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Prognosis of preterm premature rupture of membranes between 20 and 24 weeks of gestation: A retrospective cohort study

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ABSTRACT

Background: The previous study on prognosis of preterm premature rupture of fetal membranes (pPROM) near the limit of viability showed various survival rate raging from 26 to 57 %%. This may be partly due to the fact that treatment of prematurely born babies vary from one country to another, or sometimes within a single country. In Japan, resuscitation efforts are made to newborns of early gestational age, normally from 22 weeks of gestation.

Objective: To assess the natural history and short- and long-term prognosis in pregnancies complicated by preterm premature rupture of membranes (pPROM) near the limit of viability in a hospital in Japan.

Method: We conducted a single-center retrospective cohort study. Cases with diagnosis of pPROM at a gestational age of 20–23 6/7 weeks and delivered in our hospital between April 2007 and December 2017 were examined.

Result: 66 cases were included and of those, 54 (81.1 %) newborns survived to discharge. Of the neonates who survived to discharge, 42 (77.8 % of survivors) experienced severe morbidity at the time of discharge. Multivariate logistic regression analysis showed that later gestational age at pPROM and longer latency period were significantly associated with survival with no severe morbidities (per one day increase, adjusted odds ratio (OR) 1.37, 95 % CI 1.03–1.83, p = 0.033 and per one day increase, adjusted OR 1.11, 95 % CI 1.02–1.21, p = 0.015). Of 23 cases followed at 36 months, 8 (34.8 %) showed developmental delay.

Conclusion: The survival rate was significantly higher than the previous studies, yet many of the survivors experienced short-term severe morbidity. Of those who experienced short-term severe morbidity, however, more than half showed normal range development at 36 months.

Introduction

Preterm premature rupture of fetal membranes (pPROM) affects 2–4 % of pregnancies accounting for 25 % of preterm birth [1]. pPROM near the limit of fetal viability is an uncommon complication of pregnancy, affecting approximately 4 in 1000 gravidas [2]. Maternal, fetal, and neonatal complications resulting from this condition are significant including chorioamnionitis, fetal loss, pulmonary hypoplasia and complications of extreme prematurity among surviving infants [2].

When delivery is assumed near the limit of viability, families and health care teams face complex and ethically challenging decisions [3]. The past studies on the prognosis of pPROM near the limit of survival showed substantially varying prognosis with survival rate raging from 26 to 57 % [4–17]. This may be partly due to the fact that treatment of prematurely born babies vary from one country to another, or sometimes within a single country. Though protocols for resuscitation of prematurely born babies theoretically play an important role in determining the prognosis of babies, in the past studies, often they were not specified or even if they were, thresholds for resuscitation were 24 weeks of gestation or later. Thus, in most cases babies born in 22 weeks of gestation are treated with palliative care so as most of those born in 23 weeks.

In our facility in Japan, we actively treat every newborn from 22 weeks of gestation once they react to initial resuscitation. Thus, this study makes the first report of pPROM near the limit of viability in which resuscitation efforts are made uniformly once babies reach 22 weeks of gestation.

The aim of this study was to assess the natural history and short- and long-term prognoses in pregnancies complicated by pPROM between 20 and 23 6/7 weeks of gestation.

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Patients and methods

This is a single-center retrospective cohort study at Tokyo Metropolitan Ohtsuka Hospital, a tertiary referral center in Tokyo, Japan. Inclusion criteria were cases of diagnoses as pPROM at a gestational age of 20–23 6/7 weeks and delivered in our hospital from April 1, 2007, to December 31, 2017. Patients who chose to terminate pregnancy by means of immediate induction of labor and pregnancies complicated by major fetal anomalies were excluded (Fig. 1). Because it is illegal in Japan to terminate pregnancy once gestational age reaches 22 weeks, the choice of termination of pregnancy is limited to those with gestational age prior to 22 weeks of gestation.

Patient data was obtained from clinical records regarding demographic characteristics, medical and obstetric history, complications and outcomes of the mothers and their neonates. Ethical approval was obtained from the Tokyo Metropolitan Ohtsuka Hospital ethics committee. Informed written consent was waived because this study solely used the data obtained from clinical practice.

Neurodevelopmental assessments of the surviving neonates were conducted in the neonatal follow-up clinic of the hospital in 36 months corrected age using the Kyoto Scale of Psychological Development (KSPD) test. The latest version of the KSPD was standardized in 2001 for children born in Japan, and the mean and 1 SD of the developmental quotient (DQ) were 100.6 and 13.4, respectively [18,19]. A DQ score of KSPD < 70, equivalent to a Bayley III cognitive score <85, [20], was interpreted as significantly delayed development according to the protocol by the Japan Neonatal Follow-up Study Group [21].

The diagnosis of pPROM was based on visible amniotic fluid with a sterile speculum examination and confirmation by Actim® PROM (Medix Biochemica) that was based on the detection of IGFBP-1 measurement, or ROM-check Membrane Immunoassay (Adeza Biochemical) that was based on the detection of fetal fibronectin depending on the availability.

The management protocol for pPROM included bed rest, daily monitoring of vital signs, uterine contraction and nonstress testing, weekly assessment of biophysical profile, treatment with antibiotics mostly with ampicillin 1 g every 6 or 8 h and oral azithromycin 1 g. The choice of antibiotic agent or duration of administration varied due to the medical conditions of the patient, culture results and attending doctor's discretion. Tocolysis with intravascular ritodrine hydrochloride or magnesium sulfate was conducted in the existence of uterine contraction. Antenatal corticosteroids (two doses of intramuscular 12 mg betamethasone 24 h apart) were administrated when delivery is anticipated within a week. Tocolysis was terminated when a patient was in active labor or developed clinical chorioamnionitis (as diagnosed by fever without another clear source and one or more of the following; tenderness in uterus, white cell count >15,000/mm [3], purulent vaginal discharge). Resuscitation is attempted to every newborn delivered in and after 22 weeks of gestation. Considering the low survival rate of newborn delivered in 22-0/7 to 22-6/7 weeks of gestation, we did not conduct cesarean section for fetal indication for fetus with this gestational age. Otherwise, indication of cesarean section was the same as that for term deliveries.

Severe neonatal morbidity was defined as any of the following neonatal morbidities: 1) bronchopulmonary dysplasia, defined as requirement for oxygen at postmenstrual age of 36 weeks of gestation; 2) severe neurologic injury, defined as grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, diagnosed by cranial ultrasonography; and 3) severe retinopathy of prematurity, defined as stage 3 or higher or requiring treatment. Other individual neonatal outcomes included necrotizing enterocolitis stage 2 or greater, seizures, sepsis, contractures, and days to initial discharge from hospitalization.

Severe oligohydramnios was defined at a maximal vertical pocket less than 1 cm or amniotic fluid index (AFI) less than 2 cm. The diagnosis of placental abruption was mainly made on clinical ground with symptoms such as abdominal pain and sign of blood clot attached to the placenta. Gestational age in these pregnancies was based on first-trimester ultrasonogram.

The background maternal characteristics, characteristics of pPROM, and pregnancy complications were compared between

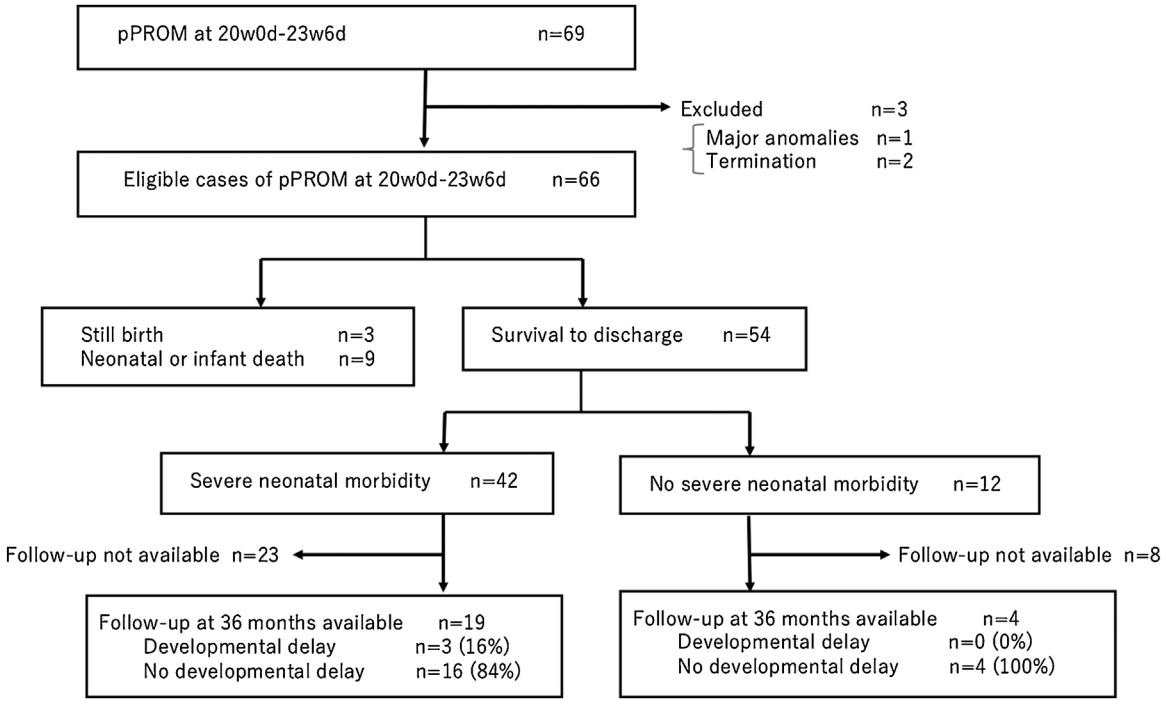

Fig. 1. Summary of outcomes of pPROM cases between 20 and 23 6/7 weeks of gestation.

pregnancies in which neonates survived to discharge and pregnancies complicated by severe neonatal comorbidities, stillbirth or neonatal death. The chi-squared test and the Fisher's exact test were used to compare categorical variables between the groups, as appropriate. Considering the small sample size, a nonparametric test (Mann-Whitney U-test) was used to compare continuous variables between the groups. We used a multivariate logistic regression analysis in order to identify factors that are independently associated with overall neonatal survival and neonatal survival without severe morbidity. Variables included in the multivariate logistic regression analysis were selected based on the previous studies [15,16] and the results of univariate analysis after being tested for multicollinearity. Statistical significance was defined with 2-sided p values of <0.05. We used odds ratios (ORs) with 95 % confidence intervals (95 % CIs). All statistical analyses were performed with The Statistical Package for Social Sciences ver. 23.0 (SPSS, Chicago, IL).

Results

69 neonates were born to women diagnosed with pPROM at a gestational age of 20–23 6/7 weeks during the study period. After excluding 2 cases where couples chose termination of pregnancy and one case with major abnormalities, 66 cases were included as the study subjects. Of the 66 cases, 54 (81.1 %) newborns survived to discharge (Fig. 1). Demographic and obstetric characteristics of the study cohort are presented in Table 1. Survivors were born at more advanced gestational age (24w6d ±14.2 days versus 23w4d ±8.6 days, p = 0.035) and had marginally longer latency period (14.8 ± 13.6 days versus 7.9 ± 8.2 days, p = 0.068), compared with those who did not survive. Survivors with no severe neonatal morbidities were less likely to be complicated by severe oligohydramnios than survivors with neonatal morbidities or non-survivors (8.3 % versus 46.3 %, p = 0.018) (Table 2). Survivors with no severe neonatal morbidities were born at more advanced gestational age (26w5.8d ±15.6 days compared with 24w1.3d ±10.8, P < 0.001), had longer latency period (25.9 days ±16.3 versus 10.8 days ±10.45, P = 0.002), and had higher birth weight (903.7 g ± 293.7 versus 623.0 g ± 202.0, P < 0.001), compared with survivors with severe neonatal morbidities or non-survivors. WBC and CRP at the diagnosis of ruptured membrane were higher in survivors with severe neonatal morbidities or non-survivors compared to survivors with no severe neonatal morbidities (11.3 (10^3 /μL) ±4.1 versus 13.7 (10^3 /μL) ±5.0, p = 0.026; 0.95 (mg/L) ±1.78 versus 1.96 (mg/L) ±2.07, p = 0.018).

Of the neonates who survived to discharge, 42 (77.8 % of survivors) had severe morbidity, 34 (63.0 %) with bronchopulmonary dysplasia, 6 (11.1 %) with severe neurologic injury, 25 (46.3 %) with severe retinopathy of prematurity (Table 3).

Table 4 shows survival rates by gestational age at the time of pPROM. The outcome was better for those with more advanced age when pPROM occurred.

Multivariate logistic regression analysis was shown in Table 5. Advanced gestational age at pPROM and longer latency period were significantly associated with survival with no severe morbidities (per one day increase, adjusted odds ratio (OR) 1.37, 95 % CI 1.03–1.83, p = 0.033 and per one day increase, adjusted OR 1.11, 95 % CI 1.02–1.21, p = 0.015, respectively). Longer latency period was marginally associated with overall survival (per one day increase, OR1.09, 95 %CI 0.99–1.20, p = 0.079). Higher serum CRP at the time of diagnosis of pPROM and severe oligohydramnios were marginally inversely associated with survival with no severe morbidities (OR 0.16, 95 %CI 0.02–1.08, p = 0.060 and OR 0.05, 95 % CI 0.01–1.08, p = 0.056 respectively).

A total of 23 of the 54 survivors were followed at 36 months corrected age. This is because many are referred to facilities closer to their residence.

Of those followed at 36 months, 8 (34.8 %) had developmental delay.

Discussion

In this study, we examined prognosis of pPROM between 20 and 23 6/7 weeks of gestation. Considering the low incidence of pPROM of this gestational age, our study presents important findings for prognosis of pPROM near the limit of viability which were

Table 1
Characteristics and pregnancy outcomes of survivors and nonsurvivors.

	All n = 66	Survivors n = 54	Nonsurvivors n = 12	P value
Characteristics				
Maternal age (year)	32.5 ± 6.1	32.6 ± 5.5	31.6 ± 8.7	0.953
Age older than 35	21 (31.8)	16(29.6)	5(41.7)	0.313
Nulliparity	37 (56.1)	29(53.7 %)	8(66.7 %)	0.413
GA at pPROM (week)	22w5.0d±6.0d	22w5.4d±5.5d	22w3.6d±7.9d	0.405
GA at pPROM 22 week or greater	54 (81.8)	46 (85.2)	8 (66.7)	0.139
Cerclage	3 (4.5)	2 (3.7)	1 (8.3)	0.416
Severe oligohydramnios	26 (39.4)	21 (38.9)	5 (41.7)	0.486
Pregnancy outcomes				
Duration of latency (days)	13.5 ± 13.0	14.8 ± 13.6	7.9 ± 8.15	0.068
Greater than 7	37 (56.1)	32 (59.3)	5 (41.7)	0.267
Greater than 14	25 (37.9)	23 (42.6)	2 (16.7)	0.086
Greater than 28	7 (10.6)	7 (13.0)	0 (0)	0.227
GA at birth (week)	24w4.4d±13.8d	24w6.1d±14.2d	23w4.5d±8.6d	**0.035**
24 or greater	41 (62.1)	35 (64.8)	6 (50.0)	0.262
25 or greater	22 (33.3)	21 (38.9)	1 (8.3)	**0.039**
26 or greater	14 (21.2)	14 (25.9)	0 (0)	**0.042**
Birth weight	667.5g ± 250.4	691.1 g ± 259.8	595.2g ± 135.3	0.146
WBC (10^3/μL)	13.3 ± 4.9	13.0 ± 5.0	14.5 ± 4.2	0.151
CRP (mg/L)	1.77 ± 2.04	1.73 ± 2.13	1.97 ± 1.64	0.345
Chorioamnionitis	53 (80.3)	44 (81.5)	9 (75.0)	0.436
Maternal sepsis	1 (1.5)	1 (1.9)	0 (0)	0.818
Placental abruption	3 (4.5)	1 (1.9)	2 (16.7)	0.083
Cord prolapse	3 (4.5)	3 (5.6)	0 (0)	0.542
Cesarean delivery	45 (68.2)	37 (68.5)	8 (66.7)	0.575

Data are mean ± standard deviation or n (%), unless otherwise specified.
Bold indicates significant P values.

Table 2
Characteristics and pregnancy outcomes of survivors without severe neonatal morbidities and survivors with severe neonatal morbidities or nonsurvivors.

	Survivors with no severe neonatal morbidities n = 12	**Neonatal morbidities or nonsurvivors n = 54**	**P value**
Characteristic			
Maternal age (year)	32.4 ± 5.3	32.4 ± 6.3	0.967
Age older than 35	3 (25.0)	18 (33.3)	0.425
Nulliparity	7 (58.3)	30 (55.6)	0.861
GA at pPROM (week)	23w0.8d±5.0d	22w4.49d±6.1d	0.064
GA at pPROM 22 week or greater	11 (91.7)	43 (79.6)	0.303
Cerclage	0 (0)	3 (5.6)	0.518
Severe oligohydramnios	1 (8.3)	25 (46.3)	**0.018**
Pregnancy outcomes			
Duration of latency (days)	25.9 ± 16.3	10.8 ± 10.45	**0.002**
Greater than 7	10 (83.3)	27 (50.0)	**0.035**
Greater than 14	9 (75.0)	16 (29.6)	**0.005**
Greater than 28	5 (41.7)	2 (3.7)	**0.002**
GA at birth (week)	26w5.8d±15.6d	24w1.3d±10.8d	<**0.001**
24 or greater	12 (100)	29 (53.7)	**0.002**
25 or greater	10 (83.3)	12 (22.2)	<**0.001**
26 or greater	8 (66.7)	6 (11.1)	<**0.001**
Birth weight	903.7 g ± 293.7	623.0g ± 202.0	<**0.001**
WBC ($10^3/\mu L$)	11.3 ± 4.1	13.7 ± 5.0	**0.026**
CRP (mg/L)	0.95 ± 1.78	1.96 ± 2.07	**0.018**
Chorioamnionitis	10 (83.3)	43 (79.6)	0.564
Maternal sepsis	0 (0)	1 (1.9)	0.818
Placental abruption	0 (0)	3 (5.6)	0.542
Cord prolapse	0 (0)	3 (5.6)	0.542
Cesarean delivery	9 (75.0)	36 (66.7)	0.425

Data are mean ± standard deviation or n (%) unless otherwise specified.
Bold indicates significant P values.

Table 3
Neonatal Morbidity Among Neonates Who Survived to Discharge.

	Survivors (n = 54)	
Outcome	n	Value
Birth weight (g)		691.1 ± 259.8
Greater than 500 g	44	81.5
Severe morbidity*	42	77.8
Bronchopulmonary dysplasia	34	63.0
Severe neurologic injury	6	11.1
Seizures	2	3.7
Necrotizing enterocolitis	5	9.3
ROP stage 3 or greater	25	46.3
sepsis	3	5.6
contractures	2	3.7
Time to discharge (days)		154.5 ± 52.6

ROP, retinopathy of prematurity.
Data are mean ± standard deviation, % [95 % confidence interval], or median (interquartile range) unless otherwise specified.
* Refers to any of the following conditions: bronchopulmonary dysplasia, severe neurologic injury(intraventricular hemorrhage grade 3 or 4 or periventricular leukomalacia), or retinopathy of prematurity stage 3 or greater.

managed in a single referral center using a standard contemporary protocol. This is also one of few studies that provided long-term prognosis of such cases.

The past studies on the prognosis of pPROM near the limit of survival showed substantially varying, but generally poor, prognosis with survival rate raging from 26 to 57 % [4–17], morbidity ratio from 37 to 83 %. This may be partly due to the fact that the past studies included different gestational ages where pPROM occurred; some included 14–23 weeks [6–9], while others included up to 28 weeks of gestational age [11]. Also, protocols for resuscitation of prematurely born babies vary though they theoretically play an important role on determining the prognosis of babies. In most studies neonates were resuscitated from 24 to 26 weeks of gestation [5,8,9] or others did not specify the threshold for resuscitation. In the study of Kibel et al. [15], each couple determined the threshold of gestational age at birth (23, 24, or 25 weeks) beyond which they would want an active resuscitation of the newborn and as a result 26 out of 104 newborns were treated with palliative care.

Our study makes the first report of prognosis of pPROM in which resuscitation efforts are made uniformly once babies reach 22 weeks of gestation. As a result, the survival rate of pPROM between 20 and 24 weeks of gestation in our study was above 80 %, which was much higher than the previous studies. In the previous report from Kibel et al. [15] of pPROM in the same periods of gestational weeks as ours, survival rate to discharge was 49.0 %.

On the other hand, of those who survived to discharge, 78 % had severe morbidities, which was higher than 47 % in the report from Kibel et al. [15] One of the reasons behind contrasting results of neonatal survival and the rate of morbidity may be derived from our protocols on neonatal resuscitation. This analysis is coherent

Table 4
Survival Rate by Gestational Age at the Time of Preterm PROM.

	Gestational Age at Time of Preterm PROM(wk)									
	20w0d-20w6d		21w0d-21w6d		22w0d-22w6d		23w0d-23w6d		Total	
Outcomes	n = 3	%	n = 9	%	n = 23	%	n = 31	%	n = 66	%
Overall survival	1	33.3	7	77.8	19	82.6	27	87.1	54	81.8
Survival without severe morbidity	0	0.0	1	11.1	3	13.0	8	25.8	12	18.2
Nonsurvival	2	66.7	2	22.2	4	17.4	4	12.9	12	18.2

Table 5
Variables Associated with Neonatal Survival: Multivariate Analysis.

	Overall Survival		Neonatal Survival with No Severe Morbidity	
	Adjusted OR (95 % CI)	p value	Adjusted OR (95 % CI)	p value
Nulliparity	0.76 (0.19–3.11)	0.706	2.98(0.26–34.63)	0.382
Gestational age at rupture (per 1 day increase)	1.08 (0.96-1.22)	0.210	1.37(1.03–1.83)	**0.033**
Latency (per 1 day increase)	1.09 (0.99–1.20)	0.079	1.11(1.02–1.21)	**0.015**
CRP (mg/L) per 1 mg/L increase	1.06 (0.75–1.45)	0.750	0.16(0.02–1.08)	0.060
Severe oligohydramnios	1.39 (0.32–6.12)	0.665	0.05(0.01–1.08)	0.056

Data are adjusted odds ratio (95 % confidence interval).
Values reflect the results of multivariable logistic regression analysis.
All the covariates that were used as adjustors are listed in the table.
Bold indicates significant associations.

with the fact that the mean gestational age and weight at birth in those who survived in Kibel's study were 26.1 weeks and 922 g, respectively, while in our study they were 24w6d and 691 g. Because the morbidity rate is largely dependent upon gestational age and weight at birth, the rise in comorbidity is explained by immaturity of newborns in our study. In other words, we might have saved the lives of less mature newborns who would have been treated with palliative care in Kibel's study.

Variables that are independently associated with better prognosis were similar to the previous studies. Gestational age at rupture of membrane and longer latency periods were associated with survival with no severe morbidities. One of the important findings in our study was that higher serum CRP at the time of diagnosis of ruptured membrane and severe oligohydramnios were inversely associated with survival with no severe morbidities. Identification of risk factors for adverse perinatal outcome will allow healthcare professionals to individualize counseling for pregnancies complicated by pPROM near the limit of viability. Higher CRP and oligohydramnios had moderate association with shorter latency, which might have resulted in increased morbidities (correlation coefficient between shorter latency and CRP was 0.405 and that for oligohydramnios was 0.284). Oligohydramnios can prohibit lung maturation and thus can affect prognosis.

We acknowledge several limitations of our study. First, a relatively small sample size due to rarity of pPROM. Second, the follow-up rate at 36 months was not very high. Of the 54 survivors, the follow-up data was obtained from only 23. Because our facility is a tertiary referral center in the urban Tokyo, babies are often referred back to their nearby hospitals once they become stable.

Yet, our findings are important because this is the first report on the prognosis of pPROM near the limit of viability from a facility in Japan where neonates were resuscitated from 22 weeks of gestation.

In summary, the overall neonatal survival rate was over 80 % for pPROM between 20 and 23 6/7 weeks of gestation, and 78 % of survived newborns were with severe morbidities at the time of discharge.

Contribution to authorship

The manuscript has been read and approved by all authors and all authors contributed to the manuscript. SS and KK conceived and designed the study. SS undertook collection, cleaning, analysis and interpretation of the data and wrote the earlier manuscript drafts. MF and KK revised subsequent manuscript drafts, reviewed records, and prepared tables and figures. YM provided expertise throughout the study and contributed to the final approval of the completed article

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Ethical approval statement

The study was approved by the Hospital Ethics Committee (Reception number 2018-64, date of approval: 3 December 2018)

Declaration of Competing Interest

The authors declare that they have no Conflict of Interest.

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