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IMPROVEMENT IN ERADICATION OF HELICOBACTER PYLORI INFECTION WITH ADDITION OF LACTOBACILLUS REUTERI---A RANDOMIZED CONTROLLED TRIAL

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Introduction & Objective: The eradication rate of *Helicobacter pylori* (HP) has decreased with different treatment regimens over the time. This study was conducted to compare the eradication rate of HP infection and improvement of symptoms treated by sequential therapy (ST) with addition of Lactobacillus Reuteri (LR) versus ST only.

Material and Methods: This open label randomized control trial was conducted in Department of Gastroenterology, Liaquat National Hospital, Karachi, from July 2020 to June 2021.A Total of 195 treatment naïve patients were included in each group. Patients of group A received ST and LR and patients of group B received ST only.Total duration of treatment was two weeks in both groups. Patients of both groups were also evaluated for severity of abdominal symptoms and its betterment after treatment according to the Gastrointestinal Symptom Rating Scale (GSRS) at first visit and on follow up visit after 4weeks. Four weeks after the treatment, HP eradication test was performed by stool antigen test (SAT) or urea breath test (UBT).

Results: A total of 390 patients were enrolled in the study and both groups consisted 195 patients each. HP eradication was successful in 116(84.7%) in group A and 94(85.5%) in Group B

(p=0.864) patients when SAT was the method of post eradication test while using UBT as post eradication test 49(84.5%) in Group A and 80(94.1%) in Group B (p=0.057) patients showed successful eradication. The symptom improvement assessed by using GSRS showed higher rates of symptom betterment in Group A 175(89.7%) as compared to Group B 53(27.2%) respectively (p=0.001).

Conclusion: This study showed that addition of LR to ST showed no increment in rates of HP eradication. However, there was an increase in effectiveness in terms of improvement of symptoms compared to the ST alone.

Trial registration: The study is registered with clinical trials.gov with first trial registered on 27/01/2023 with the registration number# NCT05701683.

Key words: *Helicobacter pylori***,** Lactobacillus Reuteri, probiotics, sequential therapy

INTRODUCTION:

Helicobacter pylori (HP) seems to be a widespread pathogen that affects approximately half of the world's population.[1] It's a major source of concern, assumed its linked to raised risk of gastric cancer, that is the third greatest cause of the mortality throughout the world.[1] Globally, the disease prevalence varied by demographic patterns, age, and socioeconomic differences, reaching up to 50%. Overall, the prevalence is higher in developing countries than the developed states.[2] In Pakistan the prevalence of HP is about 73.5% in males and 75.4% in females, and the tendency seems to increase with the increasing age.[3]According to the epidemiological studies, medical and general practitioners treat a significant number of patients who are suffering with gastrointestinal issues. Although an infection with HP can remain dormant for years and eventually result in symptomatic gastrointestinal diseases.[4] The main symptoms are epigastric pain, heart burn, acid regurgitation, nausea, vomiting, abdominal bloating and altered bowel habits. Occassionally HP is even linked with non-gastrointestinal symptoms like anemia[5]. Male gender, increasing age, obesity, shorter height, tobacco use, lower socioeconomic status along with lower educational status of parents in different studies conducted are proposed risk factors for infection[6]. Previously first-line standard triple therapy (STT), was considered the treatment of choice for HP infections over a long period of time which consisted of at least two antibiotics, combined with the proton pump inhibitors (PPIs).But for the past few decades, gradual decline in the rates of eradication achieved by conventional anti-HP medications led to further research in this topic by experts. The currently available treatments for HP are challenged by the recently revealed alarming prevalence of antimicrobial drug resistance, with the failure rate approximately 30.3%[7]. In this regard, novel treatment regimens and approaches are desperately required[8].

However, the effective implementation of these novel therapies is dependent upon having a solid comprehension of the broad applicability of HP to the gastric acidic environment as well as the complicated mechanism of the pathogen. On the other hand, a large number of probiotics have been studied so far which showed beneficial effects upon the human gut[9]. The most widely used probiotics includes Lactobacillus and Bifidum species, also among the common microbes in the gastrointestinal tract, been demonstrated to be useful in treating the HP related gastrointestinal symptoms[10]. Therefore to generate more evidence, the present study was planned to compare the eradication rate between two groups. Group A received sequential therapy (ST) plus Lactobacillus Reuteri (LR) and group B received ST alone, along with documentation of improvement in symptoms after addition of LR to the ST regimen of HP.

MATERIAL AND METHODS:

(i) STUDY DESIGN

This was a prospective open label randomized controlled trial which was designed according to CONSORT guidelines 2010, done at Out Patients Department (OPD) of Gastroenterology, Liaquat National Hospital, Karachi. Study was conducted during a period of one year from July 2020 to June 2021.The study has been approved by and began after Ethical review committee of the Liaquat National Hospital and Medical College under the reference number App#0493-2019-LNH-ERC. A written informed consent was signed by all eligible patients for their voluntary recruitment into this study. It is registered with clinicaltrial.gov with first trial registered on 27/01/2023 under the registration number NCT05701683.

(ii) INCLUSION CRITERIA

All the patients with age range of 18-60 years with positive H.P confirmed by histopathology, Rapid Urease Test---RUT, performed during endoscopy or positive result of Urea Breath Test (UBT) or stool antigen test (SAT) of either gender, were included in the study.

(iii) EXCLUSION CRITERIA

Patients were excluded from the study if they were pregnant, had chronic liver disease, renal impairment, history of previously used PPI during last 4 weeks, previous failed attempts for HP eradication and those who had allergy to antibiotics or had any contraindications to use antibiotics.

(iv) STUDY GROUPS

A total of 390 patients' were included in the study. Patients were randomized into two groups by chit/lottery method; group A (ST+LR) and B (ST) after the per protocol (PP) and intention to treat (ITT) stratification as Shown in Fig.1.

GROUP A (ST+LR):

-Esomeprazole 20mg twice daily for 2weeks
-Amoxicillin 1000 mg twice daily for first 5 days
-Clarithromycin 500 mg twice daily plus Tinidazole 500 mg twice daily for next 5 days
Addition of LR 100 mg twice daily in capsule form was given for 2 weeks.

GROUP B (ST ONLY):

-Esomeprazole 20mg twice daily for 2weeks
-Amoxicillin 1000mg twice daily for first 5 days
-Clarithromycin 500 mg twice daily plus Tinidazole 500 mg twice daily for next 5 days

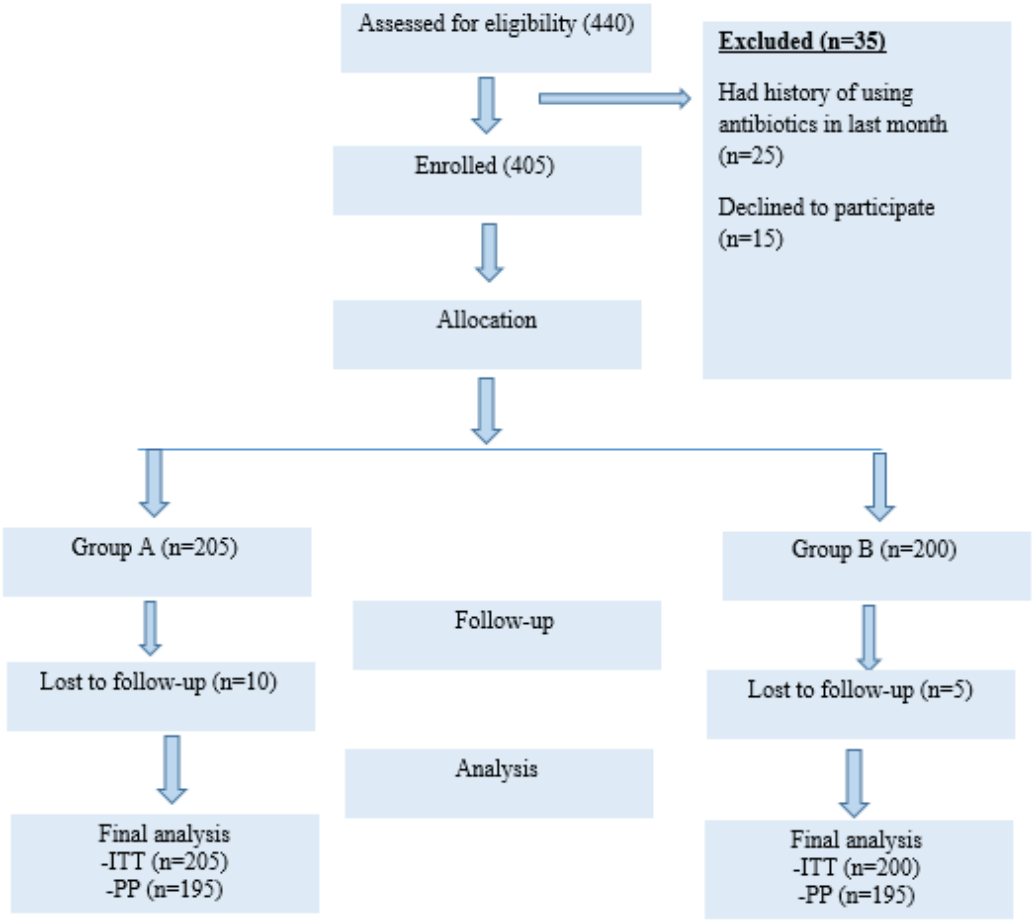


FIG.1: Flow diagram of this study with patient allocation and analysis. ITT: Intention-to-treat, PP: Per-Protocol.

(v)GASTROINTESTINAL SYMPTOMS ASSESSMENT

During the study our patients were also evaluated on the basis of severity of abdominal symptoms which made them consult gastroenterology clinics which were assessed according to the Gastrointestinal symptom rating scale (GSRS) questionnaire at 1st visit and on follow up visit after end of eradication therapy. There are 15 common symptoms included in the scale.

(vi) STUDY EVALUATION

All patients were prescribed with PPI for a total of 2weeks after which they remained off treatment for 2 weeks .On follow up visit after 4weeks HP eradication was documented by either negative results of SAT or UBT. All the information was collected via study proformas.

(vii)STUDY OUTCOMES

PRIMARY OUTCOME: Improvement in eradication rates of HP after addition of LR to the clarithromycin based ST.

SECONDARY OUTCOMES: To assess the improvement in gastrointestinal symptoms before and after eradication therapy with addition of LR between both study groups.

(viii) STATISTICAL ANALYSIS

Data entry and analysis was performed by using IBM SPSS statistics v26. For categorical variables, frequencies and percentages were calculated. Using the Shapiro-Wilk test, numerical variables were first checked for the assumption of normality. For quantitative variables having non-normal

distribution, the median with inter-quartile range (IQR) was presented. The Fisher-exact test or the Chi-square test was used to compare categorical variables between the two research groups. The threshold for statistical significance was two tallied p-value 0.05.

RESULTS:

(i) PATIENT CHARACTERISTICS

A total of 390 individuals were studied in this randomized control trial. Considering the age and gender studied in both groups no significance was noted. However statistical significance was seen in the duration of symptoms among the patients of both groups with which they consulted the GI clinic as their complaints. Table.1

(ii) PATIENTS SYMPTOM PROFILE

Both groups ST+LR and ST were analyzed for the complaints with which they first visited the GI clinics and eventually got enrolled into the study. Epigastric pain being the most common complaint or symptom that made the patient to seek clinical consult, followed by heart burn, abdominal bloating and regurgitation. Least commonly encountered complaints also included nausea vomiting, diarrhea and constipation, but no significant difference was noted between the two groups with respect to these symptoms.Table.2

Table.1 Descriptive statistics of demographic variables n=390

Variables		Study groups		p-value
		Sequential therapy + LR	**Sequential therapy**	
Age (years)		36.51±9.91	53.65±10.0	0.396
Duration of symptoms (months)		9.75±4.6	13.59±7.61	0.001
Gender	Males	87(44.6%)	91(46.7%)	0.684
	Females	108(55.4%)	104(53.3%)	
Total		195(100.0%)	195(100.0%)	

Table.2 presenting complaints of the patients n=390

Variables		Study groups		p-value
		ST + LR	**ST**	
Presenting complaints	Abdominal bloating	39(20.0%)	35(17.9%)	0.430
	Regurgitation	22(11.3%)	16(8.2%)	
	Burping	3(1.5%)	7(3.6%)	
	Constipation	2(1.0%)	7(3.6%)	
	Diarrhea	5(2.6%)	5(2.6%)	
	Epigastric pain	62(31.8%)	53(27.2%)	
	Heart burn	51(26.2%)	54(27.7%)	
	Nausea	9(4.6%)	15(7.7%)	
	Nausea/vomiting	2(1.0%)	3(1.5%)	

†Sequential therapy+Lactobacillus Reuteri=ST+LR ‡Sequential therapy=ST

(iii) HP ERADICATION AND SYMPTOMS IMPROVEMENT

After the completion of therapy, successful eradication among the both groups ST+LR and ST were assessed with the help of SAT and UBT after 4 weeks. Contrary to the title, lower eradication rates were found in the ST+LR group as compared to ST group with no statistical significance when checked via post eradication methods used in the study. However narrating to the symptoms improvement among the groups after the end of treatment, notable improvement was highlighted by the patients of ST+LR group rather than the ST group. Table.3

Table.3 Comparison of the post eradication in groups and symptoms n=390

Variables		Study groups		p-value
		ST + LR	ST	
Post eradication in SAT (n=247)	Negative	116(84.7%)	94(85.5%)	0.864
	Positive	21(15.3%)	16(14.5%)	
Post eradication in UBT (n=143)	Negative	49(84.5%)	80(94.1%)	0.057
	Positive	9(15.5%)	5(5.9%)	
Better symptoms	Yes	175(89.7%)	53(27.2%)	0.001
	No	20(10.3%)	142(72.8%)	
Total		195(100.0%)	195(100.0%)	

†SAT: stool antigen test, ‡UBT=Urea breath test, §ST: Sequential therapy, ¶LR: Lactobacillus Reuteri

(iv) GSRS ASSESSMENT

Mean GSRS score was assessed at 1st week on first visit and then at 4th week follow up visit. Symptoms assessment done with a questionnaire consisting of 15 questions. The mean score analyzed among the patients of both groups at the beginning of treatment showed comparable results. Table. 4. But for the mean score evaluated after the 4th week highlighted considerable decrease in GSRS score of ST+LR group as compared to ST group. Table. 5

Table.4 GSRS scale comparison at 1st week in both study groups n=390

GSRS questionnaire	Study groups	GSRS scale		p-value
		Mean	SD	
Pain or discomfort upper abdomen	Group A	3.70	2.52	0. .496
	Group B	3.52	2.52	
Hunger pains in the stomach during the past week	Group A	3.25	1.87	0. .919
	Group B	2.27	2.10	
Nausea during the past week	Group A	2.29	1.22	0.155
	Group B	2.50	1.59	
Heart burn during the past week	Group A	3.47	2.50	0.901
	Group B	2.44	2.36	
Acid reflux during the past week	Group A	2.57	1.64	0.426
	Group B	2.45	1.52	
Rumbling in stomach during the past week	Group A	1.46	1.03	0.192
	Group B	2.62	1.41	
Felt bloated during the past week	Group A	1.98	2.01	0.822
	Group B	1.94	2.04	
Burping during the past week	Group A	2.08	0.66	0.222
	Group B	2.18	0.96	
Passing gas or flatus during the past week	Group A	3.72	1.50	0.949
	Group B	2.73	1.63	
Diarrhea during the past week?	Group A	1.12	0.76	0.946
	Group B	2.11	0.73	
Loose stool during the past week	Group A	1.09	0.60	0.935
	Group B	2.10	0.63	
Urgent need to have a bowel movement during the past week	Group A	1.06	0.41	1.00
	Group B	2.06	0.43	
Constipation during the past week	Group A	1.05	0.50	0. 089
	Group B	2.18	0.96	
Hard stool during the past week	Group A	2.04	0.40	0.111
	Group B	2.13	0.69	
Sensation of not completely emptying the bowels	Group A	1.03	0.35	0.420
	Group B	2.06	0.39	

†Group A= Sequential therapy + LR ‡ **Group B**= Sequential therapy

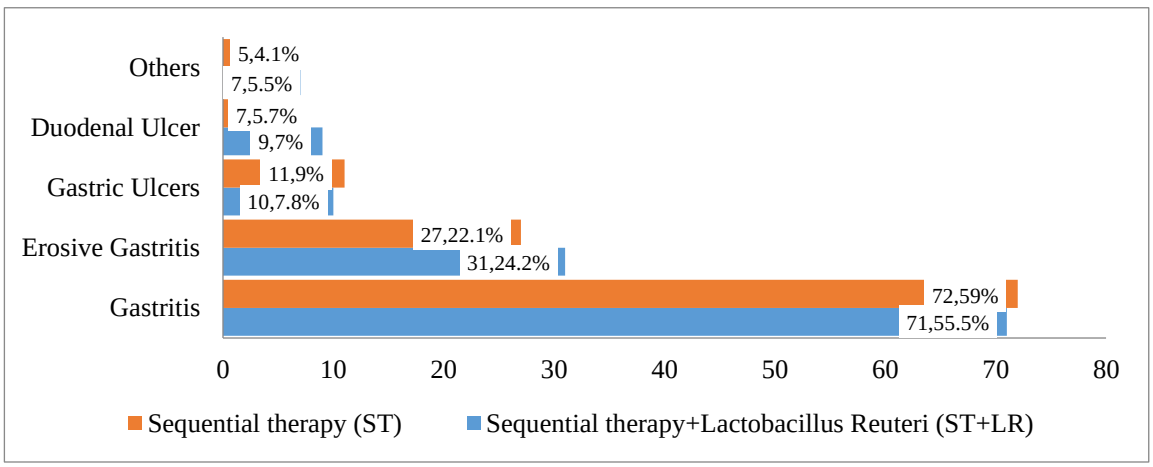
Table.5 Post therapeutic GSRS scale comparison at 4th week in both study groups n=390

GSRS questioner	Study groups	GSRS scale		p-value
		Mean	SD	
Pain or discomfort upper abdomen	Group A	0.90	1.38	0.014
	Group B	2.37	2.27	
Hunger pains in the stomach during the past week	Group A	0.61	0.97	0.000
	Group B	1.21	2.01	
Nausea during the past week	Group A	0.15	0.66	0.009
	Group B	0.45	1.42	
Heart burn during the past week	Group A	0.69	1.24	0.000
	Group B	1.33	2.19	
Acid reflux during the past week	Group A	0.24	0.75	0.235
	Group B	0.36	1.23	
Rumbling in stomach during the past week	Group A	0.23	0.51	0.010
	Group B	0.45	1.08	
Felt bloated during the past week	Group A	0.40	0.88	0.040
	Group B	0.66	1.50	
Burping during the past week	Group A	0.04	0.34	0.064
	Group B	0.16	0.85	
Passing gas or flatus during the past week	Group A	0.32	0.70	0.021
	Group B	0.57	1.33	
Diarrhea during the past week?	Group A	0.07	0.44	0.492
	Group B	0.11	0.70	
Loose stool during the past week	Group A	0.05	0.33	0.433
	Group B	0.08	0.54	
Urgent need to have a bowel movement during the past week	Group A	0.03	0.23	0.332
	Group B	0.07	0.45	
Constipation during the past week	Group A	0.03	0.30	0.041
	Group B	0.16	0.85	
Hard stool during the past week	Group A	0.02	0.25	0.051
	Group B	0.12	0.64	
Sensation of not completely emptying the bowels	Group A	0.01	0.10	0.056
	Group B	0.07	0.47	

†**Group A**= Sequential therapy + LR ‡**Group B**= Sequential therapy

(v)ENDOSCOPIC FINDINGS

During the study, a total of 250 patients underwent upper G.I endoscopy with 128 in ST+LR group and 122 in ST group. The most common endoscopic finding came across was gastritis followed by erosive gastritis, gastric & duodenal ulcers. A very few patients showed findings other than these as shown in the graph.1.



Graph.1: Endoscopic findings in both groups (ST+LR & ST).

DISCUSSION:

The eradication of HP is critical to improve the quality of life for patients with various gastrointestinal disorders. Multiple regimens are now available that emphasis the use of both acid suppressants and antibiotics in the treatment of HP. These medication groups have the potential to decrease the rate of HP eradication by increasing the prevalence of adverse responses and antibiotic resistance.[11,12] In a local HP guidelines by Kamani et al antibiotic resistance was found to be different for different antibiotics used for eradication with metronidazole being the most resistant among all[13].The quadruple 14-day therapy has replaced the previous conventional 7-day triple therapy as the first-line treatment strategy approved by the worldwide community.[14] Unfortunately, the unpredictability and length of the treatment course with increasing dosage, further reduces the rate of HP eradication. The function of probiotics in the elimination of this vicious cycle is a major endeavor that is now under progress.[15] Globally multiple studies were conducted and have shown that the use of probiotics, particularly LR, can be effective in improving the eradication of HP infection.[16]

The improvement of clinical manifestations is a valuable marker for HP for the effective therapy. The GSRS questionnaire is a frequently employed instrument in several research to evaluate the HP gastrointestinal symptoms and quality of life.[17] In our study, a standard GSRS questionnaire was employed to assess the GI symptomatic changes before and after the therapy in both groups. In this study, majorly reported symptoms were epigastrium pain, heart burn, abdominal bloating and regurgitation in both study groups. The current study shows a trend of significant decrease (89.7%) in the presentation and severity of GI symptoms in group of LR (Group A). Whereas small reduction in symptom severity were present in group B patients, indicating that symptomatic regression was not significantly achieved with ST alone (27.2%). After four weeks, the mean GSRS score was considerably lower in the interventional group (ST+ LR) than in the control group (ST) ($p= 0.05$). These results were in line with earlier multiple research studies published. Martin Buckley et al study found a tendency for a decrease in 66.7% of patients who took LR regime, with the abdominal symptoms' subgroup seeing the largest decline, with GSRS ratings falling by 16.7%.[18] The Asian study by Kumar Parth et al., also showed similar results with major decline in severity and presentation of symptoms perceived in patients' group with LR. A significant improvement in GSRS mean scores compared to conventional group-I patients.[19] The GSRS questionnaire was utilized by Suzuki Het al. and Ojetti V et al. in HP eradication and to examine symptomatic changes before and after addition of LR. It was discovered that the use of LR in the treatment of HP infection significantly improved quality of life (QOL).[20, 21]

In current study, in terms of the difference of both groups for effectiveness of eradicating HP, the results showed no significant difference in the eradication rate between the two groups. The total eradication rate reported after using both methods to check eradication in this study is 84% in conventional therapy group (Group A), which falls within a range of eradication rates from 60% to 94.4%. Whereas, group B eradication rate reached upto 89% in our study. Many studies found varying rates, which may indicate strain-specific anti-HP action.[22]. A meta analysis of RCT in 2019 by Yu M et al investigated the effect of LR in eradicating HP infection in adults. The study included randomized groups to receive either STT plus LR or STT plus a placebo. The results showed the similar current study results as no significant difference in the HP eradication rate between the two groups.[23] Ample clinical studies have investigated the use of LR as an adjunct therapy for the eradication of HP. These studies have used a range of study designs, including Randomized clinical trials (RCTs) , open-label trials, and observational studies. The results of these studies have been mixed, with some studies reporting a significant improvement in HP eradication rates with the addition of LR, while others have found no significant effect.[24] Zhu R et al., in meta-analysis found that probiotics combined with triple therapy could not increase the rate of infection eradication. Heterogeneity was significant in their study.[25] In conclusion; the evidence on the efficacy of LR in

eradicating infection is still inconclusive and debatable. Further well planned studies are required in future for further clarification.

STRENGHTS & LIMITATIONS:
It is the first RCT in Pakistan conducted to precisely denote the part played by addition of probiotics in HP eradication. Selection of clarithromycin sequential therapy the regime upon which the role of probiotics have not been studied so far in most of the previous studies conducted in different regions. Although it was a single center study mostly conducted in COVID pandemic with non-blinded open label randomization and no different strains of probiotics were used.

CONCLUSION:
This study showed that ST with inclusion of LR showed no increment in rates of HP eradication however, there is an increased effectiveness in terms of improvement of symptoms compared to the ST alone. Further studies are required to delineate the role of LR in HP management.

AUTHORS' CONTRIBUTION:
Mehreen Akmal: Data Collection, Analysis & Interpretation, Writing First Draft of Manuscript.

Prof. Lubna Kamani: Design, Analysis and Revising Manuscript

Adeel Rahat: Concept, Data Collection, Literature Search

Sajjad Jameel: Literature Search, Protocol Writing and Data Collection.

Leticia Moreira MD, PhD: Critical Second Revision of Manuscript.

Javier P.Gisbert MD, PhD: Critical Final Revision and Major Editing of Manuscript.

CONFLICT OF INTEREST:
No conflict of interest associated with this study.

DECLARATIONS:
(i) **Ethics approval and consent:** The study began after the ethical review committee of Liaquat National Hospital and Medical College under the reference number App#0493-2019 LNH-ERC.
(ii) **Fundings:** None included
(iii) **Acknowledgement:** None
(iv) **Consent for publication: "**Not applicable" for that section.

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