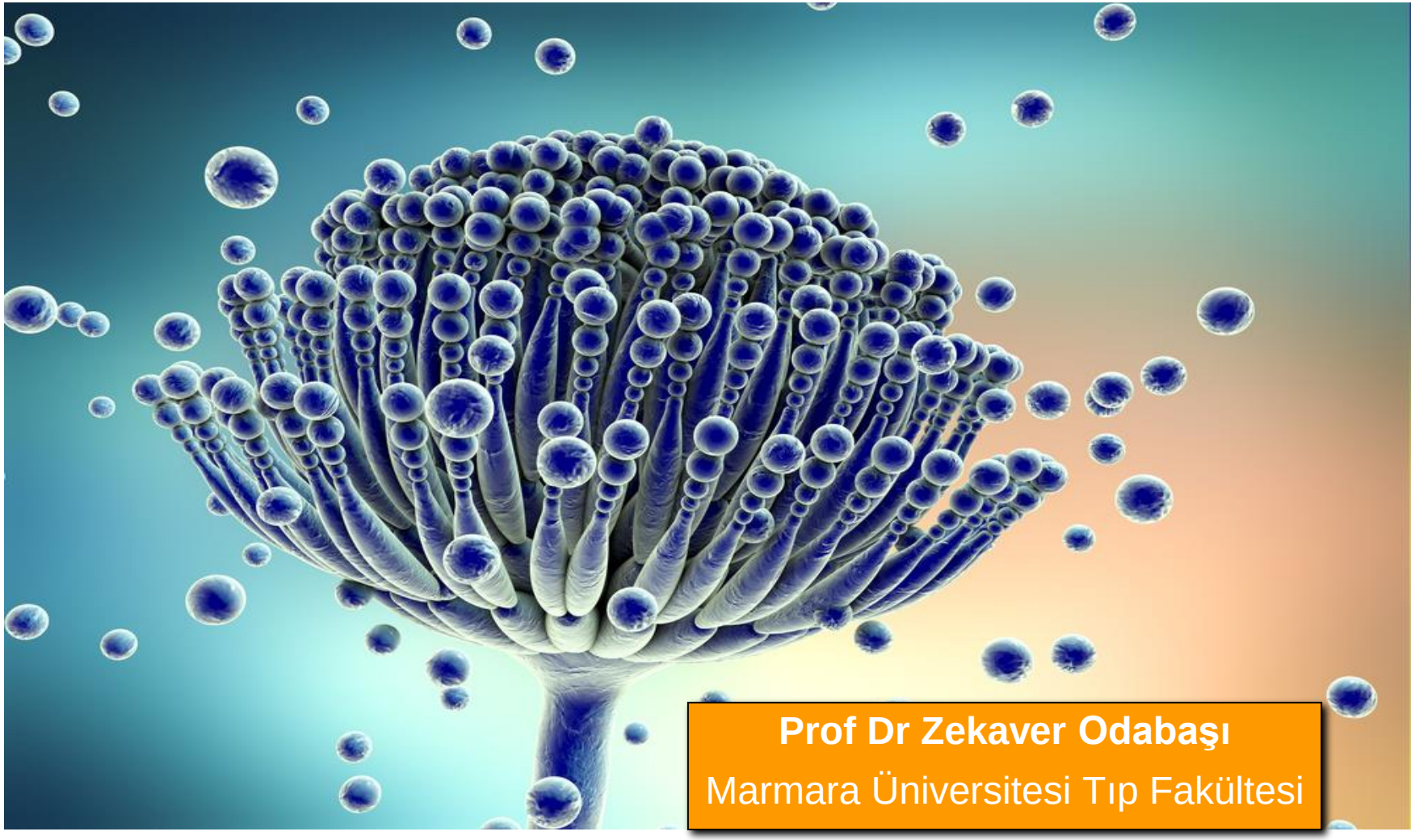
İnvaziv Aspergilloz
Erken Tanı - Doğru Tedavi



Prof Dr Zekaver Odabaşı
Marmara Üniversitesi Tıp Fakültesi

Treatment of Invasive Aspergillosis: Relation of Early Diagnosis and Treatment to Response

JOSEPH AISNER, M.D.; STEPHEN C. SCHIMPFF, M.D., F.A.C.P.; and
PETER H. WIERNIK, M.D., F.A.C.P.; Baltimore, Maryland

Aspergillus infections in patients with cancer are difficult to diagnose, and such diagnoses are frequently made at necropsy. Earlier therapy has been proposed to provide better response. We reviewed 17 consecutive patients with documented aspergillosis to determine the impact of earlier diagnosis and prompt treatment with amphotericin B. Sixteen had hematologic malignancies, and all had marked granulocytopenia. Six were diagnosed and treated within 96 h of the appearance of infiltrates. Three of these six had complete resolution of all signs and symptoms of aspergillus infection. The other three had a partial response to therapy despite continued granulocytopenia. All 11 patients in whom antifungal therapy was either delayed (six) or not given (five) for at least 2 weeks after the infiltrate was present died with progressive aspergillosis. Aggressive diagnostic methods to establish the diagnosis of aspergillosis are warranted so that antifungal therapy can be started early, which may then be successful in resolving these potentially fatal infections.

- 17 aspergilloz vakası
- 6 'sı ilk 96s içinde tanı ve tedavi almış: hepsi hayatta
- 11 vakada tedavi 2 hafta sonrasında başlanmış ve progressif aspergilloz nedeni ile kaybedilmişler.

diagnostic, transtracheal bronchial brush biopsy was done unless these methods were contraindicated by uncorrectable thrompocytopenia or coagulation defects (12). Our report on the results of bronchial brushing included four patients discussed in this study (12). None of the patients in this study underwent percutaneous or open lung biopsy.

Our definitions of documented severe infections have been previously published and include unequivocal clinical evidence of infection at the suspected site in association with appropriate systemic signs and symptoms (3, 13). The diagnosis of invasive

Aisner J, Annals of Internal Medicine, 1977

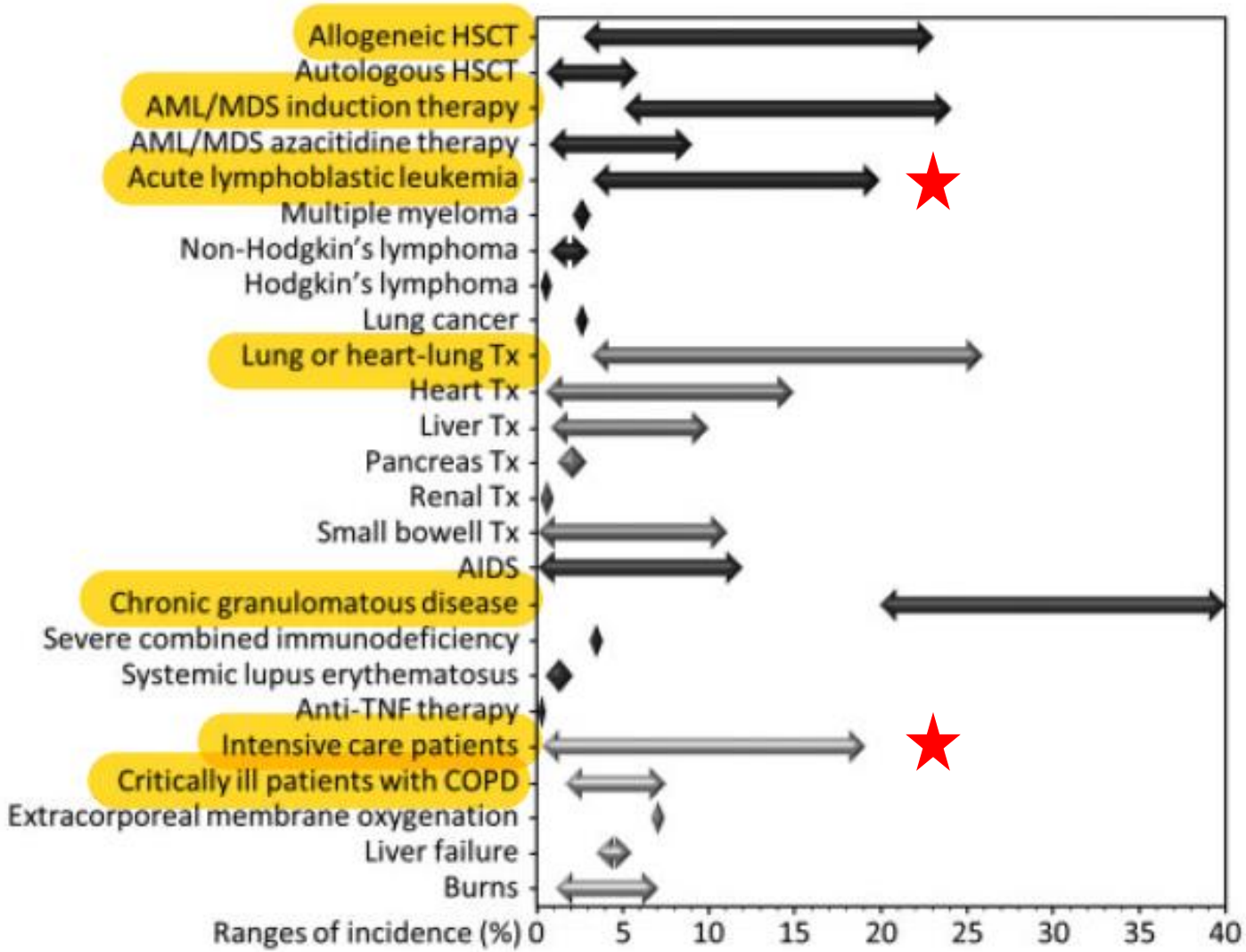
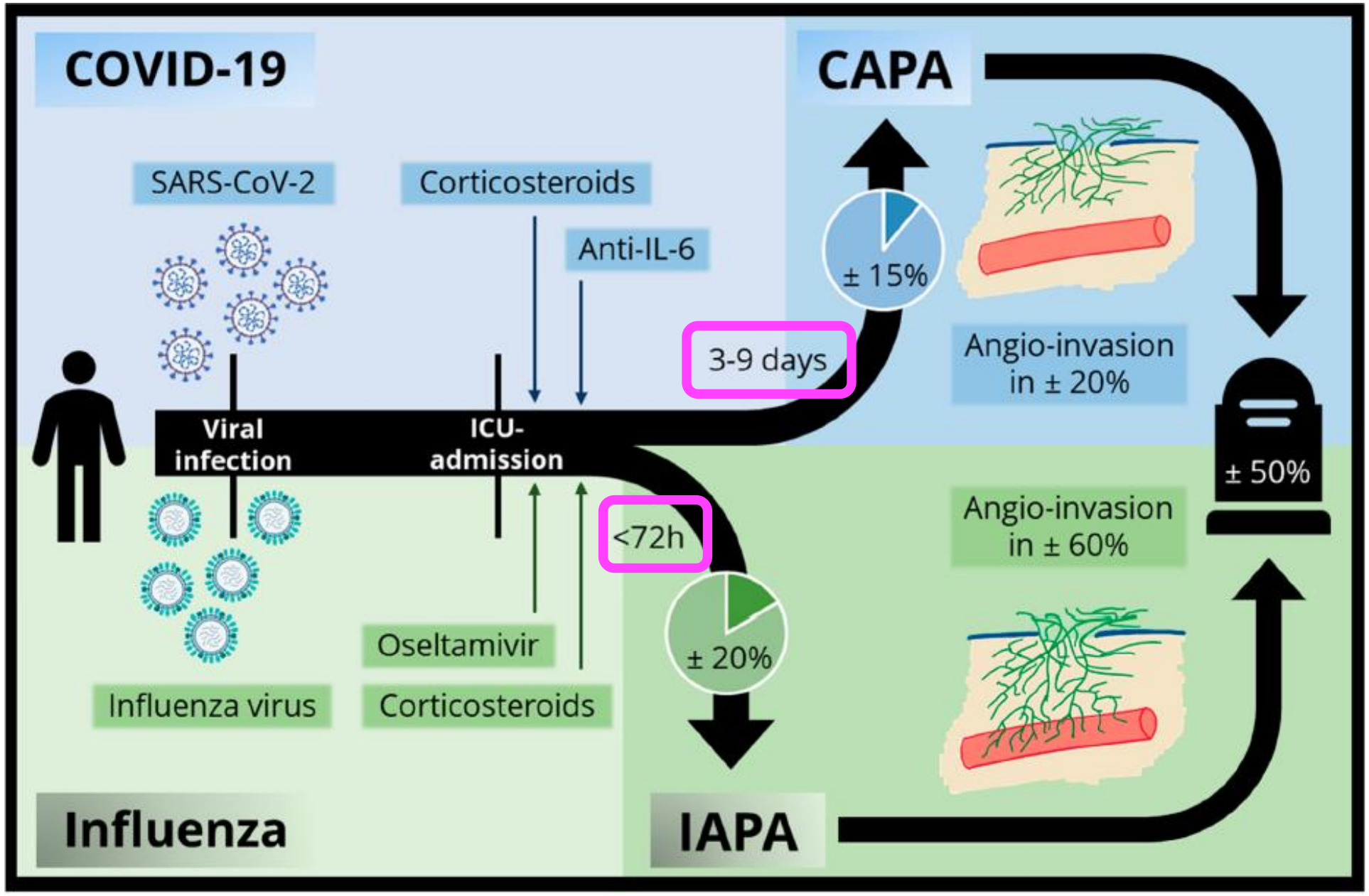


Fig. 2 Range of incidences reported in literature according to the risk group. The large variations reflect the differ conditions, inclusion of possible invasive aspergillosis in some series, evolution over time, and effect of prophylactic AML, acute myeloblastic leukemia; COPD, chronic obstructive pulmonary disease; HSCT, hematopoietic stem cell tr myelodysplastic syndrome; TNF, tumor necrosis factor; Tx, transplantation.

Marie-Pierre Ledoux, Semin Respir Crit Care Med 2020


COVID-19
CAPA
SARS-CoV-2
Corticosteroids
Anti-IL-6
± 15%
3-9 days
Angio-invasion
in ± 20%
Viral
infection
ICU-
admission
± 50%
<72h
Angio-invasion
in ± 60%
Oseltamivir
± 20%
Influenza virus
Corticosteroids
Influenza
IAPA

İnvaziv Fungal Enfeksiyonların Tanısı

	Candida	*Aspergillus*	Mucorales	*Fusarium*	*Cryptococc*
Kültür	✓	✓	✓	✓	✓
Histopatoloji	✓	✓	✓	✓	✓
Galaktomannan		✓		✓	
Beta glukan	✓	✓		✓	
Lateral Flow test	✓	✓			✓
T2 Manyetik Rezonans	✓				
PCR	✓	✓	✓	✓	✓
Mannan Anti-Mannan	✓				

Odabaşı Z, Türkiye Klin 2020

ECIL 3

	GM	Beta Glukan	Mannan - antimannan	Kriptokok antijeni	PCR
İnvazif Aspergilloz	✓	✓			✓
İnvazif Kandidiyaz		✓	✓		
Kriptokokkoz				✓	
EORTC/MSG İFİ Tanısında	**A II**	**B II**	**C II**	**A II**	**----**

Marchetti O, BMT, 2012

Test sonuçlarının klinisyene ulaşma süresi

Table 2. Commercially available non-culture-based testing for *Aspergillosis* and Mucorales.

Test Name	Example Commercial Product	Sample Source	TAT	Disadvantages	Sensitivity	Specificity	Notes
1,3-β-D-glucan (BDG)	Fungitell (Associates of Cape Cod, Inc.) and Fungitec G-MK. (Seikagaku).	Serum	Fungitell STAT (qualitative): 40–60 min Regular Fungitell: 24–72 h (d)	Cross-reactive with other fungi, False positives frequent. Often run in reference labs.	Fungitell: 33–100% Fungitec: 67–88%	Fungitell: 36–94% Fungitec: 84–85%	FDA approved.
Galactomannan	Platelia *Aspergillus* EIA /Ag (Bio-Rad)	Serum, BAL (also CSF, pleural fluid)	1–7 days	Cross-reactive with other fungi. False positives frequent.	**Neutropenic/heme malignancy** Serum: 61–79% BALF: 58–90% **Non-neutropenic:** Serum: 38–41% BALF: 65–76%	**Neutropenic/heme malignancy** Serum: 81–95% BALF: 84–96% **Non-neutropenic:** Serum: 87–89% BALF: 81–90%	FDA approved. Serially monitoring can assess treatment response.
Lateral flow devices	AspLFD (OLM Diagnostics) and the Aspergillus galactomannan LFA (IMMY)	Serum, BAL, urine	15–30 min	Serum LFD requires additional preparation steps/ pre-treatment. Sensitivity decreased with antifungals.	**AspLFD: Neutropenic/heme malignancy:** Serum: 56–68% BAL: 71–89% **Non-neutropenic:** BAL: 46–69% **LFA: Neutropenic/heme malignancy:** 89–97% **Non-neutropenic:** BALF: 65–69%	**AspLFD: Neutropenic/heme malignancy:** Serum: 87–90% BAL: 88–100% **Non-neutropenic:** BAL: 46–58% **LFA: Neutropenic/heme malignancy:** 88–98% **Non-neutropenic:** BALF: 62–68%	Available in Europe. Urinary GM-like antigen-based test also exists but needs further validation.
Aspergillus PCR	MycAssay Aspergillus (real-time PCR) AsperGenius assay (multiplex real-time PCR)	Serum, BAL	12–24 h	Sensitivity decreased by antifungal treatment. Many commercially available assays. Standardization efforts ongoing. Small clinical studies.	**Serum:** 60–79% **BALF:** 77%	**Serum:** 80–95% **BALF:** 94%	Some detect azole-resistant mutations. Independent validation still needed for most.
Mucorales PCR	MucorGenius (Pathonostics)	BAL, biopsy fluid	3 h		**90–100%**	**90–99%**	

GM ELISA testi

- Seru[illegible]0.5 ve üzerinde iki pozitiflik
- ≥ 0.7 [illegible]ger

Cut-off	studies	N	sensitivity	95%CI	specificity	95%CI
0.5	7	901	0.78	0.61-0.89	0.81	0.72-0.88
1	12	1744	0.75	0.59-0.86	0.91	0.84-0.95
1.5	17	2600	0.64	0.5-0.77	0.95	0.91-0.97

Leeflang et al The Cochrane library Issue 4 2008

EORTC – MSG İnvaziv fungal enfeksiyon tanı kriterleri revizyonu

Clinical Infectious Diseases

MAJOR ARTICLE

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

J. Peter Donnelly,[1] Sharon C. Chen,[2] Carol A. Kauffman,[3] William J. Steinbach,[4] John W. Baddley,[5] Paul E. Verweij,[6] Cornelius J. Clancy,[7] John R. Wingard,[8] Shawn R. Lockhart,[9] Andreas H. Groll,[10] Tania C. Sorrell,[11] Matteo Bassetti,[12] Hamdi Akan,[13] Barbara D. Alexander,[14] David Andes,[15] Elie Azoulay,[16] Ralf Bialek,[17] Robert W. Bradsher Jr,[18] Stephane Bretagne,[19] Thierry Calandra,[20] Angela M. Caliendo,[21] Elio Castagnola,[22] Mario Cruciani,[23] Manuel Cuenca-Estrella,[24] Catherine F. Decker,[25] Sujal R. Desai,[26] Brian Fisher,[27] Thomas Harrison,[28] Claus Peter Heussel,[29] Henrik E. Jensen,[30] Christopher C. Kibbler,[31] Dimitrios P. Kontoyiannis,[32] Bart-Jan Kullberg,[33] Katrien Lagrou,[34] Frédéric Lamoth,[35] Thomas Lehrnbecher,[36] Jurgen Loeffler,[37] Olivier Lortholary,[38] Johan Maertens,[39] Oscar Marchetti,[20] Kieren A. Marr,[40] Henry Masur,[41] Jacques F. Meis,[42] C. Orla Morrisey,[43] Marcio Nucci,[44] Luis Ostrosky-Zeichner,[45] Livio Pagano,[46] Thomas F. Patterson,[47] John R. Perfect,[14] Zdenek Racil,[48] Emmanuel Roilides,[49] Marcus Ruhnke,[50] Cornelia Schaefer Prokop,[51] Shmuel Shoham,[40] Monica A. Slavin,[52] David A. Stevens,[53] George R. Thompson III,[54] Jose A. Vazquez,[55] Claudio Viscoli,[56] Thomas J. Walsh,[57] Adilia Warris,[58] L. Joseph Wheat,[59] P. Lewis White,[60] Theoklis E. Zaoutis,[61] and Peter G. Pappas[5]

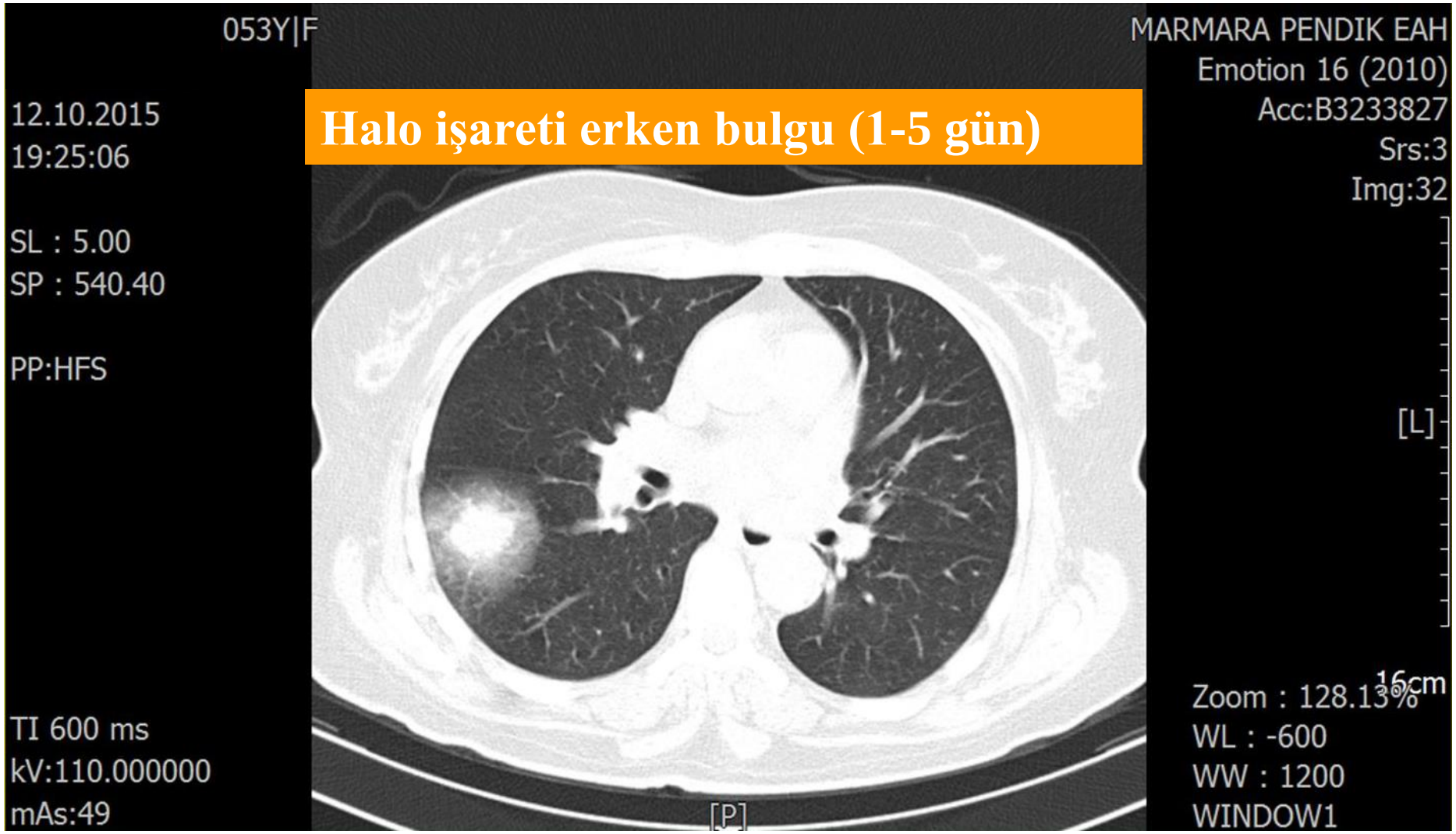
Clin Infect Dis 2019

Mycological evidence
Any mold, for example, *Aspergillus*, *Fusarium*, *Scedosporium* species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate
Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold
Tracheobronchitis
Aspergillus recovered by culture of BAL or bronchial brush
Microscopic detection of fungal elements in BAL or bronchial brush indicating a mold
Sino-nasal diseases
Mold recovered by culture of sinus aspirate samples
Microscopic detection of fungal elements in sinus aspirate samples indicating a mold
Aspergillosis only
Galactomannan antigen
Antigen detected in plasma, serum, BAL, or CSF
Any 1 of the following:
Single serum or plasma: ≥1.0
BAL fluid: ≥1.0
Single serum or plasma: ≥0.7 and BAL fluid ≥0.8

Clin Infect Dis 2019

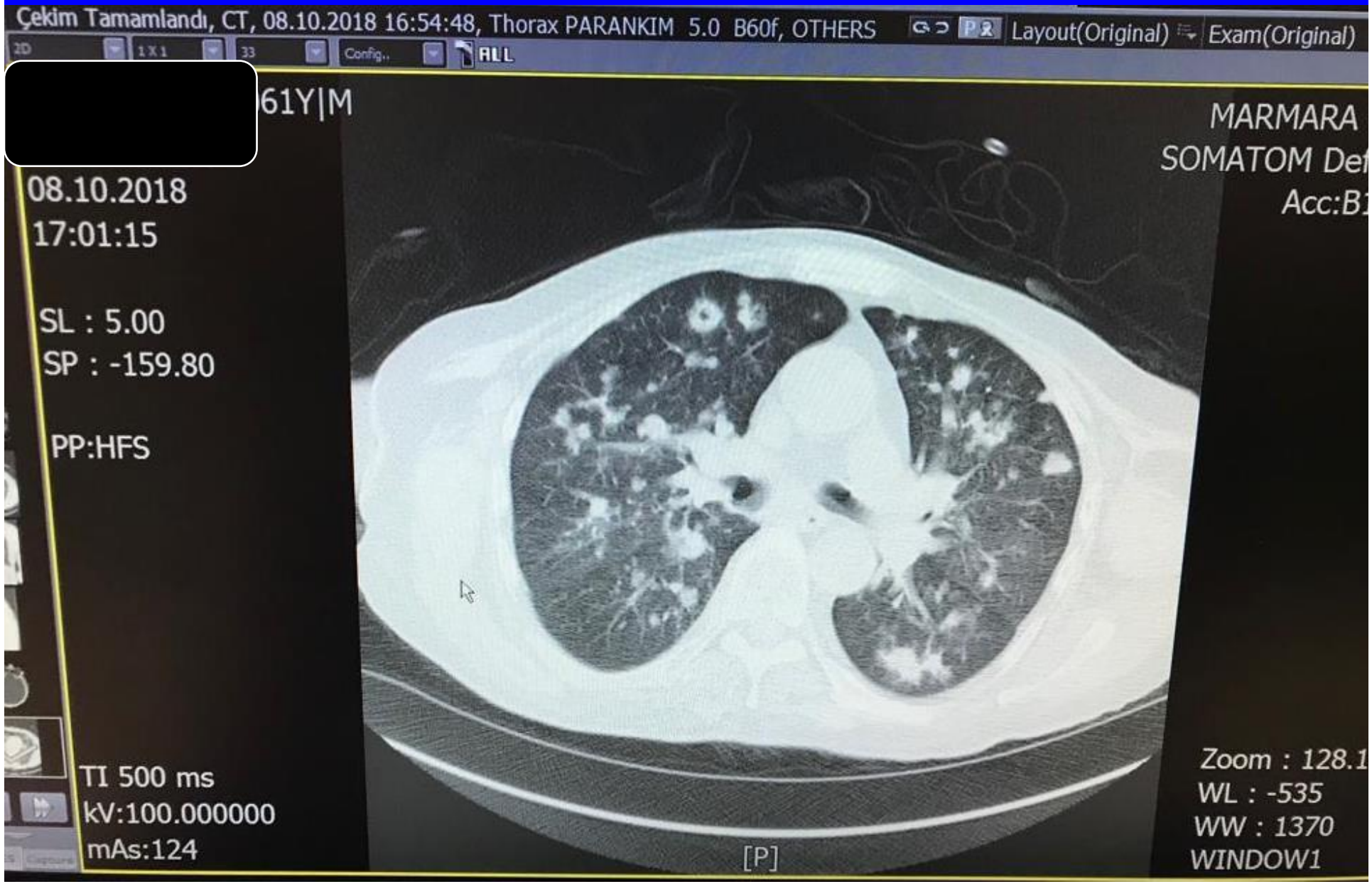
- **GM – ELISA**, önemli **dezavantajları**
- 96 kuyucuklu plate ile çalışılır, yeterli vaka sayısına ulaşılamadan çalışılmıyor
- Özel ekipmanlar gerekir (her merkezde olmayabilir) ve tecrübeli personel tarafından çalışılmalıdır

Tomografik Görüntüleme



Halo işareti erken bulgu (1-5 gün)

61 yaş, erkek, küçük lenfositik lenfoma, **ibrutinib** sonrası CT, **BAL GM** > 6, **serum GM** 5.06



Jin *et al. BMC Infectious Diseases* (2019) 19:471
https://doi.org/10.1186/s12879-019-4039-7

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Utility of CT assessment in hematology patients with invasive aspergillosis: a post-hoc analysis of phase 3 data

Jie Jin[1], Depei Wu[2*], Yang Liu[3], Sisi Pan[3], Jean Li Yan[4], Jalal A. Aram[4], Yin-jun Lou[1], Haitao Meng[1], Xiaochen Chen[1], Xian'an Zhang[3], Ilan S. Schwartz[5,6] and Thomas F. Patterson[6,7]

Jie Jin et al, BMC Infect Dis 2019

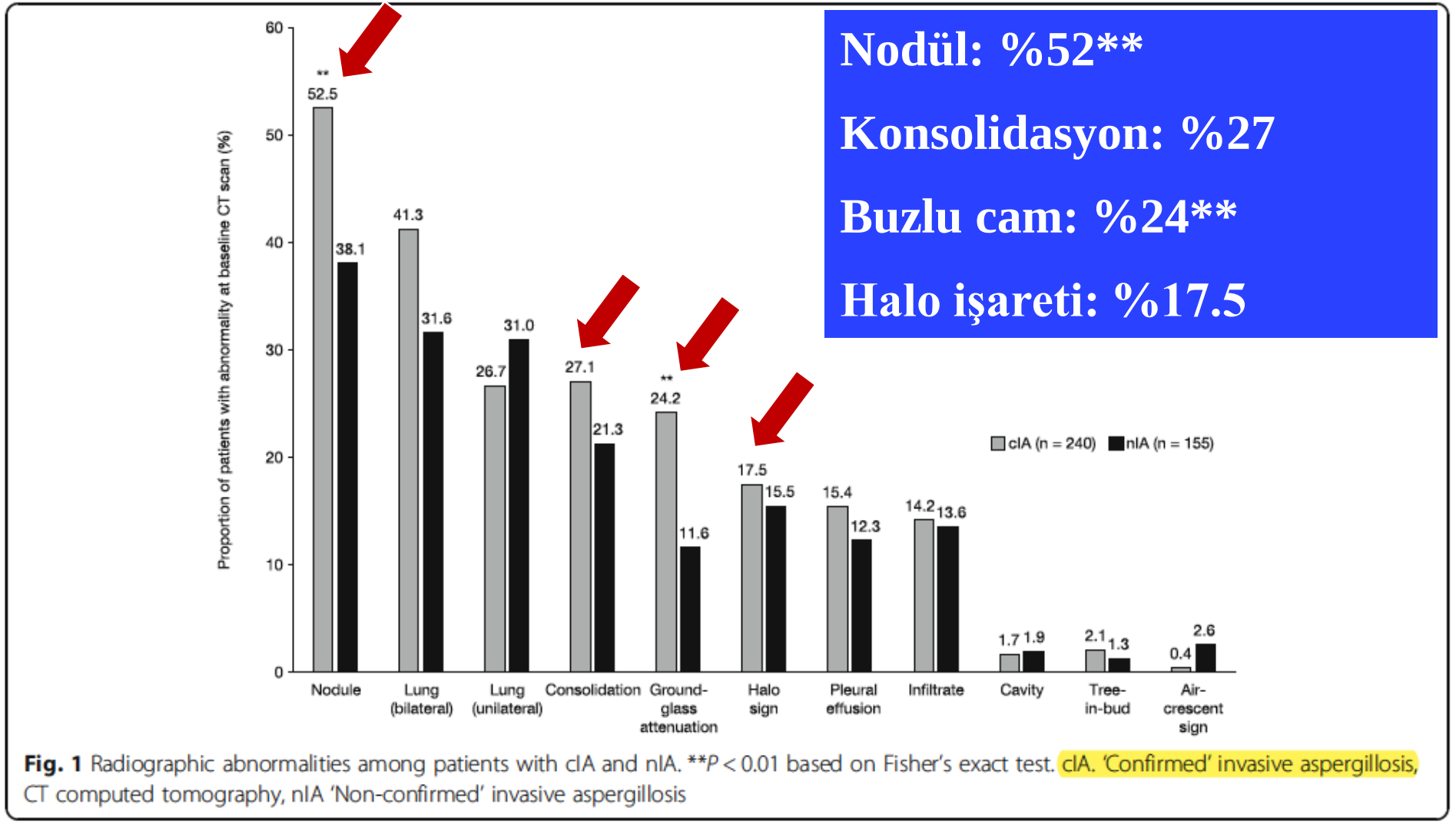


Fig. 1 Radiographic abnormalities among patients with cIA and nIA. $^{**}P < 0.01$ based on Fisher's exact test. cIA. 'Confirmed' invasive aspergillosis, CT computed tomography, nIA 'Non-confirmed' invasive aspergillosis

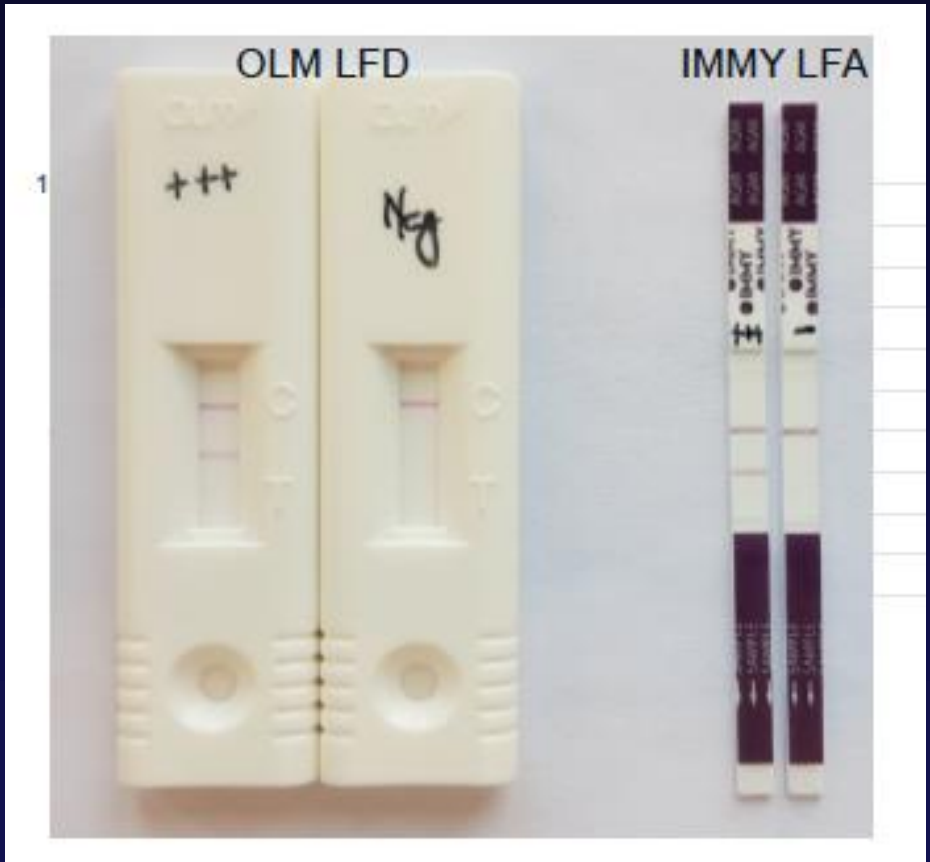
Jie Jin et al, BMC Infect Dis 2019

EORTC - MSG 2019 revize kriterler – **CT bulguları**

Clinical features
Pulmonary aspergillosis
The presence of 1 of the following 4 patterns on CT:
Dense, well-circumscribed lesions(s) with or without a halo sign
Air crescent sign
Cavity
Wedge-shaped and segmental or lobar consolidation

Clin Infect Dis 2019

Aspergillus Lateral Flow: immünokromatografi



Hızlı tanı testi:

- Serum ve BAL
- 15 – 30 dakikada sonuç

- OLM (LFD device)
  - JF5 monoklonal antikor ile **mannoprotein** tespiti

- IMMY (LFA aspergillus)
  - **Galaktomannan** tespiti

GM-ELISA: kullanılan galaktomannan özgün monoklonal antikor (EB-A2)
LFA IMMY: iki farklı monoklonal antikor

Dijital okuyucu

Numune: Serum veya BAL

Çalışma Süresi: 15 dk. manuel işlemler + 30dk. inkübasyon

300 mikrolitre serum veya BAL örneği

Sonuç şekli: Kantitatif ve semi kantitatif

Procedure:

SPECIMEN PREPARATION

Obtain 2 test tubes for each specimen: *1 screw cap, heat reistant centrifuge tube for the dilution*
1 flat-bottom tube for running the test

1

Transfer 300 µl specimen in the screw cap, heat resistant centrifuge tube 1

2

Add 100 µl Sample Pretreatment Buffer to tube 1 *(vortex as needed)*

3

Place tube 1 on heat block for 6-8 minutes at 120° C

4

Centrifuge tube 1 at 10,000 - 14,000 x g for 5 minutes

RUN TEST

5

Transfer 80 µL from tube 1 to tube 2

6

Add 40 µL of Aspergillus GM LFA Running Buffer to tube 2

7

Insert strip (↓↓ down)
Wait for **30 min.**

8

Read Test
1 line = negative
2 lines = positive

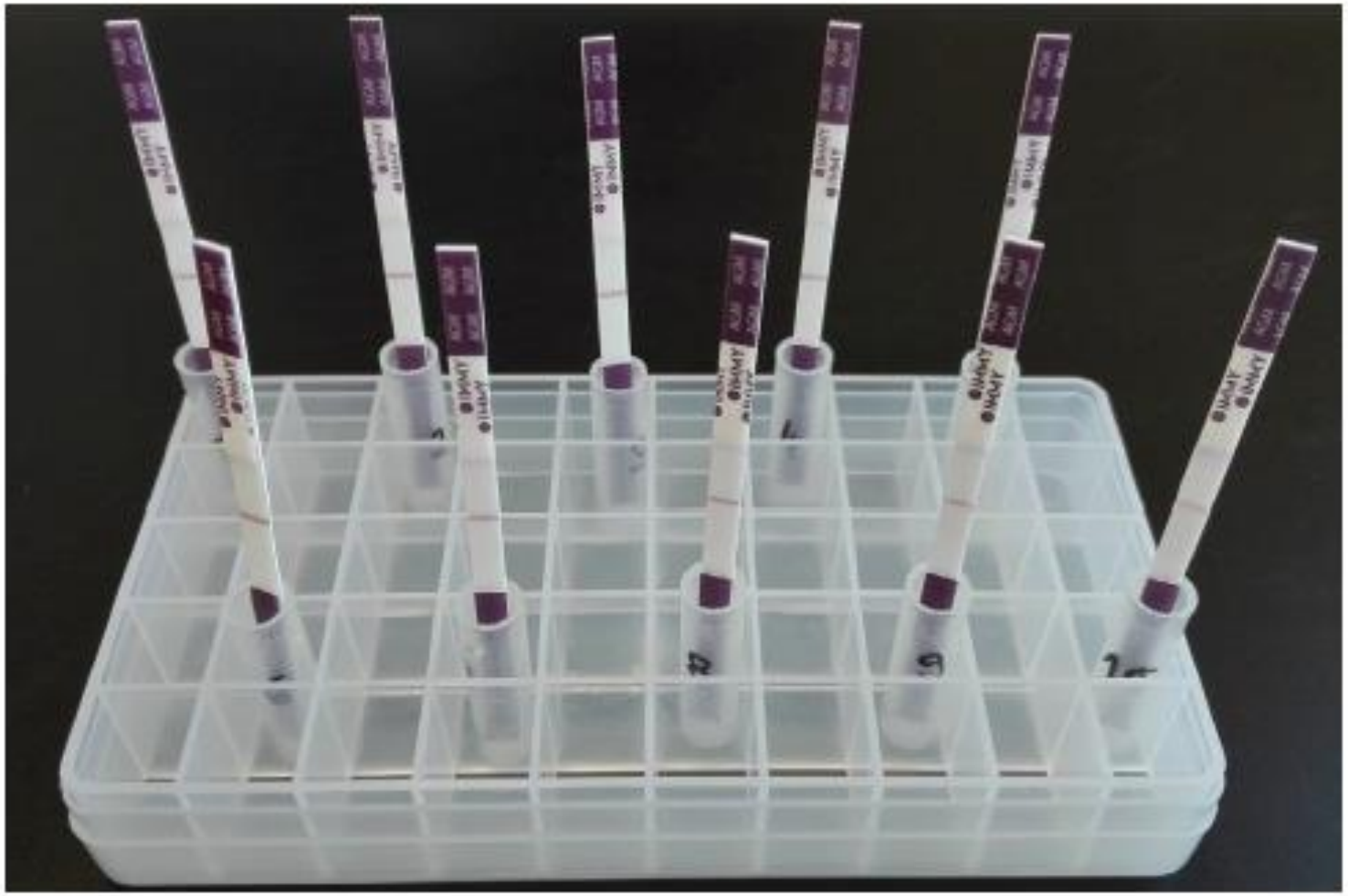


FIGURE 2 *Aspergillus*-specific lateral flow assay (LFA, IMMY) after test execution

Galaktomannan **ELISA vs Lateral flow** uyumu

Percent Agreement to Commercially Available Antigen EIA:

Serum	Asp Ag EIA	
Asp GM LFA Assay	Pos	Neg
Pos	26	1
Neg	6	116

Serum	Calculated	95% CI
% Agreement Pos	81%	64% - 93%
% Agreement Neg	99%	95% - 99.9%

BAL	Asp Ag EIA	
Asp GM LFA Assay	Pos	Neg
Pos	25	3
Neg	3	48

BAL	Calculated	95% CI
% Agreement Pos	89%	72% - 98%
% Agreement Neg	94%	84% - 99%

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INTERNATIONAL SOCIETY FOR
HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2019, 0, 1–9
doi: 10.1093/mmy/myz079
Advance Access Publication Date: 0 2019
Original Article

Original Article

Lateral flow assays for diagnosing invasive pulmonary aspergillosis in adult hematology patients: A comparative multicenter study

Toine Mercier[1,2,*], Albert Dunbar[3], Elizabeth de Kort[4], Alexander Schauwvlieghe[3], Marijke Reynders[5], Ellen Guldentops[2], Nicole M. A. Blijlevens[4], Alieke G. Vonk[3], Bart Rijnders[3], Paul E. Verweij[6,7], Katrien Lagrou[1,8] and Johan Maertens[1,2], on behalf of the Dutch-Belgian Mycosis Study Group (DB-MSG)

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LFA ve LFD 'nin **BAL örneklerinde** tanısal performansları

		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Proven IPA versus control ($n = 128$)	LFA	0.91 (0.59–1.00)	0.87 (0.80–0.93)	0.40 (0.21–0.61)	0.99 (0.95–1.00)
	LFD	0.82 (0.48–0.98)	0.87 (0.80–0.93)	0.38 (0.19–0.59)	0.98 (0.93–1.00)
Proven and probable IPA versus control ($n = 192$)	LFA	0.83 (0.72–0.90)	0.87 (0.80–0.93)	0.81 (0.70–0.89)	0.89 (0.81–0.94)
	LFD	0.69 (0.58–0.79)	0.87 (0.80–0.93)	0.78 (0.66–0.87)	0.82 (0.74–0.88)
Proven and probable IPA (GM excluded) versus control ($n = 147$)	LFA	0.87 (0.69–0.96)	0.87 (0.80–0.93)	0.63 (0.47–0.78)	0.96 (0.91–0.99)
	LFD	0.73 (0.54–0.88)	0.87 (0.80–0.93)	0.59 (0.42–0.75)	0.93 (0.86–0.97)
Probable IPA vs controls ($n = 181$)	LFA	0.81 (0.70–0.90)	0.87 (0.80–0.93)	0.78 (0.66–0.87)	0.89 (0.82–0.94)
	LFD	0.67 (0.54–0.78)	0.87 (0.80–0.93)	0.74 (0.61–0.85)	0.83 (0.75–0.89)

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DOI: 10.1111/myc.13352

ORIGINAL ARTICLE

mycoses WILEY

Serum Lateral Flow assay with digital reader for the diagnosis of invasive pulmonary aspergillosis: A two-centre mixed cohort study

Martin Hoenigl[1,2,3] | Matthias Egger[1] | Johannes Boyer[3] | Eduard Schulz[4] | Juergen Prattes[3] | Jeffrey D. Jenks[1,2,5]

LFA Cut-off/patient group	0.5 ODI		1.0 ODI	
	Sensitivity	Specificity	Sensitivity	Specificity
Overall	79% (22/28)	80% (70/87)	50% (14/28)	97% (84/87)
Haematological malignancy	85% (17/20)	72% (23/32)	55% (11/20)	97% (31/32)
Other traditional underlying diseases predisposing for IA but no haematological malignancy	83% (5/6)	76% (22/29)	50% (3/6)	93% (27/29)
COVID-19 acute respiratory failure but no other underlying disease predisposing for IA	0% (0/2)	96% (25/26)	0% (0/2)	100% (26/26)

Abbreviations: COVID-19, coronavirus disease 2019; IA, invasive aspergillosis; LFA, lateral flow assay; ODI, optical density index.

Received: 21 January 2021 | Revised: 27 February 2021 | Accepted: 3 March 2021

DOI: 10.1111/myc.13265

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases | WILEY

Serum Aspergillus galactomannan lateral flow assay for the diagnosis of invasive aspergillosis: A single-centre study

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[1]Department of Hematology, University of Health Sciences, Istanbul Training and Research Hospital, Istanbul, Turkey

[2]Department of Internal Medicine and Hematology, Istinye University, Liv Hospital ULUS, Istanbul, Turkey

Abstract

Background: Aspergillus species meet the most important group of invasive fungal diseases (IFD) in immunosuppressed patients. Galactomannan is a polysaccharide antigen located in the wall structure of Aspergillus. The most commonly used method

TABLE 3 Diagnostic performance of lateral flow assay and ELISA in predicting

ROC curve results	Galactomannan cut-off: 0.5 ODI	
	LFA	ELISA
Sensitivity	90.9%	0%
95% CI	58.7% to 99.8%	0.0% to 28.5%
Specificity	90.8%	92.1%
95% CI	81.9% to 96.2%	83.6% to 97.1%
PPV	58.8%	0%
95% CI	40.7% to 74.8%	-
NPV	98.6%	86.4%
95% CI	91.4% to 99.8%	85.6% to 87.2%
Accuracy	90.8%	80.5%
	82.7% to 96.0%	70.6% to 88.2%

School of Medicine

Evaluation of The Performance of Aspergillus Galactomannan Lateral Flow Assay 'As A Point Of Care Test' For The Early Diagnosis of Invasive Aspergillosis In Patients With Hematological Malignancies

Ö. Alhan Güncü[1], R. Saba[2], E.H. Akalin[3], B. Ener[3], Z. Türe Yüce[4], M.M. Güncü[5], B. Deveci[2], H.N. Kahveci[4], A.F. Yilmaz[1], **Z. Odabasi**[1]

[1]Marmara University Faculty of Medicine - Istanbul (Turkey), [2]Medstar Antalya Hospital - Antalya (Turkey), [3]Uludag University Faculty of Medicine - Bursa (Turkey), [4]Erciyes University Faculty of Medicine - Kayseri (Turkey), [5]Marmara University Institute of Health Sciences - Istanbul (Turkey)

Study Design

- **Risk factors for IA**
  - (i) Patients with hematological malignancies undergoing chemotherapy or with refractory disease.
  - (ii) Prolonged neutropenia (10 days, 500 neutrophils/mm3) after chemotherapy
  - (iii) Allogeneic HSCT recipient
  - (iv) Use of corticosteroids at 0.3 mg/kg for 3 weeks in the previous 60 days
  - (v) Treatment with T or B cell immunosuppressant drugs
  - (vi) Acute GVHD grade ≥2 or chronic GVHD

- **EORTC/MSG-ERC 2019**

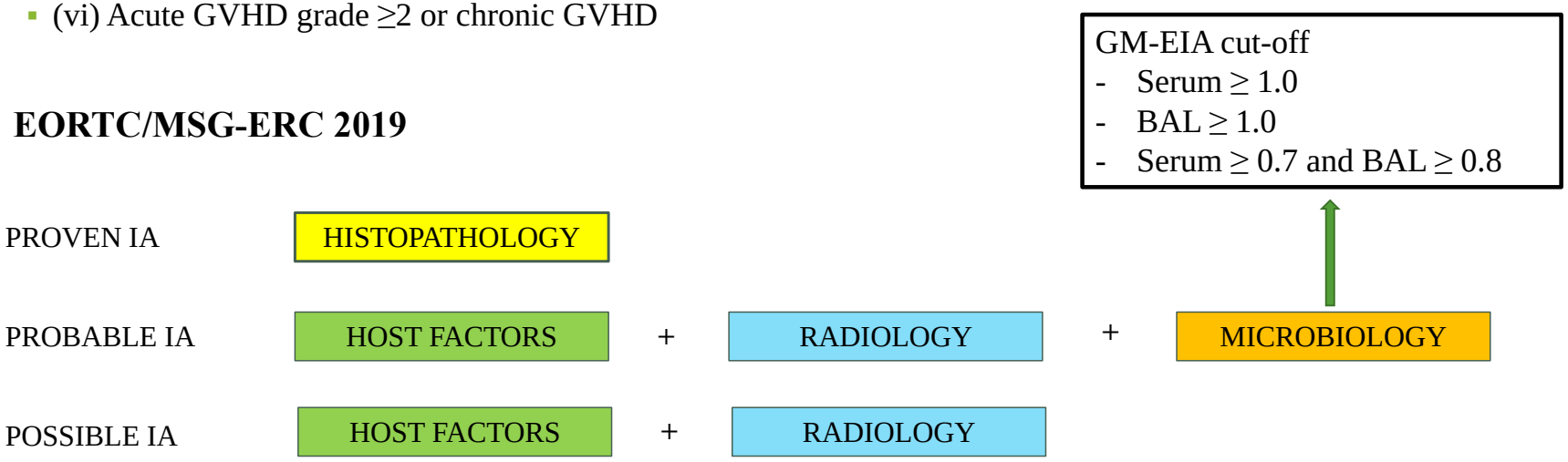


Figure-1. EORTC/MSG-2019 IA case definition

Study Design - Statistics

- IBM SPSS Statistics 26.0
- GM-LFA 0.5 and 1.0 ODI → **Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)**
- **ROC curve** analysis and values under the curve (AUC) at 95% confidence interval (95% CI)
- **Spearman** correlation analysis (quantitative variables)
- **Cohen kappa** coefficient (qualitative variables) - test positivity according to 0.5 ODI

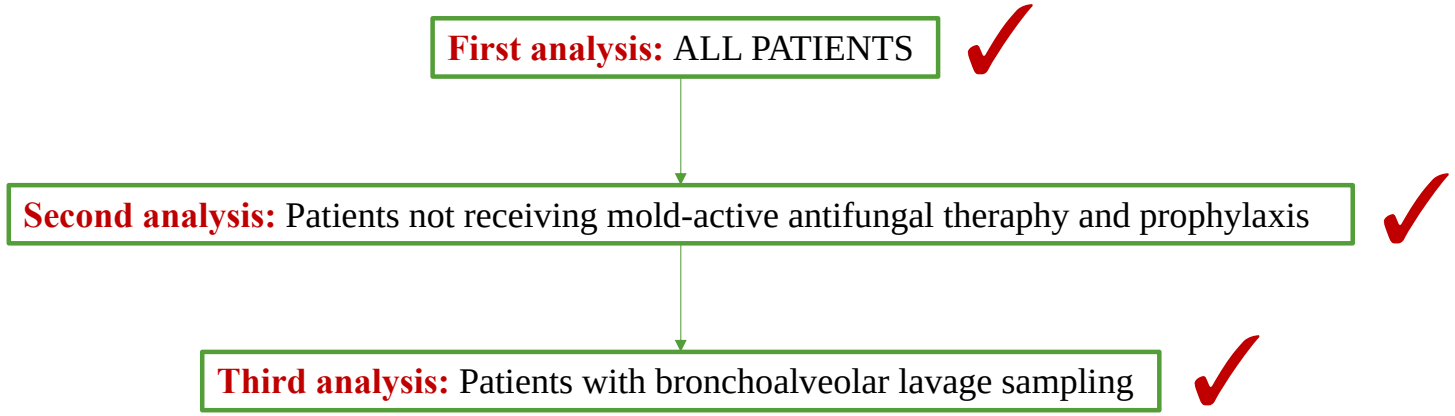


Figure-3. Analyes in the study

Table 1. Demographics of study participants

	Overall		Proven/ Probable IA		Possible IA		No IA	
Median Age, y (min-max, IQR)	54 (18-91, 27)		51 (19-73, 24)		57 (18-77, 27)		54 (18-91, 27)	
	N=171	**%**	**N=28**	**%**	**N=55**	**%**	**N=88**	**%**
Men	100	58.5	18	64.3	28	50.9	54	61.4
Hematological Malignancies								
AML	62	36.3	10	35.7	30	54.5	22	25.0
NHL	35	20.5	6	21.4	4	7.3	25	28.4
ALL	25	14.6	4	14.3	7	12.7	14	15.9
MM	20	11.7	2	7.1	4	7.3	14	15.9
HL	13	7.6	1	3.6	4	7.3	8	9.1
MDS	4	2.3	0	0	3	5.5	1	1.1
Others	12	7.0	5	17.9	3	5.5	4	4.5
HSCT								
Overall	29	17.0	3	10.7	13	23.6	13	14.8
Autologous	17	9.9	2	7.1	8	14.5	7	8.0
Allogeneic	12	7.0	1	3.6	5	9.0	6	6.8
GVHD	4	2.3	0	0	1	1.8	3	3.4

RESULTS

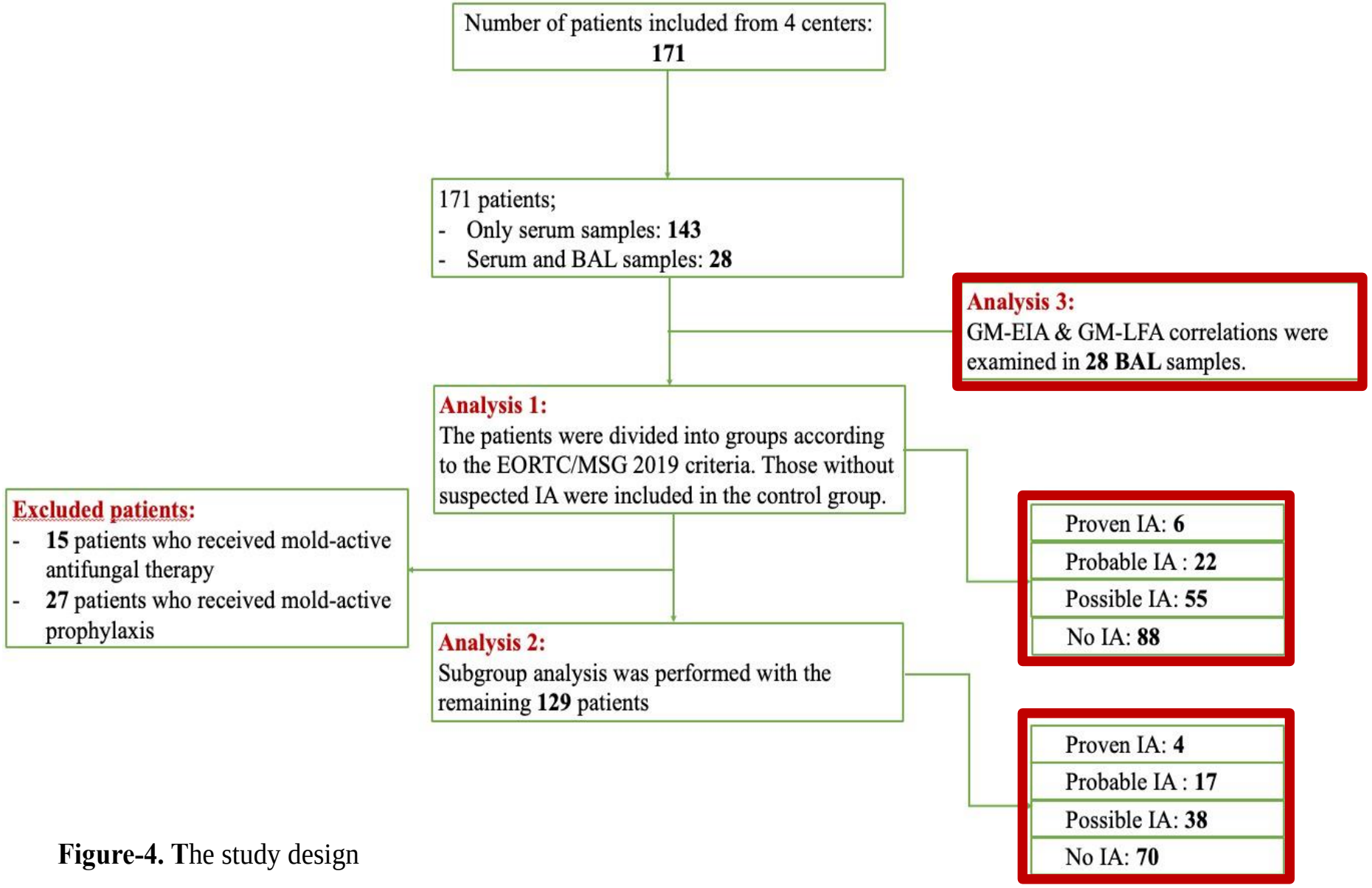
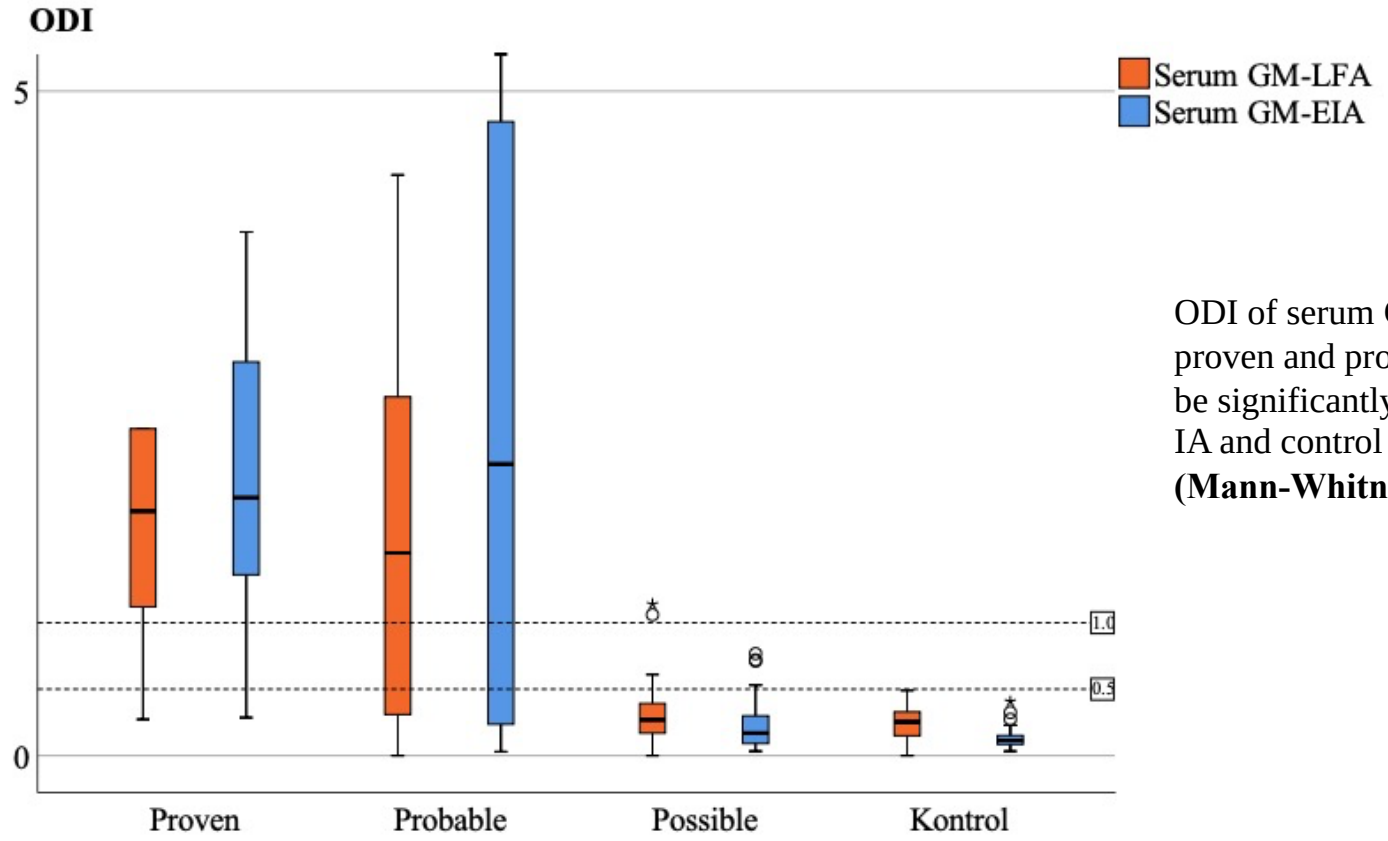


Figure-4. The study design

Table-4: Performance of the GM-LFA test at 0.5 and 1.0 cutoff points

%95 CI	ODI	Sensitivity	Specificity	PPV	NPV
Proven IA (n=6) VS No IA (n=88)					
	0.5 ODI	83.3 %	100 %	100 %	98.9 %
	1.0 ODI	83.3 %	100 %	100 %	98.9 %
Proven IA (n=6) + Probable IA (n=22) VS No IA (n=88)					
	0.5 ODI	% 75	100 %	100 %	92.6 %
	1.0 ODI	% 71.4	100 %	100 %	91.7 %

- The diagnostic accuracy values of the GM-LFA at the 0.5 ODI cutoff point:
  - Proven IA → 98.9%
  - Proven/probable IA → 93.9%



ODI of serum GM-LFA and GM EIA in proven and probable IA cases were found to be significantly higher than in both possible IA and control cases
(Mann-Whitney U test, P<0.001)

Figure-5. Clustered box plots of serum GM-LFA and GM-EIA index values in case and control groups

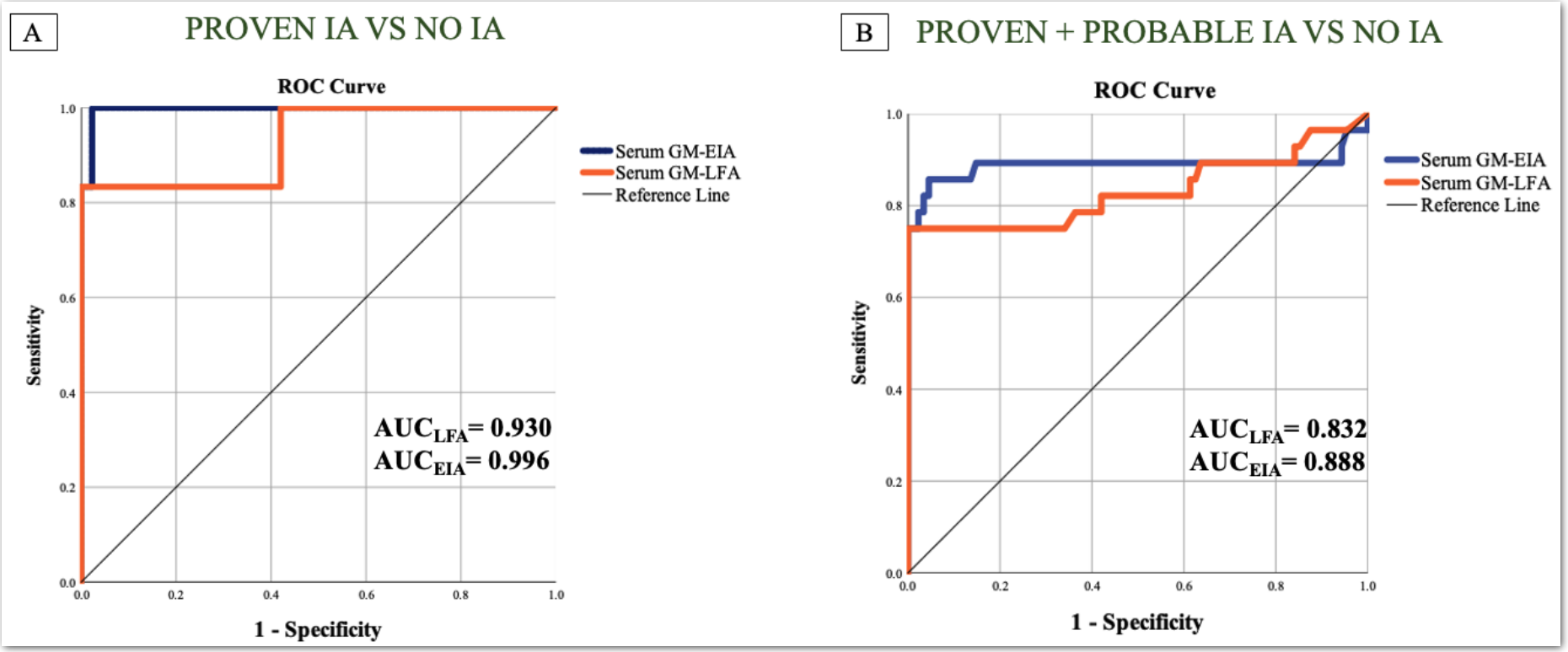


Figure-6. ROC curves of serum GM-EIA and GM-LFA in the diagnosis of IA

- Proven vs No IA → **AUC_{LFA} = 0.930** (%95CI 0.802-1.000) **(P<0.001)**
- Proven/probable vs No IA → **AUC_{LFA} = 0.832** (%95CI 0.716-0.949) (**P<0.001**)

Table-5: The agreement between GM-LFA and GM-EIA in case and control groups

A		GM LFA ≥0.5 ODI							
		Overall N=171 (%)		Proven/Probable IA N=28 (%)		Possible IA N=55(%)		No IA N=88 (%)	
		Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
GM-EIA ≥0.5 ODI	Positive	25/26 (96.1%)	0/145 (0%)	21/21 (100%)	0/7 (0%)	4/5 (80%)	0/50 (0%)	0/0 (0%)	0/88 (0%)
	Negative	1/26 (3.8%)	145/145 (100%)	0/21 (0%)	7/7 (100%)	1/5 (20%)	50/50 (100%)	0/0 (0%)	88/88 (100%)
	Overall	26	145	21	7	5	50	0	88

- **Qualitative agreement between GM-LFA and GM-EIA at 0.5 ODI**
- all cases → **99.4%**
  - Cohen's kappa coefficient **κ = 0.977**, almost perfect agreement
- proven&probable cases → **100%**
- possible cases → **98.7%**
  - **κ =0.879**, almost perfect agreement

RESULTS – ANALYSIS 2

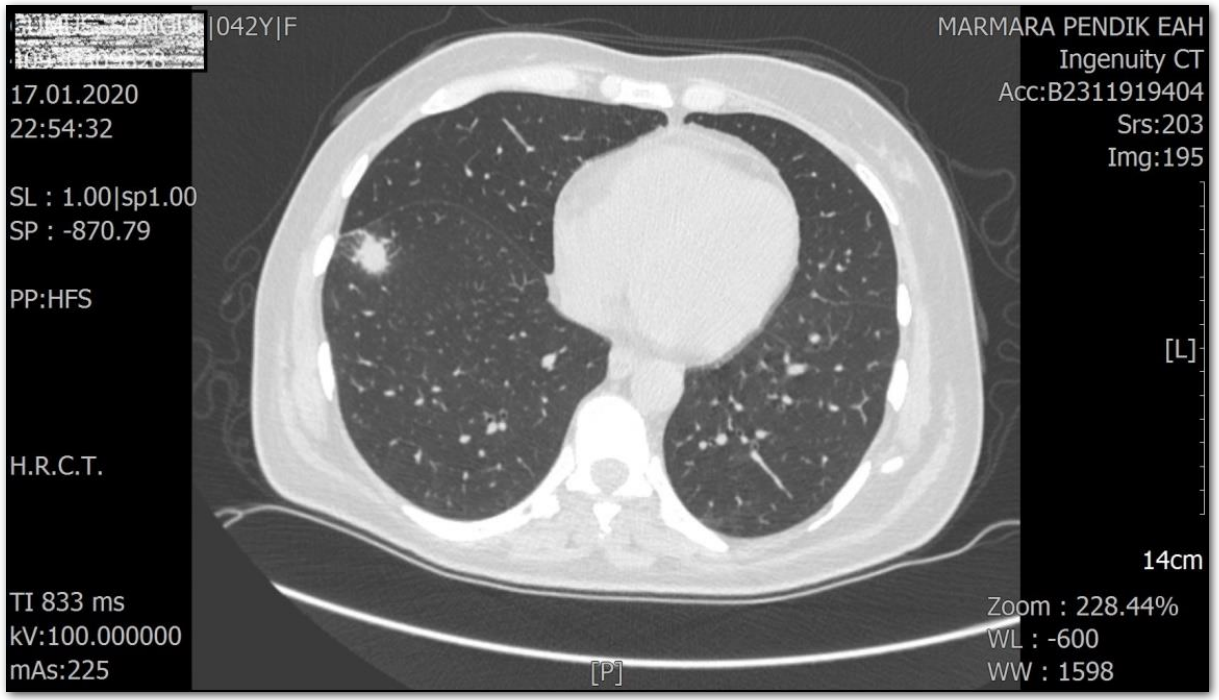
- Excluded patients :
  - **15** patients who received mold-active antifungal therapy
  - **27** patients who received mold-active prophylaxis
- the remaining **129** patients

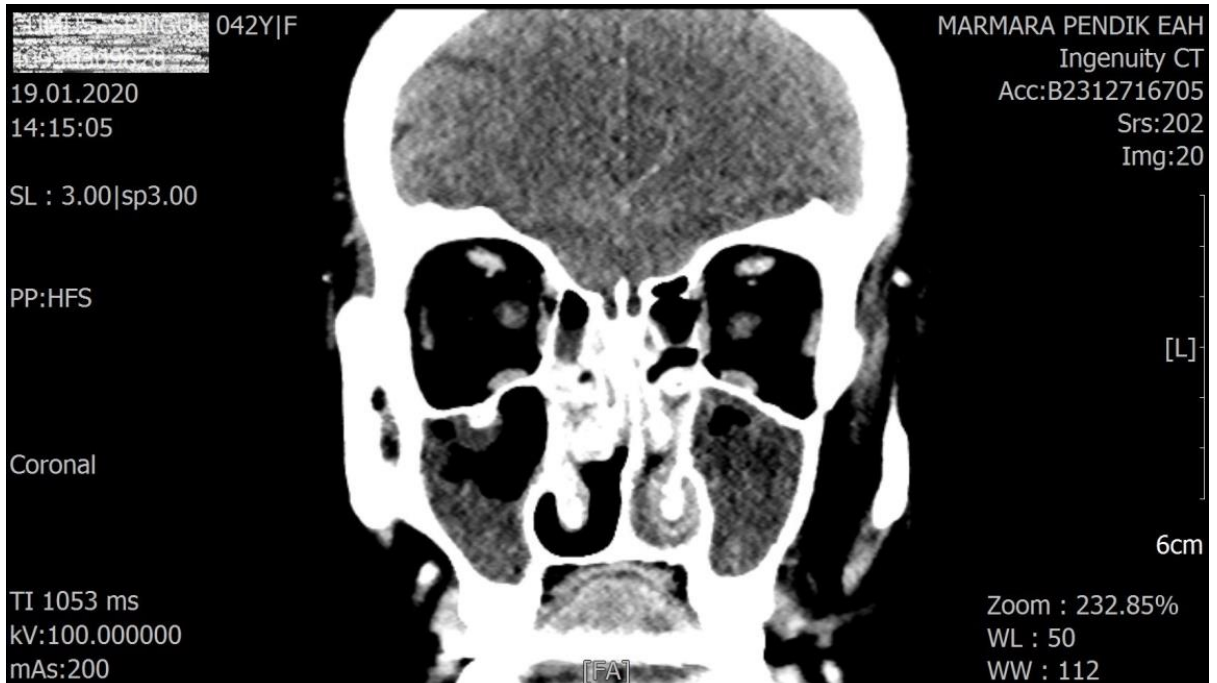
Proven IA: **4**
Probable IA : **17**
Possible IA: **38**

%95 CI	ODI	Sensitivity	Specificity	PPV	NPV
Proven IA (n=4) VS No IA (n=70)					
	0.5 ODI	100 %	100 %	100 %	100 %
	1.0 ODI	100 %	100 %	100 %	100 %
Proven IA (n=4) + Probable IA (n=17) VS No IA (n=70)					
	0.5 ODI	76.2 %	100 %	100 %	93.3 %
	1.0 ODI	71.4 %	100 %	100 %	92.1 %

- The **diagnostic accuracy** values of the GM-LFA at the 0.5 ODI cutoff point:
  - Proven IA → 100%
  - Proven/probable IA → 94.5%

- **Analysis 1:**
- Proven vs No IA:
  - sensitivity: 83.3 %; NPV: 98.9 %
- Proven+Probable vs No IA
  - sensitivity: 75 %; NPV: 92.6 %





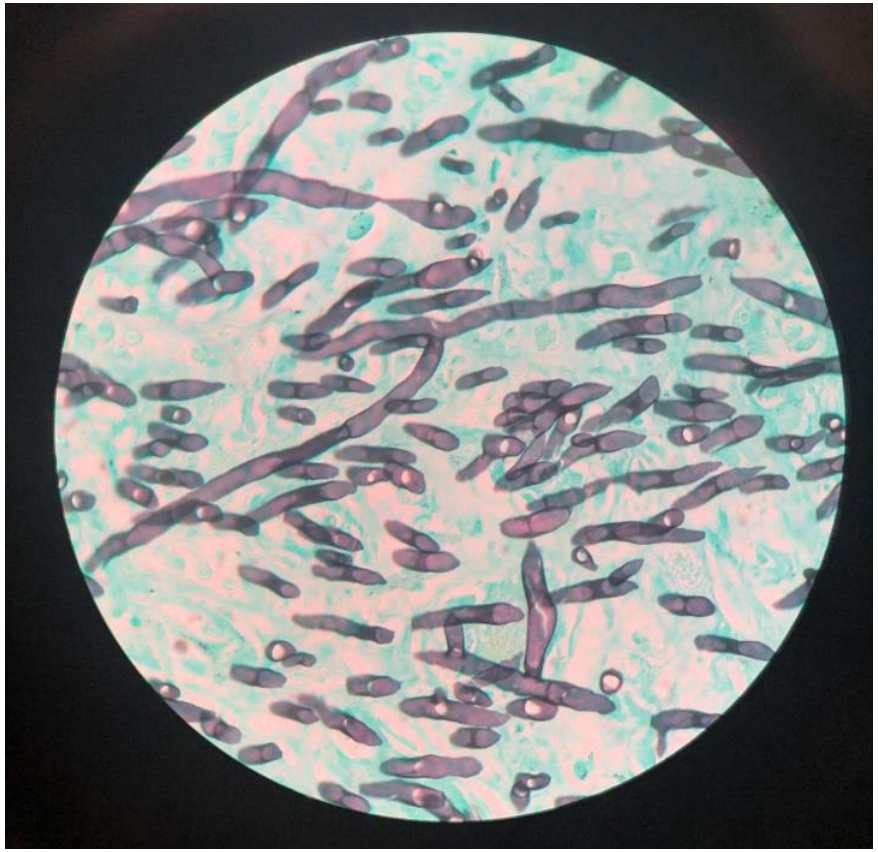
42 yaş, kadın hasta
KLL tanılı

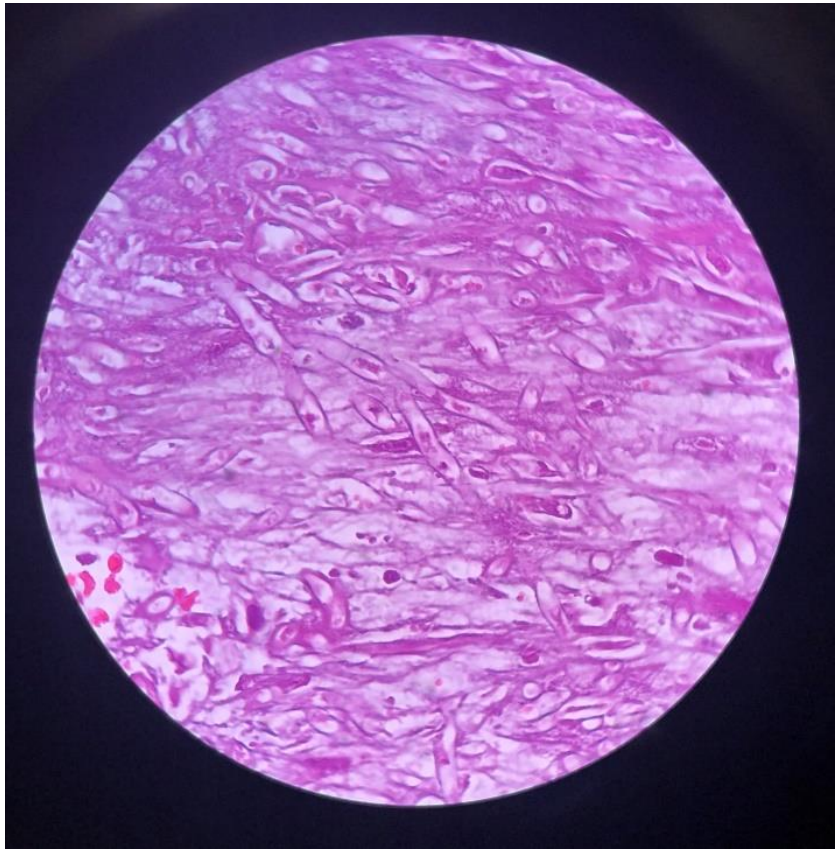
R-EPOCH tedavisi almakta (78 gündür nötropenik)

Akciğer BT: **nodül**,
Serum **GM ve LFA +**

Sinüs hassasiyeti ve Paranasal BT de sinüslerde dolgunluk +

Paranasal örneklemesinde Aspergillus spp ile uyumlu hifler





LFA Özet

- LFA testi en az GM-EIA testi kadar etkin görünüyor
- Daha hızlı sonuç veriyor
- Erken AF tedavi başlanması
- İnvaziv aspergilloz açısından hedefe yönelik tedavi başlanması
- Gereksiz ampirik AF tedavi kullanımının azaltılması sağlanabilir

ESCMID 2018 – Galaktomannan test önerileri

Table 6
Galactomannan testing in blood samples

Population	Intention	Intervention	SoR	QoE	Comment
Patients with prolonged neutropenia or allogeneic stem cell transplantation recipients **not on mould-active prophylaxis**	Prospective screening for IA	GM in blood[a] Draw samples every 3–4 days	A C	I III	Highest test accuracy requiring two consecutive samples with an ODI ≥0.5 or retesting the same sample Prospective monitoring should be combined with HRCT and clinical evaluation
Patients with prolonged neutropenic or allogeneic stem cell transplantation recipients **on mould active prophylaxis**	Prospective screening for IA	GM in blood[a]	D	II	Low prevalence of IA in this setting with consequently low PPV of blood GM test Prophylaxis may have a negative impact on sensitivity of the test or the low yield may be due to decreased incidence of IA
Patients with a haematological malignancy	To diagnose IA	GM in blood[a]			Significantly lower sensitivity in non-neutropenic patients
• Neutropenic patients			A	II	
• Non-neutropenic patients			B	II	
ICU patients	To diagnose IA	GM in blood[a]	C	II	Better performance in neutropenic than in non-neutropenic patients
Solid organ recipients	To diagnose IA	GM in blood[a]	C	II	Low sensitivity, good specificity Most data for lung SOT
Any other patient	To diagnose IA	GM in blood[a]	C	II	Piperacillin/tazobactam may no longer be responsible for false-positive results according to recent studies Cross-reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis) False-positive results reported due to ingestion of ice-pops, transfusions, antibiotics, Plasmalyt® infusion
Cancer patients	To monitor treatment	GM in blood[a]	A	II	

Ullmann AJ, Clin Microbiol Infec, 2018

ECIL-6 İnvaziv Aspergillozda Birinci basamak tedavi önerileri

	Grade	Comments
Voriconazole[a]	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole[a] + anidulafungin	C I	
Other combinations	C III	
Recommendation against use Amphotericin B deoxycholate	A I	Less effective and more toxic

[a]Monitoring of serum levels is indicated. In the absence of sufficient data for first-line monotherapy, anidulafungin, micafungin and posaconazole have n

Frederic Tissot, Haematologica 2017

IDSA İnvaziv Aspergilloz Rehberi 2016

Condition	Therapy: Primary	Therapy: Alternative
Invasive syndromes of *Aspergillus*		
IPA	Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)
Invasive sinus aspergillosis	Similar to IPA	Similar to IPA
Tracheobronchial aspergillosis	Similar to IPA	Adjunctive inhaled AmB may be useful
Aspergillosis of the CNS	Similar to IPA	Similar to IPA Surgical resection may be beneficial in selected cases
Aspergillus infections of the heart (endocarditis, pericarditis, and myocarditis)	Similar to IPA	Similar to IPA
Aspergillus osteomyelitis and septic arthritis	Similar to IPA	Similar to IPA
Aspergillus infections of the eye (endophthalmitis and keratitis)	Systemic IV or oral voriconazole plus intravitreal AmB or voriconazole indicated with partial vitrectomy	Similar to invasive pulmonary aspergillosis; limited data with echinocandins and poor ocular penetration by this class
Cutaneous aspergillosis	Similar to IPA	Similar to IPA
Aspergillus peritonitis	Similar to IPA	Similar to IPA
Empiric and preemptive antifungal therapy	For empiric antifungal therapy, Liposomal AmB (3 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (100 mg day), voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or 3–4 mg/kg q 12 h)	

ESCMID– Aspergilloz Tedavi Rehberi

Table 27
Targeted therapy of pulmonary disease—first line

Population	Intention	Intervention	SoR	QoE[1]	QoE[2]	QoE[3]	Comment
1] Neutropenia (non-allo HSCT recipients) 2] Allo-HSCT (during neutropenia) 3] Allo-HSCT (w/o neutropenia) or other non-neutropenic patients	To increase response and survival rate	Isavuconazole 200 mg IV tid day 1–2, then 200 mg qd oral	A	I	II_t	II_t	D III, if mould active azole prophylaxis fewer adverse effects than voriconazole
		Voriconazole 2× 6 mg/kg IV (oral 400 mg bid) on day 1, then 2–4 mg/kg IV (oral 200–300 mg bid)	A	I	II_t	II_t	C III for start with oral; D III, if prior mould active azole prophylaxis; TDM
		L-AmB 3 mg/kg	B	II	II_t	II_t	
		Combination of voriconazole 6/4 mg/kg bid (after 1 week oral possible (300 mg bid)) + anidulafungin 200/100 mg	C	I	II_t,	II_t,	No significant difference compared to voriconazole, in GM-positive (subgroup) better survival; TDM
		Caspofungin 70 mg qd day 1, followed by 50 mg qd (if body weight <80 kg)	C	II	II	II	
		Itraconazole 200 mg q12 h IV on day 1, then 200 mg/qd	C	III	$II_{t,a}$	$II_{t,a}$	D III for start with oral, TDM D III, if mould active azole prophylaxis
		AmB lipid complex (ABLC) 5 mg/kg	C	III	III	III	
		Micafungin 100 mg	C	III	III	III	
		AmB colloidal dispersion (ABCD) 4–6 mg/kg	D	I	II_t	II_t	
		Conventional AmB 1–1.5 mg/kg	D	I	II_t	II_t	
		Other combinations	D	III	III	III	Efficacy unproven
Life-threatening haemoptysis	Bridging until neutrophil recovery	Arterial embolization, emergency surgical intervention	B	III	III	III	

Ullmann AJ, Clin Microbiol Infec, 2018

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial

Johan A Maertens, Issam I Raad, Kieren A Marr, Thomas F Patterson, Dimitrios P K
Dionysios Neofytos, Mickael Aoun, John W Baddley, Michael Giladi, Werner J Hein
Dong-Gun Lee, Olivier Lortholary, Vicki A Morrison, Ilana Oren, Dominik Selleslag,
Rochelle M Maher, Anne-Hortense Schmitt-Hoffmann, Bernhardt Zeiher, Andrew

İzavukonazol mortalite %19

Vorikonazol mortalite %20

Summary

Background Isavuconazole is a novel triazole with broad-spectrum antifungal activity. The SECURE trial assessed efficacy and safety of isavuconazole versus voriconazole in patients with invasive mould disease.

Methods This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice–web response system, stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). We tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00412893.

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December 9, 2015
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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(15)01218-0

Department of Hematology, Universitaire Ziekenhuizen Leuven, KU Leuven, Belgium (Prof J A Maertens MD); Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial

*Johan A Maertens, Galia Rahav, Dong-Gun Lee, Alfredo Ponce-de-León, Isabel Cristina Ramírez Sánchez, Nikolay Klimko, Anne Sonet, Shariq Haider, Juan Diego Vélez, Issam Raad, Liang-Piu Koh, Meinolf Karthaus, Jianying Zhou, Ronen Ben-Ami, Mary R Motyl, Seongah Han, Anjana Grandhi, Hetty Waskin, on behalf of the study investigators**

Summary

Background Voriconazole has been recommended as primary treatment for patients with invasive aspergillosis. Intravenous and tablet formulations of posaconazole that have improved systemic absorption could be an effective alternative to voriconazole. We aimed to assess non-inferiority of posaconazole to voriconazole for the primary treatment of invasive aspergillosis.

Lancet 2021; 397: 499–509

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 5, 2021

Posakonazol invaziv aspergilloz birinci basamak tedavisinde vorikonazol ile eşdeğer

Mortalide %19 vs %19

Daha az yan etki

Lancet Şubat 2021

MAJOR ARTICLE

İnvaziv aspergillozda **mortaliteye** etki eden faktörler üzerine bir çalışma

9 yıl – 385 vaka

Factors Associated with Overall and Attributable Mortality in Invasive Aspergillosis

Yasmine Nivoix,[1] Michel Velten,[7] Valérie Letscher-Bru,[2] Alireza Moghaddam,[3] Shanti Natarajan-Amé,[3] Cécile Fohrer,[3] Bruno Lioure,[3] Karin Bilger,[3] Philippe Lutun,[4] Luc Marcellin,[5] Anne Launoy,[6] Guy Freys,[6] Jean-Pierre Bergerat,[3] and Raoul Herbrecht[3]

[1]Pharmacie, [2]Institut de Parasitologie et de Pathologie Tropicale, [3]Service d'Hématologie et d'Oncologie, [4]Service de Réanimation Médicale, [5]Service de Pathologie Générale, and [6]Service de Réanimation Chirurgicale, Hôpitaux Universitaires de Strasbourg, and [7]Laboratoire d'Epidémiologie et de Santé Publique, Faculté de Médecine, Université Louis Pasteur, Strasbourg, France

(See the editorial commentary by Kohno on pages 1185–7)

Background. Invasive aspergillosis is associated with high death rates. Factors associated with increased mortality have not yet been identified in a large population of patients with various underlying conditions.

Methods. We retrospectively reviewed 385 cases of suspected or documented aspergillosis that occurred during a 9-year period. We identified 289 episodes that fulfilled the criteria for possible, probable, or proven invasive aspergillosis according to the international definition criteria and that was treated with an anti-*Aspergillus* active antifungal drug. Clinical and microbiological variables were analyzed for their effects on overall and attributable mortality. Significant variables in univariate analysis were introduced into a multivariate Cox model.

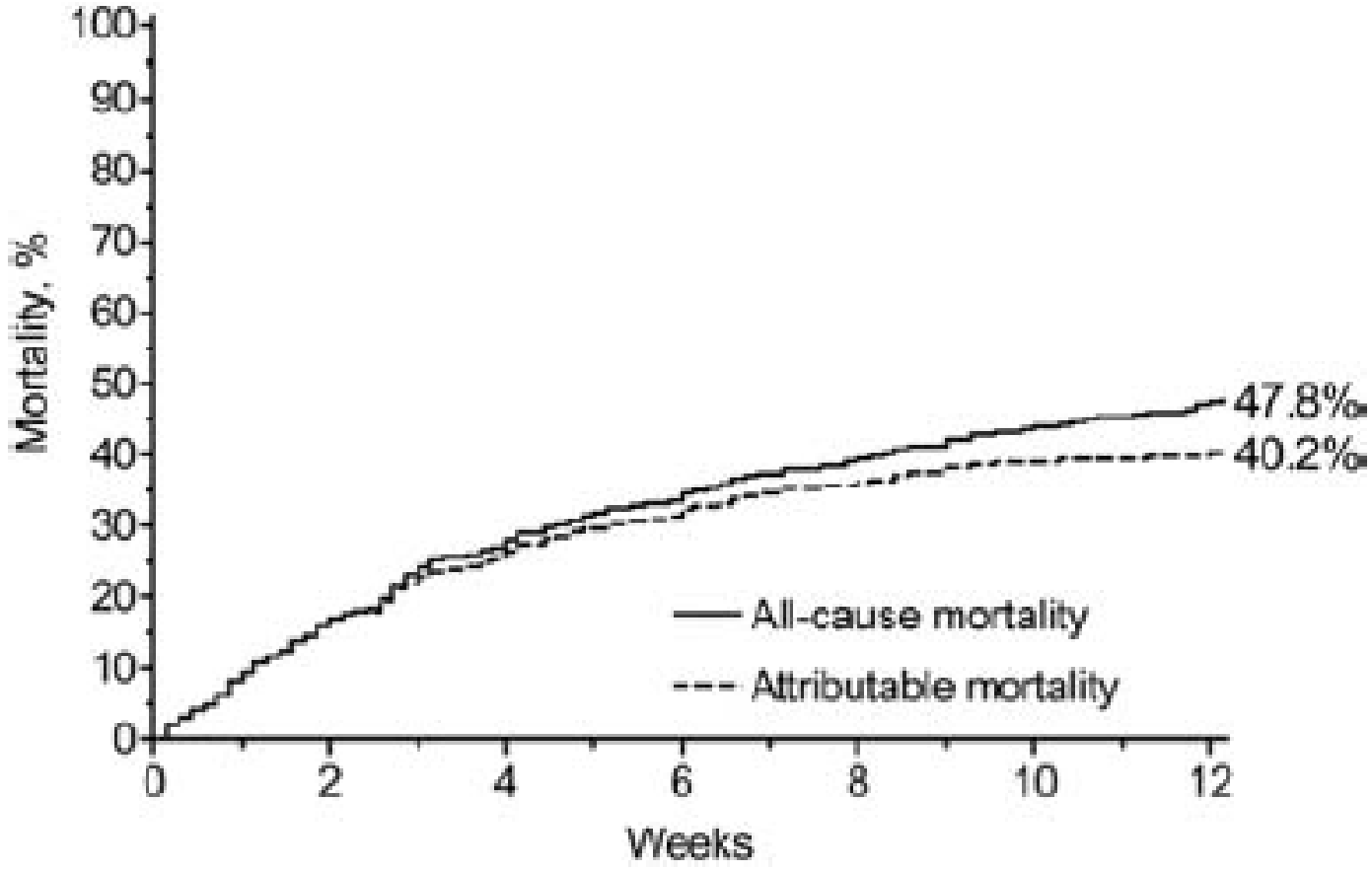


Figure 3. Probability of all-cause mortality and mortality attributable to aspergillosis.

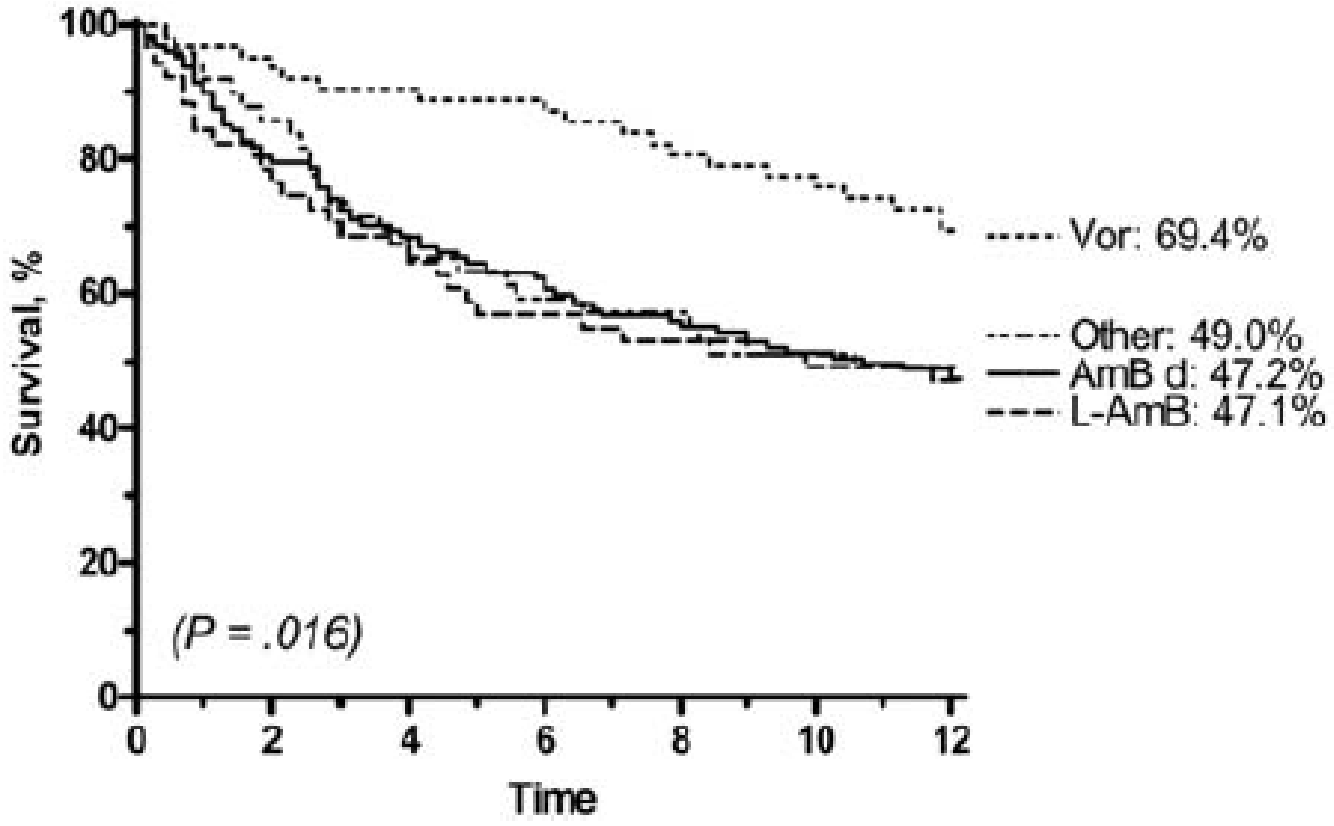


Figure 1. Kaplan-Meier probability of overall survival after initiation of treatment according to first-line therapy. AmB d, amphotericin B deoxycholate; L-AmB, liposomal amphotericin B; Vor, voriconazole.

İA için birinci basamakta kullanılan antifungallere göre sürvi

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2017, 55, 82–86
doi: 10.1093/mmy/myw114
Advance Access Publication Date: 2 December 2016
Review Article

Review Article

Invasive aspergillosis in acute myeloid leukemia: Are we making progress in reducing mortality?

Giulia Dragonetti*, Marianna Criscuolo, Luana Fianchi and Livio Pagano

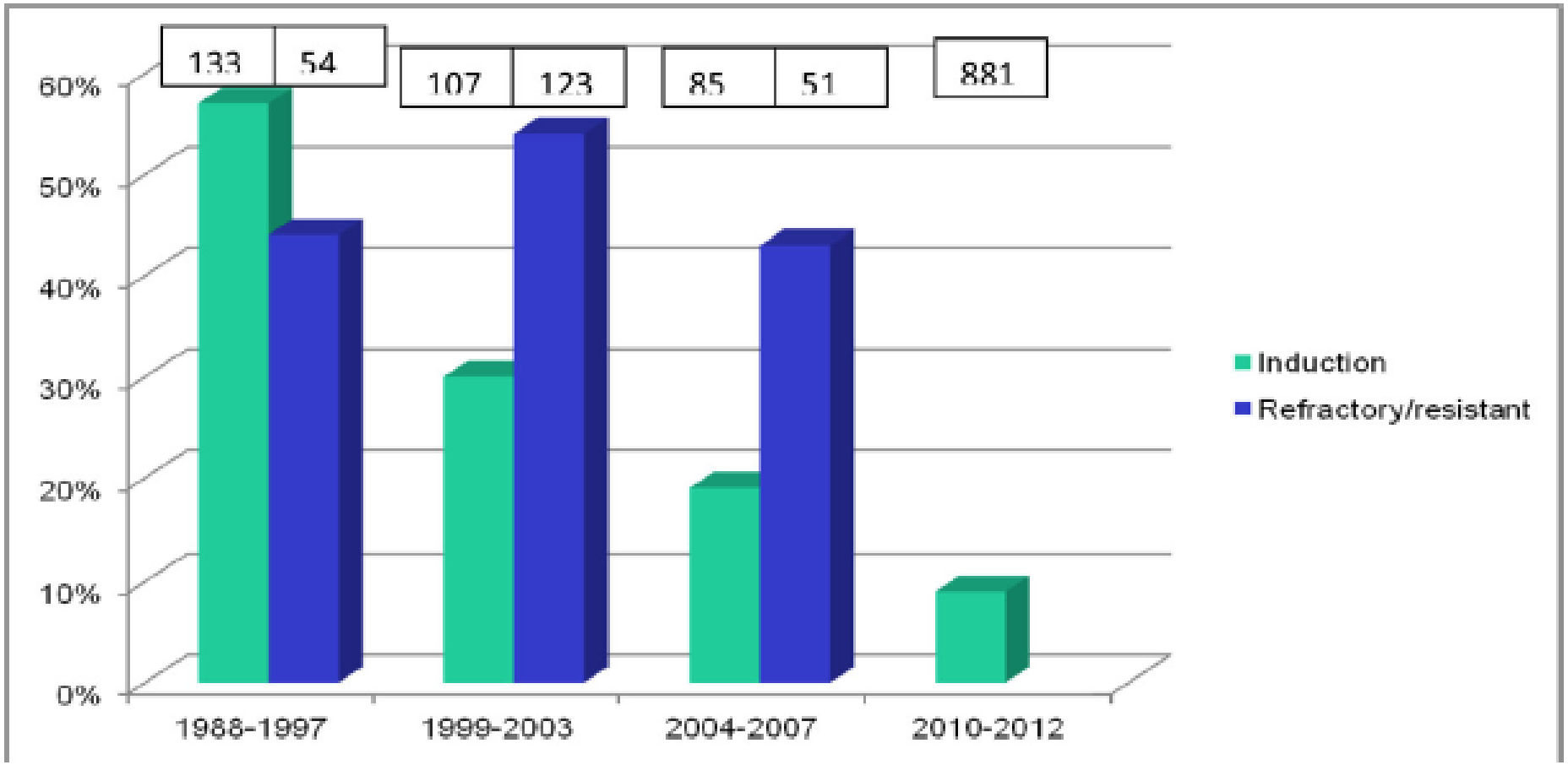
Hematology Department, Catholic University of Sacred Heart, Rome, Italy

*To whom correspondence should be addressed. Giulia Dragonetti, Medical doctor, specializing of hematology, Hematology Department, Catholic University of Sacred Heart, Largo A. Gemelli 8, I-00168 Roma Italy,
E-mail: dragonettigiulia@gmail.com

Received 30 April 2016; Revised 9 September 2016; Accepted 16 October 2016; Editorial Decision 2016 September 15

Şekil 1. İnvaziv aspergilloza atfedilen mortalite oranları

- **Remisyondaki** hastalarda son yıllarda mortalite azalırken
- **Refrakter** hastalarda mortalite halen yüksek



İnvaziv Pulmoner Aspergilloz Tedavi Süresi

Clinical Infectious Diseases

IDSA GUIDELINE

Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Thomas F. … **nnis,**[7] **Kieren A. M** … **. Wingard,**[15] **Jo-Anne H** …

[1]University of … ospital of South Manchester, U… y of Strasbourg, France; [7]Unive… e, Maryland; [9]Hennepin Co… l Sciences, and Roswell Park … Hospital/Weill Cornell Medic… y and Infectious Disease, Nati…

30. We recommend that treatment of IPA be continued for a minimum of 6–12 weeks, largely dependent on the degree and duration of immunosuppression, site of disease, and evidence of disease improvement (*strong recommendation; low-quality evidence*).

It is impo… …ed to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline

(Tables 27 and 28). Physicians should consider switching from intravenous to oral therapy in stable and pharmacokinetically reliable patients. Treatment duration depends on clinical response and on immune reconstitution or recovery from GvHD. Good partial or complete remission requires no persistent clinical, including imaging (scarring allowed), or microbiological evidence of disease. The range of the duration of treatment (3 to >50 weeks) is huge and the evidence base to support any particular recommendation is weak.

O.A. Cornely [56, 58, 60, 61, 62, 63, 64, *]

Received: 4 March 2019 | Accepted: 18 March 2019
DOI: 10.1111/ctr.13544

SPECIAL ISSUE: TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Shahid Husain[1] | Jose F. Camargo[2] on behalf of the AST Infectious Diseases Community of Practice

[1]Division of Infectious Diseases, Multi-Organ Transplant Unit, University Health Network, University of Toronto, Toronto, Ontario, Canada

[2]Department of Medicine, Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, Florida

Correspondence
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Email: shahid.husain@uhn.ca

Funding information
American Society of Transplantation

5.2 | Duration of therapy

The optimal duration of therapy for IA depends upon the response to therapy, and the patient's underlying disease(s) or immune status. Treatment is usually continued for 12 weeks; however, the precise duration of therapy should be guided by clinical response rather than an arbitrary total dose or duration. A reasonable course would be to continue therapy until all clinical and radiographic abnormalities have resolved, and until fungal biomarkers and cultures (if they can be readily obtained) no longer yield evidence of *Aspergillus*.

apy is recommended in lung transplant recipients, whereas targeted prophylaxis is favored in liver and heart transplant recipients. In these guidelines, we also discuss newer antifungals and diagnostic tests, antifungal susceptibility testing, and special patient populations.

SCIENTIFIC REPORTS

nature research

Check for updates

Short course of voriconazole therapy as a risk factor for relapse of invasive pulmonary aspergillosis

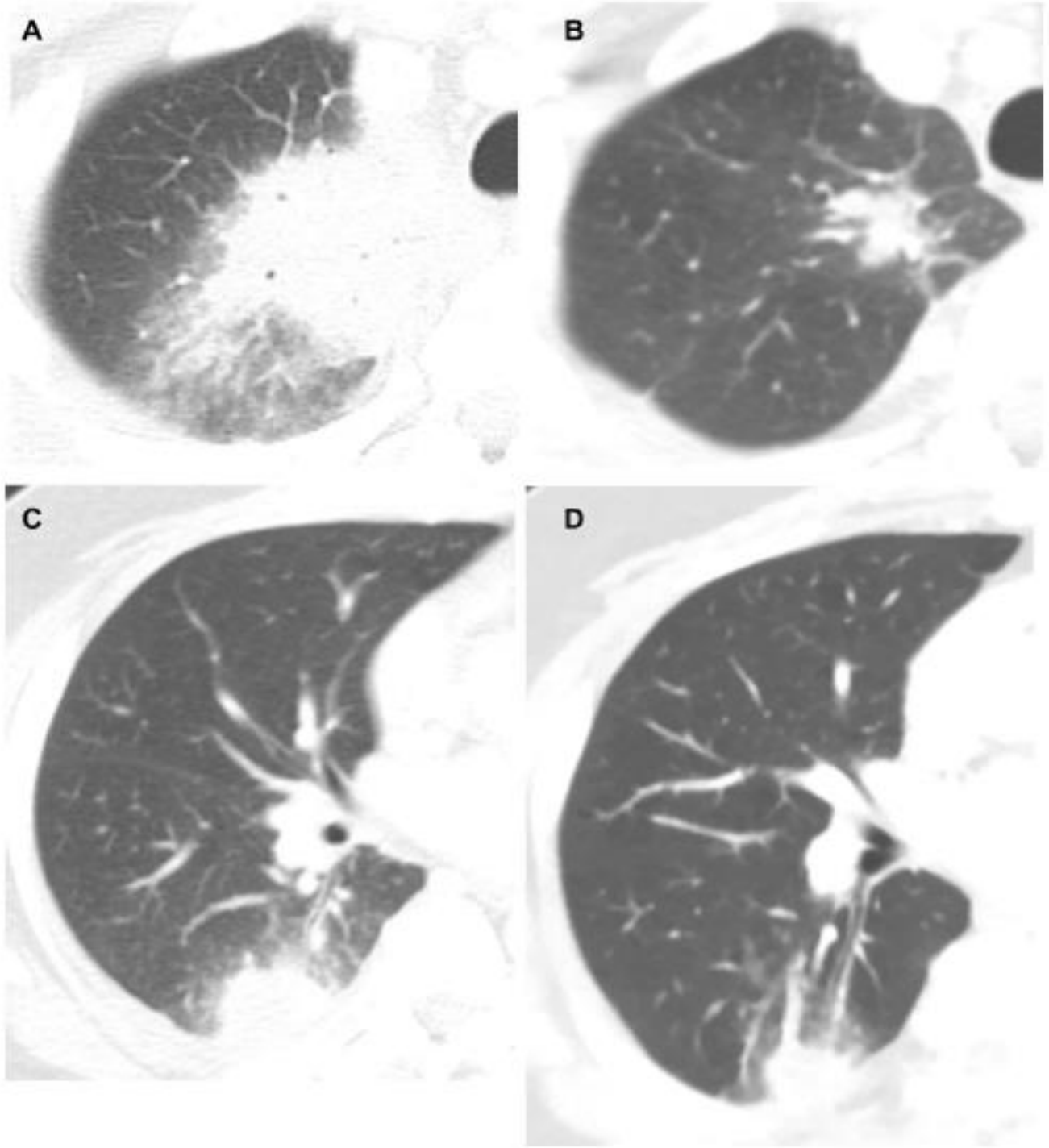
Dong Hoon Shin[1,5], Seung-Jin Yoo[2,5], Kang Il Jun[1], Hyungjin Kim[2✉], Chang Kyung Kang[1✉], Kyoung-Ho Song[1,3], Pyoeng Gyun Choe[1], Wan Beom Park[1], Ji-Hwan Bang[1,4], Eu Suk Kim[1,3], Sang Won Park[1,4], Hong Bin Kim[1,3], Nam-Joong Kim[1] & Myoung-don Oh[1]

To investigate associations of the duration of voriconazole treatment and radiological response with relapse of invasive pulmonary aspergillosis (IPA) in immunocompromised patients, we explored the risk factors for IPA relapse after successful initial treatment. All patients with proven or probable IPA who had finished voriconazole treatment between 2005 and 2019 in a tertiary-care hospital were reviewed. IPA relapse was defined as re-diagnosis of proven or probable IPA at the same site within 1 year after treatment termination. Short course of voriconazole treatment was defined as a treatment less than 9 weeks, which is a median of the recommended minimum duration of therapy from the Infectious Disease Society of America. The radiological response was defined as a reduction in IPA burden by more than 50% on chest computed tomography. Of 87 patients who had completed voriconazole treatment, 14 (16.1%) experienced IPA relapse. Multivariable Cox regression identified that short voriconazole treatment duration (adjusted hazard ratio [aHR], 3.7; 95% confidence interval [CI], 1.1–12.3; $P = 0.033$) and radiological non-response (aHR, 4.6; 95% CI, 1.2–17.5; $P = 0.026$) were independently associated with relapse of IPA after adjusting for several clinical risk factors. Longer duration of therapy should be considered for those at higher risk of relapse.

2020

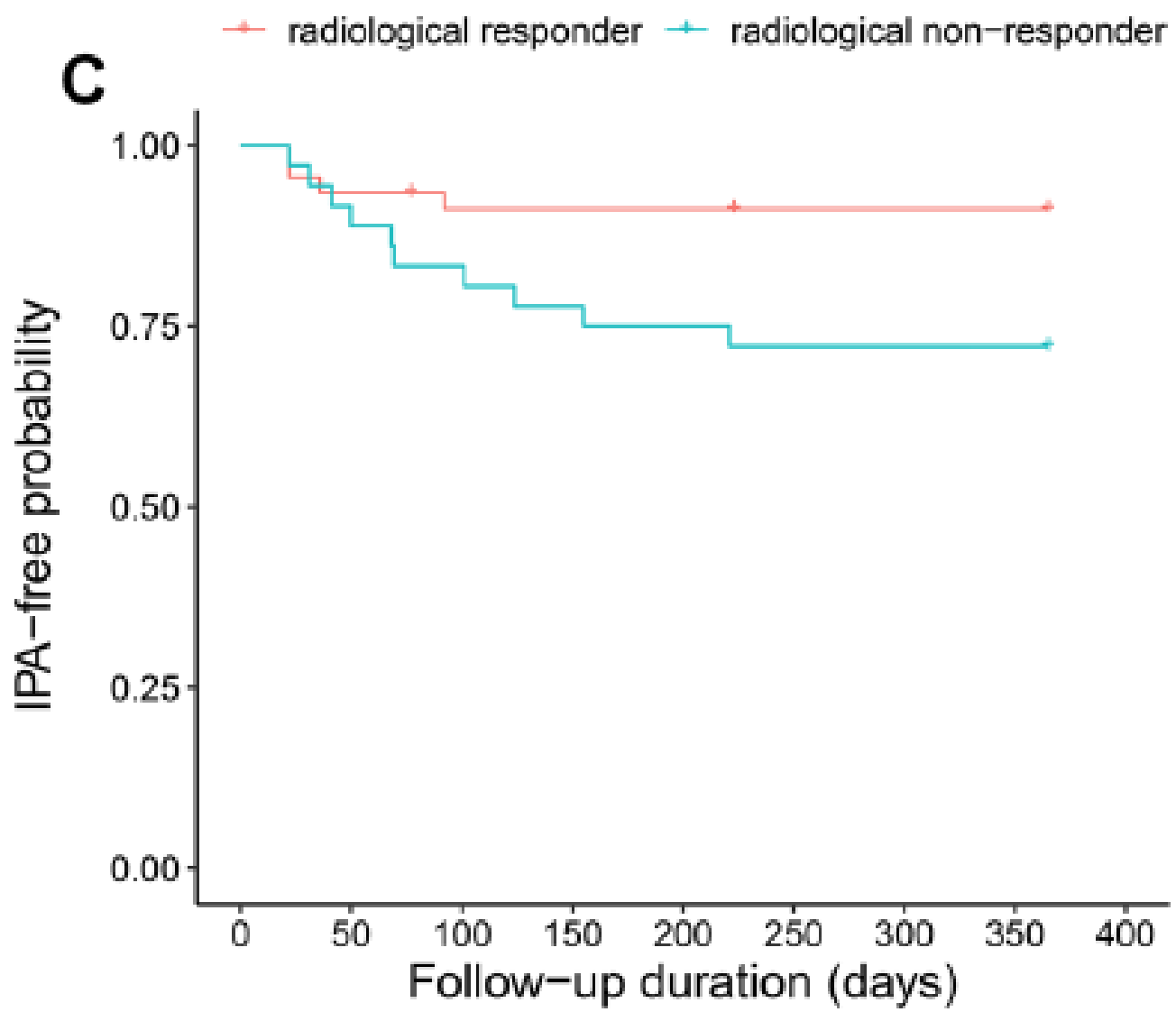
İA için relaps risk faktörleri

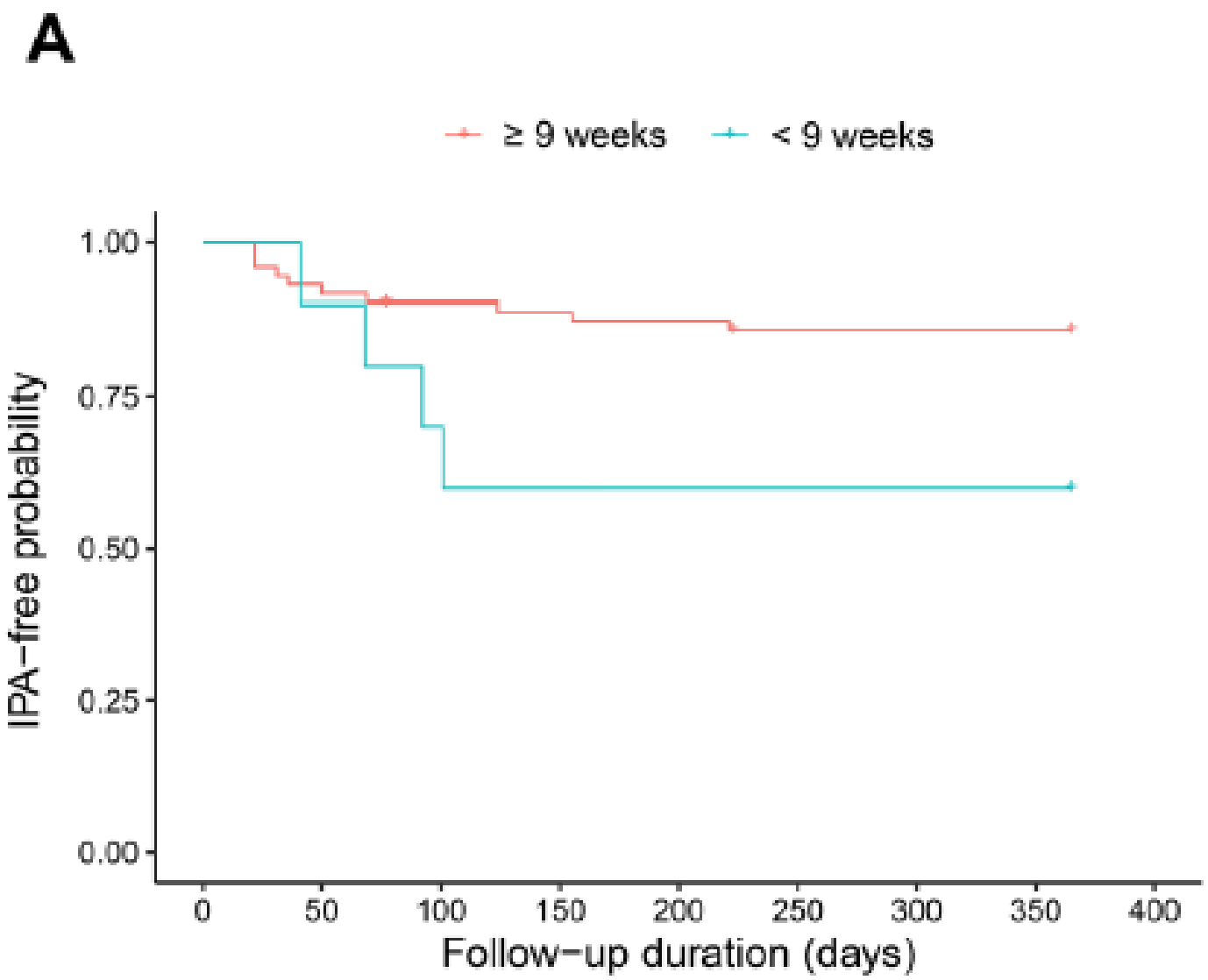
Variable	aHR (95% CI)	*P*
Age	0.9 (0.9–1.0)	0.096
Male	3.3 (0.8–13.0)	0.088
Charlson comorbidity-weighted index score	1.8 (1.2–2.6)	0.003
Number of initial involved lobes	1.1 (0.7–1.5)	0.777
Any immunosuppressive events during treatment	2.6 (0.7–10.3)	0.164
Short voriconazole treatment duration	3.7 (1.1–12.3)	0.033
Radiological non-response	4.6 (1.2–17.5)	0.026



Radyolojik düzelme (>%50)
relaps yok

Radyolojik düzelme (<%50)
relaps gelişti


C
radiological responder
radiological non−responder
IPA−free probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
250
300
350
400
Follow−up duration (days)


A
≥ 9 weeks
< 9 weeks
IPA−free probability
1.00
0.75
0.50
0.25
0.00
0
50
100
150
200
250
300
350
400
Follow−up duration (days)

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Defining Responses to Therapy and Study Outcomes in Clinical Trials of Invasive Fungal Diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer Consensus Criteria

Brahm H. Segal[1], **Raoul Herbrecht**[22], **David A. Stevens**[9,10], **Luis Ostrosky-Zeichner**[4], **Jack Sobel**[7], **Claudio Viscoli**[28,29], **Thomas J. Walsh**[12], **Johan Maertens**[30], **Thomas F. Patterson**[5], **John R. Perfect**[2], **Bertrand Dupont**[23], **John R. Wingard**[8], **Thierry Calandra**[21], **Carol A. Kauffman**[6], **John R. Graybill**[5], **Lindsey R. Baden**[15], **Peter G. Pappas**[11], **John E. Bennett**[13], **Dimitrios P. Kontoyiannis**[3], **Catherine Cordonnier**[24], **Maria Anna Viviani**[27], **Jacques Bille**[20], **Nikolaos G. Almyroudis**[1], **L. Joseph Wheat**[14], **Wolfgang Graninger**[25,26], **Eric J. Bow**[16], **Steven M. Holland**[13], **Bart-Jan Kullberg**[18,19], **William E. Dismukes**[11], and **Ben E. De Pauw**[17]

Table 3

Responses to antifungal therapy in patients with invasive mold disease

Outcome, response	Criteria
Success	
Complete response	Survival and resolution of all attributable symptoms and signs of disease; plus
	Resolution of radiological lesion(s); persistence of only a scar or postoperative changes can be equated with a complete radiological response; plus
	Documented clearance of infected sites that are accessible to repeated sampling (e.g., mold disease involving the palate, sinuses, or cutaneous lesions)
Partial response	Survival and improvement of attributable symptoms and signs of disease[a]; plus
	At least 25% reduction in diameter of radiological lesion (s); plus
	Documented clearance of infected sites that are accessible to repeated sampling (e.g., mold disease involving the palate, sinuses, or cutaneous lesions)
	In cases of radiological stabilization (defined as a 0%–25% reduction in the diameter of the lesion), resolution of all attributable symptoms and signs of fungal disease can be equated with a partial response
	In cases of radiological stabilization, biopsy of an infected site (e.g., lung biopsy) showing no evidence of hyphae and negative culture results can be equated with a partial response
Failure	
Stable response	Survival and minor or no improvement in attributable symptoms and signs of disease; plus
	Radiological stabilization (defined as a 0%–25% reduction in the diameter of the lesion); or
	Persistent isolation of mold or histological presence of invasive hyphae in infected sites
Progression of disease	Worsening clinical symptoms or signs of disease; plus
	New sites of disease or radiological worsening of preexisting lesions; or
	Persistent isolation of mold species from infected sites
Death	Death during the prespecified period of evaluation regardless of attribution

İnvaziv Aspergillozda Tedaviye Yanıtı Değerlendirme (randomize kontrollü antifungal tedavi çalışmaları)

İnvazif Aspergillozda Tedaviye Yanıt Değerlendirmesi

Başarılı

Tam başarı: Semptom ve şikayetlerin tamamen kaybolması ile birlikte **radyolojik bulguların da tamamen düzelmesi** ya da sekel /skar kalması

Kısmi Başarı: Semtom ve şikayetlerde gerileme ile birlikte radyolojik bulgularda **en az %25 gerileme olması**

Başarısız

Stabil yanıt: Semtom ve şikayetlerde hafif düzelme ya da hiç düzelme olmaması ve radyolojik görüntülemede **< %25 gerileme**

Progresyon: Semtom ve şikayetlerde artış olması ile birlikte radyolojik lezyonlarda ilerleme, yeni lezyonların eklenmesi ve kültürlerde üremelerin devamlılık göstermesi

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Journal of Antimicrobial Chemotherapy

When to change treatment of acute invasive aspergillosis: an expert viewpoint

Monica A. Slavin [1*], Yee-Chun Chen[2], Catherine Cordonnier[3], Oliver A. Cornely [4,5], Manuel Cuenca-Estrella[6], J. Peter Donnelly [7], Andreas H. Groll [8], Olivier Lortholary[9], Francisco M. Marty[10]†, Marcio Nucci [11], John H. Rex[12,13], Bart J. A. Rijnders[14], George R. Thompson III[15], Paul E. Verweij [16,17], P. Lewis White[18], Ruth Hargreaves[12], Emma Harvey[12] and Johan A. Maertens[19,20]

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- **Senaryo1**
  - Triazol profilaksi altında «**breakthrough**» fungal enfeksiyon
- **Senaryo 2**
  - Triazol altında **tedavi başarısızlığı** (duyarlılık sonucu bilinmiyor)
- **Senaryo 3**
  - Kanıtlanmış **azol direnci**

Medical Microbiology and Infectious Diseases Erasmus MC, University Medical Center, Rotterdam, The Netherlands; [15]Department of Internal Medicine, Division of Infectious Diseases, 4150 V Street, Suite G500, Sacramento, CA 95817, USA; [16]Radboudumc-CWZ Center of Expertise for Mycology, Radboud University Nijmegen Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; [17]Center for Infectious Disease Research, Diagnostics and Laboratory Surveillance National Institute for Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA Bilthoven, The Netherlands; [18]Public Health Wales Mycology Reference Laboratory, University Hospital of Wales, Heath Park, Cardiff, UK; [19]Department of Microbiology, Immunology, and Transplantation, K.U. Leuven, Leuven, Belgium; [20]Department of Hematology, U.Z. Leuven, Leuven, Belgium

Senaryo 1: Küf etkili azol profilaksisi altında breakthrough invaziv aspergilloz

- Profilaksi başladıktan kaç gün sonra gelişen enfeksiyon «breakthrough» kabul edilsin: 3 gün
- Serum düzeyi yeterli ise: Lipozomal AmB
- Eğer
  - Subterapötik posakonazol serum düzeyi varsa
  - *Aspergillus* türü azol duyarlı ise
- Vorikonazol veya İzavukonazol

Posakonazol serum düzeyinin kararlı konsantrasyona ulaşması 3-7 gün

Antifungal	Time to steady state*	Plasma elimination half-life	Dosing interval after steady State#	Reference
Echinocandins				
Anidulafungin	1 day	24 h	24 h	[140, 141]
Caspofungin	4–7 days	8–11 h	24 h	[142–144]
Micafungin	4–5 days	13–20 h	24 h	[145, 146]
Azoles				
Fluconazole	5–10 days (without loading dose)	30 h	24 h	[147]
Isavuconazole	4–7 days (with loading dose); 10–14 days (without loading dose)	80–120 h	24 h	[46, 148–153]
Itraconazole	7–14 days	30 h	12 h	[154–156]
Posaconazole	3–7 days	27 h 35 h	6–8 h (oral suspension) 24 h (tablet, iv formulation)	[157–161]
Voriconazole	1 day i.v. with loading dose; 5 days p.o. or i.v. without loading dose	6 h	12 h	[127, 162, 163]
Polyenes				
Amphotericin B, deoxycholate	4 days	24 h	24 h	[164, 165]
Amphotericin B, liposomal	4–7 days	6–24 h	≥24 h	[166–168]

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Medical Mycology, 2019, 57, S127–S137
doi: 10.1093/mmy/myy091
Review Article

Review Article

Breakthrough invasive fungal diseases in acute myeloid leukemia patients receiving mould active triazole primary prophylaxis after intensive chemotherapy: An Italian consensus agreement on definitions and management

Corrado Girmenia[1,*], Alessandro Busca[2], Anna Candoni[3], Simone Cesaro[4], Mario Luppi[5], Anna Maria Nosari[6], Livio Pagano[7], Giuseppe Rossi[8], Adriano Venditti[9] and Franco Aversa[10]

- **Breakthrough**: profilaksi başladıktan **7 gün sonra**
- **Vorikonazol** alıyorsa **LAmB** (mukor riski nedeni ile)
- **Posakonazol** alıyorsa ilaç düzeyi bakılması ya da **LAmB**

Senaryo 2: Triazol altında tedavi başarısızlığı (refrakter invaziv aspergilloz)

- **Tedavi başlandıktan en az kaç gün sonra tedavi başarısızlığı kabul edilecek: 8 gün**
  - **8 günde yeterli antifungal konsantrasyonu ve etkinliği** gelişmiş olacaktır
  - **>8 gün sonra artan GM antijeni** (öncesinde artması değil)
  - **>14 gün sonra çekilen CT** de lezyonlarda büyüme (öncesinde değil, ya da nötropeniden çıkarken değil)
- **Serum düzeyi yeterli ise: Lipozomal AmB**
- **Değil ise başka bir azole geçilmesi veya yanına ekinokandin eklenmesi düşünülebilir**

≥15	Any of the above criteria *Or* Progression of original lesions on CT (or other imaging) based on >25% growth of initial lesions in the context of no change in immune status

Senaryo 2: Triazol altında tedavi başarısızlığı (refrakter invaziv aspergilloz)

- Altta yatan hastalık oldukça agresif, kemoterapiye refrakter ya da progresyon gösteriyorsa

- Antifungal değişiminin sürvi üzerine pozitif etkisi beklenmiyor

Senaryo 3: Gösterilmiş azol direnci varsa

- Lipozomal AmB ‘ye geçilmeli

J Antimicrob Chemother 2022; **77**: 16–23
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When to change treatment of acute invasive aspergillosis: an expert viewpoint

Stable disease

Stable disease was not considered treatment failure in the real-world setting. If patients were consistently neutropenic or otherwise severely immunocompromised, then stable disease, particularly if there had been previous rapid progression, would be

Vorikonazolün Farmakokinetik Özelliklerini Etkileyen Faktörler

- CYP 2C19 genotipi
- Irk
- Yaş ve cinsiyet
- Vücut ağırlığı
- Karaciğer yetmezliği: orta – ağır yetmezlikte yükleme dozu aynı, idame dozunu %50 azalt
- Böbrek yetmezliği: kreatinin >2.5 ise İV yerine oral form tercih edilir
- İlaç etkileşimleri

Table 4 Summary of voriconazole-mediated drug–drug interactions

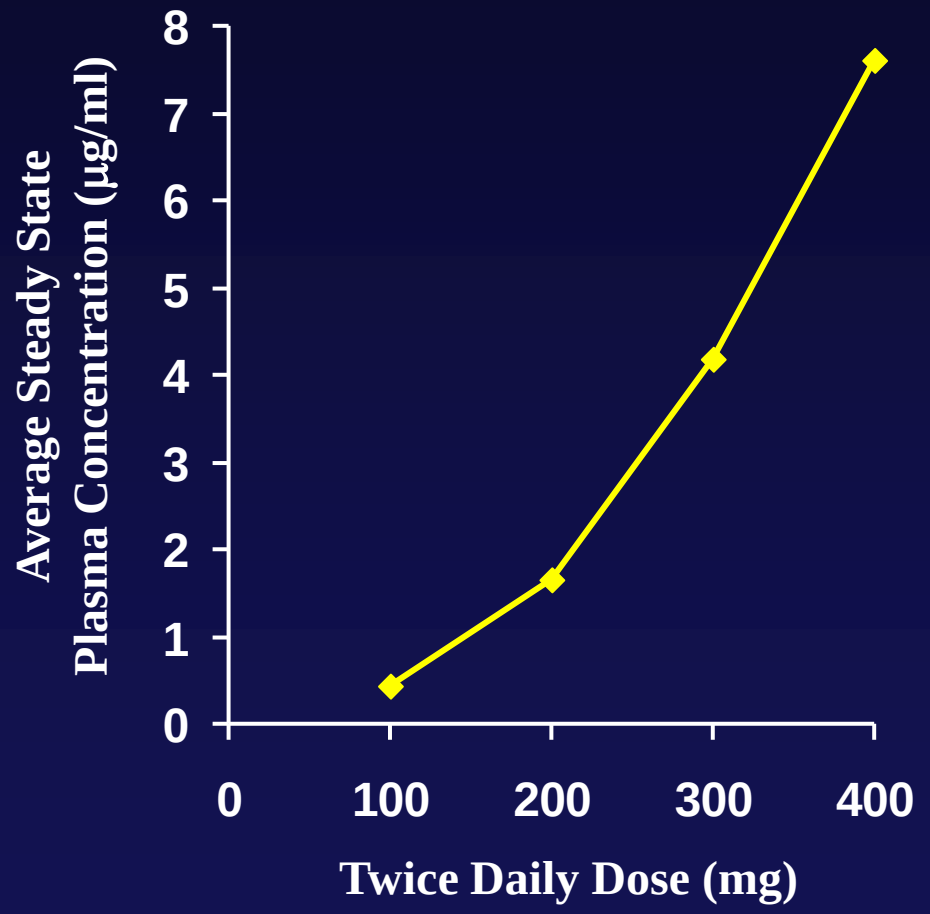
Type of interaction, drug	Recommendation
Decreases voriconazole levels	
Carbamazepine	Contraindicated
Long-acting barbiturates	Contraindicated
Rifampin	Contraindicated
Ritonavir	Avoid unless benefit outweighs risk
Levels increased by voriconazole	
Astemizole	Contraindicated
Cisapride	Contraindicated
Cyclosporine	Reduce cyclosporine dosage by half and monitor cyclosporine levels
Ergot alkaloids	Contraindicated
Omeprazole	Reduce dosage by half
Quinidine	Contraindicated
Sirolimus	Contraindicated Reduce sirolimus dose by 90% and monitor sirolimus levels
Tacrolimus	Reduce tacrolimus dosage by two-thirds and monitor tacrolimus levels

Venetoklaks

Midostaurin

Voriconazole
Non-lineer Farmakokinetik

- Doz artımına göre serum düzeyi daha yüksek oranda artar
- Oral dozu 1.7 kat arttırdığınızda kan düzeyi yaklaşık 2.4 kat artıyor



Vorikonazol Serum Düzeyi Bakılamıyorsa oral tedavi dozunun ayarlanması

- Genelde oral tedavi dozu **2 x 200** mg öneriliyor, ancak
- **Oral tedavide kilo bazlı** tedavi verilebilir
  - Uygun tablet dozuna yuvarlanır
- Ya da **tedavi yanıtı yoksa 2 x 300 mg** verilebilir
  - Günlük total 600 mg aşılmamalıdır
- **Doz tolere edilemiyorsa 50 mg dozlarla düşürülür** (200 mg ‘a kadar)
- **< 40 kilo olanlarda %50 doz azaltılır,**

Bellmann R, Infection, 2017

Voriconazole

Contents

- Obesity:
  - Use **Ideal BW**. Check trough concentrations (underdosing is common with Voriconazole).
  - Dosing using actual body weight may result in supratherapeutic concentrations, but published data are insufficient to recommend adjusted BW vs. ideal BW. Best approach for now is to use ideal BW and check serum concentrations. Refs: Antimicrob Agents Chemother 55:2601, 2011; Clin Infect Dis 53:745, 2011; Clin Infect Dis 63:286, 2016.
  - For further information, see Dosing Adjustments in Obesity.
- ECMO:

BMI ≥30 kg/m^2:

Weight-based dosing: **IV, Oral:** Initial: Use **adjusted body weight** to calculate dose based on indication. Adjust dose based on serum trough concentration to ensure efficacy and avoid toxicity (Koselke 2012; Park 2012; expert opinion).

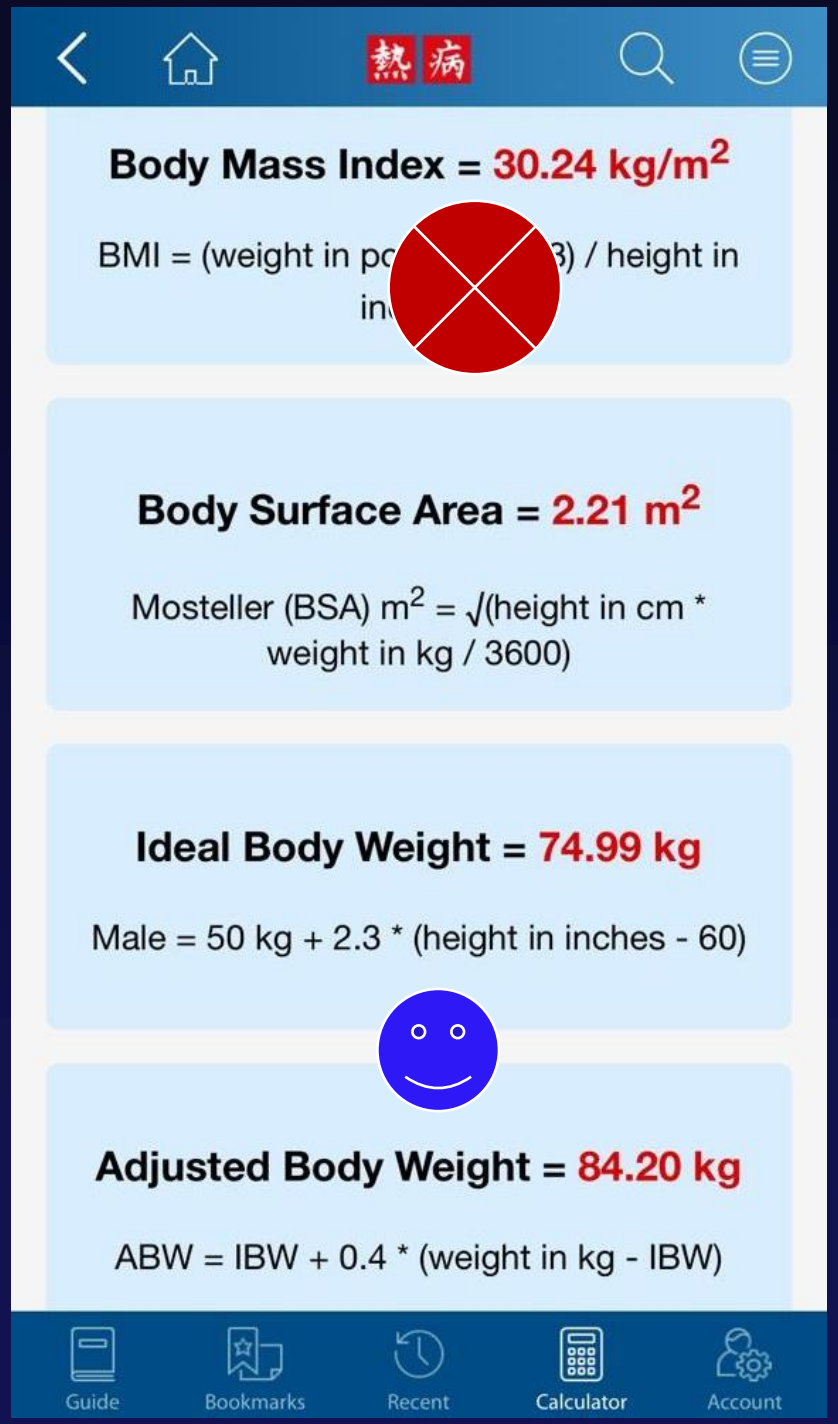
Adjusted body weight = [0.4 × (actual body weight – ideal body weight) + ideal body weight].

Fixed (non-weight-based) dosing: **Oral, IV:** Initial: Use standard doses based on indication (200 to 300 mg every 12 hours); no dosage adjustment necessary for patients who are obese (expert opinion). Adjust dose based on serum trough concentration to ensure efficacy and avoid toxicity (Koselke 2012; Park 2012).

Uptodate - Lexicomp

Kilo: **98** kg
Boy: **180** cm

Vori
6
2
4
2x4



Kilo: **80** kg
Boy: **180** cm

Body Mass Index = 24.69 kg/m^2

BMI = (weight in pounds * 703) / height in inches^2

Body Surface Area = 2.00 m^2

Mosteller (BSA) m^2 = √(height in cm * weight in kg / 3600)

Ideal Body Weight = 74.99 kg

Male = 50 kg + 2.3 * (height in inches - 60)

Adjusted Body Weight = 77.00 kg

ABW = IBW + 0.4 * (weight in kg - IBW)

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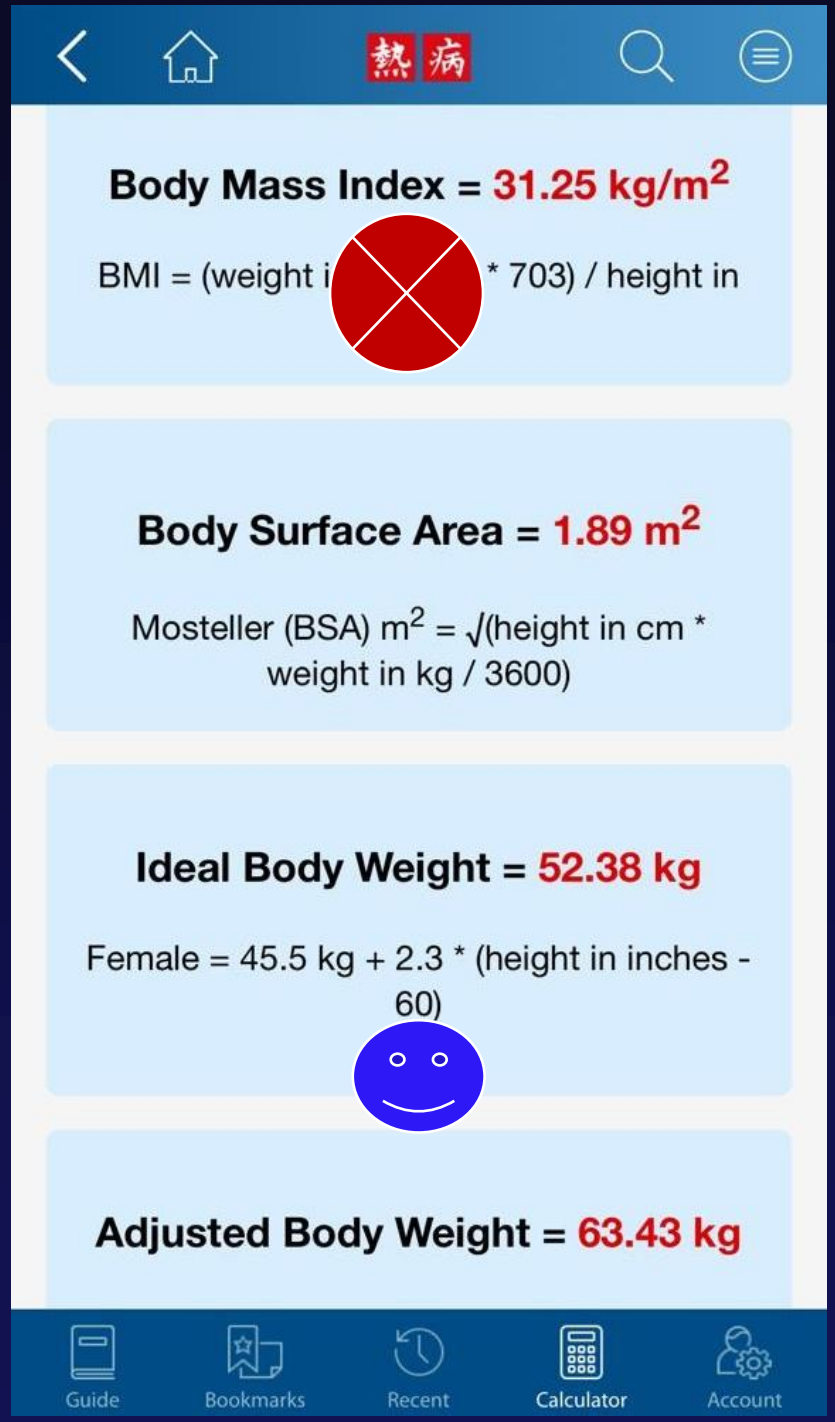
Kilo: **80** kg
Boy: **160** cm



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