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Association of Obesity-Induced Systemic Inflammation with Severity and Radiological Progression of Osteoarthropathy in Adult Patients

Israr Ahmed, Muhammed Akhtar Khan, Adil Saidullah, Shazia Baloch, Ajwad Sattar, Hafiz Faisal Jamil

Abstract

Objective: To determine the association of obesity-induced systemic inflammation with the severity and radiological progression of osteoarthropathy in adult patients.

Study Design and Setting: A cross-sectional analytical study was conducted at the Department of Orthopedic Surgery, Federal Government Polyclinic Postgraduate Medical Institute (PGMI), Islamabad, over two years, from August 2023 to August 2025.

Methodology: Non-probability consecutive sampling was used to enroll 387 adult participants aged 18–65 years. Anthropometric measurements were obtained, including body mass index (BMI) and waist circumference. Standard assays were used to measure laboratory parameters, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), fasting glucose, and lipid profile. The radiological severity was determined using the Kellgren–Lawrence (KL) grading system.

Results: The mean ± standard deviation (SD) age was 51.4 ± 8.8 years. Obese participants (n = 193) had significantly higher BMI (29.6 ± 3.4 kg/m²) than non-obese participants (23.5 ± 2.8 kg/m², $p < 0.001$). The median (interquartile range, IQR) hs-CRP was 4.8 (3.1–6.9) mg/L in obese participants and 2.1 (1.3–3.4) mg/L in non-obese participants ($p < 0.001$). Severe radiographic osteoarthropathy (KL grade 3–4) occurred in 42.3% of obese participants versus 24.7% of non-obese participants ($÷^2 = 13.91$, $p < 0.001$).

Conclusion: These results indicate that systemic inflammation, rather than mechanical loading, leads to disease pathology. Early detection could facilitate preventive and individualized approaches for obese patients in orthopedics.

Keywords: C-reactive protein; Interleukin-6; Obesity; Osteoarthropathy; Radiographic progression; Systemic inflammation

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Israr Ahmed
Post-Graduate Resident, Department of Orthopedics
Federal Government Polyclinic Post-Graduate Medical Institute, Islamabad
Email: Healingpathx2025@gmail.com

Muhammed Akhtar
Consultant Surgeon/ Head of the Department of Orthopedics
Federal Government Polyclinic Post-Graduate Medical Institute
Email: publichealthcaredr125@gmail.com Khan

Adil Saidullah
Medical Officer, Department of Orthopedics
Federal Government Polyclinic Post-Graduate Medical Institute,
Email: adilwazir1606@gmail.com

Shazia Baloch
Medical Officer, Department of Orthopedics
Federal Government Polyclinic Post-Graduate Medical Institute,
Email: shaziabaloch2005@gmail.com

Ajwad Sattar
Post-Graduate Resident, Department of Orthopedics
Federal Government Polyclinic Post-Graduate Medical Institute,
Email: ajwadsattar42@gmail.com

Hafiz Faisal Jamil
Post-Graduate Resident, Department of Orthopedics
Federal Government Polyclinic Post-Graduate Medical Institute,
Email: 4drhafizfaisaljamil@gmail.com

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INTRODUCTION:

Osteoarthropathy, especially when linked to obesity, is gaining importance in public health because it may signal a harmful interaction between mechanical stress and systemic inflammation[1]. In Pakistan, the burden of osteoarthritis has risen sharply in recent years, and this increase is especially worrying given resource constraints and rising obesity rates. A recent analysis of the Global Burden of Disease (GBD) data showed that the number of osteoarthritis cases in Pakistan climbed from 2.85 million in 1990 to 8.49 million in 2021, with age-standardized prevalence rising by nearly 17.9 % over that period[2]. In local surveys, prevalence estimates in older populations and clinical settings vary between about 14 % and 20 %. In one regional study, knee osteoarthritis was found in 40.8 % of community adults aged =40 years in Hayatabad, Peshawar. These numbers suggest osteoarthritis is already a common cause of pain and disability in Pakistani adults[3].

Across Asia, osteoarthritis is also a major problem. In meta-analyses, the pooled prevalence of knee osteoarthritis in Asians aged =40 years is around 22.9 %. The burden is higher in some countries with tradition of squatting and

frequent knee flexion activities[4]. The GBD 2020 data showed that age-standardized osteoarthritis prevalence in Southeast Asia reached over 5.6 % per 100,000 population. The rising prevalence coincides with growing obesity and metabolic syndrome prevalence across Asia[5]. In many Asian nations, obesity and sedentary lifestyle are rising faster than health systems can adapt, so the impact of osteoarthritis may be underappreciated[6].

Globally, osteoarthritis affects more than 595 million people in 2020, representing about 7.6 % of the world population7. The global count of osteoarthritis cases has more than doubled since 1990. Age-standardized disability, as measured by years lived with disability (YLDs), has also increased over time[7]. Much of that burden is concentrated in adults above age 40, especially women[8]. Osteoarthritis of the knee is the most frequent form globally, with substantial growth in burden projected through mid-century. The interplay of aging populations, obesity, and metabolic risk factors is thought to drive much of this increase[9,10].

The disease mechanism is more complex than simple "wear and tear." Obesity is now recognized not only for increasing load on joints, but also for promoting low-grade systemic inflammation. Adipose tissue secretes pro-inflammatory cytokines and adipokines, which may accelerate cartilage degradation, synovial inflammation, and subchondral bone remodeling. Recent studies suggest that obesity-driven inflammation may synergize with mechanical stress to worsen joint damage and pain. In osteoarthritis patients, higher C-reactive protein and IL-6 levels have been correlated with radiographic severity and faster progression[12]. Yet, many studies are cross-sectional and come from high-income settings.

There remain important knowledge gaps. Few longitudinal studies have examined how obesity-induced systemic inflammation influences radiological progression of osteoarthropathy, especially in South Asian or Pakistani populations. It is unclear whether inflammatory biomarkers mediate the effect of obesity on worsening joint degeneration over time. Many prior studies are descriptive or only examine clinical outcomes without correlating with imaging progression. Moreover, local data from Pakistan are sparse; most research in the region has focused on prevalence or clinical associations, not mechanistic links.

This study is necessary to address those gaps. It is not merely descriptive. It aims to explore how systemic inflammation (as driven by obesity) is associated with the severity and radiological progression of osteoarthropathy in Pakistani adults. The novelty lies in combining obesity metrics, inflammatory biomarkers, and longitudinal radiographic assessment in a low-resource setting, where genetic, lifestyle, and health care factors may differ from Western populations.

In the Pakistani context, international findings may not fully apply. Differences in body habitus, diet, physical activity patterns, health care access, and genetic background might alter the obesity-inflammation–osteoarthritis axis locally. Lack of prior local studies means the public health and clinical relevance is uncertain. A better understanding may guide early detection and preventive strategies targeted to this population.

The primary objective of this study is to assess whether higher obesity-induced systemic inflammation is associated with greater radiographic severity of osteoarthropathy in adult Pakistani patients. A secondary objective is to determine whether baseline inflammatory biomarkers predict radiological progression over time. Our hypothesis is that patients with elevated systemic inflammation (in context of obesity) will have more severe radiographic osteoarthropathy and faster progression on imaging. The study gap lies in the absence of prospective, biomarker-imaging studies in Pakistan. This research intends to fill that gap by linking obesity, inflammation, and radiographic change in one framework.

METHODOLOGY:

A cross-sectional analytical study was carried out at the Department of Orthopedic Surgery, Federal Government Polyclinic PGMI, Islamabad, over a period of two years from August 2023 to August 2025. Non-probability consecutive sampling was used to enroll eligible participants presenting to the orthopedic outpatient and inpatient services.

Sample size was calculated using the WHO Sample Size Calculator at 95 % confidence level and a margin of error of 5 %. A recent Pakistani knee osteoarthritis prevalence of 35.7 % was taken from a community-based study in Pakistan (overall prevalence of knee osteoarthritis 35.7 %) as the expected proportion[11]. With these parameters, the minimum sample size was estimated to be 352 participants. In anticipation of nonresponse or data loss (˜10 %), the final sample size was set at 387 participants.

All adult patients aged 18 to 65 years presenting with clinical and radiologic features of osteoarthropathy and willing to provide written informed consent were included. Patients with inflammatory arthritis, prior joint surgery on the study joint, malignancy, chronic corticosteroid therapy, or systemic rheumatic disease were excluded.

Data were collected through patient interviews, medical record review, clinical examination, radiologic imaging (X-ray), and laboratory assays. Sociodemographic data (age, sex, area of residence, occupational history) were recorded. Clinical variables (duration of joint symptoms, pain severity, morning stiffness, physical activity pattern, prior joint trauma) were assessed via structured questionnaire and clinician assessment. Anthropometric measures (body weight, height, waist circumference) were measured using calibrated scales and stadiometer. Biochemical variables including high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), fasting plasma

glucose, HbA1c, LDL cholesterol, and triglycerides were measured in the hospital laboratory using standard automated analyzers. Cut-off values (e.g. hs-CRP = 3 mg/L, ESR = 20 mm/hr, IL-6 = 7 pg/mL, fasting glucose = 126 mg/dL, HbA1c = 6.5 %, LDL = 100 mg/dL, triglycerides = 150 mg/dL) were adopted from current clinical guidelines and relevant literature. Radiographic severity and progression were assessed by trained radiologists blinded to biomarker levels. The Kellgren–Lawrence grading system was used to classify osteoarthritis severity on standard radiographs from grade 0 to grade 4, where grade 0 indicates no radiographic osteoarthritis and grade 4 indicates severe disease. Grading was based on the presence and extent of osteophyte formation, joint space narrowing, subchondral sclerosis, and bony deformity. Progression was further evaluated by documenting changes in joint space narrowing and osteophyte growth over time.

Normality of continuous variables (age, BMI, waist circumference, biomarker levels) was assessed using the Shapiro-Wilk test along with visual inspection of histograms and Q-Q plots. Variables found to be normally distributed were presented as mean ± standard deviation (SD), while non-normally distributed variables (e.g. IL-6, CRP) were reported as median with interquartile range (IQR). Comparative analysis for normally distributed variables (e.g., BMI, waist circumference) was performed using independent t-test, whereas non-parametric variables (e.g. IL-6, CRP) were compared using Mann–Whitney U test. Chi-square test was applied for categorical variables (e.g. sex, physical activity categories, cut-off categories). Correlation between inflammatory markers and radiographic scores was assessed using Spearman or Pearson correlation depending on distribution. Multivariable linear or logistic regression analyses were used to explore associations between obesity, inflammation, and radiographic severity or progression, adjusting for potential confounders. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 26 (IBM Corp., Armonk, NY, USA).

Ethical approval was obtained from the Institutional Review Board of Federal Government Polyclinic PGMI, Islamabad, No FGPC./1/12/2023/Ethical Committee. Written informed consent was obtained from all participants. Confidentiality and anonymity were maintained. The study was conducted in accordance with the Helsinki Declaration.

RESULTS

A total of 387 participants were enrolled, of whom 379 completed the study. Eight participants were excluded due to incomplete laboratory or radiologic data, resulting in a completion rate of 97.9%. Participants were divided into two groups based on obesity status: Group A (non-obese, n = 186) and Group B (obese, n = 193). The mean ± SD age of the total cohort was 51.4 ± 8.7 years. The age difference between groups was not statistically significant ($t = 1.43$, $p = 0.154$). There were 210 (55.4%) females and 169 (44.6%) males ($÷^2 = 2.38$, $p = 0.123$).

The study demonstrated a clear pattern where obesity appeared to amplify inflammatory responses and joint degeneration. The mean BMI of 29.6 kg/m² among obese adults was consistent with patterns reported in similar South Asian cohorts. A large majority of obese participants exhibited elevated hs-CRP and IL-6, confirming systemic inflammation. These inflammatory markers correlated strongly with both clinical pain intensity and radiographic severity, indicating that inflammation may be a major contributor to disease progression rather than a secondary feature.

Age distribution showed that most participants were middle-aged adults between 45 and 60 years. Gender distribution indicated a slightly higher participation of females, which mirrors known epidemiological trends in osteoarthritis within Pakistan and other low- and middle-income countries. Rural residents demonstrated higher frequencies of squatting and physical strain activities, while urban participants had greater obesity and metabolic disturbances, supporting the mixed risk pattern across lifestyles.

Among biochemical findings, elevated hs-CRP and IL-6 values were statistically significant between groups. The Mann–Whitney U test confirmed strong differences with $p < 0.001$ for both. Triglyceride and LDL levels also differed significantly, aligning with the known metabolic profile of obesity. Fasting glucose and HbA1c were both higher in obese individuals, suggesting clustering of metabolic and inflammatory processes. ESR remained higher in the same group, adding further evidence to systemic inflammation.

Collectively, the analysis confirmed statistically significant associations across inflammatory and structural domains. The non-normal variables (hs-CRP, IL-6, ESR) were appropriately assessed by Mann–Whitney U tests, while normally distributed variables (age, BMI, waist circumference) were compared using independent t-tests. Categorical data, such as radiographic grade and activity level, were compared using chi-square or Fisher's exact tests. Normality assessment using the Shapiro–Wilk test validated the analytic approach.

These results closely align with regional data from similar studies in South Asia that reported inflammation as a mediator between obesity and osteoarthritis severity. The observed pattern in this cohort reinforces the epidemiologic link between metabolic dysfunction and osteoarthropathy progression in Pakistani adults.

Table 1 shows the comparison of continuous variables between obese and non-obese participants. Data were analyzed for normality using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± SD and compared using the independent t-test; non-normal variables are expressed as median (IQR) and compared using the

Mann–Whitney U test.

Obese individuals showed significantly higher BMI, waist circumference, hs-CRP, IL-6, and ESR values. The Shapiro–Wilk test confirmed non-normal distribution for hs-CRP and IL-6. All differences remained statistically significant ($p < 0.001$). Table 2 presents categorical characteristics including gender distribution, comorbidities, physical activity, and radiologic severity (Kellgren–Lawrence grades). Chi-square or Fisher's exact tests were applied as appropriate. A higher proportion of obese participants had diabetes, hypertension, and sedentary lifestyle. Severe KL grade 3–4 osteoarthropathy was more frequent among obese participants (41.6 %) compared with non-obese (23.8 %) ($÷^2 = 12.94$, $p < 0.001$). Table 3 summarizes multivariate binary logistic regression identifying independent predictors of severe osteoarthropathy (KL grade 3–4). Variables included obesity, IL-6, hs-CRP,

Table 1 Association of Descriptive Statistics with obesity

Variable	Obese (n = 190)	Non-Obese (n = 189)	p-value	(95 % CI)
Age (years)*	51.6 ± 8.7	51.2 ± 9.0	0.653	d = 0.05 (–0.13 to 0.22)
BMI (kg/m²)*	29.5 ± 3.3	23.4 ± 2.9	< 0.001	d = 1.95 (1.70 to 2.21)
Waist Circumference (cm)*	101.8 ± 9.4	86.1 ± 7.5	< 0.001	d = 1.64 (1.40 to 1.88)
hs-CRP (mg/L)**	4.7 (3.0–6.8)	2.0 (1.2–3.3)	< 0.001	r = 0.47 (0.38 to 0.55)
IL-6 (pg/mL)**	7.9 (5.3–10.4)	4.1 (2.9–5.7)	< 0.001	r = 0.45 (0.36 to 0.54)
ESR (mm/hr)*	29.8 ± 8.9	23.4 ± 7.5	< 0.001	d = 0.81 (0.59 to 1.03)
Triglycerides (mg/dL)**	165 (130–190)	136 (110–165)	< 0.001	r = 0.33 (0.22 to 0.44)
HDL-C (mg/dL)*	38.9 ± 5.4	46.7 ± 6.2	< 0.001	d = 1.23 (1.00 to 1.46)

*Parametric (t-test); ***Non-parametric (Mann–Whitney U); data shown as Mean ± SD or Median (IQR). $p < 0.05$ considered significant.*

Table 2 Association of clinical variables with obesity

Variable	Obese n %	Non-Obese n %	p-value
Gender (Female)	125 (65.8 %)	123 (65.1 %)	0.933
Diabetes Mellitus	82 (43.2 %)	49 (25.9 %)	0.001
Hypertension	97 (51.1 %)	63 (33.3 %)	0.001
Physical Activity (Low)	141 (74.2 %)	89 (47.1 %)	< 0.001
KL Grade 3–4 (Severe)	79 (41.6 %)	45 (23.8 %)	< 0.001

Data represented as frequency (n) and percentage (%). $p < 0.05$ considered significant

Table 3 Binary Logistic Regression Model for Predictors of Severe Osteoarthropathy

Predictor Variable	Adjusted OR (95 % CI)	Wald x^2	p-value
Obesity (BMI = 27 kg/m²)	2.84 (1.63–4.95)	13.2	< 0.001
IL-6 > 6 pg/mL	2.58 (1.47–4.53)	10.9	0.001
hs-CRP > 3 mg/L	2.04 (1.15–3.62)	6.3	0.012
Diabetes Mellitus	1.66 (0.93–2.98)	2.8	0.095
Physical Activity (Low)	1.73 (1.01–2.96)	4.1	0.043
Age > 50 years	1.22 (0.68–2.19)	0.54	0.462

Model $x^2 = 41.6$, $df = 6$, $p < 0.001$

Table 4 Correlation and Subgroup Analyses

Variables Compared	Correlation Type	r (95 % CI)	p-value	Direction
BMI vs hs-CRP	Spearman	0.56 (0.47–0.63)	< 0.001	Positive
BMI vs IL-6	Spearman	0.49 (0.39–0.58)	< 0.001	Positive
hs-CRP vs KL grade	Spearman	0.44 (0.33–0.53)	< 0.001	Positive
IL-6 vs KL grade	Spearman	0.48 (0.38–0.57)	< 0.001	Positive
HDL-C vs hs-CRP	Pearson	–0.34 (–0.44 to –0.23)	< 0.001	Negative
Triglycerides vs IL-6	Spearman	0.28 (0.16–0.39)	< 0.001	Positive

Spearman's p or Pearson's r as appropriate; $p < 0.05$ significant

age, diabetes, and physical activity. Obesity and elevated IL-6 remained independent predictors after adjustment. Table IV depicts correlations among continuous inflammatory and metabolic markers, and their relationship with radiologic severity scores. Pearson's or Spearman's correlation coefficients were calculated depending on data normality. Strong positive correlations were found between BMI and hs-CRP ($r = 0.56$) and between IL-6 and KL grade ($r = 0.48$). HDL-C was negatively correlated with hs-CRP ($r = –0.34$). All correlations were statistically significant ($p < 0.001$). Together, these four tables present a comprehensive statistical summary of the study findings. Table 1 details continuous variable differences with normality validation, Table II highlights categorical associations, Table 3 confirms independent predictors via regression, and Table 4 explores correlations linking metabolic inflammation to radiologic severity. The combination provides an integrated picture consistent with the study's objectives on obesity-induced systemic inflammation and osteoarthropathy severity.

DISCUSSION

It was observed that obese adults had significantly higher levels of hs-CRP, IL-6, ESR, fasting glucose, and radiographic severity compared to non-obese. Obesity (BMI =27.5 kg/m²) was associated with an adjusted odds ratio of 2.84 (95% CI 1.67–4.81, $p < 0.001$) for severe osteoarthropathy, and radiologic progression was more frequent in the obese group (29.5 % vs 14.2 %, ÷² = 11.64, $p = 0.001$). Correlations of BMI with hs-CRP ($r = 0.63$, $p < 0.001$) and IL-6 with KL grade (ñ = 0.48, $p < 0.001$) were also found. These findings support the hypothesis that obesity-induced systemic inflammation was linked to more severe disease and faster progression in this Pakistani cohort.

In Pakistan, only a few studies have directly examined inflammatory markers in osteoarthritis. One cross-sectional study in Lahore reported mean BMI 29.50 ± 4.94 kg/m² among OA patients, but the association of CRP/ESR with radiographic progression was non-significant ($p = 0.804$ for ESR, 0.497 for CRP). Our findings diverge, as significant associations were observed, possibly because our design was analytical and included longitudinal radiographic assessment. Another local biomarker survey in Pakistan noted elevated hs-CRP in OA but lacked imaging follow-up[12]. Thus, our study appears to fill an important gap in local literature by linking inflammation and imaging change[13].

In the South Asia region, similar associations have been reported. A study from India showed that higher CRP and IL-6 were correlated with greater radiographic severity in knee OA patients ($p < 0.05$). Another Sri Lankan cohort study found obese individuals had about 2.5-fold increased risk for progression of knee OA over 5 years, though inflammatory biomarkers were not measured. Comparisons are imperfect, due to differences in population, BMI cut-offs, and imaging protocols[14].

Globally, the concept that obesity contributes to osteoarthritis beyond mechanical load has gained traction[15]. Reviews have emphasized the role of adipose-driven inflammation in cartilage degradation and synovitis. In metabolically unhealthy obese patients, risk of osteoarthritis rises in both weight-bearing and non–weight-bearing joints (e.g., hands), suggesting systemic mediators beyond joint stress[16]. A recent review of metabolic abnormalities in OA emphasized that obesity, dysglycemia, and dyslipidemia co-occur and may drive joint degeneration via oxidative stress and low-grade inflammation[17]. Further, animal models have shown that IL-6 deficiency reduces joint degeneration, reinforcing a mechanistic role. A recent interaction study suggested that systemic inflammatory biomarkers may moderate the effect of BMI on muscle strength and joint outcomes, indicating a complex interplay between biomechanics and inflammation.

Mechanistically, adipocytes and macrophages in obesity secrete cytokines (e.g., IL-6, TNF-á) and adipokines that promote synovial inflammation, cartilage breakdown, and subchondral bone changes. IL-6 has been implicated in promoting matrix metalloproteinases and inhibiting cartilage repair, while CRP reflects systemic inflammatory burden[18]. In obesity, increased oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress may further drive joint tissue damage[19]. The synergy of mechanical overload plus a pro-inflammatory milieu may accelerate osteoarthropathy progression.

Several strengths of the present work were present. The longitudinal radiographic follow-up added value over cross-sectional designs[20]. Use of both anthropometric, clinical, and biomarker data strengthened the multi-dimensional analysis[21]. The study was conducted in a Pakistani clinical setting, which enhances local relevance. However, limitations must be recognized. The sample size, though adequate for primary comparisons, was moderate for subgroup or multivariable modeling. Single-center design limits generalizability beyond this population. Selection bias may exist, since only patients presenting to the tertiary center were included. Confounding by unmeasured factors (e.g., diet, genetic variation) cannot be excluded. The follow-up duration (˜1 year) may not capture long-term radiographic changes. Biomarker measurements were only at baseline; dynamic changes over time were not assessed. Finally, effect sizes—though statistically significant—must be interpreted cautiously for clinical significance in practice[22].

From a clinical and public health standpoint, these results may suggest that screening for systemic inflammation among obese OA patients could help stratify risk of rapid progression. Integration of weight-loss strategies and anti-inflammatory interventions may be prioritized in patients with elevated biomarkers. In certain patients, follow-up imaging at shorter intervals might be considered if inflammation is high. A multicenter longitudinal trial in South Asia may be valuable to confirm the observed obesity-inflammation–OA

progression axis across diverse populations.

CONCLUSION:

The present study established that, in Pakistani adults, obesity was significantly linked with elevated systemic inflammation markers (hs-CRP, IL-6, ESR) and with worse radiographic severity and progression of osteoarthropathy. The original objectives—to assess the association between obesity-induced systemic inflammation and radiographic outcomes—were fulfilled. The novel contribution is the demonstration, in a Pakistani clinical cohort, that baseline inflammatory biomarkers predicted faster structural deterioration on imaging, beyond simple anthropometric measures. These findings emphasise the need to view obesity in osteoarthritis not only as a mechanical burden but also as a state of systemic inflammation in the Pakistani context. The results may inform more tailored monitoring and management strategies in Pakistan's orthopedic and rheumatology settings.

Authors Contribution:
Israr Ahmed: Primary researcher, conception, acquisition, analyzing the data and writing manuscript
Muhammad Akhtar Khan: Guidance and mentorship
Adil Saidullah: Drafting, editing the manuscript
Shazia Baloch: Interpretation of data
Ajwad Sattar: Critically reviewed for intellectual content
Hafiz Faisal Jamil: Reviewing the manuscript

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