Color Doppler Sonography in fetal growth retardation: Need of the hour

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ABSTRACT

Objective: Color Doppler sonography and flow velocimetry of fetal UA, MCA, and RA for accurate prediction of perinatal outcome in fetal growth retardation. *Material and methods*: Prospective study of 200 singleton pregnancies having FGR (24-39 weeks). BPD, HC, AC and FL were obtained for fetal weight on high end sonography machine with 2-5 MHz transducer. Color Doppler waveform measurements of fetal UA PI, MCA PI, RA PI, UA/MCA PI ratio, and RA/MCA PI ratio were calculated. *Results*: Analysis of 197 pregnant women and 197 fetuses was done. 40.6 percent pregnant women had one or more complication of pregnancy such as hypertension, diabetes, preterm membrane rupture, vaginal bleeding, and miscellaneous complications. There were 8 stillbirths and 189 live births. 103 of 189 live born neonates were hospitalized to premature baby critical care unit, 86 staying for 48 hours or more. 47 fetuses experienced perinatal problem, 8 Still births, 3 infant deaths, 1 ischemic encephalopathy of hypoxia, 1 intraventricular hemorrhage, 1 periventricular leukomalacia, 2 necrotic enterocolitis, 33 Cesarean section, 5 pH of umbilical cord less than 7.1 and 13 Apgar score less than 7 were minor outcomes. UA PI sensitivity 85.17%, MCA PI sensitivity 70.25% and RA PI sensitivity 37.50% was observed. *Conclusion:* An aberrant UA PI suggests poor perinatal results. Normal MCA PI identifies fetuses unlikely to have significant perinatal problems.

Keywords: Fetal Growth Retardation, Perinatal Outcome, Color Doppler Sonography, Umbilical Artery, Middle Cerebral Artery, Renal Artery.

1. INTRODUCTION

In India, fetal growth retardation (FGR) is very prevalent condition, caused by maternal malnutrition or fetal internal causes. When compared to fetuses with normal growth characteristics, FGR is usually linked to high chances of perinatal morbidity, mortality, delayed postnatal neurodevelopment, and potentially even adult life extension (Dobson et al., 1981; Wennergren et al., 1988; Kok et al., 1998). This places a significant cost on society and the health-care system. The health-care system urgently needs accurate FGR diagnosis and perinatal outcome prediction. Color Doppler sonography is a noninvasive modality to diagnose FGR, predict perinatal outcome, change fetal treatment, reduce fetal mortality, morbidity and prevent postnatal neurological

problems. If the fetal weight is lower than 10th percentile, then it is called fetus with growth retardation. American Congress of Gynecologists & Obstetricians recommends this definition. Sonographic biometry helps in the diagnosis of a diverse range of tiny-for-gestational-age fetuses, including those with FGR, those with a small constitutional size, and those having normal growth but misinterpreted as smaller. Major goal of prenatal care is to recognize the FGR correctly so that timely intervention may be made.

Color Doppler evaluation of umbilical artery is the most thoroughly validated noninvasive measure of fetal health (Alfirevic & Neilson, 1995; Al-sakkal & kader, 2020). Its usage in risk pregnancies has resulted in reduction of perinatal death. The brain circulation in the fetus has a high impedance and constant flow during whole cardiac cycle. In fetal hypoxia, blood flow is redistributed centrally, with additional blood flow to vital organs like heart, brain and adrenals and decreased flow to placental circulation and peripheral vessels (Peeters et al., 1979). The PI of renal artery is reduced with increasing gestation in normal fetus, implying an increase in renal blood flow. FGR fetuses have a higher renal artery PI than normal pregnancies. When compared to normal fetuses, previous studies on Color Doppler sonography assessment of fetal circulation found a remarkable increase in umbilical artery PI, a remarkable reduction in middle cerebral artery PI and a remarkable increase in renal artery PI in fetuses with FGR (van den Wijngaard et al., 1989; Arduini & Rizzo, 1991). The major aim of our study was to detect fetal impairment early enough to allow for proper intervention and prevent more significant consequences.

Objectives
To confirm Fetal Growth Retardation (FGR) using sonographic biometry, to investigate the Color Doppler flow velocimetry of fetal umbilical, middle cerebral and renal artery for an accurate prognosis of perinatal outcome in cases of FGR and to compare the performance of PI of umbilical, middle cerebral and renal arteries in perinatal outcome.

2. MATERIAL & METHODS

Prospective observational study was carried out in medical institute in Central India for 2 years, from April 2019 to March 2021, after the approval of Institutional Ethics Committee (No. NKPSIMS & RC and LMH/IEC/11/2019). Pregnant women who were suggested obstetric sonography and fulfilled the inclusion criteria of study were allowed to be part the study. Prior to examination, the expectant woman gave her written consent.200 singleton pregnancies having FGR fetus (24-39 weeks gestation), as determined by a prior sonography scan performed at 20 weeks or earlier. Abdominal circumference or fetal weights were estimated to be below 10th percentile of normal fetal intrauterine age using sonography. Multiple fetuses as well as any fetus with proven significant embryological or developmental defect, or both were excluded from study. Four standard fetal parameters, BPD, HC, AC and FL were obtained (Arbuckle et al., 1993). Hadlock model was used for determining fetal weight (Arduini & Rizzo,1990). Following sonography biometry and a complete anatomic survey, Color Doppler sonography was done. Proper diagnosis of a growth retarded fetus necessitates a precise estimation of date of delivery (EDD). The EDD is usually determined during the first antenatal checkup. The EDD was calculated as early as feasible for accurate gestational age (Uquillas et al., 2017).

According to ACOG, sonography for fetal intrauterine age determination must be done at the first antenatal appointment to avoid inaccurate LMP dates (Fong et al., 1996). Sonography in the first three months of pregnancy is the most reliable indicator for establishing EDD. At study entrance and at 34 weeks' gestational age, Color Doppler wave form measurements of UA PI, MCA PI, RA PI, UA/MCA PI ratio and RA/MCA PI ratio were performed, unless delivery had occurred. With a pregnant lady in a reclined position and a fetus in the resting phase, a Color Doppler sonography examination was done on a high-end Color Doppler sonography machine (Esaote-Mylab50). The frequency of the transducer was 2-5MHz. Color Doppler sampling volume was 2-3 mm, with 50-100Hz filter. For simplicity and uniformity, free loop of umbilical cord was preferred for umbilical artery sampling. Doppler velocimetry was the key surveillance method for growth retarded fetuses because it analyses the blood circulation resistance in fetal-placental complex.

Umbilical artery waveform showed gradual reduction of end diastolic blood flow to absent flow and finally reversal of blood flow due to placental or maternal circumstances which obstructs tiny muscle arteries in the placenta (Arbuckle et al., 1993; Anderson et al., 2007). At the sphenoid bone, along transverse plane, image of fetal head was acquired for MCA Color Doppler sonography. Circle of Willis was shown using Color Doppler flow The MCA was sampled at 10mm distance from its origin (Gramellini et al., 1992). In normal pregnancies, the fetal brain has a high concentration of neurons. Long axis picture of fetal kidney was acquired for renal artery Color Doppler sonography. The complete renal artery was visualized using Color flow imaging from its origin from aorta up to hilum of kidney, with volume sampling of renal artery from its proximal part. Five successive waveforms were recorded by using spectral Doppler waveforms from each renal artery and PI was measured from mean of successive 5 recordings (Fong et al., 1996).

The observations of Color Doppler sonography at the start of the trial were analyzed to see if they could predict perinatal outcome. If one or more of the main or minor issues listed below occurred, the perinatal result was judged negative. i) Perinatal death (excluding deadly anomalies), ii) Hypoxic-ischemic encephalopathy, iii) Major periventricular or intraventricular hemorrhage, iv) Leukomalacia around ventricles, v) Necrotic enterocolitis were the most common adverse outcomes. The UA PI,RA PI, UA/MCA PI ratio and RA/MCA PI ratio, were declared abnormal (Hadlock et al., 1982), if it was over 95th percentile of earlier studies for corresponding fetal age. If MCAPI was below 5th percentile ,it was declared abnormal (Dubiel et al., 1997). For all Color Doppler values, sensitivity, specificity, negative predictivity value, positive predictivity value and probability ratios were estimated.

3. RESULTS

One pregnancy was omitted from analysis out of 200 because of deadly congenital defects discovered after birth (trisomy18). We did not get satisfactory Doppler spectral readings from MCA in two pregnancies. Table 1 summarizes the analysis of 197pregnant women and 197 fetuses. At the start of study, 40.6 percent pregnant women had minimum one complication of pregnancy, such as hypertension (requiring medication or hospitalization) in 18.5 percent (36 of 197), diabetes mellitus (requiring insulin) in 2.5 percent (5 of 197), preterm rupture of membranes in 9.6 percent (19 of 197), vaginal bleeding (requiring hospital admission) in 6.2 percent (12 of 197) and miscellaneous complications in 15.3 percent (30 of 197). At the fetal gestational age of 32 weeks, first Color Doppler sonography was performed. Within two weeks of the initial Color Doppler, 102 neonates (51.8%) had been delivered. There were eight stillbirths (normally developed neonates) and 189 live births. 103 (54.4%) of the 189 live born neonates were hospitalized to premature baby critical care unit, with 86 staying for 48 hours or more. Three neonatal fatalities occurred, as well as two nonlethal chromosomal abnormalities (trisomy 21) and nine non-lethal minor congenital malformations.

Table 1 Analysis of 197 fetuses and pregnant women

	PARAMETERS	VALUE
1.	Health of pregnant women	
a.	Age (years)	27 ±7
b.	Parity	0 – 3
2.	Complications related to pregnancy (Total pregnant women)	80
3.	Health of fetus (fetal Gestational age on first Color Doppler)	32±2 weeks
4.	First Doppler ultrasound performed within 2 weeks of delivery	102
5.	Ultrasound biometry-	
a.	AC <10th percentile	177
b.	Estimated fetal weight <10th percentile	142
c.	Both<10th percentile	129
6.	Actual birth weight (<10th percentile)	138

Table 2 lists the characteristics of the 11 cases of prenatal mortality. A total of 47 fetuses (24.1%) experienced minimum one significant or less significant perinatal problem, with few having multiple problems. Stillbirths (n=8), infant mortality (n=3), ischemic encephalopathy due to hypoxia (n=1), hemorrhage within ventricular system of grade IV severity (n=1), cystic leukomalacia around ventricles (n=1), and necrotic entero-colitis (n=2) were the most common adverse events. Cesarean delivery for fetal hypoxia (n=33), pH of umbilical cord lower than 7.1 (n=5), Apgar score less than 7 after five minutes (n=13) were minor outcomes. Optimum spectral Doppler readings were acquired from UA and MCA in 197 fetuses, from RA in 158 fetuses at study entrance and the first Color Doppler sonography test. The analysis of PI values of UA, MCA, RA and PI ratios of UA/MCA, RA/MCA for any unfavorable neonatal outcome prediction (significant, less significant or both) were calculated using first Color Doppler sonography results (figure 1 – 4). University of Arizona's PI was the most sensitive (sensitivity 85.89 percent). MCA PI (p0.001), UA/MCA PI ratio (p0.001), RA PI (p0.001), and RA/MCA PI ratio (p=0.005) were all considerably more sensitive. The specificity of the UA PI was 68.34%, which was substantially higher than the MCA PI (p0.001), PI ratio of UA/MCA (p=0.002), PI

ratio of RA/MCA (p=0.001). PPV of the UA PI was the highest (85.17 percent). It also had a high NPV (Negative Predictive Value) (58.44 percent). RA PI showed lowest sensitivity (37.50%) but the specificity was highest (97.50%). RA PI had a Positive Predictive Value (PPV) of just 49.09 percent.

Table 3 summarizes the PI values of UA, MCA, RA and PI ratio of UA/MCA and RA/MCA for predicting poor perinatal outcome. The most sensitive PI was still the UA PI. The first Color Doppler sonography investigation was performed on 70 fetuses.

Table 2 Poor perinatal outcome

	Poor perinatal outcome	Number of fetuses
A)	Major	
1.	Stillbirth	8
2.	Neonatal Deaths	3
3.	Ischemic Encephalopathy due to hypoxia	1
4.	Hemorrhage within ventricular system of grade IV severity	1
5.	Cystic Leukomalacia surrounding ventricular system	1
6.	Necrotic Entero-colitis	2
B)	Non-Major	
1.	Delivery by Cesarean section	33
2.	pH of umbilical artery less than 7.1	5
3.	5 min APGAR score <7	13

Table 3 PI and PI ratios of UA, MCA and RA for poor perinatal outcome

|	Pulsatility index	Sensitivity	Specificity	Positive predictivity	Negative predictivity	Positive likelihood ratio	Negative likelihood ratio	Overall Accuracy
1.	Umbilical artery(n=197)	85.89 %	68.34%	85.71%	58.44%	1.78	0.32	76.14 %
2.	MCA(n=197)	70.25%	40.79%	65.38%	46.27%	1.19	0.73	58.88 %
3.	Renal artery(n=158)	37.50%	77.60%	49.09%	68.31%	1.67	0.81	62.94 %
4.	UA/ MCA ratio(n=197)	80.69%	55.67%	80.14%	45.10%	1.45	0.44	71.07 %
5.	RA/ MCA ratio(n=197)	55.17%	65.13 %	53.33%	73.47%	1.97	0.62	65.82 %
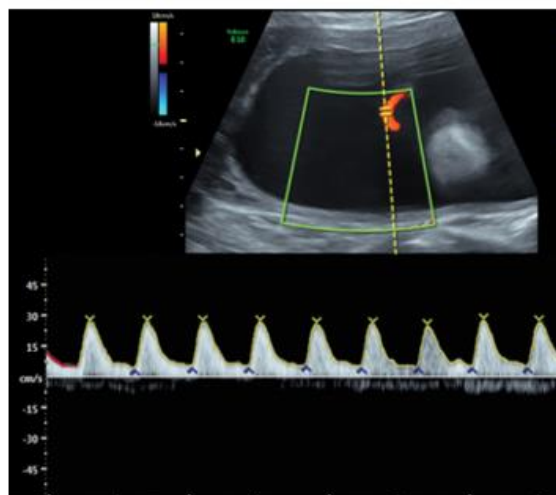
Figure 1 Showing Color Doppler sonography spectrum of umbilical artery in second trimester demonstrating normal waveforms.
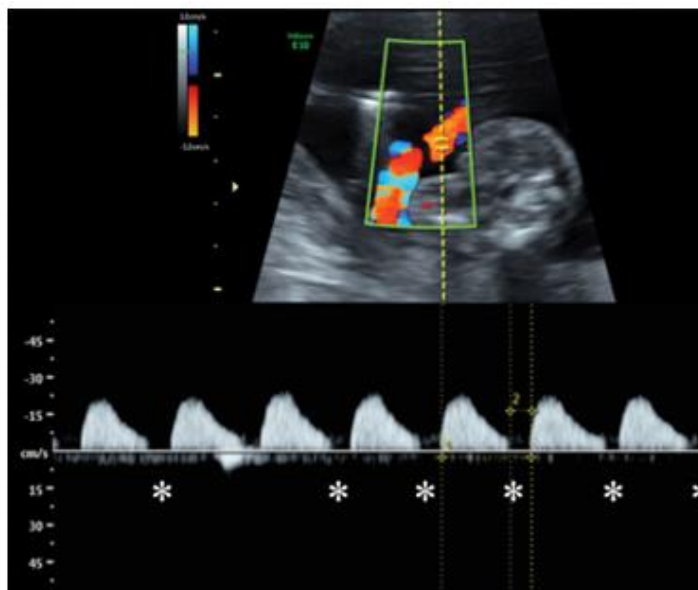
Figure 2 Showing Color Doppler sonography spectrum of umbilical artery in second trimester demonstrating end diastolic flow absence.
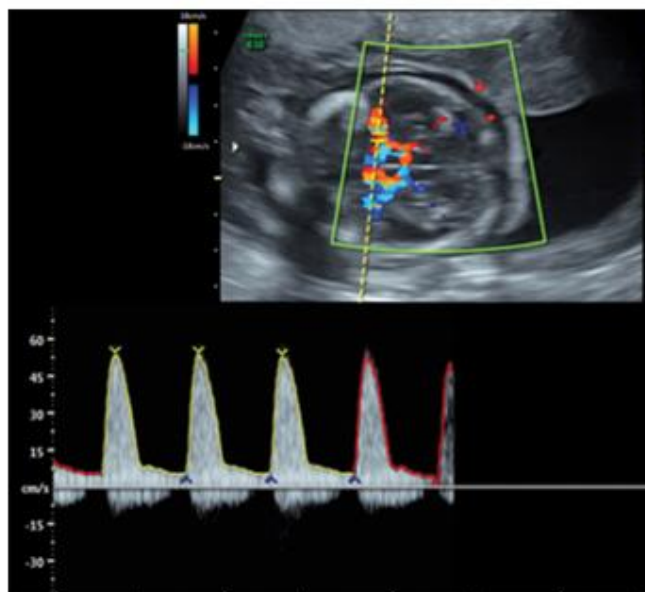

Figure 3 showing Color Doppler sonography spectrum of MCA in second trimester demonstrating normal waveforms
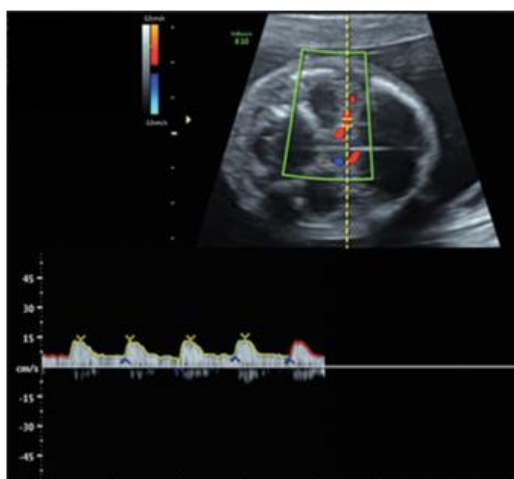

Figure 4 Showing Color Doppler sonography spectrum of MCA in second trimester demonstrating abnormal spectral waveforms.

4. DISCUSSION

A fetus is diagnosed as having fetal growth retardation, when its estimated weight is less than 10th percentile (Uquillas et al., 2017). Royal College of Gynecologists and Obstetricians believes that, below 10th percentile abdomen circumference qualifies for growth restriction. Fetal growth retardation (FGR) increase the chances of fetal death, neonatal mortality and morbidity (Resnik, 2002). Genetic factors and development limitation owing to utero-placental insufficiency lead tiny-for-gestational-age fetuses to be small. In a growth retarded fetus, the blood is diverted to heart and brain from non-essential organs in response to persistent hypoxia. Many observational studies have looked at cerebral redistribution in high-risk pregnancies to see if it can predict perinatal outcome. In the past, Color Doppler velocimetry has been intensively researched. The MCA was the most accessible conduit for examination of cerebral circulation of fetus. Acceptable flow-velocity waveforms for investigation were obtained in 91-94% fetuses in prior studies on fetal MCA (van den Wijngaard et al., 1989; Arduini & Rizzo, 1990). We could obtain optimum spectral Doppler waveforms from MCA in 99 percent participants in our investigations.

Color Doppler sonography study of fetal renal artery was more difficult as compared to UA and MCA. In 80% fetuses, we got adequate spectral Doppler waveforms from renal artery. In prior studies, success rates of 72 percent to 87 percent of normal fetuses were reported (Committee on practice bulletins, 2016; Peeters et al., 1979). The renal artery was frequently the final vessel investigated in our study and fetal movements, breathing led to reduced rate of success. The complexity of technique also resulted in renal artery PI's limited sensitivity. Arduini & Rizzo (1992) investigated test features of PI from UA, MCA and RA in 120 SGA fetuses to watch for the unfavorable fetal perinatal results. Perinatal death, cesarean section for fetal hypoxia, five-minute Apgar score lower than7 and respiratory distress requiring critical neonatal care unit admission for 48 hours or more were all reported in 46.7 percent (56 of 120) of the fetuses.

The author discovered that PI ratio of UA/MCA was the better predictor test than UA, MCA, and RA PI alone when using the initial Color Doppler result following the SGA diagnosis for analysis (sensitivity 89 percent vs 68 percent, 66 percent and 43 percent, specificity 94 percent vs 91 percent, 88 percent, and 91 percent). Fong et al., (1996) studied over 300 high-risk pregnancies. In 40.3 percent of instances, the neonatal weight was less than third percentile, and 20.1 percent (59/293) fetuses were delivered prior to 32 weeks GA. The rate of negative perinatal result (significant, less significant or both) was 25.9%. Significant unfavorable perinatal results occurred in 8.2 percent. The UA PI had a greater PPV for unfavorable perinatal results than UA/MCA PI ratio and MCA PI when the first spectral Doppler sonography results were considered for analysis is linked to higher risk of intrauterine fetal death, neonatal mortality and morbidity.

According to Uquillas et al., (2017), the hazards increased with severity of limitation. Fetuses with weight below 10th percentile and 1.5- 2.5 kg had perinatal mortality rates 5 to 30 times higher than babies with weight 10th- 90th percentile. Perinatal mortality rates were 70-100 times higher if weight of fetus was less than 1.5 kg. With abnormal UA spectral Doppler waveforms, was observed, the strong and significant connection with unfavorable perinatal results in growth retarded fetuses. Bahado-Singh et al., (1999) discovered a significant hike in prenatal mortality and morbidity in cases with aberrant cerebro-placental ratio. They used p.001 for the 10th percentile birth weight. The CP ratio was found more useful for prediction of perinatal results when compared to UA spectral Doppler waveforms. As revealed by regression analysis, the CP ratio did not correspond substantially with perinatal results in fetuses older than 34 weeks, which was an interesting discovery. Khanduri et al., (2013) found that UA PI shows the highest specificity and sensitivity with second visit at 28-32 weeks and third visit at 32-37 weeks. The total diagnostic accuracy of the MCA PI was 52.8 percent. Bellido-González et al., (2017) discovered those fetuses with growth retardation and an aberrant cerebro-placental ratio (MCA/UA PI), born at term, have increased risk of delayed and less cognitive functions till the age of 6-8 years than fetuses having normal ratio.

Our study results are consistent with those of Fong et al., (1996) and Uquillas et al., (2017) but different from the studies which have found that UA/MCA PI ratio is more reliable than UA PI in prediction of poor outcomes (Arduini & Rizzo, 1992; Gramellini et al., 1992; Arias, 1994). The UA PI was the most important information in FGR for distinguishing normal fetuses from likely to be compromised or compromised fetuses. We focused on the immediate perinatal outcomes in our research. It's unclear that cerebral diversion of blood was a protective response to fetal stress or indication of future impairment of neurodevelopment. In our study, some neonates may show long-term effects, necessitating the completion of neurological development follow-up study.

Epidemiologic studies have found a link between prenatal growth retardation and abnormal long term health effects, such as delayed cognitive development in children and in adult, disorders like heart disease, diabetes and obesity. Due to differences in study design, patient selection criteria, definitions of poor outcomes, varying cut-off values of abnormal and normal findings, different numbers of patients in the studies, apple to apple comparison of different studies was challenging. It was also not possible to compare the results because the criteria of unfavorable perinatal results differed from one study to the next. The venous system

has recently received increased attention (Mari et al., 1995). Ductus venous flow absence or flow reversal and umbilical vein pulsation are reported as warning signals of heart compromise and neonatal death (Kiserud et al., 1994; Hecher et al., 1995; Ozcan et al., 1998).

5. CONCLUSION

The most usable definition for Fetal Growth Retardation is weight of fetus below10th percentile. If the fetus is declared viable, Color Doppler sonography of umbilical artery is advisable to detect risk of unfavorable outcome and to decide delivery time. An aberrant UA PI, rather than an abnormal MCA or RA PI, suggests greater prediction of poor perinatal results. Normal MCA PI can help identify fetuses, which are unlikely to have significant perinatal results, especially before 32 gestational weeks. In fetuses having aberrant UA PI, statistically significant risk of mortality is present. In growth retarded fetuses, Color Doppler detection of fetal cerebral redistribution effect also predicts neonatal prognosis.

Abbreviations

Fetal Growth Retardation (FGR), Umbilical Artery (UA), Middle Cerebral Artery (MCA), Renal Artery (RA), Pulsatility Index (PI), Biparietal Diameter (BPD), Head Circumference (HC), Abdominal Circumference (AC), Femur Length (FL).

Authors Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Ethical Approval

The study was approved by Medical Ethics Committee of NKP Salve Institute of Medical Sciences and Research Centre with the letter number: (No. NKPSIMS & RC and LMH/IEC/11/2019).

Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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