ORIGINAL RESEARCH

Lymphocyte to C-Reactive Protein Ratio as an Early Biomarker to Distinguish Sepsis from Pneumonia in Neonates

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Background: Neonatal sepsis is an acute and severe disease that seriously threatens the life and health of newborns. Neonates with pneumonia may also have unrecognized neonatal sepsis. Early diagnosis of neonatal sepsis is beneficial for early treatment. This study aimed to evaluate the clinical significance of the lymphocyte-to-C-reactive protein ratio (LCR) as an early biomarker to distinguish sepsis from pneumonia.

Methods: This retrospective study enrolled 1635 neonates with pneumonia from February 2016 to March 2022. Among them, 182 cases were diagnosed with sepsis based on the positive blood culture results. Clinical and laboratory data were extracted from the electronic medical records. LCR was calculated as the ratio of the total lymphocyte count ($\times 10^9$ cells/L) to the C-reactive protein level (mg/L). Binary logistic regression analysis was conducted to evaluate the clinical significance of LCR as an early biomarker in distinguishing sepsis from pneumonia. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic value of LPCR in sepsis cases. All statistical analyses were conducted using Statistical Product and Service Solutions, version 24.0.

Results: The neonates with pneumonia combined with sepsis had a lower LCR than that of the neonates with pneumonia. Further analysis showed that the prevalence of neonatal pneumonia combined with sepsis was significantly higher in the low-LCR group than in the high-LCR group (20.7% vs 5.5%, P < 001). Binary logistic regression revealed that LCR was an independent risk factor for identifying pneumonia combined with sepsis. The ROC curve analysis revealed that LCR had better power than the lymphocyte count and CRP level individually in diagnosing neonatal pneumonia combined with sepsis (0.72 vs 0.65 vs 0.66, P < 0.001), with 62% sensitivity and 72% specificity.

Conclusion: LCR can be a potential early biomarker in distinguishing neonates with sepsis from those with pneumonia.

Keywords: lymphocyte to C-reactive protein ratio, neonates, pneumonia, sepsis

Introduction

Neonates are susceptible to pathogenic microorganisms and may develop into neonatal pneumonia or sepsis owing to their immature immune systems.[1] Neonatal sepsis is a severe threat to the life and health of newborns, affecting 2/1000 live births, with a high mortality rate ranging from 11% to 19%.[2] Furthermore, neonates with pneumonia may also have unrecognized neonatal sepsis. In some cases, neonates have both pneumonia and sepsis, and they are not treated according to the intervention guidelines for sepsis. Hence, these neonates cannot benefit from the early treatment of sepsis, as encouraged by the Surviving Sepsis Campaign Physician's management guidelines.[3] However, there are many difficulties and uncertainties in the early diagnosis of neonatal sepsis, such as non-specific clinical symptoms and lower rates of positive blood culture results. Therefore, exploring more convenient and accurate indicators for the early detection of neonatal sepsis is critical.

Neonatal sepsis is characterized by systemic inflammatory response syndrome,[4] indicating that inflammatory markers may be clinically relevant in identifying neonatal sepsis. Lymphocytes are the primary white blood cells that help the

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body fight infection and disease.[5,6] In sepsis, various cytokines can induce apoptosis of the lymphocytes.[7,8] Several studies have reported that lymphocytopenia is frequently observed in patients with sepsis, and persistent lymphocytopenia is associated with high mortality rates.[9–13] C-reactive protein (CRP) is a protein produced by the liver and increases significantly when there is inflammation in the body.[14] CRP is one of the most investigated and widely used laboratory parameters to evaluate the body's inflammation status.[15] Multiple studies have confirmed that CRP has high clinical significance in the early diagnosis of sepsis and is an important predictor and risk factor for poor outcomes in neonates with sepsis.[16,17] The lymphocyte-to-CRP ratio (LCR) is an index calculated as the ratio of the total lymphocyte count ($\times 10^9$ cells/L) to the CRP level (mg/L). Studies have reported that LCR decreases in patients with infectious diseases and is a helpful biomarker in the early screening and prediction of infectious diseases, such as coronavirus disease 2019 (COVID-19) and sepsis.[18–20] However, no studies have evaluated the clinical significance of LCR in distinguishing neonatal sepsis from neonatal pneumonia. Thus, we aimed to examine whether LCR can serve as an early biomarker in distinguishing sepsis from pneumonia in neonates.

Materials and Methods

Study Design and Population

This single-center retrospective observational study was conducted at Henan Children's Hospital Zhengzhou, China, between February 2016 and March 2022. The inclusion criteria for the study were aged ≤ 28 days and a diagnosis of pneumonia. The exclusion criteria were the presence of hematological system diseases, malignancies, or major congenital malformations and incomplete data during the admission, such as body temperature, CRP level, and lymphocyte count. The study followed the principles of the Declaration of Helsinki, and it was approved by the Hospital Ethics Review Board of Henan Children's Hospital. The data used in this study were retrospectively collected, and the datasets were entirely anonymized before analysis. Considering the retrospective nature of this investigation, the need for informed consent was waived by the Hospital Ethics Review Board.

Clinical Definition

The diagnosis of neonatal pneumonia is mainly based on the medical history, clinical symptoms, and laboratory test results. Medical history refers to the current presence of any high-risk factors or previous contact with infected patients. Clinical symptoms include abnormal body temperature, respiratory distress, snoring, and coughing. Laboratory findings refer to abnormal levels of inflammatory cells and markers, such as CRP and procalcitonin (PCT). Additionally, chest radiography usually shows new pulmonary infiltration. Neonatal sepsis is defined as systemic inflammatory response syndrome in the presence of a positive blood culture according to the published International Pediatric Sepsis Consensus.[21] The neonatal sequential organ failure assessment (nSOFA) score is used to assess the severity of neonatal sepsis.[22] Both neonatal pneumonia and sepsis were diagnosed by two independent doctors for these patients.

Data Collection

Clinical and laboratory data during hospital admission were extracted from the electronic medical records, including age, sex, weight, body temperature, respiratory rate, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), the length of hospital stay, PCT, CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin (ALB), creatinine (CREA) and urea nitrogen (UREA). The PCT levels were detected using Cobas® 8000 modular analyzer (Roche Diagnostics, Switzerland). The CRP levels were detected using a latex-enhanced immunoturbidimetric assay on an UPPER analyzer (Ultrasensitive CRP kit, Upper Bio-Tech, China). The ALT, AST, ALB, CREA, and UREA levels were recorded by the conventional clinical analytical approach using an automatic Beckman biochemical analyzer (Beckman Coulter, Brea, California, USA). The total white blood cells, neutrophils, lymphocytes, and platelets were recorded using an automated blood cell counter (Sysmex Corporation, Japan). In our data analysis, PCT levels>100 ng/mL or <0.02 ng/mL were defined as 101 ng/mL and 0.01 ng/mL, respectively, and CRP levels <0.8 mg/L were defined as 0.7 mg/L. The LCR was calculated as the total lymphocyte count ($\times 10^9$ cells/L)/CRP (mg/L).

Statistical Analysis

Normally distributed data are presented as means ± standard deviations. They were analyzed using independent *t*-tests or one-way analysis of variance. Non-normally distributed data are presented as medians and interquartile ranges. They were analyzed using the Mann–Whitney *U*-test. Categorical data are expressed as numbers and percentages. They were evaluated using chi-square tests. The association between the LCR and other continuous variables was assessed using Spearman correlation test. Binary logistic regression analysis was conducted to evaluate the clinical significance of LCR as an early biomarker in distinguishing sepsis from pneumonia. Receiver operating characteristic (ROC) curve was used to assess the diagnostic value of LCR in sepsis. Delong's test was used to compare the area under the ROC curves (AUC) among different variables. The optimal cut-off point was calculated using Youden's index (sensitivity + specificity − 1).[23] All statistical analyses were performed using IBM Statistical Product and Service Solutions version 24.0 (SPSS Inc., Chicago, Illinois, USA) and MedCalc version 15.2.2 (MedCalc Software, Belgium).

Results

Study Population Characteristics

This study enrolled 1635 neonates with pneumonia, of which 182 (11.1%) had sepsis and were allotted to pneumonia with sepsis group. The remaining 1453 (88.9%) neonates were included in the pneumonia group. The baseline characteristics of the two groups are presented in Table 1. Compared with the neonates in the pneumonia group, neonates

Table 1 Basic Characteristics of the Study Participants by Groups

Variables	Pneumonia (n = 1453)	Pneumonia with Sepsis (n = 182)	P
Age (days)	10.0 (5.0, 19.0)	11.0 (7.0, 16.0)	0.107
Male, n (%)	866 (59.6%)	108 (59.3%)	0.946
Weight (kg)	3.3 ± 0.6	3.0 ± 0.8	< 0.001
Temperature (°C)	36.9 ± 0.5	37.1 ± 0.9	0.026
Respiratory (rate/minute)	51.4 ±11.2	51.9 ± 12.0	0.565
Heart rate (bpm)	146.5 ± 16.2	150.8 ± 21.4	0.010
SBP (mm Hg)	76.1 ± 8.5	74.4 ± 10.8	0.049
DBP (mm Hg)	46.4 ± 8.1	44.3 ± 9.5	0.005
Biochemical parameters			
PCT (ng/mL)	0.12 (0.08, 0.26)	0.63 (0.15, 11.6)	< 0.001
CRP (mg/L)	0.7 (0.7, 0.7)	0.7 (0.7, 31.81)	< 0.001
ALT (U/L)	27.8 (21.6, 35.9)	26.0 (19.6, 38.2)	0.444
AST (U/L)	36.8 (29.1, 49.2)	37.2 (28.7, 55.1)	0.584
ALB (g/L)	33.01 ± 8.59	29.80 ± 5.87	< 0.001
CREA (mmol/L)	45.1 (34.3, 58.2)	48.7 (37.3, 77.4)	< 0.001
UREA (μmol/L)	2.7 (1.7, 3.8)	3.85 (2.7, 5.7)	< 0.001
WBC (10^6 cells/L)	10.0 (7.9, 12.5)	10.7 (7.6, 14.9)	0.080
Neutrophils (10^6 cells/L)	4.1 (2.9, 6.5)	6.0 (3.4, 9.2)	< 0.001
Lymphocytes (10^6 cells/L)	4.1 (3.0, 5.4)	3.0 (1.8, 4.5)	< 0.001

(*Continued*)

Table 1 (Continued).

Variables	Pneumonia (n = 1453)	Pneumonia with Sepsis (n = 182)	P
LCR	5.3 (3.0, 7.2)	1.9 (0.1, 5.2)	< 0.001
nSOFA	0 (0, 0)	1.0 (0, 3.0)	< 0.001
Length of hospital stay (days)	10.0 (8.0, 14.0)	17.0 (13.0, 25.0)	< 0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; CREA, creatinine; UREA, urea nitrogen; LCR, lymphocyte-to-C-reactive protein ratio; nSOFA, neonatal sequential organ failure assessment.

in pneumonia with sepsis group were older and had lower body weight, SBP, and DBP. Moreover, the body temperature, respiratory rate, and heart rate were higher, and the hospital stay was lengthier in pneumonia with sepsis group than in the pneumonia group. Laboratory tests showed that neonates in the pneumonia with sepsis group had higher PCT, CRP, CREA, and UREA levels, neutrophil count, and nSOFA scores, and lower ALB level, lymphocyte count, and LCR than those of the pneumonia group.

Association Between LCR and the Presence of Neonatal Sepsis

To further explore the association of the LCR with the presence of neonatal pneumonia combined with sepsis, the neonates were classified into the following three groups according to the LCR tertiles: low-LCR group (LCR <3.56), intermediate-LCR group (LCR, 3.56–6.29), and high-LCR group (LCR >6.29). The neonates in the low-LCR group were younger and had a higher proportion of males, higher PCT levels and nSOFA scores, and lengthier hospital stay when compared with the neonates in the other two groups (Table 2). Further analysis revealed that the prevalence of neonatal pneumonia combined with sepsis was significantly higher in the low-LCR group than in the high-LCR group (20.7% vs 5.5%, P < 0.001), while that of neonatal pneumonia was significantly lower in the low-LCR group than in the high-LCR group (79.3% vs 94.5%, P < 0.001).

Correlation Between LCR and Clinical Parameters

Spearman correlation analysis was performed to investigate the relationship between the LCR and various clinical parameters. LCR was positively correlated with age (r = 0.320, P < 0.001), body weight (r = 0.161, P < 0.001), SBP (r = 0.148, P < 0.001), DBP (r = 0.097, P < 0.001), ALT (r = 0.058, P = 0.020), and ALB (r = 0.367, P < 0.001) (Table 3). However, LCR was negatively correlated with the respiratory rate (r = –0.084, P = 0.001), PCT (r = –0.481, P < 0.001),

Table 2 Clinical and Demographic Characteristics According to the Lymphocyte-to-C-Reactive Protein Ratio Tertiles

Variables	Low LCR (< 3.56) (n = 542)	Intermediate LCR (3.56–6.29) (n = 549)	High LCR 3 (> 6.29) (n = 544)	P
Age (days)	6.0 (3.0, 13.0)	9.0 (4.0, 15.0)	13.0 (9.0, 21.0)	0.107
Male, n (%)	357 (65.9%)	316 (57.6%)	301 (55.3%)	0.001
PCT (mg/L)	0.34 (0.14, 2.35)	0.12 (0.08, 0.23)	0.10 (0.07, 0.14)	< 0.001
Clinical data				
Pneumonia, n (%)	430 (79.3%)	509 (92.7%)	514 (94.5%)	< 0.001
Pneumonia with sepsis, n (%)	112 (20.7%)	40 (7.3%)	30 (5.5%)	< 0.001
nSOFA	0 (0, 3.0)	0 (0, 0)	0 (0, 0)	< 0.001
Length of hospital stay (days)	13.0 (9.0, 19.0)	10.0 (8.0, 14.0)	9.0 (8.0, 12.0)	< 0.001

Abbreviations: LCR, lymphocyte-to-C-reactive protein ratio; PCT, procalcitonin; nSOFA, neonatal sequential organ failure assessment.

Table 3 Correlations Between LCR and Clinical Parameters

Variables	Overall Population	
	r	P
Age (day)	0.320	< 0.001
Body weight (kg)	0.161	< 0.001
Body temperature (°C)	−0.004	0.860
Respiratory rate (rate/minute)	−0.084	0.001
Heart rate (bpm)	0.006	0.808
SBP (mm Hg)	0.148	< 0.001
DBP (mm Hg)	0.097	< 0.001
PCT (ng/L)	−0.481	< 0.001
ALT (U/L)	0.058	0.020
AST (U/L)	−0.047	0.059
ALB (g/L)	0.367	< 0.001
CREA (mmol/L)	−0.290	< 0.001
UREA (μmol/L)	−0.174	< 0.001
Neutrophils (10^6 cells/L)	−0.217	< 0.001
nSOFA	−0.333	< 0.001
Length of hospital stay (days)	−0.225	< 0.001

Abbreviations: LCR, lymphocyte-to-C-reactive protein ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, pro-calcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; CREA, creatinine; UREA, urea nitrogen; nSOFA, neonatal sequential organ failure assessment.

CREA (r = –0.290, P < 0.001), UREA (r = –0.174, P < 0.001), neutrophil count (r = –0.217, P < 0.001), nSOFA score (r = –0.333, P < 0.001), and length of hospital stay (r = –0.225, P < 0.001). No significant association was found between the LCR and body weight, heart rate, and AST.

LCR as an Independent Factor in Identifying Neonatal Sepsis

Univariate and multivariable binary logistic analyses were conducted to evaluate the clinical significance of LCR as an early biomarker in distinguishing neonatal pneumonia combined with sepsis from pneumonia. Variables with a P-value <0.05 in the univariate analysis were used in the multivariable binary logistic analysis, including body weight, body temperature, heart rate, SBP, DBP, PCT, ALB, ALT, AST, CREA, UREA, and neutrophil count. After adjusting for the above variables, LCR remained an independent biomarker for identifying neonatal sepsis in neonates with pneumonia (odds ratio [OR] = 0.902, 95% confidence interval [CI] = 0.847–0.962, P = 0.002) (Table 4). Further analysis showed that the LCR tertiles were independently associated with an increased prevalence of neonatal pneumonia combined with sepsis.

Diagnostic Value of LCR in Neonatal Sepsis

ROC curve analysis was conducted to assess the efficacy of LCR in distinguishing neonatal sepsis from pneumonia in neonates. The AUC of LCR revealed that it had good power in diagnosing neonatal pneumonia combined with sepsis (AUC = 0.72, 95% CI = 0.67–0.76, P < 0.001), which was higher than that of the lymphocyte count (AUC = 0.65, 95%

Table 4 Predictive Value of the LCR for Sepsis in Neonates with Pneumonia

Variables	Univariate		Multivariate*	
	OR (95% CI)	P	OR (95% CI)	P
Presence of sepsis				
LCR	0.784 (0.739–0.831)	< 0.001	0.902 (0.847–0.962)	0.002
LCR tertiles				
Low LCR	I		I	
Intermediate LCR	0.302 (0.206–0.443)	< 0.001	0.531 (0.345–0.817)	0.004
High LCR	0.224 (0.147–0.342)	< 0.001	0.471 (0.289–0.767)	0.002

Note: *Adjusted for body weight, body temperature, heart rate, SBP, DBP, PCT, ALB, ALT, AST, CREA, UREA, and neutrophil count.
Abbreviations: LCR, lymphocyte-to-C-reactive protein ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCT, procalcitonin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREA, creatinine; UREA, urea nitrogen.

CI, 0.60–0.70, P < 0.001) and CRP (AUC = 0.66, 95% CI = 0.62–0.71, P < 0.001) (P < 0.05) (Figure 1). The optimal cut-off value of LCR in predicting neonatal pneumonia combined with sepsis was 3.35, with 62% sensitivity and 72% specificity.

Discussion

Compared with adults, neonates have limited immunological memory and an immature immune system, which makes them vulnerable to pathogenic microorganisms and the development of pneumonia and sepsis.[1] Pneumonia is a significant neonatal infection that affects the lung and has a high incidence. Compared to neonatal pneumonia, neonatal sepsis is an acute and severe disease that seriously threatens the life and health of newborns.[24] Neonatal sepsis is an infection of the bloodstream in newborn infants under 28 days old. It is the leading cause of morbidity and mortality, especially in low- and middle-income countries.[25] Oza et al[26] analyzed the neonatal mortality data from 193 countries between 2000 and 2013 and found that neonatal sepsis was the third leading cause of neonatal deaths after preterm birth and postpartum complications, accounting for 15.6% of neonatal deaths. In the late neonatal period (7–27 days), the sepsis-related mortality rate increased to 37.2%.[26] Accurate early diagnosis of neonatal sepsis can help to provide
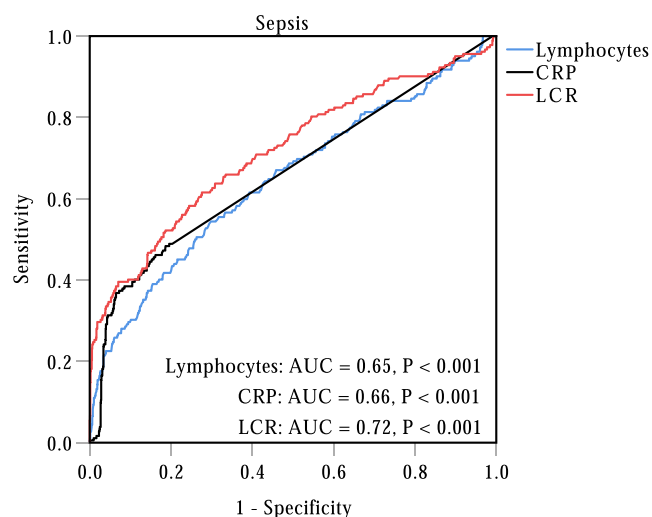

Figure 1 ROC curve of the lymphocyte count, CRP, and LCR in predicting neonatal sepsis.

treatment according to the Surviving Sepsis Campaign Physician's management guidelines.[3] However, the clinical symptoms of neonatal pneumonia and sepsis are similar, making it difficult to distinguish them based on the clinical signs. Moreover, blood culture, the gold standard method for diagnosing neonatal sepsis, usually has a long waiting time and a low positive detection rate of pathogenic microorganisms.[27] Therefore, circulating biomarkers may help to distinguish neonatal sepsis from pneumonia.

Lymphocytes are the type of white blood cells with the highest peripheral blood count in healthy newborns.[28] They comprise an essential arm of the innate immune response during sepsis and can recognize microbial antigens and present them to the T cells.[29] Moreover, lymphocytes can also release chemokines and regulatory cytokines.[30] However, during sepsis, the number of lymphocytes undergoes apoptosis, which significantly reduces their number.[7,31] Clinical studies have confirmed that patients with sepsis have a lower lymphocyte count, and lymphocytopenia is commonly observed in them.[10,32–35] The decreased lymphocyte count contributes to the immunosuppressed state, making patients susceptible to new infections.[9] CRP is an acute-phase protein produced by the liver in response to inflammation. The CRP level is the most studied and commonly used laboratory parameter in sepsis cases. Studies have confirmed that CRP significantly increases in patients with sepsis and is an independent sepsis predictor for sepsis.

Recently, the lymphocyte count and CRP level were combined to improve the potential predictive value of the individual markers. LCR is an index calculated by dividing the lymphocyte count by the CRP level. LCR has garnered increasing attention as a newly emerging inflammatory marker. It has been proven to be a helpful predictor for postoperative complications in various types of tumor diseases, such as colorectal cancer, gastric cancer, and hepatocellular carcinoma.[36–40] Furthermore, it is closely associated with infectious diseases. A meta-analysis study showed that LCR values were decreased significantly in patients with COVID-19.[41] Demirkol et al[42] further reported that the CRP-to-lymphocyte ratio (CLR) level was elevated in deceased COVID-19 patients indicating that the elevated levels were associated with poor outcomes in COVID-19 patients. Yang et al[43] reported that LCR proved more beneficial than the CRP level or lymphocyte count alone in evaluating severe COVID-19. However, published studies have not paid sufficient attention to the relationship between LCR and sepsis in adults and newborns.

In this study, we first evaluated the ability of LCR to identify sepsis in neonates with pneumonia. Our data showed that the levels of LCR were lower in neonates with pneumonia combined with sepsis than in those with pneumonia. The prevalence of neonatal pneumonia combined with sepsis was significantly higher in the low-LCR group than in the high-LCR group. Moreover, LCR correlated negatively with PCT, nSOFA score, and the length of hospital stay. However, the correlation between LCR and other indicators is not very strong ($r < 0.5$), which may be related to the physiological increase/decrease of some indicators in newborns. Multivariate analysis revealed that LCR is an independent risk factor for neonatal pneumonia combined with sepsis. ROC curve showed that LCR had better power than the lymphocyte count and CRP level alone in distinguishing sepsis from neonatal pneumonia.

This study has several limitations. First, since this was a single-center retrospective observational study, the results require further validation via future multicenter studies. Second, we did not differentiate between early-onset sepsis and late-onset sepsis due to the limited number of children diagnosed with sepsis in this study. Finally, LCR was only calculated at admission, and serial LCR measurements may prove helpful in evaluating the clinical significance of LCR in distinguishing neonatal sepsis from neonatal pneumonia.

Conclusions

This study elicited the relationship between the LCR and the presence of sepsis in neonates with pneumonia. LCR is a potentially helpful biomarker in distinguishing neonates with sepsis from those with pneumonia.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Hospital Ethics Review Board of Henan Children's Hospital, Zhengzhou, China. The study guarantees that the identity of the

participants and other related data has been kept anonymous and confidential. The requirement for informed consent was waived considering the retrospective nature of the study.

Disclosure
The authors report no conflicts of interest in this work.

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