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Bronchiectasis in Low and Middle Income countries - the importance of the wider view

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Until the early 2000s PubMed data showed there were fewer than 200 papers published on bronchiectasis per year. Since then, publications on bronchiectasis have increased rapidly to a peak of 834 publications in 2021 (for context, just over 10% of the total for COPD or asthma). The quality of the published data has also improved substantially, and now includes large epidemiology datasets, clinical insights from disease registry studies, and multiple controlled trials. This body of work has shown that bronchiectasis, far from being a disease from the history books, is increasing in incidence in high-income countries (HIC), at least in part due to the greater accessibility of CT lung scanning, and has defined severity scoring systems, causative aetiologies, novel disease phenotypes, and effective therapies[1-6]. However, a major limitation has been the very limited data published on bronchiectasis from countries other than Europe, the US, and Australasia. Bronchiectasis is the end consequence of multiple different aetiologies, many of which (such as previous severe lung infections and tuberculosis [TB]) have a higher prevalence in Low and Middle Income Countries (LMIC). As a result, the published data on bronchiectasis probably does not accurately reflect the global burden of bronchiectasis, nor provide the clinical insights needed to improve management in LMICs.

This is the knowledge gap addressed by the paper by Dhar et al in this edition of the ERJ[7] and their previous paper[8]. These papers have used data from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry (EMBARC-India) patient registry that replicates the EMBARC European registry and recruits patients from 31 sites across India. The initial EMBARC-India paper described the demography and disease characteristics for 2195 patients and compared these European, Israeli and the US datasets[8] to demonstrate that bronchiectasis in India has substantial and important differences compared to bronchiectasis from HIC. Indian patients were a median of 11 years younger, had a male rather than female preponderance, were more likely to have a clinician-defined post-infective aetiology (nearly 60% of all cases, the majority post-TB), and had more severe bronchiectasis with higher Reiff radiology scores, a greater proportion of cystic dilatation, lower FEV1 (61% predicted v 74% for the European/Israeli cohort), and a higher rate of admission to hospital for treatment of exacerbations (summarised in **Table 1**). The younger age and higher incidence of post-infective aetiology in EMBARC-India are probably predictable given the high prevalence of TB, which can cause bronchiectasis in up to 44% of cases[9], and childhood respiratory infections in India. However, the reason(s) for the male preponderance remains unclear as both TB and childhood pneumonia have an even sex distribution in India[10,11]. Furthermore, the higher severity of cases in the EMBARC-India registry compared to Western countries was perhaps less predictable. This could potentially reflect a recruitment bias for more severe cases as the registry sites include a relative over-representation of tertiary (10) compared to secondary healthcare or community sites (21), and required a CT scan to confirm the diagnosis, access to which remains limited in many LMIC settings.

The current paper by Dhar et al. uses the EMBARC-India registry data to describe the outcomes and risk factors associated with mortality, hospitalisation or exacerbations[7]. They studied a subset of 1018 patients of the registry patients with at least 12 months follow up, roughly 50% of the EMBARC-India cohort. There were no significant differences for multiple

demographic and clinical factors for the included patients compared to the overall cohort, and the data are therefore likely to be representative of all those in the registry. The analysis totalled 15,479 patient months of follow up, during which there were 51 deaths (2.3%) and 259 (25.4%) hospitalizations for severe exacerbations[7]. The total number of deaths is probably too low to have sufficient statistical power to tease out all the important risk factors associated with an increased mortality. Despite, this several risk factors were identified. As expected, increasing age was associated strongly with mortality, but interestingly not with hospitalisations or exacerbation (after 41 years of age). With the exception of COPD, the aetiology of bronchiectasis had no influence on outcomes, although some of the aetiologies associated with poorer outcome in HIC such as rheumatoid arthritis[12] were not well represented in the EMBARC-India cohort. Similar to data from HIC[13], COPD (odds ratio [OR] 2.3) and cardiovascular disease (OR 2.9) were both associated with poorer outcomes, further emphasising the importance of these comorbidities in patients with bronchiectasis. To dissect why COPD is associated with poorer outcomes in the EMBARC-India cohort will need a more detailed assessment of the causes of fixed-airflow obstruction, which in LMIC settings are less dominated by exposure to cigarette smoke, more likely to be caused by poor lung growth and exposure to non-tobacco toxic inhaled substances[14], and can also be the end result of severe bronchiectasis or previous TB. The other important associations with mortality were smoking, infection with *Enterobacterales* and specifically *Klebsiella pneumoniae* (but not *Pseudomonas aeruginosa*), exacerbation frequency, and MRC dyspnoea score. The decline in FEV1 for the overall cohort was not markedly different from that expected in healthy populations, at an estimated 24 ml per year, but was considerably higher for patients with 2 or more exacerbations per year (-79ml) and with COPD (-83ml).

Although incomplete, the sputum microbiology data from the EMBARC-India cohort is striking. In contrast to the dominance of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* in HIC, in the EMBARC-India cohort these three pathogens together were found in only 2.3% of patients (**Table 1**). Non-tuberculous mycobacteria (NTM)

were also rare. Although some of these differences may be related to ascertainment bias due to technical difficulties in culturing specific microorganisms and less surveillance for NTM, the degree of difference suggests the data are likely to reflect real biology. European studies have shown *P. aeruginosa* infection identifies patients with more severe bronchiectasis and a poorer prognosis[15]. However, despite a similar prevalence of *P aeruginosa*, in EMBARC-India patients this was not associated with poorer outcomes or increased mortality. Instead, in the EMBARC-India cohort there was a higher incidence of infection with *Enterobacterales* (9.8%), particularly *K. pneumoniae,* and this was a marker for increased mortality, hospitalisations, and exacerbations. These results demonstrate the differences in microbiology between HIC and EMBARC-India cohorts are clinically relevant. Compared to Europe, in Asia *K. pneumoniae* is a more prevalent community-acquired respiratory pathogen[16], and therefore could be more readily acquired by patients with bronchiectasis. *K. pneumoniae* is a major threat due to high levels of antibiotic resistance[17], but the EMBARC-India authors did not present data on antibiotic resistance patterns for their *K. pneumoniae* isolates and these data are needed urgently. The differences in bronchiectasis microbiology between LMIC and HICs reinforces the importance for specific antibiotic guidelines for bronchiectasis for different geographic regions. In the EMBARC-India cohort 61% of patients used inhaled corticosteroids despite these generally not being recommended for bronchiectasis outside the context of asthma or allergic bronchopulmonary aspergillosis (ABPA), and this may be highly relevant due to the association of inhaled corticosteroids with alterations in the airway microbiome[18].

Another major finding by Dhar et al. was that bronchiectasis severity scoring systems defined using HIC data performed less well in the Indian population (**Table 1**). The Bronchiectasis Severity Index (BSI) predicted mortality reasonably well (area under the curve [AUC] 0.77) but was poorer at predicting severe exacerbations (AUC 0.66), and the FACED score performed poorly at predicting both mortality and severe exacerbations (AUC 0.68 and 0.52 respectively). A new severity tool may be necessary for LMIC settings where the aetiology and demographics of affected populations are different; the EMBARC-India registry is well-placed

to develop this. Despite having significant geographic gaps in central, Eastern, and Northern India, the centres contributing to the EMBARC-India registry still include a wide range of different geographical and climatic conditions. Once the patient numbers within the EMBARC-India registry are large enough, comparisons of clinical features between centres within the cohort could identify important associations. For example, the EMBARC-India cohort could be used to assess the effect of air quality on bronchiectasis aetiology and disease progression (especially important due to the association of COPD with poorer outcomes) or how geography influences the incidence of ABPA, a disease which is driven by environmental exposure to *Aspergillus fumigatus*.

The EMBARC-India studies are the first data from a large longitudinal study of bronchiectasis from an LMIC, and reveal important differences in the clinical presentation and predictors for poorer outcomes compared to data from HIC studies (summarised in **Table 1**). Some of these differences were largely predictable but others less so, and the data suggest mitigating the health impact of bronchiectasis in LMIC settings cannot rely just on data extrapolated from HIC settings. The EMBARC-India studies demonstrate the need for country-specific data to assist clinicians treating bronchiectasis and to identify specific areas of concern such as the predominance of potentially antibiotic resistant organisms in Indian patients. As well as improving management within a geographic area, future comparisons of the clinical characteristics of bronchiectasis across different geographic areas could also reveal important insights into the pathogenesis and the clinical course of bronchiectasis relevant to all countries.

Conflict of Interests Statement:

JSB has no relevant conflicts of interest

JRH has no relevant conflicts of interest

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Table 1: Selected major differences in patient characteristics, clinical presentation, and severity associations for the EMBARC-India cohort of bronchiectasis patients compared to European and US studies. HIC data obtained from reference 8 unless otherwise stated.

Parameter	**Findings**		**Interpretation / implications**
	EMBARC-India data	**HIC data**	
Median age	56 years	67 years	Probably reflects increased dominance of post-infective causes which can occur at a younger age
Sex predominance	Male 57%	Female 61%	Increased male dominance in India partly related to reduction in dominance of idiopathic causes
Aetiology	Post-infective dominant	Idiopathic dominant	Reflects higher incidence of severe respiratory infections; plus lack of access to vaccines and healthcare
Microbiology			
P. aeruginosa	14%	15%	Reflects community exposure (*K. pneumoniae* commoner in India), some ascertainment bias? Important due to the potential for antibiotic resistance in *Enterobacterales.*
H. influenzae	0.5%	22%	
Enterobacterales	9.8%	6.1%	
Radiology Reiff score	6	4	More severe radiological disease in Indian patients
Predicted FEV1	61% (35% obstructive, 27% restrictive)	74%	High incidence of restrictive lung disease reflects post-infective damage?
% with hospital admission for an exacerbation / year	39%	26%	Reflects background severity of the bronchiectasis, and possibly the microbiology?
Long term antibiotics	16%	26%	Poorer healthcare access?
Inhaled corticosteroids	61%	29% (US data[19])	Poorer healthcare access?
Mortality associations			
Microbiology	*Enterobacterales* OR 3.13	*P. aeruginosa* OR 2.95[15]	Why the association of *P. aeruginosa* infection with mortality is lost in Indian patients is not clear. The causes of COPD are likely to differ between Indian and European populations.
COPD	OR 2.27	OR 2.22[13]	
CV disease	OR 2.87	OR 1.31[13] (Ischaemic heart disease alone)	
Severity scores	BSI score 7 (36% severe)	BSI score 6 (35% severe)	Similar BSI despite poorer lung function and higher Reiff score, possibly related to the younger age for Indian patients