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Publishing Service: AVES
Address: Büyükdere Cad. 199/6, 34394, Şişli, İstanbul, Türkiye
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

Editors in Chief:
Oğuz KILINÇ
İpek Kıvılcım OĞUZÜ.LGEN
Address: Turan Güneş Bulvarı, Koyunlu Sitesi No: 175/19 Oran, Ankara, Türkiye
Phone: +90 (312) 490 40 50
Fax: +90 (312) 490 41 42
E-mail: editorial.office@turkthoracj.org

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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.

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Original Article

Work-Related Symptoms of Spice Shop Workers and the Effect of Common Aeroallergen Sensitivity on Work-Related Symptoms

Ömür Güngör[1], Nazan Akel[2], Ceyda Şahan[3], Ahmet Uğur Demir[4], Ali Fuat Kalyoncu[5]

[1]Department of Occupational Medicine, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[2]Department of Occupational Medicine, Mehmet Akif İnan Training And Research Hospital, Şanlıurfa, Türkiye
[3]Department of Occupational Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[4]Department of Chest Diseases, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[5]Division of Allergy and Clinical Immunology, Department of Chest Diseases, Hacettepe University Faculty of Medicine, Ankara, Türkiye

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Abstract

OBJECTIVE: Spices, because of their bioactive content, can cause irritation and allergic symptoms in the respiratory system and skin. Spice shop workers are constantly exposed to spices and dried herbs as part of their jobs. This study aimed to investigate the work-related symptoms of spice shop workers. Another aim was to assess the risk status of having an atopic nature for work-related symptoms.

MATERIAL AND METHODS: This was a cross-sectional study. Our research team visited the spice shops and a questionnaire was administered to 112 workers to assess work-related symptoms. In order to determine atopy, 79 of them had skin prick tests with common aeroallergens.

RESULTS: Workers had eye complaints (19.6%), runny noses (22.3%), skin symptoms (9.8%), shortness of breath (9.8%), and coughs (19.6%) at work. The prevalence of atopy was 18%. Atopy was associated with work-related eye complaints (odds ratio (OR): 4.12, 95% CI: 1.17-14.46), work-related runny nose, and work-related cough (OR: 4.85, 95% CI: 1.44-16.32, and OR: 4.41, 95% CI: 1.30-14.97).

CONCLUSIONS: The workers in spice shops are adversely affected by spices and dried herbs in their working environment. Being sensitive to common aeroallergens poses a risk for occupational symptoms.

KEYWORDS: Spices, herbs, occupational exposure, spice shop, atopy

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INTRODUCTION

Spices are natural aromatic substances obtained by drying, grinding, or processing plant components of various plants, such as seeds, leaves, roots, bark, flower buds, or fruits. Since ancient times, spices have been used to flavor foods and beverages. Herbs are plants in which the leafy, green, or flowering parts are medicinal. In recent times, there has been a widespread use of herbal treatment methods.[1] Medicinal plants and spices are usually purchased from spice shops, which are establishments where spices and dried herbs are sold in residential areas. Spice shop workers not only ensure that products reach customers, but also provide information about spices and other related products. They also perform a number of tasks that facilitate the overall shopping experience. The process of delivering products to customers causes the dispersion of particles and the release of suspended particles, thus creating an environment that poses as an occupational hazard in stores.

Spices contain irritants and pharmacologically active ingredients that can stimulate the immune system's response.[2] Occupational inhalation of spices and skin contact can cause certain symptoms. Zuskin et al[3] revealed the immunological and irritant properties of spices on workers. Exposure was associated with acute respiratory symptoms and alterations in lung function.[3] In addition, there have been documented reports of allergy symptoms in farmers who come into contact with plants due to their occupation.[4]

Spice allergies often occur following an initial sensitization to other allergens.[2] Cross-reactivity to protein allergens appears to be an important trigger for the activation of allergic reactions to spices.[2] The cross-reaction of spices with other spices, pollen, and some foods can cause allergic symptoms in people.[5] The most widely recognized cross-reaction is the celery–mugwort–spice syndrome, which is an allergic sensitivity to the Apiaceae family.[6] The existence of similar immunogens or common epitopes tends to cause cross-reactivity, which exacerbates clinical sensitivity.

Corresponding author: Ömür Güngör, e-mail: omurgungor70@hotmail.com.tr

Atopy is an immunological predisposition that can result in an exaggerated immunoglobulin E response to various allergens.[7] The global prevalence of atopic diseases has increased in recent years.[8] Assessing the feasibility of employment for individuals with atopic conditions, in a workplace that contains a high concentration of possible allergens, is a significant concern. There are limited studies examining the impact of workplace exposure to common aeroallergens on susceptible individuals. The study primarily aims to investigate the impact of exposure to spices and dried herbs in the workplace on the eyes, respiratory tract, and skin of spice shop workers. The secondary aim is to evaluate whether having a sensitivity to common aeroallergens poses a risk of exposure to spices and dried herb powders in the workplace.

MATERIAL AND METHODS

Study Design and Population

This is a cross-sectional epidemiological study. A total of 112 currently employed spice shop workers from Spice Bazaar, Grand Bazaar in Istanbul, and Ankara spice shops were included. All participants affiliated with the association were included in the study, and all of them completed the survey. Only 79 of the participants agreed to have a skin prick test (SPT). Beforehand, consent forms were signed separately for both the questionnaire and the SPT. The study obtained ethical approval from the Hacettepe University Faculty of Medicine (approval number: 1609/2021, date: September 7, 2021).

The questionnaire was developed by the authors. It had 2 sections and was administered to the participants face-to-face by the researchers. The participants' demographic characteristics, such as age, gender, and smoking status, were collected in the first section. In the second section, the questions related to occupational characteristics and symptoms. Work-related symptoms resulting from exposure to spice dust in the workplace were defined as work-related eye symptoms (watery, red, and itchy eyes), work-related runny nose symptoms (sneezy, runny, and itchy nose), and work-related skin symptoms (itching and redness on the skin). Work-related shortness of breath and cough were defined as the presence of symptoms associated with spice dust inhalation during work. The SPT was conducted using the 3 common aeroallergens identified in a previous study.[9] The aeroallergens were pollen (*Phleum pratense*), which is the most common cause of sensitization in the region; the most common mite (*Dermatophagoides pteronyssinus*); and the allergen of cats (*Felis domesticus*), which is the most common pet in Türkiye (ALK-Abello' A/S, Horsholm, Denmark). The test was read after 15 minutes, and positive results were traced on a clear tape. A mean wheal diameter of 3 mm or more compared to the negative control was considered positive. Atopy was defined as having at least 1 positive sensitivity to one or more common aeroallergens.

Main Points

- Studies in the field of occupational health have mostly examined work-related exposure factors. However, sensitivity to common aeroallergens might significantly impact one's job comfort.
- The allergens and irritants found in spices and dry herbs have a negative impact on atopic workers in spice shops.
- In allergen-dense work environments, identifying workers sensitive to common aeroallergens and providing protective measures will have a positive impact on work health.

Statistical Analysis

The analysis was conducted using the statistical package the Statistical Package for the Social Sciences 23.0 for Windows (IBM Corp., Armonk, NY, USA). The chi-square test was performed to determine the percentages of participants in the different groups. The univariate logistic regression analysis was used to examine the correlation between the characteristics and symptoms of atopic and non-atopic workers. Considering that age, gender, smoking habits, and the presence of asthma might affect the symptoms, adjusted odds ratios were calculated using multivariable logistic regression analysis. A *P*-value less than .05 was considered statistically significant.

RESULTS

The mean age of the workers was 38.13 years and 14% were women. The mean duration of employment was 10.38 years. Non-smokers accounted for 42.9%, ex-smokers 11.6%, and current smokers 45.5%. There were 5 (4.5%) workers with physician-diagnosed asthma and 6 (5.4%) workers with any physician-diagnosed skin disease. Of these, 4 had rosacea, and 1 of them had psoriasis and alopecia areata. Atopy history in the parents (asthma, allergic rhinitis, or a dermatological disease) was present in 15 (13.4%) of the workers. In addition to the spices and herbs they sell in the shop, 12 (10.7%) workers were selling the herbs they had collected. The runny nose (n = 25, 22.3%) and eye symptoms (n = 22, 19.6%) were the most common work-related symptoms. Work-related skin symptoms and work-related shortness of breath had the same prevalence of 9.8% (n = 11). Of the 112 workers, 19.6% (n = 22) reported work-related coughing. There was no mold or dampness in any of the workplace environments. There were no complaints of noise exposure in the workplace. The detailed distribution of the characteristic features is shown in Table 1. Of the 79 workers who underwent SPT, 14 (18%) tested positive. The overall positive rates for *Phleum pratense, Dermatophagoides pteronyssinus*, and *Felis domesticus* were 13.9% (11), 6.3% (5), and 2.5% (2), respectively.

A univariate logistic regression analysis was performed to assess the risk status of individuals with atopic structures in relation to occupational symptoms. The presence of atopy was associated with work-related eye symptoms (odds ratio (OR): 4.12, 95% CI: 1.17-14.46) and work-related runny nose (OR: 4.85, 95% CI: 1.44-16.32). Simultaneously, workers with atopy were more susceptible to work-related cough (OR: 4.41, 95% CI: 1.30-14.97). There was no statistically significant association observed between atopy and work-related shortness of breath (OR: 2.26, 95% CI: 0.50-10.11). There was no significant association between atopy and work-related skin symptoms (OR: 2.68, 95% CI: 0.58-12.36). When non-smokers were used as the reference group, there was no statistical difference in smoking habits between workers with and without atopy (ex-smokers, OR: 1.38, 95%

Table 1. Characteristics of Participants

(%)	Skin Prick Test Performed	Skin Prick Test Non-Performed	All Participants
	n = 79	n = 33	n = 112
Age (mean ± SD)	40.17 ± 10.57	33.24 ± 10.57	38.13 ± 10.38
BMI (mean ± SD)	26.40 ± 3.85	25.66 ± 4.13	26.16 ± 3.93
Gender (female)	13 (16.4)	3 (9.0)	16 (14.3)
Smoking habits			
Nonsmoker	32 (40.5)	16 (48.5)	48 (42.9)
Ex-smoker	8 (10.1)	5 (15.2)	13 (11.6)
Current smoker	39 (49.4)	12 (36.4)	51 (45.5)
Physician-diagnosed asthma	4 (5.0)	1(3.0)	5 (4.5)
Physician-diagnosed skin disease	6 (7.5)	-	6 (5.4)
Atopy history in the parents	9 (11.3)	6 (18.1)	15 (13.4)
Working years in a spice shop (mean ± SD)	11.72 ± 7.55	7.15 ± 4.79	10.38 ± 7.15
Symptoms in the workplace			
Work-related eye symptoms	16 (20.2)	6 (18.1)	22 (19.6)
Work-related runny nose	22 (27.8)	3 (9.0)	25 (22.3)
Work-related skin symptoms	9 (11.3)	2 (6.0)	11 (9.8)
Work-related shortness of breath	10 (12.7)	1 (3.0)	11 (9.8)
Work-related cough	19 (24.0)	3 (9.0)	22 (19.6)
Worker who collects some medicinal herbs from the field	8 (10.1)	4 (12.1)	12 (10.7)

CI: 0.12-15.36; current smokers, OR: 3.33, 95% CI: 0.83-13.37). Atopy did not differ significantly by gender (OR: 2.48, 95% CI: 0.64-9.66) and was not different among those who collected plants (OR: 0.63, 95% CI: 0.07-5.63). The mean duration of employment in a spice shop was shorter for participants with atopy (9.09 years) than for those without atopy (12.29 years), although the difference was not statistically significant (OR: 0.93, 95% CI: 0.85-1.02). Table 2 provides comprehensive comparisons between workers with and without atopy.

Table 2. Comparison of Atopic and Non-Atopic Groups in Spice Shop Workers

n = 79 (%)	Non-Atopic Group n = 65 (82)	Atopic Group n = 14 (18)	Odds Ratio (95% CI)	*P*
Gender (female)	9 (13.8)	4 (28.6)	2.48 (0.64-9.66)	.23
Smoking habits				
Ex-smoker	7 (10.8)	1 (7.1)	1.38 (0.12-15.36)	.79
Current smoker	29 (44.6)	10 (71.4)	3.33 (0.83-13.37)	.08
Working years in a spice shop (mean ± SD)	12.29 ± 7.87	9.07 ± 5.29	0.93 (0.85-1.02)	.15[δ]
Symptoms in the workplace				
Work-related eye symptoms	10 (15.4)	6 (42.9)	4.12 (1.17-14.46)	**.03***
Work-related runny nose	14 (21.5)	8 (57.1)	4.85 (1.44-16.32)	**.01***
Work-related skin symptoms	6 (9.2)	3 (21.4)	2.68 (0.58-12.36)	.19
Work-related shortness of breath	7 (10.8)	3 (21.4)	2.26 (0.50-10.11)	.28
Work-related cough	12 (18.5)	7 (50.0)	4.41 (1.30-14.97)	**.02***
Worker who collects some medicinal herbs from the field	7 (10.8)	1 (7.1)	0.63 (0.07-5.63)	.98

Atopy was defined as a positive skin prick test for common inhalant allergens.
Odds ratio implies the probability of the first column for atopic workers.
[δ]Odds ratio implies the probability of the atopy.
**P*-value <.05 significant.

Table 3. Association of Symptoms and Atopy by Multivariate Analysis

	Odds Ratio (95% CI)*
Work-related eye symptoms	4.48 (1.18-16.96)
Work-related runny nose	4.53 (1.29-15.90)
Work-related cough	5.39 (1.09-26.77)

Odds ratio implies the probability of the symptoms.
Atopy was defined as a positive skin prick test for common inhalant allergens.
*Adjusted by age, gender, smoking, and asthma.

Significant symptoms were adjusted for confounders using multivariable logistic regression. The presence of asthma and smoking were important confounders for symptoms. While a positive trend was observed for work-related cough (OR 5.39, 95% CI 1.09-26.77), work-related eye symptoms (OR 4.48, 95% CI 1.18-16.96), and runny nose (OR 4.53, 95% CI 1.29-15.90) exhibited almost similar rates (Table 3).

DISCUSSION

Sensitivity to aeroallergens refers to a person's tendency to have a hypersensitive reaction to certain compounds present in the surrounding air. We conducted a study to examine the impact of allergenic plant particles on workers who are susceptible to common aeroallergens in their work environment. We found that atopic workers are predisposed to work-related nose, cough, and eye complaints. We did not find a relationship between work-related shortness of breath and atopy. The prevalence of atopy was 18% and this was found to be 8% lower than that in a study (26%) conducted in the different regions of Türkiye.[10] The reason for this is that workers with atopy may have quit their jobs as a result of the "healthy worker effect." We hypothesize that workers with atopy, in particular, may be forced to quit their jobs due to complaints of work-related shortness of breath. Workers may have ignored cough, nose, and eye symptoms. The present study was cross-sectional, and only those employed at the time of the study were included. This phenomenon can be further investigated with a larger study population, including those who have left work. The majority of studies conducted in the spice industry have focused on investigating the sensitization effects of only 1 or 2 spice kinds.[5,11,12,13] In addition to aeroallergens, we considered using spices and dried herbs for skin testing in our study. Compared to spice factories, our study population has been exposed to a much wider variety of spices and herbs. The type and number of herbs and spices available differ depending on the geographical area. In Türkiye, a spice shop typically offers an average of 284 plant products.[14] However, the dominant spice or herb in each shop may be different. Therefore, it was not feasible to do prick testing using a particular spice, as has been done in other studies.[5,11,12,13] A study conducted on farmers in Denmark examined the relationship between sensitivity to common aeroallergens and their occupations. Farm environments are known for high levels of exposure to a wide range of antigenic and potentially allergenic organic dusts of plant origin. The risk of sensitization to common aeroallergens and some respiratory complaints, such as wheezing, was found to be lower in farmers.[15] Similar to our study, in addition to the healthy worker effect, respiratory symptoms in particular may contribute to a lower risk of atopic sensitization to common aeroallergens. However, we believe that a potential cross-reactivity may have affected work-related symptoms. In another study conducted on saffron workers, significant cross-reactivity was reported between saffron and 3 pollens commonly found in the area. Exploring biologic cross-reactions was not the primary objective of this study. However, both the modulation against common aeroallergens and the response against occupational agents occur in the respiratory mucosa. Our investigation revealed that the fact that workers with atopy were especially prone to eye, nose, and cough complaints suggested that there might be a mucosal interaction. In the research involving 3 spice mill workers, it was observed that participants who were exposed to high levels of spice dust developed IgE-mediated responses to multiple spices. Atopy is defined as a reaction to common allergens, which may pose a risk for work-related symptoms, supporting our hypothesis.[16]

Given that spices and dried herbs have bioactive contents that can cause irritant and immunological effects, the frequent exposure to these substances can constitute a significant occupational health issue for workers in spice shops. In our study, the prevalence of shortness of breath and coughing was 9.8% and 19.6%, respectively. A survey conducted on cinnamon growers in Sri Lanka revealed that 37.5% reported experiencing cough, 22.5% reported asthma, and 22.5% reported eye issues.[17] Nasal and bronchial symptoms were reported in 16% and 6% of saffron workers, respectively.[12] In another study of female workers exposed to organic dust in food processing industries, the prevalence of all acute and chronic respiratory symptoms was found to be significantly higher among consistently exposed workers compared to control workers. The most common respiratory symptom was cough (58.7%), and the most common chronic respiratory complaint was chronic cough (40%).[18] Occupational rhinitis prevalence is reported to be 2%-87% in workplaces exposed to high molecular weight agents such as spices.[19] In a previous study, cases of occupational rhinoconjunctivitis had been reported in spice workers handling onion and garlic powders.[20]

The study found that 22% of participants experienced work-related runny nose symptoms, while 19% experienced work-related eye problems. In another study conducted on spice factory workers, 43% of them experienced oculonasal symptoms as a result of inhaling spice powder. Additionally, 11% reported wheezing in the last year, while 10% reported waking up with shortness of breath (11). In the present study, work-related skin symptoms were reported by 5.4% of participants. The skin diseases that the participants had were not IgE-mediated. Interestingly, the prevalence of rosacea among workers was 3.5% (4 patients). Among cinnamon workers in Sri Lanka, 50% had skin irritation, 37.5% hair loss, and 12.5% rash.[17] Among buckwheat workers, 18% had skin symptoms, and among saffron workers, 8% had cutaneous pruritus.[21,12] The other 2 participants had alopecia areata. Protective equipment was hardly utilized by the spice shop staff due to their focus on sales and aesthetic considerations.

In addition, the levels of airborne dust in spice shops are consistently lower compared to those found in spice manufacturers. Therefore, we believe that the prevalence of work-related symptoms is lower in spice factories. Simultaneously, there is no legal requirement for dust quantification in these shops in our country, and the precise quantity of dust in the environment is not known.

The bias may be that employees with allergic symptoms are more willing to participate in the SPT. Another bias that occurs is the tendency to hire and retain relatively healthy individuals. Individuals with atopy generally avoid working in spice shops due to the presence of irritants and dust. In conclusion, spice shop workers are at risk for respiratory and eye symptoms, although comparatively lower than other spice industries. Having an atopic constitution is a risk factor for work-related symptoms. Ensuring occupational health and safety measures is important for all employees. In addition, employees with atopic constitution need more specific protection in allergen-dense work environments.

Ethics Committee Approval: This study was approved by the Ethics Committee of Hacettepe University (approval number: 1609\2021; date: September 7, 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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Original Article

Population-Based Analysis of Local Therapies for Large (>7 cm) Non-Small Cell Lung Cancer Tumors

Deven C. Patel[1,2], Hao He[1], Douglas Z. Liou[1], Paul J. Speicher[3], Mark F. Berry[1]

[1]Department of Cardiothoracic Surgery, Stanford University, Palo Alto, CA, USA
[2]Division of Thoracic Surgery, Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, MD, USA
[3]Department of Cardiothoracic Surgery, University of Alabama at Birmingham School of Medicine, Huntsville, AL, USA

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Abstract

OBJECTIVE: This study evaluated the impact of local treatment modalities in the management of large non-small cell lung cancer (NSCLC) tumors using a nationwide population-based dataset.

MATERIAL AND METHODS: Patients with NSCLC tumors >7 cm that were cN0-1M0 in the Surveillance, Epidemiology, and End Results (SEER) registry from 2010 to 2015 were stratified by local management strategy (surgery, radiation therapy, no local treatment) and evaluated using Kaplan–Meier survival analyses, Cox proportional-hazard methods, and propensity-matched analysis.

RESULTS: A total of 3156 patients were identified, of which 1580 (50.1%) underwent surgical resection, 920 (29.2%) received radiation only, 655 (20.7%) received no local treatment. Overall, the 5-year survival of patients undergoing surgical resection was 40.7%, compared to 14.7% and 5.3% for the radiation only and no local treatment groups, respectively ($P < .001$). Surgery with or without radiation continued to have an independent association with improved survival in multivariable analysis (HR 0.23, $P < .0001$). Other factors associated with improved survival included younger age, negative nodal disease, and chemotherapy use. In propensity-matched sub-analyses, 5-year survival remained significantly better after surgery alone compared to radiation alone (38.5% vs. 13.6%, $P < .001$), while survival after radiation alone was better than no local treatment, though both were largely poor (12.4% vs. 7.5%, $P < .001$).

CONCLUSIONS: Survival of patients with large NSCLC managed non-surgically is very poor. Despite the significant long-term survival benefit with surgical intervention, nearly half of the study cohort did not undergo surgery. Patients and clinicians can use these results to estimate specific potential benefits when considering possible treatment strategies for large NSCLC tumors.

KEYWORDS: Non-small cell lung cancer, large tumors, surgery, radiation therapy, survival, comparative effectiveness

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the world, with nearly 1.76 million deaths annually.[1] Tumor size is an independent prognostic factor, and larger tumors are associated with worse survival.[2,3] Accordingly, each new iteration of the American Joint Committee on Cancer (AJCC) and International Association for the Study of Lung Cancer (IASLC) staging systems has placed a greater significance on size, specifically tumors larger than 7 cm.[4,5] The T status for a tumor larger than 7 cm was classified as T2 in the sixth edition, became T3 in the seventh edition, and is now T4 in the eighth edition.

Despite the increased recognition of the importance of tumor size on outcomes, objective data regarding the optimal management of large non-small cell lung cancer (NSCLC) tumors are generally lacking. Surgical resection and external beam radiation therapy are local treatment options, and generally combined with systemic chemotherapy, and some occasions used together as a trimodal treatment strategy. Although the risks of lung cancer resection have been well categorized and are generally well understood, the benefits of surgery relative to alternative treatments are not as well quantified, especially when considering that data from clinical trials or specialized centers may not be generalizable to all centers that treat lung cancer. Large tumors may require complex or extensive surgical resection, which clinicians or patients may avoid because of the associated perioperative risks.[6] This study was undertaken to examine treatment patterns in a nationwide population-based dataset with the primary goal of evaluating the impact of local management strategies on long-term survival for patients with NSCLC tumors >7 cm in size, and should provide objective data that can be used in the risk/benefit process of local treatment strategies, specifically surgery vs. definitive radiation when these patients are evaluated in the multidisciplinary setting.

MATERIAL AND METHODS

We conducted this retrospective secondary analysis using the Surveillance, Epidemiology, and End Results (SEER) database. Supported by the National Cancer Institute, the SEER program collects and publishes cancer incidence and survival data

Corresponding author: Mark F. Berry, e-mail: berry037@stanford.edu

from population-based cancer registries covering approximately 35% of the United States population.[7] Patients were identified using ICD-O-3 location codes for lung cancer (C34.0-C34.9) and appropriate SEER histology codes ranging from 8012 to 8576 for all possible NSCLC histologies.

Patients included in this study were those 18 years or older with NSCLC primary tumors of at least 7 cm diagnosed between 2010 and 2015. During the study period, the AJCC Cancer Staging Manual, 7th edition, classified tumors greater than 7 cm as T3. Accordingly, inclusion criteria for the current study consisted of patients with T3 tumors and size greater than 7 cm. Note, the eightedition AJCC Staging Manual, updated in 2016, has classified tumors greater than 7 cm as T4. Only patients with N0-1 disease were kept for analysis because surgery may not have a role in the setting of advanced nodal disease.[8] Of note, SEER reports TNM data using Collaborative Staging (CSv2), utilizing a combination of clinical and pathologic data to provide standardized staging and tumor size information across all SEER participants.[9] Patient age, sex, race, ethnicity, marital status, insurance status, and survival follow-up time were also extracted. Patients living longer than 7 years were right-censored. Survival data are recorded from the time of cancer diagnosis.

Our primary focus was to examine the impact of local therapies on survival for potentially resectable large NSCLCs (≥7 cm), with the caveat that chemotherapy is likely to be employed irrespective of the local treatment strategy utilized. Patients were stratified by local treatment approach (surgery with or without radiation, radiation without surgery, or no local treatment). In order to quantify factors that may have been important in the selection of local therapy, multivariable logistic regression was used to estimate predictors of surgical intervention in patients. The covariates entered in this model were those considered significant on univariate analyses, our clinical experience, and the existing literature. Unadjusted survival analyses, stratified by treatment approach, were performed using the Kaplan–Meier method. A multivariable Cox proportional hazards model was created to estimate the independent effect of local treatment modality on survival adjusted for other important patient and disease-related factors. Covariates in the Cox models included local therapy modality as well as age sex, race, marital status, insurance, N stage, tumor size (treated as continuous variable), histology, and receipt of chemotherapy.

Several additional analyses were performed to quantify the treatment and outcomes of patients with large tumors. Propensity-matched analysis was performed due to the likelihood that some patients selected for more aggressive therapy had better outcomes not only because of the therapy but also due to other unmeasured factors, such as better pulmonary function, higher functional status, and less comorbid conditions. Two propensity-matched sub-analyses were performed: comparing patients treated with surgical resection alone vs. radiation therapy alone, as well as radiation therapy alone vs. no local treatment. Propensity scores were calculated using a logistic regression model in which age, patient sex, marital status, insurance status, N stage, tumor size, and receipt of chemotherapy were included as predictors. Propensity scores between the 2 groups were matched 1:1 through a Greedy algorithm with a caliper of 0.2 standard deviations. After matching, Kaplan–Meier analysis was used to compare long-term survival. To better understand which patients may be more likely to benefit from surgical resection, a Cox proportional hazards model was created to estimate predictors of survival in the subset of patients who underwent surgery, utilizing the same covariates as above, as well as the usage of induction or adjuvant radiation therapy. Given the limited granularity regarding patient comorbidities and functional status in the SEER database, a survival sub-analysis using patients younger than 60 years, married, and insured was created to include patients more likely to tolerate aggressive cancer treatment based on age and socioeconomic support.

Main Points

- Over the past several years, there has been increased recognition for the importance of non-small cell lung cancer (NSCLC) tumor size on outcomes. Accordingly, the American Joint Committee on Cancer (AJCC) has placed greater weight on tumors larger than 7 cm; however, despite a greater appreciation for tumor size on outcomes, the optimal local treatment strategy for these large tumors is generally lacking.
- In this national analysis, we explore the current treatment trends and long-term outcomes for patients with NSCLC tumors >7 cm. This study demonstrates grim survival for patients with large NSCLC tumors managed non-surgically.
- Despite proven benefits, nearly half of the study cohort opted against surgery, influenced by factors like age, race, and insurance status.
- Treatment must be carefully considered for all patients based on their individual characteristics, but higher operative risks may be acceptable in the management of very large NSCLC tumors considering the potential survival benefit of surgery over other treatment options.

Statistical Analysis

Missing data were rare and handled with case-wise deletion. Univariate comparisons were conducted using Pearson's chi-square tests or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. A *P*-value < .05 was used to indicate statistical significance for all comparisons and analyses. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc. NC, USA).

Ethics Committee Approval

This study was considered exempt by the Institutional Review Board at Stanford University.

RESULTS

A total of 3156 patients diagnosed with NSCLC tumors of at least 7 cm between 2010 and 2015 were identified for inclusion in this study (Supplementary Figure 1). Of these, 1580 (50.1%) underwent surgical resection with or without radiation, 920 (29.2%) received radiation therapy only, and 655 (20.7%) received no local treatment. The baseline demographic characteristics of these patients are shown in Table 1,

Table 1. Baseline Patient Characteristics of the Entire Cohort and Stratified by Local Management Strategy

Patient Characteristic	Total (n = 3156)	Surgical Resection ± Radiation (n = 1580)	Radiation Only (n = 920)	No Local Treatment, (n = 655)	*P*
Age (years)					<.001
18-50	147	104 (6.6%)	31 (3.4%)	12 (1.8%)	
51-64	963	540 (34.2%)	265 (28.8%)	158 (24.1%)	
65-74	1088	563 (35.6%)	314 (34.1%)	211 (32.2%)	
75+	958	374 (23.7%)	310 (33.7%)	274 (41.8%)	
Sex					.116
Male	1972	987 (62.4%)	595 (64.7%)	390 (59.5%)	
Female	1184	594 (37.6%)	325 (35.3%)	265 (40.5%)	
Race					<.001
White	2540	1305 (82.5%)	710 (77.2%)	526 (80.3%)	
Black	384	156 (9.9%)	148 (16.1%)	80 (12.2%)	
Others	231	120 (7.6%)	62 (6.7%)	49 (7.5%)	
Marital status					<.001
Single	1357	581 (36.8%)	420 (45.7%)	356 (54.4%)	
Married	1659	936 (59.2%)	455 (49.5%)	268 (40.9%)	
Unknown	140	64 (4.1%)	45 (4.9%)	31 (4.7%)	
Insurance					.074
Uninsured	91	37 (2.3%)	33 (3.6%)	21 (3.2%)	
Insured	3024	1530 (96.8%)	873 (94.9%)	621 (94.8%)	
Unknown	41	14 (0.9%)	14 (1.5%)	13 (2.0%)	
Tumor size (>7 cm)					
Median (IQR)	8.5	8.5 (7.5, 10)	8.3 (7.6, 9.6)	8.4 (7.6, 10)	.008
Nodal stage					.001
N0	2297	1128 (72.3%)	657 (71.4%)	512 (79.1%)	
N1	830	432 (27.7%)	263 (28.6%)	135 (20.9%)	
Chemotherapy	1730	886 (56.0%)	667 (72.5%)	177 (27.0%)	<.001
Extent of surgical resection					NA
Sublobar	–	41 (2.6%)	–	–	
Lobectomy	–	1264 (80.6%)	–	–	
Pneumonectomy	–	276 (17.5%)	–	–	
Histology					<.001
Adenocarcinoma	1229	811 (51.3%)	228 (24.8%)	190 (29.0%)	
Squamous cell carcinoma	1362	566 (35.8%)	480 (52.2%)	316 (48.2%)	
Large cell neuroendocrine carcinoma	85	58 (3.7%)	17 (1.9%)	10 (1.5%)	
Adenosquamous carcinoma	55	38 (2.4%)	13 (1.4%)	4 (0.6%)	
Other non-small cell histology	425	108 (6.8%)	182 (19.8%)	135 (20.6%)	
Lymph node examined					<.001
No	1441	48 (3.0%)	786 (85.4%)	607 (92.7%)	
Yes	1702	1532 (96.9%)	125 (13.6%)	45 (6.9%)	
Unknown/NA	13	1 (0.1%)	9 (1.0%)	3 (0.5%)	
Lymph node positive					<.001
Negative	1274	1129 (71.4%)	108 (11.7%)	37 (5.7%)	
Positive	426	401 (25.5%)	17 (1.9%)	8 (1.2%)	
Not-examined/unknown/NA	1456	51 (3.2%)	795 (86.4%)	610 (93.1%)	

both for the entire cohort and stratified by management strategy. The median tumor size for the study cohort was 8.5 cm. The majority of patients across groups were male and white, with node-negative disease. Older patients were more likely to receive no local treatment for their large tumors. The majority of patients undergoing a local treatment strategy also had chemotherapy, whereas only a minority of patients who received no local treatment underwent systemic chemotherapy (surgery: 56.0% vs. radiation: 72.5% vs. no local treatment: 27.0%, $P < .001$). Among patients undergoing surgery, the vast majority underwent lobectomy (80.6%). Increasing age, Black race, squamous cell carcinoma histology, and chemotherapy use were predictors of non-surgical treatment in a multivariable logistic regression model (Figure 1). Patient sex and absolute tumor size did not have a significant association with the use of surgery, but married and insured patients were more likely to have surgery. Among patients receiving both surgery and radiation therapy, the majority of surgical patients received radiation in the postoperative setting (Supplementary Table 4).

Kaplan–Meier survival curves, stratified by treatment approach, are shown in Figure 2. The overall 5-year survival of patients undergoing surgery with or without radiation therapy was 40.7%, compared to 14.7% for the radiation therapy group, and 5.3% for the no local treatment group ($P < .001$). The results of the Cox proportional hazards survival model, adjusted for treatment strategy and available baseline and tumor characteristics, are shown in Table 2. Overall, local treatment was associated with improved survival compared to patients receiving no local treatment. However, surgery with or without radiation had the largest association with survival (HR 0.24, $P < .001$). Increasing patient age and N1 disease were associated with worse survival. Conversely, female

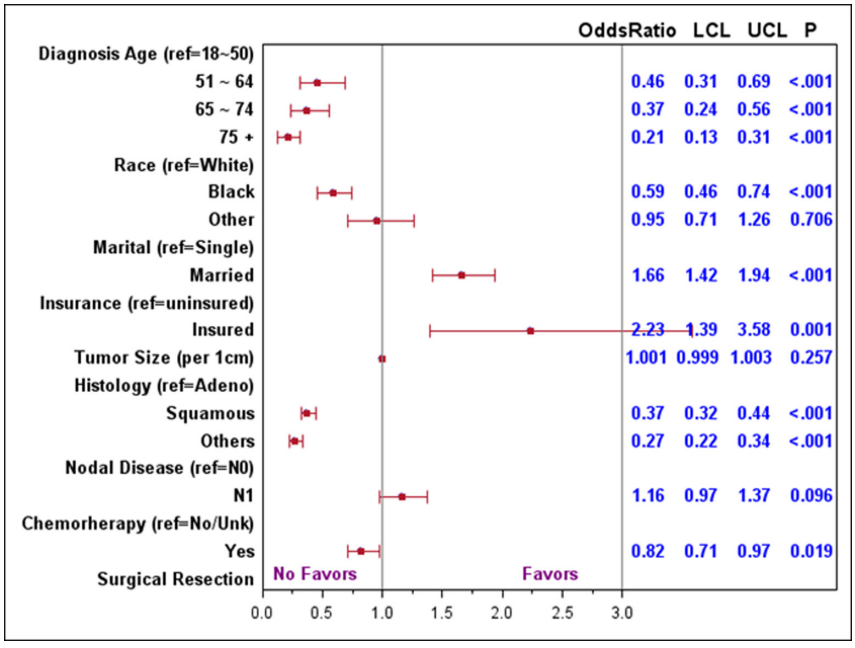

Figure 1. Predictors of surgical intervention among patients with large (at least 7 cm) NSCLC tumors.

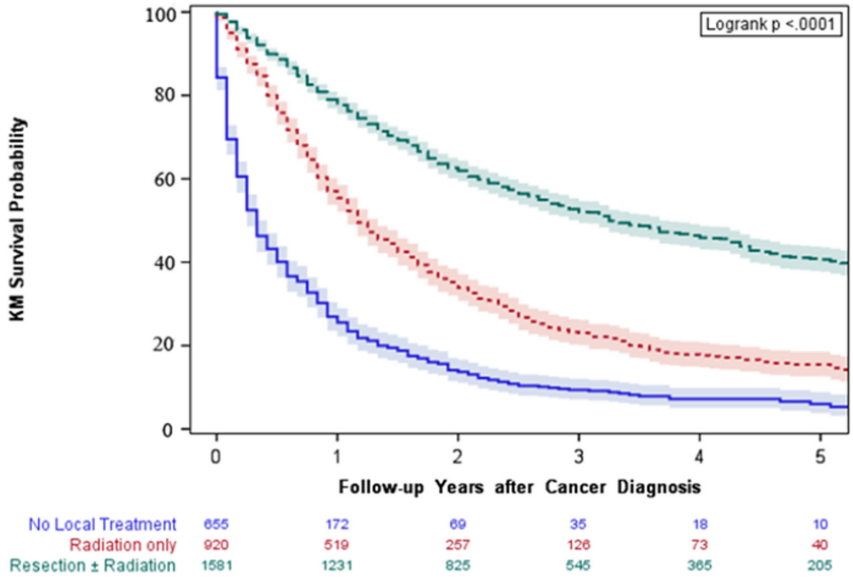

Figure 2. Kaplan–Meier survival estimates for patients with large NSCLC, stratified by treatment approach.

Table 2. Results of Cox Proportional Hazard Modeling Showing Adjusted Risk of Death in the Entire Cohort of Patients with Large NSCLC Tumors

Predictors	Hazard Ratio	95% CI		*P*
		Lower	Upper	
Local treatment approach				
No local treatment	*Ref*			
Surgical resection ± radiation	0.24	0.21	0.27	<.001
Radiation only	0.52	0.46	0.59	<.001
Age (yrs)				
18-50	Ref			
51-64	1.36	1.04	1.77	.023
65-74	1.58	1.21	2.06	.001
75+	1.82	1.39	2.38	<.001
Sex				
Male	Ref			
Female	0.84	0.77	0.92	<.001
Race				
White	Ref			
Black	0.91	0.80	1.06	.240
Others	0.74	0.62	0.89	.001
Marital status				
Single	Ref			
Married	0.91	0.83	0.99	.043
Insurance				
Uninsured	Ref			
Insured	1.06	0.80	1.41	.691
Tumor size (>7 cm)				
Per 1 cm increase	1.00	0.99	1.00	.482
Nodal stage				
N0	Ref			
N1	1.25	1.13	1.38	<.001
Histology				
Adenocarcinoma	Ref			
Squamous cell carcinoma	1.42	1.28	1.57	<.001
Others	1.39	1.23	1.58	<.001
Chemotherapy				
No/unknown	Ref			
Yes	0.55	0.50	0.61	<.001

sex, marriage, and receipt of chemotherapy all predicted improved survival. As shown in Supplementary Table 2, short-term survival rates between surgery ± radiation therapy were comparable to the radiation-only group (1 month: 97.6% vs. 95.0%, respectively).

The results of the propensity-matched sub-analysis comparing surgical resection alone vs. radiation therapy alone were consistent with the results of the main analysis. In a total of 567 matched pairs, there were no differences in patient characteristics (Supplementary Table 1). Patients who underwent surgery alone had significantly better 5-year survival than matched patients who had radiation therapy alone (38.5% vs. 13.6%, $P < .001$) (Figure 3). In the propensity-matched analysis of the subset of patients not undergoing surgery, patients undergoing radiation therapy had a substantially higher survival estimate at 1 year compared to matched patients undergoing no local treatment (51.3% vs. 33.4%). At 5 years, patients treated with radiation had a statistically significantly improvement in overall survival compared to those not undergoing treatment, though the prognosis of both groups were generally poor (12.4% vs. 7.5%, $P < .001$) (Figure 4). In a sub-analysis using patients younger than 60 years, married, and insured, short-term survival between radiation only and surgery ± radiation groups was very similar (Supplementary Table 3); however, surgery continued to demonstrate a significant survival benefit in long-term analysis (Supplementary Figure 2).

The overall 30-day and 90-day mortality after surgery was 0.51% and 4.31%, respectively. Parsed by the extent of resection, the 30-day/90-day mortality rates were as follows: sublobar resection: 0.00%/9.76%, lobar resection: 0.40%/2.62%, and pneumonectomy: 1.09%/11.31%. Table 3 demonstrates the Cox proportional hazards model using only patients who had undergone surgical resection. Surgical patients who received radiation therapy demonstrated worse survival (HR 1.34, $P = .002$). Female sex, receipt of chemotherapy, and patients who were married were associated with a survival benefit. Increasing age and N1 disease predicted worse survival. Although the Cox model showed a qualitatively, though not statistically significant difference in survival between lobar resections and pneumonectomy, survival between these extents of resections were compared and shown to be slightly different (5-year OS 41.0% for lobectomy vs. 39.1% for pneumonectomy, $P = .004$) (Supplementary Figure 3).

DISCUSSION

Large NSCLC tumors pose a challenging clinical dilemma that requires thoughtful consideration into the variety of treatment strategies. In this study, we sought to investigate whether an aggressive localized treatment strategy involving surgery would confer a long-term survival benefit that would potentially justify the perioperative risks. Using the nationwide SEER registry, we demonstrate that patients with potentially resectable NSCLC of at least 7 cm in size realize a substantial long-term survival benefit following surgical resection compared with non-operative locoregional therapy. Patients who underwent surgery were generally younger, insured, married, and less likely to have undergone systemic chemotherapy. Independent benefits to surgery were found in both multivariable survival analysis and propensity-matched analysis. Further, in a sub-analysis examining all surgical patients, the addition of radiation therapy was associated with worse survival, while chemotherapy demonstrated a survival advantage. While our results also demonstrate that radiation therapy alone confers a marginal survival benefit compared to no local treatment, outcomes when surgery is not utilized are poor.

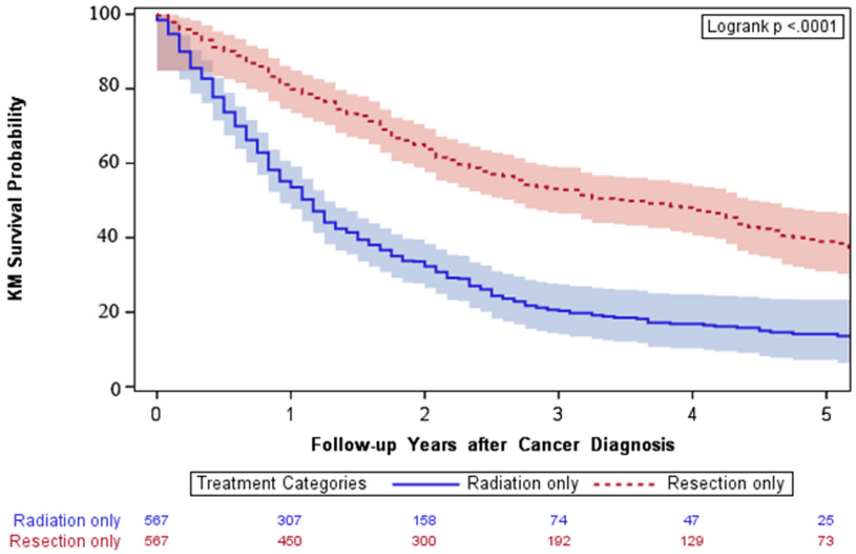

Figure 3. Kaplan–Meier survival estimates for propensity matched patients undergoing surgical resection alone vs. radiation alone for large NSCLC tumors.

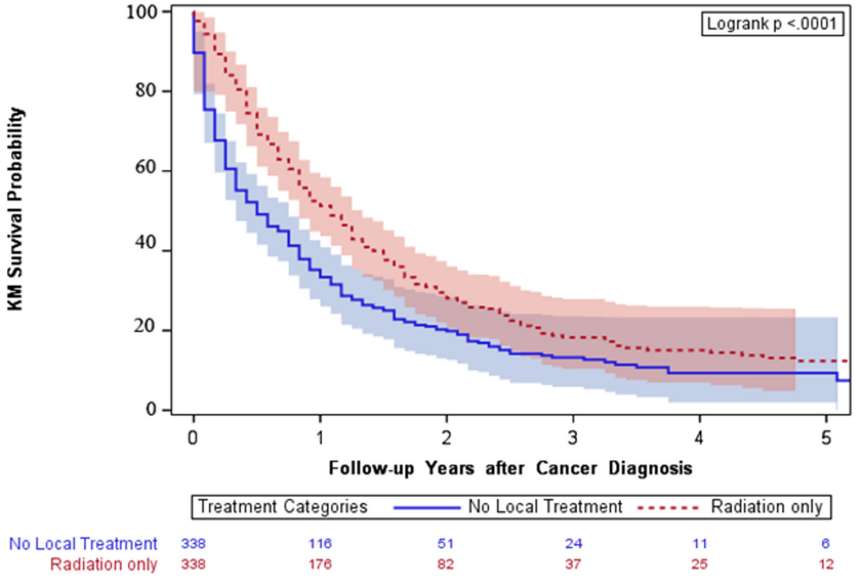

Figure 4. Kaplan–Meier survival estimates for propensity matched patients undergoing radiation alone vs. no local treatment for large NSCLC.

Despite the significant long-term survival benefit of surgical intervention, nearly 50% of the study cohort did not undergo surgery for tumors ≥7 cm in this population-based analysis. The strongest predictor for not receiving surgery was increasing age, particularly patients older than 75 years. Consistent with the existing literature in health disparities, patients of black race and those who were uninsured were less likely to undergo surgery in the current study.[10,11] For these reasons, we speculate that elderly and other patients with poor access to care or limited social support were not considered surgical candidates and possibly did not even receive a surgical evaluation. Although deferring surgery may have been appropriate in many patients, the very poor outcomes seen when surgery is not utilized suggest that all patients should at least undergo careful consideration of surgery. Patients who are turned down for surgery may benefit from a second opinion from a high-volume or more specialized center, where the risks of surgery may be less, and should at the least be discussed at a multi-disciplinary conference where both the relative risks and potential benefits are carefully considered. This current study provides quantitative data from a large cohort of patients on the benefits and alternative management options for the informed consent process prior to surgery.

The poor outcomes following non-surgical therapy, as demonstrated in this study, can likely be attributed to a number of factors related to tumor size. Generally, as tumor volume increases in many cancers, neoplastic cells outgrow their blood supply, and the subsequent hypoxia can have substantial undesirable effects on radiation penetration.[12,13] Radiation therapy alone can also lead to substantial morbidity. Effective therapy resulting in substantial tumor death can lead to a large necrotic mass in the chest cavity, the sequelae of which include abscess and infection, bronchopulmonary fistulae, and impaired pulmonary mechanics. While surgical resection also carries substantial morbidity when managing these large tumors, the short-term risks associated with non-operative therapy cannot be discounted when determining optimal

Table 3. Results of Cox Proportional Hazard Modeling Showing Adjusted Risk of Death in the Subset of Patients Who Had Surgical Resection of Large NSCLC Tumors

Predictors	Hazard Ratio	95% CI		*P*
		Lower	Upper	
Local treatment approach				
Surgical resection without radiation	*Ref*			
Surgical resection with radiation	1.34	1.11	1.61	.002
Age (yrs)				
18-40	*Ref*			
41-64	1.36	0.95	1.94	.093
65-74	1.76	1.23	2.52	.002
75+	2.08	1.43	3.01	<.001
Sex				
Male	*Ref*			
Female	0.78	0.67	0.91	.001
Race				
White	*Ref*			
Black	1.10	0.87	1.39	.422
Others	0.73	0.54	0.99	.044
Marital status				
Single	*Ref*			
Married	0.97	0.83	1.12	.658
Insurance				
Uninsured	*Ref*			
Insured	1.20	0.71	2.04	.490
Tumor size (>7 cm)				
Per 1 cm increase	1.00	0.99	1.00	.589
Nodal Stage				
N0	*Ref*			
N1	1.48	1.26	1.74	<.001
Histology				
Adenocarcinoma	*Ref*			
Squamous cell carcinoma	1.21	1.03	1.41	.019
Others	1.32	1.06	1.63	.013
Extent of surgical resection				
Sublobar	*Ref*			
Lobectomy	0.85	0.56	1.30	.460
Pneumonectomy	1.05	0.67	1.66	.820
Chemotherapy				
No/unknown	*Ref*			
Yes	0.61	0.52	0.72	<.001

management for patients. In this study, short-term survival of radiation therapy alone demonstrated slightly lower survival than surgery ± radiation therapy, suggesting potential selection bias, possibly secondary to pre-existing medical comorbidities and functional status—which cannot be fully captured by the SEER database. However, the short-term mortality for both local treatment strategies were overall very low for the first few months. Additionally, in a sub-analysis using a presumably healthier patient subset with socioeconomic support, surgery continued to demonstrate a significant long-term survival benefit. Thus, suggesting a patient's general medical conditions and functional status alone are unlikely to explain the observed benefit of surgery. Further, the short-term harm of surgery may be overstated, and morbidity from radiation may be underappreciated.

The importance of tumor size as a prognostic factor for NSCLC is well recognized.[2,3] Indeed, reasonable long-term outcomes after surgery for locally advanced tumors have been demonstrated before, including in studies used to revise T staging definitions.[4] However, objective data that compare treatment options and therefore could guide therapeutic decision are generally limited.[14-16] In a National Cancer Database study evaluating patients with >7 cm, hilar lymph node-positive NSCLC from 1999 to 2005, local therapy in the form of surgery alone demonstrated no significant difference in survival compared to patients receiving definitive chemoradiotherapy.[17] In the aforementioned study, only when chemotherapy was combined with surgery did 5-year overall survival improve compared to non-surgical treatment groups and those receiving no treatment. In the current study, surgical resection was associated with a substantial survival advantage in comparison to other non-surgical treatment strategies, even when adjusting for nodal disease and the use of chemotherapy.

The use of the SEER dataset for this analysis allowed the construction of a large cohort of patients across a wide range of institutions, enabling more generalizable results compared to studies that predominantly involve high-volume or specialized centers, and therefore provide strong data on a relatively uncommon clinical scenario. Nonetheless, this SEER analysis does have limitations, which are lessened but not eliminated by the use of propensity matching. Our results are likely limited by a notable selection bias, as treatment allocation to surgery or radiation therapy, as well as the extent of surgical resection, may be confounded by unmeasured variables including pre-existing medical comorbidities, functional status, and high risk tumor features not captured by the dataset. Although all patients included in this study are potentially resectable based on TNM staging criteria, it is likely that some of the radiation therapy patients were deemed unfit for surgery due to disease that would present a particularly challenging technical resection or invasion of adjacent organs. The results of this study are limited by the lack of granular radiation therapy data and the inability to distinguish between palliative intent and curative intent, which could underestimate the potential curative benefit of radiation. Outside of a clinical trial, delineating the impact of systemic therapy is challenging due to the potential variety of agents, doses, sequence, and number of treatments that can be used, and further compounded by the very limited granularity regarding chemotherapy in the SEER dataset. The absence of resection margin data precludes this study from commenting on the impact of an R1 or R2 resection. Residual disease was likely a major impetus for adjuvant radiation therapy and aligned

with the worse survival seen in this study for patients undergoing surgery and radiation compared to surgery alone. The lack of information on the specific mediastinal staging used to determine the nodal stage precludes us from commenting on this important aspect of the diagnostics used to determine the appropriate treatment strategy. The study period in this study was used to maximize long-term follow up, however, more modern outcomes may have provided a greater understanding of adjuvant strategies and the use of targeted therapies or immunotherapy. Finally, as SEER reports tumor size using best available clinical or pathologic information, the accuracy of the tumor size is expected to be more exact in patients undergoing upfront surgery compared to patients undergoing radiation therapy in which size was based on clinical information.

For patients with potentially resectable NSCLC tumors of 7 cm or greater, long-term outcomes after surgery are considerably better than non-surgical treatment strategies. Although radiation therapy confers marginal survival benefit compared to no local treatment, outcomes remain dismal, particularly when compared to surgical intervention. These results, which quantify the potential benefits of local treatment options, are useful to both patients and clinicians when weighing management options for large cancers. Treatment must be carefully considered for all patients based on their individual characteristics, but higher operative risks may be acceptable in the management of very large NSCLC tumors considering the potential survival benefit of surgery over other treatment options.

Ethics Committee Approval: Ethics Committee/Institutional Review Board of Stanford University exempted this study as SEER data is publicly available and de-identified.

Peer-review: Externally peer-reviewed.

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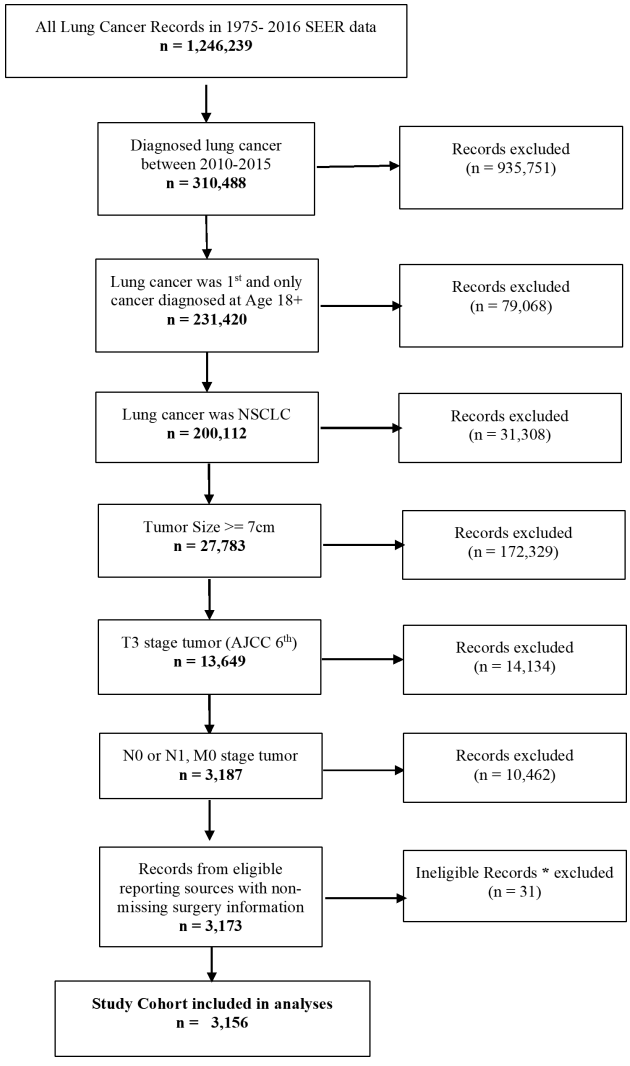
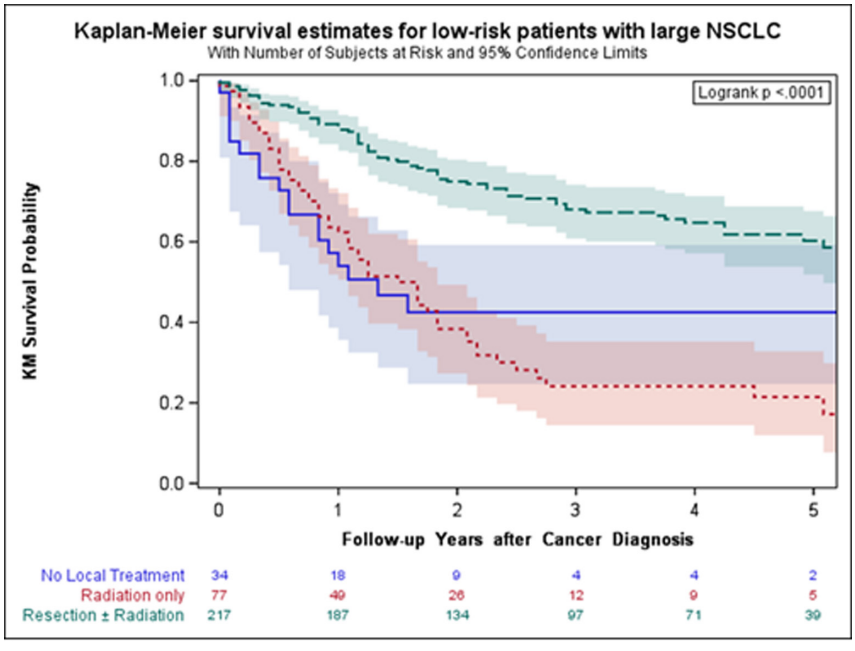
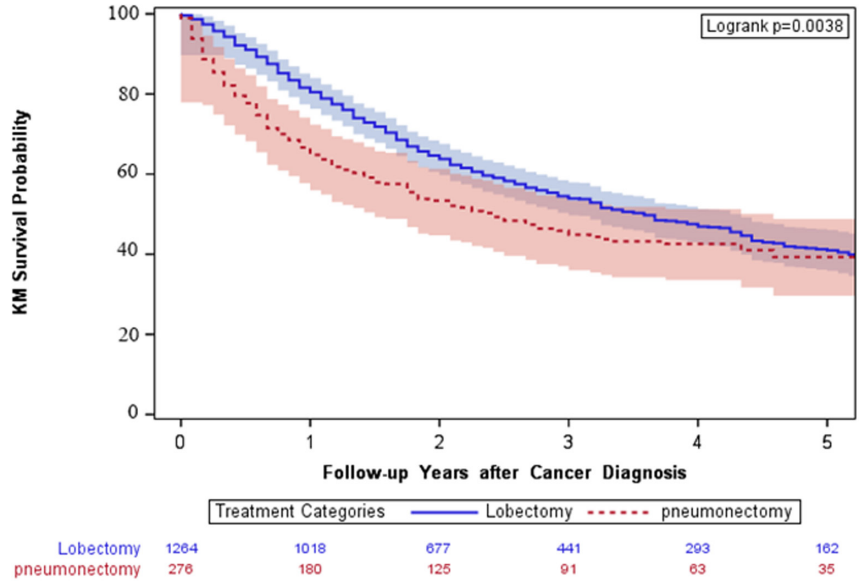


Supplementary Figure 1. Consolidated standards of reporting trails (CONSORT) diagram outlining patient selection. *Ineligible records include following sources: Laboratory Only (hospital-affiliated or independent); Nursing/Convalescent Home/Hospice; Autopsy Only; Death Certificate Only.



Supplementary Figure 2. Kaplan-Meier survival estimates for low-risk subgroup (age < 60, married, and insured), stratified by treatment approach.



Supplementary Figure 3. Kaplan-Meier survival estimates for patients with large NSCLC, stratified by extent of surgical resection, lobectomy versus pneumonectomy.

Supplementary Table 1. Baseline Patient Characteristics of Propensity-score Matched Patients Receiving Surgical Resection only Versus Radiation Therapy Only

Patient characteristic	Surgical resection only (n = 567)	Radiation therapy only (n = 567)	*P*
Age (years)			.563
18-50	25 (4.1%)	24 (4.2%)	
51-64	195 (34.4%)	178 (31.4%)	
65-74	191 (33.7%)	213 (37.6%)	
75+	156 (27.5%)	152 (26.8%)	
Sex			.459
Male	354 (62.4%)	367 (64.7%)	
Female	213 (37.6%)	200 (35.3%)	
Race			.560
White	455 (80.3%)	467 (82.4%)	
Black	64 (11.3%)	61 (10.8%)	
Others	48 (8.5%)	39 (6.9%)	
Marital status			.831
Single	247 (43.6%)	240 (42.3%)	
Married	303 (53.4%)	307 (54.1%)	
Unknown	17 (3.0%)	20 (3.5%)	
Insurance			.561
Uninsured	14 (2.5%)	16 (2.8%)	
Insured	550 (97.0%)	545 (96.1%)	
Unknown	3 (0.5%)	6 (1.1%)	
Tumor Size (>7 cm)			
Median [IQR]	8.2 [7.5, 9.8]	8.4 [7.6, 10.0]	.615
Nodal Stage			.405
N0	383 (67.6%)	397 (70.0%)	
N1	184 (32.5%)	170 (30.0%)	
Chemotherapy	379 (66.8%)	375 (66.1%)	.850

Supplementary Table 2. Short-term Survival Rates for Resection ± Radiation and Radiation Only Groups in the Study Cohort

	Months after Cancer Diagnosis					
Treatment Groups	**1 month**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**
Radiation only	95.0%/46	91.1%/82	87.5%/115	85.7%/141	79.9%/184	75.9%/222
Resection ± Radiation	97.6%/37	95.6%/68	93.7%/98	92.1%/125	89.9%/159	88.5%/179

*Short-term survival rates/cumulative death.

Supplementary Table 3. Sub-analysis, Short-Term Survival Rates for Resection ± Radiation and Radiation only Groups in Low-risk Subgroup (age < 60, insured and Married Patients)

	Months after Cancer Diagnosis					
Treatment Groups	**1 month**	**2 months**	**3 months**	**4 months**	**5 months**	**6 months**
Radiation only	97.4%/2	93.5%/5	89.6%/8	87.0%/10	83.1%/13	77.9%/17
Resection ± Radiation	98.6%/3	97.7%/5	96.3%/8	94.4%/12	94.0%/13	93.5%/14

*Short-term survival rates/cumulative death.

Supplementary Table 4. Radiation Sequence with Surgery

Sequence	**Frequency**	**Percent**
Radiation before surgery	89	2.82
Radiation after surgery	287	9.09
Radiation both before and after surgery	8	0.25
Intraoperative radiation with other radiation given before or after surgery	1	0.03
Surgery before and after radiation	3	0.10
No radiation and/or surgery as defined above	2768	87.71

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Original Article

Impact of Anxiety, Depression, and Coping Strategies on Health-Related Quality of Life in Patients with Cystic Fibrosis

Berrin Ceyhan[1], Zeynep Uslu Suner[2], Derya Kocakaya[1], Şehnaz Olgun Yıldızeli[1], Emel Eryüksel[1]

[1]Department of Pulmonary Medicine and Intensive Care, Marmara University School of Medicine, İstanbul, Türkiye
[2]Department of Pulmonary Medicine, Bahçeşehir University School of Medicine, İstanbul, Türkiye

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Abstract

OBJECTIVE: With the significant increase in the life expectancy of cystic fibrosis (CF) patients, many individuals now reach adulthood and develop specific coping strategies to maintain their physical and mental well-being. This study aims to evaluate coping styles and their relationship with mental health and Health-Related Quality of Life (H-RQoL) in adult CF patients.

MATERIAL AND METHODS: Thirty adult CF patients completed the Hospital Anxiety and Depression Scale to assess anxiety and depression, the Cystic Fibrosis Questionnaire—Revised to evaluate quality of life, and the Brief Coping Orientation to Problems Experienced questionnaire to assess coping strategies.

RESULTS: Twelve individuals (40%) met the diagnostic criteria for being at risk of experiencing anxiety and/or depression. Anxiety risk group exhibited lower life quality scores in the domains of vitality, emotional functioning, and role limitations ($P = .027$, $P = .001$, and $P = .001$, respectively). Patients reporting depressive symptoms had lower scores in emotional functioning and role limitations domains of quality of life ($P = .005$ and $P = .018$, respectively). Multivariate analysis indicated that depression and anxiety scores were significant predictors of emotional quality of life. In terms of coping strategies, "acceptance" was the most commonly preferred, while "substance use" was the least preferred strategy among all participants. Patients at risk of anxiety and/or depression often chose "avoidance" as their coping strategy.

CONCLUSION: Anxiety and depressive symptoms are prevalent and associated with poorer H-RQoL in adult CF patients. These patients preferred to employ giving up strategy when dealing with the disease. Therefore, it is essential to screen adult CF patients for mental health risks and to work on improving their coping strategies.

KEYWORDS: Anxiety, depression, cystic fibrosis, quality of life, coping

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INTRODUCTION

Cystic fibrosis (CF) is a life-limiting genetic disorder. However, advances in medical management and treatment have enabled a growing number of patients to reach adolescence and adulthood.[1] As these individuals attain greater independence from their families, they also face increased stress related to education, employment, independence, travel, fertility, and relationships. Additionally, adults with CF frequently underestimate the severity of their condition, harboring the misconception that they are healthier than they actually are.[2] Therefore, it is necessary to use indicators to follow these patients in addition to physical health parameters. Health-related quality of life (H-RQoL) outcomes serve as a valuable metric for assessing the disease's impact on both physical and psychosocial well-being.[3] To date, the impact of many clinical factors on aspects of H-RQoL has been studied in the CF population such as lung function, sex, body mass index, age, and pulmonary exacerbations that were closely associated with various domains of H-RQoL.[4]

Recently, the psychological well-being of adult CF patients has come into focus because of increased risk for depression and anxiety and their negative effects on H-RQoL in this population.[5-7] A growing body of research has identified positive mental health as a significant positive predictor of H-RQoL domains. However, there is a gap in the literature concerning the relationship between mental health and the quality of life of adult CF patients in our population. Only 1 study has been conducted in our pediatric population, revealing that depression significantly exacerbates the adverse impact of CF on the quality of life.[8]

Coping is generally understood as the comprehensive set of cognitive, emotional, and behavioral strategies employed to manage stress. Factors such as stress level, age, gender, intelligence, and cultural variations in personality types influence the selection of coping styles.[9,10] It has been reported that long-term reliance on negative coping strategies can exacerbate mood disorders and may serve as a precursor to more serious psychological issues. An optimistic, problem-solving approach to coping has been linked to better psychological well-being, while avoidance and passivity are often considered maladaptive approaches, particularly in chronic respiratory conditions.[11] This information highlights the need for a

Corresponding author: Berrin Ceyhan, e-mail: ceyhan.berrin@gmail.com

deeper understanding of the psychological burden associated with coping styles in the CF population. Previous studies in the general population have shown that a depressive mood is often accompanied by a tendency to avoid stressful situations, along with feelings of helplessness and hopelessness.[12] Research by Taylor et al[13] found that active coping strategies were associated with lower levels of depression and anxiety, and better psychological quality of life among CF patients awaiting lung transplants. In the same study, disengagement was linked to higher levels of depression, anxiety, and stress, as well as lower psychological H-RQoL. Staab et al[14] showed that positive social coping was correlated with higher quality of life, while depressive coping was inversely related. A weak correlation was also found between cognitive avoidance and poorer quality of life in CF patients. Importantly, avoidance coping strategies were shown to be associated with higher rates of non-adherence to medical and physical therapy regimens.[15] Therefore, understanding coping strategies is not just a psychological concern, but also a critical factor in the effective medical management of patients with CF. Notably, existing literature has not explored the interplay between coping mechanisms and quality of life among adult patients with CF within our population.

The central research question of this study is to define mental well-being in the adult CF population and to ascertain whether coping strategies differ between patients experiencing anxiety and/or depression and how each of these mental health conditions influences quality of life. Second, we aimed to scrutinize the relationship between quality of life and coping strategies.

MATERIAL AND METHODS

Subjects

This cross-sectional study was conducted at a tertiary CF center, and the study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (number: 09.2016.341, date: May 6, 2016). Primarily, 40 adult patients with a diagnosis of CF were enrolled. Exclusion criteria included pregnancy, a history of pulmonary transplantation, pulmonary infection in the previous month, and any mental condition that could interfere with the testing procedures. One patient with a history of lung transplantation was excluded, 9 patients did not approve participation in the study, and only 30 of 39 patients completed the study. Written and verbal informed consents were obtained from all participants.

Main Points

- This is a study conducted on 30 adult patients with cystic fibrosis to investigate various aspects including coping strategies, quality of life, mental well-being, and their relationships.
- Anxiety and depressive symptoms are prevalent in this population, and these patients have poorer quality of life.
- Acceptance emerged as the most commonly used coping strategy among all participants, and this information highlights that adult individuals with cystic fibrosis actively engage in health-care decision-making. Particularly, the subgroup with depression and/or anxiety prefer avoidance coping strategy to deal with the disease.
- The patients who use more positive coping strategies can face stressful events and have a higher quality of life. This study also identified a positive correlation between the use of seeking help from others and improved emotional well-being. Social functioning positively correlated with the employment of the humor strategy.
- That is why, it is important in clinical practice to screen patients for mental well-being and to encourage the use of adaptive coping strategies to increase patient's satisfaction with life.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item, 4-point Likert scale designed to evaluate the risk of anxiety and depression. It was initially developed to determine the risk of anxiety and depression and has been extensively used and validated in patients with different clinical problems.[16] The Turkish version of the HADS scale has been proven both valid and reliable.[17]

Brief Coping Orientation to Problems Experienced

The Brief Coping Orientation to Problems Experienced (Brief-COPE) Inventory is a derivative of the more comprehensive Carver Coping Styles Inventory and consists of 14 distinct coping strategies, each represented by 2 items.[18] Patients complete the questionnaire to describe their habitual coping mechanisms in stressful situations. The inventory has been validated and found reliable in a Turkish context.[19] Patients indicate the frequency with which they employ for each strategy on a 4-point Likert scale such as "active coping" (taking direct action to get around the problem), "planning" (making a plan of action), "positive reframing/reinterpretation" (trying to see the event in a more positive light), "acceptance" (learning to live with it), "humor" (making fun of the situation), "religion" (finding comfort in religion or spiritual beliefs), "use of emotional support" (getting emotional support from others), "use of instrumental support" (getting help and advice from other people), "self-distraction" (turning to work to take mind off things), "denial" (refusing to believe that the event has happened), "venting" (expressing negative feelings), "substance use" (using alcohol/drugs to get through the event), "behavioral disengagement" (giving up trying to deal with it), "self-blame/accusation" (self-criticism). Low scores indicate that the given dimension is less used, and high scores show that the given dimension is used more often.

Health-Related Quality of Life

The CF Questionnaire—Revised (CFQ-R) is the most commonly utilized disease-specific H-RQoL instrument for CF patients. It comprises 50 items distributed across 9 quality-of-life domains and 3 symptom scales. Each item is scored on a 4-point Likert scale, with standardized scores for each subscale ranging from 0 to 100. Higher scores indicate better H-RQoL and lower scores suggest poorer H-RQoL.[20] Health-related quality of life was examined using the following such as physical functioning (difficulty performing vigorous activities such as running, sports, lifting and carrying heavy things, climbing stairs), vitality (feeling full of energy/tired/exhausted), emotional functioning (feeling worried/useless/sad), eating disturbances (never enjoy eating, forcing to eat), treatment burden (burdened by daily inhalation and physical

therapy), health perception (better/same/deteriorated/leading a normal life), social functioning (staying at home because of health reasons), body image (thinking physically different from others, too thin), role limitations (problems at school, at work, or with other daily activities because of health reasons), weight problems (trouble gaining weight), respiratory symptoms (cough/wheezing/sputum etc), and digestive symptoms (diarrhea/abdominal pain).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 23.0 program (IBM Corp., Armonk, NY, USA). Descriptive statistics of continuous data are presented as mean±standard deviation. The chi-square test was employed for comparing categorical variables, and the Fisher's exact test was utilized when cell counts in 2 × 2 tables were fewer than 5. T-tests were applied for comparing means of normally distributed continuous variables, while the Mann–Whitney *U*-test was used for non-normally distributed data. Pearson's correlation was employed for normally distributed correlation analyses, and the Spearman rank test was utilized for non-normal distributions. A *P*-value of <.05 was considered statistically significant in all analyses. Multiple regression analyses were conducted with all HR-QoL domain scores as dependent variables, using sex, age, disease duration, anxiety and depression scores, and coping strategies as predictor variables.

RESULTS

This study was conducted on 30 adult patients diagnosed with CF. Demographic and clinical characteristics of the participants are summarized in Table 1. Of the total, 8 patients (27%) were identified as at risk for anxiety, and the same number (27%) were at risk for depression. Mean scores on the HADS were 7.4 ± 4.0 for anxiety and 5.0 ± 3.0 for depression. Anxiety scores correlated with depression scores ($r = 0.498$, $P = .005$) and depression risk increased with aging ($r = 0.366$, $P = .047$).

In the H-RQoL evaluation, the domain eating disturbances scored the highest, while the domain trouble gaining weight scored the lowest among all participants. In sociodemographic parameters, female patients exhibited lower scores in physical functioning (53.9 ± 23.9 vs. 72.4 ± 19.2, $P = .012$, respectively) and higher scores in body image (looking different from others) when compared with males (76.6 ± 33.5 vs. 61.5 ± 21.2, respectively, $P = .041$). The relationships between several clinical variables and quality of life domains were presented in Table 2. Body Mass Index (BMI) positively correlated with emotional functioning, social functioning, body image, and weight dimensions of H-RQoL. Modified Medical Research Council (mMRC) scores were negatively related to several H-RQoL dimensions including physical functioning, vitality, eating disturbances, treatment burden, role limitations, and respiratory symptoms. Lower FEV1 (range:26-114%) values which indicate greater respiratory disability were likely associated with lower levels of social functioning of H-RQoL. Concerning the relationship between psychological well-being and H-RQoL domains, patients at risk for anxiety showed poorer quality of life scores in the domains of vitality (feeling energetic), emotional functioning (feeling worried), and role limitations (limit in social area, work, and personal goals), ($P = .027$, $P = .001$, and $P = .001$, respectively), (Table 3). Patients manifesting depressive symptoms similarly reported lower H-RQoL scores in the domains of emotional functioning and role limitations ($P = .005$ and $P = .018$, respectively), (Table 3). In subgroup with symptoms of depression and/or anxiety, lower quality of life in several domains was found including emotional functioning, eating disturbances, social functioning, and role limitations domains ($P = .001$, $P = .033$, $P = .024$, and $P = .001$, respectively), (Table 3). In a multivariate model focusing on emotional H-RQoL, both anxiety and depression scores emerged as significant independent predictors ($P = .003$ and $P = .04$, respectively). Additionally, depression scores were found as a predictor of eating disturbances and gender was found as a predictor of physical functioning (Table 4). The results for these 3 dimensions were given in Table 4 because other dimensions included in the study did not show any significant relationships with the predictors examined in the model.

In terms of coping strategies, "acceptance" was the most commonly employed coping strategy, while "substance use/alcohol-drug use" was the least favored among all participants. Patients at risk for depression were less likely to use "active coping/direct action to solve problems" and more likely to employ "behavioral disengagement/giving up"

Table 1. Patient Data

Characteristics	n (%)
Patients	30 (100)
Age (years)	24 ± 4 (18-34)
Gender	
Female	17 (57)
Male	13 (43)
Marital status	
Single	26 (87)
Married	4 (13)
Educational status	
Primary school graduate	2 (7)
High school graduate	13 (43)
University graduate	15 (50)
Occupational status	
Unemployed	10 (33)
Still student	10 (33)
Employed	10 (33)
Duration of disease (years), (range)	19 ± 8 (3-30)
FEV1 % predicted (range)	64.1 ± 23.8 (26-114)
HADS	
Anxiety	8 (27)
Depression	8 (27)
Anxiety and/or depression	12 (40)

Table 2. Relationship Between Clinical Variables and Health-Related Quality of Life Domain Scores

Health-Related Quality of Life Domains	Age (Years)	Duration of Disease (Years)	FEV_1 % Predicted	BMI (kg/m²)	mMRC
Physical functioning	−.206	.242	.299	.220	−.442*
Vitality	−.007	.215	.136	.102	−.513**
Emotional functioning	.066	.065	.267	.372*	−.445*
Eating disturbances	−.020	−.125	.215	.262	−.365*
Treatment burden	−.096	.248	.276	.187	−.424*
Health perception	.037	.358	.319	.325	−.338
Social functioning	.023	.068	.438*	.384*	−.344
Body image	−.014	.036	.252	.633**	.095
Role limitations	−.063	.224	.218	.122	−.710**
Weight problems	.107	.149	.359	.563**	−.224
Respiratory symptoms	.075	.314	.445*	.338	−.536**
Digestive symptoms	−.281	.140	.049	.254	−.273

BMI, body mass index; mMRC, Modified Medical Research Council Dyspnea Scale.
Correlation analysis *$P < .05$.
**$P < .01$.

Table 3. Health-Related Quality of Life Scores for the Total Sample and Anxiety/Depression Subgroups

Health- Related Quality of Life Domains	Total	Risk of Anxiety			Risk of Depression			Risk of Depression and/or Anxiety		
	n = 30	Present n = 8	Absent n = 22	*P*	Present n = 8	Absent n = 22	*P*	Present n = 12	Absent n = 18	*P*
Physical functioning	61.9 ± 23.5	55.5 ± 20.6	24.0 ± 3.6	NS	54.4 ± 24.0	64.7 ± 23.3	NS	56.8 ± 21.5	65.3 ± 24.8	NS
Vitality	60.1 ± 23.2	43.9 ± 24.4	66.0 ± 20.1	.027*	52.4 ± 23.8	62.9 ± 22.8	NS	50.2 ± 25.2	66.7 ± 19.7	NS
Emotional functioning	69.8 ± 27.3	38.4 ± 20.1	81.2 ± 19.6	.001*	47.5 ± 26.5	77.9 ± 23.2	.005*	47.2 ± 23.3	84.8 ± 18.1	.001*
Eating disturbances	77.4 ± 29.5	63.9 ± 39.4	82.4 ± 24.2	NS	69.4 ± 29.7	80.4 ± 29.5	NS	64.8 ± 34.2	85.9 ± 23.1	.033*
Treatment burden	49.6 ± 21.5	36.3 ± 26.6	54.5 ± 17.6	NS	53.0 ± 13.1	48.4 ± 24.0	NS	42.8 ± 23.3	54.2 ± 19.6	NS
Health perception	58.6 ± 20.4	47.3 ± 16.9	62.7 ± 20.3	NS	57.0 ± 18.5	59.2 ± 21.4	NS	52.8 ± 19.3	62.4 ± 20.8	NS
Social functioning	63.3 ± 24.1	55.4 ± 25.6	66.1 ± 23.5	NS	56.1 ± 24.3	65.8 ± 24.1	NS	51.3 ± 21.8	71.2 ± 22.7	.024*
Body image	70.1 ± 29.4	68.3 ± 33.8	70.7 ± 28.4	NS	65.4 ± 34.9	71.8 ± 27.8	NS	67.8 ± 29.7	71.6 ± 29.9	NS
Role limitations	70.3 ± 25.9	42.8 ± 19.0	80.3 ± 20.2	.001*	52.1 ± 17.6	76.9 ± 25.5	.018*	48.6 ± 18.3	84.7 ± 19.3	.001*
Weight problems	47.9 ± 30.1	45.9 ± 35.5	48.6 ± 28.8	NS	50.0 ± 31.0	47.1 ± 30.4	NS	44.4 ± 29.7	50.2 ± 30.9	NS
Respiratory symptoms	53.9 ± 22.1	47.5 ± 22.3	56.2 ± 22.1	NS	48.1 ± 21.4	56.0 ± 22.4	NS	48.4 ± 20.6	57.5 ± 22.9	NS
Digestive symptoms	73.5 ± 19.6	61.3 ± 25.3	77.9 ± 15.4	NS	66.8 ± 26.7	75.9 ± 16.4	NS	64.9 ± 24.2	79.2 ± 13.7	NS

All data are presented as mean ± SD.
NS, non-significant; SD, standard deviation.

Table 4. Multivariate Analyses of the Ability of Potential Risk Factors for Predicting Health-Related Quality of Life Domain Scores

Health-Related Quality of Life Domains	Beta	95% CI		*P*
Emotional functioning domain				
Age	1.959	−.210	4.128	.075
Gender	−4.320	−19.678	11.037	.567
Anxiety score	−3.341	−5.386	−1.297	.003*
Depression score	−2.998	−5.850	−.146	.040*
Physical functioning domain				
Age	−1.359	−3.481	.763	.199
Gender	−23.897	−39.494	−8.300	.004*
Anxiety score	−.368	−2.418	1.683	.715
Depression score	−2.480	−5.378	.417	.090
Eating disturbances domain				
Age	.836	−2.268	3.940	.584
Gender	−15.651	−38.465	7.164	.170
Anxiety score	.692	−2.307	3.691	.639
Depression score	−4.280	−8.518	−.041	.048*

compared to the non-depressed group ($P = .05$ and $P = .01$, respectively). Similarly, patients at risk for anxiety were more likely to use "venting/negative feelings" and "behavioral disengagement" strategies compared to the non-anxious group ($P = .041$ and $P = .039$, respectively). In the subgroup with symptoms of depression and/or anxiety, only "behavioral disengagement" was the most frequently used coping strategy ($P = .005$) (Table 5). Both anxiety and depression scores positively correlated with the "behavioral disengagement" strategy ($r = 0.634$, $P = .001$ and $r = 0.397$, $P = .03$, respectively). Additionally, depression scores positively correlated with the "denial" coping strategy ($r = 0.409$, $P = .025$).

When correlating coping strategies with H-RQoL scores, the use of "instrumental support/seeking help and advice from others" had a positive impact, while "behavioral disengagement" had a negative impact on emotional functioning ($r = 0.409$, $P = .025$, and $r = -0.484$, $P = .007$, respectively). Social functioning positively correlated with the use of the "humor" strategy ($r = 0.393$, $P = .032$). We found a negative relationship between the vitality domain of quality of life and denial, self-blame, and planning coping styles (Table 6). However, multivariate analysis did not show any significant effect of coping skills on all H-RQoL domains.

DISCUSSION

This study offers an in-depth analysis of the prevalent coping mechanisms among adult Turkish patients with CF, while also considering essential demographic and clinical factors—most notably psychological issues—in evaluating H-RQoL. We found that 40% of participants reported elevated anxiety and/or depression symptoms and these rates are consistent with international samples of adult CF patients and these patients had poor emotional and social functioning, eating disturbances, and limits of personal goals in quality of life domains. This research is the first study focused on identifying coping styles associated with social and emotional aspects of H-RQoL within the Turkish adult CF population, using validated assessment tools. In our cohort, adults with CF predominantly employed "acceptance" as their principal coping strategy. It is a fact that these adult individuals actively want to engage in healthcare decision-making contrary to childhood period. However, the subgroup of patients who had anxiety and/or depression preferred not to take direct action to solve problems. When examining H-RQoL in relation to coping styles, we found that "instrumental support"—which involves seeking help and advice from others—was consistently linked to improved emotional well-being. Conversely, "behavioral disengagement" was consistently correlated with diminished emotional H-RQoL. Furthermore, the use of "humor" as a coping mechanism was positively associated with better social H-RQoL among our study participants.

In a large international study, elevated rates of anxiety and depression were reported among patients with CF.[5-7,21,22] Older age, reduced lung function, lower BMI, female gender, recent incidents of hemoptysis or pneumothorax, recent use of intravenous antibiotics, and being listed for a transplant were identified as factors associated with depression and/or anxiety.[5] In the same CF cohort, depression risk in 29% and anxiety risk in 31% of participants was reported from our country. Likewise, our study revealed similar rates, however, in the adult CF population (27% for both depression and anxiety). Additionally, we identified an increased risk of depression with advancing age—a finding corroborated by Modi et al,[23] who reported a 32% prevalence of depression among their adolescent and adult CF patients. The authors hypothesized that disease progression and diminishing self-esteem with age could contribute to the declining mental health. Similar high rates of clinically significant anxiety were also reported in adult CF populations in western countries such as UK (27%) and Belgium (30%).[7,22] Overall, these escalating rates of anxiety and depression underscore the growing importance of understanding the psychosocial complexities facing adults with CF.

As life expectancy for individuals with CF continued to improve and decreased mental well-being, recent clinical measures predominantly focused on H-RQoL**.** It is a fact that respiratory symptoms can significantly impair one's ability to perform tasks or participate in activities, leading to disruptions in daily life and functioning. In our study, we showed several clinical variables such as BMI, mMRC, lung function test affected the dimensions of H-RQoL. Despite a limited body of research exploring the relationship between mental health risks and H-RQoL in adults with CF, it is generally accepted that patients with depressive symptoms are less compliant with medical treatments and consequently report worse H-RQoL[6,7,15] Riekert et al[6] found that patients exhibiting both depressive symptoms and poor lung function had significantly lower H-RQoL across all domains compared to those without depressive symptoms, irrespective of lung function.[6] Our study demonstrated a clear link between

Table 5. Coping Scores for the Total Sample and Anxiety/Depression Subgroups

	Total	Risk of Anxiety			Risk of Depression			Risk of Depression and/or Anxiety		
Coping Strategies	**n = 30**	**Present n = 8**	**Absent n = 22**	***P***	**Present n = 8**	**Absent n = 22**	***P***	**Present n = 12**	**Absent n = 18**	***P***
Active coping	5.6 ± 1.7	5.5 ± 1.2	5.7 ± 1.9	NS	4.6 ± 1.7	6.0 ± 1.6	.050*	4.9 ± 1.4	6.1 ± 1.7	NS
Planning	5.3 ± 1.6	5.3 ± 1.8	5.3 ± 1.6	NS	5.0 ± 1.9	5.4 ± 1.6	NS	5.1 ± 1.7	5.4 ± 1.6	NS
Positive reframing	6.1 ± 1.6	5.9 ± 1.9	6.1 ± 1.5	NS	5.9 ± 1.2	6.1 ± 1.7	NS	5.7 ± 1.6	6.3 ± 1.5	NS
Acceptance	6.8 ± 1.2	7.3 ± 0.5	6.6 ± 1.4	NS	6.3 ± 1.2	7.0 ± 1.2	NS	6.7 ± 1.2	5.9 ± 1.3	NS
Humor	4.6 ± 2.1	4.1 ± 2.3	4.7 ± 2.1	NS	4.9 ± 1.9	4.5 ± 2.2	NS	4.1 ± 2.0	4.9 ± 2.2	NS
Religion	4.5 ± 2.1	4.8 ± 2.4	4.5 ± 2.0	NS	4.1 ± 1.6	4.7 ± 2.3	NS	4.5 ± 2.2	4.6 ± 2.1	NS
Use of emotional support	4.1 ± 2.0	4.1 ± 2.5	4.0 ± 1.8	NS	3.1 ± 1.7	4.4 ± 2.0	NS	3.7 ± 2.1	4.3 ± 1.9	NS
Use of instrumental support	4.0 ± 1.9	3.6 ± 2.0	4.1 ± 1.8	NS	3.1 ± 1.0	4.3 ± 2.0	NS	3.6 ± 1.7	4.2 ± 1.9	NS
Self-distraction	5.7 ± 1.9	6.0 ± 1.9	5.6 ± 1.9	NS	6.0 ± 1.8	5.6 ± 1.9	NS	5.8 ± 1.7	5.6 ± 2.0	NS
Denial	3.4 ± 1.5	4.1 ± 2.2	3.1 ± 1.1	NS	4.1 ± 2.1	3.1 ± 1.2	NS	3.8 ± 1.9	3.1 ± 1.2	NS
Venting	5.5 ± 1.5	6.4 ± 1.1	5.1 ± 1.6	.041*	5.0 ± 1.7	5.6 ± 1.5	NS	5.5 ± 1.6	5.4 ± 1.5	NS
Substance use	2.5 ± 1.6	3.5 ± 2.8	2.2 ± 0.5	NS	3.5 ± 2.8	2.2 ± 0.5	NS	3.0 ± 2.3	2.2 ± 0.5	NS
Behavioral disengagement	3.4 ± 1.9	4.6 ± 2.4	2.9 ± 1.4	.039*	5.1 ± 2.4	2.7 ± 1.1	.010*	4.6 ± 2.2	2.6 ± 1.6	.005*
Self-blame	4.3 ± 1.7	4.5 ± 2.2	4.3 ± 1.6	NS	4.8 ± 2.1	4.2 ± 1.6	NS	4.2 ± 2.0	4.4 ± 1.5	NS

All data are presented as mean ± SD.
NS, non-significant; SD, standard deviation.

psychological well-being and H-RQoL. Depression scores were related to poor emotional functioning, and role limitations in H-RQoL, while anxiety scores related to low vitality, poor emotional functioning, and role limitations. In multivariate analysis of the present study, only depression and anxiety scores were significantly linked to the emotional functioning domain of H-RQoL. Likewise, a study published in our country reported an association between depression and anxiety with poor psychosocial H-RQoL in CF patients. However, the study focused solely on children and adolescents not adult patients. Additionally, depression was associated with an increased likelihood of eating disturbances and gender was found as a significant factor in predicting physical functioning. Overall, these findings provide valuable insights into the relationships between mental health, gender, and physical functioning, highlighting the complexity of these interactions and their implications for quality of life.

Moving to adulthood, this unfavorable childhood disease experience will affect lifelong coping styles in patients with CF, even affecting survival.[24] In our study, "acceptance" emerged as the most commonly used coping strategy among the participants. This finding aligns with previous research on young adults transitioning to adult CF care.[25,26] When examining the impact of coping strategies on the psychosocial dimensions of H-RQoL, we found that the use of "instrumental support/seeking help and advice from others" positively influenced emotional well-being. In contrast, "behavioral disengagement/giving up" had a detrimental effect on emotional H-RQoL. Using "humor" as a coping mechanism was positively associated with better social functioning. These results are in accordance with prior studies, which have shown that higher levels of "optimism" are linked to better H-RQoL, whereas "distraction" correlates with poorer outcomes.[26] Similarly, Hugh et al[27] assessed 122 adult CF patients using the CFQ-R and Brief-COPE instruments. They discovered that "active coping" strategies were associated with better social H-RQoL and greater utilization of "religion" and "instrumental support," moreover "acceptance" was positively correlated with better emotional well-being. A negative association was reported between "distraction" and both social and emotional domains; additionally, higher "substance use" and "disengagement" were associated with lower emotional quality of life.[27] Collectively, these findings indicate the notion that enhancing coping skills can significantly improve the quality of life for CF patients.

When we assessed the effect of psychological well-being on coping styles, we observed that "behavioral disengagement" was more likely used by patients at risk for depression and/or anxiety, while "active coping" was less commonly employed among those in the depression risk group. This study's findings regarding the impact of coping styles on H-RQoL were consistent with similar studies conducted in other countries suggesting that these relationships are not solely influenced by cultural factors.[25] Clearly, individuals with mental health risks face challenges in achieving optimal H-RQoL by using different coping strategies.

This study acknowledged certain limitations, including its cross-sectional design, which may not capture temporal

Table 6. Relationship Between Coping Scores and Health-Related Quality of Life Domain Scores

	Coping Strategies													
Health- Related Quality of Life Domains	**Active Coping**	**Planning**	**Positive Reframing**	**Acceptance**	**Humor**	**Religion**	**Use of Emotional Support**	**Use of Instrumental Support**	**Self-Distraction**	**Denial**	**Venting**	**Substance Use**	**Behavioral Disengagement**	**Self-Blame**
Physical functioning	−.148	−.178	.145	.220	.140	−.040	.207	.399*	.054	−.253	.126	−.062	−.061	−.162
Vitality	−.253	−.447*	.106	.144	.207	−.352	.163	.265	−.051	−.471**	−.320	.006	−.302	−.429*
Emotional functioning	.057	−.157	.118	.160	.134	.063	.182	.409*	−.047	−.328	−.097	−.135	−.484**	−.134
Eating disturbances	.177	.059	.434*	.218	.201	−,.036	.141	.148	.263	−.132	.083	.304	−.312	.257
Treatment burden	−.136	−.156	−.040	−.242	.145	−.087	.143	.208	.244	.046	−.104	.161	.204	.021
Health perception	−.068	−.381*	.097	.183	.234	−.089	.059	.287	.084	−.174	−.321	.020	−.148	−.252
Social functioning	.211	−.115	.302	.331	.393*	.305	.075	.281	.267	−.220	.126	.236	−.204	.083
Body image	.009	−.234	.218	.246	.130	−.114	−.084	−.156	.280	−.140	−.015	.042	−.250	.031
Role limitations	.026	−.155	.218	.136	.198	−.066	.274	.389*	.138	−.429*	−.104	−.056	−,317	−.032
Weight problems	.096	−.095	.156	.081	.032	.012	.051	.004	−.101	.050	.095	−.064	−.336	.050
Respiratory symptoms	−.120	−.263	.036	.134	−.105	.188	.143	.330	.060	−.355	−.077	−.050	−.286	−.302
Digestive symptoms	−.063	−.096	.274	−.036	.041	−.064	−.153	.013	−.066	−.048	.098	−.063	−.196	.193

Correlation analysis *$P < .05$, **$P < .01$.

variations in health status and mental well-being over time. Additionally, single-center data may not be fully representative of the broader adult CF population. While self-reporting instruments are commonly used, they are subject to individual biases.

In conclusion, this study provides valuable insights into the relationship between coping strategies, psychological well-being, and H-RQoL in adult CF patients. This research indicates that patients with CF have a high risk of mental problems such as anxiety and depression. Given that maintaining a satisfactory quality of life is a central objective for healthcare providers, our study concentrated on identifying the coping strategies that serve as predictors of H-RQoL. Particularly, we found that "behavioral disengagement" was the more commonly used strategy among CF patients with risks for depression and/or anxiety, and negative mental health had an adverse impact on emotional and social aspects of H-RQoL. They tended to use less adaptive coping strategies. Finally, identifying psychological well-being and coping strategies that predict H-RQoL can help healthcare providers for better support CF patients in managing their condition and improving overall well-being.

Ethics Committee Approval: This study was approved by the Ethics Committee of Marmara University (approval number: 09.2016.341; date: May 6, 2016).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Original Article

Relative Value of Immunohistochemistry in Detection of Mycobacterial Antigen in Suspected Cases of Tuberculosis in Tissue Section

Musi Ravindra Mohan[1], Kothur Narayana-Reddy Sukumar[2], Anjaneya Amith[2]
[1]Oxford Medical College Hospital and Research Center, Bangalore, Karnataka, India
[2]Department of Respiratory Medicine, Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India

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Abstract

OBJECTIVE: Due to its infectious nature, complex immunological response, chronic progression, and the necessity for long-term treatment, tuberculosis has always been a major health burden. Immunohistochemistry (IHC) has the capacity to highlight the occurrence of mycobacterial antigens for tissue diagnosis. This study was conducted to understand the advantage of immunostaining over culture of *Mycobacterium tuberculosis*.

MATERIAL AND METHODS: A cross-sectional study was conducted on 30 samples of suspected cases of tuberculosis. Specimens received were fixed in 10% formalin and processed; 3-5 µm thick sections were made from paraffin block, stained with hematoxylin and eosin, Ziehl–Neelsen stain, and immunohistochemistry. Culture was done using Lowenstein–Jensen medium. Immunohistochemistry was interpreted as fine granular brownish cytoplasmic, coarse granular brownish cytoplasmic, and bacillus staining.

RESULTS: Out of the 30 samples studied, 12 (40.0%) were culture positive while 20 (66.7%) of them were IHC positive. Immunohistochemistry showed 17 granulomatous lesions of which 11 (55.0%) were well-formed granulomas. The sensitivity and negative predictive value were found to be high with immunohistochemistry, while specificity and positive predictive value were found to be on the lower side. Among the 20 positive IHC cases, the degree of staining was fine granular cytoplasmic staining in 13 cases (65.0%) and coarse granular staining in 7 cases (35.0%).

CONCLUSION: Immunohistochemistry is a reliable test with high sensitivity as well as high negative predictive value which can be done rapidly for establishing an etiological diagnosis of tuberculosis in histologic specimens.

KEYWORDS: Granuloma, tissues, immunohistochemistry, tuberculosis
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INTRODUCTION

Mycobacterium tuberculosis is responsible for one of the most infectious diseases known to man which is tuberculosis (TB). The estimated world prevalence of TB is 40 million, with approximately 10.6 million new cases reported each year. Also, nearly 3 million people die annually from the disease. The situation in India is shocking, where nearly 28.0% of the global burden exists, with approximately 1.8 million person developing TB every year.[1]

Due to various factors, including its high infectivity rate, intricate immunological response, progression which is lasting for many years, and the necessity for continuous management, TB has consistently been a significant health burden on healthcare system. Nowadays, the development of multidrug-resistant strains and the recent TB-HIV epidemic, associated with its severe social consequences have increased the burden. Laboratory diagnosis, treatment, and prevention of TB have embodied a permanent trial over the course of human history.[2] Clinically, TB presents in various forms, and tissue sections show very low yield of acid-fast bacilli, making diagnosis challenging.[3]

Taking into consideration the limitations in diagnostic accuracy of Ziehl–Neelsen (ZN) staining, mycobacterial culture, molecular, and serological methods, in a few cases of TB, histomorphological examination seems to be the only reasonable procedure for field diagnosis.[4] The detection limit for staining is more than 104 bacilli per slide or the presence of more than 104 bacilli per mL of specimen resulting in low sensitivity.[5] Culture of mycobacterium is considered to be one of the most sensitive techniques for identifying infections. Nevertheless, the time required for performing culture is several weeks, and its sensitivity is also low in paucibacillary conditions. Chronic granulomatous inflammation, which is a classical histological change seen in TB, is considered as the basis for the diagnosis of TB.[6]

Both immunocompromised as well as the immunocompetent patients are at high risk of developing infections and complications associated with mycobacterial infection. Hence, it is crucial to detect mycobacteria in all samples without

Corresponding author: Kothur Narayana-Reddy Sukumar, e-mail: kumarkn65@gmail.com

fail.[7] Immunohistochemistry (IHC) is a novel and powerful method. In formalin-fixed, paraffin-embedded tissues, IHC focuses on specific antigens using antigen–antibody interaction. Immunohistochemistry not only highlights the presence of mycobacterial antigens for tissue diagnosis but also could morphologically localize its distribution in different cells.[3,8]

There is a dearth of studies looking at the immunohistochemistry findings of TB, especially in those countries that are great contributors to the burden. Hence, this study was conducted to understand the advantage of immunostaining over culture methods.

MATERIAL AND METHODS

This prospective cross-sectional study was carried out at Kempegowda Institute of Medical Science (KIMS), Bangalore and JJM Institute of Medical Science (JJMMC), Davangere Medical College, after obtaining necessary permissions from Kempegowda Institute of Medical Science Institutional Ethics Committee (aproval no: KIMS/IEC/D-13/2017, date: 7-11-2017). The study was conducted for a period of 3 years. Informed written consent was obtained before initiation of the study. The study included all the suspected cases of TB on histopathology, while any autolyzed or inadequate specimens were excluded. Tuberculosis was diagnosed with the help of thorough general and systemic examinations, as well as making use of routine blood tests, chest X-rays, ultrasonography, computed tomography/magnetic resonance imaging and fine-needle aspiration.

Specimens were transported to the laboratory as soon as possible after collection. None of the samples were used if refrigerated for more than 2 days. Specimens were homogenized to free the bacilli from the mucus, cells, or tissues in which they may be embedded. All the specimens received were fixed in 10% formalin and routinely processed; 3-5 µm thick sections were made from paraffin-embedded blocks, stained with hematoxylin and eosin (H and E), Ziehl–Neelsen staining, and immunohistochemistry were performed. All samples were sent for culture using Lowenstein–Jensen (LJ) medium. For the culture process, 2 slopes per specimen were inoculated, each with one 5 mm loopful of the centrifuged sediment distributed over the surface. Measures were taken to minimize evaporation and drying of media. All cultures were inoculated at 35-37°C until growth was observed or discarded as negative after 8 weeks. Contaminated slopes were discarded. A total of 30 samples were studied. Tissue sections were deparaffinized, hydrated, and subjected to microwave antigen retrieval. The endogenous peroxidase activity was inhibited by incubating the sections with hydrogen peroxide.

Main Points

- Immunohistochemistry is a reliable test with high sensitivity as well as a high negative predictive value.
- Immunohistochemistry is capable of morphologically localizing antigen presence in various cells.
- Immunohistochemistry has advantages over polymerase chain reaction, with the former being robust and economical, and easily usable in routine laboratory settings.

The primary antibody used for IHC was the polyclonal anti-bacillus Calmette-Guérin antibody (pAbBCG) (Genxbio, India). This was done in a dilution of 1:50. One-step Envision method (HRP-streptavidin-biotin method; Dako, Germany) using diaminobenzidine as chromogen was employed for visualizing the system.

In the tissue samples collected, different areas and cells were assessed for the type of granuloma with the presence or absence of necrosis. Other findings studied included the visualization of multinucleated giant cells, lymphocytes, epithelioid cells, plasma cells, perigranuloma macrophages, necrotic zones, fibroblasts, and perigranuloma endothelial cells. The presence of staining in 10% of the epithelioid cells was considered positive staining. Comparisons were made between culture using LJ medium and immunohistochemistry. For each immunohistochemistry staining, one negative and one positive control (high leprosy bacillary positive section) were considered. Immunohistochemistry staining was interpreted as fine granular brownish cytoplasmic, coarse granular brownish cytoplasmic, and bacillus staining.

Statistical Analysis

The data were collected and entered into Microsoft Excel 365 and analyzed using the Statistical Package for the Social Sciences® version 20.0 (IBM Inc., Armonk, NY, USA). All study variables were analyzed using descriptive statistical methods such as frequencies and percentage for categorical variables, and mean with standard deviation or median with interquartile range for continuous variables. Chi-square test was performed to find the association between categorical variables. This study also assessed the specificity, sensitivity, as well as positive predictive value and negative predictive values of IHC. A P value of <.05 was considered statistically significant in this study.

RESULTS

The mean age of the study population was 32 years, with more males (17; 56.7%) than females (13; 43.3%). Regarding the nature of tissue studied, lymph nodes (30.0%) were the most common, followed by bone (20.0%), abscess (13.3%), and synovium (13.3%). Out of the 30 samples studied, 12 (40.0%) were culture positive, while 20 (66.7%) of them were IHC positive. Immunohistochemistry showed 17 granulomatous lesions, of which 11 (55.0%) were well-formed granulomas and 6 (30.0%) were ill-formed granulomas (Table 1).

There was a significant difference in the positivity rate between culture and immunohistochemistry in this study (Table 2).

Table 1. Distribution of the Samples in Terms of Organization

Organization	Frequency	Percentage
Well-formed granuloma	11	55.0%
Ill formed granuloma	6	30.0%
Necrotic tissue	3	15.0%
Total	20	100.0%

Table 2. Comparison of Ziehl–Neelsen stain with Immunohistochemistry

		Immunohistochemistry			
		Positive	**Negative**	**Total**	***P***
M. tuberculosis culture	Positive	12 (40.0%)	0 (0.0%)	12 (40.0%)	.002
	Negative	8 (26.7%)	10 (33.3%)	18 (60.0%)	
	Total	20 (66.7%)	10 (33.3%)	30 (100.0%)	

$P < .05$, hence statistically significant.

Table 3. Specificity, Sensitivity, Positive Predictive Value, and Negative Predictive Value of Immunohistochemistry in Diagnosing Tuberculosis Using Culture as the Gold Standard

	Immunohistochemistry
Sensitivity	100%
Specificity	40%
Positive predictive value	25%
Negative predictive value	100%

Table 4. Distribution of Samples in Terms of the Degree of Staining (n = 20)

Degree of Staining	**Frequency**	**Percentage**
Fine	13	65.0%
Coarse	7	35.0%
Total	20	100.0%

The sensitivity and negative predictive value were found to be high with immunohistochemistry, while specificity and positive predictive value were found to be on the lower side (Table 3).

Among the 20 positive IHC cases, the degree of staining was fine granular cytoplasmic staining in 13 cases (65.0%) and coarse granular staining in 7 cases (35.0%) (Table 4).

DISCUSSION

Considering morbidity and mortality among the various infectious diseases affecting adults in developing countries, TB still holds the top rank as the number one killer. In the case of TB, we usually reach a diagnosis based on the classical histomorphology of chronic granulomatous inflammation, which is pathognomonic of TB. A variety of techniques already exists to detect the pathogen responsible, *M. tuberculosis.* Even though quick and economical, the ZN stain is a procedure that shows positivity only in instances where there is a high bacillary load. Another drawback of ZN staining is its inability to distinguish between various Mycobacterium species. Culture is considered the gold standard for diagnosing TB. Other techniques such as enzyme-linked immunosorbent assay test and polymerase chain reaction (PCR) are intricate, requiring advanced equipment and trained individuals, costly, tardy, and not readily available.[9]

The factors that led to the preference of immunohistochemistry staining procedure in various settings are its simplicity and versatility, which are useful in the identification of mycobacterium in sputum, cultures, smears, and tissue segments.

In this study, the majority were males with a ratio of 1.2:1. This is similar to the study conducted by Mustafa et al,[6] which showed a similar ratio. Majority of the tissues were obtained from lymph nodes (30.0%), followed by bone (20.0%), abscess (13.0%), and synovium (13.0%) in this study. In the study conducted by Geol et al, lymph nodes (44.4%) were the predominant sample studied,[10] while in the case of Kohli et al,[11] most of the samples were from the gastrointestinal tract (24.0%) and bones (24.0%).

This study showed predominantly well-formed granulomas in IHC, while in the Karimi et al[3] study, ill-formed granulomas were the predominant. Immunohistochemistry positivity was found to be 66.7% in this study. Immunohistochemistry positivity ranged from 72% to 100% in various published studies by multiple authors.[9-11] Our results showed that IHC using polyclonal (anti-BCG) antisera has better sensitivity (100.0%), but lower specificity (40.0%) and high predictive value.

In the study conducted by Goel and Budhwar,[10] the sensitivity for IHC was found to be 64.0%-100.0%. They had used a monoclonal antibody instead of a polyclonal antibody for IHC. In the study conducted by Mustafa et al, both sensitivity and specificity were found to be 100% for IHC using a polyclonal antibody.[6] Barbolini et al[12] used a monoclonal antibody for IHC and found that the sensitivity and specificity were both 100.0%. In their study, they obtained tissues from extrapulmonary TB sites. In a study conducted on samples obtained from aspirates of lymph nodes, CSF, and effusion by Purohit et al,[13] both sensitivity and specificity were found to be 96.0%. In the study conducted by Prapanna et al,[14] using IHC, the sensitivity and specificity were 96.9% and 95.0%, respectively. In the study conducted using pAbBCG for IHC by Karimi et al,[15] both sensitivity and specificity were 100.0% each.

The main asset of this IHC technology is that it is readily available in routine surgical pathology laboratories and is a robust technology. Immunohistochemistry can detect fragmented tubercle bacilli with high sensitivity compared to ZN staining, which has a sensitivity of 25.0%-44.0% and requires an intact cell wall. Logani et al, in their study, concluded that the use of IHC with the help of pAbBCG generates positive outcomes in specimens with 10 bacilli per slide.[16]

The main limitation of this study was that the sample size was small. Various factors can contribute to the sensitivity of IHC, including the clinical stage of the disease and the duration of antitubercular treatment received prior to biopsy. These factors were not addressed in this study.

Immunohistochemistry was found to be dependable in diagnosing TB even in specimens with fragmented tubercle bacilli. Immunohistochemistry is a reliable test with high sensitivity as well as negative predictive value, which can be rapidly performed to establish an etiological diagnosis of TB in histologic specimens. Hence, this study has a place in the differential diagnosis of tuberculous and non-tuberculous mycobacterial diseases. Immunohistochemistry has advantages over PCR of being robust and economical, and it can easily be used in a routine laboratory.

Ethics Committee Approval: This study was approved by the Ethics Committee of Kempegowda Institute of Medical Science Institutional Ethics Committee (approval no.: KIMS/IEC/D-13/2017; date: 7/11/2017).

Informed Consent: Written consent was obtained from the patients who agreed to take part in the study.

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Original Article

Evaluation of Long-Coronavirus Disease 2019 Cases Readmitted to Intensive Care Units Due to Acute Respiratory Failure: Point Prevalence Study

Eylem Tunçay[1], Özlem Moçin[2], Özlem Ediboğlu[3], Nalan Adıgüzel[2], Sinem Güngör[2], İnsa İşcanlı[4], Berrin Er[5], Nilgün Alptekinoğlu Mendil[6], Adnan Usalan[7], Didem Yılmaz[7], Hülya Keskin[8], Gül Erdal Dönmez[2], Barış Yılmaz[2], Feyza Kargın[8], Kemal Tolga Saraçoğlu[8], Şahin Temel[9], Hayriye Cankar Dal[5], Sema Turan[5], Leyla Talan[10], Derya Hoşgün[11], Semih Aydemir[11], Hülya Sungurtekin[12]

[1]Department of Intensive Care, University of Medical Sciences Şehit Prof. Dr. İlhan Varank Training and Research Hospital, İstanbul, Türkiye
[2]Department of Intensive Care, Health Sciences University Süreyyapaşa Pulmonary Disease and Pulmonary Surgery Training and Research Hospital, İstanbul, Türkiye
[3]Department of Intensive Care, Health Sciences University Dr. Suat Seren Pulmonary Disease and Pulmonary Surgery Training and Research Hospital, İstanbul, Türkiye
[4]Department of Intensive Care, Health Sciences University Sultan Abdülhamid Han Training and Research Hospital, İstanbul, Türkiye
[5]Department of Intensive Care, TC Ministry of Health, Ankara City Hospital, Ankara, Türkiye
[6]Department of Intensive Care, TC Ministry of Health, Mersin City Hospital, Mersin, Türkiye
[7]Department of Intensive Care, Tarsus Medikalpark Hospital, Mersin, Türkiye
[8]Department of Intensive Care, Health Sciences University Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye
[9]Department of Intensive Care, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[10]Department of Intensive Care, Ankara University Faculty of Medicine, Ankara, Türkiye
[11]Department of Intensive Care, Health Sciences University Ankara Atatürk Pulmonary Disease and Pulmonary Surgery Training and Research Hospital, Ankara, Türkiye
[12]Department of Intensive Care, Pamukkale University Faculty of Medicine, Denizli, Türkiye

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Abstract

OBJECTIVE: Coronavirus disease 2019 (COVID-19) caused morbidity and mortality worldwide. Besides the acute effects, subacute and long-term effects are defined as long-COVID causing morbidity. The intensive care unit (ICU) data of long-COVID-19 cases were evaluated with the participation of 11 centers.

MATERIAL AND METHODS: Study was designed by Turkish Thoracic Society Respiratory Failure and Intensive Care Working Group to evaluate long COVID-19 patients. All patients followed up in the ICU with long-COVID diagnosis were included in point prevelance study.

RESULTS: A total of 41 long COVID-19 patients from 11 centers were included in the study. Half of the patients were male, mean age was 66 ± 14, body mass index was 27 ± 5. Hypertension, diabetes mellitus, lung cancer, malignancy, and heart failure rates were 27%, 51%, 34%, 34%, and 27%, respectively. Eighty percent had received COVID vaccine. Patients had moderate hypoxemic respiratory failure. APACHE II, SOFA score was 18 (14-26), 6 (3-8), respectively. Forty-six percent received invasive mechanical ventilator support, 42% were sepsis, 17% were septic shock. Bilateral (67%), interstitial involvement (37%) were most common in chest x-ray. Fibrosis (27%) was detected in thorax tomography. Seventy-one percent of patients received antibiotherapy (42% carbapenem, 22% linezolid). Sixty-one percent of the patients received corticosteroid treatment.

CONCLUSION: More than half of the patients had pneumonia and the majority of them used broad-spectrum antibiotics. Presence of comorbidities and malignancies, intensive care severity scores, intubation, and sepsis rates were high. Receiving corticosteroid treatment and extensive bilateral radiologic involvement due to COVID-19 might be the reasons for the high re-admission rate for the ICUs.

KEYWORDS: Post-acute COVID-19 syndrome, intensive care, respiratory failure, acute respiratory distress syndrome, hospital-acquired pneumonia, steroids

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INTRODUCTION

Nowadays, unlike other viruses transmitted by the respiratory route, the long-term effects of the coronavirus diease 2019 (COVID-19) virus, which can harm numerous organ systems and is categorized as long COVID, are emerging as a significant public health problem.[1]

Long-COVID syndrome is defined as the existence of cardiovascular, gastrointestinal, hematological, neuropsychiatric, and physical symptoms, affecting different organ systems that persist more than 4-12 weeks in a patient with a history of COVID-19, and cannot be explained by any other cause.[2-4]

Corresponding author: Tuncay Eylem, e-mail: acarturkeylem@yahoo.com

Although the risk factors for the development of long-COVID syndrome are unknown, studies have been conducted to determine which organ systems are affected and how they are affected. Furthermore, there are research on the morbidity, quality of life, and outpatient follow-up results of long-COVID-19 cases in the current literature.[5-7]

Since long-COVID syndrome has been researched in patients who were followed up on and discharged from the intensive care unit (ICU) due to serious COVID-19 infection, no adequate research on re-hospitalization of long-COVID patients in the ICU has been conducted.[8]

We aimed to evaluate the intensive care outcomes of long-COVID patients during re-admission to the ICU due to acute respiratory failure.

MATERIAL AND METHODS

Multicentered, cross-sectional, 1-day point prevalence study. Current studys' announcement was performed by e-mail through the Turkish Thoracic Society among the members currently practicing in the ICUs. Afterwards, the consent forms were shared with the centers. All ongoing symptomatic COVID-19 cases categorized in long-COVID admitted to the ICU between December 15, 2021, 08:00 AM, and December 16, 2021, 08:00 AM, were included in the study. All data from centers were obtained via e-mail. The study was approved by the University of Health Sciences İzmir Dr Suat Seren Chest Diseases and Surgery Training Hospital Ethical committee, 2020-KAEK-139, according to the Declaration of Helsinki.

Ongoing symptomatic COVID-19 patients who were discharged after being hospitalized due to severe COVID pneumonia and then admitted to the ICU for acute respiratory failure at 4-12 weeks were included in the study.

Patients definition for long-COVID-19 was provided from National Institute for Health and Care Excellence guidelines on Long-COVID. In the current study, ongoing symptomatic COVID-19 was defined as signs and symptoms developing during/after the COVID-19 infection persisting more than 4-12 weeks and also cannot be explained by any other diagnosis.

Accordingly, long-COVID consists of 2 categories as below:

- Ongoing symptomatic COVID-19, the symptoms lasting for 4-12 weeks
- Post-COVID-19 syndrome, with symptom persistence beyond 12 weeks[9]

Inclusion Criteria

- Ongoing symptomatic COVID-19 patients, previously diagnosed COVID-19 and/or thorax computed tomography (CT)

Exclusion Criteria

- Patients refused to participate in the study
- Age <18 years
- Pregnancy

Assessments

Demographic features (age, gender), smoking history, vaccination status, ICU diagnosis, comorbidities, ICU duration time, radiologic features (chest x-ray, thorax CT if available), Acute physiology health evaluation II score (APACHE II), and the Sequential Organ Failure Assessment (SOFA) scores, type of respiratory support which patients received (nasal oxygen, mask oxygen, high flow oxygen, noninvasive mechanical ventilation [NIV], IMV), presence of sepsis, septic shock, multi-organ failure, adult respiratory distress syndrome, and types of medical treatment (antibiotics, corticosteroids, anticytokine, etc.) were recorded for analysis.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences, Statistics for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive analysis was performed for patients' demographics and clinical data. For non-parametric continuous variables, the median with interquartile range was used, and for parametric continuous variables, the mean ± standard deviation (SD). Counts and percentages were used when applicable.

RESULTS

A total of 41 patients from 11 centers were included in the current study. Table 1 summarizes the demographic features, ICU admission place, comorbidities of the ongoing symptomatic COVID-19 cases at the study day. Approximately half of the cases were male, and the mean age was 66 ± 14 years. Nearly half of the cases were current smokers. The most frequent comorbidities were malignancy and diabetes mellitus, 60%, 34%, respectively. Besides, 81% of the patients had comorbidities. The COVID-19 vaccination rate was 80%.

The ICU data, treatments, type of respiratory support, length of stay, intubation/extubation duration, type of respiratory support (nasal oxygen, mask oxygen, high flow oxygen, NIV, IMV), types of medical treatment, and discharge place, were shown in Table 2. The most frequent diagnosis in ICU admission was pneumonia 28 (68%). Nearly half of the patients

Main Points

- Long-coronavirus disease (COVID) syndrome is defined as the existence of cardiovascular, gastrointestinal, hematological, neuropsychiatric, and physical symptoms, affecting different organ systems in patients with a history of COVID-19, and cannot be explained by any other cause**.**
- Long COVID consists of 2 categories as below: acute COVID-19, with symptoms lasting for 4-12 weeks, and post-COVID-19 syndrome, with symptom persistence beyond 12 weeks.
- In the present study, we aimed to evaluate the intensive care outcomes of long COVID patients during re-admission to the ICU due to acute respiratory failure.
- Ongoing symptomatic COVID-19, especially accompanying comorbidity and malignancy might have increased intensive care unit re-admission. In addition, the risk of pneumonia and need for broad-spectrum antibiotics might be increased in the group of patients receiving steroid treatment due to the sequelae of COVID-19.

Table 1. Demographic Characteristics of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to Intensive Care Units Due to Acute Respiratory Failure

Male, n (%)	21 (51)
Age, mean ± SD	66 ± 14
BMI, mean ± SD	27 ± 5
Smoking status, n (%)	
Current smoker	22 (54)
Ex-smoker	6 (15)
Non-smoker	12 (31)
Intensive care unit admission place, n (%)	
Emergency unit	14 (34)
Ward	17 (42)
Outer center ICU	7 (17)
Outer center emergency unit	3 (7)
Comorbidities, n (%)	33 (81)
Congestive heart failure	11 (27)
Hypertension	21 (51)
Diabetes mellitus	14 (34)
Coronary artery diseases	7 (17)
Chronic kidney failure	6 (15)
Alzheimer's disease	4 (10)
Parkinson disease	2 (5)
Cerebrovascular event	5 (12)
Sequelae of tuberculosis	1 (2)
Extra-pulmonary malignancy	11 (27)
Pulmonary malignancy	14 (34)
COVID vaccination, n (%)	33 (80)

BMI, body mass index; COVID, coronavirus disease 2019; ICU, intensive care unit.

Table 2. Intensive Care Data of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to the Intensive Care Units Due to Acute Respiratory Failure

ICU Diagnosis, n (%)	
COPD exacerbation	6 (15)
Pneumonia	28 (68)
Pulmonary embolism	1 (2)
Pneumothorax	1 (2)
Pulmonary edema	6 (15)
Interstitial lung disease exacerbation	4 (10)
Acute kidney failure	4 (10)
Cerebrovascular event	4 (10)
ICU Data	
P/F ratio, median (IQR)	170 (110-260)
APACHE II, median (IQR)	18 (14-26)
SOFA, median (IQR)	6 (3-8)
ARDS, n (%)	4 (10)
Sepsis, n (%)	17 (42)
Septic shock, n (%)	7 (17)
Multi organ failure, n (%)	3 (7)
Intubation, n (%)	23 (56)
Tracheostomy, n (%)	4 (10)
Extubation, n (%)	5 (12)
Type of Respiratory Support, n (%)	
Invasive mechanical ventilation	19 (46)
Non-invasive mechanical ventilation	6 (15)
Nasal oxygen	6 (15)
Mask oxygen	2 (5)
Reservoir mask oxygen	3 (7)
High flow nasal cannula oxygen	3 (7)
Intubation day, median (IQR)	9 (1-16)
Extubation day, median (IQR)	2 (1-4)
ICU length of stay, median (IQR)	10 (6-18)
Discharge site from ICU, n (%)	4 (10)
Home, n (%)	1 (2)
Ward, n (%)	3 (7)
Type of Respiratory Support After Discharge, n (%)	
LTOT	4 (10)
CPAP	1 (2)
BIPAP-ST	2 (5)
HomeVENT	2 (5)

APACHEII, acute physiology health evaluation II score; ARDS, acute respiratory distress syndrome; BIPAP-ST, bilevel positive airway pressure spontaneous/timed; CPAP, continuous positive airway pressure; ICU, intensive care unit; IQR, interquartile range; LTOT, long-term oxygen therapy; P/F ratio, partial arterial oxygen pressure to fractional inspired oxygen; SOFA, Sequential Organ Failure Assessment.

had sepsis. The APACHE II score and partial arterial oxygen pressure to fractional inspired oxygen (P/F) ratio was 18 (14-26), 170 (110-260), respectively. Intubation rate was observed to be 56% and 46% of required mechanical ventilation support. Long-term oxygen therapy was prescribed for 10% of the patients at discharge.

Table 3 summarizes the medical treatment of ongoing symptomatic COVID-19 patients. Among the study population 61% of the patients received corticosteroid, and 71% of the patients used antibiotherapy. Most frequent reason for receiving antibiotic treatment was hospital acquired pneumonia (32%). The most commonly administered antibiotics were meropenem and linezolid 42%, 22%, respectively.

Interstitial involvement was detected in 37% of patients on chest radigraphy whereas fibrosis and consolidation/ground glass involvement were detected via computerized thorax tomography, 27% respectively (Table 4).

DISCUSSION

In our study, more than half of the ongoing symptomatic COVID-19 patients were hospitalized in the ICU due to

Table 3. Medical Intensive Care Treatments of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to Intensive Care Units Due to Acute Respiratory Failure

Corticosteroid, n (%)	25 (61)
Methylprednisolone	16 (39)
Prednisolone	2 (5)
Dexamethasone	6 (15)
Hydrocortisone	1 (2)
Antibiotherapy, n (%)	29 (71)
Antibiotherapy day, mean ± SD	1.8 ± 0.5
Antibiotherapy reason, n (%)	
CAP	11 (27)
HAP	13 (32)
VIP	4 (10)
UTI	3 (7)
Catheter infection, n (%)	1 (2)
Wound infection, n (%)	2 (5)
Antibiotics, n (%)	
Meropenem, n (%)	17 (42)
Teicoplanin, n (%)	3 (7)
Linezolid, n (%)	9 (22)
Coly-Mycin, n (%)	5 (12)
Fluconazole, n (%)	4 (10)
Amphotericin B, n (%)	2 (5)
Daptomycin, n (%)	2 (5)
Levofloxacin, n (%)	4 (10)
Tigecycline, n (%)	4 (10)
Ertapenem, n (%)	2 (5)
Piperacillin–tazobactam, n (%)	3 (7)
Moxifloxacin, n (%)	2 (5)
Vancomycin, n (%)	2 (5)
Posacanazole, n (%)	1 (2)
Trimethoprim–sulfamethoxazole, n (%)	1 (2)
Fosfomycin, n (%)	1 (2)
Ceftazidime, n (%)	3 (7)
Amikacin, n (%)	1 (2)
Ceftazidim-avibactam, n (%)	1 (2)

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; UTI, urinary tract infection; VIP, ventilatory acquired pneumonia.

pneumonia and the majority of them used broad-spectrum antibiotics. In addition, the rates of comorbidities and malignancies were found to be high. Besides, intensive care severity scores (APACHE II; SOFA), intubation, and sepsis rates were high, and P/F rates were low. In the present study, it has been shown that more than half of the patients who were discharged and re-admitted to the ICU after suffering from COVID-19 had received corticosteroid therapy and had bilateral involvement due to COVID-19 on a chest x-ray. The use of steroids, lung involvement/fibrosis might be among the reasons for the severity of critical illness in ICU.

Table 4. Radiologic Features of Ongoing Symptomatic Coronavirus Disease 2019 Patients Admitted to Intensive Care Units Due to Acute Respiratory Failure

Chest X Ray	
Normal, n (%)	5 (12)
Lobar involvement. n (%)	4 (10)
Lobular involvement, n (%)	4 (10)
Diffuse involvement, n (%),	5 (12)
İnterstitial involvement, n (%)	15 (37)
Localization, n (%)	
Right	6 (15)
Left	3 (7)
Bilateral	27 (67)
Computerized thorax tomography, n (%)	
Ground glass opacity, n (%)	7 (17)
Consolidation, n (%)	2 (5)
Consalidation and ground glass opacity, n (%)	11 (27)
Fibrosis, n (%)	11 (27)
Lung opacity, n (%)	3 (7)

Recent studies revealed that the ratio of long COVID symptoms was higher in females. Factors predicting long COVID were age over 70 years, to have >5 symptoms during the presence of comorbidities, and female gender.[10-12] In the present study, gender ratios were similar, and 81% of the ongoing symptomatic COVID patients had comorbidities. Additionally, a few studies reported that males were as likely to develop long-COVID as females.[13,14]

In our study, the most frequent comorbidities were malignancy and DM among the ongoing symptomatic COVID patients admitted to the ICU. Lee et al[15] reported that 28% of the cancer patients with COVID-19 died, and mortality was associated with old age, male gender, existing comorbidities such as hypertension and cardiovascular disease. On the other hand, it was determined that the type of oncologic treatment (cytotoxic chemotherapy, immunotherapy, hormonal therapy, etc.) had no effect on mortality. In the current study, treatments of patients with malignancy were not evaluated.

Coronavirus disease-ICU group on behalf of the REVA network and the COVID-ICU investigators evaluated the risk factors of 90-day mortality during post-ICU admission among 4244 patients who survived from COVID-19. Ventilator-associated pneumonia was diagnosed in nearly half (58%) of these patients and on day 90, 1/3 of patients had died. Independent predictors of 90-day mortality were older age, immunosuppression, severe obesity, DM, higher renal and cardiovascular SOFA score components, and a lower PaO_2/FiO_2[16] ratio. In the current study, ongoing symptomatic COVID patients were admitted to the ICU mostly with the diagnosis of pneumonia (68%) and nearly half of the patients had sepsis. The APACHE II scores were high and P/F ratio was low. Half of the patients had received intubation and required mechanical ventilation support.

Ruiz-Bastiá and coworkers evaluated a total of 1251 respiratory samples from 1195 critically ill COVID-19 patients and reported that all patients received broad-spectrum antibiotherapy as an empirical treatment, and the isolated bacteria were mainly Enterobacterales followed by *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[17] In our study, 2/3 of the patients received broad-spectrum antibiotherapy, most frequently administered antibiotics were meropenem and linezolid.

Various studies consider smoking status, male gender as a risk factor for post-COVID-19 pulmonary fibrosis (PCPF).[18-20] On the contrary, in a meta-analysis male gender, smoking status, and body mass index were not found to be significant risk factors for the development of PCPF; only COPD was reported as a risk factor.[21] In a study performed on 55 COVID-19 survivors 3 months after recovery, radiological abnormalities (ground-glass opacity, consolidation, and interstitial thickening) persisted in 70% of the patients.[22] In the present study, 1/3 of the post-COVID-19 patients admitted to the ICU had fibrosis on computerized thorax tomography. Since the current study was designed as cross-sectional, previous computerized thorax tomography records were not obtained, and other factors that might cause lung fibrosis could not be investigated. Additionally, in the current study, 11% of the study population had fibrosis detected in computerized thorax tomography.

The main limitation of our study is the short time period of the study, since the study designed as a cross-sectional 1-day point prevalence study, results only reflect the study day. Follow-up results, ICU outcomes, factors affecting mortality, could not be provided. Since the study was conducted as multi-centered, data was obtained from different ICUs with various protocols which could cause heterogeneity. However, the evaluation of 11 centers could provide important data about ongoing symptomatic COVID-19 patients' ICU data.

In conclusion, among ongoing symptomatic COVID-19 cases, especially accompanying comorbidity and malignancy, ICU re-admission rate was high. In order to reveal the association between the ICU readmission and presence of comorbidity, malignancy risk analysis should be performed with a control group. In addition, the risk of pneumonia and need for broad-spectrum antibiotics might be increased in the group of patients receiving steroid treatment due to the sequelae of COVID-19. In daily clinical practice, the number of Post-COVID cases that would be increased as time passes should be followed up more closely and multidisciplinary in the ICU.

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences İzmir Dr Suat Seren Chest Diseases and Surgery Training Hospital (Approval No: 2020-KAEK-139, date: November 2020).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Research Letter

Comparison of 2005 and 2021 American Thoracic Society/ European Respiratory Society Criteria for Bronchodilator Response

Kohei Okawa[1], Toshihiro Shirai[1], Taisuke Akamatsu[1], Keita Hirai[2]

[1]Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan
[2]Department of Clinical Pharmacology and Therapeutics, Shinshu University Graduate School of Medicine, Matsumoto, Japan

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In 2021, the American Thoracic Society (ATS)/European Respiratory Society (ERS) statements were revised, and the criteria for bronchodilator response (BDR) test were changed.[1] The 2005 criteria (old criteria) were ≥12% and ≥200 mL in forced expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC) from baseline;[2] however, the 2021 criteria (new criteria) are >10% of the predicted value in FEV1 and/or FVC. The major limitation of the old criteria is that the absolute and relative changes in FEV1 and FVC are inversely proportional to baseline lung function and are associated with height, age, and sex in both health and disease.[1] The change was to reduce the association of baseline lung function (sex, age, and height differences) in assessing BDR by using the change in FEV1 and/or FVC relative to predicted values. It is unclear how changing from the old to the new criteria would change the patient population with BDR in clinical practice. This study compared cases meeting the old and new criteria in asthma patients in clinical practice. The subjects included 190 asthma patients who underwent BDR tests using short-acting β2 agonist (30 μg procaterol) inhalation according to a previous methods[3] at our hospital from April 2014 to March 2018. Bronchodilator response tests were accumulated and compared for cases meeting the old and new criteria. The Shizuoka General Hospital ethics committee approved this study (approval number: SGHIRB#2021035, date: August 26, 2021) and permitted the use of the information in the database. The data acquired were kept anonymized. Since this was a retrospective study, the Board waived patient approval or informed consent.

Among 190 patients (mean age ± standard deviation 60 ± 15 years; 106 females; median (interquartile range) body mass index, 22.9 (21.0-26.8) kg/m^2) who underwent the BDR test, 38 (20.0%) were positive by the old criteria and 34 (17.9%) by the new criteria. Thirty-one patients were positive by both old and new criteria. Table 1 and Figure 1 show the patients with negative or positive conversions between 2005 and 2021 ATS/ERS BDR criteria, that is, 2005, ≥12% and 200 mL in

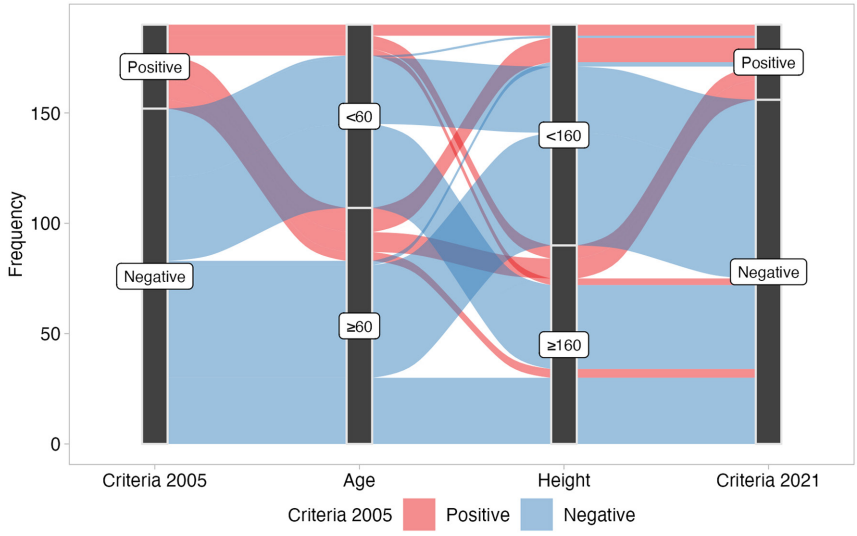

Figure 1. River plot of the relationship between positive or negative bronchodilator response, age (years), and height (cm).

Corresponding author: Toshihiro Shirai, e-mail: toshihiro-shirai@i.shizuoka-pho.jp

Table 1. Patients with Negative or Positive Conversions Between 2005 and 2021 American Thoracic Society /European Respiratory Society Bronchodilator Response Criteria

						2005 BDR					
						Changes in FVC		Changes in FEV1		2022 BDR	
Age, years		Sex	Height, cm	Weight, kg	BMI, kg/m²	mL	%	mL	%	FVC, %	FEV1, %
Negative conversion											
1	53	Male	173	60.4	20.2	10	0.2	**300**	**12.6**	0.2	8.5
2	65	Male	168	76.0	27.1	**270**	**13.6**	**240**	**24.7**	7.3	7.9
3	62	Male	165	79.3	29.2	60	2.0	**240**	**12.5**	1.6	8.0
4	59	Male	169	58.1	20.5	−30	−1.3	**230**	**14.1**	−0.8	7.1
5	70	Male	165	98.8	36.3	**200**	9.3	**200**	**12.7**	5.8	7.1
6	16	Male	176	93.0	30.1	**420**	**17.9**	**320**	**19.3**	9.2	7.6
7	75	Male	162	55.6	21.2	**310**	**21.2**	20	**2.2**	9.7	0.8
Mean, n = 7	57	NA	168*	74.5	26.4	177	9.0	221	14.0	4.7	6.7
Positive conversion											
1	70	Female	156	49.7	20.4	**250**	10.0	190	**13.9**	**10.4**	**10.1**
2	69	Female	150	59.2	26.5	**330**	11.1	140	5.0	**11.1**	5.5
3	63	Male	157	49.3	19.9	140	8.0	190	**16.4**	6.0	**10.0**
Mean, n = 3	67	NA	154	52.7	22.4	240	9.7	173	11.8	9.2	8.5
Overall mean, n = 190	60	84/106	160	62.6	24.4	79	2.8	65	4.9	2.5	2.6

The bold values meet positive criteria.
ATS, American Thoracic Society; BDR, bronchodilator response; BMI, body mass index; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable.
*$P < .007$ compared to the overall mean value.

FEV1 and/or FVC from baseline, and 2021, >10% of the predicted value in FEV1 and/or FVC, respectively. Seven patients who were positive by the old criteria but negative by the new criteria were taller and younger than the overall mean. Three patients who were negative by the old criteria but positive by the new criteria were shorter and older than the overall mean. The new criteria are based on predicted values as denominators, which become smaller in lower-height and older subjects, leading to larger BDRs.[4] A positive conversion from the old criteria to the new criteria in 3 patients was caused by this effect.

The new criteria are more stringent because the denominator is the predicted FEV1 (L), which considers height and age. Some cases went from positive to negative and vice versa. Some were negative in the FEV1 evaluation but positive in the FVC evaluation. Bronchodilator response in FVC, rather than FEV1, has been shown to better reflect the physiological processes of air trapping.[5-8] It is essential to evaluate BDR not only by FEV1 but also by FVC.

The new criteria are affected by height and age, so caution should be taken in interpreting the results. The ability of an acute response to bronchodilators to predict future clinical status other than survival is unclear, and BDR does not accurately differentiate between types of airway diseases.[9] Further evidence is needed to determine whether BDR is associated with outcomes other than survival.

Ethics Committee Approval: This study was approved by Ethics Committee of Sizuoka General Hospital, (SGHIRB#2021035, Date: August 26, 2021).

Informed Consent: Since this was a retrospective study, the Board waived patient approval or informed consent.

Peer-review: Externally peer-reviewed.

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