Hypoxic-ischaemic encephalopathy: Identifying newborns who will benefit from therapeutic hypothermia in developing countries

M Coetzee, MB ChB, DCH, FCPaed, MMed (Paed), Cert Neonatology, MPhil (Neonatology)

Division of Neonatology, Department of Paediatrics and Child Health, School of Medicine, University of Pretoria, South Africa

Corresponding author: *M Coetzee (mel.coetzee@up.ac.za)*

Hypoxic-ischaemic encephalopathy (HIE) is only one of the many causes of neonatal encephalopathy, with no definitive test to make the diagnosis and very little available in terms of neuroprotective strategies, except for the use of therapeutic hypothermia (TH). TH improves survival and neurodevelopmental outcome at 18 months of age in neonates with moderate or severe encephalopathy. Based on this evidence, the International Liaison Committee on Resuscitation has recommended TH as standard of care since 2010. Low-cost methods of administering TH in low- and middle-income countries are effective as long as intensive care facilities are available, and provided that a TH guideline based on published international trials is in place. A local guideline, taking into consideration the care capable at different hospital levels, would be valuable in a developing country with resource constraints and increasing litigation.

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Neonatal encephalopathy (NE) is the term used to describe newborns ≥35 weeks' gestation who have an abnormal level of consciousness or seizures, which may be accompanied by abnormal tone and reflexes.[1,2] Intrapartum hypoxia resulting in hypoxic-ischaemic encephalopathy (HIE) is only one of the many causes of NE, with no definitive test to make the diagnosis[1] and very little available in terms of neuroprotective strategies, except for the use of therapeutic hypothermia (TH).[2] For this reason, it is important for clinicians to conduct a comprehensive evaluation (including determining the type and timing of contributing factors, performing a neurological examination, analysing the blood gas and searching for markers of multi-organ involvement)[1] to either exclude or strengthen the diagnosis of HIE, to select newborns who may benefit from TH.

The incidence of HIE has decreased to 1 - 8 per 1 000 live term births in developed countries;[3] however, 96% of cases are still from low- and middle-income countries,[4] with an incidence reported in one South African study ranging between 8.7 and 15.2 per 1 000 live term deliveries.[5]

The outcome for newborns suspected to have suffered an intrapartum hypoxic-ischaemic insult in the pre-cooling era has been well described. In 1976, Sarnat and Sarnat[6] reported that 25% of newborns with moderate encephalopathy and 100% of newborns with severe encephalopathy had a severely abnormal neurological outcome or were dead at 1 year of age. The Thompson score, a long-term prognostication score described in 1997, reports that a maximum score ≤10 assures a normal neurological outcome at 1 year of age; however, 65% of infants with a score >10, and 92% of infants with a score >15, will have an abnormal neurological outcome at 1 year of age.[7] In South Africa, Bruckmann and Velaphi[5] reported an in-hospital mortality rate of 1.4%, 7.1% and 62.5% in mild, moderate and severe encephalopathy, respectively, in newborns with HIE prior to the introduction of therapeutic hypothermia.

Management

Resuscitative care

The current recommendation is not to practise delayed cord clamping in asphyxiated newborns requiring resuscitation.[2,8] Normothermia must be maintained during resuscitation.[2,3] Once the neonate has been stabilised and a definitive decision is made by a senior clinician to offer TH, passive cooling can be commenced in the delivery room by turning off the radiant warmer while awaiting the initiation of active cooling.[2] However, passive cooling is not a recommended method of providing prolonged TH, even in low-resource settings. Hyperthermia during resuscitation and stabilisation should be avoided as it is associated with adverse outcomes.[2,3]

It is reasonable to initiate neonatal resuscitation in term infants using air (21% oxygen) and titrating the concentration to achieve target pre-ductal saturations after delivery.[8] The optimal oxygen concentration required during cardiac compressions remains unknown,[2] but the Neonatal Guidelines Writing Group recommend increasing to 100%.[8] However, it has been shown that hyperoxia during newborn resuscitation is associated with poorer outcomes[2] and therefore the oxygen concentration should be decreased as soon as the heart rate recovers.[8] There is no evidence for the use of sodium bicarbonate infusions during neonatal resuscitation.[9]

Supportive care

Supportive care may include assisted ventilation, with care to avoid hypocarbia and hyperoxia.[2] Hypocarbia causes vasoconstriction with decreased cerebral perfusion and hyperoxia increases oxidative stress; therefore the recommended $PaCO_2$ is 40 - 55 mmHg and PaO_2 is 50 - 100 mmHg.[3] It is particularly important to avoid hypoglycaemia as this may exacerbate brain injury.[2,3] There is limited evidence to use a sodium bicarbonate infusion to correct metabolic acidosis; however, Azzopardi[10] suggests correcting a severe metabolic acidosis (pH <7) persisting for >4 hours despite adequate supportive interventions. As HIE impairs cerebral autoregulation, a critical mean blood pressure range of 40 - 60 mmHg[3] is recommended to ensure cerebral perfusion. The use of fluid boluses, inotropes or vasopressors to maintain adequate perfusion will be guided by echocardiography.[3,11] Cerebral perfusion can also be assessed directly using near infrared spectroscopy (NIRS) if available.[2] Additionally, an amplitude-integrated electroencephalogram (aEEG) should be used to identify seizures,[3,11] abnormal background patterns, and abnormalities of the sleep-wake cycle.[2] Although phenobarbital augmented hypothermic neuroprotection in a rodent model, Sarkar *et al.*[12] reported no clinical benefit of combining phenobarbital with TH in neonates with HIE. Of concern is the reported increase in the combined

outcome of death or an abnormal post-cooling magnetic resonance imaging (MRI) brain in neonates who received combination therapy.[12] Until large randomised controlled trials are available, the use of phenobarbital to augment TH cannot be recommended. Additionally, prophylactic phenobarbital should not be used to prevent seizures.[13] There is also no evidence to administer corticosteroids to prevent or treat cerebral oedema secondary to HIE.[11]

Newborns with HIE are at an increased risk of fluid overload secondary to syndrome of inappropriate antidiuretic hormone and acute kidney injury,[2] and intravenous fluids should therefore be restricted to 40 - 70 mL/kg/day[2,3] with adjustment according to the urine output. A meta-analysis has reported that a single dose of prophylactic theophylline within 1 hour of delivery may prevent acute kidney injury and can be considered in cases of suspected hypoxic-ischaemic injury; however, it must be kept in mind that, despite the immediate renal benefits of prophylactic theophylline, the long-term renal and neurological effects are unknown, and it is not yet recommended as routine practice.[14]

Medications that are excreted by the kidneys or metabolised by the liver need to be used cautiously and may require dose adjustment if there is organ dysfunction.[2] Additionally, TH may delay hepatic metabolism of some medications and newborns should be monitored for toxic effects secondary to any drugs administered.[15] Pain and stress can diminish the neuroprotective effects of TH, and it is suggested that analgesia and sedation be provided for these infants.[15] Signs of pain or distress include tachycardia (heart rate >110 beats/min.), facial grimacing and shivering.[15] For spontaneously breathing newborns, respiration must be monitored closely if providing sedation.[15]

Therapeutic hypothermia

A recent meta-analysis of 7 large randomised controlled trials has demonstrated that TH improves survival (without increasing disability) and neurodevelopmental outcome at 18 months of age in neonates with moderate or severe encephalopathy.[16] When compared with standard supportive care, there is a significant reduction in death (risk ratio (RR) 0.75, 95% confidence interval (CI) 0.63 - 0.88), major disability (RR 0.68, 95% CI 0.56 - 0.83), cerebral palsy (RR 0.62, 95% CI 0.49 - 0.78), developmental delay (RR 0.66, 95% CI 0.52 - 0.82) and blindness (RR 0.56, 95% CI 0.33 - 0.94) at 18 months of age.[16] The number of infants with HIE who need to be treated with TH to prevent death or major disability in neonates with moderate and severe encephalopathy is 6 and 7, respectively.[16] Based on these outcomes, the International Liaison Committee on Resuscitation have recommended TH as the standard of care for infants with suspected HIE since 2010.[9] In 2015, the American Heart Association stated that TH may also be practised in resource-limited settings, as long as protocols are based on those from large clinical trials, a multidisciplinary team is available for patient care, and long-term follow-up is possible.[8] However, despite the use of TH, the rate of death or disability for infants with HIE remains high (44 - 55%).[17]

In a South African web-based survey, 66% of paediatrician and neonatologist respondents stated that TH was effective, although only 42% offered TH and a further 9% referred patients to another facility for TH.[18] Twenty-four percent of respondents had not introduced TH in their unit.[18] The reluctance of almost a quarter of South African doctors to use TH as standard of care for newborns with HIE may be attributed to the lack of local published recommendations by a neonatal or paediatric association. Such a guideline, based on internationally published protocols but adjusted for South African conditions, would be valuable in a developing country with resource constraints and increasing litigation.

Timely and accurate identification of newborns who may benefit from TH is imperative so that treatment can be initiated within the 6-hour therapeutic window. However, it is advisable to initiate TH immediately if eligible, as Thoresen *et al.*[19] showed that neonates initiated before 3 hours of life had improved motor outcomes at 18 - 20 months of age. Additionally, as injury to the brain is not static the clinical neurological examination should be repeated at 1 - 2-hour intervals within the first 6 hours of life to identify neonates with progression of encephalopathy (mild to moderate/severe) who would then be eligible for TH.[2] Eligibility is defined by 3 main categories, which must be met sequentially. The eligibility criteria of the 6 largest published international trials[20-25] are summarised in Table 1. Category (A) describes general criteria such as age in hours after birth and gestational age. The majority of trials used age ≤6 hours old[20-25] and a gestational age ≥36 weeks.[20-23] Category (B) searches for evidence of possible intrapartum hypoxia-ischaemia, evidenced by either low Apgar scores (≤5 at 10 minutes),[20-22,24,25] acidosis (pH ≤7 and/or base deficit ≥16) on arterial cord blood or a blood gas done within 60 minutes of delivery,[20-24] or the need for continued resuscitation at 10 minutes of life.[20-23,25] Category (C) defines the neurological picture, including encephalopathy and/or clinical seizures and/or an abnormal background aEEG. Exclusions for TH include major congenital abnormalities,[20-25] intra-uterine growth restriction (weight <1 800 g),[20,21,23] intracranial haemorrhage[20,23,24] or stroke[22,24] and a moribund state.[21,22,25]

These 6 trials defined encephalopathy clinically using the modified Sarnat stages[26] or the Sarnat and Sarnat stages.[6] However, the Thompson score has also been used in some studies to establish eligibility for TH.[7] As described by Thompson *et al.*,[7] the following scores equated to specific Sarnat and Sarnat stages: neonates scoring 0 - 10 had mild encephalopathy (stage I), those scoring 11 - 14 had moderate encephalopathy (stage II), and those scoring >14 had severe encephalopathy (stage III). According to the current recommendations, only newborns with moderate or severe encephalopathy qualify for TH, namely a Thompson score >10. However, various TH protocols using the Thompson score include newborns with a score ≤10,[27-29] implying that neonates with mild encephalopathy, according to Thompson *et al.*,[7] are receiving TH. However, the number of neonates included in Thompson's study was small, and the numerical threshold with the best sensitivity and specificity to identify neonates with encephalopathy who will benefit from TH is yet to be validated in large clinical trials. This is of particular importance in a developing country, where the incidence of HIE is high and resources for providing TH are limited, so that the resources are offered to patients who will have the greatest benefit. There are, however, a few small studies that attempted to identify a threshold Thompson score which predicted an abnormal aEEG or an adverse outcome. Horn *et al.*[30]showed that an early Thompson score, before 6 hours of age, ≥7 had the best sensitivity and specificity (100% and 66.7%, respectively) to predict an abnormal 6-hour aEEG. This study also showed that there was no significant difference in the ability of either an early Thompson score or the modified Sarnat stages to predict an abnormal aEEG by 6 hours of age.[30] Weeke *et al.*[27] showed a significant association between the Thompson score and abnormal aEEG patterns. The scores of neonates with discontinuous normal voltage (DNV) and burst suppression (BS) were significantly different (>7 v. ≥10), as were the scores of neonates with BS and continuous low voltage (CLV)/flat trace (FT) (≥10 v. ≥12/15). The sensitivity for an abnormal outcome with a Thompson score >7 or a BS/CLV/FT background aEEG pattern was 96% and 94%, respectively, but with low specificities of 24% and 49%, respectively. The low specificity compared with Thompson's original paper may be attributed to the neuroprotective effects of therapeutic hypothermia. However, ROC analysis showed that a Thompson score ≥11 was the best cut-off value for an abnormal outcome (sensitivity 76%, specificity 83%), including death, cerebral palsy, severe visual and hearing impairments, and abnormal neurodevelopment.[27]

Table 1. Comparison of the six largest therapeutic hypothermia trials tabulated according to year published

Source	Characteristic	Description
Gluckman *et al.*[20] 2005 (CoolCap)	(A)	≥36 weeks and ≤6 hrs old
	(B)	At least 1 of the following: Apgar score ≤5 at 10 minutes **OR** continued resuscitation at 10 minutes **OR** severe acidosis* (pH <7/BD ≥16)
	(C)	Modified Sarnat or clinical seizures **AND** abnormal aEEG
	Major excl.	>5.5 hrs old, major cong. abn., head trauma with ICH, severe IUGR (<1 800 g), HC <–2 SD
	Intervention	Selective head cooling with mild systemic hypothermia (servo-control) at 34 - 35°C (R) for 72 hrs
Shankaran *et al.*[21] 2005 (NICHD)	(A)	≥36 weeks and ≤6 hrs old
	(B)	Acidosis (pH ≤7/BD ≥16) If pH 7.01 - 7.15/BD 10 - 15.9 or blood gas not available, require ≥2: Hx of an acute perinatal event **AND** the need for assisted ventilation for 10 minutes after birth **OR** an Apgar score ≤5 at 10 minutes
	(C)	Modified Sarnat or clinical seizures
	Major excl.	>6 hrs old, major cong. abn., severe IUGR (≤1 800 g), moribund
	Intervention	Whole body cooling (servo-control) at 33.5°C (OES) for 72 hrs
Azzopardi *et al.*[22] 2009 (TOBY)	(A)	≥36 weeks and ≤6 hrs old
	(B)	At least 1 of the following: Apgar score ≤5 at 10 minutes, **OR** continued resuscitation at 10 minutes **OR** acidosis* (pH <7/BD ≥16)
	(C)	Modified Sarnat or clinical seizures **AND** abnormal aEEG
	Major excl.	>6 hrs old, major cong. abn., moribund, postnatal collapse or cerebral infarction
	Intervention	Whole body cooling (servo-control) at 33 - 34°C (R) for 72 hrs
Simbruner *et al.*[23] 2010 (neo.nEURO network)	(A)	≥36 weeks and ≤6 hrs old
	(B)	At least 1 of the following: Apgar score <5 at 10 minutes, **OR** continued resuscitation at 10 minutes **OR** acidosis (pH <7/BD >16) on cord blood or any arterial sample within 60 minutes of birth
	(C)	Sarnat and Sarnat stages or clinical seizures **AND** abnormal aEEG/EEG
	Major excl.	>5.5 hrs old, BW <1 800 g, HC <3rd centile, major cong. abn., gross haemorrhage
	Intervention	Whole body cooling (manually adjusted mattress) at 33.5°C (R) for 72 hrs
Zhou *et al.*[24] 2010	(A)	≥37 weeks and ≤6 hrs old
	(B)	Apgar score ≤3 at 1 minute and ≤5 at 5 minutes **AND** cord blood gas pH<7/BD ≥16 **AND** the need for resuscitation or ventilation at 5 minutes
	(C)	Sarnat and Sarnat stages or clinical seizures
	Major excl.	BW <2 500 g, major cong. abn., infection, other cause for NE (stroke, CNS abn., ICH), severe anaemia (Hb <12g/dL)
	Intervention	Selective head cooling with mild systemic hypothermia (servo-control) at 34.5 - 35°C (R) for 72 hrs
Jacobs *et al.*[25] 2011 (ICE)	(A)	≥35 weeks and ≤6 hrs old
	(B)	≥2 of the following: Apgar score ≤5 at 10 minutes **AND/OR** continued need for mechanical ventilation at 10 minutes **AND/OR** metabolic acidosis* (pH <7/BD ≥12)
	(C)	Modified Sarnat or clinical seizures
	Major excl.	>6 hrs old, BW <2 000 g, major cong. abn., overt bleeding, require FiO_2 >80%, death imminent
	Intervention	Whole body cooling (radiant warmer off and gel packs as needed) at 33.5°C (R) for 72 hrs

aEEG = amplitude-integrated electroencephalography; excl = exclusion; cong. = congenital; abn. = abnormality; ICH = intracranial haemorrhage; IUGR = intrauterine growth restriction; HC = head circumference; SD = standard deviation; R = rectal; NICHD = National Institute of Child Health and Human Development; BD = base deficit (mmol/L); Hx = history; TOBY = total body hypothermia for neonatal encephalopathy trial; OES = oesophagaael; BW = birth weight; NE = neonatal encephalopathy; CNS = central nervous system; Hb = haemoglobin; ICE = infant cooling evaluation; FiO_2 = fraction of inspired oxygen.
*Arterial cord blood sample or arterial/venous/capillary blood sample within 60 minutes of birth.

Thorsen *et al.*[28] showed that a Thompson score ≥12 had a 3.9-fold increased odds of death before discharge and an 8.4-fold increased odds of severe seizures compared with infants with a Thompson score <12.

Similarly, the modified Sarnat stages is a clinical staging method developed to establish whether an early neurological examination performed within the first 12 hours of life could predict a persistent abnormal neurological state beyond 5 days of life or death in the first week of life comparable with an aEEG.[26] Encephalopathy was defined as the presence of 1 or more signs in at least 3 of the following 6 categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic dysfunction.[26] This study reported that an aEEG had a better specificity (89% v. 78%) and positive predictive value (73% v. 58%), with similar sensitivity (79% and 78%) and negative predictive values (90% v. 91%), compared with an abnormal clinical examination, but also reported that the combination of abnormalities in both the early clinical examination and aEEG had the highest specificity and positive predictive value for an abnormal short-term outcome (sensitivity 78%, specificity 94%, positive predictive value 85%, negative predictive value 92%).[26]

Although whole-body cooling is more commonly used owing to the ease of administration, both whole-body and selective head cooling are effective methods to provide TH and have comparable outcomes.[16] Servo-controlled (automated) devices are easier to use to maintain core body temperature within the appropriate range, but these devices are expensive to purchase and maintain and may preclude many neonatal units in resource-limited settings from implementing TH. A systematic review of TH in low- and middle-income countries showed no survival benefit, which was suggested to be secondary to the use of low-cost TH methods and the lack of neonatal intensive care facilities.[31] However, many individual studies have shown that low-cost methods of cooling are effective, so a systematic review was done to assess the use of low-cost methods in facilities where neonatal intensive care was available.[32] The 3 studies included in the present review used gel packs to provide TH. This review showed a significant reduction in mortality at discharge (RR 0.60; 95% CI 0.39 - 0.92), mortality at 6 - 24 months (RR 0.63; 95% CI 0.43 - 0.93), and neurological morbidity at discharge (RR 0.46; 95% CI 0.33 - 0.63). One study reported on outcomes at 24 months, with a significant reduction in severe neurological morbidity or mortality (RR 0.77; 95% CI 0.62 - 0.98). Two studies reported an increased survival without morbidity at 6 months (RR 1.31; 95% CI 1.09 - 1.58) and 24 months (RR 1.75; 95% CI 1.13 - 2.7), respectively.[32] A study comparing two commonly used low-cost methods of cooling, namely frozen gel packs and phase-changing material, showed that both methods are as effective as servo-controlled methods of TH with similar complication rates and short-term outcomes.[33]

It has also been investigated whether a longer duration of cooling of 120 hours or deeper cooling to 32°C or both will have further neuroprotective benefits above the current recommendations. However, both of these variations have significantly increased complications, and have not demonstrated any benefit to in-hospital survival.[17] These practices can therefore not be recommended; and existing TH guidelines recommending maintaining the core body temperature of 33°C - 34°C for 72 hours,[17] and then slowly re-warming, should be followed.

Early predictors of outcome

It has been suggested that the addition of TH to the management of newborns with HIE may alter the prognostic value of predictive tests. As the level of care offered to the newborn with HIE is often based on the perceived prognosis, information regarding predictive tests during the era of TH should be used.

The predictive value of an early clinical examination is lower in newborns receiving TH compared with those who are kept normothermic.[34] However, considering that many of the sophisticated predictive tests may only be available in specialist centres, a detailed clinical neurological examination is imperative. Shankaran *et al.*[35] reported that the persistence of moderate to severe encephalopathy at 72 hours, an abnormal neurological examination (hypertonia, fisting, abnormal movements, absent gag reflex, and an asymmetric tonic neck reflex) at discharge, or the need for gastrostomy tube feeding at discharge were all associated with an increased risk of death or disability. Importantly, the presence of seizures *per se* is not associated with an abnormal outcome; however, a high seizure burden is. Kharoshankaya *et al.*[36] showed that the odds of an abnormal outcome at 24 - 48 months of age were increased 9 times with a total seizure burden >40 minutes (p=0.001) and 8 times with a maximum seizure burden >13 minutes per hour (p=0.003), irrespective of the use of TH. Maartens *et al.*[37] also reported that neonates requiring more than two anti-epileptic drugs to control seizures had a significantly poorer outcome at 2 years of age (p<0.01).

Although TH does not alter the interpretation of cranial ultrasound, the predictive value of an abnormal cranial ultrasound remains poor, with a sensitivity of 79% and specificity of 55%.[38] A recent meta-analysis showed that the predictive value of an aEEG at 6 hours of age in newborns receiving TH is poor (post-test probability 59.1%), and the maximum predictive reliability of aEEG for death or moderate/severe disability in newborns receiving TH is at 72 hours (post-test probability 95.7%). However, the presence of an abnormal aEEG persisting beyond 48 hours also had a high predictive reliability for an adverse outcome (post-test probability 93%). Consequently, in the era of TH, the predictive reliability of aEEG is delayed from 24 - 36 hours to 48 - 72 hours of life.[39] While TH reduces brain injury on MRI, the predictive value remains unchanged[40] and MRI remains the gold standard neuroimaging modality in newborns with HIE. A meta-analysis by Van Laerhoven *et al.*[38] reported that T1/2-weighted MRI has the best predictive values of outcome for all neuroimaging investigations, with sensitivities of 84% and 98% and specificities of 90% and 76% when done in the first and second week of life, respectively. Additionally, early MRI images performed on day 4 of life after completion of TH highly correlated with late images done during the second week of life.[41] Similarly, MRI done during TH (day 2 - 3 of life) demonstrated the full extent of brain injury compared with MRI done on day 10 of life.[42] This information is essential for early prognostication in terms of family counselling and early re-direction of care.

Late predictors of outcome

Using Prechtl's assessment of general movements, Ferrari *et al.*[43] showed that cramped-synchronised general movements at 1 and 3 months of age were associated with the development of cerebral palsy at 24 months of age in infants with HIE (sensitivity 68.7%, specificity 100%). Additionally, abnormal general movements at 1 and 3 months of age correlated well with early MRI abnormalities in these infants (cramped-synchronised general movements had predominantly deep grey-matter injury on MRI). The combination of information using these two techniques had the best predictive value for outcome at 24 months.[43] Similarly, Soleiman *et al.*[44] showed that the absence of fidgety movements at 3 months of corrected age in infants who suffered from HIE was associated with abnormal neurological outcomes at 12 - 18 months of age (sensitivity 80%, specificity 100%). Cordes *et al.*[45] showed that reduced head growth by 4 months of age was highly predictive of long-term neurological abnormalities; however, normal head growth does not preclude an abnormal neurological outcome.

Conclusion

Improved survival and neurodevelopmental outcome at 18 months of age has been reported in multiple trials of TH, and it is currently the only neuroprotective strategy for neonates suspected to have suffered an intrapartum hypoxic-ischaemic event. Therapeutic hypothermia in low- and middle-income countries using low-cost methods

is effective, provided that intensive care facilities are available. However, a protocol for TH based on one of the large trials should first be in place, keeping in mind that these may require adaptation to the South African environment. In accordance with the large trials, TH should be reserved for neonates ≥36 weeks and ≤6 hours old with evidence of possible intrapartum hypoxia-ischaemia (Apgar score ≤5 at 10 minutes, or continued resuscitation at 10 minutes, or severe acidosis (pH <7/base deficit (BD) ≥16) and an abnormal neurological examination (moderate/severe encephalopathy or clinical seizures or an abnormal aEEG). Although the use of the Thompson score to determine eligibility cannot be disregarded, there is no consensus on the ideal numerical threshold that should be used as Horn *et al.*[30] suggest ≥7, Weeke *et al.*[27] suggest ≥11 and Thorsen *et al.*[28] suggest ≥12, and therefore further large studies are necessary. Institutions using the Thompson score to determine eligibility should select a threshold according to the resources available at that facility, i.e. the private sector and tertiary hospitals may use a lower threshold and regional hospitals, with fewer resources, a higher threshold.

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