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## ORIGINAL ARTICLE

## SELF-REPORTED MULTI-MORBIDITY WITH TUBERCULOSIS: DATA FROM THE KHYBER PAKHTUNKHWA INTEGRATED POPULATION HEALTH SURVEY (KPIPHS) IN PAKISTAN

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**Background:** With the rise of non-communicable diseases (NCDs) in a country that is already facing high tuberculosis (TB) burden, TB multi-morbidity is likely to pose a significant public health challenge in Pakistan. Data were analysed to determine the prevalence of TB and explore the distribution and determinants of multi-morbidity associated with TB in the population of Khyber Pakhtunkhwa -a province of Pakistan. **Methods:** This is a secondary analysis of data gathered as part of the KPIPHS survey conducted in 2016-17 in both the rural and urban areas of Khyber Pakhtunkhwa, Pakistan. An interviewer-administered questionnaire was used to collect data, from adults, on demographics, education and socioeconomic status, physical and mental health, reproductive health, child health, health-related quality of life, and self-reported cardiometabolic diseases including Diabetes, hypertension, renal disorders, cardiac failure, angina, and stroke. **Results:** A total of 20,715 participants were recruited in the survey including 52.8% (n=10,943) males and 47.2% (n=9,772) females with a mean age of 41 (13.1) years. Data on TB status was available for a total of 14452 participants. The prevalence of TB in Khyber Pakhtunkhwa was found to be 0.49% (n=72) including an almost equal number of males and females [48% (n=34) vs 51% (n=36)], respectively. The mean age of the patients with TB was 47.5 (11.6) years. A higher proportion of people with TB had cardiometabolic diseases compared to people without TB (45.9% vs. 30.9%). Amongst the cardiometabolic disorders, self-reported hypertension (OR: 1.81, 95% CI 1.08–3.02,  $p=0.02$ ), Diabetes (OR: 3.99, 95% CI 1.95-8.18,  $p<0.002$ ), and angina (OR: 3.88 95% CI 1.20–12.49,  $p=0.02$ ) were positively associated with the occurrence of TB. In the adjusted analysis, only self-reported Diabetes was positively associated with the occurrence of TB (OR: 3.33, 95% CI 1.61-6.88,  $p=0.001$ ). **Conclusion:** There is a higher burden of self-reported cardiometabolic diseases among people with TB, suggesting that this high-risk group should be screened for cardiometabolic diseases, especially Diabetes.

**Keywords:** Cardiometabolic; South Asia; Low- and middle-income countries; TB-Diabetes comorbidity

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### INTRODUCTION

Tuberculosis (TB) is one of the most commonly occurring communicable diseases, in low and middle-income countries (LMIC). Pakistan ranks 5<sup>th</sup> on the list of countries with the highest burden of TB.<sup>1,2</sup> According to the World Health Organisation, the incidence of TB in Pakistan is 230 per 100,000 population while in the province of Khyber Pakhtunkhwa, Pakistan, the incidence of TB was recorded to be even higher with 270

cases per 100,000 population. (NTP 2014).<sup>3</sup> Tuberculosis multimorbidity, a result of the clustering of certain risk factors including low immunity, drug resistance, smoking, malnutrition, low-income status, and poor quality of life, is becoming an issue of public health concern and putting a great strain on the healthcare system<sup>4,5</sup> HIV is the most common chronic communicable and depression and Diabetes are the most

commonly co-occurring non-communicable diseases (NCDs) with TB.<sup>6,7</sup>

Tuberculosis and NCDs cluster together and adversely affect health outcomes.<sup>8</sup> For instance, evidence from countries facing the double burden of Diabetes and TB shows that the risk of developing TB is three times higher in patients with Diabetes than in the general population, while globally, ~15% of the patients with Diabetes develop TB indicating a bidirectional relationship.<sup>9</sup> Almost 50% of people suffering from TB have pre Diabetes or Diabetes.<sup>10</sup> Evidence indicates a poor prognosis of TB in people living with Diabetes.<sup>11</sup> An increased risk of premature death, and development of serious complications including TB relapse, poor glycaemic control, and drug-resistant TB.<sup>12,13</sup> Similarly, in high-burden African countries like Ethiopia and Kenya, TB presents as an important risk factor for cardiac issues like pericarditis, especially in the presence of HIV.<sup>14</sup>

With the rise of NCDs in a country that is already facing a high TB burden, TB multimorbidity is likely to pose a significant public health challenge in Pakistan. There is no data available regarding the prevalence or disease burden of TB multimorbidity in Pakistan so resources can be allocated and services can be planned to lessen this potential burden. This paper aims to present the distribution and determinants of self-reported TB multimorbidity, through a community-based, self-reported survey in the province of Khyber Pakhtunkhwa, Pakistan. The community-based survey allowed the selection of a relatively large and representative sample of people from the predetermined population as opposed to an institution-based study.

## MATERIAL AND METHODS

This is a secondary analysis of data gathered as part of a survey conducted in 2016-2017 in both the rural and urban areas of 24 of 34 districts in Khyber Pakhtunkhwa.<sup>14</sup> A multistage stratified cluster sampling technique was used to recruit adult males and females (>18 years); sampling was carried out in all 24 districts with strata from urban and rural Primary Sampling Units (PSUs). The PSUs for urban areas were divided into enumeration portions based on income (low, middle, and high) groups while for rural areas, the PSUs were Mohallas (a defined neighbourhood within a town or city) and villages. Each PSU included 250–300 households. Each PSU was visited, and all households were enlisted, then through systematic random sampling technique, every 16<sup>th</sup> household was selected for data collection per rural PSU, and

every 12<sup>th</sup> household was selected per urban PSU; these were called Secondary Sampling Units (SSU's). A total of 15,724 households were selected for data collection including 3,756 households from urban areas and 11,968 households from rural areas.

In each household, all males and females aged 15 years and above were recruited for the survey. After obtaining consent from participants, an interviewer-administered questionnaire was used that included data on demographics, education, socioeconomic status, physical and mental health, reproductive health, child health, health correlated quality of life, and self-reported co-morbidities including Diabetes, hypertension, renal disorders, cardiac failure, angina, and stroke. The interviews were conducted by trained field workers with each household member separately.

Ethical approval was obtained from the ethical committee of Khyber Medical University. Detailed methodology is explained in the health survey (KP-IPHS) article published elsewhere.<sup>15</sup>

Written informed consent was obtained from all participants (or their parents/legal guardians) who participated in the survey. In the Health Questionnaire section, the respondent was asked to list any/all past or current physician-diagnosed health conditions including TB and cardiometabolic diseases including Diabetes, hypertension, renal disorders, cardiac failure, angina, and stroke. Response to these questions was used to estimate the prevalence of self-reported TB and cardiometabolic diseases. Benazir income support program was used as a guide for classifying the households into income groups as low-income <25000 PKR, middle-income 25000–50000 PKR, and high-income >50000 PKR.

Data were analysed to determine the prevalence of TB among adults in the Khyber Pakhtunkhwa population and explore the distribution and determinants of multimorbidity associated with TB in these participants. Analysis was performed using STATA-version 16 and SPSS-Version 22. Mean and standard deviation were calculated for continuous variables. Percentages and frequencies were calculated for categorical variables. Chi-square test and logistic regression were employed to determine the association between demographics (age, sex, education, area of residence) and clinical characteristics with TB status and multimorbidity. A *p*-value of 0.05 was taken as significant. Model analyses were done separately for cardiometabolic diseases (like Diabetes, hypertension, and angina) as outcomes and the presence of TB as a predictor while all models were adjusted for age, sex, education status, and monthly income.

**RESULTS**

A total of 20,715 participants were recruited in the survey including 10,943 (52.8%) males and 9,772 (47.2%) females with a mean age of ~41 (13.1) years. The proportion of people living in the rural areas was 74.3% and more than half of the participants were educated to matriculation and above. Self-reported cardiometabolic diseases (including Diabetes, hypertension, renal disorders, cardiac failure, angina, and stroke) were reported in 5,877 (28%) among which the most prevalent was hypertension (N=4,258; 20.0%) followed by Diabetes N=859;5.7%) and angina N=241; 1.6%). Out of the total study population, 72 (0.49%) had TB (Table-1).

The demographic and clinical characteristics were compared between two groups; those with TB (both past and present) and those who did not have TB (Table 2).

Out of the total 20715 participants surveyed, data on TB status was available for 14452 participants. A higher proportion of TB patients were aged above 40 years than the non-TB population with a mean age of 47.54 (11.6) years. Comparing people who had TB with those who did not have TB, people with TB had a higher

proportion of co-morbidities like hypertension (33.8% vs 22.0%,  $p=0.02$ ), Diabetes (12.5%, vs 4.5%  $p < 0.001$ ), and angina (5.1% vs 1.4%  $p=0.14$ ).

In univariable logistic regression analysis, the age group 21–30 years (OR: 0.21; 95%CI 0.07-0.62,  $p=0.005$ ; reference age group 15-20 years) and with higher education status (OR: 0.17; 95%CI 0.05-0.56,  $p=0.004$ ) were significantly less likely to be associated with TB. Amongst the self-reported cardiometabolic disorders; hypertension, Diabetes, and angina were significantly more likely to be associated with the occurrence of TB (OR: 1.81, 95%CI 1.08-3.02,  $p=0.024$ ; OR: 3.04, 95%CI 1.51-6.15,  $p < 0.002$ ; OR: 3.88 95%CI 1.20–12.49,  $p=0.02$ ), respectively. (Table 3).

Multiple logistic regression was conducted with the presence of TB as the predictor and the risk of the comorbid condition as an outcome (Table 4).

In the adjusted analysis, only Diabetes was positively associated with the occurrence of TB (AOR: 3.33, 95%CI 1.61-6.88,  $p=0.001$ ) while the association of hypertension and angina with the occurrence of TB was no longer significant ( $p=0.96$  and  $p=0.99$ , respectively) after adjusting for potential confounders (age, sex, education, monthly income).

**Table-1: Characteristics of the Khyber Pakhtunkhwa Integrated Population Health Survey (KP-IPHS) study participants (N = 20715)**

Characteristics	Overall (N=20,715)	Males (N=10,943)	Females (N=9,772)	p (Males vs. females)
	n (%)	n (%)	n (%)	
15 – 20	705 (3.49)	340 (48.2)	365 (51.8)	<0.001
21-30	4,261 (21.03)	1639 (38.5)	2622 (61.5)	
31- 40	6,278 (30.94)	2991 (47.6)	3287 (52.4)	
41- 50	4,833 (23.83)	2704 (55.9)	2129 (44.1)	
51-60	2,661 (13.12)	1853 (69.6)	808 (30.4)	
>60	1,539 (7.6)	1239 (80.5)	300 (19.5)	
<b>Education</b>				
No formal education	820 (10.93)	672 (82)	148 (18)	
Primary (5 years)	1,592 (17.31)	1243 (78.1)	349 (21.9)	
Middle (8 years)	1,710 (14.6)	1450 (84.8)	260 (15.2)	
Matriculation (10 years)	2,891 (29.86)	2453 (84.8)	438 (15.2)	
Above Matriculation (>10 years)	2,648 (27.31)	2309 (87.2)	339 (12.8)	
<b>Residence</b>				<0.001
Urban	5,401(25.63)	3613 (66.9)	1788 (33.1)	
Rural	15315 (74.37)	7330 (47.9)	7984 (52.1)	
<b>Chronic health condition</b>				
Tuberculosis	72 (0.49)	35 (48.6)	37 (51.4)	0.47
Any cardio-metabolic disease	5,854 (28.3)	2744 (46.9)	3110 (53.1)	<0.001
Diabetes	855 (5.77)	490 (57.3)	365 (42.7)	0.008
Hypertension	4,237 (20.5)	1819 (42.9)	2418 (57.1)	<0.001
Angina	237 (1.64)	116 (48.9)	121 (51.1)	0.23

**Table-2: Sociodemographic characteristics and self-reported cardiometabolic diseases presented by Tuberculosis status**

	Overall			Males			Females		
	TB (N=72) n (%)	No TB (14380) n (%)	p value	TB (N=35) n (%)	No TB (N=7726) n (%)	p value	TB (N=37) n (%)	No TB (N=6885) n (%)	p value
<b>Age in years</b>									
15 – 20	0	512 (3.54)	0.002	0	228 (2.95)	0.028	0	284 (4.12)	<0.001
21-30	4 (6.94)	3,123 (21.61)		2 (5.88)	1180 (15.27)		2 (5.56)	1941 (28.19)	
31-40	21 (29.17)	4,288 (29.67)		3 (8.82)	2204 (28.52)		18 (52.94)	2263 (32.87)	
41-50	19 (26.39)	3,436 (23.78)		13 (38.23)	1944 (25.16)		6 (16.67)	1488 (21.61)	
51-60	18 (25.00)	1,928 (13.34)		9 (26.47)	1360 (17.60)		9 (25.00)	568 (8.25)	
>60	8 (12.50)	1,165 (8.06)		7 (20.59)	939 (12.15)		1 (2.78)	225 (3.27)	
<b>Education</b>									
No formal education	6(1.5)	396(98.5)	0.007	4 (11.76)	338 (4.37)	0.021	2 (5.56)	55 (0.80)	0.16
Primary (5 years)	4(0.4)	1102(99.6)		1 (2.94)	930 (12.04)		2 (5.56)	172 (2.50)	
Middle (8 years)	7(0.6)	1170(99.4)		5 (14.71)	1037 (13.42)		1 (2.78)	133 (1.93)	
Matriculation (10 years)	5(0.3)	1812(99.7)		5 (14.71)	1589 (20.57)		0	223 (3.24)	
Above Matriculation (>10y)	4(0.2)	1621(99.8)		2 (5.88)	1454 (18.82)		2 (5.56)	167 (2.43)	
<b>Residence area</b>									
Urban	10 (13.89)	3,281 (22.43)	0.08	8 (23.53)	2220 (28.73)	0.503	2 (5.56)	1059 (15.38)	0.10
Rural	62 (86.11)	11,348 (77.57)		26 (76.47)	5506 (71.26)		34 (94.44)	5826 (84.62)	
<b>Monthly income (Pakistani Rupees)<sup>#</sup></b>									
<25000	60 (83.33)	12326 (84.25)	0.88						
25000-50000	11 (15.28)	2067 (14.12)							
>50000	1 (1.39)	237 (1.62)							
<b>Self-reported co-morbidities</b>									

**Table-3: Unadjusted association between the characteristics of study participants and the occurrence of tuberculosis**

Characteristics	Odds of having TB		
	Odds Ratio	95% CI	p
<b>Age in years</b>			
15 – 20		Ref	
21-30	0.21	0.07 - 0.62	0.005
31-40	0.63	0.29 - 1.39	0.2
41=50	0.72	0.32 - 1.59	0.4
51-60	1.21	0.54 - 2.70	0.6
<b>Sex</b>			
Male		Ref	
Female	1.19	0.74 - 1.90	0.5
<b>Education status</b>			
No formal education		Ref	
Primary (5 years)	0.18	0.05 - 0.68	0.01
Middle (8 years)	0.42	0.15 - 1.23	0.1
Matriculation (10 years)	0.19	0.06 - 0.58	0.004
Above Matriculation (>10 years)	0.17	0.05 - 0.56	0.004
<b>Monthly Income (Pakistani rupees)</b>			
<25000		Ref	
25000-50000	1.70	0.84 - 3.47	0.1
>50000	1.69	0.70 - 4.093	0.2
<b>Self-reported co-morbidities</b>			
Diabetes	3.04	1.51 - 6.15	0.002
Hypertension	1.81	1.08 - 3.02	0.02
Angina	3.88	1.20 - 12.49	0.02

**Table 4: Adjusted association between tuberculosis (Predictor) And the Co-Morbidity (Outcome)**

Model	Variables included	OR (95% CI)	p-value
<b>Association between TB and DM</b>			
1	TB	3.99 (1.95-8.18)	<.001
2	Model 1+age	3.37 (1.63-6.96)	0.001
3	Model 2+sex	3.34 (1.62-6.91)	0.001
4	Model 3+education	3.33 (1.61-6.88)	0.001
<b>Association between TB and Hypertension</b>			
1	TB	1.81 (1.08-3.02)	0.02
2	Model 1+age	1.48 (0.87- 2.50)	0.1
3	Model 2+sex	1.29 (0.75- 2.24)	0.3
4	Model 3+ education	1.32 (0.76-2.29)	0.3
<b>Association between TB and Angina</b>			
1	TB	3.88 (1.20- 12.49)	0.02
2	Model 1+age	3.53 (1.09-11.39)	0.03
3	Model 2+sex	1.15 (0.16- 8.39)	0.8
4	Model 3+education	1.19 (0.15-8.20)	0.9

## DISCUSSION

We conducted a secondary data analysis of the first community-based Khyber Pakhtunkhwa Integrated Health Survey to study the prevalence of TB and the co-occurrence of self-reported non-communicable diseases in TB patients. We found that the prevalence of TB (both past and active) in Khyber Pakhtunkhwa was 0.49%. Amongst this population with TB, self-reported cardiometabolic diseases were more common than in people without TB (45.9% vs. 30.9%); hypertension (33.9% vs. 22.1%), followed by Diabetes (12.5% vs. 4.5%) and angina (5.1% vs. 1.4%).

According to WHO and Pakistan National TB Control Programme (2014), communicable diseases in Pakistan are still a primary cause of morbidity and mortality. Likewise, non-communicable diseases are on the rise too (16,17). We found that 72 (0.49%) patients suffered from TB which is slightly higher than a country-wide survey conducted on 105,913 participants from across Pakistan (2010-2011), which reported a prevalence of 341 (0.32%) of self-reported TB in the country. However, results for the Khyber Pakhtunkhwa province showed a higher TB prevalence than the rest of the country in the previous years.<sup>18</sup>

The study shows that the younger population is at a higher risk than the older age groups, while there was no significant association with sex. In line with our study findings, a previous study showed that Pashtun (people originating from Khyber Pakhtunkhwa province and some parts of Baluchistan province in Pakistan) women and men have the same TB incidence while in the rest of the world, men get more TB than women.<sup>19</sup> These findings are also supported by findings from Stevenson *et al* who reported a greater relative risk of developing TB in younger individuals and no association between sex and the risk of developing TB.<sup>20</sup> The association between education status and TB has been reported in previous studies.<sup>21</sup> A cross-sectional study was conducted at private health institutions on 352 TB patients in Sub-Saharan Africa. The study revealed that people with low educational status were more prone to have pulmonary TB.<sup>22</sup> In Khyber Pakhtunkhwa province a low literacy rate of 53% (men and women combined) may be a barrier to accessing various sources of information and easily understanding messages related to TB prevention and management that may in turn increase the chances of TB occurrence in both men and women and the uneducated in this province.

The prevalence of self-reported Diabetes in our study is at least half compared to the reported prevalence from other studies conducted in Pakistan. Recently a systematic review and meta-analysis

reported the prevalence of Diabetes in Pakistan as 14.6% (10.7%–19.1%; 14 studies, 49,418 people) while the prevalence of Pre-diabetes was 11.4% (8.3%–15.0%; 10 studies, 26,999 people.<sup>22</sup> The included studies mostly confirmed the Diabetes status using objective measures which may likely account for the higher prevalence compared to the current study. A study by Khalid M *et al*, conducted in Punjab and Sindh provinces of Pakistan, reported the prevalence of undiagnosed Diabetes as 6.4%.<sup>23</sup> Our findings highlight a significant proportion of the population with undiagnosed Diabetes.

Self-reported hypertension in our population is almost similar to the findings of a meta-analysis by Nabi *et al* which reported that the prevalence of hypertension is 26.3% (25.9%, 26.8%; 18 studies, 42,618 people) in the Pakistani population aged 15 year or above.<sup>24</sup> A systematic review of the literature was performed in 2016 to evaluate the evidence for an association between hypertension and TB. Cross-sectional studies included in the review reported a prevalence of hypertension in TB patients ranging from 0.7% to 38.3%. However, none of the studies included in the review were designed to assess whether hypertension is a risk factor for developing active TB or vice versa.<sup>32</sup>

The higher self-reported cardiometabolic disease prevalence amongst TB patients, in our study, compared to the non-TB population is in line with the existing evidence. A meta-analysis published in 2020 found the pooled relative risk of developing coronary heart disease in patients with TB to be 1.76 (95%CI 1.05-2.95, 4 cohort studies, 83,500 TB cases) compared to patients without TB.<sup>28</sup> Similar findings were reported by Hasanain *et al.*, Chung *et al.*, and Huaman *et al.* with TB increasing the risk for coronary heart disease in all studies.<sup>29-31</sup>

The ~3 times higher risk of TB in patients with Diabetes in our study, is in agreement with the previous studies, conducted across low-middle and high-income countries, which reported a four times higher risk of TB in patients with Diabetes than those without TB.<sup>33,34</sup> These findings suggest a bidirectional relationship between the two health conditions.<sup>27-29,35-37</sup> A hospital-based cross-sectional study conducted in Lahore, Pakistan reported a slightly higher estimate of TB-Diabetes co-prevalence (14.8%) compared to our study findings (~13%). In a study by Mashal *et al*, the prevalence of self-reported TB-Diabetes co prevalence was 3.2%.<sup>9</sup>

There is a significant association between Diabetes and TB, suggesting that patients with TB should be screened for cardiometabolic diseases especially Diabetes.<sup>38</sup> Importantly, Diabetes is associated with worse TB treatment outcomes including treatment failure, relapse, and death in

people with TB. In Pakistan, which has both a high TB and high Diabetes burden, there are 570,000 cases of TB every year and almost half of all people with TB are likely to have Diabetes or pre-Diabetes.<sup>39</sup> In addition to higher healthcare needs, patients with TB and Diabetes commonly face changes in employment status or cuts in work hours which, in turn, place a high economic burden on the individual as well as the health system and national level.<sup>10,40</sup>

Our study reflects that TB multimorbidity remains a highly prevailing problem in a resource-scarce country like Pakistan and there is a paucity of literature on this issue. However, this study does have some limitations. The survey was conducted in only one (north-west) province of Pakistan, hence may not represent the whole country's population. The diseases were self-reported based on previous medical history and were not confirmed by examination or lab tests at the time of data collection. Moreover, the current disease status of the TB patients was also not confirmed. Data was collected on a limited number of risk factors and physical health conditions excluding mental health conditions. There likely were undiagnosed cases of Diabetes and hypertension that would have underestimated the prevalence rates of these conditions in this study.

## CONCLUSION

Our findings highlight the high burden of TB and self-reported cardiometabolic diseases in Pakistan and the considerable overlap between the two and call for an urgent need for integration across TB and NCD services. Akin to TB and HIV programs, active collaboration between TB and NCD, especially Diabetes, care will help to avoid needless duplication of service provision and structures and encourage optimal and coordinated use of scarce health care resources. Research is needed to identify and target high-risk populations, such as people with Diabetes, for effective prevention and treatment of TB multimorbidity. Developing countries, like Pakistan, have compromised health and social care systems that are struggling to deal with the increasing burden of multimorbidity. Thus, urgent research is needed to better understand TB multi-morbidity and evaluate the effectiveness of context-specific interventions to address this critical issue.

## DECLARATION

**Ethics Approval:** Ethical approval was obtained from Khyber Medical University's Ethics Review Board. Written informed consent was obtained from participants who participated in the survey. For participants below the age of 16 years, written informed consent was obtained from a parent/legal guardian. In addition to this, guidelines and regulations (Declaration of Helsinki) were followed.

**Consent for Publication:** Not applicable.

**Availability of Data:** All the data generated or analyzed during this study are available in the supplementary files.

**Competing Interest:** The authors have no competing interests to declare.

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## AUTHORS' CONTRIBUTION

SA, KS and ZH conceived and planned the study. ZH, SF, FK, MZH and AR carried out the study and helped in data collection. SA, SF and SH performed the analysis. SA and KS contributed to the interpretation of the results. ZH and SA took the lead in writing the manuscript. All authors provided critical feedback and helped shape the analysis and manuscript. KS provided the final review to the manuscript.

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