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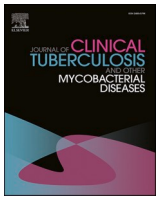

Relationship between patient sex and anatomical sites of extrapulmonary tuberculosis in Mali

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ABSTRACT

Background: Contribution of host factors in mediating susceptibility to extrapulmonary tuberculosis is not well understood.
Objective: To examine the influence of patient sex on anatomical localization of extrapulmonary tuberculosis.
Methods: We conducted a retrospective cross-sectional study in Mali, West Africa. Hospital records of 1,304 suspected cases of extrapulmonary tuberculosis, available in TB Registry of a tertiary tuberculosis referral center from 2019 to 2021, were examined.
Results: A total of 1,012 (77.6%) were confirmed to have extrapulmonary tuberculosis with a male to female ratio of 1.59:1. Four clinical forms of EPTB predominated, namely pleural (40.4%), osteoarticular (29.8%), lymph node (12.5%), and abdominal TB (10.3%). We found sex-based differences in anatomical localization of extrapulmonary tuberculosis, with males more likely than females to have pleural TB (OR: 1.51; 95% CI [1.16 to 1.98]). Conversely, being male was associated with 43% and 41% lower odds of having lymph node and abdominal TB, respectively (OR: 0.57 and 0.59).
Conclusion: Anatomical sites of extrapulmonary tuberculosis differ by sex with pleural TB being associated with male sex while lymph node and abdominal TB are predominately associated with female sex. Future studies are warranted to understand the role of sex in mediating anatomical site preference of tuberculosis.

1. Introduction

Tuberculosis (TB) remains one of the leading causes of death due to an infectious disease worldwide. In 2020, the World Health Organization (WHO) reported 1.3 million TB deaths, globally, among people not infected with HIV [1]. TB is typically considered to be a pulmonary disease, but the bacilli responsible for TB in humans, can infect non-pulmonary tissues through lymphatic or blood circulation

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and cause extra-pulmonary tuberculosis (EPTB) [2,3]. According to the WHO, any form of TB that occurs in a tissue outside the lung parenchyma is defined as EPTB [4]. EPTB can also occur when a susceptible host ingests contaminated food, usually non-pasteurized dairy products [3]. EPTB constitutes, on average, 15–20% of all incident TB cases [5]. Clinically, it is characterized by a spectrum of clinical manifestations, but the most common forms are lymph node, pleural, osteoarticular, and urogenital TB [6–8].

Host factors are thought to influence the pathogenesis of EPTB, but the mechanisms remain poorly defined. The most highly reported risk factors for EPTB are race, HIV infection, extreme age, and female sex [6,8,9]. Female sex has been consistently associated with reduced risk of pulmonary TB and favorable treatment outcomes when compared to male sex [10–12]. However, the reasons why females seem more vulnerable to EPTB, while being relatively resistant to pulmonary TB are unclear. Increased co-infection with HIV in females is one explanation [13]. For example, 63% of new HIV infections occur in females in Sub-Saharan Africa [13], a region where TB is endemic and co-infection with HIV in individuals affected by EPTB is common [5,14]. Another possible reason is biological sex, specifically sex hormones, genetic factors, and their underlying effects on immunity [15], yet the role of these biological factors in mediating sex differences in EPTB is underexplored [2].

A prerequisite for determining the role of biological sex in EPTB pathogenesis is a better understanding of the influence of patient sex on EPTB burden (i.e., incidence, prevalence, and mortality), anatomical site, clinical severity, and treatment outcomes. A recent study in Korea revealed that adult females have 48% higher odds of developing EPTB compared to adult males [16]. Historically, there has been little interest in reporting and studying risk factors of EPTB. On one hand, the impact of EPTB on the global burden of TB was not considered as substantial, given the fact that EPTB cases are usually not contagious. Thus, there is a lower likelihood of sustaining and amplifying TB transmission cycles [2]. On the over hand, the inherent challenges of diagnosing EPTB with traditional tools (chest X-ray and microscopy) limit the ability to perform in-depth clinical investigations, particularly in resource-limited settings, such as low- and middle-income countries (LMICs). In fact, patients affected with EPTB usually have no radiographic findings on chest X-ray and most EPTB cases are paucibacillary [2]. The gold standard for EPTB diagnosis is blood culture or tissue biopsy, which are not always available in LMICs [17]. However, detection of bacterial genomic DNA in affected tissues by nucleic acid amplification techniques (NAAT), such as the Xpert MTB/RIF, are now commonly used because of their sensitivity and rapid turnaround of results [17].

Gaining a better understanding of the role of biological sex on the anatomical site preference of EPTB is essential to improving clinical care and (1) could advance the goal of reducing TB-associated deaths, worldwide, by targeting people at the highest risk of developing severe forms of EPTB such as TB meningitis and pericardial TB; (2) accelerate rapid identification of sex-specific biomarkers to identify individuals, who are likely to fail treatment because of drug resistance or poor compliance to treatment; (3) provide more evidence that sex should be considered as a "biological variable" for the rational development of novel host-directed therapeutics and vaccines against TB.

The study seeks to (1) describe the sex-specific distribution of different anatomical sites of EPTB and (2) determine whether there is a sex difference in the odds of developing EPTB at a specific anatomical site. We hypothesize that biological sex is a contributor of anatomical localization of EPTB. The study was conducted in Mali, a large country in the heart of West Africa with endemic TB. Pleural, osteoarticular, and lymph node TB have reportedly accounted for 48% of all EPTB in Mali (4), but the sex-specific distribution has never been described. We believe that studying EPTB in the Malian context provides an ideal opportunity to investigate EPTB in an adult population with less confounding due to HIV infection. Indeed, prevalence of HIV infection in new and relapse TB cases is estimated to be around 8,6% in Mali [1], which is quite low compared to other Sub-Saharan African countries like South Africa where the HIV-TB co-infection rate is nearly 60% [18].

2. Methods

2.1. Study design and participants

We conducted a retrospective, cross-sectional study of EPTB patients in the TB Registry of the Department of Pneumophtisiology of the University Teaching Hospital of Point-G in Bamako, Mali, for a three-year-period (from January 2019 to December 2021). Patients are referred to this department from all over Mali as it is the only specialized center for clinical management and diagnosis of EPTB and drug-resistant TB in Mali. Therefore, data collected from the TB Registry are likely to be representative of most EPTB cases in the country. We obtained approvals from the Director of the University Teaching Hospital of Point-G and the Chief of the Department of Pneumophtisiology before submission of the protocol to the Ethics Committee. We included data available from male and female patients of any age diagnosed with EPTB and who initiated anti-tuberculosis treatment in the department. The case was recorded as EPTB based on the 2013 WHO definition, which defines EPTB as "any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs" [4]. We excluded patients without a specific EPTB diagnosis or documentation of the anatomical site of the disease in the EPTB registry.

2.2. Data collection and analysis

A paper-based data collection form, specifically designed for the study, was used to abstract patients' demographic information (age, sex, and residency), diagnosis, EPTB anatomical sites, and date of TB treatment initiation. A senior clinician and lead author, with a master's degree (MS) in Clinical Investigation at the Northwestern University, oversaw all procedures pertaining to data collection, including the design of the data collection form, training of data collectors, assignment of anonymous identification numbers to ensure anonymity and confidentiality of the data. Quality assurance was performed by audit of two clinicians in the department. De-identified data were then transferred into an Excel spreadsheet per the study protocol, followed by a second round of quality assurance. Data were analyzed using the R software. Proportions of EPTB by anatomical site were estimated by sex and compared using a Chi-square or Fisher test. Simple logistic regressions were used to estimate the odd ratios, using female as reference group, with the goal of determining whether one sex is at greater risk of developing EPTB at a specific anatomical site. A difference was considered significant if, at the 95% confidence interval (CI), the two-tailed p-value is < 0.05.

2.3. Ethical considerations

The study protocol (N°2021/191/CE/USTTB) was approved by the Ethics Committee of the University of Sciences, Techniques, and Technologies of Bamako (USTTB).

3. Results

3.1. Characteristics of study participants

The Registry included 1,304 patients with TB between January 2019 through December 2021. Of these, 1,012 (77.6%) patients were recorded as having EPTB, as shown in Fig. 1, while 271 (20.8%) had smear microscopy negative pulmonary TB and 21 (1.6%) had miliary TB, which is considered to be pulmonary TB, based on the WHO definitions used in this study [4]. Most EPTB patients were male (61%), with a male to female sex ratio of 1.59:1. Mean age was 41.0 ± 18.2 years for males and 41.1 ± 17.8 years for females (Fig. 1). Overall, the largest age group was 25–34 years for both males (23.6%) and females (22%). No

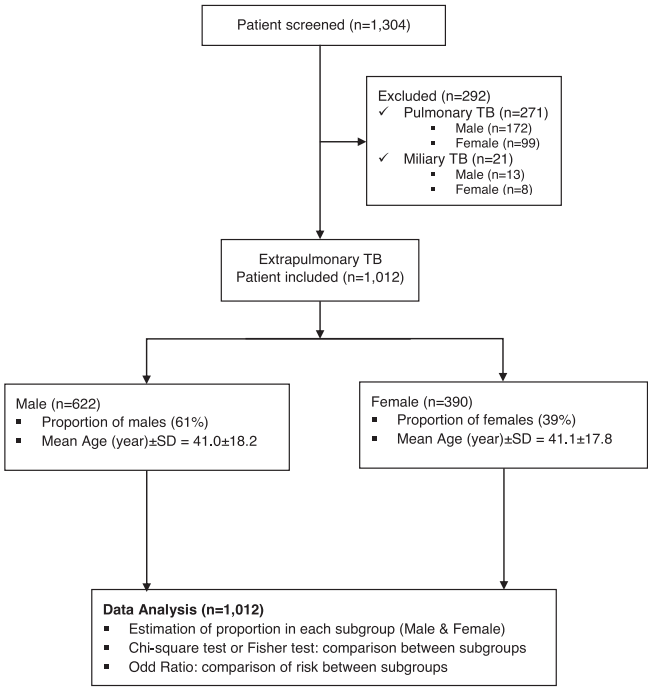

Fig. 1. Participant selection flow chart. Hospital records of 1, 304 patients were available over a 3-year period. Out of whom 1,012 subjects were confirmed to have extrapulmonary tuberculosis (EPTB), thus were included in the study. EPTB cases were disaggregated by sex and data were analyzed according to the scheme presented in this figure.

Table 1
Characteristics of study participants.

Parameter	All N = 1,012	Male N = 622	Female N = 390	*p*-value
	N (%)	N (%)	N (%)	#
Age (year)				
Under 18	71 (7.0)	42 (6.8)	29 (7.4)	0.604
18–24	119 (11.8)	79 (12.7)	40 (10.3)	
25–34	233 (23.0)	147 (23.6)	86 (22.0)	
35–44	177 (17.5)	99 (15.9)	78 (20.0)	
45–54	146 (14.4)	88 (14.1)	58 (14.9)	
55–64	147 (14.5)	90 (14.5)	57 (14.6)	
≥ 65	119 (11.8)	77 (12.4)	42 (10.8)	
Residence				
Commune I	126 (12.5)	77 (12.4)	49 (12.6)	0.051
Commune II	66 (6.5)	43 (6.9)	23 (5.9)	
Commune III	37 (3.7)	21 (3.4)	16 (4.1)	
Commune IV	125 (12.4)	81 (13.0)	44 (11.3)	
Commune V	146 (14.4)	75 (12.1)	71 (18.2)	
Commune VI	257 (25.4)	152 (24.4)	105 (26.9)	
Outside Bamako	255 (25.2)	173 (27.8)	82 (21.0)	
Year of Inclusion				
2019	488 (38.3)	261 (42.0)	127 (32.6)	0.009
2020	312 (30.8)	176 (28.3)	136 (34.9)	
2021	312 (30.8)	185 (29.7)	127 (32.6)	
Month of Inclusion				
January	66 (6.5)	36 (5.8)	30 (7.7)	0.378
February	87 (8.6)	55 (8.8)	32 (8.2)	
March	105 (10.4)	64 (10.3)	41 (10.5)	
April	79 (7.8)	58 (9.3)	21 (5.4)	
May	94 (9.3)	64 (10.3)	30 (7.7)	
June	100 (9.9)	54 (8.7)	46 (11.8)	
July	86 (8.5)	53 (8.5)	33 (8.5)	
August	75 (7.4)	44 (7.1)	31 (7.9)	
September	70 (6.9)	45 (7.2)	25 (6.4)	
October	86 (8.5)	49 (7.9)	37 (9.5)	
November	83 (8.2)	49 (7.9)	34 (8.7)	
December	81 (8.0)	51 (8.2)	30 (7.7)	

significant association ($p = 0.604$) was found between patient sex and age (Table 1). To ensure that the sex-based differences in EPTB prevalence were not an artefact of reporting bias, we stratified the data by year (Table 1). For any given year, there were more males than females in absolute numbers, with a decrease in the number of cases from 2019 to 2021. Similar results were obtained when data were categorized by month instead of year (Table 1). More males had EPTB than females, regardless of the period of the year. A greater number of EPTB cases were diagnosed between March and June each year, which corresponds to the dry season in Mali.

3.2. Sex and EPTB anatomical sites

Overall, the most frequent clinical forms of EPTB were pleural 40.4% (409), osteoarticular 29.8% (302), lymph node 12.5% (127), and abdominal 10.3% (104) TB (Table 2). Sex-specific differences were consistent for pleural, lymph node, and abdominal TB, but not for osteoarticular TB. Males were more impacted by pleural TB than females (44.2% versus 34.4%; $p = 0.002$) and females were more likely to present with lymph node and abdominal TB, $p = 0.004$ and $p = 0.015$, respectively (Table 2). No sex differences were observed for other anatomical sites. We also found that male sex was associated with 51% increased odds of developing pleural TB (OR: 1.51, 95 %CI (1.16 to 1.98), $p = 0.002$), but associated with lower odds of developing lymph node and abdominal TB (OR: 0.57 and 0.59, respectively) (Table 3).

4. Discussion

A key goal of the WHO is to reduce TB incidence by 90% by 2035 [1]. While global efforts have been successful in significantly decreasing the number of pulmonary TB cases, the number of EPTB cases has increased in many settings [8,19,20]. The impact of the HIV pandemic on the global TB epidemiology was initially thought to be a main factor of the rise in EPTB cases [21], but it is now clear that additional risk factors need to be considered. Among those, the role of sex in the susceptibility to EPTB has been raised. In this study, we sought to determine whether patient sex influences the anatomical site preference of EPTB in a cohort of patients in Mali. The most frequent clinical forms of EPTB were pleural, osteoarticular, lymph node, and abdominal TB, with striking sex-based differences in EPTB anatomical sites. Specifically, males were less likely to have lymph node and abdominal TB, but more likely to have pleural TB. Conversely, we did not find a significant association between patient age and anatomical site of EPTB.

An association between sex and incidence or prevalence of EPTB has been consistently reported [2,10,12]. In the United States (US), being female, HIV infected, and non-Hispanic black increased the risk of developing EPTB [6,9]. Similarly, in Europe, a higher prevalence of EPTB was found in Dutch females compared to males [22]. In North Africa, the predominance of female sex in EPTB was also reported with a prevalence as high as 63% [23]. While, in this study, we did not find a higher frequency of EPTB in females, we did observe that two of the

Table 2
Sex-specific clinical presentation of extrapulmonary tuberculosis.

Localization	Overall N = 1,012	Male N = 622	Female N = 390	*p*-value
	n (%)	n (%)	n (%)	
Pleural	409 (40.4)	275 (44.2)	134 (34.4)	0.002**
Osteoarticular	302 (29.8)	191 (30.7)	111 (28.5)	0.491
Lymph node	127 (12.5)	63 (10.1)	64 (16.4)	0.004**
Abdominal	104 (10.3)	52 (8.4)	52 (13.3)	0.015*
Neuro-meningeal	29 (2.9)	17 (2.7)	12 (3.1)	0.900
Genito-urinary	18 (1.8)	9 (1.5)	9 (2.3)	0.445
Cardiac	12 (1.2)	10 (1.6)	2 (0.5)	0.205
Others[†]	11 (1.1)	5 (0.8)	6 (1.5)	0.352

[†] = Eye + Breast + Skin + Ear, Nose, and Throat (ENT).

Table 3
Site-specific risk of extrapulmonary tuberculosis by sex.

Localization	Female* N = 390	Male N = 622	OR [95% CI]	*p*-value
	# (%)	# (%)		
Pleural	134 (34.4)	275 (44.2)	1.51 [1.16 to 1.95]	0.002**
Osteoarticular	111 (28.5)	191 (30.7)	1.11 [0.84 to 1.47]	0.447
Lymph node	64 (16.4)	63 (10.1)	0.57 [0.39 to 0.83]	0.004**
Abdominal	52 (13.3)	52 (8.4)	0.59 [0.39 to 0.89]	0.012*
Neuro-meningeal	12 (3.1)	17 (2.7)	0.88 [0.42 to 1.87]	0.750
Genito-urinary	9 (2.3)	9 (1.5)	0.62 [0.24 to 1.57]	0.318
Cardiac	2 (0.5)	10 (1.6)	3.17 [0.69 to 14.54]	0.138
Others[†]	6 (1.5)	5 (0.8)	0.52 [0.16 to 1.71]	0.281

*Reference
[†]Eye + Breast + Skin + Ear Nose and Throat (ENT)

most common anatomical sites of EPTB (lymph node and abdominal TB) were significantly more common in females. In contrast, pleural TB predominated in males. Our data are well aligned with studies conducted in Germany [24], India [25], and Pakistan [26], which all observed that lymph node TB was more common among females while pleural TB was more frequent in males. Therefore, sex-specific anatomical localization of EPTB do exist, but may have been masked in studies that considered all EPTB as a single disease, irrespective of the anatomical site of the disease.

The reason for higher risk of EPTB in females is still unknown. Isolating the role of biological sex from other risk factors, such as HIV infection and age, can be challenging [9,27], However, biological factors, such as sex hormones, genetic factors, and their underlying effects on immunity are possible contributing factors [15]. For example, the risk of EPTB is more pronounced in females > 45 years, who, presumably, have a reduced level of estradiol and a weaker immune system, which may reduce containment of mycobacterium within the lungs [28]. Similarly, before, puberty when sex hormonal response is at lowest and immune response is immature, infection with *Mycobacterium tuberculosis* is more likely to result in EPTB, specifically TB meningitis [2]. In contrast, EPTB is considerably less common at puberty, as the disease manifestation mirrors that of adults, primarily pulmonary TB. These findings suggest that hormonal effects on immunity appear to mediate EPTB susceptibility and outcomes. There is also evidence that testosterone and estradiol regulate immune responses to pulmonary TB in animal models [29], specifically, ovariectomized mice exhibit higher mycobacterial burden in the lungs and this phenotype is reversed by in vivo treatment with estradiol (E2), suggesting that E2 has a protective effect on infection with mycobacterium [29]. In the absence of common risk factors, such as HIV [30,31], EPTB is frequently diagnosed in foreign-born ethnic minorities such as South East Asian and Sub-Saharan Africans, who emigrate to the US and Europe, suggesting a genetic predisposition to EPTB. This hypothesis is further supported by findings that people from African ancestry are more susceptible to EPTB [6]. Moreover, two novel single nucleotide polymorphisms (SNPs), which were found to distinguish EPTB from PTB, namely rs340708 and rs1886870, have been identified from a pilot genome wide association study [32]. Therefore, there is growing evidence that sex-specific biological factors may promote EPTB in certain anatomical sites.

Female bias was observed in lymph node and abdominal TB. Lymph nodes, are secondary lymphoid tissues, enriched with immune cells and where antigen-presenting cells activate adaptive immunity to mycobacterium after infection. We hypothesize that the resulting disease is the consequence of dysregulated immune responses to mycobacteria leading to specific immunopathology in females in the absence of an optimal hormonal milieu. Conversely, while males are more susceptible to pleural TB, but not other forms of EPTB, is largely unexplained. It is, however, important to note that pleural TB is the only anatomic site of EPTB that is confined to the chest, based on the WHO definition [4], confirming that sex-based differences in TB outcomes are site-specific or tissue-specific (pulmonary versus non-pulmonary sites). Further studies are therefore needed to examine whether unique and sex-specific factors exist in these tissues, such as expression of hormone receptors, immune cell trafficking, and/or X-linked gene expression. Nonetheless, we do not propose to preclude the role of non-biological factors, such as differences in TB acquisition and exposure, between men and women. For example, certain clinical forms of EPTB have been shown to occur via zoonotic transmission by ingesting infected foods with *Mycobacterium bovis*, specifically raw milk, unpasteurized dairy products, and undercooked meats, or by inhaling aerosol from infected livestock [3]. Whether women and men have differential eating behaviors or differential exposure to livestock in Mali, also needs to be studied.

Last but not the least, the impact of smoking and alcohol in the development of pleural TB in males requires consideration. It is well established that males are more likely to smoke and drink alcohol than females [33]. The Global Burden of Disease Consortium has recently reported that the proportion of TB-associated deaths in HIV-negative individuals attributable to smoking and substance abuse was respectively 4.27 and 6.17 times higher in males compared to females, based on data gathered from more than two hundred countries and territories [34]. The data suggest that smoking and alcohol drinking are contributors of sex differences in TB outcomes. However, future research is needed to determine whether excess of pleural TB in males is associated to these non-biological factors, which are also influenced by gender.

The large sample size, assessment of EPTB burden over three years, and use of Registry records from the only EPTB Referral Center in Mali are strengths of the study. However, the cross-sectional design and lack of information on co-morbidities, such as HIV and diabetes, with potential immunologic impact are limitations of this study. Similarly, behavioral data, such as smoking, alcohol, and illegal substances use, as well as information regarding professional and socioeconomic characteristics which may be associated with TB exposure and gender, were not available. Finally, the study is limited by the lack of longitudinal follow-up to determine differences in EPTB treatment outcomes by anatomic site and sex.

In summary, we found that the anatomical sites of three forms of EPTB (pleural, lymph node, and abdominal, TB) are sex specific. Future studies are warranted to define mechanisms leading to the impact of sex and gender in the pathogenesis and treatment outcomes of EPTB.

CRediT authorship contribution statement

Bocar Baya: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft. **Ibrahim Sanogo:** Software, Formal analysis, Data curation, Writing – review & editing. **Mahamadou Kone:** Investigation, Data curation, Writing – review & editing. **Dianguina Soumare:** Validation, Resources, Writing – review & editing. **Kadidia Ouattara:** Validation, Resources, Writing – review & editing. **Amadou Somboro:** Investigation, Data curation, Writing – review & editing. **Mamadou Wague:** Investigation, Writing – review & editing. **Nadie Coulibaly:** Investigation, Writing – review & editing. **Isaac Koloma:** Investigation, Writing – review & editing. **Mariam Coulibaly:** Investigation, Writing – review & editing. **Mohamed Nantoume:** Investigation, Writing – review & editing. **Mamadou Perou:** Investigation, Writing – review & editing. **Kadidia Kone:** Investigation, Writing – review & editing. **Djeneba Coulibaly:** Investigation, Writing – review & editing. **Hawa Boukary Diarra:** Investigation, Writing – review & editing. **Bourahima Kone:** Investigation, Resources, Writing – review & editing. **Ayouba Diarra:** Software, Formal analysis, Data curation, Writing – review & editing.

Mamadou D. Coulibaly: Software, Formal analysis, Data curation, Writing – review & editing. **Moumine Sanogo:** Investigation, Resources, Writing – review & editing. **Bassirou Diarra:** Investigation, Resources, Writing – review & editing. **Mahamadou Diakite:** Resources, Supervision, Writing – review & editing. **Chad J. Achenbach:** Supervision, Writing – review & editing. **Seydou Doumbia:** Resources, Supervision, Writing – review & editing. **William R. Bishai:** Supervision, Writing – review & editing. **Sabra L. Klein:** Supervision, Writing – review & editing. **Jane L. Holl:** Supervision, Writing – review & editing. **Souleymane Diallo:** Resources, Supervision, Writing – review & editing. **Robert L. Murphy:** Supervision, Writing – review & editing. **Yacouba Toloba:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – review & editing, Supervision. **Djeneba Dabitao:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – original draft, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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