# **Original Research**

# Evaluation of the prevalence of anxiety and depression and the impact of asthma control level on these parameters among asthmatic patients

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#### **Abstract**

**Objectives:** This study is designed to assess the prevalence of anxiety and depression among asthmatic patients living in Amman, Jordan. Additionally, it evaluates the effect of asthma control levels using the correct inhaler technique on anxiety and depression. **Method:** This single-blinded, randomized, interventional, active-control study was conducted at the University of Jordan Hospital in the period between March and August of 2019. Asthmatic patients in the active group were counseled on the correct inhaler technique using placebo inhalers and using sticky labels on their prescribed inhalers. At the baseline and after three months, both groups were assessed on their asthma level of control, anxiety and depression using the asthma control test (ACT), general anxiety disorder (GAD-7) and patient health questionnaire (PHQ-9), respectively. A total of 159 asthmatic adult patients were recruited and randomized into active groups (n = 79) and control groups (n = 78) using controller inhalers, either Turbohaler or Accuhaler or both. **Results:** ACT, GAD7, and PHQ9 were assessed at the baseline and no statistically significant difference between both groups was found (P-value < 0.001). At follow-up, ACT, GAD7, and PHQ9 showed significant differences in the active group with mean ± SD of 21.21±5.26, (P-value < 0.001), 3.84 ±4.782, (P-value < 0.001), 6.4±6.4115, (P-value < 0.001), respectively. At the same time, the difference in the mean score for control group patients did not reach a significant level. **Conclusion:** The prevalence of psychological disorders among asthmatic patients is common and directly related to the asthma level of control. Improvements in the ACT can lead to significant improvements in patient anxiety and depression related to asthma.

Keywords: act; asthma-related anxiety; asthma-related depression; gag-7 score; phq-9 score

## INTRODUCTION

Asthma is a chronic inflammatory respiratory disease involving the trachea and bronchi, and it extends to the terminal bronchioles and parenchyma (GINA 2018). The degree of inflammation does not relate to asthma severity but relates to airway hyperresponsiveness (AHR).<sup>1,2</sup>

Depression is more prevalent than anxiety among asthmatic patients in China. The study showed that patients had anxiety were 25.34%, while 46% had depression.<sup>3</sup>

Anxiety and depression are associated with asthma as it affects the quality of asthmatic patients' lives. Asthma control test

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(ACT), anxiety, and depression are all significant predictors of patients' quality of life.<sup>4</sup> Significant associations between anxiety and depressive patients and emotional domains of quality of life scores, symptoms, and limited activity domains lead to the conclusion that psychological disorders significantly impact the quality of life of asthma patients<sup>6</sup>. Asthma is a chronic inflammatory respiratory disease involving the trachea and bronchi, and it extends to the terminal bronchioles and parenchyma.<sup>1</sup> The degree of inflammation does not relate to asthma severity but relates to airway hyperresponsiveness (AHR).<sup>1</sup>

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In asthmatic patients, the prevalence of predicted anxiety was 13.3%, while patients with a severe anxiety disorder had a prevalence of 56.6%. 70% were diagnosed with anxiety. Most patients diagnosed with anxiety associated with asthma were females, advanced-age patients, and of low social class. It also depends on the severity of asthma and the duration of the asthmatic attacks, but there was no correlation with lung function test value. Patients with psychological disorders such as anxiety and depression had a higher prevalence of exacerbations and emergency department referrals. In studying the association of generalized anxiety disorder (GAD) with inflammatory cytokines, cortisol, and alpha-amylase (sAA), GAD with asthma patients showed higher daily secretion of sputum IL-1, sputum IL-6 and sAA compared to healthy



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# individuals and asthma patients without GAD. There were significant links between IL-1, IL-6, sAA, cortisol, and the severity of GAD for asthma patients. The present study indicated that the pro-inflammatory cytokines, salivary cortisol, and sAA are associated with GAD in patients with asthma.9 Anxiety and depression related to psychiatric disorders and other relevant comorbidities are common in asthmatic outpatients. Strong correlations between patients who had anxiety and depression with uncontrolled asthma and patients with lower ACT scores have been shown in many studies.<sup>10</sup> In 2010, among 294 patients, a cross-sectional study was done to evaluate the correlation between anxiety, depression and asthma control, using the ACT scale and HAD (Hospital anxiety and depression score),8 it revealed that among poorly controlled patients by ACT scale, anxiety and depression percentages respectively were 63% and 49% of the population, while in well-controlled patients by ACT scale, anxiety and depression percentages respectively were 29% and 18%. The study concluded that by improving the level of asthma control from not controlled at all patients, poorly controlled, and partially controlled going to well-controlled patients, the level of anxiety and depression

This study was conducted to assess the prevalence of anxiety and depression amongst asthmatic patients living in Amman, Jordan. Additionally, we aimed to assess the impact of proper inhaler technique administration and asthma control levels on the levels of anxiety and depression.

## **METHODS**

was reduced.8

#### Study design and subjects

Patients were randomized into active and control groups. The study was performed at the University of Jordan Hospital (JUH) at the respiratory clinic in 2019. Patients included in this study were adults less than 75 years old, confirmed with the diagnosis of asthma despite the severity, with no interruption or modification to the treatment regimen in the past month, and able to be frequently followed up. Patients excluded from the study were adults using reliever inhalers only, patients who cannot speak or write Arabic, Patients who do not self-administer their medication, and patients who refuse to return for the second study visit. Patients recruited for the study were asked to sign a consent form.

Patients in the active group received counseling on the correct inhaler technique orally and by using inhaler adhesive labels at the baseline, while control group patients did not receive counseling on the correct inhaler technique at the baseline.

During the follow-up phase, both cohorts underwent a reinterview process after three months. Patients in the control group received guidance on the accurate inhalation technique during this session. At the end of the interview, patients were thanked for their help. Phone calls were used to collect patient data if the patient was unable to attend the clinic by sending videos for their inhaler administration.

The predetermined randomization number list was designed using a computer-generated randomization program (www.

#### Outcome measures at baseline

At baseline, patients' asthma inhaler administration techniques were assessed using placebo inhalers and validated inhaler technique checklists translated into Arabic. 11 The checklist contains 0-9 scores; a score of 9 was considered the correct technique for Accuhaler [Diskus], Turbuhaler and pressurized metered dose inhalers (pMDIs). For the Turbuhaler, four steps were categorized as 'essential' (little or no medication would reach the airway), and for the Accuhaler and pMDI, three steps were classified as essential. 11 A score of 4/4 for Turbuhaler and 3/3 for Accuhaler and pMDI indicates Correct Essential Technique. Due to its high price, no patients were found to be using the pMDI as a controller treatment at the JUH. It was excluded from the assessment conducted in this study.

#### Asthma level of control

Asthma control was assessed by ACT questionnaires. ACT is a validated self-administered questionnaire to determine the level of asthma control, composed of five questions. The Arabic version of ACT was used and validated by Lababidi et al. A score of less than 20 in ACT refers to uncontrolled or poorly controlled asthma, and the asthma status should be reassessed.

### Asthma-related anxiety

Anxiety was assessed using the published GAD-7 score, which consists of 7 questions to find the correlation between anxiety score and asthma using the general anxiety disorder tool,<sup>13</sup> reflecting on the number of times patients had anxiety due to asthma attacks in the past two weeks. It showed how much the patient was worried, anxious, or on edge; the ability to control the worrying; worrying too much; the ability to relax; being restless; being too annoyed; and feeling afraid as if something awful might happen.<sup>13</sup>

#### Asthma-related depression

The correlation between depression and asthma was assessed using the PHQ-9 score questionnaire, which consists of nine questions<sup>13</sup>. Showing how often the patient had depression due to an asthma attack in the past two weeks. It showed patient interest in doing things; feeling down or depressed; having trouble falling or staying asleep; feeling tired or having low energy; feeling bad about yourself; trouble concentrating on things; moving or speaking too slowly; and thinking that you would be better off dead or hurting yourself. The final scores of 0–4, 5–9, 10–14, 15–19, and 20–27 are the ranges for none, mild, moderate, moderately severe, and severe, respectively.

## Pharmaceutical care intervention

Both groups in the study sample were interviewed by direct contact with the clinical pharmacist at the respiratory clinic of the JUH. The pharmacist provides counseling on the correct inhaler administration technique for the active group patient using oral, written, and adhesive label instructions for each inhaler device with the frequency of puffs/day. The patients were happy with the service and thanked for their participation.



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#### At the follow-up

At the follow-up patient's inhaler technique was assessed by the clinical pharmacist at the clinic. Patients who could not attend the clinic for the following three months were assessed by sending videos and answering the questionnaires on the phone. The interventional group was counselled on the correct inhaler technique for Accuhaler [Diskus], Turbuhaler and pressurized metered dose inhalers (pMDIs),11 with oral and written instructions (photo label) in the respiratory clinic of the hospital (Figure 1, 2 and 3). The time required for patients' counseling on the correct inhaler technique was assessed using a timer since the pharmacist started to demonstrate the correct inhaler technique on a placebo till the patient achieved a 9/9 score on their inhaler. All the required information was collected, and the patients answered the questionnaires (study tools). At the end of the study period, there was a second interview to assess the inhaler technique again, ACT, anxiety, and depression.

# Sample size

The primary objective of this study was to assess the level of asthma control using ACT questionnaire. For the active and control groups, a sample size of 79 and 78 adult asthmatic patients, respectively, was essential to detect a significant 10% contrast in ACT scores between the groups, with a statistical power of 80% and a significance level set at 5%. The recruitment of patients was carried out over six months, from March 2019 to August 2019.

## Statistical analysis

The Chi-Square test was used to compare the active and control groups for the categorical data. A paired sample t-test was used to compare the continuous data, such as the mean within the

group at the baseline and follow-up. An independent sample t-test was used to compare the continuous data, such as the mean between both groups, either at the baseline or follow-up. McNemar's statistical test is used on paired nominal data at baseline and follow-up. It is applied to  $2\times 2$  contingency tables with a dichotomous trait with matched pairs of subjects.

#### **RESULTS**

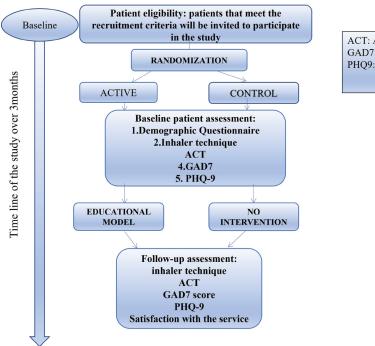
## **Demographics of study participants**

According to the study inclusion criteria, 157 asthmatic adult patients were recruited for the study. The total sample was randomized into active and control groups (n = 79, 78, respectively). At follow-up, 151 patients were re-interviewed at the respiratory clinic of JUH. Three patients out of the total sample were unable to complete the questionnaire due to another clinic appointment or time pressure (Table 1). At follow-up, three patients from the active group couldn't complete the questionnaire; two had wrong numbers, and one had died, while two patients from the control group had the wrong number, and one couldn't hear well.

#### Measured outcomes

#### Asthma level of control

The asthma control test mean score was assessed at baseline and follow-up. Results showed that there were no statistically significant differences between the mean scores of active (15.39±6.136) and control groups (14.22±5.892) at baseline (p-value 0.223, independent sample t-test) (Table 2). At follow-up, the mean scores of asthma control were significantly improved for the active group (21.21±5.267) compared to the control group (15.92±7.304, P-Value <0.001).



ACT: Asthma control test GAD7: General anxiety disorder PHQ9: patient health questionnaire

 $\textbf{Figure 1.} \ \textbf{Study protocol explains process of the study and data collected at baseline and at follow up}\\$ 



Categorical variables		Continuous variables						
Descriptive statistics (using		Normality test (Kolmogorov-Smirnov)						
frequencies)  Within group		Between groups con	nparison	Within group comparison				
Between groups comparison	comparison	Normal data	Non-normal data	Normal data	Non-normal data			
		Independent Samples Student's t-test	Mann Whitney	Paired Samples Student's t-test	Wilcoxon Signed Rank test			
Pearson's Chi-Square	e test	One-way ANCOVA	U- test	Pearson's product-moment correlation	Spearman rank order correlation			

Figure 2. Data analysis plan used in the analysis of the results

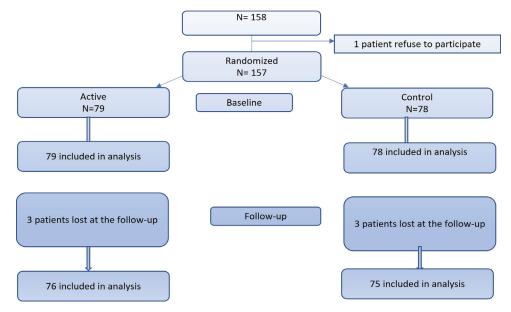


Figure 3. Consort diagram for the study sample (n=157)

	Active N= 79 (53%)	Control N=78 (47%)	Total	P-value*
Age mean ±SD	48.24±16.689	50.91±17.914	49.58±17.308	0.338 <sup>b</sup>
Gender N (%)				0.969ª
Male	15(19)	15(19.2%)	30 (19.1)	
Female	64(81)	63(80.8%)	127 (80.9)	
Marital Status N (%)				0.519ª
Married	48(60.8%)	55(71.4%)	103(66%)	
Single	21(26.6%)	15(19.5%)	36(23.1%)	
Divorced	3(3.8%)	3(3.9%)	6(3.8%)	
Widow	7(8.9%)	4(5.2%)	11(7.1%)	
Living place: N (%)				0.027 a*
Amman	48(61.5%)	57(73.1%)	105(67.3%)	
Zarqa	15(19.2%)	3(3.8%)	18(11.5%)	
Salt	7(7.7%)	6(7.7%)	12(7.7)	
Others	9(11.5%)	12(15.4%)	21(13.5%)	



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Education level N (%)				0.785 a
Illiteracy	6(8%)	5(6.4%)	11(7%)	
Elementary	16(20.3%)	19(24.4%)	35(22.3%)	
High school	21(26.6%)	15(19.2%)	36(22.9%)	
Collage	10(12.7%)	13(16.7%)	23(14.6%)	
Bachelor	26(32.9%)	26(33.3%)	52(33.1%)	
Family members				0.009 **
≤ 3	0(0%)	3(3.9%)	3(1.9%)	
4-6	41(52.9%)	54(70.1%)	95(61.3%)	
≥7	37(47.4%)	19(24.7%)	56(36.1%)	
Employment: N (%)				0.554ª
Employed	25(31.6%)	21(26.9%)	46(29.3%)	
Unemployed	35(44.3%)	39(50%)	74(47.1%)	
Student	9(11.4%)	5(6.4%)	14(8.9%)	
Retired	10(12.7%)	13(16.7%)	23(14.6%)	
Smoking N (%)				
Yes	7(8.9%)	11(14.1%)	18(11.5%)	0.530 a
No	68(86.1%)	62(79.5%)	130(82.8%)	
Ex-smoker	4(5.1%)	5(6.4%)	9(5.7%)	

Table 2. Clinical outputs for anxiety-related asthma, comparing participants in the active (n=79) and control groups (n=78) at baseline and follow-up in the active (n=76) and control (n=75) at the follow-up

Baseline					Follow-up				
Parameter N(%)	Active=79	Control=78	Total	P-Value	Active=79	Control=78	Total	P-Value	
Never anxious	38(48.1)	33(42.3%)	71(45.2%)		51(68)	28(37.3%)	79 (52.7%)		
Mild anxiety	23(29.1)	20(25.6)	43(27.4)	0.614ª	14(18.7)	19(25.3)	33(22)	<0.001°	
Moderate anxiety	11(13.9)	14(17.9)	25(15.9)		7(9.3)	12(16)	19(12.7)		
Sever anxiety	7(8.9)	11(14.1)	18(11.5)		3(4)	16(21.3)	19(12.7)		
Mean ± SD	6.11±4.977	7.07± 5.957	6.56± 5.462	0.287**	3.84 ±4.782	8.40±6.679	5.99± 6.173	<0.001**	

<sup>&</sup>lt;sup>a</sup> Chi-square test

b t-test Independent sample

Table 3. Clinical outputs for depression-related asthma, comparing participants in the active (n=79) and control groups (n=78) at baseline and the follow-up in the active (n=76) and control (n=75)

Parameter N (%)	Active=79	Control=78	Total	P-Value	Active=79	Control=78	Total	P-Value
Never depressed	20(25.3)	24(30.8%)	44(28)		38(48.1)	14(17.9)	52(33.1)	
Mild depression	20(25.3)	16(20.5)	36(22.9)		16(20.3)	20(25.6)	36(22.9)	
Moderate depression	18(22.8)	24(30.8)	42(26.8)	0.756ª	14(17.7)	20(25.6)	34(21.7)	<0.001 <sup>a</sup>
Moderately Sever depression	10(12.7)	8(10.3)	18(11.5)		3(3.8)	9(11.5)	12(7.6)	
Severe depression	10(12.7)	6(7.7)	16(10.2)		4(5.1)	12(15.4)	16(10.2)	
Mean ± SD	9.9487±6.6545	9.9± 6.400	9.9257± 6.513	0.964**	6.4±6.4115	11.2388± 7.299	8.6831± 7.237	<0.001**
<sup>a</sup> Chi-square test ** t-test Independent sample								

## Asthma-related anxiety

Uncontrolled and poorly controlled asthmatic patients were found to have more anxiety symptoms than well-controlled asthmatic patients, as the mean GAD-7 score for the well-controlled asthmatic patients was 3.66±4.383, while uncontrolled and poorly controlled had a mean of 6.67±3.803 and 8.03±5.880. The prevalence of anxiety among asthmatic patients ranged from mild to moderate to severe (n

= 43,27.4%), (n = 25,15.9%), and (n =18,11.5%), respectively. At baseline, no statistically significant difference between both groups in anxiety mean score (active=  $6.11\pm4.977$ , control=  $7.07\pm5.957$ , P=0.287, t-independent sample test) was found. At the follow-up, there was a significant improvement in the mean anxiety score of the active group ( $3.84\pm4.782$ ) and the control group ( $8.40\pm6.679$ ). The difference in anxiety score between baseline and follow-up for both the active and control



<sup>\*\*</sup> t-test Independent sample

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groups was statistically significant (active= 6.11±4.977, control= 7.07± 5.957, P=0.287, t-independent sample test). Control group patients felt that something awful might happen more than the active group (Table 3), with a statistically significant difference (P-value 0.006). For the other six questions of the GAD-7 questionnaire, no statistical difference at the baseline between both groups was found. At follow-up, patients in the active group had significantly less feelings of being afraid as if something awful might happen, not being able to stop or control worrying, being so restless that it's hard to sit still, and becoming easily annoyed or irritable (P-value <0.001, 0.001, 0.002, and <0.001 respectively). Improvement for the active group in worrying too much about different things, having trouble relaxing, and feeling afraid as if something awful might happen questions did not reach a significant level. The anxiety score had a significant impact on asthma-related quality of life. The Pearson correlation for patients at baseline and follow-up showed that (r = -0.599 and -0.595) as anxiety scores increased, AQLQ scores decreased.

## Asthma-related depression

Depression among asthmatic patients was prevalent, especially among uncontrolled and poorly controlled patients. Although (n = 44, 28%) of study participants were never depressed, (n = 36, 22.9%), (n = 42, 26.8%), (n =18,11.5%), and (n =16,10.2%) were found to have mild, moderate, moderately severe, and severe depression, respectively. There was no statistically significant difference between the active and control groups regarding the mean score of depression at baseline; patients in the active group's mean score was found (9.9487±6.6545) and patients in the control group's mean score was (9.9± 6.400), (P= 0.964, t-test Independent sample). At follow-up, the active group was found to have less depression than the control group, with a mean score of 6.4±6.4115 for the active group and 11.2388± 7.299 for the control group, with a statistically significant difference (P-Value < 0.001, t-independent test). The differences in depression scores at baseline and follow-up for both active and control groups were statistically significant (active, -3.964±5.22 and control, 1.693±4.106; P<0.001; independent sample t-test). Upon assessment of depression by the PHQ-9 questionnaire at the baseline for both the active and control groups, there was no statistically significant difference between groups at the baseline in the nine depression questionnaire questions (P-value>0.05, chi-square test). At follow-up, statistically significant differences between both groups were noticed except for three questions Feeling down, depressed, or hopeless; moving or speaking slowly enough for others to notice; or the opposite—being so fidgety or restless that you've been moving around a lot more than usual; and thoughts that you'd be better off dead or hurting yourself in some way. "This showed improvement among the active group versus the control group in depression symptoms.

Asthma control level scores had a strong correlation with depression scores among asthmatic patients at baseline and follow-up (r= -454 and -0.513, Pearson Correlation). Consequently, anxiety, depression, and quality of life are affected mainly by asthma's level of control.

#### DISCUSSION

Several studies have shown a relationship between asthma, especially severe asthma, with anxiety and depression. Recent asthma research found that asthma patients had higher-than-expected rates of anxiety disorders and severe depression. The anxiety scoring tool used in this study was the general anxiety disorder (GAD-7) score, which is a questionnaire that consists of seven questions that show how many times within the past two weeks the patient had anxiety due to an asthma attack. This study aimed to find the correlation between anxiety prevalence among asthmatic patients. The study aimed to find the correlation between anxiety prevalence among asthmatic patients.

A strong correlation was found between asthma and anxiety disorders. Patients frequently had anxiety of different severity; mild, moderate, and severe in the frequency of 27.4%, 15.9%, and 11.5%, respectively.

A previous study showed a relationship between asthma and psychiatric conditions. This was significant, especially with lifetime anxiety disorders reflecting on asthma control levels when measured by ACT.15 Exacerbation, emergency department referral, and needed healthcare utilization were all more common in patients with psychological disorders such as anxiety and depression.8 In our study, asthma level of control had a major effect on the prevalence and severity of anxiety in the study group. Patients who had a low asthma control score had a higher prevalence of anxiety with a strong correlation (R = -0.307). Similar results were noticed in a study performed on asthmatic patients to assess the correlation with anxiety disorder.8 Results showed that anxiety was prevalent among worse-controlled asthma patients with a low ACT score but not a high FEV1 value.8 At the follow-up, patients in the active group had higher ACT mean scores and a decreased prevalence of anxiety. The mean ACT score of the patients in the active group was 15.39±6.136, and at follow-up, it was increased to 21.21±5.267. So the anxiety mean score for the patients decreased from 9.9487±6.6545 to 6.4±6.4115. This reinforces the correlation between anxiety and asthma control.

Interestingly, no recent research was done to evaluate the effect of pharmacist counseling on the patient's anxiety prevalence or improvement in the anxiety level of control. This adds significant importance to this study, especially among Jordanians population, and increases the need to be studied more in the future.

Interestingly, no recent research has been done to evaluate the effect of pharmacist counseling on the patient's anxiety prevalence or improvement in the anxiety level of control. This adds significant importance to this study, especially among the Jordanian population, and increases the need to be studied more in the future.

Recent research has also looked into the relationship between asthma and depression. Results showed a strong correlation between asthma and depression, especially with poorly controlled asthma. Patients with poorly controlled asthma were found to have a higher prevalence of depression than patients with well-controlled asthma. Although asthma patients still had a higher risk of major depressive disorder than healthy



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patients.8

Asthma severity and prednisone-dependent asthma are two additional risk factors for psychiatric disorders such as depression and anxiety. This was confirmed by many studies that showed patients have more anxiety and depression as compared to patients with other asthma severity levels.<sup>16</sup>

A strong correlation was shown among the study population between asthma and depression prevalence. The frequency of the patients in our study who had depression was 112 (72%). Patients ranged in severity from mild to moderate to moderately severe to severe depression.

In our study, patients with poorly controlled and uncontrolled asthma had more prevalent for depression. The study showed that ACT score had a strong correlation with depression among asthmatic patients at baseline and follow-up (r = -0.454 and -0.513, Pearson Correlation).

The pharmaceutical care for the patients in the active group was reflected in the depression mean score and ACT score at the follow-up. Although there was no statistically significant difference between the active and control groups in the mean depression score at baseline, 9.9487±6.6545 for the active and 9.9± 6.400 for the control group (P-value 0.964), the active group had a mean score of 6.4±6.4115 and the control group had a mean score of 11.2388± 7.299 with a statistically significant difference (P-Value 0.000, t-independent test). This indicates that pharmacist counseling on inhaler technique lead to improvement in ACT score. This was similar to a study that concluded that patients with low ACT had more depressive symptoms. Also, depression was correlated with an increase in specific asthma symptoms. Asthma severity was strongly associated with an increased risk of asthma-related depression<sup>17</sup>.

Recent research has found a link between depression and quality of life in asthmatic patients. In our study, the level of depression was found to have a strong effect on asthmarelated quality of life. This was shown with Pearson correlation for patients at baseline and follow-up (r =-0.587 and-0.603),

which showed that depression scores increased and reduced the AQLQ score among the study population.

In a study performed in 2005, quality of life in the four domains was lower for asthmatic patients who had depression and were poorly controlled or not well controlled.<sup>17</sup>

## **Study limitations**

Social bias is a common limitation in many studies. Patients show up and exaggerate the level of their improvement in asthma symptoms, anxiety, and depression factors. Furthermore, this study was conducted in Amman, Jordan's capital city, and while some patients from other countries were included in the study, the levels of education and facilities in Amman are not similar to other countries, making it difficult to generalize the percentage of awareness on correct inhaler administration technique. Also, scoring was used by most researchers for evaluating anxiety and depression, and the HAD score. In our research, the GAD7 score was used to assess anxiety and the PHQ9 was used to assess depression. This may need research to evaluate if there is a difference in the results between the two-scoring systems.

#### CONCLUSION

The results of this study have demonstrated that anxiety and depression are prevalent among Jordanian asthmatic patients irrespective of asthma severity. Also, the improvement in the level of asthma control had a major role in the degree of anxiety and depression among these patients.

# **AUTHORS' CONTRIBUTIONS**

All authors were involved in all parts of the study and manuscript preparation, including literature search, study design, analysis of data, manuscript preparation, and review of the manuscript.

## **CONFLICT OF INTEREST**

No conflict of interest.

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