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Horizontal Transfer of Plasmids Bearing *bla*$_{CTX-M}$ Between Gut Commensals and Pathogenic *Escherichia coli* in Indian Patients

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Abstract

Indiscriminate use of antibiotics has exerted selective pressure on the gut microbiota, increasing the prevalence of antibiotic-resistant bacteria among the commensal population. However, in a state of intestinal dysbiosis, the patient's flora contributes to the spreading of genes bearing determinants for antibiotic-resistance via horizontal transfer of drug-resistant plasmid. Although the *in vivo* spread of antibiotic resistance through this mechanism is well-known, limited studies demonstrate evidence of it occurring between commensal and pathogenic *Enterobacteriaceae* in patients. This study investigated the possibility of horizontal transfer of plasmids bearing *bla*$_{CTX-M}$, from a gut *E. coli* to pathogenic *Enterobacteriaceae* and vice versa. Clinical specimens from twelve patients were screened for beta-lactamase producing *Enterobacteriaceae,* followed by isolating corresponding gut *Enterobacteriaceae* from stool samples. Standard bacteriological procedures and antibiotic sensitivity testing were performed to identify and confirm ESBL, AmpC beta-lactamase, and carbapenemase producers. PCR to confirm beta-lactamase genes, ERIC PCR to assess clonal similarity, PCR-based replicon typing for plasmid profiling, conjugation by broth mating assay for evaluating the horizontal transfer of plasmids, were performed to study the possibility of horizontal transfer of *bla*$_{CTX-M}$ gene between gut and pathogenic *E. coli*. In two patients, we demonstrated the potential for horizontal transfer of *bla*$_{CTX-M}$ carrying IncFIA and IncFIB plasmids between uropathogenic *E. coli* and gut *E. coli, in vivo*. This study confirms *in vivo* horizontal transfer of plasmids bearing *bla*$_{CTX-M}$ types IncFIA and IncFIB between gut commensal and uropathogenic *E. coli*, highlighting the need for stringent antibiotic stewardship to curb multidrug-resistant pathogen spread.

Keywords: HGT, Uropathogenic *E. coli,* IncFIA, IncFIB, Plasmids

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INTRODUCTION

Members of the *Enterobacteriaceae* family, a group of Gram-negative rod-shaped bacteria, are commonly associated with a wide range of clinical infections, including those affecting the urinary tract, surgical wounds, bloodstream, and respiratory system. Management of these infections frequently involves the use of antimicrobial therapy. Among the drugs most effective against these organisms are cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones.[1,2]

In pathogenic *Enterobacteriaceae* obtained from patient specimens, carbapenem and cephalosporin resistance is mainly mediated by the enzymes-carbapenemases, extended spectrum beta-lactamases (ESBLs), and AmpC beta-lactamases. Often, the genes that encode these beta-lactamases are present in plasmids.[3-5] It is well known that horizontal transfer of plasmids bearing carbapenemase, ESBL, and AmpC beta-lactamases genes results in rapid dissemination of resistance to carbapenems and cephalosporins.[6] Also, these plasmids frequently bear resistance determinants for other antibiotics such as aminoglycosides and fluoroquinolones, thereby spreading multidrug-resistance. Another mode of drug-resistance is through efflux pumps observed among clinical isolates of *Enterobacteriaceae*. The genetic determinants for efflux pumps are found on chromosomal DNA as well as on plasmids.[7]

Overuse and misuse of antibiotics to treat infections give rise to selective antibiotic pressure, resulting in intestinal opportunistic pathogens exhibiting resistance to multiple drugs. Consequently, the gastrointestinal tract acts as a reservoir pool for multidrug-resistant opportunistic pathogens, which can lead to infections in immunocompromised individuals and pose a significant risk to hospitalized patients. Salyers et al. hypothesized that antibiotic resistance genes present in the human gut can be shared with both native gut bacteria and transient microbial populations.[8] The human intestine is host to a large microbial community.[9] Regardless of the infection type community or hospital-acquired the digestive tract remains the main reservoir of *Enterobacteriaceae*. Intestinal microbiota contribute substantially to the dissemination of antibiotic resistance genes.[8] The gastrointestinal tract acts as a hotspot for resistance gene transfer, with antibiotic pressure driving the dominance of resistant bacteria. In the human intestine, microbial dysbiosis creates conditions conducive to the horizontal transmission of antibiotic resistance genes between commensals and pathogens.[10]

Although limited, there are reports on fecal carriage rates of beta-lactamase-producing *Enterobacteriaceae* among hospitalized as well as healthy individuals from our country. However, horizontal transfer of resistance genes, though a long-known mechanism of spreading antibiotic resistance *in vivo*, has not been demonstrated in *Enterobacteriaceae* between a commensal and pathogen in a patient in our country. Therefore, this study aimed to demonstrate the possibility of horizontal transfer of genes encoding beta-lactamase in *Enterobacteriaceae* between pathogenic and gut isolates.

MATERIALS AND METHODS

Study isolates

Patients with clinical specimens testing positive for *Enterobacteriaceae* harboring beta-lactamase genes were identified. Stool samples were obtained from these patients to isolate intestinal *Enterobacteriaceae* and investigate the horizontal transfer of beta-lactamase genes between pathogenic and commensal strains. A total of 12 paired *Enterobacteriaceae* isolates one from clinical specimens and the other from stool samples were obtained from patients at a tertiary care hospital in Chennai, India. This study was approved by the Institutional Human Ethics Committee (IHEC). IHEC Approval No.: UM/IHEC/01-2014-II dated 18.02.2015 and IHEC Approval No.: UM/IHEC/01-2017-I dated 26.04.2017.

Isolation and identification of bacterial isolates

Standard microbiological techniques were employed to isolate and characterize the bacterial strains. Both the pathogenic isolate and the gut isolate were then subjected to the following tests individually:

Antibiotic Sensitivity Testing (AST) by disc placement method

Detection of carbapenemase, ESBL, AmpC, inducible AmpC beta-lactamases, and combined resistance mechanisms was carried out using the one-plate method outlined by Rodrigues et al.[11] Antibiotic discs used were (imipenem 10 µg, cefotaxime 30 µg, cefoxitin 10 µg, ceftazidime 30 µg, ceftazidime + clavulanic acid 30 µg + 10 µg, aztreonam 30 µg, ceftriaxone 30 µg Hi Media Labs, Mumbai, India) were placed on the agar surface. Interpretation of the susceptibility data was performed following Clinical & Laboratory Standards Institute (CLSI) standards, with *E. coli* ATCC 25922 serving as the quality control reference strain.

PCR to detect beta-lactamase encoding genes

Genomic DNA from the bacterial isolates was extracted using the heat lysis protocol. Briefly, 1-2 bacterial colonies were suspended in 100 µL of sterile double autoclaved water in a 1.5 mL microcentrifuge tube. The suspension was boiled in a dry bath at 100 °C for 10 minutes. The suspension was then immediately kept at -20 °C for 10 minutes. It was then centrifuged, and the supernatant was used as DNA template for polymerase chain reaction (PCR) reactions. PCR was performed, targeting the following beta-lactamase genes: $bla_{\text{CTX-M}}$ grp 1, $bla_{\text{CTX-M}}$ grp 2, $bla_{\text{CTX-M}}$ grp 8, $bla_{\text{CTX-M}}$ grp 9, $bla_{\text{CTX-M}}$ grp 25, bla_{NDM}, $bla_{\text{OXA-48}}$, $bla_{\text{KPC-1}}$, bla_{IMP}, bla_{VIM} using primers and annealing conditions as described.[12,13]

Enterobacterial Repetitive Intergenic Consensus sequence-based PCR (ERIC PCR)

ERIC PCR is a quick and easy technique to divide the strains with the same serotypes into the different sub-types. Here, ERIC PCR was performed to detect clonal similarity between the isolates tested. This was done with the primers and PCR conditions as described earlier.[14]

PCR based replicon typing (PBRT)

PBRT is the most commonly used method of classifying plasmids based on the incompatibility type of the plasmid. PBRT consists of 5 multiplex PCR and 3 simplex PCR reactions. This was performed as described by Carattoli et al.[15]

Conjugation assay[16]

To evaluate the potential horizontal transfer of β-lactamase genes, a broth mating conjugation assay was performed using sodium azide-resistant *E. coli* J53 as the recipient and either a clinical pathogenic or gut-associated enterobacterial isolate as the donor. In brief, 500 µL of overnight cultures from both the donor and recipient strains were combined and incubated together at 37 °C (to mimic the human body's core temperature) for 6-7 hours, after which a loopful of the mixture was plated onto an antibiotic-azide selective plate (Mac Conkey's agar incorporated with 1 mg/L cefotaxime and 100 mg/L sodium azide) and incubated at 37 °C for 18-24 hours. Transconjugants that grew on the selective plates were subjected to AST and PCR to confirm the acquisition and horizontal transfer of beta-lactamase genes.

RESULTS

A total of 12 paired sets of *Enterobacteriaceae* isolates comprising clinical isolates and gut-derived strains (from stool samples) were collected from patients attending a tertiary care hospital. All the clinical isolates of *Enterobacteriaceae* of the 12 patients produced either one or a combination of the beta-lactamases-carbapenemases, ESBL, and AmpC beta-lactamases, detected by AST by disc placement method and further confirmed by PCR targeting specific genes. Gut-derived enterobacterial isolates producing beta-lactamases were compared with their corresponding clinical *Enterobacteriaceae* isolates to investigate the potential horizontal transfer of β-lactamase genes between commensal and pathogenic strains. It was found that, out of the 12 patients, two harbored pathogenic and gut *Enterobacteriaceae* that had a similar antibiogram pattern and produced the same beta-lactamases and were consequently examined in greater detail to investigate horizontal gene transfer of beta-lactamase genes. The results are as follows:

Evidence of horizontal transfer in non-clonally related strains

Patient A

Urine and stool samples were collected

from a 50-year-old female patient. *E. coli* was isolated and identified from urine as well as stool samples of the patient. The *E. coli* isolated from urine samples is subsequently referred to as UPEC (uropathogenic *E. coli*) and the *E. coli* isolated from stool sample is subsequently referred to as gut *E. coli*. AST by disc placement method revealed that both the UPEC and gut *E. coli* isolates showed a similar antibiogram pattern and also produced ESBL. PCR analysis confirmed the presence of bla_{CTX-M} group-1 gene in both the isolates. PBRT demonstrated that UPEC was of replicon types IncI1 and IncF1B whereas gut *E. coli* was of replicon type IncF1B only (Figure 1A). ERIC PCR showed that

Table 1. Data to indicate the horizontal transfer of bla_{CTX-M} from UPEC to gut *E. coli* to have occurred in the gut of the patient A

Experiment	Clinical isolate	Gut isolates
Bacterial identification	UPEC	Gut *E. coli*
Phenotypic test for beta-lactamase	ESBL producer	ESBL producer
bla_{CTX-M} PCR	Positive	Positive
PBRT	IncI1, IncF1B	IncF1B
Conjugation study	TC of UPEC obtained	Conjugation did not occur
Confirmation of HGT of bla_{CTX-M} in TC of UPEC		
bla_{CTX-M} PCR	Positive	
PBRT of TC	IncI1, IncF1B	

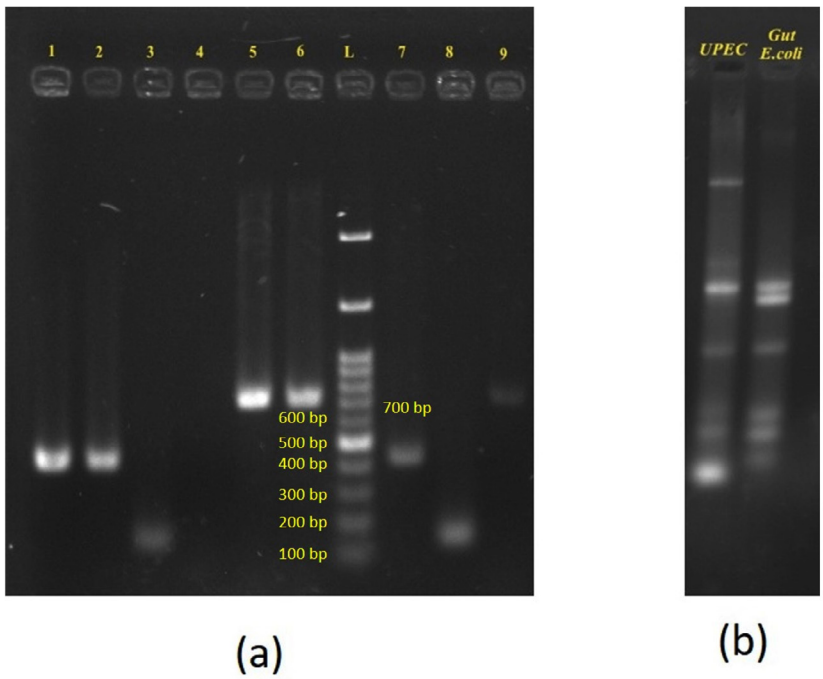

Figure 1. Gel electrophoresis demonstrating horizontal transfer of bla_{CTX-M} from UPEC to gut *E. coli* in patient A:
(a): PCR amplification of resistance gene and plasmid replicons. Lanes 1 & 2 - bla_{CTX-M} group 1 Positive for UPEC and gut *E. coli* respectively; Lanes 3 & 4 - IncI1 Positive in UPEC and - IncI1-negative in gut *E. coli* respectively; lanes 5 & 6 - IncF1B Positive for both UPEC and gut *E. coli* respectively; Lanes 7, 8 & 9 - TC UPEC positive for bla_{CTX-M} group 1, IncI1 and IncF1B respectively. L - 100 bp - 1.5 Kb ladder (bands at 100, 200, 300, 400, 500, 600, 700 bp, etc). Amplicon sizes of: bla_{CTX-M} group 1 - 415 bp; IncI1 - 139 b; IncFIB - 702 bp.
(b): ERIC PCR profile of UPEC and Gut *E. coli* - showing dissimilar banding patterns

Table 2. Data to indicate the horizontal transfer of bla_{CTX-M} between UPEC and gut *E. coli* to have occurred in the gut of the patient B

Experiment	Clinical isolate	Gut isolates
Bacterial identification	UPEC	Gut *E. coli*
Phenotypic test for beta-lactamase	ESBL and AmpC beta-lactamase producer	Carbapenemase, ESBL and AmpC beta-lactamase producer
bla_{CTX-M} PCR	Positive	Positive
PBRT	IncFIA and IncFIB	IncFIA and IncFIB
Conjugation study	TC of UPEC obtained	TC of UPEC obtained
Confirmation of HGT of bla_{CTX-M} in TC of UPEC		
bla_{CTX-M} PCR	Positive	
PBRT of TC	IncFIA and IncFIB	

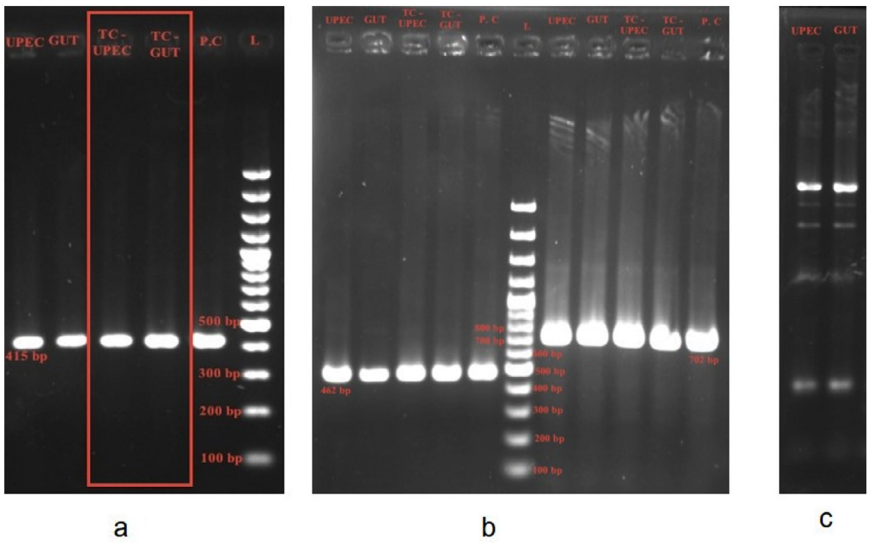

Figure 2. Gel electrophoresis demonstrating horizontal transfer of bla_{CTX-M} from UPEC to gut *E. coli* in patient B:
(a): bla_{CTX-M} group 1 - 415 bp present in: UPEC, Gut *E. coli*, TC-UPEC, TC Gut- Transconjugant Gut *E. coli*, PC - Positive control, L- ladder 100 bp - 1.5 Kb
(b): FI A - 462 bp present in UPEC, Gut *E. coli*, TC-UPEC, TC Gut, PC - Positive control, L- ladder 100 bp - 1.5 Kb FI B - 702 bp present in UPEC, Gut *E. coli*, TC-UPEC, TC Gut, PC - Positive control.
(c): ERIC PCR of UPEC and Gut *E. coli*

there was no clonal relatedness between UPEC and gut *E. coli* establishing that the two isolates, although of the same species, were two different strains (Figure 1B). Both the isolates shared IncF1B replicon types only. Two independent conjugation assays were conducted using UPEC and gut *E. coli* isolates as donors, with sodium azide-resistant *E. coli* J53 serving as the recipient. The assays were performed at 37 °C to simulate human body temperature, and transconjugants were selected on MacConkey agar plates supplemented with cefotaxime (1 mg/L) and sodium azide (100 mg/L). Transconjugants of UPEC that were obtained were positive by PCR for bla_{CTX-M} group-1 and were of replicon types IncI1 and IncF1B replicon types (Figure 1A). Transconjugants of gut *E. coli* were not obtained (Table 1).

Evidence of horizontal transfer in clonally related strains

Patient B

Urine and stool samples were collected from a 70-year-old male patient with urinary tract infection (UTI). Isolation and identification of *E. coli* from both urine and stool samples revealed UPEC and gut strains, respectively. The colony morphology of UPEC was: lactose fermenting, circular, elevated center with smooth edge and gut *E. coli* was lactose fermenting, circular, flat, dry with smooth edge. AST by disc placement method showed that while UPEC was an ESBL and AmpC beta-lactamase producer, gut *E. coli* was a carbapenemase, ESBL and AmpC beta-lactamase producer. PCR confirmed that both isolates carried bla_{CTX-M} group-1 gene. ERIC PCR showed that there was clonal relatedness between UPEC and gut *E. coli*. Both UPEC and gut *E. coli* harbored one plasmid each of similar size and was of replicon types IncFIA and IncFIB, indicating that the same plasmid was present in both the isolates. Two independent conjugation assays were conducted using UPEC and gut *E. coli* isolates as donors, with sodium azide-resistant *E. coli* J53 as the recipient strain. The assays were performed at 37 °C to simulate human body temperature, and transconjugants were selected on MacConkey agar plates supplemented with cefotaxime (1 mg/L) and sodium azide (100 mg/L). Transconjugants were obtained for both the UPEC and gut *E. coli* strains thus demonstrating the ability to horizontally transfer bla_{CTX-M} bearing IncFIA and IncFIB plasmid to recipient *E. coli* J53 (Figure 2 and Table 2).

DISCUSSION

The beta-lactam group of drugs are most diverse and widely used among all the groups of antimicrobial agents. Resistance to these drugs is often mediated by beta-lactamase enzymes, the genes for which are commonly borne on plasmids. Rapid and disseminated spread of resistance to beta-lactam drugs is known to occur by horizontal transfer of beta-lactamases borne on plasmids. Acquisition and diffusion of beta-lactam resistance immensely limits treatment options.[17] Several investigations have demonstrated the exchange of bla_{CTX-M} genes among diverse bacterial strains and species. Cho et al. reported horizontal $bla_{CTX-M-14}$ gene transfer from *Shigella sonnei* to a commensal *E. coli* strain.[18] Whole-genome sequencing by Knudsen et al. revealed the horizontal transfer of a $bla_{CTX-M-1}$ encoding plasmid between various *E. coli* strains residing in the human gut.[19] Plasmid-mediated transfer of *ISEcp1-*$bla_{CTX-M-15}$ and *aac(6')-Ib-cr* genes by conjugation to a recipient strain was observed in 49% of ESBL-producing isolates in a Lebanese study.[20] In Israel, horizontal interspecies transfer of a plasmid bearing the *KPC-3* gene from a carbapenem-resistant KPC-3 producing *K. pneumoniae* to a carbapenem-susceptible *E. coli* was suggested to occur in the gut of a patient from whom the strains were isolated.[21] There is scarce documentation of *in vitro* bacterial resistance gene transfer in studies involving both human and animal hosts.[22-24] Despite its clinical significance, *in vivo* evidence for horizontal transfer of the bla_{CTX-M} gene between two *E. coli* strains in the human gut remains scarce.[25-28] Our findings contribute to this body of knowledge by providing *in vivo* evidence of such horizontal transfer, particularly highlighting the potential for plasmid-mediated gene transfer within the human gut microbiota.

The current study aimed to investigate the potential horizontal transfer of beta-lactamase genes between gut and clinical *Enterobacteriaceae* isolates in hospitalized patients. A total of 12 patients were sampled, and two cases exhibited noteworthy findings. In the first case (patient A), both UPEC and gut *E. coli* isolates from a 50-year-old female patient produced ESBL and harbored the bla_{CTX-M} group-1 gene. Despite their identical resistance profiles, ERIC PCR demonstrated no clonal relatedness, indicating they were distinct strains. UPEC had two replicon types IncI1 and IncF1B but the gut *E. coli* had only IncF1B. To understand if the horizontal transfer of bla_{CTX-M} group-1 gene had occurred between UPEC and gut *E. coli,* conjugation experiment was performed. Transconjugants were observed only for UPEC and not for gut *E. coli*. These findings suggest that the gut *E. coli* may have acquired the bla_{CTX-M} bearing IncF1B plasmid from UPEC through horizontal gene transfer. The absence of clonal relatedness supports the hypothesis that horizontal transfer, rather than clonal expansion, facilitated the spread of the resistance gene. This demonstrates the potential for plasmid-mediated transfer of

resistance genes between different *E. coli* strains within the same host.

In the second case (patient B), involving a 70-year-old male patient, both UPEC and gut *E. coli* were positive for the bla_{CTX-M} group-1 gene, and ERIC PCR analysis showed clonal relatedness between the two isolates. Despite the clonal relatedness, there were marked differences between the two strains. Both UPEC and gut *E. coli* had different colony morphologies and dissimilar antibiogram patterns. Gut *E. coli* was resistant to imipenem by AST, but PCR targeting carbapenemase genes was negative, suggesting that imipenem resistance was not enzyme-mediated. In contrast, UPEC was sensitive to imipenem. These findings suggest that although UPEC and gut *E. coli* were clonally related, as demonstrated by ERIC PCR, they were different *E. coli* strains. Cremet et al. showed that in spite of clonal relatedness, *E. coli* can undergo phenotypic and genotypic changes.[29] Both UPEC and gut *E. coli* isolates carried a single plasmid of similar size, identified as IncFIA and IncFIB types. Conjugation assays confirmed the transferability of the bla_{CTX-M} bearing IncFIA and IncFIB plasmid to recipient *E. coli* J53 from both UPEC and gut *E. coli*. The findings from this case strongly support the *in vivo* transfer of a plasmid harboring the bla_{CTX-M} gene within the patient's gut. This case provides strong evidence of in vivo horizontal transfer of the bla_{CTX-M} bearing plasmid within the patient's intestine. The clonal relatedness between the isolates suggests that the plasmid-mediated resistance gene transfer could have occurred after the initial colonization by a single strain, facilitating the dissemination of resistance within the gut microbiota.

CONCLUSION

The findings underscore the complexity of resistance gene dynamics within the human host, where both clonal expansion and horizontal gene transfer can contribute to the spread of resistance. The study highlights the significance of the gut microbiota as a reservoir for antimicrobial resistance genes and the potential for horizontal gene transfer to pathogenic strains. These findings have important clinical implications, particularly in the context of infection control and antimicrobial stewardship. Understanding the mechanisms of resistance gene transfer can help in forming strategies to mitigate the spread of resistance within healthcare settings. Further studies are needed to explore the prevalence and mechanisms of horizontal gene transfer in diverse patient populations and settings to develop effective interventions to curb the dissemination of antimicrobial resistance.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

PS conceptualized the study. JM and PK collected resources. PK supervised the study and funding acquisition. JM and PS applied methodology. JM, PS and PK performed investigation. PS and PK wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Human Ethics Committee (IHEC), Dr. ALM PG IBMS, University of Madras, Chennai, India. (IHEC Approval No.: UM/IHEC/01-2014-II dated 18.02.2015 and IHEC Approval No.: UM/IHEC/01-2017-I dated 26.04.2017)

INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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