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ORIGINAL ARTICLE

Causes of neonatal deaths in Malaysian neonatal intensive care units in 2015-2020: a descriptive study

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Abstract

Introduction: To investigate the major causes of neonatal deaths in Malaysian neonatal intensive care units (NICUs). *Materials and Methods:* This retrospective observational study analysed prospectively collected data of neonates (gestation ≥22 weeks, birthweight ≥500g) admitted to 44 NICUs in the years 2015-2020 in the Malaysian National Neonatal Registry. Causes of death were reported using the modified Wigglesworth classification. *Results:* Out of 759,435 neonates, 1.2% (n=9470) died. Most (72.3%) were early neonatal deaths (0-7days of life), 17.5% were late neonatal deaths (8-28 days of life), and 10.2% were post-neonatal deaths (>28 days of life). Inborn extremely preterm (EPT, <28 weeks gestation) neonates had the highest death rates (427.5/1000 livebirths) and term neonates (1.7/1000 livebirths) had the lowest. Congenital malformations accounted for 33.0% of deaths; the majority were of gestation ≥28 weeks. Trisomy 18 (n=542), trisomy 13 (n=397), cardiovascular (CVS) malformations (n=371) and neurological malformations including neuro-tube defects (NTD) (n=252) were the four most common types of malformations. The three most common causes of non-malformation deaths were EPT (n=1424), sepsis (n=867, affecting all gestations), and hypoxic-ischaemic encephalopathy (HIE) in term neonates with/without multiorgan failure (n=570). Less than one-third of EPT neonates who died received respiratory support at birth. Most (85.3%) sepsis death was late-onset sepsis (≥72 hours of age). Only 27.8% term neonates dying from HIE received adequate therapeutic hypothermia. *Conclusions:* Extreme prematurity, nosocomial sepsis, HIE in term neonates, chromosomal abnormalities due to trisomy 18 and trisomy 13, ductal-dependent CVS malformations, and NTD were the six most common causes of neonatal deaths in Malaysian NICUs.

Keywords: neonatal deaths, Malaysian NICUs, malformation deaths, HIE, extreme preterm, nosocomial sepsis.

INTRODUCTION

For over 20 years (2003-2023), the neonatal mortality rates (NMR) of Malaysia hovered around 4.5 per 1000 livebirths.[1] Meanwhile, our neighbouring countries like Japan, Singapore, Korea and Thailand had declined markedly. By year 2021, the NMR of Singapore and Korea were 1.0 per 1000 livebirths, and Thailand was 5.0 per 1000 livebirths. In many developed countries, the NMR were lower than in Malaysia for years. For instance, the NMR of Australia was 2.3 per 1000 livebirths, and Germany was 2.2 per 1000 livebirths since 2018.[2] In Malaysia, more than half of under-five mortality was neonatal.[3] The United Nations Sustainable Development goal 3 advocates that to reduce the under-five mortality in a country, identifying and ending preventable neonatal deaths are targets which health care providers should aim to achieve.[4]

Over a six-year period (2015-2020), 2,998,121 livebirths were reported in Malaysia[3], and 1,792,002 (59.8%) of them were born in 44 hospitals participating in the Malaysian National Neonatal Registry (MNNR). These MNNR hospitals included all major public hospitals, several small public hospitals, one university hospital, and three small private hospitals. Trained staff of their neonatal intensive care

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units (NICUs) prospectively submitted data of neonates admitted to their NICUs to the MNNR. The present study aimed to investigate the major causes of neonatal deaths in these hospitals during this period. The ultimate aims were to provide information for future strategies to reduce Malaysian NMR.

MATERIAL AND METHODS

This was a retrospective observational study using MNNR data of neonates admitted to these 44 Malaysian NICUs in 2015-2020. The MNNR inclusion criteria were neonates with any of the following: gestation <32 weeks, 500-1500 g, gestation >35 weeks with hypoxic-ischaemic encephalopathy (HIE), had confirmed sepsis, congenital heart disease, on respiratory support, and/or died before discharge in the participating hospitals. The exclusion criteria were those who died before admission, birthweight <500g, or gestation <22 weeks. Data of eligible neonates were submitted prospectively using a standardised format. Annually, participating hospitals also submitted their hospital census of inborn livebirths and NICU admissions. The inclusion criteria for the present study were all neonatal deaths during the study period.

Autopsies were rarely performed on neonates in Malaysia. Causes of death were reported by local managing doctors using the modified Wigglesworth classification.[5] Deaths were classified as whether lethal/major congenital malformation (LCM) was present (yes/no). In neonates with LCM, whether death was due to neural tube defects (NTD), other central nervous system (CNS) abnormalities (hydrancephaly, holoprosencephaly, others), congenital cardiovascular system (CVS) such as complex heart disease, acyanotic heart disease, recognisable syndrome (Edward, Patau, Downs, others), non-recognisable syndromes (in neonates with dysmorphism and multiple malformations not associated with known syndromes), skeletal dysplasia, respiratory system abnormalities, gastrointestinal abnormalities, renal abnormalities, hydrops fetalis, or others. In neonates without LCM, whether death was due to preterm <37 weeks (yes, no); if 'yes', whether due to intraventricular haemorrhage (IVH), sepsis, patent ductus arteriosus (PDA) in heart failure, pulmonary haemorrhage, necrotising enterocolitis (NEC), pneumonia, bronchopulmonary dysplasia (BPD), pneumothorax, "extreme prematurity", acute intrapartum event, severe respiratory distress syndrome, or others. A diagnosis of "extreme prematurity" was assigned as the cause of death in neonates born <28 weeks of gestation without other causes identified. In neonates of gestation ≥37 weeks and without LCM, death was reported as whether it was due to asphyxia conditions (yes, no). Asphyxia conditions were defined as death from birth asphyxia (or hypoxic-ischaemic encephalopathy, HIE, with/without multiorgan failure), meconium aspiration syndrome (MAS), or persistent pulmonary hypertension of neonates. In neonates of gestation ≥37 weeks without LCM and asphyxia conditions, whether death was due to infection (yes, no); if yes, whether infection was due to group B streptococcal (GBS) sepsis, meningitis, congenital pneumonia, congenital infection, or other infections/sepsis (yes, no). In neonates ≥37 weeks gestation without LCM, asphyxia and infection, whether death was due to kernicterus/severe neonatal jaundice, haemorrhagic disease of newborn/vitamin K deficiency, pneumothorax, inborn error of metabolism, surgery, others, or unknown (yes, no).

Definitions

Gestation at birth was reported in completed weeks, based on antenatal ultrasound findings, maternal last menstrual period, or the New Ballard score after birth.[6] Neonates born <28 weeks gestation were defined as extremely preterm (EPT), 28-<32 weeks as very preterm (VPT), 32-34 weeks as moderate preterm (MPT), 35-<37 weeks as late preterm (LPT), 37-<42 weeks as term, and ≥42 weeks as post-term. LCM was defined as any abnormality of prenatal origin that if uncorrected or uncorrectable, significantly impaired normal physical/social function or reduced normal life expectancy. Recognisable syndromes were diagnosed clinically and/or by karyotyping. Sepsis was diagnosed in symptomatic neonates with positive blood culture. Sepsis developed at ≤72 hours of life was early-onset sepsis (EOS), and >72 hours was late-onset sepsis (LOS). NEC was diagnosed based on Bell's criteria[7], IVH and intracranial haemorrhage were diagnosed using cranial ultrasonography, and severity staged according to Papile's criteria.[8] BPD was diagnosed in preterm neonates requiring more than 28 days of oxygen and/or respiratory support since birth and still required oxygen at 36 weeks of gestation. HIE was diagnosed in those with clinically recognised encephalopathy within 72 hours of birth with history of intrapartum asphyxia, after excluding

infections, cerebral malformations, and inborn error of metabolism. MAS was diagnosed based on the presence of meconium-stained amniotic fluid, respiratory distress at birth and chest radiographic changes. Pneumothorax was diagnosed based on chest radiographic findings. Early neonatal death (ENND) was death at 0-7 days of life, late neonatal deaths (LNND) at 8-28 days of life, and post-neonatal deaths (PNND) after 28 days of life.

Ethics

The Malaysian National Institute of Health, the National Medical Research Register, and the Medical Research Ethics Committee of the Ministry of Health of Malaysia granted approval of this study (Research ID: RSCH ID-24-07064, NMRR ID-24-04087-UJJ (IIR)).

Statistical analysis

The IBM SPSS statistical program (v. 29.0.02) was used for analysis. Data of neonates admitted to multiple centres were merged. Descriptive statistics were presented as number (percentage), mean (±SD) or median (interquartile range IQR) where appropriate. Given that the MNNR received only the birth census from member hospitals, the present study calculated only the inborn annual NMR and expressed them as number of deaths per 1000 livebirths in the respective participating hospitals each year, and of each gestational age group. The proportions of all EPT neonates (both inborn and outborns) who had received basic support and all HIE neonates (both inborn and outborns) who received therapeutic hypothermia (TH) before death were also calculated. The Chi-square test was used for between group analyses. P values of <0.05 were considered statistically significant.

RESULTS

During this six-year period, of the 759,435 neonates admitted to these NICUs, 9,470 (1.2%) died. Most (72.3%) were ENND. Table 1 shows their demographic characteristics.

Death rates of inborn

There were 1,773,619 inborn neonates of gestation ≥22 weeks in these hospitals during this period; 8,217 (4.6/1000 livebirths) died before discharge. The annual inborn neonatal death rates were: 5.9/1000 livebirths in 2015, 5.5/1000 livebirths in 2016, 5.3/1000 livebirths in 2017, 6.6/1000 livebirths in 2018, 4.8/1000 livebirths in 2019 and 4.9/1000 livebirths in 2020. Inborn EPT neonates had the highest death rates (average: 427.5/1000 livebirths), and term neonates the lowest (average: 1.7/1000 livebirths) (Figure 1). The EPT death rates decreased from 466.5/1000 livebirths in 2015 to 383.0/1000 livebirths in 2020, VPT death rates from 110.5/1000 livebirths to 92.5/1000 livebirths, MPT from 33.2/1000 livebirths to 28.6/1000 livebirths, LPT from 10.8/1000 livebirths to 8.7/1000 livebirths, term and post-term deaths from 2.3/1000 livebirths to 1.9/1000 livebirths, respectively.

Death due to malformations

Of all the neonates (both inborn and outborn) who died after admission to NICUs, 33.0% (n=3,128) were due to major malformations. A majority (82.9%) were more mature preterm and term/post-term neonates (Figure 2). Malformations accounted for 52.0 % of MPT deaths, 57.1% of LPT deaths, and 43.5% of term/post-term deaths. Most (75.1%) were ENND, 15.1% were LNND, and 9.8% were PNND. There were significantly more females than males (35.9% versus 30.6%, $p<0.001$), and more inborns than outborns (34.4% versus 23.8%, $p<0.001$).

Recognisable congenital syndromes accounted for 56.8% of malformation deaths (Table 2). Trisomy 18 (Edwards syndrome) was the most common (30.5%), followed by trisomy 13 (Patau Syndrome) (22.3%), and trisomy 21 (Down Syndrome) (5.8%). Except for Down Syndrome, majority (>71.0%) were ENND.

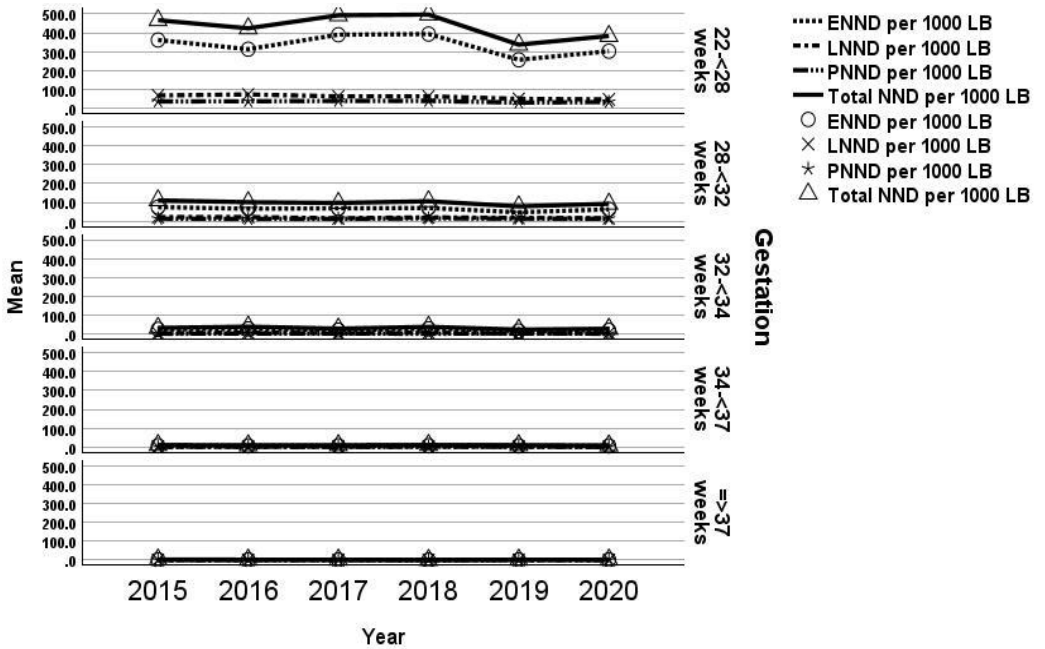
Among the non-syndromic malformations (Table 2), CVS malformations were the most common, accounting for 27.5% of the deaths. CNS malformations (including NTD) (18.7%), respiratory malformations (16.7%) and hydrops foetalis (9.3%) were the next three common. Ductal-dependent CVS anomalies accounted for 71.2% of CVS malformation deaths; median age of death was 4 days (IQR: 1, 15); 59.5% of ductal-dependent CVS malformation deaths were ENND, 25.4% were LNND and 15.2% were PNND. The median age of death of non-ductal dependent CVS malformations was 7 days (IQR: 1, 30). NTD (anencephaly, encephalocele, myelomeningocele) were the most common (52.7%) CNS malformations, and 95.5% were ENND. Congenital diaphragmatic hernia (CDH) accounted for 32.3% of respiratory malformation deaths. Among neonates dying from hydrops foetalis, no underlying causes were identified/reported in 84.9% of them.

Overall, the four most common types of lethal malformations were recognisable syndromes

Table 1: Demographic characteristics of neonates died in the 44 Malaysian neonatal intensive care units in the MNNR, 2015-2020

Variables	Deaths at all ages N=9470	Early neonatal deaths (0-7 days) N= 6851 (%)	Age died Late neonatal deaths (8-28 days) N= 1653 (%)	Post-neonatal deaths N=966 (%)
Age died, days				
Median (IQR)	2 (1-9)	1 (1-3)	13 (10-18)	57 (37-93)
Birthweight, g				
500-<1000	2898 (30.6)	2198 (32.1)	429 (26.0)	271 (28.1)
1000-1499	1449 (15.3)	978 (14.3)	287 (17.4)	184 (19.0)
1500-2499	2380 (25.1)	1645 (24.0)	459 (27.8)	276 (28.6)
2500-<3999	2665 (28.1)	1972 (28.8)	463 (28.0)	230 (23.8)
≥4000	78 (0.8)	58 (0.8)	15 (0.9)	5 (0.5)
Gestation at birth, weeks				
<28	2564 (27.1)	1988 (29.0)	362 (21.9)	214 (22.2)
28-<32	1529 (16.1)	1016 (14.8)	301 (18.2)	212 (21.0)
32-<34	708 (7.5)	515 (7.5)	126 (7.6)	67 (6.9)
34-<37	1420 (14.8)	965 (14.1)	277 (16.8)	178 (18.4)
37-<42	3226 (34.1)	2347 (34.3)	585 (35.4)	294 (30.4)
≥42	23 (0.2)	20 (0.3)	2 (0.1)	1 (0.1)
Intrauterine growth				
AGA	5941 (62.7)	4324 (63.1)	1013 (61.3)	604 (62.5)
SGA	3049 (32.2)	2171 (31.7)	557 (33.7)	321 (33.2)
LGA	480 (5.1)	356 (5.2)	83 (5.0)	41 (4.2)
Gender	N=9452	N=6838	N=1649	N=965
Female	4087 (43.2)	2907 (42.5)	721 (43.7)	459 (47.6)
Male	5260 (55.6)	3844 (56.2)	918 (55.7)	498 (51.6)
Indeterminate	105 (1.1)	87 (1.3)	10 (0.6)	8 (0.8)
Ethnic group	N=9463	N=6846	N=1652	N=965
Chinese	707 (7.5)	494 (7.2)	123 (7.4)	90 (9.3)
Malay	6015(63.6)	4300 (62.8)	1083 (65.6)	632 (65.5)
Indian	492 (5.2)	345 (5.0)	84 (5.1)	63 (6.5)
Sarawak natives	407 (4.3)	267 (3.9)	9 (5.5)	49 (5.1)
Sabah natives	654 (6.9)	521(7.6)	86 (5.2)	47 (4.9)
Other Malaysians	241 (2.6)	179 (2.6)	41 (2.5)	21 (2.2)
Foreigners	947 (10.0)	740 (10.8)	144 (8.7)	63 (6.5)
Modes of delivery	N=9461	N=6843	N=1652	N=966
SVD	4602 (48.6)	3467 (50.7)	719 (43.5)	416 (43.1)
LSCS	4208 (44.5)	2846 (41.6)	856 (51.8)	506 (52.4)
Vacuum extraction	178 (1.9)	141 (2.1)	25 (1.5)	12 (1.2)
Breech	444 (4.7)	367 (5.4)	47 (2.8)	30 (3.1)
Forceps	29 (0.3)	22 (0.3)	5 (0.3)	2 (0.2)
Birthplace	N=9469			N=965
Inborn	8217 (86.8)	5962 (87.0)	1415 (85.6)	840 (87.0)
Outborn	1252 (13.2)	889 (13.0)	238 (14.4)	125 (13.0)

Note: MNNR: Malaysian National Neonatal Registry; IQR, interquartile range; AGA, appropriate-for-gestational age; SGA, small-for-gestational age; LGA, large-for-gestational age; SVD, spontaneous vertex delivery; LSCS, lower segment Caesarean section.



ENND, early neonatal deaths; LNND, late neonatal deaths; PNND, post-neonatal deaths. LB, livebirths.

Figure 1. Mortality Rates of inborn neonates in 44 Malaysian Neonatal Intensive Care Units (NICU), 2015-2020

(26.9%), CVS (20.2%), CNS (13.1%) and respiratory (10.8%) malformations. CNS malformations (29.1%) was the most common type of malformation deaths in EPT neonates (Figure 3), recognisable syndromes the most common malformation deaths in VPT, MPT and LPT neonates, CVS malformations and recognisable syndromes the most common malformation deaths in term neonates, and CNS and respiratory malformations the most common malformation deaths in post-term neonates. Most were ENND across all gestational groups (Figure 4).

Non-malformation preterm deaths

The majority (67.0%) of neonatal deaths (both inborn and outborn) were not due to malformations. Table 3 lists their causes of death.

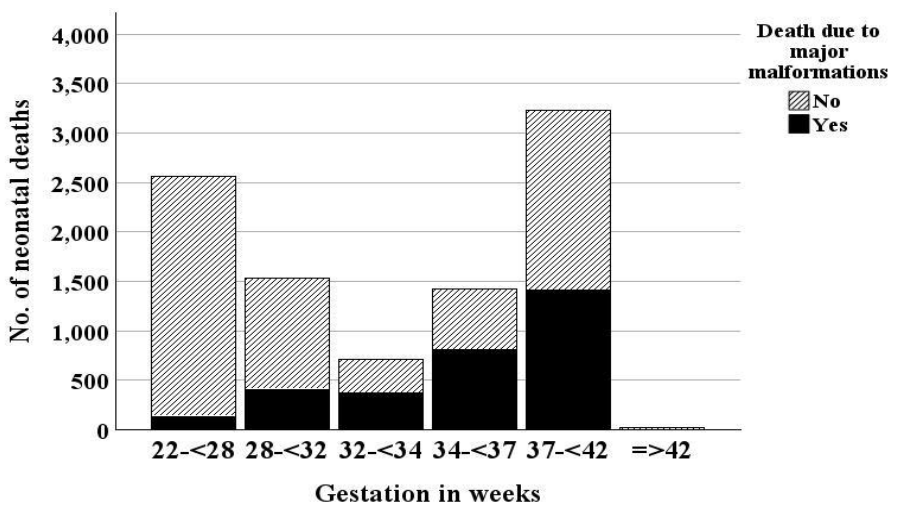


Figure 2. Frequency distribution of all neonatal deaths due to major congenital malformations in different gestational age groups in 44 Malaysian Neonatal Intensive Care Units (NICUs), 2015-2020.

Table 2: All neonatal deaths due to malformations in 44 Malaysian NICUs in years 2015-2020

Types of malformations	Deaths at all ages N = 3128 (%)	Age died		
		0-7 days n=2350 (%)	8-28 days n=473 (%)	>28 days n=305 (%)
Syndromic malformations	1777 (56.8)	1335	270	172
Trisomy 18	542	398	112	32
Trisomy 13	397	324	56	17
Trisomy 21	103	50	20	33
Other syndromes	252	180	25	47
Unrecognisable syndromes	483	383	57	43
Non-syndromic malformations	1351 (43.2)	1015	203	133
CNS and NTD	252	215	18	19
Anencephaly	105	104	0	1
Holoprosencephaly	44	32	8	4
Hydrocephalus	27	19	5	3
Hydrancephaly	18	18	0	0
Encephalocele	15	13	1	1
Myelomeningocele	13	10	0	3
Multiple CNS anomalies	5	4	1	0
Type not reported	25	24	10	9
Cardiovascular system	371	222	91	58
Ductal dependent	264	157	67	40
Non-ductal dependent	45	23	11	11
Missing data	62	42	13	7
Respiratory system	226	195	18	13
CDH	73	63	5	5
Others	128	111	11	6
Hydrops foetalis	126	114	10	2
No cause identified	107	98	8	1
Ductal dependent CVS	5	5	0	0
Non-ductal dependent CVS	8	7	1	0
Hydrocephalus	3	2	1	0
Othe CNS malformations	1	1	0	0
Respiratory malformations	1	1	0	0
Renal malformations	1	0	0	1
Skeletal malformations	68	52	9	7
Renal system	30	23	5	2
Gastrointestinal system	45	26	10	9
Not specified	233	168	42	23

Note: NICUs, neonatal intensive care units; CNS, central nervous system; NTD, neural tube defects; CDH, congenital diaphragmatic hernia; CVS, cardiovascular system.

More than two-third (71.1%) were preterm <37 weeks gestation, majority (81.9%) were ENND. Information on causes of death in 22.4% preterm deaths were missing in the database; 88.4% (n=892) of them were inborn (EPT n=393, VPT n=369, MPT n=54 and LPT n=76). Among the remainder preterm deaths, more than half (53.9%) were EPT neonates, 25.0% were VPT, 7.5% were MPT and 13.5% were LPT (Figure 5). The most common cause of preterm deaths was extreme prematurity (31.6%), followed by sepsis (13.8%), and IVH (5.4%). Almost all (99.9%) "extremely prematurity" deaths were ENND (Table 3); 76.2% of them were of gestations 24-<28 weeks. The

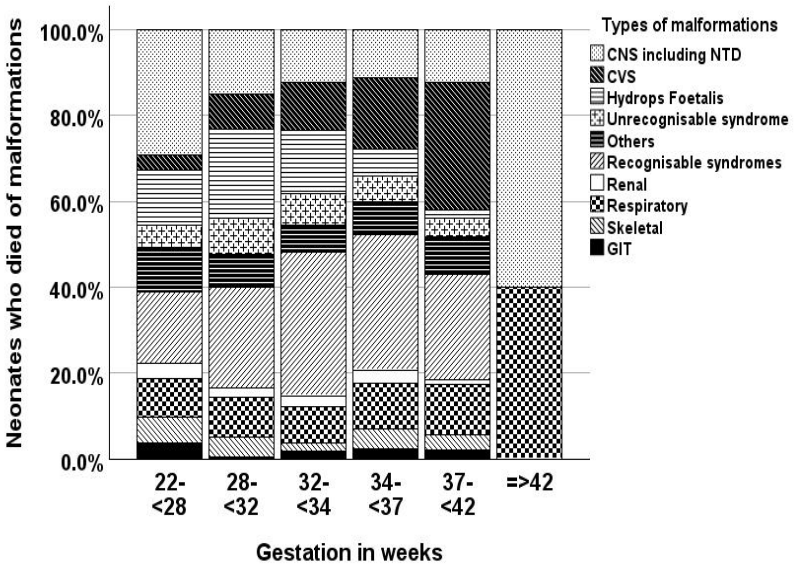


Figure 3. Proportions of all neonates dying from different types of major congenital malformation in different gestational age groups in 44 Malaysian Neonatal Intensive Care units, 2015-2020. (CNS, central nervous system; NTD, neural tube defects; CVS, cardiovascular system; GIT, gastrointestinal tract)

median age of death from "extreme prematurity" was 1.0 day (IQR: 1.0,1.0); at birth, only 13.7% of them (n=1,424) received nasal continuous positive airway pressure (nCPAP) therapy, 12.5% received bag-and-mask resuscitation at birth, 12.5% received endotracheal intubation; after admission to NICU, only 5% received nCPAP, 37.4% received mechanical ventilation, 35.2% received surfactant therapy, 17.3% received high frequency ventilation, and 19.5% received total parenteral nutrition (TPN). Of the deaths due to sepsis, 85.3% were LOS; their median

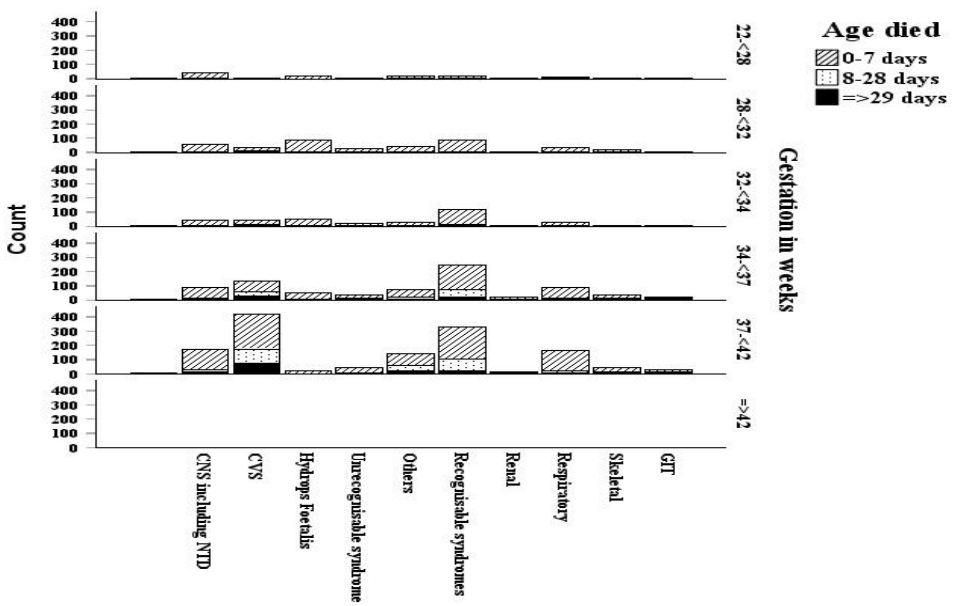


Figure 4. Age of deaths due to various major malformations in different gestational age groups in 44 Malaysian Neonatal Intensive Care Units, 2015-2020. (CNS, central nervous system; NTD, neural tube defects; CVS, cardiovascular system; GIT, gastrointestinal tract.)

Table 3: Causes of deaths in all neonates not due to malformations in 44 Malaysian NICUs, 2015-2020

Causes of deaths	Deaths in all ages N (%)	Age of death		
		0-7 days N (%)	8-28 days N (%)	>28 days N (%)
All gestations	**6342**	**4501**	**1180**	**661**
Preterm <37 weeks	**4506 (71.1)**	**3118**	**864**	**524**
Extreme prematurity	1424	1423	1	0
Severe RDS	145	120	14	11
Acute intrapartum event	215	176	28	11
Intraventricular haemorrhage	243	146	82	15
Sepsis	621	281	209	131
PDA with heart failure	22	8	4	10
Pulmonary haemorrhage	194	161	27	6
Necrotizing enterocolitis	158	35	86	37
Pneumonia	91	34	28	29
BPD/PIE	83	1	5	77
Pneumothorax	34	27	4	3
Other causes	267	147	59	61
Missing data	1009	559	317	133
Gestation ≥37 weeks	**1836 (28.9)**	**1383**	**316**	**137**
Asphyxia conditions	782	657	102	23
HIE/multiorgan failure	570	464	83	23
MAS	212	193	19	0
Infections	409	261	91	57
GBS sepsis	47	36	8	3
Other pathogenic sepsis	199	97	55	47
Meningitis	21	16	5	0
Congenital pneumonia	121	97	18	6
Congenital infections	21	15	5	1
Kernicterus/severe jaundice	5	5	0	0
HDN/vitamin K deficiency	12	12	0	0
Intracranial bleed or SAH	12	8	1	3
Pneumothorax	29	21	7	1
Pulmonary haemorrhage	40	30	7	3
Inborn error of metabolism	25	19	5	1
Surgical complications	46	32	12	2
Others	176	103	49	24
PPHN	99	86	13	0
Missing data	300	235	42	23

Note: NICUs, neonatal intensive care units; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; HIE, hypoxic-ischaemic encephalopathy; MAS, meconium aspiration syndrome; GBS, group B hemolytic streptococcal; HDN, haemorrhagic disease of newborns; SAH, subaponeurotic haemorrhage.

age of death was 9 days (IQR: 1-264). More than half (60.1%) of deaths due to IVH were ENND. Of the 215 (4.8%) preterm deaths due to acute intrapartum events, only 29.3% of them had information on the types of intrapartum events (eclampsia n=14, abruptio placenta n=37, bleeding placenta previa n=5, cord prolapse n=7).

Non-malformation deaths in term neonates

Most (75.3%) of term neonatal deaths (inborn and outborns) were ENND (Table 3, Figure 6). The two most common causes of non-malformation deaths were asphyxia conditions (42.6%), and infections (22.3%). Of the asphyxia deaths, 72.9% were due to HIE with/without multiorgan failures

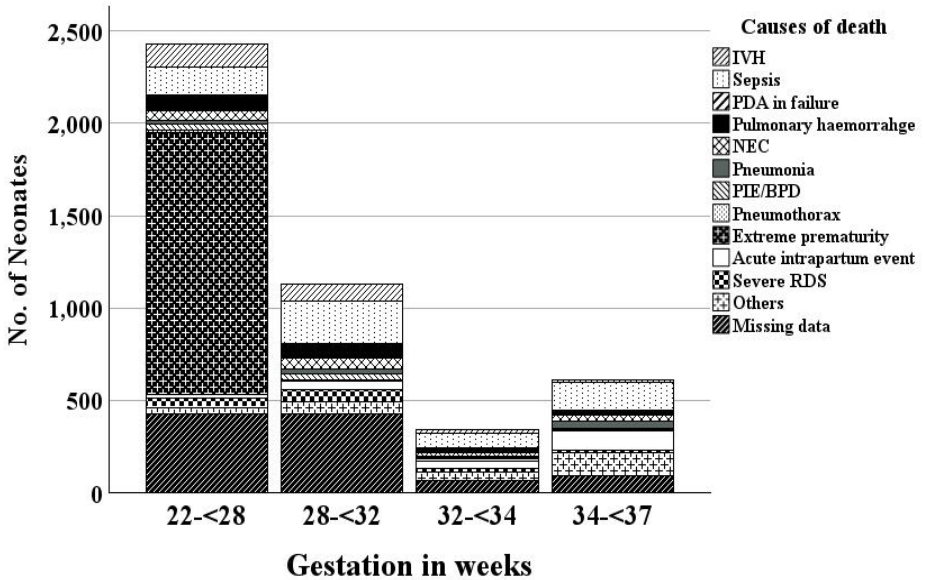


Figure 5. Frequency distribution of all preterm neonates dying from non-malformation causes in different gestational age groups in 44 Malaysian Neonatal Intensive Care Units, 2015-2020. (IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis; PIE, pulmonary interstitial emphysema; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome)

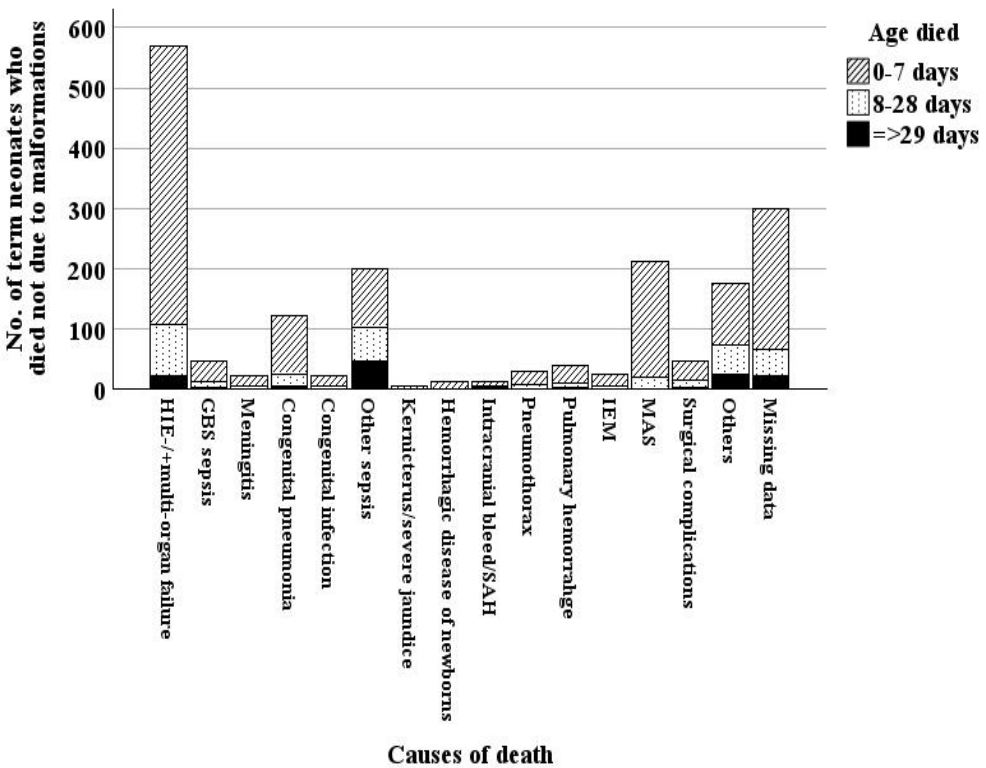


Figure 6. Frequency distribution of all term neonates dying from different non-malformation causes at different ages in 44 Malaysian Neonatal Intensive Care Units, 2015-2020. (HIE, hypoxic-ischaemic encephalopathy; GBS, group B streptococcal; SAH, subaponeurotic haemorrhage; IEM, inborn error of metabolism; MAS, meconium aspiration syndrome)

and 27.1% due to MAS. Data of HIE neonates receiving TH were available in the database only since 2016. Of the 349 neonates dying from HIE between 2016-2020, 45.3% did not receive any TH; 26.9% received TH using the passive cooling method, and only 27.8% received TH via dedicated servo-controlled cooling devices. Among those dying from sepsis, more than half (26/47, 55.3%) of the Group B *Streptococcus sepsis deaths* were EOS; 51.3% of those due to other pathogens were LOS.

DISCUSSION

This multicentre and retrospective observational study confirmed that the annual trend of Malaysian NMR is parallel with those published in the United Nations report[2] and the Malaysian Statistics Department.[1] Although there was some reduction in the NMR in our cohort, this was much less than our neighbouring countries like Singapore, Hong Kong and Korea during the same period.[2] Most of our neonatal deaths were ENND. Like other low- and middle-income countries,[9,10] EPT had the highest rate.

Our findings concurred with a recent study on neonatal mortalities in Southeast Asian countries (including Malaysia)[11] that the top four most common causes were prematurity, congenital malformations, asphyxia conditions, and sepsis. The more detailed data in the MNNR allowed us to further identify that the six most common causes of death were extreme prematurity (EPT), LOS, HIE, chromosomal abnormalities due to trisomy 18 and trisomy 13, ductal-dependent CVS malformations, and NTD.

According to the Malaysian national paediatric management guidelines[12], preterm neonates <32-week gestation should be started on early nCPAP therapy at birth and supported with mechanical ventilation via endotracheal intubation and given surfactant therapy when severe respiratory distress develops. To prevent admission hypothermia, they should be plastic-wrapped at birth and transported to NICUs in transport incubators. TPN should be commenced as soon as possible in those with birthweight 1000g-1250 g. The present study revealed that a large proportion of EPT neonates who died did not receive these supports according to the national guidelines and most died on the first day of life. Previous studies showed that preterm neonates given early nCPAP needed less invasive respiratory support and had higher survival rates;[13] those with admission hypothermia had higher death rates than those with normothermia.[14] Many countries reported improvement in survival and reduction in morbidities in EPT neonates receiving these basic supports.[15-17] Our study suggests that to further reduce Malaysian NMR, these basic neonatal facilities and supports should be provided to all preterm neonates ≥24 weeks of gestation.

Sepsis was the second most common cause of death in this cohort (n=867); 69.9% of all sepsis deaths were preterm neonates and LOS was the predominant cause. Up-scaling preventive measures against nosocomial sepsis in Malaysian NICUs should be urgently considered to reduce NMR in Malaysia. GBS sepsis was preventable and treatable; it remained an important cause of deaths in term neonates. Given that the incidence of early GBS sepsis and mortality was very high in Malaysian NICUs[18] and a significant cause of LOS in term neonate[19], improving early detection and prophylactic treatment of perinatal GBS infections may help further reduce NMR in Malaysia.

HIE with/without multiorgan damage in term neonates was the third most common cause of death in Malaysian NICUs. The present study showed that a high proportion of neonates dying from HIE did not receive TH as recommended by our national guidelines.[20] Reports elsewhere showed that timely and proper administration of TH reduced mortality and morbidity of neonatal HIE.[21] Previously[22], we have reported the lack of proper TH equipment as a significant risk factor associated with increased mortality in neonates with HIE in Malaysian NICUs. Equipping NICUs with adequate number of dedicated and functional TH devices, training staff to use them properly and monitoring compliance would be an important strategy to reduce Malaysian NMR.

One-third of all neonatal deaths in our NICUs were due to congenital malformations, accounting for 43.6% term neonatal deaths and 55.4% preterm deaths of gestation ≥32 weeks. Recognisable syndromes, CVS malformations and NTD were the three most common. More than one-third of those with NTD had anencephaly. Investigators in many countries have reported on the benefit of maternal periconceptional folic acid supplementation for the prevention of NTD and other congenital abnormalities.[23-25] This has led to the introduction of mandatory folic acid fortification of grain and/or flour in many countries. There was strong evidence that periconceptional folic acid supplementation reduced the incidence of NTDs, cardiac malformations, oral facial clefts, cleft

palate, limb reduction defects and obstructive urinary tract anomalies; moderate evidence that it prevented congenital hydrocephalus, transposition of great arteries, pyloric stenosis and omphalocele in many countries.[23,26] In Malaysia, mandatory folic acid fortification of wheat flour applied only to government-subsidized 1.0 kg packages. However, large bulk shipments made up nearly 50% of flour consumed in Malaysia. There was no legislation to mandate folic acid fortification of rice grain, the staple food of the majority of Malaysians. Among the CVS malformation deaths, 60% occurred during and 40% after the first week of life. Most died while awaiting surgery. Given that some of the CVS malformations could be prevented with maternal folic acid supplementation, mandatary folic acid fortification of rice grain and wheat flour may help reduce their incidence and mortality. Universal screening using pulse oximetry for early detection of ductal-dependent CVS malformations after birth, and training more paediatric cardiologists and cardiothoracic surgeons in Malaysia for timely definitive treatment of these neonates would further improve their outcome.

More than 50% of malformation deaths in our cohort were due to congenital syndromes, trisomy 18 and trisomy 13 being the most common. Like those reported in other countries, many died during the first week of life.[27,28,29] Unlike other countries, termination of pregnancy is not legally acceptable in Malaysia. To reduce NMR due to these conditions, research is needed to identify the risk factors associated with them.

The strengths of our study include it being the first detailed report on major causes of death in all major Malaysian public NICUs. The data were captured in a standardised format using the Wigglesworth Classification of neonatal death.

This study has several limitations: 22.4% of the preterm death had missing information; no detailed intrapartum information in 75% of neonates dying from "acute intrapartum events"; no information on NICU policy of withdrawal of treatment in EPT. The role of maternal illness and medication on malformations and neonatal deaths were not investigated. Given that a substantial proportion of data of causes of death in preterm neonates were missing, many of the preventable/ modifiable causes of death (like RDS, IVH, sepsis, NEC, pneumonia) may be underestimated. These indicate a need to improve the training of staff in data collection and to implement a more effective system of monitoring completeness and accuracy of data entry in the MNNR.

In summary, extreme prematurity, nosocomial sepsis, HIE in term neonates, chromosomal abnormalities due to trisomy 18 and trisomy 13, ductal-dependent CVS malformations, and NTD were the six most common causes of neonatal deaths in Malaysian NICUs.

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What is already known:

- Prematurity, congenital malformations, asphyxia conditions, and sepsis were common causes of neonatal deaths world-wide, including Malaysia.
- Neonatal mortality rates remained around 4.5 per 1000 livebirths in Malaysia for the past twenty years.

What is new:

- Extreme prematurity (<28 weeks gestation) is the most common cause of neonatal deaths in Malaysia.
- Nosocomial sepsis is the second most common causes of neonatal deaths in Malaysia.
- Hypoxic-ischaemic encephalopathy with or without multiorgan failure is the most common cause of death in term neonates in Malaysian neonatal intensive care units.
- Trisomy 18 and trisomy 13 were the most common congenital syndromic malformation deaths in Malaysia.
- Cardiovascular malformations and neural tube defects were the most common non-syndromic malformations.

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