Validation of actigraphy in hospitalised newborn infants using video polysomnography

Running title: Validation of actigraphy in newborn infants

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Abstract

Actigraphy has been established as a reliable sleep assessment tool in adults; however, its utility in newborns remains unknown. Validation of actigraphy in newborns may provide a significant insight into the physiological and pathological acquisition process of mature diurnal sleep patterns and subsequent morbidities in both newborns and their mothers. Thus, this study aimed to evaluate the accuracy of sleep–wake detection by overnight actigraphy in a cohort of newborns. Simultaneous recording of polysomnography and actigraphy data was performed in 40 newborns admitted to a tertiary neonatal intensive care unit (NICU). A mixed-effects logistic regression model to explain the sleep state identified by polysomnography was employed using the actigraphic activity score as a fixed independent variable and the individual newborn's identity as a random effect. To evaluate the usefulness of the actigraphic activity score as a surrogate marker of sleep, a receiver operating characteristic (ROC) curve analysis was performed using the variables that were used in the mixed-effects logistic regression model, and the area under the curve (AUC) was assessed. The results showed that polysomnography-determined sleep epochs were associated with a smaller activity index on actigraphy (odds ratio per 10 activity indices increase, 0.81; 95% confidence interval [CI], 0.79–0.84). The AUC for the ROC curve was 0.87 (95% CI, 0.87–0.88; range, 0.54–0.99). An activity score of 124 showed the maximum overall accuracy (90.2%; 95% CI, 87.7–92.1). Our study suggests that sleep–wake states of NICU-hospitalised newborns can be precisely determined using actigraphy on the ankle.

Keywords

actigraphy, newborn infant, polysomnography, sleep pattern

INTRODUCTION

Delayed acquisition of mature diurnal sleep patterns after birth is associated with serious clinical conditions in both newborns and their mothers and family members. Short-term events include poor body weight gain in newborns (Lampl & Johnson, 2011; Tikotzky et al., 2010) and sleep deficits and postpartum depression in mothers (Armitage et al., 2009; Iwata et al., 2019). Long-term neurodevelopmental impairments of children are also reported in association with early sleep problems (Chaput et al., 2017; Geva, Yaron, & Kuint, 2016; Shellhaas et al., 2017; Weisman, Magori-Cohen, Louzoun, Eidelman, & Feldman, 2011). Early screening of abnormal sleep patterns in newborns may delineate the relationship between sleep patterns and the development of pathological events and may help improve the outcomes of newborns and their family members.

Polysomnography is currently used as the gold standard for the assessment of sleep patterns. Using a set of biological information, such as electroencephalogram, electromyogram, electrocardiogram, and breathing patterns, polysomnography provides comprehensive information regarding sleep quantity and quality (Berry et al., 2012). However, polysomnography is time-consuming and requires special hardware and experts to perform and translate the findings. In addition, polysomnography is usually performed at medical facilities; thus, the sleep environment differs significantly from that at home and recorded sleep patterns may not represent the newborn's usual sleep. Hence, polysomnography is not suitable as a screening tool for abnormal sleep patterns in newborns. Sleep diaries are a simple and well-accepted alternative to polysomnography. Sleep diaries can be applied at home, with the minimum burden of recording sleep states and related events by a caregiver of the newborn (Galland, Taylor, Elder, & Herbison, 2012). However, the quality of the information can be affected by the attitude and attention of the caregiver. Observation is likely to be limited when the caregiver is asleep and/or when the caregiver does not share the bedroom with the newborn. Objective sleep assessment tools, which can be applied overnight with a small burden, need to be established for newborns.

Videosomnography provides objective information of infant's overnight sleep, however, coding of the infant sleep/awake state needs to be done manually by an experienced examiner (Camerota, Tully, Grimes, Gueron-

Sela, & Propper, 2018). Actigraphy has been established as a simple, objective, and reliable sleep assessment tool in adults (Ancoli-Israel et al., 2003). Actigraphy uses a watch device that records the magnitude and acceleration of the limb movement (Ancoli-Israel et al., 2003; Gorny SW, 2001). An activity index is calculated by taking the maximum acceleration signal within a second and then integrating it over a given epoch (Chen & Bassett, 2005). Sleep–wake states are determined for each study epoch using established algorithms (Gorny SW, 2001). According to validation studies, actigraphy showed considerably high agreement with polysomnography (80.9–93.1%) in determining sleep–wake states in healthy adults (Conley et al., 2019). Validation of actigraphy for sleep detection may significantly improve the understanding of physiological and pathological acquisition processes of diurnal sleep–wake cycles and may contribute to the prediction of a range of serious clinical conditions rooting from abnormal sleep architecture during the neonatal period. However, regarding the assessment of sleep–wake states using actigraphy in newborns, only two studies have been conducted and their findings were conflicting. Using actigraphy and polysomnography, So et al. studied eight term and preterm newborns (between 2 and 4 weeks after birth) from maternity wards and hospitals and reported good agreement between actigraphy and polysomnography in the determination of sleep–wake states (agreement rate, 80.4–93.7%; sensitivity, 80.6–96.2%; and specificity, 54.6–82.6%)(So, Buckley, Adamson, & Horne, 2005). By contrast, Rioualen et al. found that in 48 healthy newborns, who were divided into term and preterm groups and were assessed 2.5 ± 0.7 and 6.4 ± 2.8 days after birth, respectively, the agreement in sleep–wake state detection between actigraphy and polysomnography was relatively poor (agreement rate, 62.6 ± 17.1% [mean ± standard deviation]; sensitivity, 82% [78–87%]; specificity, 36% [30–42%])(Rioualen et al., 2015). Although these studies were well designed and performed, the study populations were relatively small (8 and 48) and the study duration ranged from 2 to 3.5 h. Considering that actigraphy in children and adolescents is recorded over multiple days and nights for the maximum reliability of the study (Schoch, Kurth, & Werner, 2021), the duration of these studies might be too short to conclude whether actigraphy can precisely predict sleep–wake states in newborns.

Hence, this study aimed to evaluate the accuracy of sleep–wake detection with actigraphy by obtaining an overnight simultaneous record of actigraphy and polysomnography in a cohort of newborns.

METHODS

This study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of the Kurume University School of Medicine (study number 10115). Written informed consent was obtained from the parents of each participating neonate.

Study population

This prospective observational study was conducted as part of a study that aimed to investigate the relationship between the activity patterns of limbs recorded using actigraphy and neurodevelopmental outcomes of newborns. Between June 2013 and March 2016, 914 newborns were admitted to the neonatal intensive care unit (NICU) of Kurume University Hospital. Newborns who were (i) without major congenital anomalies, (ii) older than 34 weeks post-conceptional age, and heavier than 2000 g at the time of the study, and (iii) not on invasive/non-invasive mechanical ventilation and continuous/intermittent intravenous injection, were recruited for the main actigraphy study. A subgroup of newborns who were available for an overnight polysomnography on prefixed study days (4–6 days per month, when a neonatologist and a physiological laboratory technician in charge of polysomnography data acquisition were available, were assigned in advance), were additionally recruited for this study.

Recording devices

An actigraphy device (Actiwatch 2, Phillips Respironics Inc., Murrysville, Pennsylvania, USA), which uses a piezoelectric two-axial accelerometer to monitor activity counts of limb movement every minute, was attached to either side of the ankle using a custom-made watch-belt harness (Akachan-no-Shiro, Kurume, Fukuoka, Japan) (Figure 1a,b). The ankle, to which actigraphy is attached, was checked for pressure marks at the beginning and end of the study and during a 3-hourly vital check. Video polysomnography (Sandman SD20, Covidien, Dublin, Ireland) was performed using a standard 10–20 system electrode placement with a referential system montage. The sleep scoring montage included a minimum set of four channels of

electroencephalogram (electrodes attached to Fp1, Fp2, C3, and C4), left and right electrooculogram, left and right submental electromyogram, left and right electrocardiogram, percutaneous arterial oxygen saturation, nasal and oral airflow, and chest and abdominal wall motion. The video camera depicted the newborn's whole body from oblique above (Figure 1c).

[Figure 1 about here]

Procedure

Polysomnography was applied to the newborn after regular milk feeding at 17:00, and data acquisition was performed until 7:00 the next morning. In this NICU, cycled lighting is provided, aiming at 100–200 lux between 7:00 and 19:00 and 10–30 lux between 19:00 and 7:00. The clocks of actigraphy were synchronised with those of polysomnography on the day of the study, which was assured by pressing the event markers of actigraphy and polysomnography simultaneously before the commencement of the study. Newborns were placed in the supine position during the study. When the sensors and electrodes were out of place following spontaneous body movement and cuddling, nurses reattached them (a simple troubleshooting manual was available for reference) and recorded the event on a study diary. The study was terminated at the discretion of the nurse in charge, when newborns did not tolerate the sensors and electrodes, or when too many sensors or electrodes needed reattachment.

Data processing

Each 30-s epoch of polysomnography was assessed for quality and was classified as invalid (i.e. difficult or unable to assess because of the lack of signals from certain sensors/electrodes, low signal-to-noise ratio, or excessive body motions) and valid epochs. The epochs classified as "invalid" were not considered further, and newborns whose valid epochs were <4 h were excluded from the analysis. For valid epochs, electroencephalogram was classified into low-voltage irregular, mixed, high-voltage slow, trace alternant patterns, and other undetermined patterns by an experienced neonatal physician (M.U.). Wakefulness and

active sleep, quiet sleep and indeterminate sleep were visually identified using established criteria (Berry et al., 2012; Anders, Emde, & Parmelee, 1971). Quiet sleep was characterised by behavioural quiescence, closed eyes, and regular breathing, with the electroencephalogram dominated by high-voltage slow and trace-alternant patterns; active sleep, by frequent facial movements and body activities interspersed with periods of quiescence, with electroencephalogram dominated by low-voltage irregular and mixed patterns; and wakefulness, by strong motor activity, open eyes, and irregular breathing, with electroencephalogram dominated by motion artefacts and low-voltage irregular patterns; indeterminate sleep, by combinations of findings inconsistent to active sleep or quiet sleep.

The polysomnography data were merged with the actigraphy data and sorted in chronological order on a spreadsheet such that a 60-s epoch of actigraphy contains sleep states from two successional 30-s epochs of polysomnography. Epochs of actigraphy with at least one “awake” epoch on polysomnography were regarded as awake, and epochs of actigraphy with two “sleep” epochs on polysomnography were regarded as sleep. Additional information was transferred from the study diary and video to discriminate the timing that was affected by feeding, pacifier use, diaper change, cuddling, and other nursing care.

Statistical analysis

A mixed-effects logistic regression was employed to explain the sleep epoch identified by polysomnography, with the actigraphic activity index as a fixed independent variable and the individual newborn’s identity as a random effect. To evaluate the predictive value of the activity index as a surrogate marker of sleep, receiver operating characteristic (ROC) curve analysis was performed using the variables that were used in the mixed-effects logistic regression model to assess the area under the curve (AUC). A cut-off point was identified by calculating the accuracy and 95% confidence interval (CI) for the activity index of each newborn and, subsequently, for all newborns using the meta-analysis method, and the maximum overall accuracy was employed as the cut-off point (Schwarzer, Carpenter, & Rücker, 2015). The overall sensitivity, specificity, positive predictive value, negative predictive value, and their 95% CI were also calculated using the same algorithm as previously described. In addition, the accuracy of actigraphic sleep detection was assessed in

subgroups of newborns stratified by sex, gestational age at birth (≥ 37 weeks gestation or younger), post-conceptional age at the study (≥ median value of 38.8 weeks or younger), relative fraction of the total sleep epochs to total valid epochs (≥ median value of 0.846 or smaller), and the longest sleep period (defined as the longest consecutive epochs of sleep; ≥ median value of 138 or shorter), to see the influence of these clinical backgrounds to the sleep assessment.

All statistical analyses were performed using GNU R (ver. 3.6.1, R Core Team, 2019). The lme4 package was used for the mixed-effects logistic regression analysis (Bates, Mächler, Bolker, & Walker, 2014). The pROC package was used to calculate the ROC curve and AUC (Robin et al., 2011). The meta package was used to determine the cut-off point (Balduzzi, Rucker, & Schwarzer, 2019).

RESULTS

Values are presented as median (range) or mean (standard deviation; range) unless otherwise described. Simultaneous recording of polysomnography and actigraphy data was successfully performed in 55 newborns. However, data from 15 newborns were excluded from the analysis because of insufficient number of valid epochs (early termination of the study, n = 1; excessively large invalid data due to electrode/sensor dislocation and/or poor signal quality following reattachment, n = 14). The final study cohort comprised 19 preterm and 21 term infants (38 [25–41] weeks' gestation and 2139 [645–3588] g at birth; 11.5 [3–119] days old and 39 [35–45] weeks post-conceptional age at the time of the study; Table 1). In addition, the primary indications for NICU admission were low birth weight and/or preterm birth (n = 28), birth asphyxia (n = 7), cardiopulmonary dysfunction (n = 17), infection (n = 10), maternal thyroid disease (n = 2), and Rh-incompatible pregnancy (n = 1) (Table 1). The duration of the simultaneous recording of polysomnography and actigraphy data was 703 (234; 369–1397) min. All epochs were classified as sleep (417 [205; 81–965] min; including active sleep, 215 [140; 35–627]; quiet sleep, 196 [89; 30–400]; and indeterminate sleep, 6 [4; 0–15]), awake (91 [69; 6–318] min), and invalid (195 [174; 0–736] min); invalid data were not considered further (Table 1).

[Table 1 about here]

Polysomnography-determined sleep epochs were associated with a smaller activity index on actigraphy (odds ratio per 10 activity indices increase, 0.81; 95% CI, 0.79–0.84). The AUC for the ROC curve was 0.87 (95% CI, 0.87–0.88; range, 0.54–0.99; Figure 2a,b). An activity score of 124 showed the maximum overall accuracy (accuracy, 90.2%; 95% CI, 87.7–92.1; Figure 3), and its estimated sensitivity, specificity, positive predictive value, and negative predictive value were 0.985 (95% CI, 0.981–0.988), 0.447 (95% CI, 0.379–0.517), 0.911 (95% CI, 0.885–0.933), and 0.850 (95% CI, 0.791–0.894), respectively. When the same cut-off activity index of 124 was used, the accuracy of actigraphic sleep detection was not affected by gestational age at birth (≥ 37 weeks: 90.3%; 95% CI, 86.5–93.0; < 37 weeks: 90.0%; 95% CI, 86.7–92.6), post-conceptional age at the study (≥ 38.8 weeks: 91.5%; 95% CI, 88.9–93.5; < 38.8 weeks: 88.5%; 95% CI, 84.2–91.8), and the longest sleep period (≥ 138 min: 91.6%; 95% CI, 89.1–93.6; < 138 min: 88.4%; 95% CI, 83.9–91.8). In contrast, the accuracy was relatively higher with female sex (female: 92.3%; 95% CI, 90.2–94.0; male: 87.3%; 95% CI, 82.7–90.8) and greater sleep epochs relative to total epochs (≥ 0.846: 93.2%; 95% CI, 91.6–94.5; < 0.846: 85.8%; 95% CI, 81.1–89.4).

[Figure 2 about here]

[Figure 3 about here]

DISCUSSION

Simultaneous recording of actigraphy and polysomnography data revealed that 90.2% of sleep epochs determined by polysomnography could be precisely identified by actigraphy in relatively stable NICU infants. This is the first study to validate the usefulness of actigraphy in monitoring sleep–wake patterns in neonates using a simultaneous overnight recording of actigraphy and polysomnography. With further validation, actigraphy could be used to further understand both physiological and pathological sleep patterns in newborn infants and to develop strategies to predict, identify, and prevent adverse events rooting from early abnormal sleep patterns.

Actigraphy, which has been validated as a simple and reliable sleep monitor in adults (Ancoli-Israel et al., 2003), can identify sleep epochs with a sensitivity of 96.5% and accuracy of 86.3% (Marino et al., 2013). Actigraphy has also been used in studies of young children and infants (Iwasaki et al., 2010; Nishihara, Horiuchi, Eto, & Uchida, 2002). In a previous study of 45 children aged 1 to 12 years, the agreement rates, sensitivity, specificity, and positive predictive value for the prediction of sleep determined by polysomnography ranged from 85.1% to 88.6%, 90.1% to 97.7%, 39.4% to 68.9%, and 91.6% to 94.9%, respectively (Hyde et al., 2007), suggesting a consistently high predictive value of actigraphy but a relatively low specificity in predicting polysomnographic sleep. In newborns, two validation studies assessed the predictive value of actigraphy using simultaneous recording of polysomnography; however, the studies reported contrasting findings. So et al. reported an agreement rate of 93.7% in eight newborns at 2–4 weeks of age (So et al., 2005), whereas Rioualen et al. found relatively lower agreement rate (62.6%) and specificity (41.0%) in 24 preterm and 24 full-term infants within the first week of life (Rioualen et al., 2015). The mean durations of the studies were 3.7 and 2.2 h, respectively, which might not include sufficient sleep cycles to allow intra- and inter-subject variations of findings. In our study, to validate actigraphy in a clinically relevant setting, we performed overnight studies (11.7 ± 3.95 h) of simultaneous actigraphy and polysomnography in a medium-sized cohort of 40 newborns. The average agreement rate with polysomnography, predictive value, and sensitivity to sleep were 88.1%, 88.8%, and 97.5%, respectively, which are similar to the findings of So et al. Considering that the sensitivity to the acceleration due to gravity of the actigraphy device used in our study (0.025 g) and the studies of So et al. (0.01 g) and Rioualen et al. (0.05 g) differed from each other, an actigraphy device with relatively higher motion sensitivities may facilitate a precise sleep assessment in newborns.

In our current study, a longer sleep period relative to the total valid record was associated with relatively higher accuracy of sleep detection by actigraphy. A considerably high sleep-awake ratio in newborns may in part explain high sensitivities and relatively low specificities of actigraphy in detecting sleep. Potential difficulties in discriminating wakefulness from active sleep may also related with the relatively low specificity of actigraphic sleep detection in newborns. An extensive analysis of our current data needs to be performed to clarify whether wakefulness can be discriminated from active sleep using the activity index.

Given the convincingly high predictive value of actigraphy in detecting newborn sleep, an extended use of actigraphy in newborns may significantly improve the understanding of pathological outcomes of newborns, especially that abnormal sleep patterns early in life are related to later health conditions and neurological development (Chaput et al., 2017). Weisman et al. classified sleep patterns of newborn infants at 37 weeks post-conceptional age and found that the organised group, whose sleep cycle mainly comprises sleep and wakefulness, was associated with a higher verbal and cognitive performance at 5 years old compared with the high-arousal group, whose sleep cycle mainly comprises awake, cry, and active sleeps, and the disorganised group, whose sleep cycle mainly comprises within-sleep-state changes (Weisman et al., 2011). Moreover, Geva et al. reported that poor sleep patterns at term-equivalent period were associated with lower scores in the visual-recognition-memory task at 18 months of age (Geva et al., 2016). These data consistently support the importance of evaluating the sleep pattern of newborns to understand neurological impairments in childhood. Actigraphy may be a powerful tool to provide objective sleep evaluation over weeks, with a minimum burden on newborns and their families. Nishihara et al. performed four sets of 3-day actigraphy studies in 11 mothers and their newborns and reported the presence of diurnal rhythms as early as 3 weeks after birth (Nishihara et al., 2002).

Study limitations

Using simultaneous recording of actigraphy and polysomnography data, we were able to assess the predictive value of actigraphy for the sleep–wake cycle in a medium-sized cohort of newborns. The relatively long study durations from overnight recordings allowed the comparison of sleep assessment between actigraphy and polysomnography over multiple sleep–wake cycles. However, our study has several limitations. First, although our cohort comprised relatively stable NICU infants, they were still different from normal newborns. Second, because of the limited study population, we were unable to evaluate the effect of several important clinical variables to the accuracy of sleep detection using actigraphy. For example, the activity index and subsequent accuracy of sleep detection might differ according to the limb position, to which the watch device is attached (e.g. wrist vs. ankle and right vs. left). In addition, the newborn with the lowest prediction accuracy, a full-term

infant who was born via caesarean section with a birth weight of 2664 g and Apgar scores of 8 (1 min) and 9 (5 min), had an AUC of 0.54 for the ROC curve. The polysomnography study was performed between days 3 and 4, when the newborn manifested poor oral feeding, poor activity, and little limb/trunk motions, suggesting that the importance of accounting for the influence of clinical conditions on actigraphic sleep assessment. Third, data from 15 of the 55 newborns who were initially recruited (27.2%) were not included in the analysis because of insufficient quantity or quality of polysomnography records. However, as the low quantity and poor quality of the data can be primarily attributed to the dislocation of electrodes and sensors and the subsequent difficulty in reattaching them, the exclusion of the 15 newborns was unlikely to yield a significant selection bias. Future studies are needed to assess the impact of the sleep environment, time of the day, and subsequent sleep duration to the accuracy of actigraphic sleep detection by repeating the observation at different stages of development.

Conclusions

Our study suggests that sleep periods of newborns admitted to the NICU at term-equivalent age can be precisely determined using actigraphy on the ankle. The simple and non-invasive nature of actigraphy, which allows long-period recordings of sleep patterns even in newborns, could help identify sleep patterns that are associated with later health conditions and neurodevelopmental outcomes. Moreover, such approach may contribute to the prediction, early diagnosis, prevention, and treatment of sleep disorders, neurological impairments, and cognitive dysfunction.

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable requests to the corresponding author.

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Figure legends

FIGURE 1 Actigraphy and video polysomnography data acquisition. Acquisition of actigraphy and polysomnography data was performed using a custom-made watch-belt harness (a, b) and electroencephalogram (c), respectively

FIGURE 2 Receiver operating characteristic curve of sleep determined by actigraphy and polysomnography. The area under the curve (AUC) for the receiver operating characteristic (ROC) curve for each newborn (a) and the entire study cohort (b). The AUC for the ROC curve of the sleep epoch determined by actigraphy to predict sleep based on polysomnography was 0.87 (95% confidence interval, 0.87–0.88), indicating a good discriminatory capability of actigraphy

FIGURE 3 Accuracy curves against cut-offs for each participant. Accuracy and its 95% confidence interval were calculated for the activity index for each newborn and for all newborns using the meta-analysis method. The maximum overall accuracy was used as the cut-off point

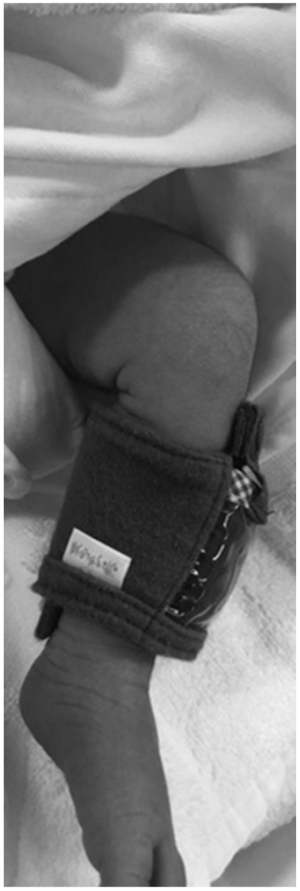
Table caption

TABLE 1 Clinical Background of the Study Participants

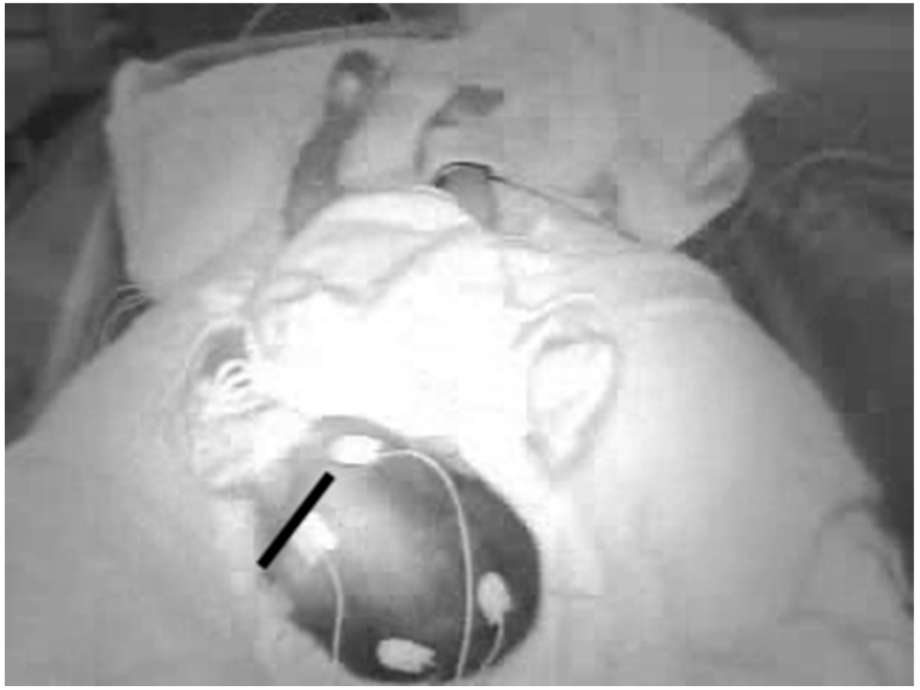
Note: Values are shown as numbers, medians (range), or means (standard deviation).

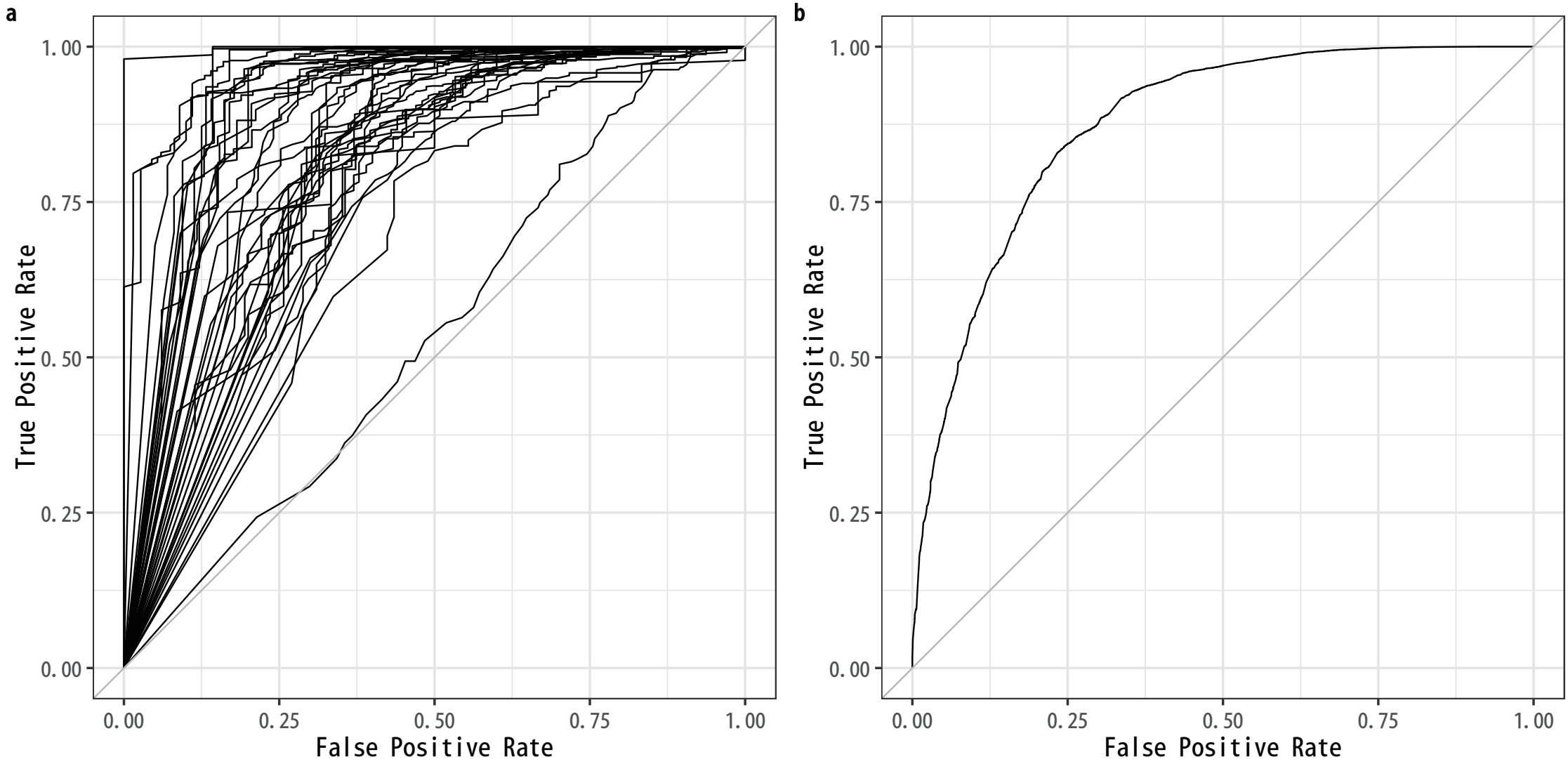
a

b



c




a
b
True Positive Rate
False Positive Rate
0.00
0.25
0.50
0.75
1.00

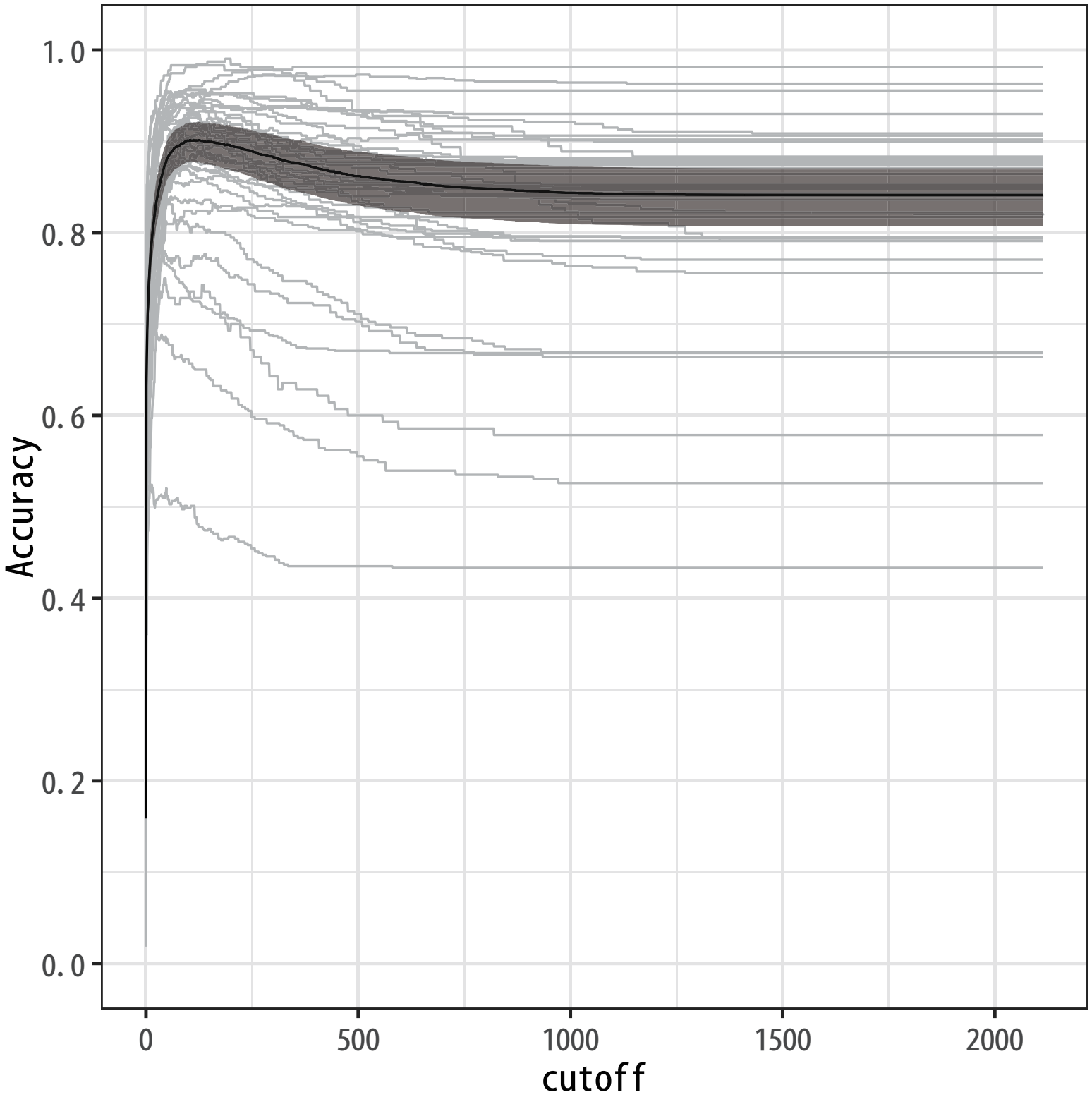

1.0
0.8
0.6
0.4
0.2
0.0
Accuracy
0
500
1000
1500
2000
cutoff

TABLE 1 Clinical Background of the Study Participants

Variable	n = 40
Male sex, number (%)	20 (50.0%)
Multiple birth, number (%)	6 (15.0%)
Delivery mode	
Spontaneous, number (%)	16 (40.0%)
Vacuum, number (%)	3 (7.5%)
Elective caesarean, number (%)	8 (20.0%)
Emergency caesarean, number (%)	13 (32.5%)
Gestational age in week, median (range)	38 (25–41)
Birth weight in g, median (range)	2139 (645–3588)
Apgar score at 1 min, median (range)	8 (1–9)
Apgar score at 5 min, median (range)	9 (6–9)
Postnatal age at study in day, median (range)	11.5 (3–119)
Post-conceptional age at study in week, median (range)	38.8 (35.3–45.3)
Study duration in min, mean (standard deviation)	703 (237)
Sleep time in min, mean (standard deviation)	417 (205)
Awake time in min, mean (standard deviation)	91 (69)
Invalid epochs in %, mean (standard deviation)	26.7 (21.2)