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ORIGINAL ARTICLE

Pulmonary hypertension in preterm infants with moderate-to-severe bronchopulmonary dysplasia (BPD)

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Abstract

Aim: To describe clinical characteristics of pulmonary hypertension (PH) associated with moderate to severe BPD (MSBPD) in premature infants born ≤32 weeks gestation.

Methods: This was a single centre retrospective cohort study, with reanalysis of echocardiographic studies for PH of infants born ≤32 weeks gestation with MSBPD admitted to a tertiary surgical neonatal service.

Results: In total, 268 babies with MSBPD were included in the study. Incidence of BPD-associated PH (BPD-PH) was 12.6% (34), of which 41% infants were observed to have severe PH. On multivariate analysis, need for positive pressure respiratory support at 36 weeks post menstrual age (PMA) was independently associated with PH ($p = 0.001$; 95% CI 2–13.5) Presence of PH and severity of PH were associated with increased mortality. Of babies with MSBPD-PH, 32% died before discharge from the neonatal unit.

Conclusion: Babies with MSBPD and PH are more likely to die before discharge from the neonatal unit. Need for positive pressure respiratory support at 36 weeks PMA is independently associated with PH. Babies with MSBPD with less than severe PH are also associated with increased mortality when compared to babies with MSBPD with no PH.

KEYWORDS
bronchopulmonary dysplasia with pulmonary hypertension, echocardiography, extreme prematurity, pulmonary hypertension

1 | INTRODUCTION

Preterm infants affected by pulmonary hypertension associated with moderate-to-severe bronchopulmonary dysplasia (MSBPD) are at high mortality risk, with a rate that varies between 42% and 50% by 2 years of age.[1] Abnormal vasoregulation, impaired gas exchange, systemic hypertension, left ventricular hypertrophy and development of systemic to pulmonary collateral vessels may complicate the clinical course.[2,3]

Abbreviations: BPD, bronchopulmonary dysplasia; BPD-PH, bronchopulmonary dysplasia associated pulmonary hypertension; LTSPH, less than severe pulmonary hypertension; MSBPD, moderate-to-severe bronchopulmonary dysplasia; MSBPD-PH, moderate-to-severe bronchopulmonary dysplasia associated with pulmonary hypertension; NHLBI, National Heart, Lung and Blood Institute; NICHD, National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; PDA, persistent ductus arteriosus; PH, pulmonary hypertension; PMA, post menstrual age.

Recent efforts to identify PH in infants with BPD using echocardiography have shown that this modality may provide an opportunity for implementation of preventive or treatment strategies to improve long-term outcomes.[4,5] Several recent studies have reported cardiovascular outcomes of PH in preterm infants.[6,7] A recent retrospective study suggested that BPD with PH is a possible independent risk factor for neurodevelopmental impairment at 3 years of age.[8] Currently, there are no international standardised guidelines regarding screening and follow-up of PH in infants with MSBPD.

2 | AIM

The aim of this study was to describe the incidence and outcomes of infants with pulmonary hypertension in preterm infants with MSBPD and identify the risk factors associated PH, which may inform development of a screening protocol for PH in infants with MSBPD.

> **Hypothesis 1.** Premature infants born at ≤32 weeks gestation with MSBPD who need positive pressure respiratory support at 36 weeks post menstrual age (PMA) are at increased risk of PH.

3 | MATERIALS AND METHODS

This was a retrospective cohort study of all preterm infants born ≤32 weeks gestational age with MSBPD admitted to St George's University Hospital Neonatal Intensive Care Unit, NICU (London, The United Kingdom) between June 2010 and July 2020. St. George's Hospital NICU is a large tertiary neonatal surgical centre that cares for an average 120 babies born ≤32 weeks gestation every year. We observed that over last 10 years although total number of babies born ≤32 weeks admitted to the unit have not changed, unit has been caring for more lower gestational babies (<26 weeks). All screening echocardiograms that were performed on these babies during their stay on neonatal unit were reanalysed prospectively for pulmonary hypertension by a single observer, accredited in Paediatric Echocardiography using objective definition described below. The observer was blinded to clinical data including echocardiography reports. Study images were reviewed offline on Phillips IntelliSpace PACS programme. This study was registered locally as audit/practice evaluation study (registration number: AUDI000824).

Clinical data concerning pregnancy, birth and outpatient follow-up were collected from each patient's electronic medical records. The data collected included gestational age at birth, birth weight, small for the gestational age (<3rd centile), gender, birth place (inborn or outborn), single or multiple gestation pregnancies, respiratory distress syndrome, duration of mechanical ventilation, mode of ventilation, tracheostomy, persistence of ductus arteriosus, necrotising enterocolitis (Bell's stage II and above), grade 3 or 4 intraventricular haemorrhage, maternal chorioamnionitis, maternal diabetes, oligohydramnios, antenatal and postnatal steroids, blood stream infections and antibiotics use.

Key Notes

- 13% of the babies born at ≤32 weeks gestation with moderate to severe BPD (MSBPD) develop pulmonary hypertension, associated with up to 32% mortality risk before 2 years of age.
- Need for positive pressure respiratory support at 36 weeks post menstrual age (PMA) in babies born ≤32 weeks gestation with MSBPD is independently associated with pulmonary hypertension (PH).
- Babies with MSBPD with less than severe PH are also associated with increased mortality compared to babies with MSBPD no PH.

For this study, the time point of echocardiographic screening of pulmonary hypertension was assigned to any echocardiogram done closest to 36 weeks PMA ideally from 32 weeks PMA until discharge. An objective and pragmatic definition for diagnosing of no PH, less than severe PH and severe PH forms was used as presence of one of three criteria shown in Table 1. We classified BPD severity as per NICHD (United States National Institute of Child Health and Human Development) and NHLBI (United States National Heart, Lung and Blood Institute)[9] regulations as shown in Table 2. We stratified respiratory support as

A Infants needing positive pressure support: It included invasive ventilation, continuous positive airway pressure support (CPAP) and high flow, humidified nasal cannula oxygen (HHHFNC).
B Infants needing supplemental oxygen without positive pressure (low flow nasal cannula).

If infants were already transferred to another hospital by 36 weeks PMA, it was determined whether they had met the above BPD criteria before discharge from the local neonatal unit and/or whether the presence of BPD/PH was confirmed during outpatient follow-up.

3.1 | Statistical analysis

The patient characteristics of the population and the prevalence of different forms of pulmonary hypertension were described with descriptive statistics. Data were presented, depending on the distribution of the variable, as mean ± standard deviation (SD), median and interquartile range (IQR) or frequencies with percentages. We performed two-sided tests, and p values <0.05 were considered significant. Univariate regression was performed to determine associations of BPD and/or PH. In addition, multivariate logistic regression was performed to determine the independent association between variables and pulmonary hypertension. Kaplan–Meier curves were used to depict the survival of the preterm infants and a log-rank test

TABLE 1 Echocardiographic criteria of pulmonary hypertension forms (Presence of one of the criteria was sufficient to diagnose PH forms).

	Absent	Less than severe	Severe
TR velocity	<3 m/s	>3–<4 m/s	>4 m/s
Intra/Extra cardiac shunt	Left to right	Left to right	Bidirectional
Interventricular septal flattening	Absent	End systole	Throughout cardiac cycle

performed to compare the different groups. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0.

4 | RESULTS

A total of 268 infants were identified with MSBPD. A total of 250 infants underwent echocardiographic assessment during the stay on neonatal unit. The remaining 18 babies with MSBPD did not have an echocardiography assessment during their stay in NICU. None of those babies had clinical concerns about PH. An echocardiography assessment was done for 26 of the 250 infants before 32 weeks PMA. None of the scans showed evidence of PH. Of the remaining 224 babies who underwent echocardiography, assessment >32 weeks PMA, and images of echocardiography were available and prospectively reviewed for 190 babies (Figure 1).

The median gestational age at birth was 25 + 4 weeks (range: 22 + 6–31 + 6 weeks), and the median birth weight was 737.5 g (range: 390–2690 g). Fifty-three patients (19.77%) were small for gestational age at birth, defined as weight below the 3rd percentile for the estimated gestational age. The median age of investigation was 36 + 4 weeks PMA. Chorioamnionitis was diagnosed in 86 cases and 35 infants underwent surgical treatment of persistent ductus arteriosus (PDA). Thirty-four babies had pulmonary hypertension associated with MSBPD, with an incidence of 13%. Severe pulmonary hypertension was observed in 14 of these infants (41%).

4.1 | Comparison between the infant groups with and without pulmonary hypertension

On univariate analysis (Table 3), most of the variables analysed were associated with significant pulmonary hypertension. The mean birth weight and median gestational age at birth of the PH group were lower than the no-PH group. Prevalence for the oligohydramnios, male gender and use of antenatal steroids were similar between the groups and had no statistical significance. Chorioamnionitis was seen more in the PH group (52% vs. 29%, $p = 0.005$).

The pulmonary hypertension group required more positive pressure respiratory support days (138 vs. 98 days, respectively, $p < 0.001$), as well as having an increased need for treatment of persistent ductus arteriosus (50% vs. 30%, respectively, $p = 0.003$) and postnatal steroid use (55% vs. 22%, respectively, $p < 0.001$).

Logistic regression analysis demonstrated the need for positive pressure respiratory support at 36 weeks PMA was independently associated with PH ($p = 0.001$; 95% CI 2–13.5; Table 3).

Most of the infants in the non-PH group were on low flow nasal cannula oxygen at 36 weeks corrected gestational age ($n = 209$). The remaining 25 cases had non-invasive respiratory support, including high flow nasal cannula, continuous positive airway pressure or non-invasive pressure ventilation.

4.2 | Respiratory support at 36 weeks PMA and PH

Babies who were on positive pressure respiratory support at 36 weeks PMA (41%) were more likely to develop PH as compared to babies in low flow oxygen at 36 weeks PMA (7%) as shown in Figure 2 (OR = 10.2; 95% CI 4.2–20.74; $p < 0.0001$). In addition, babies who were on positive pressure respiratory support at 36 weeks cGA were more likely to develop severe PH (OR 25.4, CI 6.7 to 96.1 $p < 0.0001$).

4.3 | Outcome and prognosis

Twenty-one babies died during the study, with overall mortality of 7% in babies with MSBPD. Median age at time of death was 52 weeks PMA. The mortality for the PH group was higher than the non-PH group (32% vs. 4%; $p < 0.001$). Babies with PH died by a median age of 55 weeks PMA (range: 49 + 2–66 + 5 weeks) which was a median of 216 days (range: 153–304 days).

Presence of PH in babies with MSBPD was associated with death ($p = 0.003$, 95% CI 1.8–17). Severe PH associated with MSBPD had a 57% mortality. We compared mortality outcomes for babies with MSBPD with no PH (lowest risk group for mortality) with four other groups as shown in Table 4. We observed that babies with MSBPD with less than severe PH were more likely to die when compared to babies with MSBPD and no PH (OR: 3.9, 95% CI 0.99–15.7; $p = 0.05$; Table 4). As expected other two groups, MSBPD with PH and MSBPD with severe PH were associated with increased mortality. Infants with severe PH were more likely to die compared to less than severe PH forms (OR: 7.5, 95% CI 1.5–38; $p = 0.01$).

According to Kaplan–Meier curve, survival probability was reduced in the pulmonary hypertension group, with a mortality peak between 200 and 220 days of life (Figure 3).

All babies with MSBPD-PH severe forms that were discharged from our unit survived until their second birthday.

5 | DISCUSSION

We discuss incidence, associated factors and outcomes of PH associated with MSBPD in premature babies born at single tertiary neonatal centre over 10-year study period. In babies with MSBPD, respiratory support at 36 weeks PMA was independently associated with PH. PH was associated with late mortality.

Pulmonary hypertension remains a serious comorbidity associated with significant bronchopulmonary dysplasia in extremely low-birth-weight infants. It is thought to result from a combination of intrinsic, secondary and acquired abnormalities of the pulmonary vasculature.[2,10–12] The epidemiology of BPD continues to demonstrate that birth weight or gestational age is most predictive of BPD. Correlations of BPD with chorioamnionitis are clouded by the foetal exposure to inflammation.[11]

5.1 | Incidence and associations

This study reports incidence and factors related to PH associated with MSBPD, as well as the long-term survival up to 2 years of age. Current literature describes the incidence of PH in babies with MSBPD to be between 25% and 45%[2,6] compared to 12% in our study. In our patient population, 4 out of 10 babies with MSBPD who were needing either positive pressure respiratory support at 36 weeks PMA, were observed to have PH. 7% of babies with MSBPD who were in low flow oxygen at 36 weeks PMA, were observed to have pulmonary hypertension. Hyo Soon An et al. observed that the incidence of PH was 58% in babies with severe BPD and 9.5% in moderate BPD, but none in the mild BPD form.[6] Data from Hyo Soon An et al was from 2004 until 2008. Even though the incidence reported was higher than in our study population, the observations were similar. During the study period, we have observed improved survival of babies born less than 26 weeks gestation. The above observation may suggest that even though the incidence of MSBPD is increasing with improved survival of extremely premature babies, the incidence of PH is probably improving. During the study period, threshold for initiating treatment for PH had not changed. Eighteen babies of PH group (52%) received medical treatment. Sildenafil was used in all 18 babies. One baby received Levosimendan in addition to Sildenafil.

In a large retrospective study involving 1677 infants <32 weeks gestation, Lagatta et al observed that ventilator support at 36 weeks' post-menstrual age, duration of ventilation and high respiratory severity score were associated with PH.[13] A systematic review by Chen et al observed that severe BPD is associated with increased risk of pulmonary hypertension.[14] We observed that the need for positive pressure support at 36 weeks PMA was independently associated with PH in babies with MSBPD. This information can be used to develop screening protocol for babies with MSBPD.

5.2 | Screening echocardiography

The strength of this study is that all echocardiography assessments were reviewed prospectively with objective pragmatic criteria, in a reasonably large recent cohort from a tertiary neonatal intensive care unit. In our study, the median age for echocardiography screening was 36 + 3 weeks PMA. A retrospective study done by Kemani et al in 2007, observed PH at a median postnatal age of 4.8 months.[2] Timing of the echocardiogram has been variable in different studies and there is no current consensus on the appropriate time for screening preterm infants for pulmonary hypertension.[15,16] Bhat et al, in a prospective cohort trial including 145 extremely low birth weight babies, observed no difference in mortality in early vs. late pulmonary hypertension groups in babies with BPD.[4]

Few teams across the world have proposed algorithm regarding diagnosis and therauptic strategies for BPD-associated PH.[17–19]

Transthoracic echocardiography is the only non-invasive method currently available to diagnose pulmonary hypertension in the vulnerable extremely preterm babies, but they have limitations as far as diagnosing PH in babies with chronic lung disease is concerned.[19]

We used a pragmatic and practical definition for presence of PH and severity. TR velocity and septal flattening are used by many researchers as surrogate marker of PH.[11,12] In addition, we used intra or extra cardiac shunting as an addiotnal parameter to stratify less than sever and severe PH forms, as used by Arjaans et al.[16] In our study, we reviewed echocardiography scans done over 10 years. The definition we used allowed us to be consistent with the diagnosis.

5.3 | Mortality

Several studies have demonstrated that PH in babies with MSBPD is associated with increased mortality. Lagatta et al, in a large

TABLE 2 Definition of bronchopulmonary dysplasia.

BPD severity	Criteria
Mild	Supplemental oxygen required ≥28 days, termination of supplemental oxygen by 36 weeks cGA or discharge
Moderate	Supplemental oxygen required ≥28 days, requirement of <30% oxygen at 36 weeks cGA or discharge
Severe	Supplemental oxygen required ≥28 days, requirement of ≥30% oxygen and/or continuous positive airway pressure or mechanical ventilation at 36 weeks cGA or discharge

retrospective study including 370 babies with PH and MSBPD, noted that PH was associated with increased mortality.[13] Khemani et al in a retrospective study including 42 premature infants with PH observed that on multivariate analyses, severe pulmonary artery hypertension and small birth weight for gestational age were associated with worse survival rates.[2] In our study, when corrected for gestational age, birth weight, gender, antenatal steroids, chorioamnionitis, duration of positive pressure respiratory support, PDA treatment, on multivariate analysis, the presence of PH was independently associated with death in babies with established MSBPD. ($p = 0.003$ CI 1.8–17.9).

Mortality in babies with MSBPD PH has been reported to be between 38% and 46%[13,19] and unfortunately, it is usually late mortality. Arjaans et al described 11%, 30%, 42% at 1, 3 and 7 months' respective mortality rates from 36 weeks post menstrual age in babies with PH.[16] Death rate is mostly reported within the first 6 months, although Khemani et al have described late mortality up to 24 months of life in babies with PH.[2] In our study, we observed death as outcome up to 2-year corrected gestational age with a 32% mortality rate in the MSBPD-PH group. None of the babies from the MSBPD-PH group who were discharged from the neonatal unit died up to two-year corrected age, although some babies stayed in hospital up to 390 days of life. This may suggest the need for gradual weaning of respiratory support, close monitoring and clinical care using a multidisciplinary team approach.

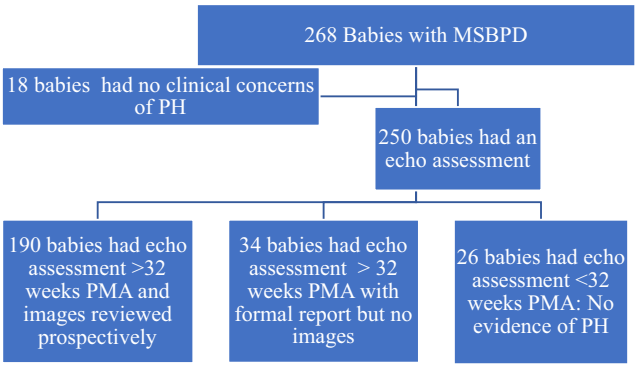

FIGURE 1 Flow chart of the study population.

5.4 | Severity of PH and mortality

We chose to compare mortality rates between MSBPD with no PH group and the rest of categories as shown in Table 4.

Severe PH is associated with worse outcomes when compared to babies with non-severe PH.[2] This observation was similar to what we noted in our study. However, in our study, we observed that babies with less than severe PH and MSBPD are at increased risk of mortality when compared to babies with MSBPD and no PH. This highlights the importance of ongoing close monitoring and follow-up of babies with less than severe pulmonary hypertension associated with MSBPD.

5.5 | Secondary PH

Even though PH is a manifestation of lung disease in preterm babies, pulmonary vein stenosis is a well-described cause for pulmonary hypertension in this population.[20,21] In our cohort, one baby had pulmonary vein stenosis, with positive clinical course, not needing intervention.

5.6 | Limitations

Probably one of the biggest limitations of this study is the fact that it was a single centre, retrospective study done over a 10-year

TABLE 3 Data analysis.

Variable	Babies with PH ($n = 34$)	Babies with no PH ($n = 234$)	p Value univariate analysis	p Value multivariate analysis 95% confidence intervals
Gestation age at birth (Median, range)	25 + 6 (23 + 1–29 + 2)	26 + 1 (22 + 6–31 + 6)	0.038	0.576 (0.8–1.4)
Birth weight (Median, range)	724 (390–1350)	804 (399–2690)	0.034	0.549 (0.99–1.02)
IUGR (n, %)	6 (18%)	47(20%)	0.7387	
Male gender (n, %)	20 (58%)	142 (60%)	0.836	
Chorioamnionitis (n, %)	18 (52%)	68 (29%)	0.005	0.217 (0.7–2.3)
Positive pressure respiratory support (days) (Median)	138	98	<0.001	0.198 (0.9–1.0)
Tracheostomy (n, %)	3 (9%)	13 (6%)	0.452	
Postnatal steroids (n, %)	19 (55%)	53 (22%)	<0.001	0.599 (0.7–4.5)
Positive pressure respiratory support at 36 weeks PMA (n, %)	18 (52%)	25 (10%)	<0.001	0.001 (2–13.5)
PDA treatment (n, %)	17 (50%)	72 (30%)	0.003	0.197 (0.7–4.4)

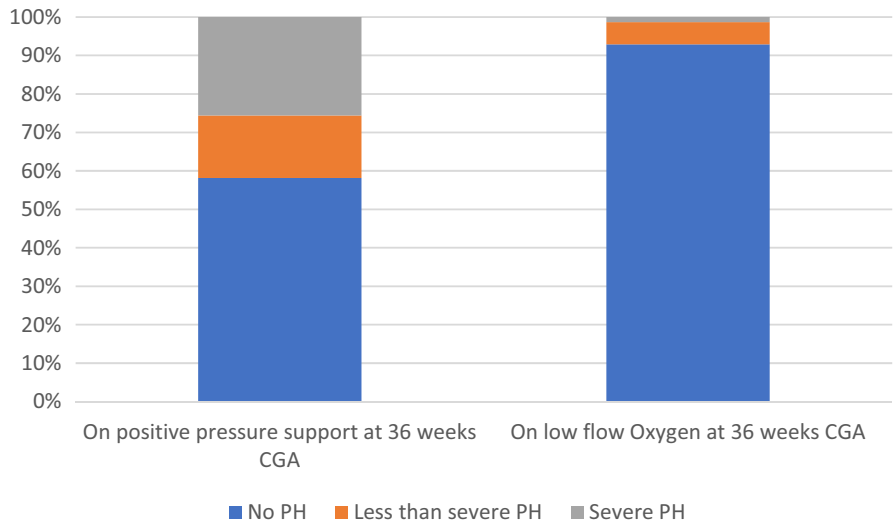

FIGURE 2 Kaplan–Meier curve – high mortality in infants with BPD and sustained pulmonary hypertension (PHT).

	Death/No. of babies	Mortality (%)	OR vs. MSBPD with no PH	*p* Value
MSBPD	21/268	7.80	1.9 (0.87–4.13)	0.1
MSBPD + No PH	10/234	4.27		
MSBPD + PH	11/34	32	10.71 (4.1–27.9)	<0.0001
MSBPD + LTSPH	3/20	15	3.9 (0.99–15.7)	0.05
MSBPD + Severe PH	8/14	57	29.8 (8.69–102.54)	<0.0001

TABLE 4 Mortality outcomes for high-risk population when compared to lowest risk group (MSBPD with no PH).

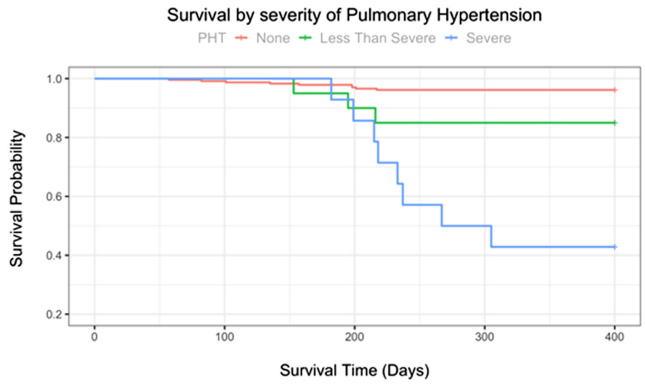

FIGURE 3 Figure showing relationship of PH forms with respiratory support at 36 weeks PMA/cGA.

period. In addition, not every infant with BPD in the study underwent echocardiography screening. This may cause selection bias. In 18 infants of the total cohort who did not have echocardiography assessments, no clinical concerns for PH were documented. They were included in the MSBPD with no PH group. Time of screening echocardiography was indeed variable with different infants. Majority of infants underwent echocardiography at more than 32 weeks PMA.

This study informed high-risk population for PH in premature infants with MSBPD and informed screening programme for PH in infants with MSBPD on our neonatal unit. This data also may inform future prospective trials involving infants with MSBPD.

6 | CONCLUSIONS

Our study has identified that in extremely premature infants with moderate-to-severe bronchopulmonary dysplasia admitted to our centre, the need for positive pressure support at 36 weeks corrected gestational age was independently associated with PH. In our study population, none of the infants with significant pulmonary hypertension associated with moderate to severe BPD that were discharged from the neonatal intensive care unit died at 2 years of age. Although severe PH is associated with worse outcome, less than severe PH is also associated with increased mortality in babies with MSBPD.

AUTHOR CONTRIBUTIONS

Dr Kulkarni, Dr Shetty, Dr Richards and Dr Vladareanu designed the study and approved the final manuscript as submitted; Dr Branescu collected the data and submitted the first draft of the manuscript. Dr Kulkarni designed the statistical analysis and analysed the data. All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

FUNDING INFORMATION

The authors declare that no funds, grants or other support were received during the preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data given in tables and as text in manuscript.

ETHICAL APPROVAL

This was a retrospective study that added no new interventions requiring patient consent; therefore, it was registered locally as audit/practice evaluation project with local audit department approval.

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