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Quality of Life and C-Reactive Protein in Patients with Schizophrenia: A Cross-Sectional Study

ABSTRACT

Objective: The connection between chronic inflammation and the quality of life (QOL) in individuals diagnosed with schizophrenia lacks clarity. This study aimed to achieve 2 primary objectives: (1) assess the QOL among outpatients with schizophrenia and (2) explore the potential correlation between reduced QOL and heightened levels of C-reactive protein (CRP) in patients with schizophrenia.

Methods: The research included 129 outpatients diagnosed with schizophrenia who were receiving care at the psychiatry department of the University Hospital Mohamed VI in Marrakech, Morocco. Disease severity was evaluated using the Positive and Negative Syndrome Scale (PANSS), while the QOL was measured using the Moroccan Arabic version of The Schizophrenia Quality of Life questionnaire. Patients were categorized into 2 groups based on their CRP levels: normal CRP (≤5.0 mg/L) and high CRP (>5.0 mg/L). A comparative analysis of sociodemographic, clinical, biological, and quality of life factors was conducted between the 2 groups (normal CRP and high CRP).

Results: The group with elevated CRP levels exhibited higher scores in various PANSS categories, including PANSS total score ($P \leq .01$), PANSS positive score ($P \leq .01$), PANSS negative score ($P \leq .01$), and PANSS general score ($P \leq .01$). After adjusting for sociodemographic and clinical variables, individuals with elevated CRP levels demonstrated lower QOL compared to those with normal CRP levels (OR = 0.57, 95% CI = 0.46-0.68). Significant associations were noted between male gender (OR = 0.047, 95% CI = 0.01-0.26), earlier onset of the condition (OR = 0.54, 95% CI = 0.33-0.82), current tobacco smoking (OR = 0.015, 95% CI = 0.00-0.08), and heightened CRP levels.

Conclusion: Our study suggests that higher CRP is associated with lower QOL levels in schizophrenia.

Keywords: Schizophrenia, quality of life, chronic inflammation, C-reactive protein

Introduction

Schizophrenia is a persistent and severe mental illness recognized as a significant public health concern both nationally and globally. Its prevalence varies between 0.4% and 1.6%.[1] This condition manifests through diverse psychotic symptoms, disorganized behavior, negative symptoms, and cognitive impairments. All these symptomatic facets significantly impact the quality of life (QOL) experienced by individuals with schizophrenia. Indeed, patients with schizophrenia have reported significantly poorer QOL than those in the general population.[2] In the context of schizophrenia, demographic factors (like gender and educational background) and clinical aspects (such as positive and negative symptoms, as well as medication side effects) have been identified as influential factors affecting QOL.[3]

The etiology of schizophrenia is not fully understood, but there is now increasing evidence of immune system dysfunction and chronic inflammation in patients with schizophrenia.[4] Many studies have reported CRP elevations,[5] increased serum concentration of several pro-inflammatory cytokines,[6] the significance of irregularities in blood lymphocytes,[7] and oxidative stress anomalies in schizophrenia.[8] Indeed, in individuals diagnosed with schizophrenia, high

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C-Reactive Protein (CRP) levels are connected with negative symptoms,[9] impaired cognitive functions,[10] high psychotic symptoms,[11] and a resistance to treatment.[12] All the clinical traits associated with elevated CRP levels in schizophrenia are recognized as factors linked to a lower QOL. Despite limited research on the connection between CRP levels and QOL, a single cross-sectional study has reported an inverse relationship between CRP levels and QOL in individuals diagnosed with schizophrenia.[13]

Enhancing the QOL has been acknowledged as a crucial objective in the treatment of individuals with schizophrenia. It is particularly vital to assess the determining factors of QOL in people with schizophrenia to mitigate the impact of the disorder and enhance their overall well-being. Quality of life is a multifaceted concept with no well-known determinants; therefore, identifying biological factors that can influence QOL holds significant implications for clinical practice. Substantial evidence indicates that inflammatory pathways, mediated by cytokines, play a crucial role in various QOL domains.[14] Additionally, the literature suggests consistent involvement of dopaminergic and serotonergic pathways in emotional functioning, social functioning, and overall well-being.[14]

Previous studies reported the association between low QOL levels and high CRP levels among non-schizophrenic populations.[15] Additionally, CRP is involved in various domains of QOL, such as fatigue and emotional functions.[14] Moreover, elevated CRP levels are also associated with high cardiovascular risk and metabolic syndrome.[13] Therefore, if we can identify CRP as a factor involved in QOL in patients with schizophrenia, we will be able to better target preventive strategies and specific support, such as interventions inducing lifestyle and behavioral changes, psychological therapy, and pharmacological treatment.

The aims of this study were twofold: (1) to assess the QOL among outpatients diagnosed with schizophrenia. (2) To explore potential correlations between reduced QOL and increased CRP levels in patients diagnosed with schizophrenia.

Material and Methods

Patient Enrollment

The cross-sectional study prospectively examined 129 patients from September 2021 to October 2022, who were receiving care at the psychiatry department of the University Hospital Mohamed VI in Marrakech, Morocco. Inclusion criteria involved individuals aged 18 or older, diagnosed with schizophrenia according to the criteria specified in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[16] Eligible participants were considered stable, with no hospitalization or treatment changes for at least 3 months before assessment, and were native speakers of Moroccan Arabic. Exclusion criteria included patients currently undergoing a psychotic crisis, those diagnosed with schizoaffective disorder, depression, bipolar disorder, individuals with organic pathology or a fever exceeding 37.9°C, and those undergoing treatment with antibiotics, anti-inflammatory drugs, or antipyretic medications.

The study received approval from the Ethics Committee of the University of Cady Ayyad Faculty of Medicine and Pharmacy in Marrakech (Approval Number: 023/20; Date: January 9, 2020). Before participating, all patients received detailed information about the study and provided written informed consent.

Data Collection

Information extraction from the charts was conducted using a predesigned form that encompassed sociodemographic measures and clinical characteristics.

- Sociodemographic information
  We gathered sociodemographic data encompassing variables such as gender, age, educational level, marital status, and the participants' family history.
- Assessment of schizophrenic symptoms
  This segment encompassed details regarding the age of onset, duration of the illness, and utilization of licit and illicit substances. Assessment of schizophrenic symptomatology involved employing the Positive and Negative Syndrome Scale (PANSS), which includes three subscales (positive, negative, and general psychopathology). Of the 30 items, 7 are positive symptoms, 7 are negative symptoms, and 16 are general psychopathology symptoms. Symptom severity for each item is rated according to which anchoring points in the 7-point scale (1 = absent; 7 = extreme).[17] Additionally, global functioning was evaluated utilizing the Global Assessment of Functioning (GAF) scale.
- Measurement of QOL
  The assessment of QOL involved using the Moroccan Arabic version of the SQoL-18 questionnaire, specifically designed and validated for evaluating QOL in individuals diagnosed with schizophrenia.[18] This self-administered questionnaire is utilized in Europe and Latin America and is a multidimensional tool developed from the perspectives of patients to gauge their current QOL. It comprises 18 items that delineate eight dimensions: psychological well-being (PsW), self-esteem (SE), family relationships (RFa), relationships with friends (RFr), resilience (RE), physical well-being (PhW), autonomy (AU), and sentimental life (SL). Additionally, it provides a total score (index). Scores for each dimension and the overall index range from 0 (indicating the lowest QOL) to 100 (representing the highest QOL).

Detection and Analysis of C-Reactive Protein

Blood samples were collected from each patient in the morning following a 10-hour fasting period. The serum levels of CRP were assessed using nephelometry, and the results were quantified in milligrams per liter (mg/L). A predetermined cutoff threshold of 5 mg/L was chosen, categorizing patients into 2 groups based on their CRP levels – 85 patients with normal CRP levels (≤5.0 mg/L) and 44 patients with elevated CRP (>5.0 mg/L). This threshold was determined by referencing data from existing literature and similar studies.[19]

Statistical Analysis

The collective characteristics of the entire group were depicted utilizing measures of central tendency (mean) and dispersion (standard deviation) for continuous data, while frequency distribution was

MAIN POINTS

- *The presence of a connection between the quality of life (QOL) and chronic inflammation in individuals diagnosed with schizophrenia.*
- *Poorer QOL in schizophrenia patients was significantly associated with higher C-reactive protein (CRP) levels.*
- *Schizophrenic patients exhibiting heightened levels of CRP experience notably more severe psychotic symptoms.*

employed for categorical variables. To compare sociodemographic, clinical, biological, and QOL factors between the 2 groups (normal CRP and high CRP), the chi-squared test was utilized for categorical variables, whereas Welch's *t*-test was preferred for continuous variables. The utilization of Welch's *t*-test instead of Student's *t*-test was decided due to our data not meeting the assumptions of normality and homoscedasticity, which is usually the case in psychological research.

A multivariate logistic regression model was conducted to determine the adjusted odds ratio (OR) and its respective 95% CI concerning the relationship between the SQoL 18 index and CRP levels. This analysis included adjustment for confounding factors selected from the univariate analysis based on a significance threshold with a *P*-value of .2 (age, matrimonial status, education level, current tobacco smoking, age at onset, PANSS total, lymphocyte cells, and SQoL 18 index). The GAF score ($P < .0001$) was excluded as it is highly correlated with the SQoL 18 index. Gender, body mass index, and the use of atypical antipsychotics were integrated into the analysis owing to their significance in sociodemographic and clinical contexts.

Statistical significance was defined as $P < .05$. The statistical analysis was conducted utilizing R statistical Software (v4.2.3; R Core Team 2023) environment.

Results

Sociodemographic and Medical Features

The study involved 129 outpatients diagnosed with schizophrenia. Table 1 presents the demographic characteristics of the sample. The majority of the participants (84.5%) were male, with an average patient age of 28.29 years (±7.76). The mean age at the onset of schizophrenia was 21.05 years (±2.78), and the average PANSS total score recorded was 68.99 (±11.78).

Comparison of Patients with Normal C-Reactive Protein Level and High C-Reactive Protein

Overall, 44 patients (34.10%) exhibited abnormal CRP levels. These abnormal CRP levels showed a notable association with a younger age at the onset of schizophrenia ($P = .012$), current tobacco smoking ($P = .018$), and a current cannabis use disorder ($P = .021$) (Table 2).

Concerning clinical features, the group with elevated CRP levels exhibited notably higher scores in various PANSS categories (Table 2): PANSS total score ($P \leq .0001$), PANSS positive score ($P \leq .0001$), PANSS negative score ($P = .0002$), and PANSS general score ($P \leq .0001$). Of biological parameters, only lymphocytes were significantly associated with the level of CRP ($P \leq .0001$) (Table 3).

Quality of Life

We observed a significant impairment in the QOL among individuals with abnormal CRP levels compared to those with normal CRP levels. Among the various dimensions of the SQoL 18 questionnaire, the most affected in the entire sample were relationships with friends, self-esteem, and sentimental life, respectively. In the group with normal CRP levels, the most impacted dimensions were relationships with friends, family relationships, and self-esteem, respectively. Meanwhile, in the group with abnormal CRP levels, the most affected dimensions were relationships with friends, sentimental life, and physical well-being, respectively. Additionally, patients with elevated CRP levels reported lower QOL scores for both the SQoL 18 index and all dimensions covered by the SQoL 18 questionnaire (Table 4).

Table 1. Univariate Association Between Sociodemographic Characteristics with Abnormal C-Reactive Protein (CRP) Level (>5 mg/L)

	Whole Sample (N = 129)	Normal CRP ≤ 5.0 mg/L (N = 85)	High CRP > 5.0 mg/L (N = 44)	Normal CRP vs High CRP *P*
Gender (male), n (%)	109 (84.5)	72 (84.71)	37 (84.09)	.927
Age (years), mean (SD)	28, 29 (7.76)	29, 13 (8.32)	26, 66 (6.32)	.063
Residency (urban), n (%)	100 (77.52)	67 (78.82)	33 (75)	.622
Matrimonial status (single), n (%)	107 (82.95)	67 (78.82)	40 (90.91)	.084
Education level (>primary), n (%)	83 (64.34)	50 (58.82)	33 (75)	.069
Professional activity (yes), n (%)	19 (14.73)	12 (14.12)	7 (15.91)	.785
Lower socioeconomic status (yes), n (%)	82 (63.57)	54 (63.53)	28 (63.64)	.990

Table 2. Univariate Association Between Clinical Characteristics with Abnormal C-Reactive Protein (CRP) Level (>5 mg/L)

	Whole Sample (N = 129)	Normal CRP ≤ 5.0 mg/L (N = 85)	High CRP > 5.0 mg/L (N = 44)	Normal CRP vs High CRP *P*
Age at onset, mean (SD)	21.05 (2.78)	22.5 (3.81)	21.05 (2.78)	**.012**
Duration of illness, mean (SD)	6.29 (6.05)	6.58 (6.56)	5.73 (4.93)	.411
Body mass index, mean (SD)	25.04 (1.62)	24.96 (1.74)	25.21 (1.34)	.370
Current tobacco smoking (yes), n (%)	110 (85.27)	77 (90.59)	33 (75)	**.018**
Current cannabis use disorder (yes), n (%)	82 (63.57)	60 (70.59)	22 (50)	**.021**
Presence of atypical antipsychotics, n (%)	72 (55.81)	50 (58.82)	22 (50)	.339
PANSS total score, mean (SD)	68.99 (11.78)	64.51 (8.38)	77.66 (12.6)	**<.0001**
PANSS positive score, mean (SD)	23.74 (6.11)	22.05 (5.12)	27.02 (6.59)	**<.0001**
PANSS negative score, mean (SD)	13.64 (3.03)	13.02 (2.79)	14.84 (3.12)	**.002**
PANSS general score, mean (SD)	31.6 (7.33)	29.44 (5.56)	35.8 (8.51)	**<.0001**
GAF score, mean (SD)	51.4 (17.43)	61.33 (9.37)	32.3 (12.11)	**<.0001**

Values in bold indicate statistical significance. PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning.

Table 3. Univariate Association Between Biological Characteristics with Abnormal C-Reactive Protein (CRP) Level (>5 mg/L)

	Whole Sample (N = 129)	Normal CRP ≤ 5.0 mg/L (N = 85)	High CRP > 5.0 mg/L (N = 44)	Normal CRP vs High CRP *P*
Biological parameters				
CRP (mg/L), mean (SD)	4.61 (3.61)	2.36 (1.31)	8.94 (2.5)	**<.0001**
White blood cells (10^3/mL), mean (SD)	8.22 (1.23)	8.19 (1.11)	8.28 (1.44)	.717
Neutrophil cells (10^3/mL), mean (SD)	5.38 (1.23)	5.42 (1.01)	5.31 (1.58)	.684
Lymphocyte cells (10^3/mL), mean (SD)	1.38 (0.67)	1.19 (0.54)	1.74 (0.76)	**<.0001**

Statistical significance was defined as $P < .05$.

Table 4. Univariate Association Between QOL Assessment with Abnormal C-Reactive Protein (CRP) Level (>5 mg/L)

	Whole Sample (N = 129)	Normal CRP ≤ 5.0 mg/L (N = 85)	High CRP > 5.0 mg/L (N = 44)	Normal CRP vs High CRP *P*
SQoL 18 index, mean (SD)	50.29 (17.46)	60.55 (8.62)	30.49 (12.38)	**<.0001**
Psychological well-being, mean (SD)	54.39 (23.59)	66.17 (15.77)	31.63 (19.15)	**<.0001**
Self-esteem, mean (SD)	49.55 (23.28)	58.82 (19.08)	31.63 (20.1)	**<.0001**
Family relationships, mean (SD)	51.91(23.73)	55.44 (20.9)	45.08 (27.38)	**.031**
Relationships with friends, mean (SD)	27.71 (23.54)	35.44 (21.89)	12.78 (19.16)	**<.0001**
Resilience, mean (SD)	56.33 (24.22)	67.02 (15.49)	35.69 (24.81)	**<.0001**
Physical well-being, mean (SD)	58.79 (24.29)	73.09 (13.29)	31.16 (15.02)	**<.0001**
Autonomy, mean (SD)	53.2 (23.24)	64.12 (15.16)	32.1 (21.63)	**<.0001**
Sentimental life, mean (SD)	50.48 (25.65)	60.55 (8.62)	23.86 (22.53)	**<.0001**

Values in bold indicate statistical significance.

Factors Linked to Elevated C-Reactive Protein

In the multivariate analyses presented in Tables 5 and 6, the correlation between the SQoL 18 index score and CRP level sustained significance even after accounting for sociodemographic, clinical, and biological characteristics. Male gender, earlier onset age of schizophrenia, and tobacco smoking status retained significant associations with elevated CRP levels.

Upon exploring the different dimensions of the SQoL 18, it was observed that all dimensions, except for the family relationships dimension, exhibited a negative association with high CRP levels.

Discussion

In this study, we found an impaired QOL of patients with schizophrenia in all dimensions of the SQoL 18. A noteworthy finding was the substantial negative correlation between elevated CRP levels and lower QOL across all dimensions measured by the SQoL 18 scale.

Assessing QOL in mental health has become increasingly significant, particularly since the deinstitutionalization movement. Integrating QOL measures into clinical practice might enhance adherence to therapeutic interventions and ultimately lead to improved health outcomes in schizophrenia.[20] However the results concerning the determinants of QOL in schizophrenia are contradictory and remain not thoroughly understood. It has been demonstrated that QOL depends on a series of factors such as the severity of the psychopathological symptoms, unmet needs, insight into the symptoms of the disorder, social support, self esteem.[21,22]

The meta-analysis conducted by Eack and Newhill revealed a strong association between poor QOL in outpatients diagnosed with schizophrenia and the presence of positive and negative symptoms. Additionally, it highlighted a consistent negative correlation

Table 5. Factors Associated with High CRP: Multivariate Analysis

Variables	Adjusted Odds Ratio	95 % CI	*P*
Gender (male)	0.047	0.01-0.26	**.002**
Age (years)	1.048	0.88-1.27	.622
Matrimonial status (single)	0.079	0.00-2.03	.138
Education level (>primary)	0.092	0.01-0.62	**.028**
Age at onset (years)	0.549	0.33-0.82	**.010**
Current tobacco smoking (yes)	0.015	0.00-0.08	**<.0001**
Presence of atypical antipsychotics	0.422	0.07-2.48	.334
PANSS total score	1.037	0.96-1.14	.400
Lymphocyte cells (10^3/mL)	2.437	0.73-9.10	.157
SQoL 18 index	0.579	0.46-0.68	**<.0001**

Statistical significance was defined as $P < 0.05$.

Table 6. SQoL 18 Dimensions Scores Associated with High CRP: Multivariate Analysis

SQoL 18 Dimensions	Adjusted Odds Ratio	95% CI	*P*
Psychological well-being	0.893	0.85-0.93	**<.0001**
Self-esteem	0.932	0.90-0.96	**<.0001**
Family relationships	0.979	0.96-1.00	.052
Relationships with friends	0.951	0.91-0.98	**.008**
Resilience	0.904	0.85-0.95	**<.0001**
Physical well-being	0.838	0.78-0.88	**<.0001**
Autonomy	0.899	0.85-0.94	**<.0001**
Sentimental life	0.862	0.81-0.90	**<.0001**

Statistical significance was defined as $P < 0.05$.

between general psychopathology and QOL among these individuals.[23] Furthermore, the severity of psychotic symptoms may predict the quality of well-being in both inpatients and outpatients diagnosed with schizophrenia. In our study, the group with high scores of severity of symptoms has low QOL in all dimensions of SQoL 18. Our findings corroborate with other studies conducted in other countries (such as Kuwait, Tunisia, and France) using different scales of QOL.[21,24,25] Moreover, the dimension of relationships with friends was the most impaired. This is due to the social stigma, as schizophrenia is often associated with perceived dangerousness, leading to social isolation.

Furthermore, QOL in schizophrenia encompasses several aspects, including neurobiological features in addition to clinical characteristics. Indeed, the literature suggests that high CRP levels were connected with low QOL in both psychiatric and nonpsychiatric populations.[26] In a sample of 2837 healthy participants, positive affect was inversely associated with levels of CRP and interleukin 6.[27] Additionally, low-grade inflammation could forecast mortality in older individuals, irrespective of the existence of any particular disease or health condition.[28] Although the biological mechanisms of positive psychology remain poorly understood, there is considerable evidence suggesting the relevance of inflammatory pathways, mediated by cytokines, in influencing various domains of QOL. Additionally, evidence indicates an association between genetic polymorphisms in genes responsible for cytokines and their receptors, involved in crucial pathways, with QOL.[14]

In our study, we found a negative association between chronic inflammation and low QOL in stable individuals diagnosed with schizophrenia. Our results were in accordance with the study of Faugere et al.[13] Our study further revealed that individuals with heightened CRP levels exhibited higher total PANSS scores and elevated subscale scores in PANSS compared to those in the normal CRP group. Exploring the relationship between the biological status of patients and the assessment of psychopathological signs in schizophrenia has been the subject of several studies with controversial results.[5,29,30,31]

Multivariate analysis revealed a significant correlation between education level and smoking habits with CRP levels, aligning with the anticipated outcomes. These findings are in line with previous studies. Smoking can activate pro-inflammatory cytokines, which stimulate the production of CRP.[32] A low education level and a low socioeconomic level have been related to chronic inflammation.[33,34] We also found that male patients had higher CRP levels, whereas in another study, women had higher CRP levels than men.[34] Interestingly, an earlier age at the onset of schizophrenia remained associated with high CRP levels. Inflammatory biomarkers have been shown to be elevated in individuals with first-episode psychosis.[4] Moreover, individuals identified as being at ultra-high risk for psychosis demonstrated elevated concentrations of IL-6 in comparison to healthy control subjects.[4]

There are several limitations of our study. First, the cross-sectional design of our study restricted our ability to infer causation or determine cause-and-effect relationships. Second, our study sample might not be entirely representative of all individuals diagnosed with schizophrenia. The sample size was not calculated beforehand, and we were limited by resource constraints such as time and number of researchers. Third, we did not evaluate metabolic syndrome, which is considered a potential confounding factor of CRP. Fourth, our study evaluated only CRP as a marker of inflammation. Subsequent studies necessitate a comprehensive evaluation of inflammatory markers to achieve a more thorough characterization of patients. Lastly, we did not account for cognitive impairment in our study.

Our study yielded noteworthy findings. Firstly, individuals with schizophrenia who had elevated CRP levels showed more severe symptoms and a lower QOL. Secondly, a significant correlation was observed between CRP levels and reduced QOL in individuals diagnosed with schizophrenia. The consistent affirmation of this association between QOL and CRP in schizophrenia in our study aligns with previous research. Nevertheless, to fully grasp the intricate biological and molecular mechanisms influencing the concept of QOL in schizophrenia, additional extensive studies are warranted.

Availability of Data and Materials: *The data that support the findings of this study are available on request from the corresponding author.*

Ethics Committee Approval: *The study received approval from the Ethics Committee of the University of Cady Ayyad Faculty of Medicine and Pharmacy in Marrakech (Approval No.: 023/20. Date: January 9, 2020).*

Informed Consent: *All patients have their informed consent to participate in this study.*

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