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ORIGINAL ARTICLE

Outcome of Ibrutinib in chronic lymphocytic leukemia-Real world experience from a developing country.

Kubra Razzaq[1], Quratulain Rizvi[2], Aisha Jamal[3], Aisha Arshad[4], Laraib Majeed[5], Nida Anwar[6]

ABSTRACT… Objective: To evaluate the efficacy and safety of ibrutinib, a bruton tyrosine kinase inhibitor, in previously untreated or relapsed/refractory CLL patients from Pakistan. **Study Design:** Cross-sectional study. **Setting:** National Institute of Blood Diseases and Bone Marrow Transplantation. **Period:** January 2023 to December 2024. **Methods:** A total of 35 CLL patients were included in the study. Patients were administered 420 mg of oral ibrutinib daily until disease progression or emergence of intolerable side effects. Descriptive analysis was calculated as means and percentages using the statistical package for the social sciences version 23.0. Survival analysis was performed using the Kaplan-Meier method. **Results:** The median age of the patient was 56 years. Del17p was detected in eight patients (22.9%). The median follow-up period in patients receiving ibrutinib as first line therapy was 29 months while it was 41 months in relapsed/refractory group. Results showed an overall response rate of 50% for first-line ibrutinib therapy and 45.5% for second-line treatment. Median overall survival could not be established. Hematologic recovery was observed in patients with pre-existing cytopenia(s). Grade 3–4 hematological toxicities were neutropenia, thrombocytopenia, and anemia. **Conclusion:** The study demonstrated the safety and efficacy of ibrutinib in Pakistani CLL patients, both as first-line and subsequent therapy.

Key words: Bruton Tyrosine Kinase Inhibitors (BTKi), Chronic Lymphocytic Leukemia (CLL), Hematologic Parameters, IBRUTINIB, Overall Response Rate.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is one of the prevailing forms of leukemia observed in adults residing in western countries and has an annual incidence rate of 4-6 cases per 100,000 individuals.[1,2] The majority of patients diagnosed with CLL are aged 65 years and above, with a higher incidence observed in men as compared to women with a ratio of 1.7:1.[2]

In the past, chemo-immunotherapy (CIT) was the conventional approach for treating CLL, with the combination of fludarabine and cyclophosphamide along with rituximab (FCR) being the most potent treatment option for patients deemed appropriate for intensive treatment.(1-5) However, with the emergence of therapeutic strategies that specifically target kinases linked to the B-cell receptor (BCR) pathway, particularly the Bruton tyrosine kinase inhibitors (BTKi) have brought about a significant transformation in the prognosis for individuals diagnosed with CLL.[1,3,5] BCR signaling plays a pivotal role in the onset, progression, and sustenance of these disorders.[3,5] This approach has not only enhanced progression-free survival (PFS) but has also been shown to be promising in certain investigations by enhancing the overall survival (OS) rate.[1,2,4,5]

Ibrutinib, a novel BTK inhibitor, was the first of its kind to effectively hinder BCR signaling in CLL cells by forming a covalent bond with a cysteine-481 amino acid within the active site of BTK.[3,5-9] Ibrutinib, administered orally as a single agent, has proven to be the most effective treatment for patients with symptomatic CLL patients.[7,8] Its efficacy is particularly pronounced in those who have experienced treatment failure with prior CIT, as well as in patients receiving it as a primary treatment strategy.[4,6-9]

1. MBBS, Resident Clinical Hematology, National Institute of Blood Diseases and Bone Marrow Transplantation.
2. MBBS, FCPS, Assistant Professor, National Institute of Blood Diseases and Bone Marrow Transplantation,
3. MBBS, FCPS, Assistant Professor, National Institute of Blood Diseases and Bone Marrow Transplantation,
4. Ph.D (Hematology), Hematologist, National Institute of Blood Diseases and Bone Marrow Transplantation,
5. B.S (Biochemistry), Clinical Research Associate, National Institute of Blood Diseases and Bone Marrow Transplantation,
6. MBBS, FCPS, FRCP (UK), FRCPath (UK), Professor, Consultant Hematologist, National Institute of Blood Diseases and Bone Marrow Transplantation,
Correspondence Address:
Dr. Nida Anwar
Plot #Special D-3 Block 6 PECHS, Karachi, 75400, Sindh, Pakistan.
drnidairfan@yahoo.com

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Regardless of high-risk genomic features such as complex karyotype, like del (17p) or TP53 mutations, del(11q), and/or unmutated IGHV in the RESONATE-2 trial, which evaluated Ibrutinib as a first-line single-agent therapy, patients treated with ibrutinib experience clinically significant and long-lasting responses.[3,5-7] Likewise, the iLLUMINATE study investigating first-line ibrutinib combined with obinutuzumab demonstrated favorable outcomes.

The efficacy of single-agent ibrutinib was found to be superior to that of ofatumumab in the phase 3 Study of Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia.[4,6,7,9]

In phase III RESONATE-2 trial, the efficacy of ibrutinib monotherapy was found to be superior to that of chlorambucil in the initial treatment of elderly patients with CLL/SLL.[6,7,9]

Moreover, the current knowledge regarding the long-term effects of ibrutinib has provided a comprehensive understanding of its toxicity profile which includes cardiac arrhythmias especially atrial fibrillation, bleeding, infections, diarrhea, arthralgia, and hypertension that hold clinical significance.[7-9]

Nevertheless, as most studies on ibrutinib outcomes and toxicity have been conducted in the developed countries and very limited data from developing countries is available, the objective of this study was to evaluate the efficacy and safety of single-agent ibrutinib in previously untreated or relapsed/refractory CLL patients from Pakistan.

METHODS

This cross-sectional study was conducted at the National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, Pakistan. A total of 35 CLL patients were enrolled in the study from January 2023 to December 2024.The study was approved by the Institutional Review Board (IRB) (NIBD/IRB-284/14-2023). All participants were presented with a comprehensive overview of the research and provided written consent for the collection and analysis of data.

Inclusion Criteria

The study included individuals aged ≥18 years who were diagnosed with CLL according to the WHO criteria. An Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, an absolute neutrophil count of at least 1000 cells/mm^3, a platelet counts of 50,000 cells/mm^3 or greater, and adequate liver and kidney function.
Patients requiring treatment and harboring the del17p/TP53 mutations.
Patients who did not respond to a chemo immunotherapy regimen or those who demonstrated disease progression within 24 months after the completion of prior therapy.

Exclusion Criteria

The exclusion criteria included autoimmune hemolytic anemia, immune-mediated thrombocytopenia, Richter transformation (RT), and the presence of other malignancies or chronic cardiovascular conditions.

Patients were administered 420 mg of oral ibrutinib daily until disease progression or emergence of intolerable side effects. Adjustment of the dosage was permitted in accordance with the manufacturer's guidelines and at the discretion of the attending physician. The patients were monitored once a month, and their hematological (complete blood counts) and biochemical parameters (liver and renal functions) were recorded at each visit.

The primary endpoints were overall survival (OS) and treatment response.

The key secondary endpoints included sustained hematologic improvement and safety. Sustained hematological response was defined as a persistent increase in hematological parameters for at least 60 days without transfusion or growth factors. This was measured by a minimum 50% rise in platelet or absolute neutrophil counts from baseline or a hemoglobin increase of at least 2 g/dL. For patients with baseline cytopenia, the criteria included hemoglobin level > 1 g/dL, platelet count > 100,000/mm^3, or absolute neutrophil count greater than 1500/mm^3.

Treatment toxicity was evaluated using the National

Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (AE) version 3.0, except for hematological adverse events, which were graded according to the iWCLL grading scale for hematologic toxicity in studies. Adverse events (AE) of grade 3 or higher were generally recorded, whereas any grade of AE was reported for hemorrhage, diarrhea, arthralgia, atrial fibrillation, and blood counts.

Responses were assessed according to the International Workshop on CLL criteria.[7] The assessment was predominantly performed through clinical evaluation, with only minimal diagnostic tests, specifically a hemogram and abdominal ultrasound.[10] Hence, treatment response was assessed as unconfirmed complete remission (CRu), partial remission (PR), progressive disease (PD), stable disease (SD).

Statistical Analysis

Descriptive analysis was calculated as means and percentages using the statistical package for the social sciences version 23.0. Survival analysis was performed using the Kaplan-Meier method. OS was defined as the time from diagnosis to the date of the last follow-up or death, regardless of cause.

RESULTS

This study included 35 patients diagnosed with CLL who underwent treatment with ibrutinib at our institution. Of these patients, 24 (68.6%) were administered ibrutinib as their initial line of therapy, whereas 11 (31.4%) received ibrutinib as a subsequent line of treatment. The median duration of treatment was 16 months, with an interquartile range (IQR) of 3–31 months.

The median age of the study population was 56 years (interquartile range [IQR]: 48–63 years), with male predominance (n = 23, 65.7%). Thirteen patients (37.1%) exhibited an ECOG performance status of 2. Most patients were diagnosed with advanced disease, of which 16 (45.7%) were categorized under Rai stages 3–4. Nine patients (25.7%) were smokers, and 12 (34.3%) had bulky disease. The median hemoglobin (Hb) level was 9.7 g/dL (IQR: 8–11.1), total leukocyte count (TLC) was 84.6 × 10^3/μL (IQR: 26–193), absolute neutrophil count (ANC) was 5.3 × 10^3/μL (IQR: 2.3–8.45), and the median absolute lymphocyte count (ALC) was 70.24 × 10^3/μL (IQR: 7.93–158). Additionally, the median platelet count was 129 × 10^3/μL (IQR, 60–201). Del17p was detected in eight patients (22.9%). In this cohort, 10 patients (28.7%) had comorbidities, with hypertension (HTN) being the most common, recorded in eight patients (22.9%). Diabetes mellitus was also present, affecting 3 patients (8.7%). Additional baseline information, including clinical and laboratory parameters for the two cohorts, is presented in Table-I.

TABLE-I

Patients initial characteristics according to treatment line:

Parameters	First line n=24	Later Line n=11
Median age at diagnosis, years(range)	56(47-65)	52(43-60)
Gender, n(%)		
Male	17(68%)	6(54.5%)
Female	8(32%)	5(45.5%)
ECOG performance status, n (%)		
0	10(40%)	4(36.4%)
1	8(32%)	1(9.1%)
2	7(28%)	6(54.5%)
Rai stage III or IV, n (%)	12(50%)	4(36.4%)
Bulky disease ≥5 cm, n (%)	7(28%)	5(45.5%)
Smokers, n (%)	6(24%)	3(27.3%)
Hemoglobin ≤10 g/dL, n (%)	13(52%)	4(36.4%)
Platelet count ≤100 × 109/L, n (%)	4(16%)	6(54.5%)
del(17p) n/N (%)	6/24(25%)	2/11(18.2%)

Of the 35 participants in the study, 11 were initially not treated with ibrutinib. These individuals were administered alternative treatment regimens, which comprised RB (rituximab + bendamustine) for 1 patient (2.9%), FCR (fludarabine, cyclophosphamide, rituximab) for 4 patients (11.4%), and chlorambucil in 6 patients (17.6%). However, owing to refractoriness to earlier treatment, these patients were subsequently switched to advanced ibrutinib therapy.

Twenty-four (68.6%) patients received ibrutinib as first-line treatment. The overall response rate

(ORR) for the 24 participants who were treated with ibrutinib as first-line therapy was 50%, including 2 unconfirmed complete responses (uCR), 10 partial responses (PR), 2 deaths, 2 patients were lost to follow-up (LTF), 4 patients with progressive disease (PD), and 4 patients with stable disease (SD).

However, in 11 patients who received ibrutinib as second-line treatment, the overall response rate (ORR) was 45.5%, including 1 uCR and 4 PR. Notably, death was reported in one patient, two in LTF, and three in PD.

The data illustrating hematologic recovery in individuals with preexisting cytopenia are presented in Figure-1. During the treatment phase, consistent improvement in anemia (Figure-1a) and thrombocytopenia (Figure-1b) was observed. The initial phase of therapy was marked by a rapid increase in mean neutrophil count, followed by a period of stabilization. (Figure-1c)

FIGURE-1(a)

Hematological recovery of hemoglobin levels in CLL patients with time

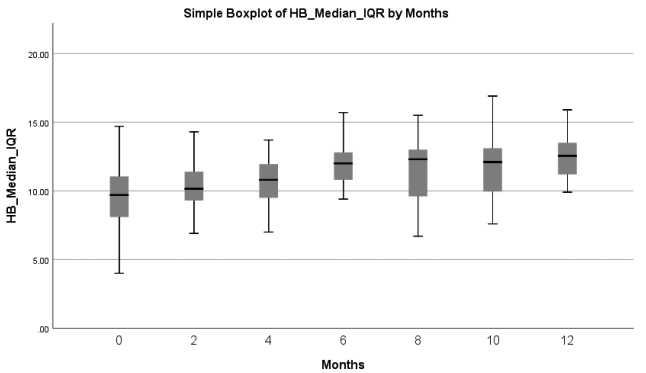


FIGURE-1(b)

Hematological recovery of platelet counts in CLL patients with time

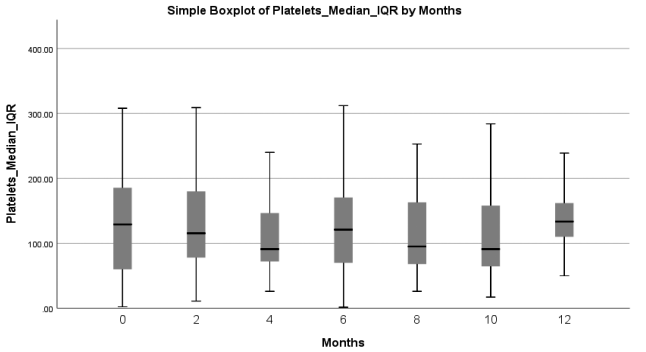
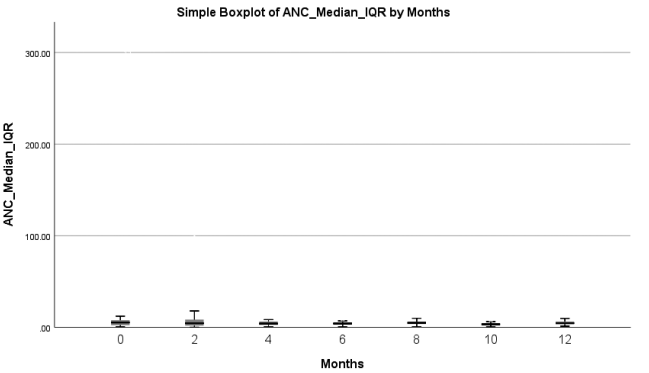


FIGURE-1(c)

Hematological recovery of absolute neutrophils counts in CLL patients with time



A standard starting dose of 420 mg/day was administered to all the patients. A total of 3 patients (8.6%) underwent dose reduction due to non-hematological adverse effects, including recurrent respiratory tract infection in 1 patient (2.9%) and nausea and vomiting in 2 patients (5.7%). Treatment was temporarily halted in 18 instances, with a total of 23 reported non-hematological adverse events. These included pneumonia (n=6, 17.1%), diarrhea (n=5, 14.3%), dysentery (n=1, 2.9%), tumor lysis syndrome (n=1, 2.9%), fungal infections (n=1, 2.9%), ear infections (n=1, 2.9%), financial difficulties (n=2, 5.7%), and refractory anemia (n=1, 2.9%). Treatment was discontinued in seven patients and was switched to another therapy, four due to PD, two had persistent cytopenia, and one had recurrent infection. Four patients died during the initial phase of treatment, and the cause was not ascertained. Eleven patients were lost to follow-up as their symptoms improved after the initiation of treatment. However, 13 patients were still undergoing treatment.

Among the 35 patients evaluated, 25 exhibited at least one form of hematological toxicity. The analysis revealed 28 hematological adverse events among the patients, including 14 episodes of neutropenia (grade 4 in 2 cases, grade 3 in 5 cases, and grade 2 in 2 patients), 3 episodes of anemia (grade 3 in 2 patients and grade 1 in 1 case), and 11 episodes of thrombocytopenia (grade 4 in 1 case, grade 3 in 3 cases, grade 2 in 3 cases, and grade 1 in 4 cases). One patient experienced grade 4 anemia

owing to an autoimmune mechanism unrelated to the therapeutic effects of ibrutinib. Two patients had their treatment regimen modified because of cytopenia persistence. In the other 26 instances, patients with cytopenia recovered without any modifications to their administration schedule.

The median follow-up period for patients who received ibrutinib as first-line treatment was 29 months (range 18.5-35 months). The median overall survival (OS) for the patients in this study could not be established, as the majority of patients were alive at the end of the study (n=21, 87.5%), while only three patients died (Figure-2).

FIGURE-2

Survival analysis of CLL after first line therapy First line therapy

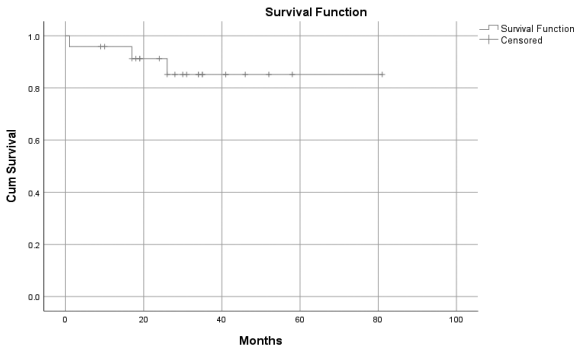
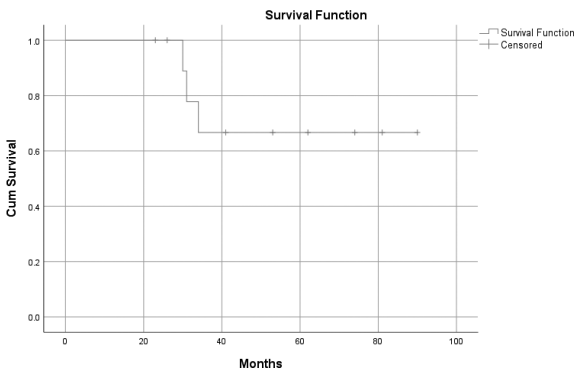


FIGURE-3

Survival analysis of CLL after later line therapy First line therapy



The median follow-up duration for patients who received ibrutinib as later-line therapy was 41 months (range 23-69 months). By the end of the study, the overall survival for this treatment group had not been achieved, as eight patients (72.7%) were alive and three patients died (Figure-3). Disease progression was observed in four patients (16.66%) from first-line ibrutinib therapy and three (27.27%) from ibrutinib as later-line therapy.

DISCUSSION

The recent introduction of single-agent ibrutinib has revolutionized the traditional frontline CIT approaches, impacting both younger fit patients and older less fit individuals, regardless of the presence of del(17p) or TP53 mutation.[5,7,11] Clinical trials have demonstrated the efficacy of ibrutinib in patients with relapsed and refractory disease, suggesting its use as an initial salvage therapy with superior outcomes as compared to its administration at later stages of the disease.[5] Moreover, it is regarded as the primary option for frontline therapy in patients with CLL who present with high-risk cytogenetic and molecular characteristics.[5,6]

The significance of real-world results for patient cohorts treated outside the framework of prospective clinical trials is increasingly being recognized in the context of hematologic malignancies. It has been observed that CLL patients included in community-based confirmatory trials exhibited poorer responses and experienced a higher incidence of side effects compared to those reported in earlier pivotal studies.[3] Nevertheless, limited literature is available for lower-middle-income countries (LMICs). To the best of our knowledge, this is the first study from our country to demonstrate the effectiveness of ibrutinib based on real-world experiences in patients receiving first-line or subsequent line treatment.

The current study evaluated the efficacy of ibrutinib in 35 patients who received the drug as either first-line therapy or subsequent treatment following failure of conventional CIT. The median age of the study population was 59 years, which is consistent with the findings of other studies.[1,7] Interestingly, most studies conducted in the western populations indicate a higher prevalence among older individuals.[3,5,6] Sixteen (45.7%) patients had a high-risk disease at the time of diagnosis, contrary to the findings of the aforementioned studies.[3,12] In our study, 17 (48.5%) patients harbored del (17p), while the PCYC-1102 trial reported an incidence of 6%. This is in contrast to the phase 3 RESONATE-2

trial, which did not enroll any subjects with del(17p) because of its presence as an exclusion criterion.[5,6]

Previous studies have reported substantial response rates in both frontline and pretreated settings (50.0% and 45.45%, respectively). However, the number of complete responses in our study was relatively low (8.3% and 1%, respectively), as previously indicated in registration trials, and consistent with existing real-world evidence for relapsed and refractory patients.[3,5] Overall, seven (20%) of our patients had progressive disease, which is contrary to the findings of previous studies.[5] However, none of the study population underwent Richter's transformation.

After a median follow-up of 29 months in patients receiving ibrutinib as primary therapy, the overall response rate (ORR) was 50%, notably higher than data reported by western countries.[3-5] The ORR in a relapsed/refractory setting after a median follow-up of 41 months was 45.5%, which differed from that reported in the PCYC-1102 trial.[5] As the majority of patients were alive at the end of the study, the median overall survival (OS) for both groups could not be established. A more extended follow-up period is necessary to ensure a more credible assessment of outcomes. However, the differences between patients receiving second- or later-line treatment in our study and those in clinical trials may be partly attributed to additional comorbidities during routine treatment, which can affect therapy adherence, adverse events, and treatment outcomes.[13,14]

In our study, patients receiving ibrutinib exhibited restored bone marrow function and showed steady improvement in cytopenia, with a higher rate of sustained improvement in hematologic parameters. This is clinically significant as bone marrow failure often complicates CLL, with anemia and thrombocytopenia frequently prompting treatment, indicating indirect evidence that ibrutinib contributes to tumor regression in the bone marrow.[3,5,6]

Real-world research insights are crucial to determine the safety and practicality of drug use. Our clinical observations indicated that ibrutinib is a safe treatment option that can be effectively managed alongside other therapies or by adjusting the dosage, leading to hospitalization in only a small percentage of cases.[7] The most frequent grade 3 or 4 adverse events observed in our patients were neutropenia (20%), thrombocytopenia (11.42%), and anemia (5.7%). Notably, we did not encounter any cases of atrial fibrillation or bleeding in our cohort, both of which are significant concerns for ibrutinib treatment.[7,15,16] Additionally, the occurrence of severe infectious adverse events was low, with respiratory tract infections being the most common adverse event. Interestingly, some of our patients discontinued follow-up after starting therapy, believing that their symptoms had improved enough and that they did not require further treatment and follow-up. However, this highlights the concept of patient counseling and awareness regarding the disease course and treatment outcomes in our part of the world, where it is believed that such improvements signify a complete cure. Moreover, there were four unexplained reports of sudden death of unascertained cause.

While our study outcomes revealed insightful observations, the study had certain limitations. The relatively small samples may restrict the generalizability of our findings. Another major limitation was the short follow-up period, which hindered our ability to draw firm conclusions regarding long-term survival rates and disease progression. The absence of a control group receiving alternative treatments significantly limited direct comparisons, making it difficult to assess the relative effectiveness of ibrutinib against other treatment options. The loss of follow-up for some patients complicates the assessment of the long-term response rates and survival outcomes. Furthermore, the lack of comprehensive molecular profiling in all patients limits our understanding of how genetic variation affects treatment efficacy.

CONCLUSION

Our study revealed the safety and efficacy of ibrutinib in patients with CLL, applicable to both first-line treatment and in cases of relapsed or refractory disease. The overall response rates and improvements in hematologic parameters observed in our study further established ibrutinib as a fundamental component of CLL treatment strategies. Moreover, our findings showed a

lower rate of atrial fibrillation and bleeding events compared to previous studies. However, challenges such as ensuring treatment adherence, addressing patient misconceptions regarding the possibility of a cure, and the requirement for extended follow-up must be carefully considered. Future prospective studies with larger cohorts and longer follow-up are vital to substantiate these findings and to refine the long-term management strategies for CLL utilizing ibrutinib.

Institutional Review Board Statement and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of NIBD Research Ethics Committee. (NIBD/IRB-284/14-2023). Informed consent was obtained from all subjects involved in the study.

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Data Availability Statement

The data and materials supporting the findings of this study are available from the corresponding authors upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Kubra Razzaq:** Manuscript writing.
2	**Quratulain Rizvi:** Data collection.
3	**Aisha Jamal:** Concept, design.
4	**Aisha Arshad:** Literature search.
5	**Laraib Majeed:** Data analysis.
6	**Nida Anwar:** Critical revisions.