

The CRP/Albumin Ratio Predicts Survival And Monitors Chemotherapeutic Effectiveness In Patients With Advanced Pancreatic Cancer

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Purpose: The CRP/albumin (Alb) ratio, a recently reported predictor, has shown value for prognosis in various human cancers. This study aimed to determine the prognostic value of baseline CRP/Alb and to explore the relevance between postchemotherapy CRP/Alb and the efficacy of chemotherapy in advanced pancreatic cancer patients.

Patients and methods: Five hundred and ninety-five patients diagnosed with locally advanced or metastatic adenocarcinoma of the pancreas were enrolled. Cut-off Finder was used to calculate the best cut-off value for baseline CRP/Alb. The primary endpoint was overall survival, which was analyzed by Kaplan-Meier survival curves with 95% confidence intervals. The log rank test and Cox proportional hazard model were used to evaluate the univariate and multivariate analyses.

Results: The optimal cut-off value for baseline CRP/Alb was determined to be 0.18. Both the baseline CRP/Alb (CRP/Alb $\geq$ 0.18 vs. CRP/Alb $<$ 0.18, hazard ratio [HR] = 2.506; $p < 0.001$) and postchemotherapy CRP/Alb (CRP/Alb $\geq$ 0.18 vs. CRP/Alb $<$ 0.18, HR = 1.854; $p = 0.002$) were significant predictors of overall survival according to multivariate analysis and were independent of other factors. Patients with a baseline and postchemotherapy CRP/Alb $\geq$ 0.18 had the worst prognosis.

Conclusion: CRP/Alb is a strong and useful indicator of prognosis for advanced pancreatic cancer. Both baseline and postchemotherapy CRP/Alb can be used in predicting the survival of patients and monitoring the effectiveness of chemotherapy in clinical practice.

Keywords: CRP/Alb ratio, pancreatic cancer, prognosis, chemotherapy

Introduction

Pancreatic cancer, which is considered one of the most deadly and aggressive malignant tumors, has risen gradually to become the 4th leading cause of cancer-related death worldwide.¹⁻³ The annual incidence of this disease is approximately equal to its annual mortality rate, and the overall 5-year survival rate is only 8%.¹ According to the statistics, only 10–20% of the patients suffering from pancreatic cancer have a chance to undergo radical surgery.⁴ Therefore, more than 80% of patients are at the advanced stage at the onset of diagnosis, and chemotherapy is one of the most crucial treatments for them.⁵ Currently, one of the most important prognostic factors for pancreatic cancer is the tumor-node-metastasis (TNM) staging system, which is suggested to play an important role in clinical practice. In addition, a great deal of research on identifying other novel indicators has emerged in recent years.⁶⁻⁸ Notwithstanding, for patients suffering from advanced

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pancreatic cancer, there is limited knowledge about predictive factors that can predict the prognosis and chemotherapy response.

Previous research has demonstrated that systemic inflammatory responses play a pivotal part in the progression of various malignancies and are closely related to poor prognosis in patients.^{9,10} Multiple inflammatory markers that are used to predict the prognosis of patients with malignant tumors can be obtained easily from peripheral blood samples;¹¹ these predictive indices include the modified Glasgow prognostic score (mGPS),¹² platelet-lymphocyte ratio (PLR),¹³ and neutrophil-lymphocyte ratio (NLR).¹⁴ Among these inflammatory markers, the C-reactive protein/albumin (CRP/Alb) ratio has been demonstrated as a prognostic indicator for several cancers, such as hepatocellular carcinoma,¹⁵ esophageal cancer,¹⁶ gastric cancer,¹⁷ lung cancer,¹⁸ newly diagnosed pancreatic cancer,¹⁹ renal cancer,²⁰ and ovarian cancer.²¹ However, its role in predicting prognosis and accessing chemotherapeutic effectiveness has not yet been elucidated in patients with advanced pancreatic cancer.

This study aimed to determine the prognostic value of baseline CRP/Alb and to explore the relevance between postchemotherapy CRP/ALB and the efficacy of chemotherapy in advanced pancreatic cancer patients.

Research Design

A retrospective, follow-up cohort analysis was performed on patients with locally advanced or metastatic adenocarcinoma of the pancreas from March 2011 to September 2016 at Shanghai Cancer Center, Fudan University, China. According to the American Joint Committee on Cancer (AJCC), 7th edition, TNM staging for pancreatic cancer, locally advanced pancreatic cancer is defined as a tumor involving the celiac axis or the superior mesenteric artery or common hepatic artery without distant metastasis.²² All patients involved were diagnosed according to histologic or cytologic evidence. Exclusion criteria included the following: patients with prior treatment for primary tumors and major metastases, patients without follow-up data or who were lacking serum CRP and albumin levels at diagnosis, and patients with second malignancies or multiple primary malignancies or evidence of infection or other inflammatory conditions. Surviving patients with a follow-up time of less than 6 months were also excluded. In total, 595 patients were recruited for our cohort. Most of the patients enrolled

(485/595, 81.5%) underwent chemotherapy, and 92.6% of them (449/485) were treated with gemcitabine-based chemotherapy. The remaining 7.4% (36/485) were subjected to other chemotherapy protocols. Chemotherapy patients are patients who receive 2 or more cycles of chemotherapy. For patients who have never received chemotherapy, the variable of chemotherapy appears to be a no. All chemotherapy was based on the latest version of the National Comprehensive Cancer Network (NCCN) Guidelines.

Clinicopathological data, including sex, age, tumor diameter, tumor location, disease stage, and serum CA19-9 concentration, were collected from the patients' medical history from Shanghai Cancer Center. The baseline serum levels of CRP and Alb used for evaluation were determined prior to the initial treatment. The CRP/Alb ratio was defined as the serum concentration of CRP (mg/L) divided by that of Alb (g/L). The postchemotherapy CRP/Alb ratio after two cycles of chemotherapy was also calculated. All patients were regularly followed-up by telephone. The onset of follow-up was the date of the first diagnosis of pancreatic cancer, and the terminal date was December 2017 or death. This retrospective study was

Table 1 Clinicopathologic Characteristics Of All Patients

Variables	n	CRP/ Alb<0.18	CRP/ Alb≥0.18	p value
Patients (N)	595	392 (65.9%)	203 (34.1%)	
Sex				0.062
Male	380	240 (61.2%)	140 (69.0%)	
Female	215	152 (38.8%)	63 (31.0%)	
Age (years)				0.249
≥65	233	147 (37.5%)	86 (42.4%)	
<65	362	245 (62.5%)	117 (57.6%)	
Location of tumor				0.025
Head	197	142 (36.2%)	55 (27.1%)	
Body or tail	398	250 (63.8%)	148 (72.9%)	
Tumor diameter (cm)				<0.001
<4	258	191 (48.7%)	67 (33.0%)	
≥4	337	201 (51.3%)	136 (67.0%)	
Tumor spread				<0.001
Locally advanced	388	226 (57.7%)	162 (79.8%)	
Metastatic	207	166 (42.3%)	41 (20.2%)	
CA19-9 (U/mL)				0.151
<37	116	83 (21.2%)	33 (16.2%)	
≥37	479	309 (78.8%)	170 (83.8%)	

Abbreviation: CRP/Alb, C-reactive protein/albumin ratio.

approved by the Ethics Board of Shanghai Cancer Center, Fudan University. The patient/next of kin consent was written informed consent, and this study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Overall survival (OS) was the primary endpoint, and it was considered to be the time between the first date of diagnosis and the date of death for any reason. OS was analyzed using Kaplan-Meier survival curves with 95% confidence intervals (CIs). Univariate and multivariate analyses were calculated according to the log rank test and the Cox proportional hazard model, respectively. Clinicopathologic characteristics between groups were compared using the Pearson χ^2 or Fisher's exact tests. The optimal cut-off values for baseline CRP/Alb were

determined using an R software-engineered, web-based system designed by Budczies J et al.²³ Statistical analyses were performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL). Differences were considered statistically significant at $p < 0.05$.

Results

The general information and clinical indexes of the patients included in the cohort are listed in Table 1. All patients received a histological or cytological diagnosis for primary pancreatic lesions or metastases. Of all the patients, 380 (63.9%) were males, and 215 (36.1%) were females. The median age of the patients recruited at diagnosis was 62 years old (range 33–84), and the numbers of patients with locally advanced and metastatic disease were 207 (34.8%) and 388 (65.2%), respectively.

Table 2 Univariate And Multivariate Analyses For The Overall Survival Of All Patients According To Baseline CRP/Alb

Variables	n	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p value	HR	95% CI	p value
Entire cohort	595						
Age (years)							
<65	233	1					
≥65	362	1.034	0.857–1.248	0.724			
Location of tumor							
Body or tail	398	1					
Head	197	1.009	0.832–1.224	0.928			
Sex							
Female	215	1			1		
Male	380	1.139	0.942–1.379	0.180	1.114	0.920–1.350	0.268
Tumor diameter (cm)							
<4	258	1			1		
≥4	337	1.468	1.218–1.768	<0.001	1.276	1.054–1.544	0.012
Chemotherapy							
Yes	485	1			1		
No	110	1.562	1.246–1.958	<0.001	1.393	1.103–1.758	0.005
CA19-9 (U/mL)							
<37	116	1			1		
≥37	479	1.588	1.234–2.043	<0.001	1.593	1.236–2.053	<0.001
Tumor spread							
Locally advanced	207	1			1		
Metastatic	388	2.048	1.671–2.509	<0.001	1.829	1.488–2.249	<0.001
Baseline CRP/Alb							
<0.18	392	1			1		
≥0.18	203	2.237	1.849–2.706	<0.001	1.840	1.510–2.242	<0.001

Abbreviations: HR, hazard ratio; CRP/Alb, C-reactive protein/albumin ratio.

The median tumor size was 4.2 cm, and the tumor size was ≥ 4 cm in 337 patients (56.6%). One hundred ninety-seven patients (33.1%) had primary pancreatic head tumors. The serum levels of CA-199 in 116 patients (19.5%) were within the normal range (<37 U/mL). The median baseline CRP/Alb was 0.08 (range 0–7.02), and the optimal cut-off value for baseline CRP/Alb was calculated to be 0.18 for the OS using the biostatistical tool Cut-off Finder.²³ The patients were divided into two cohorts by cut-off values according to the baseline CRP/Alb. A total of 203 (34.1%) patients had baseline CRP/Alb levels higher than the cut-off value. Correlations between the CRP/Alb ratio and the clinicopathological characteristics were analyzed using χ^2 tests, as shown in Table 1. The baseline CRP/Alb ratio was not associated with age ($p = 0.249$). It was, however, associated with tumor location ($p = 0.025$), tumor diameter ($p < 0.001$) and disease stage ($p < 0.001$). Although there was no significant difference, male patients ($p = 0.062$) and patients with elevated CA19-9 levels ($p = 0.151$) showed a tendency for a higher CRP/Alb ratio.

The median follow-up time of the present study was 7.3 months, and the median survival time was 7.6 months. The 1-year OS and 2-year OS were 18.0 and 24.1%, respectively. Table 2 indicates the relationship between the clinicopathological variables and OS. In the univariate analysis, the OS was significantly correlated with tumor diameter, disease stage, CA19-9 level, chemotherapy and baseline CRP/Alb. Although not statistically significant, male patients presented with a worse prognosis trend. The multivariate analysis revealed the following as independent prognostic factors for OS: tumor diameter ≥ 4 cm (HR = 1.276; $p = 0.012$), lack of chemotherapy (HR = 1.393; $p = 0.005$), CA19-9 ≥ 37 U/mL (HR = 1.593; $p < 0.001$), metastatic diseases (HR = 1.829; $p < 0.001$) and baseline CRP/Alb ≥ 0.18 (HR = 1.840; $p < 0.001$). Survival was significantly better for patients with a baseline CRP/Alb ratio < 0.18 than for those with a baseline CRP/Alb ratio ≥ 0.18 , as shown in Figure 1A. Regardless of the locally advanced or metastatic cohort classification, prognosis was significantly worse for patients with a baseline CRP/Alb ≥ 0.18 than for those with a baseline CRP/Alb < 0.180 (Figure 1B and C).

Two hundred thirteen patients had CRP/Alb ratio data after two cycles of chemotherapy. According to a univariate

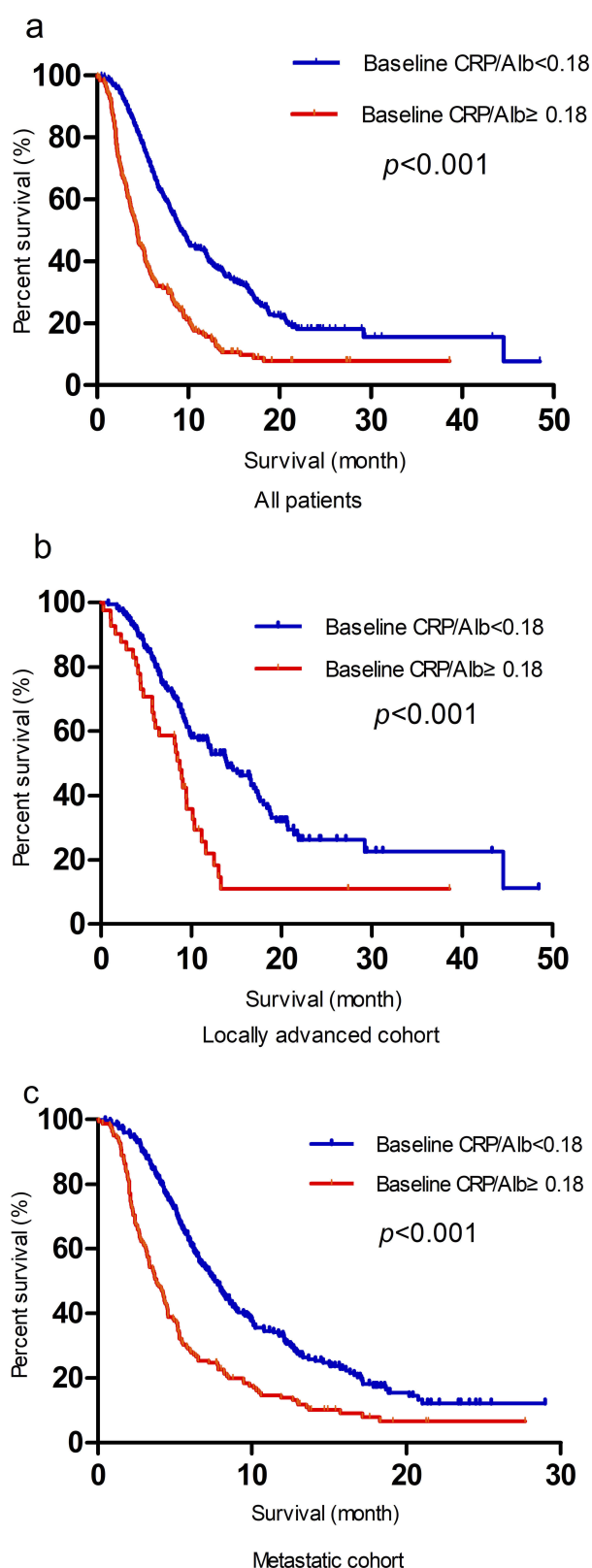


Figure 1 Kaplan-Meier analysis of OS according to baseline CRP/Alb in all patients (A), in the locally advanced (B) and metastatic cohorts (C).

Table 3 Univariate And Multivariate Analyses For The Overall Survival Of Patients According To Baseline And Postchemotherapy CRP/Alb

Variables	n	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p value	HR	95% CI	p value
Entire cohort	213						
Age (years)							
<65	142	1					
≥65	71	1.087	0.756–1.563	0.653			
Location of tumor							
Body or tail	137	1					
Head	76	1.006	0.716–1.413	0.972			
Sex							
Female	73	1			1		
Male	140	1.339	0.940–1.907	0.105	1.207	0.842–1.731	0.306
Tumor diameter (cm)							
<4	102	1			1		
≥4	111	1.273	0.916–1.769	0.150	1.072	0.76–1.513	0.691
CA19-9 (U/mL)							
<37	47	1			1		
≥37	166	1.373	0.902–2.090	0.139	1.486	0.971–2.275	0.068
Tumor spread							
Locally advanced	80	1			1		
Metastatic	133	2.140	1.492–3.609	<0.001	1.926	1.330–2.790	0.001
CRP/Alb							
Baseline <0.18 Postchemotherapy <0.18	135	1			1		
Baseline ≥0.18 Postchemotherapy <0.18	17	1.582	0.861–2.908	0.140	1.356	0.725–2.536	0.341
Baseline <0.18 Postchemotherapy ≥0.18	29	2.272	1.447–3.568	<0.001	2.158	1.355–3.437	0.001
Baseline ≥0.18 Postchemotherapy ≥0.18	32	3.639	2.310–5.732	<0.001	3.132	1.952–5.025	<0.001

Note: Two hundred and thirteen patients had postchemotherapy CRP/Alb ratio data after two cycles of chemotherapy.

Abbreviations: HR, hazard ratio; CRP/Alb C-reactive protein/albumin ratio.

analysis, male patients (HR = 1.339; $p=0.105$) with a tumor diameter ≥ 4 cm (HR = 1.273; $p=0.150$) and CA19-9 ≥ 37 U/mL (HR = 1.373; $p=0.139$) had a worse prognosis trend. Disease stage and postchemotherapy CRP/Alb were significant independent predictors of OS according to both univariate analysis and multivariate analysis (Table 3). The clinical value of postchemotherapy CRP/Alb (HR = 2.456; $p<0.001$ (Figure 2A)) in predicting the prognosis of patients after two cycles of chemotherapy was better than that of baseline CRP/Alb (HR = 1.890; $p=0.001$). To confirm the value of CRP/Alb for monitoring chemotherapeutic effectiveness, the patients were further divided into 4 subgroups according to whether the baseline and postchemotherapy CRP/Alb ratios were ≥ 0.18 . Among the 4 subgroups, the patients with baseline and postchemotherapy CRP/Alb ratios ≥ 0.18 had the worst prognosis (HR = 3.132; $p<0.001$), followed by

patients with baseline CRP/Alb ratios < 0.18 and postchemotherapy CRP/Alb ratios ≥ 0.18 (HR = 2.158; $p=0.001$ (Figure 2B)). No significant differences were observed for OS between patients with baseline and postchemotherapy CRP/Alb ratios <0.18 and patients with baseline CRP/Alb ratios ≥ 0.18 and postchemotherapy CRP/Alb ratios <0.18 (HR = 1.356; $p=0.341$).

Discussion

Because of both the cell-intrinsic and cell-extrinsic processes of cancer cells, cancer is regarded as a complicated disease.⁹ Inflammation can promote tumorigenesis and development by affecting the microenvironment of cancer.¹⁰ Studies have shown that some inflammatory mediators, such as acute phase and inflammatory proteins, chemokines, immune cells and cytokines,^{24,25} play a

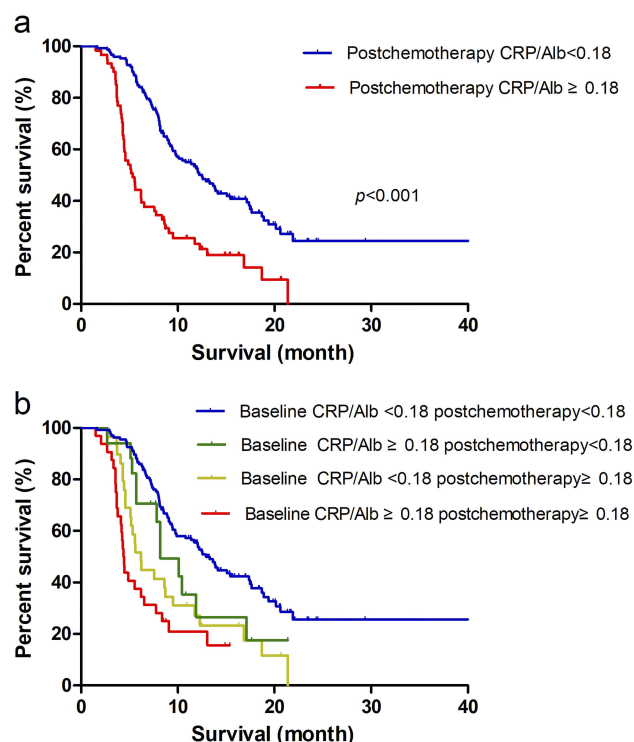


Figure 2 (A) Kaplan-Meier analysis of OS in patients after two cycles of chemotherapy according to postchemotherapy CRP/Alb. **(B)** OS of the patients after two cycles of chemotherapy according to baseline and postchemotherapy CRP/Alb.

pivotal role in cancer development, angiogenesis, invasion and metastasis. A variety of inflammatory markers, including NLR, PLR, CRP/Alb and mGPS, have been used to evaluate the outcome of pancreatic cancer.^{6,19,26}

As an acute phase protein, CRP is synthesized in the liver and induced by pro-inflammatory cytokines, and is considered to be a predictor of infection. It can also be elevated in the metastasis process of tumors. Alb is a circulating protein in the plasma that can be involved in the inflammatory response.²⁷ The CRP/Alb ratio can represent the potential inflammatory status of the body. It was developed as a prognostic score for patients with sepsis and was later widely used for various neoplastic diseases.^{20,28,29} It is widely acknowledged that the inflammatory response and innutrition are closely associated with low quality of life and have detrimental effects on therapeutic efficacy in cancer patients.^{30,31} As a quantifiable continuous variable, CRP/Alb can reflect the inflammation and nutritional status of cancer patients during treatment. A study showed that for patients who underwent pancreatic resection, a higher CRP/Alb ratio was a useful and remarkable predictor of poor OS.²⁹ However, studies on the prognostic value of baseline and postchemotherapy CRP/Alb for final outcomes for advanced pancreatic cancer patients after chemotherapy are rare.²⁸

Our study used multivariate analyses to demonstrate that both baseline and postchemotherapy CRP/Alb ratios were independent predictors of the estimated final prognosis for advanced pancreatic cancer patients after chemotherapy. Furthermore, in the subsequent subgroup assessment, patients with baseline CRP/Alb < 0.180 showed a notably better clinical outcome than patients with baseline CRP/Alb ≥ 0.18, regardless of their locally advanced or metastatic cohort classification. Postchemotherapy CRP/Alb is better than baseline CRP/Alb for predicting survival and can help us to predict the chemotherapy response in a timely manner. Patients with baseline CRP/Alb ≥ 0.18 and postchemotherapy CRP/Alb < 0.18, which means they could benefit from chemotherapy, have similar prognoses as patients with baseline and postchemotherapy CRP/Alb < 0.18. In addition, patients with baseline and postchemotherapy CRP/Alb ≥ 0.18 had a HR of 3.132, suggesting that baseline and postchemotherapy CRP/Alb ratios ≥ 0.18 are the most useful and important prognostic factors for patients receiving chemotherapy.

Our present research first discussed the role of CRP/Alb in indicating the outcomes for advanced pancreatic cancer patients who have received chemotherapy. In addition, we found that postchemotherapy CRP/Alb can be used for both monitoring the effectiveness of chemotherapy and predicting the survival of patients with advanced pancreatic cancer. As chemotherapy is the main alternative treatment for these patients and its effectiveness is closely related to patient's final outcome, it is very important to find a simple and effective method to predict the effect of chemotherapy. This tool could help to identify which groups of advanced pancreatic cancer patients will benefit most from chemotherapy and help doctors make clinical decisions. We set 0.18 as the CRP/Alb cut-off value by using Cut-off Finder, but other studies have set different cut-off values. These variations may be related to the different background characteristics of the patients.

There were some limitations to this study. First, because CRP is not a unique biomarker for inflammation, it could be elevated in a large number of systematic diseases. Second, although our sample size is relatively large compared with other related studies, the sample size becomes relatively small after division into subgroups, which also means that our results need further verification in future multicenter prospective studies.

Conclusion

CRP/Alb is a strong and useful predictor of prognosis for patients with advanced pancreatic cancer. Both baseline

CRP/Alb and postchemotherapy CRP/Alb can be used for monitoring the effectiveness of chemotherapy and predicting survival. CRP can be used as a routine test for decision making during chemotherapy for the clinical treatment of advanced pancreatic cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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