



Sleep disturbance in primary brain tumor: prevalence, risk factors, and patient preferences

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Abstract

Purpose Primary brain tumor (PBT) patients report sleep disturbance due to their disease and treatment, yet few studies have utilized validated measures to understand the extent of patients' concerns and preferences for treatment. The purpose of this quality improvement project was to determine the prevalence and associated risk factors of sleep disturbance among PBT patients in our clinic and to evaluate interest in treatment for sleep disturbance.

Methods PBT patients completed validated measures of sleep disturbance and health during routine neuro-oncology visits. Patients also reported on sleep-related symptom management and their preferences for pharmacological and/or behavioral treatment.

Results Sleep disturbance was common, with 61.5% of PBT patients ($N=119$; $M_{\text{age}}=52.60$ years; 50% male) reporting poor sleep quality and 21.5% endorsing symptoms of insomnia. Insomnia could be explained by increased fatigue and corticosteroid use; sleep quality could be explained by fatigue. Patients in our clinic with higher grade tumors, significant sleep disturbance, of minority racial/ethnic status, and those not already taking sleep medications were more likely to report their symptoms and were *not* well-addressed by their medical team. Patients indicated a similar interest in pharmacological and behavioral treatment, warranting the availability of both in our clinic.

Conclusions Findings indicate a high prevalence of sleep disturbance in PBT patients, highlighting the need for increased screening, monitoring, and treatment in our neuro-oncology clinic. Future research would benefit from assessing the efficacy of behavioral treatments for sleep disturbance in this population.

Keywords Primary brain tumor · Sleep disturbance · Insomnia · Neuro-oncology · Psycho-oncology

Introduction

Sleep disturbance—including short sleep duration, poor quality of sleep, and sleep inefficiency—is one of the most common and consequential symptoms reported by cancer survivors [1]. As many as 60% of cancer patients report

symptoms of sleep disturbance, a rate 2–3 times higher than that of the general population [2, 3]. More recent studies suggest that nearly a third of cancer patients endorse severe insomnia with nearly two-thirds advocating for more consistent assessment of their sleep as part of their cancer care [4, 5]. Among individuals with cancer, sub-optimal sleep is associated with a range of adverse physical, psychological, and functional consequences including increased pain, fatigue, and depression [6, 7]. Despite the advent of safe and effective behavioral treatments for sleep disturbance [8], screening for sleep disorders in oncology settings is still limited, and pharmacological treatments remain the norm [9, 10].

Individuals with primary brain tumors (PBT) frequently report sleep disturbance and rate this problem as one of the most distressing symptoms [11, 12]. One study reported that 38% of patients with PBT on steroids reported sleep disturbance [12]. Sleep disturbance is particularly problematic

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for this specific cancer population given their unique vulnerabilities: PBT patients are at a higher risk for cognitive impairment, and problems with sleep may magnify any neuropsychological deficits resulting from both the brain tumor and its treatment [13]. Furthermore, the side effects of prescribed sleep medications may also impair cognition and exacerbate PBT patients' risk of falls, fractures, and motor vehicle accidents [14]. Lastly, given that poor sleep quality is associated with higher levels of inflammatory biomarkers such as interleukin-6 (IL-6), prolonged difficulties with sleep may also increase PBT patients' risk for tumor progression and worsen their already poor prognoses [15, 16].

Despite the wide array of consequences associated with sleep disturbance in neuro-oncology, PBT patients have often been excluded from sleep research—perhaps, as reported in a review of PBT representation in quality of life research [17], due in part to presumed cognitive impairment. Two recent review articles [11, 18] highlight major drawbacks of extant research: first, the use of well-validated sleep measures is scarce, with past research predominantly relying on health-related quality of life measures or single-item, self-report measures of sleep. Secondly, study samples were often small, composed of mixed brain cancer groups, or largely focused on patients with benign brain tumors in long-term remission from total tumor resection [11]. These methodological limitations inevitably obscure the prevalence of sleep disturbance in PBT and limit the generalizability of the existing knowledge base. To date, there is only one published study which directly analyzed the prevalence of sleep disturbance using validated sleep measures in a sample of Australian brain cancer patients (including both PBT and metastatic brain tumors) [19]. This study found that over half of the sample reported significant poor sleep quality, and 15% endorsed clinically significant symptoms of insomnia. Nevertheless, follow-up analyses with a sample of strictly PBT patients are needed to replicate these initial prevalence rates.

Information is also limited regarding potential risk factors for sleep disturbance among PBT patients, which might be useful in clarifying underlying mechanisms. In the larger sleep disturbance literature, certain demographic variables (e.g., female gender and advanced age) are known predisposing factors for developing insomnia [20], yet there has been no data to date that confirms this in neuro-oncology. Medical providers in neuro-oncology appear to attribute sleep disturbance solely to the use of corticosteroids and/or previous mood disorders [21]. However, Jeon and colleagues [19] reported that other variables, such as participants' Karnofsky performance status (KPS) scores and levels of fatigue, were significant predictors of sleep quality in their *mixed* sample of primary and metastatic brain tumor patients. Other preliminary data in mixed neuro-oncology samples suggests radiation treatment, tumor bilaterality, and depressive

symptoms may interfere with sleep [22, 23]. Further elucidating the etiology and underlying mechanisms of sleep disturbance in PBT are important steps in tailoring treatment to address these concerns.

Perhaps most importantly, existing research has not yet examined PBT patients' preferences for treatment or the extent to which they believe their reported symptoms are well-managed by their medical team. This information is especially important as a recent study found that only 20% of surveyed medical professionals in neuro-oncology routinely assessed for sleep disturbance, even though these providers perceived a high prevalence of sleep disturbance in their clinics [21]. This study also found that neuro-oncology providers were most likely to offer advice or prescribe medication to treat sleep disturbance, yet this study did not assess the *patients'* preferences for treatment, including their interest in non-pharmacological approaches (e.g., behavioral therapy). This is especially important as behavioral treatments have been shown to be highly effective [8] and are the preferred treatment option of other chronically ill samples who similarly have complex medication and treatment regimens [24]. Given the ubiquity and significance of sleep-related concerns in this vulnerable population, a more thorough examination of the prevalence and risk factors for sleep disturbance—using comprehensive, validated sleep disturbance questionnaires—as well as PBT patients' beliefs and preferences for treatment is warranted. These inquiries will help inform the next steps of our neuro-oncology physicians in their treatment of sleep-related concerns.

The purpose of the present quality improvement project was threefold: (1) to determine the prevalence of sleep disturbance among PBT patients in our clinic, (2) to identify risk factors associated with sleep disturbance in our patient sample, and (3) to evaluate our PBT patients' beliefs about how well their medical team is currently managing their sleep-related symptoms and assess their interest in pharmacological and/or behavioral treatments for sleep disturbance. The prevalence of sleep disturbance was hypothesized to be comparable to that of previous research in neuro-oncology with fatigue, age, and corticosteroid use explaining greater sleep disturbance. We also hypothesized that a significant prevalence of sleep disturbance in our sample would translate into a strong belief that their symptoms are not well-managed by their medical team, especially considering recent research suggesting sleep disturbance is infrequently assessed in neuro-oncology. Finally, given what has been found in previous research with other medical populations [24], PBT patients were hypothesized to be most interested in behavioral over pharmacological treatments for sleep disturbance.

Methods

Design and study population

Patients were asked to respond to an anonymous, voluntary quality improvement survey during their routine neuro-oncology visits at an urban National Cancer Institute-designated cancer center. Our IRB board ruled that our quality improvement survey did not necessitate review. Due to COVID-19 restrictions, visits occurred both in-person and via telehealth. During in-person visits, clinic nurses provided patients with the online Qualtrics survey to complete via iPad while waiting for care in private exam rooms. For telehealth appointments, patients were emailed a link to the survey to complete at home. Patients were required to be adults (+ 18), diagnosed with a PBT, and literate in English to participate.

Measures

Demographic and clinical factors Patients self-reported demographic (e.g., age, gender, race/ethnicity) and clinical characteristics (e.g., tumor type, tumor grade, time since diagnosis, and corticosteroid medication use). Tumor type was categorized as glioblastoma, astrocytoma, oligodendroglioma, meningioma, or “other.” Tumor grade was categorized dichotomously as low (grades I and II) or high (grades III and IV). Time since diagnosis was investigated as date of survey completion minus date of diagnosis, rounded to the nearest month. Current corticosteroid medication use was categorized dichotomously as either yes or no.

Insomnia Severity Index (ISI) [25] The ISI is a widely used screening measure of insomnia and has been validated in cancer populations [26]. Total scores on the ISI range from 0 to 28, with higher scores corresponding to greater insomnia severity. The ISI has the following established cut-off scores: 0–7 (no clinically significant insomnia symptoms), 8–14

(subthreshold scores), 15–21 (clinical insomnia, moderate severity), and 22–28 (clinical insomnia, severe). Cronbach’s alpha for the ISI in the current sample was 0.90.

Pittsburgh Sleep Quality Index (PSQI) [27] The PSQI is a 19-item measure which assesses past-month sleep quality and produces seven component scores ranging from 0 to 3, with higher scores corresponding to poorer sleep quality. Components include subjective sleep quality, sleep onset latency, sleep duration, sleep efficiency [(% of time spent sleeping / time spent in bed) × 100], sleep disturbances, sleep medication use, and daytime dysfunction. Component scores are totaled to produce a global score ranging from 0 to 21, with scores above 5 indicative of poor sleep quality [27]. Cronbach’s alpha for PSQI in the current sample was 0.72.

Brief Fatigue Inventory (BFI) [28] One item from the BFI was used to determine participants’ level of fatigue during the past month on a scale from 0 (*no fatigue*) to 10 (*as bad as you can imagine*). The use of a single item for assessing fatigue is consistent with previous research [29, 30], though these studies did not use single items from the BFI specifically.

Napping A single-item asked patients to report the average number of hours per day spent napping in the past month.

Patient beliefs and interests Patients were also asked to report on the following: (1) their beliefs regarding how well their symptoms of insomnia were managed by their medical team and (2) their interest in insomnia treatment (i.e., pharmacological and/or behavioral treatment). Insomnia management was rated from 0 (*not at all well-managed*) to 10 (*very well-managed*); treatment interests were rated from 0 (*strongly dislike*) to 10 (*strong prefer*). For each of these questions, participants could also mark *not applicable* (i.e., no insomnia symptoms). See Table 1 for researcher-developed questions.

Table 1 Researcher developed questions assessing patients’ beliefs of symptom management and patients’ interests in treatment

Patient beliefs item	Rating scale
1. To what extent do you believe your insomnia symptoms are well-managed by your medical providers?	0 (<i>not at all well-managed</i>) to 10 (<i>very well-managed</i>)
Patient treatment interests items	Rating scale
1. Insomnia can be treated with medications and/or techniques aimed at changing behaviors and lifestyle factors. How would you describe your feelings towards medication treatment?	0 (<i>strongly dislike</i>) to 10 (<i>strongly prefer</i>)
2. Insomnia can be treated with medications and/or techniques aimed at changing behaviors and lifestyle factors. How would you describe your feelings towards behavioral treatment?	0 (<i>strongly dislike</i>) to 10 (<i>strongly prefer</i>)

Note: For each item, participants could also mark *not applicable/no insomnia symptoms*

Data analytic plan

Descriptive analyses were computed to characterize the sample and estimate the prevalence of sleep disturbance. Patients with clinically elevated insomnia symptoms ($ISI \geq 15$) or poor sleep quality ($PSQI > 5$) were categorized as experiencing sleep disturbance. Two logistic regressions were performed to identify demographic and clinical factors associated with sleep disturbance; variables included age, gender, race/ethnicity, time since diagnosis, tumor type, tumor grade, corticosteroid medication use, and fatigue severity. Patients' beliefs about how well their symptoms were managed by their medical team and their treatment interests (i.e., pharmacological and/or behavioral treatment) were assessed using frequencies. Patients' beliefs and interests were collapsed into two categorical responses, where responses of 0–4 were negative/low and responses of 6–10 were positive/high. Lastly, we used both one-way ANOVA and Pearson correlations to determine how these beliefs and interests differed across demographic (e.g., age, gender, race/ethnicity) and clinical (e.g., time since diagnosis, tumor type, tumor grade, corticosteroid medication use, sleep medication use, fatigue severity, ISI total, and PSQI total) variables.

Results

Patient characteristics

A total of 121 PBT patients participated in the survey. Two patients did not complete both the ISI and PSQI and thus were excluded, yielding a sample size of 119 for analysis. Patients were predominantly male (50.4%), White (74.4%), and middle-aged ($M = 52.60$ years; $SD = 15.39$; range, 21–83 years). Most patients reported high-grade brain tumor (61.3%), and glioblastoma multiforme (GBM) was the most commonly reported tumor type (37%). The average time since PBT diagnosis was 65.08 months ($SD = 72.06$; range, 1–367 months). One fifth of patients (20.2%) reported that they were currently prescribed corticosteroids. Finally, the patients' mean fatigue level during the previous two weeks was 4.39 ($SD = 2.71$; range, 0–10). See Table 2 for complete participant demographics and clinical characteristics.

Prevalence of sleep disturbance

In terms of insomnia, patients' average score on the ISI was within the sub-clinical range ($M = 8.81$, $SD = 6.69$). Based on established cut-offs, the breakdown of scores on the ISI was as follows: 44.6% no clinically significant insomnia,

31.4% sub-clinical symptoms, 17.4% moderate symptoms, and 4.1% severe symptoms.

In terms of sleep quality, over half (61.5%) of patients had poor sleep quality based on the PSQI total score (> 5). Average sleep duration was 8.58 h/night ($SD = 1.95$ h/night), with 52.1% of participants reporting a sleep efficiency score below 85%, a common cut-off indicative of poor sleep quality.

Participants with insomnia as measured by the ISI all endorsed poor sleep quality ($PSQI > 5$), while 34.7% of participants who endorsed poor sleep quality ($PSQI > 5$) also scored above the cut-off for insomnia ($ISI \geq 15$).

Sleep medication use was also prevalent, with 24% of participants using over-the-counter medication and 12.4% taking prescription sleep medication. Based on the ISI, insomnia severity for participants taking any kind of sleep medication ($M = 11.90$, $SD = 6.72$) was nearly twice as high as those not taking medication ($M = 6.46$, $SD = 5.69$; $F(1,116) = 22.63$, $p < 0.001$). Moreover, of those taking sleep medication, 62.7% screened positive for insomnia on the ISI.

Finally, daytime napping was common (69.7%) with an average of 1.41 h ($SD = 1.41$; range, 0–6 h) of reported daytime sleep per day.

Risk factors of sleep disturbance

Two logistic regressions were used to determine risk factors for sleep disturbance and insomnia, using the PSQI and ISI as outcome variables. In the first logistic regression, explaining insomnia correctly classified 82.8% of participants (sensitivity = 50%; specificity = 92.2%). Nagelkerke R^2 suggested that the model accounted for approximately 52.5% of the variance in insomnia. Specifically, corticosteroid medication use ($OR = 5.97$; CI, 1.15, 31.07) and fatigue severity ($OR = 1.66$; CI, 1.23, 2.25) were each found to significantly increase the likelihood of insomnia.

By contrast, the second logistic model explained 29.4% of the variance in sleep quality and correctly classified 71.9% of participant's sleep quality (sensitivity = 50%; specificity = 84.7%). Only fatigue severity explained the presence of poor sleep quality ($OR = 1.29$; CI, 1.07, 1.56). Supplemental Table 1 provides the full results of the logistic regressions.

Patients' beliefs about management of sleep-related symptoms

Of those who positively screened for insomnia ($ISI \geq 15$), most patients (64%) reported these symptoms were *not* well-managed (rating of 0–4) by their medical team, and only 24% reported that these symptoms were indeed well-managed (rating of 6–10; $M = 3.64$; $SD = 2.46$). Similarly, in patients who reported clinically significant sleep disturbance ($PSQI > 5$), more patients indicated their symptoms were

Table 2 Demographic and clinical characteristics of primary brain tumor sample ($N=119$)

Variable			Frequency	Mean/percent (SD)
Age			119	52.60 years (range 21–83 years)
Gender	Male		60	50.4
	Female		58	48.7
Race	White		88	73.9
	African American		23	19.3
	Other		8	6.6
Tumor type	Meningioma		18	15.1
		Grade I	8	6.7
		Grade II	8	6.7
	Astrocytoma		27	22.7
		Grade II	13	10.9
		Grade III	13	10.9
	Oligodendroglioma		21	17.6
		Grade II	5	4.2
		Grade III	12	10.1
	Glioblastoma multiforme			
		Grade IV	44	37.0
	Other/unknown		9	7.6
Tumor grade	Low	Grades I and II	35	21.8
	High	Grades III and IV	73	61.3
Time since diagnosis			119	65.08 mos. (72.06)
			> 1 year	16.8
			1–3 years	36.0
			3–5 years	14.0
			5–10 years	10.4
			10+ years	20.4
Corticosteroid Rx	Yes		24	20.2
	No		91	76.5
	Unsure		4	3.4
Sleep medication	No		68	57.1
	Yes		51	42.9
		Prescribed	15	12.6
		Over-the-counter	29	24.4
ISI total			118	8.81 (6.70)
PSQI total			117	7.19 (4.27)

Note: ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Inventory

not well-managed (48.3%) than managed (38.3%; $M=4.48$; $SD=3.37$).

Using both one-way ANOVA and Pearson correlations, we determined whether any demographic or clinical characteristics were related to patients' beliefs regarding how well their symptoms were managed. The results revealed that patients were more likely to believe their symptoms were *not* well-managed if they had higher grade tumors ($F(1, 57)=6.75$, $p=0.01$), were currently prescribed corticosteroids ($F(1, 61)=4.70$, $p=0.03$), were of a minority racial/ethnic background ($F(1, 62)=4.61$, $p=0.04$), were

not already taking a prescription sleep medication, ($F(1, 32)=4.55$, $p=0.04$), or had higher ISI scores ($r=-0.35$, $p<0.01$). No other demographic or clinical variables were significantly associated ($ps>0.05$).

Patients' interests in treatment

Of those who positively screened for insomnia ($ISI\geq 15$), 48% reported interest in pharmacological treatment and 41.7% in behavioral treatment. Of those who positively screened for sleep disturbance ($PSQI>5$), 40.5% reported

interest in pharmacological treatment and 38.5% in behavioral treatment.

Using both one-way ANOVA and Pearson correlations, we assessed whether any demographic or clinical variables determined an interest in pharmacological and/or behavioral treatment. Patients with poorer sleep quality as measured by the PSQI ($r=0.34$, $p<0.01$) and patients who were already taking sleep medications ($F(1, 75)=5.11$, $p=0.03$) were more likely to rate pharmacological treatment more highly; no other demographic or clinical variables were found to be significantly related, $ps>0.05$.

Discussion

This study sought to better understand the prevalence and risk factors of sleep disturbance in a sample of PBT patients receiving care at a National Cancer Institute (NCI)-designated neuro-oncology clinic. This data represents the first known investigation to use validated questionnaires of insomnia and sleep disturbance (i.e., Insomnia Severity Index and Pittsburgh Sleep Quality Index) in exclusively PBT patients, a sample with myriad vulnerabilities to sleep disturbance and its treatment. We found that over half of patients reported poor sleep quality and over a fifth endorsed moderate-to-severe symptoms of insomnia. Increased fatigue was found to explain both insomnia and sleep disturbance, whereas corticosteroid use was found to be only an indicator of insomnia. Our investigation also had the unique goal of elucidating patients' beliefs on how well these symptoms were being managed by their medical team as well as patients' interests in treatment moving forward. Those experiencing sleep disturbance did not feel their symptoms were properly addressed by their medical team, yet there was a similar interest in both pharmacological and behavioral treatments across the board. These findings suggest that our patients may potentially benefit from (1) additional screening of insomnia by medical staff and (2) behavioral interventions for insomnia by one of our two staff psychologists or our clinical psychology practicum students. Further, the results may prompt and guide other neuro-oncology clinics to enhance their care of sleep disturbance in their own patient populations.

The prevalence of insomnia in our sample was comparable to a recent study which examined sleep among patients with either primary or metastatic brain tumors [19] but lower than a prior study of patients with recurrent gliomas where insomnia was screened using an adverse event scale [31]. One possible reason for this discrepancy may be the relatively higher rate of sleep medication use in our sample, which may mask some of the symptoms of sleep disturbance. One study found that hypnotic medication might be helpful to improve sleep, mood, and cognitive functioning

for patients with brain tumors [32]. The risk factors for sleep disturbance among our patients were consistent with past research. For example, one study found that 89% of patients with PBT who were categorized as having insomnia endorsed fatigue [31, 33]. These findings are clinically relevant given that fatigue is known to adversely affect both the quality of life (e.g., disrupting mood) and functioning of PBT patients [34, 35]. Similarly, the association between corticosteroids use and sleep disturbance has been shown in previous investigations [31]. While previous research suggests that certain demographic variables [36], such as female gender or advanced age, predispose one to experience insomnia, this was not the case among our patients. However, the lack of an association between these demographic variables and sleep disturbance is consistent with other research examining sleep in patients with PBT [19, 31].

Given that previous findings have uncovered infrequent assessment of sleep disturbance in neuro-oncology [21], it is perhaps not surprising our data revealed a high rate of dissatisfaction with how well their sleep-related symptoms were managed by their medical team. Indeed, most of our patients with clinically significant sleep disturbance indicated that their symptoms were *not* properly addressed by their medical team. To manage the tumor and its side effects (e.g., edema), neuro-oncologists often prescribe medications and treatments that may negatively impact sleep (e.g., corticosteroids, radiation therapy). Thus, frequent assessment and routine monitoring of sleep disturbance is warranted, especially in those with higher grade tumors, those of a minority racial/ethnic background, those prescribed corticosteroids, and those not already taking sleep medications, as these individuals in our clinic were less likely to believe their symptoms were being addressed. Validated, brief instruments such as the ISI and PSQI may be two possible, practical additions to improve assessment in our NCI-designated, fast-paced, neuro-oncology clinic. Both measures may also assist with monitoring symptoms across the disease trajectory as they are sensitive to therapeutic change [26].

Increasing the identification of sleep disturbance is merely the first step in improving quality of life of PBT patients; patients will also need an appropriate treatment. Our findings indicate that patients in our clinic have a similar interest in both pharmacological and behavioral treatment for insomnia, regardless of whether they have clinically significant insomnia. Only those with poor sleep quality and those already taking sleep medications indicated a higher interest in medication as treatment. Previous findings suggest that pharmacological treatment is the norm in neuro-oncology [9, 21, 37], and many of our patients reported using an over-the-counter or prescription sleep medication. Of note, however, the majority of those using sleep medications still screened positive for insomnia—perhaps suggesting the need for combined pharmacological and behavioral

treatment for these patients. While behavioral treatments are less likely to be recommended by individual medical providers [21], cognitive behavioral therapy for insomnia (CBT-I) is the recommended frontline treatment for insomnia by the American College of Physicians [8] and American Academy of Sleep Medicine [38]. CBT-I specifically targets dysfunctional sleep routines and attitudes without the use of medication. Many chronically ill patients prefer behavioral treatment such as CBT-I over medication given the risk of polypharmacy [24]; this is especially relevant to PBT patients who are often prescribed a variety of medications, including psychostimulants [39]. While CBT-I has been found to be efficacious in improving sleep disturbance in other cancer populations [37], PBT patients have been historically excluded from these trials. Overall, the significant proportion of interest in behavioral treatment identified in our sample warrants the availability of such treatments moving forward, though future investigations of CBT-I in PBT are also needed.

Limitations

The present study is not without limitations. First, the cross-sectional design precludes our ability to establish temporal relationships between clinical risk factors and sleep disturbance in PBT patients. Secondly, though the use of well-established measures of sleep disturbance is a strength relative to past research, self-report measures are subject to reporting bias. Future research would also benefit from comprehensive scales of fatigue. Finally, given that these findings are based on a quality improvement project, additional clinical factors of interest, such as emotional distress, history of previous treatments, or functional status, were not assessed. Future research would benefit from examining a larger population and a broader range of relevant clinical variables to determine their association to sleep among this patient population.

Conclusion

Sleep disturbance and insomnia are highly prevalent among patients in our clinic with PBT. Patients with poor sleep are dissatisfied with the management of their symptoms and report an openness to either pharmacological or behavioral interventions for insomnia. These findings underscore the need for better screening of sleep disturbance by healthcare providers in our clinic and for future research to assess the efficacy of both pharmacological and behavioral interventions.

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Data availability Data are available upon reasonable request from the corresponding author.

Code availability Not applicable.

Declarations

Ethics approval This is a quality improvement, needs assessment study. The Institutional Review Board at VCU has confirmed that no ethical approval is required as this data does not qualify as research and was collected for clinical purposes.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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