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ABOUT

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Thoracic Research and Practice is a bimonthly journal that is published in English in January, March, May, July, September, and November.

Journal History

Thoracic Research and Practice started its publication life following the merger of two journals which were published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2008. From 2008 to 2022, the journal was published under the title "Turkish Thoracic Journal". Archives of the journals were transferred to Thoracic Research and Practice.

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Thoracic Research and Practice covers a wide range of topics related to adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery, including diagnostic methods, treatment techniques, and prevention strategies. The journal is interested in publishing original research that addresses important clinical questions and advances the understanding and treatment of these conditions. This may include studies on the effectiveness of different treatments, new diagnostic tools or techniques, and novel approaches to preventing or managing pulmonary diseases.

Thoracic Research and Practice publishes clinical and basic research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, systematic reviews and meta-analyses, letters to the editor and editorials. Conference proceedings may also be considered for publication.

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LETTERS TO THE EDITOR

Thorac Res Pract. 2025;26(4):155-175 DOI: 10.4274/ThoracResPract.2024.24081

Original Article

Global Burden of Tracheal, Bronchus, and Lung Cancer in Adults Over 55 Years Old Based on Socio-demographic Status and Geographical and Gender Differences from 2010-2021

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Abstract

OBJECTIVE: This study presented the tracheal, bronchus, and lung cancer (TBLC) trend in adults ≥55 based on the Socio-demographic Index and geographical regions.

MATERIAL AND METHODS: We obtained annual TBLC data from 2010 to 2021 from the 2021 Global Burden of Disease (GBD) Study and analyzed the incidence, death rates, and disability-adjusted life years (DALYs) rates across different geographical classifications of 204 national and territorial.

RESULTS: In adults ≥55 years, the TBLC incidence rate decreased from 2010 to 2021 by globally 20.9% and 9.6% in males, while increasing by 3.8% in females. Approximately 60% of TBLC cases occurred in Asian countries. European countries exhibit the highest incidence rate (169.16 per 100,000). Males across all continents showed a decreasing trend, only the Americas reported a decreasing trend for women, with a noted change of 17.3%. The Western Pacific Region (World Health Organization region), East Asia (GBD region), Monaco, and countries with advanced health systems reported the highest incidence, death, and DALY numbers and rates for all genders. World Bank Upper middle-income countries recorded the highest DALY numbers and rates, incidence, and death numbers, all showing a downward trend, similar to high-income countries.

CONCLUSION: The global burden of TBLC is predominantly in Asian countries (mainly East Asia), with a slower decrease in incidence, death, DALY, and burden rates. Therefore, reducing exposure to risk factors, expanding screening and diagnostic programs, especially for high-risk male smokers and females, and improving treatment procedures to reduce the progression of this cancer are urgent.

KEYWORDS: 'Tracheal, bronchus, and lung cancer', socio-demographic index, incidence, death, burden

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INTRODUCTION

Tracheal, bronchus, and lung cancer (TBLC) presents a significant global health burden.[1] In 2019, 2.26 million new cases and 2.04 million deaths were attributed to TBLC, resulting in 45.9 million disability-adjusted life years (DALYs).[2] In addition, TBLC-related symptoms and treatment side effects can substantially diminish patients' quality of life and functional status. Smoking is the main cause of TBLC, but environmental exposures like air pollution and occupational carcinogens are also significant.[3] However, the relative contribution of each risk factor to mortality varies by sex, geography, and individual exposures.[4] Despite advancements in cancer treatment and technology, socioeconomic and geographic disparities affect access to appropriate care for TBLC patients.[5] Given the multifaceted nature of factors influencing TBLC burden, it is imperative to investigate their impact comprehensively. On the other hand, understanding the complex interplay of risk factors and their varying impact across demographics and regions is essential for developing targeted interventions to decrease the burden of TBLC worldwide.[6]

Due to physiological changes in lung aging, the incidence of TBLC increases with age,[7,8] and TBLC is considered one of the most important health challenges in old age.[9] Meanwhile, the symptoms of TBLC in old age are misleading and make screening and diagnosis challenging; a significant percentage of elderly people with TBLC do not show a desire to receive treatment services.[9-11] Given that the world population has shifted toward older ages,[12] it is of particular importance to examine statistics related to TBLC as an old age disease. Because proper policymaking and optimal implementation of cancer management programs require up-to-date and complete data, this study aims to investigate the burden of TBLC in adults aged ≥55 years, based on gender disparities among Socio-demographic Index (SDI) classifications and different geographical divisions. This is done by using the most up-to-date data from the Global Burden of Disease (GBD) study 2021 and its trend from 2010 to 2021.

MATERIAL AND METHODS

This study extracted data from the GBD 2021 online platform on the incidence, deaths, and DALYs of TBLC ≥55 from 2010 to 2021, which covers 369 diseases across 204 countries. The data were classified under the International Classification of Diseases-10 code (C33, C34.0–C34.92, Z12.2, Z80.1–Z80.2, and Z85.1–Z85.20).[13] Data were analyzed using classifications based on global trends, SDI, continents, World Bank regions, World Health Organization (WHO) regions, GBD regions, and national and territorial divisions by gender and age groups. Old age in the GBD begins at age 55 and extends to the age group of ≥70. Therefore, we decided to present data for individuals aged 55 and older. SDI is a measure that identifies where countries sit on the development spectrum and is expressed on a 0 to 100 scale; 0 being the lowest SDI value and 100 being the highest. SDI is based on three measures: lag-distributed income per capita, average years of schooling in ages 15 and older, and total fertility rate for females under age 25. Countries and territories are stratified into five groups based on SDI values: low SDI (<0.45), low-middle SDI (≥0.45 and <0.61), middle SDI (≥0.61 and <0.69), high-middle SDI (≥0.69 and <0.80), and high SDI (≥0.80).[14] The World Bank classifies economies into four income groups (low, medium-low, medium-high, and high) based on per capita gross national income, using the Atlas method to account for exchange rate fluctuations.[15] The study employs DALYs to measure the burden of TBLC, combining years of life lost due to premature death and years lived with disability.[16] To calculate total DALYs, years of life lost and years lived with disability were estimated and combined. GBD 2021 defined a summary measure of personal health care access and quality for a given location as the Healthcare Access and Quality (HAQ) Index. HAQ Index is based on risk-standardized mortality rates from causes that, in the presence of high-quality health care, should not result in death-also known as amenable mortality. Based on HAQ, countries and territories are classified into four groups: Advanced Health System, Basic Health System, Limited Health System, and Minimal Health System.[17]

Main Points

- In 2021, more than 66% of new tracheal, bronchus, and lung cancer (TBLC) cases were in men globally.
- In adults' ≥55 years, the TBLC incidence rate decreased from 2010 to 2021 globally by 20.9%.
- The TBLC incidence rate decreased by 9.6% in males and increased by 3.8% in females.
- Approximately 60% of TBLC cases occurred in Asian countries.
- European countries exhibiting the highest incidence rate.

Ethical Consideration

The Jahrom University of Medical Sciences Ethical Research Committee approved this study (approval no: IR.JUMS.REC.1401.094, date: 23.11.2022). Because utilizing anonymous online datasets, informed consent was not required.

Statistical Analysis

The incidence, mortality, and DALY rates were calculated per 100,000 population with a 95% confidence interval. Selected epidemiological metrics are delineated individually for each classification. Definitions of the terms utilized are available at: https://www.healthdata.org/terms-defined and https://www.healthdata.org/gbd/

RESULTS

The Global Trend of TBLC Among Aged ≥55 Years

In 2021, 2,021.521 new cases of TBLC were recorded globally, 66% in males and 34% in females. TBLC incidence rate (per 100,000) with a 5.1% decrease compared to 2010 reached 190.704 in 2021. Also, 1,808.810 deaths related to TBLC were recorded globally, 66.6% in males and 33.4% in females. TBLC death rate (per 100,000) with a 7.1% decrease compared to 2010 reached 121.725 in 2021. The DALYs numbers related to TBLC were recorded as 37,632.985, globally, 67.8% in males and 32.2% in females. TBLC DALY rate (per 100,000) with a 9.2% decrease compared to 2010 reached 2,532.526 in 2021. Between 2010 and 2021, the TBLC incidence, death, and DALY rates decreased by 9.6, 11.2, and 13.3% in males, respectively. In contrast, females recorded a 3.8, 2.3, and 0.7% increase in incidence, death, and DALY rates, respectively (Tables 1, 2, 3 and, Figure 1).

Table 1. Incidence of TBLC in ≥55 years old in 2021 and its changes from 2010 to 2021

Location	Both genders			Males			Females		
	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)
Global	2021521	136.039	-0.051	1334012	190.704	-0.091	687509	87.417	0.038
	(1826641_2220212)	(122.925_149.41)	(-0.135_0.034)	(1173641_1502454)	(167.779_214.784)	(-0.198_0.029)	(602528_761779)	(76.612_96.861)	(-0.051_0.142)
SDI									
High SDI	695752	201.660	-0.109	419104	260.958	-0.161	276647	150.017	-0.032
	(632877_730778)	(183.436_211.812)	(-0.137_-0.086)	(389630_438888)	(242.605_273.276)	(-0.19_-0.132)	(242064_295776)	(131.264_160.39)	(-0.062_-0.006)
High-middle SDI	646561	186.502	-0.001	447354	281.754	-0.073	199207	106.016	0.182
	(565073_738061)	(162.997_212.896)	(-0.122_0.14)	(372730_528061)	(234.754_332.585)	(-0.228_0.105)	(166192_236098)	(88.446_125.649)	(-0.008_0.406)
Low SDI	20925	25.501	0.047	15046	37.409	0.015	5880	14.053	0.170
	(17842_24404)	(21.743_29.74)	(-0.081_0.188)	(12703_17955)	(31.584_44.644)	(-0.113_0.172)	(4830_6851)	(11.543_16.374)	(-0.002_0.383)
Low-middle SDI	103032	42.737	0.043	72323	62.569	0.022	30710	24.471	0.130
	(93995_113138)	(38.988_46.929)	(-0.07_0.144)	(66413_79644)	(57.457_68.904)	(-0.109_0.144)	(26657_34612)	(21.241_27.581)	(0.013_0.254)
Middle SDI	553323	117.764	0.041	378875	169.338	0.005	174448	70.879	0.153
	(461703_641449)	(98.264_136.52)	(-0.124_0.215)	(301061_459098)	(134.559_205.194)	(-0.199_0.235)	(146345_205815)	(59.461_83.624)	(-0.034_0.378)
World Bank income level									
World Bank high-income	756867	193.124	-0.107	467439	258.101	-0.164	289427	137.299	-0.016
	(687279_791117)	(175.367_201.863)	(-0.129_-0.091)	(436661_485057)	(241.106_267.828)	(-0.186_-0.145)	(251864_309385)	(119.48_146.767)	(-0.042_0.007)
World Bank low income	20065	41.829	-0.066	14134	61.810	-0.075	5931	23.628	-0.039
	(15622_25292)	(32.567_52.727)	(-0.171_0.064)	(10925_18343)	(47.776_80.217)	(-0.178_0.075)	(4278_7622)	(17.043_30.366)	(-0.206_0.133)
World Bank lower middle-income	204928	46.489	0.031	147975	69.961	0.000	56952	24.837	0.148
	(178963_227155)	(40.598_51.531)	(-0.098_0.135)	(129646_164293)	(61.295_77.676)	(-0.135_0.111)	(47588_65604)	(20.754_28.61)	(0.02_0.288)
World Bank upper middle-income	1037726	171.810	0.030	703147	248.081	-0.020	334579	104.373	0.165
	(870368_1217969)	(144.101_201.652)	(-0.135_0.206)	(557692_861192)	(196.762_303.841)	(-0.222_0.223)	(275202_398729)	(85.85_124.385)	(-0.046_0.419)
Continents									
Africa	41556	38.582	-0.011	31111	60.396	-0.010	10445	18.586	0.050
	(36441_47343)	(33.833_43.955)	(-0.114_0.122)	(27337_35519)	(53.07_68.953)	(-0.121_0.141)	(8826_11903)	(15.705_21.181)	(-0.099_0.205)
America	320264	138.088	-0.209	174764	163.517	-0.237	145500	116.355	-0.173
	(293708_335006)	(126.638_144.445)	(-0.229_-0.191)	(164613_181694)	(154.02_170.001)	(-0.26_-0.217)	(128872_153723)	(103.057_122.93)	(-0.198_-0.15)

Table 1. Continued

Location	Both genders			Males			Females		
	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)
Asia	1207198	137.507	0.036	818012	193.518	-0.002	389185	85.496	0.141
	(1027784_1393003)	(117.071_158.672)	(-0.117_0.189)	(657720_980997)	(155.597_232.075)	(-0.191_0.213)	(325424_454644)	(71.489_99.876)	(-0.045_0.349)
Europe	449726	169.159	-0.077	308258	262.897	-0.156	141467	95.197	0.101
	(420474_469822)	(158.156_176.718)	(-0.109_-0.048)	(290221_322467)	(247.514_275.014)	(-0.191_-0.124)	(127226_150238)	(85.614_101.099)	(0.062_0.139)
WHO Regions									
African Region	26886	32.276	-0.039	18867	48.501	-0.046	8019	18.061	0.034
	(23986_30233)	(28.794_36.294)	(-0.128_0.068)	(16910_21457)	(43.471_55.16)	(-0.143_0.072)	(6783_9123)	(15.277_20.546)	(-0.1_0.175)
Eastern Mediterranean Region	41935	56.333	-0.037	33332	86.299	-0.059	8603	24.018	0.070
	(36862_48146)	(49.519_64.677)	(-0.155_0.105)	(29062_38683)	(75.243_100.151)	(-0.185_0.101)	(7079_10248)	(19.765_28.612)	(-0.112_0.259)
European Region	456888	164.202	-0.086	313519	255.369	-0.163	143369	92.213	0.090
	(426699_477162)	(153.352_171.488)	(-0.117_-0.057)	(295418_327900)	(240.625_267.082)	(-0.197_-0.133)	(128947_152150)	(82.937_97.861)	(0.051_0.126)
Region of the Americas	320264	138.088	-0.209	174764	163.517	-0.237	145500	116.355	-0.173
	(293708_335006)	(126.638_144.445)	(-0.229_-0.191)	(164613_181694)	(154.02_170.001)	(-0.26_-0.217)	(128872_153723)	(103.057_122.93)	(-0.198_-0.15)
South-East Asia Region	141386	45.774	0.070	97459	65.526	0.045	43927	27.430	0.144
	(120733_158579)	(39.088_51.34)	(-0.083_0.203)	(84186_110334)	(56.602_74.183)	(-0.13_0.198)	(35304_51396)	(22.045_32.093)	(-0.007_0.296)
Western Pacific Region	1020528	204.484	0.051	687437	287.748	0.011	333090	128.027	0.160
	(852097_1200801)	(170.736_240.606)	(-0.12_0.233)	(538078_846822)	(225.229_354.464)	(-0.205_0.266)	(270000_400439)	(103.778_153.914)	(-0.051_0.407)
Health System Grouping Level									
Advanced Health System	865692	183.297	-0.103	554171	259.245	-0.161	311521	120.500	-0.005
	(793798_901757)	(168.075_190.934)	(-0.124_-0.085)	(522373_575080)	(244.369_269.026)	(-0.184_-0.139)	(272657_332329)	(105.467_128.548)	(-0.033_0.017)
Basic Health System	1037237	156.528	0.033	695751	219.963	-0.005	341486	98.595	0.139
	(863044_1209508)	(130.24_182.525)	(-0.134_0.206)	(545234_853562)	(172.377_269.856)	(-0.212_0.247)	(283663_405417)	(81.9_117.054)	(-0.068_0.383)
Limited Health System	110509	33.509	0.058	78322	49.135	0.025	32187	18.890	0.194
	(99227_123189)	(30.088_37.353)	(-0.095_0.19)	(69613_87243)	(43.672_54.731)	(-0.141_0.176)	(28051_37003)	(16.462_21.716)	(0.036_0.367)
Minimal Health System	6155	30.847	0.032	4458	47.156	-0.001	1697	16.162	0.110
	(4732_8415)	(23.717_42.175)	(-0.111_0.203)	(3312_6511)	(35.03_68.869)	(-0.145_0.178)	(1310_2127)	(12.474_20.261)	(-0.101_0.38)

Table 1. Continued

Location	Both genders			Males			Females		
	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)
GBD Region									
Central Europe, Eastern Europe, and Central Asia	158210	139.200	-0.083	116847	251.347	-0.158	41363	61.580	0.130
	(149274_166827)	(131.337_146.782)	(-0.131_-0.036)	(109046_123778)	(234.566_266.255)	(-0.215_-0.109)	(38125_44195)	(56.761_65.797)	(0.062_0.2)
Central Asia	8883	61.052	-0.245	7035	110.138	-0.279	1848	22.645	-0.153
	(7934_9825)	(54.529_67.526)	(-0.321_-0.161)	(6237_7829)	(97.65_122.57)	(-0.355_-0.201)	(1640_2066)	(20.087_25.31)	(-0.252_-0.044)
Central Europe	74924	202.344	0.011	51121	315.904	-0.081	23803	114.187	0.253
	(69374_79915)	(187.354_215.824)	(-0.057_0.077)	(46938_54757)	(290.056_338.375)	(-0.149_-0.015)	(21711_25785)	(104.15_123.693)	(0.155_0.347)
Eastern Europe	74403	119.852	-0.107	58692	245.376	-0.170	15711	41.172	0.075
	(67454_80970)	(108.659_130.43)	(-0.186_-0.029)	(52241_64937)	(218.408_271.484)	(-0.26_-0.084)	(14108_17298)	(36.97_45.33)	(-0.023_0.181)
High-income	691861	194.495	-0.112	424106	258.003	-0.164	267755	139.935	-0.029
	(626369_724173)	(176.084_203.578)	(-0.134_-0.094)	(392777_440963)	(238.944_268.258)	(-0.187_-0.144)	(232204_286604)	(121.355_149.786)	(-0.056_-0.006)
Australasia	15257	172.707	-0.063	8652	205.931	-0.108	6606	142.578	0.002
	(13607_16731)	(154.02_189.387)	(-0.139_0.022)	(7746_9578)	(184.379_227.976)	(-0.204_-0.005)	(5708_7247)	(123.205_156.415)	(-0.069_0.085)
High-income Asia Pacific	148952	211.270	0.029	104651	323.420	-0.011	44301	116.137	0.111
	(128808_160986)	(182.697_228.337)	(-0.03_0.087)	(94133_111703)	(290.915_345.215)	(-0.07_0.045)	(34126_50605)	(89.464_132.662)	(0.024_0.186)
High-income North America	238470	211.909	-0.214	125182	239.398	-0.247	113288	188.049	-0.178
	(218679_250417)	(194.322_222.525)	(-0.234_-0.195)	(117851_130919)	(225.377_250.369)	(-0.271_-0.223)	(99655_120365)	(165.42_199.796)	(-0.203_-0.153)
Southern Latin America	15313	104.055	-0.158	9959	151.383	-0.230	5354	65.792	0.005
	(14002_16597)	(95.147_112.78)	(-0.223_-0.08)	(9099_10796)	(138.306_164.11)	(-0.298_-0.158)	(4754_5917)	(58.418_72.717)	(-0.084_0.122)
Western Europe	273869	183.639	-0.089	175662	254.760	-0.173	98207	122.479	0.080
	(251000_289406)	(168.305_194.057)	(-0.124_-0.057)	(162467_184723)	(235.624_267.902)	(-0.21_-0.137)	(86593_105674)	(107.995_131.792)	(0.036_0.119)
Latin America and Caribbean	67647	63.680	-0.076	40387	82.915	-0.129	27260	47.391	0.026
	(61809_72854)	(58.185_68.582)	(-0.13_-0.023)	(37458_43429)	(76.902_89.16)	(-0.185_-0.069)	(24411_29522)	(42.439_51.324)	(-0.04_0.093)
Andean Latin America	5057	51.046	-0.032	2781	58.751	-0.059	2276	43.995	0.009
	(3955_6224)	(39.919_62.826)	(-0.223_0.182)	(2188_3439)	(46.22_72.659)	(-0.25_0.155)	(1706_2836)	(32.99_54.817)	(-0.203_0.25)
Caribbean	10041	108.453	-0.054	6712	154.337	-0.069	3329	67.810	-0.006
	(8895_11264)	(96.069_121.661)	(-0.166_0.056)	(5885_7636)	(135.322_175.597)	(-0.19_0.045)	(2855_3798)	(58.154_77.358)	(-0.125_0.119)
Central Latin America	20093	46.983	-0.126	11994	61.013	-0.158	8099	35.048	-0.061
	(17757_22694)	(41.522_53.065)	(-0.217_-0.022)	(10444_13663)	(53.131_69.507)	(-0.258_-0.049)	(6975_9309)	(30.183_40.282)	(-0.173_0.056)

Table 1. Continued

Location	Both genders			Males			Females		
	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)	Incidence number	Incidence rate per 100,000	Changes (2010-2021)
Tropical Latin America	32456	73.267	-0.040	18900	94.649	-0.124	13555	55.717	0.115
	(30008_34298)	(67.741_77.426)	(-0.08_0.001)	(17679_19936)	(88.534_99.837)	(-0.167_-0.074)	(12277_14483)	(50.464_59.531)	(0.059_0.17)
North Africa and Middle East	57987	76.064	-0.052	46835	121.381	-0.079	11152	29.621	0.072
	(50384_67122)	(66.091_88.047)	(-0.179_0.104)	(40247_55213)	(104.308_143.095)	(-0.213_0.084)	(9313_13049)	(24.736_34.659)	(-0.116_0.268)
North Africa and Middle East	57987	76.064	-0.052	46835	121.381	-0.079	11152	29.621	0.072
	(50384_67122)	(66.091_88.047)	(-0.179_0.104)	(40247_55213)	(104.308_143.095)	(-0.213_0.084)	(9313_13049)	(24.736_34.659)	(-0.116_0.268)
South Asia	75444	30.385	0.120	54583	44.856	0.060	20861	16.476	0.357
	(63426_85929)	(25.545_34.608)	(-0.076_0.307)	(44305_62935)	(36.41_51.72)	(-0.155_0.269)	(17666_24390)	(13.953_19.264)	(0.113_0.63)
South Asia	75444	30.385	0.120	54583	44.856	0.060	20861	16.476	0.357
	(63426_85929)	(25.545_34.608)	(-0.076_0.307)	(44305_62935)	(36.41_51.72)	(-0.155_0.269)	(17666_24390)	(13.953_19.264)	(0.113_0.63)
Southeast Asia, East Asia, and Oceania	945194	186.095	0.046	633796	260.209	0.010	311398	117.803	0.146
	(776899_1113883)	(152.96_219.307)	(-0.142_0.242)	(485921_790433)	(199.498_324.518)	(-0.222_0.293)	(253934_374308)	(96.064_141.602)	(-0.083_0.418)
East Asia	836971	213.447	0.060	559211	294.799	0.023	277760	137.214	0.169
	(676469_1012020)	(172.515_258.089)	(-0.147_0.286)	(415219_715425)	(218.891_377.151)	(-0.241_0.344)	(219672_341439)	(108.518_168.671)	(-0.088_0.477)
Oceania	936	75.821	0.035	675	104.490	0.023	260	44.298	0.082
	(712_1289)	(57.697_104.419)	(-0.149_0.254)	(500_958)	(77.331_148.228)	(-0.164_0.259)	(191_363)	(32.468_61.819)	(-0.12_0.31)
Southeast Asia	107288	93.657	-0.010	73910	138.841	-0.026	33378	54.431	0.021
	(88294_123475)	(77.076_107.787)	(-0.147_0.118)	(61861_86517)	(116.206_162.524)	(-0.178_0.127)	(25868_39814)	(42.185_64.927)	(-0.127_0.174)
Sub-Saharan Africa	25179	32.306	-0.035	17458	48.360	-0.040	7721	18.454	0.037
	(22424_28362)	(28.771_36.39)	(-0.124_0.076)	(15514_19997)	(42.974_55.394)	(-0.139_0.08)	(6510_8808)	(15.56_21.053)	(-0.098_0.184)
Central Sub-Saharan Africa	3657	40.525	0.090	2672	64.810	0.046	985	20.100	0.154
	(2612_5501)	(28.944_60.966)	(-0.137_0.369)	(1780_4271)	(43.176_103.613)	(-0.19_0.325)	(718_1312)	(14.654_26.764)	(-0.148_0.529)
Eastern Sub-Saharan Africa	7448	27.545	0.013	5166	40.112	-0.026	2281	16.114	0.143
	(6459_8794)	(23.887_32.526)	(-0.142_0.169)	(4375_6190)	(33.968_48.064)	(-0.202_0.152)	(1796_2752)	(12.685_19.439)	(-0.061_0.381)
Southern Sub-Saharan Africa	8232	84.559	-0.104	5320	131.656	-0.148	2912	51.137	-0.009
	(7487_9135)	(76.905_93.832)	(-0.186_-0.009)	(4708_6004)	(116.508_148.582)	(-0.243_-0.035)	(2545_3304)	(44.686_58.02)	(-0.132_0.119)
Western Sub-Saharan Africa	5843	18.177	-0.004	4300	28.557	0.026	1542	9.028	0.088
	(4876_6946)	(15.17_21.608)	(-0.127_0.154)	(3615_5113)	(24.008_33.959)	(-0.12_0.21)	(1204_1833)	(7.047_10.731)	(-0.092_0.303)

SDI: socio-demographic index, TBLC: tracheal, bronchus, and lung cancer, WHO: World Health Organization

Table 2. Death of TBLC in ≥55 years old in 2021 and its changes from 2010 to 2021

	Both genders			Males			Females		% Changes (2010-2021)
	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	
Global	1808810	121.725	-0.071	1203940	172.110	-0.112	604871	76.910	0.023
	(1632909_1986037)	(109.887_133.651)	(-0.153_0.013)	(1060249_1353298)	(151.568_193.462)	(-0.215_0.003)	(529955_670701)	(67.384_85.28)	(-0.068_0.124)
SDI									
High SDI	566616	164.230	-0.112	345357	215.039	-0.165	221259	119.982	-0.030
	(514794_597233)	(149.21_173.104)	(-0.14_-0.089)	(321174_361385)	(199.981_225.018)	(-0.193_-0.137)	(192124_237407)	(104.182_128.738)	(-0.062_-0.004)
High-middle SDI	582299	167.966	-0.048	403726	254.276	-0.116	178573	95.035	0.124
	(511627_660153)	(147.58_190.423)	(-0.163_0.081)	(337465_472938)	(212.543_297.867)	(-0.26_0.049)	(149964_210287)	(79.809_111.913)	(-0.047_0.333)
Low SDI	22438	27.343	0.043	16134	40.115	0.012	6304	15.067	0.166
	(19157_26265)	(23.346_32.008)	(-0.085_0.184)	(13646_19298)	(33.93_47.981)	(-0.121_0.165)	(5177_7388)	(12.373_17.658)	(-0.006_0.384)
Low-middle SDI	109722	45.512	0.036	76881	66.513	0.015	32841	26.169	0.122
	(99966_120661)	(41.465_50.05)	(-0.077_0.138)	(70636_84716)	(61.11_73.292)	(-0.116_0.135)	(28508_37098)	(22.717_29.561)	(0.006_0.245)
Middle SDI	525850	111.917	-0.015	360568	161.156	-0.048	165282	67.155	0.085
	(440585_608749)	(93.77_129.56)	(-0.163_0.141)	(287772_433959)	(128.62_193.958)	(-0.236_0.162)	(139632_193715)	(56.733_78.707)	(-0.081_0.297)
World Bank income level									
World Bank high-income	626018	162.533	-0.111	392179	220.118	-0.169	233838	112.968	-0.014
	(568180_655898)	(147.517_170.291)	(-0.133_-0.095)	(365014_406461)	(204.871_228.134)	(-0.189_-0.151)	(201889_250862)	(97.533_121.192)	(-0.041_0.007)
World Bank low income	21409	40.639	-0.067	15049	60.407	-0.075	6360	22.903	-0.043
	(16684_27216)	(31.67_51.663)	(-0.172_0.062)	(11657_19562)	(46.791_78.52)	(-0.176_0.075)	(4538_8223)	(16.342_29.615)	(-0.211_0.132)
World Bank lower middle-income	214183	50.487	0.027	154337	75.737	-0.003	59846	27.147	0.139
	(187232_237375)	(44.135_55.954)	(-0.102_0.129)	(134984_171526)	(66.24_84.172)	(-0.141_0.108)	(49854_69003)	(22.615_31.301)	(0.013_0.28)
World Bank upper middle-income	945308	151.829	-0.028	641094	219.509	-0.075	304214	92.032	0.097
	(798105_1106833)	(128.187_177.772)	(-0.18_0.131)	(509699_781793)	(174.52_267.684)	(-0.264_0.146)	(253302_360235)	(76.63_108.979)	(-0.095_0.326)
Continents									
Africa	44412	41.233	-0.017	33260	64.567	-0.016	11152	19.845	0.040
	(38953_50628)	(36.165_47.004)	(-0.118_0.116)	(29195_38124)	(56.676_74.01)	(-0.124_0.137)	(9422_12750)	(16.766_22.688)	(-0.108_0.195)
America	273626	117.980	-0.200	152706	142.878	-0.231	120921	96.699	-0.159
	(250592_286741)	(108.048_123.634)	(-0.222_-0.181)	(143216_158884)	(133.999_148.659)	(-0.253_-0.21)	(107198_128030)	(85.724_102.384)	(-0.184_-0.135)
Asia	1084447	123.525	-0.007	736097	174.139	-0.043	348349	76.525	0.092
	(922965_1246915)	(105.131_142.031)	(-0.151_0.141)	(593111_882222)	(140.313_208.708)	(-0.225_0.167)	(291907_405627)	(64.126_89.108)	(-0.085_0.294)
Europe	403667	151.834	-0.087	280133	238.910	-0.162	123534	83.129	0.091
	(376617_421943)	(141.66_158.709)	(-0.118_-0.058)	(263696_292863)	(224.892_249.767)	(-0.198_-0.131)	(110439_131653)	(74.317_88.592)	(0.052_0.124)

Table 2. Continued

	Both genders			Males			Females		% Changes (2010-2021)
	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	
WHO Regions									
African Region	28698	34.451	-0.045	20120	51.722	-0.050	8578	19.319	0.024
	(25638_32262)	(30.777_38.729)	(-0.133_0.064)	(18069_22935)	(46.449_58.958)	(-0.146_0.068)	(7255_9804)	(16.34_22.08)	(-0.108_0.167)
Eastern Mediterranean Region	45076	60.553	-0.044	35838	92.786	-0.066	9238	25.792	0.062
	(39671_51738)	(53.292_69.502)	(-0.162_0.097)	(31310_41579)	(81.063_107.65)	(-0.189_0.092)	(7601_10984)	(21.223_30.667)	(-0.117_0.248)
European Region	410799	147.638	-0.095	285364	232.436	-0.170	125434	80.678	0.079
	(383052_429581)	(137.666_154.388)	(-0.127_-0.067)	(269234_298225)	(219.297_242.911)	(-0.204_-0.14)	(112256_133582)	(72.202_85.918)	(0.04_0.112)
Region of the Americas	273626	117.980	-0.200	152706	142.878	-0.231	120921	96.699	-0.159
	(250592_286741)	(108.048_123.634)	(-0.222_-0.181)	(143216_158884)	(133.999_148.659)	(-0.253_-0.21)	(107198_128030)	(85.724_102.384)	(-0.184_-0.135)
South-East Asia Region	149227	48.313	0.060	102636	69.007	0.036	46591	29.093	0.132
	(127373_167292)	(41.238_54.161)	(-0.089_0.191)	(88586_116132)	(59.561_78.081)	(-0.138_0.186)	(37479_54510)	(23.403_34.038)	(-0.017_0.281)
Western Pacific Region	888144	177.959	-0.001	598886	250.682	-0.039	289258	111.180	0.102
	(738679_1042408)	(148.01_208.869)	(-0.168_0.171)	(468194_737822)	(195.977_308.839)	(-0.248_0.211)	(235036_347349)	(90.339_133.508)	(-0.103_0.346)
Health System Grouping Level									
Advanced Health System	729231	154.404	-0.106	474485	221.967	-0.165	254745	98.538	-0.002
	(666188_761007)	(141.055_161.132)	(-0.128_-0.087)	(445938_493326)	(208.613_230.781)	(-0.188_-0.144)	(222127_272230)	(85.921_105.301)	(-0.031_0.02)
Basic Health System	953998	143.966	-0.027	640528	202.504	-0.063	313470	90.506	0.071
	(798590_1107650)	(120.514_167.153)	(-0.18_0.133)	(505842_781342)	(159.923_247.023)	(-0.253_0.163)	(263446_369619)	(76.063_106.718)	(-0.12_0.288)
Limited Health System	117102	35.508	0.050	82881	51.995	0.017	34222	20.084	0.182
	(105226_130499)	(31.907_39.57)	(-0.102_0.179)	(73724_92328)	(46.25_57.921)	(-0.147_0.167)	(29807_39274)	(17.493_23.049)	(0.026_0.348)
Minimal Health System	6593	33.043	0.026	4771	50.472	-0.008	1822	17.350	0.105
	(5058_9047)	(25.348_45.342)	(-0.119_0.202)	(3552_6952)	(37.578_73.536)	(-0.147_0.171)	(1397_2296)	(13.308_21.867)	(-0.104_0.382)
GBD Region									
Central Europe, Eastern Europe, and Central Asia	150860	132.733	-0.097	110971	238.706	-0.173	39889	59.387	0.120
	(142404_158787)	(125.293_139.707)	(-0.141_-0.052)	(103788_117408)	(223.256_252.552)	(-0.227_-0.127)	(36725_42578)	(54.675_63.391)	(0.056_0.184)

Table 2. Continued

	Both genders			Males			Females		% Changes (2010-2021)
	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	
Central Asia	9109	62.605	-0.261	7180	112.416	-0.294	1929	23.631	-0.176
	(8144_10065)	(55.974_69.179)	(-0.334_-0.181)	(6358_7953)	(99.55_124.514)	(-0.368_-0.219)	(1713_2154)	(20.983_26.392)	(-0.269_-0.071)
Central Europe	74575	201.401	0.013	50792	313.870	-0.082	23783	114.092	0.265
	(69151_79336)	(186.754_214.26)	(-0.052_0.076)	(46712_54314)	(288.661_335.637)	(-0.149_-0.017)	(21677_25710)	(103.99_123.336)	(0.172_0.352)
Eastern Europe	67176	108.211	-0.139	52999	221.577	-0.200	14177	37.151	0.031
	(61079_72932)	(98.389_117.482)	(-0.214_-0.065)	(47449_58260)	(198.373_243.571)	(-0.283_-0.119)	(12739_15580)	(33.382_40.829)	(-0.061_0.128)
High-income	561913	157.964	-0.114	349411	212.563	-0.167	212502	111.058	-0.030
	(508470_590518)	(142.94_166.005)	(-0.137_-0.097)	(324274_362986)	(197.271_220.821)	(-0.188_-0.149)	(182869_228329)	(95.571_119.33)	(-0.058_-0.008)
Australasia	11554	130.792	-0.092	6741	160.438	-0.127	4814	103.907	-0.042
	(10292_12717)	(116.497_143.946)	(-0.166_-0.008)	(6032_7455)	(143.577_177.446)	(-0.215_-0.027)	(4166_5305)	(89.911_114.514)	(-0.111_0.027)
High-income Asia Pacific	112940	160.191	0.045	79137	244.570	0.005	33803	88.615	0.127
	(96202_122466)	(136.45_173.702)	(-0.011_0.096)	(70914_84035)	(219.155_259.707)	(-0.041_0.05)	(25676_38993)	(67.309_102.221)	(0.046_0.194)
High-income North America	188320	167.345	-0.211	101358	193.837	-0.243	86962	144.350	-0.175
	(172395_198522)	(153.193_176.41)	(-0.232_-0.192)	(95110_105954)	(181.888_202.625)	(-0.27_-0.221)	(76277_92754)	(126.614_153.964)	(-0.2_-0.151)
Southern Latin America	15778	107.213	-0.172	10278	156.232	-0.239	5500	67.584	-0.020
	(14424_17161)	(98.016_116.617)	(-0.234_-0.095)	(9431_11146)	(143.364_169.42)	(-0.308_-0.167)	(4882_6104)	(59.989_75.012)	(-0.105_0.087)
Western Europe	233320	156.450	-0.099	151897	220.295	-0.179	81423	101.547	0.065
	(212064_246994)	(142.196_165.618)	(-0.133_-0.066)	(140457_159822)	(203.703_231.788)	(-0.214_-0.147)	(70954_87822)	(88.491_109.528)	(0.023_0.101)
Latin America and Caribbean	70597	66.458	-0.087	41724	85.661	-0.139	28873	50.196	0.011
	(64558_76143)	(60.773_71.678)	(-0.141_-0.034)	(38584_44880)	(79.213_92.14)	(-0.192_-0.082)	(25745_31373)	(44.757_54.542)	(-0.053_0.079)
Andean Latin America	5439	54.906	-0.055	2991	63.182	-0.081	2448	47.332	-0.014
	(4247_6628)	(42.874_66.907)	(-0.243_0.154)	(2334_3677)	(49.308_77.675)	(-0.269_0.135)	(1829_3058)	(35.366_59.117)	(-0.217_0.23)
Caribbean	9558	103.231	-0.070	6107	140.434	-0.092	3450	70.278	-0.017
	(8476_10756)	(91.545_116.176)	(-0.178_0.032)	(5382_6866)	(123.765_157.888)	(-0.205_0.012)	(2976_3926)	(60.622_79.976)	(-0.13_0.1)
Central Latin America	21342	49.904	-0.138	12696	64.588	-0.169	8646	37.412	-0.076
	(18903_24063)	(44.201_56.266)	(-0.229_-0.039)	(11076_14471)	(56.343_73.617)	(-0.268_-0.062)	(7411_9959)	(32.071_43.096)	(-0.188_0.039)
Tropical Latin America	34258	77.336	-0.049	19930	99.804	-0.130	14329	58.895	0.100
	(31582_36215)	(71.295_81.753)	(-0.089_-0.006)	(18588_21030)	(93.082_105.314)	(-0.173_-0.081)	(12907_15329)	(53.053_63.006)	(0.045_0.154)

Table 2. Continued

	Both genders			Males			Females		% Changes (2010-2021)
	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	Changes (2010-2021)	Death number	Death rate per 100,000	
North Africa and Middle East	**62269**	**81.682**	**-0.058**	**50281**	**130.314**	**-0.085**	**11988**	**31.841**	**0.063**
	(54488_72079)	**(71.475_94.55)**	**(-0.184_0.098)**	**(43336_59239)**	**(112.315_153.53)**	**(-0.217_0.079)**	**(10014_13939)**	**(26.598_37.025)**	**(-0.121_0.26)**
North Africa and Middle East	**62269**	**81.682**	**-0.058**	**50281**	**130.314**	**-0.085**	**11988**	**31.841**	**0.063**
	(54488_72079)	**(71.475_94.55)**	**(-0.184_0.098)**	**(43336_59239)**	**(112.315_153.53)**	**(-0.217_0.079)**	**(10014_13939)**	**(26.598_37.025)**	**(-0.121_0.26)**
South Asia	**79596**	**32.057**	**0.111**	**57538**	**47.285**	**0.052**	**22058**	**17.422**	**0.342**
	(66946_90425)	**(26.962_36.418)**	**(-0.084_0.294)**	**(46646_66292)**	**(38.334_54.479)**	**(-0.159_0.256)**	**(18694_25775)**	**(14.765_20.358)**	**(0.103_0.612)**
South Asia	**79596**	**32.057**	**0.111**	**57538**	**47.285**	**0.052**	**22058**	**17.422**	**0.342**
	(66946_90425)	**(26.962_36.418)**	**(-0.084_0.294)**	**(46646_66292)**	**(38.334_54.479)**	**(-0.159_0.256)**	**(18694_25775)**	**(14.765_20.358)**	**(0.103_0.612)**
Southeast Asia, East Asia, and Oceania	**856734**	**168.678**	**-0.019**	**575428**	**236.246**	**-0.052**	**281305**	**106.419**	**0.075**
	(707838_1006822)	**(139.363_198.229)**	**(-0.191_0.164)**	**(442793_715500)**	**(181.792_293.753)**	**(-0.265_0.207)**	**(231638_335834)**	**(87.629_127.047)**	**(-0.135_0.325)**
East Asia	**742883**	**189.452**	**-0.012**	**497183**	**262.100**	**-0.047**	**245700**	**121.376**	**0.090**
	(600890_895412)	**(153.241_228.351)**	**(-0.207_0.194)**	**(371156_635002)**	**(195.662_334.754)**	**(-0.293_0.246)**	**(195934_301544)**	**(96.791_148.963)**	**(-0.148_0.379)**
Oceania	**999**	**80.941**	**0.029**	**722**	**111.783**	**0.017**	**276**	**47.028**	**0.073**
	(759_1382)	**(61.46_111.976)**	**(-0.164_0.256)**	**(531_1029)**	**(82.141_159.28)**	**(-0.173_0.254)**	**(201_388)**	**(34.215_65.929)**	**(-0.137_0.31)**
Southeast Asia	**112852**	**98.514**	**-0.023**	**77523**	**145.629**	**-0.040**	**35329**	**57.613**	**0.007**
	(92675_130034)	**(80.9_113.513)**	**(-0.158_0.106)**	**(64911_90474)**	**(121.936_169.956)**	**(-0.188_0.109)**	**(27315_42107)**	**(44.543_68.666)**	**(-0.135_0.161)**
Sub-Saharan Africa	**26841**	**34.439**	**-0.040**	**18586**	**51.484**	**-0.045**	**8256**	**19.732**	**0.028**
	(23894_30298)	**(30.657_38.873)**	**(-0.13_0.07)**	**(16551_21344)**	**(45.847_59.123)**	**(-0.143_0.075)**	**(6970_9434)**	**(16.659_22.547)**	**(-0.107_0.178)**
Central Sub-Saharan Africa	**3863**	**42.808**	**0.081**	**2816**	**68.309**	**0.037**	**1047**	**21.359**	**0.145**
	(2751_5728)	**(30.482_63.482)**	**(-0.145_0.365)**	**(1864_4526)**	**(45.215_109.804)**	**(-0.198_0.318)**	**(759_1418)**	**(15.484_28.936)**	**(-0.161_0.535)**
Eastern Sub-Saharan Africa	**7993**	**29.563**	**0.011**	**5549**	**43.089**	**-0.026**	**2444**	**17.259**	**0.139**
	(6934_9422)	**(25.647_34.848)**	**(-0.145_0.167)**	**(4711_6646)**	**(36.582_51.603)**	**(-0.199_0.147)**	**(1923_2956)**	**(13.58_20.878)**	**(-0.067_0.372)**
Southern Sub-Saharan Africa	**8679**	**89.148**	**-0.113**	**5569**	**137.813**	**-0.156**	**3110**	**54.614**	**-0.022**
	(7892_9621)	**(81.065_98.827)**	**(-0.193_-0.02)**	**(4937_6273)**	**(122.169_155.231)**	**(-0.248_-0.045)**	**(2711_3517)**	**(47.615_61.765)**	**(-0.141_0.103)**
Western Sub-Saharan Africa	**6307**	**19.621**	**-0.010**	**4651**	**30.891**	**0.021**	**1655**	**9.688**	**0.079**
	(5288_7499)	**(16.451_23.33)**	**(-0.131_0.146)**	**(3909_5520)**	**(25.96_36.658)**	**(-0.124_0.203)**	**(1299_1967)**	**(7.605_11.512)**	**(-0.1_0.296)**

SDI: socio-demographic index, TBLC: **tracheal, bronchus, and lung cancer,** WHO: World Health Organization

Table 3. Burden of TBLC in ≥55 years old in 2021 and its changes from 2010 to 2021

	Both genders			Males		Changes (2010-2021)	Females		Changes (2010-2021)
	DALY number	DALY rate per 100,000	Changes (2010-2021)	DALY number	DALY rate per 100,000		DALY number	DALY rate per 100,000	
Global	37632985	2532.526	-0.092	25527865	3649.352	-0.133	12105120	1539.174	0.007
	(33897815_41367880)	(2281.166_2783.867)	(-0.175_-0.003)	(22421782_28746491)	(3205.319_4109.472)	(-0.236_-0.015)	(10799610_13346792)	(1373.178_1697.054)	(-0.09_0.111)
SDI									
High SDI	10792988	3128.284	-0.151	6684375	4162.062	-0.206	4108613	2227.971	-0.061
	(10005640_11267790)	(2900.076_3265.902)	(-0.174_-0.13)	(6296548_6982975)	(3920.58_4347.987)	(-0.232_-0.179)	(3677289_4344500)	(1994.077_2355.884)	(-0.089_-0.036)
High-middle SDI	12375134	3569.641	-0.071	8743270	5506.714	-0.135	3631864	1932.845	0.100
	(10857873_14081882)	(3131.983_4061.957)	(-0.185_0.059)	(7333050_10300126)	(4618.525_6487.258)	(-0.279_0.029)	(3071972_4280983)	(1634.875_2278.3)	(-0.077_0.307)
Low SDI	531329	647.505	0.045	383439	953.372	0.014	147891	353.477	0.165
	(450859_625379)	(549.44_762.119)	(-0.085_0.191)	(320621_462061)	(797.185_1148.856)	(-0.122_0.174)	(122508_173716)	(292.81_415.202)	(-0.008_0.383)
Low-middle SDI	2561649	1062.559	0.038	1816661	1571.675	0.017	744988	593.638	0.126
	(2328237_2826848)	(965.741_1172.562)	(-0.08_0.143)	(1659387_2006821)	(1435.609_1736.19)	(-0.117_0.141)	(644455_845617)	(513.529_673.823)	(0.005_0.254)
Middle SDI	11330969	2411.571	-0.038	7872000	3518.392	-0.069	3458969	1405.400	0.064
	(9498761_13120367)	(2021.622_2792.408)	(-0.188_0.118)	(6286261_9507920)	(2809.646_4249.567)	(-0.253_0.143)	(2945011_4042403)	(1196.575_1642.453)	(-0.103_0.274)
World Bank income level									
World Bank high-income	11990750	3113.167	-0.150	7626601	4280.581	-0.209	4364150	2108.335	-0.044
	(11112158_12425474)	(2885.057_3226.034)	(-0.168_-0.134)	(7218473_7867798)	(4051.511_4415.958)	(-0.228_-0.192)	(3896101_4611811)	(1882.219_2227.981)	(-0.068_-0.023)
World Bank low income	504793	958.214	-0.064	360168	1445.697	-0.072	144626	520.844	-0.037
	(390955_643948)	(742.122_1222.361)	(-0.171_0.067)	(275522_473148)	(1105.932_1899.195)	(-0.176_0.082)	(104173_185762)	(375.16_668.99)	(-0.205_0.144)
World Bank lower middle-income	5060236	1192.806	0.034	3684724	1808.179	0.004	1375512	623.960	0.154
	(4403727_5609606)	(1038.053_1322.305)	(-0.098_0.14)	(3223864_4101232)	(1582.024_2012.57)	(-0.135_0.119)	(1133792_1595101)	(514.311_723.571)	(0.017_0.307)
World Bank upper middle-income	20039185	3218.568	-0.056	13830414	4735.493	-0.100	6208771	1878.297	0.068
	(16910136_23501422)	(2716_3774.651)	(-0.208_0.106)	(11037818_16968317)	(3779.316_5809.902)	(-0.284_0.12)	(5149757_7361950)	(1557.921_2227.16)	(-0.125_0.297)
Continents									
Africa	1051133	975.899	-0.013	792427	1538.334	-0.012	258706	460.354	0.050
	(915828_1200187)	(850.278_1114.285)	(-0.119_0.126)	(692495_910200)	(1344.336_1766.967)	(-0.124_0.144)	(217076_297011)	(386.276_528.517)	(-0.105_0.212)
America	5518481	2379.404	-0.210	3130441	2928.981	-0.245	2388040	1909.685	-0.160
	(5156140_5739149)	(2223.173_2474.549)	(-0.23_-0.19)	(2972652_3248259)	(2781.346_3039.217)	(-0.267_-0.224)	(2175171_2509784)	(1739.456_2007.042)	(-0.185_-0.138)
Asia	22589353	2573.068	-0.033	15591105	3688.398	-0.067	6998247	1537.372	0.066
	(19058755_26066482)	(2170.911_2969.135)	(-0.181_0.12)	(12566132_18760446)	(2972.778_4438.171)	(-0.248_0.153)	(5924316_8150802)	(1301.451_1790.565)	(-0.115_0.265)

Table 3. Continued

	Both genders			Males		Changes (2010-2021)	Females		Changes (2010-2021)
	DALY number	DALY rate per 100,000	Changes (2010-2021)	DALY number	DALY rate per 100,000		DALY number	DALY rate per 100,000	
Europe	8418281	3166.436	-0.112	5976514	5097.047	-0.184	2441767	1643.122	0.068
	(7964899_8758645)	(2995.902_3294.46)	(-0.143_-0.084)	(5672625_6243635)	(4837.877_5324.861)	(-0.22_-0.152)	(2238368_2579953)	(1506.25_1736.11)	(0.032_0.103)
WHO Regions									
African Region	678416	814.413	-0.043	480517	1235.253	-0.050	197899	445.708	0.034
	(602331_768340)	(723.075_922.363)	(-0.133_0.07)	(427493_551386)	(1098.945_1417.434)	(-0.149_0.073)	(166748_226701)	(375.55_510.576)	(-0.104_0.183)
Eastern Mediterranean Region	1048108	1407.974	-0.037	838752	2171.564	-0.056	209356	584.524	0.063
	(920181_1208097)	(1236.124_1622.895)	(-0.16_0.107)	(725863_977752)	(1879.291_2531.442)	(-0.189_0.105)	(171894_251043)	(479.929_700.914)	(-0.126_0.255)
European Region	8586034	3085.755	-0.120	6103222	4971.216	-0.191	2482812	1596.908	0.057
	(8131189_8934955)	(2922.287_3211.154)	(-0.15_-0.092)	(5798726_6374982)	(4723.197_5192.57)	(-0.226_-0.16)	(2276653_2623280)	(1464.31_1687.255)	(0.021_0.092)
Region of the Americas	5518481	2379.404	-0.210	3130441	2928.981	-0.245	2388040	1909.685	-0.160
	(5156140_5739149)	(2223.173_2474.549)	(-0.23_-0.19)	(2972652_3248259)	(2781.346_3039.217)	(-0.267_-0.224)	(2175171_2509784)	(1739.456_2007.042)	(-0.185_-0.138)
South-East Asia Region	3451022	1117.280	0.057	2404574	1616.713	0.032	1046448	653.439	0.137
	(2949843_3877262)	(955.022_1255.277)	(-0.096_0.191)	(2076744_2731231)	(1396.297_1836.341)	(-0.143_0.185)	(834081_1239276)	(520.829_773.847)	(-0.017_0.298)
Western Pacific Region	18087358	3624.186	-0.035	12400755	5190.725	-0.070	5686603	2185.714	0.068
	(14967716_21430920)	(2999.1_4294.14)	(-0.202_0.144)	(9580340_15453131)	(4010.152_6468.393)	(-0.279_0.188)	(4628024_6849611)	(1778.836_2632.73)	(-0.145_0.316)
Health System Grouping Level									
Advanced Health System	14400136	3049.014	-0.140	9594310	4488.278	-0.197	4805825	1858.944	-0.030
	(13500388_14917720)	(2858.506_3158.605)	(-0.159_-0.121)	(9133841_9942508)	(4272.867_4651.167)	(-0.22_-0.176)	(4327401_5059018)	(1673.884_1956.882)	(-0.055_-0.01)
Basic Health System	20273158	3059.385	-0.050	13818091	4368.623	-0.084	6455067	1863.733	0.047
	(16921208_23603532)	(2553.549_3561.966)	(-0.203_0.111)	(10895294_16959756)	(3444.574_5361.868)	(-0.27_0.146)	(5389161_7623352)	(1555.98_2201.045)	(-0.143_0.261)
Limited Health System	2759867	836.847	0.047	1971760	1236.972	0.013	788107	462.528	0.187
	(2476217_3086161)	(750.839_935.786)	(-0.104_0.183)	(1748041_2199335)	(1096.624_1379.74)	(-0.15_0.167)	(682644_908593)	(400.633_533.239)	(0.026_0.356)
Minimal Health System	158909	796.401	0.041	115584	1222.644	0.010	43325	412.627	0.113
	(120507_220790)	(603.94_1106.529)	(-0.11_0.222)	(84839_170546)	(897.425_1804.026)	(-0.145_0.198)	(33108_54601)	(315.316_520.022)	(-0.101_0.395)

Table 3. Continued

	Both genders			Males		Changes (2010-2021)	Females		Changes (2010-2021)
	DALY number	DALY rate per 100,000	Changes (2010-2021)	DALY number	DALY rate per 100,000		DALY number	DALY rate per 100,000	
GBD Region									
Central Europe, Eastern Europe, and Central Asia	3436982	3024.001	-0.116	2597087	5586.517	-0.185	839896	1250.434	0.091
	(3243146_3614237)	(2853.456_3179.957)	(-0.162_-0.072)	(2423068_2752545)	(5212.191_5920.919)	(-0.24_-0.138)	(780004_895430)	(1161.268_1333.113)	(0.029_0.156)
Central Asia	225236	1548.039	-0.236	180539	2826.658	-0.272	44697	547.577	-0.129
	(199859_249566)	(1373.625_1715.253)	(-0.315_-0.15)	(158975_200718)	(2489.04_3142.592)	(-0.351_-0.191)	(39419_50226)	(482.909_615.31)	(-0.235_-0.012)
Central Europe	1637723	4422.930	-0.038	1137575	7029.726	-0.125	500147	2399.289	0.205
	(1519791_1740836)	(4104.436_4701.403)	(-0.105_0.022)	(1046989_1216922)	(6469.941_7520.053)	(-0.192_-0.062)	(458229_541753)	(2198.199_2598.876)	(0.112_0.29)
Eastern Europe	1574023	2535.517	-0.135	1278973	5347.074	-0.190	295051	773.196	0.027
	(1421402_1713742)	(2289.666_2760.583)	(-0.215_-0.057)	(1140364_1411538)	(4767.586_5901.3)	(-0.278_-0.105)	(264892_325059)	(694.162_851.833)	(-0.072_0.133)
High-income	10617887	2984.879	-0.153	6690445	4070.107	-0.209	3927442	2052.573	-0.058
Australasia	221657	2509.066	-0.106	129015	3070.831	-0.146	92642	1999.635	-0.047
	(201708_240799)	(2283.253_2725.74)	(-0.173_-0.03)	(117303_141515)	(2792.057_3368.337)	(-0.229_-0.054)	(82235_100662)	(1775.02_2172.759)	(-0.108_0.018)
High-income Asia Pacific	1821752	2583.922	-0.063	1328767	4106.494	-0.093	492985	1292.376	0.002
	(1605467_1950856)	(2277.149_2767.039)	(-0.11_-0.018)	(1215044_1403103)	(3755.04_4336.227)	(-0.135_-0.052)	(391676_555628)	(1026.791_1456.594)	(-0.069_0.065)
High-income North America	3702193	3289.836	-0.226	2030321	3882.771	-0.262	1671872	2775.178	-0.183
	(3456812_3866920)	(3071.786_3436.215)	(-0.246_-0.207)	(1925297_2109910)	(3681.924_4034.977)	(-0.288_-0.239)	(1509181_1764424)	(2505.124_2928.807)	(-0.206_-0.16)
Southern Latin America	333680	2267.447	-0.188	221030	3359.792	-0.257	112649	1384.341	-0.019
	(307219_363305)	(2087.64_2468.757)	(-0.251_-0.111)	(203004_239645)	(3085.782_3642.747)	(-0.323_-0.187)	(101207_124359)	(1243.72_1528.239)	(-0.107_0.09)
Western Europe	4538605	3043.297	-0.132	2981312	4323.758	-0.213	1557293	1942.183	0.044
	(4219045_4755438)	(2829.021_3188.691)	(-0.163_-0.102)	(2802822_3113953)	(4064.897_4516.126)	(-0.246_-0.183)	(1397833_1659560)	(1743.313_2069.725)	(0.005_0.079)
Latin America and Caribbean	1503628	1415.459	-0.090	892265	1831.834	-0.146	611363	1062.868	0.017
	(1385991_1618090)	(1304.72_1523.209)	(-0.144_-0.036)	(826670_958313)	(1697.165_1967.432)	(-0.202_-0.085)	(554373_662268)	(963.789_1151.367)	(-0.048_0.088)
Andean Latin America	109922	1109.598	-0.044	60516	1278.403	-0.068	49406	955.119	-0.007
	(84946_135856)	(857.485_1371.387)	(-0.243_0.168)	(47086_75150)	(994.704_1587.544)	(-0.265_0.166)	(36647_61666)	(708.459_1192.127)	(-0.228_0.244)
Caribbean	201540	2176.819	-0.070	129853	2985.910	-0.090	71687	1460.135	-0.020
	(178389_227376)	(1926.765_2455.877)	(-0.184_0.033)	(113689_146980)	(2614.218_3379.728)	(-0.209_0.018)	(61848_81914)	(1259.747_1668.454)	(-0.136_0.104)
Central Latin America	447580	1046.574	-0.132	268449	1365.641	-0.164	179131	775.161	-0.063
	(394104_508099)	(921.53_1188.086)	(-0.227_-0.023)	(233134_306854)	(1185.987_1561.012)	(-0.272_-0.049)	(153638_207069)	(664.847_896.062)	(-0.182_0.062)

Table 3. Continued

	Both genders			Males		Changes (2010-2021)	Females		Changes (2010-2021)
	DALY number	DALY rate per 100,000	Changes (2010-2021)	DALY number	DALY rate per 100,000		DALY number	DALY rate per 100,000	
Tropical Latin America	744586	1680.864	-0.063	433447	2170.609	-0.150	311140	1278.887	0.100
	(699950_783162)	(1580.098_1767.946)	(-0.103_-0.021)	(407199_457307)	(2039.167_2290.098)	(-0.194_-0.101)	(284939_330791)	(1171.193_1359.659)	(0.045_0.153)
North Africa and Middle East	1425166	1869.467	-0.057	1164707	3018.571	-0.082	260458	691.805	0.056
	(1235874_1644515)	(1621.163_2157.199)	(-0.185_0.096)	(998361_1367526)	(2587.452_3544.217)	(-0.215_0.083)	(218063_303375)	(579.198_805.797)	(-0.131_0.258)
North Africa and Middle East	1425166	1869.467	-0.057	1164707	3018.571	-0.082	260458	691.805	0.056
	(1235874_1644515)	(1621.163_2157.199)	(-0.185_0.096)	(998361_1367526)	(2587.452_3544.217)	(-0.215_0.083)	(218063_303375)	(579.198_805.797)	(-0.131_0.258)
South Asia	1887377	760.135	0.103	1375271	1130.202	0.044	512106	404.471	0.343
	(1585172_2154999)	(638.423_867.919)	(-0.095_0.291)	(1114965_1585848)	(916.281_1303.254)	(-0.168_0.248)	(432833_600824)	(341.86_474.542)	(0.092_0.623)
South Asia	1887377	760.135	0.103	1375271	1130.202	0.044	512106	404.471	0.343
	(1585172_2154999)	(638.423_867.919)	(-0.095_0.291)	(1114965_1585848)	(916.281_1303.254)	(-0.168_0.248)	(432833_600824)	(341.86_474.542)	(0.092_0.623)
Southeast Asia, East Asia, and Oceania	18124029	3568.357	-0.044	12361382	5075.046	-0.075	5762647	2180.031	0.047
	(14918989_21439691)	(2937.331_4221.162)	(-0.216_0.137)	(9504105_15443049)	(3901.972_6340.244)	(-0.285_0.188)	(4712955_6910714)	(1782.929_2614.349)	(-0.165_0.293)
East Asia	15502899	3953.603	-0.044	10532324	5552.328	-0.076	4970575	2455.468	0.056
	(12467252_18831949)	(3179.441_4802.588)	(-0.236_0.166)	(7844220_13557156)	(4135.239_7146.929)	(-0.318_0.224)	(3937268_6141452)	(1945.014_3033.883)	(-0.184_0.342)
Oceania	23751	1924.455	0.045	17139	2651.737	0.032	6612	1124.782	0.093
	(17906_33090)	(1450.868_2681.206)	(-0.146_0.283)	(12523_24470)	(1937.553_3785.944)	(-0.171_0.279)	(4797_9362)	(816.098_1592.629)	(-0.122_0.355)
Southeast Asia	2597379	2267.371	-0.014	1811918	3403.722	-0.030	785460	1280.895	0.015
	(2133351_3004461)	(1862.299_2622.731)	(-0.154_0.123)	(1498353_2137437)	(2814.684_4015.215)	(-0.185_0.128)	(604070_944581)	(985.091_1540.382)	(-0.138_0.182)
Sub-Saharan Africa	637916	818.476	-0.039	446707	1237.409	-0.044	191209	457.008	0.038
	(565855_727509)	(726.018_933.427)	(-0.131_0.077)	(394235_516681)	(1092.057_1431.243)	(-0.147_0.08)	(161649_219338)	(386.357_524.238)	(-0.102_0.191)
Central Sub-Saharan Africa	97294	1078.229	0.099	71677	1738.744	0.056	25617	522.673	0.160
	(68062_145954)	(754.272_1617.479)	(-0.138_0.408)	(47308_115842)	(1147.591_2810.089)	(-0.19_0.342)	(18512_34459)	(377.711_703.078)	(-0.155_0.559)
Eastern Sub-Saharan Africa	188817	698.349	0.003	131554	1021.454	-0.036	57263	404.440	0.138
	(163819_225570)	(605.894_834.283)	(-0.151_0.167)	(111725_159739)	(867.491_1240.292)	(-0.212_0.143)	(44794_69457)	(316.378_490.569)	(-0.07_0.376)
Southern Sub-Saharan Africa	206656	2122.752	-0.116	136927	3388.552	-0.158	69729	1224.518	-0.015
	(187456_229595)	(1925.536_2358.384)	(-0.2_-0.016)	(121076_154957)	(2996.291_3834.761)	(-0.254_-0.043)	(61196_79052)	(1074.656_1388.228)	(-0.137_0.121)
Western Sub-Saharan Africa	145149	451.571	0.000	106549	707.597	0.029	38600	225.926	0.096
	(120032_174006)	(373.428_541.349)	(-0.126_0.165)	(88698_128227)	(589.046_851.563)	(-0.12_0.222)	(29706_46355)	(173.866_271.317)	(-0.097_0.316)

SDI: Socio-demographic Index, TBLC: tracheal, bronchus, and lung cancer, WHO: World Health Organization, GBD: Global Burden of Disease

The Global Trend of TBLC Among Aged ≥55 Years by Continents

In 2021, approximately 60% of TBLC incidence, death, and DALY cases were recognized in Asian countries, but more TBLC incidence, death, and DALY rates were reported in European countries, with 169.159, 151.834, and 3,166.436 cases per 100,000 population, respectively. While between 2010 and 2021, the TBLC incidence rate (per 100,000) increased by 3.6% in Asia, other continents reported a downward trend of up to 20.9% (America). Males on all continents experienced a decreasing trend in the observed factor, but among women, only America reported a downward trend (17.3%). At this time, the TBLC death and DALY rates (per 100,000) in all continents decreased; the highest decrease was reported in America by 20 and 21%, respectively. Also, males in all continents reported a decreasing trend, but for women, only America experienced a downward trend of 15.9% (Tables 1, 2, 3 and, Figure 1).

The Global Trend of TBLC Among Aged ≥55 Years by Socio-demographic Index

In 2021, most TBLC incidence cases (34.4%) were recorded in high SDI countries. High-middle SDI countries exhibited the highest TBLC deaths (32.2%) and DALYs (32.9%). High SDI countries experienced the highest decreasing trend in TBLC incidence, death, and DALY rates (per 100,000) by a 10.9, 11.2, and 15.1% decrease, respectively, compared to 2010. TBLC incidence rate for males decreased in high and high-middle SDI countries from 2010 to 2021, while only high SDI countries recorded a decreasing trend for females. TBLC death and DALY rates for males increased in low and low-middle SDI countries from 2010 to 2021, while only for females high SDI countries recorded a slight decreasing trend in TBLC death and DALY rates by 3% and 6.1%, respectively (Tables 1, 2, 3 and, Figure 2).

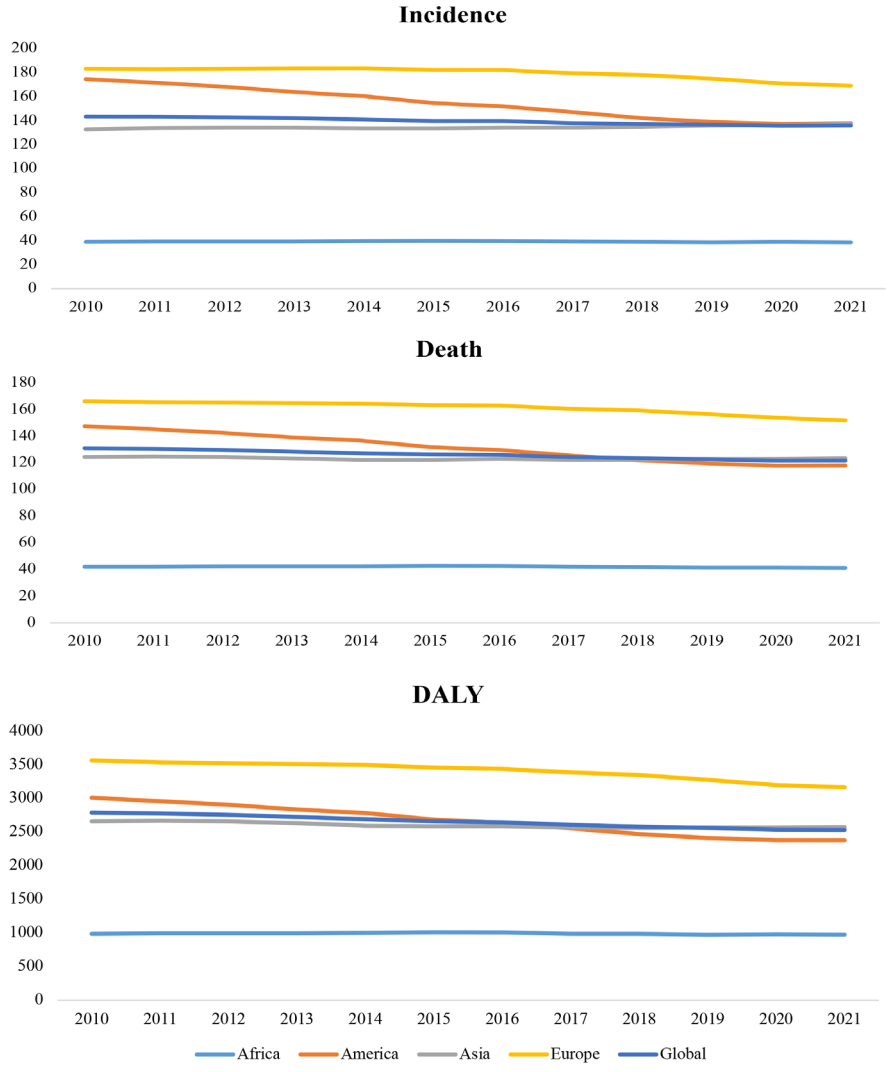

Figure 1. Temporal trend of incidence, death and DALYs rates (per 100,000 population) of TBLC based on continents and comparison with global data from 2010 to 2021

TBLC: tracheal, bronchus, and lung cancer

The Global Trend of TBLC Among Aged ≥55 Years by World Bank Income Levels

In 2021, the highest TBLC incidence, death, and DALYs rates (per 100,000) were reported in World Bank high-income countries with an incidence rate of 193.124, high-income countries with a death rate of 162.533, and upper middle-income countries with DALYs of 3,218.568, respectively. World Bank high-income countries experienced the highest downward trends of 10.7, 11.1, and 15.0% in incidence, death, and DALYs rates (per 100,000) between 2010 and 2021, respectively. The male TBLC incidence rate (per 100,000) decreased in all World Bank groups except World Bank lower middle-income, which reported a stable trend. The male TBLC death and DALY rates (per 100,000) decreased in all World Bank groups, up to 16.9% and 20.9%, in the World Bank high-income group, respectively. The TBLC incidence rate for females increased up to 16.8% in the World Bank upper middle-income countries. The TBLC death and DALY rates for females increased by 13.9% and 15.4%, respectively, in countries classified by the World Bank as lower middle-income (Tables 1, 2, 3).

The Global Trend of TBLC Among Aged ≥55 years in WHO Regions

In 2021, the Western Pacific Region exhibited the highest incidence rate of TBLC for both genders. The region of the Americas experienced a downward trend of 10.7%, 23.7%, and 17.3% for both genders, males, and females in the TBLC incidence rate compared to 2010. The Western Pacific region exhibited the highest death rate of TBLC for both genders. The Region of the Americas experienced a downward trend in TBLC death rates of 20% for both genders, 23.1% for males, and 15.9% for females compared to 2010. The Western Pacific Region exhibited the highest DALY rate of TBLC for both genders. The region of the Americas experienced a downward trend of 21%, 24.5%, and 16% for both genders combined, males, and females, TBLC DALY rate compared to 2010. Female TBLC incidence, death, and DALY rates, in all WHO regions increased, except the region of the Americas (Tables 1, 2, 3 and, Figure 3).

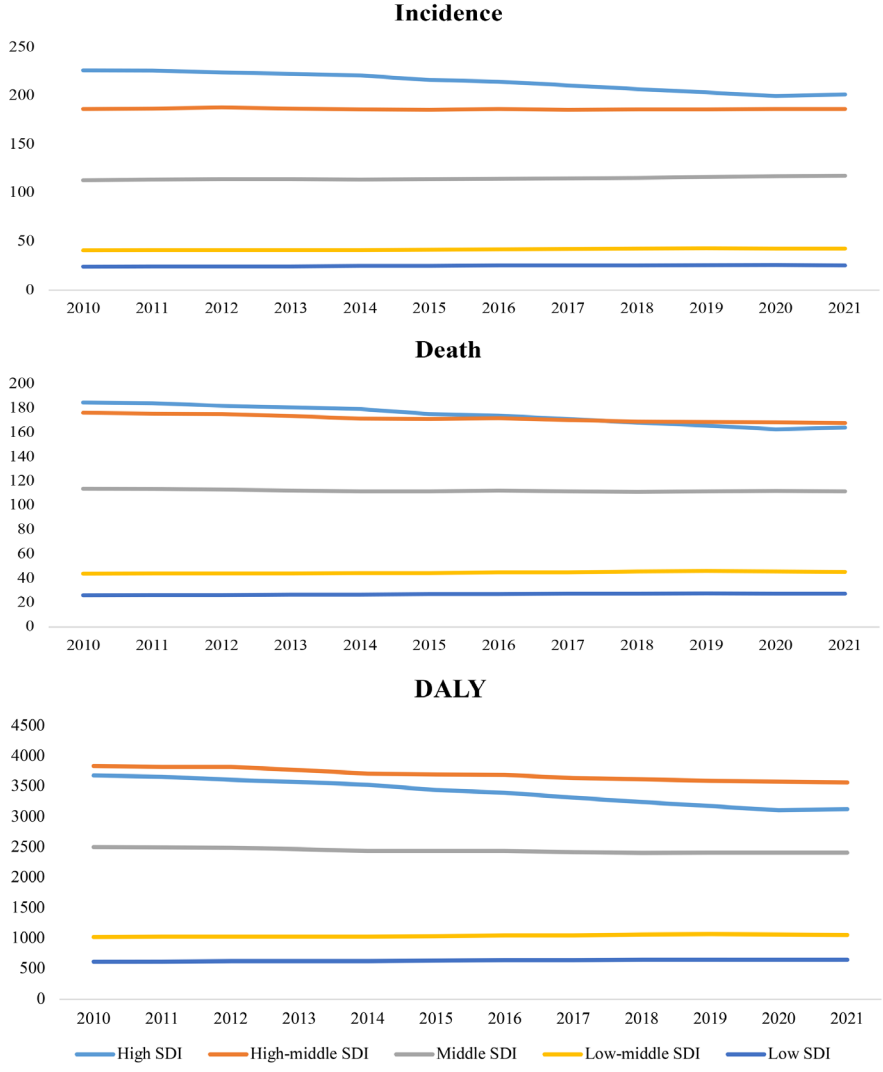

Figure 2. Temporal trend of incidence, death, and DALYs rates (per 100,000 population) of TBLC based on SDI from 2010 to 2021

SDI: socio-demographic index, TBLC: tracheal, bronchus, and lung cancer

The Global Trend of TBLC Among Aged ≥55 Years by Health System Advancement Levels

Countries with Advanced Health Systems reported the highest TBLC incidence, death, and DALY rates with 183.297, 154.404, and 3,059.385 per 100,000 people, respectively, and the highest decreasing trend of 10.3, 10.6, and 14% compared to 2010 for these indicators. In contrast, the most notable increasing trend in TBLC incidence, death, and DALY rates is observed in females living in countries with Limited Health Systems, experiencing respective increases of 19.4%, 18.2%, and 18.7% (Table 1).

The Global Trend of TBLC Among Aged ≥55 Years in GBG Regions

In 2021, among GBG regions, the highest TBLC incidence rate (per 100,000) was allocated to East Asia with 213.477. Between 2010 and 2019, 15, 18, and 6 regions of GBD regions reported a downward trend in TBLC incidence number and rate (per 100,000) for both genders, males, and females, respectively. The highest increase was observed in South Asia (12%), Western Europe (6%), and Central Latin America and the high-income Asia Pacific (35.7%) for both genders, males, and females, respectively. The highest decrease was observed in Central Asia (24.5%), East Asia (27.5%), and North Africa and Middle East and North America (17.8%) for both genders, males, and females, respectively (Table 1, Figures 4, 5).

The highest TBLC death rate (per 100,000) was recorded in Central Europe (201.401). Between 2010 and 2019, 16, 17, and 9 GBD regions reported a downward trend in TBLC death number and rate (per 100,000) for both genders, males, and females, respectively. The highest increase was observed in South Asia, with increases of 11.1%, 5.2%, and 34.2% for both genders, males, and females, respectively. The highest decrease was observed in Central Asia with a 26.1%, 29.4%, and 17.6% decrease for both genders, males, and females, respectively (Table 2, and, Figures 4, 5).

The highest TBLC DALY rate (per 100,000) was recorded in Central Europe (4,422.930). Between 2010 and 2019, 17 GBD regions, 17 for males, and 9 for females reported a downward trend in TBLC DALY number and rate (per 100,000) for both genders, males, and females, respectively. The highest increase

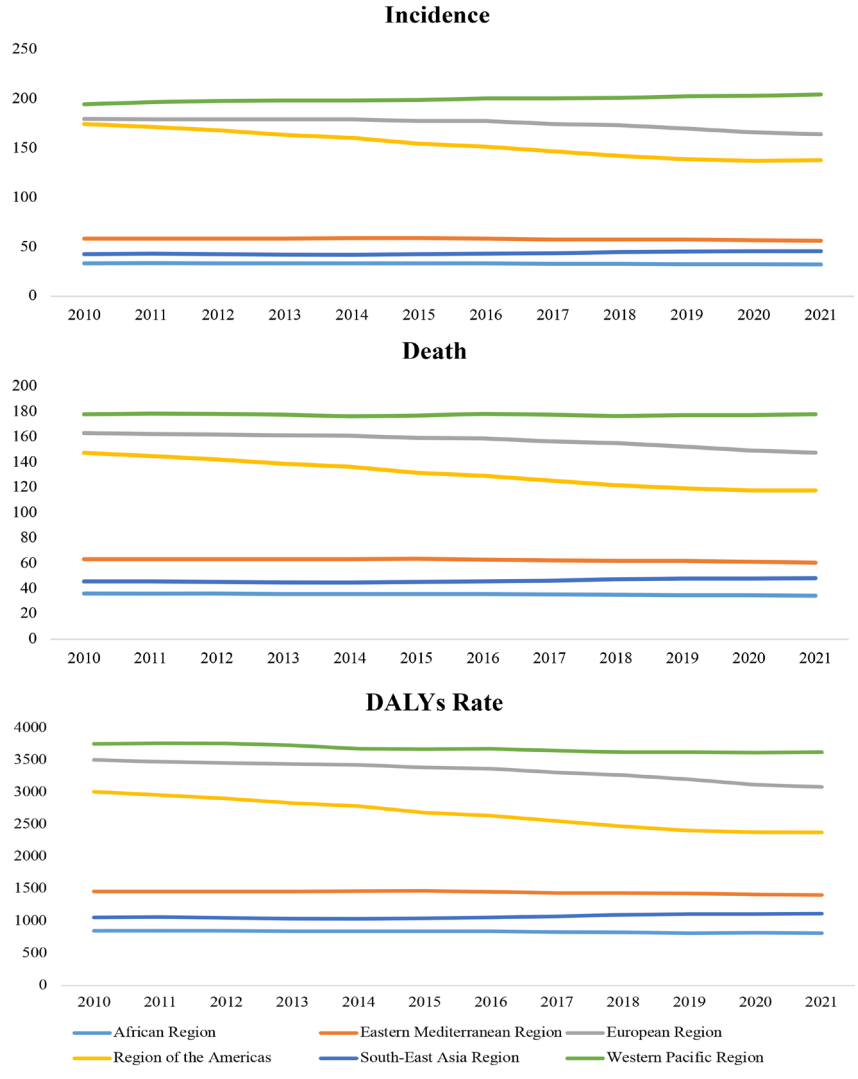

Figure 3. Temporal trend of incidence, death, and DALYs rates (per 100,000 population) of TBLC based on WHO regions from 2010 to 2021

TBLC: tracheal, bronchus, and lung cancer, WHO: World Health Organization

	Incidence			Death			DALY		
	Both	Male	Female	Both	Male	Female	Both	Male	Female
Andean Latin America	51.046	58.751	43.995	54.906	63.182	47.332	1109.598	1278.403	955.119
Australasia	172.707	205.931	142.578	130.792	160.438	103.907	2509.066	3070.831	1999.635
Caribbean	108.453	154.337	67.810	103.231	140.434	70.278	2176.819	2985.910	1460.135
Central Asia	61.052	110.138	22.645	62.605	112.416	23.631	1548.039	2826.658	547.577
Central Europe	202.344	315.904	114.187	201.401	313.870	114.092	4422.930	7029.726	2399.289
Central Latin America	46.983	61.013	35.048	49.904	64.588	37.412	1046.574	1365.641	775.161
Central Sub-Saharan Africa	40.525	64.810	20.100	42.808	68.309	21.359	1078.229	1738.744	522.673
East Asia	213.447	294.799	137.214	189.452	262.100	121.376	3953.603	5552.328	2455.468
Eastern Europe	119.852	245.376	41.172	108.211	221.577	37.151	2535.517	5347.074	773.196
Eastern Sub-Saharan Africa	27.545	40.112	16.114	29.563	43.089	17.259	698.349	1021.454	404.440
High-income Asia Pacific	211.270	323.420	116.137	160.191	244.570	88.615	2583.922	4106.494	1292.376
High-income North America	211.909	239.398	188.049	167.345	193.837	144.350	3289.836	3882.771	2775.178
North Africa and Middle East	76.064	121.381	29.621	81.682	130.314	31.841	1869.467	3018.571	691.805
Oceania	75.821	104.490	44.298	80.941	111.783	47.028	1924.455	2651.737	1124.782
South Asia	30.385	44.856	16.476	32.057	47.285	17.422	760.135	1130.202	404.471
Southeast Asia	93.657	138.841	54.431	98.514	145.629	57.613	2267.371	3403.722	1280.895
Southern Latin America	104.055	151.383	65.792	107.213	156.232	67.584	2267.447	3359.792	1384.341
Southern Sub-Saharan Africa	84.559	131.656	51.137	89.148	137.813	54.614	2122.752	3388.552	1224.518
Tropical Latin America	73.267	94.649	55.717	77.336	99.804	58.895	1680.864	2170.609	1278.887
Western Europe	183.639	254.760	122.479	156.450	220.295	101.547	3043.297	4323.758	1942.183
Western Sub-Saharan Africa	18.177	28.557	9.028	19.621	30.891	9.688	451.571	707.597	225.926

Figure 4. The incidence, death, and DALYs rates (per 100,000) of TBLC among over 55 years people based on GBD regions and genders from 2010 to 2021

TBLC: tracheal, bronchus, and lung cancer, GBD: Global Burden of Disease

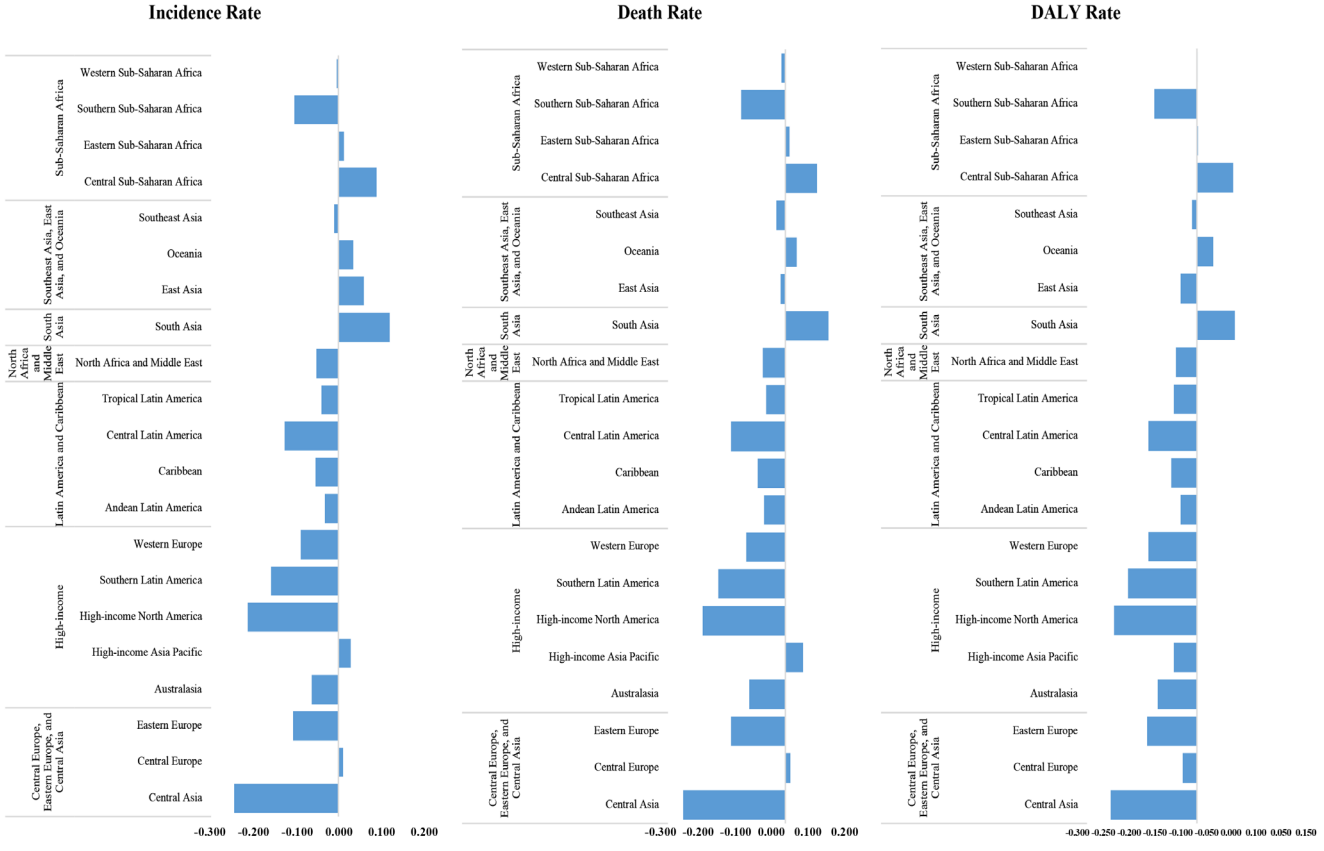

Figure 5. The relative change in incidence, death, and DALYs rates (per 100,000) of TBLC among over 55 years people based on GBD regions and genders from 2010 to 2021

TBLC: tracheal, bronchus, and lung cancer, GBD: Global Burden of Disease

was observed in South Asia (10.3%), Central Sub-Saharan Africa (5.6%), and a third region with an increase of 34.3%, for both genders combined, and separately for males and females, respectively. The highest decrease was observed in Central Asia (23.6%), Central Asia (27.2%), and High-income North America (18.3%) decrease for both genders, males, and females, respectively (Table 3, Figures 4, 5).

National Comparison of the Global Trend of TBLC Among Aged ≥55 Years

In 2021, Monaco, with 414.333, 540.472, and 301.309, exhibited the highest TBLC incidence rates (per 100,000) for both genders, males, and females, respectively. Between 2010 and 2019, 64; 48; and 130 out of 204 countries and territories experienced an increasing trend in TBLC incidence rates (per 100,000) for both genders, males, and females, respectively. The highest increase was observed in Cabo Verde (27.9%) and Bulgaria (43.7%) for both genders, males, and females, respectively. In contrast, the highest decrease was observed in the United Arab Emirates (53.4%) and Kuwait (45.1%) for both genders.

Also, Monaco exhibited the highest TBLC death rates (per 100,000) of 370.074 for both genders, 488.984 for males, and 263.527 for females, respectively. Between 2010 and 2019, 58 43 and 120 out of 204 countries and territories experienced an increasing trend in TBLC death rates (per 100,000) for both genders, males, and females, respectively. The highest increase was observed in Cabo Verde (23.6% for both genders, 28.8% for males), and Bulgaria (45.0% for females). In contrast, the highest decrease was observed in the United Arab Emirates (53.8%), Saudi Arabia (58.7%), and Kuwait (46.4%) for both genders, males, and females, respectively.

Also, Monaco (7,091.097), Monaco (9,522.039), and Greenland (5,583.999) exhibited the highest TBLC DALY rates (per 100,000) for both genders, males, and females, respectively. Between 2010 and 2019, 62, 45, and 125 out of 204 countries and territories experienced an increasing trend in TBLC DALY rates (per 100,000) for both genders, males, and females, respectively. The highest increase was observed in Cabo Verde (36.8%), Cabo Verde (45.2%), and Bulgaria (43.6%) for both genders, males, and females, respectively. In contrast, the highest decrease was observed in the United Arab Emirates (54.1%), United Arab Emirates (58.1%), and Kuwait (46.1%) for both genders, males, and females, respectively.

DISCUSSION

The results of the present study showed that global TBLC incidence, mortality, and DALYs decreased in adults ≥55 years from 2010 to 2021. In 2021, more than 66% of new TBLC cases occurred in men, and the incidence rate declined by 9.6% in men. Contrarily, females experienced a 3.8% increase from 2010. While males account for the majority of TBLC burden, it is important to pay attention to the higher growth rate of women and the associated risk factors.[18]

TBLC mortality is generally increasing among patients aged 70 and older, and, due to the growing geriatric population, managing TBLC in this population is becoming a greater concern.[18] Older patients often have reduced functional reserves and limited ability to receive proper treatments. Moreover, a higher prevalence of underlying diseases results in unfavorable treatment outcomes.[19]

The burden of TBLC is primarily influenced by smoking in both men and women.[20] East Asia, Western Europe, and high-income North America bear a higher TBLC burden due to historical smoking patterns.[21] TBLC mortality typically peaks 30-40 years after the peak smoking prevalence in a population.[22] Therefore, implementing effective approaches to reduce smoking could help reduce the burden of the disease, particularly in low SDI populations.[23] In East Asia, where female smoking rates are low, indoor air pollution from cooking and heating emerges as a major factor in TBLC incidence.[24] This study confirms distinct gender variations in the global burden of TBLC due to occupational carcinogens, aligning with previous studies.[25] Additionally, female TBLC rates increased in World Bank middle-income countries, where smoking among women is steadily rising because it is becoming normalized due to social media, globalization, and marketing efforts.[26] The gender gap could be attributed to variations in smoking rates and biological responses to tobacco between men and women. Exposure to sex hormones and molecular characteristics could heighten women's vulnerability to TBLC.[27]

Air pollution, occupational exposures, second-hand smoking, low fruit intake, and elevated fasting plasma glucose levels are known to contribute to death and DALYs from TBLC.[28] High fasting plasma glucose is an important risk factor among older men in developed countries.[29] Therefore, TBLC screening should be included in routine diabetes assessments.[30]

In 2021, approximately 60% of TBLC cases occurred in Asian countries, while European countries exhibited the highest TBLC incidence rate. In contrast with the global decreasing trend, the TBLC incidence, death, and DALY rates in Asia increased. Rezaei et al.'s[4] study showed a decrease in the age-standardized incidence rate of TBLC in Asia, but our study, which considered a cutoff of ≥55 years and a longer period, found an increase in the TBLC incidence. The high geographical variation observed in the epidemiological rates and trends of TBLC in this study highlights the need for tailored global disease burden control strategies, taking into account the discrepancies in healthcare resources and opportunities for diagnosis and treatment.

There are uneven burdens across the five SDI quintiles, reflecting inequalities in healthcare access. Our study found that TBLC DALY and death rates for males increased in low and low-middle SDI countries, while high and high-middle SDI countries saw a decrease in TBLC DALY and death rates. For females, only high SDI countries showed a decreasing trend in incidence rates. The high death and DALY rates in high-middle SDI countries reflected industrialization and cumulative occupational exposures from decades ago.[31] Previous studies have estimated a 20-fold variation in TBLC incidence rates by region, largely reflecting the maturity of the tobacco epidemic and historical patterns of tobacco exposure, including intensity, duration, cigarette types, and degree of inhalation.[32] Currently, 80% of the world's smokers live in low- and middle-income countries.[33] In low-middle and low SDI quintiles, the top

risk factors for TBLC deaths and DALYs include air pollution, tobacco, and dietary risks.[34] Occupational exposure to silica was the primary risk factor for TBLC in individuals aged 20-39 and 40-59, whereas asbestos exposure was the primary risk for those aged 60-79 and over 80. This difference is likely due to the latency period between exposure and TBLC morbidity.[35] Therefore, occupational asbestos exposure remains a significant risk factor in high SDI countries.[31]

On the other hand, late diagnosis results in poor prognosis for patients. The failure to implement and manage appropriate screening programs in governments and health systems, along with the failure to establish primary prevention laws, leads to increasing trends in all TBLC indicators, especially in women.[36] The American Cancer Society recommends annual low-dose helical computed tomography for TBLC screening in older adults. Effective screening programs can significantly reduce TBLC incidence and mortality.[37] However, differences in equipment, resources, and personnel skills affect early detection rates.[4] Generally, given that TBLC is largely preventable, effective management and intervention by healthcare systems is essential. Moreover, prioritizing early diagnosis is crucial for improving TBLC prognosis.[38] These findings highlight the need for adaptable control strategies tailored to local conditions to mitigate the global burden of this disease.[33]

Interpretation of the results of this study should be interpreted with caution because using online data presents limitations, such as potential errors in stored data, delays in data access, changes in coding practices over time, and reliability gaps in cancer reporting and registries, particularly low-SDI countries.

CONCLUSION

The global burden of TBLC is predominantly in Asian countries (mainly East Asia), with a slower decrease in incidence, death, DALY, and burden rates compared to other regions. Therefore, measures are recommended to reduce the progression of TBLC, such as reducing exposure to risk factors, expanding screening and diagnostic programs, especially for high-risk male smokers, and improving treatment procedures. In addition, more research are needed to investigate the causes of the increasing trend of TBLC in women. controlling related risk factors in women needs urgent and effective preventive interventions.

Ethics

Ethics Committee Approval: The Jahrom University of Medical Sciences Ethical Research Committee approved this study (approval no: IR.JUMS.REC.1401.094, date: 23.11.2022).

Informed Consent: Because utilizing anonymous online datasets, informed consent was not required.

Footnotes

Authorship Contributions

Concept: H.S., A.M., F.R., Data Collection or Processing: A.M., E.S., Z.S., Analysis or Interpretation: H.S., F.S.-S., A.M., Literature Search: A.M., E.S., F.R., F.S.-S., Z.S., L.A., H.S., Writing: A.M., E.S., F.R., F.S.-S., Z.S., L.A., H.S.

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

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

Latent Tuberculosis Infection in Inflammatory Rheumatic Diseases Before Biological and Synthetic DMARD Treatment: Results from Three Rheumatology Centers in Different Regions of Türkiye

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Abstract

OBJECTIVE: The objective of this study was to investigate the prevalence of latent tuberculosis (TB) infection (LTBI) and its associated factors in patients with inflammatory rheumatic diseases (IRDs) prior to the administration of biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs/tsDMARDs).

MATERIAL AND METHODS: A total of 402 patients with IRDs who were receiving bDMARDs/tsDMARDs from tertiary rheumatology centers in three different geographical regions were included in the study. Demographic, clinical, and TB-related characteristics were documented. The patients were divided into two groups, namely those with LTBI and non-LTBI, and their data were subjected to comparative analysis. The impact of various factors on LTBI was evaluated by regression analysis.

RESULTS: The prevalence of LTBI was 50.7% (204/402) before bDMARD/tsDMARD therapy. The proportion of male patients [108 (52.9%) vs. 84 (42.3%); $P = 0.03$] and the prevalence of smoking [102 (50.0%) vs. 64 (32.3%); $P = 0.001$] were statistically higher in the LTBI group. The preference for adalimumab was statistically lower in patients with LTBI (30.4%, 62/204 vs. 45.9%, 91/198; $P = 0.021$). Smoking [odds ratio (OR) 95% confidence interval (CI): 1.46 (1.16-1.65); $P = 0.007$], and duration of bDMARD use [OR 95% CI: 1.10 (1.03-1.17); $P = 0.013$] were significantly associated with LTBI. Isoniazid was used as the prophylactic agent in 96.45% (190/204) of patients, whereas there were no cases of TB reactivation among the three cohorts.

CONCLUSION: The present study demonstrated that more than half of patients with IRDs undergoing advanced therapies have LTBI, with this infection being associated with male sex, smoking status, and duration of bDMARD use. Furthermore, this study indicates that appropriate screening and treatment of LTBI in patients with rheumatic diseases are associated with favorable clinical outcomes.

KEYWORDS: Latent tuberculosis infection, interferon-gamma release tests, rheumatic disease, epidemiology, biologic disease-modifying antirheumatic drugs, targeted-specific synthetic disease-modifying antirheumatic drugs

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INTRODUCTION

Tuberculosis (TB) is an infectious disease that represents a significant public health concern.[1] Latent TB infection (LTBI) is defined as a persistent immune response to tubercle bacilli that does not manifest clinically.[2] Although dormant tubercle bacillus may remain asymptomatic in the lungs for years, they may cause active TB in approximately 10% of cases.[1] Over the past two decades, the rise in immunosuppressive therapies has increased the risk of TB reactivation in individuals with LTBI.[1,2]

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Biologic disease-modifying antirheumatic drugs (bDMARDs) and target-specific synthetic disease-modifying antirheumatic drugs (tsDMARDs) utilized in the treatment of inflammatory rheumatic diseases (IRDs) exert immunosuppressive effects through disparate mechanisms, including anticytokine, co-stimulator, and antibody blockade.[3] In the context of TB infection, in which a T cell-mediated response is of significance, the reactivation of LTBI may be observed as a consequence of these drugs.[3,4]

The World Health Organization has identified early recognition and treatment of LTBI as a crucial strategy for controlling reactivation TB in patients with IRDs who are immunosuppressed.[2] It is estimated that approximately one-quarter of the global population will be infected with LTBI.[5] For this reason, both clinical practice and guidelines recommend that LTBI screening be performed before bDMARD and tsDMARD therapies.[1,4] Furthermore, patients should undergo clinical evaluation for TB at 3-month intervals after the commencement of treatment.[2,6,7]

The prevalence of LTBI in IRD may vary according to demographic characteristics, such as regional differences, and various clinical features, such as differences in immune mechanisms in rheumatic diseases.[4,8] In addition, a comparative presentation of the results of latent TB diagnosis, treatment, and follow-up among patients from different rheumatology centers will provide important information on the management of LTBI.[7]

Accordingly, in this study, we aimed to reveal the frequency of LTBI and related factors in patients with rheumatic diseases prior to bDMARD/tsDMARD therapy in tertiary rheumatology centers located in three different regions of Türkiye.

MATERIAL AND METHODS

Patients and Rheumatology Centers

The study included 402 patients with IRDs [ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, familial Mediterranean fever (FMF), Behçet's disease, juvenile idiopathic arthritis, large vessel vasculitis (LVV) and deficiency of adenosine deaminase 2 disease] who were to be started on biologic or targeted DMARD therapy. Patients were recruited from tertiary rheumatology centers across different regions. Rheumatology centers were selected from different geographical regions in Türkiye, with consideration given to the potential for variations in the prevalence of latent TB between regions. The selected regions were the West Black Sea region (Kastamonu), the East Anatolia region (Erzurum), and the Marmara region (İstanbul), which ranged from rural to urban (from low to high population density). Patients aged below 18 years with multiple concurrent rheumatic diseases, solid or hematologic malignancies, using immunosuppressive drugs for non-rheumatic indications, on drugs causing pulmonary toxicity and with active TB infection before the start of bDMARDs/tsDMARDs therapy were excluded from the study.

Data on patients between 2010 and 2024 were retrospectively obtained from the hospital electronic records. Informed consent was not obtained from the patients because of the retrospective study design.

The patient data set comprised demographic data (age, gender, weight, height) and clinical data, including diagnosis, disease duration, smoking status, comorbidities, medications, duration of medication use, and clinical measurements of the diagnosis and treatment of LTBI. The study protocol was approved by the Karabük University Faculty of Medicine Ethics Committee for Clinical Research (protocol number: 2024/1863; date: 10.09.2024). The study was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice.

Biological and Synthetic DMARD Therapy

The current utilization of bDMARDs, including adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, secukinumab, ixekizumab, ustekinumab, tocilizumab, abatacept, anakinra, and canakinumab, and tsDMARDs, including tofacitinib, baricitinib, and upadacitinib, were recorded. The duration of use and concomitant administration of glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, and/or immunosuppressive agents, including azathioprine, mycophenolate, and cyclophosphamide, were also documented.

Latent Tuberculosis Diagnosis, Treatment, and Reactivation

In accordance with national and global guidelines, a diagnosis of LTBI was made when a patient exhibited a TB skin test (TST) result of 5 mm or greater and/or a positive interferon gamma release assay (IGRA) test [T-SPOT.TB test (T-SPOT), Oxford Immunotec Ltd., Oxford, UK or QuantiFERON-TB (QFT, Cellestis Ltd., Carnegie, Australia or Qiagen, Hilden, Germany)] without any signs or symptoms.[9,10]

Rheumatic patients with LTBI are referred to the TB dispensaries (the primary health center where patients are seen for follow-up and treatment of TB), which are widely distributed throughout Türkiye and provide a nine-month course of isoniazid (INH)

Main Points

- Latent tuberculosis (TB) infection (LTBI) occurs in more than half of patients with inflammatory rheumatic diseases (IRDs) scheduled for biologic disease-modifying antirheumatic drugs/target-specific synthetic disease-modifying antirheumatic drugs (bDMARD/tsDMARD) therapy.
- Smoking, male gender, and duration of bDMARD use are associated with LTBI.
- In patients with LTBI in whom adalimumab was less preferred, no TB reactivation was detected in any patient in the three centers, despite a longer duration of bDMARD use.
- Prior to commencing bDMARD/tsDMARD therapy, the TB skin test was performed to screen for LTBI in >85% of patients, with >95% of LTBI patients with IRD receiving full-dose isoniazid.
- The present study indicates that appropriate screening and treatment of LTBI in patients with rheumatoid arthritis are associated with favorable clinical outcomes.

treatment.[9] Rifampicin (RIF) is used as monotherapy for a period of four months when INH is contraindicated. The use of INH for 9 months or RIF for 4 months in LTBI prophylaxis is expressed as the full dose.[9,11] Conversely, the administration of these agents for periods shorter than the aforementioned durations is classified as an insufficient dose.[9,11]

Follow-up of patients with LTBI is conducted at TB dispensaries in collaboration with tertiary rheumatology centers. The medication used for LTBI, duration of treatment, and any drug-related adverse effects are documented. Patients who experience reactivation of TB during rheumatology follow-up are also recorded.

Statistical Analysis

The statistical analyses were conducted using IBM Statistical Package for the Social Sciences statistics 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to ascertain data normality. The mean±standard deviation was used to represent average distribution values for numerical data that exhibited a normal distribution. The median and minimum-maximum values for the non-normally distributed variable, as well as the frequencies for the categorical data, are presented. A comparison of the LTBI and non-LTBI groups was conducted using the independent *t*-test to assess differences in numerical variables with a normal distribution, the chi-square test, and Fisher's exact test to compare categorical data. In the case of numeric variables lacking a normal distribution, the Mann-Whitney U test was used for analysis. Univariate and multivariate logistic regression analysis were utilized to assess the association between LTBI (the dependent variable) and other variables. Odds ratios (ORs) with 95% confidence intervals (CI) for LTBI were calculated. The threshold for statistical significance was set at $P < 0.05$.

RESULTS

Of the 402 patients included in the study, 204 (50.7%) were diagnosed with LTBI, whereas 198 (49.3%) did not. The mean age of patients with LTBI was 47.9 (±12.5) years, while the mean age of patients without LTBI was 46.1 (±14.5) years. The proportion of male patients was significantly higher in the LTBI group (52.9%) than in the non-LTBI group (42.3%) ($P = 0.03$). No significant differences were observed in mean weight, height, or disease duration between the two groups. Additionally, a higher prevalence of smoking was observed in the LTBI group [102 (50.0%) vs. 64 (32.3%); $P = 0.001$].

When the frequency of LTBI was compared according to the rheumatology centers, it was similar in all 3 centers ($P = 0.32$). Although not statistically significant, the prevalence of LTBI was higher in the Marmara region (55.0%) than in the Eastern Anatolia region (53.9%) and the Western Black Sea region (47.0%) from more populated to less populated areas.

Regarding the frequency of LTBI according to diagnosis, no significant difference was found for any disease diagnosis ($P > 0.05$) (Table 1). When patients with and without LTBI were compared according to medical treatments, the duration of biologic drug use was significantly longer in the LTBI group than in the non-LTBI group [3.0 (0.25-18.0) vs. 1.5 (0.25-14.0); $P = 0.008$, respectively] (Table 1).

Table 2 illustrates the comparative frequency of rheumatic drug selection between patients with and without LTBI. Adalimumab was significantly more preferred in the non-LTBI group than in the LTBI group (45.9%, 91/198 vs. 30.4%, 62/204; $P = 0.021$). Except for adalimumab, all drug use preferences were similar between the groups.

In patients with IRD, TST (175; 85.8%) was the most frequently used method for diagnosing LTBI before treatment. This was followed by the QuantiFERON and T-SPOT tests, which were used in (21; 10.3%) and (8; 3.9%) of the cases, respectively (Figure 1). The majority of patients (190; 96.45%) received the full dose of INH for LTBI prophylaxis, 5 patients (2.54%) received an insufficient dose of INH, and 2 patients (1.02%) developed INH-related adverse effects (hepatotoxicity in two patients). Additionally, 8 patients (80%) received full-dose prophylaxis for RIF, 1 patient (10%) received an insufficient dose, and 1 patient (10%) developed RIF-related side effects (cutaneous reaction in a patient) (Figure 2). Notably, there were no cases of reactivation of TBIs among the 402 patients receiving biologic or tsDMARD therapy.

The effects of various factors on LTBI was assessed by univariable and multivariable regression analysis. The univariate analysis indicated that cigarette smoking [OR=1.48 (1.25-1.64); $P < 0.001$], male gender [OR=1.35 (1.03-1.56); $P = 0.035$], and duration of bDMARD use [OR=1.11 (1.04-1.18); $P = 0.001$] were independent factors that increased the frequency of LTBI. In the multivariable model, cigarette smoking [OR=1.46 (1.16-1.65); $P = 0.007$] and duration of bDMARD use [OR=1.10 (1.03-1.17); $P = 0.013$] remained significantly associated with LTBI, whereas gender, disease duration, and glucocorticoid dose were not significantly related with LTBI (Table 3).

DISCUSSION

The findings of this study indicate that the prevalence of LTBI among patients with IRD undergoing advanced rheumatic therapies (bDMARD/tsDMARD) is higher in males, with a higher prevalence of smoking among these patients and a longer duration of bDMARD use. Additionally, this study revealed that adalimumab, a monoclonal tumor necrosis factor (TNF) antibody, was less frequently selected as a drug for the treatment of patients with LTBI.

TB has the potential to reactivate in patients undergoing treatment with bDMARDs or tsDMARDs in the presence of LTBI. The management of TB in patients with rheumatoid arthritis may vary depending on the specific rheumatoid disease and treatment regimen involved. Additionally, local recommendations from countries and recommendation sets from international organizations and associations serve as valuable resources in clinical practice.[9,12] It is recommended that clinical assessment along with one of the TST or IGRA tests and chest radiography be performed in every patient who is considered to start bDMARD or tsDMARD treatment for screening LTBI.[12]

In addition to the general recommendations, it is important to consider the epidemiological and demographic differences associated with TB infection. The present study revealed a higher

Table 1. Clinical and demographic characteristics of rheumatic patients with and without LTBI

	All patients from three centers (n=402)	Patients with LTBI (n=204)	Patients without LTBI (n=198)	*P* value
Age, year, mean (±SD)	47.0 (±13.5)	47.9 (±12.5)	46.1 (±14.5)	0.18[β]
Sex (male; %)	210 (52.1%)	108 (52.9%)	84 (42.3%)	**0.03**[γ]
Weight, kg, mean (±SD)	74.1 (±12.4)	74.9 (±11.1)	73.2 (±13.5)	0.19[β]
Height, cm, mean (±SD)	166.4 (±9.6)	167.5 (±8.8)	165.1 (±10.3)	0.14[β]
Disease duration, year, mean (±SD)	11.3 (±8.4)	12.1 (±8.3)	10.6 (±8.4)	0.09[β]
Smoking	168 (41.3%)	102 (50.0%)	64 (32.3%)	**0.001**[γ]
Diabetes mellitus	50 (12.5%)	26 (12.7%)	24 (12.1%)	0.86[γ]
Hypertension	96 (23.9%)	49 (24.0%)	47 (23.7%)	0.94[γ]
CKD	11 (2.7%)	4 (1.9%)	7 (3.5%)	0.33[γ]
COPD	12 (3.0%)	6 (2.9%)	6 (3.0%)	0.95[γ]
Rheumatology center				
West Black Sea region (Kastamonu)	200 (49.7%)	94 (47.0%)	106 (53.0%)	
The Eastern Anatolia region (Erzurum)	102 (25.3%)	55 (53.9%)	47 (46.1%)	0.32[γ]
Marmara region (İstanbul)	100 (24.9%)	55 (55.0%)	45 (45.0%)	
Diagnosis				
AS	227 (56.4%)	122 (59.8%)	105 (53.0%)	0.17[γ]
RA	115 (28.5%)	55 (26.9%)	60 (30.0%)	0.45[γ]
PsA	36 (8.9%)	14 (6.9%)	22 (11.1%)	0.13[γ]
FMF	8 (2.1%)	3 (1.5%)	5 (2.5%)	0.49[δ]
Behçet's disease	6 (1.5%)	4 (1.9%)	2 (1.0%)	0.68[δ]
JIA	5 (1.2%)	2 (1.0%)	3 (1.5%)	0.68[δ]
LVV	4 (1.0%)	3 (1.5%)	1 (0.5%)	0.62[δ]
DADA2	1 (0.2%)	1 (0.5%)	-	-
Medications				
NSAID	165 (41.0%)	85 (41.6%)	80 (40.4%)	0.79[γ]
csDMARDs	146 (36.3%)	70 (34.3%)	76 (38.3%)	0.39[γ]
bDMARDs	369 (91.8%)	185 (90.7%)	184 (92.9%)	0.86[γ]
Duration of current bDMARD therapy (years), median (min-max)	2.0 (0.25-18.0)	3.0 (0.25-18.0)	1.5 (0.25-14.0)	**0.008**[α]
tsDMARDs	33 (8.2%)	19 (9.3%)	14 (7.1%)	0.40[γ]
Duration of current tsDMARD therapy: year, median (min-max)	0.5 (0.25-6.0)	0.5 (0.25-6.0)	0.5 (0.25-3.0)	0.24[α]
Glucocorticoid dose, milligrams, mean (±SD)	1.09 (±2.07)	0.89 (±1.76)	1.29 (±2.34)	0.053[β]
Immunosuppressive	8 (2.0%)	5 (2.4%)	3 (1.5%)	0.72[δ]

[α]: Mann-Whitney U test; [β]: Student's t-test; [γ]: Chi-square test; [δ]: Fisher's exact test.

LTBI: latent tuberculosis infection, NSAID: non-steroidal anti-inflammatory drug, csDMARD: conventional synthetic disease-modified anti-rheumatic drug, bDMARD: biological disease-modified anti-rheumatic drug, tsDMARD: target synthetic disease-modified anti-rheumatic drug, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, AS: ankylosing spondylitis, RA: rheumatoid arthritis, PsA: psoriatic arthritis, FMF: familial mediterranean fever, BH: Behçet's disease, JIA: juvenile idiopathic arthritis, LVV: large vessel vasculitis, DADA2: deficiency of adenosine deaminase 2, SD: standard deviation, min-max: minimum-maximum

prevalence of LTBI in men than in women. Similarly, the prevalence of LTBI in the national TB data of Türkiye was 42.3% in women and 57.7% in men.[9] However, although male sex was found to be associated with LTBI in the univariate analysis, no such association was found in the multivariate analysis. This discrepancy can be attributed to the covariance effect, which is likely influenced by the high rate of smoking among male patients.

The prevalence of respiratory TB infection is higher in urban areas with high population density than in rural areas.[8] In this study, although no significant difference was observed between the regions, LTBI was detected more frequently (55.0%) in İstanbul (in the Marmara region), which has the highest population density, than in the other centers. In contrast, in Kastamonu (in the West Black Sea region), the most rural of the three centers, LTBI was the least frequent (47.0%).

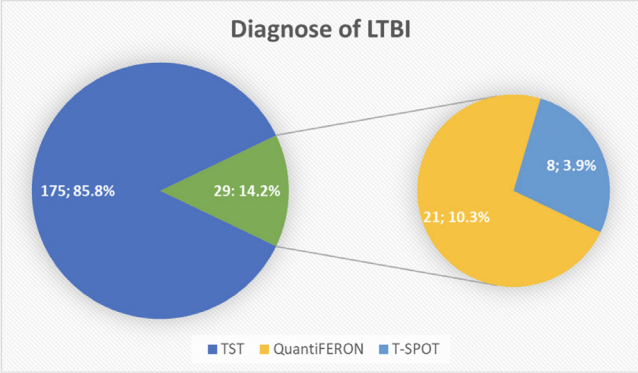

Figure 1. Frequency of tests used for LTBI diagnosis

LTBI: latent tuberculosis infection, TST: tuberculosis skin test

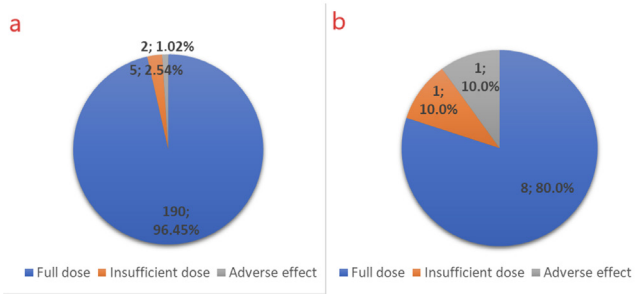

Figure 2. LTBI therapy for patients with rheumatic disease [(a) isoniazid, (b) rifampicin]

LTBI: latent tuberculosis infection

The relationship between IRDs and LTBI has been the subject of numerous studies.[13-15] The available evidence suggests that the presence of several RDs is associated with an increased prevalence of LTBI, irrespective of the pharmacological agents employed by the patients.[13-15] It has been documented in the literature that the prevalence of LTBI is higher in individuals with rheumatoid arthritis than in the general population, independent of biological therapy.[13,14] Furthermore, the risk of TB is elevated in patients with high disease activity across a range of rheumatic diseases.[7,15] However, in none of the IRDs included in this study, an increase in the frequency of LTBI was observed compared with the other IRDs. Additionally, a comparison of the results with the healthy population and an evaluation of LTBI risk according to disease activity were not conducted because they were not within the scope of this study's design.

In this study, we observed that adalimumab was less preferred in the LTBI group than in the non-LTBI group. A meta-analysis identified the highest risk of TB with monoclonal anti-TNF therapy, whereas the risk was low with etanercept and non-TNF biologic therapy.[4] Notwithstanding the elevated risk of TB reactivation, biological drugs are safely employed in rheumatic patients with suitable prophylaxis and meticulous periodic follow-up.[12] In our study, despite the LTBI group having undergone bDMARD therapy for a significantly longer duration, no cases of TB reactivation were identified.

In a study conducted in South Korea, the risk of LTBI infection in patients with rheumatoid arthritis was found to be equal between patients receiving biological therapy and those receiving JAK inhibitors (tsDMARDs).[16] Furthermore, the risk of active TB was found to be lower in patients receiving JAK inhibitors compared with those receiving biological therapy.[16] In our study, the preference for JAK inhibitors was similar between the groups with and without LTBI.

Table 2. Drug selection in rheumatic patients with and without LTBI

n (%)	LTBI (n=204)	Non-LTBI (n=198)
Methotrexate	26 (12.7)	19 (9.6)
Leflunomide	20 (9.8)	28 (14.1)
Sulfasalazine	12 (5.9)	14 (7.0)
Hydroxychloroquine	2 (1.0)	2 (1.0)
Colchicine	4 (1.9)	8 (4.0)
Combination of csDMARDs	6 (2.9)	5 (2.5)
csDMARD combined with bDMARD/ tsDMARD	70 (34.3)	76 (38.3)
Azathioprine	5 (2.4)	3 (1.5)
Anti-TNFIs		
Adalimumab	62 (30.4)	91 (45.9)*
Etanercept	35 (17.1)	22 (11.1)
Infliximab	11 (5.4)	7 (3.5)
Golimumab	30 (14.7)	18 (9.0)
Certolizumab pegol	17 (8.3)	16 (8.1)
Secukinumab	11 (5.4)	10 (5.1)
Ixekizumab	1 (0.5)	3 (1.5)
Ustekinumab	1 (0.5)	3 (1.5)
Tocilizumab	13 (6.4)	6 (3.0)
Abatacept	1 (0.5)	2 (1.0)
Anakinra	0 (0)	1 (0.5)
Canakinumab	3 (1.5)	5 (2.5)
JAKinibs (tsDMARDs)	19 (9.3)	14 (7.1)
Tofacitinib	10 (4.9)	5 (2.5)
Baricitinib	2 (1.0)	4 (2.0)
Upadacitinib	7 (3.4)	5 (2.5)

*$P < 0.05$.

LTBI: latent tuberculosis infection, csDMARD: conventional synthetic disease-modified anti-rheumatic drug, bDMARD: biological disease-modified anti-rheumatic drug, tsDMARD: target synthetic disease-modified anti-rheumatic drug, Anti-TNFIs: anti-tumor necrosis factor inhibitor

Glucocorticoids are frequently prescribed in rheumatology, yet their chronic use has been linked to an increased risk of TB.[17] The duration and dose of glucocorticoids in immunosuppression are heterogeneous. However, studies have indicated that a prednisolone equivalent of >15 mg/day for >4 weeks is a risk factor for TB.[12,18] In accordance with the literature review, this study demonstrated that the mean glucocorticoid dose was lower in the LTBI group.

The TST is a commonly employed diagnostic tool in screening for LTBI, despite inherent limitations such as measurement sensitivity and cross-reactivity with the Bacille Calmette-

Table 3. Univariable and multivariable regression analysis results (dependent variable LTBI)

Independent variables	Univariable OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Age (older)	0.99 (0.97-1.01)	0.184		
Sex (male)	1.35 (1.03-1.56)	**0.035**	1.01 (0.61-1.66)	0.956
Smoking	1.48 (1.25-1.64)	**<0.001**	1.46 (1.16-1.65)	**0.007**
Disease duration	0.98 (0.96-1.00)	0.091	0.98 (0.95-1.01)	0.180
Rheumatology center	1.18 (0.94-1.50)	0.157		
Diagnosis of rheumatic disease	1.03 (0.87-1.21)	0.754		
NSAID	1.05 (0.71-1.56)	0.797		
csDMARD	0.84 (0.56-1.26)	0.396		
bDMARD	0.98 (0.91-1.05)	0.600		
Duration of current bDMARD therapy	1.11 (1.04-1.17)	**0.001**	1.10 (1.03-1.17)	**0.013**
tsDMARD	0.91 (0.65-1.28)	0.606		
Duration of current tsDMARD therapy	0.65 (0.34-1.26)	0.202		
Glucocorticoid dose (low)	1.10 (0.99-1.21)	0.053	1.05 (0.94-1.17)	0.361

Bold values indicate $P < 0.05$.
LTBI: latent tuberculosis infection, csDMARD: conventional synthetic disease-modified anti-rheumatic drug, bDMARD: biological disease-modified anti-rheumatic drug, tsDMARD: target synthetic disease-modified anti-rheumatic drug, OR: odds ratio, CI: confidence interval, NSAID: non-steroidal anti-inflammatory drug

Guérin vaccine.[19] As the test was commonly employed in the Tuberculosis Dispensaries and hospitals in Türkiye, the TST was identified as the most frequently utilized test in this study. IGRA tests do not suffer from the aforementioned limitations, and there are two main types of IGRA tests. These are the T-SPOT. TB and QuantiFERON-TB tests.[10] The tests have been employed with increasing frequency in our country, particularly in recent years, and have been used exclusively in tertiary care centers, as evidenced by their use in 14.9% of patients in this study. The TST test is the primary recommendation for LTBI screening in accordance with the National Tuberculosis Diagnosis and Treatment Guidelines. In immunosuppressive patient groups (chronic renal failure, chemotherapy planned due to hematological malignancy, rheumatic patients before bDMARD treatment, before long-term steroid use of 15 mg/day and before transplantation), one of the IGRA tests is recommended in conjunction with a negative two-step TST test and clinically highly suspected TB infection.[9,20]

The American Thoracic Society has established a series of treatment protocols for the management of LTBI.[11,21] The National Tuberculosis Guideline in Türkiye recommends INH treatment (300 mg/day) for 9 months as the first-line treatment. In patients who cannot tolerate INH or who have resistance, RIF treatment is provided for 4 months.[9] In this retrospective study, >95% of patients with LTBI received INH prophylaxis, whereas only 8 patients received full-dose RIF therapy.

This study has several potential limitations. The first limitation is that disease activation could not be evaluated due to its retrospective nature. Second, the relatively small number of patients in the study sample with less advanced therapies in the treatment protocol (FMF, Behçet's disease, etc.) and rarer rheumatic diseases (LVV, etc.) represents a limitation. On the other hand, the study's multicentre design, comparison of different geographical regions and high sample size represent its main strengths.

CONCLUSION

A recent study indicated that more than half of patients with rheumatic diseases prior to bDMARD/tsDMARD therapies is diagnosed with LTBI. Furthermore, the findings revealed that smoking and male gender were significant factors associated with LTBI. In patients with LTBI in whom adalimumab was less preferred, no TB reactivation was detected in any patient in the three centers, despite a longer duration of bDMARD use. It can be argued that the periodic follow-up of patients for LTBI and high rates of full-dose LTBI prophylaxis led to favorable clinical outcomes. These results provide valuable insight into the management of LTBI in patients with rheumatic diseases undergoing advanced therapy in rheumatology centers across Türkiye.

Ethics

Ethics Committee Approval: The study protocol was approved by the Karabük University Faculty of Medicine Ethics Committee for Clinical Research (protocol number: 2024/1863, date: 10.09.2024).

Informed Consent: Informed consent was not obligated from patients due to retrospective design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., C.A., S.B., Concept: A.K., C.A., S.B., Design: A.K., C.A., S.B., Data Collection or Processing: A.K., C.A., S.B., Analysis or Interpretation: A.K.,

C.A., S.B., Literature Search: A.K., Critical Review: C.A., S.B., Writing: A.K.

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Original Article

Transbronchial Mediastinal Cryobiopsy Diagnostic Yield and Perioperative Patient Management: A Single Tertiary Center Experience

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Abstract

OBJECTIVE: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is widely used to diagnose mediastinal lesions; however, small cytology samples from EBUS-TBNA may be inadequate in cases of benign lung diseases, hematologic disorders, and to assess the molecular profile of primary lung cancer (PLC). EBUS-guided transbronchial mediastinal cryobiopsy (TMC) obtains histological samples and potentially implies a higher diagnostic yield (DY) than EBUS-TBNA. The clinical impact of this technique and the perioperative patient management are still unclear. Our aim was to critically analyze our experience with TMC.

MATERIAL AND METHODS: A single center retrospective study was conducted to evaluate TMC DY and perioperative routine over 11 months (February 2023-January 2024).

RESULTS: Forty-one patients were included. The overall DY was 41.5% and 95.1% for EBUS-TBNA and TMC, respectively. TMC provided a higher DY than EBUS-TBNA in cases of hematologic disorders, benign diseases, and uncommon tumors (31% for EBUS-TBNA and 100% for TMC; 95% confidence interval (CI): 52.1-85.8, $P < 0.001$). For PLC, the DY and the assessment of immunohistochemical marker expression did not significantly differ between the two techniques (80% for EBUS-TBNA and 100% for TMC; 95% CI: -4.79-44.8, $P = 0.13$). The management of antithrombotic therapy was the same as that of EBUS-TBNA. Sedatives were administered to achieve deep sedation. After the procedure, no step-up in the level of care was observed, either in outpatients or in patients with a Charlson Comorbidity Index ≥5.

CONCLUSION: TMC had a better DY than EBUS-TBNA in hematologic disorders, benign lung disease, and uncommon tumors, with an optimal tolerability profile.

KEYWORDS: Bronchoscopy, diagnostic methods, endobronchial ultrasound-guided transbronchial needle aspiration, lung cancer, mediastinal diseases, perioperative care

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INTRODUCTION

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique with a broad capability of obtaining cytologic samples from mediastinal lesions. However, some controversies about its diagnostic yield (DY) remain unsettled. Firstly, the sensitivity of EBUS-TBNA in mediastinal restaging of primary lung cancer (PLC), after induction treatment with chemoradiotherapy, is lower (67-76%) compared with the sensitivity for the initial staging (81-93%). Therefore, confirmation of negative EBUS-TBNA with surgical mediastinoscopy is advised for a conclusive diagnosis.[1,2] Secondly, for PLC staging, the likelihood of malignant nodal involvement after negative EBUS-TBNA ± transesophageal bronchoscopic ultrasound-guided fine needle aspiration (EUS-B-FNA) is

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13-15%. Both American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) Guidelines suggest additional mediastinoscopy before surgery.[1,3,4] Thirdly, the DY for lymphoproliferative disorders is between 31-65%, and the 2011 statement of British Thoracic Society guidelines, "insufficient evidence to recommend EBUS-TBNA for routine use in the diagnosis of lymphoma," remains valid.[5,6] Lastly, the sensitivity of the technique in benign mediastinal diseases is around 60%. Further resource-consuming efforts are commonly needed due to the clinical overlap of benign disorders, which demand completely different therapies (i.e., infective versus autoimmune diseases).[7] Transbronchial biopsy with a cryoprobe of large outer diameter (1.9/2.4 mm), has been widely used for sampling lung parenchyma in the diagnosis of diffuse lung diseases, a setting in which the DY of traditional forceps biopsy is limited by crushing artifacts. Similarly, EBUS-guided transbronchial mediastinal cryobiopsy (TMC) is a minimally invasive technique, allowing to obtain large, architecturally preserved histology samples from mediastinal lesions, using a thin cryoprobe (outer diameter 1.1 mm). Data from published literature suggest that EBUS-TMC has a better DY than EBUS-TBNA in hematologic diseases, benign lung disorders, and typically, but not always, in uncommon tumors, potentially addressing diagnostic limitations with cytology samples.[8-11] Despite its growing use, a clear indication for TMC application is still subject to ongoing debate, and the technical aspects are not standardized. We hypothesized that TMC implementation may favorably impact cases in which the diagnostic performance of EBUS-TBNA is suboptimal, potentially improving patient outcomes (i.e., avoidance of repeated procedures and/or mediastinoscopy, with their associated morbidity), ultimately enhancing the cost-effectiveness of the procedure. In this study, we aimed to evaluate the DY of TMC and describe the peri-procedural management of patients undergoing TMC.

MATERIAL AND METHODS

Study Design and Participants

We retrospectively evaluated all patients who consecutively underwent TMC at our large tertiary facility, the Interventional Pulmonology Unit of Cardarelli Hospital, Naples, Italy, over 11 months from February 17, 2023, to January 31, 2024. The primary outcome was the DY of TMC, defined as a conclusive diagnosis obtained from histological samples. Analogously, EBUS-TBNA was considered conclusive if the specimens provided a formal cytological or histopathological diagnosis. All patients provided written informed consent before bronchoscopy. Subject characteristics, including age, sex, Charlson Comorbidity Index, antithrombotic therapy (ATT), type of hospital admission, and reason for bronchoscopy, were traced using the hospital's electronic medical records. Chest computed tomography (CT) with contrast was performed in all patients, and the ultrasonographic characteristics of the target lesion(s) were reviewed. All patients undergoing TMC were routinely provided multimodal intravenous analgosedation with midazolam + propofol±fentanyl, administered by an interventional pulmonologist not directly involved in the procedure, for patients categorized as American Society of Anesthesiologists (ASA) class I-III, or by an anesthesiologist for patients ASA III-IV. Sedation was maintained to target a Ramsay sedation scale score of 4-5 [that is, deep sedation (DS)]. Furthermore, for breathing support, all patients were connected to the ventilator through a Mapleson C circuit after placement of a laryngeal mask airway (LMA). One highly experienced interventional pulmonologist performed three passes of EBUS-TBNA using a convex probe ultrasound bronchoscope (BD UC180F, Olympus, Tokyo, Japan) at the point where the target lesion had the closest contact (≤1 cm) to the tracheobronchial wall. The choice of needle size (19G or 21G, ViziShot 2, Olympus, Tokyo, Japan) was at the operator's discretion. All passes were performed at the same angle as the first TBNA, aiming to facilitate the tunnelling process and widen the airway puncture. At the end of the third needle pass, needle lenght was progressively shortened, and the needle sufficiently agitated at every proximal retraction. This technique created a continuous pathway through the tracheobronchial wall and the capsule of the node, finally allowing for the insertion of the 1.1 mm cryoprobe (Erbecryo 20402-401, Tubingen, Germany). After ensuring in Doppler mode, that intralesional vessels were avoided, the cryoprobe was cooled down for 4 seconds, and the frozen biopsy tissue was retracted en bloc with the scope and probe.[12] All patients had a post-procedural chest X-ray (CXR). The collected adverse events (AEs) were: pneumothorax, pneumomediastinum, mediastinitis, bleeding (mild: no intervention other than intermittent suctioning±cold saline instillation; moderate: need for continuous suctioning±blockade balloons; severe: any other additional intervention, including bronchoscopic intervention, blood product administration, or change in level of care), and death. AEs were monitored 2 hours after bronchoscopy and after 24 hours (via phone call for outpatients). To ensure that any difference in DY by technique (TMC and EBUS-TBNA) did not depend on patient characteristics or target lesion echo features, we examined multiple variables according to the outcome of EBUS-TBNA (that is, the diagnostic EBUS-TBNA group and the non-diagnostic EBUS-TBNA group). After verifying the homogeneity of the sample, the DY of each technique was analyzed to distinguish between neoplastic and non-neoplastic diseases.

Main Points

- Transbronchial mediastinal cryobiopsy (TMC) obtains diagnostic tissue both in benign and malignant lung diseases.
- TMC is safe in comorbid patients and in outpatient setting.
- Management of antithrombotic therapy may be the same as with endobronchial ultrasound-guided transbronchial needle aspiration.
- Deep sedation allows for a smooth procedure.

Ethical Considerations

The study received approval from the Research Ethics Committee of Cardarelli Hospital (Campania 3, AORN_063) (approval number: 00023093, date: 10.10.2024). The requirement for consent was waived owing to the retrospective nature of the study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, as revised in 2013.

Statistical Analysis

Continuous variables are presented as mean and standard deviation (SD), and categorical variables as frequencies and percentages. ANOVA test for continuous variables and Pearson's chi-square test for categorical variables were performed. The primary outcome was analyzed using Pearson's chi-square test. A $P < 0.05$ level of significance was used. All tests were performed using the Jamovi software, version 2.3 (The Jamovi Project 2024, Sydney, Australia).

RESULTS

The study included 41 subjects (20 males, 21 females), of whom 23 were outpatients and 18 inpatients. The reasons for bronchoscopy were suspicion of PLC (n = 12, 29.3%), hematologic disorders and benign lung diseases (n = 18, 43.9%), recurrence of known solid cancer (n = 6, 14.6%), and recurrence of known hematologic malignancy (n = 5, 12.2%). Nineteen patients were on ATT (antiplatelet and/or anticoagulant therapy), but the therapy was discontinued in preparation for bronchoscopy, only in seven cases. The management of ATT was the same as that of EBUS-TBNA: both low-dose aspirin (primary and secondary prevention of cardiovascular events) and low-molecular-weight heparin (prophylaxis of venous thromboembolism) were not discontinued.[13,14] Oral anticoagulants were stopped, however, when the thromboembolic risk outweighed the procedural risk of bleeding (i.e., pulmonary embolism, thrombosis of large venous vessels), parenteral anticoagulants were continued. The descriptive characteristics of the sample and target lesion(s) according to EBUS-TBNA DY are reported in Table 1. In brief, the average diameter of the lesions was 2.4 cm ± 1; the most biopsied lymph node station was 7 (n = 28, 65.1%); in 3 cases, EBUS-TBNA + TMC was performed directly on centrally-located mass (hilo-perihilar), with a mean diameter of 7 cm ± 3.2; the mean number of cryoprobes per station was 2.7±0.6.

Table 1. Descriptive characteristics of the sample by EBUS-TBNA diagnostic yield

	Diagnostic EBUS-TBNA n = 15	**Non-diagnostic EBUS-TBNA n = 26**	**Overall n = 41**	***P***
Age, years	61.1±14.2 (30.0-75.0)	59.1±13.9 (19.0-80.0)	59.8±13.9 (19.0-80.0)	0.65
Sex				0.27
Male	9 (60.0%)	11 (42.3%)	20 (48.8%)	
Female	6 (40.0%)	15 (57.7%)	21 (51.2%)	
Charlson Comorbidity Index				0.067
≤5	6.0 (40.0%)	18 (69.2%)	24 (58.5%)	
5+	9 (60.0%)	8 (30.8%)	17 (41.5%)	
Number of cryobiopsies				0.72
2	4 (26.7%)	9 (34.6%)	13 (31.7%)	
3	8 (53.3%)	14 (53.8%)	22 (53.7%)	
4	3 (20.0%)	3 (11.5%)	6 (14.6%)	
Largest EBUS-TBNA needle, G				0.21
21	11 (73.3%)	23 (88.5%)	34 (82.9%)	
19	4 (26.7%)	3 (11.5%)	7 (17.1%)	
Diagnostic group				0.017
N miss	0	2	2	
Non-PLC	8 (53.3%)	21 (87.5%)	29 (74.4%)	
PLC	7 (46.7%)	3 (12.5%)	10 (25.6%)	
Final diagnosis				0.26
PLC	7 (46.7%)	3 (11.5%)	10 (24.4%)	
Sarcoidosis	3 (20.0%)	7 (26.9%)	10 (24.4%)	
Other lung granulomatosis	2 (13.3%)	4 (15.4%)	6 (14.6%)	
Rare solid malignant tumor	1 (6.7%)	3 (11.5%)	4 (9.8%)	
Benign reactive lymphadenitis	0 (0.0%)	4 (15.4%)	4 (9.8%)	
Castleman disease	1 (6.7%)	2 (7.7%)	3 (7.3%)	
Lymphoma	1 (6.7%)	1 (3.8%)	2 (4.9%)	
Non-diagnostic	0 (0.0%)	2 (7.7%)	2 (4.9%)	

Table 1. Continued

	Diagnostic EBUS-TBNA n = 15	Non-diagnostic EBUS-TBNA n = 26	Overall n = 41	*P*
Target size on CT (short axis), cm	2.7 (0.8) (1.6-4.2)	2.2 (1.0) (0.9-5.5)	2.4 (1.0) (0.9-5.5)	0.11
Lymph node shape				0.39
Irregular	13 (68.4%)	12 (48.0%)	25 (56.8%)	
Round	4 (21.1%)	8 (32.0%)	12 (27.3%)	
Oval	2 (10.5%)	5 (20.0%)	7 (15.9%)	
Echogenicity				0.51
Homogenous	8 (42.1%)	14 (51.9%)	22 (47.8%)	
Heterogeneous	11 (57.9%)	13 (48.1%)	24 (52.2%)	
Calcifications				0.58
No	15 (78.9%)	23 (85.2%)	38 (82.6%)	
Yes	4 (21.1%)	4 (14.8%)	8 (17.4%)	
Target station				0.32
7	11 (57.9%)	17 (70.8%)	28 (65.1%)	
11R	6 (31.6%)	1 (4.2%)	7 (16.3%)	
10L	1 (5.3%)	1 (4.2%)	2 (4.7%)	
11L	1 (5.3%)	2 (8.3%)	3 (7.0%)	
4R	0 (0.0%)	2 (8.3%)	2 (4.7%)	
10R	0 (0.0%)	1 (4.2%)	1 (2.3%)	

Patient characteristics and target lesion sonographic features according to EBUS-TBNA diagnostic yield. Data are presented as n (%) or mean±SD. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, PLC: primary lung cancer, CT: computed tomography, SD: standard deviation

Thirty-nine patients (95.1%) had a definite diagnosis based on the mediastinal specimens: PLC (n = 10, 24.4%), uncommon tumors (n = 4, 9.8%), hematologic disorders (n = 9, 22.0%), and benign lung diseases (n = 16, 39.0%). In two patients, neither technique established a definite diagnosis. The overall DYs were 41.5% for EBUS-TBNA and 95.1% for TMC. TMC showed a DY comparable to EBUS-TBNA for patients with PLC (80% for EBUS-TBNA and 100% for TMC, 95% confidence interval (CI): -4.79-44.8, p=0.13), however, TMC showed a significantly better DY in case of non-PLC pathologies: uncommon tumors (25% for EBUS-TBNA and 100% for TMC, 95% CI: 32.5-100, $P < 0.02$), hematologic disorders (28.6% for EBUS-TBNA and 100% for TMC, 95% CI: 50.6-100, $P < 0.001$), and benign lung diseases (37.5% for EBUS-TBNA and 100% for TMC, 95% CI: 38-70, $P < 0.001$) (Table 2). In nine subjects with a history of previous non-diagnostic EBUS-TBNA, EBUS-TBNA continued to result non-diagnostic, whereas TMC was diagnostic in all cases. AEs were mild bleeding (n = 4, 9.7%), nonspecific chest discomfort (n = 2, 4.8%), and dysphonia (n = 1, 2.4%), which regressed after a short course of oral corticosteroids. No higher incidence of bleeding was observed in patients on ATT than in patients who did not receive ATT, or those who discontinued ATT.

DISCUSSION

In this retrospective analysis, we found that TMC provided a higher DY than EBUS-TBNA in cases of hematologic disorders (benign or malignant), benign lung diseases, and uncommon tumors. The DY was 31% for EBUS-TBNA and 100% for TMC (95% CI: 52.1-85.8, $P < 0.001$). For PLC, the DY, as well as the assessment of immunohistochemical marker expression, did not significantly differ between the two techniques (80% for EBUS-TBNA and 100% for TMC; 95% CI: -4.79-44.8, $P = 0.13$) (Figure 1). The DY of EBUS-TBNA samples may be hampered by blood and bronchial cell contamination, crushing artifacts and necrosis; furthermore, the diagnostic discordance between cytologic and histologic specimens and the fact that cytological findings of different lesions often resemble one another (i.e., granulomatous components are present in lymphoma, tuberculosis and sarcoidosis) are the main limiting factors to the use of EBUS-TBNA in hematologic disorders as well as in benign lung diseases.[15,16] Since TMC obtains intact histology samples, cryobiopsies could definitively overcome the cytopathology issues of EBUS-TBNA, giving a conclusive diagnosis in these conditions, as the results of this study confirm, in accordance with literature.[8-11,17,18] In our sample, in case of suspicion of relapsed/refractory (R/R) hematological malignancies after chemoradiotherapy (n = 5, 12.2%), TMC established a diagnosis in four patients thanks to the high-quality specimens (one patient: confirmation of R/R disease, with biopsy adequate both for subtyping and determining the histologic grade; three patients: benignant lymphadenitis, no R/R disease), with no need of further sampling procedures (negative follow-up after six months of radiological surveillance). Conversely, also in real-life scenarios, when EBUS-TBNA is negative for R/R hematological malignancies, it is deemed insufficient for a reliable result; thus, invasive histologic confirmation is required.[19] Future research should address the role of TMC as a decision support tool in this specific patient population. In the group finally diagnosed with PLC, the

Table 2. EBUS-TBNA and TMC diagnostic yields by pathologies

Diagnostic yield by pathologies	EBUS-TBNA n = 41	TMC n = 41	Overall n = 82	*P*
Overall	17 (41.5%)	39 (95.1%)	56 (68.3%)	<0.001
PLC	8 (80.0%)	10 (100%)	18 (90.0%)	0.13
Non-PLC	9 (31.0%)	29 (100%)	38 (65.5%)	<0.001
Uncommon tumors	1 (25.0%)	4 (100%)	5 (62.5%)	0.028
Hematologic disorders	2 (28.6%)	9 (100%)	11 (61.1%)	<0.001
Lung granulomatosis	6 (37.5%)	16 (100%)	22 (68.8%)	<0.001

Data are presented as n (%).
EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, TMC: transbronchial mediastinal cryobiopsy, PLC: primary lung cancer

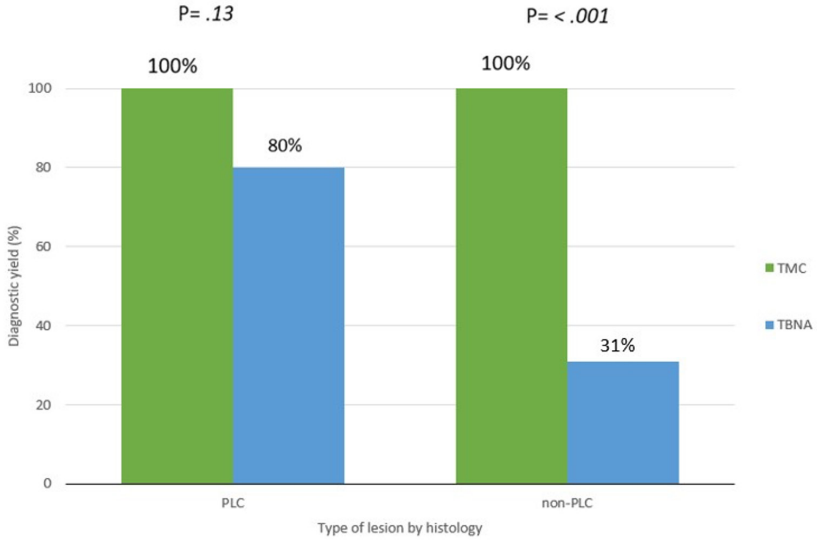

Figure 1. Diagnostic yield by technique in case of PLC and non-PLC diseases (uncommon tumors, hematologic disorders and benign lung disorders): TMC provides 69% a higher diagnostic yield than EBUS-TBNA in case of non-PLC diseases [31% for EBUS-TBNA and 100% for TMC; 95% confidence interval (CI): 52.1-85.8, $P < 0.001$]; for PLC, the diagnostic yield does not significantly differ between the two techniques (80% for EBUS-TBNA and 100% for TMC; 95% CI: 4.79-44.8, $P = 0.13$)

PLC: primary lung cancer, TMC: transbronchial mediastinal cryobiopsy, EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration

sensitivity of EBUS-TBNA was slightly lower than the existing literature (80% versus 91-93%), probably due to a high prevalence in our cohort, of patients (n = 8, 80%) with extensively necrotic lymph-nodes on CT scan.[3,4] Furthermore, we found the sensitivity of EBUS-TBNA for the diagnosis of granulomatous disorders below the range reported in the literature (37.5% versus 60%).[7] This result also deviates from our practice as regular EBUS-endoscopists (EBUS-TBNA DY for lung granulomatosis at our interventional pulmonology unit is 57%, unpublished data); factors that may have negatively impacted the DY in this group were history of previous non-diagnostic EBUS-TBNA (n = 6, 27.2%) and recent course of steroids administered for other reasons, (n = 5, 22.7%) possibly partially attenuating inflammation. However, given the retrospective nature of the study, there were unmeasurable variables that may have introduced a bias toward the null hypothesis (more diagnostically challenging procedures were performed with EBUS-TBNA + TMC, given its theoretical advantage). Furthermore, we could not assess any eventual improvement in the DY for non-malignant lung diseases when utilizing a 19G needle versus TMC. Indeed, among the seven patients in whom the procedure was performed with the larger needle, only one had a final diagnosis of benignancy (sarcoidosis) on the TBNA specimen. Also if the choice of the needle size was at the operator's discretion, we tended to use a 19G needle only at the beginning of our learning curve with TMC to facilitate the insertion of the cryoprobe by creating a larger entry point rather than on the basis of suspected benign disease; this is in accordance with guidelines on EBUS-TBNA, suggesting using either a smaller (21G) or a larger (19G) needle in patients with suspected benign disease.[20] However, studies comparing the DY of the two techniques, in which EBUS-TBNA was performed using only 19G needles, reported that TMC overcame EBUS-TBNA in cases of benign disorders, including infection and sarcoidosis.[21,22] It is noteworthy that in all our patients who repeated bronchoscopy because of diagnosis initially missed by EBUS-TBNA, the latter continued to be non-diagnostic, while a diagnosis was reached by cryobiopsy in all

cases, suggesting that TMC could be the investigation of choice in this population. In two patients, neither EBUS-TBNA nor TMC could establish a diagnosis: one underwent bronchoscopy for suspicion of relapsing gray zone lymphoma after chemotherapy, the other one, for restaging of primary lung adenocarcinoma after induction chemoradiotherapy; in these clinical scenarios, lymph nodes undergo fibrosis and necrosis, and residual malignant cells may be heterogeneously distributed within the node (center as well as subcapsular zone).[23,24] This aspect could be particularly relevant because, unlike EBUS-TBNA, which allows a bronchoscopist to extensively sample different zones of the target lesion ("fanning technique"), cryobiopsies may be performed only along the track originally created by the EBUS needle.[25] Future research could explore how to increase DY in these patients (i.e., higher number of cryo-passes, use of elastography, creation of more tracks within the nodes). The ACCP guidelines released on September 2024, on the acquisition and handling of EBUS-TBNA samples, recommend performing four or more needle passes over three or fewer needle passes in patients with suspected malignant and non-malignant diseases: a greater number of passes provides adequate specimens for molecular and immunological assessments of malignancies and facilitates the recognition of the characteristic pathology of benign diseases.[20] However, when we introduced TMC in our practice (February, 2023) and for all the study period (February, 2023-January, 2024), we complied with the guidelines on EBUS-TBNA in force at that time, and performed three separate needle passes per sampling site, so we cannot exclude the possibility that this factor favored cryobiopsy's DY.[26] However, the number of EBUS-TBNA passes to execute before TMC is not standardized across the studies, ranging from two, to three, to four.[8,9,12,27,28] Only one study reported up to five passes of EBUS-TBNA before cryobiopsy, and even so TMC outperformed EBUS-TBNA in the diagnosis of uncommon tumors and benign disorders;[29] a uniform methodology should be employed in this matter. The minimum number of cryobiopsies that should be conducted on each target lesion is not yet well established and can range between one and four. Kho et al.[29] found that the DY of TMC plateaued after 2-3 cryo-passes; accordingly, in our study, we found that the DY of two cryo-passes was the same as that of three or more cryo-passes. The ideal cryoprobe activation time is undefined, ranging from three to seven seconds.[8-12,25,30] In our experience, cooling down the cryoprobe for no more than four seconds allowed for an easy retraction of the scope from the airway, a longer time may translate into a progressive ascending cooling down of the probe, beyond the blunt tip, with increased resistance opposed by the tracheobronchial wall to the removal of the scope. We did not face technical difficulty with TMC performed on hilar (10R/L) and lobar (11R/L) lymph-nodes. In general, TMC is smoother when the cryoprobe enters the needle track at a near-perpendicular angle (i.e., stations 4R and 7), preventing the sliding of the probe in the sub-mucosal layers above the lesion. Soo et al.[31] described that cryobiopsy may present some difficulties for posterior tracheal lesions, and Ariza Prota et al.[12] ranked the lymph node stations accessibility for TMC, from easiest to most challenging, as follows: 11L, 11Ri, 7, 11Rs, 4R, 2L, 2R, 10R, 10L, 3p, and 4L. However, experience from larger studies shows that any station, from 2 to 12, may be safely biopsied via TMC.[30] In other studies, TMC has been performed through an oral bite under conscious sedation, or through an endotracheal tube under general anesthesia (GA), respectively.[8-10,17,18] However, GA, has some critical drawbacks, including pronounced hemodynamic and respiratory impact, prolonged recovery phase, and high costs. These drawbacks could be disproportionate to the relatively simple technical needs of the procedure. Meanwhile, conscious sedation, in which verbal contact with the patient is possible at all times, may not always be ideal for both the patient's tolerance and the operator's comfort.[32] In our patients, anesthetics were titrated to target a state of DS. Since the heart of the procedure lies in the insertion of the cryoprobe into the target lesion through the tunnel created by the EBUS needle, DS helped the operator to maintain the same angle in which the initial puncture was made by reducing cough and excessive transpulmonary swings, causing access limitation. By manually squeezing the bag of the Mapleson circuit connected to the LMA, episodes of inadequate spontaneous ventilation due to DS were easily corrected. LMA placement could be particularly advantageous in patients undergoing TMC when compared with oral bite, because it allows smooth, fast, and repeated entrances of the scope owing to better laryngeal exposure and avoids contact between the cooled cryoprobe with the attached frozen biopsy and the pharynx. Furthermore, the use of the LMA, compared to the endotracheal tube, makes TMC easier to perform on the upper paratracheal lymph nodes. In our study, there was no pneumothorax or pneumomediastinum, and the overall low incidence of these two AEs in the literature might call into question the appropriateness as well as the cost-effectiveness of performing CXR after the TMC.[33,34] No instances of mediastinitis were observed, and antibiotics were not routinely administered after the procedure, except in the case of necrotic target lesion(s); notably, the use of LMA could be advantageous in this regard, reducing the contamination of the bronchoscope and, by inference the cryoprobe as well, by oropharyngeal pathogens. In all observed cases, bleeding post TMC was mild and easily controlled; our findings suggest that the management of ATT could be similar to EBUS-TBNA, traditionally considered a procedure with a low relative bleeding risk.[13] However, at our center, in case of severe airway bleeding, it is possible to convert the procedure to rigid endoscopy: while waiting for further evidence, the capabilities of the center in managing uncontrolled bleeding should be taken into account when considering ATT discontinuation for patients undergoing TMC. TMC was safe even in the presence of a Charlson Comorbidity Index ≥5, and no patient needed a step-up in the level of care after the procedure, delineating a good tolerability profile in the outpatients. In light of the findings of this study, the following recommendations could be implemented for use in daily practice: combined EBUS-TBNA and TMC is preferable to EBUS-TBNA alone in cases of suspected hematologic diseases, lung granulomatosis, CT features suggestive of uncommon lung tumors, history of diagnosis initially missed by EBUS-TBNA, and largely necrotic lesion(s) on CT scans. The decision to perform TMC as the first step in the diagnosis of PLC, in order to ensure adequate tissue acquisition for advanced molecular testing, should be weighed according to the local joint expertise of both interventional pulmonologists and pathologists (i.e., acquisition, handling and processing of the sample, trained personnel, availability of reliable novel tests).

This study has several limitations: importantly, it is a retrospective, single-center study with a relatively small sample size that allows for indication bias, thus making it unclear when TMC should be used. Furthermore, TMC was performed only by expert interventional pulmonologists; however, the technique is not intuitive and requires a learning curve.

CONCLUSION

In conclusion, TMC appears to be a valuable option for all diseases burdened by a low DY from EBUS-TBNA, probably leading to cost savings in specific diagnostic scenarios. The good tolerability profile makes TMC suitable for outpatients and patients with multiple comorbidities.

Ethics

Ethics Committee Approval: The study received approval from the Research Ethics Committee of Cardarelli Hospital (Campania 3, AORN_063) (approval number: 00023093, date: 10.10.2024).

Informed Consent: The requirement for consent was waived owing to the retrospective nature of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.C., A.P., S.C., G.F., Concept: N.C., A.P., G.F., Design: N.C., A.P., A.F., G.F., Data Collection or Processing: N.C., A.P., A.F., S.C., G.F., Analysis or Interpretation: N.C., A.P., A.F., L.Z., G.F., Literature Search: N.C., A.P., S.C., L.Z., G.F., Writing: N.C., A.P., A.F., S.C., L.Z., G.F.

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Original Article

The Role of Pulmonary Genetic Variations in the Pathogenesis of Pediatric Postinfectious Bronchiolitis Obliterans

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Abstract

OBJECTIVE: Postinfectious bronchiolitis obliterans (PIBO) is a chronic airway disease. The severity of the damage and the subsequent obstructive and inflammatory processes varies from one individual to another. The objective was to identify genetic variations that may be associated with pulmonary diseases in patients with PIBO.

MATERIAL AND METHODS: This retrospective descriptive study was carried out to define potential genetic changes that may be associated with PIBO. Medical records were used to obtain sociodemographic characteristics. Neutrophil, lymphocyte, platelet counts, immunoglobulins and C-reactive protein values, thoracic computed tomography (CT) findings and genetic analysis results for pulmonary panel using next-generation sequencing technology were recorded.

RESULTS: Sixteen patients were enrolled. Median age at diagnosis was 27.5 months (range: 7-195 months). Wheezing was the most common presenting symptom. The most prevalent finding on thoracic CT was a mosaic pattern. In all but one, a wide range of variations genes related to both pulmonary structure and function were identified. The genes identified included those related to primary ciliary dyskinesia (*DNAH* genes), surfactant metabolism disorder (ABCA3, CSF2RB), pulmonary fibrosis (MUC5B, SFTP), and bronchiectasis (SCNN1B).

CONCLUSION: Heterozygous variations associated with pulmonary diseases, including the *MUC5B* and *DNAH* genes, and CSF2RB, were identified in most patients diagnosed with PIBO, which may have clinical significance. These data are valuable in hypothesis formation that may lead to the evaluation of these three genes in the pathogenesis of PIBO in children.

KEYWORDS: Postinfectious bronchiolitis obliterans, next generation sequencing, whole exon study, genetics

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INTRODUCTION

Postinfectious bronchiolitis obliterans (PIBO) is a rare, chronic obstructive lung disease that is characterized by injury to the bronchiolar epithelium, followed by an inflammatory response and non-uniform luminal obliteration of the small airways. The fundamental mechanism is the injury of the airway epithelium, followed by the proliferation of fibroblasts and peribronchiolar fibrosis. Although PIBO frequently develops in children following adenovirus, influenza, measles, or respiratory syncytial virus infections, it may also occur following other lower respiratory tract infections.[1-3]

Although the role of an increased inflammatory response and peribronchial inflammation that occur with infection in the pathogenesis of BO is well-established, there are still some unresolved questions regarding its emergence. Some children infected with the same virus develop BO, while others recover without sequelae. However, a subset of these children develops severe structural and functional lung disease. This discrepancy may be attributable to a combination of genetic predisposition, the nature of the viral infection, and environmental factors. It is important to consider the role of primary structural, immunological, and functional genetic substructure in that affect the pulmonary immune response and fibrotic process. As is the case with many diseases, genetic predisposition may influence the individual's response

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to infection. Previous research has shown an association between the genetic variants of dynein axonemal heavy chain 1 (DNAH1) and mannose binding lectin.[4,5] Moreover, epigenetic changes associated with the disease were reported, such as the presence of dysfunctional miRNAs that have a role in cytokine-cytokine receptor interaction, transforming growth factor-beta (TGF-β) signaling, and FoxO signaling pathway.[6]

The identification of specific genetic variants associated with the development of PIBO, and the elucidation of their impact may help establish evidence-based diagnostic strategies. Additionally, it may aid in the development of individualized medical therapies to improve the quality of life of patients with certain rare lung diseases with which they may be associated. Therefore, the objective of this study was to identify genetic variations that may be associated with pulmonary diseases in patients with PIBO.

MATERIAL AND METHODS

Research Design and Ethical Approval

This retrospective descriptive study was approved by the Institutional Review Board of Manisa Celal Bayar University Ethics Committee (no: 20.478.486/1521, date: 21.09.2022).

Study Population

A total of 16 children aged 0-18 years who were diagnosed with PIBO based on history, clinical and radiological findings between January 2017 and December 2022 in our Pediatric Pulmonology clinic were included in the study. Genetic screening for lung-related diseases was performed in these patients.

The diagnosis of PIBO can be made on the basis of a history of acute severe respiratory tract infection in childhood, particularly in the early years. It requires the presence of clinical findings such as persistent or recurrent wheezing and airway obstruction that persists after findings revealed by lung function tests, if available. The lack of an expected response to systemic steroids and bronchodilators, along with the presence of a mosaic pattern, air trapping, and/or bronchiectasis, or atelectasis on thoracic computed tomography (CT) also supports the diagnosis, as well as the exclusion of other diseases that may cause chronic lung disease.[7,8] The diagnosis of PIBO was made on the basis of clinical features, chest X-ray, and thorax CT findings, after excluding other causes of chronic lung disease as suggested by Teper et al.[8]

Informed consent was obtained from the parents of all patients.

Data Collection

The complaint at presentation to our center, presence of bacterial co-infection in the history requiring the first hospitalization, antibiotic use, glucocorticoid use, mechanical ventilation, duration of hospital stay, and treatments received were recorded from the files. Sociodemographic characteristics and previous medical history, including age, gender, mode of delivery, birth week, presence of postnatal respiratory distress, and whether there was neonatal intensive care unit hospitalization, were also noted. Family history was documented regarding the smoking habits of the mother and father, the mother's smoking during pregnancy, the quantity of cigarettes smoked, and the presence of chronic lung diseases in the family. Moreover, physical examination findings, such as the severity of respiratory distress and the auscultation findings, were recorded.

The genetic results of the pulmonary panel were evaluated.

Thorax CT images were evaluated, and the findings reported by the pediatric radiology specialist of our institution, as well as echocardiography findings routinely performed by the pediatric cardiology specialist at our institution, were recorded.

Moreover, the results of the spirometry, which is routinely performed by the lung function test nurse according to the ATS and ERS guidelines, were obtained.[9]

Genetic Screening for Lung Diseases

In our clinic, all patients with chronic lung symptoms who are followed up with a pre-diagnosis of interstitial lung disease, cystic fibrosis, primary ciliary dyskinesia (PCD), and PIBO are screened for genes that may be associated with lung diseases. Next-generation sequencing technology is used for genetic analysis with the Illumina MiSeq system and compatible reagent kits, and the variants detected are classified according to American College of Medical Genetics and Genomics 2015 criteria.

NGS DNA Extraction

Genomic DNA was extracted from peripheral venous blood using the QIAamp® DNA Mini Kit (QIAGEN, Ankara, Türkiye).

Sequencing for Pulmonary Panel

Virtual panel analysis containing 60 genes (*ACVRL1, BLOC1S6, BMPR2, CAV1, CCDC39, CCDC40, CFTR, CHRNA3, CHRNA5, DNAAF1, DNAAF2, DNAH11, DNAH5, DNAI1, DNAI2, DNAL1, DOCK8, DSP, DTNBP1, EDN3, EFEMP2, ELMOD2, ELN, ENG, FBLN5, FLCN, FOXF1, GDNF, GSTP1, HPS1, HPS4, IL10, IL13, IL2RA, IL4, IL4R, KCNK3, LTBP2, LTBP4, MFAP4, MUC5B, NME8, PHOX2B, RPGR, RSPH4A, RSPH9, SCNN1A, SCNN1B, SCNN1G, SERPINA1, SFTPA1, SFTPA2, SFTPD, SMAD9, SOD3, STAT3, TERT, TGFβ1, TSC1, TSC2*) associated with pulmonary diseases was performed on the patients. Clinical Exome Solution V2 (CES v2) by Sophia Genetics was used for the exome enrichment. All procedures were carried out according to the manufacturer's protocols. Paired-end sequencing was performed on an Illumina NextSeq 500 system with a read length of 150 by 2. Base calling and image analysis were performed using Illumina's Real-Time Analysis software. The BCL (base calls) binary file was converted to FASTQ using the Illumina bcl2fastq package.

Bioinformatics Analysis

All bioinformatics analyses were performed on Sophia DDM™ platform, which includes algorithms for alignment, calling SNPs and small indels (Pepper®), calling copy number variations (Muskat®) and functional annotation (Moka®). Raw reads were aligned to the human reference genome (GRCh37/hg19). Variant filtering was performed on Sophia DDM™. Variant interpretation was evaluated according to American College of Medical Genetics criteria. Integrative Genomics Viewer was used for Bam file visualization.

Whole Exome Sequencing

Whole-exome sequencing was applied to the genomic DNA extracted from peripheral blood lymphocytes. Sequencing libraries were generated using the MGIEasy Exome Capture V4 Probe Set, and the samples of the patients were sequenced on a MGISEQ-2000 sequencing platform (MGI Tech Co. Ltd., Shenzhen). "Variant Annotation and Filter Tool (VarAFT)" and "SEQ Platform (Genomize Inc.)" were used for annotating the the variant-calling file and filtering the variants. According to the lung disease phenotype of the patients, the gene list titled "abnormal respiratory system physiology (HP: 0002795)" in the Human Phenotype Ontology database was used for analysis. Variant interpretation was evaluated according to American College of Medical Genetics criteria.

Sanger Sequencing

Familial segregation analyses of the variants were performed using the Sanger sequencing method.

Statistical Analysis

The Jamovi program was used for data analysis. We described categorical data as number and percentage, and continuous data as means, median, and standard deviation.

RESULTS

Sociodemographic and Background Characteristics

A total of 16 patients diagnosed with PIBO were included in the study. The study included 12 male patients (75%) and 4 female patients (25%). No parents or siblings of the patients had been diagnosed with PIBO. The median age at diagnosis was 27.5 months (minimum-maximum range: 7-195 months). Two patients (12.5%) were born prematurely at 34 and 36 weeks' gestation, while six patients (37.5%) were delivered via normal delivery. Three patients (18.8%) were admitted to the hospital due to respiratory distress during the neonatal period. Two patients (12.5%) had a mother who smoked one to two cigarettes per day during pregnancy. However, these two patients did not experience respiratory distress in the neonatal period. Following birth, 10 patients (62.5%) were exposed to domestic cigarette smoke.

Clinical and Treatment Characteristics

A total of three patients (18.8%) presented to our clinic with cough, eight patients (50%) with wheeze, four patients (25%) with cough and wheeze, and one patient (6.3%) with cough and dyspnea. Six (37.5%) of the PIBO patients exhibited no history of recurrent respiratory tract infection and no findings indicative of disease before the first severe infection occurred. According to the anamnesis obtained from the families, 15 patients (93.8%) were hospitalized during the period of severe respiratory symptoms. The median duration of hospitalization was 6.5 days (minimum 0 days, maximum 30 days). Antibiotics were administered to 14 patients (87.5%), and steroids were given to 8 patients (50%) during hospitalization. Five patients required oxygen support. One patient was intubated and subsequently monitored.

Laboratory Investigations

Four patients (25%) had positive respiratory viral panel results, and all were positive for adenovirus.

The sweat test was found to be within normal limits in all cases in the examinations performed until the time of diagnosis.

Imaging Results

The echocardiography of three patients included in the study revealed pathological findings. One patient exhibited a right arcus aorta, one patient had atrial and ventricular septal defects, and one patient had increased left ventricular thickness. Flexible bronchoscopy revealed no anatomical abnormalities in any of the patients. The most prevalent finding in patients whose contrast-enhanced thoracic CT scans were evaluated, was the mosaic pattern, observed in 10 patients (62.5%). Additionally, air trapping was observed in 10 patients (62.5%). In the remaining patients, in addition to the mosaic pattern, two patients (12.5%) exhibited atelectasis, another two (12.5%) bronchiectasis, and two more (12.5%) both atelectasis and bronchiectasis. The CT specimens of the patients who were followed up are available for sharing (Figures 1-4).

Main Points

- Postinfectious bronchiolitis obliterans (BO) is a chronic airway disease that occurs after severe damage to the lower airways in childhood.
- The severity of this damage and the subsequent obstructive and inflammatory process varies individually.
- It should be taken into account that this difference may be related to the character of the viral infection and the environment, as well as genetic predisposition.
- In our study, a wide range of genetic variations in molecular structural or functional genes in the lung were demonstrated in patients with BO.
- These data suggest that BO is not a random process and that one or more primary molecular causes should be sought.

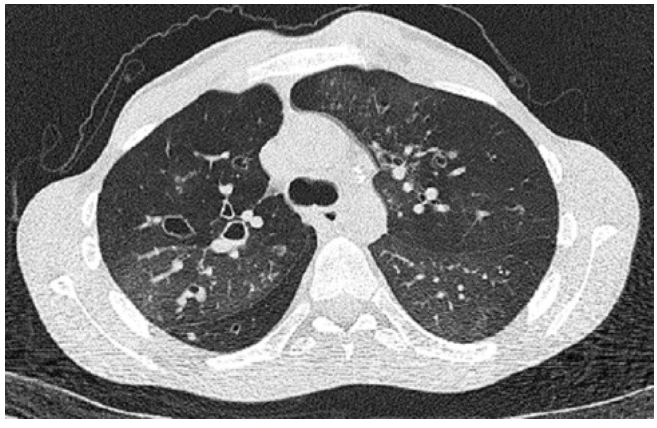

Figure 1. Fourteen years old, bronchiectatic segments with localized secretion-air leveling and bilateral ventilation asymmetries

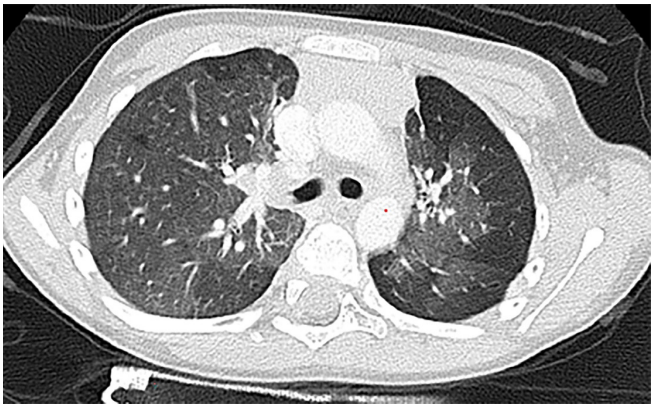

Figure 2. One year of age, diffuse patchy ground-glass areas and ventilation asymmetries from both apices to the lower lobes

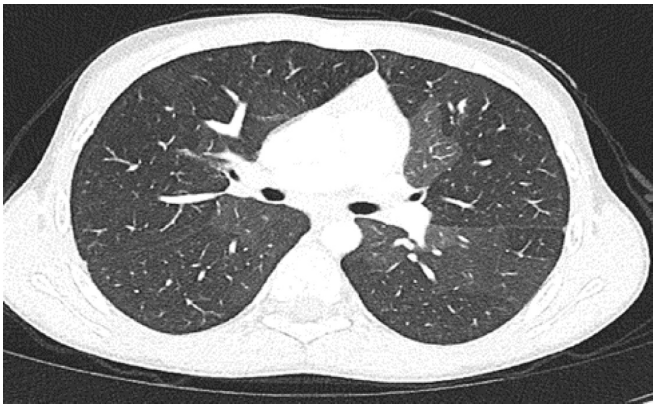

Figure 3. Nine years of age, peribronchial thickening and bilateral ventilation asymmetries

Pulmonary Function Test Evaluations

At the time of admission, 6 patients (cases 2, 4, 6, 7, 9, 14) underwent spirometry, the others were younger than 6 years or did not comply with the test. The results showed that one (case 2) had restrictive lung dysfunction; the others were normal.

Genetic Panel Results

As the cases had recurrent or prolonged respiratory symptoms and developed chronic lung disease process, the pulmonary panel was studied and 99% of all exons and exon-intron junctions (up to 20 bases) encoded by the studied genes were sequenced and analyzed. This study was performed with next-generation sequencing technology using the Illumina NextSeq® system and compatible reagent kits. In total, 17 different variations were

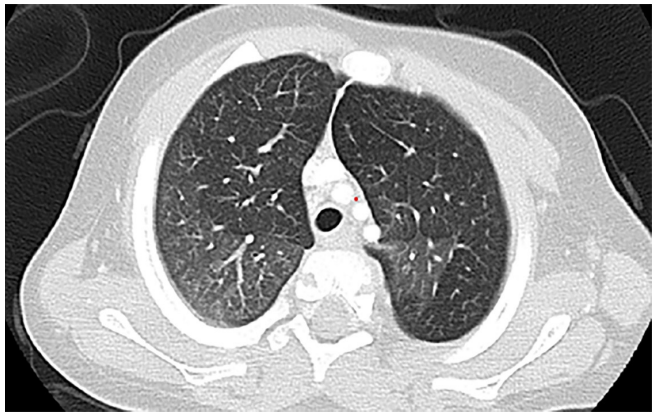

Figure 4. Two years old, bilateral mosaic perfusion appearance, more prominent in the right lung

Table 1. Gender and age distribution of patients with bronchiolitis obliterans and genetic results

Age (in years)	Gender	Genetic result
2	Girl	Normal
14	Boy	*CSF2RB, DNAAF4, DNAH1, DNAH 5, DNAH9, MUC5B* heterozygous
1	Boy	*CCDC40* heterozygous
8	Boy	*DNAI2* heterozygous
1	Boy	*CSF2RB, DNAH9* heterozygous
9	Boy	*MUC5B* heterozygous
6	Girl	*NLRP12* heterozygous
1	Boy	*MUC5B, SCNN1B* heterozygous
16	Boy	*DOCK8* heterozygous, *FLNA* hemizygous
1	Boy	*CSF2RB, DNAH5, MUC5B* heterozygous
3	Girl	*FLNA* heterozygous
4	Boy	*HYDIN, SCNN1G* heterozygous
2	Boy	*DNAH11* heterozygous
16	Boy	*MUC5B* heterozygous
1	Boy	*CCDC40, DNAH11, DNAH5* heterozygous
4	Girl	*ABCA3, CARMIL2* heterozygous

ABCA3: ATP binding cassette subfamily A member 3, *CARMIL2*: Capping protein regulator and myosin 1 linker 2, *CDC40*: Coiled-coil domain 40 molecular ruler complex subunit, *CSF2RB:* Colony stimulating factor 2 receptor subunit beta, *DNAAF4:* Dynein axonemal assembly factor 4, *DNAH1*: Dynein axonemal heavy chain 1, *DNAH5:* Dynein axonemal heavy chain 5, *DNAH9*: Dynein axonemal heavy chain 9, *DNAH11*: Dynein axonemal heavy chain 11, *DNAI2*: Dynein axonemal intermediate chain 2, *DOCK8*: Dedicator of cytokinesis 8, *FLNA*: Filamin A, *HYDIN:* Axonemal central pair apparatus protein, *MUC5B*: Mucin 5B, oligomeric mucus/gel-forming, *NLRP12*: NLR family pyrin domain containing 12, *SCNN1B*: Sodium channel epithelial 1 subunit beta, *SCNN1G:* Sodium channel epithelial 1 subunit gamma

detected. The results of the pulmonary panel were evaluated by the department of medical genetics in accordance with the individual characteristics of each patient and reported in the table (Table 1).

DISCUSSION

The findings of our study indicated that there is a considerable diversity of genetic variations in structural or functional genes, that have been shown to be associated with distinct lung diseases in patients diagnosed with PIBO. This explains the patient-specific risk factors for the development of PIBO following a respiratory tract infection.

BO describes a common pathological change in the small airways that occurs following a variety of diseases with different etiologies and characteristics. PIBO is frequently linked to a range of viruses and bacteria, including adenovirus, influenza, respiratory syncytial virus, and *Mycoplasma pneumoniae*. In our study, as most patients presented to our center weeks or months after the acute infection period, it was not possible to determine the presence of an associated pathogen in 75% of cases. Clinically, the condition is characterized by tachypnoea, rales, wheezing, and hypoxemia, which persists for a long time after the onset of symptoms or recurrent episodes.[10-12] Cough and wheezing were the most prevalent symptoms observed in our patient cohort. No hematological or biochemical pathology was identified in the blood tests conducted at the initial presentation, and there was no apparent immunoglobulin deficiency.

The diagnosis of bronchiolitis is typically based on typical clinical findings, fixed airway obstruction on pulmonary function tests, and radiological findings, especially a mosaic pattern on CT.[8,12,13] Although atelectasis, peribronchial thickening, air trapping, and bronchiectasis form the other CT changes, only the mosaic pattern was included in the PIBO score by Teper et al.[1,8,14] Consistent with this information, all the subjects enrolled had a mosaic pattern among lung CT findings.

Differential diagnosis of PIBO has been reported to include asthma in previous research. Onay et al.[15] have reported that about one third of their PIBO patients had been diagnosed with asthma before presenting to their clinic. Moreover, if PIBO is associated with bronchiectasis, then other etiologies related to bronchiectasis need to be considered, such as cystic fibrosis, PCD, and tuberculosis. Lee et al.[16] have demonstrated that PIBO was the underlying reason in 14% of the subjects with bronchiectasis in their Korean population. All subjects enrolled had sweat chloride testing, immunoglobulin levels, and tuberculin skin tests performed to rule out these diagnoses.

The most crucial step is to forecast the progression of PIBO, in a select group of children with respiratory tract infections, as well as the specific children who are most susceptible to developing severe complications. Although the pathogenesis of PIBO remains incompletely understood, it is becoming increasingly clear that the microbiological factors thought to be effective in the development of the disease are associated with genetic predisposition in affected individuals. An example of this is the development of PIBO in PCD patients with DNAH1 mutation more commonly than in those with a CCDC39 mutation.[17-19] Although we had subjects with DNAH mutations, none of them were diagnosed with PCD. Therefore, mutations that would lead to PCD if present as compound heterozygous or homozygous may be associated with the development of PIBO if present as a heterozygous mutation. However, this interpretation needs to be tested in a larger cohort.

Previous research identified genetic disorders related to surfactant dysfunction as causes of severe respiratory distress and childhood interstitial lung disease in infants.[20] Genetic surfactant dysfunction is the result of variations in genes encoding proteins that are crucial for surfactant production and function. Four proteins that are highly expressed in the lung are designated (SP)-A, -B, -C and -D. SP-B and SP-C reduce surface tension and are encoded by the *SFTPB* and *SFTPC* genes, respectively. One of the principal causes is associated with pathogenic variants, such as ABCA3 (ATP-binding cassette, subfamily A, member 3) and CSF2RB (granulocyte-macrophage colony-stimulating factor receptor, beta). ABCA3 is responsible for transporting phospholipids, which are essential for surfactant function, to the lamellar body. This process is encoded by a single *ABCA3* gene. The *NKX2.1* gene, which encodes the thyroid transcription factor 1 protein, has been demonstrated to affect the expression of the surfactant genes SFTPB, SFTPC, and ABCA3.[21] However, although many of these genes lead to severe clinical findings or respiratory distress when homozygous, the clinical outcome is not known for heterozygous or partially inactive genes. The genetic screening in our study population revealed a heterozygous mutation in the *ABCA3* gene. Surfactant protein mutations may be associated with PIBO due to the immunoprotective effects of these proteins.

Similarly, MUC5B (MUCIN 5, subtype B, tracheobronchial) has been linked to pulmonary fibrosis, while pathogenic variants of SCNN1B (sodium channel, non-voltage-gated 1, beta subunit) have been associated with small airway disease, which can lead to bronchiectasis.[20,21] We have detected MUC5B mutations in four of the subjects with PIBO enrolled in our study population. This may be related to the mucous quality changes in these children; therefore, further physiological studies on its quality are required.

The most significant limitation of this study is its descriptive nature. Nevertheless, the objective of this study is to provide a foundation for future observational studies. The most significant strength of this study is that it is one of the few to examine genetic variations in cases of BO. This study will contribute to the elucidation of the pathogenesis of this condition.

CONCLUSION

In conclusion, the data indicate that PIBO is not a random process, and genetic variations in genes related to dynein, mucous quality, and surfactant metabolism may be associated with increased risk. The objective of this descriptive study is to develop a hypothesis. The potential role of these genes in the development of PIBO needs to be elucidated with further research linking genetic analysis with protein function analysis.

Ethics

Ethics Committee Approval: This retrospective descriptive study was approved by the Institutional Review Board of Manisa Celal Bayar University Ethics Committee (no: 20.478.486/1521, date: 21.09.2022).

Informed Consent: Informed consent was obtained from the parents of all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.N.T., G.K., Ö.Y., M.Ö., H.Y., Concept: S.N.T., Ö.Y., H.Y., Design: S.N.T., Ö.Y., H.Y., Data Collection or Processing: S.N.T., G.K., Ö.Y., M.Ö., H.Y., Analysis or Interpretation: S.N.T., G.K., Ö.Y., M.Ö., H.Y., Literature Search: S.N.T., Ö.Y., H.Y., Writing: S.N.T., G.K., Ö.Y., M.Ö., H.Y.

Conflict of Interest: The author of this article, Özge Yılmaz, is a member of the Editorial Board of the Thoracic Research and Practice. However, she did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

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Original Article

Premature Deaths and Socio-economic Status: The Role of Fine Particulate Matter in Türkiye (2019)

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Abstract

OBJECTIVE: Air pollution, particularly particulate matter (PM), is a leading environmental risk factor contributing to global morbidity and premature mortality. The World Health Organization's (WHO) AirQ+© software is a vital tool for assessing the health impacts of air pollution. Our study used this software to estimate premature deaths attributable to long-term particulate matter ($PM_{2.5}$) exposure in Türkiye in 2019 and explored its relationship with each province's socio-economic status.

MATERIAL AND METHODS: We conducted an ecological study using annual average $PM_{2.5}$ levels from air quality stations. Due to limited $PM_{2.5}$ measurements (only 16% of stations), we derived $PM_{2.5}$ values from PM_{10} data using WHO's conversion coefficient for Türkiye.

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Abstract

RESULTS: We identified the provinces with the highest $PM_{2.5}$ concentrations and associated mortality: Iğdır, Şırnak, Çorum, Düzce, and Kahramanmaraş had the highest concentrations, while Erzurum, Çorum, Iğdır, Sinop, and Kütahya had the highest mortality rates per 100,000 population. No significant correlation was found between premature deaths and the socio-economic development index of each province. Our study estimated 37,768 premature deaths attributed to long-term $PM_{2.5}$ exposure in adequately monitored provinces.

CONCLUSION: In 2019, Türkiye faced persistent air pollution, with $PM_{2.5}$ levels exceeding WHO's 2021 limits across all provinces and stations. Türkiye lacks specific $PM_{2.5}$ limits legislation. Our findings provide a fresh insight into the literature, highlighting policy reform needs. However, data deficiencies hindered analysis in some provinces, affecting nearly 20% of the population aged 30 and above and 31% of the total surface area. Therefore, the actual burden of air pollution-related deaths may be higher than our estimates, underscoring the need to address these challenges urgently.

KEYWORDS: Air pollution, particulate matter, software tool, premature death, socio-economic status

INTRODUCTION

Air pollution is a major public health issue globally, with 99% of the world's population breathing air exceeding World Health Organization (WHO) pollutant limits.[1] Key pollutants include particulate matter (PM_{10}, $PM_{2.5}$), nitrogen oxides (NO_2, NO_x), ozone (O_3), volatile organic compounds, carbon monoxide (CO), and sulfur dioxide (SO_2). PM is composed of solid/liquid particles, including dust, dirt, soot, smoke, and airborne liquid droplets.[2] These pollutants, which are among the main air pollutants in Türkiye, consist of carbon, heavy metals, inorganic ions, and polycyclic aromatic hydrocarbons. Wood stoves and forest fires are examples of primary PM sources, while power plants and coal burning are examples of secondary PM sources, which are generated in the atmosphere through intricate chemical reactions involving compounds like SO_2 and NO. Factories, cars, trucks, and construction sites can be primary or secondary sources of pollution.[2]

Particles ranging from 2.5 to 10 μm in diameter are categorized as PM_{10}, also known as coarse particles, while those with a diameter of ≤2.5 μm are labeled as $PM_{2.5}$, referred to as fine particles.[3] Air pollution affects human health in a variety of ways, with particularly prominent health issues in the respiratory, cardiovascular, and cerebrovascular systems. It has been proven that the pathogenic effect of $PM_{2.5}$ is greater on various body systems through the systemic circulation.[4,5] Epidemiological studies indicate that $PM_{2.5}$ poses a greater risk factor compared to PM_{10} concerning premature mortality and long-term health impacts.[6] WHO reports that air pollution causes about 7 million premature deaths annually.[1] Studies, such as those by Badyda et al.[7] in Poland, link $PM_{2.5}$ exposure to increased mortality rates from lung cancer and cardiopulmonary diseases.

Main Points

- In 2019, Türkiye faced persistent air pollution issues, with particulate matter ($PM_{2.5}$) levels exceeding World Health Organization-recommended limits across all provinces and stations.
- Still, Türkiye lacks specific legislation on $PM_{2.5}$ limits.
- The study estimated 37,768 premature deaths attributed to long-term $PM_{2.5}$ exposure in adequately monitored provinces.
- The actual burden of air pollution-related deaths may be higher than the estimates, underscoring the urgent need to address these challenges.

According to the United States Environmental Protection Agency (EPA), vulnerable groups include children, pregnant women, elderly individuals, and those with pre-existing heart and lung conditions.[8] Socio-economic status (SES) also influences susceptibility to air pollution. Air pollution is associated with low education and low income.[9,10] $PM_{2.5}$ exposure is assessed with a comprehensive socio-economic indicator [Socio-economic Development Ranking Research (SEGE)] that is not limited to education and income. Segments of society with low socio-economic levels live in air-polluted regions and industrial peripheries. The relationship between $PM_{2.5}$ exposure and SES remains complex and context dependent. While some studies indicate that higher SES regions may experience increased $PM_{2.5}$-related mortality due to greater industrial activity, energy consumption, and urbanization, others suggest a protective effect driven by improved healthcare infrastructure, environmental regulations, and economic investments in pollution control.[11] The variability in findings highlights the importance of considering spatial and socio-economic heterogeneity when analyzing air pollution's health impacts. Studies that rely on broader geographic units, such as province- or city-level data, may overlook localized inequalities, limiting the accuracy of assessments. Therefore, understanding the interaction between $PM_{2.5}$ exposure and SES at a finer spatial resolution is crucial for developing targeted policies that address environmental justice and public health disparities. An investigation conducted under the Air Pollution and Health: A European Approach 2 project examined the short-term effects of ambient particles on mortality across 29 European cities, highlighting modifications in effects. It revealed that a 10 μg/m³ increase in PM_{10} or black smoke concentrations in short-term exposures resulted in a 0.6% rise in mortality (95% confidence interval=0.4-0.8%), with slightly higher impacts among the elderly. Additionally, the study demonstrated that variations in effect parameters among cities indicate genuine effect modifications, attributed to distinct city characteristics.[12] The countries that suffer the highest exposure to air pollution are low- and middle-income countries.[1] It is understood that both outdoor air pollution and SES have negative effects on respiratory outcomes.[13,14] While the direct impact of $PM_{2.5}$ on mortality has received extensive attention in research, its function as a modifier in relation to the SES-mortality relationship has been infrequently assessed.[15] A recent study indicates that neglecting SES factors might underestimate the influence of $PM_{2.5}$.[16] Another recent study revealed that, in general, each 10 μg/m³ increase in the annual mean $PM_{2.5}$ level corresponded to a 3.8% increase in all-cause mortality.[11] Stratified analysis of the same study revealed that districts with lower SES experienced significantly greater health

effects from $PM_{2.5}$ exposure. The analysis was conducted by dividing districts into quartiles based on key SES indicators, including literacy rate, university education rate, urbanization rate, and gross domestic product (GDP) per capita. The impact estimates for the lowest quartile of these indicators were 6.0%, 4.4%, 3.5%, and 4.9%, respectively, compared to their counterparts in the highest quartile. This demonstrates that populations in districts with lower SES are more vulnerable to the adverse health effects of $PM_{2.5}$ exposure, likely due to reduced access to healthcare, higher baseline exposure levels, and compounded environmental inequalities. These results were statistically significant ($P < 0.05$).[11]

Outdoor air pollution is also a public health problem for Türkiye. Research indicates that solely due to coal-fired power plants, Türkiye experiences approximately 2,876 premature deaths, 4,311 hospitalizations, and 637,643 instances of workplace absenteeism annually.[17] In a study conducted in Türkiye in 2018, it was found that a total of 44,617 individuals had premature mortality as a result of long-term exposure to $PM_{2.5}$. This study revealed that the provinces of Iğdır and Kahramanmaraş exhibited the highest estimated mortality rates associated with $PM_{2.5}$, while the provinces of Manisa and Afyonkarahisar recorded the highest estimated number of deaths per 100,000 population.[18]

Türkiye lacks a comprehensive analysis of $PM_{2.5}$ exposure and its associated burden on premature mortality, particularly in the context of socio-economic disparities. Existing studies often focus on global or regional scales, leaving country-specific data for Türkiye underrepresented. Moreover, the integration of socio-economic development indicators in assessing the health burden of $PM_{2.5}$ exposure remains limited. The aim of this study is to explore the relationship between $PM_{2.5}$-related mortality in Türkiye for 2019 and the socio-economic development levels of cities, using the WHO's AirQ+© software, providing a unique framework for understanding the interplay between air pollution and social determinants of health. By highlighting the regional disparities and the magnitude of the problem, this research aims to contribute to the existing literature and guide national strategies for air quality improvement and public health protection.

MATERIAL AND METHODS

This ecological study used WHO's AirQ+© (v.2.2) software (Regional Office for Europe, European Centre for Environment and Health, Bonn office, Germany), developed by the WHO Regional Office for Europe, to calculate the health impact of air pollution on specific populations.[19] AirQ+© has the ability to determine the proportion of a particular health outcome attributable to specific air pollutants in any urban area, country, or region. Additionally, it can predict potential changes in health impacts resulting from changes in air pollution levels compared to current conditions. Concentration/response functions and epidemiological studies provide the foundation for all of AirQ+©'s computations. The software's concentration/response functions are derived from a meta-analysis and systematic review of epidemiological studies. AirQ+© was employed to predict premature mortality from long-term $PM_{2.5}$ exposure.[20] Calculations involved using the annual average $PM_{2.5}$ level, converted from PM_{10} using WHO's conversion coefficient for Türkiye (0.66327),[21,22] since it is measured only in 16.6% of the stations. Additional components of the calculations included the region's surface area, the population aged 30+, and the mortality rate of this population, excluding external injuries. Data from 2019 were used to avoid Coronavirus disease-2019 impacts on air pollution levels and mortality rates. The annual average $PM_{2.5}$ levels for the provinces in 2019 were sourced from the Ministry of Environment, Urbanization, and Climate Change's air quality stations with sufficient data (90% and above).[23] The annual PM_{10} averages were obtained from the validated data shared in the 2019 Air Quality Bulletin.[24] According to these data, provinces with a data availability rate below 90% were excluded. To determine the annual average $PM_{2.5}$ concentration for a province in 2019, we summed the measured or converted annual average $PM_{2.5}$ concentrations from all air quality stations in that province and divided the total by the number of stations.

Provincial surface areas were sourced from the data in the document "Provincial and District Surface Areas" of General Directorate of Maps,[25] and population aged 30+ data from the Turkish Statistical Institute (TUIK) "Population by Age Groups-2019 Year" database.[26] The number of deaths for the 30+ population was calculated by excluding the total number of deaths from external injuries and poisonings in the 0-29 age group by using TUIK "Statistical Regional Units Classification, deaths by gender and age group, 2019" and "External injuries and poisonings" databases.[27] To obtain the death rate (per thousand) for the population aged 30+ years, excluding external injuries and poisonings, divide the number of deaths calculated according to provinces by the population aged 30+, and then multiply by 1,000. The map and graphic works were created using the Aldus FreeHand program.

The socio-economic development of the provinces was determined according to the index value of the "SEGE-2017" prepared by the Republic of Türkiye Ministry of Industry and Technology for the year 2017.[28] SEGE-2017 is a comprehensive study aimed at measuring the socio-economic development levels of districts in Türkiye. The research evaluates various indicators, including education, health, income levels, employment, infrastructure, social services, and environmental factors. Specifically, SEGE-2017 assesses income levels, literacy rates, accessibility and quality of health services, construction and infrastructure investments, industrial and commercial activities, and overall environmental conditions and quality of life at the district level. Since this study used publicly available air quality and statistical data and did not involve any human participants or identifiable personal information, it did not require ethical committee approval or informed consent.

Statistical Analysis

Data were analyzed statistically using IBM Statistical Package for the Social Sciences statistics, version 29.0 software (IBM Corp., Armonk, NY, USA), and correlation coefficient analyses were performed to assess relationships between variables.

RESULTS

Twenty provinces (Afyonkarahisar, Ağrı, Artvin, Bingöl, Bitlis, Bolu, Denizli, Elazığ, Eskişehir, Hakkari, Karabük, Kastamonu, Konya, Malatya, Mersin, Muğla, Muş, Tunceli, Uşak, Zonguldak) out of 81 were not included in the study due to the data rate being below 90%. Adana and Hatay were not included in the study due to the average $PM_{2.5}$ level being below 10 μg/m³, which is the WHO-recommended limit value from 2005. As a result, the study contained data from 59 different cities. PM_{10} was measured in 64% of a total of 347 stations, and only 37.5% of these stations had measurement data covering more than 90% of the time period. $PM_{2.5}$ was not measured in 71% of the total 347 stations, and only about half (54.5%) of the measuring stations had sufficient $PM_{2.5}$ measurements. Overall, 16% of the total stations had measurements above 90%.

The annual mean $PM_{2.5}$ concentration for Türkiye in 2019, based on data from cities with adequate measurements, was found to be 32.2 μg/m³. The provinces with the highest $PM_{2.5}$ concentration (μg/m³), were Iğdır (78.93), Şırnak (54.27), Çorum (52.45), Düzce (44.14) and Kahramanmaraş (42.48) and the lowest ones were Hatay (8.84), Adana (9.31), Rize (15.61), Afyonkarahisar (16.08) and Nevşehir (16.75) (Figures 1, 2).

Iğdır (33.94), Şırnak (23.38), Çorum (22.56), Düzce (18.55), and Kahramanmaraş (17.76) were the provinces with the highest mortality rate (%) attributable to $PM_{2.5}$ exposure, while Rize (3.31), Nevşehir (3.95), Kırşehir (6.12), Bayburt (7.08), and Balıkesir (7.09) had the lowest rates (Table 1).

Erzurum (614.4), Çorum (263.7), Iğdır (228.8), Sinop (228.68), and Kütahya (196.05) were the provinces with the highest number of mortality cases per 100,000 population attributable to $PM_{2.5}$ pollution, while Rize (35.25), Nevşehir (40.11), Van (53.5), Diyarbakır (53.51), and Mardin (59.36) were the lowest (Table 1, Figure 3).

In provinces with adequate measurements, the total number of premature deaths attributed to air pollution in 2019 was found to be 37,768, with which 5,869 in İstanbul, 2,709 in Ankara, 2,534 in Bursa, 2,394 in Erzurum, and 2018 in İzmir (Table 1).

The correlation of premature deaths related to $PM_{2.5}$ with the socio-economic development index of the provinces was examined. There was no correlation found between the SES of the provinces and premature deaths related to $PM_{2.5}$.

DISCUSSION

In 2019, Türkiye continued to face significant air pollution issues, with annual average $PM_{2.5}$ levels exceeding WHO's recommended limits across all provinces and stations.

Short- and long-term PM exposure is a major cause of morbidity and mortality, linked to respiratory and cardiovascular diseases.[4,5,14] Additionally, PM and outdoor air pollution are classified as human group 1 carcinogens by the International Agency for Research on Cancer, correlating with bladder and lung cancer.[29] Pope et al.'s[30] study indicates a 4% increase in overall mortality and a 6% increase in heart-lung disease mortality for every 10 μg/m³ increase in $PM_{2.5}$. In Türkiye, circulatory system diseases (36.8%), neoplasms (18.4%), and respiratory system diseases (12.9%) were the leading causes of death in 2019.[27] 39.1% of deaths from circulatory system diseases were attributable to ischemic heart disease, followed by cerebrovascular diseases (22.2%), other heart diseases (25.7%), and hypertensive disorders (7.9%). One important etiological factor of these common diseases, which are responsible for the majority of deaths that occurred in Türkiye in 2019, is continuous exposure to $PM_{2.5}$. Our findings align with these outcomes, highlighting that air pollution significantly reduces life expectancy, as shown by studies indicating a 0.61±0.20-year increase in life expectancy with a 10 μg/m³ reduction in $PM_{2.5}$ levels.[5] That's why air pollution, particularly that which is caused by $PM_{2.5}$, represents a highly significant issue for public health, with its preventability being a crucial aspect.

Despite the severe health impacts, PM pollution monitoring in Türkiye was inadequate. PM_{10} was measured in 64% of stations,

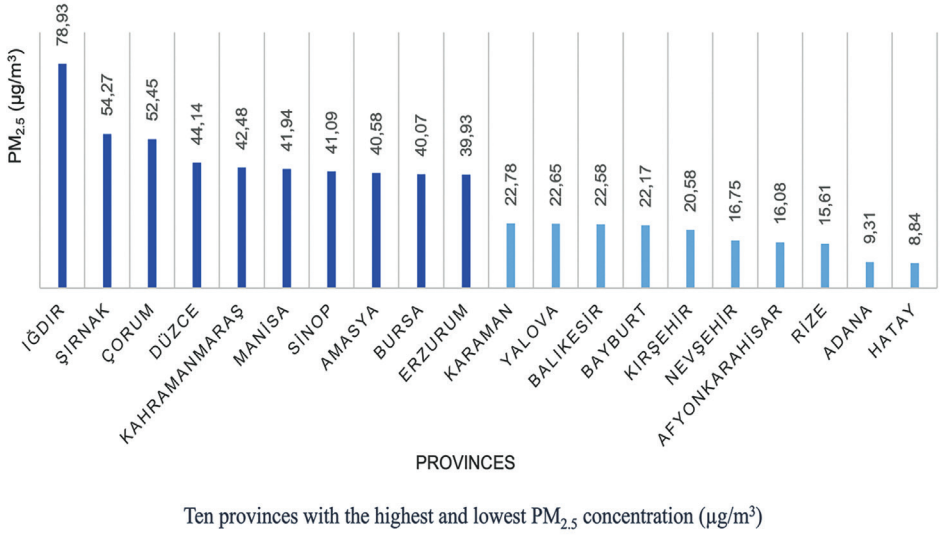

Figure 1. Ten provinces with the highest and lowest $PM_{2.5}$ concentration (μg/m³)

$PM_{2.5}$: particulate matter

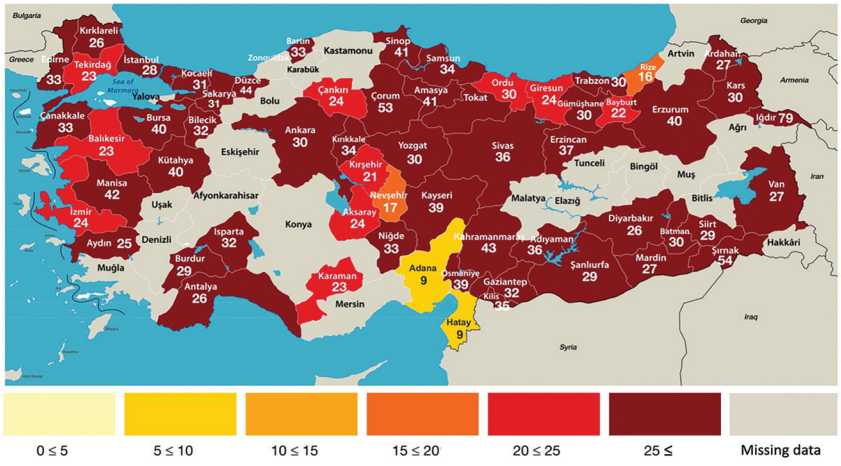

Figure 2. The $PM_{2.5}$ concentrations in provinces of Türkiye (μg/m³)

$PM_{2.5}$: particulate matter

Table 1. Estimated attributable proportion, the total number of premature deaths, premature mortality cases per 100,000 population and SES by province, attributed to $PM_{2.5}$ exposure (2019)

Province	Attributable proportion (%)	Number of attributable cases per 100,000 population at risk	Total number of attributable cases			Socio-economic status
	Central	Central	Central	Lower	Upper	
Adıyaman	14.28	105.26	335	224	434	-0.926
Aksaray	8.08	66.02	152	100	198	-0.271
Amasya	16.81	191.17	409	275	527	0.054
Ankara	11.18	80.30	2709	1803	3524	2.718
Antalya	9.34	62.08	948	629	1237	1.642
Ardahan	9.54	101.83	57	38	74	-0.983
Aydın	8.52	92.43	655	433	856	0.599
Balıkesir	7.19	90.15	740	489	970	0.476
Bartın	12.92	149.84	194	129	251	-0.14
Batman	11.05	64.48	165	110	215	-1.324
Bayburt	7.08	69.24	31	20	40	-0.629
Bilecik	12.50	138.38	188	125	244	0.556
Burdur	10.96	125.52	213	141	277	0.211
Bursa	16.41	136.43	2534	1703	3265	1.336
Çanakkale	12.61	150.28	537	358	697	0.548
Çankırı	7.69	101.56	126	83	165	-0.379
Çorum	22.56	263.70	890	606	1134	-0.262
Diyarbakır	9.25	53.51	419	278	547	-1.074
Düzce	18.55	176.47	409	276	524	0.2
Edirne	12.82	159.90	432	288	560	0.534
Erzincan	15.02	158.60	215	144	278	-0.15
Erzurum	16.50	614.40	2394	1610	3085	-0.531
Gaziantep	12.48	86.22	858	572	1114	0.25

Table 1. Continued

Province	Attributable proportion (%)	Number of attributable cases per 100,000 population at risk	Total number of attributable cases			Socio-economic status
	Central	Central	Central	Lower	Upper	
Giresun	8.13	102.28	299	198	392	-0.323
Gümüşhane	11.07	109.68	102	68	133	-0.623
Iğdır	33.94	228.80	217	152	271	-1.179
Isparta	12.18	134.63	361	241	469	0.564
İstanbul	9.99	64.61	5869	3896	7650	4.051
İzmir	7.86	72.38	2018	1334	2640	1.926
Kahramanmaraş	17.76	130.97	802	540	1031	-0.416
Karaman	7.30	68.42	100	66	131	0.177
Kars	11.40	148.60	210	140	274	-1.125
Kayseri	15.96	124.91	1001	672	1279	0.56
Kırıkkale	13.08	135.92	232	155	300	0.211
Kırklareli	7.63	107.72	256	170	334	0.557
Kırşehir	6.12	63.40	92	61	121	-0.085
Kilis	13.88	147.62	104	69	134	-0.57
Kocaeli	11.60	81.52	920	612	1196	1.787
Kütahya	16.21	196.05	715	481	922	0.17
Manisa	17.36	176.32	1577	1062	2028	0.49
Mardin	9.83	59.36	215	143	281	-1.396
Nevşehir	3.95	40.11	72	47	95	-0.015
Niğde	13.00	122.16	248	165	321	-0.395
Ordu	11.50	122.21	590	393	767	-0.486
Osmaniye	16.06	119.83	358	241	462	-0.367
Rize	3.31	35.25	76	50	100	0.174
Sakarya	11.97	115.00	698	465	906	0.832
Samsun	13.34	130.84	1079	721	1398	0.242
Siirt	10.70	64.70	85	57	111	-1.405
Sinop	17.06	228.68	332	223	427	-0.317
Sivas	14.22	153.18	569	381	736	-0.137
Şanlıurfa	11.02	60.42	498	331	648	-1.35
Şırnak	23.38	110.26	208	142	264	-1.788
Tekirdağ	7.58	62.10	395	261	517	1.014
Tokat	14.99	170.91	641	430	828	-0.381
Trabzon	11.07	108.20	538	358	700	0.389
Van	9.94	53.50	253	168	330	-1.452
Yalova	7.24	63.66	107	70	140	0.796
Yozgat	11.07	128.17	321	214	418	-0.589
	Total	**7280.14**	**37768**	**25211**	**48970**	

SES: socio-economic status, $PM_{2.5}$: particulate matter

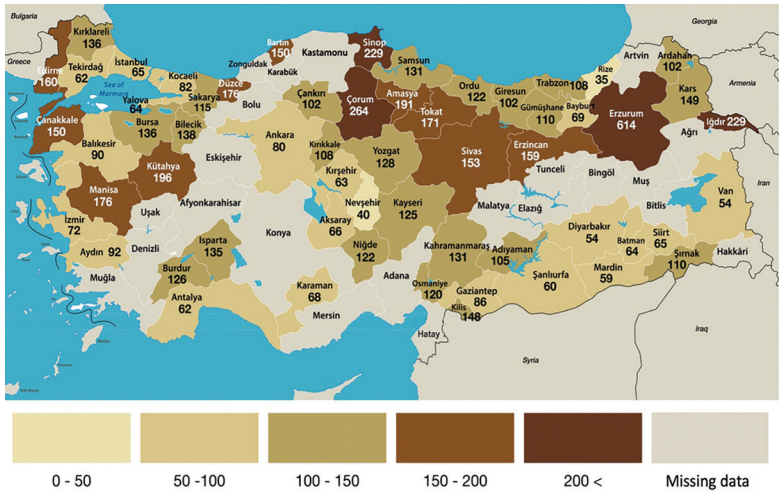

Figure 3. The mortality cases per 100,000 population attributable to $PM_{2.5}$ exposure by province

$PM_{2.5}$: particulate matter

with only 37.5% providing sufficient data. $PM_{2.5}$ was measured in only 16% of stations with sufficient data. The scarcity of reliable data, especially in regions with high pollution levels and vulnerable populations, clearly demonstrates the urgent need for improved and widespread monitoring capabilities to address the concrete reality of the public health crisis caused by air pollution in Türkiye.

The estimated mortality rate from long-term $PM_{2.5}$ exposure exceeded 20% in Iğdır, Şırnak, and Çorum, and surpassed 10% in 36 other provinces. We could not determine how $PM_{2.5}$ exposure contributes to Türkiye's leading causes of death due to insufficient data, highlighting the need for further research.

In 2019, $PM_{2.5}$ exposure led to an estimated 37,768 premature deaths in Türkiye (95% confidence interval 25,211-48,970). While this figure is lower than the 44,617 deaths estimated in 2018, it is important to note that the 2019 study covered fewer provinces (59 vs. 72) and used stricter data criteria (90% vs. 75% station data) (Table 2). These stricter criteria were implemented to ensure higher data accuracy but led to the exclusion of 20 provinces due to insufficient data coverage and two provinces due to average $PM_{2.5}$ levels falling below the limit value. These exclusions represent a significant portion of Türkiye, raising concerns about the underrepresentation of certain regions. These exclusions represent 20.3% of Türkiye's population aged 30+ and 31.2% of the country's total area, creating a significant gap in the study's geographic and demographic representation. The underrepresentation of these regions introduces significant uncertainty into the analysis. Many of the excluded provinces, especially in rural and industrialized areas, may have different pollution profiles or high exposure levels due to local $PM_{2.5}$ emission sources such as agricultural burning, industrial processes, or transportation corridors. Moreover, the population and geographic areas excluded from this study are not evenly distributed, which may skew the findings. For example, rural areas often lack adequate monitoring infrastructure despite potentially higher exposure levels due to unregulated pollution sources. On the other hand, urban centers such as İstanbul, Ankara, and İzmir, where most premature deaths are recorded, benefit from more comprehensive monitoring. This urban bias further emphasizes the need for even distribution of monitoring stations to ensure that the health impacts of air pollution are fully captured across all regions of the country. The lack of data from these regions may underestimate the true burden of premature $PM_{2.5}$-related deaths in Türkiye.

When compared to European Union (EU) member countries, where the highest annual mean $PM_{2.5}$ concentrations in urban areas were recorded in Bulgaria (19.6 μg/m^3), Poland (19.3 μg/m^3), and Romania (16.4 μg/m^3) in 2019, the findings in Türkiye indicate a substantially higher pollution burden.[31] The overall annual mean $PM_{2.5}$ concentration in Türkiye, based on cities with adequate measurements, was 32.2 μg/m^3-more than double the EU average (12.6 μg/m^3) and far exceeding the WHO-recommended limit of 10 μg/m^3. Additionally, certain provinces, such as Iğdır, Şırnak, Çorum, Düzce, and Kahramanmaraş, exhibit $PM_{2.5}$ levels that are significantly higher than those reported in the most polluted EU countries. In comparison with Poland, which holds the highest concentration of $PM_{2.5}$ among EU countries, where $PM_{2.5}$-related deaths ranged from 106 to 242 per 100,000, Türkiye's 11 largest cities (İstanbul, Ankara, İzmir, Kocaeli, Bursa, Konya, Şanlıurfa, Gaziantep, Antalya, Adana, Mersin) had $PM_{2.5}$ levels of 9.3-40.1 μg/m^3, with premature death rates between 60-176 per 100,000. Poland's geographical structure, energy resources, and industrial and heating policies may contribute to higher values compared to our country. From another point of view, if sufficient measurements were taken at the stations in these 11 largest cities in Türkiye, similar results could be obtained.

Despite a 23% decrease in air pollution-related deaths in 27 European countries between 2009 and 2019, Türkiye saw no reduction and ranked as the third worst in Europe for preventing air pollution-related premature deaths.[32] In 2019, European countries averaged 59.78 $PM_{2.5}$-related deaths per 100,000, while this study found rates in Türkiye between 35.25 and 614.40. A global meta-analysis estimated 25.3 $PM_{2.5}$-related

Table 2. Comparison of premature deaths attributable to long-term $PM_{2.5}$ exposure in Türkiye, 2018[18] and 2019

Features	2018	2019
Total number of stations, n	338	347
Number of provinces that included in the measurements, n	72	59
MD for 365 days a year (≥%)	75	90
Station measuring PM_{10} of over MD, n (%)	114 (33.7)	130 (37.5)
Station measuring $PM_{2.5}$ of over MD n (%)	63 (18.6)	57 (16.6)
Total number of premature deaths attributed to $PM_{2.5}$, n	44,617	37,768

MD: measurement data, $PM_{2.5}$: particulate matter

deaths per 100,000, which is a figure below Türkiye's lowest estimate, highlighting the country's challenges in addressing air pollution.[33]

In 2019, Türkiye's crude mortality rate was 5.3 per thousand, with 435,941 total deaths.[27] In other words, approximately one-ninth of the total number of deaths can be interpreted as premature deaths attributable to $PM_{2.5}$. Erzurum province had the highest estimated $PM_{2.5}$-related mortality, surpassing even the crude death rate of 530 per 100,000.

Vulnerable populations, particularly those of lower SES, are more susceptible to the effects of air pollution.[34] It is well known that SES and outdoor air pollution have a negative impact on the functioning of the respiratory and cardiovascular systems.[13,14] A study showed a 3.8% increase in all-cause mortality for every 10 μg/m³ rise in $PM_{2.5}$, with greater impacts in districts with lower SES.[11] Districts with lower SES had greater health effects from exposure, according to stratified analysis. The districts with the lowest quartiles of literacy, university enrollment, urbanization rate, and GDP per capita were estimated to have had an impact of 6.0%, 4.4%, 3.5%, and 4.9%, respectively. There was strong evidence that districts in the lowest quartile compared to those in the highest quartile had a higher risk of $PM_{2.5}$-related mortality across all socio-economic factors ($P < 0.05$). A meta-analysis suggests that the negative effects of $PM_{2.5}$ on mortality may be underestimated if SES factors are disregarded.[16] However, this study found no correlation between SES and $PM_{2.5}$-related premature deaths in Türkiye. This may be sourced from several situations. First of all, in Türkiye, there is a need to investigate the relationship between SES, social classes, air pollution, and individual health levels in the smallest possible settlements. Another issue is that $PM_{2.5}$ was not measured at all stations, and the stations were far from representing the districts and the city. Additionally, the lack of correlation may stem from the geographic scale of the analysis. Most studies on SES and air pollution focus on smaller regions, such as neighborhoods or districts, where environmental inequalities are more pronounced. However, due to data availability and the current air pollution monitoring structure in Türkiye, province-level analysis remains the most feasible approach. While this broader scale may obscure localized disparities, it provides the best possible assessment within the existing framework. Future research incorporating finer spatial analyses would offer a more nuanced understanding of the relationship between SES and $PM_{2.5}$-related health outcomes, but this would require an extensive monitoring network, which is currently lacking.

WHO recommends a 5 μg/m³ annual mean $PM_{2.5}$ limit and a 15 μg/m³ annual mean PM_{10} limit.[35] In the relevant regulations, only a national limit is specified for PM_{10}. As of January 1, 2019, the national annual average limit for PM_{10} has been set at 40 μg/m³, according to the Air Quality Assessment and Management Regulation (Official Gazette No: 26898, 2008). The lack of a national limit value for $PM_{2.5}$ in Türkiye is an important problem. Therefore, Türkiye should accept the PM_{10} limits recommended by WHO as soon as possible and determine the national $PM_{2.5}$ limit. This will be an important milestone toward preventing the morbidity and mortality caused by air pollution. According to WHO, national conversion coefficients can be used to calculate $PM_{2.5}$ values, over PM_{10} values in the event that $PM_{2.5}$ is not directly measured at stations. However, these calculated values may differ from region to region, and $PM_{2.5}$ calculations based on PM_{10} measurements may fail to reflect actual $PM_{2.5}$ concentrations.

Worldwide, several additional studies utilized the AirQ+© program. Cardito et al.[36] conducted an analysis of the concentration levels of six air pollutants (benzene, ground-level O_3, CO, nitrogen dioxide, and PM) that were observed by 37 stations in Campania, Italy, in the years 2019-2021. Based on the AirQ+© software's assessment of the health effects of air pollution, there was a notable decrease in adult mortality in 2020 compared to 2019 and 2021. The potential health benefits of reducing $PM_{2.5}$ exposure in Eastern Mediterranean Region (EMR), countries in 2019 were estimated by Faridi et al.[37] using WHO AirQ+© (v.2.1) software. In different EMR countries, it was estimated that lowering the annual mean $PM_{2.5}$ exposure level to 5 μg/m³ would result in a 16.9-42.1% decrease in all natural-cause mortality in adults (ages 30+). Reaching the 25 μg/m³ annual mean $PM_{2.5}$ would help all countries, as it would lower all-cause mortality by 3-37.5%. The health effects of long-term $PM_{2.5}$ exposure on years of life lost (YLL) and expected life remaining (ELR) indices in Ahvaz city between 2008 and 2017 were investigated by Zallaghi et al.[38] using the AirQ+© software. According to the results, over a ten-year period, the highest and lowest YLLs for all age groups were respectively, 137,760.49 (2010) and 5035.52 (2014). Additionally, the ELR index strongly correlated with the $PM_{2.5}$ concentration and was lower than the EPA and Iranian standards. Using PM data from 25 monitoring stations spread across the region between 2011 and 2019, Arregocés et al.[39] estimated the mortality rate attributed to yearly $PM_{2.5}$ exposure in Colombia's northern Caribbean region. An estimated 11.6% of acute lower respiratory disease deaths in children under 4 years old, 16.1% of deaths from chronic obstructive pulmonary disease (COPD), and 26.6% of deaths from ischemic heart

disease in adults are attributed to prolonged exposure to $PM_{2.5}$. It was estimated that the annual rates of lung cancer and stroke attributable to PM exposure were 9.1% and 18.9%, respectively. It is estimated that PM pollution directly causes 738 deaths annually. The adult population (aged 18+) had the highest annual death rate, averaging 401 events. The annual average risk of bronchitis prevalence in children due to air pollution was 109 per 100,000 individuals.

In order to quantitatively estimate the number of specific health outcomes from long- and short-term exposure to atmospheric pollutants in São Paulo, Southeastern Brazil, Wikuats et al.[40] applied the AirQ+© model to analyze the 2021 data. Lowering São Paulo's $PM_{2.5}$ levels, as recommended by WHO, could avert 113 COPD deaths and 24 lung cancer deaths annually. Additionally, it might prevent 258 hospital admissions for respiratory disorders and 163 admissions for cardiovascular disorders, both, brought on by $PM_{2.5}$ exposure. The findings showed that O_3-related excess deaths from cardiovascular and respiratory illnesses were 228 and 443, respectively. In the Marmara Region, which is the area with the highest concentration of urban and industrial mobility in Türkiye between 2016 and 2019, Kahraman and Sivri[41] used AirQ+© software to estimate mortality rates in the metropolitan cities of İstanbul, Bursa, Kocaeli, Balıkesir, Sakarya, and Tekirdağ. From 2016 to 2019, a total of 46,920 premature deaths were attributed to exceeding the WHO limit values, with 11,895, 13,853, 11,748, and 9,429 recorded for each year. Thus, AirQ+© is a helpful software that facilitates the development and application of air pollution control measures, to reduce death and economic costs associated with $PM_{2.5}$ exposure in Türkiye.

The strength of our study lies in its contribution to the body of literature by using AirQ+© software to calculate, for the first time, the estimated number of premature deaths in Türkiye in 2019 that can be attributed to long-term exposure to $PM_{2.5}$. It is also unique in that it considers the particular conditions of Türkiye and employs data specific to that country. It serves as a catalyst for related research, helps clarify the impacts of air pollution, and establishes the framework for further investigation. This enables us to better comprehend the connection between public health outcomes and air pollution. Calculating the risk of premature death from $PM_{2.5}$ can help influence political changes such as updating environmental regulations and air quality standards, thereby improving the creation of health policies through public health measures.

This study has several notable limitations. Premature deaths attributable to $PM_{2.5}$ exposure could not be calculated for the entire population aged 30 and above, and across the entire area, due to data deficiencies and values falling below the threshold in some provinces. These excluded provinces account for a significant portion of Türkiye's population, meaning the overall burden of $PM_{2.5}$-related health outcomes may be underestimated.

Additionally, $PM_{2.5}$ was not measured in 71% of all air quality monitoring stations, and even where measurements were taken, only a small fraction (16%) had data above the 90% reliability threshold. Due to the limited availability of direct $PM_{2.5}$ measurements, $PM_{2.5}$ values were derived from PM_{10} using a conversion coefficient. This situation may limit the accuracy of the analysis. Understanding the actual $PM_{2.5}$ levels is essential for revealing the morbidity and mortality associated with long-term exposure. However, in Türkiye, there is currently no specified limit value for $PM_{2.5}$ in air quality regulations, which further complicates efforts to quantify the full scope of health impacts.

Lastly, the analysis was conducted at the provincial level, which may obscure localized environmental inequalities and their associated health impacts. Studies focusing on smaller geographic units, such as districts or neighborhoods, are needed to better capture these disparities.

CONCLUSION

Despite these limitations, this study is the first in Türkiye to estimate premature deaths attributed to $PM_{2.5}$ using AirQ+© software for 2019. The findings indicate that 37,768 premature deaths could have been prevented in 2019 alone if the $PM_{2.5}$ limit value recommended by the WHO had been adopted and implemented. Considering the limitations in $PM_{2.5}$ measurement capabilities, the actual number of deaths attributed to air pollution is likely underestimated. These findings highlight the necessity of establishing a more comprehensive air quality monitoring network and ensuring direct $PM_{2.5}$ measurements to enhance the reliability of health burden assessments. Expanding the measurement infrastructure would provide more accurate data, allowing for better estimation of the true health impacts of air pollution. Additionally, these findings reinforce the importance of annual measurement and control strategies to evaluate and improve national ambient air quality standards, which are critical for protecting public health and reducing premature mortality caused by air pollution. By addressing existing gaps, this study contributes to the scientific literature and strengthens advocacy efforts for improved air quality policies and monitoring infrastructure.

Ethics

Ethics Committee Approval-Informed Consent: Since this study used publicly available air quality and statistical data and did not involve any human participants or identifiable personal information, it did not require ethical committee approval or informed consent.

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Footnotes

Concept: N.A., A.T., C.H.Ç., K.P., Design: N.A., S.Ç.K., A.T., C.H.Ç., K.P., Data Collection or Processing: All authors, Analysis or Interpretation: All authors, Literature Search: N.A., S.Ç.K., M.E.K., O.T.S., S.S.O., N.K.Ç., A.T., C.H.Ç., K.P., Writing: S.Ç.K, N.A., M.E.K., O.T.S., S.S.O., N.K.Ç., A.T.

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Research Letter

Considering Patient Perspective Through Visual Representatives: Telemedicine Gives Voice to Rare Interstitial Lung Disease Patients

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KEYWORDS

Telemedicine, education, interstitial lung disease, patient perspective, patient perspective, patient-based learning, rare ILD, videoconference

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INTRODUCTION

Rare diseases, also known as orphan diseases, are characterized by their low prevalence, affecting fewer than one person in 2000. Both diagnosis and treatment of rare diseases, even among individuals with the same condition, can be challenging due to their rarity. These conditions are often neglected due to their small patient populations. Medical expertise is scarce, knowledge and research are limited, and care services are inadequate.[1] In a survey conducted by Powell et al.,[2] the majority of healthcare professionals expressed the need for education on rare lung diseases. They recommended that educational resources be developed in collaboration with organizations such as the European Respiratory Society and integrated into meetings and events organized by these organizations. Additionally, 95% of patients believe that they should play a role in clinician education. However, barriers such as language, travel costs, and poor health conditions hinder patients' access to educational activities.[2]

Patient-centered medicine aims to improve health outcomes by considering patients' goals, preferences, and values, and determining the best intervention for each patient, while placing greater value on heterogeneity, observations, and exceptions.[3] The development of patient-centered medicine can be achieved by increasing patient-focused research.

An innovative idea emerged among the team members, who discussed the possibilities of extending the advantages of telemedicine through shared experiences. A panel presentation was proposed to the Turkish Thoracic Society Congress. Recordings of video consultations (VCs) between healthcare providers and patients with rare interstitial lung diseases (ILDs), with informed consents from the patients, were shared with the congress attendees, primarily to discuss the patient perspective through patients' own narratives shared in pre-recorded VCs of four rare ILD patients [lymphangioleiomyomatosis, Birt-Hogg-Dubé syndrome, pulmonary alveolar microlithiasis (PAM), pulmonary alveolar proteinosis], with informed consents from the patients.

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A survey questionnaire was administered to evaluate the audience's perspectives on the case presentations. The questionnaire primarily consisted of multiple-choice questions with predetermined answers on the following topics: specialty, work title, duration of work since graduation from medical school, opinion on considering patients' perspectives in scientific meetings, and if affirmative, opinion on discussing patients' perspectives using the method based on pre-recorded VC compared with the patient's in-person presence in. Additionally, it covered the effects of the meeting on the participants' own medical practice. This article aimed to evaluate the impacts of this novel method on clinicians in the context of a holistic approach to rare ILDs (Ethics Committee of Pamukkale University Faculty of Medicine; approval number: 15, date: 19.09.2023).

All 14 participants agreed on the benefit of considering patients' perspective through the representations of patients. Half of the applicants declared that the effect of using VC recordings is similar to in-person presentation of the patient, while the other half favored pre-recorded VCs over in-person presence of the patient. Watching VCs has been reported by all participants as having a positive effect on their medical practice. The participants' views on the session, in the context of the impact on medical practice, approach to telemedicine, and the use of VC recordings in medical/specialty education, are summarized in Table 1. The applicants mentioned observing the effect of telemedicine in giving each patient as much time as needed and a chance to communicate effectively, even through an interface. The answers were all supportive of the potential of telemedicine in providing healthcare service, as they presented an alternative to presupposition while observing the technique for the first time. The use of pre-recorded VCs for both undergraduate and postgraduate medical education was found inspiring and affirming by all the participants.

This study describes a method that enables the integration of patient perspectives through pre-recorded interviews with patients with rare ILD, used not only in medical/specialty education but also within the scope of postgraduate education, to discuss the patient perspective at a congress with the patients' consent. This made it possible for patients to participate in the congresses remotely and express themselves, allowing the diseases to be evaluated holistically with their biopsychosocial aspects. Evaluating the experiences of the participants in the congress session, who were at different stages of their medical careers, highlights the impressive and motivating power of watching patient interviews and hearing the process from the patients themselves.

The common problems attributed to rare diseases have been mentioned as 1) being "invisible" to the healthcare systems, 2) the paucity of experts, 3) the lack of appropriate treatments, and 4) the social exclusion faced by patients and their families.[4] Rare diseases pose challenges for patients, physicians, and researchers.[5] General physicians and clinicians in community hospitals may have less experience with rare diseases, which can lead to delays in diagnosis and referral to expert centers. In our study, although the participating physicians had extensive professional experience, a significant portion had not previously managed patients with rare ILDs. The educational needs of both patients and physicians need to be identified and addressed, as discussed in a comprehensive review.[6] The patient perspective is crucial in the education of physicians and researchers; however, this topic is primarily discussed through presentations by medical professionals on most occasions. One of the noteworthy comments from the participating physicians was that, in future national and international congresses, symposiums, and similar events, it should be possible and necessary to hear the patient's perspective directly using this method.

As highlighted in a review article, one of the main challenges for the future is to shorten the diagnostic delay through increasing physician awareness for rare lung diseases, and educating them on how to get help and access expertise for difficult cases.[6] For the PAM patient presented at a recent panel discussion, who had already reached the physician in her country through telemedicine from hundreds of kilometers away, this process offered the opportunity to receive a third opinion from an international expert thousands of kilometers away. During the latest consultation, provided through the pre-recorded VC, the health status of the patient could be observed, and radiological images could be evaluated even though it was not in real-time (Figure 1).

CONCLUSION

In conclusion, patients with rare diseases not only face clinical problems related to the disease but also bear psychosocial burdens. The impact of meetings where patients are central

Table 1. Participants' evaluations about the panel discussion session

Question	Code	Number of participants (n)
Impact on medical practice	Positive	8
	Allocating necessary time to the patient	5
	Sense of feasibility and motivation	4
Approach to telemedicine	Overcoming prejudices	7
	Consideration of applying to one's own practice	4
	Should be implemented in the future	10
Use of video consultation recordings in medical/specialty education	Continuous education independent of time and place	4
	Opportunity for repeated viewing	3
	Retention	3

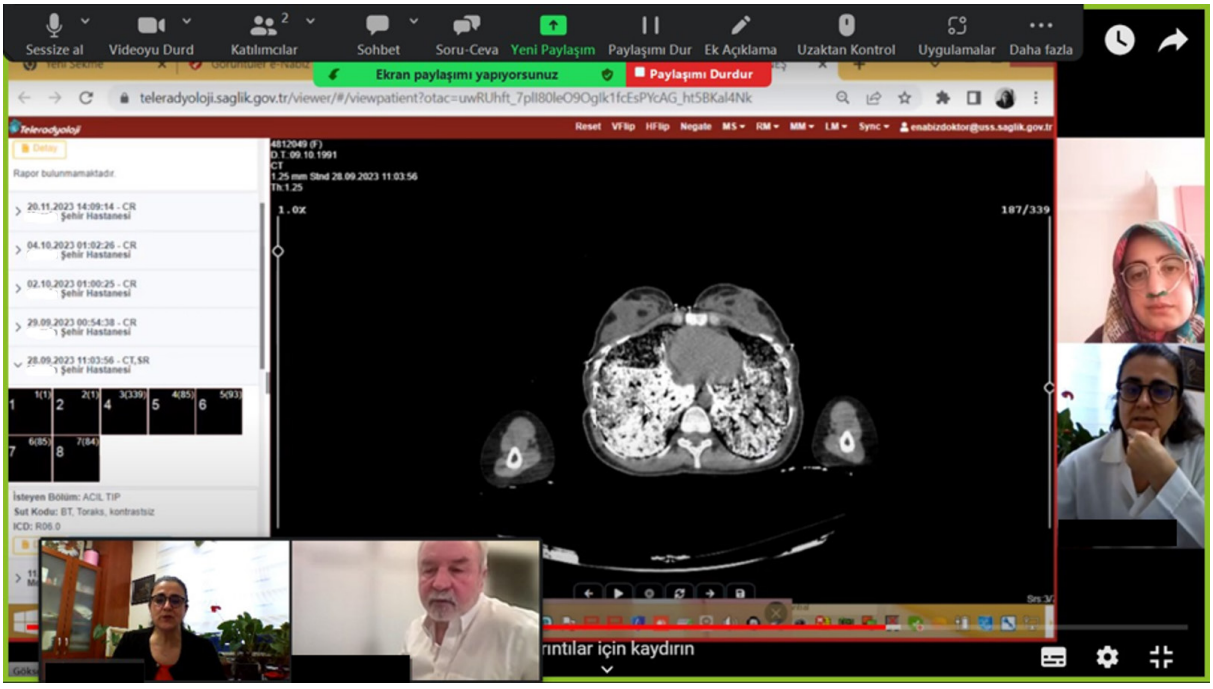

Figure 1. Teleconsultation via video conferencing and save-and-share methods involves, after detailed anamnesis, evaluating current examinations simultaneously with Prof. Francis X. McCormack at Cincinnati University. The distance between the physician and patient in Türkiye is 750 km, and the distance from Türkiye to Cincinnati is 9500 km

participants is significant for providing a holistic approach to diseases and increasing awareness and educational level of physicians on this matter. The educational method based on telemedicine through VCs and the recordings with the patient's consent is a novel method that can amplify patients' voices on scientific platforms in different cities or even different countries.

Ethics

Ethics Committee Approval: This study was carried out in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Pamukkale University Faculty of Medicine (approval number: 15, date: 19.09.2023).

Informed Consent: Consent for the use of patient interview records and anonymous medical information of patients in medical/specialist education and in the article was obtained from the patient and his/her relatives.

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We sincerely thank our patients who guaranteed us their consent to allow congress attendees to view their video recordings.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., Concept: N.Ç., G.A., Design: N.Ç., G.A., Data Collection or Processing: N.Ç., S.S.O., U.T., P.D.Ç., G.A., F.X.M., Analysis or Interpretation: N.Ç., G.A., Literature Search: N.Ç., Writing: N.Ç., S.S.O., U.T., P.D.Ç., G.A., F.X.M.

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Letter to the Editor

Response to: Long-term Effects of COVID-19 on Sleep Patterns

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DEAR EDITOR,

We appreciate the opportunity to respond to the comments made by Professor Al-Mendalawi[1] regarding our recent study published in Thoracic Research and Practice, which examined the long-term impact of Coronavirus disease-2019 (COVID-19) and the prevalence of sleep disorders among COVID-19 survivors.[2] We thank him for his thoughtful engagement with our study and for highlighting the importance of using robust and validated tools to assess sleep quality.

In response to his comments, we would like to clarify a few key points regarding our methodology. Our primary objective was to determine the prevalence of specific sleep symptoms-such as daytime sleepiness, insomnia, and other sleep-related issues-among COVID-19 survivors, rather than assessing overall sleep quality. This focus guided our choice of a customized survey, which allowed us to capture detailed information on these specific symptoms.

While the Pittsburgh Sleep Quality Index (PSQI)[3] is indeed a well-validated and widely used tool, its application in our study presented several challenges. First, the participant burden associated with the PSQI, which comprises 19 items, was a significant concern. To minimize participant fatigue, we opted for a more streamlined approach to data collection.

Second, since the PSQI assesses sleep quality during the previous month and is prefaced by the phrase "During the past month ...", we did not find the tool well-suited to our study objectives. Our research required participants to recall their sleep experiences from the time of their COVID-19 infection, which in many cases occurred more than a year prior. As such, the PSQI's timeframe did not align with the need to assess retrospective sleep symptoms. Instead, we developed a tailored survey to capture specific sleep-related issues directly relevant to our study aims.

Although other short sleep assessment tools are available and provide fast and reliable assessment of sleep quality,[4,5] the sleep measures in these questionnaires only include graded response categories and do not provide quantitative data, and therefore the number of hours of sleep cannot be determined. Similarly, the Brief-PSQI,[6] although less burdensome to the study participants, has excluded daytime sleepiness and was performed only among a Spanish-speaking population, and the findings cannot be generalized.

We fully acknowledge the value of the PSQI in assessing sleep quality in many contexts and agree that its use could facilitate direct comparisons with other populations and studies. However, for the specific objectives of our research, we believe the survey methodology we employed was more appropriate and practical.

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We share your concern regarding the significant proportion of sleep disturbances observed in our study cohort. These findings underscore the need for further research into tailored interventions to improve sleep health and overall quality of life for individuals recovering from COVID-19.

Thank you again for your insightful comments, which contribute to the ongoing dialogue about the best methods for studying sleep disturbances in post-COVID-19 populations. We remain committed to refining our methodologies and welcome future discussions and collaborations in this important area of research.

Footnotes

Authorship Contributions

Concept: S.B-A., O.S.F., S.F.Q., Writing: S.B-A., O.S.F., S.F.Q.

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Letter to the Editor

Comment on: Long-term Effects of COVID-19 on Sleep Patterns

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DEAR EDITOR,

The study published by Batool-Anwar et al.,[1] in the January 2025 issue of the Thoracic Research and Practice is intriguing. Batool-Anwar et al.,[1] found that Coronavirus disease-2019 (COVID-19) infection imposed negative influences on sleep, and a significant proportion of individuals exhibited daytime sleepiness and insomnia beyond one year after recovering from the initial COVID-19 infection. Batool-Anwar et al.[1] stated six impactful study limitations, and we address another one. It is common for individuals to be concerned about their disturbed sleep quality and its negative effects on daytime functioning. The tools to quantify sleep quality, like polysomnography, are not always favored by practicing clinicians and researchers in their daily work because they are time-consuming, costly, and not practical for research. Therefore, numerous self-report questionnaires have been constructed.[2] Among them, the Pittsburgh Sleep Questionnaire Index (PSQI) is widely utilized in research and clinical settings. It is a 19-item questionnaire which was formulated and initially validated in adults by Buysse et al.,[3] to gauge sleep quality, yielding a global score that helps in comparing scores between groups/individuals over time. It had good validity and internal reliability.[4] Moreover, the scores of sleep quality, both scale and global sleep quality risk scores, were found to reliably correspond with academic performance and mental health, thus highlighting the value of good sleep for individuals.[5] To facilitate PSQI implementation in different populations, various versions have been developed and validated. In the study methodology, Batool-Anwar et al.[1] employed a survey, which involved questions pertaining to many points, such as the amount of sleep, daytime sleepiness, difficulties in initiating/maintaining sleep, snoring, difficulties in breathing while asleep, history of hypnagogic hallucinations/vivid dreams, and utilizing sleeping aids before and after COVID-19 diagnosis. Regrettably, it was not explicit why Batool-Anwar et al.[1] referred to that survey in the study methodology, rather than the widely recommended and precise PSQI to assess sleep patterns among the study population. We believe that referring to the PSQI could yield a better insight into sleep disorders among the study participants. Irrespective of the study limitations, the significant proportion of sleep disturbance among cohort 1 is alarming. Tailored measures to enhance healthy sleep and encourage a positive quality of life are, therefore, recommended.

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Letter to the Editor

A New Global Epidemic of Silicosis Due to Artificial Stone: is Türkiye Next?

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DEAR EDITOR,

Twenty years ago, Türkiye faced a devastating outbreak of silicosis among young workers employed in denim sandblasting workshops. Thousands developed the disease, with many succumbing to respiratory failure in early adulthood. Although silica-based sandblasting was banned in 2009, survivors continue to grapple with chronic and debilitating forms of silicosis.[1] The attention once focused on Türkiye's denim sandblasting crisis now echoes in a different form, in different countries, driven by a different industry—yet the underlying threat of occupational silicosis persists.[2] Today, a new and deadlier wave of silicosis is unfolding—this time among workers in the artificial stone industry. Widely used as a modern alternative to natural stones such as marble and granite, artificial stone contains over 90% crystalline silica. Cutting, polishing, and installing these materials release microscopic silica dust, leading to irreversible pulmonary damage. Globally, this market is valued at more than $25 billion annually, yet it carries an invisible burden of disease.[3] What began in isolated regions is now reported with alarming frequency across the globe. In Israel, fatal cases have been identified among young workers. In the United States, severe disease clusters have been reported in California, Colorado, Texas, and Washington.[4] In 2024, Australia became the first country to ban artificial stone products altogether. Reports from Italy, Belgium, and the United Kingdom suggest that this epidemic respects no borders—and Türkiye is unlikely to remain exempt from its consequences.[2,5] Clinical observations indicate that patients exposed to artificial stone dust not only develop silicosis but also exhibit radiologic patterns that can resemble sarcoidosis or other interstitial lung diseases. Notably, many affected individuals are young, with exposure histories as brief as four years. These patients often experience a progressive disease course, leading to severe complications such as emphysema, spontaneous pneumothorax, and in some cases necessitating lung transplantation.[3,5] Standard safety measures—dust masks, wet cutting, and ventilation—are proving inadequate against such intense exposure. There is an urgent need for systemic regulatory reform. Early data from Australia show that legislative bans can drive innovation towards low-silica or silica-free alternatives.[3]

In Europe and North America, the expert consensus now recommends reducing silica content in these materials to less than 5%.[3] This looming crisis demands immediate attention. Silicosis in the artificial stone industry is not only a worker's disease; it is a societal failure of prevention.

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Footnotes

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