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ORIGINAL ARTICLE

Evaluation of neurological behaviour in late-preterm newborn infants using the Hammersmith Neonatal Neurological Examination

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Aim: We hypothesise that clinically well late-preterm infants (LPI) (34^{+0}–36^{+6} weeks) are neurologically more immature than their term counterparts, and this immaturity persists even when these infants reach term-corrected age (TCA). The primary aim of our study was to characterise and contrast the neurodevelopmental profile of well LPI with full-term infants (FTI) (39^{+0}–41^{+6} weeks) using the Hammersmith Neonatal Neurological Examination (HNNE). Our secondary aim was to obtain local reference ranges for the 34 items in the HNNE in an Asian-dominant population.

Methods: LPI were assessed at two time points: 12–72 h of life and at TCA of 39^{+0}–41^{+6} weeks, while FTI were assessed at 12–72 h of life using the HNNE. Each of the 34 items on the HNNE was assigned an optimality score (OS) of 0, 0.5 or 1, totalling up to 34. A quantitative comparison of the neurobehavioral patterns was made using two-sample *t*-tests.

Results: A total of 212 infants (79 LPI and 133 FTI) were recruited. Mean OSs for LPI and FTI at birth were $(25.11 \pm 3.36)/34$ and $(31.19 \pm 1.50)/34$, respectively, with a mean difference of 6.08 (*P* value <0.0001). The mean OS for LPI on reaching TCA was $(28.91 \pm 2.30)/34$, with a mean difference of 2.28 (*P* value <0.0001). Reference OSs for the 34 items on the HNNE were also obtained.

Conclusion: LPI are more immature than their term counterparts even on reaching TCA, with discrepancies most apparent in 'tone' and 'movement'. We provide reference OSs of 34 items in the HNNE for infants in an Asian-dominant population.

Key words: full-term infants; Hammersmith Neonatal Neurological Examination; late-preterm infant; optimality score; raw score; term-corrected age.

What is already known on this topic

1. The Hammersmith Neonatal Neurological Examination (HNNE) is a validated tool to objectively assess the neurology of newborn infants.
2. Reference ranges for optimality scores for each of the items on the HNNE have been published in term infants in largely Western cohorts.
3. The fetus undergoes a critical and rapid period of brain growth during the last 6 weeks of gestation; late-preterm infants (LPI) born between 34^{+0} and 36^{+6} weeks are not shielded by natural *in utero* protection, potentially leading to neuronal networks developing differently had the pregnancy progressed to term.

What this paper adds

1. This is the first study conducted in an Asian-dominant population using the HNNE.
2. It provides longitudinal data on neurodevelopmental profile of LPI at birth and at term-corrected age.
3. It confirms our hypothesis that LPI are more immature than their term counterparts, and this immaturity persists even on reaching term-corrected age.

Late-preterm infants (LPI), infants born between 34^{+0} and 36^{+6} weeks account for 75% of preterm deliveries and are often viewed as 'small full-term' infants, with little regard for their unique set of medical and developmental needs that could place them at increased risk for morbidity and mortality.[1]

The human brain experiences a critical period of rapid growth, acquiring 35% of the total fetal brain and 47% of the cortical volume during the last 6 weeks of gestation. Similarly, the myelinated white matter undergoes a fivefold increase between 34 and 41 weeks' gestation, and the grey matter volume increases at a rate of 1.4% or 15 mL/week.[2,3] Hence, preterm infants undergo brain growth post-natally without the *in utero* protection that they would have otherwise been accorded. Hence, the neuro networks that develop might differ from natural *in utero* progression.[3] This raises questions regarding the neurodevelopment of

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Conflict of interest: EYJ Chin received, in her third year of medical school, a start-up study grant from Duke-NUS Medical School Singapore to pursue her research interest. The grant was utilised to buy essential stationary and a video camera for the study and enabled her to present her research at an overseas conference.

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LPI compared to their term counterparts, both at birth and at a term-corrected age (TCA).

The Hammersmith Neonatal Neurological Examination (HNNE) developed by Dubowitz *et al.*[4] is an objective assessment of an infant's neurology. It consists of 34 items assessing tone, tone patterns, reflexes, movements, abnormal signs and behaviour of the newborn infant. Using the HNNE, we aimed to characterise the neurodevelopmental profile of well, LPI at 12–72 h from birth and at TCA and compare it with full-term infants (FTI) at 12–72 h from birth. Our hypothesis was that clinically well LPI assessed within 72 h from birth exhibit neurological immaturity when compared to their term counterparts, and this pattern persists on reaching TCA.

Methods

Study participants

This prospective study involved clinically well, low-risk, full-term (39^{+0}–41^{+6} weeks) and late-preterm (34^{+0}–36^{+6} weeks) newborn infants born over a 12-month period in 2016 at Singapore General Hospital. Based on a two-sided two-sample *t*-test at the 0.05 significance level, group sample sizes of 59 LPI and 118 FTI needed to be recruited to achieve 81% power.

A total of 1808 infants were born during this period, of which 963 infants met the inclusion criteria for gestational age (GA) (LPI 177). Of the 963 infants, 212 infants who met the inclusion criteria (79 LP1 and 133 FTI) were recruited (Fig. 1). The study was a third-year research project undertaken by a medical student (J Chin), and recruitment into the study was dictated by the student's time and availability over the 12-month recruitment period or the availability of either of the two trainees (I Ereno and K Low) to perform the HNNE. Hence, 75 LPIs were not recruited as a result of this, while 17 LPIs were clinically unwell, and parents declined participation for 6 LPIs.

GA was calculated from the first trimester dating ultrasound scan. When antenatal ultrasound scan was not available, the gestation was determined using the Dubowitz *et al.*[5] or Ballard *et al.*[6] assessment of GA against the mother's last menstrual period.

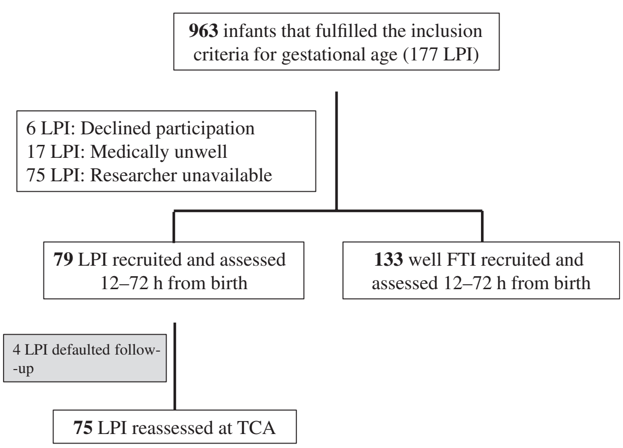


Fig. 1 Screening and recruitment of study subjects. FTI, full-term infant; LPI, late–preterm infant; TCA, term-corrected age.

Exclusion criteria included infants who were clinically unwell, neonatal infections, infants with major congenital or chromosomal anomalies, birth injuries, significant hyperbilirubinemia (serum bilirubin of >200 μmol/L within 72 h of life) and infants who failed their hearing test at discharge.

Informed consent was obtained from the parents at routine newborn screening examinations at 12–24 h from birth. The examination was videotaped as part of the quality audit to ensure that examination standards were fulfilled by study investigators. The study was approved by the Hospital Ethics Committee (CIRB Ref No. 2015/2929).

Study procedure and follow-up

Clinically well FTIs and LPIs were examined using the HNNE at 12–72 h from birth. Examination was limited to three assessors, two neonatal registrars (IE and KL) and the first author (JC), all of whom underwent training in the use of the HNNE to minimise inter-rater variability. The examinations were performed in a quiet room with infants undressed on an open bed or in their cot and placed under a radiant warmer with infants in state 4 or 5 of the Brazelton Neonatal Behavior Assessment scale.[7] Where possible, the examination was performed midway between two feeds, with infants settled, alert and comfortable. LPIs were re-examined at TCA of 39^{+0}–41^{+6} weeks during their scheduled post-discharge follow-up visits, with infants who missed their follow-up visits re-assessed through a home visit.

Hammersmith Neonatal Neurological Examination

Each of the 34 items was scored on a 5-point scale. If an item fell between two categories, it was given the appropriate half score between categories. These scores denote the 'raw score' (RS), which were then converted into an 'optimality score' (OS) designed and introduced primarily for the use of research and validated on a population of 224 low-risk term infants, as originally described by Dubowitz *et al.*[8] The distribution of the study population was plotted for each item, and the 5th/95th and 10th/90th centiles were used as cut-off values. A RS between the 10th and 90th centile was given an OS of 1. RSs between the 5th and 10th or 90th and 95th centiles were given an OS of 0.5, and a score of '0' was given for infants at the extreme ends of <5th or >95th centile. To illustrate an example, if one were to score 'Arm recoil' (as part of Tone assessment) at 39–40 weeks, a RS of 3 or 4 would correspond to an OS of 1, a RS of 2.5 to an OS of 0.5 and RSs less than 2.5 or 5 to an OS of 0.[8]

Statistical analysis

Performance on the HNNE was quantified by conversion of the RS to the OS. Comparison was made at two time points: 12–72 h from birth and at TCA of 39^{+0}–41^{+6} weeks. The OSs of infants born late preterm at 12–72 h from birth and at TCA of 39^{+0}–41^{+6} weeks were compared with that of their term counterparts using the two-sample *t*-test assuming normality. A *P* value of ≤0.05 was considered statistically significant, and a cut-off of ≥30.5/34 was used to define the ideal 'optimal' score in an infant based on the results from a previously similar study cohort.[9]

Table 1 Demographics and characteristic profile of infants at 12–72 h from birth

Variable	Late-preterm infants (GA = 34^{+0}–36^{+6}), *n* = 79			Full-term infants (GA = 39^{+0}–41^{+6}), *n* = 133	*P* value
	GA = 34 weeks, *n* = 14	GA = 35 weeks, *n* = 28	GA = 36 weeks, *n* = 37		
Gender (male), *n*	7	11	25	57	0.0478
Mean birthweight, g, mean ± SD	2111.43 ± 283.26	2281.25 ± 343.60	2613.24 ± 355.89	3261.0 ± 340.45	<0.0001
Age at examination, h, mean ± SD	49.29 ± 17.26	43.18 ± 17.69	38.31 ± 19.80	30.74 ± 14.78	0.0001
Brazelton score on examination					0.109
Stage 2/3	3	1	4	10	
Stage 4	9	27	32	117	
Stage 5	2	0	1	6	
Mean optimality score at birth, mean ± SD	22.46 ± 3.23	24.41 ± 3.05	26.65 ± 2.85	31.19 ± 1.50	<0.0001

GA, gestational age; SD, standard deviation.

One-way analysis of variance was used to compare the birthweight, age at examination (hours of life) and OSs at 12–72 h from birth and at TCA among the subgroups of LPI, (34, 35 and 36 weeks' gestation) and FTI. Pairwise comparisons were performed using the least significant difference *t*-test approach.

To evaluate the range and distribution frequency of the OSs among subgroups of LPI at TCA and that of the FTI, the distribution of RSs for the cohort of clinically well, low-risk infants was plotted for each of the 34 items.

Results

A total of 212 infants who fulfilled the inclusion criteria (79 LPI and 133 FTI) were enrolled in the study (Table 1).

Neurological maturity varied with gestation with increasing OS of 22.46 ± 3.23, 24.41 ± 3.05, 26.65 ± 2.85 and 31.19 ± 1.50 for infants born at 34, 35, 36 weeks' gestation and at term, respectively. As expected, the mean OSs between the LPI and FTI cohort 12–72 h from birth were statistically and significantly different, with a mean score of (25.11 ± 3.36)/34 and 31.18/34, respectively ($P < 0.0001$) (Table 2). LPIs were re-assessed at a mean corrected age of 40.2 weeks, and the OSs were recalculated at this gestation. In contrast, term infants had a mean GA of 39.9 weeks at enrolment ($P < 0.01$).

Of the 79 LPIs, 75 were reassessed at the corrected age of term, with 4 infants withdrawing from participating in a follow-up assessment. The mean OS of these 75 LPIs at term was (28.91 ± 2.30)/34 as compared to (31.19 ± 1.50)/34 for FTIs, with a mean difference of 2.28 ($P < 0.0001$) (Table 2). Further analysis revealed that the two main subcategories where LPIs lagged behind were tone and movement, with a median difference of 1.5 and 1 ($P < 0.0001$), respectively. For example, there were persistent differences in flexor tone in the limbs both on flexion and traction in LPI even at term. The difference in flexor tone was also observed in scores on posture, with FTIs attaining a higher median score noted at column 4, which denotes 'legs well-flexed and adducted near abdomen'. In contrast, LPIs had median scores in column 3, which describes a 'well-flexed with minimal or no adduction' posture. Similarly, our findings showed increased popliteal angle in the LPI population even at TCA. Interestingly, on pull-to-sit from supine (head lag) and ventral suspension, the median score of our LPIs, whilst closer to the full-term cohort, remained lower than the FTIs, with relatively more marked decrease in 'head lag' than that of 'ventral suspension' (as noted in the 'tone pattern' subsection). The median scores of both the flexor and extensor tone components of head control of LPIs at TCA were lower than the FTIs, with minimal difference between both the flexor and extensor states in LPIs. The potential explanation for the discrepancies in tone will be discussed below.

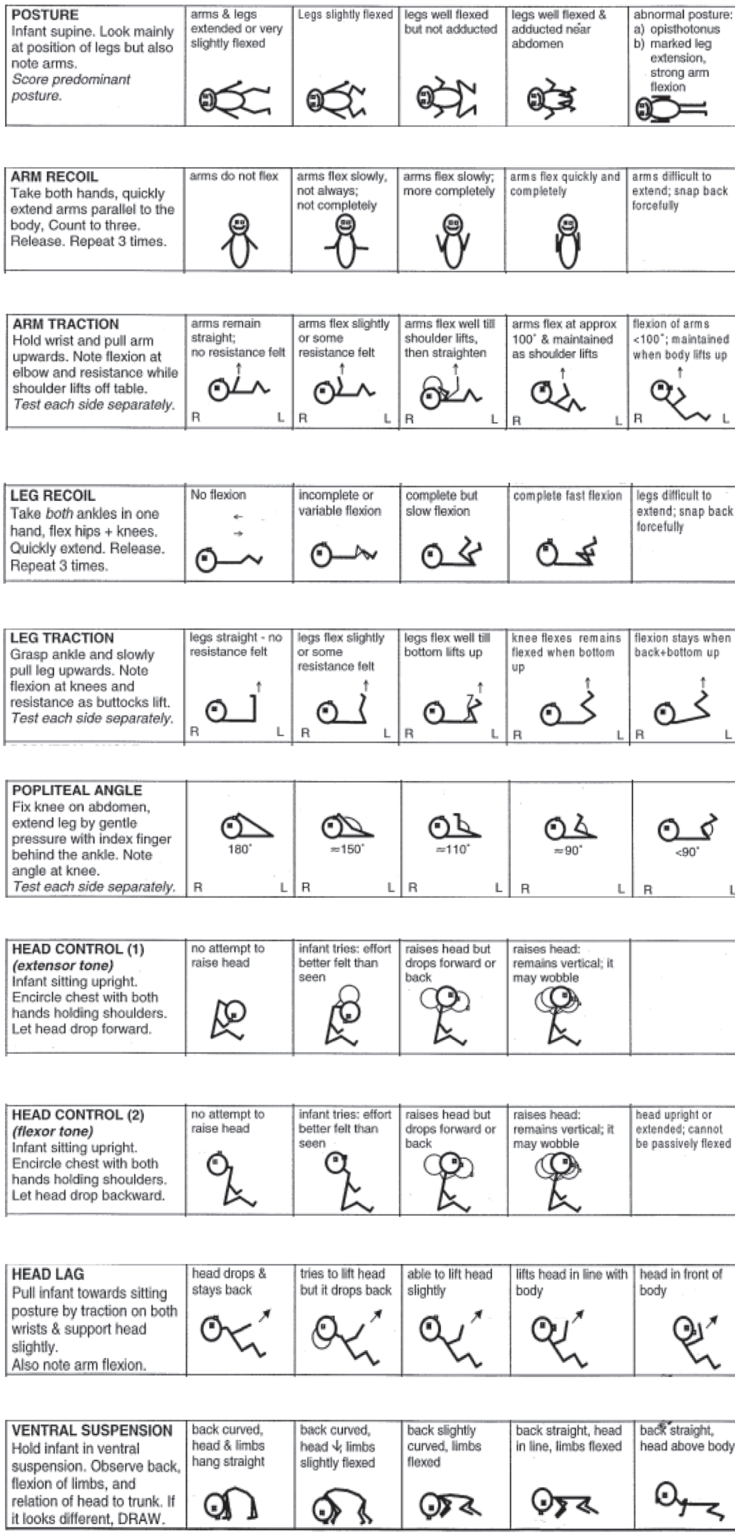
With regard to the 'movements' subsection, our findings indicate that LPIs at 34 and 35 weeks' gestation are more likely to display frequent 'isolated' movements compared to frequent 'generalised' movements found in infants born at 36 weeks' or greater. In our study, there was, however, no difference in the median score for the 'quality' of spontaneous movement among the subgroups. Likewise, LPIs had lower scores in the 'Head Raising Prone' component in this subsection.

Table 2 Optimality scores in late-preterm infants (LPIs) and full-term infants (FTIs) at birth and at term-corrected age (TCA)

	LPI	FTI	Mean difference (*P* value)
Optimality score at 12–72 h from birth, mean	(25.11 ± 3.36)/34	(31.19 ± 1.50)/34	6.07 (<0.0001)
Mean GA at TCA, weeks	40.2 ± 0.68	39.9 ± 0.57	0.30, *P* < 0.01 (0.0081)
Optimality score at TCA, mean	(28.91 ± 2.30)/34	(31.19 ± 1.50)/34	2.28 (<0.0001)

GA, gestational age.

Posture and Tone



1	.5	2	.5	3	.5	4	.5	5	Gestational age
0	0	4	2	8	0	0	0	0	GA= 34
0	0	3	3	22	0	0	0	0	GA= 35
0	0	1	2	30	0	4	0	0	GA= 36
0	0	1	2	58	6	8	0	0	LPI at TCA
0	0	0	0	14	24	95	0	0	FTI
0	1	4	3	6	0	0	0	0	GA= 34
0	0	6	6	15	1	0	0	0	GA= 35
0	0	5	8	20	2	2	0	0	GA= 36
0	0	10	13	40	3	9	0	0	LPI at TCA
0	0	0	0	23	16	94	0	0	FTI
0	1	9	3	1	0	0	0	0	GA= 34
0	0	9	6	12	1	0	0	0	GA= 35
0	0	6	7	16	5	3	0	0	GA= 36
0	0	6	19	36	4	10	0	0	LPI at TCA
0	0	0	1	8	9	115	0	0	FTI
0	0	3	7	3	1	0	0	0	GA= 34
0	0	0	5	17	2	4	0	0	GA= 35
0	0	1	2	15	3	13	0	0	GA= 36
0	0	5	6	35	5	24	0	0	LPI at TCA
0	0	0	0	14	11	108	0	0	FTI
0	1	5	5	3	0	0	0	0	GA= 34
0	0	5	4	19	0	0	0	0	GA= 35
0	0	2	7	14	8	6	0	0	GA= 36
0	0	3	10	47	5	10	0	0	LPI at TCA
0	0	0	0	5	6	122	0	0	FTI
0	0	10	2	2	0	0	0	0	GA= 34
0	0	18	1	9	0	0	0	0	GA= 35
0	0	14	2	19	2	0	0	0	GA= 36
0	0	0	3	54	3	15	0	0	LPI at TCA
0	0	0	0	23	7	103	0	0	FTI
0	0	6	2	6	0	0	0	0	GA= 34
0	0	4	6	18	0	0	0	0	GA= 35
0	0	3	6	27	0	1	0	0	GA= 36
0	0	1	6	47	7	14	0	0	LPI at TCA
0	0	0	1	23	23	86	0	0	FTI
0	0	4	3	7	0	0	0	0	GA= 34
0	0	4	7	16	1	0	0	0	GA= 35
0	0	6	4	26	0	1	0	0	GA= 36
0	0	0	8	47	8	12	0	0	LPI at TCA
0	0	0	2	24	23	84	0	0	FTI
0	0	7	5	2	0	0	0	0	GA= 34
0	0	4	11	13	0	0	0	0	GA= 35
0	0	8	8	20	1	0	0	0	GA= 36
0	0	2	12	50	6	5	0	0	LPI at TCA
0	0	0	1	47	50	35	0	0	FTI
0	0	5	3	6	0	0	0	0	GA= 34
0	0	9	7	12	0	0	0	0	GA= 35
0	0	4	6	23	3	1	0	0	GA= 36
0	0	0	10	47	8	10	0	0	LPI at TCA
0	0	0	2	22	54	55	0	0	FTI

Fig. 2 Distribution frequency of each item in the Hammersmith Neonatal Neurological Examination of late-preterm infants (LPI) and full-term infants (FTI) at 12–72 h from birth and at term-corrected age (TCA). Boxes shaded in grey denote the median score. GA, gestational age.

Tone Patterns						1	.5	2	.5	3	.5	4	.5	5	Gestational age
FLEXOR TONE (1) (on traction: arm versus leg) Compare scores of arm traction with leg traction.		Score for arm flexion less than leg flexion	Score for arm flexion equal to leg flexion	Score for arm flexion more than leg flexion but difference of 1 column or less	Score for arm flexion more than leg flexion but difference more than 1 column	0	0	5	0	8	0	1	0	0	GA= 34
						0	0	8	0	19	0	1	0	0	GA= 35
						0	0	14	0	19	0	4	0	0	GA= 36
						0	0	19	0	46	0	10	0	0	LPI at TCA
						0	0	13	0	115	0	5	0	0	FTI
FLEXOR TONE (2) (arm versus leg) Posture in supine			Arms and legs flexed	Strong arm flexion with strong leg extension *intermittent*	Strong arm flexion with strong leg extension *continuous*	0	0	0	0	14	0	0	0	0	GA= 34
						0	0	0	0	28	0	0	0	0	GA= 35
						0	0	0	0	37	0	0	0	0	GA= 36
						0	0	0	0	75	0	0	0	0	LPI at TCA
						0	0	0	0	133	0	0	0	0	FTI
LEG EXTENSOR TONE Compare scores of leg traction and popliteal angle		Score for leg traction more than score for popliteal angle	Score for leg traction equal to score for popliteal angle	Score for leg traction less than score for popliteal angle by 1 column only	Score for leg traction less than score for popliteal angle by more than 1 column	0	0	4	0	8	0	2	0	0	GA= 34
						0	0	12	0	13	0	3	0	0	GA= 35
						0	0	22	0	12	0	3	0	0	GA= 36
						0	0	8	0	48	0	18	0	1	LPI at TCA
						0	0	52	0	132	0	12	0	0	FTI
NECK EXTENSOR TONE (SITTING) Compare scores of head control 1 and 2		Score for head extension less than head flexion	Score for head extension equal to head flexion	Score for head extension more than head flexion but difference is 1 column or less	Score for head extension more than head flexion but difference is more than 1 column	0	0	1	0	13	0	0	0	0	GA= 34
						0	0	1	0	26	0	1	0	0	GA= 35
						0	0	2	0	29	0	6	0	0	GA= 36
						0	0	1	0	71	0	3	0	0	LPI at TCA
						0	0	0	0	130	0	3	0	0	FTI
INCREASED EXTENSOR TONE (HORIZONTAL) Compare scores of head lag and ventral suspension		Score for ventral suspension less than head lag	Score for ventral suspension equal to head lag	Score for ventral suspension more than head lag but difference of 1 column or less	Score for ventral suspension more than head lag but difference more than 1 column	0	0	2	0	4	0	8	0	0	GA= 34
						0	0	5	0	19	0	4	0	0	GA= 35
						0	0	4	0	19	0	14	0	0	GA= 36
						0	0	10	0	49	0	15	0	1	LPI at TCA
						0	0	18	0	65	0	50	0	0	FTI

Fig. 2 (Continued)

Interestingly, 12 LPIs had a lower OS at term follow-up compared to that originally obtained at their first assessment after birth. The items where LPIs scored lower at term compared to what they did when first examined included 'Head Raising Prone', 'Head Control' and 'Arm Traction'. We were unable to explain why this was the case (see Study limitations).

Distribution frequency of each of the 34 items of the subgroups of LPI at TCA as well as that of infants born at term is shown in Figure 2, with the median value for each item indicated in grey.

Discussion

This is the first study conducted in an Asian-dominant population using the HNNE and provides longitudinal data on the neurodevelopmental profile of LPIs at birth and at TCA using the OS introduced by Dubowitz *et al*.[8]

Our results show that LPIs are neurologically immature at birth and fail to 'catch up' with their term counterparts at TCA, with a statistically significant mean difference of 6.07 points at birth and 2.28 points at TCA of 39^{+0}–41^{+6} weeks' gestation ($P < 0.0001$).

Our study concurs with the findings from Romeo *et al*.,[10] which showed that the median and range of neurological scores were wider in the preterm infants than their term counterparts. In the report by Mercuri *et al*.[9] on clinically well, low-risk term infants, a global score of ≥30.5/34 was defined as 'optimal'. In our study, 3 of 79 LPIs (3.79%) attained an optimal score of ≥30.5/34 compared to 90 of 133 FTI (67.66%) at 12–72 h from birth. At TCA, only 20 of 75 (26.66%) LPIs attained an optimal score of ≥30.5. This suggests that LPIs not only 'lag behind' their term counterparts at birth but also have suboptimal scores even at TCA. In addition, approximately 16% of the LPIs (12/75 LPIs) had lower OSs at TCA compared to that at birth. This group of LPIs deserves closer monitoring of their developmental performance at subsequent follow-up visits.

The frequency distribution of the 34 items of the HNNE provides an estimate of neurodevelopmental profiles of clinically well, predominantly Asian LPIs and FTIs at 12–72 h after birth and at TCA (Fig. 2). LPIs had a lower tone at birth compared with their term counterparts, and this difference persisted at TCA (Fig. 2). This finding aligns with that of Romeo *et al*.[11] who compared neurological outcomes in LPIs and FTIs at 6, 9 and 12 months corrected age. They were assessed using the infant version of the HNNE applicable to older babies (the Hammersmith Infant Neurological Examination), and LPIs had lower scores in tone and reflexes that persisted even at 12 months. This continuing difference in flexor tone in the limbs between LPIs and FTIs, also highlighted in our study, is likely to be explained by the longer exposure to intra-uterine pressure in a flexed posture in the FTIs. In contrast, LPIs are less flexed *in utero* and are

Reflexes

Reflex					
TENDON REFLEX Test biceps, knee, ankle jerks.	absent	Felt not seen	seen	"exaggerated" (very brisk)	clonus
SUCK/GAG Little finger into mouth with pulp of finger upwards.	No gag/ no suck	Weak irregular suck only No stripping	Weak regular suck Some stripping	Strong suck: (a) Irregular (b) Regular Good stripping	No suck but strong clenching
PALMAR GRASP Put index finger into the hand and gently press palmar surface. Do not touch dorsal surface. *Test each side separately.*	No response R L	Short, weak flexion of the fingers R L	Strong flexion of the fingers R L	Strong finger flexion shoulder raised R L	Very strong grasp; infant can be lifted off couch R L
PLANTAR GRASP Press thumb on the sole below the toes. Test each side separately.	No response R L	Partial plantar flexion of toes R L	Toes curve around the examiner's finger R L		
PLACING Lift infant in an upright position and stroke the dorsum of the foot against a protruding edge of a flat surface, *Test each side separately.*	No response R L	Dorsiflexion of ankle only R L	Full placing response with flexion of hip and knee and placing sole on surface R L		
MORO REFLEX One hand supporting the infant's head in midline, the other at the back. Raise infants to 45° and when infant is relaxed, let head fall through 10°. note if jerky. Repeat 3 times	No response, or opening of hands only	Full abduction at shoulder and extension of the arms; no adduction	Full abduction, but only delayed or partial adduction	Partial abduction at shoulder and extension of arms followed by smooth adduction	-minimal abduction or adduction -no abduction or adduction; only forward extension of arms

Reflex										Group
Tendon reflex	0	0	6	0	8	0	0	0	0	GA= 34
	0	0	12	0	16	0	0	0	0	GA= 35
	0	0	11	0	26	0	0	0	0	GA= 36
	0	0	45	0	30	0	0	0	0	LPI at TCA
	0	0	42	0	91	0	0	0	0	FTI
Suck/gag	1	0	3	0	4	1	5	0	0	GA= 34
	0	0	1	1	3	3	20	0	0	GA= 35
	0	0	3	1	8	0	25	0	0	GA= 36
	0	0	0	1	0	0	74	0	0	LPI at TCA
	0	0	0	0	10	0	123	0	0	FTI
Palmar grasp	0	0	0	1	10	0	3	0	0	GA= 34
	0	0	1	1	12	1	13	0	0	GA= 35
	0	0	1	3	9	1	23	0	0	GA= 36
	0	0	4	2	43	0	26	0	0	LPI at TCA
	0	0	1	0	32	0	100	0	0	FTI
Plantar grasp	0	0	0	0	14	0	0	0	0	GA= 34
	0	0	0	0	28	0	0	0	0	GA= 35
	0	0	0	0	37	0	0	0	0	GA= 36
	0	0	2	0	72	0	1	0	0	LPI at TCA
	0	0	2	0	131	0	0	0	0	FTI
Placing	0	0	2	0	12	0	0	0	0	GA= 34
	0	0	1	0	27	0	0	0	0	GA= 35
	0	0	0	1	36	0	0	0	0	GA= 36
	0	0	8	1	65	0	1	0	0	LPI at TCA
	0	0	4	0	129	0	0	0	0	FTI
Moro reflex	0	0	0	0	6	0	8	0	0	GA= 34
	0	0	0	0	5	1	22	0	0	GA= 35
	0	0	0	0	9	3	25	0	0	GA= 36
	0	0	1	0	29	6	39	0	0	LPI at TCA
	0	0	0	0	16	10	107	0	0	FTI

Fig. 2 (Continued)

nursed supine in a relatively extended posture for several weeks after birth.[12] This difference in tone was further confirmed by a difference in popliteal angle, head lag and ventral suspension among LPIs at TCA, which is likely to be a reflection of reduced tone in LPIs compared to their term counterparts. Previous studies have also noted the presence of transient neurologic abnormalities in 40–80% of well preterm infants, which increases in frequency with lower GA and birthweight.[13]

Reflexes, apart from suck and gag, were generally unremarkable except in LPIs at 34 weeks, with a majority demonstrating 'weak, irregular/regular' suck and 1 of 13 infants having 'no suck/no gag' response (in spite of palatal stimulation). Studies have shown that preterm infants develop the skills necessary to start oral feeding as they attain a post-conception age (PCA) that supports co-ordinated breathing, swallowing with oral–motor functioning and ability to maintain physiological stability.[14] Studies show that both the palmar and plantar grasp reflex can generally be elicited in all normal preterm infants as early as 25 weeks' PCA.[15] Likewise, Moro reflex has been noted in the majority by 30 weeks of PCA.[16]

In our study, although LPIs had less generalised movements than FTIs, there was no difference in the median score for the 'quality' of spontaneous movement among the subgroups. This is consistent with findings by Spittle *et al*. in their assessment of OSs in moderate–late-preterm and term infants.[17]

'Irritability', 'consolability' and 'cry' were comparable between the LPIs and FTIs, and this is expected given that study infants were clinically well. In response to auditory stimulation, FTIs were shown to be more likely to respond with shifting of eyes and, at times, slight turning of head in search for the source compared to an 'auditory startle' (when the infant brightens and stills but does not show true orientation), which is more common in the LPIs. As all infants recruited had normal newborn audiology screening, this difference could be due to the level of alertness and ability to 'focus' or duration of attention span, which is known to vary with gestational maturity. FTIs and LPIs at TCA in our study had more sustained attention when awake and were more able to 'look at stimuli' (red ball) but often lost them, compared to looking 'briefly' as noted in LPIs at 12–72 h from birth.

Movements

	1	2	3	4	5
SPONTANEOUS MOVEMENT (quantity) Watch infant lying supine	No movement	Sporadic and short isolated movements	Frequent isolated movements	Frequent generalized movements	Continuous exaggerated movements
SPONTANEOUS MOVEMENT (quality) Watch infant lying supine	Only stretches	Stretches and random abrupt movements; some smooth movements	Fluent movements but monotonous	Fluent alternating movements of arm and legs. Good variability	-cramped, synchronized; -mouthing -jerky or other abnormal movements
HEAD RAISING PRONE Infant in prone, head in midline	No response	Infant rolls head over, chin not raised	Infants raises chin, rolls head over	Infant brings head and chin up	Infant brings head up and keeps it up

Item	1	.5	2	.5	3	.5	4	.5	5	Gestational age
Spontaneous movement (quantity)	0	0	1	0	8	0	5	0	0	GA= 34
	0	0	0	0	13	1	14	0	0	GA= 35
	0	0	2	0	10	0	25	0	0	GA= 36
	0	0	0	0	9	1	65	0	0	LPI at TCA
	0	0	0	0	15	0	118	0	0	FTI
Spontaneous movement (quality)	0	0	0	1	4	0	9	0	0	GA= 34
	0	0	0	0	11	1	16	0	0	GA= 35
	0	0	0	0	5	0	32	0	0	GA= 36
	0	0	0	0	3	1	71	0	0	LPI at TCA
	0	0	0	0	1	0	132	0	0	FTI
Head raising prone	1	0	11	0	1	1	0	0	0	GA= 34
	2	0	19	3	3	0	1	0	0	GA= 35
	0	0	10	3	23	0	1	0	0	GA= 36
	1	0	34	1	34	2	3	0	0	LPI at TCA
	0	0	2	0	41	15	75	0	0	FTI

Abnormal signs/ patterns

	1	2	3	4	5
ABNORMAL HAND OR TOE POSTURE		Hands open, toes straight most of the time	Intermittent fisting or thumb adduction	Continuous fisting or thumb adduction; index finger flexion, thumb opposition	Continuous big toe extension or flexion of all toes
TREMOR		No tremor, or tremor only when crying or only after Moro Reflex	Tremor occasionally when awake	Frequent tremors when awake	Continuous tremors
STARTLE	No startle even to sudden noise	No spontaneous startle but reacts to sudden noise	2-3 spontaneous startles	More than 3 spontaneous startles	Continuous startles

Item	1	.5	2	.5	3	.5	4	.5	5	Gestational age
Abnormal hand or toe posture	0	0	0	0	14	0	0	0	0	GA= 34
	0	0	0	0	28	0	0	0	0	GA= 35
	0	0	2	1	33	0	1	0	0	GA= 36
	0	0	1	0	72	0	2	0	0	LPI at TCA
	0	0	5	1	120	6	1	0	0	FTI
Tremor	0	0	8	0	6	0	0	0	0	GA= 34
	0	0	9	0	17	0	2	0	0	GA= 35
	0	0	7	0	27	0	3	0	0	GA= 36
	0	0	52	0	22	0	1	0	0	LPI at TCA
	0	0	64	1	63	1	4	0	0	FTI
Startle	0	0	12	0	2	0	0	0	0	GA= 34
	0	0	17	0	11	0	0	0	0	GA= 35
	0	0	18	1	17	0	1	0	0	GA= 36
	0	0	63	1	9	0	2	0	0	LPI at TCA
	0	0	102	1	27	0	3	0	0	FTI

Fig. 2 (Continued)

The findings of a lower level of alertness to stimuli serve to remind care providers of the impact of these neurological responses on the infant's ability to acquire basic survival skills like feeding.[18]

Study limitations and future directions

While the numbers of infants recruited was sufficiently powered to answer our study question, the numbers in individual sub-groups of LPIs were small. We recruited a cohort of 212 infants from an eligible population of 963 infants. This discrepancy was mainly because of the non-availability of the study researchers to perform the clinical examination at the time of the births. The low fraction of eligible infants recruited could be a potential source of bias, as might be the time interval of performing the clinical examination. These were performed at 12–72 h to reflect clinical practice and practical realities in terms of the time of performing the first newborn screening, trainee availability and experience from comparable studies.[17] A larger population might have enabled a better representation of the neurodevelopmental profile at individual GAs in LPIs, aiding in prompt recognition of problems and their timely intervention.

Orientation and behaviour

EYE APPEARANCE	Does not open eyes		Full conjugated eye movements	*Transient* -nystagmus -strabismus -roving eye movements -sunset eyes	*Persistent* --nystagmus -strabismus -roving eye movements Abnormal pupils
AUDITORY ORIENTATION Infant awake. Wrap infant. Hold rattle 10-15 cm from ear	No reaction	Auditory startle; brightens and stills; no true orientation	Shifting of eyes, head might turn towards the source	Prolonged head turn to stimulus; search with eyes; smooth	Turns head (jerkily, abruptly) and eyes towards noise every time
VISUAL ORIENTATION Warp infant, wake up with rattle if needed or rock gently. Note if baby can see and follow red ball.	Does not follow or focus on stimuli	Stills, focuses, follows briefly to the side but loses stimuli	Follows horizontally and vertically; no head turn	Follows horizontally and vertically; turns head	Follows in a circle
ALERTNESS Tested as response to visual stimuli (with a red ball)	Will not respond to stimuli	When awake looks only briefly	When awake, looks at stimuli but loses them	Keeps interest in stimuli	Does not tire (hyper-reactive)
IRRITABILITY In response to stimuli	Quiet all the time, not irritable to any stimuli	Awakes, cries sometimes when handled	Cries often when handled	Cries always when handled	Cries even when not handled
CONSOLABILITY Ease to quiet infant	Not crying; consoling not needed	Cries briefly; consoling not needed	Cries; becomes quiet when talked to	Cries; needs picking up to be consoled	Cries; cannot be consoled
CRY	No cry at all	Whimpering cry only	Cries to stimuli but normal pitch		High-pitched cry; often continuous

1	.5	2	.5	3	.5	4	.5	5	Gestational age
0	0	0	0	14	0	0	0	0	GA= 34
0	0	0	0	28	0	0	0	0	GA= 35
0	0	0	0	37	0	0	0	0	GA= 36
0	0	0	0	75	0	0	0	0	LPI at TCA
1	0	0	0	132	0	0	0	0	FTI
0	0	12	1	1	0	0	0	0	GA= 34
0	0	23	1	4	0	0	0	0	GA= 35
0	0	26	1	10	0	0	0	0	GA= 36
0	0	45	2	28	0	0	0	0	LPI at TCA
0	0	62	4	66	0	1	0	0	FTI
4	1	8	0	1	0	0	0	0	GA= 34
1	0	22	3	2	0	0	0	0	GA= 35
3	1	23	4	6	0	0	0	0	GA= 36
0	0	51	8	16	0	0	0	0	LPI at TCA
3	0	73	10	43	3	1	0	0	FTI
0	2	9	0	3	0	0	0	0	GA= 34
0	0	24	2	2	0	0	0	0	GA= 35
0	0	22	0	15	0	0	0	0	GA= 36
0	0	29	3	42	1	0	0	0	LPI at TCA
0	0	49	2	81	1	0	0	0	FTI
0	0	4	2	5	1	2	0	0	GA= 34
0	0	17	0	10	0	1	0	0	GA= 35
0	0	14	2	20	1	0	0	0	GA= 36
1	0	32	0	39	2	1	0	0	LPI at TCA
0	1	63	3	60	2	4	0	0	FTI
0	0	4	0	4	0	6	0	0	GA= 34
0	0	18	0	9	0	1	0	0	GA= 35
0	0	12	1	20	1	3	0	0	GA= 36
1	0	21	0	45	0	8	0	0	LPI at TCA
0	0	49	4	67	1	12	0	0	FTI
0	0	3	0	11	0	0	0	0	GA= 34
0	0	11	0	17	0	0	0	0	GA= 35
0	0	7	0	30	0	0	0	0	GA= 36
1	0	13	0	61	0	0	0	0	LPI at TCA
0	0	37	3	93	0	0	0	0	FTI

Fig. 2 (Continued)

Given the time limitations of the study period and priority to ensure compliance with follow-ups of those recruited, the infants were re-assessed with a repeat HNNE at a single time point only. Hence, it is unclear at what time point LPIs attain neuro-maturity and if and when they do eventually 'catch up' with their term counterparts.

Among the 75 LPIs who were re-assessed at TCA, 13% were noted to paradoxically have lower OSs at term compared to their initial scores. Factors that can potentially impact neurodevelopmental outcomes (e.g. social environment, maternal health) were not studied, and interventions that might positively influence neuro-maturity, such as physiotherapy, oral feeding and various aspects of developmental care, were also not considered.

Conclusion

Our study shows that LPIs are neurologically less matured than their term counterparts, and this immaturity persists even when they reach TCA. Our study also provides longitudinal data on all 34 items of the HNNE in an Asian-dominant population. This will enable us to better understand the neuro-maturity of this group of vulnerable, yet often neglected, infants and facilitate early identification of problems and timely intervention, thereby limiting future neurological morbidity and adverse neurodevelopmental outcomes.

References

1 Bastek JA, Sammel MD, Pare E *et al*. Adverse neonatal outcomes: Examining the risks between preterm, late preterm, and term infants. *Am. J. Obstet. Gynecol.* 2008; **199**: 367.
2 Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: A review. *Semin. Perinatol.* 2006; **30**: 81–8.
3 Melnyk BM, Feinstein N, Fairbanks E. Two decades of evidence to support implementation of the COPE program as standard practice with parents of young unexpectedly hospitalized/critically ill children and premature infants. *Pediatr. Nurs.* 2006; **32**: 475–81.
4 Dubowitz LM, Dubowitz V, Mercuri E. *Neurological Assessment of the Preterm and Fullterm Newborn Infant*, 2nd edn. London: Mac Keith Press; 1999.
5 Dubowitz LMS, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J. Pediatr.* 1970; **77**: 1–10.
6 Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard score, expanded to include extremely premature infants. *J. Pediatr.* 1991; **119**: 417–23.
7 Brazelton TB. The Brazelton Neonatal Behavior Assessment scale: Introduction. *Monogr. Soc. Res. Child Dev.* 1978; **43**: 1–13.
8 Dubowitz L, Mercuri E, Dubowitz V. An optimality score for the neurologic examination of the term newborn. *J. Pediatr.* 1998; **133**: 406–16.
9 Mercuri E, Guzzetta A, Laroche S *et al*. Neurologic examination of preterm infants at term age: Comparison with term infants. *J. Pediatr.* 2003; **142**: 647–55.
10 Romeo DM, Luciano R, Corsello M *et al*. Neonatal neurological examination of late preterm babies. *Early Hum. Dev.* 2013; **89**: 537–45.
11 Romeo DMM, Guzzetta A, Scoto M *et al*. Early neurologic assessment in preterm-infants: Integration of traditional neurologic examination and observation of general movements. *Eur. J. Paediatr. Neurol.* 2008; **12**: 183–9.
12 Ricci D, Romeo DMM, Haataja L *et al*. Neurological examination of preterm infants at term equivalent age. *Early Hum. Dev.* 2008; **84**: 751–61.
13 Lenke MC. Motor outcomes in premature infants. *Newborn Infant Nurs Rev* 2003; **3**: 104–9.
14 Thoyre SM, Shaker CS, Pridham KF. The early feeding skills assessment for preterm infants. *Neonatal Netw.* 2005; **24**: 7–16.
15 Futagi Y, Toribe Y, Suzuki Y. The grasp reflex and Moro reflex in infants: Hierarchy of primitive reflex responses. *Int. J. Pediatr.* 2012; **2012**: 191562.
16 Allen MC, Capute AJ. The evolution of primitive reflexes in extremely premature infants. *Pediatr. Res.* 1986; **20**: 1284–9.
17 Spittle AJ, Walsh J, Olsen JE *et al*. Neurobehaviour and neurological development in the first month after birth for infants born between 32–42 weeks' gestation. *Early Hum. Dev.* 2016; **96**: 7–14.
18 White-Traut RC, Nelson MN, Silvestri JM *et al*. Effect of auditory, tactile, visual, and vestibular intervention on length of stay, alertness, and feeding progression in preterm infants. *Dev. Med. Child Neurol.* 2002; **44**: 91–7.