Does Early Cerebral Near-Infrared Spectroscopy Monitoring Predict Outcome in Neonates with Hypoxic Ischaemic Encephalopathy? A Systematic Review of Diagnostic Test Accuracy

Aisling A. Garvey^{a, b} Andreea M. Pavel^{a, b} Deirdre M. Murray^{a, b}
Geraldine B. Boylan^{a, b} Eugene M. Dempsey^{a, b}

^aINFANT Research Centre, Cork, Ireland; ^bDepartment of Paediatrics and Child Health, University College Cork, Cork, Ireland

Keywords

Near-infrared spectroscopy · Hypoxic ischaemic encephalopathy · Early biomarker · Neonatal encephalopathy

Abstract

Introduction: Hypoxic ischaemic encephalopathy (HIE) remains one of the top 10 contributors to the global burden of disease. Early objective biomarkers are required. Near-infrared spectroscopy (NIRS) may provide a valuable insight into cerebral perfusion and metabolism. We aimed to determine whether early NIRS monitoring (<6 h of age) can predict outcome as defined by grade of encephalopathy, brain MRI findings, and/or neurodevelopmental outcome at 1–2 years in infants with HIE. **Methods:** We searched PubMed, Scopus, Web of Science, Embase, and The Cochrane Library databases (July 2019). Studies of infants born $\geq 36^{+0}$ weeks gestation with HIE who had NIRS recording commenced before 6 h of life were included. We planned to provide a narrative of all the studies included, and if similar clinically and methodologically, the results would be pooled in a meta-analysis to determine test accuracy. **Results:** Seven studies were included with a combined total of 161 infants. Only 1 study includ-

ed infants with mild HIE. A range of different oximeters and probes were utilized with varying outcome measures making comparison difficult. Although some studies showed a trend towards higher cSO_2 values before 6 h in infants with adverse neurodevelopmental outcomes, in the majority, this was not significant until beyond 24 h of life. **Conclusion:** Very little data currently exists to assess the use of early NIRS to predict outcome in infants with HIE. Further studies using a standardized approach are required before NIRS can be evaluated as a potential objective assessment tool for early identification of at-risk infants.

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Introduction

Hypoxic ischaemic encephalopathy (HIE) is the leading cause of acquired brain injury in term newborns and accounts for 1–3/1,000 live births [1]. HIE results from an initial insult due to cerebral hypoxia and ischaemia resulting in energy depletion and lactate accumulation secondary to anaerobic metabolism. This is followed by a secondary insult, termed the reperfusion injury, following circulatory restoration [2, 3]. HIE is clinically graded

as mild, moderate, and severe based on neurological examination after birth, and long-term neurodevelopmental outcome correlates with grade of encephalopathy. Therapeutic hypothermia (TH) is the current approved treatment for infants with moderate and severe grades of HIE and should be commenced within 6 h of life, before the secondary energy failure commences, to be most effective [3–5]. Historically, infants with mild grades of encephalopathy were thought to have normal outcomes [6]; however, it is becoming more apparent that these infants are at increased risk of adverse neurodevelopmental outcome, specifically significant levels of learning, emotional, and behavioural difficulties [7].

This presents significant challenges as the current methods of identifying such infants at risk of long-term neurodevelopmental difficulties are somewhat limited. It is clear that some infants who have difficulties later are currently falling below the threshold for therapeutic intervention [7]. The earliest available tools including Apgar score, pH, and lactate levels do not correlate with outcome, rather they succeed in focusing attention on newborns at risk of HIE [8–10].

Currently, assessment is centred around clinical evaluation, and the modified Sarnat and Thompson scores [6, 11] are most commonly used in clinical practice. Originally validated to examine infants repeatedly in the first week of life [6, 11], when used in the first 6 h of life, they can be influenced by factors including mode of delivery and maternal analgesia.

Electroencephalography (EEG) plays a key role in both prognostication and detection of seizures in infants with HIE. Amplitude-integrated EEG (aEEG) in the first 6 h of life was the most useful tool in predicting outcome in the pre-TH era; however, this predictive ability has now altered if TH is commenced very early, and the best predictive ability is now seen at 48 h [12]. Continuous, multi-channel EEG requires expert interpretation, and most units do not have 24-h access to a neonatal neurophysiologist or neurologist.

Hypoxic injury is not evident on conventional MRI until the first to second week of life [13] and is therefore not helpful in detecting or grading encephalopathy in the early postnatal period [14]. Early MRI scans may be helpful in ascertaining the timing of the initial injury [15–17], although there were concerns that early diffusion weighted imaging scans may underestimate the extent of the injury [17, 18].

Prediction of long-term outcome remains challenging, and it is important to consider other confounding factors in the neonatal unit and beyond. However, at present, we

have no single test to accurately identify infants at risk of long-term neurodevelopmental outcome in the setting of HIE. Alternative methods of identification are thus required.

HI injury results in a period of hypoperfusion at the time of initial insult followed by circulatory restoration [3]. Cerebral blood flow (CBF) has been shown to increase in the first 24 h following HI injury likely due to a disruption in haemodynamic control [19, 20]. This early hyperperfusion has been shown to be associated with increased risk of brain injury [21]. Clinicians commonly associate time of injury with time of birth, which is not always the case and may explain why studies on the use of early near-infrared spectroscopy (NIRS) as a prognostic tool are conflicting, but beyond 24 h of life, NIRS, specifically cerebral oxygenation (cSO₂) and metabolism, appears to be a good predictor of neurodevelopmental outcome [22, 23]. Data on NIRS in the first 6 h of life (within the therapeutic window) may aid in prognostication and objective identification of cases for therapeutic intervention. The aim of this systematic review is to determine whether early cerebral NIRS monitoring (<6 h of age) can predict neonatal outcome as defined by grade of encephalopathy (defined clinically using Thompson or Sarnat scoring or electrophysiologically using visual EEG analysis), brain MRI findings, and/or neurodevelopmental outcome at 1–2 years of age.

Methods

As per the Preferred Items for Systematic Reviews and Meta-Analysis Statement, a systematic stepwise approach was taken to search various databases [24].

Search Strategy

Relevant articles were identified from the following databases by 2 authors, A.G. and A.P.: PubMed, Scopus, Web of Science, Embase, and The Cochrane Library. Searches were filtered to include human studies published in the English language in the last 30 years (January 1988 to July 2019). Three broad search terms were used (Neonate, HIE, and NIRS) along with their corresponding synonyms and MeSH terms (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000518687). Additional published reports identified in review articles or screened articles were subsequently included.

Study Selection

All articles were indexed to EndNote, and duplicates were removed. Articles were initially screened based on the title and then by abstract by 1 author (A.G.). The remaining articles were then screened independently for inclusion criteria by both A.G. and E.D., and any discrepancies were discussed and resolved.

Fig. 1. PRISMA diagram of literature search. The PRISMA diagram displays the number of articles identified from each database searched, screening process, and number of studies and reasons for subsequent exclusion from analysis. NIRS, near-infrared spectroscopy.

Inclusion criteria consisted of the following:

1. Observational cohort study or clinical randomized or quasi-randomized controlled trials.
2. Human study.
3. Newborn infants born at ≥ 36 weeks gestational age.
4. Neonatal HIE defined clinically, using Thompson or Sarnat scoring, and/or electrophysiologically, using amplitude-integrated (aEEG) or continuous EEG (cEEG).
5. Cerebral NIRS monitoring commenced early, defined as before 6 h of age.

Animal studies, studies that were not in English, or conference abstracts were not included.

Strategy for Data Analysis

We planned to include a narrative of all the studies included, detailing the early findings of NIRS monitoring. If the studies were similar clinically and methodologically, we planned to pool the results of the studies in a meta-analysis. Data from each study would be summarized in a 2×2 table (true-positives, false-positives, false-negatives, and true negatives) and the sensitivity and specificity for each study calculated. A coupled forest plot displaying the sensitivity and specificity and corresponding 95% CIs for each study and a summary plot displaying the sensitivity-specificity point for each study would be created. Heterogeneity among studies would be investigated by visual inspection of these plots. If no substantial heterogeneity was observed, pooled sensitivity and specificity estimates and corresponding 95% CIs would be calculated for studies with a common threshold using the bivariate random effects regression model or the univariate random-effects model (if the number of studies is small). If different thresholds

were reported in the individual studies, a hierarchical summary receiver operating characteristic curve would be created and a global summary of test accuracy calculated. The analysis would be performed using Stata (version 13.0; StataCorp LP, College Station, TX, USA).

Risk of Bias (Quality) Assessment

Studies were critically appraised using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess their validity and applicability. Each article was scored by both reviewers independently. The review protocol was published on the International prospective register of systematic reviews (PROSPERO) prior to conducting database search (Registration No. PROSPERO 2019 CRD42019127907).

Results

Our initial search identified 3,826 articles. Figure 1 provides a flow diagram of the search results.

From these articles, 1,116 duplicates were removed and 2,590 articles were excluded based on title or abstract. One hundred and twenty full-text articles were assessed for eligibility criteria, and from these, we identified 7 original articles that described the use of NIRS in infants with HIE within the first 6 h of life. The details of included articles are summarized in Table 1. The principle reasons

Table 1. Studies included in systematic review, NIRS measurement commenced <6 h, outcome method used, and synopsis of main findings

Author	n	Grade of HIE (n)	NIRS device	Location of sensor	NIRS measure reported	MRI brain	Long-term outcome	Summary of findings
Ancora et al. [29]	12	Moderate (8), severe (4)	NIRO 200	Bifrontal	TOI	n/a	Griffiths at 18 months	No difference in TOI at 6 h. Significantly higher TOI values at 24 h in the adverse outcome group
Goeral et al. [28]	32	Moderate (32)	INVOS 5100C neonatal sensor	Frontoparietal	cSO ₂ , FTOE	First 2 weeks	Not done	No difference in cSO ₂ /FTOE values at 6 h in those with favourable/unfavourable MRI outcomes
Gucuyener et al. [32]	10	Moderate (6), severe (4)	NIRO 200	Parietal	TOI, FTOE	Day 7	Bayleys at 24 months	Early NIRS (TOI, FTOE) did not predict long-term outcome
Lemmers et al. [24]	39	Moderate, severe* (39)	INVOS 4100-5100 adult sensor	Frontoparietal	cSO ₂ , FTOE	Day 4–6	Griffiths at 18 months	No difference in early cSO ₂ or FTOE. Significantly higher cSO ₂ beyond 24–72 h in the adverse outcome group
Nakamura et al. [31]	11	Mild (4), moderate (6), severe (1)	TRS 10	Forehead	cSO ₂ , CBV	Day 7–14	Kyoto Scale of Psychological Dev & exam at 12–18 months	No difference in early cSO ₂ . Significantly higher CBV at 6 h in the adverse outcome group. Significantly higher cSO ₂ and CBV at 24 h in the adverse outcome group
Niezen et al. [30]	39	Moderate, severe* (39)	INVOS 5100 paediatric sensor	Left or right frontoparietal	cSO ₂	Day 4–13	GMFCS and Bayleys at 30 months	No difference in early cSO ₂ . Significantly higher cSO ₂ beyond 24–72 h in the adverse outcome group
Peng et al. [27]	18	Moderate (8), severe (10)	Fore-sight	Bifrontal	cSO ₂	Day 2–3 and 10	Not done	Higher cSO ₂ values at all time points in infants with evidence of MR injury

NIRS, near-infrared spectroscopy; TOI, tissue oxygen extraction; cSO₂, cerebral oxygen saturation; FTOE, fractional tissue oxygen extraction; CBV, cerebral blood volume.
 * Numbers of each grade not specified.

Table 2. Assessment of risk of bias of included studies using quality assessment of diagnostic accuracy tests – 2

	Risk of bias				Applicability concerns		
	patient selection	index test	reference standard	flow and timing	patient selection	index test	reference standard
Ancora et al. [29]	Low	Unclear	Low	Low	Low	Low	Low
Goeral et al. [28]	Low	Unclear	Low	Low	Low	Low	Low
Gucuyener et al. [32]	Unclear	Unclear	Unclear	High	Low	Low	Low
Lemmers et al. [24]	Low	Unclear	Low	Low	Low	Low	Low
Nakamura et al. [31]	High	Unclear	High	Low	Low	Low	Low
Niezen et al. [30]	Low	Unclear	Unclear	Low	Low	Low	Low
Peng et al. [27]	Unclear	Unclear	Low	Low	Unclear	Low	Low

for non-inclusion are outlined in online supplementary Table 2, but predominantly were related to a NIRS device not being used (e.g., MRI to measure cerebral metabolism and blood flow), start time of NIRS recording not documented, or NIRS monitoring commenced after 6 h of life.

Included Studies

Details of included studies are outlined in Table 1, and a brief narrative is included below.

Early NIRS to Determine Grade of Encephalopathy

In all of the included studies, grade of encephalopathy was determined at or before time of enrolment using standardized assessment tools such as the Sarnat or Thompson score. Six of the 7 trials focused on moderate to severe encephalopathy only. Early NIRS was not assessed for its ability to predict grade of encephalopathy nor were they correlated with the individual grades. Only 1 study included infants with mild encephalopathy, and no study included a control group.

Early NIRS Monitoring to Predict Outcomes

a. MR injury only: only 2 studies addressed.

Peng et al. [25] found consistently higher cSO₂ values in moderately or severely encephalopathic infants receiving TH with later evidence of injury on MRI. In a cohort of 32 cooled infants with moderate encephalopathy, Goeral et al. [26] found no difference in cSO₂ or FTOE values at 6 h in those with favourable or unfavourable MRI outcomes.

b. Long-term outcome only: only 1 study addressed.

Examining the ability of NIRS to predict long-term outcome, Ancora et al. [27] reported a trend towards a higher TOI at 6 h of life in infants with an adverse outcome at 18 months (80.0% ± 10.5 vs. 66.9% ± 7.0, $p =$

0.057), and this difference was statistically significant by 24 h of life (79.7% ± 9.4 vs. 67.1% ± 7.9, $p = 0.034$). These infants all received TH for moderate or severe grades of encephalopathy.

c. Composite outcome of MR or long-term outcome: 4 studies addressed.

Both Lemmers et al. [22] and Niezen et al. [28] found that early cSO₂ and FTOE values did not differentiate between infants with a favourable or adverse outcome. They included infants with both moderate and severe grades of HIE undergoing TH. However, in both studies, the predictive ability of these NIRS measurements improved beyond the first 24–72 h of life at which time cSO₂ was significantly higher in the adverse outcome group.

Nakamura et al. [29] also found no difference in cSO₂ values at 6 h between those with a favourable and unfavourable outcome across all grades of encephalopathy. Mean CBV at 6 h, however, was significantly higher in the infants who had an adverse outcome (3.1 ± 0.4 vs. 2.4 ± 0.5 mL/100 g brain, $p = 0.03$). At 24 h after birth, both cSO₂ and CBV were higher in the infants with an adverse outcome, and they found that combining CBV and cSO₂ at 24 h after birth had a 100% sensitivity, specificity, and positive and negative predictive values for neurological outcome.

Gucuyener et al. [30] noted that 3 infants in their cohort, all of which were cooled for moderate grade of encephalopathy, had low TOI and high FTOE before the initiation of TH. These same infants had repetitive seizures as confirmed by aEEG within the first few hours of life, suggesting increased oxygen consumption during seizures, and by the end of TH, their values were within normal ranges. Although 2 of these infants had an abnormal MRI on day 7, all 3 had normal Bayleys scores at 2 years of age, highlighting the importance of long-term

follow-up as an abnormal MRI is not synonymous with adverse neurodevelopmental outcome.

Quality Assessment

Quality of the included studies was assessed using the QUADAS-2 tool (Table 2). Regarding patient selection, it was unclear in some studies as to whether patients were consecutively enrolled or selected randomly, thus avoiding selection bias. In all studies, it was unclear as to whether the index test was interpreted without knowledge of the reference standard, and similar issues with blinding were present in some studies regarding the interpretation of the outcome data. Generally, concerns regarding applicability were low in the majority of studies.

Discussion

HIE is one of the top 10 contributors to the global burden of disease and has life-long effects for survivors and their families [31]. Use of TH in infants with moderate and severe encephalopathy has improved neurological outcomes. However, with significant disability still reported in over 1 million survivors [32], further improvement in therapy is required. Early NIRS monitoring may have an important role to play, not only in prediction of poor neurodevelopmental outcome but also in objective selection of infants for therapeutic intervention.

One of the main findings from this systematic review was the variation in methodology seen, specifically the device and sensors used, the measurements reported, and the outcome milestones assessed. Due to this heterogeneity, we were unable to perform a quantitative meta-analysis. In the 7 included studies, 6 different devices or sensors were used making it very difficult to draw firm conclusions. Although normative ranges for term infants have been suggested, these values have a narrow range and vary greatly between configurations of devices and sensors used [33, 34]. Using the INVOS oximeter, for example, cSO_2 values vary up to 10% depending on whether the neonatal or adult probes are used. In addition, the INVOS oximeter truncates values at 95%, the range above which an adverse outcome may be expected and is an important point to consider when neonatal probes are used. Reapplication of a sensor in the same area may also result in variability of values of up to 6% [35]. Furthermore, there is significant variation in the probe location used in the above studies, for example, frontal, parietal, and frontoparietal. Some studies obtained measurements bilaterally and some did not specify whether it was right or left.

This is important, as different NIRS systems have different penetration depths, so values may vary depending on the site used [36].

There was also variation in the short- and long-term outcome assessment methods used. Overall, 6 of the studies examined the ability of NIRS to predict brain injury on MRI, but the timing of these scans differed with some performing MRI in the first week of life and others into the second week of life. Long-term neurodevelopmental assessment also varied from 12 to 30 months of age. Furthermore, it is also unclear in many of the studies whether the authors were blinded to the NIRS values when assessing the outcome data and vice-versa, raising concerns for the potential for bias.

It is important, however, to also consider the timing of injury. As previously mentioned, timing of injury is frequently tacked to time of birth when in fact the timing of the sentinel event may vary and the resultant asphyxia may be acute, chronic, or acute-on-chronic [37], placing the infant at different stages along the injury pathway at time of birth. Nonetheless, NIRS provides an indirect measure of cerebral perfusion and oxygen consumption and has been shown to be very sensitive to acute changes in cerebral oxygenation [38]. Alterations in cerebral oxygenation and metabolism are pathognomonic of HIE, supporting the theoretical benefit of NIRS as a potential bedside biomarker. CBF has been shown to increase in the first 24 h following HI injury [19, 20]. In the pre-TH era, a low resistance index as measured by Doppler ultrasound was a good predictor of outcome in infants with HIE indicating impaired cerebral vasodilation and blood flow. This is no longer the case in the advent of TH [39]. However, in infants receiving TH, Wintermark et al. [21] found decreased CBF on day of life 1 in infants who later demonstrated hypoxic ischaemic injury on MRI. Therefore, early cerebral NIRS measurements of cerebral oxygenation, metabolism, and blood flow may contain important information that could aid in the prediction of outcome.

It is also necessary to address any potential confounding influencers on cSO_2 . cSO_2 values comprised arterial, venous, and capillary saturations with a largely venous component (75%). For this reason, care is needed in its interpretation as it portrays the fine balance between oxygen delivery and consumption and can thus be influenced by many variables including blood pressure, cardiac output, ventilator status, and concomitant medication. Nonetheless, trends in NIRS values can give important clues as to the haemodynamic status of the individual organs being monitored [40–42]. Sedation was

described in 4 of the studies in which all infants received sedation as routine [27–30]. Three studies described the use of inotropes but found no difference in the use of inotropes between infants with a favourable or unfavourable outcome [22, 25, 26]. The impact of TH on NIRS is unclear. TH is thought to reduce metabolism and thus may decrease oxygen extraction. However, TH is also known to cause bradycardia which may influence cardiac output and thus oxygen delivery. Only Lemmers et al. [22] and Nakamura et al. [29] provided cSO_2 values during both hypothermia and normothermia; however, they did not address the impact of TH on cerebral oxygenation.

Previous studies have shown that cSO_2 levels beyond 24 h of life correlate with MRI findings and long-term neurodevelopmental outcome [22, 23]. Persistently higher cSO_2 values are seen in infants with subsequent MRI injury and poor neurological outcomes [23, 43]. We set out to determine if early cerebral NIRS monitoring before 6 h of life could predict both short- and long-term outcomes and thereby aid in the identification of infants who would benefit most from TH. Although 2 studies demonstrated higher cSO_2 and CBF values before 6 h in infants with adverse outcomes, in the majority, this difference was not significant until beyond 24 h of life [25–30].

Cerebral NIRS may be used in combination with blood pressure to assess autoregulation in infants with HIE [44]. Studies have used NIRS to determine the optimal mean arterial blood pressure at which autoregulation is maintained. Studies to date have found that infants who spent longer outside this optimal pressure range had a greater risk of adverse outcome [45]. This approach did not form part of our review, but information pertaining to early cerebral autoregulation could be beneficial in enabling early identification of infants at risk.

NIRS can also be used in combination with other modalities such as EEG or aEEG. As discussed, aEEG in the first 6 h of life was the most useful tool in predicting outcome in the pre-TH era. Although its predictive ability is now best seen at 48 h following the introduction of TH [12], the combination of NIRS and aEEG in the first 6 h of life may be useful in predicting outcome and thus the need for TH. Lemmers et al. [22] found that when aEEG and cSO_2 scores were combined, both positive and negative predictive values improved to 70–91% and 90–100%, respectively. Goeral et al. [26] found that a combination of both cSO_2 and aEEG predicted MRI outcome as early as 18 h.

Cerebral NIRS is both a feasible and acceptable monitoring tool in the neonatal unit. However, whether it re-

sults in a meaningful benefit to the neonatal HIE population remains to be seen. Based on limited available data, methodological heterogeneity in design, execution and available findings, early cerebral NIRS has not been evaluated for prediction of grades of HIE and is not associated with prediction of MRI evidence of brain injury or neurodevelopmental outcome.

The included studies in this review focused primarily on continuous wave NIRS to measure cerebral oxygenation. Other available methods include broadband NIRS or diffuse correlation spectroscopy which measure changes in cytochrome c oxidase and the cerebral metabolic rate of oxygen. These devices however are not commercially available and are therefore predominantly used in a research setting [46].

Whilst research to date has primarily focused on the value of NIRS monitoring as a trend monitor, signal processing techniques have shown that the NIRS signal itself may be rich in information [41]. Perhaps it is not the absolute values, rather the variation in values over time or quantitative analysis of the signal itself that is useful in outcome prediction. Quantitative analysis has the potential of providing an objective, continuous, and scalable analysis of the NIRS signal, but further research in this area is required. Future research should also focus on obtaining early measurements and including all grades of HIE. Combining NIRS with other monitoring modalities such as EEG and BP may enhance its predictive ability; however, it is also important that saturation values are measured using the same device, sensors, and methods.

This review is limited by the fact that it only includes articles written in English and was filtered to include human studies only as we wished to assess the usefulness of NIRS in clinical practice. As discussed, a small number of studies with varying methodologies were identified, so a meta-analysis was not feasible; however, this review was systematic and transparent. All full-text articles were independently reviewed, and we have clearly outlined reasons for inclusion and exclusion of studies in a PRISMA flowchart.

In conclusion, cerebral NIRS has the potential to be an important monitoring tool in infants with HIE. It can be used early after birth as it is quick and easy to apply and can provide continuous, non-invasive measurements. Unlike other monitoring modalities such as EEG, NIRS interpretation requires little training, and values are available instantaneously with a high sampling frequency. However, there are many questions to be answered before NIRS can be incorporated as an objective tool for identifying at-risk infants. Only 161 infants in total were in-

cluded in the studies reviewed, and individually the studies had insufficient numbers to address their primary objectives. Only 4 infants with mild HIE were included in the studies, and therefore we are unable to determine whether there is a benefit to NIRS monitoring in this group. Furthermore, differing methodologies and conflicting results make it very difficult to draw any firm conclusions. There may be a trend towards higher cSO₂ values at 6 h of life in infants with HIE who subsequently have adverse outcomes, but larger studies using a standardized approach and including all grades of encephalopathy are required. Furthermore, more precise measures of oxygen metabolism are likely required to identify the impairment in cerebral metabolism which occurs in the early stages of HIE prior to its incorporation into the neonatal unit as a predictive or decision-making tool.

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Statement of Ethics

The study is exempt from ethics committee approval as it involved a systematic review of the current published literature.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.G. and A.P. conducted the literature search. All studies were screened by title and abstract by A.G. Remaining studies were screened for inclusion/exclusion criteria by A.G. and E.D. A.G. drafted the manuscript, and all authors contributed to reviewing and editing the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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