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Very Low Birth Weight Infants – Mortality and Predictive Risk Factors

J K Chye, C T Lim

ABSTRACT

Aims: To determine the survival rates and risk factors associated with mortality in premature very low birth weight or VLBW (≤ 1500 grams) infants.

Methods: This is a part-retrospective and part-prospective study of VLBW infants admitted into the Special Care Nursery, University Hospital Kuala Lumpur, between August 1994 and July 1996.

Results: Of the 184 infants without lethal congenital malformations, 144 (78%) infants survived till discharge. The causes of death included respiratory diseases (63%), infections (30%), gastrointestinal abnormalities (5%) and intracerebral haemorrhage (2%). On multivariate logistic regression analysis, birth weight of 1 kg or less [odds ratio (OR) 3.88, 95% Confidence Interval (CI) 2.22, 6.67, p < 0.001], gestational age of 28 weeks or less [OR 1.78, 95% CI 1.03, 3.03, p = 0.038], ventilatory support [OR 2.68, 95% CI 1.46, 4.92, p = 0.002] and male gender [OR 1.83, 95% CI 1.10, 3.06, p = 0.021] were significant predictive factors for increased mortality. In a subgroup of 87 infants who were ventilated for severe respiratory distress syndrome, their survival was predicted by birth weight above 1 kg, gestational age greater than 28 weeks, appropriate for gestational age and surfactant replacement therapy.

Conclusions: Mortality remains high for the very low birth weight and very premature infants. Prolonging the duration of pregnancy and administrating exogenous surfactant to ventilated infants with RDS are two important measures to improve survival amongst VLBW infants.

Keywords: infants (VLBW), mortality, risk factors, exogenous surfactant

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INTRODUCTION

Premature infants with birth weights ≤ 1500 g (very low birth weight or VLBW infants) form a significant proportion of neonates admitted to a neonatal intensive care unit. The high mortality rate amongst VLBW infants was found to be the main predictor of neonatal mortality in industrialised countries[1]. With recent advances and improvement in obstetrics and neonatal care, improving survival rates have been reported[2-6].

This study aims to determine the survival rate and the risk factors for mortality in our population of VLBW infants over a 2-year period from August 1994 to July 1996.

MATERIALS AND METHODS

From August 1994 to July 1996, all VLBW infants admitted to the Special Care Nursery (SCN), University Hospital Kuala Lumpur, a tertiary neonatal intensive care unit, were enrolled into this part-retrospective and part-prospective observational study. Perinatal and neonatal data were obtained from the infants' medical notes.

All live-born premature infants were assessed by the paediatric team at the time of their births. The decision to resuscitate premature infants of less than 27 weeks' gestation or birth weight below 700 g was left to the attending doctors. All resuscitated infants were admitted directly to the SCN, unless the unit was full, then would the infants be transferred to the paediatric intensive care unit. Due to the chronic shortage of ventilator beds in the SCN, there were few out-born VLBW infants.

Infants with birth weights below 1250 g received intermittent mandatory ventilation (IMV) early if they had respiratory distress syndrome (RDS). Heavier and more matured infants with respiratory disorders were put on trials of nasal continuous positive airway pressure (CPAP) support initially, failing which IMV was used. Failure of CPAP was considered if the infant had recurrent apnoeas and bradycardias, frequent desaturations, $PaO_2 < 6.5$ kPa or $PCO_2 > 7$ kPa, or required $FiO_2 > 40\%$. As of February 1995, exogenous surfactant (Survanta, Ross Laboratories) was administered to infants with severe RDS (intubated, $FiO_2 > 40\%$ and PaO_2/PAO_2 ratio < 0.22). Infants with patent ductus arteriosus were treated conservatively with fluid restrictions, diuretics and oral indomethacin. The use of postnatal dexamethasone to wean infants off the ventilators or supplemental oxygen was not practised. Enteral feeds were started within the first 2 – 3 days of life if the infants were stable. Total parenteral nutrition or intralipid supplement was from 3 – 4 days of life, as with the percutaneous insertion of central venous catheters. All newly admitted infants with either suspected infection (septicaemia or pneumonia) or at high risk

for sepsis, were treated with intravenous penicillin and gentamicin till the blood culture results were known. Second line antibiotics with intravenous amikacin and cloxacillin, and third line antibiotics with vancomycin, the third-generation cephalosporins and/or imipenem were used for late-onset suspected or confirmed sepsis.

The following definitions were used in this study: mortality referred to hospital deaths which occurred within the SCN; RDS was diagnosed on both clinical and radiographic criteria; initial hypoglycaemia as the first blood glucose reading of ≤ 2.5 mmol/L obtained within 2 hours of SCN admission (using the Boehringer Ingelheim Reflolux glucometer or hospital laboratory testing); intrauterine growth retardation (IUGR) for birth weight below 10th centile[7]; gestational age was assessed using the Ballard's scores[8], completed course of antenatal dexamethasone if 2 doses or more were given at least 12 hours before delivery; sepsis was based on a combination of clinical, and supportive haematological and microbiological evidence; and necrotising enterocolitis (NEC) was diagnosed using the Bell's criteria[9]. Unbooked cases referred to mothers having either no antenatal care or were cared for by medical practitioners outside the University Hospital, prior to their deliveries. As requests for postmortem on all the deceased infants were declined, due to cultural and religious reasons, the causes of death were made clinically by the attending clinicians.

Data were analysed using SPSS[10]. Chi-square statistics, Fisher's exact test and Student's t-test were used for univariate analyses. Multivariate logistic regression analyses using the backward likelihood ratio method were performed (on covariates with p values < 0.30) to determine the independent risk factors for mortality or survival. The statistical significance level was taken at $p < 0.05$. Analysis was also made on the subgroup of infants who had RDS and received IMV, to ascertain the impact of surfactant on their survival rates.

RESULTS

Over the 2-year study period, 187 VLBW infants were admitted to the SCN. Of these, 3 infants with lethal congenital malformations (one infant with severe hydrops fetalis of unknown cause, and two infants with major multiple organ anomalies) were excluded from the analysis. As only 3 infants were outborn, distinction was not made on the place of birth.

The means (standard error of mean or SEM), and 95% Confidence Intervals [CI] of the birth weight and gestational age of the 184 infants were 1167 (18) g, [1131 g – 1204 g] and 30.2 (0.2) weeks [29.8 weeks – 30.6 weeks] respectively. The racial distribution was 98 (53%) Malays, 40 (22%) Indians and 46 (25%) Chinese. Amongst these infants, 53 (29%) were infants with birth weight ≤ 1000 g (extremely low birth weight or ELBW infants), 52 (28%) were ≤ 28 weeks' gestation, 69 (38%) were IUGR, 93 (51%) males, 27 (15%) had Apgar scores (AS) ≤ 3 at 1 minute and 14 (8%) had AS ≤ 5 at 5 minutes, 50 (27%) were intubated at birth, 86 (47%) had initial hypoglycaemia, 85 (46%) had admitting rectal temperature of ≤ 35°C, and 93 (51%) had RDS but only 87 (47%) of these infants received IPPV. Only 37 ventilated infants with RDS were given surfactant replacement therapy.

The means (SEM) and 95% CI for the 172 mothers' age, gravida and parity were 28.4 (0.5) years [27.5 years – 29.3 years], 2.4 (0.1) [2.1 – 2.6] and 1.0 (0.1) [0.8 – 1.2] respectively. Eight mothers had twin pregnancies and one had quintuplet pregnancy. Only 69 (40%) mothers were booked cases. The reasons for premature births were pregnancy-induced hypertension [66 (36%)], antepartum haemorrhages [32 (17%)], prolonged rupture of membranes, suspected or confirmed maternal infections [21 (11%)], medical illnesses [18 (10%)] and unknown cause [47 (26%)]. Of the 66 (36%) mothers who were given antenatal dexamethasone, 47 (26%) had at least 2 doses.

One hundred and forty four (78%) VLBW and 22 (42%) ELBW infants survived till discharge from the SCN. The mortality rates increased with decreasing birth weight and gestational age (Figs 1 and 2). Infants below 28 weeks' gestation had higher

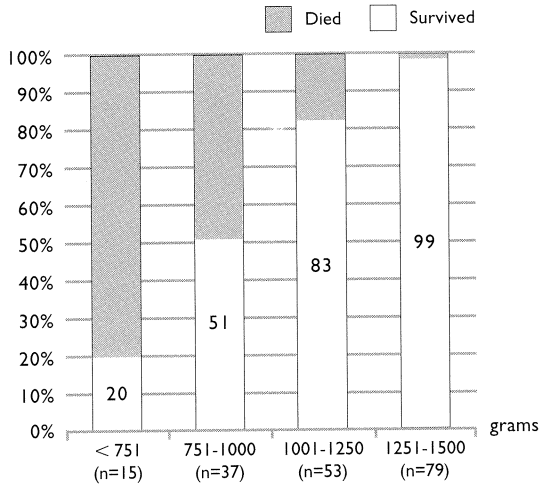

Fig 1 – Survival rates by birth weight. Numbers inside the histograms indicate the percentages of survival in each birth weight category. The trend for increasing survival rates with increasing birth weight is statistically significant ($\chi^2 = 18$, df = 3; $p < 0.001$).

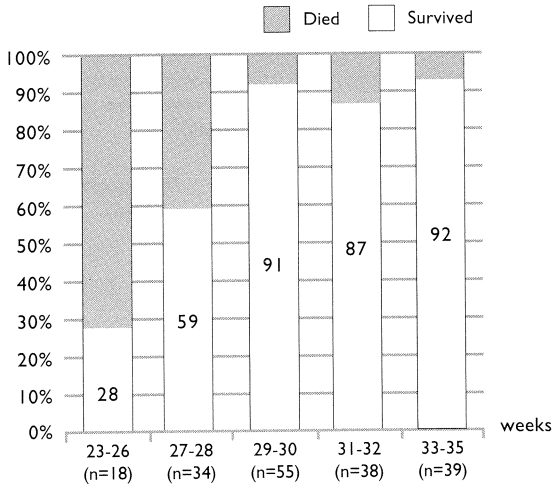

Fig 2 – Survival rates by gestational age. Numbers inside the histograms indicate the percentages of survival in each gestational age category. The trend for increasing survival rates with increasing geatational age is statistically significant ($\chi^2 = 53$, df = 4; $p < 0.001$).

rates of mortality. The number of surviving infants according to gestational age were as follows: 0 of 3 (0%) for 23 weeks; 1 of 2 (50%) for 24 weeks; 0 of 3 (0%) for 25 weeks; 4 of 10 (40%) for 26 weeks; and 5 of 10 (50%) for 27 weeks. The main causes of death (Table I) were due to RDS and its complications [25/40 (63%)], which also played an important role in causing death within the first week of life [21/24 (88%)]. In comparison, infection-related deaths, including 4 cases of NEC (stages II & III), tended to occur after the first week [10/16 (63%)]. One infant, the surviving twin of a foetus with anencephaly, died within 24 hours with unsuspected congenital fungal septicaemia (*Candida albicans* was isolated from blood and all superficial body swabs). Single and multiple bacteria (*Klebsiella proteus pseudomonas, E coli,* and *Streptococcal species*) were isolated in blood or peritoneal fluids of only 6 of the other 11 infants who had infection-related deaths. An infant with gastroschisis collapsed and died within 3 hours after arrival from another hospital, and another infant with RDS and exomphalos deteriorated after sustaining a cardio-respiratory arrest intraoperatively. A surviving twin sustained a massive uncontrollable unilateral intracerebral bleed from the first day of life, and subsequently died from associated multiorgan failure in the second week of life.

Table I – Causes and timing of deaths in 40 VLBW infants

	< 24 hours	1-7 days	8-28 days	> 28 days
Respiratory 25 (63%)				
RDS	9	9	-	-
Pulmonary haemorrhage	-	2	-	-
Chronic lung disease	-	-	-	3
Pneumonia	-	-	1	-
Pulmonary hypoplasia	1	-	-	-
Infection 12 (30%)				
Sepsis/NEC	1	1	4	6
Gastrointestinal Tract 2 (5%)				
Ventral wall defects	1	-	1	-
Central Nervous System 1 (2%)				
Intracerebral haemorrhage	-	-	1	-
Total no. (%)	12 (30)	12 (30)	7 (18)	9 (22)

VLBW: very low birth weight; RDS: respiratory distress syndrome; NEC: necrotising enterocolitis

Table II – Risk factors for mortality in 184 VLBW infants (univariate analysis with Student's t-test)

	Deceased* (n=40)	Survivors* (n=144)	P values
Birth weight (g)	877 (35)	1248 (16)	< 0.001
Gestational age (weeks)	28.1 (0.5)	30.1 (0.2)	< 0.001
Apgar scores at 1 minute	4.5 (0.3)	6.5 (0.2)	< 0.001
Apgar scores at 5 minutes	7.0 (0.4)	8.8 (0.1)	< 0.001
Admitting temperature (°C)	34.6 (0.2)	35.2 (0.1)	0.002
Maternal age (years)	27.7 (0.9)	28.6 (0.5)	0.420
Maternal gravida	2.1 (0.2)	2.5 (0.1)	0.170
Maternal parity	0.8 (0.2)	1.1 (0.1)	0.267

VLBW: very low birth weight; *mean (standard error of mean)

On univariate analyses, infants who died were more likely to have had lower mean birth weight, gestational age, Apgar scores (AS) and admitting rectal temperature (Table II). They also tended to have birth weight ≤ 1 kg, gestational age ≤ 28 weeks, ventilatory support, RDS, intubation at birth, AS ≤ 3 and ≤ 5 at 1 and 5 minutes respectively, and admitting temperature ≤ 35°C (Table III). There were no significant differences in the maternal age, gravida and parity (Table II) or the initial hypoglycaemia, booked case, completed course of antenatal dexamethasone, the mode of delivery (vaginal versus Caesarean section), IUGR, infants' gender and race (Table III) between these 2 groups of infants. On logistic regression analysis (using the covariates in Table III), increased risks of mortality were only associated with infants who were ELBW [OR 3.88, 95% CI 2.22, 6.67, p < 0.001], gestational age of ≤ 28 weeks [OR 1.78, 95% CI 1.03, 3.03, p = 0.038], required ventilatory support [OR 2.70, 95% CI 1.47, 5.00, p = 0.002] and of male gender [OR 1.83, 95% CI 1.09, 3.13, p = 0.021].

As for the 87 infants who had RDS and received IMV, 52 (60%) infants survived. Mortality was significantly increased in infants with birth weight ≤ 1000 g, gestational age ≤ 28 weeks, initial hypoglycaemia, IUGR, and not given exogenous surfactant (Table IV). On logistic regression analysis, survival was predicted by birth weight above 1 kg [OR 2.29, 95% CI 1.19, 4.42, p = 0.014], gestational age greater than 28 weeks [OR 2.73, 95% CI 1.24, 6.02, p = 0.013], non-IUGR [OR 2.13, 95% CI 1.03, 4.42, p = 0.041] and surfactant replacement therapy [OR 3.02, 95% CI 1.49, 6.10, p = 0.002].

DISCUSSIONS

The prognosis for premature infants has improved considerably over the past two decades with the advances made in neonatal intensive care. Although our overall survival rates for VLBW infants compared favourably with some larger centres in the Western countries (Table V), the survival rates for our ELBW infants, especially those less than 27 weeks' gestation at birth, lag far behind the experience of other centres (Table VI).

For a neonatal unit in a developing nation, we face several key issues which could help explain these differences in mortality rates. The problems of shortage and high turnover rate of nursing and medical staff, who are trained in neonatal care, are of major importance. The roster of only 3 nurses on night duty to manage on the average 4 ventilated infants and 13 high dependency care infants was a marked deviation to the recommended one nurse to one ventilated neonate and one to three high dependency infants ratio. Similarly, most of the after-hours medical

Table III – Risk factors for mortality in 184 VLBW infants (univariate analysis with chi-square statistics and Fisher's exact test)

	Deceased* (n=40)	Survivors* (n=144)	OR (95% CI)	P vlaues
ELBW	30 (75)	22 (15)	16.64 (7.13, 38.82)	< 0.001
Gestation ≤ 28 weeks	27 (68)	25 (17)	9.89 (4.49, 21.78)	< 0.001
Ventilation	33 (83)	61 (42)	6.41 (2.66, 15.47)	< 0.001
RDS	31 (78)	61 (42)	4.68 (2.08, 10.56)	< 0.001
Intubated at birth	21 (53)	29 (20)	4.38 (2.09, 9.21)	< 0.001
AS ≤ 3 at 1 minute	11 (28)	16 (11)	3.03 (1.28, 7.22)	0.010
AS ≤ 5 at 5 minutes	8 (20)	6 (4)	5.75 (1.86, 17.73)	0.003
Temperature ≤ 35°C	25 (63)	60 (42)	2.33 (1.13, 4.80)	0.020
Initial hypoglycaemia	24 (60)	62 (43)	2.00 (0.97, 4.05)	0.060
Booked case	13 (33)	63 (44)	0.62 (0.30, 1.30)	0.200
Antenatal steroids	9 (23)	42 (29)	0.71 (0.31, 1.61)	0.400
Vaginal delivery	14 (35)	47 (33)	1.11 (0.53, 2.32)	0.780
IUGR	16 (40)	53 (37)	1.14 (0.56, 2.35)	0.716
Male gender	24 (60)	69 (48)	1.63 (0.80, 3.32)	0.180
Race				
Malay	23/98 (23%)			0.830
Indian	8/40 (20%)			
Chinese	9/46 (20%)			

*: number (percentages); VLBW: very low birth weight; OR: odds ratio; CI: Confidence Interval; ELBW: extremely low birth weight; RDS: respiratory distress syndrome; AS: Apgar score; IUGR: intrauterine growth retardation

Table IV – Risk factors for mortality in 87 VLBW infants with RDS who received IPPV (univariate analysis with chi-square statistics and Fisher's exact test)

	Deceased* (n=35)	Survivors* (n=52)	OR (95% CI)	P vlaues
ELBW	26 (74)	11 (21)	10.77 (3.93, 29.52)	< 0.001
Gestation ≤ 28 weeks	24 (69)	16 (31)	4.91 (1.95, 12.38)	< 0.001
Initial hypoglycaemia	19 (54)	13 (25)	3.56 (1.43, 8.89)	0.007
IUGR	14 (40)	10 (20)	2.80 (1.07, 7.56)	0.033
Surfactant therapy	10 (29)	27 (52)	0.37 (0.15, 0.92)	0.046
Temperature ≤ 35°C	22 (63)	22 (42)	2.31 (0.96, 5.56)	0.081
AS ≤ 3 at 1 minute	9 (26)	11 (21)	1.29 (0.47, 3.54)	0.616
AS ≤ 5 at 5 minutes	8 (20)	6 (4)	2.35 (0.68, 8.11)	0.211
Intubated at birth	20 (57)	24 (46)	1.56 (0.66, 3.69)	0.383
Booked case	12 (34)	21 (40)	0.77 (0.32, 1.88)	0.655
Antenatal steroids	9 (26)	13 (25)	1.04 (0.39, 2.78)	1.000
Vaginal delivery	13 (37)	18 (35)	1.11 (0.46, 2.72)	0.823
Male gender	20 (57)	29 (56)	1.06 (0.45, 2.51)	1.000
Race				
Malay	20/50 (40%)			0.997
Indian	6/15 (40%)			
Chinese	9/22 (40%)			

*: number (percentages); VLBW: very low birth weight; RDS: repiratory distress syndrome; IPPV: intermittent positive pressure ventilation; OR: odds ratio; CI: Confidence Interval; ELBW: extremely low birth weight; IUGR: intrauterine growth retardation; AS: Apgar score.

coverage were provided by junior and senior doctors, posted from other paediatric wards and disciplines, unlike the dedicated teams of medical doctors working in such units in advanced countries. This would obviously incur a greater strain on the hospital budget.

The physically small and overcrowded SCN, and low staff-patient ratio most likely contributed to the high late infection-related deaths amongst our infants, even though hand washing, and sterile techniques and procedures have been stressed. As very premature and small infants are at higher risk for late-onset sepsis[1-7], early diagnosis of suspected or confirmed sepsis and NEC are essential and this includes low threshold for empirical treatment with antibiotics. However, of concern with this mode of antibiotics usage is the increasing emergence of multi-resistant strains of gram-negative organisms in our unit and hospital. The policy for judicious avoidance of prolonged antibiotic use is necessary. Prevention of infection and infection control, such as proper care of the endotracheal tubes, arterial and venous catheters, and isolation of infected neonates, are some of the vital steps to reduce this complication and an important cause of late-deaths.

Exogenous surfactant, as a prophylactic[18,19] or rescue treatment[20] has made a tremendous impact on the improved survival rates of premature infants with RDS world-wide. In our unit, this rescue therapy is restricted to infants with documented severe RDS as their parents have to pay for this expensive drug and most belong to the low income group. Some subsidy from the hospital's limited emergency fund is available only to the few parents who cannot bear the full cost. For this financial reason, prophylactic administration of surfactant in the labour room or SCN is not considered appropriate, as we may be treating infants with either no RDS or a mild disease. The other setback is the late administration of surfactant; the average time of administration is at the 6th hour of life (unpublished data). The delay is mainly due to the time needed to stabilise the infants, establish vascular access, obtain arterial blood gases and chest radiographs, and to wait for the sole after-hours medical officer to give the surfactant. Earlier administration[21,22] and more liberal use of exogenous surfactant in ventilated infants instead of what is currently practised would result in better survival, but this would involve more financial expenditure.

Fortunately, the use of tocolytic agents and antenatal steroids for premature labour are widely practised by our obstetrics colleagues. However, a study to examine the further causes of premature labour, and ways to prevent or to control it would be helpful in reducing the number of premature births. The large number of our mothers who were not given or had received inadequate doses of antenatal dexamethasone were mainly due to their imminent deliveries on arrival to the labour ward, as reflected by the high proportion of unbooked and walk-in cases, and medical contraindications such as severe maternal pre-eclampsia. The benefits of antenatal steroids in reducing the incidence of RDS and increasing the survival rates of VLBW infants[23,24] and including an additive effect with surfactant use[25], have been well

Table V – Comparative survival rates of VLBW and ELBW infants

Reference	Cohort	Number of infants	Percentage of survivors
VLBW infants			
Hack[11]	1987 – 88	1765	74
Phillip[2]	1982 – 91	950	78
Rapisardi[12]	1987 – 92	273	75
Present study	1994 – 96	184	78
ELBW infants			
Phillip[2]	1982 – 91	401	58
Keith[13]	1985 – 92	581	54
Rapisardi[12]	1987 – 92	96	60
Present study	1994 – 96	52	42

VLBW: very low birth weight; ELBW: extremely low birth weight

Table VI – Comparative survival rates of infants born between 23 – 26 weeks' gestation

Reference	Cohort	Gestational age			
		23 weeks % (no.)	24 weeks % (no.)	25 weeks % (no.)	26 weeks % (no.)
Hack[11]	1987 – 88	23	34	54	-
Synnes[14]	1983 – 89	16 (56)	43 (108)	55 (160)	63 (177)
Allen[15]	1988 – 91	15 (40)	56 (34)	79 (39)	-
Rennie[16]	1977 – 93	16 (375)	35 (834)	48 (1387)	57 (1735)
Present study	1994 – 96	0 (3)	50 (2)	0 (3)	40 (10)

* number of infants in each gestational age group were not given; -: no data

demonstrated. Our failure to show this in the present study may be due to the small number involved and the non-randomised nature of the study design.

Other recent advances, as in newer modes of ventilation, such as the high frequency oscillatory[26] and partial liquid ventilation[27], and the use of nitric oxides[28] for persistent pulmonary hypertension of the newborn, offer hope of improving survival rates. However, these techniques are very new and experimental (except for high frequency oscillatory ventilation), which require further trials and are not yet available in this country.

Whilst it is known that male infants have poorer neonatal survival rates[5,14,29], as compared to female infants, the reasons are not obvious. The notion that infants who are growth retarded fare better than infants who are appropriate for their gestational age, has been recently challenged[30]. It is not at all clear how IUGR influences early outcome in these infants. Although there was no significant difference in the overall mortality rates between the IUGR and gestational age of infants in our study, IUGR infants who had RDS requiring IPPV had higher mortality rates than their non-IUGR counterparts.

In conclusion, the prognosis for our VLBW, but not the ELBW infants, is comparable to those of the developed countries. Appropriate remedial attention is needed for the various deficiencies in our neonatal unit. Only when the set-up in the neonatal unit matches that of leading units in developed countries will the survival rates of the ELBW infants be comparable, and hopefully, so will the morbidity outcomes[31]. The difficult question remains as to what priority and how much of the current limited hospital resources be allocated to saving the ELBW infants. As the boundaries of foetal viability are gradually being advanced in this country, questions currently asked in the Western societies will also be echoed here[32].

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