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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The predictive value of the Haller index for recurrent pneumothorax risk after primary spontaneous pneumothorax

Primer spontan pnömotoraks sonrası tekrarlayan pnömotoraks riski için Haller indeksinin öngördürücü değeri

Mesut Buz, Yunus Emre Özsaray, Mehmet İlhan Sesigüzel, Mahmut Talha Doğruyol, Rıza Berk Çimenoğlu, Attila Özdemir, Recep Demirhan

Department of Thoracic Surgery, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

ABSTRACT

Background: In this study, we aimed to evaluate the predictive value of the Haller index for recurrence risk in primary spontaneous pneumothorax patients.

Methods: Between January 2018 and December 2023, a total of 285 patients (260 males, 25 females; median age: 23 years; range, 17 to 35 years) with primary spontaneous pneumothorax who underwent thoracic computed tomography and followed for at least one year were retrospectively analyzed. The patients were divided into two groups as the non-recurrence group (n=170) and recurrence (n=115) group. The Haller index was calculated from computed tomography scans at presentation and its predictive value for recurrent pneumothorax was estimated.

Results: The median age was significantly higher in the non-recurrence group than in the recurrence group (p<0.001). The median time to recurrence was two (IQR 1-3) months. The diagnostic validity of Haller index for predicting recurrence showed an area under the receiver operating characteristic of 0.824 (95% confidence interval [CI]: 0.775-0.866) (p<0.001). The optimal cut-off value of Haller index (>2.4) showed a sensitivity of 70.43% (95% CI: 61.2-78.6) and specificity of 76.47% (95% CI: 69.4-82.6).

Conclusion: A high Haller index is associated with increased recurrent pneumothorax risk in primary spontaneous pneumothorax patients. Traditionally used for pectus excavatum severity, incorporating Haller index in the management of these patients may help to identify high-risk patients and guide personalized management strategies.

Keywords: Haller index, primary spontaneous pneumothorax, recurrence.

ÖZ

Amaç: Bu çalışmada primer spontan pnömotoraks hastalarında nüks riski için Haller indeksinin öngördürücü değeri incelendi.

Çalışma planı: Ocak 2018 - Aralık 2023 tarihleri arasında toraks bilgisayarlı tomografiye giren ve en az bir yıl takip edilen primer spontan pnömotorakslı toplam 285 hasta (260 erkek, 25 kadın; medyan yaş: 23 yıl; dağılım: 17-35 yıl) retrospektif olarak incelendi. Hastalar nüks izlenmeyen grup (n=170) ve nüks grubu (n=115) olmak üzere iki gruba ayrıldı. Başvuru sırasında bilgisayarlı tomografi görüntülerinden Haller indeksi hesaplandı ve bunun pnömotoraks nüksü için öngördürücü değeri tahmin edildi.

Bulgular: Medyan yaş, nüks olmayan grupta, nüks grubuna göre anlamlı olarak daha yüksekti (p<0.001). Nükse kadar geçen medyan süre iki (IQR 1-3) ay idi. Haller indeksinin nüksü öngörme konusundaki tanısal geçerliliği, alıcı işletim karakteristiğinin altında kalan alanının 0.824 (%95 güven aralığı [GA]: 0.775-0.866) (p<0.001) olduğunu gösterdi. Optimal Haller indeksinin kesim değeri (>2.4), %70.43 (%95 GA: 61.2-78.6) duyarlılık ve %76.47 (%95 GA: 69.4-82.6) özgüllük gösterdi.

Sonuç: Yüksek Haller indeksi, primary spontan pnömotoraks hastalarında artmış nüks pnömotoraks riski ile ilişkilidir. Geleneksel olarak pektus ekskavatum şiddeti için kullanılan Haller indeksinin, bu hastaların tedavisine dahil edilmesi, yüksek riskli hastaların tespitine ve kişiselleştirilmiş tedavi stratejilerine rehberlik etmeye yardımcı olabilir.

Anahtar sözcükler: Haller indeksi, primer spontan pnömotoraks, nüks.

One of the most common pathologies affecting the pleural cavity is the abnormal accumulation of gas within the space, known as pneumothorax.[1] Pneumothorax can cause severe symptoms such as shortness of breath and chest pain, necessitating immediate medical intervention due to its critical

Corresponding author: Mesut Buz.
E-mail: mesutbuzmd@gmail.com

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nature. Although the incidence of hospitalization due to pneumothorax varies by region, it has been reported as 11.1 per 100,000 population annually (16.6/100,000/year for men and 5.8/100,000/year for women).[2]

Despite the complexity and varying classification sources, pneumothorax is most divided into two main categories based on etiology: spontaneous and traumatic. The spontaneous category is further divided into three subgroups: primary, secondary, and catamenial, while the traumatic category is divided into two subgroups: iatrogenic and non-iatrogenic.[3] The most frequently encountered type of pneumothorax is primary spontaneous pneumothorax (PSP).[4] Recurrent pneumothorax is common following the initial episode of PSP; therefore, one of the most important factors in the management of PSP is considering the likelihood of recurrence and the need for interventions to prevent recurrence.[5] Therefore, identifying the etiologies that cause PSP is of strategic importance in managing patients after PSP and predicting the recurrence of pneumothorax.

Although some etiological factors for PSP have been identified to date, the exact etiology still remains unclear.[6,7] The majority of the studies have particularly argued that changes in alveolar pressure due to chest wall deformities can contribute to the formation of subpleural bullae, which are among the main risk factors for PSP.[8] While this finding suggests that the anatomical structure of the chest wall may influence the dynamics and pathologies of thoracic respiration, the limited research in this area is notable. The anatomical structure of the chest wall has been examined in studies through the lens of common anterior chest wall deformities (rib cage deformity), such as pectus excavatum (PE), and it has been argued that PE may predispose individuals to the development of PSP and be considered among the etiological factors of spontaneous pneumothorax.[9]

The Haller index (HI) is a ratio of thoracic width to height, measured from axial computed tomography (CT) images, used to describe the internal dimensions of the chest cavity. The HI is a commonly used measurement method in the management of PE.[10] It was developed specifically to determine the severity of chest wall deformities.[11] However, Haller et al.,[12] followed by Daunt et al.,[13] also used the HI to describe thoracic dimensions in individuals without pectus deformities. Research also exists on the impact of chest wall deformities identified using the HI on the development of PSP.[8,9] However, studies on the potential role of the HI in predicting the recurrence of pneumothorax, the most common complication in PSP patients, are limited.

In the present study, we aimed to evaluate the impact of the HI on the risk of recurrent pneumothorax in patients with PSP.

PATIENTS AND METHODS

Study design and study population

This single-center, retrospective study was conducted at the Department of Thoracic Surgery of Kartal Dr. Lütfi Kırdar City Hospital between January 2018 and December 2023. The study included patients who were treated for PSP and followed for at least one year. A written informed consent was obtained from each patient. The study protocol was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (date: 28.02.2024, no: 010.99/1). The study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 499 patients who received a diagnosis of PSP at the Emergency Department (ED) and Thoracic Surgery clinic of the study center were screened. Inclusion criteria were having a clinically and radiologically confirmed diagnosis. Patients without chest CT scans, those with secondary spontaneous pneumothorax (SSP), traumatic pneumothorax, underlying severe lung diseases, lost to follow-up, or incomplete hospital data were excluded from the study. A total of 214 patients were excluded from the study. Finally, 285 patients (260 males, 25 females; median age: 23 years; range, 17 to 35 years) were included. The patients were divided into two groups as the non-recurrence group (n=170) and recurrence (n=115) group. The study flowchart is shown in Figure 1.

Data collection

Data were retrospectively collected from the hospital information management system using the International Classification of Diseases (ICD)-10 diagnosis codes J93 (pneumothorax), J93.0 (spontaneous tension pneumothorax), J93.1 (another spontaneous pneumothorax), J93.8 (other pneumothorax), and J93.9 (pneumothorax unspecified). Demographic data, clinical assessments, imaging results, and follow-up data were obtained from electronic health records. The primary variables included pneumothorax recurrence, age, sex, smoking status, the HI measured at the initial presentation with a PSP diagnosis, the affected lung side, pleural

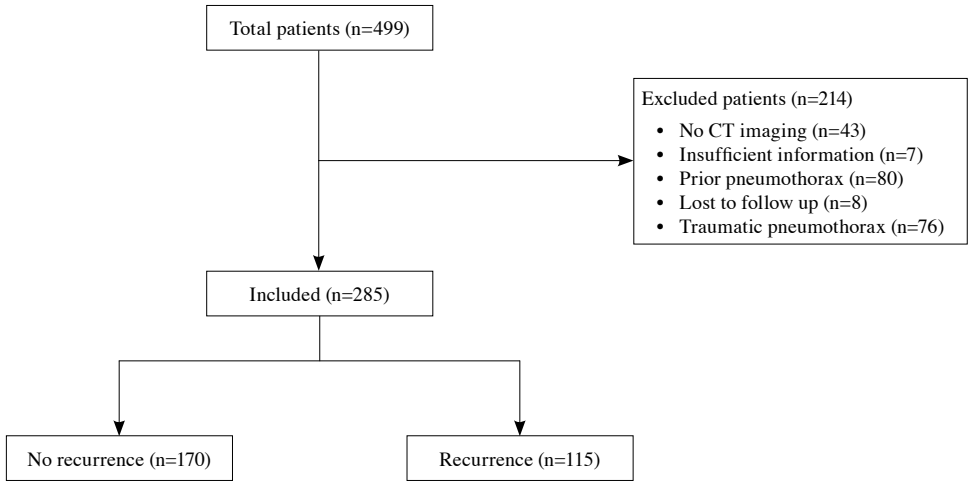

Figure 1. Study flowchart.
CT: Computed tomography.

effusion, pneumomediastinum, the presence of bullae, and the type of treatment administered following the initial PSP presentation. Treatments for PSP are classified into two main categories:

1. Non-surgical treatments: This includes conservative management such as observation with or without supplemental oxygen, and minimally invasive interventions such as needle aspiration and tube thoracostomy.
2. Surgical treatments: This involves invasive surgical interventions, including thoracotomy and video-assisted thoracoscopic surgery (VATS).

Definition of recurrence

Recurrence of pneumothorax was determined by assigning pneumothorax diagnosis codes (J93, J93.1, J93.8, and J93.9) during the data collection period following the initial treatment. Patients identified as having PSP and presenting with similar diagnosis codes at the study center within one year, demonstrating clinical and imaging evidence of recurrent pneumothorax, or those recorded with similar diagnosis codes at other hospitals on the national patient registry platform, with clinical and new pneumothorax findings, were considered to have a recurrence.[14] In this study, only recurrences of pneumothorax that occurred on the same side as the initial pneumothorax were considered as events. This approach was adopted to ensure consistency and accuracy in evaluating the recurrence rates.

Measurements from thoracic CT

In this study, the HI was measured by two independent thoracic surgery specialists who were blinded to the patients' recurrence status. Both specialists used the same PACS to ensure consistency in measurements. The interobserver variability was assessed using the intraclass correlation coefficient (ICC), which demonstrated excellent agreement between the two observers, with an ICC value of 0.70. This process validated the HI measurements and ensured their reliability for analysis.

The HI is calculated using anatomical measurements obtained from chest CT scans. Specifically, it is determined by dividing

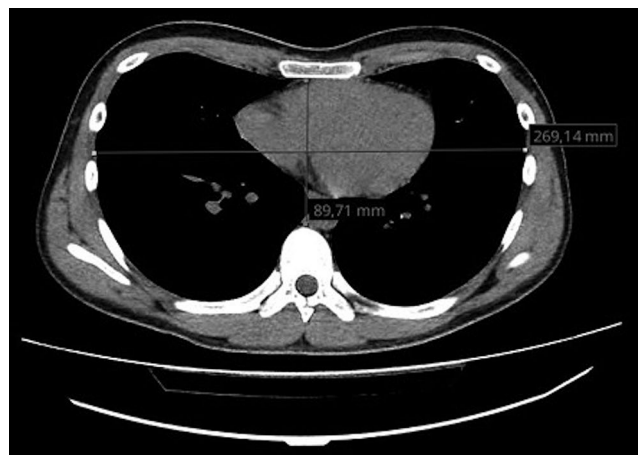

Figure 2. Measurement of the Haller index.

Table 1. Baseline characteristics of patients by recurrence status

Variables	All (n=285)					Non recurrence (n=170)					Recurrence (n=115)						
	n	%	Mean±SD	IQR	Median	n	%	Mean±SD	IQR	Median	n	%	Mean±SD	IQR	Median	*p*	MD	95% CI
Age (year)				18.5-32	23				20-35	27				17-26	21	<0.001		
Sex																		
Female	25	8.8				15	8.8				10	8.7				0.970		
Smoking (smoker)	120	42.1				74	43.5				46	40				0.554		
Pneumothorax side (right)	152	53.3				90	52.9				62	53.9				0.872		
Pleural effusion	8	2.8				6	3.5				2	1.7				0.305		
Pneumomediastinum	12	4.2				9	5.3				3	2.6				0.213		
Bullae	246	86.6				141	57.3				105	42.7				0.056		
Non-surgical treatments	198	69.5				85	50				113	98.3				<0.001		
ACCP (large)	184	64.6				117	68.8				67	58.3				0.067		
BTS (large)	129	45.3				85	50				44	38.3				0.051		
Haller index			2.38±0.51					2.15±0.36					2.73±0.50			<0.001	0.58	0.48-0.68

SD: Standard deviation; IQR: Interquartile range; MD: Mean difference; ACCP: American College of Chest Physicians; BTS: British Thoracic Society.

the transverse diameter of the chest by the anteroposterior (AP) distance on the axial slice that shows the smallest distance between the anterior surface of the vertebral body and the posterior surface of the sternum (Figure 2). The HI can vary depending on the vertebral level at which it is measured and is typically largest at the upper levels. To ensure consistency, it is recommended to calculate the HI at the deepest point of the sternum. A normal chest is characterized by a HI of less than 2.0, while mild PE ranges from 2.0 to 3.2, moderate excavatum ranges from 3.2 to 3.5, and severe excavatum is indicated by a HI greater than 3.5. Corrective surgery for PE is usually considered when the HI is 3.25 or higher.[15,16]

The criteria of the American College of Chest Physicians (ACCP) and the British Thoracic Society (BTS) are standard measures used to assess the size and severity of pneumothorax. In this study, pneumothorax size was differentiated as "large" or "small" based on the presence of a visible rim of >2 cm between the lung margin and the chest wall at the level of the hilum. This measurement was consistently performed using the digital imaging system (PACS) to ensure accurate classification.[17] According to the ACCP criteria, pneumothorax is classified based on the distance from the apex of the lung to the top of the thoracic cavity. If this distance is less than 3 cm, it is considered a small pneumothorax.[18]

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 29.0 software (IBM Corp., Armonk, NY, USA) and MedCalc version 20.104 software (MedCalc Software Ltd., Ostend, Belgium). Descriptive data were presented in mean ± standard deviation (SD) or median [IQR 25^{th}-75^{th}] values for continuous variables and in number and frequency for categorical variables. Normality of data distribution was assessed using the Shapiro-Wilk test and histograms. Group comparisons were conducted using the Pearson chi-square test for categorical variables (or Fisher exact test when assumptions were violated) and the Student t-test or Mann-Whitney U test for continuous variables. For the multivariate analysis, logistic regression was used to identify independent predictors of recurrent pneumothorax. Variables that showed a p value of less than 0.2 in the univariate analysis were included in the multivariate model. The logistic regression results were expressed as odds ratios (ORs) with 95% confidence intervals

(CIs). Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, and the predictive capability of the model was evaluated with the Nagelkerke R^2 and Cox & Snell R^2 values. The receiver operating characteristic (ROC) curves were generated for diagnostic validity tests, and sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios were calculated for the cut-off values with the highest Youden index for statistically significant parameters. A two-sided *p* value of <0.05 was considered statistically significant.

RESULTS

The median age in the non-recurrence group was significantly higher than in the recurrence group (p<0.001) (Table 1). No significant difference in sex distribution was observed between the groups (p=0.970). The smoking rate in the study cohort was 42.1% (n=120), with no significant difference between the groups (p=0.554). The side of the lung affected by pneumothorax was similar across both groups (p=0.872). There were no statistically significant differences in the frequencies of pleural effusion, pneumomediastinum, and bullae between the groups (p=0.305, p=0.213, and p=0.056, respectively). Non-surgical treatments were performed in 69.5% (n=198) of the patients at their initial presentation due to PSP; the rate of non-surgical treatments at initial presentation due to PSP in the recurrence group (98.3%, n=113) was significantly higher than in the non-recurrence group (50%, n=85) (p<0.001). According to the ACCP classification, 64.6% (n=184) of the patients had a large pneumothorax, with no significant difference between the non-recurrence (68.8%, n=117) and recurrence (58.3%, n=67) groups (p=0.067). The BTS classification identified 45.3% (n=129) of the patients with a large pneumothorax, again showing no significant difference between the non-recurrence (50%, n=85) and recurrence (38.3%, n=44) groups (p=0.051). The mean HI was significantly higher in the recurrence group (2.73±0.50) compared to the non-recurrence group (2.15±0.36), with a mean difference of 0.58 (95% CI: 0.48-0.68) (p<0.001).

The median time to recurrence for the included patients was two (IQR 1-3) months (Table 2). In these patients, a large pneumothorax was observed in 40.9% (n=47) according to the ACCP criteria and in 27% (n=31) according to the BTS criteria.

A multivariate logistic regression analysis was conducted to identify independent predictors of recurrent pneumothorax in patients with PSP. The variables included in the analysis were age, presence of bullae, initial treatment approach (non-surgical *vs.* surgical), BTS classification of pneumothorax size, and HI (Table 3).

The results indicated that non-surgical treatments were significantly associated with a higher risk of recurrence, with an OR of 48.68

Table 2. Characteristics of recurrence group (n=115)

Variables	n	%	Median	IQR
Time to recurrence (month)			2	1-3
ACCP (large)	47	40.9		
BTS (large)	31	27		

IQR: Interquartile range; ACCP: American College of Chest Physicians; BTS: British Thoracic Society.

Table 3. Multivariate analysis of factors associated with recurrent pneumothorax

Variables	*p*	OR	95% CI
Age	0.053	0.956	0.921-1.002
Bullae	0.129	0.359	0.096-1.370
Non-surgical treatments	<0.001	48.68	9.73-243.48
BTS (large pneumothorax)	0.002	0.332	0.164-0.674
Haller index	<0.001	35.75	10.84-117.9

OR: Odds ratio; CI: Confidence interval; BTS: British Thoracic Society.

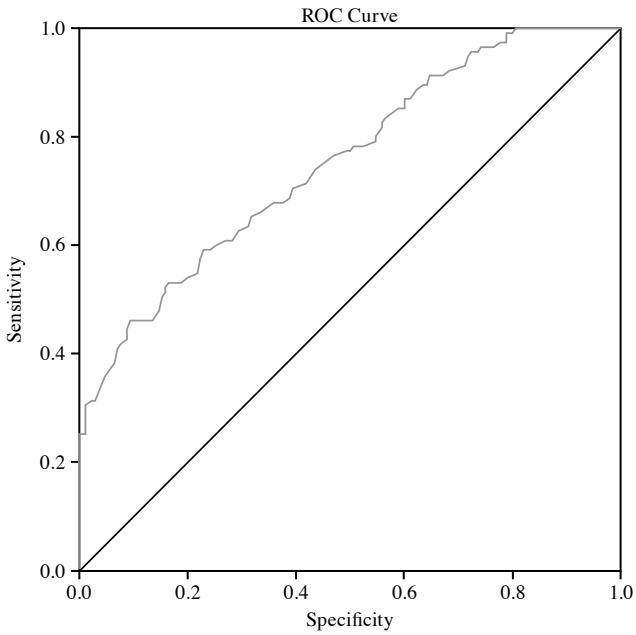

Figure 3. Receiver operating characteristic curve (ROC) for prediction of recurrent pneumothorax based on Haller index.

(95% CI: 9.73-243.48, p<0.001). Similarly, a higher HI was a strong independent predictor of recurrence, with an OR of 35.75 (95% CI: 10.84-117.9, p<0.001). The BTS classification of large pneumothorax was associated with a lower risk of recurrence (OR: 0.332, 95% CI: 0.164-0.674, p=0.002).

Age was not a statistically significant predictor of recurrence (OR: 0.956, 95% CI: 0.921-1.002, p=0.053), although there was a trend toward younger patients being at a higher risk. The presence of bullae did not reach statistical significance as an independent predictor (OR: 0.359, 95% CI: 0.096-1.370, p=0.129).

Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test, which indicated a good fit (p=0.664). The Nagelkerke R^2 value was 0.638, and the Cox & Snell R^2 was 0.472, indicating a moderate to strong predictive capability of the model.

The diagnostic validity analysis of the HI for predicting recurrent pneumothorax showed an area under the ROC (AUROC) of 0.824 (95% CI: 0.775-0.866) (p<0.001) (Figure 3). Using the Youden index for the optimal cut-off value (>2.4), the sensitivity was 70.43% (95% CI: 61.2-78.6), specificity was 76.47% (95% CI: 69.4-82.6), positive likelihood ratio was 2.99 (95% CI: 2.23-4.02), and negative likelihood ratio was 0.39 (95% CI: 0.29-0.52).

DISCUSSION

In the present study, we evaluated the impact of the HI on the risk of recurrent pneumothorax in patients with PSP. Our study results showed that the mean HI significantly higher in patients who were treated for PSP and subsequently experienced recurrent pneumothorax. This finding suggests that patients with higher HI values may be more prone to recurrent episodes, indicating that the HI can be used as a simple and effective standard measurement tool for predicting recurrence.

Most recurrent pneumothorax cases following PSP occur within the first year, with an incidence ranging from 25 to 50%, and the recurrence rate is the highest within the first 30 days.[19] In our study, the incidence and timing of recurrent pneumothorax are consistent with the literature.

Considering the etiological factors, PSP is typically associated with the rupture of subpleural bullae, whereas the etiology of SSP includes various lung diseases. Primary spontaneous pneumothorax classically occurs in tall, thin males, typically between the ages of 10 and 30, with a family history of the condition, and smokers with subpleural bullae. It is thought that the development of subpleural bullae may be due to either the increased negative pressure at the apex of the lungs during growth, increased mechanical alveolar stretch, or a congenital phenomenon where the lung tissue at the apex grows faster than its vascular supply, thereby outstripping the blood flow.[20] These etiological foundations highlight three primary factors in PSP patients: First, patient demographics, which include factors such as sex, age, and genetic predispositions. Second, idiopathic phenomena which lead to deformities in the chest wall and lung parenchyma. Third, predisposing factors, with smoking being a significant contributor. Our research examined the incidence and emergence of recurrent pneumothorax in PSP patients in relation to these key factors. The established risk factors for the recurrence of PSP are contralateral, bilateral, or life-threatening PSP; high-risk occupations or hobbies; prolonged air leakage after thoracostomy.[21] However, there is a limited number of studies investigating the impact of etiological factors causing PSP on its recurrence.

The first etiological foundation of PSP is demographic factors. Primary spontaneous pneumothorax more frequently occurs in individuals aged 15 to 34 years, particularly in tall and thin males, as a result of the spontaneous collapse of lung

tissue.[22] While sex and age are significant factors in PSP, research indicates that they do not significantly affect pneumothorax recurrence.[23] In our study, although the overall average age was young, the average age of patients with recurrent pneumothorax was significantly lower compared to those without recurrence. Additionally, while our study population was predominantly male, consistent with the literature, we did not find a significant difference in recurrence rates between exes. This contrasts with other studies that have observed higher recurrence rates in men or women.[24,25]

Upon reviewing the literature, it is evident that research on the etiological causes of PSP frequently focuses on genetic factors and idiopathic phenomena leading to chest wall and lung parenchyma deformities, particularly the structure of subpleural bullae.[26,27] In our study, bullae were identified in 86.6% of patients with PSP, which is consistent with the literature. However, no significant difference was found in the presence of bullae between patients with recurrent pneumothorax and those without recurrence. Although the anatomical lesion known as a bulla was first described by Miller[6] in 1947, its mechanisms of formation still remain debated.[28] The key to understanding both PSP and recurrent pneumothorax in treated PSP patients lies in accurately identifying the main etiological factor. Primary spontaneous pneumothorax occurs without primary lung disease and without thoracic trauma, involving the presence of a bulla (connective tissue disorder) and its rupture, leading to air leakage into the pleural cavity.[29] In this context, our research focused on the anatomical structure of the chest and its influence on PSP and recurrent pneumothorax, specifically examining the HI. We observed that higher HI values were associated with recurrent pneumothorax. This finding suggests that the anatomical dynamics of the chest can serve as a simple yet effective predictive tool for pneumothorax recurrence. Our study is consistent with previous research suggesting that PE deformities in the chest wall can predispose individuals to PSP, supporting the notion that PE is an etiological factor in PSP development.[9] Furthermore, our findings emphasize the significance of chest anatomy in the recurrence of pneumothorax. Considering the polygenic nature and variable penetrance of these conditions, it is plausible that both PSP and recurrent pneumothorax may originate from a common etiological factor: the anatomical structure of the chest wall.

The chest wall is a complex three-dimensional structure which reflects the intrathoracic contents and functions of the chest. Traditionally, the HI is used to measure the severity of PE, the most common chest wall deformity. This index is calculated as the ratio of the widest transverse diameter of the chest to the AP diameter at the deepest point of the deformity. Conditions with a HI above 3.25 are usually considered severe PE and may require surgical intervention. The use of the HI is not limited to this context but has also been investigated for evaluating postoperative complications. Mortellaro et al.[30] found no correlation between preoperative HI ratios of PE patients and age, surgery duration, postoperative bar infection, or length of hospital stay; however, a correlation was observed with the development of pneumothorax. Our study also examined the potential of the HI to predict the risk of recurrence in PSP patients and found significantly higher HI values in patients who developed pneumothorax. This novel application may provide clinicians with an additional tool for risk stratification and management of PSP patients.

Another etiological factor for PSP is smoking, which is a global public health issue today. Smoking is considered a predisposing factor which influences PSP, SSP, and recurrent pneumothorax.[31,32] In our study, smoking rates were high among PSP patients; however, no significant difference was found between recurrent pneumothorax patients and those without recurrence.

While recommending treatment approaches for PSP, non-surgical treatments remain among the first suggestions, and the role of surgical treatments like VATS as a primary treatment for PSP remains unclear.[33] Video-assisted thoracoscopic surgery is recommended for patients with PSP or SSP who have a clear indication for a procedure, based on its high efficacy and lower adverse effect profile compared to thoracotomy.[34,35] However, in our study, it was observed that conservative treatment was frequently preferred at the initial presentation of patients who later developed recurrent pneumothorax.

The current guidelines emphasize the need for further research to better determine the optimal timing of operative intervention, the most effective operation, and the management of recurrence after observation, tube thoracostomy, or surgical intervention in the management of PSP patients.[28] In the present study, we examined the role of the anatomical structure of the chest wall, an etiological factor in the development of recurrent pneumothorax following PSP, using the HI, which was developed for standardizing the management of the most common

chest wall deformity. The findings indicated that patients with a high HI following PSP had a higher rate of recurrent pneumothorax, suggesting that this scoring method could be used as a predictor of recurrence after PSP.

Nonetheless, this study has several limitations. The main limitation is that it was conducted in a single center, and only patients who presented to the ED and thoracic surgery clinic with PSP, who underwent thoracic CT during the diagnostic process before treatment, were included. In the diagnosis and management of PSP, the initial step typically involves a chest X-ray, and chest CT is not a mandatory examination within the treatment approach. However, due to the necessity of using chest CT for accurate HI measurement, patients whose management was based solely on chest X-rays were not included in this study. This limitation could potentially introduce bias into our study.

In conclusion the Haller index is a commonly used, standard, and simple measurement method for evaluating patients with chest wall deformities. Based on our findings, the Haller index can be an important predictor for the development of recurrent pneumothorax after PSP. Further large-scale, prospective studies are needed to establish more definite conclusions on this subject.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, design, data analysis, literature review, drafting the article, critical review: M.B.; Data collection, data analysis, literature review Y.E.Ö., M.İ.S.; Concept, design, data collection, data analysis: M.T.D.; Design, critical review: R.B.Ç.; Data analysis and interpretation, critical review: A.Ö.; Concept, design, supervision, critical review: R.D.

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