# GÖĞÜS HASTALIKLARINDA GÜNCEL YAKLAŞIMLAR: TANI, TEDAVİ VE KLİNİK YÖNETİM

Editör:
**HÜSEYİN FATİH SEZER**



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# BÖLÜM 1

# ACUTE PULMONARY EMBOLISM IN CONTEMPORARY PRACTICE: FROM DIAGNOSTIC STRATEGY TO RISK-ADAPTED REPERFUSION

AHMET RIDVAN BİLGİÇ[1]

## INTRODUCTION

Acute pulmonary embolism (PE) is one of the major clinical manifestations of venous thromboembolism and remains a time-critical cardiovascular emergency. Its presentation is highly variable, ranging from an incidental filling defect in a stable patient to obstructive shock or cardiac arrest. For that reason, management cannot be reduced to confirmation of clot within the pulmonary arteries. A clinically useful approach combines pretest probability, definitive imaging, right ventricular (RV) performance, evidence of myocardial injury, bleeding risk, and the possibility that reperfusion may be needed. Current European recommendations and the 2026 AHA/ACC multi-association guideline reflect this risk-based approach; direct oral anticoagulants (DOACs) are preferred in many eligible patients, whereas advanced reperfusion is reserved for selected situations (Creager et al., 2026; Konstantinides et al., 2020).

The chapter follows the sequence of decisions faced in practice. The first is whether PE can be safely excluded or must be confirmed urgently. The second is whether a confirmed event carries a meaningful risk of early deterioration. The third is how far treatment should be escalated beyond anticoagulation. Catheter-based treatment and mechanical thrombectomy are discussed within this framework, because their expanding use has made patient selection at least as important as technical availability.

### Clinical Architecture and Pathobiology

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Most acute pulmonary emboli arise from thrombi formed in the deep veins of the lower extremities or pelvis. Venous thromboembolism is common in cardiovascular practice, and its incidence rises markedly with age. Rates reported across populations are not identical, reflecting differences in demographic structure, inherited susceptibility, provoking exposures, access to health care, and diagnostic intensity (Sørensen et al., 2011; Tormene et al., 2011; White, 2003).

Virchow's triad remains a useful way to understand why venous thrombosis develops: stasis, endothelial injury, and hypercoagulability often coexist rather than act in isolation. In clinical terms, these mechanisms are represented by factors such as major surgery or trauma, prolonged immobilization, active malignancy, pregnancy and the postpartum period, estrogen exposure, previous venous thromboembolism, inherited thrombophilia, advanced age, obesity, heart failure, and selected inflammatory or systemic disorders. Whether a provoking factor is transient or persistent also matters later, because it influences decisions about secondary prevention and treatment duration (Anderson & Spencer, 2003; Pomp et al., 2008).

The hemodynamic consequences of PE are determined largely by the response of the right ventricle to an abrupt increase in pulmonary vascular resistance. As RV afterload rises, dilatation, wall stress, ischemia, and impaired contractility may follow. Once RV output falls, left ventricular filling and systemic cardiac output also decline, creating a pathway to hypotension, obstructive shock, and death. Gas exchange is impaired in parallel through ventilation-perfusion mismatch, bronchoconstriction, neurohumoral effects, and inflammatory endothelial activation. Thus, early mortality is driven primarily by acute RV failure rather than by anatomic clot burden alone (Konstantinides et al., 2020; Peracaula et al., 2024).

**From Clinical Suspicion to Diagnostic Confirmation**

The first branch point in the diagnostic pathway is hemodynamic status. In an unstable patient, waiting for a conventional work-up may be unsafe. Bedside transthoracic echocardiography (TTE) can rapidly identify acute RV pressure overload and help exclude other causes of shock. Compression ultrasonography may provide additional support by demonstrating proximal deep vein thrombosis when computed tomography pulmonary angiography (CTPA) cannot be obtained immediately. Once the patient can be transported safely, urgent CTPA remains the preferred test for confirmation (Creager et al., 2026; Konstantinides et al., 2020).

In a stable patient, clinical probability determines the next diagnostic step. The Wells and revised Geneva rules are useful because they organize pretest probability and guide the use of D-dimer rather than because either score can establish PE on its own. With a low or intermediate probability - or a classification of PE unlikely in a two-level strategy - a negative high-sensitivity D-dimer can exclude PE without imaging. For patients older than 50 years, an age-adjusted threshold of age x 10 microg/L can improve specificity when fibrinogen-equivalent-unit assays are used. By contrast, a high clinical probability should generally lead directly to imaging (Klok et al., 2008; Righini et al., 2014; Wells et al., 2001).

CTPA is the first-line imaging study for most patients with suspected acute PE. In addition to showing intraluminal filling defects, it can reveal alternative thoracic diagnoses and provide information about RV enlargement. The scan should still be interpreted in the context of pretest probability, especially when the only finding is an isolated subsegmental defect. Ventilation/perfusion scintigraphy remains valuable when iodinated contrast is undesirable, including selected patients with pregnancy, severe renal dysfunction, or a history of severe contrast reaction. A positive proximal compression ultrasound may establish venous thromboembolism in the appropriate setting, but a negative study

does not rule out PE (Konstantinides et al., 2020; Stein et al., 2006; van Belle et al., 2006).

Other tests have supporting, not confirmatory, roles. Sinus tachycardia and patterns of RV strain may appear on electrocardiography, while arterial blood gases can show hypoxemia and hypocapnia. Chest radiography is more useful for identifying competing diagnoses than for diagnosing PE itself. Once PE has been confirmed, cardiac troponin and natriuretic peptides contribute to prognostic assessment. TTE may demonstrate RV dilatation, an increased RV/LV ratio, or reduced tricuspid annular plane systolic excursion; however, a normal examination does not exclude PE in a hemodynamically stable patient (Kurnicka et al., 2016; Lang et al., 2015; Stein et al., 1991).

*Table 1. Practical Diagnostic Decision Framework for Suspected Acute Pulmonary Embolism*

| **Clinical setting** | **Preferred sequence** | **Key implication** |
|---|---|---|
| Hemodynamic instability | Immediate bedside TTE +/- compression ultrasonography; urgent CTPA when feasible | Evidence of acute RV overload in a compatible shock state may justify emergency reperfusion when definitive imaging cannot be obtained without unsafe delay. |
| Stable, high clinical probability | Proceed directly to CTPA | A negative D-dimer should not be used as the principal exclusion strategy. |

| Clinical setting | Preferred sequence | Key implication |
|---|---|---|
| Stable, low/intermediate probability or PE unlikely | High-sensitivity D-dimer; CTPA if positive | A negative D-dimer can exclude PE; age-adjusted thresholds may be used in patients >50 years. |
| CTPA unsuitable or contraindicated | Ventilation/perfusion imaging and/or compression ultrasonography according to the clinical context | Alternative imaging should be selected according to renal function, pregnancy, contrast history, and local availability. |

Source: (Creager et al., 2026; Konstantinides et al., 2020; Righini et al., 2014; van Belle et al., 2006)

**Risk Stratification as a Treatment Decision Tool**

After PE has been confirmed, risk stratification becomes a treatment decision rather than a descriptive exercise. Hemodynamic instability defines high-risk PE. This includes cardiac arrest, obstructive shock requiring vasopressor support despite adequate volume status, or persistent hypotension not attributable to another cause. In these patients, acute RV failure is the immediate threat, and reperfusion must be considered without delay (Creager et al., 2026; Konstantinides et al., 2020).

The assessment is more nuanced in normotensive patients. PESI or sPESI summarizes the clinical risk profile, while RV dysfunction on imaging and elevation of cardiac troponin add information about cardiopulmonary stress. Their combination separates intermediate-low from intermediate-high risk. A patient with preserved blood pressure but both RV dysfunction and myocardial injury belongs to the intermediate-high-risk group. Routine primary systemic thrombolysis is not recommended in this setting, but close surveillance is warranted because early

deterioration may trigger rescue reperfusion (Aujesky et al., 2005; Donzé et al., 2008; Righini et al., 2011).

Low-risk PE also requires more than a reassuring score. Early discharge or outpatient treatment is most appropriate when predicted mortality is low, hemodynamics are stable, bleeding risk is acceptable, and there is no clinically important RV dysfunction when it has been assessed. Practical issues matter as well: the patient must be able to adhere to treatment and obtain prompt medical review if symptoms worsen. The Hestia criteria are useful in this respect because they identify medical and social reasons that favor inpatient care (Zondag et al., 2013).

*Table 2. Risk Strata and Immediate Management Implications in Acute Pulmonary Embolism*

| **Risk category** | **Core profile** | **Immediate management implication** |
|---|---|---|
| High risk | Hemodynamic instability: cardiac arrest, obstructive shock, or persistent hypotension | Urgent reperfusion strategy plus anticoagulation and organ support; systemic thrombolysis is standard when not contraindicated. |
| Intermediate-high risk | Normotensive; adverse clinical score plus RV dysfunction and positive cardiac troponin | Therapeutic anticoagulation with monitored care; no routine primary thrombolysis; rescue reperfusion if deterioration occurs. |

| Risk category | Core profile | Immediate management implication |
|---|---|---|
| Intermediate-low risk | Normotensive; adverse clinical score with only one or neither of RV dysfunction/troponin positivity | Anticoagulation; inpatient management according to comorbidity, oxygen requirement, bleeding risk, and clinical course. |
| Low risk | Low clinical mortality score, stable physiology, and no major exclusion to ambulatory care | Consider early discharge or outpatient anticoagulation after Hestia/social assessment. |

Source: (Aujesky et al., 2005; Creager et al., 2026; Konstantinides et al., 2020; Righini et al., 2011; Zondag et al., 2013)

## Anticoagulation: Matching Drug Strategy to Clinical Context

Anticoagulation remains the basis of treatment for nearly every patient with acute PE. When clinical probability is high, bleeding risk is acceptable, and definitive imaging will be substantially delayed, treatment may be started before confirmation. The initial agent should be chosen with the whole clinical setting in mind - hemodynamic stability, renal and hepatic function, possible invasive procedures, pregnancy, active cancer, drug interactions, body weight, and the likelihood that rapid reversal could become necessary (Creager et al., 2026; Ortel et al., 2020; Stevens et al., 2021).

Unfractionated heparin (UFH) is particularly useful when clinicians need rapid titration and reversibility, as may occur in high-risk PE, advanced renal dysfunction, or before an anticipated reperfusion procedure. For stable patients who require parenteral anticoagulation, low-molecular-weight heparin (LMWH) is generally more convenient because its pharmacokinetics are

predictable and routine laboratory monitoring is usually unnecessary. Fondaparinux is another once-daily option for stable patients with adequate renal function (Büller et al., 2003; Ortel et al., 2020; Stevens et al., 2021).

For many hemodynamically stable patients, a DOAC offers the simplest oral strategy. Apixaban and rivaroxaban can be started immediately using their intensified initial regimens. Dabigatran and edoxaban, in contrast, are introduced only after at least 5 days of parenteral anticoagulation. Randomized trials established efficacy comparable with conventional therapy for prevention of recurrent venous thromboembolism, with an overall favorable bleeding profile. On that basis, current guidelines prefer DOACs to vitamin K antagonists when no important contraindication is present (Agnelli et al., 2013; EINSTEIN-PE Investigators, 2012; Creager et al., 2026).

Several patient groups require a different approach. Vitamin K antagonists remain preferred in triple-positive antiphospholipid syndrome, and DOACs are avoided during pregnancy. In active cancer, either a DOAC or LMWH may be suitable, although gastrointestinal and genitourinary malignancies warrant particular attention to mucosal bleeding and drug-drug interactions. Standard-dose apixaban or rivaroxaban can be considered in severe obesity. After bariatric surgery, however, uncertain absorption may make parenteral anticoagulation or a vitamin K antagonist more appropriate (Lyman et al., 2021; Martin et al., 2021; Stevens et al., 2021).

*Table 3. Selected Anticoagulant Regimens for Acute Pulmonary Embolism*

| Agent | Initial regimen | Ongoing regimen / practical note |
|---|---|---|
| Unfractionated heparin | 80 U/kg IV bolus (or 5,000 U), then 18 U/kg/h infusion | Titrate according to institutional aPTT/anti-Xa protocol; useful when rapid reversal or reperfusion is anticipated. |
| Enoxaparin | 1 mg/kg subcutaneously every 12 h (alternative 1.5 mg/kg once daily in selected patients) | Preferred parenteral option in many stable patients; renal function must be considered. |
| Fondaparinux | <50 kg: 5 mg once daily; 50-100 kg: 7.5 mg once daily; >100 kg: 10 mg once daily | Avoid in severe renal impairment (creatinine clearance <30 mL/min). |
| Rivaroxaban | 15 mg orally twice daily for 21 days | Then 20 mg once daily; 10 mg once daily may be considered in selected patients during extended therapy. |
| Apixaban | 10 mg orally twice daily for 7 days | Then 5 mg twice daily; 2.5 mg twice daily may be considered in selected patients during extended therapy. |
| Dabigatran | At least 5 days of therapeutic parenteral anticoagulation | Then 150 mg orally twice daily. |

| Agent | Initial regimen | Ongoing regimen / practical note |
|---|---|---|
| Edoxaban | At least 5 days of therapeutic parenteral anticoagulation | Then 60 mg orally once daily, with dose modification when indicated by renal function, body weight, or interacting drugs. |

Source: (Agnelli et al., 2013; Büller et al., 2003; EINSTEIN-PE Investigators, 2012; Ortel et al., 2020; Stevens et al., 2021)

## Reperfusion Therapy: Escalation Beyond Anticoagulation

Reperfusion is indicated because of clinical instability, not simply because CTPA shows a large clot burden. For high-risk PE and an acceptable bleeding profile, systemic thrombolysis remains the fastest widely available pharmacologic option. Alteplase 100 mg over 2 hours is the conventional regimen. The price of this rapid effect is bleeding risk, particularly intracranial hemorrhage, which is why primary systemic thrombolysis should not be used routinely in stable intermediate-risk PE. In PEITHO, fibrinolysis reduced hemodynamic decompensation but increased major and intracranial bleeding, illustrating the central risk-benefit trade-off (Meyer et al., 2014; Konstantinides et al., 2020).

If systemic thrombolysis is contraindicated or unsuccessful, the next option depends on urgency, anatomy, available expertise, and local resources. Catheter-directed thrombolysis aims to achieve reperfusion with a lower local fibrinolytic dose. Mechanical thrombectomy and aspiration systems take a different approach by removing thrombus with little or no thrombolytic exposure. The 2022 ESC clinical consensus document and the 2026 AHA/ACC guideline support catheter-based reperfusion in selected high-risk patients and as rescue treatment after clinical deterioration. They do not support routine first-line intervention in every hemodynamically

stable intermediate-high-risk patient (Creager et al., 2026; Pruszczyk et al., 2022).

The evidence base for device-based reperfusion is growing, although the strength of evidence differs among studies. In FLARE, FlowTriever thrombectomy reduced the RV/LV ratio at 48 hours in intermediate-risk PE with a low major bleeding rate. FLASH subsequently reported early reductions in pulmonary artery pressure and RV strain in routine practice, and the nonrandomized FLAME study described favorable in-hospital outcomes in selected high-risk patients treated with FlowTriever. EXTRACT-PE showed a comparable short-term fall in RV/LV ratio with the Indigo aspiration system, and most patients did not receive intraprocedural thrombolysis. PEERLESS provided a direct randomized comparison of large-bore mechanical thrombectomy and catheter-directed thrombolysis in intermediate-risk PE. Its hierarchical composite endpoint favored thrombectomy, largely because of less clinical deterioration or rescue therapy and lower intensive-care use; a clear mortality or major-bleeding advantage was not demonstrated (Jaber et al., 2025; Silver et al., 2023; Sista et al., 2021; Toma et al., 2023; Tu et al., 2019).

These findings are clinically important, but they should not be overinterpreted. Several device studies are single-arm and many rely on surrogate outcomes such as RV/LV ratio or pulmonary artery pressure. It remains uncertain whether early hemodynamic improvement translates into lower mortality, fewer recurrent events, better functional recovery, or less chronic thromboembolic disease. This uncertainty is one reason a multidisciplinary Pulmonary Embolism Response Team (PERT) can add value in difficult cases, where shock severity, bleeding risk, clot location, comorbidity, procedural risk, and institutional capability must all be weighed together.

Surgical pulmonary embolectomy remains a definitive reperfusion option when thrombolysis cannot be given or has failed,

particularly if catheter-based treatment is unavailable, unsuitable, or unsuccessful. Results are influenced by how early surgery is performed, the experience of the surgical team, and the degree of circulatory collapse before intervention. In carefully selected patients with refractory shock or cardiac arrest, mechanical circulatory support can be used as a bridge to definitive treatment (Goldberg et al., 2023).

*Table 4. Contemporary Reperfusion Options and Evidence Considerations*

| **Strategy** | **Typical clinical role** | **Evidence / limitation** |
|---|---|---|
| Systemic thrombolysis | First-line reperfusion for high-risk PE when bleeding risk is acceptable; rescue option after deterioration | Rapid, widely available reperfusion; major bleeding and intracranial hemorrhage constrain use in stable intermediate-risk PE. |
| Catheter-directed thrombolysis | High-risk PE when systemic thrombolysis is contraindicated/unsuccessful; selected rescue scenarios | SEATTLE II demonstrated improvement in RV/LV ratio, but the single-arm design does not prove superior safety versus systemic thrombolysis. |
| FlowTriever mechanical thrombectomy | Selected intermediate-risk or high-risk PE requiring rapid thrombus extraction without systemic lysis | FLARE, FLASH, and FLAME support short-term hemodynamic improvement; mortality benefit remains uncertain. |

| Strategy | Typical clinical role | Evidence / limitation |
|---|---|---|
| Indigo aspiration thrombectomy | Selected intermediate-risk PE when aspiration-based reperfusion is favored | EXTRACT-PE showed reduced RV/LV ratio with very limited use of intraprocedural thrombolysis. |
| Large-bore thrombectomy vs catheter-directed thrombolysis | Selected intermediate-risk PE considered for catheter intervention | PEERLESS favored thrombectomy for a hierarchical composite outcome driven mainly by clinical deterioration/rescue therapy and ICU use, not a proven mortality advantage. |
| Surgical embolectomy | High-risk PE when thrombolysis is contraindicated/failed or catheter treatment is unsuitable | Potentially lifesaving but highly dependent on rapid referral, surgical expertise, and perioperative support. |

Source: (Creager et al., 2026; Goldberg et al., 2023; Jaber et al., 2025; Piazza et al., 2015; Pruszczyk et al., 2022; Silver et al., 2023; Sista et al., 2021; Toma et al., 2023; Tu et al., 2019)

## Duration of Therapy and Prevention of Recurrence

A minimum 3-month course of anticoagulation is required for acute PE unless an exceptional contraindication develops. Three months is often sufficient when the event was provoked by a major transient risk factor that has resolved. Longer treatment deserves consideration when the recurrence risk persists - for example after unprovoked PE, recurrent venous thromboembolism, active cancer, persistent risk factors, or selected high-risk thrombophilias - provided that the expected benefit remains greater than the bleeding risk (Prandoni et al., 2007; Stevens et al., 2021).

The decision to continue anticoagulation beyond the initial treatment phase should be revisited over time rather than treated as permanent by default. Renal and hepatic function, interval bleeding, interacting drugs, cancer activity, recurrence risk, and patient preference may all change. For selected patients continuing a DOAC, reduced-dose apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily can be used for extended prevention. In active cancer, treatment may continue beyond 3-6 months while the malignancy remains active and bleeding risk is acceptable (Lyman et al., 2021; Stevens et al., 2021).

## CONCLUSION

Management of acute PE is best approached as a sequence of risk-based decisions. Pretest probability determines how D-dimer and imaging are used; after diagnosis, hemodynamic status, RV function, myocardial injury, and the broader clinical profile determine the level of monitoring and the need for reperfusion. Anticoagulation is sufficient for most patients, and DOACs are preferred in many who are eligible for oral therapy. Reperfusion, however, should follow clinical instability and bleeding risk rather than clot burden in isolation. Systemic thrombolysis remains the standard rapid reperfusion treatment for high-risk PE when it can be given safely. Catheter-directed therapy, mechanical thrombectomy, and surgical embolectomy broaden the options when thrombolysis is contraindicated, ineffective, or when the patient deteriorates. The unresolved issue is no longer whether advanced devices can improve short-term hemodynamics; it is which patients gain a durable clinical benefit. Future randomized studies should therefore focus on mortality, functional recovery, recurrent events, chronic thromboembolic disease, and patient-centered outcomes in addition to imaging-based surrogate endpoints (Creager et al., 2026; Jaber et al., 2025; Pruszczyk et al., 2022).

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# BÖLÜM 2

## ASTIM TEDAVİSİNDE BİYOLOJİK AJANLAR VE REMİSYON KAVRAMININ KILAVUZLARA GİRİŞİ

**Ümmühan Tuğba TÜMÜKLÜ**[1]

### Giriş

GINA'nın en güncel tanımına göre astım, hava yollarında kronik enflamasyonla seyreden heterojen bir hastalık olup hışıltı, nefes darlığı, göğüste sıkışma hissi ve öksürük gibi zamana ve şiddete göre değişkenlik gösteren solunumsal yakınmalar kiniği ve değişken ekspiratuar hava akımı kısıtlanmasının bir arada bulunması olarak tanımlanmaktadır (Global Initiative for Asthma, 2025). Kliniğe genellikle hava yolu hiperreaktivitesi de eşlik etmektedir. Semptomlar ve akciğer fonksiyonları tedaviyle birlikte zaman içinde normale dönebilse de hastalık ilerledikçe hava akımı kısıtlanması kalıcı hale gelebilir. 2021 yılı verilerine göre dünya genelinde yaklaşık 260 milyon kişi astımla yaşmaktadır. Yaş standardize prevalans oranı 1990'dan bu yana yaklaşık %40 azalmış olsa da, nüfus artışı nedeniyle 2050 yılına kadar hasta sayısının 275 milyona ulaşması beklenmektedir (GBD 2021 Asthma and Allergic Diseases Collaborators, 2025). Bu denli yaygın bir hastalıkta tedavi yaklaşımı uzun yıllar boyunca büyük ölçüde semptom kontrolü ve alevlenme

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sayısını azaltmak üzerine yürütülmekte iken son on yılda bu tabloda köklü bir değişim yaşanması dikkat çekicidir. Tip 2 inflamasyonu hedefleyen biyolojik ajanların klinik kullanıma girmesiyle birlikte tedavi hedefi yalnızca semptomları baskılamak değil, mümkünse tamamen durdurmak olarak değişiklik gösterdi.

Önce alevlenme sıklığını ve oral kortikosteroid ihtiyacını azaltmak amacıyla anti-interlökin-5 (anti-IL-5), anti-interlökin-4/interlökin-13 (anti-IL-4/IL-13) ve anti-timik stromal lenfopoietin (anti-TSLP) grubundaki ilaçlar geliştirildi. Bu tedaviler kullanılmaya başlanıp gerçek yaşam verileri toplandıkça, bir kısım hastanın tedavi altında neredeyse tamamen semptomsuz kaldığı, akciğer fonksiyonlarının stabilize olduğu ve alevlenme geçirmediği tespit edildi. Bu gözlem 'klinik remisyon' kavramını ortaya çıkardı.

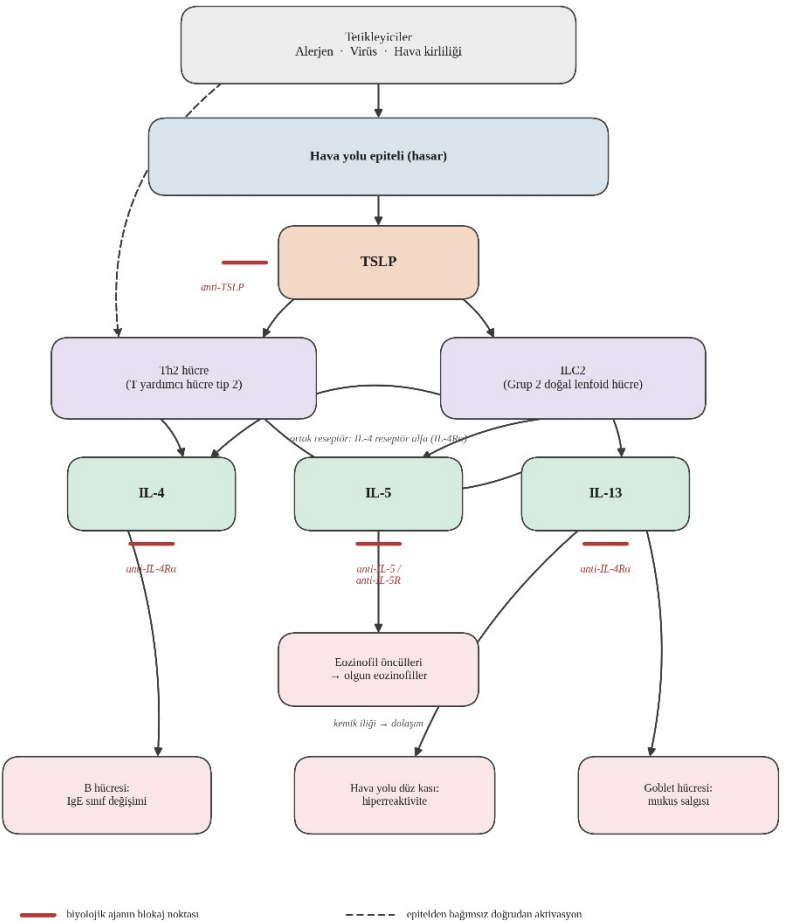
**Astımda Tip 2 İnflamasyon ve Biyolojik Hedeflerin Patofizyolojik Temeli**

Astım hastalarının önemli bir kısmında hava yolu inflamasyonu, T yardımcı hücre tip 2 (Th2) yanıtı üzerinden ilerler. Bu yanıtta en önemli rol, allerjenlere veya epitel hasarına karşı aktive olan Th2 hücreleri ve grup 2 doğal lenfoid hücreler (ILC2) tarafından sentezlenen interlökin-4 (IL-4), interlökin-5 (IL-5) ve interlökin-13 (IL-13) sitokinlerine aittir. IL-5, kemik iliğinde eozinofil öncüllerinin olgunlaşmasını ve dolaşıma katılmasını sağlarken IL-4 ve IL-13 ise B hücrelerinde immünoglobulin E (IgE) sınıf değişimini tetikleyerek hava yolu düz kasında hiperreaktiviteyi artırır ve mukus salgısını uyarır. Bu iki sitokin, interlökin-4 reseptör alfa (IL-4Rα) adlı ortak bir reseptör alt birimi üzerinden sinyal iletir.

Epitel hücrelerinden salgılanan TSLP, bu yanıtın biraz daha yukarısında, alarmin adı verilen bir grup sitokinin parçasıdır. Alerjen, virüs veya hava kirliliği gibi tetikleyicilerle hasarlanan epitel TSLP salgılar; bu da hem dendritik hücreleri hem ILC2'leri

aktive ederek tip 2 yanıtı başlamasını tetikler. TSLP'nin yolağın en üst basamağında yer alması, ona yönelik planlanan tedavilerin eozinofil sayısından bağımsız olarak etki edebilmesini sağlar (ŞEKİL1).

*Şekil 1. Astımda Tip 2 (Th2) Enflamasyon Yolağı ve Biyolojik Ajanların Etki Noktaları*




Kaynak: Yazar tarafından oluşturulmuştur.

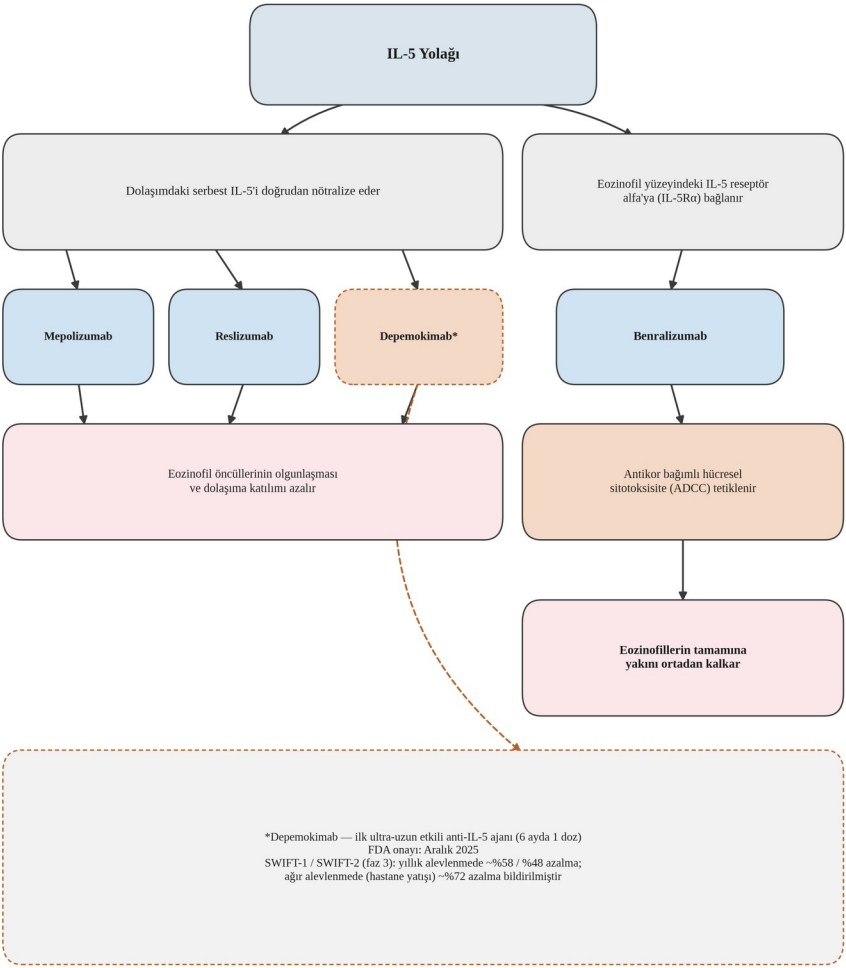
**Anti-IL5/IL5R Tedaviler**

IL-5 yolağını hedefleyen üç ajan, mepolizumab, reslizumab ve benralizumab, eozinofilik astımda uzun süredir klinik kullanımdadır. Mepolizumab ve reslizumab dolaşımdaki IL-5'i doğrudan nötralize ederken, benralizumab eozinofil yüzeyindeki IL-5 reseptör alfa (IL-5Rα) alt birimine bağlanır ve antikor bağımlı hücresel sitotoksisite yoluyla eozinofillerin tamamına yakınını ortadan kaldırmaktadır.

Mepolizumabın etkinliği, kan eozinofil sayısı yüksek ve tekrarlayan alevlenmeli hastalarda yürütülen MENSA çalışmasında gösterilmiştir. Bu çalışmada alevlenme sıklığının anlamlı ölçüde azaldığı bildirilmiştir (Ortega ve ark., 2014). Benralizumab için de SIROCCO çalışmasında benzer bulgular elde edilmiş, ayrıca oral kortikosteroide bağımlı hastalarda idame doz azaltımını değerlendiren ZONDA çalışmasıyla bu bulgular desteklenmiştir (Bleecker ve ark., 2016; Nair ve ark., 2017). Reslizumab ise kilogram başına dozlanarak intravenöz yoldan uygulanması ile diğer iki ajandan ayrılarak farklılık göstermektedir.

Bu grupta en yeni gelişme, Depemokimabın Aralık 2025'te ABD Gıda ve İlaç Dairesi'nden (FDA) onay almasıyla yaşanmıştır. Depemokimab, IL-5'e yüksek afinite ile bağlanan ve altı ayda bir uygulanan ilk ultra-uzun etkili biyolojik ajandır. SWIFT-1 ve SWIFT-2 faz 3 çalışmaları ile yıllık alevlenme oranının sırasıyla yaklaşık yüzde 58 ve yüzde 48 azalma sağladığının ve hastaneye yatış gerektiren ağır alevlenmelerde ise havuzlanmış analizde yüzde 72'ye varan bir azalma sağlandığının bildirilmesi depemokimabı kısa sürede alanda dikkatini çeken bir ajan hâline getirmiştir Jackson ve ark. (2024). Aynı zamanda yılda iki enjeksiyonla idame sağlanabilmesi, tedaviye uyumun sık sorun olduğu bir hasta grubunda pratik bir avantaj sağlamaktadır (Şekil 2).

*Şekil 2. Anti-IL-5/IL-5R Ajanlarının Etki Mekanizması Algoritması*




Kaynak: Yazar tarafından oluşturulmuştur.

## Anti-IL4/IL13 Tedaviler

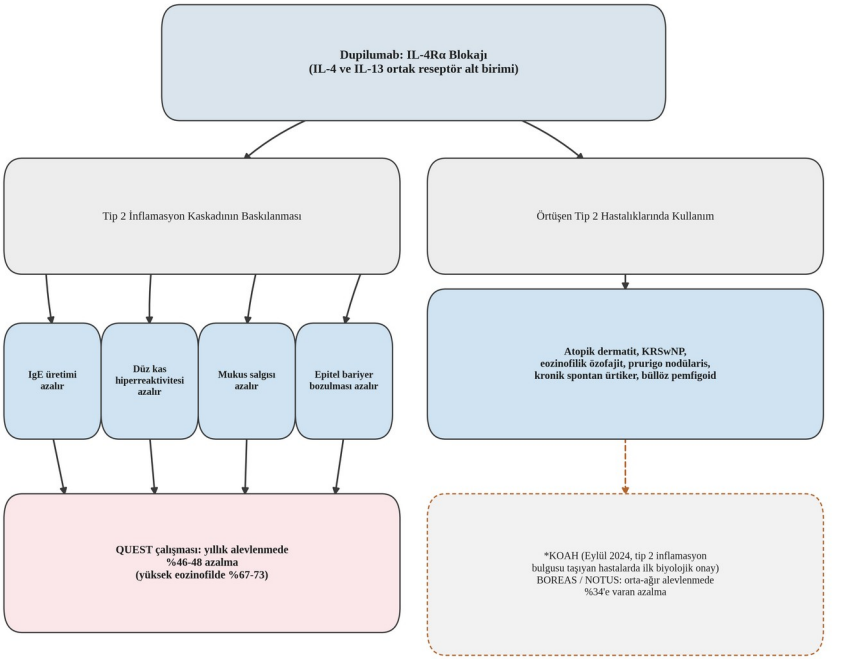
Dupilumab, IL-4 ve IL-13'ün ortak kullandığı IL-4Rα alt birimini bloke ederek her iki sitokinin sinyalini aynı anda durdurmaktadır. Böylece ajanın IgE üretiminden hava yolu düz kas hiperreaktivitesine, mukus salgısından epitel bariyer bozulmasına

kadar geniş bir etki alanı ortaya çıkmaktadır. Dupilumabın diğer biyolojik ajanların aksine ortak reseptör üzerinden iki sitokini birden hedef alması onu diğerlerinden ayıran önemli bir özelliktir.

Dupilumabın astımdaki etkinliği LIBERTY ASTHMA QUEST çalışmasında orta-ağır kontrolsüz astımlı hastalarda yıllık ağır alevlenme oranını plaseboya göre yüzde 46-48 azalması ve başlangıç kan eozinofil sayısı 300 hücre/µL ve üzerinde olan hastalarda bu azalma yüzde 67-73'e kadar çıkarması ile kanıtlanmıştır (Castro ve ark., 2018). Endikasyon kararında genellikle kan eozinofil sayısı veya FeNO değeri eşik olarak kullanılması, dupilumabı diğer anti-IL5 ajanlarından biyobelirteç profili açısından ayırmaktadır.

Atopik dermatit ve KRSwNP başta olmak üzere birçok tip 2 hastalıkta aktif rol oynayan IL-4/IL-13 yolağını etkilemesi nedeniyle dupilumab, atopik dermatit, KRSwNP, eozinofilik özofajit, prurigo nodülaris, kronik spontan ürtiker ve büllöz pemfigoid gibi farklı endikasyonlarda kullanılmaktadır. BOREAS ile NOTUS çalışmalarında orta-ağır alevlenmede plaseboya göre yüzde 34'e varan azalma sağlayarak Eylül 2024'te, tip 2 inflamasyon bulgusu taşıyan kronik obstrüktif akciğer hastalığında (KOAH) kullanılan ilk biyolojik ajan olması ise dikkat çekicidir. Aynı patofizyolojik mekanizma üzerinden gelişen hastalık birlikteliklerinde tek bir ajanın kullanılabilmesi, tedaviyi basitleştirdiği için önemli bir avantaj sağlamaktadır (Şekil 3).

*Şekil 3. Dupilumab (Anti-IL4/IL13) Etki Mekanizması ve Kullanım Alanları Algoritması*




Kaynak: Yazar tarafından oluşturulmuştur.

## Anti-TSLP Tedaviler

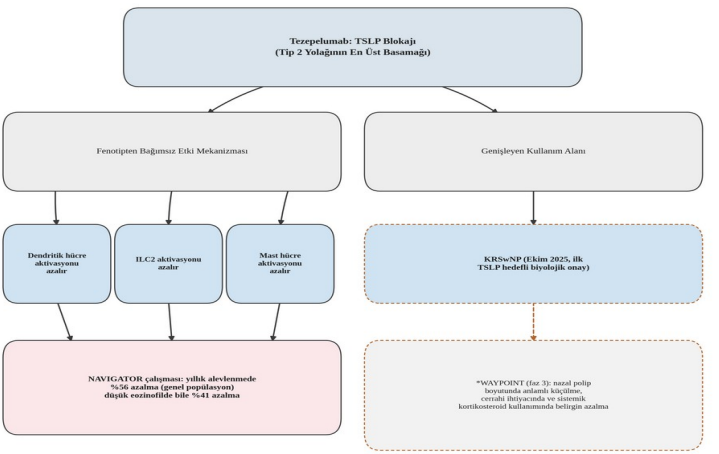
Epitelden salgılanan TSLP'yi nötralize ederek tip 2 yanıtın en üst basamağında etki gösteren tek onaylı biyolojik ajan tezepelumabdır. Ajanın hem dendritik hücreleri hem ILC2'leri hem de mast hücrelerini aktive eden bir alarmin olan TSLP nin bloke etmesi tek bir sitokini değil, yolağın başlangıç noktasını hedeflemesi bakımından önemlidir. Bu özellik tezepelumabı eozinofil sayısından bağımsız kılarak ve hem eozinofilik hem de non-eozinofilik astımlı hastalarda kullanılabilir hale getirmektedir.

NAVIGATOR çalışmasında tezepelumabın etkinliği yıllık alevlenme oranını plaseboya göre genel popülasyonda yüzde 56 azaltması; başlangıç kan eozinofil sayısı 300 hücre/µL'nin altında olan, düşük tip 2 biyobelirteç profiline sahip hastalarda bile bu

azaltmanın yüzde 41'e kadar ulaşması ele kanıtlanmıştır (Menzies-Gow ve ark., 2021). Dört haftada bir subkütan uygulanan tezepelumab, biyobelirteç eşiği aranmaksızın reçete edilebilen ilk ajan olması avantajıyla fenotipleme yapılamayan veya sınırda değerlere sahip hastalarda tercih edilmektedir.

Bu ajanın Ekim 2025'te FDA onayı alan KRSwNP endikasyonu en güncel gelişmedir. Tezepelumabın WAYPOINT faz 3 çalışmasında nazal polip boyutunda anlamlı küçülme sağlaması, cerrahi ihtiyacını neredeyse ortadan kaldırması ve sistemik kortikosteroid kullanımını belirgin şekilde azaltması vurgulanmıştır. Böylece tezepelumab, TSLP yolağını hedefleyerek KRSwNP'de kullanılan ilk biyolojik ajan olmakla beraber astımla birlikte nazal polip taşıyan hastalarda artık Dupilumaba alternatif bir tedavi seçeneği sunmuştur (ŞEKİL 4).

*Şekil 4. Tezepelumab (Anti-TSLP) Etki Mekanizması ve Fenotipten Bağımsız Etkinlik Algoritması*




Kaynak: Yazar tarafından oluşturulmuştur.

**Biyolojik Ajan Seçiminde Klinik Karar Süreci**

Güncel GINA kılavuzuna göre biyolojik ajan seçiminde önce kan eozinofil sayısı, FeNO düzeyi, total IgE ve alevlenme sıklığı gibi biyobelirteçler değerlendirilmektedir (Global Initiative for Asthma [GINA], 2026).

Anti-IgE tedavisi için allerjen duyarlılığı ve dozlama aralığında IgE düzeyi aranırken, anti-IL5/IL5R tedavileri kullanılan ajana göre 150 veya 300 hücre/μL eşiğinin üzerinde eozinofil sayısı gerekmektedir. Anti-IL4Rα tedavisi (dupilumab) için eozinofil sayısının 150-1500 hücre/μL aralığında olması, FeNO değerinin 25 ppb'nin üzerinde olması veya idame oral kortikosteroid ihtiyacının bulunması yeterli sayılmaktadır. Anti-TSLP tedavisi ise geçen yıl içinde alevlenme öyküsü olması koşuluyla, biyobelirteç düzeyinden bağımsız olarak da düşünülebilmektedir.

Komorbiditeler de biyobelirteçler kadar tedavi seçimini yönlendirmektedir. Atopik dermatit veya nazal polip birlikteliği olan hastalarda Dupilumab, hem astımı hem de eşlik eden hastalığı tek ajanla kontrol altına alma avantajı sunmaktadır. Yüksek eozinofil sayısı ve sık alevlenme öyküsü anti-IL5/IL5R ve anti-IL4Rα tedavilerine yanıtı güçlü şekilde öngörmekte iken yüksek FeNO ve nazal polip varlığı anti-TSLP tedavisine yanıtla ilişkilendirilmektedir (GINA, 2026). Klinik pratikte doz sıklığı, uygulama yolu (subkütan veya intravenöz), maliyet ve hasta tercihi de önem taşımaktadır.

Tedaviye yanıt genellikle 3-4 ay sonra değerlendirilmesi gerekirken yanıt belirsiz ise süre 6-12 aya kadar uzatılabilmektedir. depemokimab gibi altı ayda bir uygulanan ajanlarda ise ilk değerlendirme için uygulamadan sonraki altı ayın sonu önerilmektedir (GINA, 2026).

İyileşmesi kriterleri arasında alevlenme sıklığının azalması, semptom kontrolünün düzelmesi, akciğer fonksiyonlarının iyileşmesi, oral kortikosteroid ihtiyacının azalması ve yaşam kalitesinin artması sayılmaktadır. Ancak GINA, bunun için henüz net bir eşik tanımlanmadığını belirtmektedir. Yanıt alınamayan hastalarda tedavi kesilip uygun olduğu takdirde farklı bir hedefe yönelik ajana geçilmesi gerekirken kısmi yanıt durumunda altta yatan tanının yeniden gözden geçirilmesi önerilmektedir. Kan eozinofili gibi biyobelirteçlerin zaman içinde belirgin dalgalanma gösterebilmesi nedeniyle, tedaviye uygunluk kararından önce ölçümün en az bir-iki hafta arayla birkaç kez tekrarlanması önerilmektedir (GINA, 2026).

**"Klinik Remisyon" Kavramının Tanımı ve Kriterleri**

Biyolojik tedavilerin bir kısım hastada alevlenmeyi neredeyse tamamen ortadan kaldırdığının görülmesiyle gündeme klinik remisyon kavramı gelmiştir. 2020 yılında yayımlanan uzman uzlaşı çerçevesinde remisyon için:

- Alevlenme yokluğu
- Semptom kontrolünün sağlanması (Astım Kontrol Testi [ACT] skorunun 20 ve üzerinde olması veya Astım Kontrol Anketi [ACQ] skorunun 0,75'in altında olması)
- Akciğer fonksiyonlarının stabilizasyonu veya optimizasyonu
- Oral kortikosteroidsiz kontrol şartlarının sağlanması gerektiği aynı zamanda bu durumun en az on iki aylık bir süre boyunca eş zamanlı olarak sağlanmalı belirtilmiştir (Menzies-Gow ve ark., 2020).

Klinik remisyon tanımı hastalığın biyolojik olarak ortadan kalktığını değil tedavi altında remisyon sağlandığı anlamında değerlendirilmektedir (GINA, 2026).

**Remisyon Hedefinin Güncel Kılavuzlara Girişi**

Klinik remisyon kavramı henüz GINA kılavuzuna resmi olarak girmemiştir. Klavuz birincil hedef olarak hâlâ "iyi kontrollü astım"ı tanımlamaktadır. Ancak GINA, biyolojik tedavi alan bazı ağır astım hastalarının klinik remisyona ulaştığını kabul etmekle ve remisyonu öngören etkenleri:

- Daha az semptom,
- Daha iyi akciğer fonksiyonu,
- Düşük komorbidite yükü,
- Erken yaşta başlayan astım
- Başlangıçta düşük doz oral steroid kullanılması veya hiç idame oral kortikosteroid kullanılmaması olarak tanımlamaktadır (GINA, 2026). Bu yaklaşım, remisyonun kılavuzlara gözlemlenen ve izlenmesi önerilen bir sonuç olarak girdiğini göstermekle beraber kavram açısından kılavuz düzeyinde henüz tam bir uzlaşıya ulaşmadığını, ancak kavramın literatüre de yerleştirilmeye çalışıldığını göstermesi bakımından dikkat çekicidir.

Gerçek yaşam verileri, biyolojik tedavinin remisyon oranlarını belirgin şekilde artırdığını göstermektedir İsviçre Ağır Astım Kayıt Sistemi'nden elde edilen 2025 tarihli bir kohort çalışmasında, dört ölçütün (alevlenme yokluğu, iyi kontrol, oral kortikosteroidsiz durum, korunmuş akciğer fonksiyonu) tümünü birden karşılayan hasta oranı biyolojik tedavi alanlarda yüzde 24,2 iken, biyolojik tedavi almayan hastalarda yüzde 6,2 olarak bildirilmiştir. Eğer tanım esnetilirse (alevlenme yokluğu, kontrol,

oral kortikosteroidsiz durum) bu oranların sırasıyla yüzde 45,7 ve yüzde 15,6'ya çıktığı gösterilmiştir. Bu fark, biyolojik tedavinin yalnızca semptomları baskılamadığını, bir kısım hastada hastalığı klinik olarak geri planda tutabildiğini ortaya koyması bakımından önemlidir.

**Tedavi Süresi ve Tedavinin Kesilme Kriterleri**

Biyolojik tedavinin ne zaman kesilebileceği sorusu, tartışmalıdır. Önerilen kesilme kriterleri:

- İyi semptom kontrolü (ACQ<1,5 veya ACT>19),
- Düzenli veya atak nedenli oral kortikosteroid kullanılmaması,
- Alevlenme geçirilmemesi,
- Akciğer fonksiyonunun normalleşmesi (FEV1≥%80)
- Baskılanmış inflamasyon (kan eozinofil sayısının 300 hücre/µL'nin, FeNO değerinin 50 ppb'nin altında olması) yer almaktadır. Bu ölçütleri karşılayan hastalar "süper yanıtlı" olarak tanımlanmakta ve kesilme denemesi için en uygun aday kabul edilmektedir.

Omalizumab tedavisi kesilen hastaların yaklaşık yüzde 48'i kontrolünü korurken, mepolizumab kesildikten sonra ACQ skorunda hafif bir kötüleşme bildirilmiştir. Dolayısıyla kılavuzlar şimdilik kesin bir süre önermek yerine, hasta bazında değerlendirmeyi öne çıkarmaktadır.

**Yeni Tedavi Yaklaşımları**

Geliştirme aşamasındaki ajanlar arasında ön planda olanlar epitelden salınan bir diğer alarmin olan IL-33'ü hedefleyen İtepekimab ve Tozorakimab gibi moleküllerdir. Ancak bu grubun

astımdaki seyrinin beklendiği kadar parlak olmadığı gösterirken bu durum IL-33 yolağının klinik etkisinin TSLP kadar güçlü olmayabileceğini düşündürmektedir. Buna karşılık, bispesifik antikor tasarımları (tek moleküle iki sitokini birden hedefleme) ve inhaler yoldan uygulanan biyolojik ajanlar hem etkiyi artırmak hem de sistemik yan etkileri azaltmak amacıyla üzerinde çalışılan güncel yaklaşımlar arasında yer almaktadır.

**Sonuç**

Biyolojik tedaviler astımda, tip 2 inflamasyonu farklı basamaklardan hedefleyerek hem alevlenmeyi hem oral kortikosteroid ihtiyacını azaltan, seçilmiş hastalarda ise neredeyse tam kontrol sağlayan bir tedavi ailesi haline gelmiştir. Ajan seçimi artık tek bir biyobelirteçle değil; eozinofil sayısı, FeNO, komorbiditeler ve hastanın tercihiyle birlikte şekillenen bireyselleştirilmiş bir süreç olarak yönetilmektedir.

Bu ilerlemenin getirdiği en belirgin değişim ise astımda daha önce gündemde olmayan bir hedef olan klinik remisyonun tartışmanın merkezine oturmasıdır. Remisyon kavramı henüz kılavuzlarda resmi bir hedef olarak yer almasa da, biyolojik tedavinin ulaşabildiği en ileri nokta olarak klinik pratiği şimdiden yönlendirmektedir.

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# BÖLÜM 3

# GLP-1/GIP RESEPTÖR AGONİSTLERİ İLE OBSTRÜKTİF UYKU APNESİ TEDAVİSİNDE YENİ DÖNEM

**ÜMMÜHAN TUĞBA TÜMÜKLÜ**[1]

## Giriş

Obstrüktif uyku apnesi (OSA), uyku sırasında üst hava yolunun tekrarlayan tam veya kısmi kollapsına bağlı olarak gelişen, kronik aralıklı hipoksemi ve uyku parçalanmasıyla seyreden yaygın bir solunum bozukluğudur (Kapur ve ark., 2017). Obeziteyle yakın ilişkisi nedeniyle göğüs hastalıkları pratiğinde sıklıkla iç içe geçmiş iki klinik tablo olarak karşımıza çıkar ve toplum sağlığı açısından önemli bir yük oluşturur.

Pozitif hava yolu basıncı (PAP) tedavisi hâlâ altın standart olma özelliğini korusa da, uzun dönem hasta uyumundaki güçlükler nedeniyle etkili bir farmakolojik alternatif arayışı onlarca yıldır sürmektedir. Bu arayış, tip 2 diabetes mellitus ve obezite tedavisi için geliştirilen glukagon benzeri peptit-1 (GLP-1) ve glukoza bağımlı insülinotropik polipeptit (GIP) reseptör agonistlerinin OSA üzerindeki etkisinin fark edilmesiyle yeni bir aşamaya girmiştir. 2024 yılında yayımlanan SURMOUNT-OSA çalışması (Malhotra ve

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ark., 2024) ve onu izleyen FDA onayı, alanı bir dönüm noktasına taşımıştır.

Bu bölümde, OSA'nın epidemiyolojisi ve obeziteyle ilişkisinden başlanarak, mevcut tedavi yaklaşımlarının sınırlılıkları, GLP-1/GIP reseptör agonistlerinin farmakolojik temeli, klinik kanıtlar, güvenlik profili ve göğüs hastalıkları pratiğine yansımaları güncel literatür ışığında ele alınacaktır.

## OSA'nın Tanımı, Epidemiyolojisi ve Obezite ile İlişkisi

Amerikan Uyku Tıbbı Akademisi'nin (AASM) tanı ölçütlerine göre OSA, polisomnografi veya ev tipi uyku testi ile saptanan saatlik apne-hipopne indeksinin (AHI) semptomatik bireylerde ≥5, semptomu bulunmayan bireylerde ise ≥15 olmasıyla tanımlanır (Kapur ve ark., 2017). Hastalık şiddeti de yine AHI değerine göre hafif (AHI: 5-14,9/saat), orta (AHI: 15-29,9/saat) ve ağır (AHI: ≥30/saat) olmak üzere üç kategoride sınıflandırılır (Kapur ve ark., 2017). Bu sınıflama yalnızca tanı koymak için değil, tedavi kararlarını yönlendirmek açısından da klinik önem taşır; ilerleyen bölümlerde ele alınacak farmakolojik tedavi çalışmalarının çoğu, hasta popülasyonunu bu AHI eşiklerine göre tanımlamaktadır.

Bu tanı çerçevesiyle değerlendirildiğinde OSA, dünya genelinde 30 yaş üstü yetişkinlerin önemli bir kısmını etkileyen, sıklıkla tanı almadan seyreden bir halk sağlığı sorunudur. Benjafield ve arkadaşlarının (2019) literatür temelli küresel yük analizine göre dünyada 936 milyondan fazla erişkin, hafif dereceyi de kapsayan tanı ölçütlerine göre OSA ile uyumlu bulgular taşımaktadır; bu erişkinlerin yaklaşık 425 milyonu orta-ağır şiddette hastalığa karşılık gelmektedir. Bu rakamlar güncelliğini korumakta olup, alanın 2025 tarihli derlemelerinde de (Iannella ve ark., 2025) hâlâ referans olarak kullanılmaya devam etmektedir. Türkiye'den elde edilen ulusal veriler de bu küresel tabloyu doğrulamaktadır: çok merkezli TURKAPNE kohortunun 7.130 hastayı kapsayan analizinde, kadın

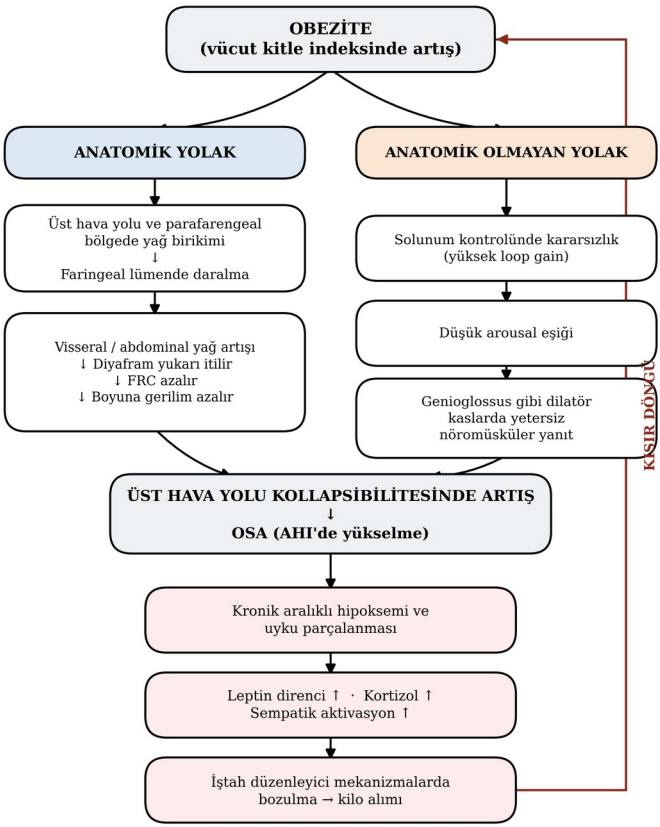
hastaların erkeklere kıyasla daha ileri yaşta ve daha yüksek vücut kitle indeksiyle başvurduğu, buna karşın ortalama AHI değerlerinin kadınlarda daha düşük seyrettiği (29,8±24,1'e karşı 36,8±26,2 olay/saat) gösterilmiş; buna rağmen kadın hastalarda insomni, baş ağrısı, duygudurum değişiklikleri ve diyabet, hipertansiyon, hipotiroidi gibi komorbiditelerin daha sık görüldüğü bildirilmiştir (Pihtili ve ark., 2025). TURKAPNE, Türkiye'de uyku apnesi alanında yürütülen ilk ulusal, çok merkezli prospektif kohort olması bakımından da ayrıca önem taşımaktadır (Fırat ve ark., 2018).

Obezite, OSA gelişiminde bilinen en güçlü ve değiştirilebilir risk faktörüdür. Messineo ve arkadaşlarının (2024) güncel derlemesinde vurgulandığı gibi, bu ilişki basit bir mekanik yük artışından ibaret değildir; anatomik ve anatomik olmayan faktörler bir arada rol oynar. Anatomik düzlemde, üst hava yolu çevresindeki ve parafarengeal bölgedeki yağ birikimi faringeal lümeni daraltırken, artan viseral ve abdominal yağ kütlesi diyaframı yukarı iterek fonksiyonel rezidüel kapasiteyi azaltır; akciğer hacmindeki bu düşüş, üst hava yolunun boyuna gerilimini zayıflatarak kollapsibiliteyi artırır. Anatomik olmayan boyutta ise obezite, solunum kontrolündeki kararsızlık (yüksek loop gain), düşük arousal eşiği ve genioglossus gibi dilatör kasların yetersiz nöromüsküler yanıtı üzerinden de hastalığa katkıda bulunabilir; bu da obez olmayan bireylerde dahi OSA'nın neden ortaya çıkabildiğini açıklamaya yardımcı olur (Messineo ve ark., 2024).

Bu ilişki tek yönlü değildir. OSA'ya bağlı kronik aralıklı hipoksemi ve uyku parçalanması; leptin direnci, kortizol düzeyinde artış ve sempatik aktivasyon üzerinden iştah düzenleyici mekanizmaları bozarak kilo alımını kolaylaştırabilir (Messineo ve ark., 2024; Romero-Corral ve ark., 2010), böylece obezite ile OSA arasında kendi kendini besleyen bir kısır döngü oluşabilir. Bu karşılıklı pekiştirici ilişki, göğüs hastalıkları pratiğinde OSA tedavisinin yalnızca üst hava yolu obstrüksiyonunu hedeflemekle

sınırlı kalamayacağını, altta yatan obezitenin de eş zamanlı ele alınması gerektiğini ortaya koymaktadır (bkz. Şekil 1).

*Şekil 1. Obezite ile obstrüktif uyku apnesi arasındaki çift yönlü (kısır döngü) patofizyolojik ilişki*




Kaynak: Yazar tarafından, Messineo ve ark. (2024) esas alınarak oluşturulmuştur.

## Mevcut Tedavi Yaklaşımları ve Farmakolojik Arayışın Gerekçesi

Pozitif hava yolu basıncı (PAP) tedavisi, üst hava yolunu pnömatik olarak açık tutarak AHI'yi neredeyse tamamen normalize edebilmesi nedeniyle orta-ağır OSA'da hâlâ birinci basamak tedavi ve altın standarttır. Ancak tedavinin etkinliği büyük ölçüde düzenli

ve uzun süreli kullanıma bağlıdır; klasik derlemelerinde Weaver ve Grunstein (2008), kullanılan uyum tanımına göre çalışmalar arasında hastaların %46-83 gibi geniş bir aralıkta uzun dönemde tedaviye yeterince uyum sağlayamadığını bildirmiştir. Maske intoleransı, klostrofobik yakınmalar, burun tıkanıklığı ve cihazın günlük yaşamda pratik olmayışı, bu uyumsuzluğun başlıca nedenleri arasında sayılmaktadır. Bu durum, PAP etkin bir tedavi olmasına karşın toplum düzeyinde beklenen faydayı tam olarak sağlayamamasına yol açmaktadır.

Oral apareyler, özellikle mandibular ilerletme cihazları, PAP'ı tolere edemeyen hafif-orta OSA hastalarında alternatif bir seçenek sunar; ancak etkinlikleri PAP'a kıyasla daha değişkendir ve ağır OSA'da, yüksek vücut kitle indeksine sahip hastalarda yanıt oranı belirgin şekilde düşer (Manetta ve ark., 2022). Üst hava yolu cerrahisi (örn. uvulopalatofarengoplasti, maksillomandibular ilerletme) seçilmiş olgularda anatomik obstrüksiyonu doğrudan hedefleyebilse de, sonuçlar hastadan hastaya büyük farklılık gösterir, invaziftir ve her hastaya uygulanabilir değildir. Bu nedenle ne oral apareyler ne de cerrahi, PAP'ın yerini toplum düzeyinde alabilecek evrensel bir çözüm oluşturmamaktadır.

Bu tabloda, hastanın günlük uyumuna bağlı olmayan, basit ve tekrarlanabilir bir farmakolojik seçeneğe duyulan ihtiyaç onlarca yıldır gündemdedir. Ne var ki geçmişte denenen ajanların çoğu bu beklentiyi karşılayamamıştır: teofilin, doksapram ve asetazolamid gibi santral solunum uyarıcıları, uyku kalitesini bozarak AHI üzerinde ya hiçbir etki göstermemiş ya da beklenenin aksine olumsuz sonuçlar vermiştir (Jaganathan ve ark., 2024). Noradrenerjik-antimuskarinik kombinasyonlar (örn. atomoksetin-oksibutinin) sonraki çalışmalarda mütevazı ama tutarlı bir etkinlik göstermiş olsa da, tek başına klinik pratiği değiştirecek düzeyde güçlü bulunmamıştır (Jaganathan ve ark., 2024). Bu birikmiş başarısızlıklar ve kısmi başarılar, araştırmacıları farklı bir hedefe —

hastalığın altında yatan obeziteyi doğrudan azaltan ajanlara — yöneltmiş ve GLP-1/GIP reseptör agonistlerinin bu alanda değerlendirilmesinin önünü açmıştır.

## GLP-1/GIP Reseptör Agonistlerinin Farmakolojik Temeli ve OSA'daki Etki Mekanizmaları

Glukagon benzeri peptit-1 (GLP-1) ve glukoza bağımlı insülinotropik polipeptit (GIP), bağırsaktan besin alımına yanıt olarak salgılanan, pankreastan glukoza bağımlı insülin salınımını uyaran doğal inkretin hormonlarıdır. Tirzepatid, bu iki reseptörü aynı anda ve dengeli şekilde aktive edebilen sentetik bir peptit olup, GLP-1 etkisiyle tokluk hissini artırıp iştahı baskılarken, GIP etkisiyle insülin duyarlılığını ve genel metabolik homeostazı güçlendirir (Fang ve ark., 2026). Bu dual agonizm, molekülün yalnızca semaglutid gibi seçici GLP-1 agonistlerine kıyasla daha belirgin kilo kaybı sağlamasının farmakolojik temelini oluşturur.

OSA üzerindeki etkisinin en iyi anlaşılan bileşeni, kilo kaybı yoluyla dolaylı yoldur. Vücut ağırlığındaki azalma, üst hava yolu çevresindeki ve parafarengeal bölgedeki yağ dokusunu küçültürken, viseral yağ kütlesindeki gerileme diyafram üzerindeki baskıyı azaltarak akciğer hacimlerini ve üst hava yolunun boyuna gerilimini iyileştirir; bu da faringeal kollapsibiliteyi doğrudan azaltır (Ellberg ve ark., 2025). Nitekim GLP-1/GIP agonistleriyle sağlanan AHI azalmasının büyük kısmının, sağlanan kilo kaybı miktarıyla orantılı olduğu gösterilmiştir.

Ancak biriken kanıtlar, etkinin yalnızca kilo kaybına indirgenemeyeceğini düşündürmektedir. Hayvan çalışmalarında GLP-1 sinyalizasyonunun genioglossus gibi üst hava yolu dilatör kaslarının tonusunu doğrudan artırarak kollaps eğilimini azaltabildiği gösterilmiş olsa da, bu etkinin insanlarda hava yoluna özgü klinik kanıtı hâlâ sınırlıdır (Fang ve ark., 2026). Bunun yanı sıra tirzepatidin, monosit kemotaksisini baskılama, makrofaj

kaynaklı inflamatuar yanıtı azaltma ve AMP ile aktive edilen protein kinaz (AMPK) aracılı nükleer faktör kappa B (NF-κB) sinyal yolağının baskılanması gibi mekanizmalarla anti-inflamatuar etki gösterdiği bildirilmektedir (Fang ve ark., 2026); bu özellikle önemlidir, çünkü kronik aralıklı hipoksemiye bağlı düşük dereceli sistemik inflamasyon (TNF-α, IL-6, CRP yüksekliği) obeziteyle ilişkili OSA'nın patofizyolojisinde kendi başına rol oynamaktadır.

Özetle, GLP-1/GIP reseptör agonistlerinin OSA üzerindeki etkisi büyük ölçüde kilo kaybı aracılı olsa da, üst hava yolu nöromüsküler fonksiyonu ve sistemik inflamasyon üzerinden kilo kaybından bağımsız katkılar da içerebilecek çok bileşenli bir mekanizma olarak değerlendirilmelidir. Bu çok yönlü etki profili, bir sonraki bölümde ele alınacak klinik çalışma sonuçlarının neden bu denli güçlü olduğunu kısmen açıklamaktadır.

## Klinik Kanıtlar: SCALE Sleep Apnea ve SURMOUNT-OSA Çalışmaları

GLP-1 agonistlerinin OSA üzerindeki etkisine ilişkin ilk düzeyde kanıt, günde bir kez subkütan uygulanan liraglutid 3,0 mg ile yürütülen SCALE Sleep Apnea çalışmasından gelmiştir (Blackman ve ark., 2016). Obez ve orta-ağır OSA'sı olan 359 hastanın (ortalama başlangıç AHI: 49,2/saat) randomize edildiği bu 32 haftalık çalışmada, liraglutid kolunda AHI ortalama 12,2 olay/saat azalırken, plasebo kolunda bu azalma 6,1 olay/saat ile sınırlı kalmıştır; tedavi farkı istatistiksel olarak anlamlı bulunmuştur (p=0,015). Vücut ağırlığındaki azalma da liraglutid grubunda plaseboya kıyasla belirgin şekilde daha fazlaydı (%5,7'ye karşı %1,6). Bu çalışma, mütevazı büyüklükteki etkisine karşın, GLP-1 reseptör agonizminin OSA şiddetini azaltabileceğine dair ilk sağlam randomize kontrollü kanıtı sunması bakımından alan için bir kilometre taşı olmuştur.

Sekiz yıl sonra yayımlanan SURMOUNT-OSA çalışması (Malhotra ve ark., 2024), dual GLP-1/GIP agonisti tirzepatidin etkisini çok daha büyük bir örneklemde ve gerçek klinik pratiği yansıtan iki ayrı kohortta test etmiştir: PAP tedavisini kullanamayan/kullanmak istemeyen hastalar ile PAP tedavisine devam eden hastalar, toplam 469 katılımcı içinde ayrı ayrı değerlendirilmiştir. 52 haftalık tedavi sonunda tirzepatid, her iki kohortta da AHI'yi ortalama 25-29 olay/saat azaltırken, plasebo kolunda bu azalma yalnızca 5-6 olay/saat düzeyinde kalmıştır. Hastalığın remisyonuna (AHI<5/saat) veya hafif dereceye gerilemesine ulaşan hasta oranı tirzepatid kolunda %42-50 iken, plasebo kolunda %14-16'da kalmıştır. Vücut ağırlığındaki azalma %18-20 ile SCALE Sleep Apnea'da gözlenenin çok üzerinde seyretmiş; ayrıca sistolik kan basıncında 7,6-9,6 mmHg düşüş ve hsCRP düzeylerinde iyileşme gibi kardiyometabolik yararlar da eşlik etmiştir.

İki çalışmanın karşılaştırmalı özeti Tablo 1'de sunulmuştur. Aradaki etki büyüklüğü farkı büyük ölçüde tirzepatidin dual agonizminin sağladığı belirgin kilo kaybı üstünlüğüyle açıklanabilir; ancak bir önceki bölümde tartışılan kilo kaybından bağımsız mekanizmaların da bu farka katkıda bulunmuş olabileceği düşünülmektedir.

*Tablo 1. GLP-1/GIP reseptör agonistleri ile OSA'da yürütülen iki anahtar randomize kontrollü çalışmanın karşılaştırmalı özeti*

| **Özellik** | **SCALE Sleep Apnea (Blackman ve ark., 2016)** | **SURMOUNT-OSA (Malhotra ve ark., 2024)** |
|---|---|---|
| İlaç | Liraglutid 3,0 mg (GLP-1 agonisti) | Tirzepatid (GLP-1/GIP dual agonisti) |
| Hasta sayısı | 359 | 469 |
| Tedavi süresi | 32 hafta | 52 hafta |
| Başlangıç AHI (ortalama) | 49,2/saat | Orta-ağır OSA (kohorta göre değişken) |
| AHI değişimi - ilaç | -12,2/saat | -25 ila -29/saat |

| | | |
|---|---|---|
| kolu | | |
| AHI değişimi - plasebo kolu | -6,1/saat | -5 ila -6/saat |
| Kilo kaybı (ilaç vs plasebo) | %5,7 vs %1,6 | %18-20 vs %2 |
| Remisyon / hafif dereceye gerileme | Bildirilmemiş | %42-50 vs %14-16 |
| Ek kardiyometabolik bulgu | Bildirilmemiş | Sistolik KB: -7,6 ila -9,6 mmHg; hsCRP iyileşmesi |

Kaynak: Blackman ve ark. (2016) ve Malhotra ve ark. (2024) verilerinden yazar tarafından derlenmiştir.

SURMOUNT-OSA'nın sonuçları, yalnızca akademik açıdan değil, düzenleyici açıdan da belirleyici olmuştur: bu çalışmanın bulguları, bir sonraki bölümde ayrıntılı ele alınacak olan FDA onayının doğrudan dayanağını oluşturmuştur.

## FDA Onayı ve Klinik Pratiğe Yansımaları

SURMOUNT-OSA çalışmasının sonuçları temel alınarak, Amerikan Gıda ve İlaç Dairesi (FDA) 20 Aralık 2024 tarihinde tirzepatidi (ticari adıyla Zepbound), obeziteyle ilişkili orta-ağır OSA'sı olan yetişkinlerde kullanım için onaylamıştır (Eli Lilly and Company, 2024). Bu onay, OSA'ya özgü endikasyonla ruhsat almış ilk farmakolojik ajan olması bakımından tarihi bir gelişmedir; onay öncesinde bu alanda kullanılan hiçbir ilaç doğrudan OSA endikasyonuyla ruhsatlandırılmamıştır. Amerikan Uyku Tıbbı Akademisi (AASM), onayı hastalığın yükünü azaltmada kritik bir ilerleme olarak nitelendirerek desteklemiştir (American Academy of Sleep Medicine, 2024).

Onaylanan endikasyon, vücut kitle indeksi ≥30 kg/m² olan ve AHI ≥15/saat ile orta-ağır OSA tanısı almış yetişkinlerle sınırlıdır. Tedavi, haftada bir kez subkütan uygulama şeklinde, 2,5 mg başlangıç dozuyla başlatılıp en az dört haftalık aralıklarla 2,5 mg artırılarak 10-15 mg/hafta idame dozuna ulaşılacak şekilde titre edilir (American Academy of Sleep Medicine, 2025). Medüller tiroid

karsinomu veya çoklu endokrin neoplazi tip 2 kişisel/aile öyküsü, ağır gastrointestinal hastalık ve gebelik, tedavinin kontrendike olduğu başlıca durumlardır.

Klinik pratik açısından belki de en kritik nokta, tirzepatidin PAP tedavisinin yerini almak üzere değil, onu tamamlayıcı bir seçenek olarak konumlandırılmış olmasıdır. AASM'in klinisyenlere yönelik rehberliğinde, Zepbound'un PAP tedavisi, oral aparey veya cerrahi gibi mevcut yaklaşımların yerine geçmemesi, aksine bu yöntemlerle birlikte veya PAP'ı tolere edemeyen hastalarda bir alternatif olarak değerlendirilmesi gerektiği vurgulanmaktadır (American Academy of Sleep Medicine, 2025). SURMOUNT-OSA'nın PAP kullanan kohortunda dahi anlamlı ek fayda gözlenmiş olması, bu iki tedavi yaklaşımının rakip değil tamamlayıcı olarak düşünülmesi gerektiğine işaret etmektedir. Tedavi süresince AHI'deki iyileşmeye paralel olarak PAP basınç ihtiyacının yeniden değerlendirilmesi önerilmekte, ancak birçok hastanın uzun dönemde PAP tedavisine bir şekilde devam etmeye ihtiyaç duyacağı belirtilmektedir (American Academy of Sleep Medicine, 2025).

Bu denli güçlü bir etkinlik profiline karşın, tirzepatidin klinik kullanımı bazı güvenlik uyarıları ve sınırlılıklarla birlikte değerlendirilmelidir; bu konu bir sonraki bölümde ele alınmaktadır.

## Güvenlik Profili, Sınırlılıklar ve Tartışmalı Noktalar

Tirzepatidin en sık bildirilen yan etkileri doza bağlı gastrointestinal yakınmalardır; bulantı, ishal, kusma ve karın rahatsızlığı hastaların önemli bir kısmında görülmekte, özellikle doz artırım döneminde belirginleşmektedir. Sıvı alımının günde yaklaşık 2 litre düzeyinde tutulması, akut böbrek hasarı riskini azaltmak açısından önerilmektedir. Molekül, medüller tiroid karsinomu ve akut pankreatit riskine ilişkin kutulu uyarı (boxed warning) taşımakta; safra kesesi hastalığı öyküsü olan, gastroparezi,

kontrolsüz diyabet, yeme bozukluğu veya gebelik durumundaki hastalarda dikkatli kullanım gerekmektedir (Robards, 2025).

Klinik kullanımı sınırlayan bir diğer önemli nokta, uzun dönem veri eksikliğidir. SURMOUNT-OSA çalışması 52 hafta ile sınırlı kalmış olup, tedavinin yıllar süren kullanımda güvenlik ve etkinlik profilinin nasıl seyredeceği henüz netlik kazanmamıştır. Daha da önemlisi, SURMOUNT-4 çalışmasının tedavi kesimi sonrası analizinde, tirzepatid tedavisi durdurulduğunda sağlanan kilo kaybının büyük ölçüde geri döndüğü ve buna paralel olarak kardiyometabolik yararların da zayıfladığı gösterilmiştir. Bu bulgu, OSA'daki AHI iyileşmesinin de tedavinin sürekliliğine bağımlı olabileceğini, dolayısıyla molekülün geçici bir kür değil, süresi belirsiz — muhtemelen uzun süreli — sürdürülmesi gereken bir tedavi olarak düşünülmesi gerektiğini düşündürmektedir (Robards, 2025).

Maliyet ve erişim, klinik pratikte belki de en somut sınırlılığı oluşturmaktadır. Amerika Birleşik Devletleri'nde liste fiyatı kutu başına yaklaşık 1.086 dolar olan ilacın sigorta kapsamı büyük ölçüde değişkendir ve çoğu sigorta planı ön onay (prior authorization) şartı koşmaktadır; hatta bazı büyük sağlık sigortası sağlayıcıları Zepbound'u kapsam dışı bırakma kararı almıştır (Robards, 2025). Türkiye başta olmak üzere birçok ülkede ise ilacın OSA endikasyonuyla geri ödeme kapsamına alınıp alınmayacağı henüz belirsizdir; bu durum, ilacın klinik etkinliğinin ötesinde, hangi hastaların bu tedaviye gerçekten erişebileceği sorusunu gündemde tutmaktadır.

AASM'in de vurguladığı gibi, tirzepatid OSA yönetiminde "bir araçtır, tek başına çare değildir"; diyetisyen ve davranışsal destek uzmanlarını içeren çok disiplinli bir yaklaşımla, düzenli takip altında ve onaylanmamış bileşik (compounded) formülasyonlardan kaçınılarak kullanılması önerilmektedir (Robards, 2025). Bu sınırlılıklar göz önünde bulundurulduğunda, GLP-1/GIP reseptör

agonistlerinin göğüs hastalıkları pratiğindeki yerinin nasıl konumlandırılması gerektiği, bölümün sonraki ve son kısmında tartışılacaktır.

## Göğüs Hastalıkları Pratiği İçin Değerlendirme ve Gelecek Yönelimler

Türkiye'de tirzepatid, Mounjaro ticari adıyla tip 2 diabetes mellitus ve obezite endikasyonlarıyla ruhsatlı ve reçetelenebilir durumdadır; ancak yazının hazırlandığı tarih itibarıyla molekülün ülkemizde doğrudan OSA endikasyonuyla bir ruhsatı ve bu endikasyona özgü bir geri ödeme kapsamı bulunmamaktadır. Bu durum, göğüs hastalıkları uzmanlarının, obeziteyle ilişkili orta-ağır OSA'sı olan ve mevcut ruhsatlı endikasyon (obezite/tip 2 diyabet) kapsamına giren hastalarında molekülü kayıtlı endikasyon üzerinden değerlendirebileceği, ancak OSA'ya özgü klinik gerekçelendirmenin reçete ve geri ödeme süreçlerinde ayrı bir belgeleme gerektirebileceği anlamına gelmektedir. Alanın hızla geliştiği göz önüne alındığında, bu durumun önümüzdeki dönemde güncellenmesi beklenebilir.

Alandaki araştırma boşlukları da göz ardı edilmemelidir. Mevcut kanıtların neredeyse tamamı obez, orta-ağır OSA'sı olan yetişkinlerden elde edilmiştir; normal kilolu veya hafif dereceli OSA'sı olan hastalarda, çocuk ve adolesan popülasyonda ya da farklı GLP-1/GIP moleküllerinin karşılaştırmalı etkinliğine ilişkin veri sınırlıdır. Semaglutidin tip 2 diyabet ve obezitesi olan, eşlik eden OSA'sı bulunan hastalardaki etkisini değerlendiren yeni bir randomize çalışma (ClinicalTrials.gov kayıt no: NCT07281196) hâlâ devam etmektedir; bu tür çalışmaların, gözlenen etkinin tirzepatide özgü mü yoksa sınıf etkisi mi olduğunu netleştirmesi beklenmektedir. Ayrıca, PAP ile GLP-1/GIP agonistlerinin birlikte kullanıldığı kombinasyon stratejilerinin uzun dönem kardiyovasküler sonuçlar üzerindeki etkisi ve tedavinin kesilmesi

durumunda AHI'nin ne kadar sürede ve ne ölçüde eski haline döndüğü gibi sorular da yanıt beklemektedir.

Bu veriler ışığında, göğüs hastalıkları pratiği için makul bir konumlandırma şöyle özetlenebilir: GLP-1/GIP reseptör agonistleri, PAP tedavisini tolere edemeyen veya tam uyum sağlayamayan, obeziteyle ilişkili orta-ağır OSA hastalarında — özellikle eşlik eden tip 2 diyabet veya kardiyometabolik risk faktörleri varsa — değerlendirilmeye değer bir tamamlayıcı seçenektir. Ancak bu hastaların tedavi öncesi ve sonrası nesnel uyku çalışmalarıyla (polisomnografi veya ev tipi uyku testi) izlenmesi, PAP ihtiyacının AHI'deki değişime göre yeniden gözden geçirilmesi ve tedavinin süreklilik gerektirebileceği konusunda hastanın baştan bilgilendirilmesi gerekmektedir.

**Sonuç**

Obstrüktif uyku apnesi, obeziteyle karşılıklı besleyici bir ilişki içinde seyreden, toplum düzeyinde büyük bir yük oluşturan ve göğüs hastalıkları pratiğinde günlük olarak karşılaşılan bir hastalıktır. PAP tedavisi hâlâ birinci basamak yaklaşım olma özelliğini korusa da, uzun dönem uyum sorunları onlarca yıldır etkili bir farmakolojik alternatif arayışını canlı tutmuştur. GLP-1/GIP reseptör agonistleri, önce liraglutid ile sağlanan mütevazı ama anlamlı etkiyle, ardından dual agonist tirzepatid ile elde edilen çok daha güçlü sonuçlarla bu arayışa somut bir yanıt sunmuş; SURMOUNT-OSA çalışmasının bulguları, Aralık 2024'te FDA'nın OSA'ya özgü ilk farmakolojik onayını vermesinin doğrudan dayanağı olmuştur.

Bu etkinin büyük ölçüde kilo kaybı aracılı olduğu, ancak üst hava yolu nöromüsküler fonksiyonu ve sistemik inflamasyon üzerinden kilo kaybından bağımsız katkıların da olası olduğu görülmektedir. Bununla birlikte, gastrointestinal yan etkiler ve nadir ama ciddi güvenlik uyarıları, sınırlı uzun dönem veri ve tedavi

kesildiğinde yararların geri dönebilmesi, yüksek maliyet ve değişken geri ödeme kapsamı gibi gerçek sınırlılıklar da göz ardı edilmemelidir.

Göğüs hastalıkları uzmanları için pratik çıkarım nettir: GLP-1/GIP reseptör agonistleri, PAP tedavisinin yerini alan değil, onu tamamlayan; hasta seçimi, nesnel uyku çalışmalarıyla izlem ve gerçekçi beklenti yönetimi gerektiren bir tedavi seçeneği olarak değerlendirilmelidir. Alanın önümüzdeki yıllarda hızla gelişmeye devam edeceği ve bu bölümde sunulan kanıt tabanının güncellenmeye açık olduğu unutulmamalıdır.

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# BÖLÜM 4

# THE FEF25-75/FVC RATIO IN THE DIAGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: PHYSIOLOGICAL BASIS, DIAGNOSTIC PERFORMANCE, AND METHODOLOGICAL LIMITS

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## Introduction

In clinical medicine, the definition of a disease and the criterion by which that disease is diagnosed are two distinct concepts. The definition describes the pathological essence of the condition; the criterion determines how it is to be identified in practice. The narrower the distance between them, the more reliable the diagnosis becomes; the wider it grows, the more misclassification becomes inevitable. Chronic obstructive

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*This chapter is derived from the medical specialty thesis titled "Role of FEF25-75/FVC Ratio in the Diagnosis of Chronic Obstructive Pulmonary Disease" (Hatay Mustafa Kemal University, Faculty of Medicine, 2020).*

pulmonary disease (COPD) is one of the conditions in which this distance is most clearly observable, and for that reason it merits examination as an instructive case in the theory of diagnostic criteria.

COPD is defined as a preventable and treatable disease characterised by a non-infectious chronic inflammatory response in the airways and lung parenchyma following prolonged exposure to noxious gases and particles, resulting in persistent and progressive airflow limitation (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2020). This definition points to a heterogeneous entity encompassing at least two distinct pathological processes: small airway disease and emphysematous parenchymal destruction. The diagnosis of the disease, by contrast, has been reduced to a single spirometric ratio falling below a single threshold: a post-bronchodilator FEV1/FVC of less than 0.70.

The practical rationale for this reduction is evident. The fixed ratio is arithmetically simple, requires no reference equations, and can be applied identically across countries. These properties have allowed the diagnosis of COPD to be disseminated from tertiary pulmonary function laboratories to primary care settings. Yet, as with any reduction, there is a cost. Because the FEV1/FVC ratio declines physiologically with age, a fixed threshold tends to classify healthy older individuals as diseased and young smokers as healthy (Swanney et al., 2008; Uysal, 2013). A false-positive diagnosis exposes an individual without disease to unnecessary and potentially harmful treatment. A false-negative diagnosis deprives a genuinely affected individual of treatment at precisely the stage at which the disease is most amenable to intervention (Hangaard et al., 2017). The clinical consequences of both errors are compounded in a setting in which an estimated 60 to 85 per cent of individuals with COPD remain undiagnosed (Kocabaş et al., 2014).

This chapter examines a parameter that has been proposed as a means of narrowing that diagnostic gap: the FEF25-75/FVC ratio.

It first considers the anatomical origin of airflow limitation in COPD and the primacy of the small airways in its pathogenesis. The mechanics of forced expiration are then elaborated in order to establish which spirometric segment carries information about which generation of the bronchial tree. Subsequently, the metrological limits of the fixed threshold, the structural constraints of the raw parameter derived from the mid-expiratory segment (FEF25-75), and the conceptual basis of the indicator obtained by normalising that parameter to forced vital capacity are discussed. The existing literature on the ratio — which spans dysanapsis physiology, airway responsiveness, and one prior report specifically addressing early COPD diagnosis — is then reviewed. Against that background, data from an independent case-control series of two hundred participants conducted by the author are presented and interpreted. The chapter concludes with an assessment of the parameter's position in clinical practice and of the study designs capable of altering that position.

**The Problem of the Defining Criterion and Underdiagnosis**

COPD is a multifactorial and heterogeneous disease. Patients differ markedly both in anatomical and pathological terms and in clinical course (Welte et al., 2015). In one case emphysematous parenchymal destruction predominates; in another, chronic bronchitis and small airway disease are foremost. Exacerbation frequency, comorbidity profile, symptom burden, and the annual rate of decline in lung function vary between individuals.

This heterogeneity is conceptually at odds with the reduction of diagnosis to a single threshold. A singular criterion can be considered reliable only if the quantity it measures is impaired in a comparable manner across all phenotypes of the disease. Since airflow limitation is the common denominator of COPD, the FEV1/FVC ratio satisfies this condition approximately. Situations in

which the ratio is normal despite the presence of disease, and in which the ratio is reduced in the absence of disease, nevertheless constitute a zone of uncertainty in which the diagnostic criterion fails to encompass the definition.

Prevalence varies across countries, across geographical regions within a given country, and according to the genetic constitution of the population, psychosociocultural structure, age, and sex (Abul & Özlü, 2013). On the basis of the Burden of Obstructive Lung Disease (BOLD) programme and comparable large-scale studies, the global number of COPD cases in 2010 was estimated at approximately 384 million, corresponding to a global prevalence of 11.7 per cent (GOLD, 2020). In Türkiye the reported figures diverge widely, and the divergence is itself instructive. Prevalence has been estimated by three distinct methods: physician-assigned diagnosis, symptom questionnaire, and, since 2003, post-bronchodilator spirometry interpreted against GOLD criteria (Abul & Özlü, 2013). In a population aged thirty and over in Trabzon, the prevalence was 0.98 per cent under GOLD criteria but 2.8 per cent under those of the American Thoracic Society — a near-threefold difference produced by the choice of criterion alone. In İzmir the figure was 10.2 per cent among adults aged forty to sixty-nine, and in the BOLD-Adana study 19.1 per cent among those over forty, the latter obtained under the fixed-ratio criterion (Abul & Özlü, 2013; Kocabaş et al., 2014); within that study the disparity between the sexes was marked, at 28.5 per cent in men and 10.3 per cent in women (Kocabaş et al., 2014). That a single population should yield two prevalences differing by a factor of three according only to which threshold is applied is the clearest available demonstration that the diagnostic criterion is not a neutral instrument for counting a pre-existing disease, but a partial determinant of how much disease is found.

Behind these figures lies the fundamental problem that obscures the epidemiological profile of the disease. It has been reported that between 60 and 85 per cent of individuals with COPD remain undiagnosed, and that this undiagnosed group consists predominantly of those with mild to moderate disease (Kocabaş et al., 2014). The overlap between the undiagnosed group and the group that would derive the greatest benefit from intervention magnifies the clinical weight of the problem.

Two sources of the diagnostic gap may be distinguished. The first is attributable to the patient: symptoms such as dyspnoea, chronic cough, and sputum production are, in the early stages, attributed to smoking or to ageing, are disregarded, and the individual does not present to a health facility (GOLD, 2020). The second is attributable to the test: even when the individual does present, the sensitivity of the diagnostic criterion in early disease is limited, and spirometry is not performed to standard in every centre. The present chapter is concerned with the second source.

The economic burden of the disease is likewise considerable. Within the European Union, the direct costs of respiratory diseases constitute approximately 6 per cent of total health expenditure, and the treatment of COPD alone accounts for approximately 56 per cent of that sum (38.6 billion euros) (GOLD, 2020). A survey spanning twelve countries demonstrated that the annual direct cost per patient ranged from 504 US dollars in South Korea to 9,981 US dollars in the United States, with inpatient hospitalisation and home oxygen therapy the principal drivers (Foo et al., 2016). Disease severity, exacerbation frequency, and the presence of comorbidities are the principal determinants of cost (López-Campos et al., 2016; Smith & Wrobel, 2014). The annual global mortality attributable to the disease is estimated at approximately three million (GOLD, 2020), and COPD is projected to remain among the leading causes of death worldwide (Mathers & Loncar, 2006; Negewo et al., 2015). That

exacerbations become more frequent as the disease advances, and that they constitute the largest single component of cost, also establishes the economic rationale for early diagnosis.

**The Anatomical Origin of Airflow Limitation**

The characteristic airflow limitation of COPD arises from two processes whose relative contributions vary between individuals: small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) (GOLD, 2020). These two processes arrive at the same physiological outcome by different mechanisms.

In small airway disease, the membranous bronchioles of less than 2 mm internal diameter develop inflammatory cell infiltration, wall thickening, smooth muscle hypertrophy, mucus plugging, and peribronchiolar fibrosis; the lumen narrows and resistance increases. In emphysema, by contrast, destruction of the alveolar walls reduces the elastic recoil force of the lung. Elastic recoil maintains the patency of the small airways through the radial traction exerted upon them by the surrounding parenchyma. When this traction is weakened, the airways become liable to collapse, particularly during expiration. In both pathways, FEV1 declines progressively, the lungs fail to empty adequately during expiration, and static and dynamic hyperinflation develop (Kocabaş et al., 2014). The process is regarded as a multifactorial pathobiological pathway shaped by the interaction of genetic determinants, lung growth, and environmental stimuli.

That the small airways constitute the first link in this pathogenetic chain carries a decisive diagnostic consequence, the appreciation of which requires attention to the geometry of the bronchial tree. The airways branch at each generation from trachea to alveolus. Although the cross-sectional area of each individual branch is smaller than that of its parent, the number of branches

increases exponentially, so that the total cross-sectional area expands markedly towards the periphery. Whereas the cross-sectional area of the trachea is of the order of a few square centimetres, the total cross-sectional area at the level of the terminal bronchioles reaches several hundred square centimetres.

Since, by Poiseuille's law, resistance is inversely related to cross-sectional area, the greater part of total airway resistance in the healthy individual originates in the large and medium-sized airways. The contribution of the small airways to total resistance is comparatively small. The diagnostic corollary is that early pathological changes in the small airways may progress for a considerable period without producing a measurable increase in total resistance. The obstruction of a large number of bronchioles is reflected only marginally in total resistance, owing to the parallel resistance of the remaining pathways. This is the reason for which the small airways are designated in the literature as the silent zone. The disease originates in this region, yet a parameter weighted towards the large airways, such as FEV1, cannot detect it in the early stages.

The phenotypic distinction acquires meaning in this context. In the emphysema-predominant case, loss of elastic recoil is foremost: total lung capacity and residual volume increase, and the diffusing capacity for carbon monoxide declines. In the case in which chronic bronchitis and small airway disease predominate, luminal narrowing is determinative and diffusing capacity may be relatively preserved. Although both phenotypes reduce the FEV1/FVC ratio, this reduction does not proceed at the same rate in the early stages of the disease. In the small-airway-predominant phenotype, parameters measuring the late expiratory segment would be expected to become abnormal earlier. This expectation constitutes the physiological foundation of the interest in FEF25-75.

## The Mechanics of Forced Expiration and Flow Limitation

Maximal expiration, initiated after a deep inspiration to total lung capacity and sustained to residual volume, constitutes the expiratory limb of the flow-volume loop (Ulubay et al., 2019). Flow rate along this limb is not governed by the same physiological laws from the beginning of the manoeuvre to its end; the curve divides into two qualitatively distinct segments.

During the initial moments of the manoeuvre — in the brief interval from total lung capacity until peak expiratory flow is attained — flow rate is directly proportional to the expiratory muscle force generated by the patient. Early parameters such as peak expiratory flow and FEF25 are therefore effort-dependent and are influenced substantially by the patient's cooperation and motivation and by the quality of instruction in the manoeuvre.

Once peak flow has been reached, however, flow rate does not increase despite increasing effort. This phenomenon, termed flow limitation, is explained by the equal pressure point theory. During forced expiration, the expiratory muscles generate a positive pressure within the pleural space. The pressure within the alveolus equals the sum of this pleural pressure and the elastic recoil pressure of the lung. As air travels from alveolus towards mouth, it loses pressure progressively through friction. At some point along the airway, the intraluminal pressure becomes equal to the pleural pressure surrounding it externally; this point is the equal pressure point. Downstream of it, towards the mouth, intraluminal pressure falls below the surrounding pressure and the airway is dynamically compressed.

The resulting inference is decisive. When the patient exerts greater effort, pleural pressure rises, but airway compression increases proportionately, and the two effects offset one another. The variables determining flow in this segment are therefore not effort

but the elastic recoil pressure of the lung and the resistance of the airways upstream of the equal pressure point. These two variables coincide with the two variables impaired in COPD: emphysema reduces elastic recoil, and small airway disease increases upstream resistance. The mid and late expiratory segments are accordingly both relatively effort-independent and directly sensitive to the two principal pathological processes of COPD (Saryal & Ulubay, 2018; Ulubay et al., 2019).

FEF25-75, which measures the mean flow rate between 25 and 75 per cent of forced vital capacity, describes precisely this segment. Herein lies the physiological foundation of the claim that the parameter reflects the small airways. It should be noted, however, that this attribution has been contested: because flow measured at the mouth is affected by thoracic gas compression, and because a reduction in flow at low lung volumes may equally result from increased peripheral pressure loss or from diminished elastic recoil, a low FEF25-75 does not identify a specific anatomical locus of disease.

A consequence of effort dependence for test quality must also be noted. Since FEV1 is in part effort-dependent, submaximal effort may reduce this value and create a spurious impression of obstruction. A prematurely terminated manoeuvre, by contrast, reduces FVC and thereby falsely elevates the FEV1/FVC ratio, potentially masking genuine obstruction. When a borderline ratio is encountered, visual inspection of the spirogram and verification that the manoeuvre satisfies the acceptability criteria must precede interpretation of the numerical value.

**Definition of Spirometric Parameters and Measurement Validity**

Spirometry is a non-invasive, low-cost, and reliable diagnostic technique that may be performed by trained health

personnel (GOLD, 2020; Kocabaş et al., 2014). Spirometers meeting the criteria of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) should be selected (Saryal & Ulubay, 2018). The parameters employed in the remainder of the chapter are summarised in Table 1.

*Table 1. Principal dynamic spirometric parameters used in the diagnosis of COPD*

| Parameter | Definition | Unit | Physiological correlate |
|---|---|---|---|
| FEV1 | Volume expelled during the first second of forced expiration following maximal inspiration | L | Partly effort-dependent; reflects predominantly the large and medium airways |
| FVC | Total volume expelled during forced expiration following deep inspiration | L | Volume indicator; reduced in restriction and in advanced hyperinflation |
| FEV1/FVC | Tiffeneau ratio | dimensionless (%) | Volume-normalised early-segment flow; diagnostic criterion for obstruction |
| FEF25-75 | Mean flow rate between 25 and 75 per cent of FVC | $L \cdot s^{-1}$ | Relatively effort-independent; held to reflect medium and small airways, but volume-dependent |
| FEF25-75/FVC | Ratio of FEF25-75 to FVC | $s^{-1}$ | Surrogate for airway size relative to lung size (dysanapsis); volume-normalised late-segment flow |

*Definitions compiled from Saryal and Ulubay (2018) and Ulubay et al. (2019); interpretation of FEF25-75/FVC after Mead (1980) and Litonjua et al. (1999).*

The validity of measurement depends upon the test being performed by an experienced technician or physician and upon adherence to the criteria of acceptability and repeatability (Graham et al., 2019; Miller et al., 2005; Saryal & Ulubay, 2018; Uysal, 2013).

The principal criteria are as follows: time to peak flow must be less than 120 milliseconds; back-extrapolated volume must not exceed 5 per cent of FVC or 150 mL; the spirogram must be free of artefact and there must be no cough during the manoeuvre; the manoeuvre must not be terminated prematurely, and expiration should be extended to fifteen seconds where necessary in elderly or obstructed individuals; there must be no leak at the mouthpiece, and the mouthpiece must not be occluded by tongue or teeth; the difference between the two largest FVC values and between the two largest FEV1 values must not exceed 150 mL; and at least three acceptable manoeuvres must be obtained from each individual.

In the diagnosis of COPD, spirometry must be repeated after administration of an appropriate dose of a short-acting inhaled bronchodilator and after the interval recommended by guidelines has elapsed, in order to minimise variability. The diagnosis rests upon post-bronchodilator values; a diagnosis founded upon pre-bronchodilator measurement is, by definition, invalid.

The measurement of FEF25-75 carries three particular vulnerabilities. The first is that the parameter is calculated over percentile fractions of the individual's own FVC; when FVC differs between two manoeuvres in the same patient, the volume interval over which the parameter is computed likewise differs, which renders the repeatability of FEF25-75 inferior to that of FEV1. The second is that the ATS and ERS recommend that the parameter be reported from the manoeuvre yielding the largest sum of FVC and FEV1 (Saryal & Ulubay, 2018); combining the value across different manoeuvres is erroneous. The third is that a prematurely terminated manoeuvre reduces FVC, shifting upward the window over which FEF25-75 is computed and thereby falsely elevating the parameter.

A convention of reporting must also be established. In the present chapter, FEF25-75/FVC is expressed in reciprocal seconds ($s^{-1}$), obtained by dividing FEF25-75 in litres per second by FVC in

litres. Some investigators multiply this quantity by one hundred and report it as a percentage, and cut-off values derived under the two conventions therefore differ by two orders of magnitude. Any study reporting this ratio should state its scaling convention explicitly, since otherwise thresholds cannot be compared across reports.

**The Metrological Limits of the Fixed FEV1/FVC Threshold**

The lung is an ageing organ. The structure of the elastin fibres deteriorates, elastic recoil force diminishes, and the radial traction that maintains the patency of the small airways is weakened. Chest wall compliance falls, and the respiratory muscles lose strength. The spirometric expression of these changes is that FEV1 declines more rapidly than FVC, and that the FEV1/FVC ratio consequently falls with age as a physiological phenomenon. Such a decline is not pathological: in a healthy, never-smoking, asymptomatic individual of seventy-five years, an FEV1/FVC ratio below 0.70 is an expected observation.

Because the fixed threshold does not accommodate this phenomenon, it generates an asymmetrical, bidirectional misclassification. In advanced age, the age-related physiological decline is interpreted as pathological obstruction, and the disease is over-diagnosed in individuals who have never smoked (Swanney et al., 2008; Uysal, 2013). In younger individuals, by contrast, the FEV1/FVC ratio of a smoker may remain above 0.70 even when it is significantly reduced for that person's age, and the disease escapes detection by the criterion (Uysal, 2013). The second error carries the graver clinical consequences, since the patient who is missed is at the very stage at which smoking cessation may slow the rate of decline in lung function.

The ATS and ERS recommend that the definition of obstruction be founded upon the lower limit of normal (LLN) calculated for the individual's age, sex, height, and ethnicity

(Hangaard et al., 2017; Quanjer et al., 2012). The LLN corresponds to the fifth percentile of the healthy reference population; equivalently, a z-score below −1.645 defines obstruction. The Global Lung Function Initiative (GLI) 2012 equations rendered this approach practicable by providing reference values spanning the age range of 3 to 95 years across multiple ethnic groups (Quanjer et al., 2012).

Although the LLN approach has been shown to reduce misclassification substantially, two obstacles persist. The first is that the approach requires the availability of population-appropriate and current reference equations, a condition that is frequently unmet in primary care and resource-limited settings, where spirometry is most needed. The second is that the LLN is itself ultimately a statistical threshold and, by definition, classifies 5 per cent of healthy individuals as abnormal; it reduces misclassification without eliminating it. The magnitude of the residual error should not, however, be overstated. Uysal (2013) puts the combined rate of missed and mistaken diagnoses at approximately 5 per cent, with ethnicity, age and sex the principal contributors. The fixed threshold is thus not a crude instrument but a slightly miscalibrated one, and it is precisely this that makes the misclassification it produces so easy to overlook.

A further blind spot of the fixed ratio is the group designated preserved ratio impaired spirometry (PRISm). These individuals, in whom the FEV1/FVC ratio is preserved while FEV1 falls below 80 per cent of predicted, do not receive a diagnosis of COPD under current GOLD criteria; they nevertheless exhibit increased respiratory symptoms, systemic inflammation, and mortality, and the pattern was found in 12.3 per cent of the COPDGene cohort (Wan et al., 2014). The existence of the PRISm group constitutes direct evidence that the diagnostic criterion fails to encompass the definition of the disease, and it is noteworthy that this group can be

identified only by way of the denominator of the ratio — that is, through volumetric impairment.

Finally, the FEV1/FVC ratio is not specific to COPD. Comorbidities such as heart failure may likewise reduce the ratio; asthma, bronchiectasis and obliterative bronchiolitis figure, alongside heart failure, in the differential diagnosis of COPD (Gentry & Gentry, 2017). A diagnosis founded solely upon the ratio documents not the presence of disease but the fact that a numerical value has crossed a threshold. This is the rationale for the insistence of international guidelines (ACP, GOLD, NICE) that the diagnosis be confirmed within the context of history and physical examination (Gentry & Gentry, 2017; GOLD, 2020). Where the ratio is borderline (in the range of 0.65 to 0.75), the decision should rest upon the joint evaluation of exposure history, symptom profile, physical examination, and, where possible, the LLN value; where doubt persists, lung volumes, diffusing capacity, and thoracic computed tomography should be added to the assessment.

Uysal (2013) states the underlying difficulty without embellishment: because COPD originates in the peripheral airways, no simple and sensitive spirometric test is at present available that can register the early rise in residual volume. The question is therefore not merely which threshold should be applied to FEV1/FVC, but whether that ratio interrogates the appropriate region of the lung at all. This tension between the fixed ratio and the LLN legitimises the search for an indicator that is relatively independent of age, unaffected by volume, and impaired at an earlier stage of the disease.

**The Structural Limitations of FEF25-75**

It has long been known that FEF25-75 falls during the initial stages of obstructive disease. Because it is relatively effort-independent and samples the late expiratory segment, the parameter

has been regarded as an early indicator of small airway disease and has been widely reported in asthma, early COPD, and occupational exposure screening. Three obstacles nevertheless stand in the way of its full incorporation into clinical decision-making.

The first and most important is volume dependence. By definition, FEF25-75 is computed over the middle half of the individual's own FVC. In a person with a small FVC, this percentile window shifts downward on the scale of absolute lung volume, into the region near residual volume where flow rates are naturally low. Since the expiratory limb of the flow-volume curve becomes progressively steeper and approaches zero at low volumes, the mean flow measured falls as the window descends, even within the same healthy lung. Consequently, FEF25-75 may be measured as low in an individual whose airways are entirely normal and whose FVC alone is small. The reduction of FEF25-75 in a restrictive case in the absence of any obstruction is explained by this mechanism. The same mechanism causes the parameter to be systematically low in individuals of short stature, in women, and in advanced age. This is not a measurement error but a structural property embedded in the definition of the parameter. A further consequence deserves emphasis: because residual volume rises as obstruction develops, the FVC of a given patient comes to be exhaled from progressively higher absolute lung volumes over the course of the disease. Since it is not practicable to express flow as a percentage of total lung capacity, a percentage of FVC is used as a surrogate, with the result that even the serial measurements of a single individual are not strictly comparable to one another.

The second obstacle is the width of the normal range in the healthy population, which weakens the specificity of the parameter. The lower limit of normal for this parameter varies markedly across age strata, so that a threshold expressed as a fixed percentage of the predicted value carries a different meaning at different ages. A low

FEF25-75 value may accordingly belong to a diseased individual or equally to an individual at the lower end of the healthy distribution, and the interpretation of an isolated reduction in FEF25-75 as early small airway disease is therefore not defensible.

The third obstacle is the questioning of the parameter's incremental clinical contribution. In a large analysis of routine spirometric records from four tertiary laboratories, comprising 11,654 white males and 11,113 white females aged 3 to 94 years, Quanjer et al. (2014) found that FEF25-75 lay below the lower limit of normal while FEV1, FVC, and FEV1/FVC all remained within normal limits in only 2.75 per cent of cases. Their conclusion — that the mid-expiratory flow contributes nothing useful to clinical decision-making over and above FEV1, FVC, and FEV1/FVC — is the most serious objection levelled at the parameter and the fundamental question that any study defending an FEF25-75-derived indicator must answer.

Of the three limitations enumerated, only the first is amenable to mathematical correction. It is to that correction, and to the literature it has generated, that the chapter now turns.

## The FEF25-75/FVC Ratio: Conceptual Basis

### Dysanapsis and the received interpretation

Green, Mead, and Turner (1974) introduced the term dysanapsis to describe the independent and disproportionate growth of airway calibre and lung parenchymal volume, invoking it to account for the observation that maximal expiratory flows exhibit greater inter-subject variability than does forced vital capacity among healthy adults. Even among healthy individuals, in other words, two persons with identical lung volumes may possess markedly different airway cross-sectional areas.

Mead (1980) subsequently quantified this disproportion. Examining the ratio of a measurement sensitive to airway size (maximal expiratory flow divided by static recoil pressure at 50 per cent of vital capacity) to one sensitive to lung size (vital capacity) in twenty-one men aged 20 to 50 years, he showed that the ratio declined approximately as the inverse four-thirds power of vital capacity — a result consistent with airway diameter being independent of, but airway length dependent upon, lung size. Mead accordingly proposed the ratio of maximal expiratory flow at 50 per cent of vital capacity to FVC as an index of airway size relative to lung size.

The extension of this reasoning to FEF25-75 followed. Litonjua, Sparrow, and Weiss (1999), studying 929 middle-aged and older men in the Normative Aging Study, treated FEF25-75/FVC explicitly as a surrogate measure of airway size relative to lung size and demonstrated that it was significantly associated with the degree of methacholine airway responsiveness after adjustment for age, height, baseline FEV1, smoking, eosinophil count, and IgE ($\beta = -0.37$; $p < 0.001$). Notably, radiographic measures of airway calibre relative to lung area were themselves attenuated when FEF25-75/FVC was entered into the same model, and the association persisted after exclusion of subjects with FEV1/FVC below 0.70 and of all subjects with any smoking history. Parker, Abu-Hijleh, and McCool (2003) subsequently confirmed the relationship in a broader sample of 764 consecutive subjects aged 4 to 91 years, encompassing both sexes.

The received interpretation of the FEF25-75/FVC ratio is therefore established: it is a surrogate for the geometric relationship between airway calibre and lung volume. As airway diameter decreases, or as lung volume increases, the ratio falls.

**A supplementary reading: the emptying rate constant**

To this established interpretation a second, complementary reading may be added, which the present chapter proposes rather than reports. The quantity obtained by dividing FEF25-75 ($L \cdot s^{-1}$) by FVC (L) carries the unit $s^{-1}$. Dimensionally, what results is not a velocity but a rate constant, expressing the fraction of its own volume that the lung empties per unit time in the mid-expiratory segment. Its reciprocal (FVC/FEF25-75), expressed in seconds, corresponds to a conceptual emptying time. A value of 0.50 $s^{-1}$, for instance, signifies that in the mid-expiratory segment the lung empties half of its own vital capacity per second. This quantity bears a structural kinship to the time constant that describes passive lung emptying ($\tau$ = resistance × compliance): as resistance increases, or as compliance increases — as in emphysema — emptying slows and the rate constant diminishes.

The two readings are not in conflict. Reduced airway calibre relative to lung volume (dysanapsis) is precisely the condition under which the lung empties a smaller fraction of its volume per unit time. The dimensional reading simply makes explicit why the ratio should be expected to behave as it does.

That the logic of normalisation is already familiar in clinical practice reinforces the point. The FEV1/FVC ratio is the product of the same operation: the volume expelled in the first second expressed as a fraction of the total expellable volume. The durability of the Tiffeneau ratio as an indicator derives from its comparability across individuals irrespective of lung size. The FEF25-75/FVC ratio applies this principle to the later segment of expiration, which is less effort-dependent and more sensitive to peripheral resistance and elastic recoil.

**A testable prediction**

This proposition contains a prediction that may be formulated in advance and tested empirically. If the operation of normalisation

genuinely removes volume dependence, then no significant correlation should be observed between the resulting indicator and FVC; a positive correlation, by contrast, should be observed between raw FEF25-75 and FVC.

A corollary follows for restrictive physiology. Although lung volume is reduced in restrictive disease, the accompanying increase in elastic recoil opposes airway collapse during the latter portion of the FVC manoeuvre; the FEF25-75/FVC ratio would therefore be expected to rise rather than fall. This asymmetry — the ratio falling in obstruction and rising in restriction — is a further consequence of its dimensional structure.

## Prior Literature on the FEF25-75/FVC Ratio in Obstructive Disease

Several investigations have assessed the relationship between FEF25-75/FVC and obstructive lung disease. Beyond the airway-responsiveness studies described above, DeMeo et al. (2004) reported familial aggregation of both FEF25-75 and FEF25-75/FVC in families with severe, early-onset COPD, a finding consistent with the ratio's capturing a heritable geometric predisposition rather than acquired obstruction alone.

Of direct relevance to the present chapter is the report of Mirsadraee, Boskabady, and Attaran (2013), who proposed the ratio of maximal mid-expiratory flow to forced vital capacity — a designation they explicitly equate with FEF25-75/FVC — as a feasible spirometric parameter permitting the diagnosis of COPD earlier than the prevailing GOLD criteria allow. Their prospective case–control study recruited 109 participants: 40 with established obstruction, 37 who presented with the clinical features of COPD while their FEV1 and FEV1/FVC remained within the normal range (designated the at-risk group), and 32 never-smoking controls in whom airway hyperresponsiveness had been excluded by

methacholine challenge. Lung volumes were measured by body plethysmography. The authors framed the ratio explicitly as an index of dysanapsis, citing Mead (1980), and traced the practice of volume-adjusting the mid-expiratory flow to Cockcroft and Berscheid (1980), whose adjustment referred the flow to a fixed volume below total lung capacity rather than dividing it by FVC. Subsequent work has employed the ratio for the classification of spirometric lung disease more broadly.

They reported a mean ratio of 0.90 ± 0.24 in controls, 0.73 ± 0.19 in the at-risk group, and 0.31 ± 0.17 in the obstructive group, the three distributions being distinct from one another. The ratio correlated with GOLD stage (Spearman's ρ = 0.82; p = 0.0001). In a receiver operating characteristic analysis directed at the detection of COPD among individuals whose FEV1 and FEV1/FVC were normal, the area under the curve for the ratio was 0.849, marginally exceeding that for FEV1/FVC at 0.843; a cut-off of 0.8 was recommended, yielding a sensitivity of 86 per cent and a specificity of 68 per cent.

The present series affords an independent test of the two values that both studies report. For the control group, Mirsadraee et al. found 0.90 ± 0.24 and the present series 0.86 ± 0.27; for the group with established obstruction, 0.31 ± 0.17 and 0.35 ± 0.09 respectively. The agreement is close, and the residual discrepancy lies in the direction the sampling frames would predict: the controls of Mirsadraee et al. were never-smokers screened by methacholine challenge, whereas the present control group was drawn from consecutive clinic attenders, 47 per cent of whom were current smokers. Two populations, two countries, two instruments, and an interval of seven years thus yield concordant central values.

The cut-off values, by contrast, diverge substantially: 0.8 in the earlier report against 0.512 $s^{-1}$ here. This is not a contradiction but a direct consequence of case definition. The positive class of

Mirsadraee et al. included the at-risk group, whose mean ratio was 0.73; no threshold below that value could have detected them. The positive class of the present series comprised only individuals with established obstruction, whose mean ratio was 0.35, for which a considerably lower threshold suffices. A cut-off derived from a receiver operating characteristic analysis is a property of the case mix that generated it, and not of the parameter it purports to characterise.

A further comparison bears upon the interpretation of both studies. In the earlier report the ratio marginally outperformed FEV1/FVC (0.849 against 0.843), whereas in the present series FEV1/FVC was marginally superior. Neither result should be read as evidence about the parameters themselves, because in each study the definition of a case determined the outcome in advance. Mirsadraee et al. selected cases in whom FEV1/FVC was, by inclusion criterion, normal; the fixed ratio was thereby handicapped by construction. The present series selected cases in whom FEV1/FVC lay below 0.70; the fixed ratio was thereby favoured by construction. The two designs err in opposite directions, and the conclusion that follows from their conjunction is that neither has yet established the relative standing of the two indices.

Two observations follow. First, the FEF25-75/FVC ratio is not a novel parameter; it possesses a lineage extending from Green et al. (1974) through Mead (1980) and Litonjua et al. (1999) to Mirsadraee et al. (2013). Any contemporary contribution must therefore be framed not as the introduction of a new measure but as the independent evaluation of an existing one. Second, and more consequentially, the study designs differ in a manner that bears directly on what each can establish. Mirsadraee et al. included an at-risk group with normal spirometry, and were thereby positioned — at least in principle — to test the claim of earlier diagnosis. A design comparing established COPD patients with healthy volunteers, as in

the series presented below, cannot test that claim, for reasons developed in the section on methodological limitations. What such a design can establish is whether the ratio discriminates, whether normalisation succeeds in removing volume dependence, and whether the ratio outperforms the existing criterion within the range over which that criterion is applied. These are worthwhile questions, and they are the questions the present series addresses. The contribution of the present series is accordingly one of independent evaluation rather than introduction. Its case–control contrast rests upon 200 participants rather than 72, and it places the ratio in direct receiver operating characteristic comparison with the fixed criterion within a single cohort, while demonstrating empirically that normalisation to FVC abolishes the volume dependence of the raw parameter.

## An Independent Case-Control Evaluation

### Design

In order to evaluate the diagnostic performance of the ratio in an independent population, 100 patients with COPD aged between 30 and 80 years who presented to the pulmonary medicine outpatient clinics of a tertiary university hospital over a five-month period were compared with 100 volunteers who had not previously received a diagnosis of COPD and in whom the absence of chronic lung disease was demonstrated spirometrically. Individuals with contraindications to spirometry (haemoptysis of unknown origin, pneumothorax, recent thoracic, cerebral, or abdominal surgery, recent myocardial infarction, known aneurysm), those with a history of lung surgery, those who had undergone endobronchial volume reduction therapy, and those with a diagnosis of solid organ or haematological malignancy were excluded.

Measurements were performed with a spirometer conforming to ERS criteria, after participants had rested for a

minimum of thirty minutes. The study was conducted with the approval of the institutional clinical research ethics committee and with the written informed consent of all participants.

Continuous variables were compared between groups using the independent-samples t test and categorical variables using the chi-square test; with one hundred participants per group, reliance on the central limit theorem for the comparison of means is defensible. Associations between spirometric indices were quantified with the Pearson product-moment correlation coefficient. Diagnostic discrimination was assessed by receiver operating characteristic (ROC) analysis, in which the state variable was the presence of physical examination findings consistent with COPD rather than the case–control label itself; this choice is examined in the section on methodological limitations. The area under the curve (AUC), the optimal cut-off value, sensitivity, and specificity were computed. The threshold of significance was set at $p < 0.05$.

**Participants**

Cumulative tobacco consumption was markedly higher in the patient group (38.1 ± 29.1 versus 14.1 ± 21.5 pack-years; $p < 0.001$), and 89 per cent of the patient group were current smokers, compared with 47 per cent of the control group ($p < 0.001$). The majority of patients exhibited mild (52 per cent) or moderate (45 per cent) airflow limitation; only 3 per cent were in the severe category. This distribution indicates that the series is weighted towards earlier disease, since no parameter would be expected to encounter diagnostic difficulty in severe cases.

**Spirometric findings**

Comparison of the spirometric parameters revealed a notable pattern (Table 2). Whereas all parameters measuring flow were significantly reduced in the patient group, FVC — which measures volume alone — did not differ between the groups ($p = 0.083$). This

finding accords with the physiological expectation that the fundamental abnormality in COPD is flow limitation rather than volume loss. It supports the internal validity of the series and simultaneously strengthens the rationale for normalisation, since the FVC in the denominator functions as a relatively neutral scaling factor unaffected by the disease.

*Table 2. Spirometric parameters in patients with COPD and in the control group*

| Parameter | Control (n = 100) | COPD (n = 100) | p |
|---|---|---|---|
| FEV1 (L) | 2.68 ± 0.71<br>2.59 (1.22–4.91) | 1.86 ± 0.68<br>1.79 (0.69–3.84) | < 0.001 |
| FVC (L) | 3.30 ± 0.88<br>3.23 (1.53–5.61) | 3.08 ± 0.94<br>2.89 (1.39–5.56) | 0.083 |
| FEV1/FVC (%) | 81.43 ± 5.75<br>81.80 (70.1–93.4) | 59.42 ± 8.36<br>60.45 (28.8–69.9) | < 0.001 |
| FEF25-75 (L·s⁻¹) | 2.79 ± 0.95<br>2.67 (0.94–6.12) | 1.08 ± 0.48<br>1.05 (0.29–2.42) | < 0.001 |
| FEF25-75/FVC (s⁻¹) | 0.86 ± 0.27<br>0.82 (0.29–1.75) | 0.35 ± 0.09<br>0.36 (0.17–0.53) | < 0.001 |

*Values are presented as mean ± standard deviation, with the median and range beneath. The independent-samples t test was applied.*

## Testing the prediction

Correlation analysis tested directly the prediction formulated above (Table 3). Raw FEF25-75 was, as anticipated, moderately correlated with FVC ($r = 0.486$; $p < 0.001$), thereby confirming volume dependence empirically. No significant relationship, by contrast, was detected between the FEF25-75/FVC ratio and FVC ($r = 0.040$; $p = 0.576$). The operation of normalisation eliminated the dependence it was designed to remove. The same analysis established that the ratio was very strongly correlated with FEV1/FVC ($r = 0.896$; $p < 0.001$), a finding of decisive importance for the interpretation offered below.

*Table 3. Correlations among spirometric parameters across all participants*

| | FVC | FEV1/FVC | FEF25-75 | FEF25-75/FVC |
|---|---|---|---|---|
| FEV1 | 0.878*** | 0.561*** | 0.811*** | 0.458*** |
| FVC | — | 0.132 (p = 0.062) | 0.486*** | 0.040 (p = 0.576) |
| FEV1/FVC | — | — | 0.820*** | 0.896*** |
| FEF25-75 | — | — | — | 0.840*** |

*Values are Pearson correlation coefficients (r). *** p < 0.001.*

## Diagnostic performance

ROC analysis demonstrated that both parameters discriminated COPD with high accuracy and that the areas under the curve were identical (AUC = 0.998). For FEV1/FVC, sensitivity was 0.981 and specificity 0.979 at a cut-off of 71.65 per cent; for FEF25-75/FVC, sensitivity was 0.971 and specificity 0.968 at a cut-off of 0.512 $s^{-1}$ (Table 4).

*Table 4. Diagnostic performance of the FEV1/FVC and FEF25-75/FVC ratios*

| Parameter | AUC | Standard error | 95% CI | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| FEV1/FVC | 0.998 | 0.001 | 0.996–1.000 | 71.65% | 0.981 | 0.979 |
| FEF25-75/FVC | 0.998 | 0.002 | 0.994–1.000 | 0.512 $s^{-1}$ | 0.971 | 0.968 |

*AUC: area under the curve; CI: confidence interval. p < 0.001 for both parameters. The state variable was the presence of physical examination findings consistent with COPD. The FEF25-75/FVC cut-off is expressed in reciprocal seconds; multiplication by 100 yields the percentage convention used by some investigators.*

## Interpretation of the Findings

The inferences supported by the series must be distinguished from those it does not support.

The first inference is that the operation of normalisation achieved its purpose. The FEF25-75/FVC ratio has been divested of volume dependence; the near-zero correlation with FVC (r = 0.040; p = 0.576) constitutes direct evidence of this. The dependence

evident in the raw parameter (r = 0.486) was abolished by normalisation. The practical corollary is that in heterogeneous populations in which variability in lung volume predominates — screening settings in which individuals of differing height, sex, age, and ethnicity are assessed together — the ratio possesses a conceptual advantage over raw FEF25-75. In settings lacking reference equations, this property may translate into a practical advantage. The finding is consistent with the interpretation of the ratio as a surrogate for airway size relative to lung size (Litonjua et al., 1999; Mead, 1980).

The second inference is that the ratio discriminates individuals with COPD from healthy individuals. The value in the patient group is approximately 40 per cent of that in the control group (0.35 versus 0.86 $s^{-1}$), and the difference is marked both statistically and in magnitude. This corroborates, in an independent population and with a larger sample, the direction of the effect reported by Mirsadraee et al. (2013).

The series does not, however, support the inference that the ratio is superior to FEV1/FVC. The areas under the curve for the two parameters are identical (0.998); their sensitivities and specificities are almost the same, and FEV1/FVC is marginally superior on both. This result is unsurprising in light of the correlation of 0.896 between them. The two ratios share a common denominator and carry largely overlapping information; FEV1 and FEF25-75 are themselves strongly correlated (r = 0.811). It would not, mathematically, have been expected that two ratios derived from two different segments of the same curve, each divided by the same volume, should carry independent information. The objection raised by Quanjer et al. (2014) — that FEF25-75-derived measures add little once FEV1, FVC, and FEV1/FVC are known — is thus not refuted by the present data. The statement supported by the series is that the ratio functions,

but that within the range over which the existing criterion operates it does not function better.

A further observation concerns the boundary of the fixed threshold. Physical examination findings consistent with COPD were recorded in 52.5 per cent of participants — in every member of the patient group and in five members of the control group. The FEV1/FVC ratios of those five individuals lay between 70.3 and 73.9 per cent, that is, immediately above the diagnostic threshold, and each was therefore classified as free of obstruction. Their FEF25-75/FVC values were 0.294, 0.439, 0.470, 0.481, and 0.584 $s^{-1}$; four of the five fell below the cut-off of 0.512 $s^{-1}$ identified above. The number is far too small to support any inference, and the observation is offered as hypothesis-generating rather than as evidence. It nevertheless illustrates, within the present data, the configuration that the preceding sections have described in the abstract: in symptomatic individuals whose FEV1/FVC lies just above 0.70, the normalised mid-expiratory flow may already be abnormal. The fixed ratio, although a robust criterion, is on its own neither definitively diagnostic nor definitively exclusionary.

## Methodological Limitations

Four methodological limitations must be borne in mind in interpreting these findings. They pertain not only to the series presented but to a substantial portion of the diagnostic accuracy literature, including several of the studies reviewed above.

**Spectrum bias.** The series compared patients whose diagnosis had already been established with volunteers free of any respiratory pathology. The population encountered by the clinician in practice, by contrast, is concentrated in the zone of uncertainty between these two extremes: smokers who are asymptomatic, borderline spirometric values, elderly individuals with heart failure, cases of asthma-COPD overlap. An AUC of the order of 0.998

therefore reflects less the discriminative power of the test than the distance separating the two groups compared. In designs comparing extreme groups, almost any test performs highly; performance under real-world conditions may be expected to be substantially lower.

**Incorporation bias.** This is the more serious constraint, and it defines what the present design can and cannot establish. The ratio was tested in a patient group defined by the very criterion accepted as the gold standard — FEV1/FVC < 0.70. The condition of inclusion in the patient group is, in other words, the result of the test against which the comparison is made. The ROC analysis mitigated this only partially: its state variable was the presence of physical examination findings, which is formally independent of spirometry but which coincided with case status in 195 of the 200 participants. Under such circumstances, the performance of the new test is inevitably constrained to converge upon that of the old, and the high correlation observed between the two ratios is in part an artefact of that constraint. The only means of demonstrating whether the new parameter identifies cases missed by the established criterion is either to include a group in whom the established criterion is negative but disease is clinically suspected — the design adopted by Mirsadraee et al. (2013) — or to employ a reference standard external to spirometry altogether: quantification of air trapping and emphysema on thoracic computed tomography, long-term clinical course (rate of FEV1 decline, exacerbation frequency, mortality), or histopathological confirmation. The strongest statement that may be extracted from the present data is that the ratio is concordant with the existing criterion, not that it precedes it.

**Single-centre design and threshold transferability.** The participants reside in the same geographical region and carry comparable comorbidities. Given that the prevalence of COPD varies markedly across countries, regions, genetic constitution, sociocultural structure, age, and sex (Abul & Özlü, 2013), it is

evident that the cut-off value of 0.512 $s^{-1}$ identified here cannot be transferred directly to other populations. Cut-off values derived from ROC analysis belong to the sample from which they are derived and cannot be generalised until tested in an independent validation cohort. The divergence between the threshold obtained here and the value of 0.8 reported by Mirsadraee et al. (2013) illustrates the point: the two figures reflect two different case mixes rather than two measurements of the same quantity. The discrepancy between thresholds reported across the literature is compounded by inconsistent scaling conventions, as noted above.

**Unadjusted confounding.** The two groups were neither matched nor statistically adjusted for the principal determinants of the FEV1/FVC ratio. Age, sex, height, and cumulative tobacco exposure all influence forced expiratory indices, and the last of these differed markedly between the groups. Since the ratio declines physiologically with age, any imbalance in that variable acts in the same direction as disease and cannot be separated from it in an unadjusted comparison. The estimates reported here should accordingly be read as crude rather than adjusted.

**Scope.** The failure to examine chronic bronchitis, one of the principal components of COPD, and the spirometric changes that accompany it constitutes a shortcoming; in Türkiye, and defined by symptoms rather than by spirometry, the prevalence of chronic bronchitis has been reported as 13.5 per cent in a rural district of Kayseri (Cetinkaya et al., 2000) and 14.1 per cent in the city centre of Gümüşhane (Tutar et al., 2013). Furthermore, the failure to analyse emphysema-predominant and airway-predominant phenotypes separately precluded any determination of the phenotype in which the ratio is more informative. Since diffusing capacity and lung volumes were not measured, this distinction cannot be made retrospectively either.

## Interpretation in the Context of Differential Diagnosis

Where the FEF25-75/FVC ratio is found to be reduced, it must be borne in mind that the ratio is not specific to COPD. Small airway involvement is prominent in uncontrolled asthma, and the ratio falls; indeed, its established association is with airway responsiveness rather than with any single diagnosis (Litonjua et al., 1999; Parker et al., 2003). The distinction rests upon bronchodilator reversibility testing (an increase in FEV1 of 12 per cent and 200 mL), symptom variability, and age at onset. Bronchiolitis obliterans is a primary disease of the small airways and reduces the ratio markedly and early. In bronchiectasis, airway deformation and mucus accumulation diminish late-segment flow. Congestive heart failure may also reduce the ratio, a possibility clinicians are advised to keep in view (Gentry & Gentry, 2017). Technical artefacts — a prematurely terminated manoeuvre, cough, leakage at the mouthpiece — may likewise produce spurious reduction.

Conversely, a normal ratio does not exclude COPD. The ratio may be preserved, particularly in the emphysema-predominant phenotype and in the PRISm group. In restrictive disease the ratio tends to be elevated rather than reduced, since the accompanying increase in elastic recoil opposes airway collapse during the latter portion of expiration.

The FEF25-75/FVC ratio is accordingly not a disease-specific marker but an indicator of the geometric and mechanical relationship between airway calibre and lung volume. An abnormal value conveys no information as to the disease from which the abnormality arises.

## Clinical Positioning and Research Priorities

The present level of evidence does not support the replacement of FEV1/FVC by the FEF25-75/FVC ratio. The defensible domain of application of the ratio is complementarity

rather than substitution. In a symptomatic case with a borderline FEV1/FVC value (0.65 to 0.75) and a significant history of exposure, a markedly reduced FEF25-75/FVC value may strengthen diagnostic suspicion and justify further evaluation: calculation of the LLN, lung volumes, diffusing capacity, and thoracic computed tomography. Conversely, a normal ratio in a borderline case may deter the initiation of unnecessary treatment. Such use constitutes a decision-supporting signal rather than a diagnostic criterion, and it must be presented to the clinician as such. To present a parameter as stronger than it is may prove more harmful than disregarding it altogether, since it engenders unnecessary diagnosis and unnecessary treatment.

Studies capable of advancing the parameter beyond this position must possess the following characteristics.

The reference standard must be changed. Rather than spirometry, either imaging (quantitative air trapping and percentage of low-attenuation area on computed tomography) or long-term clinical outcome (rate of FEV1 decline, exacerbation frequency, mortality) must serve as the diagnostic criterion, since only such a design can eliminate incorporation bias.

A design incorporating all consecutive attenders at a pulmonary medicine clinic, rather than established patients and healthy volunteers, is the sole means of removing spectrum bias. Where this is not feasible, the inclusion of a symptomatic at-risk group with spirometry within the normal range, as in Mirsadraee et al. (2013), represents a partial remedy.

A multicentre and ethnically diverse sample would render possible the derivation of population-specific reference values and of a lower limit of normal for the ratio, together with the standardisation of its scaling convention.

The incremental contribution of the ratio when added to FEV1/FVC must be tested by measures such as the net reclassification improvement and the integrated discrimination improvement, beyond the comparison of areas under the curve. Comparing the AUC of two tests does not demonstrate what one adds when appended to the other, and it is precisely the question of incremental value that Quanjer et al. (2014) answered in the negative for the raw parameter and that remains unanswered for the ratio.

Performance must be evaluated separately in emphysema-predominant and airway-predominant phenotypes, with concurrent measurement of diffusing capacity and lung volumes.

Finally, a longitudinal design testing whether individuals with a normal baseline FEV1/FVC but a reduced FEF25-75/FVC subsequently develop COPD constitutes the only genuine test of the claim that the ratio becomes abnormal at an earlier stage. Given the familial aggregation of the ratio reported in kindreds with severe, early-onset COPD (DeMeo et al., 2004), the relatives of such probands would represent a particularly informative population in which to conduct that test.

**Conclusion**

The definition of COPD rests upon a heterogeneous pathology, whereas its diagnostic criterion rests upon a single spirometric threshold; the distance between these two levels constitutes the source of misclassification. Although the fixed threshold of FEV1/FVC < 0.70 affords ease of application, it leads to over-diagnosis in advanced age and to under-diagnosis in the young. Because the small airways contribute only marginally to total airway resistance, they constitute a diagnostically silent zone, and early disease within this zone is not reflected in FEV1 for a considerable period.

The segment of forced expiration following peak flow is relatively effort-independent, and the variables that determine flow within it — elastic recoil pressure and the resistance upstream of the equal pressure point — coincide with the two variables impaired in COPD. The parameter that measures this segment, FEF25-75, is nevertheless volume-dependent, possesses a wide normal range, and was shown by Quanjer et al. (2014) to be abnormal in isolation in only 2.75 per cent of routine spirometric records.

Normalising FEF25-75 to FVC yields a quantity, expressed in reciprocal seconds, that has been used since the work of Mead (1980) and Litonjua et al. (1999) as a surrogate for airway size relative to lung size, and that Mirsadraee et al. (2013) proposed as a means of diagnosing COPD earlier than current guidelines permit. The independent series presented here confirms that normalisation removes volume dependence — the ratio was uncorrelated with FVC ($r = 0.040$; $p = 0.576$) — and that the ratio is substantially reduced in COPD. It nevertheless exhibited diagnostic performance equivalent to that of FEV1/FVC and demonstrated no superiority (AUC = 0.998 for both); the correlation of $r = 0.896$ between the two ratios accounts for this result. The high AUC observed in both parameters is in large measure a product of spectrum bias.

So long as the FEV1/FVC ratio is employed as the reference standard and established patients are compared with healthy volunteers, the claim that the FEF25-75/FVC ratio permits earlier diagnosis cannot be tested. At the present level of evidence, the place of the ratio should be established not as a diagnostic criterion but as a decision-supporting indicator that justifies further evaluation in borderline cases. Clarification of its clinical value depends upon multicentre, longitudinal studies of consecutive attenders employing a reference standard external to spirometry.

## Declaration

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