763, 0.737), moaning (0.732, 0.728) and noisy sounds (0.638, 0.621) loaded together, respectively. The remaining domain features loaded to form the second component in the 2-factor model; while for the 3-factor model crying (0.750), requesting help (0.602), howling (0.598) and screaming (0.375) loaded together; and loudtalk (0.771), sighing (-0.754) and screaming (0.539) loaded together. Voice domain scores ranged from 0-9 (*M* = 0.6, *SD* = 1.11, *Md* = 0.0, *IQR* = 0.0-1.0). Figure 2 provides further details on Voice domain scores for a) dichotomized pain intensities, i.e., low and high and b) four pain intensities (No, Mild, Moderate and Severe pain).

Figure 2. Boxplot depicting voice domain score across pain intensity categories



a) Two category pain plot. *Note: Voice domain cores for low and high pain ranged from 0-6 (M = 0.4, SD = 0.8, Md = 0.0, IQR 0.0-1.0) and 0-9 (M = 3.0, SD = 1.6, Md = 3.0, IQR 2.0-4.0), respectively.*



b) Four category pain plot. *Note: Voice domain scores ranged from 0-5 (M=0.2 SD=0.5 Md=0.0 IQR 0.0-0.0) for no pain, 0-6 (M=1.2 SD=1.2 Md=1.0 IQR 0.0-2.0) mild pain, 0-8 (M=2.5 SD=1.4 Md=4.0 IQR 2.0-3.0) moderate pain, and 0-9 (M=3.8 SD=1.7 Md=4.0 IQR 3.0-5.0) for severe pain.*

Discussion

In this study we described pain-specific vocal expressions of people living with advanced dementia during assessment of their pain. As such, it becomes the first study to do so by analyzing the data from a large database of over 20,000 pain assessments conducted in clinical settings.

Our findings suggest that the presence of vocalization is associated with higher median pain scores, therefore providing evidence to associations of vocalization behaviors not only in relation to pain presence but its intensity as well. Additionally, analysis of identified vocalizations during different pain categories revealed specific patterns that were more prevalent dependent on whether subjects experienced severe pain or mild pain. These results support existing evidence that has suggested that there is a change in voice parameters in patients experiencing pain (19-21).

Vocalized expressions of pain are produced in response to noxious stimuli, perhaps to support the survival instinct of senders through attracting attention from perceivers or listeners or warning others from existential danger. (32,33) Through auditory broadcastings of the pain experience, vocalizations may alert listeners to the experienced threat. (33) Thus, supported by their acoustic features, vocalizations may be deemed genuine communication cues to the experience of pain and pain intensity. (34) Our study suggests that vocalized expressions of pain are graded behaviors rather than discrete. This is congruent with several studies in other population groups (e.g., infants). (35,36)

Recently, Veldwijk-Rouwenhorst *et al.* found that higher frequencies of vocalizations characterized with vocal behaviors such as higher levels of screaming, were correlated with higher levels of antipsychotic use as well as aberrant motor behaviors, anxiety, night-time behaviors and euphoria in residents with dementia. (37) A strong association between screaming and pain intensity found in our study provides evidence to support this. In this context, it is also worth mentioning that presence of pain has been previously shown to be associated with higher severity of neuropsychiatric behaviors in people with dementia. (38)

This study has a number of strengths which are primarily related to the large and representative database that stems from clinical practice. The database is automatically compiled after pain assessments are completed using a POC tool and the data then are transmitted via cloud computing to support documentation processes. Additionally, the study benefits from the consistency in the pain assessment process enabled by a validated pain assessment tool used across assessments, and different sites, and trained assessors that ensured competency in the pain assessment process. However, the study also has a number of limitations including the fact that different types of dementia were not accounted for, and the data were not labelled to account for the degree or severity of cognitive impairment. Pain experience can be affected by these aspects especially considering that various dementia types involve different neural processing mechanisms and brain regions which as a result may affect the pathways through which pain is processed. (39) Additionally, we did not account for potential confounding effects of medications and other medical conditions including the impact of non-pain related impact of neuropsychiatric symptoms. Further research is needed to study the implications of these factors in the context of pain and vocalizations. Also, further research exploring the relationship of individual and combined vocalization behaviors with other pain behaviors would be beneficial in order to phenotype the multidimensionally aspects of pain experience.

Nonetheless, our findings contribute to the existing literature by providing new insights related to vocalization behaviors and the presence and intensity of pain, therefore supporting their diagnostic value. Furthermore, considering the relationships between neuropsychiatric symptoms, vocalization behaviors and pain, findings of this study could inform clinical practice and therefore have implications in relation to a timelier assessment of pain and its intensity, and subsequent reduction of pain-related complications such as BPSD. Furthermore, our findings raise the possibility of digital phenotyping of vocalizations emerging as a broader clinically-relevant biomarker of clinical evaluation of later- stage dementia. The need for mechanistic phenotyping and therefore individualization of pain management in dementia has been recently raised by Collins *et al.*, whereas Soiza as well as Close in separate editorials highlighted the value of harnessing big data to inform clinical practice. (40,41,42). In this regard, digital phenotyping of vocalizations, enabled by big data availability and analysis could assist with identification of previously unrecognized patterns of pain experience by the person with dementia. This has potential to contribute towards individualization and improvement of pain management.

Conclusions

Our findings provide evidence from clinical practice contributing to further insights into the occurrence and relationship of vocalized behaviors with the presence and intensity of pain in people living with dementia unable to self-report. As such, the study confirms the diagnostic value of vocalized behaviors in assessing pain in nonverbal people with dementia. Our findings suggest that the identification of increased vocalized behaviors should prompt clinicians to consider the presence of significant pain, and therefore complete a formal multidimensional pain assessment using a validated multidimensional pain assessment tool to confirm the intensity of pain and therefore direct appropriate treatment. The above considerations as well as the opportunity for digital phenotyping of vocalizations can provide valuable clinical information that may contribute towards individualized pain assessment and management in people living with dementia.

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The study was approved (HR10/2014) by the Human Research Ethics Committee (HREC) of Curtin University (Bentley, WA, Australia). Permission was also granted by PainChek Ltd (Sydney, NSW, Australia) to provide the dataset.

Declaration of Conflicts of Interest

KH, MA, and JH are co-inventors of the original PainChek® instrument (branded ePAT at the time), which was acquired and subsequently commercialized by PainChek Ltd. They are shareholders of PainChek Ltd. KH is employed as a consultant by PainChek, while also serving as a Professor at the University of Prishtina, Kosovo and is an Adjunct at the Curtin Medical School, Curtin University, WA, Australia. MA previously held the position of a Senior Research Scientist

(October 2018–May 2020) at PainChek Ltd., and currently serving the position of Research and Practice Lead at The Dementia Centre, HammondCare. JH currently holds the position of Chief Scientific Officer at PainChek Ltd., while serving as an Emeritus Professor at Curtin Medical School. The co-inventors had authored a patent titled "A pain assessment method and system; PCT/AU2015/000501" which was assigned to PainChek Ltd. and who have, to date, received granted patents in the jurisdictions of China, Japan, and the United States. PC was paid as an independent consultant to complete the data analysis for the project. PC is the Principal Consultant of DATaR Consulting providing independent biostatistical services, while also serving as Associate Professor at the University of Notre Dame Australia and adjunct at Edith Cowan University in Western Australia.

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