

# ACLF'da Medikal Tedavinin Yeri

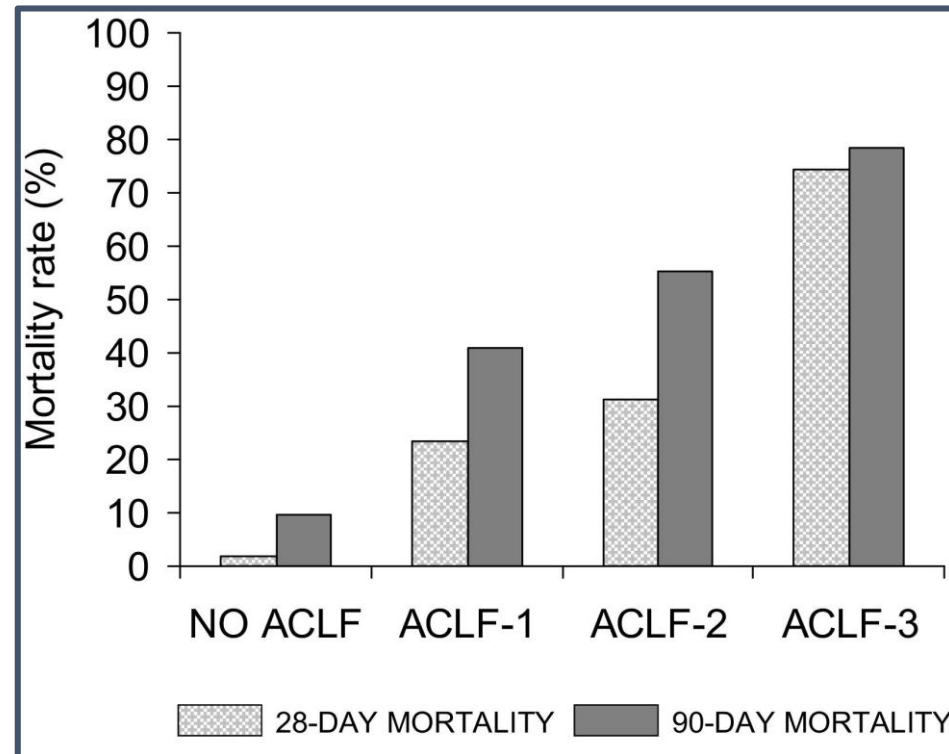
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Gupse Adalı

SBÜ İstanbul Ümraniye Eğitim ve Araştırma Hastanesi

# ACLF Mortalite

CANONIC Study, n= 415 ACLF, 28 günlük mortalite % 32.8, 90 günlük mortalite % 51.2

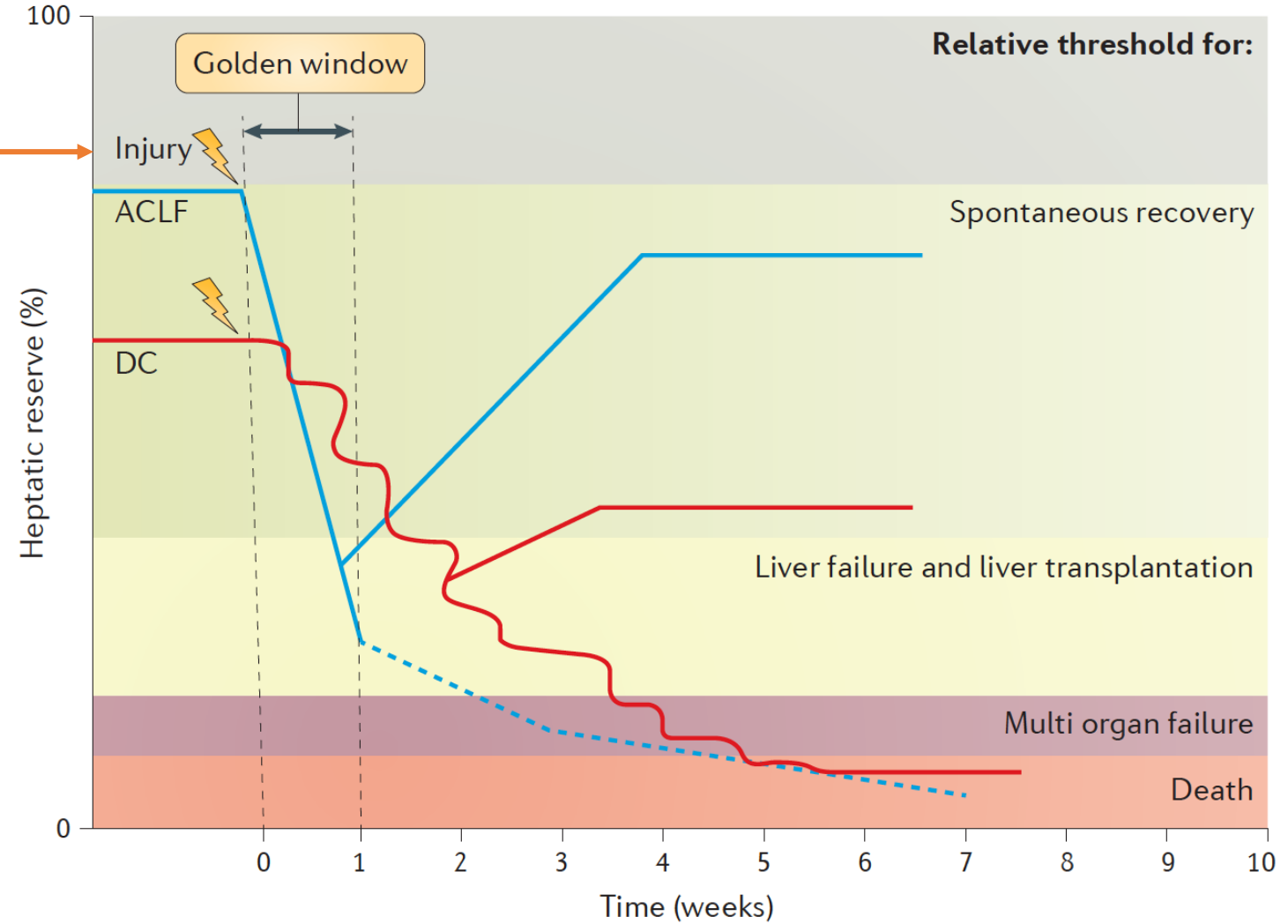


EASL-CLIF, European Association for the Study of the Liver-chronic liver failure

# ACLF'da tedavi zamanı ?

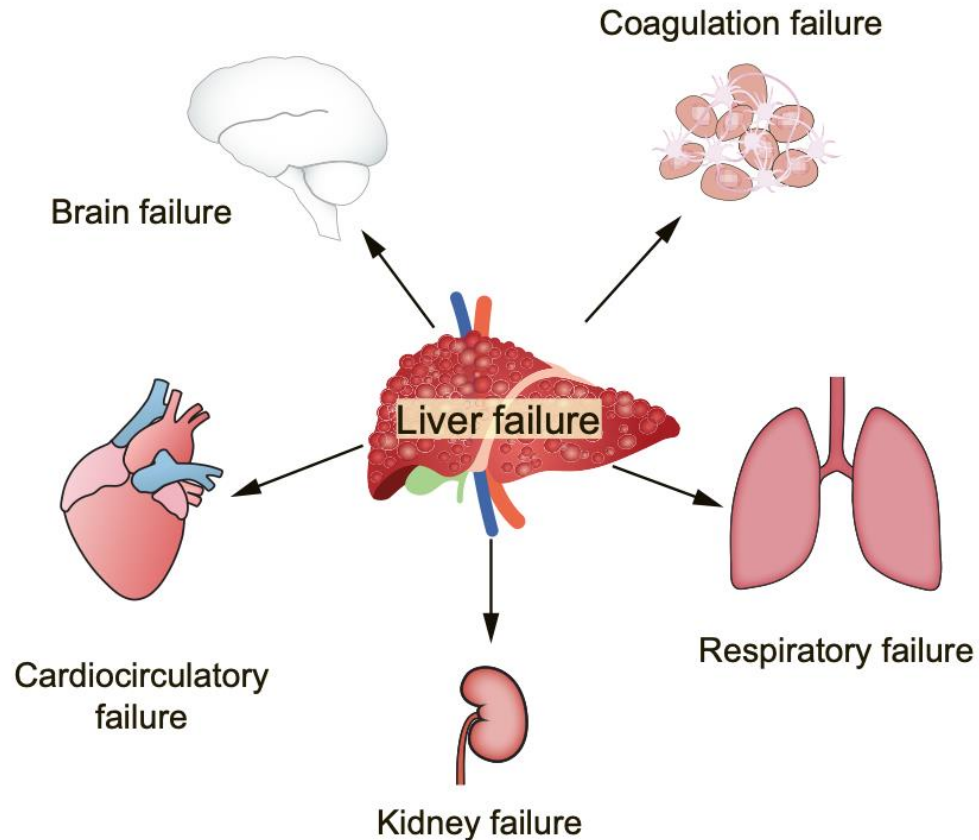
## Presipitan faktörler:

- ✓ Etanol
- ✓ HBV reaktivasyonu
- ✓ Viral hepatitler
- ✓ Otoimmün hepatit
- ✓ DILI
- ✓ Wilson alevlenmesi
- ✓ Cerrahi
- ✓ Enfeksiyonlar
- ✓ Bilinmeyen



# ACLF'da medikal tedavinin ana bileşenleri

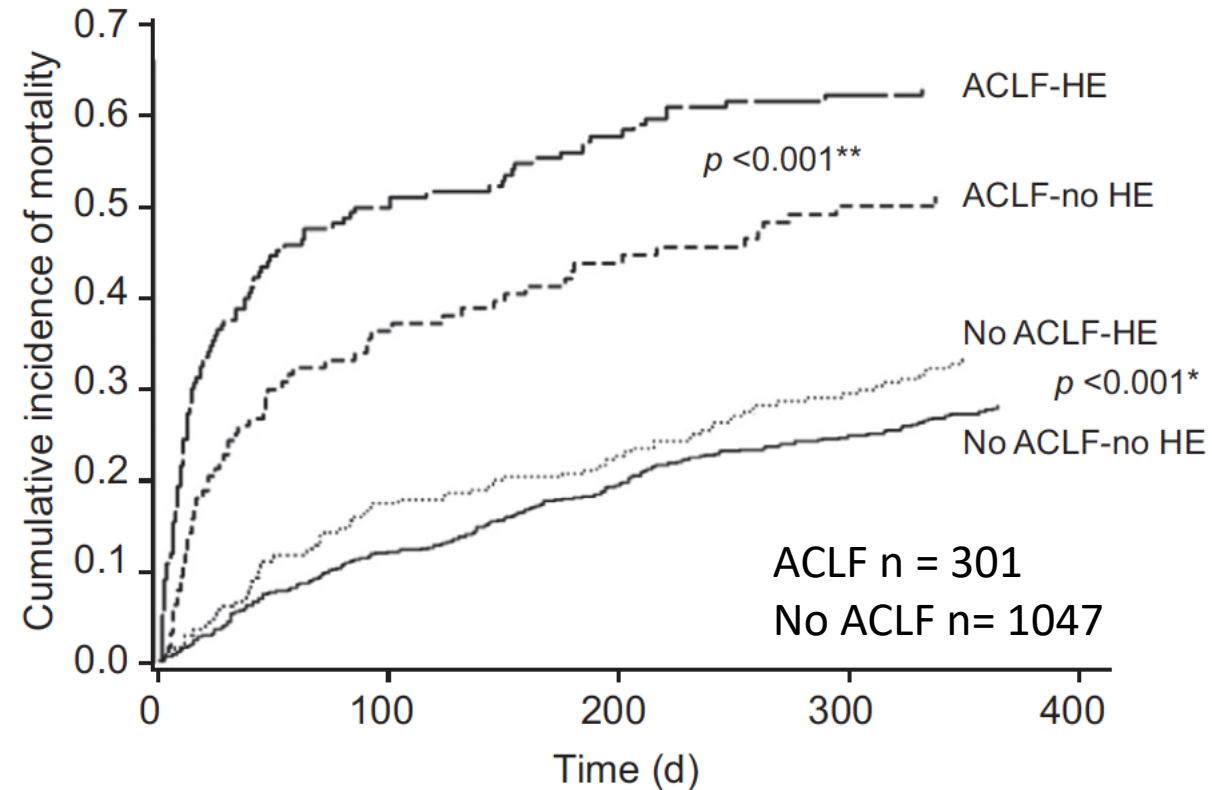
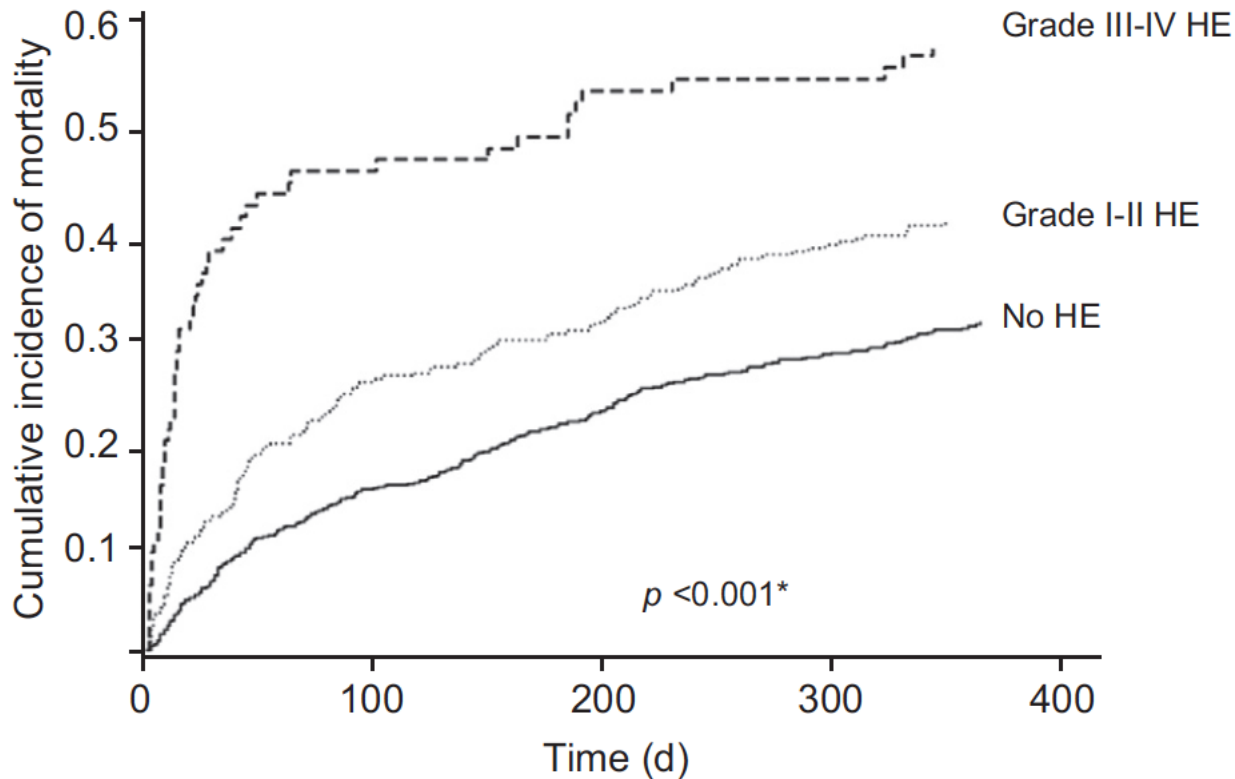
Acute-on-chronic liver failure



- ✓ Multidisipliner organ yetmezlikleri tedavisi
- ✓ Yakın İzlem – YBÜ
- ✓ Presipitan faktör tedavisi
- ✓ Enfeksiyon / Sepsis tedavisi
- ✓ Diğer destek tedaviler - Liver-assist devices ?

# ACLF'de organ yetmezliklerine yaklaşım – Beyin – Grade III/IV HE

HE Grade 3 / 4 → Sedasyon, kısa etkili → Dexmedetomidine = Precedex  
Presipitan faktör ve enfeksiyon tedavisi, laktuloz, rifaximin, NH<sub>3</sub> ↓



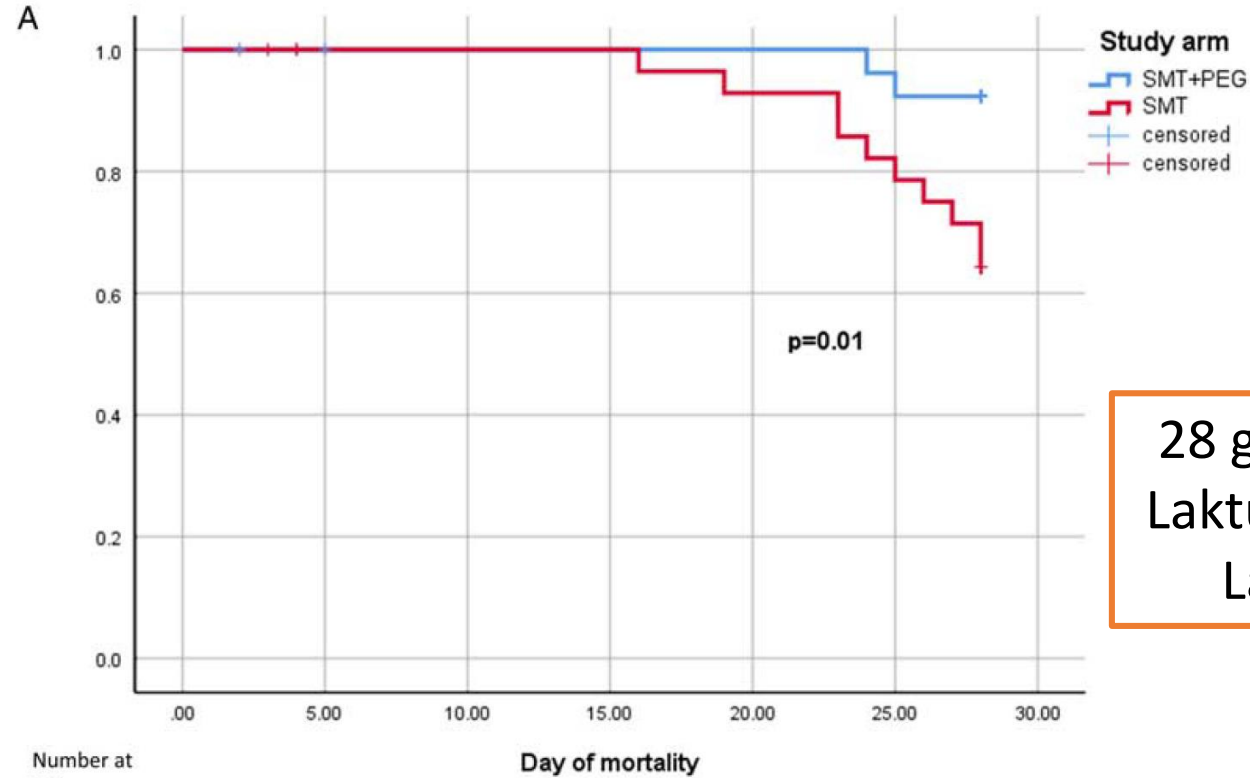
Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. *Am J Gastroenterol*. 2022.

Sarin SK, Choudhury A, Sharma MK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL). *Hepatol Int*. 2019.

Cordoba J et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). *J Hepatol*. 2014.

# ACLF'da HE - Laktuloz

ACLF ve HE grade  $\geq 2$  olan hastalar: 29 hasta Laktuloz + PEG vs 31 Laktuloz  
HE skorunda gerileme % 62 vs % 32, HE rezolüsyonu süresi 4.5 gün vs 9 gün



28 günlük sağkalım  
Laktuloz + PEG % 93  
Laktuloz % 67

# ACLF'da HE – Profilaktik Rifaximin

TABLE 3 Non-infectious liver complications developed during follow-up and deaths in the rifaximin and control groups

Patient number	ACLF at admission	ACLF resolution	Non-infectious liver complications developed during follow-up	Number of complications	Death
Rifaximin group					
1	No		No	0	Yes
6	No		Gastrointestinal bleeding. <b>ACLF 2</b> (Liver and cerebral).	3	Yes
12	ACLF 2 (Liver and coagulation)	no	Progressed to ACLF 3a for renal failure. Mild HE	2	No
13	No		Ascites	1	No
14	No		No	0	Yes
15	ACLF 1 (Liver failure)	Yes	Ascites	1	No
18	No		Ascites. Acute kidney injury	2	No
Control group					
1	ACLF 2 (Liver and renal)	No	Ascites. Mild HE	2	No (OLT)
2	No		<b>ACLF 2</b> (Liver and coagulation). Gastrointestinal bleeding	3	Yes
3	No		Mild HE. <b>ACLF 2</b> (Liver and kidney)	3	Yes
4	No		Gastrointestinal bleeding (massive). Acute kidney injury	2	Yes
5	ACLF 2 (Liver and coagulation)	No	Progressed to ACLF 3b for cerebral and renal failure)	2	Yes
6	No		Gastrointestinal bleeding. Mild HE. <b>ACLF 1</b> (Liver failure)	3	Yes
8	ACLF 2 (Liver and renal)	Yes	No	0	Yes
9	No		Ascites. <b>ACLF 3</b> (Renal, respiratory and cerebral)	4	Yes
10	No		Severe HE	1	No
16	No		<b>ACLF 2</b> (Liver and respiratory)	2	Yes
17	No		<b>ACLF 3a</b> (Liver, respiratory and cerebral)	3	Yes
18	No		Mild HE. Ascites	2	No
20	No		<b>ACLF 1</b> (renal)	1	No
21	ACLF 1 (liver)	No	Progressed to ACLF 2 for renal failure	1	No (OLT)
27	No		Ascites	1	No
30	ACLF 1 (liver)	Yes	Severe HE	1	No
32	No		Severe HE	1	No
33	No		Mild HE. Gastrointestinal bleeding. Ascites	3	No
36	ACLF 2 (Liver and renal)	No	Ascites. Mild HE. Gastrointestinal bleeding	3	Yes
37	No		<b>ACLF 2</b> (Liver and renal failure)	2	Yes
38	No		Ascites. <b>ACLF 3a</b> (Liver, Renal and cerebral)	4	Yes
39	No		Ascites	1	No
40	No		Ascites. Gastrointestinal bleeding. <b>ACLF 3b</b> (Liver, renal, respiratory and circulatory)	6	Yes
41	No		Mild HE. Ascites	2	No

Abbreviations: ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy; OLT, orthotopic liver transplantation.

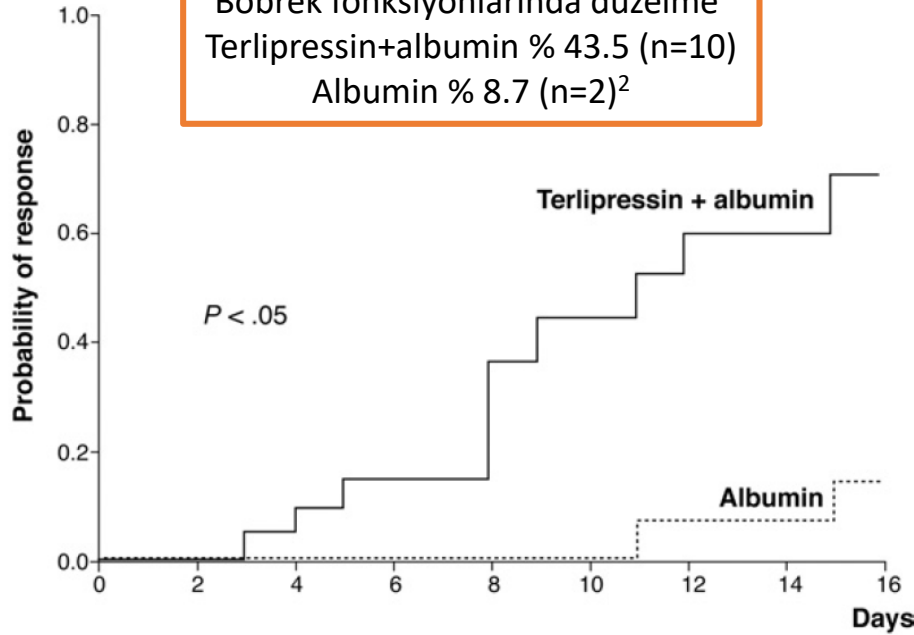
Ağır alkolik hepatit  
RFX n=41 vs Kontrol n= 42  
RFX 1200 mg/gün- 90 gün

RFX grubunda n=1 ACLF  
Kontrol grubunda n=10 ACLF

# ACLF'da böbrek yetmezliği - Albumin

Albumin tek başına HRS-Akut böbrek hasarı tedavisinde efektif değil  
Vazokonstrüktör tedaviler (Terlipressin, Noradrenalin) ile beraber öneriliyor (albumin -  
volüm arttırıcı ve antiinflamatuvar etkili)<sup>1</sup>

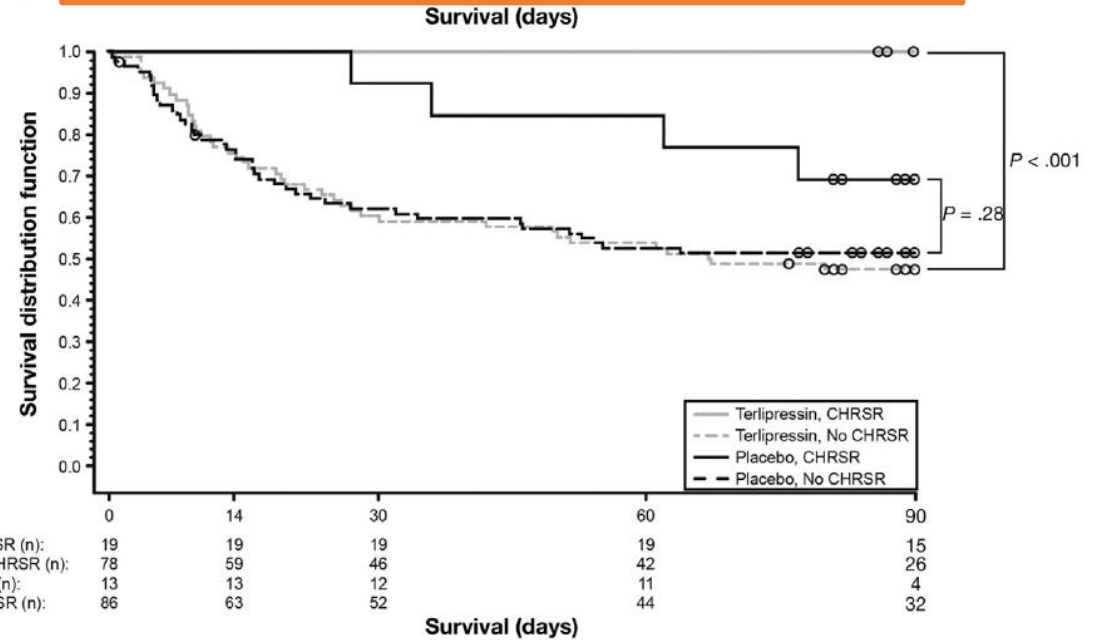
Böbrek fonksiyonlarında düzelme  
Terlipressin+albumin % 43.5 (n=10)  
Albumin % 8.7 (n=2)<sup>2</sup>



Patients at risk:

—	23	22	19	17	14	12	12	11	10
-----	23	21	18	18	17	16	16	15	15

90 günlük sağkalım  
Terlipressin+albumin ile HRS'de düzelme olanlarda %100  
Albumin ile HRS'de düzelme olanlarda % 69.2<sup>3</sup>



Terlipressin, CHRSR (n):	19	19	19	19	15
Terlipressin, No CHRSR (n):	78	59	46	42	26
Placebo, CHRSR (n):	13	13	12	11	4
Placebo, No CHRSR (n):	86	63	52	44	32

<sup>1</sup>Bajaj JS et al. Acute-on-Chronic Liver Failure Clinical Guidelines. *Am J Gastroenterol*. 2022.

<sup>2</sup>Martín-Llahí M et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology*. 2008.

<sup>3</sup>Boyer TD et al. Terlipressin Plus Albumin Is More Effective Than Albumin Alone in Improving Renal Function in Patients With Cirrhosis and Hepatorenal Syndrome Type 1. *Gastroenterology*.2016.



# ACLF'da böbrek yetmezliği - Vazokonstrüktörler

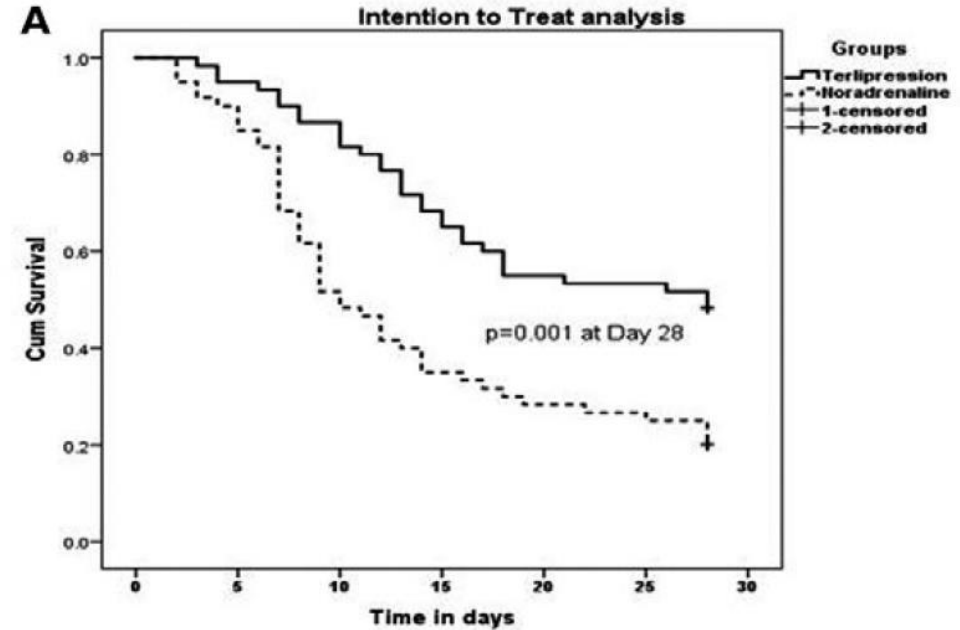
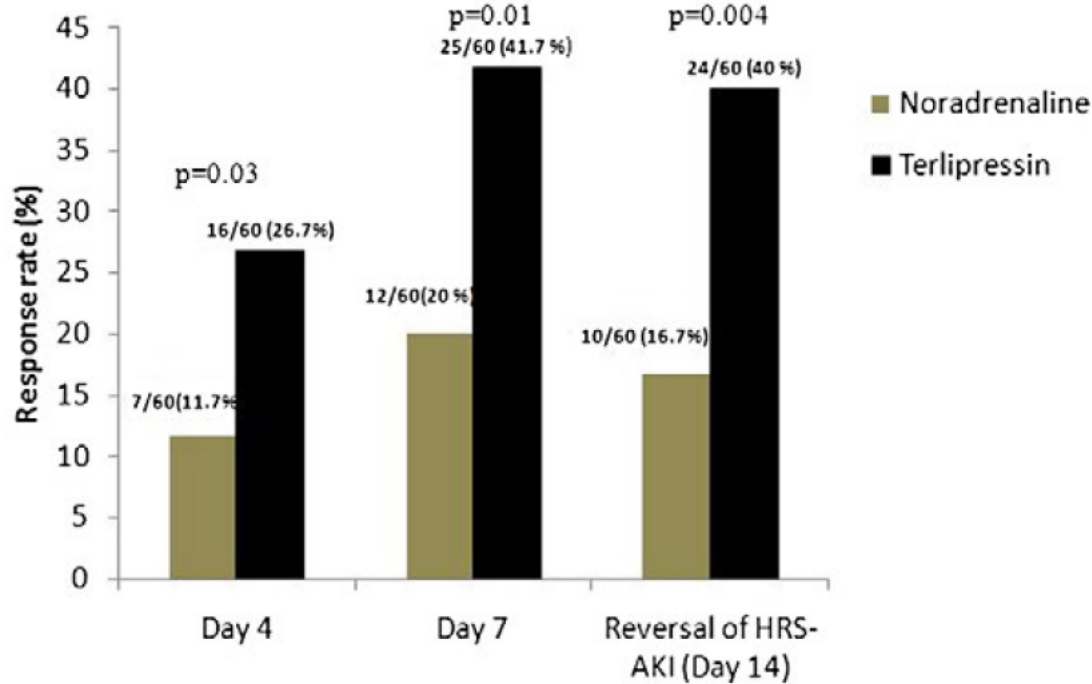
Terlipressin  
ACLF'da Te

**Vazokonstrüktör tedaviler Stage 2 ve 3 AKI'de öneriliyor**  
Stage 2: sCr  $\geq$  2.0–3.0 kat  $\uparrow$  bazale göre  
Stage 3: sCr  $\geq$  3.0 kat  $\uparrow$  bazale göre VEYA sCr 4.0 mg/dL +0.3mg/dL  
akut artış VEYA RRT başlanması

da daha etkili  
ak gerekli<sup>1,2</sup>

HRS-AKI düzeme:  
Terlipressin vs Noradrenalin  
Daha erken ve yüksek oranlarda

28 günlük sağkalım:  
Terlipressin %48.3 vs Noradrenalin %20



<sup>1</sup>Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. *Am J Gastroenterol*. 2022.

<sup>2</sup>Sarin SK, Choudhury A, Sharma MK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL). *Hepatol Int*. 2019.

<sup>3</sup>Arora V et al. Terlipressin Is Superior to Noradrenaline in the Management of Acute Kidney Injury in Acute on Chronic Liver Failure. *Hepatology*. 2020.

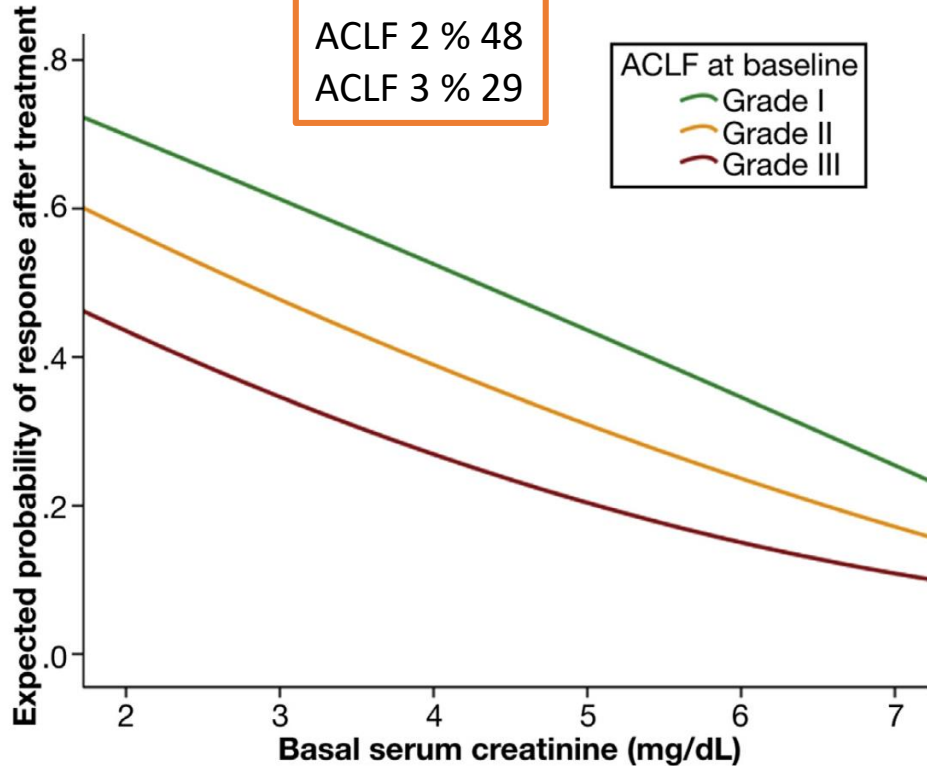
# ACLF'da böbrek yetmezliği - Terlipressin

HRS-AKI'de Terlipressin ile yanıt oranı ~ % 44

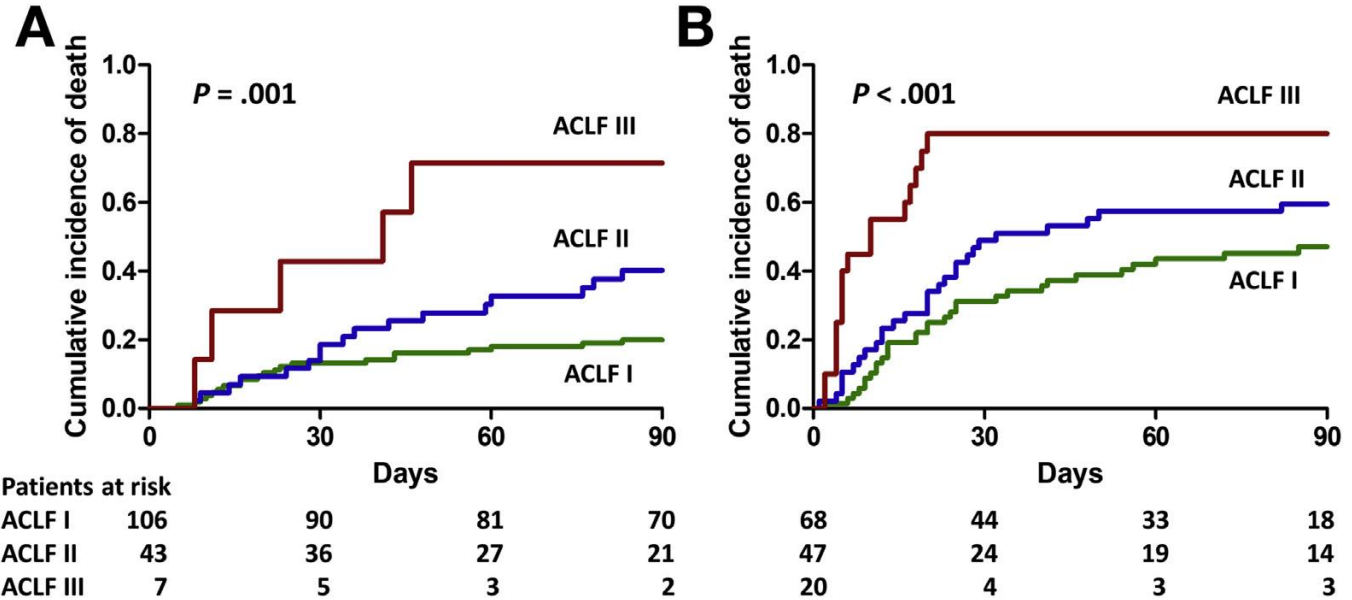
Cevap oranı ACLF evresi arttıkça azalıyor

ACLF 3 hastalarda Terlipressin kullanırken solunum yetmezliği açısından dikkatli olunmalı

ACLF 1 % 60  
ACLF 2 % 48  
ACLF 3 % 29



Terlipressin cevaplı hastalarda 90 günlük mortalite:  
ACLF 1 ve ACLF 2'da azalıyor  
ACLF 3'da Terlipressin cevaplı vs cevapsız fark yok

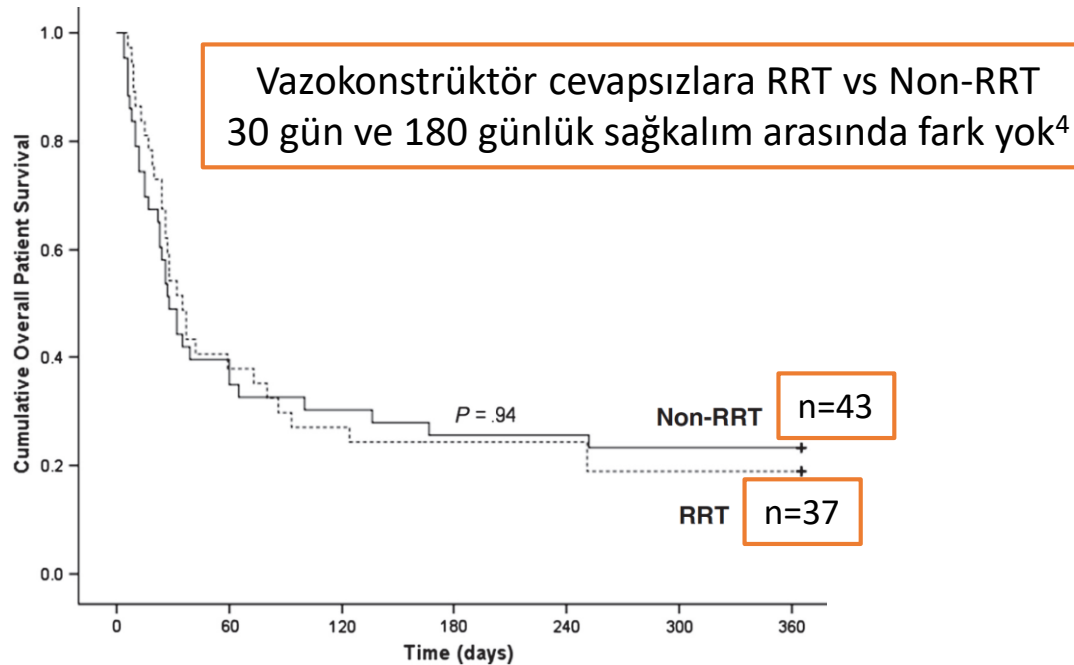


Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. *Am J Gastroenterol*. 2022.

Piano S et al. Association Between Grade of Acute on Chronic Liver Failure and Response to Terlipressin and Albumin in Patients With Hepatorenal Syndrome. *Clin Gastroenterol Hepatol*. 2018.

# ACLF'da böbrek yetmezliği -Renal replasman tedavisi (RRT)

RRT sadece vazokonstrüktör tedaviye cevapsız veya ciddi volüm yüklenmesi, hiper K, hipo Na, metabolik asidoz varsa  
LT adayı ise köprü olarak ve Continuous Renal Replacement Therapy (CRRT) tercih edilerek planlanmalı<sup>1,2,3</sup>



Summary of the effects of RRT status and baseline characteristics on HRS patient survival by univariate and multivariate analyses

	Multivariate analysis		
	OR	95% CI	P
Overall patient survival—30 d			
RRT unadjusted	0.811	0.336-1.957	.642
RRT adjusted for all confounders	1.203 <sup>a</sup>	0.409-3.542 <sup>a</sup>	.737 <sup>a</sup>
Overall survival—180 d			
RRT unadjusted	0.830	0.304-2.266	.717
RRT adjusted for all confounders	0.487 <sup>a</sup>	0.122-1.951 <sup>a</sup>	.310 <sup>a</sup>
Survival in patients not transplanted—30 d			
RRT unadjusted	1.058	0.372-3.011	.916
RRT adjusted for all confounders	1.408 <sup>a</sup>	0.355-5.590 <sup>a</sup>	.627 <sup>a</sup>
Survival in patients not transplanted—180 d			
RRT unadjusted	0.646	0.109-3.826	.603
RRT adjusted for all confounders	0.328 <sup>a</sup>	0.015-7.112 <sup>a</sup>	.477 <sup>a</sup>

<sup>1</sup>Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal syndrome. *Nat Rev Dis Primers*. 2018.

<sup>1</sup>Sarin SK, Choudhury A, Sharma MK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL). *Hepatol Int*. 2019.

<sup>3</sup>Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. *Am J Gastroenterol*. 2022.

<sup>4</sup>Zhang Z, Maddukuri G, Jaipaul N, Cai CX. Role of renal replacement therapy in patients with type 1 hepatorenal syndrome receiving combination treatment of vasoconstrictor plus albumin. *J Crit Care*.

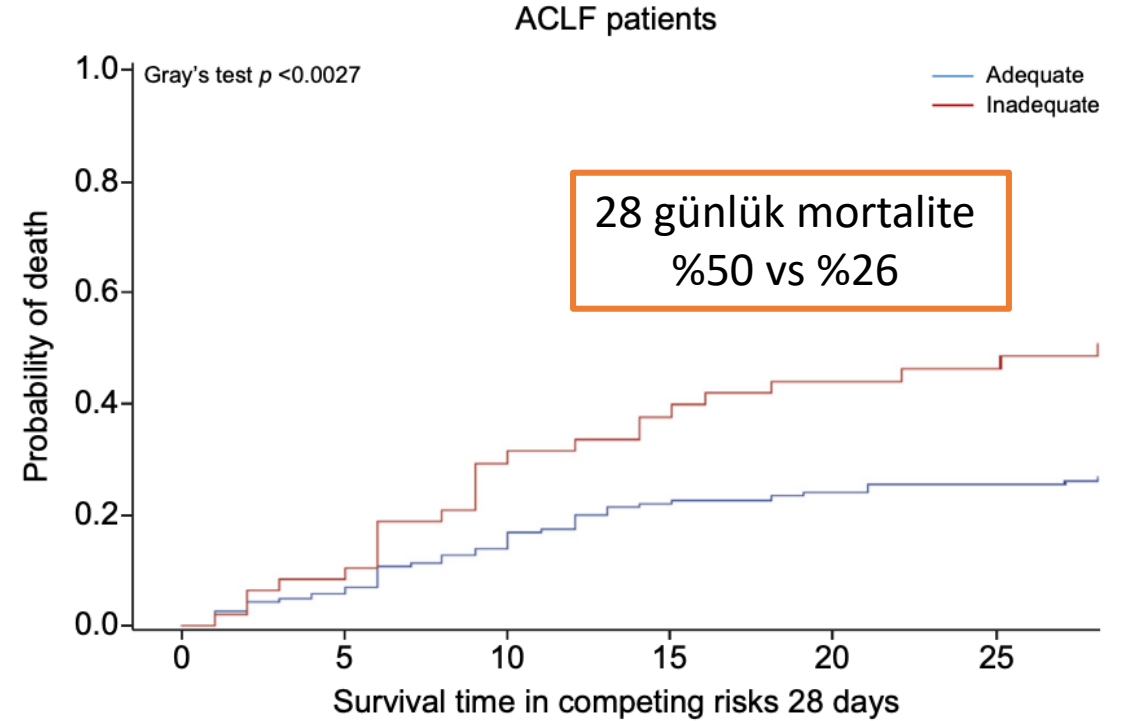
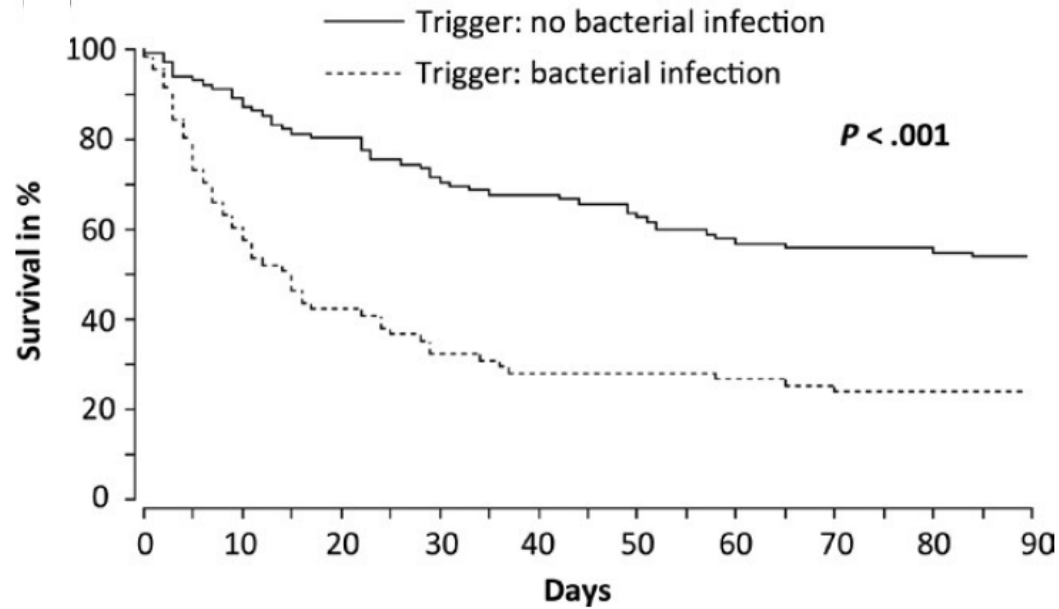
# ACLF'da bakteriyel enfeksiyon tedavisi

Enfeksiyon varlığı ACLF'da kötü prognostik faktör  
Ampirik antibiyoterapi seçimi: Klasik 1.basamak antibiyotik rejimi yerine MDR kapsayan geniş spektrumlu rejim ACLF'da kısa süreli mortaliteyi azaltıyor

ACLF bacterial inf vs no bacterial inf - sağkalım

30 gün % 72 vs % 34

90 gün % 54 vs % 25



Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. *Am J Gastroenterol*. 2022.

Mücke MM, Rumyantseva T, Mücke VT, et al. Bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality. *Liver Int*. 2018.

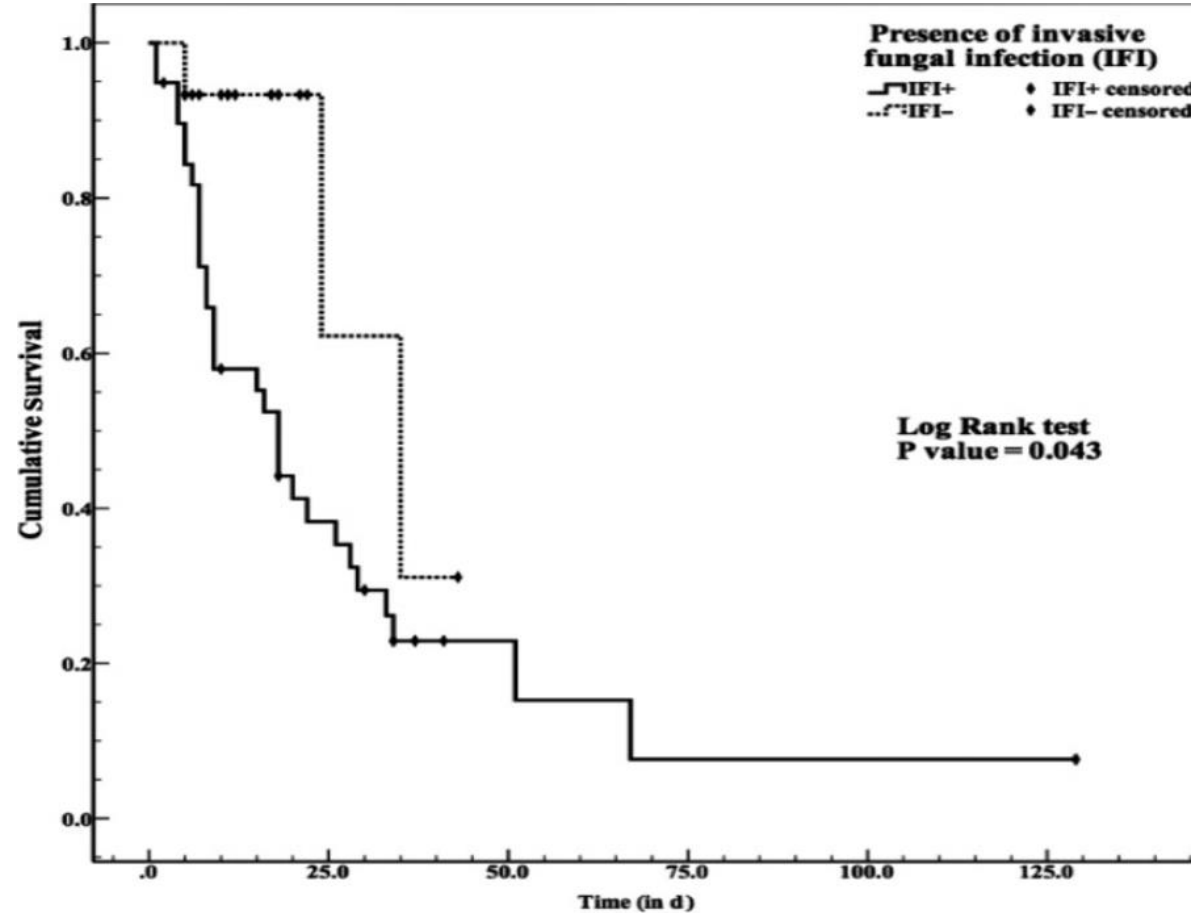
Fernández J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. *J Hepatol*. 2019

# ACLF'da invaziv fungal enfeksiyon

ACLF'da bakteriyel enfeksiyon var ve antibiyotik cevapsız ise MDR organizma veya fungal enfeksiyondan şüphelenilmeli – fungal enfeksiyon ile mortalite ↑

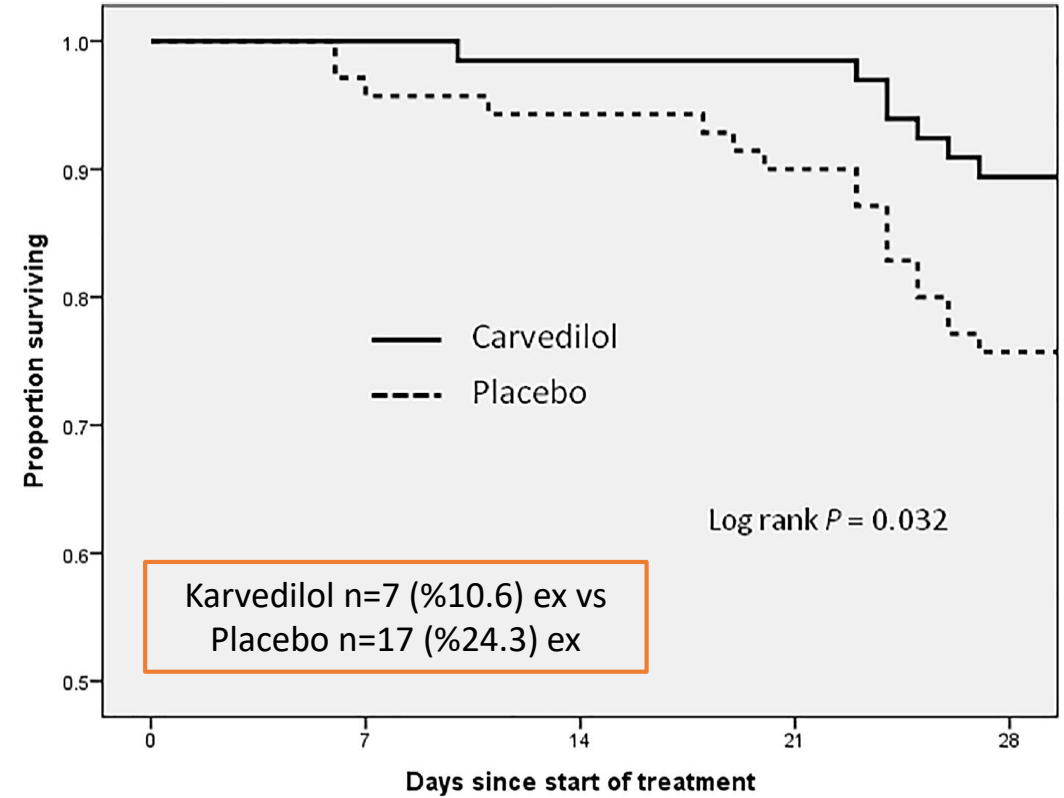
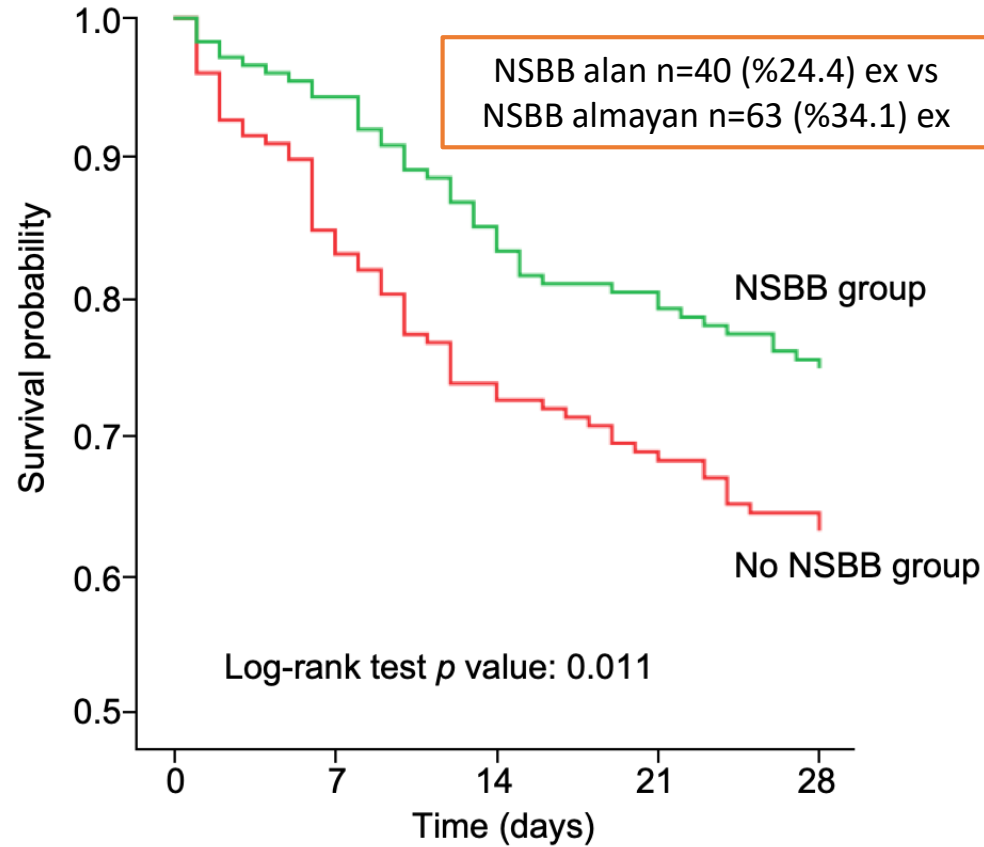
n= 264 ACLF  
IFI n= 39 (%14.7)

30 günlük sağkalım  
IFI varsa % 29 vs  
IFI yoksa % 62



# ACLF'da NSBB

Nonselektif beta-blokerler (NSBB) bakteriyel translokasyonu azaltabilir  
ACLF'da sağkalımı arttırdığını gösteren 2 çalışma var <sup>1,2</sup>  
ACLF hastaları genelde optimal dozu tolere edememekte



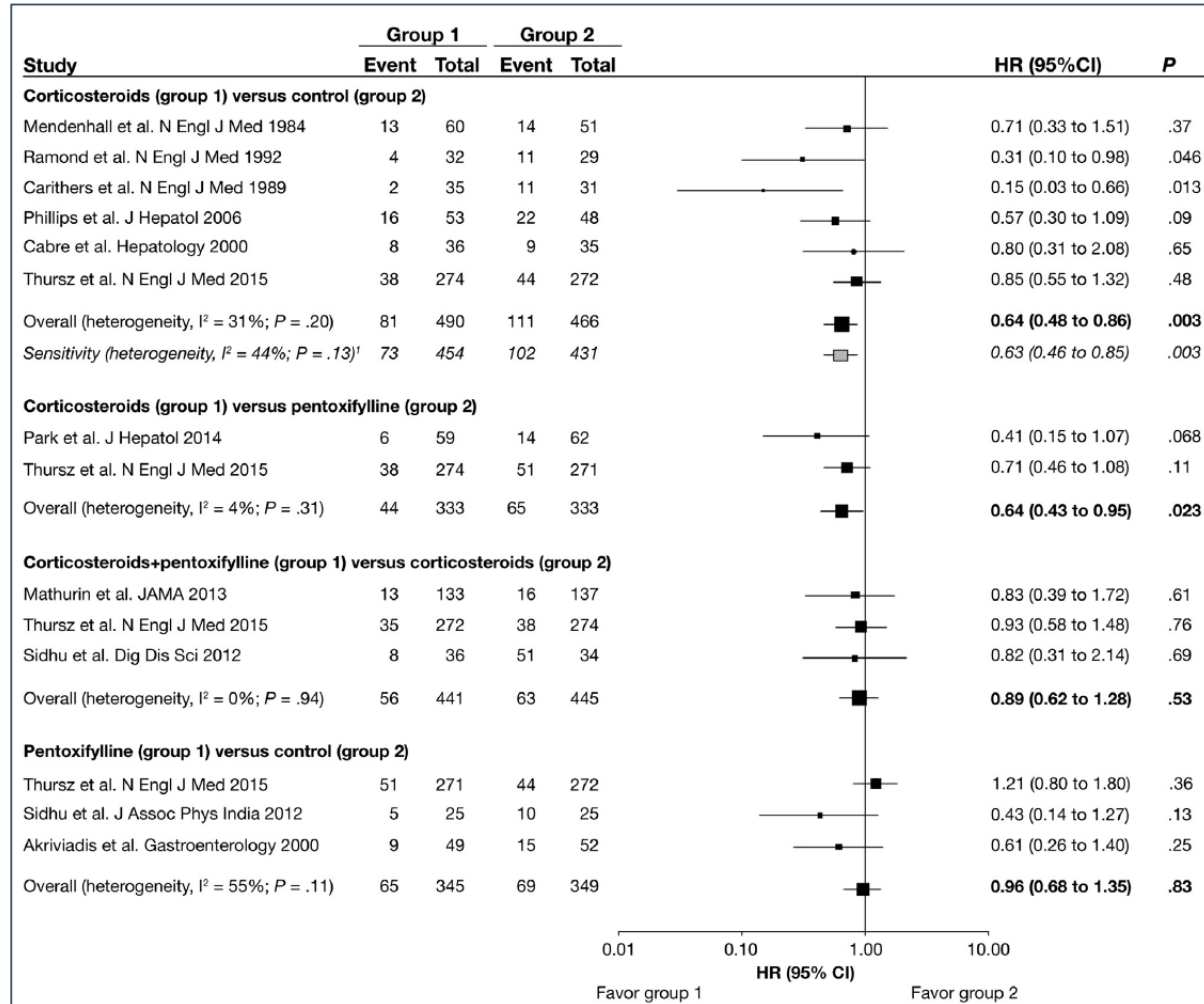
<sup>1</sup>Mookerjee RP, CANONIC Study Investigators of the EASL-CLIF Consortium. Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol.* 2016

<sup>2</sup>Kumar M et al. Treatment with carvedilol improves survival of patients with acute-on-chronic liver failure: a randomized controlled trial. *Hepatol Int.* 2019

# ACLF & Akut alkolik hepatit

Ağır AAH'de (Maddrey discriminant function  $\geq 32$ , MELD  $\geq 20$ ) kontrendikasyon yoksa prednisolone veya prednisone (40 mg/gün) 28 günlük mortaliteyi azaltıyor. Pentoxifilin önerilmiyor

Meta-analiz 11 çalışma  
n= 2111  
KS kullanımını 28 günlük  
mortalite riskini azaltıyor  
  
(HR 0.64;  
95% CI 0.43–0.95)



# HBV reaktivasyonuna bađlı ACLF

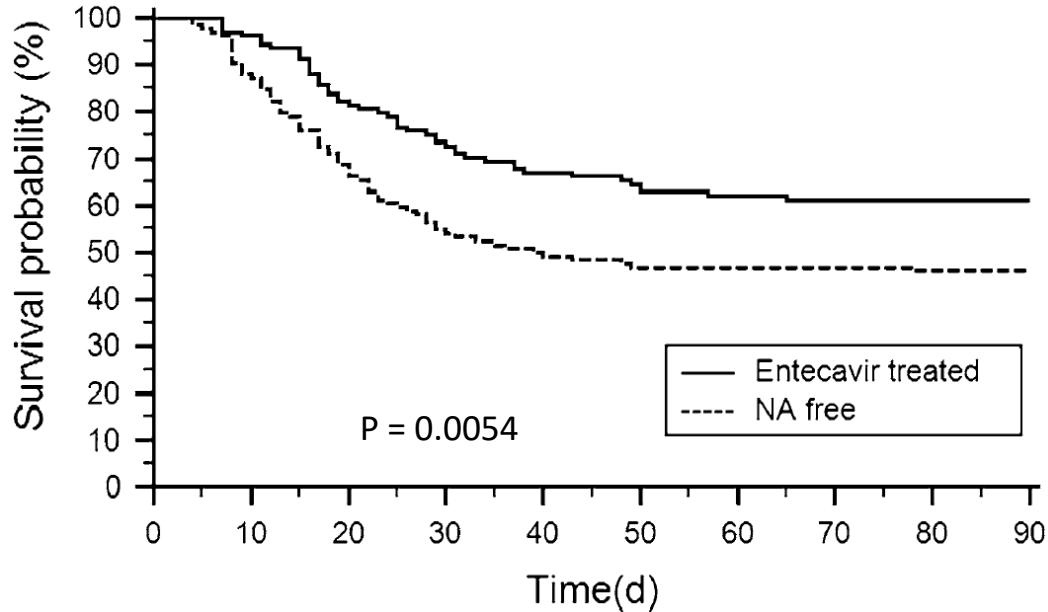
Nukleoz(t)ide analogları tanı anında HBV DNA beklenmeden hemen başlanmalı

ETV, TDF ve TAF gibi potent antiviraller kullanılmalı<sup>1</sup>

ETV vs NA almayan HBV ACLF<sup>2</sup>

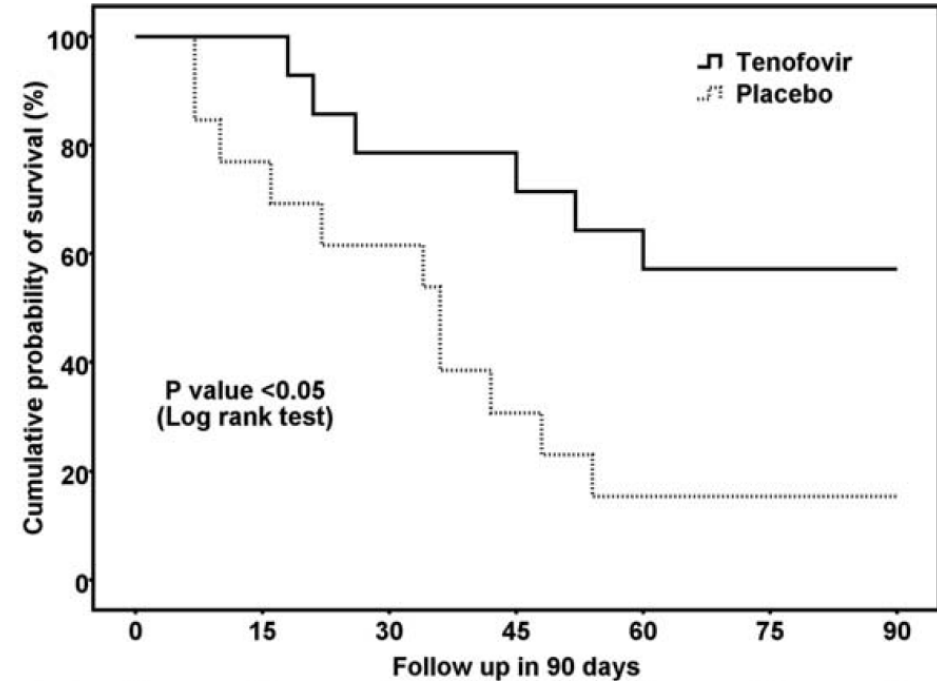
1-aylık sağkalım %73 vs %53, P= 0.002

3-aylık sağkalım %61 vs %46, P = 0.022



TDF vs NA almayan HBV ACLF<sup>3</sup>

3-aylık sağkalım %57 vs %17



<sup>1</sup>Sarin SK, Choudhury A, Sharma MK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL). *Hepatol Int.* 2019.

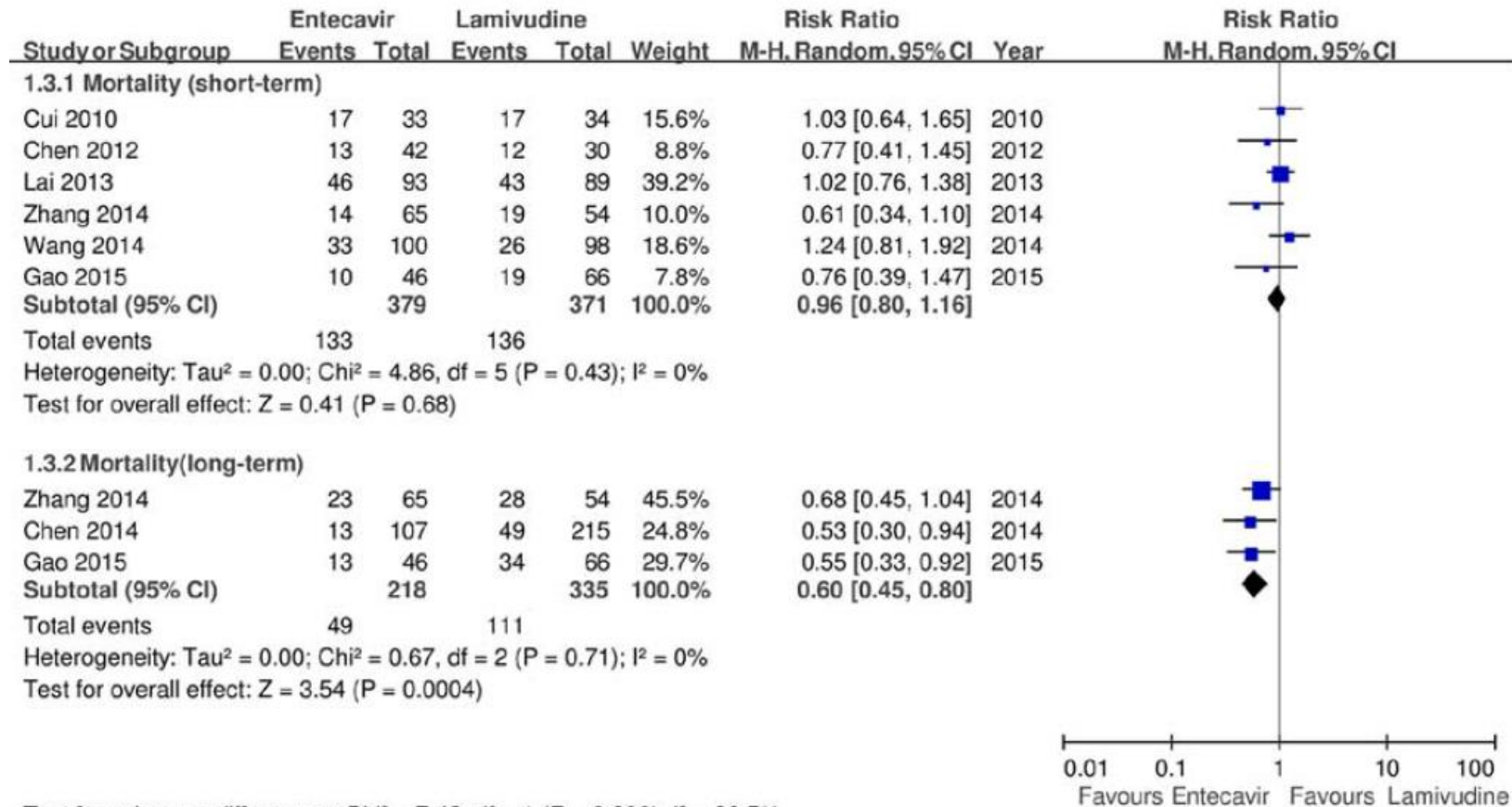
<sup>2</sup>Ma K et al. Entecavir treatment prevents disease progression in hepatitis B virus-related acute-on-chronic liver failure: establishment of a novel logistical regression model. *Hepatol Int.* 2012.

<sup>3</sup>Garg H, Sarin SK, Kumar M, et al. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology.* 2011



# HBV reaktivasyonuna bağlı ACLF

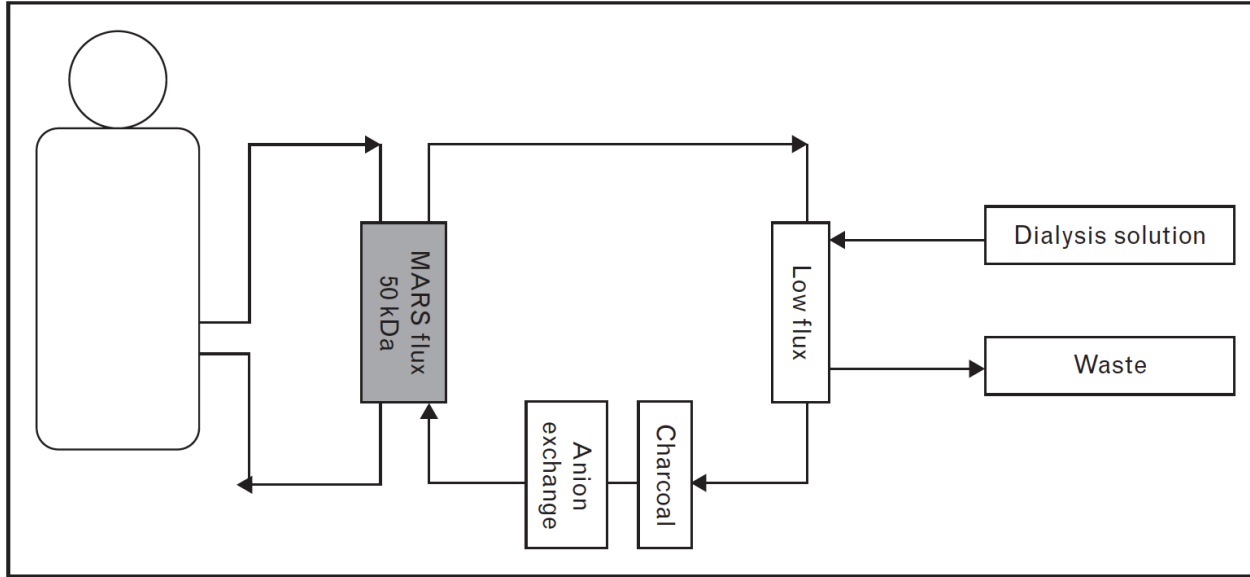
HBV ACLF'da ETV vs LAM kısa dönem (< 4 ay) mortalite oranları benzer  
ETV ile LAM'a göre uzun dönem mortalite oranları daha düşük



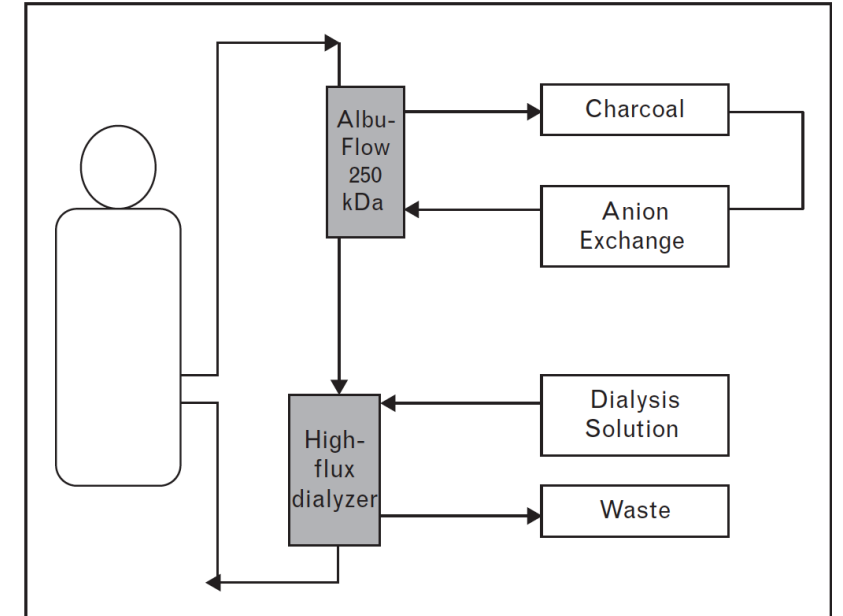
# ACLF'da karaciğer destek cihazları «Liver-assist devices»

Yapay karaciğer destek sistemlerinin (biyolojik komponenti var/yok) klinik faydası belirsiz  
Plazma değişiminin ALF'da sağkalımı arttırdığı gösterilmiş, fakat ACLF'da etkisi bilinmiyor

MARS: molecular adsorbent recirculating system

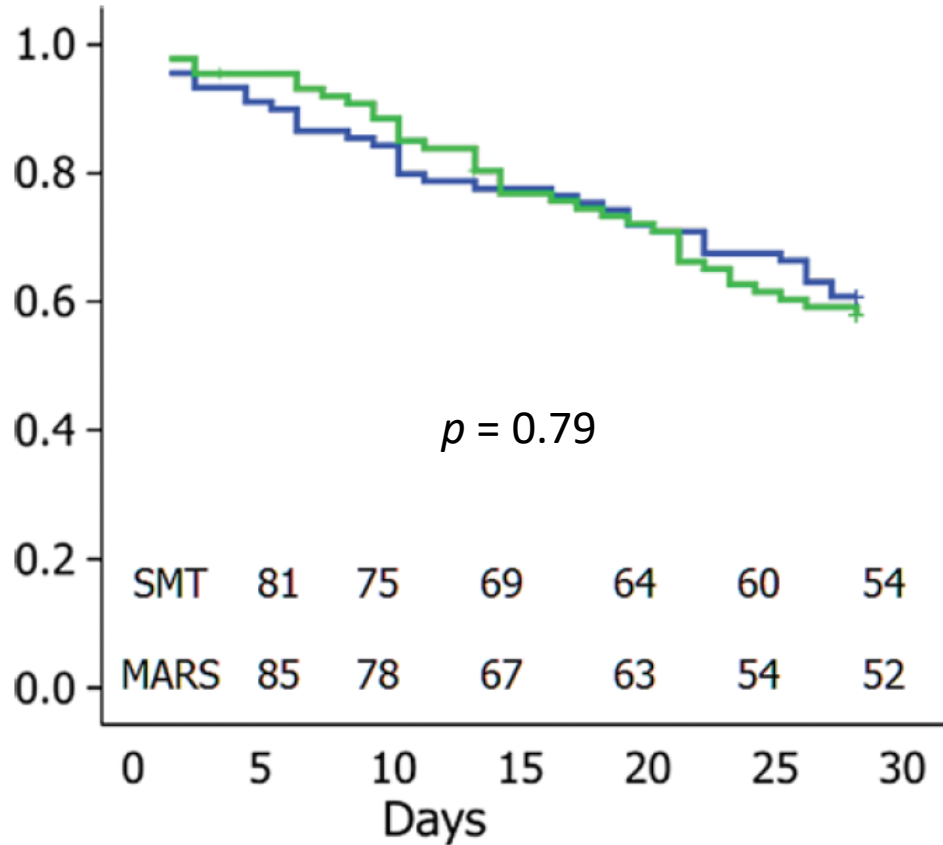


Prometheus (FPSA): fractionated plasma separation and adsorption

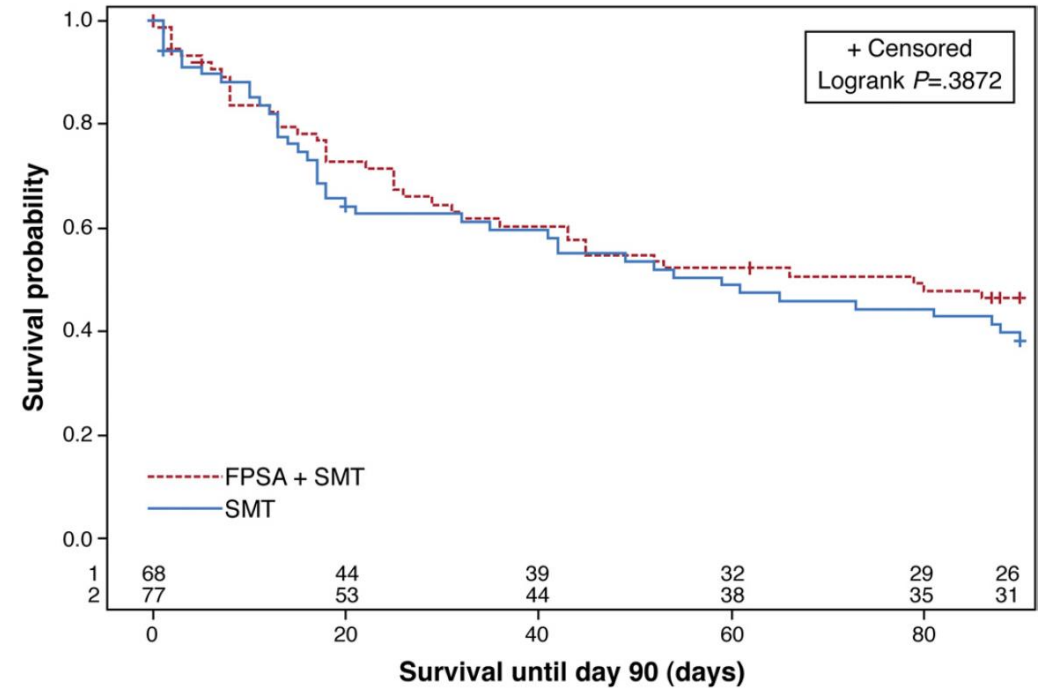


# ACLF'da karaciğer destek cihazları

MARS + Standart tedavi vs Standart tedavi  
28 günlük transplantsız sağkalım: % 60.7 vs %58.9



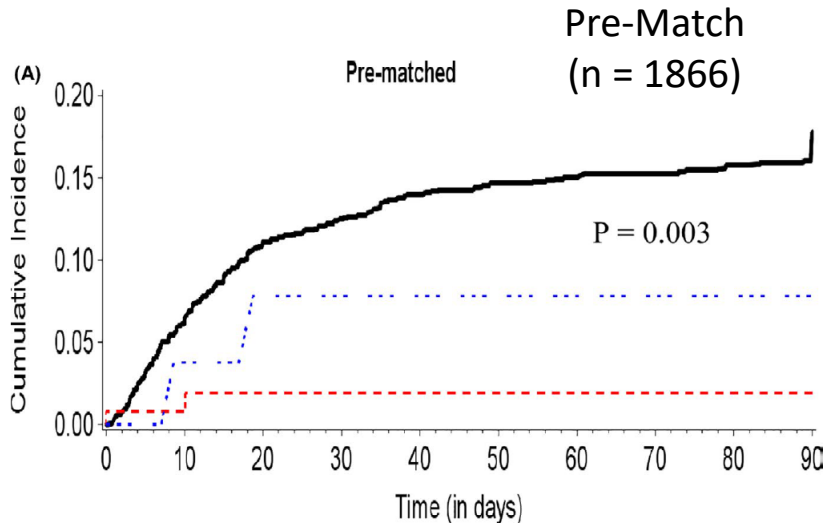
Prometheus + Standart tedavi vs Standart tedavi  
28 günlük sağkalım: % 66 vs %63  $p=0.70$   
90 günlük sağkalım %47 vs %38  $p=0.35$



# ACLF'da plazma deęişimi «plasma-exchange»

PE ile kc yetmezlięi ilişkili ölüm insidansı SMT ve Prometheus'a göre 30.gün ve 90. gün ↓  
PE, MOF gelişiminin engellenmesi ve sağkalım açısından SMT ve Prometheus'a üstün

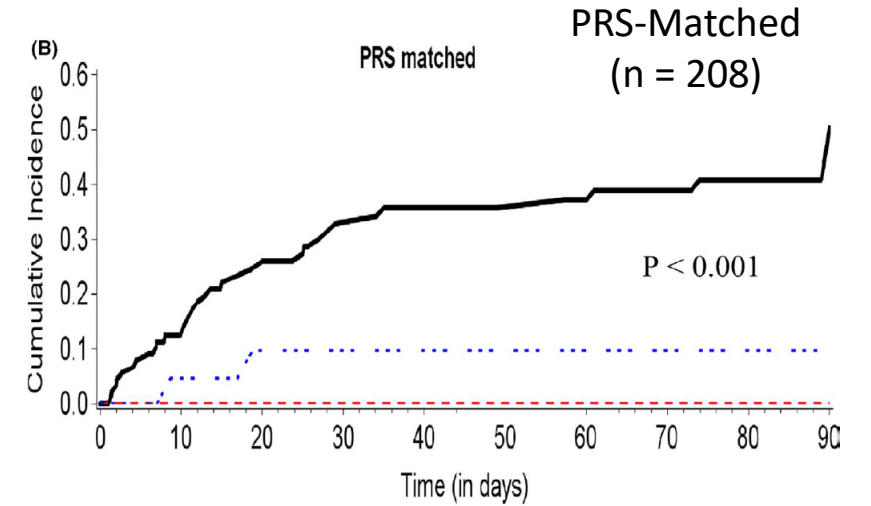
AARC (APASL ACLF Research Consortium) - Çok merkezli, çok uluslu veritabanı



– Standart medikal tedavi

••• Prometheus

--- Plazma exchange



Tüm hastalar ve propensity risk score ile eşleştirme yapılmış hastalarda  
SMT vs Prometheus vs PE tedavilerinin karaciğer ilişkili ölüm kümülatif insidansı

# ACLF'da plazma deęişimi «plasma-exchange»

HBV-ACLF n= 524 - Chinese Acute-on-chronic Liver Failure (CATCH-LIFE)

n=358 SMT vs n=166 SMT + PE

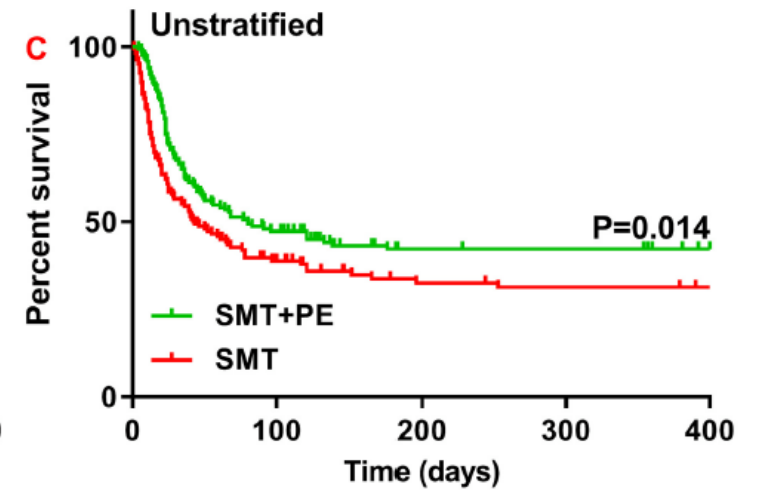
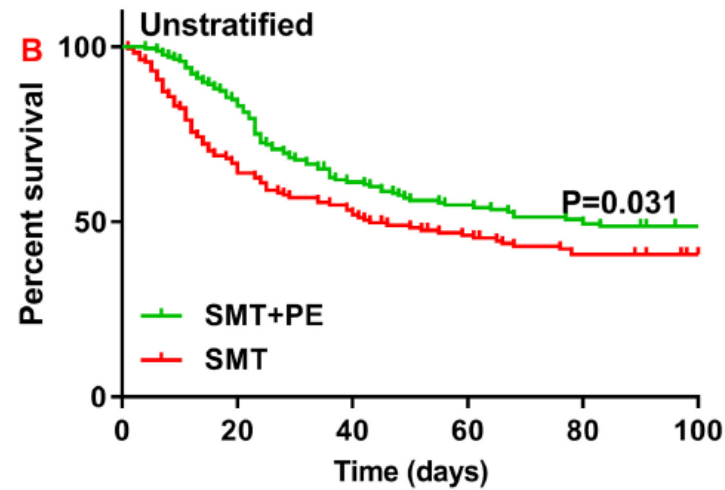
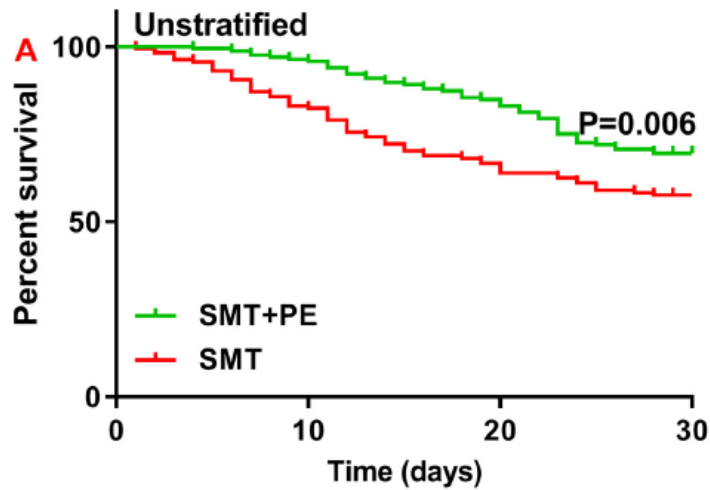
PSM → 166 SMT vs 166 SMT + PE

Saękalım PE grubunda daha yüksek

28 gn %69.5 vs.%57.6

90 gn %48.7 vs. %40.7

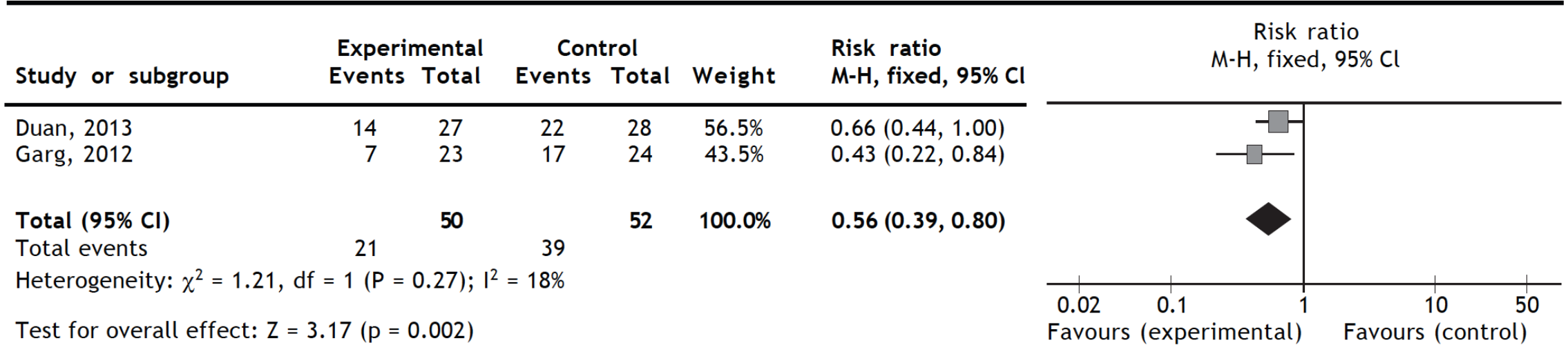
1 yıl %42.20 vs. %31.3



# ACLF'da Granulocyte colony-stimulating factor

ACLF'da G-CSF verilmesi kısa dönem mortaliteyi Asya'daki kohortlarda azaltmış, fakat Batı kohortlarında azaltmamış – rutinde kullanılması tartışmalı

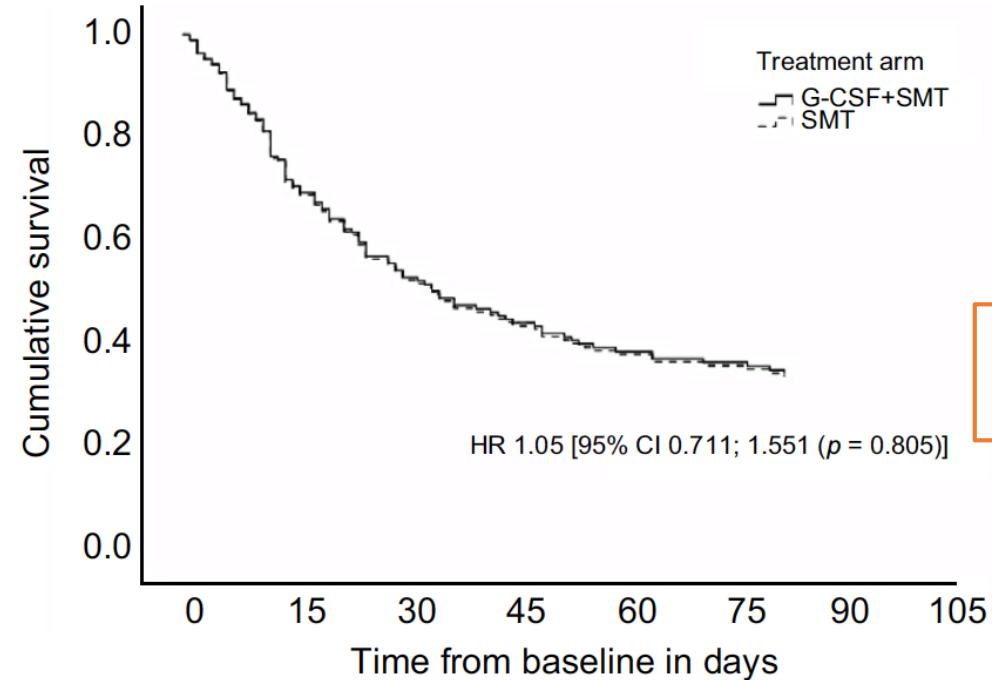
Meta-analiz, Hindistan ve Çin'den 2 çalışma  
G-CSF tüm nedenlere bağlı mortaliteyi azaltmış (RR 0.56; 95% CI 0.39, 0.80; P = 0.002)  
Yan etki: Ateş, herpes zoster reaktivasyonu, bulantı ve raş



K.i.nden CD34 + hücreleri mobilize ederek hepatik rejenerasyon → Sepsis ve MOF gelişimini engelliyor

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Çok merkezli, prospektif, kontrollü, open-label Faz 2,  
176 ACLF (EASL-CLIF criteria) randomize: G-CSF (5 µg/kg günlük -5 gün ve 3 günde bir 26.güne kadar) + SMT vs SMT  
30 gün ve 360 günlük transplant-free sağkalım, tüm sağkalım, CLIF-C OF skoru, MELD skoru, enfeksiyon gelişimi  
açısından fayda görülmemiş



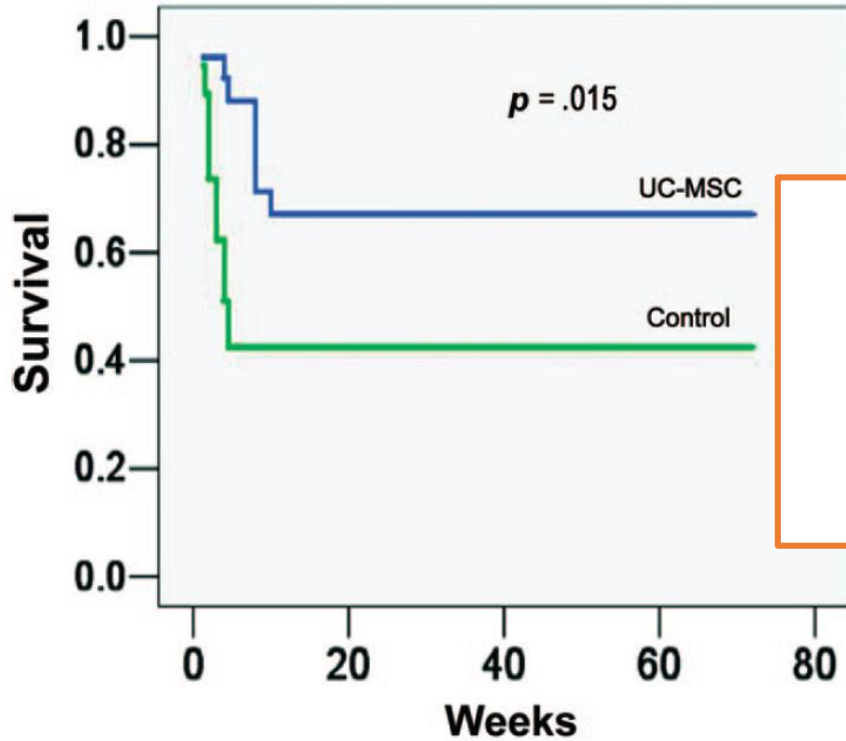
90 günlük ölüm veya LT:  
% 61.4 G-CSF+SMT vs. %58 SMT

Patients at risk	
G-CSF + SMT	88 61 42 35 29 28 27
SMT	88 54 43 35 31 28 26

# ACLF'da kök hücre tedavisi «Stem cell therapy»

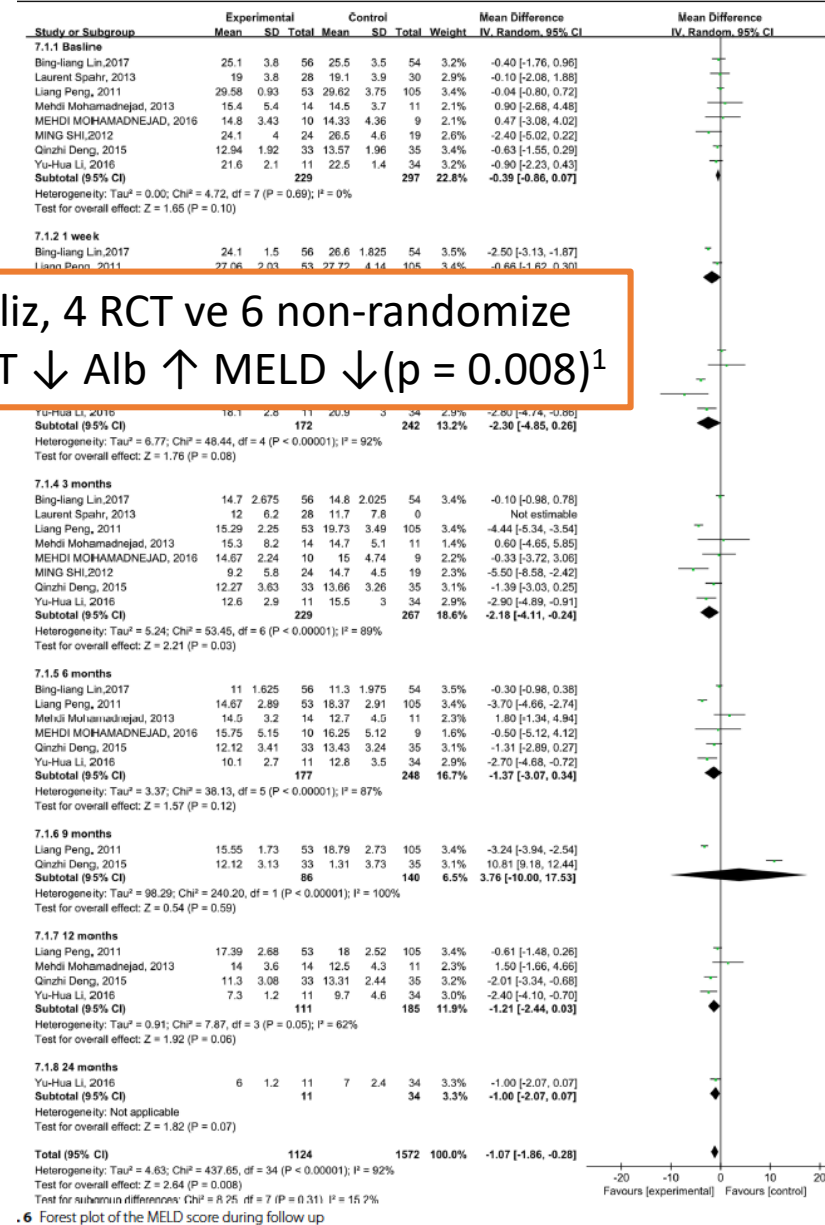
Kök hücre tedavisi yeni ve umut vaat eden – köprü tedavisi olabilir

Henüz rutin klinik kullanımı için veri az



HBV ACLF  
 n=24 umbilical cord MSC (UC-MSC)  
 n=19 kontrol  
 72 hafta - Ölüm oranı:  
 Kök hücre grubunda daha az  
 %21 vs %47%<sup>2</sup>

Meta-analiz, 4 RCT ve 6 non-randomize  
 Total bil, ALT ↓ Alb ↑ MELD ↓ (p = 0.008)<sup>1</sup>



<sup>1</sup>Xue R et al. Clinical performance of stem cell therapy in patients with acute-on-chronic liver failure: a systematic review and meta-analysis. *J Transl Med.* 2018.

<sup>2</sup>Shi M et al. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Transl Med.* 2012



Soru: ACLF'da bbrek yetmezliđi tedavisi iin en etkili ajan hangisidir ?

- A. Albumin
- B. Noradrenalin
- C. Midodrin
- D. Terlipressin

*Teşekkürler*

