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Research Article

The Tolerability and Side Effect Profile of Venlafaxine in a Clinical Outpatient Pediatric Population

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Abstract

Background: Major depressive disorder (MDD) in youth is a prevalent and debilitating mental health condition, with approximately 20% of adolescents estimated to be affected prior to adulthood. **Objective:** Our objective was to review the tolerability and efficacy of venlafaxine in adolescents with MDD.**Methods:** We conducted a retrospective chart review spanning January 2020 to December 2022 from the Royal Ottawa Mental Health Centre. Patients were included if they were between 7 and 18 years old, had a diagnosed MDD, and were on Venlafaxine for at least six weeks and were excluded if they didn't have enough follow-ups, resulting in a sample size of 45 patients. The primary outcomes were the tolerability and side effect profile of venlafaxine, assessed through changes in symptomatology, documented new symptoms, and functional side effects. **Results:** The study population comprised 67% females (n=30). Males were treated significantly longer (19 months) than females (9.61 months) (p=.015). Most patients (53.3%) maintained a consistent dosage throughout treatment. Approximately 11.1% of patients experienced new symptoms, and 6.7% reported functional side effects. Improvement in mood was noted in 51.1% of patients, with additional benefits observed in sleep (26.7%), anxiety reduction (24.4%), and mood stabilization (15.6%). Overall, 68.9% of patients reported improvements in symptoms over the course of treatment. **Conclusions:** Venlafaxine appears to be a well-tolerated and effective treatment option for adolescents with MDD. These findings support the potential use of venlafaxine in cases where first-line treatments are inadequate, highlighting the need for further research on its safety and efficacy.

Keywords: Antidepressants; Depressive disorders; Child and Adolescent Psychiatry; Venlafaxine; Major depressive disorder.

Introduction

Major depressive disorder (MDD) stands as a prevalent mental health diagnosis globally across all age groups, exerting a discernible and disabling impact. An estimated 20% of adolescents will experience MDD prior to adulthood [1]. Depression interferes with an individual's ability to form social connections, succeed in academic pursuits, and foster necessary confidence [2]. A diagnosis of MDD in youth has been shown to predict adverse outcomes later in life, including substance use disorders, lower socioeconomic status, and poor occupational and educational attainment [2]. Given the detrimental short and long-term ramifications, treatment is critical. Research has shown that first-line pharmaceutical options such as fluoxetine result in a positive clinical response about 60% of the time in children and adolescents [3,4]. More recently, it's been suggested that up to 30% of adolescents will have persistent symptoms despite using evidence-based methods such as first-line selective serotonin reuptake inhibitors (SSRIs) [5]. This highlights the importance of considering secondary and tertiary options when managing the multifaceted challenges in youth depression [3].

While many pharmacologic treatment options for adults exist, few options have been approved by the U.S. Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE) for patients under the age of 18. Fluoxetine stands as the sole approved medication for children aged 7 to 12 years, while fluoxetine and escitalopram are the only options approved for adolescents [6,7]. This lack of approval is typically related to insufficient testing, rather than demonstratable differences in efficacy [8]. However, these are not the only medications prescribed for this population. Due to sub-optimal clinical results, other SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) are prescribed off-label as secondary and tertiary options [3], despite not being approved to treat children and adolescents as per health Canada.

Fluoxetine and escitalopram are used clinically as first-line pharmaceutical options due to their safety profiles. While some studies suggest that the use of SNRIs, particularly venlafaxine, may result in the worsening of suicidal ideation as well an increase in diastolic blood pressure and skin problems [3,9,10], other studies did not draw the same conclusions [11]. Notably, treatment-emergent suicidality has also been reported in current first-line SSRIs [10]. Meanwhile, venlafaxine has been previously reported to be generally well tolerated among children and adolescents [12]. Thus, the conflicting evidence suggests it is not clear whether worsening suicidal ideation is the result of the SNRI itself, or patient differences, comorbidities, or other extraneous factors.

Although venlafaxine is recommended as a third-line option according to the CANMAT guidelines [13], its use in youth has promising results (Brent et al, 2008; Brent et al., 2018). One study found that adolescents treated with venlafaxine demonstrated significantly greater improvement on validated depression scales when compared to a placebo [14]. Another study reported that 10% of patients demonstrated improvement after six months on venlafaxine, indicating that prior trials may not have tested the drug for an adequate period of time to uncover significant findings [15]. Furthermore, this may represent a feasible secondary or tertiary option for the minority who do not respond well to first-line pharmacological options. There is also evidence to suggest that venlafaxine is useful in treatment-resistant depression. As per the TORDIA trial, where most information on inadequate first-line response comes from, switching from an insufficient first-line SSRI to either venlafaxine or a secondary SSRI yielded similar clinical responses [5,3]. Overall, the existing body of literature in this field is sparse and further exploration is indeed necessary to understand venlafaxine's role in youth depression treatment.

Due to the limited existing research on venlafaxine use in youth depression, the present study aimed to retrospectively assess and summarize the documented use of venlafaxine as a therapeutic treatment option in youth with MDD. We hypothesized that over two years, youth diagnosed with MDD with or without another concurrent psychiatric disorder, would both tolerate and demonstrate benefits from venlafaxine.

Methods

Approval to conduct the retrospective review of charts was obtained from the Royal Ottawa Mental Health Centre research ethics board (REB).

Participants

A retrospective chart review was conducted on adolescent patients seen over a two-year span (January 2020 to December 2022) by three board certified child psychiatrists at the Royal Ottawa Mental Health Center. Patients were included if they were between the ages of 7 and 18 years, had a diagnosed MDD as per the DSM-V, and were on Venlafaxine for at least six weeks with disregard to inpatient or outpatient status.

Patients were excluded if no follow up data was available, or if the patient was below the age of 7 years or above the age of 18 years. The initial sample size yielded 589 patients between the ages of 7 and 18 years diagnosed with a depressive disorder.

An initial screening of all 589 patients that was conducted via chart review excluded 443 patients who were not diagnosed with any depressive disorder. The 146 remaining patients, 36 were excluded after screening for patients without a sufficient number of follow-up reports available, 8 were excluded for not taking any SNRI during their treatment, and 57 were excluded for patients

with repeated files (only repeats were removed), yielding a final sample size of 45 patients who met the study criteria, and thus were subsequently enrolled for chart review and data extraction (Figure 1).

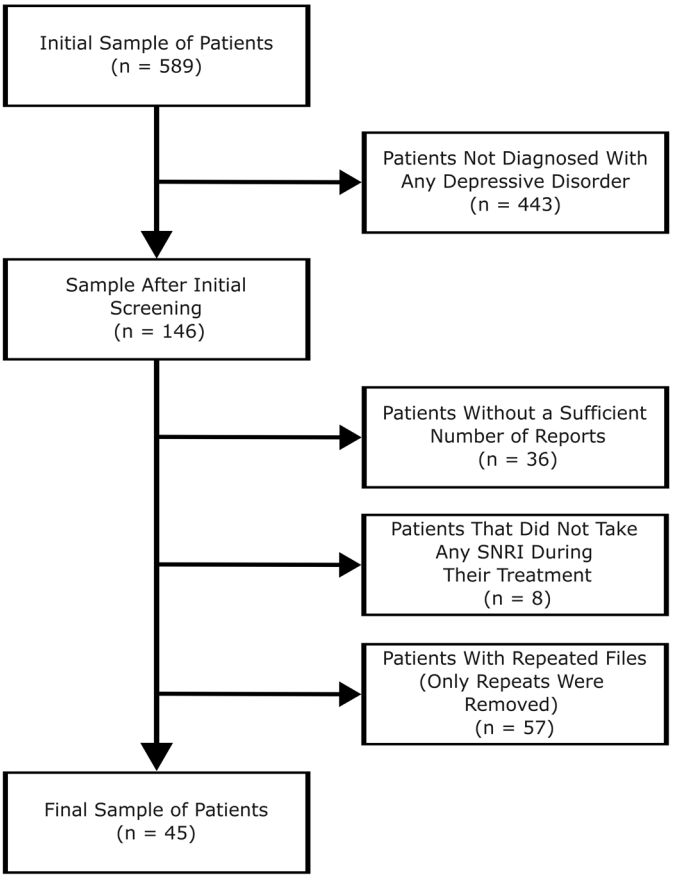

Figure 1: Screening Flowchart.

Data Extraction

Data extracted from patient charts included the patients age, sex, medial history, diagnoses, treatment plan and duration, patient progress, medication side effects, and inpatient/outpatient status at the time of assessment. Variable definitions were standardized to ensure consistency in data extraction. Extracted data were recorded and aggregated on an excel database.

Interrater Reliability

Three independent raters conducted data extraction. Interrater reliability amongst raters were established via consistent extracted data items amongst a sample of 4 test patient charts, following standardized item definitions. Consistency across raters and any conflicts were established and resolved by the principal investigator (PI), respectively. Upon consistent data items across raters, data extraction proceeded for the enrolled patient sample.

Statistical Analysis

Descriptive statistics were conducted to quantitatively summarize the trend, course, and length of venlafaxine treatment, and reported symptomology and side effects, by sex. Differences in the duration of venlafaxine treatment across sex was also assessed *via* t-test. The statistical software used was R. Assumption testing was conducted to ensure homogeneity of variance and normality of the data. Despite a Shapiro-Wilk test indicating non-normality in female treatment length data, the normality assumption is tentatively maintained due to small sample size and potential outliers. Q-Q plots support this. Levene's test suggests unequal variances between genders, hence a Welch t-test is employed, bypassing the assumption of equal variances.

Results

Patient Characteristics

Females comprised majority of the study population (n=30, 67%) in comparison to males (n=15, 33%). Approximately 27% (n=8) of females presented with a comorbid depressive and anxiety disorders, whereas 70% (n=21) of females presented with a depressive disorder and an additional comorbid disorder. Only 3.3% (n=1) of females presented with a depressive disorder only. Furthermore, over 50% (n=8) of males presented with a depressive disorder and an additional comorbid disorder, whereas approximately 25% (n=4) presented with a comorbid depressive and anxiety disorders. Twenty percent (n=3) of males presented with only a depressive disorder. Clinical characteristics are summarized in Table 1.

	Female (N=30)	Male (N=15)	Total (N=45)
Patient Diagnosis			
Depressive Disorder and Other Comorbidities	21 (70.0%)	8 (53.3%)	29 (64.4%)
Depressive Disorder and Anxiety Disorder	8 (26.7%)	4 (26.7%)	12 (26.7%)
Depressive Disorder only	1 (3.3%)	3 (20.0%)	4 (8.9%)
Age			
Mean (SD)	17.15 (0.69)	17.19 (1.16)	17.2 (0.86)
Unreported	0 (0%)	1 (6.67%)	1 (2.2%)

Table 1: Patient Characteristics.

Tolerability and Side Effect Profile

Venlafaxine was most used as a second line of therapy across females (n=12, 40%) and males (n=8, 53.3%), and less commonly as a first line of therapy (females: n=9, 30%; males: n=5, 33.3%) (Table 2). The average treatment length for Venlafaxine was 13 months, with males having spent a significantly longer duration of time on Venlafaxine (19 months) than females (9.61) (p=.015).

	Female (N=30)	Male (N=15)	Total (N=45)
Venlafaxine Line of Therapy			
1	9 (30.0%)	5 (33.3%)	14 (31.1%)
2	12 (40.0%)	8 (53.3%)	20 (44.4%)
3	3 (10.0%)	1 (6.7%)	4 (8.9%)
4+	1 (3.3%)	0 (0%)	1 (2.2%)
Unreported	5 (16.7%)	1 (6.7%)	6 (13.3%)
Length of treatment on Venlafaxine (months)			
Mean (SD)	9.61 (5.75)	19.0 (11.6)	13.0 (9.39)
Unreported	7 (23.3%)	2 (13.3%)	9 (20.0%)

Table 2: Course of Treatment with Venlafaxine.

Approximately 79.2% (n=19) females and 20.8% (n=5) males maintained a consistent dosage of Venlafaxine throughout the treatment course, for a total of 53.3% (n=24) of the sample. Approximately 10% (n=5) of patients discontinued use during their course of treatment. Moreover, 17.8% (n=8) of patients experienced an adjustment (increase) in their Venlafaxine dosage. Approximately 89% (n=40) and 94% (n=42) of patient charts did not document new symptoms or functional side effects during the course of Venlafaxine, respectively. Females reported more new symptoms (13.3%; n=4) than males (6.7%; n=1) male, for a total of approximately 11% (n=5) of patients. New reported symptoms included an increase in anxiety, mild bruising, a nosebleed, nausea, and periorbital edema. Three patients (6.7%) reported functional side effects, which included increased agitation, suicidal ideation, skin picking, and hair pulling (Table 3). Functional side effects were reported in only 4.4% (n=2) of patients, with documented increases in agitation, suicidal ideation, skin picking, and hair pulling.

	Female (N=30)	Male (N=15)	Total (N=45)
Course of Venlafaxine Over Time			
Maintained dosage	19 (63.3%)	5 (33.3%)	24 (53.3%)
Increased dosage	6 (20.0%)	2 (13.3%)	8 (17.8%)
Discontinued (effective)	0 (0%)	2 (13.3%)	2 (4.4%)
Discontinued (ineffective)	1 (3.3%)	2 (13.3%)	3 (6.7%)
Unreported[A]	4 (13.3%)	4 (26.7%)	8 (17.8%)
Documented New Symptoms			
Yes[B]	4 (13.3%)	1 (6.7%)	5 (11.1%)
Unreported	26 (86.7%)	14 (93.3%)	40 (88.9%)
Functional Side Effects			
Yes[C]	1 (3.3%)	1 (6.7%)	2 (4.4%)
Unreported	28 (93.3%)	14 (93.3%)	42 (93.3%)
Unknown[D]	1 (3.3%)	0 (0%)	1 (2.2%)

Table 3: Tolerability and Side Effect Profile; [A]) Unreported refers to a chart in which the variable of interest was not documented or not reported by the patient; [B]) New symptoms include increased anxiety (1 patient), mild bruising and nose bleed (1 patient), nausea (1 patient) and puffiness around eyes (1 patient); [C]) Functional side effects include increased agitation and suicidal ideation (1 patient) and skin picking and hair pulling (1 patient); [D]) Unknown side effects that resolved after 1 week (1 patient).

There were a variety of reported resolving or improved symptoms following a course of venlafaxine. There were trends for reported improvements in mood (n=23, 51.1%) and sleep (n=12, 26.7%), reported reductions in anxiety (n=11, 24.4%), suicidal ideation (n=7, 15.6%), and thoughts of self-harm (n=6, 13.3%), and reported stabilization of mood (n=7, 15.6%).

Additional reported effects while on Venlafaxine include reported improvements in depressive symptoms (n=4, 9%), concentration (n=3, 7%), energy (n=3, 7%), daily functioning (n=2, 4%), motivation (n=2, 4%), insight (n=1, 2%), school performance (n=1, 2%), and stress management (n=1, 2%), reductions in social anxiety (n=2, 4%), panic attacks (n=1, 2%), fatigue (n=1, 2%), and smoking and drinking habits (n=1, 2%), Furthermore, a proportion of patients reported having become more future oriented (n=2, 4%) while on Venlafaxine. Moreover, 31.1% (n=14) of patient charts did not document the resolution or improvement of symptoms while on Venlafaxine (Table 4).

	Female (N=30)	Male (N=15)	Total (N=45)
Symptoms	20 (66.7%)	11 (73.3%)	31 (68.9%)
Mood improvement	13 (43.3%)	10 (66.7%)	23 (51.1%)
Sleep improvement	8 (26.7%)	4 (26.7%)	12 (26.7%)
Reduced anxiety	11 (36.7%)	0 (0%)	11 (24.4%)
Mood stabilization	4 (13.3%)	3 (20%)	7 (15.6%)
Reduced suicidal ideation	5 (16.7%)	2 (13.3%)	7 (15.6%)
Reduced feelings of self harm	5 (16.7%)	1 (6.7%)	6 (13.3%)

	Female (N=30)	**Male (N=15)**	**Total (N=45)**
Improved appetite	5 (16.7%)	0 (0%)	5 (11.1%)
Unreported[A]	10 (33.3%)	4 (26.7%)	14 (31.1%)
Other[B]	8 (26.7%)	6 (40%)	14 (31.1%)

Table 4: Proportion of patients with resolved or improved symptoms; [A]) Unreported refers to a chart in which the variable of interest was not documented or not reported by the patient; [B]) Other includes improvement in depression symptoms (2 females, 2 males), improved concentration (2 females, 1 male), improved energy (1 female, 2 males), future oriented (1 female, 1 male), improved functioning (2 males), improved motivation (1 female, 1 male), reduced social anxiety (1 female, 1 male), improved insight (1 female), improved school work (1 male), improved stress management (1 female), less fatigued (1 male), reduced panic attacks (1 female), smoking and drinking cessation (1 female).

Discussion

The goal of the present study was to retrospectively assess and summarize the tolerability and side effects profile associated with the use of Venlafaxine in a Canadian clinical outpatient pediatric population. We hypothesized that over two years, youth diagnosed with MDD would both tolerate and demonstrate benefits from venlafaxine. Over all our findings suggest that venlafaxine seems to be a safe and well tolerated therapeutic option for pediatric patients suffering from MDD, with reported concurrent improvements in an array of symptoms. These findings are in keeping with previous research suggesting the potential benefits of Venlafaxine in pediatric MDD [3,14].

Our study found that venlafaxine was more often used as a second-line of therapy (44.4%) than a first line of therapy (31.1%), across both females (40%) and males (53.3%), in the context of study findings yielding safe, tolerable, and beneficial outcomes – a trend which aligns with the suggestions posited by the TORDIA trial [5,3]. This suggests the potential feasible use of Venlafaxine as a secondary line of therapy for the proportion of pediatric patients that do not respond well to first-line pharmacological options. Interestingly, length of treatment on Venlafaxine was significantly longer in males than females. This was an unexpected finding and could shine light on unexplored sex differences important to the tolerability and side effects experienced on Venlafaxine.

More than 70% of patients remained on venlafaxine upon follow-ups with the treating psychiatrist, suggesting that there may have been therapeutic benefits experienced upon commencing their respective course. Only a small minority of patients (6.7%) discontinued use due to reported ineffectiveness of the medication. Furthermore, a small minority also discontinued use in the context of improved or resolving symptoms (4.4%).

This trend reinforces a possible positive tolerability profile for Venlafaxine experienced by adolescents experiencing MDD, findings which were also previous established in the literature [14]. One aspect not entirely well assessed was side effect profiles. A small proportion of patients experienced either new symptoms (11.1%) or functional side effects (6.7%) upon commencing Venlafaxine, however we were not able to confirm whether the majority of patients experienced any side effects at all, as we could not assume whether no documented side effects on the chart constituted a lack there-of. The incidence of treatment-emergent adverse events such as headache, nausea, and abdominal pain have previously been reported in longitudinal studies [15], thus, the importance of monitoring for side effects in this population still requires further up-to-date research.

There have previously been documented risks concerning an increase in suicidal ideation while on venlafaxine. Hetrick and colleagues (2021)[10] reported an increased risk of suicidal ideation in some patients on antidepressant, which included Venlafaxine. To the contrary, Gibbons and colleagues [16] found that antidepressant use, including venlafaxine, reduced suicidal thoughts and behavior in adults and geriatric patients. Our study did not find a significant degree of reported suicidal ideation in adolescents. Although the existing literature suggests that the risk for experiencing a worsening in suicidal ideation may vary across different age groups, one may theorize that Gibbons and colleagues [16] findings may indirectly relate and support findings from our present study, associating the lack of reported worsening or new suicidal ideation to the Venlafaxine.

A total of 68.9% of patients reported improvements in symptoms over the course of treatment while prescribed venlafaxine. Notably, a significant proportion of our sample demonstrated improvements in mood, sleep quality, and reduced anxiety, which are important in the overall management of depression. This is consistent with findings from Emslie and colleagues [15] who observed significant improvements in depression scores among adolescents treated with venlafaxine compared to a placebo, suggesting that

venlafaxine seems to offer a considerable advantage in cases where first-line SSRIs have failed to produce the desired clinical response. Moreover, reduced feelings of suicidal ideation and feelings of self-harm were prevalently reported, further supporting the findings postulated by Gibbons and colleagues [16] that Venlafaxine may reduce these feelings in depressed patients. A significant finding that cannot be ignored is the indiscernible data on reported improved or resolved symptoms, that was accounted for across over 30% of patients. It is uncertain whether this missing or unreported information would have yielded stronger findings, or whether this data reflects a subset of adolescents not experiencing any changes in symptoms while on Venlafaxine.

Our findings shed light on the potential utility of Venlafaxine as a safe and tolerable second-line of therapy, with non-causal evidence suggesting improved depressive symptoms and functional outcomes in adolescents suffering from MDD. Further exploration of venlafaxine's efficacy in treating pediatric MDD is critical, given the substantial impact of this condition on youth development, academic performance, and overall quality of life. Current research, including our study, suggests that venlafaxine holds promise as a treatment option for adolescents, particularly those who have not benefited from first-line SSRI treatments. However, the retrospective nature of our study and limitations on causal inferences call for further substantive research. Prospective studies are warranted to more accurately assess venlafaxine's efficacy and safety in this population, ideally incorporating larger sample sizes, utilize standardized measures, and longer follow-up periods to capture the long-term outcomes of treatment.

Limitations and Future Directions

There are several limitations to the study. First, the study utilized a retrospective chart review methodology, thus causal inferences from reported tolerability and improvement in symptoms cannot be deduced from Venlafaxine. Our sample size was also small at 45 patients, thus the degree of generalizable external validity from these findings may be called into scrutiny. It should also be noted that despite having pre-defined variables of interest, several key data points were quantitatively collated from qualitative patient reports, and thus leaves room for interpretation due to a lack of standardization of the available data – one cannot be certain that the reported information by the patient was adequately captured and described in the chart. Moreover, the inconsistencies in language used to describe similar symptoms and side effects further contributes to the difficulties of standardization dealt with during data collection. It is also possible that the patient charts did not capture the entire tolerability and side effect profile experienced while on Venlafaxine due to potential underreporting by patients. Moreover, dosages of venlafaxine could not be controlled across patients, and in some instances were not clear-thus further inferences to be made about improvements from venlafaxine is not only limited to methodology but also to unknown Venlafaxine dosage variability. Expanding upon this is the confound of dual-therapy effects not controlled for (both pharmacological and psychotherapy) which further hinders any conclusions to be made about the tolerability and side effects profile of Venlafaxine.

Future studies should aim to conduct an up-to-date literature review on the use of Venlafaxine not only in North America but world-wide. Furthermore, future efforts should also be directed to conducting a meta-analysis which could yield significant findings to strongly inform prospective trials. An effort should also be put in place to further expand upon our retrospective study results, with more rigorous criteria on controlling for reported outcomes on dual therapies, utilizing a large multi-center cohort. Moreover, future studies should closely monitor reported side effects as its prevalence rates are not entirely known. Lastly, prospective studies should examine the efficacy of Venlafaxine at different lines of therapy (i.e., first, second, third), and assess whether prior SSRI treatment may influence Venlafaxine's efficacy as a second or third line of therapy, considering our study yielded promising findings coming from a cohort of adolescents whom majority received Venlafaxine following a previously prescribed course of SSRI.

Conclusion

The use of venlafaxine in pediatric populations for the treatment of major depressive disorder (MDD) represents a significant area of clinical interest, given the complex nature of these disorders in adolescents. Current research, including our study, suggests that venlafaxine holds promise as a treatment option for adolescents, particularly those who have not benefited from first-line SSRI treatments. This is consistent with the broader literature, which indicates that a significant portion of pediatric patients with MDD may not respond to initial antidepressant therapy, necessitating alternative treatment strategies [5,3].

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Conflict of Interest Disclosures

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Data Sharing Statement

The data are available from the corresponding author by reasonable request.

Credit Author Statement

Mohammad Alatoom: Data curation, Investigation, Writing – review & editing. **Elham Almajarresh:** Data curation, Investigation, Writing – review & editing. **Abdalkarim Alnajjar:** Formal Analysis, Software, Writing – original draft, Writing – review & editing. **Asma Alamri:** Writing – original draft, Writing – review & editing. **Khalid Bazaid:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Kevin R Simas:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Logan Reynolds:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Sami S Alharthi:** Methodology, Writing – review & editing. **Zaid Taweel:** Data curation, Investigation, Writing – original draft, Writing – review & editing.

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