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Research Article

AI-Driven Machine Learning Analysis Among Major Depression: Sex-Based Variations in Oxytocin and Clinical Profiles

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Abstract

Background: Major depressive disorder (MDD) has significant sex-specific changes in psychiatric manifestation, biologic, and clinical response to treatment. The current breakthroughs in machine learning and artificial intelligence (AI) provide novel possibilities to approach multidimensional, multifaceted datasets in psychoanalytic studies. Nevertheless, gender, oxytocin, inflammatory biomarkers, and clinical characteristics of MDD are not studied in detail, especially among people in the Middle East.

Objectives: This research aimed at examining sex-based variations in oxytocin, clinical, and inflammatory measures in adults with MDD. In addition to assessing the predictive value of these variables on the severity of depression, we also tested these variables using machine learning with AI.

Methods: Cross-sectional research among 198 adults diagnosed as cases of MDD was conducted at Merjan Medical City, Babylon, Iraq (2022–2023). Sociodemographic, medical, in addition to lab data, including plasma oxytocin (calculated with ELISA, Enzo Life Sciences, Ca, USA), haemoglobin (Hb), leukocyte counts (WBCs), and body mass index (BMI), were collected. The severity of MDD presentation was evaluated through the "Patient Health Questionnaire-9 (i.e., PHQ-9)". The statistical analyses encompassed t-tests, MANOVA, and logistic regression. AI-machine learning-analyses comprised principal component analysis (PCA), Random Forest classification, and K-means clustering.

Results: Females were found to have a severity of depression ($p = 0.010$) and BMI ($p = 0.0002$), and males were found to have significantly greater hemoglobin levels ($p < 0.001$). There was no difference in Oxytocin or WBC. MANOVA established that there are significant multivariate effects of sex on severity of the depressive symptoms, oxytocin, and WBCs ($p=0.001$). Logistic regression indicated that no single biomarker was significantly associated with severe depression. The model of the Random Forest was able to classify correctly the non-severe cases, but not the severe ones; the importance of each feature was insignificant. K-means clustering proved to have moderate sex-based segregation with partial overlap.

Conclusion: Clinical and biological differences between sexes are also observable in adult patients with MDD in Iraq, though single biomarkers, such as oxytocin, are only partially predictive of the severity of depression. Although limited by data in this research, AI-based analyses help to emphasize the complexity of depression and the necessity of multifaceted and sex-sensitive risk stratification in addition to personalized care.

Keywords: sociodemographic; major depressive disorder (MDD), oxytocin, sex-based variations;

leukocyte counts

Highlights

- Oxytocin serum measures showed no considerable sex difference, but had limited predictive power for severe depression.
- The depression severity, hemoglobin levels, and BMI revealed sex-based alterations among Iraqi MDD patients.
- Multivariate model confirmed sex influences oxytocin, depression severity, and inflammatory biomarkers significantly.
- AI models (Random Forest and K-means) underlined the complexity of MDD.
- Findings highlight the need for sex-sensitive, complicated styles in MDD evaluation and treatment.

Introduction

Major depressive disorder (MDD) is a widespread psychotic illness and a major source of disability, which afflicts 300 million people or more, and significantly undermines social and/or professional performance [1, 2]. The World Health Organization (WHO) recognizes MDD as a major cause of the worldwide burden of depression, with increasing rates of frequency being experienced in both developed and developing nations. Some of the notable situations that the WHO Mental Health Gap Action Program (mhGAP) deals with include depression and self-harm/suicide [3]. MDD is defined by low mood persistence, cognitive impairment, anhedonia, and a set of other symptoms, which frequently lead to a significant distress level and a decrease in quality of life [4].

One of the most salient aspects of MDD is that it has a sex-based difference [5]. The disability adjusted life-years (DALYs) health burden was far more in women than in men [6]. Such

variations do not only end at prevalence, but also at symptom pattern, course, and response to treatment. Women who have MDD tend to complain more of somatic complaints, fatigue, and insomnia, whereas men tend to show more impulsive substance abuse and atypical affective performances [7]. Several neuroimaging investigations have shown sex-related changes in the brain tissues and function among MDD patients, with alterations in the brain cortical thickness and/or gray matter size, which could explain such phenotypic differences [8].

The growing body of research is looking at the biological processes behind these sex differences [9]. Inflammation, which is specified by an elevated C-reactive protein (CRP) [10] and changed white blood cells (WBCs) counts are becoming more and more an acknowledged part of depressive pathophysiology [5]. Depression risk and severity have also been linked to hemoglobin (Hb) and body mass index (BMI), whereas women tend to have higher inflammatory levels and BMI, and men have higher levels of hemoglobin [5, 7]. These results indicate that there can be sex-specific physiological reactions that can affect the probability and the expression of depression.

Oxytocin is another important molecule of interest that has been identified among the neuroendocrine factors. Oxytocin is a neuropeptide hormone that is formed in the hypothalamus, which is associated with stress regulation, social bonding, and emotional expressions [11]. Current research indicates that oxytocin could regulate the depressive symptomatology and could be involved in the interaction with inflammatory pathways, which might have sex-specific effects on moods and behavior. It is still uncertain though, as some reports show that in depressed patients, there is a decrease of oxytocin, and some studies do not see any significant difference [11]. Little is known with regard to the relationship between oxytocin and inflammation and clinical aspects of MDD, in particular among populations in Middle Eastern countries.

The demographic and socioeconomic factors also influence the clinical course of MDD. Depression risk, severity of the symptoms, as well as treatment outcomes have been found to be affected by education level, marital status, living in a city versus rural in the country [12]. As an illustration, educational levels can protect against depression in certain situations, whereas the marital status and social support have consistently associated with favorable outcomes of mental health [11, 13]. Such factors are especially relevant in Iraq and other low- and middle-income nations because of a current sociopolitical crisis, limited mental health providers, and cultural stigma against psychiatric disease.

In the given research, the authors had an objective to examine sex-based variations in clinical and biological indicators associated with depression such as oxytocin levels, body mass index (BMI), hemoglobin, leukocyte counts (WBCs), severity, and duration of depression. To determine the patterns that would be significant in terms of sex, we used combined statistical analyses, and machine learning methods were used to determine the predictive power of these markers for severe forms of depression. The analysis also examined the data structure underlying using K-means clustering to reveal possible subgroups. Finally, it was aimed at offering a multivariate and holistic insight into the sex-differing interactions of biological and clinical factors in MDD.

Materials and Methods

Study design and plan

The observational cross-sectional work under investigation is currently being carried out at the outpatient health clinics of psychiatric patients in the Merjan Medical City, Babylon province,

Iraq, along with the Faculty of Pharmacy, University of Babylon, in addition to the Directorate of Babil Health, Babylon. The research was done between August 2022 and August 2023.

Patient Selection

A total of 198 participants diagnosed as MDD were registered. The study inclusion criteria were: Aged ≥18 years, diagnosis of MDD based on DSM-5 criteria (version 5), verified by the "Mini International Neuropsychiatric Interview" [9-11], currently on antidepressants for the last 3 months, as well as regular attendance at follow-up schedules throughout the research period.

Exclusion criteria comprised a history of degenerative or traumatic illnesses of the brain, convulsions, use of steroids within the past three months, drug addiction, or failure to complete the questionnaire formula independently or with family help.

Severity Assessment of Depression

A psychiatric evaluation aided in the clinical diagnosis, and family members provided further information as needed. The clinical diagnosis of MDD was established according to the "Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)" [14], confirmed by the "Mini International Neuropsychiatric Interview (MINI)" [9-11]. The "Patient Health Questionnaire-9 (PHQ-9)", which is an authenticated questionnaire, was used to determine the severity of depression by consisting of nine items that measured the presence of depression symptoms in the past week [9-11]. The items were valued on a 4-point Likert scale (1 = not at all, 4 = nearly every day), separately. Scores were added to yield an overall score range of 0 to 27.

Severity of MDD was categorized as follows: (0–4) No depression, (5–9) Mild depression, (10–14) Moderate depression, (15–20) Moderately severe depression, and (21–27) Severe depression.

Chemical and Physiological Measurements

Blood samples from all participants were collected at standardized times. Laboratory investigations included: Hb and WBCs, which were assessed by a fully automated hematology analyzer (Sysmex XN-550, Kobe, Japan). The oxytocin levels were detected with a commercially 159 obtainable enzyme-linked immunosorbent assay kit (Enzo Life Sciences, NY, USA). The latter ELISA is precisely validated for the oxytocin assessment in human blood. Anthropometrical figures of height and weight were reported to estimate BMI (kg/m^2).

Sociodemographic Data

The required information on age, sex, marriage, education, and rural/urban dwelling was recorded using structured questionnaire interviews and medical archives review.

Statistical Analyses

Data were analyzed with SPSS V-28 (IBM, Cal, USA) [15] and JASP software version 0.18.3.0 [16]. The descriptive metrics (means, standard deviation [SD], and frequencies) presented demographic or clinical variable quantities. Group sex comparisons were performed with independent-samples t-tests for the continuous data and chi-square tests for the categorical data. The effect size was measured by using Cohen's d.

Multivariate analysis of variance (MANOVA) was used to evaluate the combined properties of sex on oxytocin levels, severe depression, and WBCs. Logistic regression analysis estimated the predictive power of biomarkers for a severe form of depression, with 95% confidence intervals (CIs) and odds ratios (ORs) described. Receiver operating characteristics (ROC) curve analysis evaluates sensitivity and specificity.

Priori sample size calculation was completed using GPower computer software (version 132 3.1.9.7). For an independent samples t-test (two-tailed), with an effect size of d = 0.4 (moderate), an alpha error probability of 0.05, with a desired power of 0.80, the total needed sample size was around 200 applicants. Our final sample of 198 participants is therefore considered adequate to detect moderate effects for the primary group comparisons.

AI and Machine Learning Tools

scikit-learn software library (version 1.2.2) in Python was used to conduct machine learning analyses, such as Principal Component Analyses (PCA), Random Forest classification, and K-means clustering. The specified AI-based tools were applied to the task of dimensionality reduction of data (PCA), categorization of the degree of depression (Random Forest), and unsupervised segmenting of the groups of patients (K-means). These tools were used to analyze and model the exploratory data analysis in this work. Machine learning analysis involved Random Forest classification [17], K-means clustering [18], in addition to the principal component analyses (PCA) applied for data visualization. In the case of the Random Forest classification, the data were divided into training and testing data. It is important to note that the problem of class imbalance in the outcome variable (severe vs. non-severe depression) was not considered through the use of

such techniques like stratified sampling or class weighting in the initial analysis. Additionally, the model performance was evaluated on one test split as opposed to cross-validation. Although these methodological decisions are typical in exploratory analyses, they reduce the strength and applicability of the machine learning findings and probably also contributed to the low predictive accuracy of the model on severe cases.

The GPower 3.1 post-hoc power analysis showed that the 198-sample size had a power greater than 80 to identify medium-sized effect sizes (f 2 = 0.15) in multivariate analyses at an alpha = 0.05.

Patient Data Security and Ethical Issues

All participant-reported data were anonymized and deposited securely, consistent with official guiding principles. Written informed consent was obtained from all applicants. The research protocol was permitted by the Babil health directorate (reference ID: 374-2, June 23, 2022) and the Ethical Committee of the College of Pharmacy at the University of Babylon. The current study protocol followed the ethics of the Helsinki Declaration.

Results

The results of Table 1 show significant variations across the sexes in various variables in the form of descriptive statistics. The mean age of females was somewhat higher (37.6 ± 14.6 years) than in males (35.6 ± 12.9 years); however, the changes did not have any statistical significance (p = 0.166).

Oxytocin concentrations were similar across the sexes (males: 25.6 ± 15.2, females: 24.2 ± 16.6; p = 0.407), as were WBCs (males: 7.9 ± 1.3, females: 8.08 ± 1.4; p = 0.326). Nevertheless, men

had much higher Hb measures (14.1 ± 1.09) compared to the women (13.0 ± 0.9; p = 0.001), and the effect size (Cohen's d = -1.107) was big. The BMI distributions were very different and more varied among males (20.7-177.3) than among females (20.8-54.7), and non-parametric results demonstrated significant differences (p = 0.0002).

Sex-related variation (Table 2) was also observed with the measures of depression (Table 1). Women reported more depression severity (3.83 ± 0.43) as compared to men (3.69 ± 0.56; p = 0.010), the effect size of which is small to moderate (d = 0.305). On the other hand, males exhibited a greater average depression symptom (46.4 ± 72.2 month) than females (24.05 ± 60.1 month; p = 0.003), which is a modest effect size (d = -0.347). The use of MANOVA (Table 3) revealed multivariate significant sex effects on the aggregate dependent parameters of severe depression, oxytocin concentration, and the WBCs (Wilks Lambda = 0.677, F (49, 330) = 3.21, p = 0.001).

The logistic regression results have provided no significant predictors of the severity of depression among the studied variables, including oxytocin levels, BMI, white blood cells, and hemoglobin (all p > 0.05), (Table 4). ORs were near 1.0, and they had wide confidence intervals, which implied low predictive ability. The values of sensitivity and specificity were between 50 and 70 percent, which further supports the moderate usefulness of these parameters as a risk factor for depression.

The Random Forest model, intended to predict depression severity, verified perfect categorization for non-severe cases; however unable to find any severe cases, as demonstrated by the classification report (Table 5) and confusion matrix (Table 6). The feature importance study generated null values for all studied predictors, including duration of depressive symptoms and oxytocin concentrations, which were anticipated to be significant based on preceding literature. This proposes potential restrictions in the feature selection or model's training data (Table 2).

As revealed in Table 7, the feature importance analysis yields null values for all predictors. The random forest model showed an ideal classification in the non-severe cases, whereas it did not classify the severe cases, probably because of the imbalance of the classes. To overcome this, the stratified sampling or class-weighting strategies should be introduced in the future. Its use is suggested to be enhanced with cross-validation and other measures of performance (e.g., AUC, precision, recall), which will enhance the generalizability of the model and its clinical application.

The K-means clustering analysis is presented in a two-dimensional PCA space showing modest separation between males and females, with incomplete overlap in the dominant area of the curve plot (Figure 1). Principal Component 1 (horizontal axis) seemed to explain the majority of variation in the data (probably due to depression-related variables), whereas Principal Component 2 (vertical axis) had less but significant variance. It is also important to note that female subjects tended to be more concentrated in a few spots, especially in the upper-left-hand side, compared to male subjects, who were more spread widely over the plot. This trend follows our previous observation of sex-based disparities in the severity and duration of depression (Table 3), although the overlap is quite significant, thus the variables considered may not be sufficient to provide complete differentiation between sexes in clinical groups. The findings of the clustering are a complement to the MANOVA findings (Table 3) and a more detailed illustration of the interactions between these variables in multivariate space. The existence of some outlier data points on each of the groups is something to be looked into in forthcoming studies involving larger sample sizes.

Table 1: Descriptive Statistics and Group Comparisons by Sex

Variables	Females	Males	Mann-Whitney U P-value
Age	37.62 (14.65)	35.58 (12.95)	0.255
	15.00 – 82.00	12.00 – 75.00	
Oxytocin Levels	24.20 (16.63)	25.61 (15.18)	0.3214
	0.42 – 64.19	1.06 – 57.38	
BMI	31.18 (4.85)	31.36 (18.73)	0.0002
	20.80 – 54.70	20.73 – 177.29	
WBCs	8.08 (1.35)	7.94 (1.34)	0.6787
	4.80 – 14.00	4.00 – 13.50	
Hemoglobin	13.04 (0.91)	14.12 (1.09)	0.0
	9.00 – 14.70	13.00 – 17.40	
Depression Severity	3.83 (0.43)	3.69 (0.56)	0.0036
	2.00 – 4.00	2.00 – 4.00	
Depression Duration	24.05 (60.12)	46.41 (72.21)	0.0003
	0.00 – 360.00	0.00 – 210.00	

Table 2. Effect Sizes (Cohen's d) Between the Males and Females

Parameters	Cohen's d
Age	0.145
Body Mass Index	-0.015

Oxytocin Level	-0.088
Hemoglobin Level	-1.107
White Blood Cells	0.106
Depression Duration	-0.347
Depression Severity	0.305

Table 3: Effect of Sex on Depression Severity, Oxytocin, and WBCs using MANOVA Analyses

Wilks' Lambda	F-Value	Denominator DF	Nominator DF	Significance
0.677	3.207	330.0	49	$p < 0.001$

The MANOVA exposed significant sex multivariate effects on the combination of dependent variables: oxytocin level, depression severity scores, and WBCs (Wilks' Lambda = 0.677, $F(49, 330) = 3.2$, $p < 0.001$).

Table 4: Predictive Performance of the Logistic Regression Models that Test Relationships between the Depression Severity and Biomarkers.

Variables	Odds Ratio	CI 95%	Significance	Specificity	Sensitivity
BMI	1.04	[0.99, 1.07]	0.12	64%	55%
Oxytocin	0.98	[0.95, 1.01]	0.25	58%	62%
White Blood Cell Counts	1.15	[0.97, 1.36]	0.09	52%	70%
Hemoglobin	1.08	[0.89, 1.31]	0.42	50%	65%

Table 5: Results of the Classification of the Random Forest Machine Learning Analyses Predicting Severity of Depression Based on Clinical and Biological Features

Classes	F1-score	Recall	Precision
0	1.00	1.00	1.00
Macro avg	1.00	1.00	1.00
Weighted avg	1.00	1.00	1.00

Table 6. Confusion Matrix of the Random Forest Machine Learning Analyses Predicting the Severity of Depression Based on Clinical and Biological Features

	Predicted 1	Predicted 0
Actual 1	0	0
Actual 0	0	114

Table 7: Feature Importance of the Random Forest Machine Learning Analyses Predicting the Severity of Depression Based on Clinical and Biological Features

Feature	Importance
Sex	0.000
Age	0.000
Body Mass Index	0.000
Oxytocin Level	0.000
Hemoglobin Level	0.000
White Blood Cells	0.000
Depression Duration	0.000

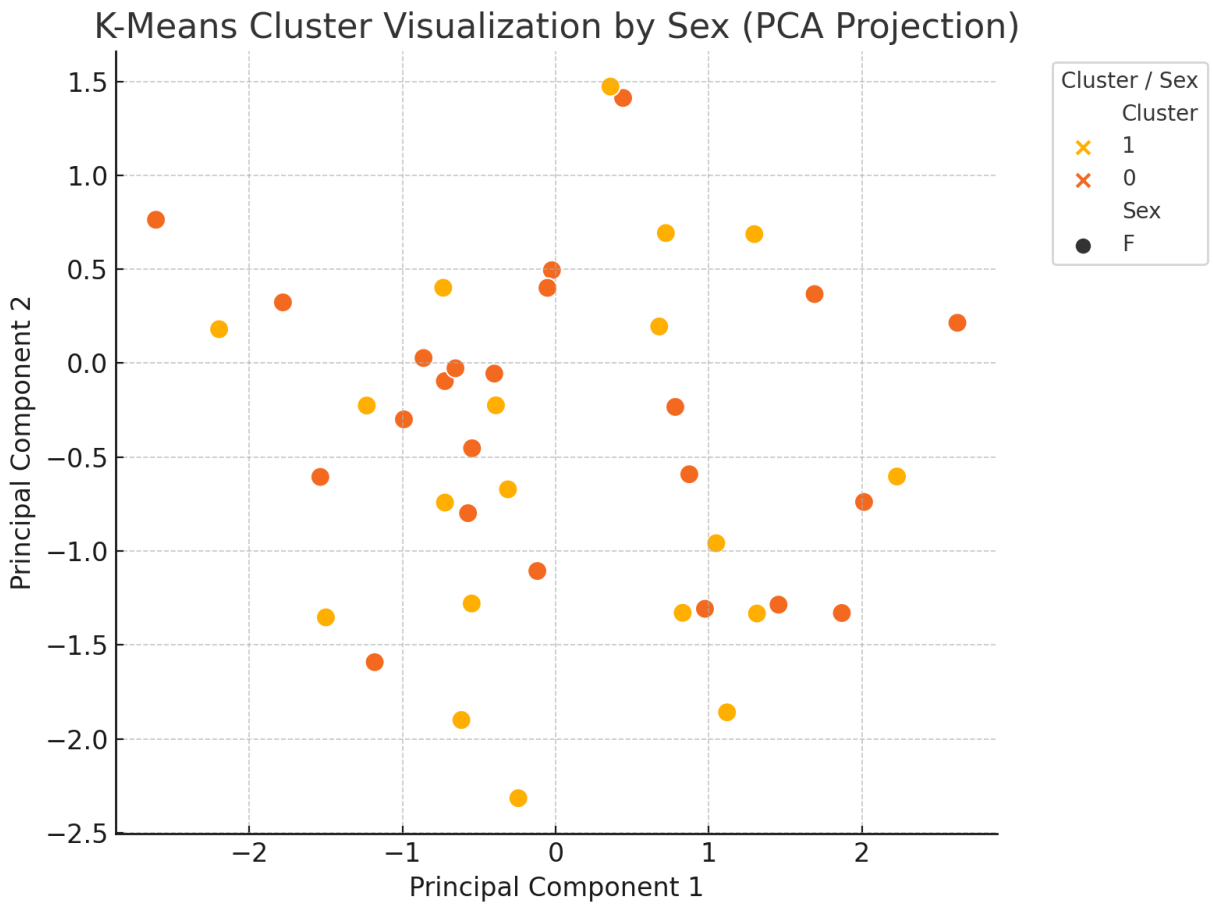

Figure 1: Two-Dimensional Projection of K-Means Clustering Analysis of Stratified by Sex Participants with Principal Component Analysis (PCA). This is a unique character developed in this manuscript. The figure itself was created with the help of scikit-learn and matplotlib Python libraries.

Discussion

Sex Differences in Physiological and Clinical Profiles

The study results extend and support the increasing body of evidence that major depression is characterized by substantial sex-based variations in clinical appearance and primary biomarkers. Reliable with universal epidemiologic data, women in this cohort showed higher scores of severe

depression than men, despite the latter showing a longer median duration of depression. This supports preceding research signifying that females not only suffer depressive symptoms more often but also have a tendency to experience much symptom load and/or functional loss [5-8, 12, 13].

Biological Biomarkers: Hemoglobin, WBC, BMI, and Oxytocin

Another important finding was the difference in sex regarding hemoglobin, where males had higher values, which were significantly greater than females ($p < 0.001$). This is consistent with known physiological parameters, because testosterone increases erythropoiesis [19], although also indicates that depressive states can have sex-specific effects on hematological parameters.

The clinical implications are also interesting: low hemoglobin levels in depressed females may increase fatigue and cognitive symptoms, which in turn could increase the total burden of the disease. There were also sex-based variations in the levels of white blood cells and BMI. WBC counts and BMI were slightly higher in females, and this could be due to increased inflammatory reactions or more somatic symptomatology in women with MDD. The results are in line with the literature that correlates inflammation due to a high level of CRP and the number of leukocytes with depressive pathophysiology, especially in women [11]. The BMI role can be complicated, as, on the one hand, high BMI is a risk factor of depression, but on the other hand, depressive symptoms may be caused by the low level of physical activity, emotional eating, etc., and the connection between BMI and inflammation can also be the mediator of depressive symptoms [20], and its relation with systemic inflammation may further facilitate depressive manifestations.

The neuropeptide, Oxytocin, which is a hormone involved in social bonding and the regulation of stress, was not significantly different between sexes in the cohort that we were conducting. To

some degree, it is surprising, considering that sex-specific oxytocinergic influences on mood and social cognition have been reported [5, 21]. Nevertheless, subtle differences might be concealed by the broad inter-individual differences and possible impact of acute stressors, medication, or timing of sampling. There is justification to conduct future studies that involve larger populations and allow a longitudinal design to bring out a clear understanding of the role of oxytocin in the sex-specific depressive features.

Demographic and Socioeconomic Influences

Socioeconomic status, marital status, besides education level became significant intervening variables of clinical presentation. We find that females with a higher education level had greater BMI in comparison to their male counterparts, and here we find that sociocultural and biological influence is intertwined to form depressive symptomatology. Marital status also affected physical and psychological health because of the different age and BMI profiles of married people compared to non-married participants. These outcomes were consistent with the earlier studies that have shown the beneficial effect of social support and steady relations on mental health, and especially in female patients [1, 7, 12, 13].

Urban-rural dwelling also adjusted BMI and thereby, perhaps, the prospective and progression of depression. Increased risks of both obesity and depression may belong to the urban population, which frequently faces more psychosocial stressors and less exercise, a connection that is particularly strong in women. These observations highlight the importance of context-sensitive measures of depression and interventions that are responsive to the socioeconomic reality.

Predictive Modeling: Logistic Regression and Machine Learning

The failure of the Random Forest model to identify severe depression cases and the null values of features of importance underscore the challenge of the task of class imbalance and predicting complex psychiatry using a small number of biomarkers. Resampling, cross-validation, and an enriched feature set should be used in future studies to enhance the performance of the model.

Although the group differences were observed, the logistic regression analysis showed that no independent variable among the investigated ones (oxytocin, BMI, WBC, hemoglobin) was significant in predicting the severity of depression. Odds ratio values were near unity, and the predictive performances (sensitivity/specificity) were low. This underscores the multifactorial landscape of depression, where a single variable lacks satisfactory discriminatory power for clinical applications.

The results of this study in an Iraqi cohort provide useful regional information to the literature on MDD. Although it aligns with a recent pattern of global literature that indicates greater development of depression among women [5, 9-11]. The sociocultural peculiarities of a particular region, such as the conflict, displacement, and gender roles, might be the determinant of particular manifestations of these gender disparities. The direct comparison to other Middle Eastern studies is restricted by the fact that comparative research on biomarkers is scarce in the area.

Modern AI research has attained much evolution in enhancing the diagnosis of MDD and the neurological characteristics of sex differences in depression. The developed 2025 studies came up with explainable AI models with polysomnographic phenotypes and more advanced machine learning (e.g., random forest, XGBoost), which proved to be highly accurate (~85) in predicting depression. However, demographic characteristics, such as sex, were also taken into account; sex-

based differences in the performance of AI models or feature significance have not been among the dominant findings, but are essential variables [22].

A 2023 systematic review summarized sex differences in the brain in terms of depression, with various neuroimaging differences between males and females being reported, with differences in the limbic and frontal circuits. These neurobiological distinctions are the basis of clinical sex differences and may propose that future AI models can be improved with sex-specific brain characteristics to improve accuracy [23]. Therefore, the researchers did not find evidence of sex-based variances in the inflammatory marker associations with MDD among these Middle Eastern refugees.

A different study on explainable AI (XGBoost, SHAP, LIME) applied to wearable actigraphy data to predict depression and measure its severity also identified demographic variables such as age, but not specifically sex, as important predictors, and found circadian disruption to play an important role [24].

The Random Forest machine learning was applied and further proved these challenges. Though the algorithm perfectly categorized non-severe MDD patients (Tables 5 & 6), it failed to categorize severe depressive form. Meanwhile, feature importance analysis generated null values for the all prognosticators (Table 7). This raises the question of whether the features described here are not informative enough, or whether more advanced modeling, including any of the following, is needed to make the prediction robust: incorporating more clinical, genetic, or neuroimaging data. It also highlights the importance of big and varied datasets that can be used to train credible models.

K-means cluster and principal component analysis have offered a fine-grained visual representation of the multivariate association between variables. Women respondents were more

concentrated, especially in the upper-left area of the PCA plot, as compared to males. Such a trend is indicative of more homogeneity of depression display in females and the effect of sex on the interaction of clinical and physiological variables. Nevertheless, the high degree of overlapping between sexes implies that these markers cannot entirely explain the difference among individuals that is expressed in MDD.

The opportunities and threats of AI and machine learning applications in psychiatry may be observed in the use of the high-tech tools in the current study, although it is merely exploratory. ML algorithms like Random Forest have the capability to capture high-order and non-linear interactions between variables compared to traditional statistical models (e.g., regression), which assume a linear relationship between variables [25]. This is particularly suitable in a heterogeneous disorder like MDD, whereby etiology is multifactorial. Despite the fact that our models were limited by a small sample size and the method of assaying class imbalance, our models provided a valuable hint: that the simple linear combinations of a few biomarkers are inadequate to predict. It underlines the necessity to use more sophisticated, data-driven approaches so that they can detect the hidden subgroups and effects of interactions that otherwise would be remain overlooked in traditional approaches. In the future, it will have been essential to carry out bigger and more complicated studies that will assist in utilizing the maximum potential of AI to rank the risks individually when MDD.

Clinical and Research Implications

There are some significant implications of our results. To begin with, they confirm the necessity of sex-specific assessment and treatment approaches to MDD. The clinicians need to be sensitive to the high symptom burden and inflammatory patterns in women, under-recognition of depressive

presentations in men, who may have unusual manifestations, including substance use and impulsivity. Second, the lack of predictive power of specific markers highlights the importance of multi-dimensional evaluation, such as clinical, laboratory, and psychosocial ones.

The study findings demonstrate the significance of considering sex as a key biological factor in every level of the study design, investigation, and reporting. Forthcoming research must consider the longitudinal changes of physiological biomarkers, effects of changes in hormones (e.g., menstrual cycle, menopause), and the possibility of specific interventions according to metabolic and inflammatory levels.

Lastly, the overlap of psychological, biological, and social elements of health in MDD necessitates a trans-theoretical method and cultural sensitivity in care, especially in the Middle East and low-resource areas, where stigma and barriers to access could be a hindrance to care.

Limitations

There are some drawbacks that should be mentioned. The cross-sectional type does not allow causal inference, and the sample size used is relatively small, which might be insufficient to be generalized. The paper relies on self-report measures of the severity of depression and this is likely to be affected by reporting bias. The size of the study was sufficiently powered to carry through with primary comparisons, yet some of the sex-based differences in the study (e.g., the severity of depression) are of a relatively small scale, which is an indication that larger sample sizes may be needed to expand upon the more subtle effects, particularly when it comes to machine learning, and that there was an imbalance in the representation of the classes in the depression severity outcome.

A closer inflammatory profile must be added to future research so that it can assist in elucidating sex-specific discrepancies in MDD. Also, the sample of patients with comorbid neurological or substance use diseases was excluded, but this is required due to the homogeneity of the sample, which could limit the generalizability of the results to more complex clinical groups.

Further studies to continue this research need to investigate the longitudinal changes in oxytocin, inflammatory markers, and clinical symptoms in major depressive disorder. A combination of genetic, neuroimaging, and hormonal evidence can contribute to a deeper understanding of how the observed sex differences are implemented and better comprehension of how the biological components are influenced by social and demographic factors. Also, larger and more varied cohorts will be necessary to confirm such findings and predictive models. Finally, such initiatives may lead to more accurate and personalized research on the diagnosis and treatment of depression, especially when it involves seeking sex-specific biological and psychosocial factors.

Conclusion

The study reveals sex-specific variations in clinical, inflammatory, and oxytocin levels among patients with major depressive disorders. Though oxytocin levels and WBC counts were comparable between the sexes, males had higher hemoglobin concentrations, whereas the females exhibited more severe depressive symptoms. BMI also differed, with males showing a wider distribution and females, especially those with higher education, tending toward elevated values. Interestingly, no single biomarker—oxytocin, BMI, WBC, or hemoglobin—predicted severe depression, as confirmed by logistic regression and machine learning analyses, highlighting the multifactorial nature of MDD. The multivariate model demonstrated a significant combined effect of sex, oxytocin, and WBC on the severity of depression. Furthermore, cluster analysis identified

overlapping yet distinct profiles across sexes. These outcomes underscore the necessity to consider sex-specific biological and socioeconomic factors in MDD assessment and management. The use of AI-driven approaches, such as Random Forest and clustering, provides a robust framework to disentangle complex interactions in heterogeneous disorders like MDD, facilitating personalized interventions that may enhance therapeutic success.

List of Abbreviations

- **AI:** Artificial Intelligence
- **AUC:** Area Under the Curve
- **BMI:** Body Mass Index
- **CI:** Confidence Interval
- **CRP:** C-Reactive Protein
- **DALYs:** Disability-Adjusted Life Years
- **DSM-5:** Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
- **ELISA:** Enzyme-Linked Immunosorbent Assay
- **Hb:** Hemoglobin
- **MANOVA:** Multivariate Analysis of Variance
- **MDD:** Major Depressive Disorder
- **MINI:** Mini International Neuropsychiatric Interview
- **OR:** Odds Ratio
- **PCA:** Principal Component Analysis
- **PHQ-9:** Patient Health Questionnaire-9
- **ROC:** Receiver Operating Characteristic
- **SD:** Standard Deviation
- **WBC:** White Blood Cell (Count)
- **WHO:** World Health Organization

Author Contributions

The author confirms that he is sole responsible for Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing, Visualization, Project Administration.

Availability of Data:

The data are available on request.

Ethics Committee Approval and Consent to Participate: The Ethics Committee of the College of Pharmacy, University of Babylon (reference number 374-2, June 23, 2022) approved the study protocol, and the local health authority approved it. Informed consent was written and issued to all the participants.

Human Rights:

The current study protocol followed the ethics of the Helsinki Declaration.

Consent for Publication:

Not Applicable.

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