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Differentiating Pulmonary Tuberculosis from Bacterial Pneumonia: The Role of Inflammatory and Other Biomarkers

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ABSTRACT

Introduction: To investigate the values of procalcitonin (PCT) and laboratory parameters in differentiating tuberculosis (TB) pneumonia from community-acquired pneumonia (CAP).

Methods: Between 01.01.2018 and 01.01.2020, 4,133 patients diagnosed with CAP or TB pneumonia in a reference hospital for chest diseases and TB were retrospectively screened. Patients with a history of close contact with someone with TB, night sweats, weight loss, or cavitary infiltration that may be typical for TB in the chest X-ray were evaluated clinically and radiologically as high TB suspects and were excluded from the study. Demographic characteristics, comorbidities, medications, admission complaints, radiological findings, microbiology results, and laboratory parameters were recorded. CURB-65 and pneumonia severity index scores were calculated. Patients were grouped as TB (n=70) and CAP (n=506) based on the final diagnosis. The parameters of the two groups were compared.

Results: The mean age of 576 patients was 55, and 423 (73%) were male. While sodium (Na) [95% confidence interval (CI): 0.716-0.914, p=0.001], blood urea nitrogen (BUN) (95% CI: 0.910-0.986, p=0.008), alanine aminotransferase (ALT) (95% CI: 0.913-0.998, p=0.043) and oxygen saturation (95% CI: 1.007-1.268, p=0.037) were found as independent biomarkers for differentiating TB and CAP, PCT had no significant influence on the differential diagnosis.

Conclusion: Prompt differential diagnosis between TB and CAP is important for public health in endemic TB areas. We recommend the evaluation of Na, ALT, and BUN for this purpose.

Keywords: Biomarkers, tuberculosis pneumonia, procalcitonin, community-acquired pneumonia, hyponatremia

Introduction

Community-acquired pneumonia (CAP) is a severe disease frequently encountered despite the use of many effective antibiotics and vaccines. However, tuberculosis (TB) continues to be a public health problem, the dimensions of which are increasing in our country and many developing countries, as it is in most of the world's geography (1).

CAP is one of the most common infections that cause death in adults and is the main reason for hospitalizations (2). Prompt diagnosis and early appropriate antibiotic therapy are essential to reduce morbidity and mortality from CAP. In countries where TB is common, *Mycobacterium tuberculosis* is a common cause of CAP (3-5). Differential diagnosis of TB from CAP is difficult because of the clinical and radiographic findings that vary according to the age and comorbidity of the patient and the low sensitivity of acid-fast bacillus microscopy (6,7). Therefore, the additional diagnostic method that can be used to differentiate between the two diseases will be of clinical importance in terms of isolating patients with TB and initiating appropriate anti-TB drug therapy at an early stage.

Diagnostic methods and early indicators of the extent of the inflammatory response can help in our initial treatment decisions.

Patients admitted to hospitals with CAP are often treated empirically for multiple organisms while awaiting research results. This costly approach may develop antibiotic resistance while exposing patients to potentially harmful pharmacotherapy or overdosage. Ultimately, it can lead to inappropriate treatment, negatively affecting morbidity and mortality. At the same time, even if the current diagnosis is TB, empirical antibiotic therapy facilitates the mechanisms that lead to the development of resistance to the major drugs used in treating TB.

C-reactive protein (CRP) is an acute phase protein and a non-specific marker of systemic inflammation (8). Procalcitonin (PCT) is a 116 amino acid protein with the same sequence as the prohormone calcitonin.

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It is synthesized by leukocytes and is found in high concentrations in the blood in bacterial infections and inflammatory response syndrome (9,10).

TB is associated with high circulating inflammatory cytokine levels, especially tumor necrosis factor-alpha (11,12). This cytokine has been shown to induce PCT production independent of the presence of bacterial endotoxins (13) and may explain the high PCT levels found in conditions other than bacterial sepsis, such as malaria (14) and systemic fungal infections (15).

Studies on the role of serum CRP concentration in determining the etiology of CAP and predicting its prognosis have been conducted (16-18), and it has been found that PCT is a better alternative to CRP in guiding antibiotic therapy in acute exacerbations of CAP and COPD (19,20). This result was attributed to the ability to distinguish between patients with and without bacterial infections. On the other hand, it was observed that PCT did not significantly increase in patients with pulmonary tuberculosis (PTB) (21,22). It can be concluded that it could be used as an attractive rapid differential diagnosis method to differentiate PTB from bacterial CAP.

PTB and CAP are common causes of lower respiratory tract infections and may have similar clinical and radiological features. It is important to accelerate the diagnosis and treatment planning in highly contagious disease groups such as TB pneumonia and to start isolation and specific treatment early to protect public health. For this reason, it is important to guide the physicians of other branches working in primary and secondary healthcare centers in differential diagnosis and treatment management.

The primary aim of this study was to investigate the diagnostic value of serum PCT and CRP sedimentation levels, which are inflammatory markers, to differentiate TB pneumonia in patients evaluated with the diagnosis of pneumonia. Its secondary purpose is to evaluate the auxiliary role of other laboratory markers and findings in diagnosing TB. The objective of the study was to facilitate the differential diagnosis between two common diseases to accelerate the diagnosis and consider microbiologic samples and initiating isolation for TB at the earliest to protect public health.

Methods

The study is a single-center and retrospective study that was conducted after being approved by the University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Board and Ethics Committee (approval number: 2021-102, date: 25.03.2021).

From the Hospital Information Management System between 01.01.2018 and 01.01.2020, 4,133 patients diagnosed with bacterial pneumonia and TB pneumonia by our hospital chest diseases clinics and TB clinic were identified. The files of all patients were re-evaluated, and patients under the age of 18, non-infective pneumonia cases, human immunodeficiency virus (+) patients, patients with high clinical suspicion (cough, night sweats, weight loss, close contact with someone with active TB) and radiological typical TB appearance (presence of cavitary infiltration in localizations that may coincide with lung areas where TB is common, such as upper lobe posterior and lower lobe superior), pregnant patients, patients who had undergone trauma or recent surgery, those with a lung cancer diagnosis, and additional immunosuppressive disease, patients with systemic inflammatory comorbidity, bronchiectasis patients, and multidrug-resistant (MDR) TB patients were excluded. A total of 576 patients (506 CAP, 70 TB) with all available baseline data recorded for the study were included (Figure 1).

Final diagnostic criteria: presence of clinical complaints such as cough and sputum with pneumonic infiltration without cavitary appearance in the chest X-ray, meeting the criteria for inclusion in the study, and monitoring clinical and radiological response after the treatment started.

TB diagnostic criteria: Presence of radiological lobar, multilobar or bronchopneumonic involvement and presence of acid-fast bacilli in sputum or bronchoalveolar lavage fluid, provided that cases with high clinical suspicion of TB. and radiological typical cavitary lesions are excluded.

CAP diagnostic criteria: Presence of radiological lobar, multilobar, or bronchopneumonic involvement in the presence of appropriate symptoms and physical examination findings, absence of acid-fast bacilli in the tests performed for the detection of the causative microorganism.

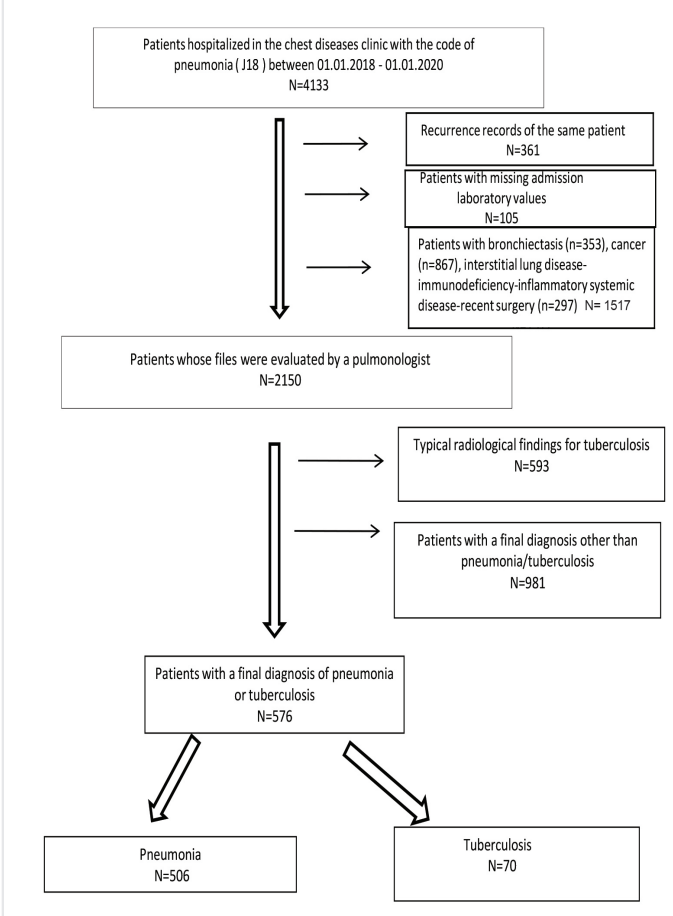

Figure 1. Flowchart for patient inclusion

Recorded Data

Patient age, gender, comorbidities, medications, admission complaints, radiological findings, basal hemogram, biochemistry data, arterial blood gas values, microbiological culture results, and direct examination results were recorded. Drug resistance patterns of TB patients were investigated. The CURB-65 score and pneumonia severity index (PSI) were calculated. Among the biochemistry data, urea, creatinine, PCT, CRP, aspartate aminotransferase, alanine aminotransferase (ALT), sodium (Na), potassium, chlorine (Cl), alkaline phosphatase, bilirubin, gamma glutamyl transferase, lactate dehydrogenase (LDH), and uric acid levels were recorded.

Statistical Analysis

Quantitative data are expressed as mean ± standard deviation and qualitative data are expressed as frequencies. Chi-square and Student's t-tests were used to evaluate the data obtained from the intergroup comparison. Variables found significant in univariate analysis were then incorporated into multiple logistic regression analysis. The cut-off value was determined for markers with $p<0.01$ in multi-way analyzes. The cut-off values for Na and blood urea nitrogen (BUN) levels were obtained from receiver operating characteristic (ROC) curves. All statistical analyzes were carried out using a statistical software package system (SPSS for Windows, version 16.0; SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

The mean age of all 576 patients was 55, and 423 (73%) were male. The most common complaints at admission were dyspnea (n=430, 75%) and cough (n=300, 52%), while 6 patients were asymptomatic. The final diagnosis was TB in 70 (12%) patients and pneumonia in 506 (88%) patients.

While smear positivity in 48 (69%), mycobacteria PCR positivity in 48 (69%), and culture positivity in 65 patients were recorded in PTB patients, the diagnosis was made hytopathologically in 5 patients. At least one non-MDR drug resistance, most commonly isoniazid, was recorded in 11 patients (Table 1).

When PTB and CAP patients were compared, it was seen that PTB patients were younger (51±20 vs. 65±15, $p<0.0001$) and the frequency of comorbid disease was lower (43% vs. 71%, $p<0.0001$). In CAP patients, dyspnea, and sputum were more common, and fatigue and weight loss were less frequent.

Among the additional diseases, heart failure (15% vs. 6%, $p=0.041$), renal failure (9% vs. 2%, $p=0.047$), and chronic obstructive pulmonary disease (COPD) (46% vs. 20%, $p<0.0001$) were more frequent in CAP patients. The frequency of TB history or index cases was less common in CAP patients (%14 vs. %23, $p<0.0001$).

Among the vital signs, tachypnea was detected more frequently in CAP (42% vs. 24%, $p=0.005$). CURB-65 and PSI scores were higher in CAP patients.

In laboratory findings in one-way analysis, PTB patients had lower leukocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), higher platelet (PLT) (pneumonia 283 TBC 338), lower platelet distribution width (PDW) lower, neutrophil (Ne) lower, eosinophils (Eo) higher, CRP lower, BUN lower, Na, ALT, and LDH lower, saturation was higher and statistically significant compared to CAP patients (Table 1).

WBC, MCV, Ne, PLT, CRP, Eo, BUN, LDH, Na, ALT, and saturation values, which were found to be significant between the two groups, were included in the logistic regression analysis. Accordingly, among the laboratory parameters, Na [odds ratio (OR): 0.809, 95% confidence interval (CI): 0.716-0.914, $p=0.001$], BUN [OR: 0.947, 95% CI: 0.910-0.986, $p=0.008$, ALT (OR: 0.955, %) 95 CI: 0.913-0.998, $p=0.043$] and oxygen saturation (OR: 1.133, 95% CI: 1.007-1.268, $p=0.037$) were found to be independent markers in the differentiation of PTB and CAP (Table 2).

Na and BUN were found to be predictors of PTB in ROC analysis. The predictor value for Na is 137 [area under the curve (AUC): 0.627: $p=0.001$, 56% sensitivity and 55% specificity] (Figure 2).

The preditor value for BUN is 37 (AUC: 0.760, $p<0.0001$, 75% sensitivity and 72% specificity) (Figure 3).

Discussion

In our study, when laboratory findings of PTB patients were compared with CAP patients, leukocytes, MCV, and MCH were lower, PDW was lower, Ne lower, CRP lower, BUN lower, Na, ALT, and LDH lower, PLT and Eo were higher, and saturation was higher and found to be significant compared to CAP patients. In multivariate analyzes baseline Na, BUN, ALT, and saturation values were independently significant for the two diseases.

PTB patients were younger and had fewer comorbidities. COPD was the most common comorbidity, followed by cardiovascular diseases. Since the CAP patients were older, COPD was observed more frequently as a comorbid disease, and these patients had more dyspnea, sputum complaints, and more deterioration in vital values such as hypotension, tachypnea, and low oxygen saturation. These patients had no history of TB or close contact with someone with active TB. In addition to the clinical and radiological evaluation, adequate medical history and investigation of risk factors are also important in determining the differential diagnosis and empirical treatment.

Pneumonia produces an inflammatory response that releases acute phase proteins. The fact that erythrocyte sedimentation rate (ESR) and leukocyte count, which are used to measure this response, can be affected by many infectious and inflammatory factors, reducing their sensitivity, and many studies on the acute phase response have shown that CRP levels have a superior diagnostic efficiency in determining bacterial pneumonia in adults (23). Our study found no significant difference in ESR levels; leukocyte and CRP levels were lower in PTB patients.

When PCT values were examined, no distinctive statistically significant difference was found between the two diseases. Although it was stated in the current studies that low PCT was a predictor in favor of TB in the differentiation of TB pneumonia and CAP, no distinctive statistically significant difference was found between the two diseases in our study.

Table 1. Comparison of recorded clinical findings according to the final diagnosis

	All patients	Pneumonia	TBC	p-value
	(n=576)	(n=506)	(n=70)	
Gender (n, %)				
Male	423 (73)	373 (74)	50 (71)	0.667
Female	153 (27)	133 (26)	20 (29)	
Mean age; (years ± SD, minimum-maximum)	63.1±16.6 (17-100)	65±15	51±20	<0.0001
Admission complaints (n, %)				
Shortness of breath	430 (75)	397 (79)	33 (47)	<0.0001
Cough	300 (52)	261 (52)	39 (56)	0.527
Sputum	193 (35)	187 (37)	17 (24)	0.045
Temperature	155 (27)	142 (28)	13 (19)	0.113
Weakness	67 (12)	51 (10)	16 (23)	0.004
Hemoptysis	47 (8)	37 (7)	10 (14)	0.06
Pain (back/chest)	56 (10)	50 (10)	6 (10)	0.833
Weight loss	14 (2)	8 (2)	6 (9)	0.004
Other	53 (9)	42 (9)	8 (14)	0.068
Asymptomatic	6 (2)	2	4	0.054
Presence of additional disease (n, %)	388 (67)	358 (71)	30 (43)	<0.0001
Additional diseases (n, %)				
IHD	123 (21)	109 (22)	14 (20)	0.877
CHF	80 (14)	78 (15)	4 (6)	0.041
CKD/AKF	47 (8)	46 (9)	1 (2)	0.032
Liver disease	4 (1)	4	0	0.998
CVA	9 (2)	8 (2)	1 (2)	0.998
DM	125 (22)	112 (22)	13 (19)	0.541
COPD	246 (43)	232 (46)	14 (20)	<0.0001
Hypertension	46 (8)	44 (9)	2 (3)	0.102
Asthma	8 (1)	8 (2)	0	0.607
TBC history (n, %)	84 (15)	68 (14)	16 (23)	<0.0001
Antibiotics use before admission (n, %)	266 (48)	261 (53)	30 (48)	0.590
Vital values (n, %)				
Temperature (<35/>40)	122 (22)	113 (23)	9 (13)	0.112
HR >125	121 (21)	105 (21)	17 (25)	0.429
RR >30	225 (40)	209 (42)	16 (24)	0.005
BP >90	22 (4)	19 (4)	3 (5)	0.736
CURB-65 mean score	1.9±0.9	1.9±0.8	1.3±0.9	<0.0001
CURB-65 score (n, %)				
0	33 (6)	22 (4)	11 (6)	-
1	152 (26)	121 (24)	32 (47)	-
2	254 (44)	235 (47)	19 (28)	<0.0001
3	125 (22)	118 (24)	7 (10)	-
4	8 (1)	8 (2)	0	-
PSI group (n, %)				
0	2 (0.3)	2 (0.4)	0	-
1	93 (16)	65 (13)	29 (41)	-
2	89 (16)	76 (15)	13 (20)	<0.0001
3	120 (21)	111 (22)	10 (15)	-
4	207 (36)	193 (38)	14 (20)	-
5	61 (11)	57 (11)	4 (7)	-

SD: Standard deviation, BP: Blood pressure, CHF: Congestive heart failure, CKD/AKF: Chronic kidney disease/acute kidney injury, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, CVA: Cerebrovascular accident, DM: Diabetes mellitus, HR: Heart rate, IHD: Ischemic heart disease, PSI: Pneumonia severity index, RR: Respiratory rate

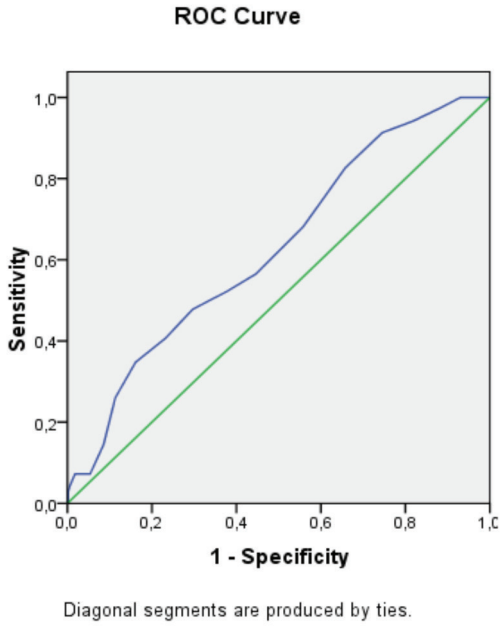

Figure 2. ROC curve for sodium
ROC: Receiver operating characteristic

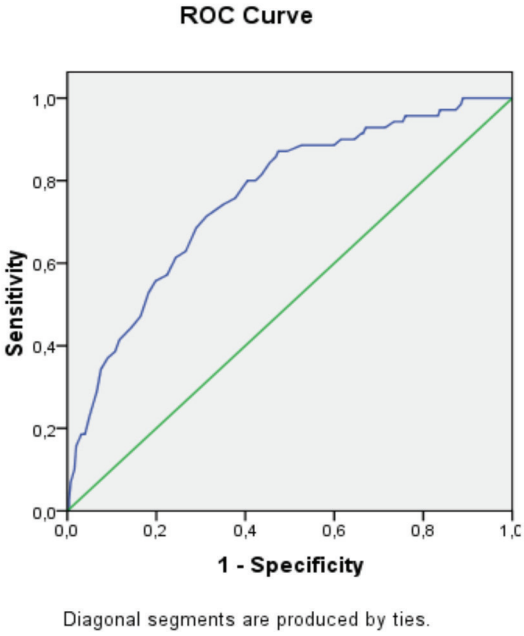

Figure 3. ROC curve for blood urea nitrogen levels (BUN)
ROC: Receiver operating characteristic, BUN: Blood urea nitrogen

This current finding may be due to the significant difference between our sample sizes and atypical bacterial agents and viral infections that do not cause a significant increase in PCT. In our study, the responsible bacterial or viral agents in each infection could not be determined, and it was determined that there were not sufficient tests for the isolation of the agent in some data. At the same time, since our hospital is a tertiary education and research hospital, the fact that the patients spent the first

Table 2. Multiple logistic regression analysis according to the final diagnosis

	OR	95% CI	p-value
WBC	1.009	0.702-1.452	0.960
MCV	0.979	0.895-1.071	0.647
Ne	0.909	0.609-1.358	0.642
PLT	1.004	0.999-1.009	0.138
CRP	0.998	0.990-1.005	0.518
Eo	1.603	0.126-10.419	0.716
BUN	0.947	0.910-0.986	**0.008**
LDH	1.005	0.999-1.011	0.120
Na	0.809	0.716-0.914	**0.001**
ALT	0.955	0.913-0.998	**0.043**
Saturation	1.133	1.007-1.268	**0.037**

ALT: Alanine transaminase, BUN: Blood urea nitrogen, CRP: C-reactive protein, Eo: Eosinophil, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, Na: Sodium, Ne: Neutrophil, PLT: Platelet, WBC: White blood cell, CI: Confidence interval, OR: Odds ratio

24-48 hours from the onset of symptoms until they applied to us may also have a role in this.

A comparative study by Quist and Hill (24) on TB, bacterial, and Pneumocystis carinii pneumonias found that LDH levels were high in 73% of bacterial pneumonias, and AST and ALT levels were high in 74%.

It has been reported that elevated LDH, BUN, and ALT levels are associated with poor prognosis and mortality in CAPs (25). In our study, where ALT and LDH levels were significantly lower in TB pneumonia patients, we can also attribute this to the fact that our CAP patients were older patients with comorbid diseases.

Hyponatremia, an electrolyte disorder, is relatively common in patients presenting with pneumonia and has been associated with disease severity. The exact mechanism is not fully understood, but inappropriate antidiuretic hormone (ADH) secretion is thought to play a role in the etiology, and low serum Na level has been associated with a poor prognosis (26-29). Zilberberg et al. (27) found that pneumonia patients with hyponatremia had more intensive care and extended hospital stays.

Factors such as interleukin-6, one of the inflammatory cytokines, stress, hypoxia, and nausea are associated with the non-nosmotic stimulus of ADH (30). In addition to pneumonia, ADH stimulation can be seen in infections such as TB and malaria.

The low BUN, which usually occurs due to not meeting the amount of protein needed by the body with nutrition, may also be due to excessive fluid consumption. In addition to the low socioeconomic level in TB patients, anorexia, and malnutrition that develops with the chronic course of the disease, the anabolic process in which the body enters may explain the low BUN, which is more pronounced in TB than in pneumonia.

In countries where TB is common, it is important to distinguish between TB pneumonia and CAP, take isolation precautions earlier, and start appropriate anti-tuberculous treatment to protect public health. It can be challenging to distinguish between diseases based on physical examination, radiological findings, and clinical features. For this reason,

the diagnostic algorithm can also include laboratory parameters understood to be supportive and distinctive.

Study Limitations

To fully evaluate our results, we must consider the limitations of this study. First, TB pneumonia patients were younger than CAP patients, few had advanced comorbidity, and the sample size was smaller.

Conclusion

Although additional studies with a higher number of TB pneumonia patients will provide us with more reliable information, it is important to correctly distinguish between TB pneumonia and CAP in countries where TB is common. Na, ALT, and BUN levels can be considered among the distinguishing laboratory parameters of the two diseases.

Ethics Committee Approval: The study is a single-center and retrospective study that was conducted after being approved by the University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Board and Ethics Committee (approval number: 2021-102, date: 25.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: No conflict of interest was declared by the authors.

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