



## Association of patient-reported outcomes with hospitalization risk in atrial fibrillation<sup>☆</sup>

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### ABSTRACT

**Background:** Patient-reported outcomes in atrial fibrillation (AF) are increasingly used to evaluate treatment efficacy and as endpoints in clinical trials. Few studies have related patient-reported outcomes in AF to clinical events and outcomes. We examined the association between patient-reported outcomes and hospitalization risk in individuals with AF receiving care at a regional healthcare system.

**Methods and results:** We related the AF Effect on Quality of Life (AFEQT), a validated measure (range 0–100) with higher scores indicating superior AF-specific patient-reported outcomes, to hospitalization events in a cohort with prevalent AF. We determined incidence rates for hospitalization events (all-cause, cardiac, or AF-related) across quartiles of AFEQT scores. We used the Andersen-Gill method to account for multiple hospitalization events per individual and compared the risks of hospitalization across AFEQT quartiles in multivariable-adjusted models. In 339 individuals with AF (age  $72.3 \pm 10.1$  years; 43% women) followed for median 2.6 years (range 0–3.4 years), we observed 417 total hospitalization events. We identified increased incidence rates of hospitalization with progressively decreased AFEQT quartile. Relative to those in the highest AFEQT quartile, individuals in the lowest AFEQT quartile had 3-fold greater risk of all-cause hospitalization (95% Confidence Interval [CI] 1.67–6.57,  $p < 0.001$ ) and 5-fold greater risk of cardiac hospitalization (95% CI 1.66–13.80,  $p = 0.004$ ).

**Conclusions:** We identified a progressive association between patient-reported outcomes in AF and risk of hospitalization events. Our results underscore the relevance of patient-reported outcomes to clinical adversity and prognosis in AF.

### 1. Introduction

Atrial fibrillation (AF) is an increasingly prevalent heart rhythm disorder with marked adverse effects on patient-reported outcomes such as quality of life [1]. Patients with AF may have complicated treatments for the condition, insults from other chronic diagnoses, or be directly affected by the tachyarrhythmia and its associated morbidity [2]. Multiple measures have emerged to identify and track patient-reported outcomes in AF [3–5]. Professional society guidelines have emphasized patient-reported measures as metrics to gauge and modify treatment for AF, indicating their importance to AF management [6]. Such measures have likewise been incorporated in clinical trials as secondary outcomes to assess symptoms specific to AF and general physical and

psychological health [7–9]. Likewise, patient-reported outcomes have been incorporated into registries to identify factors that influence clinical outcomes in AF [10,11].

We determined to investigate the associations between patient-reported and clinical outcomes. Our rationale was several-fold: first, to date the data describing patient-reported outcomes in AF in relation to clinical adversity remains limited. Second, we appreciated that substantive examination of the association between patient-reported measures and AF may yield insights to enhance and direct patient-centered care, particularly to identify individuals at increased risk of clinical adversity. Third, as patient-reported outcomes are used more frequently as endpoints in clinical trials and studies, how they are affected by AF treatment strategies merits continued exploration.

<sup>☆</sup> **Subject term list:** Atrial fibrillation, Quality and Outcomes

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To conduct our investigation we employed the AF Effect on Quality of Life (AFEQT) questionnaire, which has emerged as the most widely used patient-reported measure in AF [12,13]. The AFEQT employs 20 questions in four domains – symptoms, daily activities, treatment concern, and treatment satisfaction – and has been used in clinical trials, including a multicenter, randomized controlled trial of ablation which identified improvement in quality of life as a prominent endpoint [9]. We consequently examined the association between patient-reported outcomes, assessed by the AFEQT, and hospitalization risk in a cohort of individuals with prevalent AF. We hypothesized that individuals with worse measurement of patient-reported outcomes (i.e., lower AFEQT scores) would experience increased risk of hospitalization even after adjustment for AF treatment.

## 2. Methods

### 2.1. Cohort selection

We enrolled individuals receiving care at selected ambulatory facilities affiliated with the University of Pittsburgh Medical Center (UPMC) in Pittsburgh, PA, a large, regional healthcare system. We identified individuals with prevalent AF by screening the electronic health record and then making direct contact during clinic visits, by physician or provider referral, or by self-referral. Eligibility criteria included age  $\geq 18$  years, history of non-valvular AF as documented by the electronic health record, CHA<sub>2</sub>DS<sub>2</sub>-VaSc [14] (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease [history of MI, PVD, or aortic atherosclerotic disease], and sex category) score  $\geq 2$ , having been prescribed oral anticoagulation for AF, and English-speaking at a level appropriate to participate in this research protocol. Exclusion criteria included history of ischemic or hemorrhagic stroke, AF secondary to non-cardiac issues, AF within 30 days of any cardiothoracic surgery, and individuals who did not pass a three-item screening instrument prior to informed consent. From 2016 to 2018, we identified 1093 eligible individuals from the electronic health record. Recruitment was conducted primarily as part of regularly scheduled visits and constitutes a convenience sample of the individuals identified as eligible as we have previously described [15–17]. We approached 486 individuals to invite their participation in this study, of whom 339 enrolled. Written informed consent was collected for each participant. The study was approved by the University of Pittsburgh institutional review board.

### 2.2. Covariates

Age, sex, race, and smoking status were obtained by self-report. Clinical history pertinent to the CHA<sub>2</sub>DS<sub>2</sub>-VaSc and body mass index were extracted from the electronic health record. AF treatment including history of electrical or chemical cardioversion, pulmonary vein isolation, and anticoagulant and antiarrhythmic medications (amiodarone, dofetilide, flecainide, lidocaine propafenone, and sotalol) were likewise identified from the electronic record. Social factors obtained from participant self-report included annual household income (<\$19,000, \$20,000–\$49,999, \$50,000–\$99,999, or >\$100,000), and level of education (high school or vocational training, some part of college or an associate degree, bachelor's degree, or any graduate or professional school degree or enrollment).

Patient-reported outcomes specific to AF were collected with the AFEQT, a validated 20-item instrument scored from 0 to 100, where higher scores indicate a superior outcome over the prior 4 weeks [12]. The AFEQT includes a global score and 4 domain scores (symptoms, daily activities, treatment concerns, and treatment satisfaction). A difference of 5 or more has been identified as a clinically meaningful change in an individual [18].

### 2.3. Outcomes ascertainment

Hospitalization events were extracted for each individual by review of the UPMC longitudinal electronic health record, from the date of enrollment to the last date of contact, through March 16, 2020 or date of death

as identified by the electronic health record. A hospitalization event was defined as a hospital admission with duration  $\geq 24$  h. Each hospitalization event was classified as all-cause, cardiac-related, and/or AF-related upon review of the electronic health record and determination of the primary indicator for hospitalization. Scheduled admissions for elective procedures (such as cardioversion or ablation) were not defined as hospitalization events.

### 2.4. Statistical analysis

We summarized continuous variables according to their means and standard deviation, and categorical variables as frequencies and percentages. We compared the baseline characteristics according to AFEQT quartile using chi-squared tests for categorical variables and analysis of variance for continuous variables. We then determined the number of hospitalizations events by AFEQT quartile, and calculated incidence rates by incorporating person-years of observation to report differences in hospitalization incidence across quartiles. We graphically represented the number of hospitalizations per patient over time using mean cumulative function of hospitalization curves.

Next, we utilized the Andersen-Gill model to analyze recurrent hospitalizations and calculated hazard ratios by the AFEQT quartile for all-cause, cardiac-, and AF-related hospitalization. The Andersen-Gill model accounts for the correlation of recurrent events within the same individual; in contrast to the standard time-to-first-event analysis of a Cox proportional hazards model, we gain the additional benefit of using all events for each participant rather than censoring at the first end-point [19,20]. We employed multivariable-adjusted models to examine the relation of the AFEQT to hospitalization endpoints. Multivariable models were constructed sequentially to adjust for demographic factors consisting of age, sex, and race (Model 1), then additionally adding clinical factors consisting of body mass index, heart failure, hypertension, diabetes, and vascular disease, and treatment for atrial fibrillation (ablations, cardioversion, antiarrhythmic medications) (Model 2), and finally adding the socioeconomic factors of annual household income and educational attainment (Model 3). All statistical analyses were conducted with SAS version 9.4 (Cary, North Carolina).

## 3. Results

Baseline characteristics at study enrollment are presented in Table 1. There were 339 participants enrolled in the study with a median 2.6-year length of follow-up (range 0–3.4 years). The average age was  $72.3 \pm 10.1$  years, and 144 (42.5%) were women. Most study participants had an annual household income in the \$20,000–\$49,999 range ( $n = 100$ , 29.5%), while education for most participants was at the high school or vocational level ( $n = 117$ , 34.5%).

The AFEQT quartiles were: 0 to <66.6 (Quartile 1); 66.6 to <80.0 (Quartile 2); 80.0 to 90.0 (Quartile 3); and >90.0 to 100.0 (Quartile 4). There were no significant differences in age, sex, or race/ethnicity across AFEQT quartiles. While a greater proportion of participants with heart failure belonged to the higher AFEQT quartiles, the distributions of hypertension, diabetes, and vascular disease were consistent across quartiles. Of the 339 individuals enrolled in the study, there was a cumulative total of 417 hospitalizations, among which 175 were categorized as cardiac-related (42.0%) and 64 (15.3%) as related to AF. The frequency of all-cause hospitalization ranged from one ( $n = 54$  individuals) to 15 ( $n = 1$ ); cardiac hospitalization from one ( $n = 42$ ) to 9 ( $n = 1$ ); and AF hospitalization from one ( $n = 24$ ) to 6 ( $n = 1$ ).

Table 2 presents the number of events and incidence rates for all-cause and cardiac-related hospitalization by AFEQT quartile. We noted an overall increase in the incidence of both categories of hospitalization with progressive decrease in AFEQT quartile. The hospitalization incidence rate per patient-year for individuals in the lowest AFEQT quartile was approximately 4-fold that of those in the highest AFEQT quartile (Quartile 1, 0.72; Quartile 4, 0.19). The incidence rate of cardiac-related hospitalization

**Table 1**  
Characteristics of the study cohort ( $n = 339$ ) by AFEQT quartile.

Characteristic	All participants	Quartile 1 ( $< 66.6$ )	Quartile 2 ( $66.6$ to $< 80.0$ )	Quartile 3 ( $80.0$ to $90.0$ )	Quartile 4 ( $> 90.0$ )
	$n = 339$	$n = 78$	$n = 94$	$n = 85$	$n = 81$
Age, years	72.3 $\pm$ 10.1	69.9 $\pm$ 9.8	72.8 $\pm$ 11.1	73.2 $\pm$ 10.9	72.9 $\pm$ 7.8
Female sex	144 (42.5%)	42 (53.8%)	39 (41.5%)	33 (38.8%)	30 (37.0%)
White race	320 (94.4%)	72 (92.3%)	86 (91.5%)	83 (97.6%)	78 (96.3%)
Body mass index (m/kg <sup>2</sup> )	31.2 $\pm$ 7.2	33.2 $\pm$ 8.3	31.4 $\pm$ 7.5	29.1 $\pm$ 5.6	31.0 $\pm$ 6.4
Smoking history					
Never	169 (49.9%)	32 (41.0%)	49 (52.1%)	46 (54.1%)	41 (50.6%)
Former	152 (44.8%)	37 (47.4%)	44 (46.8%)	36 (42.4%)	35 (43.2%)
Current	18 (5.3%)	9 (11.5%)	1 (1.1%)	3 (3.5%)	5 (6.2%)
Heart failure (any)	111 (32.7%)	34 (43.6%)	40 (42.6%)	24 (28.2%)	13 (16.0%)
Preserved	61 (18.0%)	16 (20.5%)	28 (29.8%)	10 (11.8%)	7 (8.6%)
Reduced	44 (13.0%)	17 (21.8%)	10 (10.6%)	11 (12.9%)	6 (7.4%)
Not specified	6 (1.8%)	1 (1.3%)	2 (2.1%)	3 (3.5%)	0 (0.0%)
Hypertension	243 (71.7%)	57 (73.1%)	71 (75.5%)	56 (65.9%)	59 (72.8%)
Diabetes	82 (24.2%)	21 (26.9%)	22 (23.4%)	21 (24.7%)	18 (22.2%)
Vascular disease	82 (24.2%)	23 (29.5%)	17 (18.1%)	20 (23.5%)	21 (25.9%)
Education					
High school/vocational	117 (34.5%)	30 (38.5%)	39 (41.5%)	26 (30.6%)	21 (25.9%)
Some college	67 (19.8%)	12 (15.4%)	22 (23.4%)	15 (17.6%)	18 (22.2%)
Bachelor's	79 (23.3%)	26 (33.3%)	12 (12.8%)	21 (24.7%)	20 (24.7%)
Graduate	76 (22.4%)	10 (12.8%)	21 (22.3%)	23 (27.1%)	22 (27.2%)
Income					
< \$19,999	35 (10.3%)	15 (19.2%)	9 (9.6%)	5 (5.9%)	6 (7.4%)
\$20,000-49,999	100 (29.5%)	25 (32.1%)	33 (35.1%)	23 (27.1%)	18 (22.2%)
\$50,000-99,999	97 (28.6%)	20 (25.6%)	29 (30.9%)	25 (29.4%)	23 (28.4%)
> \$100,000	64 (18.9%)	10 (12.8%)	8 (8.5%)	22 (25.9%)	24 (29.6%)
Refused/no answer	43 (12.7%)	8 (10.3%)	15 (16.0%)	10 (11.8%)	10 (12.3%)
AFEQT	76.4 $\pm$ 17.6	50.4 $\pm$ 12.6	73.3 $\pm$ 4.0	85.8 $\pm$ 2.8	94.8 $\pm$ 2.6

Continuous measures expressed as mean  $\pm$  standard deviation, and categories by their distribution and percentages. AFEQT indicates Atrial Fibrillation Effect on Quality of Life.

for individuals in the lowest AFEQT quartile was 8-fold that of those in the highest AFEQT quartile (Quartile 1, 0.40; Quartile 4, 0.05). Supplemental Table 1 presents the number of events and incidence rates for AF-related hospitalization stratified by AFEQT quartile. The incidence rate of AF-related hospitalization for those in the lowest AFEQT quartile was 10-fold that of those in the highest AFEQT quartile (Quartile 1, 0.10; Quartile 4, 0.01).

Fig. 1A presents the graded associations between AFEQT quartile and all-cause hospitalization events over follow-up. Likewise, Fig. 1B presents the association between AFEQT and cardiac-related hospitalizations, also stratified by AFEQT quartile. Supplementary Fig. 1 presents AF-related hospitalization events by AFEQT quartile. The figures consistently demonstrate the strong, prospective associations between lower AFEQT scores and increasing frequency of hospitalization events.

Table 3 presents the associations between health-related quality of life as measured by the AFEQT and risk of all-cause and cardiac-related

**Table 2**  
Incidence of hospitalization events in study cohort by AFEQT quartile.

	Hospitalization events	Person-time at risk (yrs)	Incidence rate <sup>a</sup>
All-cause hospitalization			
Quartile 1 ( $n = 78$ )	142	198.6	0.72
Quartile 2 ( $n = 94$ )	148	244.9	0.60
Quartile 3 ( $n = 85$ )	89	219.7	0.41
Quartile 4 ( $n = 81$ )	38	204.5	0.19
Cardiac-related hospitalization			
Quartile 1 ( $n = 78$ )	79	198.6	0.40
Quartile 2 ( $n = 94$ )	54	244.9	0.22
Quartile 3 ( $n = 85$ )	31	219.7	0.14
Quartile 4 ( $n = 81$ )	11	204.5	0.05

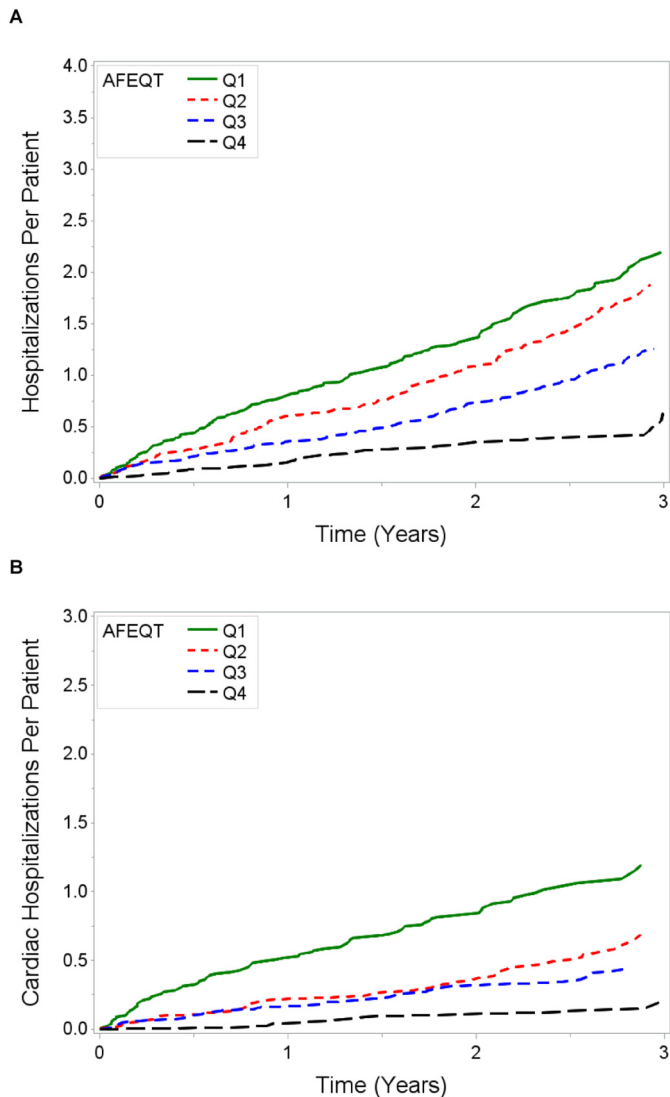
<sup>a</sup> Incidence rate reported as number of hospitalizations per patient-year. AFEQT indicates Atrial Fibrillation Effect on Quality of Life.

hospitalization in multivariable-adjusted models. With the highest AFEQT quartile serving as the referent, the risk of hospitalization in both categories progressively increased across lower AFEQT quartiles. Individuals in the lowest AFEQT quartile had approximately 3-fold the risk of overall hospitalization as individuals in the highest AFEQT quartile after adjustment for demographic, clinical, and socioeconomic factors (95% CI 1.67–6.57,  $p < 0.001$ ). For cardiac hospitalization, the progressive increase in risk with decrease in AFEQT quartile was more pronounced. Individuals in the lowest AFEQT quartile had nearly five-fold the risk of cardiac hospitalization as individuals in the highest AFEQT quartile (CI 1.66–13.80,  $p = 0.004$ ). Supplemental Table 2 presents the associations between the AFEQT and risk of AF hospitalization. The progressive increase in risk with decrease in AFEQT quartile was most pronounced with AF hospitalization. Individuals in the lowest AFEQT quartile had approximately 16 times the risk of AF hospitalization as individuals in the highest AFEQT quartile (CI 2.00–133.10,  $p = 0.009$ ).

#### 4. Discussion

In a moderate-sized cohort of individuals with AF, we identified significant and consistent associations between validated, AF-specific patient-reported outcomes and adverse clinical events, specifically hospitalization. We noted a graded increase in risk of hospitalization as patient-reported outcomes declined. Our results underscore the importance of patient-reported outcomes as informative measures of health risk and clinical adversity in individuals with AF.

Our study is particularly relevant as patient-reported outcomes are increasingly used in clinical trials as primary endpoints. For example, the AFEQT was used in a multicenter randomized trial of over 2000 patients comparing catheter ablation and antiarrhythmic drug therapy in AF [9]. The AFEQT has also been used to investigate the merits of earlier cardioversion to maintain sinus rhythm in recent-onset AF [21]. Our results are consistent with a prior study, which showed that lower quality of life, a central



**Fig. 1.** A and B. Mean cumulative function of (A) all-cause and (B) cardiac-related hospitalization after study enrollment according to AFEQT quartile scores. AFEQT indicates Atrial Fibrillation Effect on QualiTy of life, and categorization into quartiles, labeled as Q1-Q4 in the figure, is as defined by the text.

**Table 3**  
Risks of all-cause and cardiac-related hospitalization according to AFEQT quartile.

	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>All-cause hospitalization</b>						
Quartile 1	4.22 (2.39, 7.44)	<0.001	3.56 (1.80, 7.02)	<0.001	3.32 (1.67, 6.57)	<0.001
Quartile 2	3.14 (1.70, 5.72)	<0.001	2.95 (1.48, 5.89)	0.002	2.75 (1.41, 5.37)	0.003
Quartile 3	2.15 (1.20, 3.83)	0.009	1.75 (0.85, 3.58)	0.12	1.69 (0.83, 3.43)	0.15
Quartile 4 (referent)	-	-	-	-	-	-
<b>Cardiac-related hospitalization</b>						
Quartile 1	7.41 (3.17, 17.20)	<0.001	5.43 (1.94, 15.10)	0.001	4.79 (1.66, 13.80)	0.004
Quartile 2	3.88 (1.60, 9.29)	0.002	3.30 (1.22, 8.85)	0.018	3.28 (1.21, 8.83)	0.019
Quartile 3	2.71 (1.12, 6.51)	0.026	2.23 (0.78, 6.37)	0.13	2.05 (0.70, 5.99)	0.19
Quartile 4 (referent)	-	-	-	-	-	-

Model 1 adjusted for age, sex, and race.

Model 2 adjusted for Model 1 covariates, body mass index, heart failure, hypertension, diabetes, vascular disease, and treatment for atrial fibrillation (ablations, cardioversion, antiarrhythmic medications).

Model 3 adjusted for Model 2 covariates, annual household income, and educational attainment.

AFEQT indicates Atrial Fibrillation Effect on QualiTy of Life; HR, hazard ratio; CI, confidential interval.

patient-reported outcome in AF, was associated with higher hospitalization risk [22]. In contrast to being conducted in a large-sized, multi-center registry, our study was conducted in a single regional healthcare system, in which we expect individuals would have decreased heterogeneity in the evaluation and management of AF. In addition, AF treatment history and relevant medications, which may influence patient-reported outcomes, are accounted for in our multivariable-adjusted analyses. In sum, our study extends our understanding of the relation of patient-reported to clinical outcomes in AF.

We consider that our findings have important implications for patient care. The delivery of patient-centered care is essential to improving outcomes in cardiovascular disease. A higher level of patient engagement in decision-making and symptom management has been associated with better clinical outcomes in AF [23]. Implementation of patient-centered care may reduce length of hospital stay, enhance physical functioning, and increase self-efficacy in cardiovascular disease [24,25]. In our study, we established that patient-centered outcomes are associated with clinical outcomes in AF, even after consideration of demographic, socioeconomic, AF treatment history, and comorbid factors included in our multivariable adjustment. Measuring patient-reported outcomes in AF patients may identify individuals at increased hospitalization risk and thereby facilitate strategic interventions to prevent clinical adversity.

Strengths of our study include the use of a moderate-sized cohort within a single-center regional healthcare system, use of a disease-specific instrument that measures patient-reported outcomes with domains pertinent to the patient experience of AF, and inclusion of cardiac and AF-specific endpoints. Our study has several limitations. First, although the use of a moderate-sized, regional-based cohort enhanced the validity of our results, our cohort's generalizability is limited. Second, our analysis may not account for health care delivery factors that may affect the associations between patient-reported outcomes and the risk of hospitalization that we identified here. For example, it is possible that patients received attention and services not accounted for by this analysis. Third, we are unable to exclude the presence of additional covariates which may have confounded our analyses. Finally, although we identified an association between patient-reported outcomes and hospitalization, we did not account for a broad array of measures such as psychological function, functional status, and general health perceptions that may be relevant [26,27]. Future research is needed to identify the causal mechanisms that may explain the complicated mechanisms by which patient-reported outcomes may mediate hospitalization risk as observed in our study.

### 5. Conclusion

In conclusion, we identified a significant association between disease-specific patient-reported outcomes and hospitalization risk in a moderate-

sized cohort of individuals with prevalent AF. Our findings extend our understanding of the relevance of patient-reported outcomes to clinical adversity in AF. Our study specifically validates the importance of assessing patient-reported outcomes to improve and focus care.

### CRedit authorship contribution statement

**Yimin Chen:** Conceptualization, Methodology, Validation, Investigation, Writing- Original draft preparation, Visualization. **Tarryn Tertulien:** Writing- Reviewing and Editing. **Andrew D. Althouse:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Visualization. **Amber Johnson:** Writing- Reviewing and Editing. **Brittany Gisi:** Writing- Reviewing and Editing. **Jared W. Magnani:** Conceptualization, Methodology, Investigation, Writing- Review & Editing, Supervision, Project administration, Funding acquisition.

### 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.ahjo.2021.100007>.

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