

Article

Blood sLOX-1 Is Beneficial for Determining Severity of Neonatal Hypoxic–Ischemic Encephalopathy: A Nationwide Prospective Cohort Study

Takuya Oshima ^{1,2}, Yoshinori Aoki ^{1,2,†} , Tomohisa Akamatsu ^{3,‡}, Yutaka Matsuyama ⁴, Naoto Takahashi ² , Toshimasa Obonai ⁵, Masaki Shimizu ⁶, Kaoru Okazaki ⁷ , Jun Shibasaki ⁸, Osuke Iwata ⁹ , Takafumi Sakakibara ¹⁰ , Reiko Kushima ¹¹ , Kenichi Masumoto ¹², Masahiro Kinoshita ¹³ , Daigo Kajikawa ¹⁴ , Yumi Kono ¹⁵ , Yasuki Maeno ¹⁶, Ken Nagaya ¹⁷ , Kentaro Shirai ¹⁸, Atsushi Naito ¹⁹, Akira Oka ^{2,20} and Masayuki Itoh ^{1,*} 

- ¹ Department of Biochemistry and Cellular Biology (Mental Retardation and Birth Defect Research), National Center of Neurology and Psychiatry, Tokyo 187-8502, Japan
 - ² Department of Pediatrics, Faculty of Medicine, The University of Tokyo, Tokyo 113-8655, Japan
 - ³ Department of Pediatrics, National Center for Global Health and Medicine, Tokyo 162-8655, Japan
 - ⁴ Department of Biostatistics, School of Public Health, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan
 - ⁵ Department of Pediatrics, Tokyo Metropolitan Tama-Hokubu Medical Center, Tokyo 189-8511, Japan
 - ⁶ Department of Neonatology, Saitama Prefectural Children's Medical Center, Saitama 330-8777, Japan
 - ⁷ Department of Neonatology, Tokyo Metropolitan Children's Medical Center, Tokyo 130-8575, Japan
 - ⁸ Department of Neonatology, Kanagawa Children's Medical Center, Kanagawa 232-8555, Japan
 - ⁹ Department of Pediatrics and Neonatology, Nagoya City University, Nagoya 467-8601, Japan
 - ¹⁰ Department of Pediatrics, Nara Medical University, Kashihara 634-8521, Japan
 - ¹¹ Department of Neonatology, Tokyo Metropolitan Bokutoh Hospital, Tokyo 130-8575, Japan
 - ¹² Department of Neonatology, Faculty of Medicine, Toho University, Tokyo 143-8540, Japan
 - ¹³ Department of Pediatrics and Child Health, Kurume University School of Medicine, Fukuoka 830-0011, Japan
 - ¹⁴ Department of Neonatology, Ibaraki Children's Hospital, Ibaraki 311-4145, Japan
 - ¹⁵ Department of Pediatrics, Jichi Medical University, Shimotsuke 329-0498, Japan
 - ¹⁶ Division of Neonatology, St. Mary's Hospital, Kurume 830-8543, Japan
 - ¹⁷ Department of Pediatrics, Asahikawa Medical University, Asahikawa 078-8510, Japan
 - ¹⁸ Department of Pediatrics, Tsuchiura Kyodo General Hospital, Tsuchiura 300-0028, Japan
 - ¹⁹ Department of Neonatology, Yamanashi Prefectural Central Hospital, Yamanashi 400-8506, Japan
 - ²⁰ Saitama Prefectural Children's Medical Center, Saitama 330-8777, Japan
- * Correspondence: itoh@ncnp.go.jp; Tel.: +81-423412711
- † Current addresses: Department of Pediatrics, University of Miyazaki, Miyazaki 889-1692, Japan.
- ‡ Current addresses: Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Saitama 350-8550, Japan.

Abstract

Background/Objectives: Neonatal hypoxic–ischemic encephalopathy (HIE) is a major cause of neurodevelopmental diseases. In a previous retrospective study, we revealed that the levels of the soluble form of lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) are linked to HIE severity. We conducted a prospective investigation to evaluate the association between sLOX-1 levels and HIE severity using the Sarnat staging system, as well as a multicenter study to assess neurodevelopmental sequelae in the short term. **Methods:** A total of 193 infants were enrolled in the study between April 2018 and March 2021. We divided the infants into groups as follows: infants without HIE were assigned to a normal control group, and those with HIE to mild, moderate, and severe HIE groups. We measured 191 samples, excluding three participants. The distribution of 191 participants was as follows: 88 normal samples of 50 umbilical cord (UC) arteries and 38 venous blood samples (control; CTL), as well as 103 HIE samples of 34 mild, 55 moderate, and 14 severe HIE samples. All the plasma samples were collected until 6 h after birth. **Results:** The mean



Academic Editor: Jiangning Yang

Received: 18 May 2026

Revised: 24 June 2026

Accepted: 9 July 2026

Published: 14 July 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

sLOX-1 value in the CTL group was 613 pg/mL (IQR: 474–925 pg/mL) and that in the UC group was 497 pg/mL (IQR: 337–693 pg/mL), with no significant difference ($p = 0.136$). The mean sLOX-1 value in the mild HIE group was 1030 pg/mL (IQR: 658–1547 pg/mL), 1026 pg/mL (IQR: 710–2051 pg/mL) in the moderate HIE group, and 1444 pg/mL (IQR: 766–3927 pg/mL) in the severe HIE group. There were significant differences between the CTL and HIE groups ($p = 0.006$) and between the CTL and mild HIE groups ($p < 0.05$), but not between the mild HIE and the moderate and severe HIE groups ($p = 0.088$). The other blood markers exhibited no correlation with Sarnat severity. Interestingly, blood sLOX-1 levels increased with Sarnat severity. **Conclusions:** The results of this study indicated that sLOX-1 level was correlated with Sarnat severity. Moreover, early assessment of sLOX-1 level may be useful for deciding whether to induce therapeutic hypothermia and/or other treatments, and sLOX-1 may serve as a short-term outcome biomarker of HIE.

Keywords: neonatal hypoxic–ischemic encephalopathy (HIE); severity; biomarker; soluble form of lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1)

1. Introduction

Neonatal hypoxic–ischemic encephalopathy (HIE), which occurs in approximately 1.5 to 2.96 cases per 1000 births each year in developed countries [1–3], is a perinatal brain injury that is often associated with death or severe neurodevelopmental impairments in survivors. This pathology leads to major brain damage via acute respiratory and circulatory failure, which occurs following asphyxia in the fetal and/or neonatal period. Although mild and transient brain hypoxia and ischemia are often reversible, severe and prolonged damage can be irreversible and lead to serious brain damage that can progress to cerebral palsy, epilepsy, and various psychomotor developmental problems [1].

Therapeutic hypothermia is currently the only effective treatment option for this condition; however, it only partially improves the mortality rate and neurodevelopmental impairments among infants with moderate and severe HIE. In addition, therapeutic hypothermia needs to be initiated within 6 h after birth. An early decision regarding the severity of the condition is usually made on the basis of the widely used Sarnat classification or its modification [4]. However, neurological assessment using these scales requires specialized knowledge, training, and skills, thereby limiting the pool of examiners to skilled neonatologists and neurologists. On the other hand, studies have indicated that the neuron-specific enolase, S100B, tau, ubiquitin carboxy-terminal hydrolase L1 protein, and brain-derived neurotrophic factor could serve as biomarkers for diagnosing and determining the severity of HIE [5,6]. However, these biomarkers are not sufficient for clinical use in acute-phase assessment and in determining short- or long-term outcomes.

We previously described the soluble form of lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) as a potential biomarker [7]. LOX-1 is a scavenger receptor of oxidized low-density lipoprotein (oxLDL) whose expression is induced by oxidant species, inflammatory cytokines, and ischemia–reperfusion in thrombocytes, endothelial cells, neurons, and macrophages [8,9]. Furthermore, sLOX-1 is expressed in the blood and has been used as a predictive factor for acute coronary syndrome, stroke and preeclampsia [10–15]. In an HIE model, we revealed that the expression of LOX-1 was increased in microglial cells and the LOX-1-neutralizing antibody was effective for acute-phase treatment [16,17]. Here, we validated whether blood sLOX-1 levels are supportive for assessing HIE severity.

2. Materials and Methods

This multicenter prospective observational study, conducted to evaluate the association between sLOX-1 and HIE severity, was approved by the Ethics Committees of the National Center of Neurology and Psychiatry (A2017-113) and the 23 consortium institutions and hospitals. We obtained consent for participation from the parents of all enrolled infants. A total of 193 infants were enrolled in the study between April 2018 and March 2021. The study design was developed as a large prospective cohort study, with the methodology based on that of a previous study [7]. Specifically, the inclusion criteria for the HIE and control groups included a gestational age ≥ 36 weeks and a birth weight ≥ 1800 g. The inclusion criteria for infants with HIE were based on those used for the randomized controlled trial on therapeutic hypothermia in HIE infants conducted by the National Institute of Child Health and Human Development (NICHD); they included a pH ≤ 7.0 or a base deficit ≥ 16 mmol/L in any blood sample obtained within 60 min after birth, as well as a 10 min APGAR score ≤ 5 or resuscitation with assisted ventilation for ≥ 10 min after birth. Infants meeting these criteria were classified as having HIE. Infants in the control group were those who met the inclusion criteria but did not have HIE. The exclusion criteria included chromosomal abnormalities, congenital infections, congenital heart disease, major malformations, and incomplete clinical information.

We classified the infants with HIE into mild, moderate, and severe HIE groups according to the modified Sarnat staging system. We examined neurologic conditions in the following 6 categories: consciousness, spontaneous activity, posture, tone, primitive reflexes (such as sucking and the Moro reflex), and the autonomic nervous system (including pupillary reactions and heart rate). Infants with abnormalities in 3 or more categories were classified as having moderate or severe HIE, and infants with abnormalities in 2 or fewer categories were classified as having mild HIE. Moderate and severe HIE were distinguished by the number of moderate or severe HIE signs, and if the number of signs was equal, the distinction was made on the basis of the infant's level of consciousness. Therapeutic hypothermia was performed for infants with moderate and severe HIE without severe complications, such as disseminated intravascular coagulation or severe pulmonary hypertension. Neurosensory impairments were defined as feeding disorders (necessitating tube feeding at discharge), hearing disorders, seizures, and severe hypotonia. Intact survival was defined as the absence of these abnormalities at discharge. We performed automated auditory brainstem response (ABR) testing (NatusALGO 3i; Atom Medical, Tokyo, Japan) at 35 dB nHL in all infants at discharge. Infants exhibiting poor responses underwent diagnostic ABR testing (Neuropack S1 MEB 9402; Nihon Kohden, Tokyo, Japan). An infant demonstrating prolonged latencies or indistinct waves at 80 dB SPL on ABR examination was classified as having a hearing disorder.

Plasma samples were obtained at regular intervals until 6 h after birth as available. Blood samples of 0.5 mL were collected from a vein or an artery of neonates in the Neonatal Intensive Care Unit (NICU) and from an umbilical artery of infants in the obstetrics clinic; each sample was collected in an EDTA-2K (ethylenediaminetetraacetic acid dipotassium salt dihydrate) tube and immediately centrifuged for 15 min at 3000 rpm at 4 °C. The supernatant was preserved as a plasma sample at -80 °C until measurements were performed. The sLOX-1 levels were measured via a sandwich enzyme-linked immunosorbent assay (ELISA) using 2 types of monoclonal antibodies against the extracellular domain of LOX-1.

In addition, we collected maternal and neonatal clinical and biological data at birth and discharge, including neurological symptoms of paralysis, abnormal muscle tone, seizure, and death.

Statistical analyses were performed using SPSS Statistics version 24.0 (IBM, Armonk, New York, NY, USA) and SAS version 9.4 (Statistical Analysis System, SAS Institute, Singapore). Statistical analyses were performed on maternal clinical characteristics, clinical information of participants at the time of admission, and items related to participants' admission and short-term outcomes (Tables 1–3, respectively). Categorical variables were compared using the Mantel-trend test, chi-square test, and Fisher test, and continuous variables were compared through analysis of variance (contrasts). Statistical analyses of sLOX-1 values were conducted using log-transformed data to reduce the influence of outliers (Table 4). We performed a multiple regression analysis to examine the differences between groups, and expressed the intergroup differences in interest as contrast coefficients, which were then tested.

Adjusted covariates were pH, base deficit, Apgar score 5 min, placental abruption, where missing covariate values were imputed by the mean for each group (Table 4). The correlations of blood sLOX-1 with the severity groups were examined using Spearman's rank correlation coefficient and a Wilcoxon rank sum test (Table 5). The distribution of sLOX-1 is shown as a boxplot in Figures S1–S3. Statistical analysis was performed using a t-test and a Mann–Whitney test, with significant differences indicated by $p < 0.05$.

Table 1. Maternal clinical features.

	HIE (Sarnat Staging)					Statistical Differences (Between Each Group) (<i>p</i> -Value)				
	Umbilical Cord (UC)	Control (CTL)	Mild	Moderate	Severe	All *	UC vs. CTL **	UC vs. HIE **	CTL vs. HIE **	Mild vs. Moderate + Severe **
age (years, (mean $\pm$ SD))	34.3 $\pm$ 4.4	33.0 $\pm$ 3.9	34.4 $\pm$ 3.8	33.2 $\pm$ 5.1	34.0 $\pm$ 3.0	0.498	0.165	0.587	0.314	0.458
gravida (median (IQR))	2 (1–2)	2 (1–3)	2 (1–3)	1 (1–2.25)	1 (1–2)	0.228	0.469	0.410	0.089	0.097
parity (median (IQR))	1 (0–2)	0 (0–1)	0.5 (0–1)	0 (0–1)	0 (0–1)	0.553	0.359	0.133	0.667	0.330
non-reassuring fetal status (N (%))	11 (23.4)	12 (31.6)	24 (72.7)	46 (88.5)	13 (92.6)	<0.001	0.399	<0.001	<0.001	0.034
emergency cesarean delivery (N (%))	11 (22)	10 (26.3)	13 (39.4)	37 (67.3)	8 (61.5)	<0.001	0.688	<0.001	0.001	0.011
Complication of pregnancy (N (%))										
total	5 (10.6)	6 (15.8)	11 (32.4)	17 (31.5)	4 (28.6)	0.172	0.351	0.006	0.065	0.880
hypertension	2 (4.3)	5 (13.2)	4 (11.8)	7 (12.7)	1 (7.1)	0.707	0.139	0.124	0.505	0.607
diabetes	3 (6.4)	2 (5.3)	1 (2.9)	2 (3.6)	2 (14.3)	0.485	0.601	0.484	0.608	0.464
placental abruption	0 (0)	0 (0)	10 (29.4)	10 (18.2)	2 (14.3)	0.099	-	0.001	0.002	0.162
pre-eclampsia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	-	-	-	-
Intrapartum complications (N (%))										
total	12 (25.5)	15 (40.5)	24 (72.7)	47 (88.7)	13 (92.9)	<0.001	0.144	<0.001	<0.001	0.031
non-reassuring fetal status	11 (23.4)	12 (31.6)	24 (72.7)	46 (88.5)	13 (92.9)	<0.001	0.399	<0.001	<0.001	0.034
cord prolapse	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)	0.085	-	0.662	0.731	0.673
coiling of cord	2 (4.0)	6 (16.7)	3 (9.4)	5 (9.4)	1 (7.7)	0.285	0.053	0.214	0.180	0.614
maternal fever	0 (0)	1 (2.8)	0 (0)	4 (7.5)	1 (7.7)	0.189	0.419	0.123	0.487	0.132
others	0 (0)	0 (0)	0 (0)	3 (5.7)	2 (15.4)	0.012	-	0.123	0.203	0.132

Abbreviations: HIE, hypoxic–ischemic encephalopathy; IQR, interquartile range; UC, umbilical cord; CTL, control; N, number. *, Analysis of Variance, **, *t*-test for continuous variables, Chi-square test or Fisher’s exact test for categorical variables. Bold, statistic significance.

Table 2. Clinical summary of participants at admission.

	HIE (Sarnat Staging)					Statistical Differences (Between Each Group) (<i>p</i> -Value)				
	Umbilical Cord (UC)	Control (CTL)	Mild	Moderate	Severe	All *	UC vs. CTL **	UC vs. HIE **	CTL vs. HIE **	Mild vs. Moderate + Severe **
N	50	38	34	55	14					
sex, male–female	21:29	26:12	21:13	27:28	3:11					
birth weight (g, mean ± SD)	3089 ± 375	2922 ± 465	2833 ± 439	2946 ± 483	2958 ± 447	0.131	0.085	0.032	0.917	0.246
gestational age (weeks, median (IQR))	39.2 (38.4–40.4)	39.0 (37.3–40.0)	39.2 (38.5–40.2)	39.4 (38.2–40.4)	38.5 (37.5–40.4)	0.076	-	0.295	0.044	0.897
APGAR score, 1 min; 5 ≤ (N (%))	0 (0)	9 (23.7)	27 (79.4)	54 (98.2)	14 (100)	<0.001	-	<0.001	<0.001	0.012
APGAR score, 5 min; 5 ≤ (N (%))	0 (0)	1 (2.6)	16 (47.1)	46 (83.6)	11 (78.6)	<0.001	-	<0.001	<0.001	<0.001
APGAR score, 10 min; 5 ≤ (N (%))	0 (0)	0 (0)	5 (14.7)	18 (37.2)	9 (64.3)	<0.001	-	<0.001	<0.001	0.111
intubation in delivery room (N (%))	0 (0)	0 (0)	10 (29.4)	31 (56.7)	10 (71.4)	<0.001	-	<0.001	<0.001	0.004
resuscitation at 10 min (N (%))	0 (0)	2 (5.4)	24 (79.4)	48 (87.3)	12 (85.7)	<0.001	-	<0.001	<0.001	0.031
blood gas value in first 60 min (pH, median (IQR))	7.34 (7.31–7.37)	7.24 (7.17–7.30)	7.18 (7.08–7.37)	7.06 (6.93–7.20)	6.87 (6.77–7.00)	<0.001	-	<0.001	<0.001	<0.001
blood gas value in first 60 min (base deficit, median (IQR))	1.3 (0.1–3.1)	5 (3.1–7.0)	10 (5.5–13.5)	14.9 (11.9–19.8)	24.8 (16.1–27.7)	<0.001	-	<0.001	<0.001	<0.001
main blood examination at admission										
RBCs (median (IQR)), ×1000	not examined	4375 (4162.5– 5337.5)	4835 (4467.5– 5132.5)	4555 (4097.5–4910)	4665 (4212.5–4750)	0.112	-	-	0.609	0.054
WBCs (median (IQR))	not examined	20,505 (18,788– 21,735)	19,285 (15,125– 24,050)	19,700 (16,000– 25,775)	20,300 (16,800– 22,805)	0.926	-	-	0.755	0.562
PLTs (median (IQR)), ×1000	not examined	270 (229.5–297)	286 (222–307.25)	226 (189.5–276)	213.5 (135.75– 290.75)	0.098	-	-	0.501	0.022
CK (median (IQR))	not examined	582 (406–624)	1284 (704–1936)	1141 (581–1758)	1276 (504–3294)	0.029	-	-	0.191	0.029
LDH (median (IQR))	not examined	545 (520–578)	623 (526–779)	700 (608–1170)	823 (686–1162)	0.054	-	-	0.159	0.037
CRP (median (IQR))	not examined	0.04 (0.01–0.09)	0.02 (0.01–0.07)	0.03 (0.01–0.10)	0.04 (0.02–0.30)	0.793	-	-	0.445	0.834
sLOX-1 (pg/mL, (median (IQR))	497 (337–693)	613 (474–925)	1030 (658–1547)	1026 (710–2051)	1444 (766–3927)	<0.001	0.054	<0.001	<0.001	0.075

Abbreviations: HIE, hypoxic–ischemic encephalopathy; IQR, interquartile range; RBCs, red blood cells; WBCs, white blood cells; PLTs, platelets; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein; sLOX-1, soluble form of lectin-like oxidized LDL receptor-1. *, Analysis of Variance, **, *t*-test for continuous variables, Chi-square test or Fisher's exact test for categorical variables. Bold, statistic significance.

Table 3. In-hospital and short-term outcomes (at approximately 1 month of age).

	HIE (Sarnat Staging)					Statistical Differences (Between Each Group) (<i>p</i> -Value)				
	Umbilical Cord (UC)	Control (CTL)	Mild	Moderate	Severe	All *	UC vs. CTL **	UC vs. HIE **	CTL vs. HIE **	Mild vs. Moderate + Severe **
death or neurosensory impairments (N (%))	0 (0)	0 (0)	1 (3.4)	5 (10.0)	10 (76.9)	<0.001	-	0.073	0.279	0.017
hypothermia (N (%))	0 (0)	0 (0)	11 (32.4)	55 (100)	13 (92.9)	<0.001	-	<0.001	<0.001	<0.001
oxygen inhalation (N (%))	1 (8.3)	32 (84.2)	27 (84.4)	53 (98.1)	13 (100)	0.008	-	<0.001	0.076	0.013
mechanical ventilation (N (%))	0 (0)	3 (7.9)	19 (55.9)	54 (98.2)	14 (100)	<0.001	-	<0.001	<0.001	<0.001
death (N (%))	0 (0)	0 (0)	0 (0)	0 (0)	5 (35.7)	<0.001	-	0.132	0.200	0.125
complications (N (%))										
total	0 (0)	0 (0)	3 (9.1)	15 (28.3)	8 (61.5)	<0.001	-	0.033	<0.001	0.006
persistent pulmonary hypertension	0 (0)	0 (0)	3 (9.1)	5 (9.49)	1 (7.7)	0.143	-	0.343	0.055	0.632
disseminated intravascular coagulation	0 (0)	0 (0)	1 (3.0)	7 (13.2)	5 (38.5)	<0.001	-	0.206	0.012	0.030
sepsis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	-	-	-	-
multiorgan failure	0 (0)	0 (0)	0 (0)	0 (0)	3 (23.1)	0.002	-	0.707	0.374	0.292
neurosensory impairments (N (%))										
total	0 (0)	0 (0)	1 (3.4)	5 (10.0)	8 (72.7)	<0.001	-	0.099	0.323	0.024
feeding problems	0 (0)	0 (0)	1 (2.9)	3 (5.6)	6 (46.2)	<0.001	-	0.236	0.036	0.089
seizure requiring anticonvulsants	0 (0)	0 (0)	0 (0)	2 (3.7)	2 (18.2)	0.010	-	0.561	0.265	0.187
hearing problems	0 (0)	0 (0)	0 (0)	0 (0)	5 (55.6)	<0.001	-	-	0.676	0.128
hypotonia	0 (0)	0 (0)	0 (0)	0 (0)	1 (10.0)	0.069	-	0.866	0.719	0.660
length of hospitalization (days, median (IQR))	6 (6–8)	8 (6–12)	18 (13–21)	24.5 (17.3–33.8)	39 (25.3–75.3)	<0.001	0.582	<0.001	<0.001	<0.001
length of oxygen inhalation (days, median (IQR))	0 (0–0)	2 (1–4)	4 (1–7.3)	6 (5–9)	13.5 (9.5–23)	<0.001	0.610	0.008	0.001	<0.001
length of mechanical ventilation (days, median (IQR))	0 (0–0)	0 (0–0)	1 (0–4.8)	5 (5–6)	7.5 (5–17.8)	<0.001	0.953	0.019	<0.001	<0.001
full feeding (days, median (IQR))	4 (4–4)	4 (3–5)	6 (5–8)	8 (7–9)	11 (9–23)	<0.001	0.991	0.003	<0.001	<0.001

Abbreviations: HIE, hypoxic–ischemic encephalopathy; IQR, interquartile range. *, Analysis of Variance, **, *t*-test for continuous variables, Chi-square test or Analysis of Variance for categorical variables. Bold, statistic significance.

Table 4. Adjusted analyses of blood sLOX-1 values and HIE severity.

	Contrast Estimate (95% Confidence Interval)	Two-Sided <i>p</i> -Value
Global	-	<0.001
UC vs. CTL	0.29 (−0.09, 0.68)	0.136
UC vs. HIE (mild + moderate + severe) *	1.05 (0.42, 1.69)	0.001
CTL vs. HIE (mild + moderate + severe) *	0.76 (0.22, 1.30)	0.006
UC + HIE (mild) vs. HIE (moderate + severe) **	0.77 (0.28, 1.26)	0.002
CTL + HIE (mild) vs. HIE (moderate + severe) **	0.62 (0.17, 1.07)	0.007
HIE (mild) vs. HIE (moderate + severe) ***	0.36 (−0.05, 0.78)	0.088
Linear trend among UCB, HIE (mild), HIE (moderate), and HIE (severe) ****	4.39 (1.82, 6.95)	0.001
Linear trend among CTL, HIE (mild), HIE (moderate), and HIE (severe) ****	3.50 (1.18, 5.83)	0.003

Severity (normal (CTL), mild, moderate, and severe) is based on modified Sarnat classification. Adjusted variables: blood gas value (pH), blood gas value (base deficit), APGAR score (5 min), placental abruption. Abbreviations: HIE, hypoxic-ischemic encephalopathy; IQR, interquartile range; UC, control of umbilical cord artery; CTL, control. *: Contrast coefficients (Normal (CTL), Mild, Moderate, Severe) = (−1, 1/3, 1/3, 1/3). **: Contrast coefficients (Normal (CTL), Mild, Moderate, Severe) = (−0.5, −0.5, 0.5, 0.5). ***: Contrast coefficients (Normal (CTL), Mild, Moderate, Severe) = (0, −1, 0.5, 0.5). ****: Contrast coefficients (Normal (CTL), Mild, Moderate, Severe) = (−3, −1, 1, 3).

Table 5. Correlation of blood sLOX-1 values with severity groups.

Spearman's Rank Correlation Coefficient	Z Value or Correlation Coefficient (95% CI)	<i>p</i> -Value
test between UC and each group	0.43 (0.30, 0.55)	<0.001
UC vs. CTL *	2.39	0.017
UC vs. Mild *	4.41	<0.001
UC vs. Moderate *	4.72	<0.001
UC vs. Severe *	2.68	0.007
test between UC + CTL and each group	0.41 (0.27, 0.53)	<0.001
UC + CTL vs. Mild *	4.17	<0.001
UC + CTL vs. Moderate *	4.57	<0.001
UC + CTL vs. Severe *	2.58	0.01
test between CTL and each group	0.22 (0.04, 0.39)	0.019
CTL vs. Mild *	−2.22	0.026
CTL vs. Moderate *	−2.34	0.019
CTL vs. Severe *	1.9	0.057

Abbreviations: UC; umbilical cord, CTL; control. * Wilcoxon rank sum test. Severity (normal (CTL), mild, moderate, and severe) is based on modified Sarnat classification.

3. Results

Of 193 participants, one case each of congenital duodenal atresia and partial deletion of the long arm of chromosome 20, both of which were diagnosed after hospitalization, was excluded, and the remaining 191 cases were included in the study. We collected 191 samples, including 88 normal samples (50 from umbilical cord (UC) arteries and 38 venous blood samples from the patients' bodies (CTL)), and 103 HIE samples (34 mild, 55 moderate, and 14 severe according to Sarnat staging). All of HIE samples were arterial or venous blood. The healthy participants included 50 babies presenting with no problems at birth at an obstetrics clinic. The 38 CTL participants were patients admitted to the NICU without a diagnosis of HIE; 18 were diagnosed with transient tachypnea, five with pneumothorax, and three with respiratory failure. All blood samples were collected within 6 h after birth before any treatments. The participants with moderate and severe HIE underwent therapeutic hypothermia after blood sampling.

3.1. Maternal and Neonatal Clinical Features

Maternal and neonatal clinical features are presented in Tables 1 and 2. There were no significant differences in maternal conditions between the UC and CTL groups. Moreover, age, gravida, and parity exhibited no significant differences between groups, while placental abruption, non-reassuring fetal status (NRFS), and emergency cesarean delivery demonstrated significant differences between the UC and CTL groups and the HIE group. These results indicate that fetal heart rate abnormality may represent a risk factor for HIE due to placental dysfunction and could lead to emergency cesarean section.

The clinical features of all neonatal participants at delivery or upon admission to the neonatal care unit (NICU) are shown in Table 2. There were no differences in birth weight and gestational age between all groups. The majority of participants in the HIE groups were admitted to private obstetrics clinics without neonatal care and transported to medical facilities with NICUs. It is reasonable that the APGAR score, intubation and/or resuscitation procedures, blood gas pH, and base deficit of the UC and CTL groups are significantly higher than those of the HIE groups. The results of the APGAR scores and blood gas tests, as well as resuscitation for 10 min or more, which are also used as diagnostic criteria for HIE, showed significant differences between the HIE group and healthy newborns, with the differences being more pronounced the more severe the condition. The blood examination indicated that creatine kinase (CK) and sLOX-1 levels were significantly different between all groups, suggesting that these two biomarkers may help to diagnose HIE. Interestingly, sLOX-1 values correlated with HIE severity (Figure S1), and platelet counts, CK, and lactate dehydrogenase (LDH) levels exhibited significant differences between mild HIE and moderate and severe HIE.

Table 3 outlines the clinical condition of participants during neonatal care hospitalization and at discharge. In the HIE group, the patients underwent some kind of intervention or treatment, such as therapeutic hypothermia, oxygen inhalation, or mechanical ventilation. The results indicate that almost all neonates with moderate and severe HIE underwent therapeutic hypothermia and ventilation, and show a high rate of death in those with severe HIE. Neurosensory impairments and other complications were observed as sequela of moderate and severe HIE, with the severity and frequency of these symptoms, as well as the duration of hospitalization, oxygen inhalation, ventilation, and feeding, increasing with rising HIE severity.

3.2. Statistical Analyses of sLOX-1 Values and Sarnat Staging

The distribution of sLOX-1 is shown in Figure S1 and Table 2. The mean sLOX-1 value in the UC group was 497 pg/mL (interquartile range (IQR): 337–693 pg/mL), 613 pg/mL (IQR: 474–925 pg/mL) in the CTL group, 1030 pg/mL (IQR: 658–1547 pg/mL) in the mild HIE group, 1026 pg/mL (IQR: 710–2051 pg/mL) in the moderate HIE group, and 1444 pg/mL in the severe HIE group (IQR: 766–3927 pg/mL). We detected four outliers in the moderate and severe HIE groups, so we logarithmically transformed the sLOX-1 values for the statistical analyses (Tables 4 and 5).

There was no significant difference between the UC and CTL groups ($p = 0.136$, Figure S1 and Table 4). However, there were significant differences between the UC and HIE groups and between the CTL and HIE groups ($p = 0.006$, Figure S1, Tables 4 and 5). Figure S2 showed the advantage of sLOX-1 measurement alongside the Sarnat score to facilitate the decision to administer therapeutic hypothermia, with therapeutic hypothermia generally employed for babies with moderate and severe HIE. However, the Area Under the Curve (AUC) by the Receiver Operating Characteristic curve (ROC) was 0.628.

In addition, we also confirmed significant differences in groups of patients who were clinically intact at the time of discharge and those with neurological and/or other sequelae or death at discharge (Figure S3).

4. Discussion

The present study demonstrated that blood sLOX-1 values within 6 h after birth were correlated with Sarnat staging. Additionally, there was a significant difference in sLOX-1 levels between the CTL and HIE groups, indicating that it is a useful biomarker for the diagnosis of HIE. We found that sLOX-1 levels parallel the severity of HIE and might be useful for discriminating babies with moderate and severe HIE from healthy babies and for deciding whether hypothermia therapy should be administered. The high levels of sLOX-1 may indicate moderate or severe brain damage. We also found that sLOX-1 levels decline rapidly from 24 h after birth in both infants with HIE and healthy infants. This is consistent with our previous pilot study and a previous study on acute coronary syndrome [7,14].

As a novel biomarker, early blood sLOX-1 levels, alongside the clinical severity of HIE and neurologic symptoms within approximate one-month old, may be useful for severity staging and as a short-term prognostic biomarker of HIE. We speculated that blood sLOX-1 levels would be high in infants with HIE, given the high sLOX-1 levels previously observed in a rat model of HIE (unpublished data). In fact, sLOX-1 levels in the first 6 h after birth tended to increase in a stepwise manner with increasing HIE severity, in accordance with a previous report linking sLOX-1 levels to the number of lesions in acute coronary syndrome [14]. Moreover, sLOX-1 levels differed between infants with intact survival and those who died or exhibited neurosensory impairment from the result of Figure S3. However, we cannot effectively set the cutoff value because of the AUC of 0.7428. In the future, an increase in the number of patients with severe HIE is expected to enable the determination of a meaningful cutoff value.

Previous reports on the long-term prognosis of HIE (at 18 months of age) showed neurosensory impairment in 22% of the mild HIE group, and the frequency of death or neurosensory impairment was reported to be 44% to 55% in the moderate and severe HIE groups treated with hypothermia [18,19]. Applying these to the present study, it is estimated that of the included patients, approximately 38 to 45 cases of neurosensory impairment or death will occur. Of the cases who are intact at the time of discharge, approximately 20 may be diagnosed with neurosensory disorders as they grow older. The results of this study suggest that it is difficult to determine whether sLOX-1 levels at birth are intact at the time of discharge, but a correlation between sLOX-1 levels at birth and long-term prognosis may be observed based on the results of developmental tests at 18 months and 3 years of age after discharge. When applied to the patients without therapeutic hypothermia, blood sLOX-1 levels may better predict death or neurosensory impairment.

The placenta strongly expresses LOX-1, which may explain the physiologically increased sLOX-1 levels seen in control group infants at birth [15]. All groups included cases of maternal hypertension due to pregnancy, but the proportion was small, and no significant differences were observed between the groups in Table 1. Therefore, in this study, it was predicted that maternal hypertension during pregnancy would have little effect on the comparison of sLOX-1 in umbilical cord blood or infant blood between each group. In addition, the number of placental abruption did not change significantly in the UC and CTL groups, but increased significantly in the HIE groups. All blood samples were derived directly from newborns and not from potentially contaminated placental blood. Therefore, there is little possibility that fetal stress from maternal distress induced LOX-1. However, there were no significant differences between each HIE group. Thus, we can speculate that there was no need to consider placenta factors. On the other hand, microglia

markedly expressed LOX-1 in an HIE rat model and an in vitro HIE model [20]. The blood sLOX-1 value may reflect brain damage primarily from activated microglia as a result of hypoxic–ischemic insult.

Early severity staging of HIE is important for ensuring the initiation of therapeutic hypothermia within the first 6 h after birth [21–24]. MRI and amplitude-integrated electroencephalography (aEEG) may be useful as biomarkers of HIE. The NICHD MRI brain injury pattern of HIE is simple and closely correlated with the developmental outcome of HIE [17,19]. In our cohort, all infants with the most severe brain injury had a poor outcome. However, MRI may not be appropriate for severity staging in the acute phase of HIE. In a meta-analysis, it was reported that a persistently abnormal aEEG 48 h after birth or later was related to poor outcomes, but that aEEG 6 h after birth was not related to outcomes [24]. Our data suggest that sLOX-1 may be sensitive to these physiological biomarkers, given that levels were associated with both early severity of HIE and neurosensory impairments. HIE pathophysiology is thought to include ischemia, followed by reperfusion and induction of cytokines, the activation of which induces functional deficit and neuronal apoptosis [25–27]. LOX-1 can be induced by the same condition in early HIE. Microglia are related to neural inflammation in HIE, and their activation is induced by hypoxic–ischemic insult [18]. It may be speculated that LOX-1 is expressed in endothelial cells and microglia of the human brain during HIE. Thus, it is considered that hypoxic–ischemic insult induces LOX-1 up-regulation and activation in microglia. LOX-1 activation induces cytokines or other stress materials through self-positive feedback and enhances cytotoxic inflammation in neonatal brains.

We propose a potential HIE treatment using LOX-1 inhibitors and neutralizing antibodies. BI-0115, a selective small-molecule inhibitor of LOX-1, blocks cellular uptake of oxLDL [28], and rat ischemic stroke models were found to exhibit improved neurological function following combination therapy of rt-PA (recombinant tissue-type plasminogen activator) and BI-0115 and/or MMP-9 (matrix metalloproteinase 9) [29]. Another study using an HIE rat model showed pathological and biological improvement following antibody treatment [17]. Thus, we believe that early diagnosis of HIE and early treatment with LOX-1 inhibitor(s) or neutralizing antibodies could improve rates of intact survival.

The expression of LOX-1 has been found to be closely related to the pathology of brain injuries in rats and humans with HIE. The combination of these factors with sLOX-1 may serve as a powerful biomarker of HIE. As such, sLOX-1 levels may be useful for deciding whether to induce hypothermia and/or other treatments, as well as for evaluating the under- and overtreatment of patients, making prognoses, and planning medical care.

We did not find clearly stratified relationships between mild and moderate HIE or between moderate and severe HIE. Therefore, confirmation of sLOX-1 as a useful staging biomarker of HIE requires further studies with larger samples. In addition, further assessment of long-term outcomes in a study with multiple hospitals would support the usefulness of sLOX-1 as a diagnostic and prognostic biomarker of HIE. The results of this study suggest that early blood sLOX-1 measurement in combination with the Sarnat system could assist in determining HIE severity.

5. Limitations

In this study, we could only obtain a small number of patients with severe HIE, because its incidence is extremely rare in Japan. Therefore, the results might be insufficient to draw conclusions about severe HIE cases. In addition, while the timing of blood sampling was within 6 h after birth, it was difficult to determine the exact sampling times while performing procedures and administering treatment in the NICU. However, the results of this study would support HIE diagnosis and consideration of HIE severity.

The observation interval of this study was also limited to one to just a few months. The long-term neurological and developmental follow-up study is underway to confirm the diagnostic value of blood sLOX-1.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/medsci14030391/s1>: Figure S1: sLOX-1 distribution of participants within 6 h after birth; Figure S2: sLOX-1 levels for therapeutic hypothermia; Figure S3: Correlation of short-term outcomes and sLOX-1 values.

Author Contributions: T.O. (Takuya Oshima) summarized the clinical data, drafted the initial manuscript, and reviewed and revised the manuscript. Y.A. curated, analyzed, and visualized the data. Y.M. (Yutaka Matsuyama) performed statistical analyses. N.T., T.O. (Toshimasa Obonai), M.S., K.O., J.S., O.I., T.S., R.K., K.M., T.A., M.K., D.K., Y.K., Y.M. (Yasuki Maeno), K.N., K.S., A.N. and A.O. collected clinical data, carried out the initial analyses, and reviewed and revised the manuscript. M.I. designed the study, coordinated and supervised data collection, and critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by grants 18gk0110033h0001 and 22gn0110060h0001 from the Japan Agency for Medical Research and Development (AMED). No products or other forms of assistance were provided for this study.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the National Center of Neurology and Psychiatry (A2017-113 and 2 March 2018). Registry name: Clinical study for severity of neonatal hypoxic–ischemic encephalopathy; registration number: UMIN000038267; link to study on registry webpage: https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000043621 (accessed on 2 March 2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

Acknowledgments: We thank all participants and their families for taking part in this study. N. Okawa (Juntendo University Shizuoka Hospital, Shizuoka, Japan) and E. Tsuchida (Asahikawa-Kosei General Hospital, Hokkaido, Japan) also collected blood samples and clinical data. In addition, we thank the late Sachio Takashima for his contributions to perinatal medicine.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

sLOX-1	soluble form of lectin-like oxidized low-density lipoprotein receptor-1
HIE	neonatal hypoxic–ischemic encephalopathy
CTL	control
oxLDL	low-density lipoprotein
ABR	automated auditory brainstem response
UC	umbilical cord
NICU	Neonatal Intensive Care Unit
IQR	interquartile range
aEEG	amplitude-integrated electroencephalography

References

1. Douglas-Escobar, M.; Weiss, M.D. Hypoxic-ischemic encephalopathy: A review for the clinician. *JAMA Pediatr.* **2015**, *169*, 397–403. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Kurinczuk, J.J.; White-Koning, M.; Badawi, N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum. Dev.* **2010**, *86*, 329–338. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Shipley, L.; Gale, C.; Sharkey, D. Trends in the incidence and management of hypoxic-ischaemic encephalopathy in the therapeutic hypothermia era: A national population study. *Arch. Dis. Child. Fetal Neonatal.* **2021**, *106*, 529–534. [\[CrossRef\]](#)
4. Sarnat, H.B.; Sarnat, M.S. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch. Neurol.* **1976**, *33*, 696–705. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Massaro, A.N.; Chang, T.; Baumgart, S.; McCarter, R.; Nelson, K.B.; Glass, P. Biomarkers S100B and NSE predict outcome in hypothermia-treated encephalopathic newborns. *Pediatr. Crit. Care Med.* **2014**, *15*, 615–622. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Massaro, A.N.; Wu, Y.W.; Bammler, T.K.; Comstock, B.; Mathur, A.; McKinstry, R.C.; Chang, T.; Mayock, D.E.; Mulkey, S.B.; van Meurs, K.; et al. Plasma Biomarkers of Brain Injury in Neonatal Hypoxic-Ischemic Encephalopathy. *J. Pediatr.* **2018**, *194*, 67–75. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Akamatsu, T.; Sugiyama, T.; Aoki, Y.; Kawabata, K.; Shimizu, M.; Okazaki, K.; Kondo, M.; Takahashi, K.; Yokoyama, Y.; Takahashi, N.; et al. A Pilot Study of Soluble Form of LOX-1 as a Novel Biomarker for Neonatal Hypoxic-Ischemic Encephalopathy. *J. Pediatr.* **2019**, *206*, 49–55. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Taye, A.; El-Sheikh, A.A.K. Lectin-like oxidized low-density lipoprotein receptor 1 pathways. *Eur. J. Clin. Investig.* **2013**, *43*, 740–745. [\[CrossRef\]](#)
9. Pirillo, A.; Norata, G.D.; Catapano, A.L. LOX-1, oxLDL, and atherosclerosis. *Mediat. Inflamm.* **2013**, *2013*, 152786. [\[CrossRef\]](#)
10. Jin, P.; Cong, S. LOX-1 and atherosclerotic-related diseases. *Clin. Chim. Act.* **2019**, *491*, 24–29. [\[CrossRef\]](#)
11. Kita, T.; Kume, N.; Minami, M.; Hayashida, K.; Murayama, T.; Sano, H.; Moriwaki, H.; Kataoka, H.; Nishi, E.; Horiuchi, H.; et al. Role of Oxidized LDL in Atherosclerosis. *Ann. N. Y. Acad. Sci.* **2001**, *947*, 199–205. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Hofmann, A.; Brunssen, C.; Wolk, S.; Reeps, C.; Morawietz, H. Soluble LOX-1: A Novel Biomarker in Patients with Coronary Artery Disease, Stroke, and Acute Aortic Dissection? *J. Am. Heart Assoc.* **2020**, *9*, e013803. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Inoue, N.; Okamura, T.; Kokubo, Y.; Fujita, Y.; Sato, Y.; Nakanishi, M.; Yanagida, K.; Kakino, A.; Iwamoto, S.; Watanabe, M.; et al. LOX index, a novel predictive biochemical marker for coronary heart disease and stroke. *Clin. Chem.* **2010**, *56*, 550–558. [\[CrossRef\]](#)
14. Kume, N.; Mitsuoka, H.; Hayashida, K.; Tanaka, M.; Kominami, G.; Kita, T. Soluble lectin-like oxidized LDL receptor-1(sLOX-1) as a sensitive and specific biomarker for acute coronary syndrome—Comparison with other biomarkers. *J. Cardiol.* **2010**, *56*, 159–165. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Tuten, A.; Erman, H.; Korkmaz, G.G.; Oncul, M.; Gelisgen, R.; Sozer, V.; Acikgoz, S.; Simesek, G.; Uzun, H. Comparison of maternal and umbilical cord blood soluble lectin-like oxidized low-density lipoprotein receptor 1 levels in early-and late-onset preeclampsia. *Arch. Gynecol. Obstet.* **2014**, *290*, 1007–1013. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Akamatsu, T.; Dai, H.; Mizuguchi, M.; Goto, Y.; Oka, A.; Itoh, M. LOX-1 is a novel therapeutic target in neonatal hypoxic-ischemic encephalopathy. *Am. J. Pathol.* **2014**, *184*, 1843–1852. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Akamatsu, T.; Sugiyama, T.; Oshima, T.; Aoki, Y.; Mizukami, A.; Goishi, K.; Shichino, H.; Kato, N.; Takahashi, N.; Goto, Y.; et al. Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1-Related Microglial Activation in Neonatal Hypoxic-Ischemic Encephalopathy: Morphologic Consideration. *Am. J. Pathol.* **2021**, *191*, 1303–1313. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Chalak, L.F.; Nguyen, K.A.; Prempunpong, C.; Heyne, R.; Thayyil, S.; Shankaran, S.; Lupton, A.R.; Rollins, N.; Pappas, A.; Koclas, L.; et al. Prospective research in infants with mild encephalopathy identified in the first six hours of life: Neurodevelopmental outcomes at 18–22 months. *Pediatr. Res.* **2018**, *84*, 861–868. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Shipley, L.; Mistry, A.; Sharkey, D. Outcomes of neonatal hypoxic-ischaemic encephalopathy in centers with and without active therapeutic hypothermia: A nationwide propensity score-matched analysis. *Arch. Dis. Child. Fetal Neonatal* **2022**, *107*, 6–12. [\[CrossRef\]](#)
20. Aoki, Y.; Dai, H.; Furuta, F.; Akamatsu, T.; Oshima, T.; Takahashi, N.; Goto, Y.I.; Oka, A.; Itoh, M. LOX-1 mediates inflammatory activation of microglial cells through the p38-MAPK/NF-κB pathways under hypoxic-ischemic conditions. *Cell Commun. Signal.* **2023**, *21*, 126. [\[CrossRef\]](#) [\[PubMed\]](#)
21. Azzopardi, D.V.; Strohm, B.; Edwards, A.D.; Dyet, L.; Halliday, H.L.; Juszczak, E.; Kapellou, O.; Levene, M.; Marlow, N.; Porter, E.; et al. Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy. *N. Engl. J. Med.* **2009**, *361*, 1349–1358. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Zhou, W.H.; Cheng, G.Q.; Shao, X.M.; Liu, X.Z.; Shan, R.B.; Zhuang, D.Y.; Zhou, C.L.; Du, L.Z.; Cao, Y.; Yang, Q.; et al. Selective Head Cooling with Mild Systemic Hypothermia after Neonatal Hypoxic-Ischemic Encephalopathy: A Multicenter Randomized Controlled Trial in China. *J. Pediatr.* **2010**, *157*, 367–372. [\[CrossRef\]](#) [\[PubMed\]](#)
23. El-Dib, M.; Inder, T.E.; Chalak, L.F.; Massaro, A.N.; Thoresen, M.; Gunn, A. Should therapeutic hypothermia be offered to babies with mild neonatal encephalopathy in the first 6 h after birth? *Pediatr. Res.* **2019**, *85*, 442–448. [\[CrossRef\]](#) [\[PubMed\]](#)

24. Chandrasekaran, M.; Chaban, B.; Montaldo, P.; Thayyil, S. Predictive value of amplitude-integrated EEG (aEEG) after rescue hypothermic neuroprotection for hypoxic ischemic encephalopathy: A meta-analysis. *J. Perinatol.* **2017**, *37*, 684–689. [[CrossRef](#)] [[PubMed](#)]
25. Drury, P.P.; Bennet, L.; Gunn, A.J. Mechanisms of hypothermic neuroprotection. *Semin. Fetal Neonatal Med.* **2010**, *15*, 287–292. [[CrossRef](#)] [[PubMed](#)]
26. Ge, X.; Zhang, D.M.; Li, M.M.; Zhang, Y.; Zhu, X.Y.; Zhou, Y.; Peng, X.; Shen, A.G. Microglial LOX-1/MAPKs/NF- κ B positive loop promotes the vicious cycle of neuroinflammation and neural injury. *Int. Immunopharmacol.* **2019**, *70*, 187–200. [[CrossRef](#)] [[PubMed](#)]
27. Alkholi, U.M.; Abdalmonem, N.; Zaki, A.; Ali, Y.F.; Mohamed, S.A.; Abdelsalam, N.I.; Abu Hashim, M.I.; Abou Sekkien, M.; Elsherbiny, Y.M. Early predictors of brain damage in full-term newborns with hypoxic ischemic encephalopathy. *Neuropsychiatr. Dis. Treat.* **2017**, *13*, 2133–2139. [[CrossRef](#)] [[PubMed](#)]
28. Schnapp, G.; Neubauer, H.; Büttner, F.H.; Handschuh, S.; Lingard, I.; Heilker, R.; Klinder, K.; Prestle, J.; Walter, R.; Wolff, M.; et al. A small-molecule inhibitor of lectin-like oxidized LDL receptor-1 acts by stabilizing an inactive receptor tetramer state. *Commun. Chem.* **2020**, *3*, 75. [[CrossRef](#)] [[PubMed](#)]
29. Arkelius, K.; Wendt, T.S.; Andersson, H.; Arnou, A.; Gottschalk, M.; Gonzales, R.J.; Ansar, S. LOX-1 and MMP-9 Inhibition Attenuates the Detrimental Effects of Delayed rt-PA Therapy and Improves Outcomes After Acute Ischemic Stroke. *Circ. Res.* **2024**, *134*, 954–969. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.