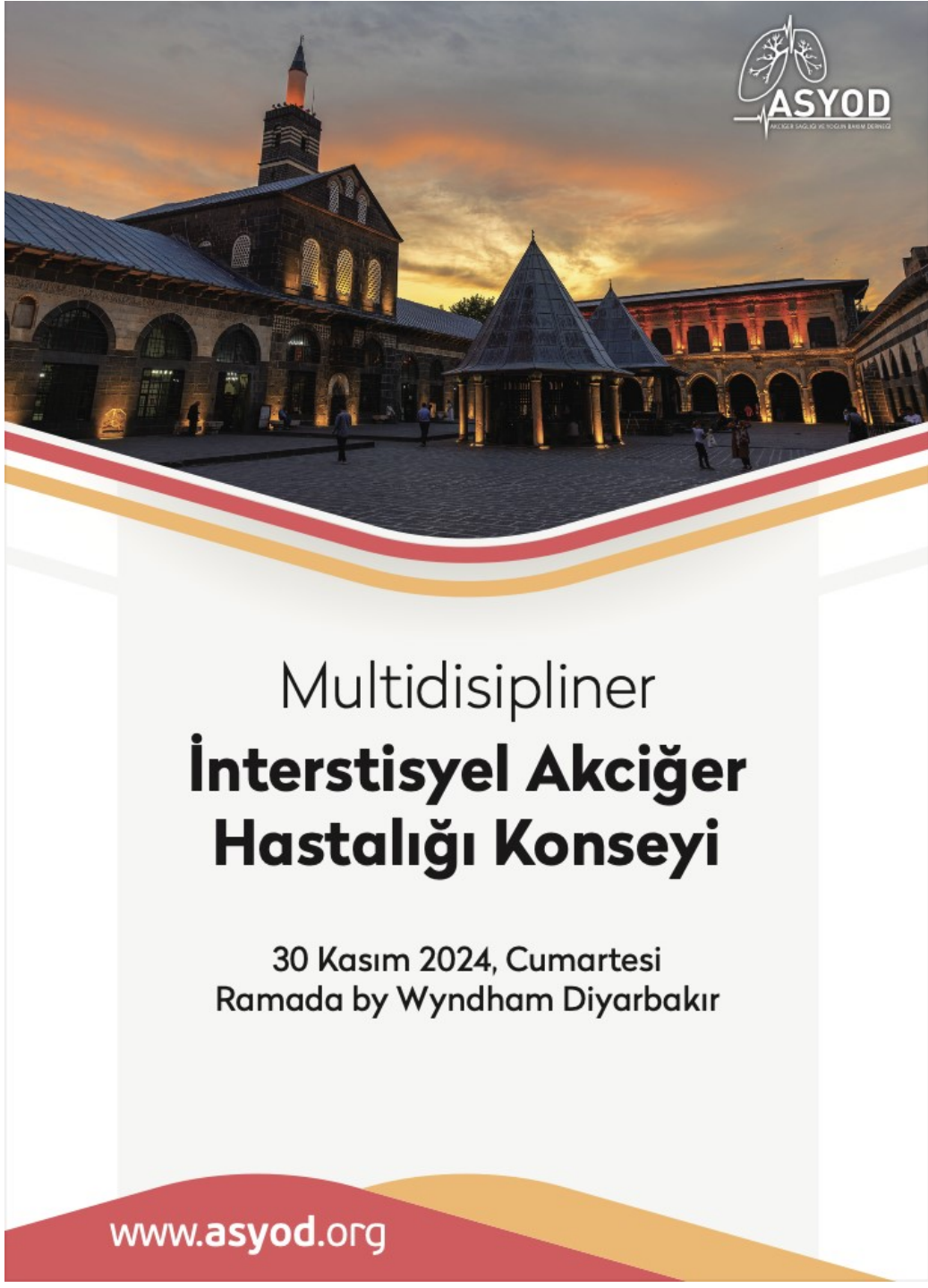
Olgu Sunumu: İPF

Dr. Dildar Duman

S.B.Ü Süreyyapaşa Göğüs Hastalıkları ve
Göğüs Cerrahisi Eğitim Araştırma Hastanesi



Başvuru 2021

- 65 yaş erkek hasta

Şikayetleri:

- Nefes darlığı
- Öksürük
- Çabuk yorulma
- Göğüs ağrısı

İnterstisyel akciğer hastalıkları polikliniğine yönlendiriliyor

Özgeçmiş

- Emekli bankacı
- 40 pk/yıl sigara, 10 yıldır exsmoker
- Bilinen maruziyet veya hobi yok
- Ek hastalık: KOAH
- Kullandığı ilaçlar : İKS/LABA ve LAMA
- Soy geçmiş: ağabeyi MI dan ex

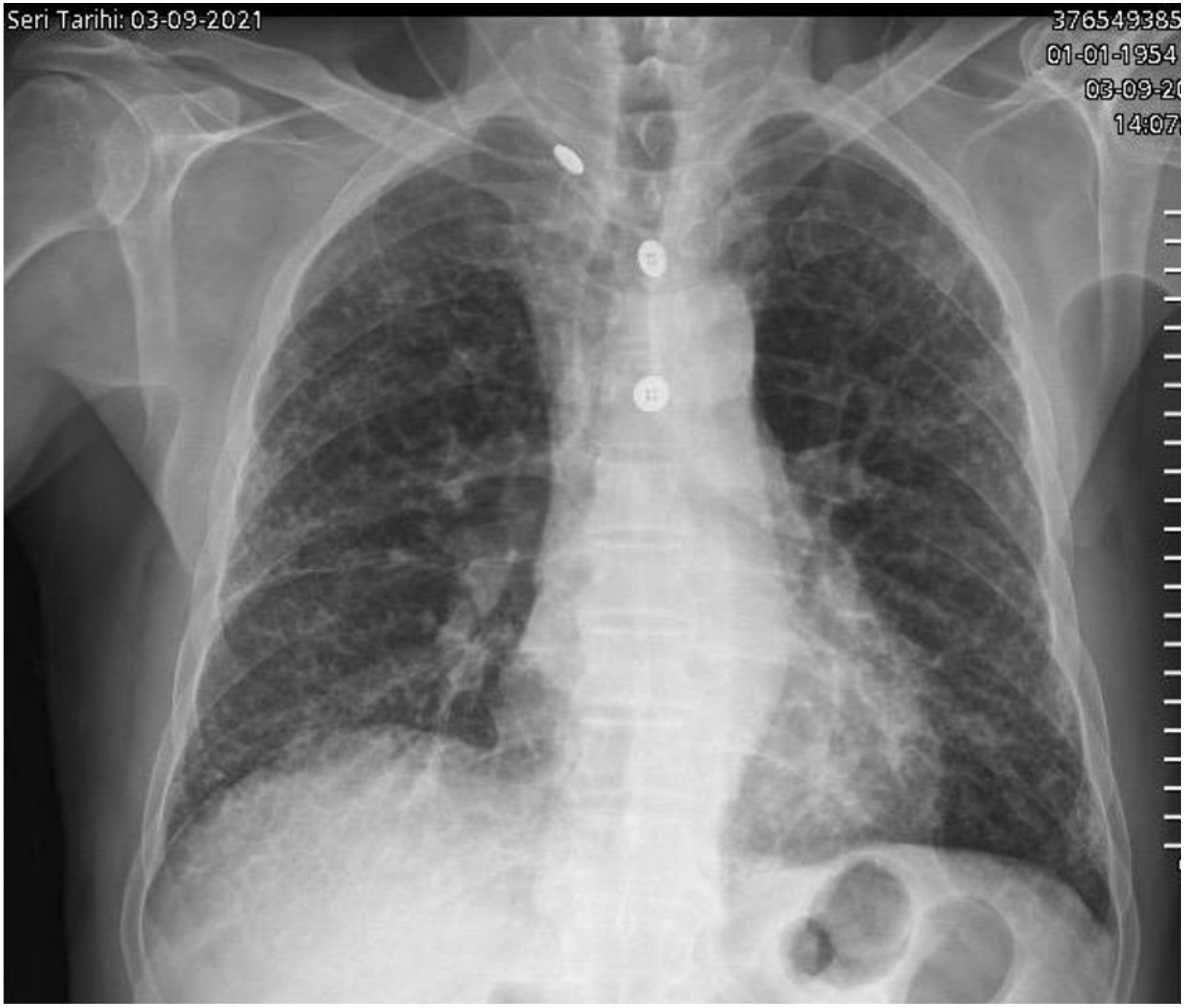
Fizik Muayene

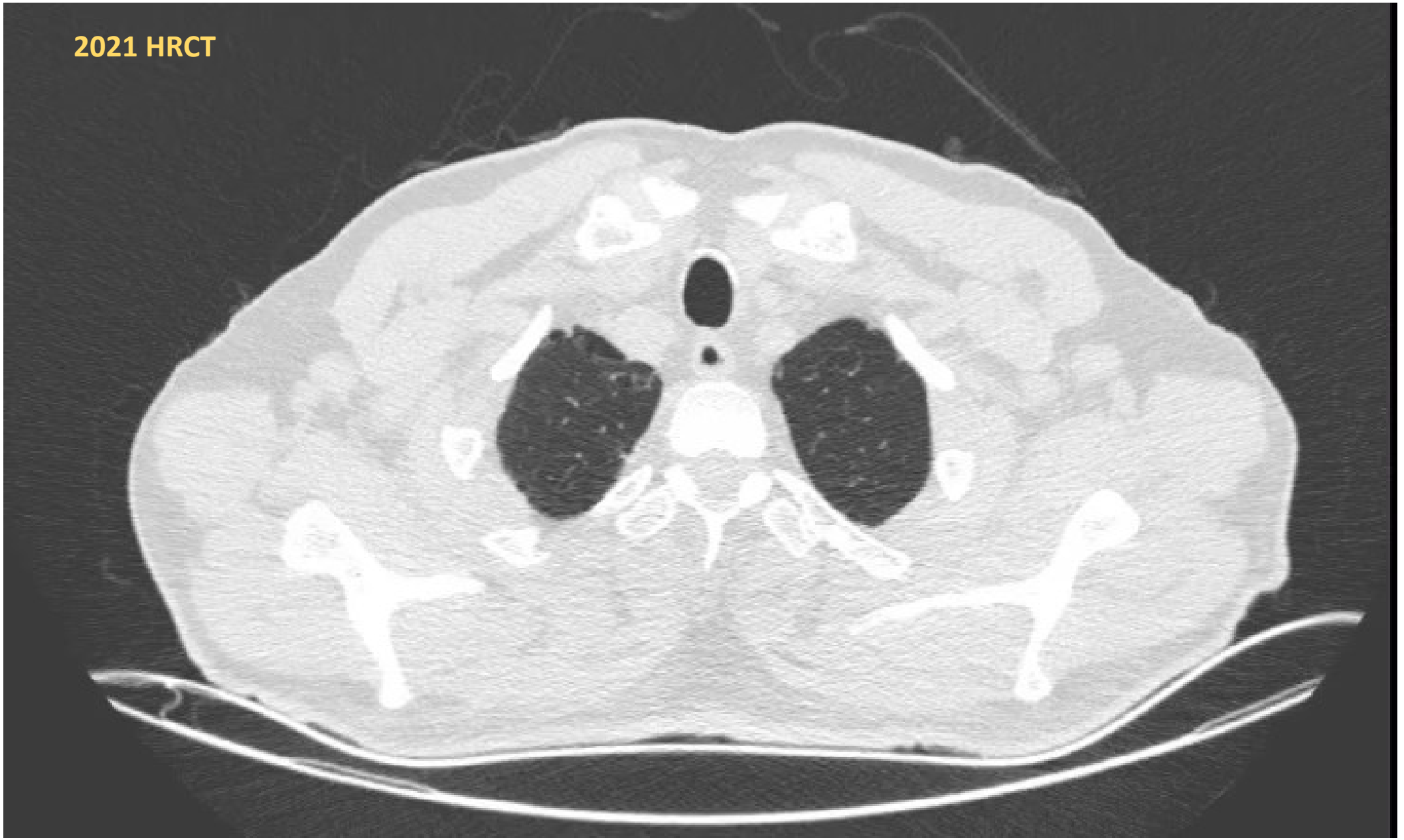
- Genel durumu orta, bilinci açık, oryante, koopere
- TA:110/75 mmHg, NDS:92/dk, DSS:18/dk, SpO2:%97(fio2 %21) Ateş: 36,5 ˚C
- Solunum sistemi: Her iki hemitoraks solunuma eşit katılıyor ,bilateral alt zonlarda velcro raller++ expiryum uzun++
- Çomak parmak (-) , ellerde Raynaud uyumlu renk değişikliği + , sklerodaktili +
- KVS: S1+ S2+ ek ses, üfürüm yok, periferik nabızlar alınıyor

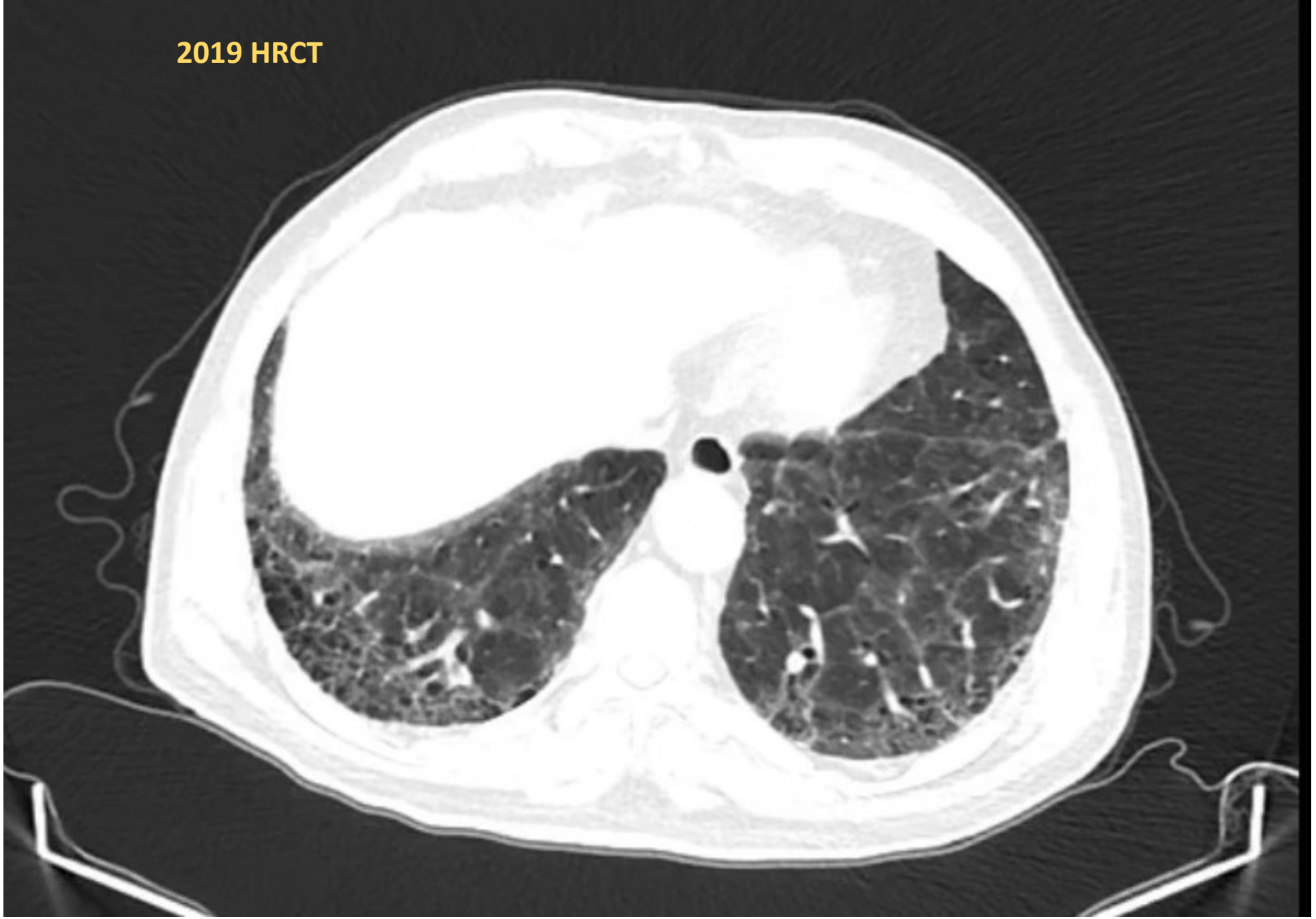
- Baş-Boyun: Tiroid nonpalpabl. LAP yok.
- GİS: Batın rahat, defans yok, rebound yok, hepatosplenomegali yok
- GÜS : KVAH -/-
- Ekstremite: PTÖ -/- ,
- Tek taraflı ısı artışı - , homans-
- Nörolojik muayene: doğal
- Diğer sistem muayeneleri doğal

2021 Başvuru

PAAC Grafi




2021 HRCT


2019 HRCT

Laboratuvar

- **Hemogram**
- Wbc: 6040/mm³
- Hgb: 13.9 g/dl
- Plt: 258000/mm³
- Neu:3950/mm³
- Lenf:2000/mm³
- Mon:700/mm³
- Eos:110/mm³
- Bas:3/mm³

Biyokimya

Glukoz:	87 mg/dl
Üre:	10 mg/dL
Kreatinin:	0,69 mg/dL
CRP:	**16,5 mg/dl (0-5)**
ALT:	11 U/L
AST:	12 U/L
Na:	140
D-Dimer:	0,3 mg/L (0-0,5)
APTT:	26 sn
PT:	16 sn
İNR:	1,15

Laboratuvar

- Troponin: 5,57 ng/L (0-14)
- Pro BNP: 64,28 ng/L (0-125)
- Procalcitonin: 0,03µg/L (0-0,5)
- Sedimantasyon: 20/sa (0-20)

Anti nükleer antikor(ANA) : Pozitif 1/640
Romatoid Faktör : Negatif (13U/mL)
Anti-CCP: Negatif
Anti ds-DNA: Negatif
Anti-JO1:Negatif
Anti-SSB: Negatif
Anti topoizomeraz(SCL-70): negatif
Anti-U1RNP: Negatif
C-ANCA(PR-3): Negatif
P-ANCA(MPO): Negatif

2021 SFT_DLCO

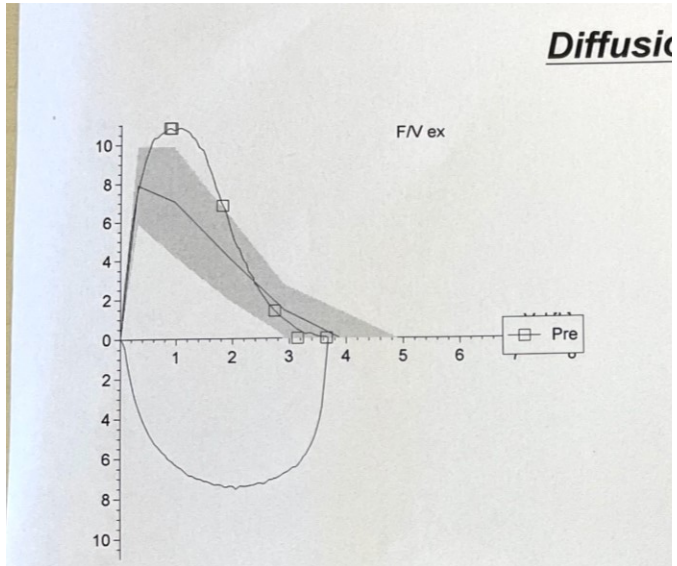
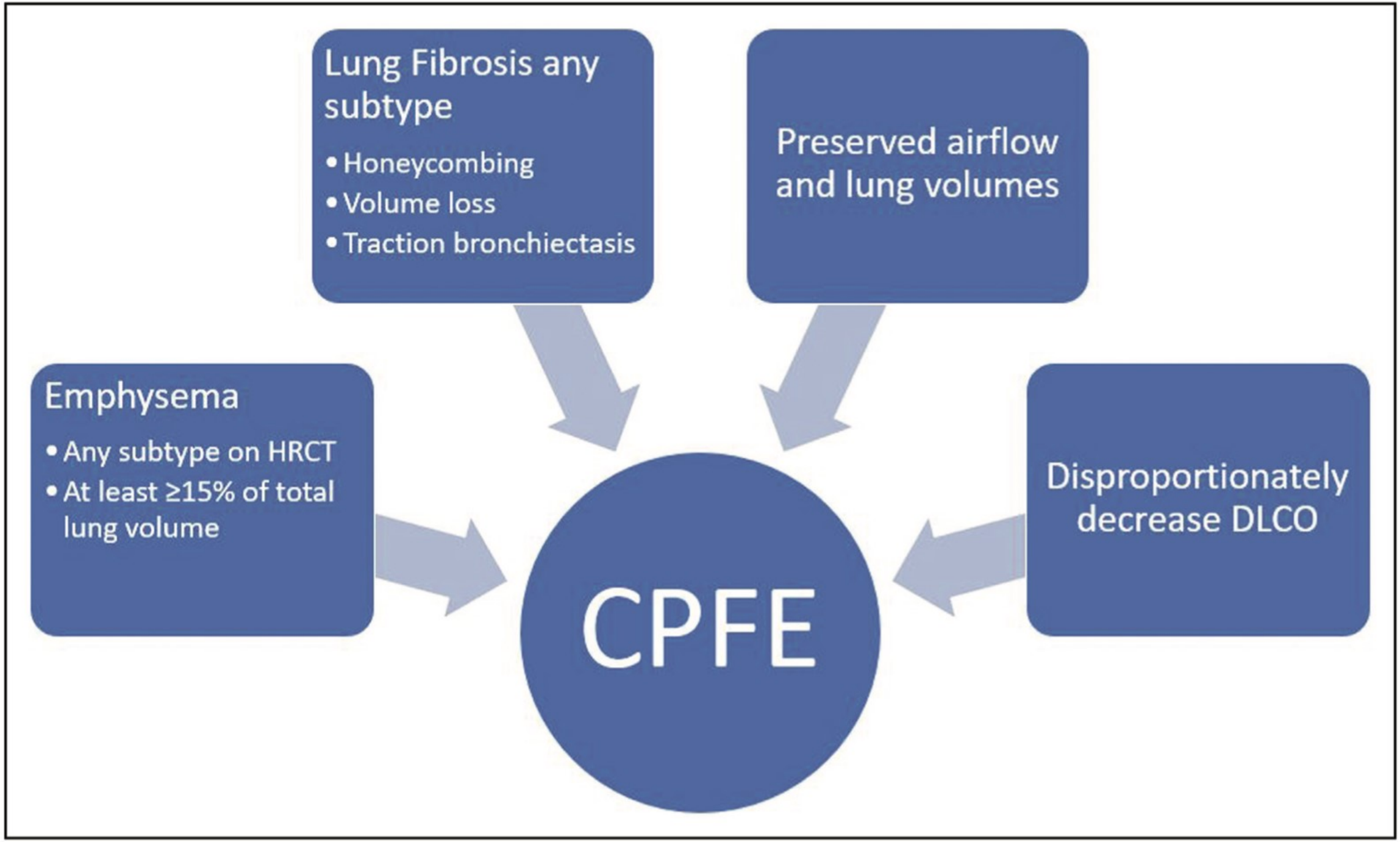


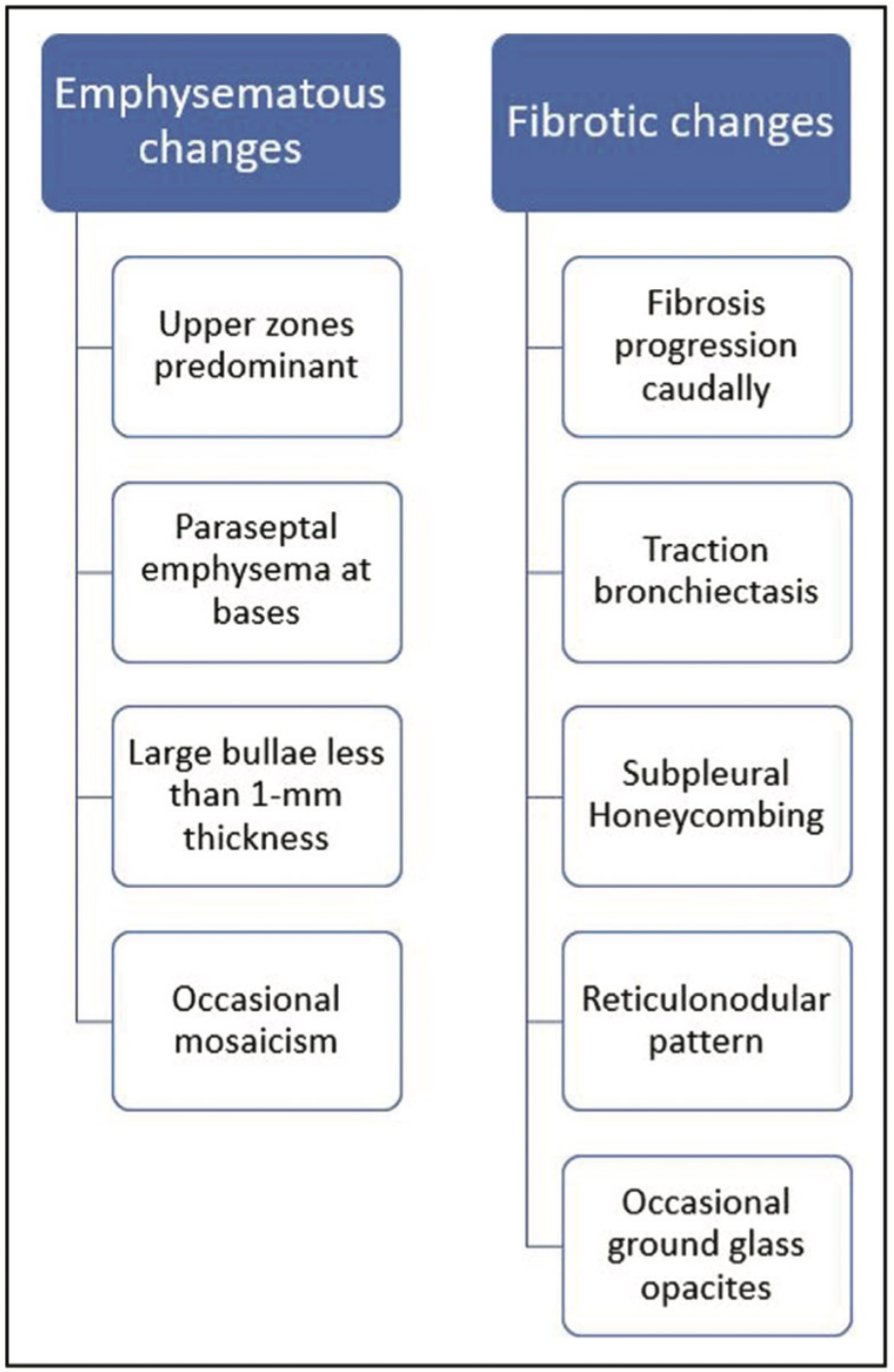
Table 4. Main Characteristics of Pulmonary Function in Combined Pulmonary Fibrosis and Emphysema

Pulmonary Function Test Measurement	Typical Abnormality Seen in CPFE	Typical Abnormality Seen in fILD without Emphysema
FVC	Decreased or normal (but preserved compared with idiopathic pulmonary fibrosis alone)	Decreased
FEV_1	Decreased or normal	Decreased
FEV_1/FVC	Variable (normal, decreased, or increased)	Normal or increased
TLC	Variable (normal, decreased, or increased)	Decreased
FRC	Variable (normal, decreased, or increased)	Decreased
Residual volume	Variable (normal, decreased, or increased)	Decreased
D_{LCO}	Disproportionately decreased	Decreased
Transfer coefficient for carbon monoxide	Severely decreased	Normal or decreased
Saturation during exercise	Severe desaturation	Desaturation
Peak oxygen uptake	Decreased	Decreased

	Pred	Pre	%(Pre/Pred)
FVC	3.88	3.65	94
FEV 1	3.01	3.15	105
FEV 1 % FVC	75.15	86.18	115
MMEF 75/25	3.18	4.48	141
PEF	7.89	10.84	137
MEF 75	7.03	10.81	154
MEF 50	4.13	6.80	165
MEF 25	1.43	1.38	97

		Pred	Best	%(Best/Pred)
DLCO_SB	mmol/(min*kPa)	8.77	4.05	46
KCO_SB	mmol/(min*kPa*L)	1.30	0.79	61
VIN_SB	L	4.03	3.38	84
VA_SB	L	6.59	5.13	78
Hb	g(Hb)/dL		14.20	
DLCOcSB	mmol/(min*kPa)	8.77	4.10	47
KCOc_SB	mmol/(min*kPa*L)	1.30	0.80	61
Level date			03.09.21	
Level time			15:15	


Lung Fibrosis any subtype
• Honeycombing
• Volume loss
• Traction bronchiectasis
Preserved airflow and lung volumes
Emphysema
• Any subtype on HRCT
• At least ≥15% of total lung volume
CPFE
Disproportionately decrease DLCO



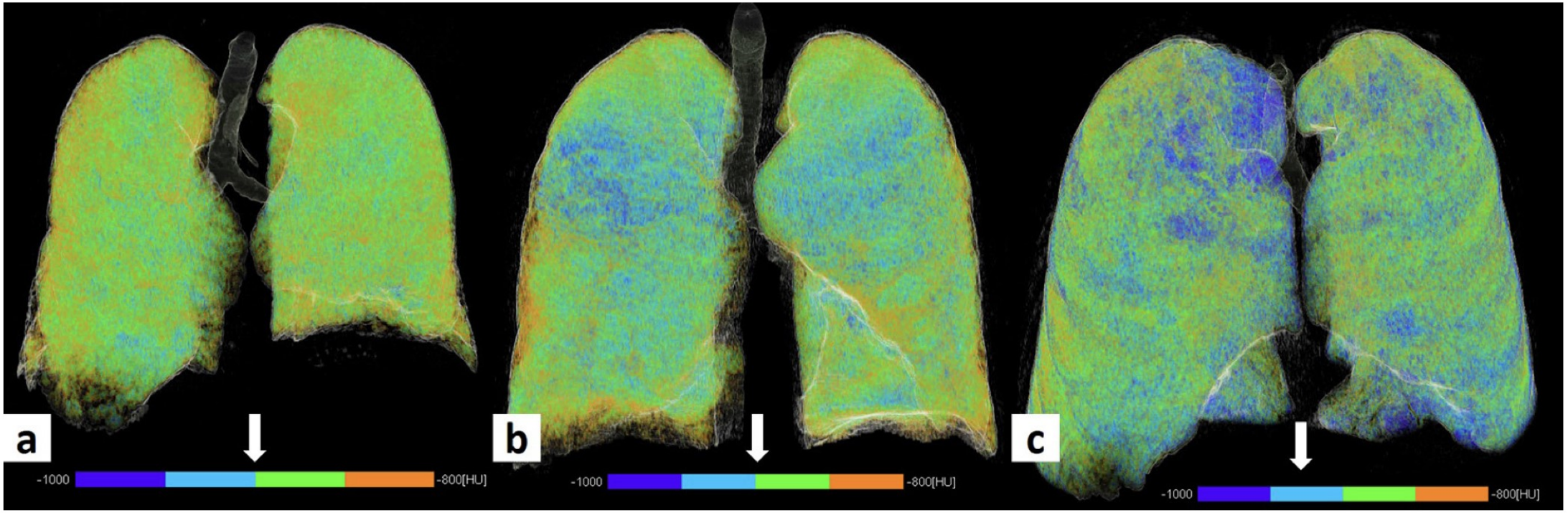
Kombine Pulmoner Fibrozis Amfizem (KPFA)

KEY POINTS

- Combined pulmonary fibrosis and emphysema (CPFE) is a clinical-radiological diagnosis mainly affecting men with more than 40 pack-year smoking history.
- Imaging is classically characterized by upper lobe emphysema and lower lobe fibrosis, although zone predilection is not required for diagnosis.
- A disproportionately low diffusing capacity of the lungs is common with minimal to relatively normal spirometric values.
- Patients have a higher risk of developing pulmonary hypertension and lung cancer.

Kombine Pulmoner Fibrozis Amfizem (KPFA)

Akciğer volümleri korunur



A-idiopathic pulmonary fibrosis,
B-combined pulmonary fibrosis and emphysema
C-emphysema only

blue color : low density, that is, emphysema, and orange :high density, that is, reticular density-fibrosis.

KPFA Tedavi

Table 13. Key Points of Current Practice Management in Patients with Combined Pulmonary Fibrosis and Emphysema

General measures	Smoking cessation
	Pulmonary rehabilitation
	Vaccination against influenza, *Pneumococcus*, and COVID-19
	Supplemental oxygen therapy as per recommendations (286, 290)
	Consider lung transplantation
Pulmonary fibrosis	Lack of evidence specific to CPFE
	Individual management and decisions about pharmacologic treatment (e.g., antifibrotic medication, immunosuppressants) should be discussed by a multidisciplinary team based on type of fILD, relative predominance of fibrosis versus emphysema, and disease progression
	Consider antifibrotic medications at first presentation of patients with IPF with CPFE, and in other forms of pulmonary fibrosis with CPFE, progressing despite management
Pulmonary emphysema	Lack of evidence specific to CPFE
	Consider inhaled bronchodilators and inhaled corticosteroids as per indications in COPD
Complications and comorbidities	Lack of evidence related to treatment of PH specific to CPFE
	Management of comorbidities, especially cardiovascular disease and lung cancer

American Journal of Respiratory and Critical Care Medicine Volume 206 Number 4 | August 15 2022

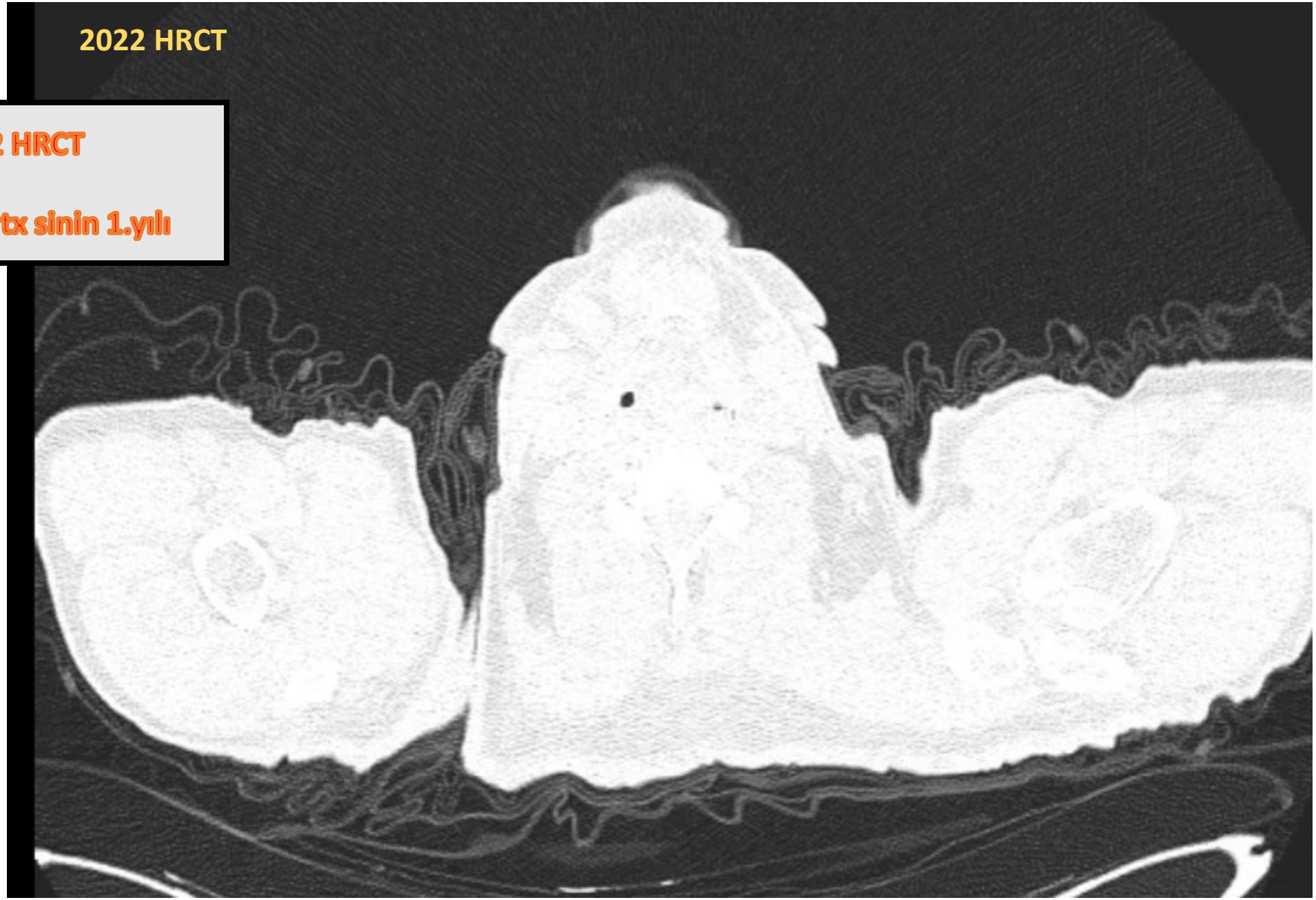
Antifibrotik Tedavi

- Pirfenidon 200 mg tb ile başlanıp

- İlk hafta 4x1
- İkinci hafta 4x2
- Üçüncü hafta 4x3

- Titrasyon sonrası
  tam doz 2400 mg/gün(600 mg tb 4x1) ile devam edildi

2022 HRCT

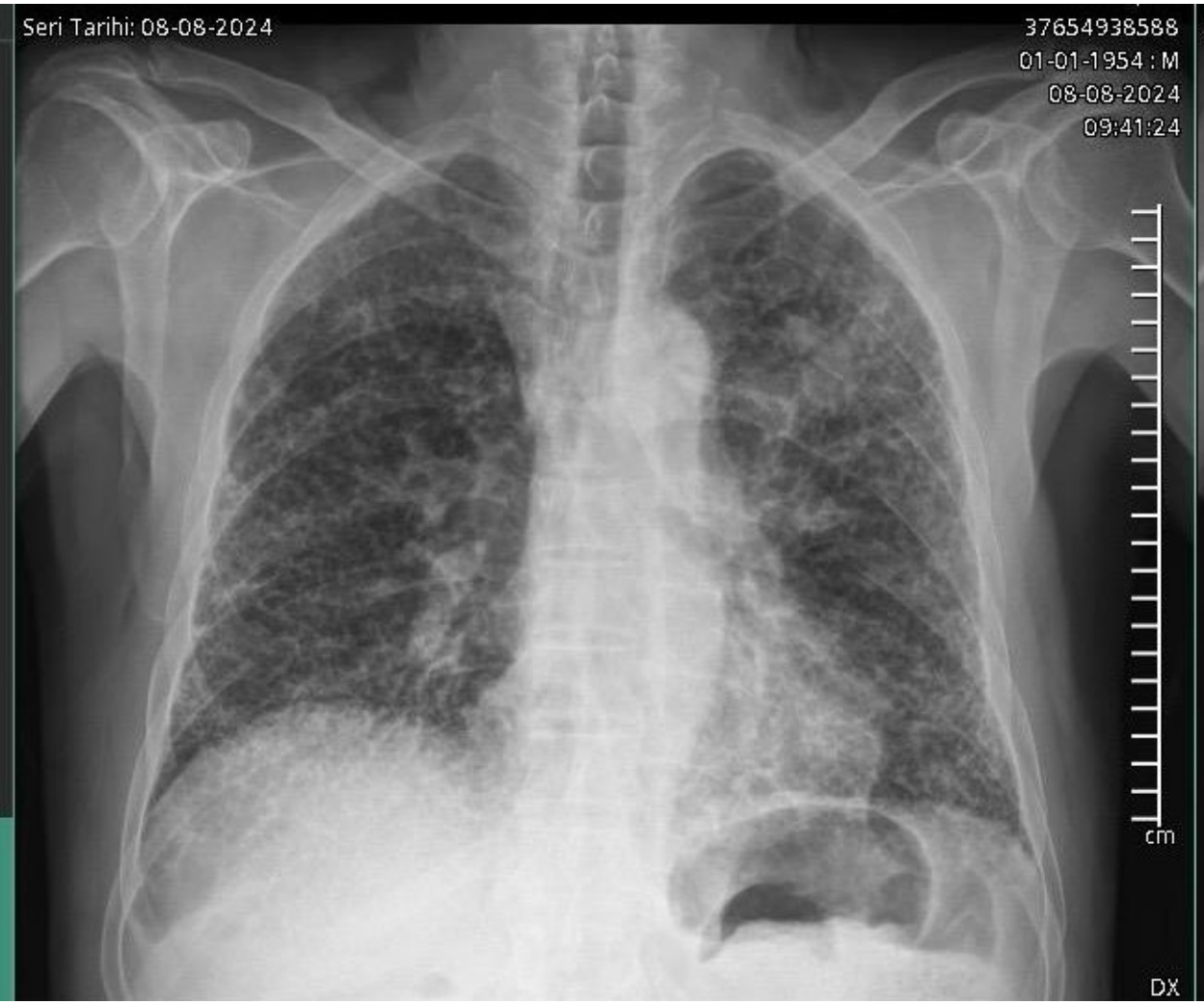


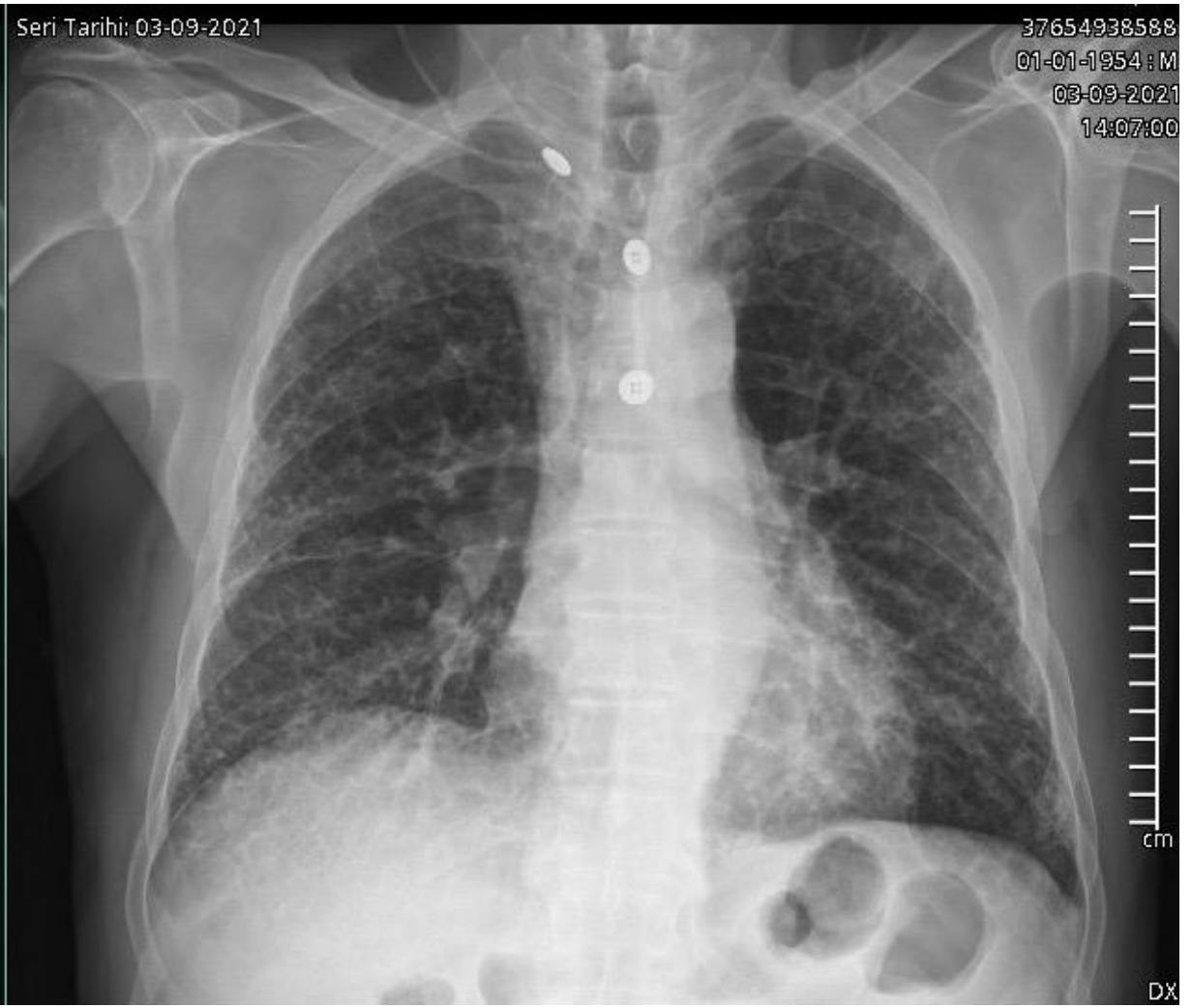
2022 HRCT

Pirfenidon tx sinin 1.yılı

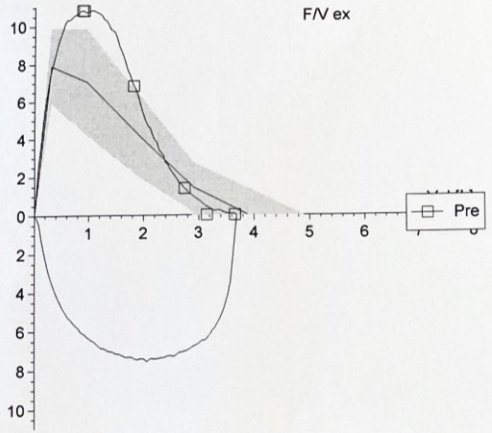
2024- 2021

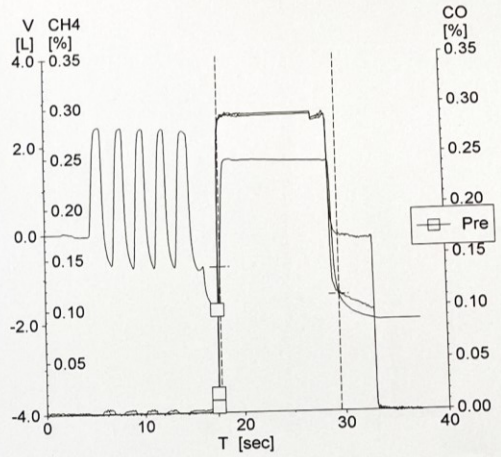
PAAC Grafi





Diffusion SB



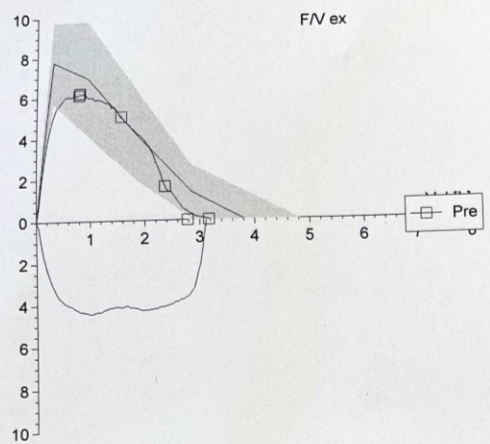


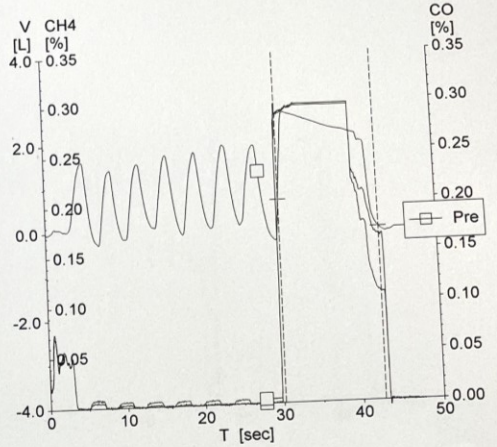
	Pred	Pre	%(Pre/Pred)
FVC	3.88	3.65	94
FEV 1	3.01	3.15	105
FEV 1 % FVC	75.15	86.18	115
MMEF 75/25	3.18	4.48	141
PEF	7.89	10.84	137
MEF 75	7.03	10.81	154
MEF 50	4.13	6.80	165
MEF 25	1.43	1.38	97

		Pred	Best	%(Best/Pred)
DLCO_SB	mmol/(min*kPa)	8.77	4.05	46
KCO_SB	mmol/(min*kPa*L)	1.30	0.79	61
VIN_SB	L	4.03	3.38	84
VA_SB	L	6.59	5.13	78
Hb	g(Hb)/dL		14.20	
DLCOcSB	mmol/(min*kPa)	8.77	4.10	47
KCOc_SB	mmol/(min*kPa*L)	1.30	0.80	61

Level date		03.09.21
Level time		15:15

Diffusion SB

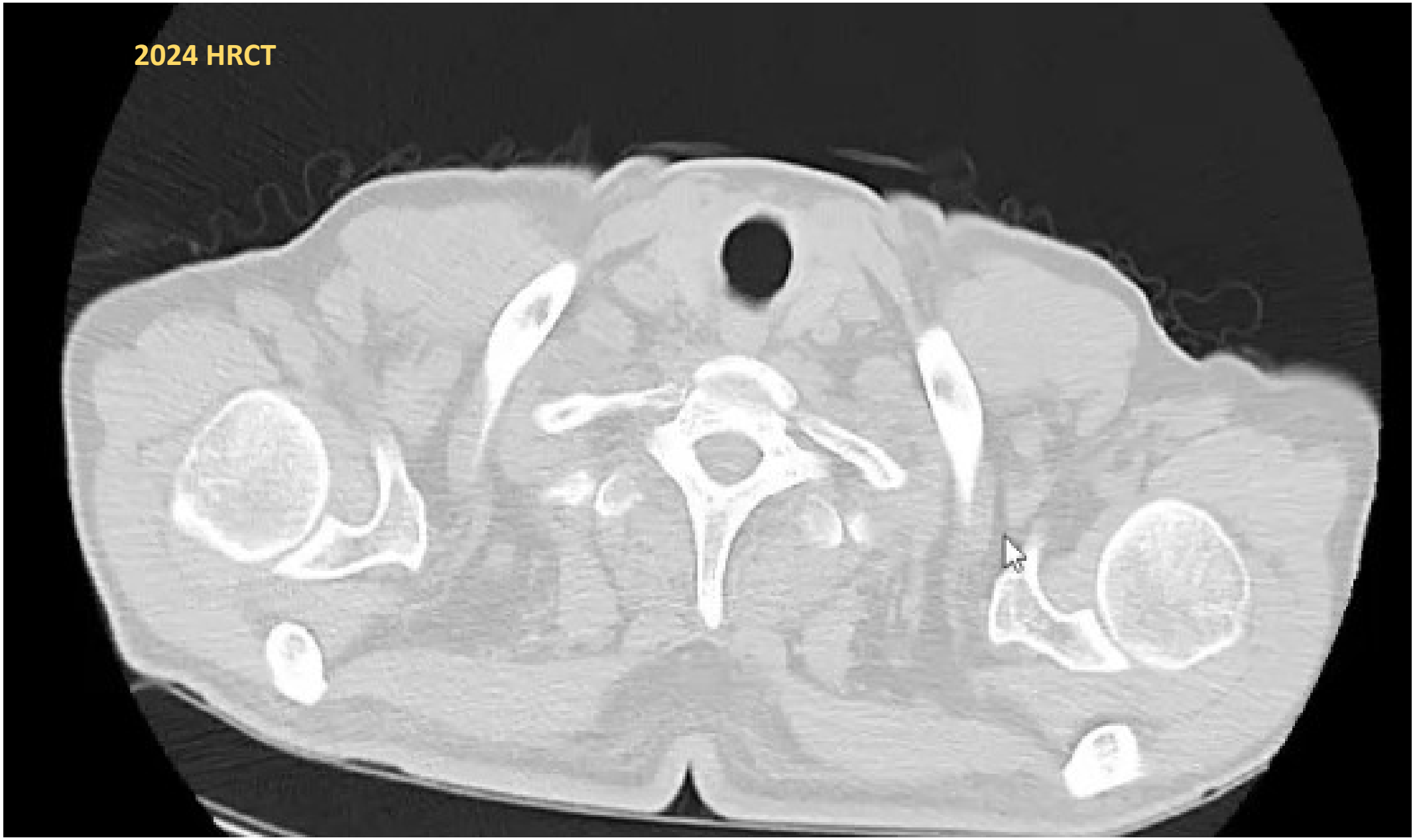




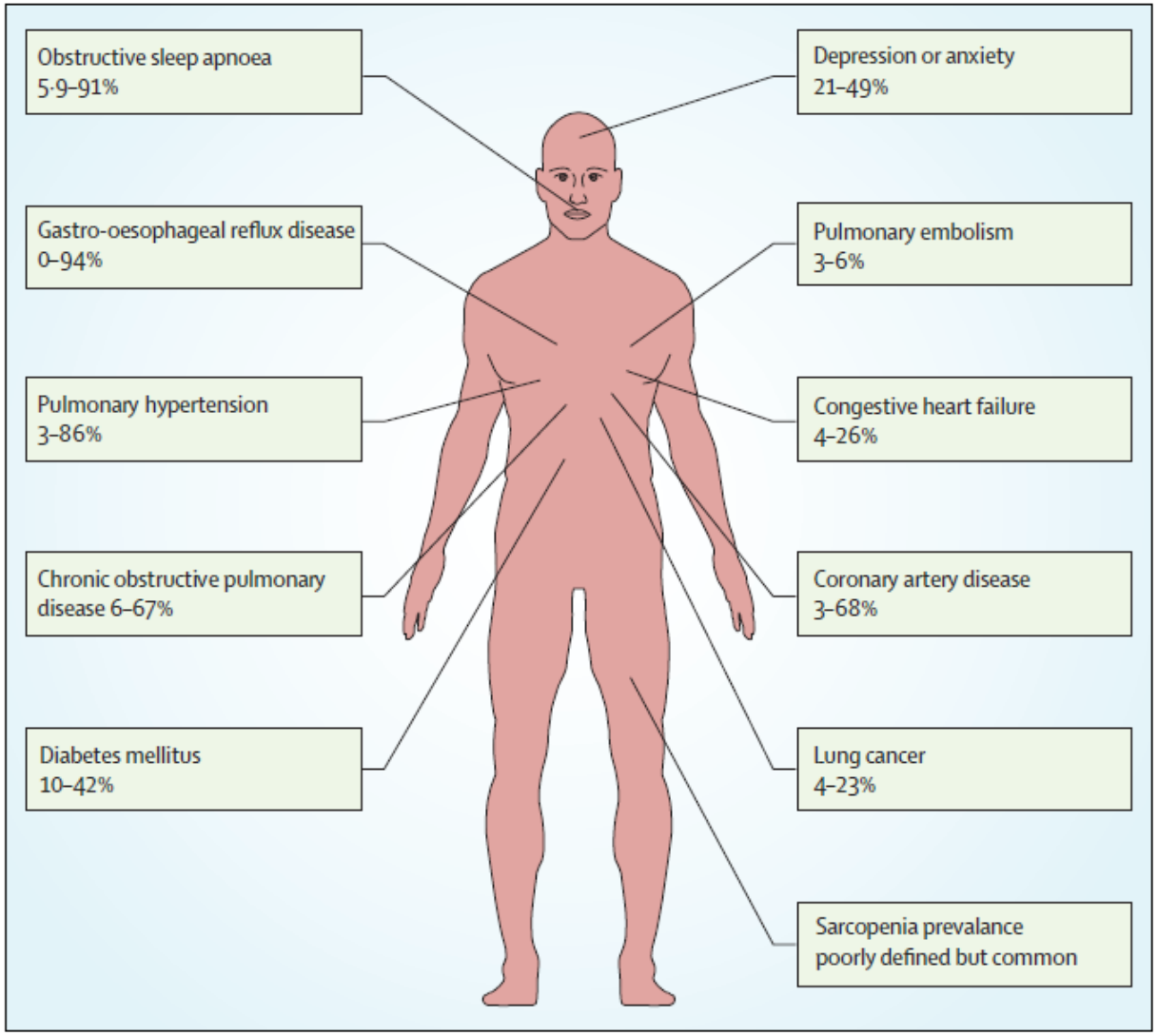
	Pred	Pre	%(Pre/Pred)
FVC	3.80	3.16	83
FEV 1	2.92	2.78	95
FEV 1 % FVC	74.61	87.91	118
MMEF 75/25	3.05	4.25	140
PEF	7.76	6.19	80
MEF 75	6.95	6.10	88
MEF 50	4.04	5.01	124
MEF 25	1.36	1.61	119

		Pred	Best	%(Best/Pred)
DLCO_SB	mmol/(min*kPa)	8.57	3.92	46
KCO_SB	mmol/(min*kPa*L)	1.27	0.78	62
VIN_SB	L	3.94	2.91	74
VA_SB	L	6.59	5.00	76
Hb	g(Hb)/dL		11.80	
DLCOcSB	mmol/(min*kPa)	8.57	4.30	50
KCOc_SB	mmol/(min*kPa*L)	1.27	0.86	68

Level date		08.08.24
Level time		14:06


2024 HRCT

İPF- Komorbiditeler



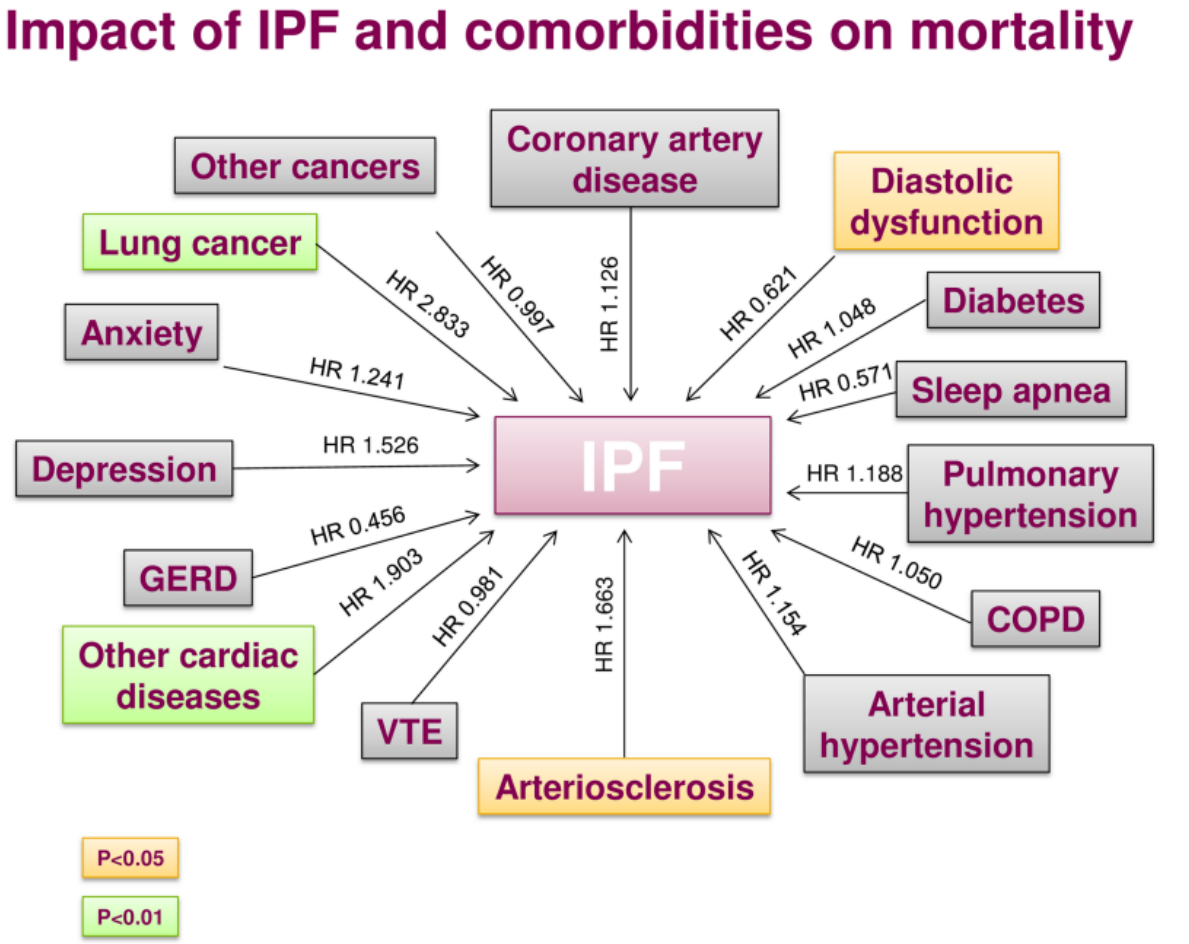


Fig 5. Impact of idiopathic pulmonary fibrosis and comorbidities on mortality. Hazard ratios (HR) have been determined using a predictive multivariate Cox proportional hazards regression model.

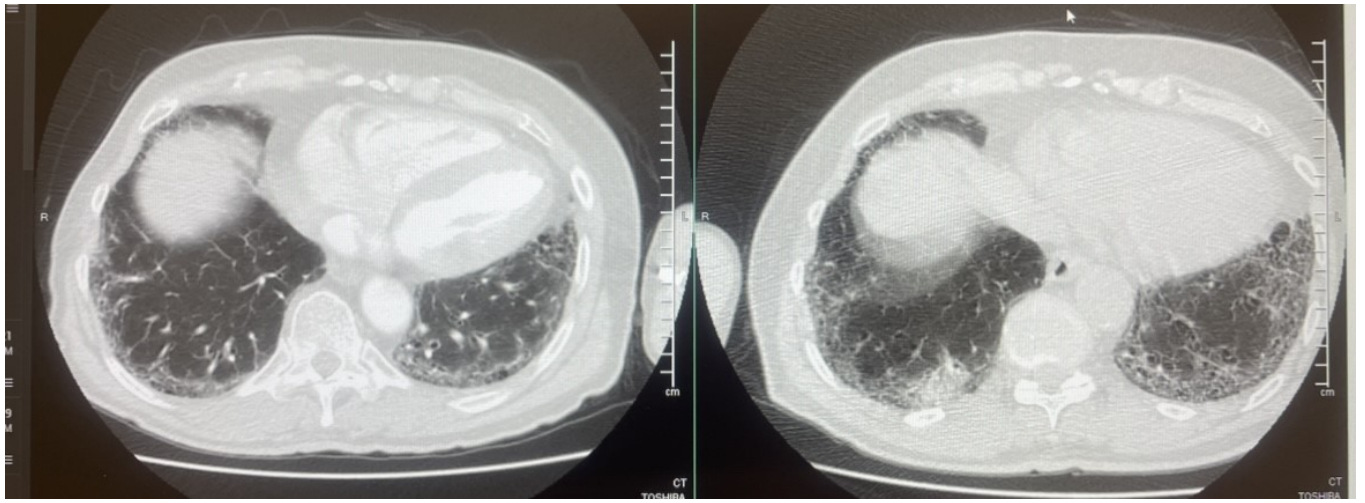
doi:10.1371/journal.pone.0151425.g005

İPF → Akciğer kanseri

- İPF'li hastalarda akciğer kanseri görülme sıklığı zamanla artar
- 1. yılda %3,
- 3,5. yılda %15,4
- 10. yılda %54,7.
- En sık görülen histolojik tümör tipi skuamöz hücreli karsinom
- Tümörlerin %81'i akciğer periferinde, %56'sı ise alt lobda yerleşir.
- çoğunluğu (%70) fibrotik bölgede görülür.

İPF ➡ Akciğer kanseri

- İPF'li yüksek riskli hastalarda, özellikle KPFA li ve/veya yoğun sigara içme öyküsü olanlarda, düşük doz BT ile yıllık akciğer kanseri taraması düşünülebilir.
- İPF'de klinik kötüleşme gösteren veya yeni atipik semptomlar gelişen hastalarda BT düşünülmelidir.
- Pirfenidon ve nintedanib'in antiproliferatif etkileri ve antitümör aktivitesi, mevcut kemoterapötik rejimlerle sinerjistik bir etkiye sahip olabilir.



İPF- Ac ca

Original article

Reduced incidence of lung cancer in patients with idiopathic pulmonary fibrosis treated with pirfenidone

Table 4 – Outcome and causes of death.

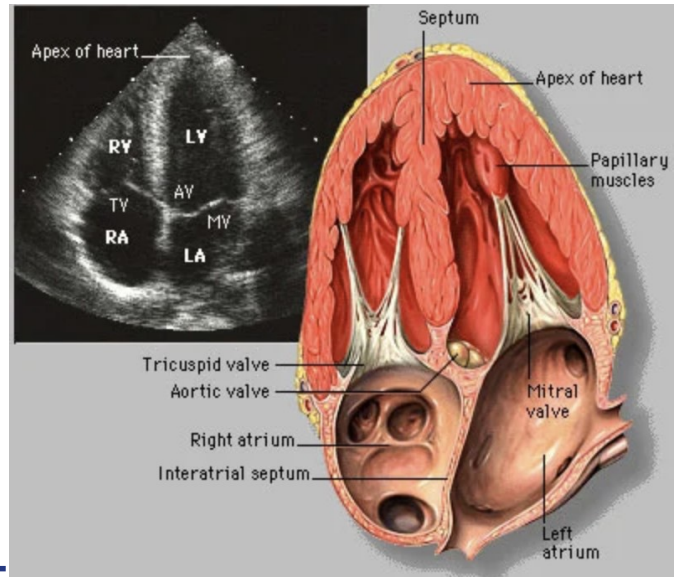
	Pirfenidone	Non-pirfenidone
Alive	36 (43.4)	76 (42.7)
Dead	29 (34.9)	56 (31.5)
Causes of death		
Acute exacerbation	10 (34.5)	28 (50.0)
Respiratory failure	9 (31.0)	4 (7.1)
Infection	4 (13.8)	7 (12.5)
Lung cancer	1 (3.5)	9 (16.1)
Acute myocardial infarction	0	1 (1.8)
Other organs cancers	0	1 (1.8)
Gastrointestinal bleeding	0	1 (1.8)
Unknown	5 (17.2)	5 (8.9)
Transferred to other hospitals	18 (21.7)	46 (25.8)

Data are presented as n (%).

A B S T R A C T

Background: Idiopathic pulmonary fibrosis (IPF) is a disease with a worse prognosis than some types of cancer. In patients with IPF, lung cancer is critical because of the associated high mortality rate from its progression and fatal complications from anticancer treatments. Therefore, preventing lung cancer in patients with IPF is primordial. Pirfenidone is an anti-fibrotic agent that reduces the decline in forced vital capacity. This study aimed to assess the effect of pirfenidone in the development of lung cancer in patients with IPF.
Methods: Data from 261 patients with IPF with and without pirfenidone were retrospectively reviewed, and the incidence of lung cancer was analyzed.
Results: In the pirfenidone group, the incidence of lung cancer was significantly lower than in the non-pirfenidone group (2.4% *vs.* 22.0%, $P < 0.0001$). Multivariate Cox proportional hazards regression analysis demonstrated that pirfenidone decreased the risk of lung cancer (hazard ratio, 0.11; 95% confidence interval, 0.03 to 0.46; $P = 0.003$), whereas coexisting emphysema increased the incidence of lung cancer (hazard ratio, 3.22; 95% confidence interval, 1.35 to 7.70; $P = 0.009$).

Kardiyoloji

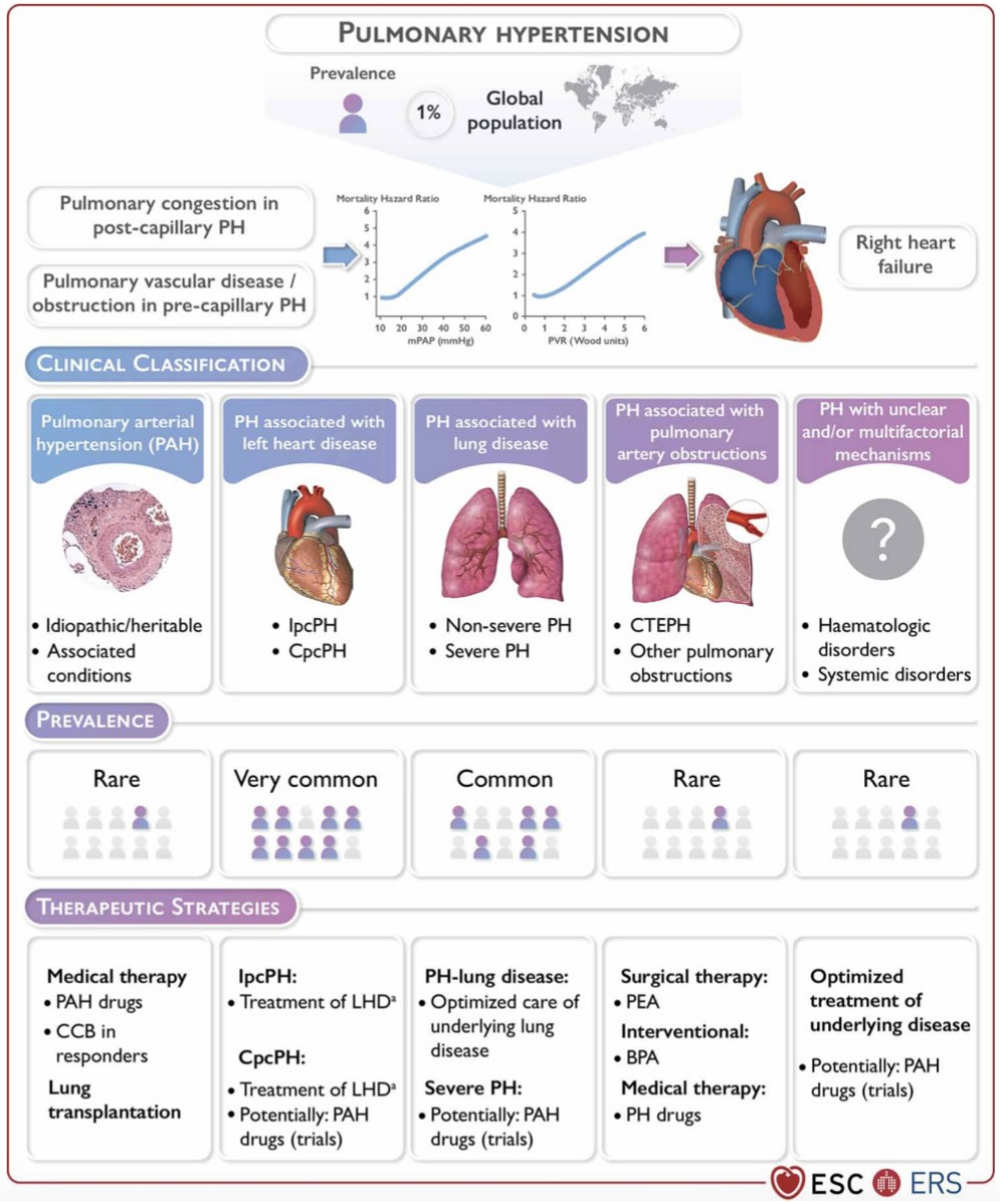


EKG: Erken atrial vuru

Ekokardiyografi:

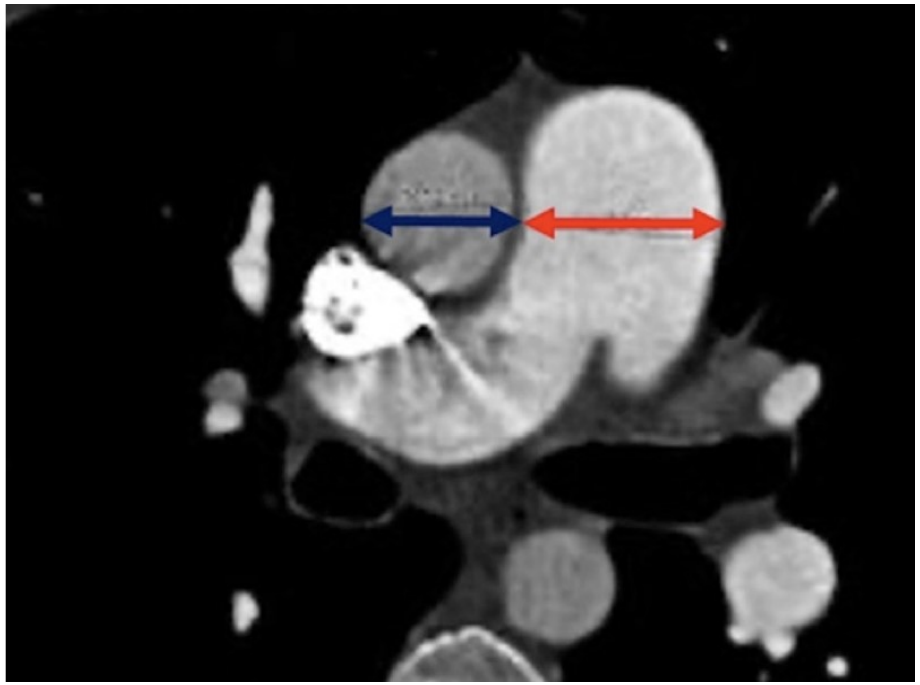
- Sol ventrikül sistolik fonksiyonları normal, EF: %65 .
- Sol ventrikül diyastolik disfonksiyonu
- Sol atrial dilatasyon
- Hafif Mitral yetersizlik, hafif triküspit yetersizlik
- PAP: 40 mmHG
- EFOR ++

İPF ➡ Pulmoner hipertansiyon



PA/aorta diameter > 1:1

PA>29 mm : PA ectasia



Treatment for disease complications

Pulmonary rehabilitation

Pulmonary hypertension: inhaled treprostinil

Respiratory failure: oxygen

End-stage disease: lung transplant

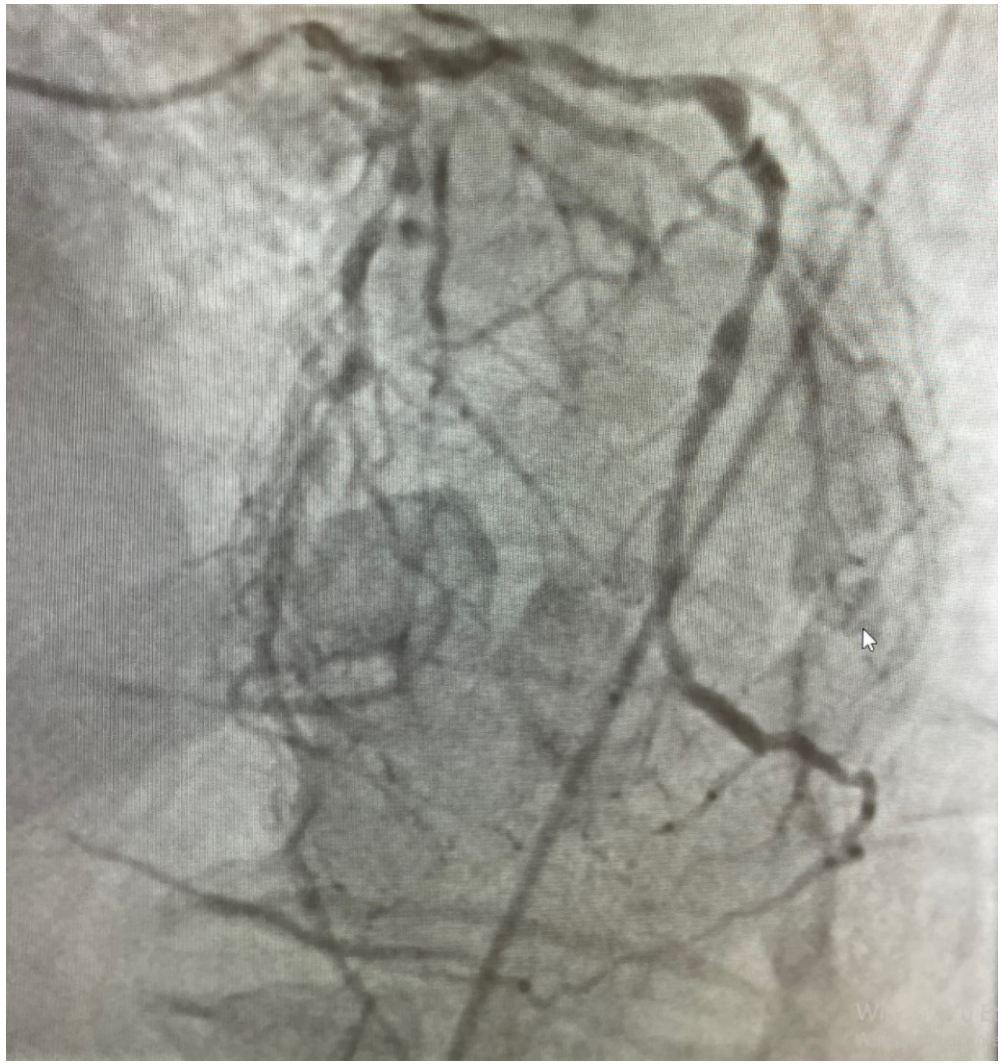
Management of symptoms (eg, cough and breathlessness)

Koroner anjiografi

LMCA ve LAD başarılı

✓**PTCA +STENT İMPLANTASYONU**

Clopidogrel ve ASA tedavisi planlanıyor ancak biyopsi işlemine kadar DMAH ile devam ediliyor



İPF → İKH riskini artırır

Risk Factors for Cardiovascular Disease in People With Idiopathic Pulmonary Fibrosis

İPF Kardiyovaskuler hastalık için risk faktörüdür

İPF hastalarında ilk İKH riski kontrol grubuna göre 2 kat fazladır

RESULTS: We identified 3,211 cases of IPF and 12,307 control subjects. Patients with IPF were more likely to have a record of hypertension (OR, 1.31; 95% CI, 1.19-1.44), and diabetes (OR, 1.20; 95% CI, 1.07-1.34) compared with control subjects; they were also more likely to have been prescribed several CV drugs. The rate of first-time IHD events was more than twice as high in patients than control subjects (rate ratio, 2.32; 95% CI, 1.85-2.93; $P < .001$), but the incidence of stroke was only marginally higher ($P = .09$). Rate ratios for IHD and stroke were not altered substantially after adjusting for CV risk factors.

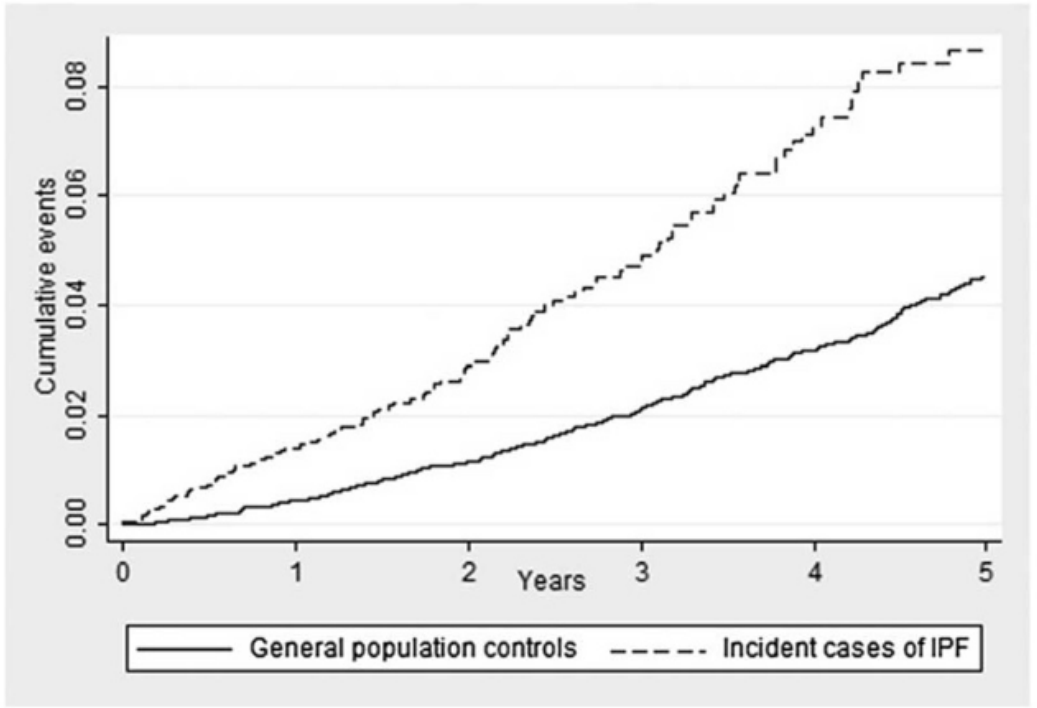


Figure 1 – *Cumulative incidence of ischemic heart disease in incident cases of IPF and general population control subjects. IPF = idiopathic pulmonary fibrosis.*

CHEST 2015; 147(1):150-156

İPF ve KOAH hastaları karşılaştırıldığında KAH İPF'de daha sık görülür ve mortalitesi daha fazladır!!

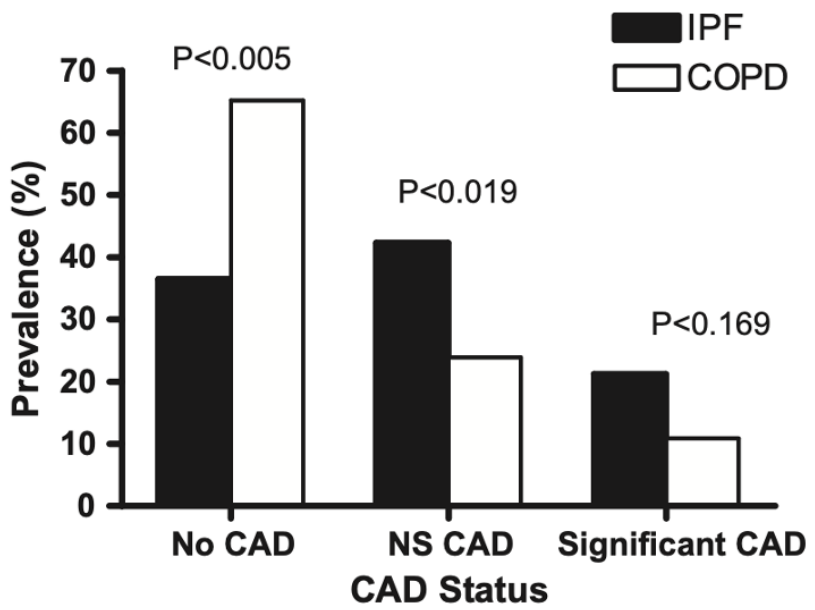


Figure 2 Coronary artery disease (CAD) status as defined by left heart catheterization in those IPF ($N = 61$) and COPD ($N = 46$) patients in whom CAD status was unknown at the time of the catheterization. Abbreviations: CAD = coronary artery disease, NS = non-significant.

Respiratory Medicine (2010) **104**, 1035–1041

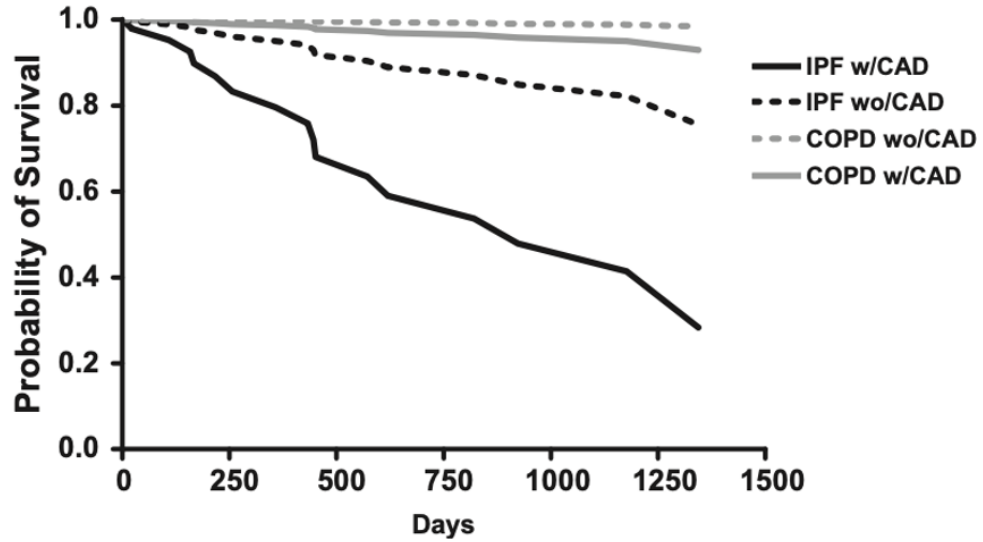
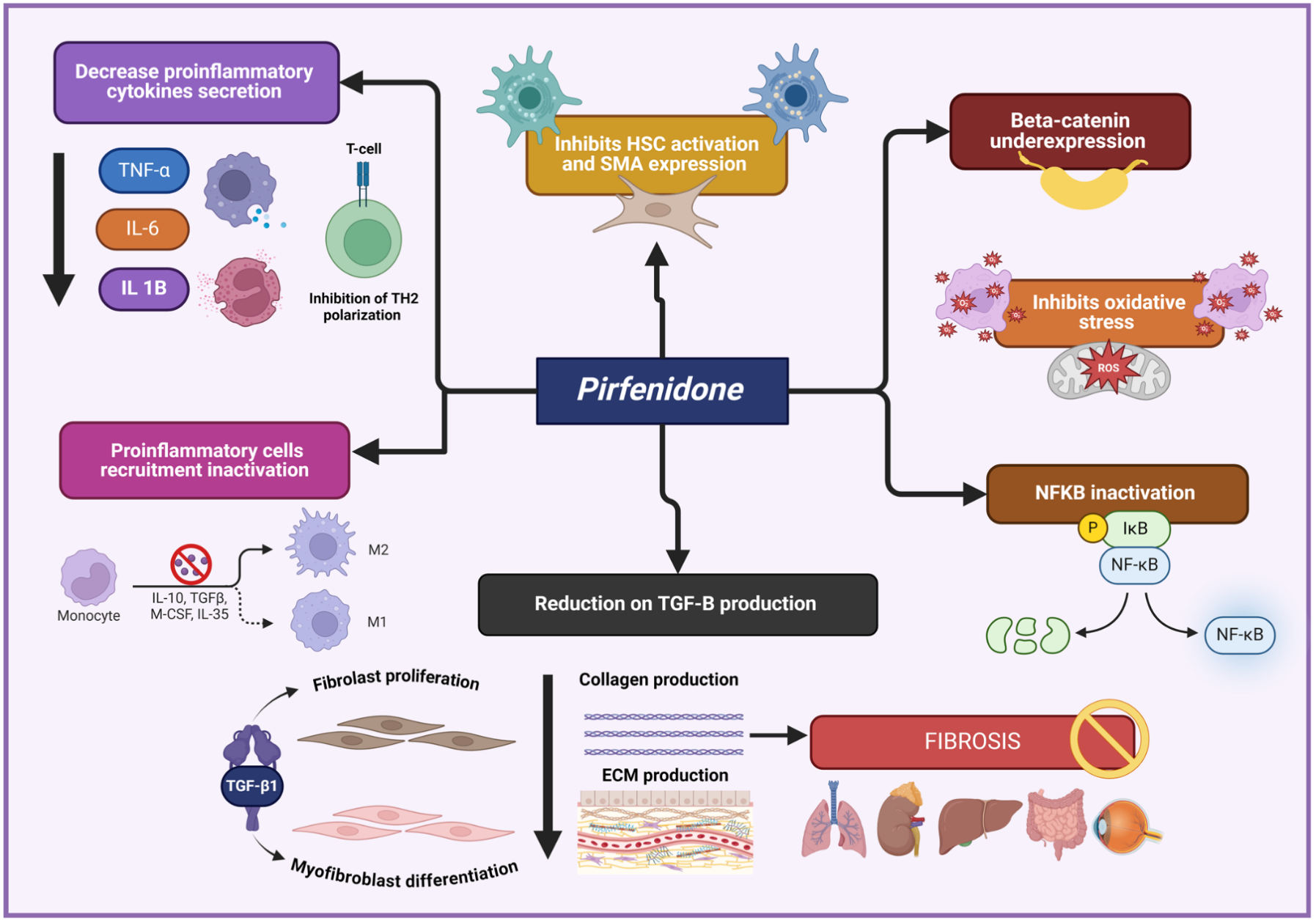


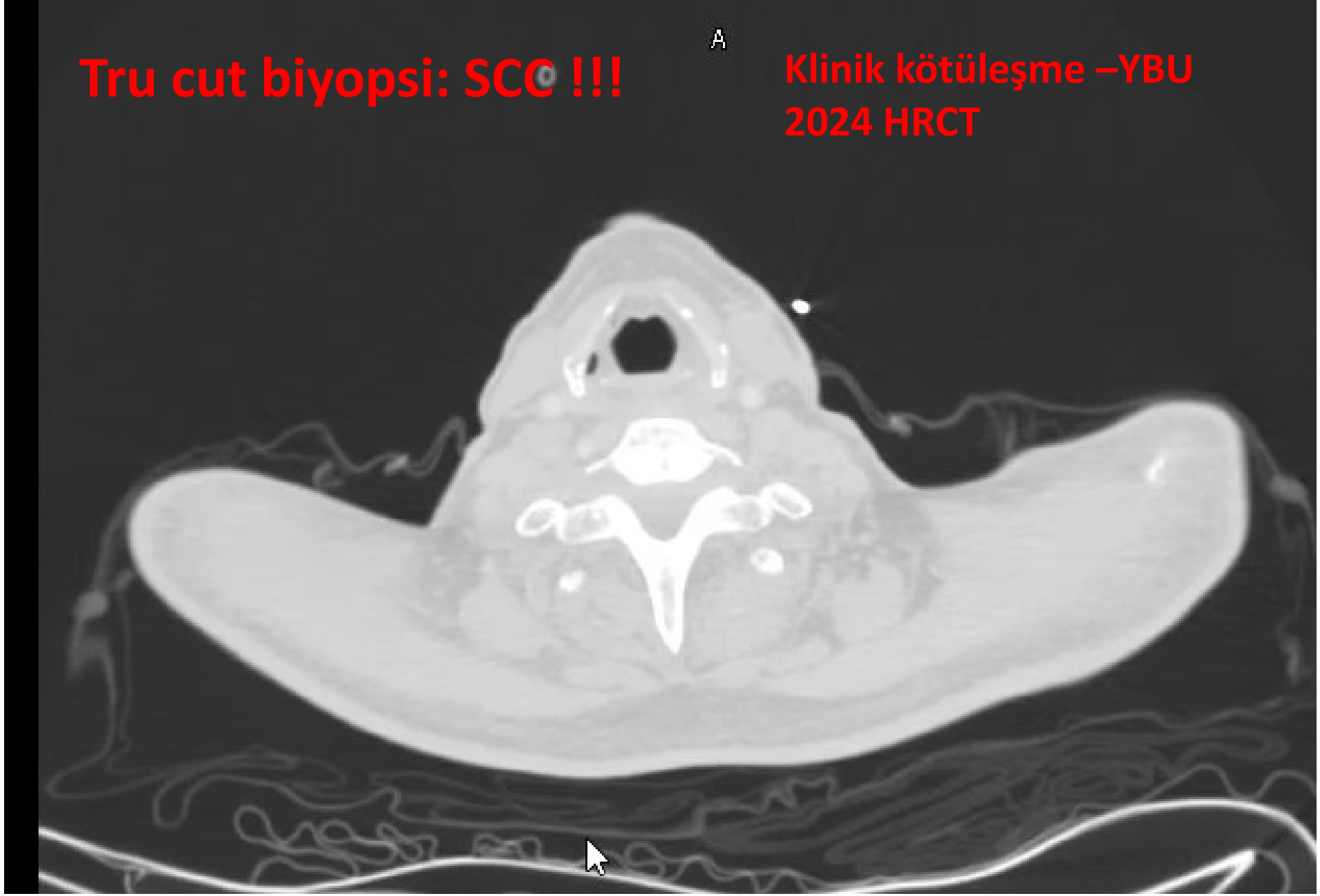
Figure 4 Results of Cox proportional hazards model adjusting for IPF ($p < 0.008$), CAD ($p < 0.059$), male ($p < 0.479$), age ($p < 0.565$), FVC% predicted ($p < 0.744$), and DL_{CO}% predicted ($p < 0.358$). Abbreviations: IPF = idiopathic pulmonary fibrosis; CAD = coronary artery disease; FVC = forced vital capacity; and DL_{CO} = single breath diffusing capacity for carbon monoxide.

İPF → KAH

- **İPF ve KAH arasında güçlü bir ilişki vardır.**
- **İnterlökin-4 (IL-4), İnterlökin-8 (IL-8) ve tümör nekroz faktörü-α (TNF-α), İPF'de yüksek olan anjiyogenezden sorumlu ortak unsurlardır.**
- **İPF de hipoksi anginanın kötüleşmesine yolaçar.**
- **Kardiyak komorbidite varlığı AC nakli yapıln hastalarda sağ kalımı azaltmıştır.**
- **Hastane yatış süresinin uzaması ve hastane içi mortaliteyle ilşkili bulunmuştur.**

Pirfenidon Etki Mekanizması




A
Tru cut biyopsi: SCC !!!
Klinik kötüleşme –YBU
2024 HRCT

İPF’de mortalite nedenleri

1. Solunum yetmezliği (%60)
2. Kardiyovasküler hastalık (%8.5)
3. Akciğer kanseri (%2.9)

Pirfenidon ASCEND

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

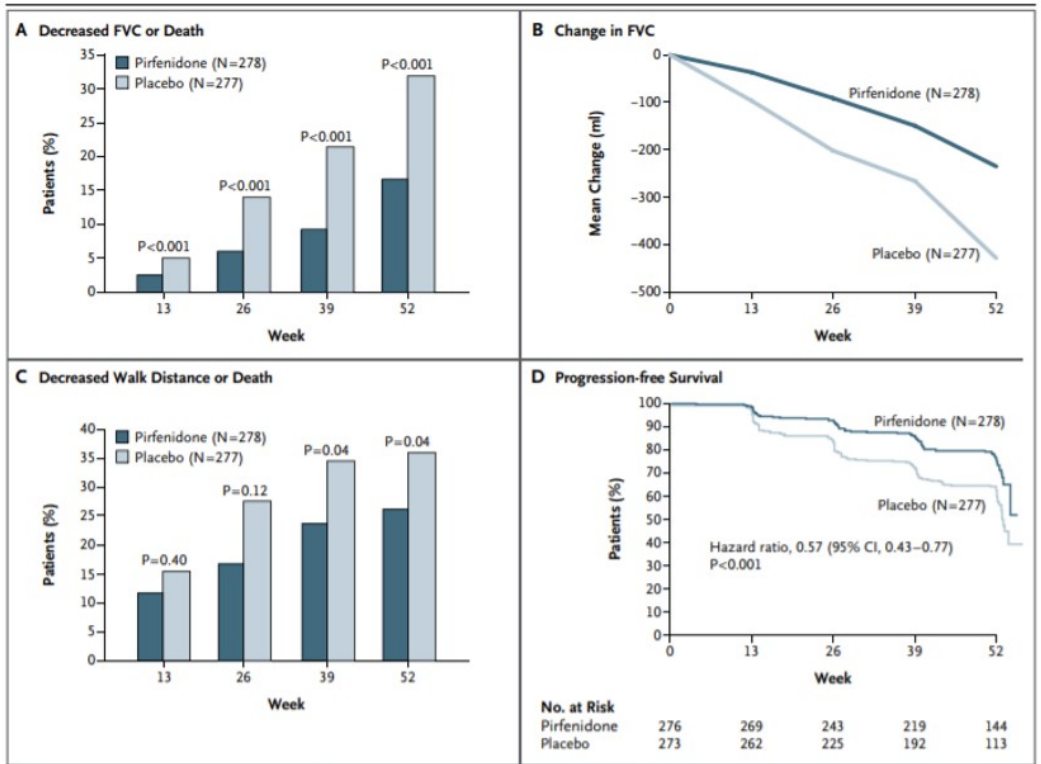


Figure 2. Primary and Key Secondary Efficacy Outcomes during the 52-Week Study Period.

Panel A shows the proportion of patients who had a decreased percentage of the predicted FVC (defined as a decline of at least 10 percentage points from baseline) or who died. Panel B shows the mean change from baseline in FVC. Panel C shows the proportion of patients who had a decreased walk distance (defined as a decline of 50 m or more in the distance walked in 6 minutes) or who died. P values shown in Panels A, B, and C were calculated with the use of ranked analysis of covariance. Panel D shows the Kaplan–Meier distribution for the probability of progression-free survival. The P value was calculated with the use of the log-rank test.

BACKGROUND

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

METHODS

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

RESULTS

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC ($P<0.001$). Pirfenidone reduced the decline in the 6-minute walk distance ($P=0.04$) and improved progression-free survival ($P<0.001$). There was no significant between-group difference in dyspnea scores ($P=0.16$) or in rates of death from any cause ($P=0.10$) or from idiopathic pulmonary fibrosis ($P=0.23$). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause ($P=0.01$) and from idiopathic pulmonary fibrosis ($P=0.006$). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

Pirfenidon ile sağkalım ortalama 8.7 yıldır ve en iyi destek tedaviden 2.5 yıl fazladır

Predicting Life Expectancy for Pirfenidone in Idiopathic Pulmonary Fibrosis

Mark Fisher, MSc; Steven D. Nathan, MD; Christian Hill, BSc; Jade Marshall, MSc; Fred Dejonckheere, MD; Per-Olof Thuresson, MSc; and Toby M. Maher, MD

TABLE 4 Comparison of Survival in Patients Receiving Pirfenidone and BSC Using the Weibull Distribution

	Survival (Years)		
	Pirfenidone	BSC	Difference
Median	7.25	4.67	2.58
Mean (95% CI)	8.72 (7.65-10.15)	6.24 (5.38-7.18)	2.47 (1.26-4.17)

BSC = best supportive care; CI = confidence interval.

J Manag Care Spec Pharm. 2017;23(3-b):S17-S24.

Teşekkürler..