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The association between fingolimod and mental health outcomes in a cohort of Multiple Sclerosis patients with stress

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Abstract. – OBJECTIVE: The primary objective was to study the association between fingolimod and the frequency of depression, anxiety, and insomnia symptoms among a cohort of Multiple Sclerosis (MS) patients with stress. The secondary objective was to examine the association between patient characteristics and these psychiatric symptoms.

PATIENTS AND METHODS: Patients with MS and stress were recruited according to the Arabic version of the Perceived Stress Scale (PSS). Psychiatric outcomes were measured by validated scales. Logistic regression was used to estimate adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Data from 324 participants were analyzed.

RESULTS: Fingolimod was associated with a significantly lower adjusted odds ratio for depression (aOR 0.58, 95% CI 0.35-0.97, $p<0.05$) but less associated with anxiety (aOR 0.63, 95% CI 0.35-1.01, $p=0.05$) and insomnia (aOR 0.88, 95% CI 0.52-1.51, $p=0.64$).

CONCLUSIONS: Close monitoring of mental health is required for patients with MS using disease-modifying therapies.

Key Words:
Fingolimod, Mental health, Multiple sclerosis.

Introduction

Multiple sclerosis (MS) is a chronic progressive autoimmune demyelinating disease resulting in plaques in different brain locations leading to a wide range of signs, symptoms, and complications[1]. MS affects around 2.5 million people worldwide[2], and the relapsing-remitting MS (RRMS) type accounts for most cases.

MS itself is a stressor. Around 70% of MS patients reported an unusual amount of stress before the onset of the disease and during the disease's course compared to healthy subjects[3-5]. Chronic and uncontrolled psychological stress could lead to depression, anxiety, and insomnia, all playing a role in the deterioration of the quality of life of individuals and MS patients[6-9].

According to the literature, about 50% of MS patients suffer from depressive symptoms that deteriorate their quality of life[10,11]. Depression is accompanied by anxiety and insomnia. For example, anxiety prevails in 22% to 54% of patients[12]. Also, insomnia rates in MS patients could reach up to four folds the general population[13]. Reportedly, 42% of MS patients had difficulty initiating sleep, 53% reported frequent awakenings, and 58% reported waking after sleep onset[14].

Disease-modifying therapies (DMTs) are the mainstay for MS, they include fingolimod, interferons, dimethyl fumarate, and others[15,16].

Fingolimod is an oral medication that is used for the treatment of MS patients by modulating SPHIN-gosine-1-phosphate-receptor[17]. Studies[17,18] showed that fingolimod prevents lymphocytes from egressing from lymph nodes, which leads to decreased infiltration of these lymphocytes to the central nervous system.

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Fingolimod therapy is very common in RRMS patients due to its efficacy and convenience of use compared to injectable DMTs such as interferons[15,16,18]. Therefore, it can be suggested that using an effective therapy can reduce MS relapses and subsequently improve mental health outcomes.

The studies on the impact of DMTs on psychological well-being are still emerging, controversial, and inconclusive[19-21]. While fingolimod demonstrated improvement in depressive symptoms in MS patients in some studies[15,22], these results were not replicated in another study[23]. Similarly, data from other DMTS studies[24,25] did not show consistency in mood improvement.

Stressed patients with RRMS are highly predisposed to other psychiatric disturbances such as depression, anxiety, and insomnia. In addition, evaluating the mental health status of these patients is quite important.

Therefore, the current research's primary objective was to study the association between fingolimod and the severity of depression, anxiety, and insomnia symptoms among a cohort of MS patients without the known psychiatric disease, but at risk for these conditions due to stress symptoms. The secondary objective was to examine the association between demographical factors and the severity of psychiatric symptoms.

Patients and Methods

Study Design and Settings

Patients were recruited for a longitudinal study; however, the current work represents the analysis of their baseline status using a cross-sectional design. MS patients who attended the MS clinic at Al-Bashir Hospital, Amman during the period of May-June 2022 were included in this study. Al-Bashir Hospital is the largest hospital (more than 1,000 bed facility), to which MS patients with the Ministry of Health government insurance are referred. The government covers all the direct costs of MS treatment, including the cost of DMTs for Jordanian patients.

Patients waiting in the MS pharmacy were approached and then assessed for their eligibility to participate in the study according to the inclusion criteria (Figure 1).

Inclusion Criteria

RRMS patients diagnosed according to the 2017 McDonald criteria[26], receiving a DMT for at least 6 months and exceeding the threshold for clinically significant stress (a score above 14) according to the Perceived Stress Scale (PSS) Arabic version. The Arabic version of the Perceived Stress Scale was used to screen the patients for stress before enrollment. The PSS was developed by Cohen et al[27] and includes 14 items that are designed to measure individual stress for the last 30 days with a cut-off score of 14 reflecting clinically significant stress.

Covariates

A self-administered structured online questionnaire was employed to cover the participants' demographical and clinical data, including marital status, sex, age, education [undergraduate or graduate (earned a university degree)], employment, duration of MS, smoking, presence of chronic somatic diseases (diabetes, hypertension, etc.), presence or absence of relapses for the past year and the duration of DMT treatment. The DMT used were fingolimod (Pharma International Company, Amman, Jordan), dimethyl fumarate (Hikma, Amman, Jordan), and different interferons, including interferon beta-1a (Biogen) and interferon beta-1b (Bayer).

Outcome Variables

Depression

The Patient Health Questionnaire-9 (PHQ-9) Arabic-validated version was used. The PHQ-9 is a short, self-administered scale based on the nine Diagnostic and Statistical Manual of Mental Disorders-IV criteria for diagnosing depression[28]. The PHQ-9 has a sensitivity of 88% and specificity of 88% for severe depression and was previously used in Arab-speaking MS patients, with a cut-off score of 15[29].

Anxiety

The General Anxiety Disorder-7 (GAD-7) is a short, self-administered scale with a cut-off point of 10 that has a sensitivity of 89% and a specificity of 82% for diagnosing generalized anxiety disorder[30]. The GAD-7 has previously been used in Arab-speaking patients with a cut-off score of 15[30].

Insomnia

The insomnia severity index – Arabic version ISI-A was used to evaluate sleep quality. The ISI consists of 7 questions with Likert-type answers and a score range between 0-28, where a score above 15 indicates clinically significant insomnia. The ISI is validated to be used in the Arabic language[31,32].

Statistical Analysis

Data were analyzed through SPSS software version 21 (IBM Corp., Armonk, NY, USA). The

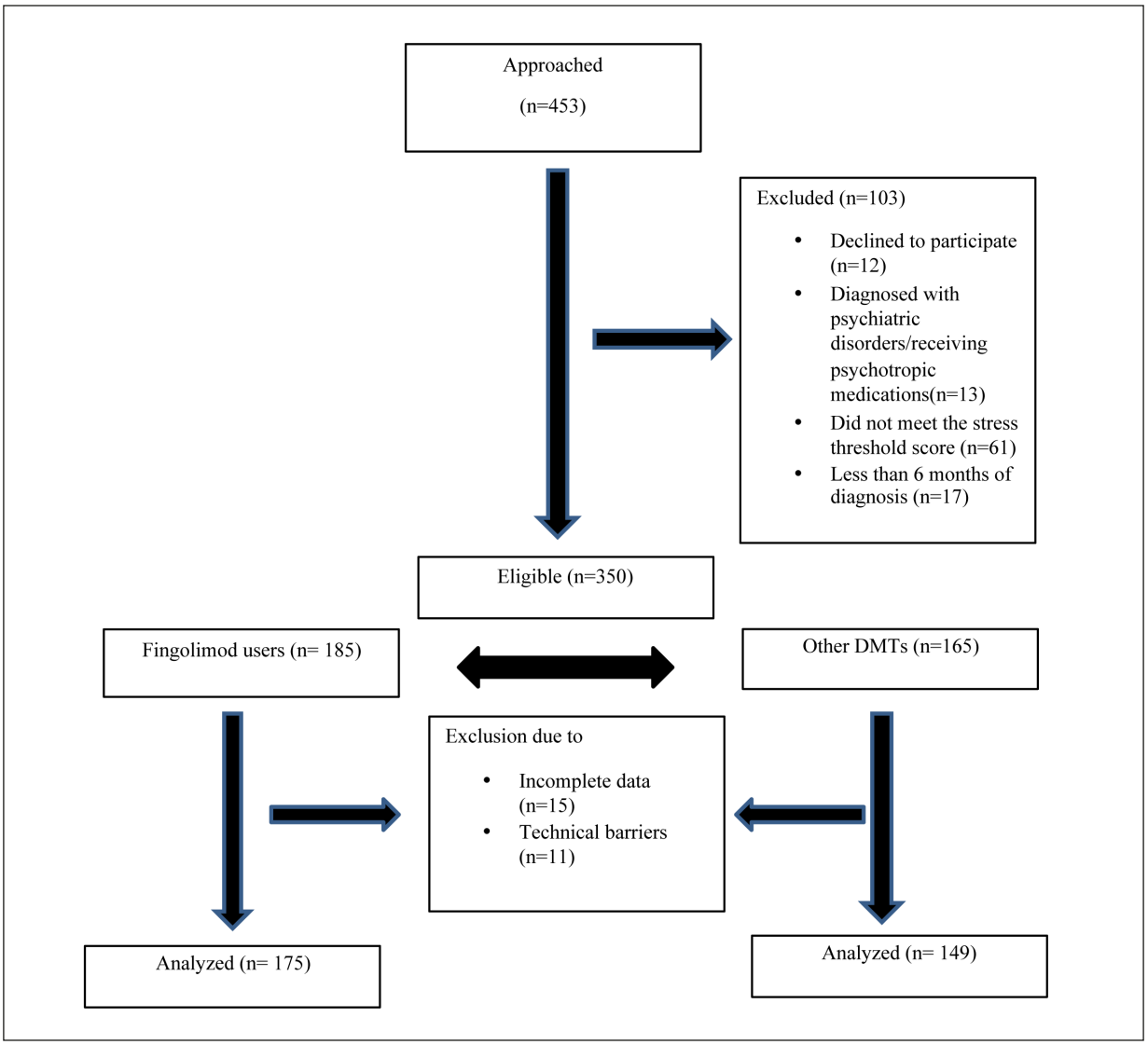

Figure 1. Study flow chart.

distribution of the covariates between the study groups was analyzed using descriptive and frequency analysis and the Chi-Square test. To study the primary objective, we analyzed the distribution of potential confounding factors in the two exposure groups by frequency analyses and the Chi-Square test (Table I). We also assessed the potential association between the covariates and the outcome variables with univariate linear regression using a cut-off value of $p<0.10$ to include covariates in the multivariate model. Afterward, a multivariable logistic regression model was carried out, including sex, age, body mass index, presence of other chronic diseases, education, DMT treatment duration, MS duration, and the number of relapses during the last year as adjustment variables. Smoking was not adjusted as it could be inversely associated with the outcome variables. For the secondary objective analysis, an initial univariate analysis was performed to screen for confounding variables having a cut-off value of $p<0.10$. Then, these variables were used to build a backward stepwise multiple regression model to determine what covariates are independently associated with the outcome variables, only covariates with $p<0.05$ were kept in the final model. The confidence intervals were set at 95% and significance at p-value of 0.05.

Results

Sample Characteristics

From the total approached patients (n=453), 324 patients consented to participation and fulfilled all inclusion criteria (Figure 1). Of these, 175 received fingolimod (54.0%), 81 interferons, and 68 dimethyl fumarates. Most of the study sample were females (n=235, 72.4%), and about half of the patients were 35 years or less (n=164, 50.7%). In addition, the majority had marital status other than single (n=207, 63.9%), had graduate education level (n=189, 58.4%), unemployed (n=211, 65.1%), non-smokers (n=215, 66.3). Among the whole study sample, 148 patients (45%) reported PHQ-9 scores above the cut-off value, 119 (36%) reported GAD-7 scores above the cut-off value, and 83 (25%) reported ISI-A scores above the cut-off value. Table I summarizes the variables stratified per the two study groups.

Primary Outcome: Fingolimod Association with Depression, Anxiety, and Insomnia

There was a significant association between the DMT used and psychiatric symptoms in the multivariate logistic regression model adjusted for sex, age, body mass index, presence of other chronic diseases, education, DMT treatment duration, MS duration, and the number of relapses during the last year. The patients using fingolimod had significantly lower aOR for depression (aOR 0.58, 95% CI 0.35-0.97, p=0.03) and a lower OR for anxiety (aOR 0.63, 95% CI 0.35-1.01, p=0.05). The odds for insomnia were 0.88, (95% CI 0.52-1.51, p=0.64, Table II).

Table I. Variables according to the type of Disease Modifying Treatment (DMT).

Factors	Categories	Fingolimod n (%)	Other DMTs n (%)	Chi-square *p*-value
Gender	female	119 (50.6)	116 (49.4)	0.061
	male	56 (62.9)	33 (37.1)	
Age	35 years old or less	97 (60.6)	63 (39.4)	0.020*
	more than 35 years old	78 (47.6)	86 (52.4)	
Marital status	single	68 (58.1)	49 (41.9)	0.297
	others	107 (51.7)	100 (48.3)	
Education level	undergraduate	63 (46.7)	72 (53.3)	0.032*
	graduate	112 (59.3)	77 (40.7)	
Employment	no	100 (47.4)	111 (52.6)	0.002*
	yes	75 (66.4)	38 (33.6)	
Chronic diseases	no	43 (43.9)	55 (56.1)	0.021*
	yes	132 (58.4)	94 (41.6)	
MS diagnosis and DMT initiation	2 years or less	67 (42.9)	89 (57.1)	0.001*
	more than 2 years	108 (64.3)	60 (35.7)	
Relapse necessitating, I.V methylprednisolone use during the last year	none	66 (49.3)	68 (50.7)	0.174
	more than once	109 (57.4)	81 (42.6)	
Body Mass Index	below 25	95 (55.5)	76 (45.5)	0.35
	25 and above	75 (52.8)	67 (47.2)	

Undergraduate: did not complete a university degree, graduate: completed a university degree . Chronic diseases: hypertension, diabetes, thyroid, etc. *p<0.05.

Table II. The association between DMT with outcome variables.

	Proportion above the cut-off n (%)			
Outcome	Fingolimod n=175	Other DMT n=149	Crude OR (95% CI)	Adjusted OR (95% CI)
Depression	70 (40)	78 (52)	0.60 (0.38- 0.90)*	0.58 (0.35-0.97)*
Anxiety	56 (32)	63 (42.3)	0.70 (0.43-1.14)	0.60 (0.35-1.01)
Insomnia	43 (24.6)	40 (26.8)	0.88 (0.53-1.46)	0.88 (0.52-1.51)

Multivariate logistic regression adjusted for sex, age, body mass index, presence of other chronic diseases, education, DMT treatment duration, MS duration and the number of relapses during the last year. Depression was measured by the Patient Health Questionnaire (PHQ-9) scale with a cut-off value for clinically significant depression of 15. Anxiety was measured using the Generalized Anxiety Disorder 7-item (GAD-7) scale with a cut-off score of 15 for significant anxiety. Insomnia severity was measured by the Insomnia Severity Index (ISI) with a cut off value of 15 indicating significant insomnia. *p<0.05.

Table III. Multiple regression to examine the association between the covariates with the outcome variables.

		Depression				Anxiety				Insomnia			
Factors	**Categories**	**Above cut-off (%)**	***p*-value univariate**	**aOR (CI)**	***p*-value multivariate**	**Above cut-off (%)**	***p*-value univariate**	**aOR (CI)**	***p*-value multivariate**	**Above univariate**	***p*-value**	**aOR (CI)**	***p*-value multivariate**
Gender	Females (n=235)	(44.7)	0.56			(38.8)	0.34			(24.3)	0.36		
	Males (n=89)	(48.3)				(32.6)				(29.2)			
Age	Below 35 years (n=160)	(36.3)	0.001	0.49 (0.31-0.78)	0.003	(35.6)	0.68			(23.8)	0.45		
	35 years and above (n=164)	(54.9)				(37.8)				(27.4)			
Chronic diseases	No (n=98)	(35.7)	0.018			(27.6)	.024			(15)	0.093		
	Yes (n=226)	(50.0)				(40.7)				(28)			
MS Diagnosed since	Less than 5 Years (n= 132)	(39.4)	0.025			(34.1)	0.28			(25.8)	0.96		
	5 years and more (n=192)	(50.0)				(38.5)				(25.5)			
Did you suffer last year from an acute relapse?	No (n=131)	(39.6)	0.031			(33.6)	0.23			(22.4)	0.25		
	Yes (n=190)	(50.0)				(38.9)				(27.9)			
DMT use duration	2 years or less (n=156)	(44.7)	0.61			(36.5)	0.96			(27.6)	0.44		
	More than 2 years (n=168)	(47)				(36.9)				(23.8)			
Smoker	No (n=215)	(41.4)	0.03	0.61 (0.38-0.98)	0.04	(32.6)	0.029	0.53 (0.32-0.89)	0.02	(22)	0.058	0.59 (0.32-0.92)	0.02
	Yes (n=109)	(54.1)				(45)				(32)			
Education	Undergraduate (n=135)	(58.5)	0.001	2.22 (1.39-3.52)	0.001	(50.4)	0.001	2.18 (1.33-3.57)	0.002	(29.6)	0.16		
	Graduate (n= 189)	(36.5)				(27)				(22.8)			
Marital status	Single (n=117)	(39.3)	0.085			(30.8)	0.095			(20.5)	0.11		
	Married & other (n=207)	(49.3)				(40.1)				(28.5)			
Employment	No (n=211)	(50.7)	0.013			(43.1)	0.001	2.10 (1.20-3.67)	0.009	(28.9)	0.065	1.90 (1.07-3.36)	0.03
	Yes (n=113)	(36.3)				(24.8)				(19.5)			

The backward stepwise multiple regression performed to examine which covariates are independently associated with the outcome variables, the choice of covariates was informed by the p-value<0.1 from the univariate analysis. Depression was measured by the Patient Health Questionnaire (PHQ-9) scale with a cut-off value for clinically significant depression of 15. Anxiety was measured using the Generalized Anxiety Disorder 7-item (GAD-7) scale with a cut-off score of 15 for significant anxiety. Insomnia severity was measured by the Insomnia Severity Index (ISI) with a cut-off value of 15 indicating significant insomnia. Undergraduate: did not complete a university degree, graduate: completed a university degree, chronic diseases (hypertension, diabetes, thyroid).

Secondary Outcomes

The backward stepwise multiple regression was performed to examine which covariates are independently associated with the outcome variables. The results showed that age below 35 years was associated with lower depression frequency (aOR 0.49, 95% CI 0.31-0.78, p=0.003). Undergraduate educated patients had higher odds for depression and anxiety (aOR 2.22, 95% CI 1.39-3.52, p=0.001) and (aOR 2.18, 95% CI 1.33-3.57, p=0.002), respectively. Unemployment was associated with higher odds for anxiety and insomnia (aOR 2.1, 95% CI 1.20-3.67, p=0.02) and (aOR 1.90, 95% CI 1.07-3.36, p=0.03), respectively. Non-smokers reported lower odds for depression, anxiety, and insomnia (aOR 0.61, 95% CI 0.38-0.98, p=0.04, aOR 0.53, 95% CI 0.32-0.89, p=0.02 and aOR 0.54, 95% CI 0.32-0.92, p=0.02, respectively) (Table III).

Discussion

The current study aimed to study the association of fingolimod to symptoms of depression, anxiety, and insomnia among otherwise psychiatric healthy MS patients suffering from stress adjusted for a range of relevant covariates. We report that fingolimod use was associated with a lower risk of depression and anxiety. Additionally, we report that in stressed patients with MS, older age, unemployment status, and lower education were independently associated with mental health outcomes.

The findings of this study are consistent with the findings of Hunter et al[33], which showed that depression was lower in patients treated with fingolimod compared to injectable disease-modifying therapy. Moreover, a previous post hoc analysis[22] from Evaluate Patient Outcomes (EPOC) study demonstrated an improvement in depressive symptoms following a switch to fingolimod compared to glatiramer acetate, Interferon-β-1a, or Interferon-β-1b. This consistency in the findings suggests that fingolimod treatment could reduce depression symptoms in MS patients. On the other hand, some studies[34] reported no significant impact of fingolimod on depression and anxiety.

Anxiety is a frequent condition encountered by MS patients due to several factors, such as the announcement of the diagnosis, the start or change of long-term disease-modifying treatment and reaching a functionally important threshold of disability[35]. Therefore, the treatment strategies have long-term implications for the patient's well-being. Injectable therapies such as Interferon-β1 increased anxiety levels due to concerns about side effects, initiation and self-administration injectables, and the need for day hospitalization[12]. However, initiating oral therapies such as fingolimod could present different psychological challenges for the patients. Moreau et al[36] studied the anxiety levels in Multiple Sclerosis patients who started using fingolimod as a treatment strategy. In this study, the Hospital Anxiety and Depression Scale score was markedly reduced four months after the initiation of fingolimod therapy compared to the beginning of the therapy. Another study[23] compared the anxiety scores between MS patients who are using intravenous therapy (natalizumab) and fingolimod. Anxiety scores were lower in patients using fingolimod compared to natalizumab.

Our findings could be explained by reduced inflammatory activity as fingolimod is a more effective therapy than injectable DMTs[19]. In addition, the patient's convenience, low side effects, and satisfaction with fingolimod over other injectable DMTs[22] could enhance the patient's adherence and improve the therapeutic outcome.

Evidence suggests that inflammation is the common ground between MS and psychiatric symptoms[37]. Higher levels of pro-inflammatory cytokines such as Interleukin-1, Interleukin-6, Interferon-γ, and Tumor Necrosis Factor-α (TNF- α) were found to be associated with the development of depression and anxiety[38,39]. Fingolimod was able to alleviate neuronal damage and oxidative stress in addition to improvement of depression-like behaviors and cognitive function in rats exposed to daily chronic unpredictable mild stress. This was associated with the anti-inflammatory effects of fingolimod that can be related to its efficacy in lowering the number of MS attacks and, therefore, better mental health outcomes[40].

In this study, low levels of education and unemployment were associated with a higher risk for depression and anxiety. Our findings are consistent with previous works[2], for example, unemployment and low education levels were risk factors for anxiety in MS patients41. We hypothesize that education and employment help provide better perception, adaptation, and coping strategies that are reflected in well-being.

This is the first study that tried to study the impact of fingolimod on depression, anxiety, and insomnia in a stressed cohort of MS patients with reliable sample size. Depression, anxiety, insomnia,

and choice of medication are topics of great importance for both patients and health personnel. There are also few studies[16,23] of psychological distress in MS patients from Arabic-speaking countries.

Limitations

This study has some limitations. The cross-sectional design makes it difficult to study the direction of association or causality, and we relied on screening tools and not formal psychiatric diagnoses. Unmeasured confounding could also impact our results. The results may not be representative for patients that have a manifest psychiatric illness or who are not stressed. Future studies will carry out a follow-up trial to monitor the changes in the patient's psychological outcomes.

Conclusions

In conclusion, DMT, including fingolimod, may impact mental health outcomes in stressed RRMS patients, follow-up studies are required to fully understand the direction and mechanisms behind this association.

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Conflict of Interest

Marte-Helene Bjørk: Honoraria for lecturing from Teva, Lilly, Eisai, and Novartis, consultancy honoraria from Jazz Pharmaceuticals, Angelini Pharma, Lundbeck, and Novartis, and institutional contract research fees from Sanofi. The other authors have no conflicts of interest.

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Ethics Approval

This study was approved by the Ethical Committee of the Yarmouk University Institutional Review Board (IRB, No. 16/2022).

Informed Consent

All participants signed consent forms before the study began.

Authors' Contributions

Conceptualization: Omar Gammoh, Suha Al-Habahbeh, Feras Weshah, Wail Ennab. Methodology and design: Omar Gammoh, Abdelrahim Alqudah, Suha Al-Habahbeh, Feras Weshah, Abdel-Ellah Al-Shudifat. Investigations: Ahmed Al-Smadi, Abdelrahim Alqudah, Suha Al-Habahbeh, Feras Weshah, Wail Ennab, Abdel-Ellah Al-Shudifat. Data acquisition and analysis: Omar Gammoh, Ahmed Al-Smadi, Wail Ennab, Abdel-Ellah Al-Shudifat. Data analysis: Ahmed Al-Smadi, Abdelrahim Alqudah Feras Weshah. Data interpretation: Ahmed Al-Smadi, Abdelrahim Alqudah Suha Al-Habahbeh, Marte-Helene Bjørk. Manuscript writing: Omar Gammoh, Ahmed Al-Smadi, Marte-Helene Bjørk. Manuscript editing: Omar Gammoh, Marte-Helene Bjørk.

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