Comparison of a Paper-Based Perinatal Infection Risk Score and the Neonatal Sepsis Calculator by Kaiser Permanente

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Abstract
Objective
We aimed to compare a paper-based perinatal infection risk (PIR) score with a validated computer-based early onset sepsis calculator by Kaiser Permanente (KP-EOSC) to assess their respective performance on neonatal sepsis detection.

Methods
All newborn babies admitted at the department of neonatology with an increased infection risk between January 2019 and December 2021 were retrospectively included. The PIR score was designed to support the decision whether to perform additional monitoring, tests, and/or administer antibiotics. A PIR score and KP-EOSC score were calculated and compared. A PIR score ≥6 or a KP-EOSC score ≥1/1000 would trigger further investigations and observation.

Results
A total of 105 babies were included, corresponding to 3.4% of the local newborn population. Of all patients born at Jan Palfijn Hospital (Antwerp, Belgium), culture proven sepsis incidence was 0.09%. When comparing the PIR score and KP-EOSC score for well appearing children, a minimal correlation was seen (Cramér's V 0.199, Cohen' Kappa -0.014, p=0.077) but scores tended to yield similar outcomes more frequently when clinical appearance shifted to equivoqual (Cramér's V 0.180, Cohen' Kappa 0.022, p=0.190).

Conclusion
When comparing the PIR tool and the KP-EOSC tool, the PIR tool looks less specific but has an overall good sensitivity in identifying children with neonatal sepsis. In this pilot study, it appears that neonatal risk stratification can be done based on several scores, while the need for a computer and/or clinician might limit the KP-EOSC tool in certain circumstances. Additional studies are warranted to validate these findings.

Introduction

Early onset sepsis (EOS) remains a challenge with an overall incidence of 0.49 to 2.20 per 1000 live births (1,2). Neonatal sepsis mortality ranges between 11 and 19%. EOS is the third leading cause of neonatal mortality in neonatal intensive care units (NICUs) worldwide (3). Newborn babies have a higher risk to develop life-threatening infections due to several risk factors such as their underdeveloped immune system. Without antibiotics, they can rapidly develop septic shock and multiple organ failure which might lead to significant morbidity and mortality. Other consequences of early onset sepsis may include intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy or meningitis (4).

Distinguishing the presence of a bacterial infection in neonates remains a clinical challenge and often leads to a low threshold to initiate antibiotic treatment due to the high morbidity and mortality in case of delayed or untreated sepsis. However, antibiotics come with side-effects including a changing microbiome, gastro-intestinal symptoms, etc. In addition, the widespread utilization of antibiotic treatment contributes to the growing worldwide problem of antimicrobial resistance whilst also having a distinct impact on the neonatal microbiome. Furthermore, antibiotic use can lead to separation between mother and neonate, prolonged hospitalization and an increased risk of developing secondary conditions such as allergies or diabetes (1,5).

TABLE 1: Perinatal infection Risk (PIR) tool.

PIR score	0	1	2	3	4
Postmenstrual age	≥ 37w ≤ 42w		< 37w > 42w		
Maternal fever*	< 38.0°C			≥ 38.0°C	
Neonatal fever **- One hour after birth** **- Rectal**	< 38.0°C			≥ 38.0°C	
GBS status	Negative Positive or unknown with adequate antibiotic prophylaxis				Positive with inadequate prophylaxis Unknown with inadequate prophylaxis
Fetal distress	None	Suboptimal CTG	Meconial amniotic fluid	Abnormal CTG (with or without meconium amniotic fluid)	
Apgar score after five minutes	7 or more				< 7
Rupture of membranes	< 18 hours				≥ 18 hours

Total score: 4-5: Do a blood test with white blood cell count and CRP after 12 and 24 hours. / 6-7: All the above is performed and the patient is admitted at department of neonatology. / 8 or more: All the above is performed. Start treatment after discussion with pediatrician. / * Take maternal temperature at admission and each 4 hours until first care postpartum.

Historically, several tools have been developed and validated to assist clinicians in the assessment of antibiotic initiation in neonates. A systematic review and meta-analysis, performed by Deshmukh et al., highlighted a reduction of antibiotics when using a risk stratification model. In this analysis, the number needed to treat to prevent one infection using antibiotics was estimated to be 22. This study also showed a significant reduction in antibiotics in the EOS calculator group in comparison to a control group (OR 0.22 (0.14–0.36), p<0,0001) (6). Currently, one of the mostly used calculators worldwide is the early onset sepsis calculator developed by Kaiser Permanente (KP-EOSC) (7,8). This calculator estimates a relative EOS risk, based on six variables, in three different clinical categories, namely well-appearing, clinical equivocal and clinical ill. Based on the estimated relative risk of EOS, different clinical management strategies are recommended. In contrast, the Jan Palfijn Hospital in Antwerp has been using a self-developed paper-based tool since 2012. The paper-based Perinatal Infection Risk (PIR) tool assesses infection risk based on multiple factors, including postmenstrual age, Group B *Streptococcus* (GBS) status and fetal or infant distress. It offers risk stratification without the need for online access or real-time clinical evaluation.

This pilot study aimed to determine whether the PIR tool performs comparably to validated screening methods for neonatal sepsis. A secondary objective was to assess whether it can contribute to more targeted antibiotic use in neonates without overlooking cases of culture-proven EOS.

Materials and Methods

PIR tool

The PIR tool, used to determine which patients were admitted at the department of neonatology for increased infection risk, includes the following topics: postmenstrual age (PMA) with a higher score if born below 37 weeks or above 42 weeks, maternal temperature 38.0°C or higher during labour, neonatal temperature 38.0°C or higher one hour after birth, GBS unknown or positive with insufficient intrapartum prophylaxis, fetal distress, Apgar below 7 at five minutes after birth and prolonged rupture of membranes (ROM). For each topic, points are given between zero and four and a total score is subsequently generated (Table 1). Neonates were excluded if the PIR document was missing from the patient file. If the PIR document was present but incomplete, missing data were retrieved from the medical records whenever possible. As per the local protocol, the total score implied further actions. When the PIR score was four or more, blood count and CRP were performed 12 and 24 hours after birth, but the baby could remain at the maternity ward. With six or more as total PIR score the same blood tests were performed and the neonate was hospitalized for close observation at the neonatal ward. With eight or more all the above measures were taken and the pediatrician was consulted to discuss further evaluation and/or IV antibiotic treatment.

Early Onset Sepsis calculator by Kaiser Permanente (KP-EOSC)

The KP-EOSC score (Table 2) was developed in California to guide decision-making on empirical antibiotic treatment in newborns (9). The tool was derived from a large case–control study including more than 608 000 live births (10). It combines six perinatal variables (baseline population incidence of early-onset sepsis, gestational age, highest maternal intrapartum temperature, duration of rupture of membranes, maternal GBS status, and type of intrapartum antibiotic administration) with the infant's clinical condition classified as well-appearing (WE), equivocal (E), or clinically illness (CI). Based on these data, the calculator estimates the relative risk of early-onset sepsis per 1 000 live births and provides corresponding management recommendations. When the estimated risk is <1 per 1 000 births, routine care is advised. For risks between 1–3 per 1 000 births, blood culture and enhanced clinical observation are recommended. If the risk is >3 per 1 000 births, initiation of empiric antibiotic therapy is advised. In this pilot study, the numbers published in the result and discussion section correspond to the risk per 1 000 births. Predictors used in KP-EOSC were retrospectively extracted from the PIR score for each baby that was included and complemented by the assumptions outlined below.

TABLE 2: Kaiser Permanente (KP-EOSC) tool.

Incidence of Early-Onset Sepsis	- 0.1/1000 live births - 0.2/1000 live births - 0.3/1000 live births (KPNC incidence) - 0.4/1000 live births - 0.5/1000 live births (CDC national incidence) - 0.6/1000 live births - 0.7/1000 live births - 0.8/1000 live births - 0.9/1000 live births - 1/1000 live births - 2/1000 live births - 4/1000 live births
Gestational age	In weeks and days
Highest maternal antepartum temperature	In Fahrenheit or Celsius
Rupture of membranes (hours)	Exact number
Maternal GBS status	- Negative - Positive - Unknown
Type of intrapartum antibiotics	- Broad spectrum antibiotics >4hrs prior to birth - Broad spectrum antibiotics 2-3.9hrs prior to birth - GBS specific antibiotics >2hrs prior to birth - No antibiotics or any antibiotics <2hrs prior to birth

Based on predictors and clinical exam total score:

Risk for early onset sepsis per 1 000 births <1: no culture, no antibiotics. Perform routine care. / Risk for early onset sepsis per 1 000 births 1-3: perform a blood culture and check vitals every 4 hours for 24 hours in total. / Risk for early onset sepsis per 1 000 births >3: start empiric antibiotics. Perform vitals per NICU

Converting PIR data to Kaiser Permanente (KP-EOSC)

In this study, the PIR value was compared with the well appearing (WA) and equivocal (E) score obtained from the KP-EOSC. To obtain a KP-EOSC for each neonate, several assumptions were made. An incidence rate of 0.5 cases of EOS per 1 000 newborns was assumed. This decision was made based on the incidence of a neonatal sepsis according to the Centers for Disease Control. The gestational age for babies born before 36 weeks was defaulted to 36 weeks. Data on maternal temperature were converted accordingly: if points were given for maternal fever in the PIR score, we assumed the mother had a temperature of ≥38.5 degrees Celsius. If no points were given, we choose a default temperature of 37.0 degrees Celsius. If the exact duration of ROM was not retrieved, but points were given for a prolonged rupture of membranes, ROM was set at 24 hours. When no points were given, ROM was set at 10 hours. Finally, if the mother had a negative GBS status, we assumed that no antibiotics were given <2 hours prior to birth. If the PIR file showed a positive GBS status but received enough antibiotics, we assumed this was for more than 4 hours prior to birth. If there was a positive or an unknown GBS status and no antibiotics or an insufficient amount of antibiotics was given, we chose 'no antibiotics or any antibiotics <2 hours prior to birth' in the KP-EOSC.

Inclusion and exclusion criteria

A retrospective study was performed. All cases, born in Jan Palfijn Hospital between January 1th, 2019, and December 31st, 2021, considered to be at a higher risk for congenital infection were admitted at the department of neonatology. These infants were elegible for inclusion. The department hospitalizes premature babies with a minimal postmenstrual age of 33 weeks. Patients were excluded if hospitalization at the department of neonatology was necessary for any other indication than increased infection risk. Individual patient record files were screened for the PIR file. This document was completed for every baby born at Jan Palfijn at time of birth and added to the medical record, whether or not there was an increased risk of infection. Each PIR document was therefore already completed and collected before the start of the study and was retrospectively retrieved.

In line with good clinical practice guidelines and national legislation, we obtained ethical approval by ZNA Hospital, Antwerp, Belgium. The study complied with the Helsinki declaration for investigations in human subjects.

Statistical analysis

To summarize quantitative variables, we used descriptive statistics consisting of proportions, means and ranges. For both the PIR score and KP-EOSC score, continuous variables for each outcome were used. The PIR score was dichotomized into two groups: neonates with a PIR score of 6 or 7, and those with a score of 8 or higher. This approach was selected based on the local clinical protocol whereby antibiotics are possibly initiated only in neonates with a PIR score of 8 or higher. The KP-EOSC score was categorized according to its predefined recommendations: relative risk <1 per 1 000 births , 1–3 per 1 000 births or >3 per 1 000 births. To assess the correlation between the two scoring systems, a likelihood ratio test, Cramér's V coefficient and Cohen's kappa coefficient were calculated. Descriptive statistics were analyzed using Microsoft Excel. The likelihood ratio test, Cramér's V coefficient and Cohen's kappa coefficient were analyzed using SPSS version 29.0.2.0.

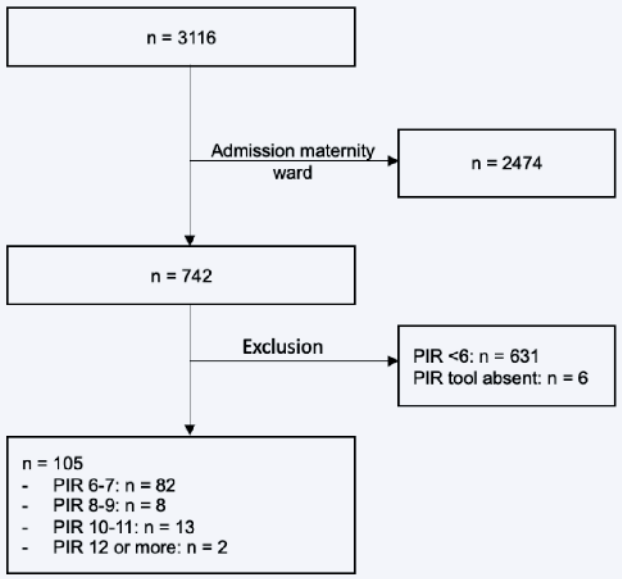
Results

In total, 3116 babies were born at Jan Palfijn Hospital between January 1st 2019 and December 31st, 2021, of whom 742 needed to be admitted at the department of neonatology (23.8%). Of these 742 babies, 111 (3.5%) were admitted due to an increased infection risk with a PIR ≥6, corresponding with 14.9% of all babies admitted at the department of neonatology (Figure 1). Non-infectious admissions included hyperbilirubinemia (6.6%), respiratory symptoms (10.5%) or preterm birth (10.1%).

Six patients at increased risk of infection were excluded because their PIR scores were unavailable. In total, 105 infants were included in the final analysis (Table 3). Of these, 57.1% were male. Almost half of the mothers (47.6%) were GBS positive or unknown with insufficient prophylaxis and 14.2% of all mothers developed fever during delivery. Most babies were born at term, corresponding to 75.2% of the included population. We observed only a minority of neonates presenting with neonatal fever (2.9%) or an Apgar score below 7 at 5 minutes of birth (14.2%). In total, three neonates developed a culture proven sepsis, corresponding with an incidence of 0.09%. Of these three individuals, two have been included in this study with a PIR of six and ten respectively

(Table 4). The corresponding KP-EOSC score was 0.10 when well appearing and 1.21 when appearing equivocal for baby one. For baby two, the KP-EOSC score was 0.20 when well appearing and 2.41 when looking equivocal. There was a third neonate, not included in the main study due to a PIR of 0, with a positive hemoculture during the inclusion period. The hemoculture for these three patients became positive for *Streptococcus viridans* for baby one, Group B *Streptococcus* for baby two and *Escherichia coli* for baby three.

FIGURE 1: Patient inclusion.



In 78.1% of cases, the PIR score was 6 or 7, corresponding to a mean KP-EOSC score of 0.17 for well appearing infants and 2.06 for those with equivocal presentations. In 7.6% of cases, the PIR score was 8 or 9, with a mean KP-EOSC score of 0.24 (WA) and 3.09 (E). A total of 12.3% of cases had a PIR score of 10 or 11, corresponding to KP-EOSC scores of 0.34 (WA) and 4.12 (E), respectively. Finally, 1.9% of cases had a PIR score of 12 or higher, which corresponded to KP-EOSC scores of 0.86 (WA) and 10.35 (E).

When comparing KP-EOSC scores across the predefined PIR groups (PIR 6–7 vs. ≥8), the likelihood ratio was 0.077 for well-appearing infants and 0.195 for those with equivocal clinical signs. The association between the PIR and KP-EOSC scores was indicated by a Cramér's V of 0.199 (WA) and 0.180 (E), and a Cohen's Kappa of −0.014 (WA) and 0.022 (E), suggesting minimal but positive agreement. Assuming all infants were well-appearing, one (1.2%) of those in the PIR 6–7 group would require frequent monitoring (every four hours) according to the corresponding KP-EOSC score. In the subgroup with PIR scores ≥8, two (9.5%) would require frequent monitoring. None of the infants in this cohort would meet the criteria for antibiotic administration under the KP-EOSC algorithm. Assuming all infants presented with equivocal clinical signs, 31 (37.8%) in the PIR 6–7 group would require frequent monitoring, and 12 (14.6%) would warrant admission for intravenous antibiotics. Among infants with PIR scores ≥8 and equivocal presentations, 9 (42.8%) would require frequent monitoring and 6 (28.6%) would require IV antibiotics (Table 5).

TABLE 3: Baseline characteristics.

Perinatal Infection Risk value	6-7		≥8
Number of babies	82 (78.1%)		23 (21.9%)
Mean birth weight (g)	3 504		3 200
Male sex	47 (57.3%)		13 (56.5%)
Postmenstrual age (weeks + days)	38 + 6		38 + 3
Postmenstrual age <37 or >42	17 (20.7%)		9 (39.1%)
Maternal fever	10 (12.2%)		5 (21.7%)
Neonatal fever	0 (0%)		3 (13.0%)
Prolonged rupture of membranes	28 (34.1%)		9 (39.1%)
GBS positivity	38 (46.3%)		12 (52.2%)
Fetal distress	38 (46.3%)		11 (47.8%)
Apgar below 7 at 5 minutes of birth	7 (8.5%)		8 (34.8%)
Positive cultures	1 (1.2%)		1 (4.3%)
Early Onset Sepsis Calculator (well appearing)	0.17	PIR 8-9 PIR 10-11 PIR 12 or more	0.36 0.24 0.34 0.86
Early Onset Sepsis Calculator (equivocal appearing)	2.06	PIR 8-9 PIR 10-11 PIR 12 or more	4.37 3.09 4.12 10.35

Discussion

This study compares the effectiveness of a paper-based neonatal risk calculator with an electronic, internationally validated sepsis score in a regional Belgian hospital. The observed incidence of neonatal sepsis in our population was 0.09%, which was slightly higher than the incidence used to calibrate in KP-EOSC (0.05%) and compared to recent Belgian data (0.037%) (11).

Numerous perinatal risk factors, such as premature rupture of membranes, GBS colonization, maternal infection, low gestational age, low birth weight and intrauterine distress (i.e. meconium-containing amniotic fluid or perinatal asphyxia) have been identified as contributors to early onset sepsis. These findings were further corroborated by Procianoy et al. (12,13). All these risk factors, except for low birth weight, are included in the PIR tool. Low birth weight was excluded due to the predominance of appropriate birth weight neonates in our population and very low birth weight infants were typically transferred to tertiary hospitals (14,15). The PIR tool also includes maternal fever, a clinical sign of maternal infection, as well as intrauterine distress, which is assessed using the 'fetal distress' and 'Apgar score' parameters. Therefore, the PIR tool provides a decision-making instrument, taking almost all the applicable perinatal risk factors into consideration. Conversely, the KP-EOSC calculator excludes birth weight and intrauterine distress, focusing instead on maternal risk factors such as GBS status, antibiotic administration and maternal temperature during labor.

TABLE 4: Characteristics of patients with culture proven sepsis.

N	PIR score							KP-EOSC score			Causing organism
	PML	MF	NF	GBS	Fetal distress	Apgar score at 5 minutes <7	PROM	WA	E	CI	
1	39+2	No	No	Yes	Yes	No	No	0.10	1.21	5.12	S. viridans
2	36+2	No	No	Yes	No	No	Yes	0.20	2.41	10.14	GBS

MF: maternal fever; NF: neonatal fever; GBS: Group B Streptococcus; PROM: Prolonged rupture of membranes; KP-EOSC: Early Onset Sepsis Calculator by Kaiser Permanente; WA: Well appearing; E: Equivoqual; CI: Clinical illness

To obtain a KP-EOSC score for each baby within our analysis, several assumptions were made to meet the score requirements. These assumptions made a direct comparison of the scores challenging. More specifically, maternal fever and duration of rupture of membranes as these were not retrievable from all the implicated patient records. We used a maternal temperature of 38.5°C and defined prolonged rupture of membranes as >24 hours, based on existing literature (16,17). When looking at the different predictors, the PIR score considers different parameters in comparison to KP-EOSC such as the Apgar score after five minutes, the presence of fetal distress prenatal and the neonatal temperature. In comparison, a study performed at the Clinical Department of Neonatology of the University Children's Hospital in Ljubljana showed that neonates with a sepsis are more likely to need immediate postnatal help and have lower Apgar scores than neonates without sepsis. Additionally, temperature instability (i.e., < 36.0°C or > 38.5°C) is more common in neonates with confirmed or probable sepsis, further supporting the inclusion of temperature as a key predictor in the PIR tool (18,19).

When comparing the KP-EOSC with the PIR score for each patient, the PIR score appeared to be less specific in identifying neonates at genuine risk for EOS although it demonstrated reasonably good sensitivity overall. When applying the PIR score to our dataset, a higher proportion of infants would require frequent monitoring and/or intravenous antibiotics if appearing well or showing equivocal signs (Table 5). In contrast, for the two neonates in our cohort who developed culture-proven sepsis, the PIR score would have recommended frequent monitoring in both cases and immediate initiation of antibiotic treatment in one. The KP-EOSC calculator however would have suggested routine care if the infant was well appearing and frequent monitoring if the infant was clinically 'equivocal'. Given the low incidence of culture-confirmed sepsis in this population, definitive conclusions regarding the safety of adapting the KP-EOSC calculator remain limited. Similar challenges have been noted in other studies (20). Measures of association, including Cramér's V and Cohen's Kappa, indicated a minimal correlation between the PIR and KP-EOSC scores, although a slightly stronger association was observed among infants with equivocal clinical signs compared to those who were well-appearing. This finding may reflect limitations related to the small sample size and the low number of confirmed sepsis cases within the cohort. Nonetheless, a consistent trend was observed whereby higher mean PIR scores were associated with higher KP-EOSC scores, suggesting a potential alignment between the two scoring systems that warrants further investigation in larger study populations.

The PIR score can support users in the decision-making process and provide a risk stratification for performing further examinations or antibiotics. However, this should not replace clinical evaluation. A study by Cavigioli et al. demonstrated that the combination of an online tool with serial clinical evaluation can reduce the use of antibiotics (21). Within our data set, one neonate with a positive hemoculture was not captured by the PIR score (PIR 0). Corresponding incidence calculated by Kaiser Permanente was 0.06 (if WA), 0.70 (if E) and 2.98 (if CI was present). This neonate was diagnosed based on clinical signs (e.g. prolonged grunting), which underscores the importance of continuous clinical monitoring alongside predictive tools. Recent studies have highlighted the limitations of relying solely on risk calculation tools. A Belgian study found that 40% of EOS patients did not receive antibiotic therapy in the first 24 hours when using the KP-EOSC, while another international meta-analysis found that 42% of EOS cases were missed (11,22). Therefore, we recommend supplementing any score in clinical practice with thorough and extensive clinical monitoring.

When comparing the PIR score with the KP-EOSC score, several strengths of the PIR tool can be identified. Unlike the KP-EOSC, the PIR score can be used without digital infrastructure, which is particularly useful in settings with limited resources (23). Additionally, it remains functional even in the presence of

TABLE 5: Management differences between KP-EOSC and PIR tool based on well appearing (A) or equivocal appearing (B) neonate.

Table 5A: Management differences between KP-EOSC and PIR tool based on well appearing (WA) neonate

	PIR score	KP-EOSC (assumption of well appearing neonate)
Admission maternity ward	0	102
Admission neonatal ward **- Only frequent monitoring** **- Consider starting antibiotics**	105 82 23	3 3 0

Table 5B: Management differences between KP-EOSC and PIR tool based on equivocal (E) neonate

	PIR score	KP-EOSC (assumption of equivocal appearing neonate)
Admission maternity ward	**0**	**47**
Admission neonatal ward **- Only frequent monitoring** **- Consider starting antibiotics**	105 82 23	58 40 18

missing data (i. e. when the neonate's temperature one hour postpartum has not been recorded) whereas the KP-EOSC cannot generate a result in such cases. The PIR score also allows for risk calculation in the absence of specialized clinicians and does not require immediate clinical evaluation in contrast to the KP-EOSC. However, there are also limitations to consider. During our research, we experienced a prolonged period of online inaccessibility, which highlighted the reliance of the KP-EOSC on stable internet access. It is also important to note that in this dataset, only neonates with PIR values more than six were included, therefore excluding all neonates admitted to the maternity ward.

Conclusion

When comparing our paper-based PIR tool to the KP-EOSC calculator, the PIR tool looks less specific but has an overall good sensitivity in identifying children with a neonatal sepsis. The PIR score doesn't need immediate clinical evaluation or internet access which is a major advantage in big parts of the world. Our pilot study confirmed prior observations that not only risk calculators, but also clinical evaluation remains important. Yet it remains important to note that further prospective analyses and larger sample sizes are needed to further validate our findings.

Statements

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Ethics approval and consent

In line with good clinical practice guidelines and national legislation, we obtained ethical approval by ZNA Hospital, Antwerp, Belgium with EC approval n° 5515. The study complied with the Helsinki declaration for investigations in human subjects.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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