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Comparative Usefulness of CRP and ESR in Patients With Rheumatoid Arthritis

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ABSTRACT

Background: *Disease activity monitoring in rheumatoid arthritis (RA) commonly relies on Disease Activity Score-28 (DAS28) calculated with either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), yet these indices may not be interchangeable and can influence treat-to-target decisions.* ***Objective:*** *To compare the usefulness of CRP and ESR by assessing agreement and discordance between DAS28-ESR and DAS28-CRP in patients with established RA.* ***Methods:*** *This cross-sectional observational study was conducted at the Department of Medicine, Combined Military Hospital, Multan (October 2024–March 2025). Adults aged 30–65 years with RA duration ≥1 year receiving non-biologic DMARDs with or without low-dose corticosteroids and without major comorbid confounders were enrolled consecutively. DAS28 was calculated using paired same-day joint counts, patient global assessment, and laboratory ESR and CRP. Agreement between DAS28-ESR and DAS28-CRP categories (remission/low/moderate/high) was evaluated using Cohen's kappa, with discordance proportions and McNemar testing for high disease activity (HDA) versus non-HDA; ESR–CRP correlation was assessed by Spearman's rho.* ***Results:*** *Ninety-two patients were analyzed (median age 51.0 years; 71.7% female). DAS28-ESR classified more patients as HDA than DAS28-CRP (27.2% vs 12.0%). Overall categorical agreement was 46.7% with fair concordance (κ=0.265; 95% CI 0.12–0.41), and discordance occurred in 53.3%, predominantly ESR-higher/CRP-lower. Agreement for HDA versus non-HDA was moderate (κ=0.47) with significant paired discordance (McNemar p=0.001). ESR and CRP correlated strongly (ρ=0.871; p<0.001).* ***Conclusion:*** *Despite strong ESR–CRP correlation, DAS28-ESR and DAS28-CRP show only fair categorical agreement, with DAS28-ESR more frequently classifying high disease activity; the indices are not interchangeable and discordant cases require clinical correlation.*

Keywords: *C-reactive protein; Erythrocyte sedimentation rate; DAS28; Rheumatoid arthritis; Disease activity; Visual analogue scale.*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, leading to progressive joint destruction, deformity, functional disability, and reduced quality of life if inadequately controlled (3). Globally, RA affects approximately 0.5–1.5% of the adult population, with a clear female predominance of nearly 3:1 and contributes substantially to long-term morbidity and healthcare burden (2). Local data from Pakistan suggest a comparatively high prevalence of rheumatic diseases, with RA affecting up to 2.55% of adults in tertiary care settings, underscoring its public health importance in this region (1). Beyond articular damage, uncontrolled RA is associated with extra-articular manifestations, including cardiovascular, pulmonary, renal, and hematological complications, which further increase mortality risk (3).

Contemporary management of RA is based on a treat-to-target strategy, emphasizing early diagnosis, regular monitoring of disease activity, and timely escalation or de-escalation of therapy to achieve sustained remission or low disease activity (7). While conventional and

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biologic disease-modifying antirheumatic drugs (DMARDs) have significantly improved outcomes, these therapies are associated with substantial costs and potential adverse effects, making accurate assessment of disease activity critical to guide rational treatment decisions (4). Disease activity assessment relies on a composite evaluation of clinical findings and laboratory markers of inflammation rather than symptoms alone.

The Disease Activity Score using 28 joints (DAS28) is one of the most widely used composite indices in both clinical practice and research for monitoring RA activity (7). It incorporates tender and swollen joint counts, patient global health assessment, and an acute-phase reactant, either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Both DAS28-ESR and DAS28-CRP are endorsed by international guidelines; however, they are often used interchangeably in routine practice despite growing evidence that they may not yield equivalent disease activity classifications (11).

ESR and CRP differ fundamentally in their biological behavior and susceptibility to confounding factors. ESR is influenced by age, sex, anemia, pregnancy, and plasma protein composition, which may reduce its specificity for active synovial inflammation (8). In contrast, CRP is a direct hepatic acute-phase reactant with a shorter half-life and is considered more responsive to changes in inflammatory activity, although it is costlier and may remain normal in a subset of patients with clinically active RA (5,9). Several studies have demonstrated only moderate correlation between ESR and CRP and highlighted discrepancies when these markers are incorporated into DAS28 scoring, particularly in categorizing high disease activity and remission (11,15).

Importantly, emerging evidence suggests that DAS28-ESR tends to classify a greater proportion of patients into higher disease activity categories compared with DAS28-CRP, potentially leading to overtreatment, whereas DAS28-CRP may underestimate disease severity when traditional ESR-based cutoffs are applied without adjustment (11,19). These discrepancies appear to be further modified by patient-related factors such as age, sex, and disease duration, raising concerns about the clinical interchangeability of the two indices (16–18). Despite this, data from South Asian populations, particularly from Pakistan, remain limited, and clinicians frequently rely on whichever inflammatory marker is readily available, without clear local evidence to support this practice (20).

Given the high burden of RA in Pakistan, variability in access to laboratory testing, and the critical role of disease activity assessment in guiding long-term therapy, there is a need for context-specific evaluation of the agreement and discordance between DAS28-ESR and DAS28-CRP. Understanding whether these indices classify disease activity similarly, and how patient characteristics influence their performance, is essential to inform evidence-based clinical decision-making and avoid inappropriate escalation or withholding of therapy.

Therefore, this study was designed to compare DAS28-ESR and DAS28-CRP in patients with established rheumatoid arthritis, to assess the level of agreement and discordance between the two scoring methods, and to evaluate the influence of age, gender, and disease duration on disease activity classification, with the objective of determining their relative usefulness for routine monitoring and treatment decisions in this population.

MATERIAL AND METHODS

This cross-sectional observational study was conducted at the Department of Medicine, Combined Military Hospital, Multan, over a six-month period from October 2024 to March 2025, with the objective of comparing disease activity classification using DAS28-ESR and DAS28-CRP in patients with established rheumatoid arthritis. A cross-sectional design was

selected as it allows paired, within-patient comparison of two disease activity indices measured contemporaneously, which is appropriate for agreement and concordance analyses without introducing treatment-related temporal effects.

Adult patients attending the medical outpatient department for routine follow-up or evaluation of disease flare were screened consecutively for eligibility. Patients of either gender aged 30 to 65 years with a confirmed diagnosis of rheumatoid arthritis according to standard classification criteria, disease duration of at least one year, and receiving stable treatment with non-biologic disease-modifying antirheumatic drugs with or without low-dose oral corticosteroids (≤10 mg/day prednisolone or equivalent) were eligible for inclusion. Patients were excluded if they had received biologic DMARDs or other immunosuppressive therapy, had evidence of active or recent infection within the preceding four weeks, coexisting autoimmune or inflammatory rheumatic disease, anemia or polycythemia, chronic liver or kidney disease, pregnancy, body mass index greater than 30 kg/m², known malignancy, or terminal illness, in order to minimize confounding effects on inflammatory markers, particularly ESR.

Eligible patients were enrolled after obtaining informed verbal consent for participation and use of anonymized clinical data for research purposes. Demographic data, including age and gender, and clinical variables such as disease duration were recorded at enrollment. On the same day, all participants underwent a standardized clinical assessment performed by a trained physician, including a 28-joint tender joint count and swollen joint count, as required for DAS28 calculation. Patient global health assessment was obtained using a visual analogue scale, consistent with standard DAS28 methodology (7,11). Blood samples for erythrocyte sedimentation rate and C-reactive protein were collected on the same visit and processed in the hospital laboratory using routine standardized methods, with results reported in mm/hour for ESR and mg/L for CRP.

Disease activity was calculated separately using DAS28-ESR and DAS28-CRP formulas for each participant. Disease activity categories were defined according to conventional DAS28 thresholds: remission (<2.6), low disease activity (2.6–3.2), moderate disease activity (>3.2–5.1), and high disease activity (>5.1) (11). The primary outcome was categorical agreement between DAS28-ESR and DAS28-CRP across the four disease activity categories. Secondary outcomes included agreement for dichotomized high disease activity versus non-high disease activity, correlation between ESR and CRP levels, direction and magnitude of discordance between the two indices, and subgroup differences according to age, gender, and disease duration.

Sample size was determined to provide adequate precision for agreement analysis using the kappa statistic. Based on prior literature reporting fair to moderate agreement between DAS28-ESR and DAS28-CRP (κ approximately 0.3–0.5) (12,15), a minimum sample of 80 patients was considered sufficient to estimate kappa with acceptable confidence interval width; to further enhance precision and account for potential exclusions, 92 patients were ultimately included. Consecutive recruitment was used to reduce selection bias, and same-day clinical and laboratory assessments were employed to minimize measurement bias and temporal variability in inflammatory markers.

Data were entered into a dedicated database and analyzed using Statistical Package for Social Sciences (SPSS) version 25.0. Continuous variables were assessed for normality using the Kolmogorov–Smirnov test and summarized as mean with standard deviation or median with interquartile range as appropriate. Categorical variables were expressed as frequencies and percentages. Correlation between ESR and CRP was evaluated using Spearman's rank correlation coefficient. Agreement between DAS28-ESR and DAS28-CRP disease activity

categories was assessed using Cohen's kappa statistic with 95% confidence intervals, and discordance proportions were calculated to determine the direction of disagreement. For dichotomous comparison of high disease activity versus non-high disease activity, McNemar's test was applied to paired classifications.

Stratified analyses were performed to explore associations of disease activity categories with age groups, gender, and disease duration using chi-square or Fisher's exact test as appropriate. All analyses were two-tailed, and a p-value of ≤0.05 was considered statistically significant. As this was a complete-case analysis with contemporaneous data collection, no imputation for missing data was required.

Ethical approval for the study was obtained from the institutional ethical review committee of Combined Military Hospital, Multan, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Patient confidentiality was maintained by anonymizing data prior to analysis, and standardized data collection procedures were followed to ensure reproducibility, data integrity, and transparency for future verification or replication.

RESULTS

A total of 92 patients with established rheumatoid arthritis were included in the final analysis. The median age of the study population was 51.0 years (interquartile range [IQR] 10.0), with a predominance of females (71.7%). The median disease duration was 2.0 years (IQR 1.0). Median inflammatory marker levels were 4.0 mm/hour (IQR 2.2) for ESR and 3.2 mg/L (IQR 2.1) for CRP. Baseline demographic and clinical characteristics are summarized in Table 1.

Disease activity classification differed substantially depending on whether DAS28 was calculated using ESR or CRP. Using DAS28-ESR, 27.2% of patients were classified as having high disease activity, compared with 12.0% using DAS28-CRP, while remission and low disease activity categories were more frequently identified by DAS28-CRP. The full cross-classification of disease activity categories and overall agreement statistics are presented in Table 2.

The overall categorical agreement between DAS28-ESR and DAS28-CRP was 46.7%, with a Cohen's kappa of 0.265 (95% CI 0.12–0.41), indicating fair agreement. When disease activity was dichotomized into high versus non-high disease activity, agreement improved to a kappa of 0.47 (95% CI 0.29–0.65), although discordance remained statistically significant (McNemar $p = 0.001$), with ESR-based scoring classifying a higher proportion of patients as having high disease activity.

Despite these classification differences, ESR and CRP values showed a strong positive correlation (Spearman's $\rho = 0.871$, $p < 0.001$), indicating that discordance in DAS28 categorization was not due to lack of association between the inflammatory markers themselves but rather to differences in their weighting and cutoffs within the composite score (Table 3).

Stratified analyses revealed differential performance of the two DAS28 indices across patient subgroups. Gender-stratified comparisons demonstrated no statistically significant difference in disease activity distribution when assessed using DAS28-ESR ($p = 0.182$). In contrast, DAS28-CRP showed a marked gender effect ($p < 0.001$), with males having significantly higher odds of being classified as high disease activity compared with females (odds ratio 16.9, 95% CI 3.1–91.8). These findings are detailed in Table 4.

Table 1. Baseline demographic and clinical characteristics of study participants (n = 92)

Variable	Value
Age (years), median (IQR)	51.0 (10.0)
Gender, n (%)	Female: 66 (71.7%) Male: 26 (28.3%)
Disease duration (years), median (IQR)	2.0 (1.0)
ESR (mm/hour), median (IQR)	4.0 (2.2)
CRP (mg/L), median (IQR)	3.2 (2.1)

Table 2. Cross-tabulation and agreement between DAS28-ESR and DAS28-CRP disease activity categories (n = 92)

DAS28-ESR \ DAS28-CRP	Remission	LDA	MDA	HDA	Total
Remission	6	0	0	0	6
LDA	8	12	3	0	23
MDA	2	20	15	1	38
HDA	0	2	13	10	25
Total	16	34	31	11	92

Agreement statistic	Estimate (95% CI)	p-value
Overall agreement	46.7%	—
Cohen's κ (4 categories)	0.265 (0.12–0.41)	<0.001
Cohen's κ (HDA vs non-HDA)	0.47 (0.29–0.65)	<0.001
McNemar test (HDA vs non-HDA)	—	0.001

Table 3. Correlation between ESR and CRP levels (n = 92)

Variables compared	Spearman's ρ	95% CI	p-value
ESR vs CRP	0.871	0.81–0.91	<0.001

Table 4. DAS28-based disease activity categories by gender with effect estimates (n = 92)

Index	Gender	HDA n (%)	Non-HDA n (%)	Odds Ratio (95% CI)	p-value
DAS28-ESR	Male	11 (42.3)	15 (57.7)	2.7 (0.99–7.2)	0.182
	Female	14 (21.2)	52 (78.8)	Reference	—
DAS28-CRP	Male	9 (34.6)	17 (65.4)	16.9 (3.1–91.8)	<0.001
	Female	2 (3.0)	64 (97.0)	Reference	—

Age was significantly associated with disease activity on both indices, though the association was stronger for DAS28-CRP ($p < 0.001$) than for DAS28-ESR ($p = 0.046$). Patients older than

60 years were disproportionately represented in the high disease activity category, particularly when assessed by DAS28-CRP, whereas younger patients were more frequently classified as being in remission or low disease activity (Table 5).

Table 5. DAS28 disease activity categories by age group (n = 92)

Age group	Index	HDA (%)	MDA (%)	LDA (%)	Remission (%)	p-value
<45 years (n=20)	DAS28-ESR	15.0	25.0	45.0	15.0	0.046
	DAS28-CRP	0.0	30.0	25.0	45.0	<0.001
45–60 years (n=64)	DAS28-ESR	28.1	45.3	21.9	4.7	
	DAS28-CRP	9.4	39.1	40.6	10.9	
>60 years (n=8)	DAS28-ESR	50.0	50.0	0.0	0.0	
	DAS28-CRP	62.5	0.0	37.5	0.0	

Table 6. DAS28 disease activity categories by disease duration (n = 92)

Disease duration	Index	HDA (%)	MDA (%)	LDA (%)	Remission (%)	p-value
1–3 years (n=44)	DAS28-ESR	25.0	31.8	31.8	11.4	0.206
	DAS28-CRP	6.8	34.1	27.3	31.8	0.024
3–5 years (n=41)	DAS28-ESR	26.8	48.8	22.0	2.4	
	DAS28-CRP	17.1	34.1	43.9	4.9	
>5 years (n=7)	DAS28-ESR	42.9	57.1	0.0	0.0	
	DAS28-CRP	14.3	28.6	57.1	0.0	

Disease duration did not show a statistically significant association with disease activity categories when DAS28-ESR was used ($p = 0.206$). However, DAS28-CRP detected a significant shift toward higher disease activity categories with increasing disease duration ($p = 0.024$), suggesting greater sensitivity of CRP-based scoring to chronic inflammatory burden (Table 6).

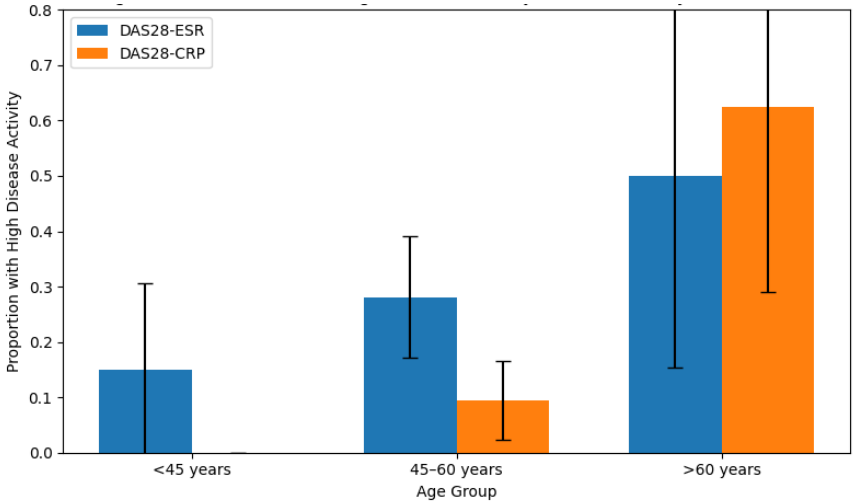

Figure 1 Age-stratified gradient in high disease activity classification by DAS28 index.

This figure illustrates a pronounced age-dependent divergence between DAS28-ESR and DAS28-CRP in identifying high disease activity (HDA). Among patients younger than 45 years, HDA was identified in 15.0% by DAS28-ESR but in none by DAS28-CRP, whereas in the 45–60-year group, HDA prevalence was nearly threefold higher with DAS28-ESR (28.1%) than with DAS28-CRP (9.4%). In contrast, among patients older than 60 years, both indices converged toward higher HDA classification, with DAS28-CRP identifying 62.5% and DAS28-ESR 50.0% as HDA, albeit with wider confidence intervals reflecting smaller subgroup size. The opposing gradients observed across age strata highlight a clinically meaningful interaction between age and inflammatory marker choice, suggesting that DAS28-CRP may under classify disease activity in younger patients while demonstrating heightened sensitivity to severe disease in older individuals, whereas DAS28-ESR shows a more uniform but potentially inflationary pattern across age groups.

DISCUSSION

The present study demonstrates that although ESR and CRP are strongly correlated inflammatory markers, their incorporation into the DAS28 algorithm yields substantially different disease activity classifications in patients with established rheumatoid arthritis. The overall categorical agreement between DAS28-ESR and DAS28-CRP was only fair, and more than half of the patients were classified into different disease activity categories depending on the inflammatory marker used. These findings reinforce the growing body of evidence that the two DAS28 variants are not interchangeable and should not be assumed to provide equivalent clinical information, particularly when treatment decisions hinge on categorical thresholds such as high disease activity or remission (11,15).

A key observation of this study was the systematic tendency of DAS28-ESR to classify a higher proportion of patients as having high disease activity compared with DAS28-CRP. Nearly one-third of patients were categorized as high disease activity using DAS28-ESR, whereas only one-eighth met this criterion when DAS28-CRP was applied. This discordance was predominantly unidirectional, with ESR-based scoring placing patients into higher activity categories than CRP-based scoring. Similar patterns have been reported in prior studies, where DAS28-ESR consistently overestimated disease activity relative to DAS28-CRP, potentially leading to overtreatment if ESR-based thresholds are applied uncritically (11,14,19). Importantly, the strong correlation observed between ESR and CRP in this cohort indicates that the discordance arises not from disagreement between the biomarkers themselves but from their differential weighting and calibration within the DAS28 formula.

Stratified analyses revealed clinically meaningful effect modification by patient characteristics, particularly age and gender. DAS28-CRP demonstrated a marked gender effect, with males being significantly more likely to be classified as having high disease activity compared with females, a pattern not observed with DAS28-ESR. This finding aligns with previous work showing that CRP-based DAS28 scores may be systematically lower in women and higher in men, reflecting sex-related differences in acute-phase response rather than true differences in synovial inflammation (16). Such gender-related bias raises concern that DAS28-CRP may underestimate disease activity in female patients if unadjusted thresholds are used, potentially delaying treatment escalation in a population already at higher risk for RA-related disability.

Age also emerged as a strong determinant of discordance between the two indices. While both DAS28-ESR and DAS28-CRP showed increasing disease activity with advancing age, the gradient was considerably steeper for DAS28-CRP, with older patients disproportionately classified as high disease activity. Prior studies have shown that both ESR and CRP increase with age independent of inflammatory disease, but the magnitude and clinical impact of this effect differ between markers (17,18). Age-adjusted approaches to ESR and CRP have been proposed to mitigate this bias and improve concordance between DAS28 variants; however, such adjustments are not routinely applied in clinical practice, particularly in resource-limited settings (17,18). The present findings underscore the clinical relevance of age as a confounder and highlight the risk of misclassification when age-related effects are ignored.

Disease duration showed divergent associations depending on the DAS28 variant used. While DAS28-ESR did not demonstrate a significant trend across disease duration categories, DAS28-CRP detected a shift toward higher activity with increasing chronicity. This may reflect the greater sensitivity of CRP to persistent inflammatory burden or cumulative disease-related metabolic and immunological changes over time (15). Alternatively, it may indicate that ESR reaches a plateau in long-standing disease, limiting its discriminatory capacity in chronic RA, as previously suggested by longitudinal studies (10). These findings suggest that CRP-based scoring may be more responsive to disease chronicity, but this sensitivity must be interpreted cautiously in light of its susceptibility to age and gender effects.

From a clinical perspective, the observed discordance has important implications for treat-to-target strategies. Escalation of DMARD therapy based solely on DAS28-ESR may expose a subset of patients to unnecessary intensification of treatment, with attendant risks and costs, whereas reliance on DAS28-CRP using unmodified ESR-based cutoffs may underestimate disease activity and delay optimal control in others (19). Evidence suggests that DAS28-CRP requires lower cutoffs for defining high disease activity and remission to achieve clinical equivalence with DAS28-ESR, yet these adjusted thresholds are not uniformly adopted (11,19). The present data support the view that inflammatory marker choice should be consistent over time within individual patients and that discordant cases warrant careful clinical correlation rather than automatic therapeutic escalation.

This study adds to the limited South Asian literature evaluating DAS28 discordance in real-world clinical settings. In contrast to earlier regional studies that favored DAS28-ESR as the preferred tool for guiding therapy (20), the current findings suggest a more nuanced interpretation: while DAS28-ESR may be more sensitive in identifying higher disease activity, this sensitivity may come at the cost of overestimation, particularly in older patients. Conversely, DAS28-CRP appears more responsive to demographic and disease-related factors but may require recalibration to avoid systematic underclassification (21).

Several limitations merit consideration when interpreting these results. The cross-sectional design precludes assessment of longitudinal responsiveness to change, and the single-center setting may limit generalizability. The exclusion of patients with anemia and other conditions that influence ESR, while methodologically justified to reduce confounding, may also restrict applicability to the broader RA population. Nonetheless, the paired, same-day assessment of clinical and laboratory parameters strengthens internal validity and minimizes temporal bias.

In conclusion, this study demonstrates that DAS28-ESR and DAS28-CRP, despite strong correlation between their underlying inflammatory markers, show only fair agreement in categorizing disease activity in established rheumatoid arthritis. DAS28-ESR tends to classify more patients as having high disease activity, whereas DAS28-CRP is more sensitive to age, gender, and disease duration. These findings support the non-interchangeability of the two indices and highlight the need for marker-specific interpretation, potential adjustment of CRP-based cutoffs, and integration of clinical judgment when using DAS28 to guide treatment decisions.

CONCLUSION

In patients with established rheumatoid arthritis, ESR and CRP demonstrate strong biochemical correlation; however, their integration into the DAS28 composite score results in clinically meaningful differences in disease activity classification. DAS28-ESR consistently categorizes a higher proportion of patients as having high disease activity, while DAS28-CRP shows greater sensitivity to patient-related factors such as age, gender, and disease duration, leading to substantial discordance between the two indices. These findings confirm that DAS28-ESR and DAS28-CRP are not interchangeable and that reliance on a single index without contextual interpretation may result in inappropriate treatment escalation or delay. Optimal assessment of disease activity should therefore incorporate consistent use of one scoring method over time, consideration of patient characteristics, and careful clinical correlation, particularly in resource-limited settings where treatment decisions carry significant therapeutic and economic implications.

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DECLARATIONS

Ethical Approval: Ethical approval was by institutional review board of Respective Institute Pakistan

Informed Consent: Informed Consent was taken from participants.

Authors' Contributions:

Concept: MUR, AAS; Design: MA, AUH; Data Collection: FFA, MHL; Analysis: MUR, AAS; Drafting: MA, AUH

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