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Calprotectin in the blood plasma as a new biomarker for assessing the activity of rheumatoid arthritis

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ABSTRACT

Aim. To study the potential use and information value of calprotectin in the blood plasma as a new biomarker for determining the activity of rheumatoid arthritis (RA).

Materials and methods. The study included 113 people. The treatment group consisted of 79 patients diagnosed with RA; the average age was 58 (± 11.66) years, the median duration of the disease was 10 [6; 15] years. The control group encompassed 34 healthy volunteers; the average age was 40 (± 11.14) years. RA activity was determined according to the Disease Activity Score (DAS) 28 and the Clinical Disease Activity Index (CDAI). The concentration of calprotectin in the blood plasma was determined by the solid-phase enzyme-linked immunosorbent assay. The obtained results were compared with laboratory and clinical parameters, as well as with composite indices (DAS28, CDAI) of RA activity. For mathematical data processing, Spearman's rank correlation coefficient, linear discriminant analysis, and ROC analysis were used.

Results. In the group of patients with RA, the level of calprotectin in the blood was higher than in the control group. A statistically significant relationship was revealed between the level of calprotectin in the blood and all standard parameters of RA activity. The ROC analysis showed that the sensitivity, specificity, and diagnostic accuracy in assessing articular syndrome, as well as moderate and high RA activity according to the composite indices DAS28 and CDAI were higher for calprotectin than for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The linear discriminant analysis showed that a combination of ESR and calprotectin levels was the most informative; following it, the probability of correct classification of RA activity, according to the DAS28 index, was 71%. For the CDAI index, only one marker, calprotectin, resulted in a statistically significant classification with a probability of 70.5 %.

Conclusion. Calprotectin in the blood plasma is a promising laboratory biomarker for assessing synovitis activity in RA demonstrating higher accuracy, sensitivity, and specificity than traditional acute-phase reactants.

Keywords: rheumatoid arthritis, activity, calprotectin

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at Almazov National Medical Research Center of the Ministry of Health of the Russian Federation (Protocol No. 06-19 of 13.05.2019).

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Кальпротектин в плазме крови как новый биомаркер в оценке активности ревматоидного артрита

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РЕЗЮМЕ

Цель. Изучить возможность применения и информативность кальпротектина плазмы крови в качестве нового биомаркера для оценки активности ревматоидного артрита (РА).

Материалы и методы. В исследование включены 113 человек, 79 пациентов с диагнозом РА (основная группа); средний возраст 58 (± 11,66) лет, медиана длительности заболевания 10 [6; 15] лет. Группу контроля составили 34 здоровых добровольца; средний возраст 40 (± 11,14) лет. У пациентов с РА активность заболевания определялась по индексу DAS28 (Disease Activity Score), а также по клиническому индексу CDAI (Clinical Disease Activity Index). Концентрация кальпротектина в плазме крови определялась методом твердофазного иммуноферментного анализа. Полученные данные сопоставлялись с лабораторными и клиническими параметрами, а также композитными индексами (DAS28, CDAI) активности РА. Для математической обработки данных использовались ранговая корреляция по Спирмену, дискриминантный и ROC-анализы.

Результаты. В группе больных РА содержание кальпротектина в крови было более высоким по сравнению с контрольной группой. Выявлена значимая связь уровня кальпротектина крови со всеми параметрами активности РА. При проведении ROC-анализа диагностическая точность, чувствительность и специфичность уровня кальпротектина в плазме крови были выше для оценки суставного синдрома, а также композитных индексов CDAI и DAS28 в сравнении с содержанием скорости оседания эритроцитов (СОЭ) и С-реактивного белка (СРБ). По данным дискриминантного анализа, наиболее информативным оказалось сочетание уровней СОЭ и кальпротектина, для которых вероятность правильной классификации активности РА, согласно индексу DAS28, составила 71%. Для индекса CDAI статистически значимую классификацию давал только кальпротектин с вероятностью 70,5%.

Заключение. Кальпротектин плазмы крови – перспективный лабораторный биомаркер в оценке активности синовита при РА, демонстрирующий более высокую информативность, чем традиционные острофазовые показатели.

Ключевые слова: ревматоидный артрит, активность, кальпротектин

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common human systemic autoimmune disease, where inflammation mainly targets peripheral joints with development of erosions and destructive changes in them. Currently, determining RA activity is an important clinical task and a time-consuming and lengthy process [1]. In order to determine RA activity, a number of clinical and laboratory evaluation parameters are used, such as the tender joint count (TJC) and swollen joint count (SJC), acute-phase reactants (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), as well as subjective assessments by the patient (patient global assessment (PGA), the visual analogue scale (VAS)) and the physician (physician global assessment (PhGA)) [2, 3].

Since these parameters separately do not fully reflect RA activity, composite indices are currently widely used for assessing the disease activity, such as Disease Activity Score (DAS) 28 and Clinical Disease Activity Index (CDAI). However, the conducted studies show that indices do not always allow researchers to reliably determine disease activity. According to the studied composite indices, in some patients with RA in remission, X-ray detected disease progression. The information value of traditional acute-phase reactants is insufficient, and composite indices are difficult to use and subjective to a certain extent, which makes it relevant to search for and introduce into clinical practice new biomarkers that accurately reflect immunological and inflammatory processes in the joints.

Calprotectin is a heterodimeric complex protein consisting of two subunits (S100A8 / S100A9) with the molecular mass of 36 kDa and Ca2+ / Zn2+ binding sites. Currently, this marker is used in gastroenterology to assess inflammatory infiltrates in the intestine in patients with inflammatory diseases [6]. This biomarker is an alarmin with proinflammatory properties [7]. Earlier studies on the new biomarker suggest that it can be quite effective in assessing RA activity [8–15].

The aim of this study was to investigate the potential use and information value of calprotectin in the blood plasma as a new biomarker for determining the activity of RA.

MATERIALS AND METHODS

We examined 113 people. The treatment group included 79 patients diagnosed with RA, and the control group encompassed 34 healthy volunteers. The inclusion criterion was compliance of patients with RA of any disease activity, regardless of the chosen treatment, with the criteria of the American College of Rheumatology / the European League Against Rheumatism (ACR / EULAR) published in 2010 [16]. The exclusion criteria were patient's refusal to participate in the study; the presence of active infection; cancer during the period of the study; other autoimmune diseases, except for secondary Sjogren's syndrome; decompensated chronic non-communicable diseases; pregnancy and lactation.

Upon admission, all patients were tested for the articular syndrome using TJC, SJC, VAS, PGA, and PhGA. RA activity was assessed using composite indices, such as DAS28-ESR and CDAI. Laboratory tests included an analysis of acute-phase reactants for ESR and CRP, rheumatoid factor (RF), and cyclic citrullinated peptide antibodies (anti-CCP). The level of plasma calprotectin was measured with the enzyme-linked immunosorbent assay (ELISA). A reagent kit for the analysis was developed by the staff of Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences. The kit included biotin-conjugated protein antibodies derived from rats. ELISA was conducted in accordance with standard protocols on the multi-mode microplate reader CLARIOstar Plus (BMG LABTECH, Germany).

Gastrointestinal pathology is detected in 13–62% of patients with RA and is one of the main extra-articular manifestations of this disease. Associated gastrointestinal lesion in patients with RA can significantly affect the concentration of both fecal and plasma calprotectin. Therefore, we thoroughly collected complaints and anamnestic data regarding the gastrointestinal pathology in all patients participating in this study and assessed the presence of symptoms for intestinal and extraintestinal manifestations of possible inflammatory bowel diseases. All patients with RA who participated in this study underwent esophagogastroduodenoscopy (EGD) during hospitalization as part of an inpatient examination. Colonoscopy (CS) was not a mandatory examination for the participation in this study in the absence of indications for it.

The results obtained were analyzed using Prism 8.0 and Statistica 12.0 software packages. The normality test was used to determine if a data set was well-modeled by a normal distribution. In the absence of normal distribution, the Mann – Whitney *U*–test and the Spearman's rank correlation coefficient were used. The differences between the groups were considered significant at $p < 0.05$. ROC analysis was performed; we calculated the area under the curve (AUC) and marker sensitivity, specificity, and diagnostic accura-

cy. A discriminant analysis was used to determine the differences between the new biomarker and traditional acute-phase reactants.

RESULTS

The average age of the patients with RA was 58 ± 11.66 years, this group included 11 men and 68 women; the control group included 15 men and 19 women whose average age was 40 ± 11.14 years. The demographic characteristics of the groups did not differ significantly. In the group of patients with RA, the median duration of the disease was 10 years [6; 15]. In this group, a total of 68 people (86%) were tested positive for anti-CCP, and 66 patients (83.5%) were tested positive for RF. The patients in the treatment group were distributed according to the degree of RA activity based on the studied indices (DAS28, CDAI). The clinical characteristics of patients with RA and laboratory data of the examined groups are presented in Tables 1 and 2.

Table 1

Clinical, laboratory, and demographic data of patients in the treatment group

Parameter	Value
Age, years, $M \pm SD$	58 (± 11.66)
Disease duration, years, $Me[Q_1; Q_3]$	10 [6; 15]
Male / female ratio, *n*	11 / 68
TJC, $Me\ [Q_1; Q_3]$	10 [6; 18]
SJC, $Me\ [Q_1; Q_3]$	4 [2; 6]
VAS, score, $Me\ [Q_1; Q_3]$	5 [4; 6.5]
DAS28 index, score, $Me\ [Q_1; Q_3]$	5.1 [4.38; 6.11]
DAS28–ESR activity, *n* (%):	
remission	5 (6.3)
low	4 (5)
moderate	29 (36.8)
high	41 (51.9)
CDAI activity, $Me\ [Q_1; Q_3]$	23.5 [16; 30]
remission	4 (5.06)
low	4 (5.06)
moderate	30 (37.97)
high	41 (51.89)
Steinbrocker staging of the disease, n:	
I	2
II	33
III	25
IV	19

Table 2

The comparison of acute-phase reactants in patients of the studied groups, $Me\ [Q_1; Q_3]$

Parameter	Control group	RA patients	*p*
ESR, mm / h	9 [5.5; 12.5]	29 [18; 51]	< 0.05
CRP, mg / l	2 [1.2; 2.1]	7.9 [2.5; 17.5]	< 0.005

The calprotectin level was significantly higher in patients with RA compared with the control group (Fig.1). According to the Mann – Whitney test, the differences in biomarker concentrations in both groups were highly statistically significant ($p < 0.0001$). It should be mentioned that calprotectin levels of four patients did not correspond to the calprotectin level range in the treatment group. A detailed analysis of the results showed that these RA patients were in remission. Remission was detected by a lower plasma calprotectin concentration.

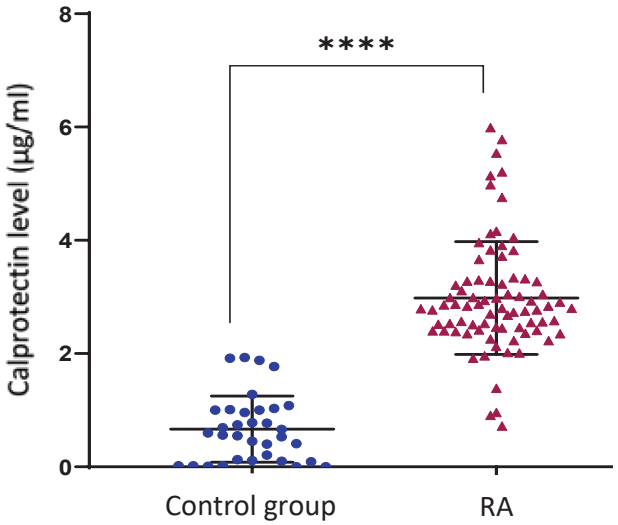


Fig. 1. Comparison of blood calprotectin levels in RA patients and the control group. $Me\ [Q_1; Q_3]$, $p < 0.0001$ (****)

With the Spearman's rank correlation coefficient, a statistically significant correlation was revealed between plasma calprotectin concentration and all components of RA activity. However, the correlation between the new biomarker and the articular component as well as composite indices was more statistically significant, while the correlation between traditional acute-phase reactants and the mentioned parameters was less statistically significant. The rank correlation coefficients are presented in Table 3.

Since DAS28 includes three main domains, including one of the acute-phase reactants (ESR / CRP), in order to exclude the markers that could affect test results, we used CDAI index containing only two domains in subsequent statistical tests.

To conduct ROC analysis, RA patients were divided into 2 groups depending on the articular syndrome. The first group consisted of patients who had TJC ≤ 8 and SJC ≤ 1. The second group included patients with TJC > 8 and SJC > 1. ROC curve plots are shown in

Figures 2 and 3. According to the assessment of TJC, calprotectin had the greatest sensitivity, specificity, and diagnostic accuracy, while ESR and CRP were characterized by the lowest values (Fig. 2*a*). The calprotectin level with higher diagnostic accuracy, sensitivity, and specificity reflected the association with SJC if compared with ESR and CRP (Fig. 2*b*). The data on the test are given in Table 4.

Table 3

Spearman's rank correlation coefficients for calprotectin and acute-phase reactants with clinical data, VAS, as well as DAS28 and CDAI indices

Parameter	Calprotectin	ESR	CRP	TJC	SJC	VAS	CDAI	DAS28
Calprotectin	–	0.316*	0.198	0.441*	0.227*	0.310*	0.419*	0.494*
ESR	0.316*	–	0.651*	0.143	0.124	0.282*	0.236*	0.597*
CRP	0.198	0.651*	–	0.078	0.113	0.191	0.158	0.443*
TJC	0.441*	0.143	0.072	–	0.559*	0.414*	0.838*	0.702*
SJC	0.227*	0.125	0.113	0.559*	–	0.324*	0.715*	0.639*
VAS	0.310*	0.282*	0.191	0.414*	0.324*	–	0.582*	0.597*
CDAI	0.419*	0.236*	0.158	0.838*	0.715*	0.582*	–	0.875*
DAS28	0.494*	0.597*	0.443*	0.702*	0.637*	0.597*	0.875*	–

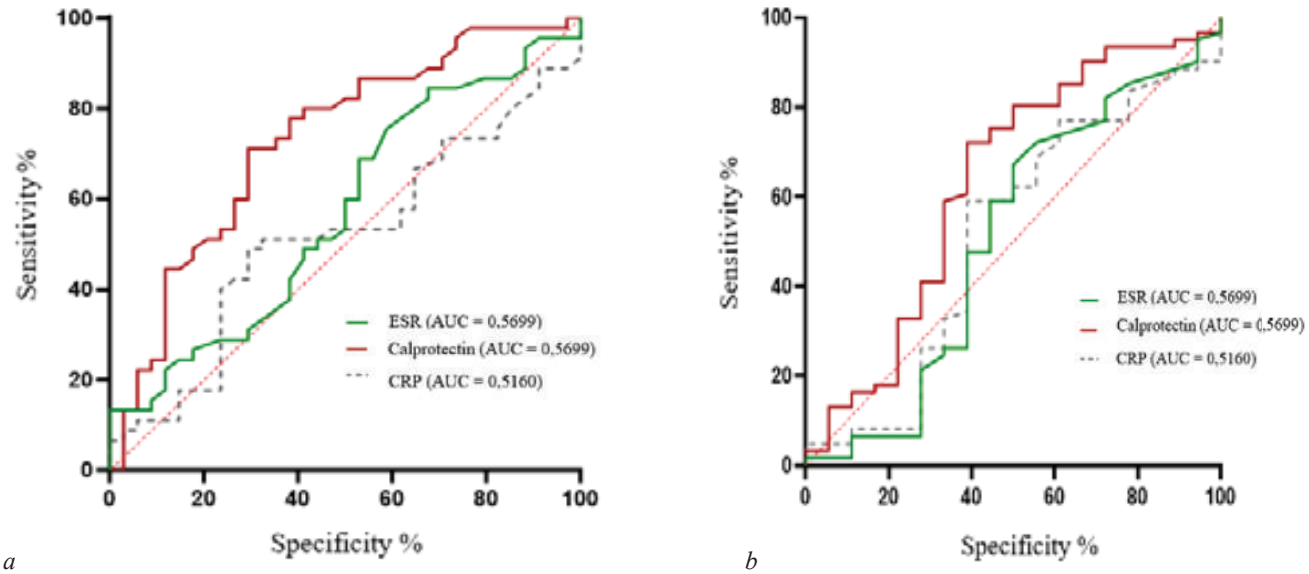
* values with $p < 0.05$.

Table 4

ROC analysis parameters for calprotectin compared with acute-phase reactants in the assessment of articular syndrome

Parameter	Calprotectin		ESR		CRP	
	TJC	SJC	TJC	SJC	TJC	SJC
Threshold	2.78	2.55	19.5	21	9.8	6
Sensitivity	71.11	72.13	75.56	67.21	48.89	59.02
Specificity	70.59	61.11	41.18	50.00	70.59	61.11
Diagnostic accuracy	70.85	66.62	58.37	58, 6	59.74	60.06
Area under the curve	0.73	0.63	0.57	0.51	0.52	0.51
LB	0.61	0.47	0.44	0.34	0.39	0.35
UB	0.84	0.79	0.70	0.68	0.65	0.68
p	0.0005	0.0868	0.2894	0.9162	0.8083	0.8562

Note: TJC is the tender joint count; SJC is the swollen joint count. LB is the lower bound and UB is the upper bound of the 95% confidence interval.



a *b*

Fig. 2. ROC curves for the correlation between laboratory markers and RA activity: *a* – with TJC; *b* – with SJC

b

When determining the correlation between the studied markers and VAS, we found no differences between the parameters for calprotectin (AUC = 0.63, $p = 0.16$), ESR (AUC = 0.64, $p = 0.14$) and CRP (AUC = 0.56, $p = 0.57$), but the values obtained were not statistically significant ($p > 0.05$).

ROC analysis was conducted to assess the correlation between all markers and the degree of RA activity determined by CDAI. Taking into account the predominance of moderate and high RA activity, we included patients in remission and those with low and moderate RA activity in one group (CDAI < 22) and compared it with patients with high RA activity (CDAI > 22). The results of the analysis showed that calprotectin levels had higher diagnostic accuracy, sensitivity, and specificity (ACC = 73.04) compared with ESR (ACC = 65.82) and CRP (ACC = 61.32) (Fig. 3).

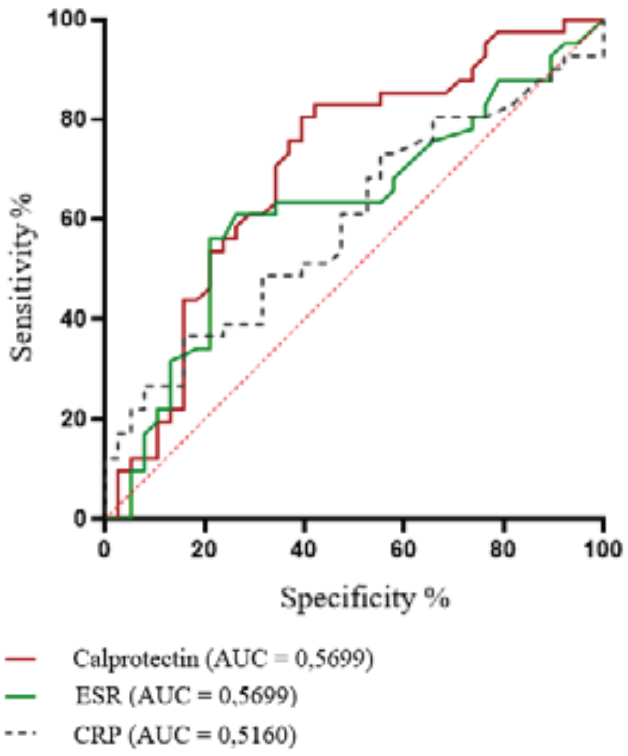


Fig. 3. ROC curves for all markers depending on the disease activity (CDAI >22)

The ROC analysis showed that the sensitivity, specificity, and diagnostic accuracy in assessing articular syndrome, as well as moderate and high RA activity according to the CDAI were higher for calprotectin than for traditional acute-phase reactants.

When the discriminant analysis was conducted, patients in remission and those with low RA activity according to DAS28 and CDAI were grouped together. According to the test results, only the combined use of ESR and calprotectin values was informative; following it, the probability of correct classification of RA activity, according to the DAS28 index, was 71%. According to the CDAI index, only calprotectin resulted in a statistically significant classification with a probability of 70.5 %.

Thus, according to a multivariate statistical analysis of data on the level of new RA activity biomarker, the diagnostic value of calprotectin not only remained competitive, but also showed better results.

According to the results of EGD, 38% of patients with RA showed signs of chronic gastritis without any signs of active inflammation. Gastric ulcer was visualized in 21% of patients, and duodenal ulcer was visualized in 8% of patients. According to EGD, in 1% of patients of the treatment group, gastric epithelial polyps were detected without atypical histologic features. According to EGD, the remaining 32% of patients had intact stomach and initial sections of the duodenum. During the period of hospitalization in the rheumatology department, none of the patients had indications for colonoscopy.

DISCUSSION

We identified statistically significant differences in the calprotectin level in patients with RA and healthy volunteers, since calprotectin is a proinflammatory cytokine involved in the development of immunological and inflammatory processes in RA. Calprotectin plays an important role in inflammation, as it interacts with the receptors of innate immunity, therefore, it was identified as a marker associated with RA [8, 9].

In our study, the calprotectin level correlated with the degree of RA activity, but especially close relationships were observed with the articular component of composite indices, as opposed to ESR and CRP. Our findings are confirmed by literature, where the study of local and systemic calprotectin production showed a statistically significant correlation of the marker level with the intensity of local inflammation, as well as with the clinical parameters of RA activity [10–15]. A meta-analysis conducted by S.-C. Bae et al. also showed that serum and synovial fluid calprotectin level correlated with RA activity [11]. Studies by H.B. Hammer et al. and J. Hurnakova et al. indicated that, based on ultrasound, serum calprotectin level correlated with synovitis, which did not correlate with the levels of ESR and CRP in patients with RA [12, 13]. Indeed, unlike CRP, calprotectin is produced locally and is not produced by hepatocytes in response to

stimulation by inflammatory cytokines, which makes it more informative and reliable [7–9, 15].

According to the conducted clinical and laboratory comparisons of data in ROC analysis, the level of the new biomarker showed the best results in assessing the articular syndrome and moderate and high disease activity, according to CDAI. According to the results of a large SONAR study, it was noted that the concentration of serum calprotectin was associated with SJC, as well as with CDAI. The biomarker level was statistically different in patients with different degrees of disease activity, according to DAS28, which weakly correlated with CRP. The multivariate analysis showed that calprotectin was independently associated with ultrasound parameters of synovitis, unlike CRP.

According to ROC analysis and DAS28, calprotectin turned out to be a more accurate marker in assessing RA activity in contrast to CRP, with AUC of 0.8 and 0.71 [14]. Thus, the authors of the study suggest that serum calprotectin levels accurately reflect the degree of local inflammation. These observations were confirmed by a prospective study, the results of which revealed the association between serum calprotectin level and RA activity according to DAS28 index in patients with normal CRP levels.

CONCLUSION

Plasma calprotectin level is a promising laboratory biomarker for assessing synovitis activity in RA demonstrating higher accuracy, sensitivity, and specificity than traditional acute-phase reactants.

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Korolkova A.A. – database formation, analysis and interpretation of the results obtained, drafting of the manuscript. Khizha V.V. – laboratory research, database formation. Kozlova D.I. – organization of laboratory research, database formation, analysis and interpretation of the data. Maslyansky A.L. – conception and design, substantiation of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Vavilova T.V. – substantiation of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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