

Original Article

Surveillance on pediatric bacterial meningitis in Gondar University Hospital, Ethiopia from 2012 to 2021: Retrospective analysis

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Abstract

Introduction: Acute Bacterial meningitis is still a major cause of death in under-five children. Surveillance on Pediatric Bacterial Meningitis has been set up by the World Health Organization to generate data on vaccine preventable causes of Meningitis in under-five children. Ethiopia is one of the countries conducting the surveillance and Gondar University Hospital is one of the sentinel surveillance sites. In this study we described the epidemiological data on Bacterial meningitis in under-five children at Gondar University Hospital from 2012-2021.

Methods: Data were extracted directly from Gondar University Hospital surveillance database collected from under-five children admitted to the Hospital with suspected meningitis from January 1st, 2012 to December 31st, 2021. Socio-demographic and clinical characteristics were collected using standard pretested questioners. All under-five children with suspected meningitis over the 10-years period were included and descriptive statistics like frequency, percentage, mean, median and standard deviations were used for the characteristics of under-five Children with Suspected Bacterial Meningitis.

Results: In this study, a total of 4311 under-five admitted with suspected bacterial meningitis from 2012 to 2021 were enrolled. The majority, 71% of suspected meningitis were reported in infants. The mortality rate in suspected meningitis during the study period was 1%. The majority (92.4 %) had fever at presentation followed by seizure (62.7 %), altered consciousness (58.9 %) and bulged fontanel in 48.3 %, respectively. The commonest bacteria identified by CSF culture and Polymerase Chain Reaction was *Streptococcus pneumoniae* (SPN). There was a reduction of confirmed meningitis cases from 2012 to 2021 (26 cases in 2012 and 6cases in 2021).

Conclusions: *Streptococcus pneumoniae* was the commonest cause of PBM. Bacterial detection by culture was low which showed that Polymerase Chain Reaction (PCR) test should be encouraged to improve bacterial detection.

Keywords: Under-five, Surveillance, meningitis, Gondar

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Introduction

In under-five children bacterial meningitis is still one of the major and fatal public health problems. Despite Antibiotic therapy and updated vaccination strategies, Acute Bacterial Meningitis is persisting to be a risk to under-five children with high morbidity and mortality. Under-five children are predominantly affected by Bacterial Meningitis because of their lower immunity specially for polysaccharide containing bacteria out of which *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common worldwide pathogens causing meningitis particularly in countries with limited resources like Ethiopia. To reduce the mortality and significant morbidity due to ABM, implementing primary prevention by routine vaccination has significant effect with lower cost especially for those with least access to health care (1, 2). In Asia and Africa even if there are reports showing in overall reduction, the three common organisms are still dominant causes of ABM

for which strong surveillance system is one of the best solutions to assess vaccine efficacy and reduction of morbidity and mortality (3, 4, 5). Constraints in vaccine administration and coverage may contribute to this persistent problem in resource limited areas. To reduce such problem, continuous surveillance is mandatory which determines the distribution of serotypes/groups of bacteria causing Meningitis in under-five children across countries to help develop sustainable and effective vaccination programs. (6). A research done before introduction of both Hib and PCV-10 vaccines in Ethiopia reported that *S. pneumoniae* serotypes 14, 19F, 20, 1, 18 and 5 account for 76% of cases and 97% of the *H. influenzae* isolates were type b (7). Implementation of Hib and PCV-10 vaccination programs started in Ethiopia in 2007 and 2011, respectively. However, the impact of these vaccines on the disease epidemiology and

clinical features are investigated only in few international studies with no adequate local evidence (8).

Implementing strong Surveillance system on vaccine-preventable diseases can provide critical information for policymakers in guiding further vaccine introduction, monitoring vaccine impact, and describing changes in disease epidemiology over time (9). The objectives of Invasive Bacterial Vaccine Preventable Disease (IB-VPD) surveillance network are to describe the epidemiology and estimate the burden of invasive bacterial vaccine preventable diseases, in establishing a surveillance platform to measure vaccine impact, and characterize the circulating bacterial serotypes/serogroups in under-five children (10). Gondar University Hospital has started the sentinel surveillance since 2007 in collaboration with the African Pediatric Bacterial Meningitis (PBM) surveillance network with the support of WHO and global immunization partners. We used data collected as part of PBM surveillance from 2012-2021 with the aim of describing the etiology, serotype/serogroup, epidemiology, and clinical presentations of pediatric bacterial meningitis in Gondar University Hospital. There are no reports about Pediatric Bacterial Meningitis activities in the study area and there are few reports from Ethiopia even if the surveillance has been done for more than 20years which was the main rationale of our study.

Materials and Methods

Study Design and Period

A retrospective analysis to assess the characteristics and patterns of Pediatric Bacterial meningitis was conducted at the University of Gondar Hospital from January 1st, 2012 to December 31st, 2021.

Study Area

This retrospective study was conducted at the University of Gondar Hospital, Department of Pediatrics and Child Health. The hospital is located in Gondar town 741km northwest of the capital city, Addis Ababa. Gondar University Hospital is one of the oldest Hospitals in Ethiopia. It has conducted Pediatric Bacterial Meningitis surveillance since January 2008.

Study Population

The study population of our study was all under-five children with suspected Bacterial Meningitis and admitted at Gondar University Hospital, Department of Pediatrics and Child Health from January 1st, 2012 to December 31st, 2021.

Inclusion and Exclusion Criteria

All under-five children with suspected bacterial meningitis admitted at Gondar University Hospital with analyzed CSF samples were included and children with unknown outcomes were excluded.

Case Enrollment

Active case-based Pediatric Bacterial meningitis surveillance is being conducted in Gondar University

Hospital starting from January 2008 as one of the sentinel surveillance sites in Ethiopia which are being supported by WHO in the African region. Those under-five children admitted to the Hospital with suspected bacterial meningitis with CSF results were included in the surveillance.

Definition of Suspected meningitis (WHO Meningitis case definition): an illness in under-five child admitted to a hospital with sudden-onset fever (>38.5°C rectal or 38°C axillary) and one of the following signs: neck stiffness, altered consciousness with no other alternative diagnosis, or other meningeal signs; or illness in any patient under-five child who is hospitalized with a clinical diagnosis of meningitis

Data Collection process

Once enrolled, Socio-demographic data, medical history, and clinical characteristics were collected using standard pretested questioners. Bacterial identification were done using conventional microbiological methods and polymerase chain reactions (PCR) as a routine activity in the Hospital, and analysis of extracted data was performed using SPSS statistical software (Version-26). We collected the data directly from the Hospital Surveillance database by a structured data collection tool. The surveillance data has gathered important information from enrolled under-five children. Demographic data, medical history, and clinical characteristics were collected by trained clinical nurses and pediatric residents using the already prepared format by WHO at each ward of Gondar University Hospital, Pediatrics department. For each patient, standardized case investigation form nationally prepared containing information on patient demographics, clinical signs/symptoms, outcome, and laboratory results were completed. Demographic information was obtained from patient's caregiver. Pre-admission clinical history was obtained from the patients' chart, but in the event of missing or unclear information, it was obtained from the caregiver. Physical findings and other clinical information were collected from the patient's medical record. A lumbar puncture (LP) was performed, and cerebrospinal fluid (CSF) was analyzed as a routine diagnostic test for suspected Bacterial Meningitis. Results of laboratory diagnostics were then used to classify suspected meningitis cases. Data were entered into an access data base which was prepared and distributed in collaboration with WHO and transferred on a monthly basis to Ethiopian Public Health Institute and to WHO country Support Team. CSF samples were examined for complete white blood cell count (WBC), protein and glucose concentrations, Gram stain and bacterial culture were also done on all CSF Specimens. When available, Latex Agglutination Test (LAT) specific for HIB, SPN and NM was done. Standard definitions for suspected, probable, and confirmed bacterial meningitis were used after CSF analysis in the Hospital laboratory. If the patient fulfills one of the laboratory meningitis case definitions

(Probable or suspected), the CSF was sent to the Ethiopian Public Health Institute (EPHI) for Polymerase Chain Reaction (PCR) confirmation and possible stereotyping and randomly selected samples were sent to South African regional laboratory for the purpose of quality control.

Data Processing and Analysis

Data were cleaned, coded, entered and analyzed using SPSS version-26. Descriptive statistics like frequency, percentage, mean, median and standard deviations were used for the characteristics of under-five Children with Suspected Bacterial Meningitis each year from 2102-2021. Tables and figures were used for data presentation

ETHICAL CONSIDERATION

Ethical clearance was obtained from Institutional Review Board of University of Gondar (Ref. No: VP/RTT/05/894/2022). Permission to access the collected data was secured from the University of Gondar Hospital director office. Privacy of the participants was respected and confidentiality was protected by, using codes and keeping questionnaires locked.

RESULTS

Sociodemographic Characteristics of under-five children

A total of 4311 under-five children with suspected bacterial meningitis were enrolled at the sentinel hospital from 2012 to 2021 and for all (100%) Lumbar Puncture was done and CSF samples were analyzed. Overall, 58.8% (2533/4311) of children were male and the median age was 3 months with SD 13.8. Majority (71%) (3061/4311) of Suspected Bacterial Meningitis cases were reported in children aged 0–11 months. The mortality rate was found to be 1% (43/4311) (Table 1).

Table 1. Summary of Sociodemographic Characteristics of under-five children

Characteristics	Category	Number (%)
Age (in months)	0-11	3061(71%)
	12-23	490(11.4%)
	24-59	755 (17.5%)
Sex	Unknown	5(0.1%)
	Female	1726(40%)
	Male	2533 (58.8%)
Antibiotic before admission	Unknown	52(1.2%)
	Yes	83(1.9%)
	No	3244(75.2%)
Discharge Dx	Unknown	984(22.8)
	Meningitis	980(22.7%)
	Sepsis	1150 (26.7%)
Outcome	Pneumonia	862(20%)
	Unknown	1319 (30.6%)
	Discharged alive	2619(60.8%)
Total cases with suspected Meningitis	Died	43(1%)
	Unknown	1649(38.2%)
		4311(100%)

The clinical presentations of children at enrollment revealed that majority 92.4 % (3975/4311) has fever at presentation followed by seizure in 62.7% (2703/4311), altered consciousness in 58.9% (2539/4311) and bulged fontanel in infants with 48.3 % (2082/4311), respectively (Table 2).

Table 2. Clinical signs/symptoms and Clinical Characteristics of under-five children at presentation

Results of CSF Analysis and Bacterial identification

Symptom/sign at presentation	Number (%)
Fever	3975(92.4)
Bulged fontanel	2082(48.3)
Altered consciousness	2539(58.9)
Seizure	2703(62.7)
Neck stiffness	2526(58.6)

Lumbar Puncture and CSF analysis were done for all the 4311 suspected cases and majority 93.5% (4029/4311) of the CSF samples were reported to be crystal and 4.8% (203/431) were reported as turbid. Only 6.6 % (283/4311) of CSF samples were found to have cell counts above 100cells/mm³ and 7 % (300/4311) CSF samples were reported as having protein level above 100mg/dl whereas 4.7 (201/4311) had glucose below 100mg/dl. Gram stain which was

done on 3814 (88.5%) CSF samples but positive result was reported only in 2.5 % (94/3814). Culture was done on 4144 (96.1%) CSF samples with positive result of 0.8 % (34/4144) (Table 3).

Table 3. Characteristics of Cerebrospinal Fluid in under-five children at Gondar University Hospital, from 2012-2021

HI=H.Influenzae
SPN=S.Pneumoniae

Characteristic	Number (%)
Cerebrospinal fluid appearance:	
Clear	4029(93.5%)
Turbid	203(4.8%)
Xanthochromic	9(0.2%)
Blood stained / Traumatic	51(1.2%)
Unknown	19(0.4)
White blood cell count (cells/mm³):	
≤10	3375(78.3%)
10 to 100	173(4.0%)
>100	283(6.6%)
Unknown/not done	470(11%)
Protein (mg/dL) :	
<100	574(13.3%)
≥100	300(7%)
Unknown/not done	3437(79.7%)
Glucose (g/dL) :	
<40	201(4.7%)
≥40	828(19.2%)
Unknown/not done	3282(76.1%)
Latex Agglutination Test (LAT) :	
Done	121(2.8%)
Not done	4190 (97.2%)
LAT Result:	
HIB	21(17.4%)
SPN	4(3.3%)
NM	5(4.1%)
Others	1(0.8%)
Negative	90(74.4%)
Gram Stain Result:	
Gram +ve	61(1.4%)
Gram-Ve	32(0.7%)
No organism:	3721(86.3%)
Not done:	497(11.5%)
Culture Result:	
HI	7(0.2%)
SPN	24(0.6%)
NM	3(0.1%)
Others	38(0.9%)
Negative	406(94.3%)
Not done	167(3.9%)

PCR test done on 66 cases:

HI	10(15.2%)
SPN	14(21.2)
NM	3(4.5%)
HIB+SPN	2(3.0%)
Negative	23(34.8%)
Inconclusive	14(21.2%)

NM=N.Meningitidis

Latex agglutination and Polymerase Reaction (PCR) were done and reported positive in only 24.8 % (30/121) and 41 % (27/66), respectively (fig.1). Latex agglutination and Polymerase Chain reaction tests were not routinely done for all suspected cases due to unavailability and frequent interruption of tests in the country.

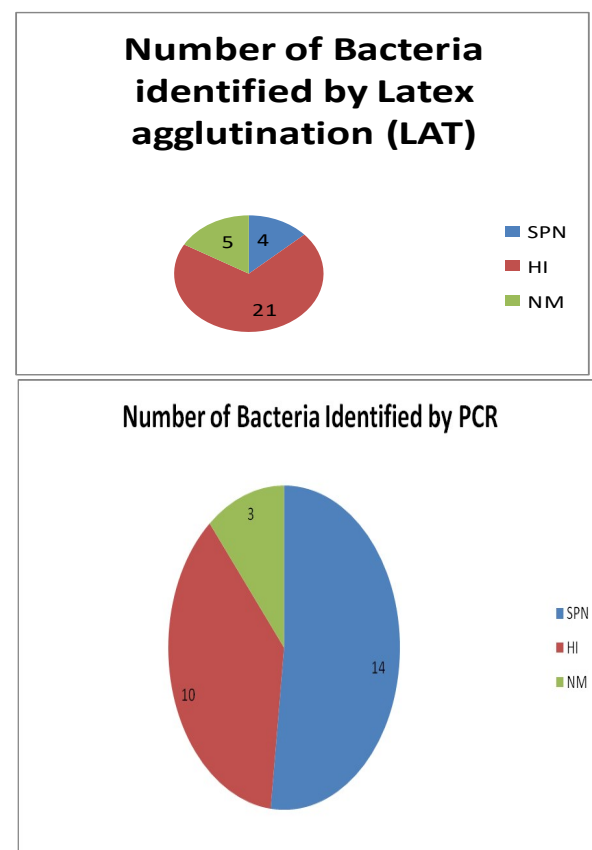


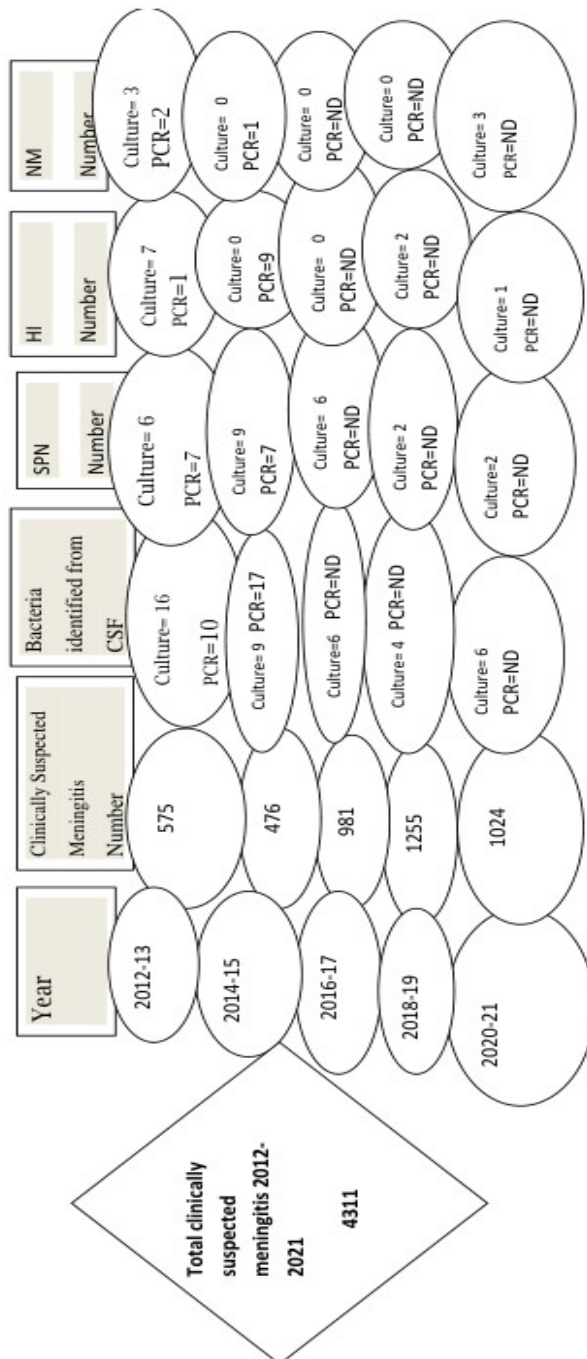
Fig.1. Bacterial detection by LAT and PCR

The number of Clinically suspected Meningitis cases in under-five children was found to be increasing (575 in 2012-13 to 1024 in 2020-2021) but the percentage of bacteria identified by CSF culture revealed a significant decrement (2.8% in 2012-13 to

0.6 in 2020-2021) (fig.2). Positive CSF culture results at Gondar University Hospital were sent to EPHI for confirmation and serotyping and reported that Stereotyping were done on 14 positive CSF samples for Pneumococcus and identified only 6 serotypes as 1, 2, 3 and 8 each and 2cases of 23F. Stereotyping performed on 8cases of *H. influenzae*– Positive CSF samples reported only 2 *HIB* isolates and *Meningococcal* serogrouping performed on 8 positive CSF samples reported only 1 case of serotype W-135.

HI=*H.Influenzae*

SPN=*S.Pneumoniae*



NM=N.Meningitidis

ND=Not done

Fig.2. Year to year Distribution of Bacterial Meningitis isolates in Gondar University Hospital, 2012–2021

Discussion

Assessment of the burden of ABM, knowing major etiologic agents, and showing the changes in epidemiology are vital to establish effective and functional preventive strategies of diseases. Three sentinel sites of which Gondar University Hospital is one have been actively doing the under-five PBM surveillance in Ethiopia. A total of 4311 under-five children with suspected meningitis were enrolled at the Hospital over the last 10 years. Majority (71%) of suspected cases were infants below 12months of age; the commonest bacteria identified by CSF culture and PCR was SPN, and the overall mortality rate was 1%. These Findings support earlier evidences which revealed SPN as the leading cause of bacterial meningitis in the same Hospital (11), and also a report from Senegal found that SPN was the leading cause (50%) of ABM in under-five children (12). Reports from these studies showed that ABM due to HIB is decreasing perhaps due to early introduction of HIB vaccine in the centers. A multi-centered Hospital Surveillance done in Turkey on children below 18yrs of age identified that NM is the leading cause of ABM accounting for nearly 71% of cases which is in contrary to our study (13). This difference may be due to the difference in age difference of participants, i.e., the Turkey study included older children up to 18rs while participants in our study were only under-five children which may bring differences in bacterial etiologies of ABM. Another reason could be the difference in setups, i.e., the study in Turkey used PCV-13 vaccine which may reduce SPN cases, while we used PCV-10 vaccine. . An Indian study also reported that SPN is a leading cause (40.8%) of ABM both in children and adults which is similar with our report (14).

Another report from Brazil reported that using PCR for CSF sample with negative culture result showed 65% positive which indicating that using PCR can improve the speed and accuracy of acute bacterial meningitis diagnosis in a clinical setting as a complement to classical immunological and bacteriological assays in CSF. It is very useful for CSF culture-negative acute bacterial meningitis (15). Another study from Iran reported that PCR has a higher rate of bacterial detection from CSF than culture (52% vs46%) (16).

The results showed that using PCR testing will have significant value in bacterial identification which is also observed in our research; even if PCR is done only on 66 CSF samples, it revealed 3 additional cases of HIB and 10 cases of SPN which were reported

to be culture negative. So, utilization of PCR test in CSF samples is recommended for clinical benefit.

Similar studies done in Ghana and Senegal based on sentinel Surveillance revealed that suspected bacterial meningitis are decreasing and identified SPN as a major cause of ABM with serotypes 19A and 23F being major contributors(17,18). This is in line with our findings. Another study done in Colombia reported NM to be the commonest (75%) cause of ABM followed by SPN (19).

In this study, only a few bacterial pathogens were isolated using culture methods, likely due to high rates of antibiotic use prior to hospitalization and LP which may be an indicator to use more sensitive methods specially to detect *HIB* such as LAT which is not routinely practiced and done only in 2.8% (121/4311). In this study, LAT detected more *HIB* (17.4%) than *SPN* (3.3%) and *NM* (4.1%). A report from 5 sentinel Hospitals from Nigeria reported that nearly 2.9% of suspected cases were confirmed to have PBM with mortality rate of 15%, and the dominant pathogen was found to be SPN which is almost comparable with our study except mortality in our case was only 1%. In our study, majority (5/6) of SPN serotypes were caused by serotypes that are included in PCV-vaccine which is also the case in Nigerian study which reported that nearly half of the pneumococcal meningitis cases were due to serotypes covered by PCV-10. Our study identified 2 cases of *HIB* serotypes and a single case of serotype W of *Meningococcal* meningitis which is in agreement with other studies (20-22).

We have found that our Hospital is having very limited utilization of LAT and PCR which were done only in 2.8% and 1.5%, respectively which might have contributed to the lower pathogen detection rate. Utilization of LAT and PCR tests showed significant improvement in detection of common organisms and also helped identify other pathogens from different countries. Studies examining bacterial meningitis in the last decade using sensitive methods such as LAT or polymerase chain reaction (PCR) have detected *HIB* in 18 to 35 per cent of likely childhood bacterial meningitis cases (23, 24, 25).

Indian Studies reported that Multiplex PCR was more sensitive than culture or antigen detection, and employing this assay can significantly increase the speed and accuracy of identification of the pathogen.

In lack of PCR, using the combination of Gram staining, culture, and LAT can increase the sensitivity and specificity close to 100%. Using Gram staining and LAT together can achieve a detection rate of nearly 85% of cases of ABM (26, 27).

So, applying Molecular techniques are more effective for establishing the etiological diagnosis of pyogenic meningitis, although they cannot completely replace conventional tests.

Studies from Central African Republic and India reported that applying PCR was able to detect bacteria missed by Culture in 20% and 10.5% of cases,

respectively(28, 29). Therefore PCR is a sensitive method that can be introduced in different laboratories to increase detection and help assess the performance of Surveillance and vaccinations programs.

In remote areas of Niger where proper laboratories are not available, storing CSF and applying PCR test showed significant result in identifying pathogens from CSF (30). Again recommending PCR test in resource limited areas where routine tests like Culture are not reliable due to different reasons including technicalities, using PCR will have significant impact since it can be done on small volume of CSF, it doesn't need viable bacteria, and samples can be transported easily which is one of the commonest problems of CSF culture yield.

In conclusion; our study showed that Suspected ABM cases are increasing from 2012-2021 but confirmed cases of bacterial meningitis are significantly decreasing. The increment of suspected meningitis cases in the last years is most probably due to the inclusion of neonatal ages below 1months, for whom CSF analysis is done for every neonate suspected of Sepsis to rollout meningitis with no clear evidence of meningitis unlike older children which made the lower CSF positive result in the surveillance activity of our Hospital. *Streptococcus pneumoniae* is found to be the commonest cause of community acquired bacterial meningitis. Molecular diagnosis is gaining momentum for a rapid detection of etiological agents with high sensitivity and specificity since it is unaffected by viability of the organisms. Hence, PCR should be introduced in the diagnosis to overcome the dependency on conventional methods and to improve the low detection rate of CSF culture.

The major Limitation of the study is being a retrospective one which was done on data collected at the sentinel site for the last 10years (2012-2021); some of the information was not complete: final diagnosis, outcome, sequelae and only few PCR tests were done and had it been a prospective study such gaps could have been filled.

Declarations

Availability of data and materials

Data set: The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The author declared that there is no conflict of interest in conducting this study.

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Authors' contribution

The author (MA) was fully involved in designing the research work, cleaning data, did the analysis and write up of the manuscript. The Author read and ap-

proved the final manuscript.

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