International Journal of Scientific Research and Management (IJSRM)
||Volume||11||Issue||04||Pages||MP-2023-836-843||2023||
Website: www.ijsrm.in ISSN (e): 2321-3418
DOI: 10.18535/ijsrm/v11i04.mp1

Medication Adherence after Myocardial Infarction: The Impact of Anxiety and Depression

[1]Arafat Khalaf Yousef Zubi. MD, [1]Laith Taye Hasan Al-jarrah. MD, [1]Najib Elbert Alqsous. MD, [1]Mohammad Wa'el Hindeyeh. MD, [1]Yazan Rateb Al sarayrah. MD

[1]Department of Psychiatry and Mental Health, Royal Medical Services, Amman 11134, Jordan

Abstract

Objective: To investigate the effect of anxiety and depression on medication adherence among patients who had previously been diagnosed with a myocardial infarction in Jordan.

Methods: This was a multicenter, descriptive cross-sectional study of Jordanian patients diagnosed with post-myocardial infarction and attending the cardiology and/or internal medicine outpatient clinics between January 2021 and December 2022. Anxiety, depression, and medication adherence were assessed using the Hospital Anxiety and Depression Scale (HADS) and the General Medication Adherence Scale (GMAS).

Results: A total of 300 patients were included in the study, with a mean age of 52.75 ± 10.36 years. Ninety-nine (33%) patients did not adhere to their medications. The patient behavior subscale had the lowest mean in GMAS (1.57 ± .77). The mean of medication adherence with regard to anxiety subscales was 22.98 ± 5.90 for normal, 21.80 ± 6.10 for borderline, and 14.56 ± 6.46 for anxiety. The mean of medication adherence with regard to depression subscales was 20.03 ± 6.95 for normal, 18.85 ± 7.30 for borderline, and 13.66 ± 5.58 for anxiety. Anxiety, depression, and gender were considered significant predictors for medication non-adherence (P<.05).

Conclusion: Anxiety and depression were prevalent among patients post-myocardial infarction. Patients were less likely to take their medicine as their anxiety and depression symptoms got worse. The study highlights the need for screening for anxiety and depression among these patients, as well as medication adherence, in order to intervene earlier

Keywords: Anxiety, depression, medication adherence, myocardial infarction, psychological health

Introduction:

Yearly, cardiovascular diseases (CVDs) account for about one-third of all deaths globally (1). In Jordan, 42 % of total deaths are from CVDs (2), putting Jordan at level 46 in the world based on the adjusted death rate (3). Myocardial infarctions (MIs) are one of these CVDs that are most commonly caused by blockage in the coronary arteries related to coronary artery disease (4). Acute MI patients require a comprehensive and complex treatment strategy (5). Pharmacological treatment is essential for controlling symptoms, reducing readmission rates, and increasing survival rates after MI. Therefore, patients can reduce their risk of hospitalization and mortality by adhering to their treatment plan (6). Medication adherence has been found in prior study of MIs to be between 40% and 60%. (7). Inconsistent medication use is influenced by a wide range of circumstances. The World Health Organization classified these variables into five categories: patient, therapy, health care system, socioeconomic, and condition-related (8).

Condition-related issues include psychological problems, including anxiety and depression; personality factors, character traits, social isolation, and life stress, which may affect patients' ability to adhere to their recommended treatment regimen (9). Patients with MIs are at high risk for anxiety (HR = 5.06, 95% CI: 4.61–5.54) and depression (HR = 7.23, 95% CI: 4.88–10.88) (10). A recent study reported the prevalence of anxiety and depression in patients with acute MI as 43% and 22%, respectively (11). Those patients with anxiety and depression were 1.76–2.3 times more likely to be non-adherent compared to those who were not depressed (12, 13).

In Jordan, several studies were conducted on medication adherence (6,14,15), but none of those studies addressed medication adherence among patients with CVDs. Therefore, this study aimed to investigate the

effect of anxiety and depression on medication adherence among patients previously diagnosed with MI in Jordan.

Method:

Study design, setting and participants

This was a multicenter, descriptive cross-sectional study of Jordanian patients diagnosed with post-myocardial infarction and attending the cardiology and/or internal medicine outpatient clinics in King Hussien Hospital, Queen Alia Center for Heart Disease, and Queen Alia Military Hospital between January 2021 and December 2022. The definition of MI used in the current study was based on the third universal definition of myocardial infarction (16).

Patients were eligible for the study if they met the following inclusion criteria: A) adults patients aged 18 years and older who had MI for more than 6 months; B) attending the outpatient clinic in the selected settings for more than 3 months; C) having no chronic mental health disorders as indicated by their medical records; and D) being able to read, write, and understand Arabic. Participants were excluded if they did not meet any of the inclusion criteria mentioned previously.

Measures

Socio-demographic characteristics included age, sex (male vs. female), marital status (single, widow, divorced, or married dichotomized as single vs. married), employment status (employed vs. unemployed), educational level (primary, secondary, or high school dichotomized as primary vs. high school), income (dichotomized as < 500 JD and >500 JD), and Social support. Social support was measured by asking, "Do you have as much contact as you would like with someone you feel close to, someone in whom you can trust and confide?" (yes/no) (17).

Risk factors include smoking (current, past or never-smoked, dichotomized as current vs. non-smoker), previous chronic diseases prior to MI occurrence such as hypertension, diabetes mellitus, hypercholesterolemia, heart failure, cardiac arrhythmias (classified as; no chronic disease, one chronic disease or two or more chronic diseases).

Current drugs were classified according to important cardiac medication classes, such as self-reported blood pressure management, usage of beta-blocker agents, angiotensin-converting enzyme (ACE) inhibitors, antiarrhythmic agents, calcium antagonists, antiplatelet, or nitrates.

The assessment of medication adherence utilized the General Medication Adherence Scale (18), which consists of 11 items measuring the level of medication adherence among patients. The scale consists of three subscales: non-adherence due to patient behavior (5 items), non-adherence due to additional disease and pill burden (4 items), and non-adherence due to financial constraints (2 items). Each item is scored from 0 to 3, with 0 for always, 1 for mostly, 2 for sometimes, and 3 for never. The scoring of the final outcome was classified as poor (0–10), low (11–16), partial (17–26), good (27–29), or high adherence (30–33). To determine the prevalence of medication adherence, it was classified into two categories: non-adherence (0–16) and adherence (>16–33), according to Meng et al. (19). The reliability of the Arabic version of the GMAS was ensured in the study of Mahmoud et al. (2020), as Cronbach Alpha was 0.834 (20).

The assessment of anxiety and depression utilized the Hospital Anxiety and Depression Scale (21), which consists of two sub-scales: one for anxiety and one for depression. Each subscale consists of seven items scored on a zero-to-three Likert scale type. The scores for each sub-scale ranged from 0 to 21. Higher scores indicate higher levels of anxiety and depression symptoms. Scores are categorized on the scale as follows: 0–7 for a normal case, 8–10 for a borderline case, and 11–21 for an anxiety and depression case. The reliability of the Arabic version of the HAD scale was ensured in the study by Terkawi et al. (2017), as the Cronbach Alpha for the anxiety subscale was 0.83 and 0.77 for the depression subscale (22).

Data collection

After identifying the eligible patients, the researchers explained the purpose and significance of the study to the patients. A paper-based questionnaire was delivered to the patients along with an invitation letter and a consent form. All patients who agreed to participate were asked to sign the informed consent form, fill out the questionnaires, and hand the completed questionnaires to the researchers after they finished. Each respondent took approximately 20 minutes to fill out the questionnaires and hand them over manually to the researchers.

Ethical consideration

The present study was approved by the Ethics and Review Board at Royal Medical Services.

Data analysis

Data were entered and analyzed statistically using Statistical Package for Social Science (IBM-SPSS) version 22. Descriptive statistics (means ±SD), frequency, and percentages were used to identify the level of medication adherence and the level of anxiety and depression among the study participants. An independent sample t test was utilized to compare the mean score of medication adherence between female and male participants. Multiple linear regressions (stepwise method) were used to find out whether anxiety and depression predict adherence to medication among patients.

Result:

Socio-demographics and medical characteristics

In total, 380 patients were invited to participate in the study, and 300 agreed, resulting in a 78.9% response rate. Their mean age was 52.75 ± 10.36 years, ranging from 22 to 66 years. 54.3% of patients were male. The majorities of patients were married (71%), had a primary school education (69%), and had an income less than 500 JD (72.3%). Sixty-one percent of patients were employed, and 42.3% were smokers. Regarding social support, 89.3% reported that they had social support. More than half of patients were healthy (56.3%), 29% had one chronic disease, and 14.7% had two or more chronic diseases. The most common cardiovascular medication received by patients was antiplatelet (78%), followed by statins (70.3%). Table 1

Medication adherence

Two hundred and one patients (67%) reported adherence to their medication, while the rest of them (33%) reported non-adherence to their medication. Table 2

Medication adherence subscales

Overall, the mean score of the GMAS was 19.68 ± 7.18; the female mean score (21.19 ± 7.29) was significantly higher than the male mean (18.40 ± 6.85) (P<.05). The mean of the financial constraint subscale (2.04 ± .83) was the highest compared to the additional disease and pill burden (1.59 ± .79) and patient behavior subscales (1.57 ± .77). In the patient behavior and financial constraint subscales, female patients had significantly higher mean medication adherence (P<.05). Table 3

Severity of anxiety and depression and medication adherence

Medication non-adherence increases with the severity of anxiety and depressive symptoms. The mean of medication adherence with regard to anxiety subscales was 22.98 ± 5.90 for normal, 21.80 ± 6.10 for borderline and 14.56 ± 6.46 for anxiety. The mean of medication adherence with regard to depression subscales was 20.03 ± 6.95 for normal, 18.85 ± 7.30 for borderline and 13.66 ± 5.58 for depression. Table 4

Predictors of medication adherence

Multiple linear regressions (stepwise method) were carried out to investigate whether participants' socio-demographics, medical characteristics, and psychological symptoms could significantly predict their medication adherence. The results of the multiple linear regression showed that model 1 (including anxiety only) explained 19.9% of the variance and was a significant predictor of participants' medication adherence, F (1, 298) = 73.84, P<.001. The results of the multiple linear regression showed that model 2 (including anxiety and depression) explained 24.3% of the variance and was a significant predictor of participants' medication adherence, F (2, 297) = 49.06, P<.001. Furthermore, the multiple linear regression results showed that model 3 (including anxiety, depression, and gender) explained 26.5% of the variance and was a significant predictor of participants' medication adherence, F (3, 296) = 35.52, P<.001. Table 5

Table 1. Baseline socio-demographic and medical characteristics for the study patients (*n* = 300)	
Age (years) mean ± SD	52.75 ± 10.36
Sex	
Male vs female (%)	163 (54.3%) vs 137 (45.7%)
Marital status	
Single vs married (%)	87 (29%) vs 213 (71%)
Education	
Primary vs high school	207 (69%) vs 93 (31%)
Income	
< 500 JD vs > 500 JD	217 (72.3%) vs 83 (27.7%)
Employment	

Unemployed vs employed	117 (39%) vs 183 (61%)
Smoking	
Non-smoking vs current	173 (57.7%) vs 127 (42.3%)
Social support	
Absent vs present	32 (10.7%) vs 268 (89.3%)
Chronic disease	
One vs Two or more chronic diseases	87 (29%) vs 44 (14.7%)
Cardiovascular medication	
Beta-blocker agents	117 (39%)
Angiotensin-converting enzyme (ACE) inhibitors	112 (37.3%)
Antiarrhythmic agents	75 (25%)
Calcium antagonists	97 (32.3%)
Antiplatelet	234 (78%)
Statin	211 (70.3%)
Diuretics	67 (22.3%)

Table 2. Medication adherence in patients post MI

GAMS	n	%
Adherence	201	67
Non-adherence	99	33

Table 3. General Medication Adherence Scale mean with regard to gender

General Medication Adherence Scale	Total	Male	Female	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
GMAS (Total)	19.68 ± 7.18	18.40 ± 6.85	21.19 ± 7.29	.001
Patient behavior	1.57 ± .77	1.47 ± .73	1.69 ± .80	.017
Additional disease and pill burden	1.59 ± .79	1.50 ± .77	1.66 ± .82	.086
Financial constrains	2.04 ± .83	1.90 ± .86	2.20 ± .76	.002

Table 4. Medication adherence of participants by severity of anxiety and depression

Severity	N (%)	Mean GMAS score ± SD
HADS-A (0-7)	85 (28.3)	22.98 ± 5.90
HADS-A (8-10)	113 (37.7)	21.80 ± 6.10
HADS-A (11-21)	102 (34)	14.56 ± 6.46
HADS-D (0-7)	150 (50)	20.03 ± 6.95
HADS-D (8-10)	81 (27)	18.85 ± 7.30
HADS-D (11-21)	69 (23)	13.66 ± 5.58

Table 5. Predictors of medication adherence in patients post MI

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% CI for B	95.0% CI for B
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	26.493	1.029		25.738	< .001	24.467	28.518
	HADS-A	-.845	.098	-.446	-8.593	< .001	-1.038	-.651
	F (1, 298) = 73.84 P < 0.001				R Square = .199 Std. Error of the Estimate = 6.467			
2	(Constant)	29.277	1.180		24.821	< .001	26.956	31.598
	HADS-A	-.676	.103	-.357	-6.583	< .001	-.878	-.474
	HADS-D	-.550	.124	-.240	-4.435	< .001	-.794	-.306
	F (2, 297) = 49.06 P < 0.001				R Square = .243 Std. Error of the Estimate = 6.273			

3	(Constant)	28.265	1.233		22.919	< .001	25.838	30.692
	HADS-A	-.655	.102	-.345	-6.415	< .001	-.856	-.454
	HADS-D	-.555	.123	-.243	-4.518	< .001	-.797	-.313
	Gender	1.855	.723	.128	2.566	.011	.433	3.278
	F (3, 296) = 35.52 R Square = .265 P < 0.001 Std. Error of the Estimate = 6.215							

Discussion

Even in a healthcare context, where patients' psychological conditions appear to be less important than the physical ones, there is still a necessity for a comprehensive assessment of patients' well-being, which is what sparked the necessity of researching the role that anxiety and depression play in post-MI patients. This is the first study that, to the best of our knowledge, not only evaluates the degree of medication adherence in Jordanian patients who have had a myocardial infarction, but it also evaluates the effect of anxiety and depression on medication adherence.

In the present study, anxiety (34%) and depressive symptoms (23%) were prevalent in patients' post-MI. A recent descriptive study assessed the prevalence of anxiety and depression in patients post-cardiac event, including MI, at three time points: close to the time of their event, early (2–4 months post-event), and late (6–12 months post-event) convalescence, and reported the prevalence as 43, 28, and 27%, respectively, for anxiety and 22, 17, and 15%, respectively, for depression (23). Kala et al. investigated anxiety and depression by using the Beck Depression Inventory II and the Self-Rating Anxiety Scale. At 3, 6, and 12 months after MI, anxiety was experienced by 10.4%, 15.4%, and 13.8% of patients, whereas depression was experienced by 4.5%, 10.8%, and 6.2% of patients at the same time periods (24). Anxiety and depression are up to four times as common in those who have had a cardiac event (11). Both post-event anxiety and depression are associated with an increased risk of mortality, emphasizing the significance of recognizing these individuals as soon as possible to ensure that they get the appropriate treatment (25, 26).

In terms of medication adherence, almost one third of the study participants' showed non-adherence to their medications. Subscales of GMAS indicated that financial constraints had the greatest mean score compared to patient behavior, additional disease and pill burden subscales, suggesting that financial domain had minimal influence on medicine non-adherence. The study's settings, military hospitals where most patients had military insurance, may explain this. Shang et al. reported that only 50.9% of patients had good adherence in the study conducted among 4001 patients after MI (27). Non-adherence behavior and discontinuation of medication treatment after an ischemic event occur soon after hospital discharge (28), despite being associated with a increase in the incidence of acute ischemic events, the rate of re-hospitalization (29, 30), and decreased survival (31). The presence of depression and anxiety at that time may help to explain this (11). Since then, patients experiencing depressive symptoms had a 3.6-fold risk of non-adherence, while those experiencing anxiety symptoms had a 3.2-fold risk (32). According to the results of this study, patients were less likely to take their medicine as their anxiety and depression symptoms got worse. The degree of medication adherence was shown to decrease in concordance with an increase in the mean severity of both anxiety and depression. Similar results were also reported in the Lissker et al. study (33).

In terms of medication adherence predictors, anxiety, depression, and gender were considered significant predictors. Sandoval et al. (2014) examined psychosocial variables and medication adherence in Santiago, Chile's Cardiovascular Health Program (CHP) hypertension patients. 513 hypertensive patients aged 30–68 were randomly chosen among 1,484 patients. Drug treatment adherence was 36.6%, with women doing better (38.4% vs. 28.9%; < 0.001). Multivariate analysis linked non-adherence to males, poor patient-physician interactions, and severe emotional stress and depression (34). Tang et al. (2014) surveyed heart failure patients on depression and medication adherence. 244 CHF adolescents completed the survey. Self-reported medication non-adherence differed significantly between depressed and non-depressed respondents ($p = 0.008$), but not objectively assessed non-adherence ($p = 0.72$). Self-reported medication non-adherence was 2.3 times higher in depressed patients ($p = 0.006$) (35). A clinical review constituting five studies examined the relationship between depression and CVDs. The study found that depression is a key driver of quality of life and patient adherence to medication and lifestyle treatments (36).

As a side issue, anxiety could be a symptom, disorder, or trait. Medication adherence in CAD patients was shown to be inversely related to state anxiety. Trait anxiety, as opposed to state anxiety, appears to have a protective effect on drug adherence, as demonstrated by Carney et al. (1998). Carney et al.'s hypothesis that state anxiety is linked to greater medication non-adherence in patients with CAD is supported by the Herrmann

investigation (37, 38), since the anxiety subscale of the HADS has a substantial correlation with the state subscale of the State-Trait-Inventory (38).

Limitation

Our findings should be interpreted with caution due to many limitations. Our first survey was a cross-sectional study. As a result, we were unable to draw any conclusions about the cause and effect of our results. It is not known if medication adherence affects depression and anxiety symptoms or whether the relationship is inverse. Hence, randomized controlled studies are needed to verify the direction of the observed associations. Second, the analysis of time related decreases or increases in medication adherence wasn't estimated. Lastly, rather than utilizing continuous scale scores, we dichotomized patients' GMAS results to better reflect their adherence to their prescribed medications. It was required to dichotomize patients' GMAS scores to determine prevalence rates of medication adherence in the study, even though the latter method may be deemed more statistically powerful.

However, our survey's strengths include the use of validated tools for evaluating anxiety and depression, as well as medication adherence. Moreover, the sample size of our survey is rather large.

Conclusion

Anxiety and depression were prevalent among patients post myocardial infarction. Our results emphasize the significance of the impact of depressive symptoms on medication adherence in patients with CAD. In addition, they show that the actual magnitude of medication non-adherence among those individuals is higher than initially assumed. Medication non-adherence is associated with more than just depression; state anxiety also plays a significant role. Increases in the mean severity of anxiety and depression were shown to be associated with a reduction in the degree of medication adherence.

Conflict of interest

The authors declare that they do not have any financial conflicts of interest related to this article.

Funding Statement

No funding source

Authors' contributions

All authors of the present study contributed to the writing and data collection processes. Arafat and Laith analyzed and interpreted the patient data regarding patients' demographics, the General Medication Adherence Scale, and the Hospital Anxiety and Depression Scale. All authors read and approved the final manuscript.

References

1. Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., ... & Muntner, P. (2017). Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *circulation*, *135*(10), e146-e603.
2. WHO. (2022). Jordan implements WHO HEARTS in primary health care to strengthen management of cardiovascular diseases and related risks. 2023 as cited in: https://www.emro.who.int/jor/jordan-infocus/jordan-implements-who-hearts-in-primary-health-care-to-strengthen-management-of-cardiovascular-diseases-and-related-risks.html
3. Elhneiti, M., & Al-Hussami, M. (2017). Predicting risk factors of heart disease among Jordanian patients. *Health*, *9*(02), 237.
4. Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., Morrow, D. A., & White, H. D. (2018). Executive group on behalf of the joint European society of cardiology (ESC)/American college of cardiology (ACC)/American heart association (AHA)/World heart federation (WHF) task force for the universal definition of myocardial infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*, *138*(20), e618-e651.
5. Kosobucka, A., Michalski, P., Pietrzykowski, Ł., Kasprzak, M., Obońska, K., Fabiszak, T., ... & Kubica, A. (2018). Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. *Patient preference and adherence*, 333-340.

6. Basheti, I. A., El Hait, S. S., Qunaibi, E. A., Aburuz, S., & Bulatova, N. (2016). Associations between patient factors and medication adherence: a Jordanian experience. *Pharmacy Practice (Granada)*, *14*(1), 0-0.
7. Shah, D., Simms, K., Barksdale, D. J., & Wu, J. R. (2015). Improving medication adherence of patients with chronic heart failure: challenges and solutions. *Research Reports in Clinical Cardiology*, 87-95.
8. Pednekar, P. P., Agh, T., Malmenäs, M., Raval, A. D., Bennett, B. M., Borah, B. J., ... & Peterson, A. M. (2019). Methods for measuring multiple medication adherence: a systematic review–report of the ISPOR medication adherence and persistence special interest group. *Value In Health*, *22*(2), 139-156.
9. Liu, J., Zhu, X., Yan, J., Gong, L., Wu, X., Liu, M., & Mao, P. (2021). Association Between Regulatory Emotional Self-Efficacy and Immunosuppressive Medication Adherence in Renal Transplant Recipients: Does Medication Belief Act as a Mediator?. *Frontiers in Pharmacology*, *12*, 559368.
10. Feng, H. P., Chien, W. C., Cheng, W. T., Chung, C. H., Cheng, S. M., & Tzeng, W. C. (2016). Risk of anxiety and depressive disorders in patients with myocardial infarction: A nationwide population-based cohort study. *Medicine*, *95*(34).
11. Murphy, B., Le Grande, M., Alvarenga, M., Worcester, M., & Jackson, A. (2020). Anxiety and depression after a cardiac event: prevalence and predictors. *Frontiers in psychology*, *10*, 3010.
12. Riegel, B. (2014). The Role of Depression in Medication Adherence Among Heart Failure Patients. *Clinical Nursing Research*, *23* (3), 231-244. http://dx.doi.org/10.1177/1054773813481801
13. Grenard, JL., Munjas, BA., Adams, JL., Suttorp, M., Maglione, M., McGlynn, EA., Gellad, WF. (2011). Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. *J Gen Intern Med*. *26* (10):1175-82. doi: 10.1007/s11606-011-1704-y. Epub 2011 May 1. PMID: 21533823; PMCID: PMC3181287.
14. Canali, G., Tittle, V., & Seita, A. (2018). Medication adherence by Palestine refugees living in Jordan who have diabetes: a cross-sectional study. *The Lancet*, *391*, S13.
15. Jarab, A. S., Rababa'h, A. M., Almousa, A., Mukattash, T. L., & Bsoul, R. (2020). Non-adherence to pharmacotherapy and its associated factors among patients with angina in Jordan. *Journal of Pharmaceutical Health Services Research*, *11*(1), 61-65.
16. ESC Committee for Practice Guidelines (CPG), Jeroen J. Bax (CPG Chairperson)(The Netherlands), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), ... & Mendis, S. (2012). Third universal definition of myocardial infarction. *Journal of the American College of Cardiology*, *60*(16), 1581-1598.
17. Williams, R. B., Barefoot, J. C., Califf, R. M., Haney, T. L., Saunders, W. B., Pryor, D. B., ... & Mark, D. B. (1992). Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. *Jama*, *267*(4), 520-524.
18. Naqvi, AA., Hassali, MA., Rizvi, M., Zehra, A., Iffat, W., Haseeb, A., Jamshed, S. (2018). Development and Validation of a Novel General Medication Adherence Scale (GMAS) for Chronic Illness Patients in Pakistan. *Front Pharmacol*. *9*:1124. doi: 10.3389/fphar.2018.01124. PMID: 30356775; PMCID: PMC6189444.
19. Meng, X., Li, D., Li, S., Lv, Q., Wang, X., Wang, Y., ... & Wang, L. (2022). Rasch Analysis of Novel General Medication Adherence Scale (GMAS) for Chronic Illness Patients in China.
20. Mahmoud, M. A., Islam, M. A., Ahmed, M., Bashir, R., Ibrahim, R., Al-Nemiri, S., ... & Yousif, M. A. (2021). Validation of the arabic version of general medication adherence scale (GMAS) in sudanese patients with diabetes mellitus. *Risk management and healthcare policy*, 4235-4241.
21. Zigmond, AS., Snaith, RP. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand 67*(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x. PMID: 6880820.
22. Terkawi, A. S., Tsang, S., AlKahtani, G. J., Al-Mousa, S. H., Al Musaed, S., AlZoraigi, U. S., ... & Altirkawi, K. A. (2017). Development and validation of Arabic version of the Hospital Anxiety and Depression Scale. *Saudi journal of anaesthesia*, *11*(5), 11.
23. Murphy, B. M., Higgins, R. O., & Jackson, A. C. (2016). Anxiety, depression, and psychological adjustment after an acute cardiac event. *Handbook of psychocardiology*.
24. Kala, P., Hudakova, N., Jurajda, M., Kasparek, T., Ustohal, L., Parenica, J., ... & Kanovsky, J. (2016). Depression and anxiety after acute myocardial infarction treated by primary PCI. *PLoS One*, *11*(4), e0152367.

25. Watkins, L. L., Koch, G. G., Sherwood, A., Blumenthal, J. A., Davidson, J. R., O'Connor, C., & Sketch Jr, M. H. (2013). Association of anxiety and depression with all-cause mortality in individuals with coronary heart disease. *Journal of the American Heart Association*, *2*(2), e000068.
26. Wu, Y. T., Kralj, C., Acosta, D., Guerra, M., Huang, Y., Jotheeswaran, A. T., ... & Prina, A. M. (2020). The association between, depression, anxiety, and mortality in older people across eight low-and middle-income countries: Results from the 10/66 cohort study. *International journal of geriatric psychiatry*, *35*(1), 29-36.
27. Shang, P., Liu, G. G., Zheng, X., Ho, P. M., Hu, S., Li, J., ... & Krumholz, H. M. (2019). Association between medication adherence and 1-year major cardiovascular adverse events after acute myocardial infarction in China. *Journal of the American Heart Association*, *8*(9), e011793.
28. Castellano, J. M., Fuster, V., Jennings, C., Prescott, E., & Bueno, H. (2017). Role of the polypill for secondary prevention in ischaemic heart disease. *European journal of preventive cardiology*, *24*(3_suppl), 44-51.
29. Collet, J. P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D. L., ... & Karia, N. (2021). 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *European heart journal*, *42*(14), 1289-1367.
30. Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., ... & Bax, J. J. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal*, *41*(3), 407-477.
31. Du, L., Cheng, Z., Zhang, Y., Li, Y., & Mei, D. (2017). The impact of medication adherence on clinical outcomes of coronary artery disease: A meta-analysis. *European journal of preventive cardiology*, *24*(9), 962-970.
32. Dempe, C., Jünger, J., Hoppe, S., Katzenberger, M. L., Möltner, A., Ladwig, K. H., ... & Schultz, J. H. (2013). Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. *Journal of psychosomatic research*, *74*(2), 122-127.
33. Lissåker, C. T., Wallert, J., Held, C., & Olsson, E. (2017). Emotional distress as a predictor of statin non-adherence among Swedish first-time myocardial infarction patients, 2006–2013. *Journal of Psychosomatic Research*, *97*, 30-37.
34. Sandoval, D., Chacón, J., Muñoz, R., Henríquez, Ó., Koch, E., & Romero, T. (2014). Influence of psychosocial factors on adherence to antihypertensive drug therapy. Results from a Cardiovascular Health Program cohort followed in the Metropolitan Region of Santiago, Chile Influencia de factores psicosociales en la adherencia al tratamient.
35. Tang, H. Y., Sayers, S. L., Weissinger, G., & Riegel, B. (2014). The role of depression in medication adherence among heart failure patients. *Clinical nursing research*, *23*(3), 231-244.
36. Hare, D. L., Toukhsati, S. R., Johansson, P., & Jaarsma, T. (2014). Depression and cardiovascular disease: a clinical review. *European heart journal*, *35*(21), 1365-1372.
37. Carney, R. M., Freedland, K. E., Eisen, S. A., Rich, M. W., Skala, J. A., & Jaffe, A. S. (1998). Adherence to a prophylactic medication regimen in patients with symptomatic versus asymptomatic ischemic heart disease. *Behavioral Medicine*, *24*(1), 35-39.
38. Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale-a review of validation data and clinical results. *Journal of psychosomatic research*, *42*(1), 17-41.