KRONİK ZEMİNDE GELİŞEN AKUT KARACİĞER YETMEZLİ (ACLF) Karaciğer Nakli Zamanlaması

Prof. Dr. Ramazan İDİLMAN
Ankara Üniversitesi Tıp Fakültesi
Gastroenteroloji Bilim Dalı

“The current era of organ shortage requires using donor allograft in the most judicious way.”

Olgu Sunumu

- 54 yaşında kadın hasta
- HBV'ye bağlı kompanse siroz hastası
  - 1 ay önce ortaya çıkan sarılık, koagülopati ve ensefalopati olması
  - Öyküde: Antiviral ilacını sonlandırmış
  - FM:
    - İkter, Grade 2 ensefalopati

Laboratuvar

- AST: 658 IU/ml
- ALT: 444 IU/ml
- T. Bilirubin: 24 mg/dl
  - Direkt bilirubin: 14 mg/dl
- PTZ> 28 sn
- Trombosit: 66.000
- Albumin: 2.7 gr/dl
- Kreatinin: 1.6 mg/dl

Kronik zeminde gelişen karaciğer yetmezliği

Akut, ani başlangıçlı, heterogenous

- Sarılık
- Koagülopati
- Hepatik ensefalopati
- Karaciğer dışı organ yetmezliği
- Yüksek mortalite oranı

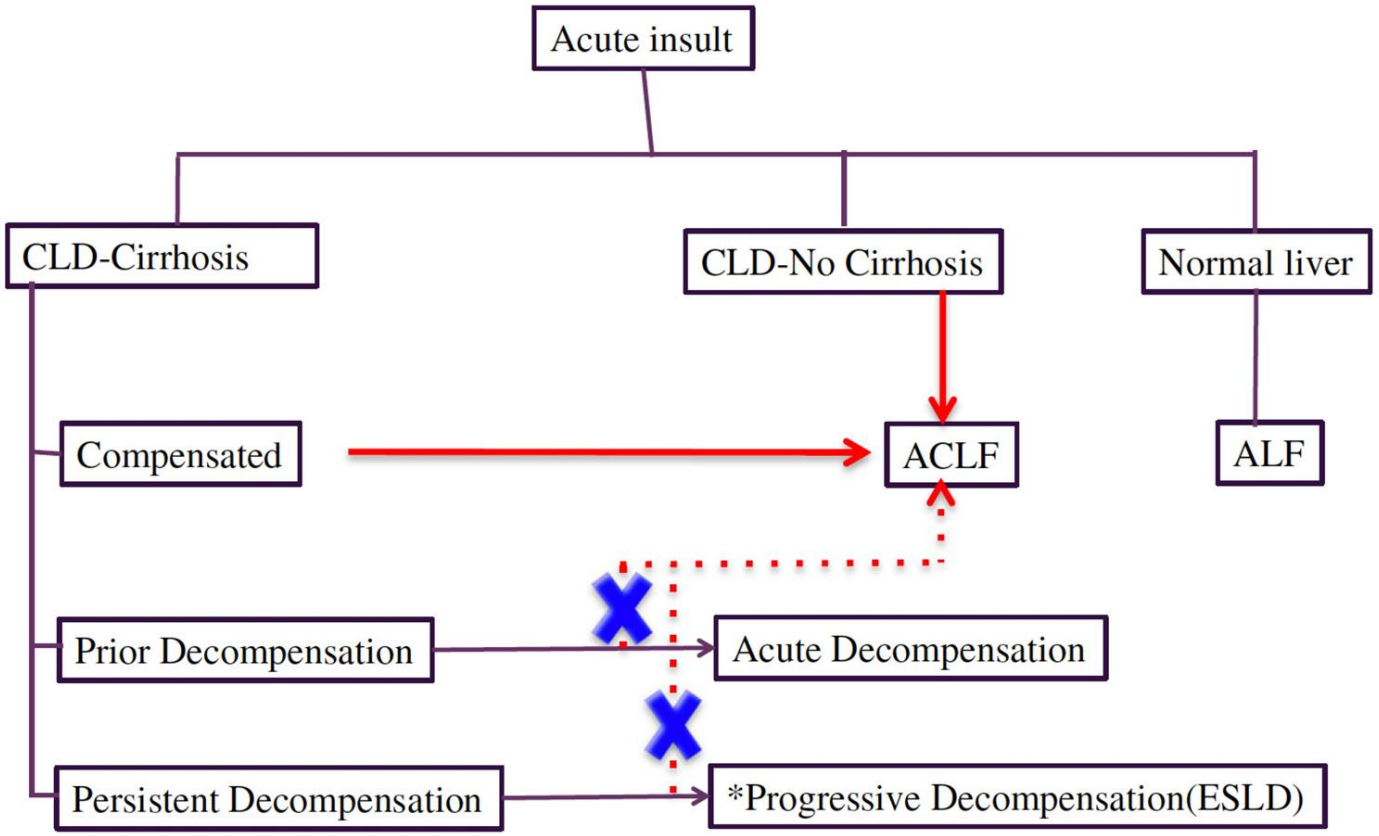
Bajaj J, et al. Am J Gastroenterol 2022
Karvellas CJ, et al. Transplantation 2021

ACLF: Tanımlama

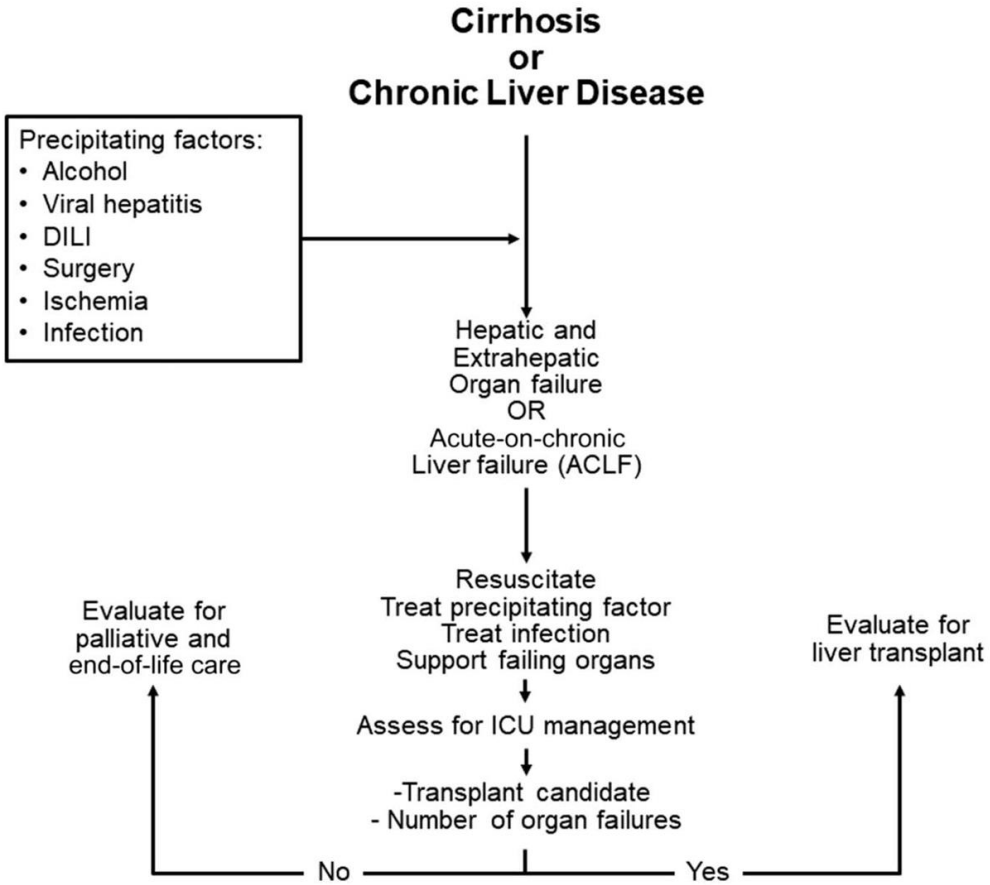
APASL	EASL CLIF	NACSELD	WGO
Kr KC Hastalığı Siroz olanlar	Siroz varlığı Akut dekompanse	Siroz varlığı Akut dekompanse	Kr KC Hastalığı Siroz olanlar
Bilirubin ≥ 5mg/dl INR ≥ 1.5 4 hafta içinde assit Ya da HE gelişimi	Hepatik ve ekstrahepatik organ yetmezliği	Ekstrahepatik organ yetmezliği	Belirtilmemiş
	No ACLF ACLF1 ACLF2 ACLF3	No ACLF ACLF1 ACLF2	Tip A Tip B Tip C
30 gün-mortalite %25	28 gün-mortalite >%15	30 gün-mortalite %49	

Karvellas CJ, et al. Transplantation 2021

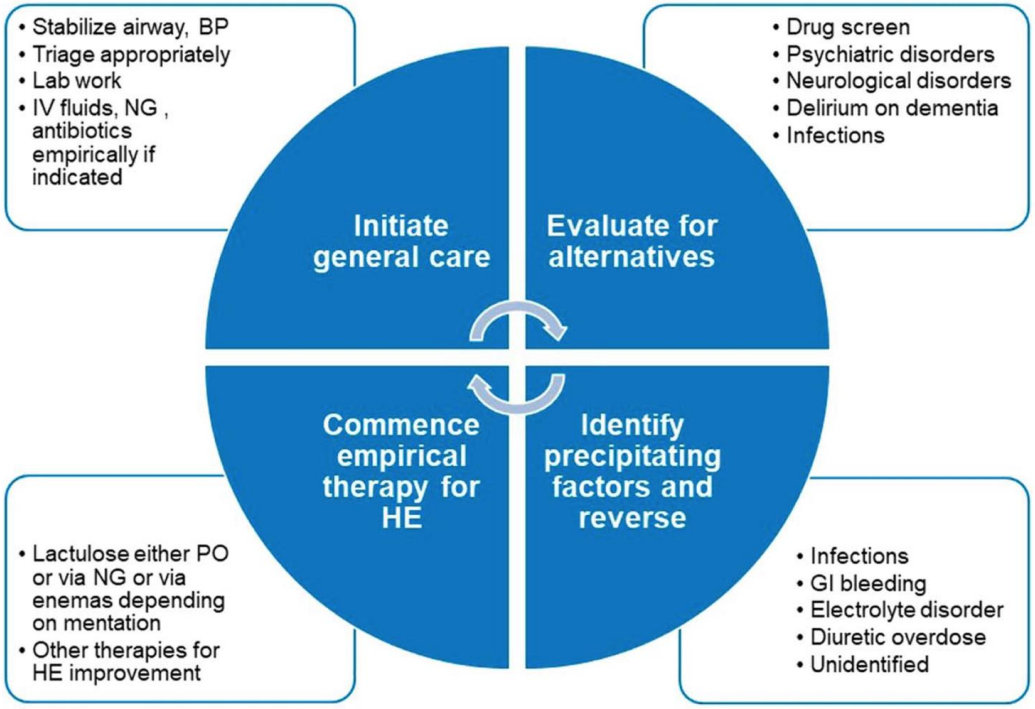
ALF vs ACLF vs Dekompensasyon



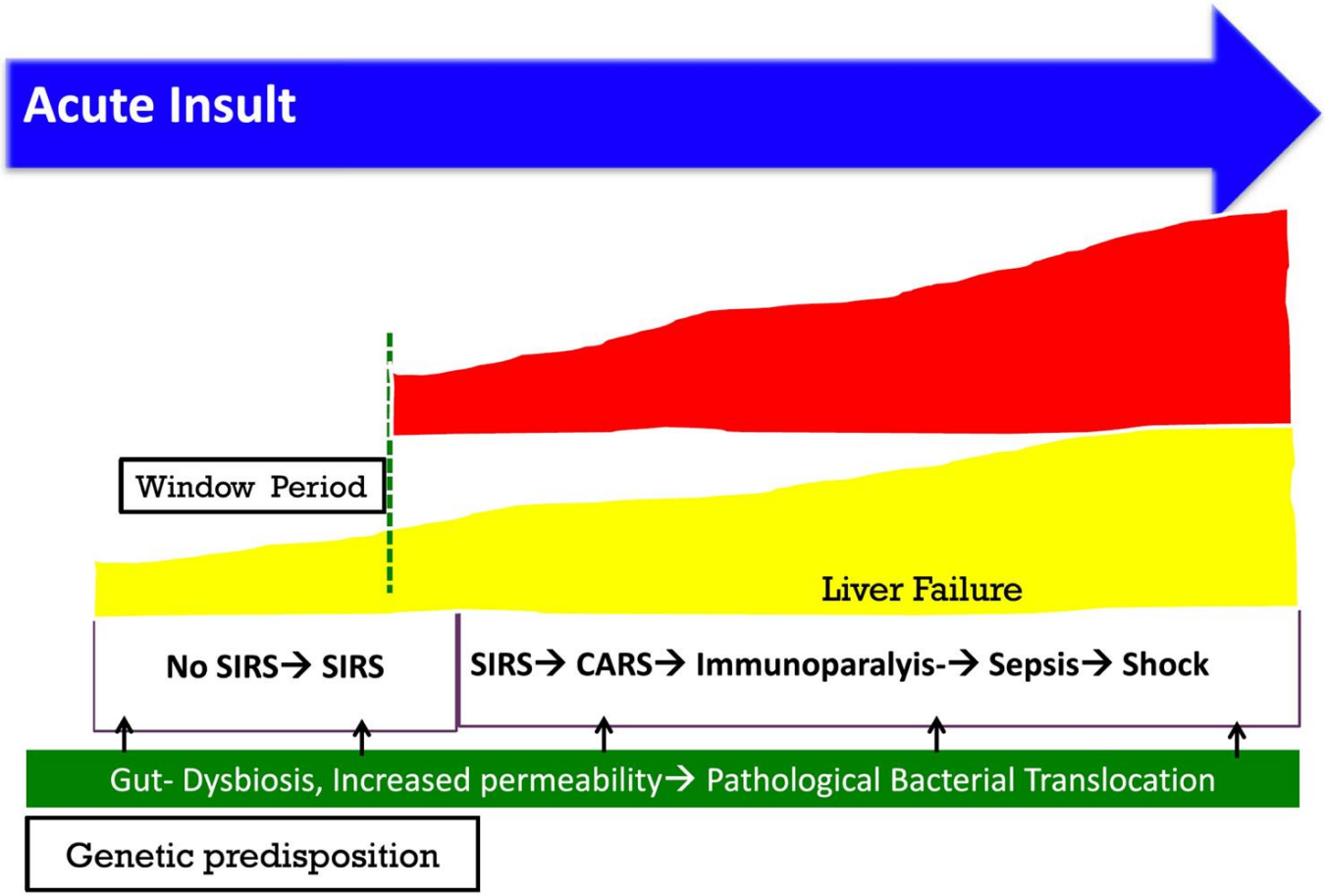
Doğal Seyir


Cirrhosis
or
Chronic Liver Disease
Precipitating factors:
• Alcohol
• Viral hepatitis
• DILI
• Surgery
• Ischemia
• Infection
Hepatic and
Extrahepatic
Organ failure
OR
Acute-on-chronic
Liver failure (ACLF)
Resuscitate
Treat precipitating factor
Treat infection
Support failing organs
Assess for ICU management
-Transplant candidate
- Number of organ failures
No
Yes
Evaluate for
palliative and
end-of-life care
Evaluate for
liver transplant

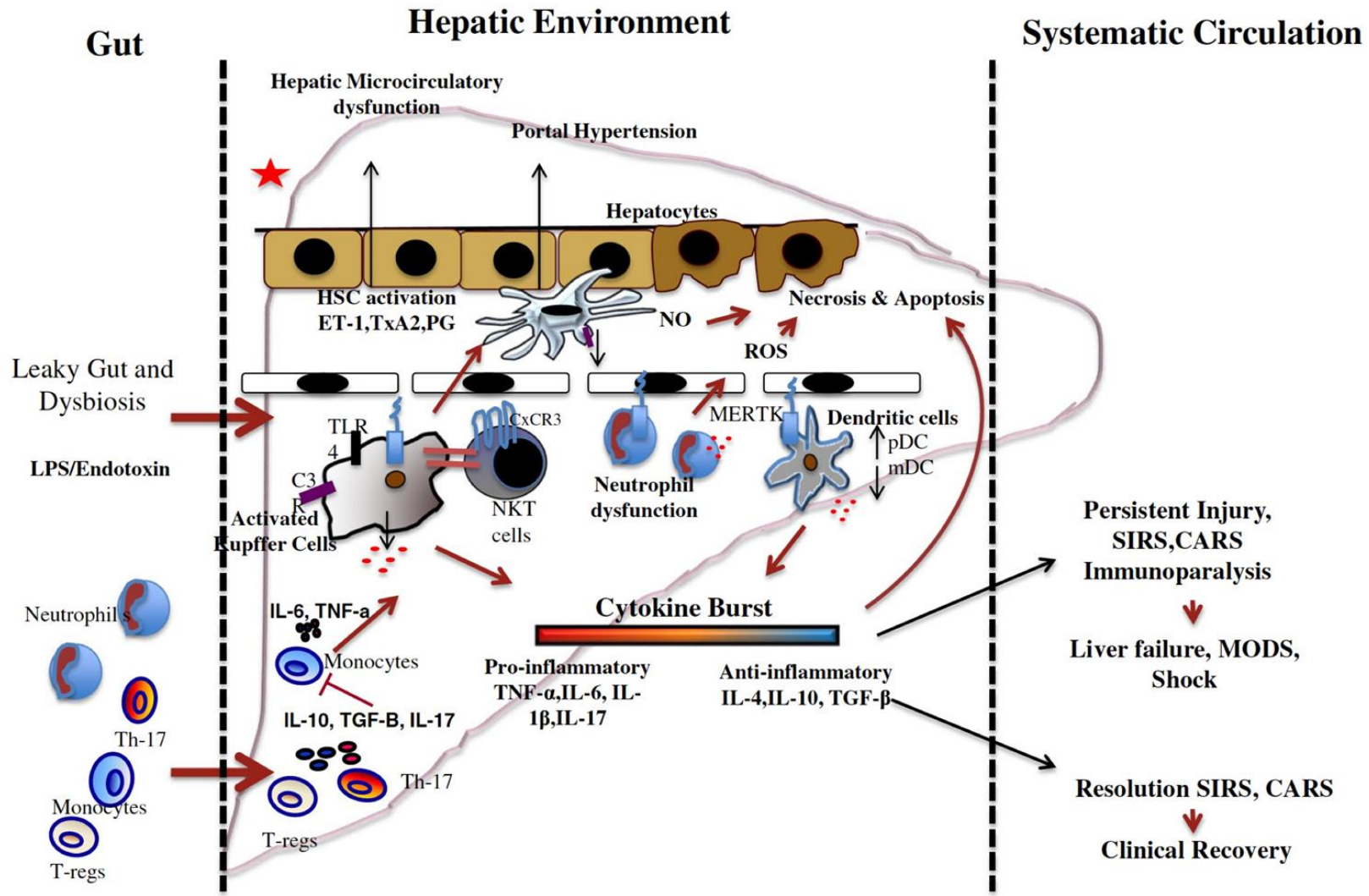
Genel Yaklaşım Prensipleri



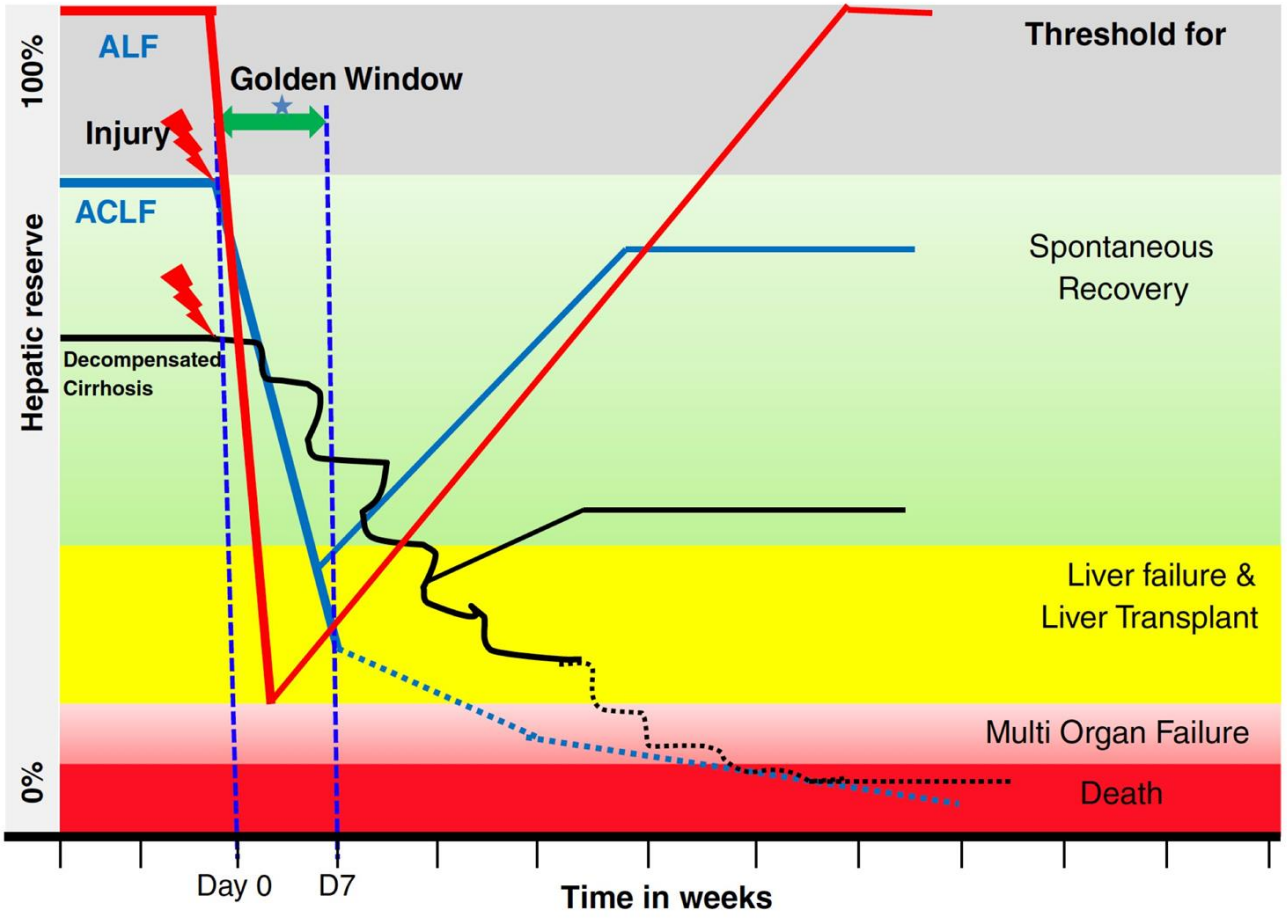
Organ yetmezliği gelişimi



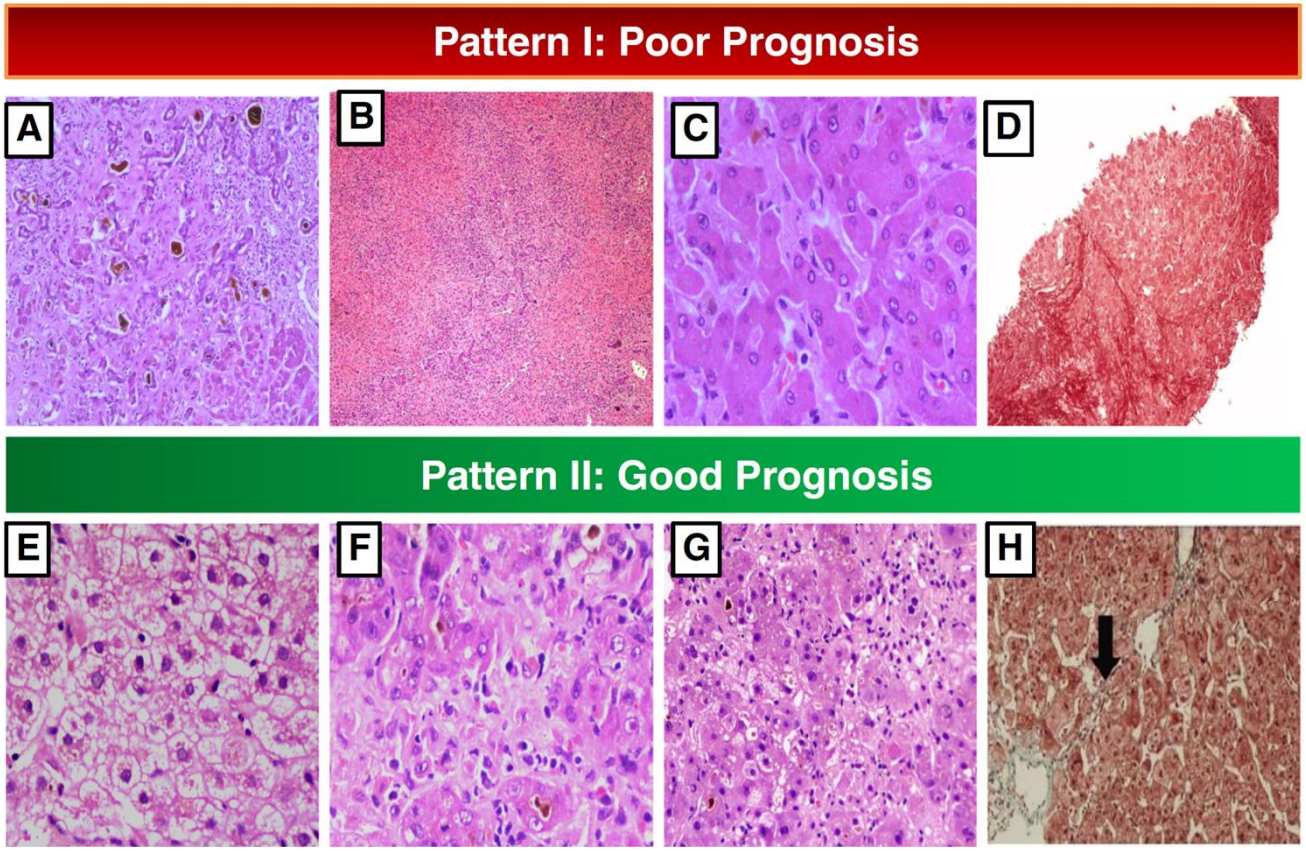
Patogenetik Mekanizmalar



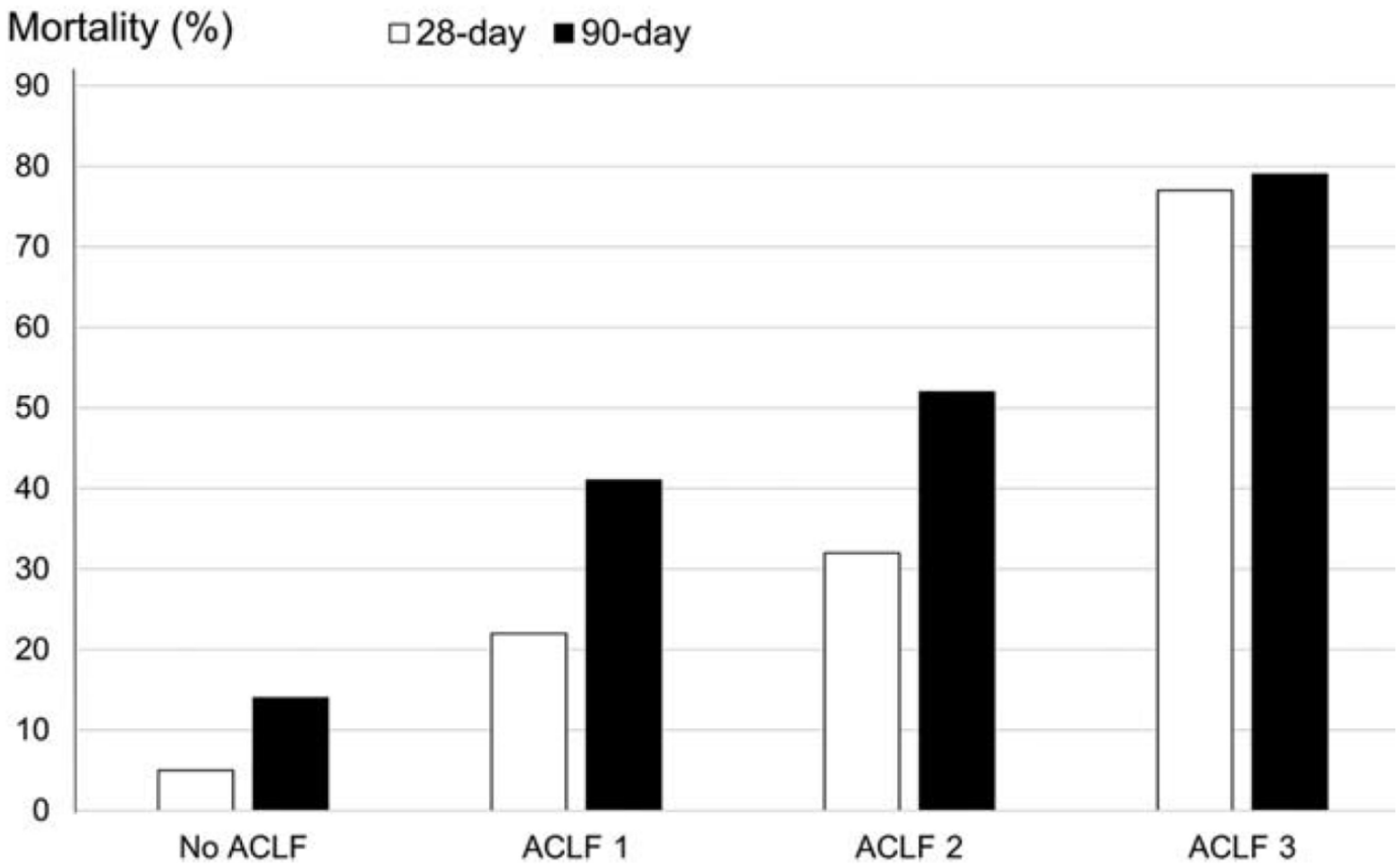
Olmak yada olmamak



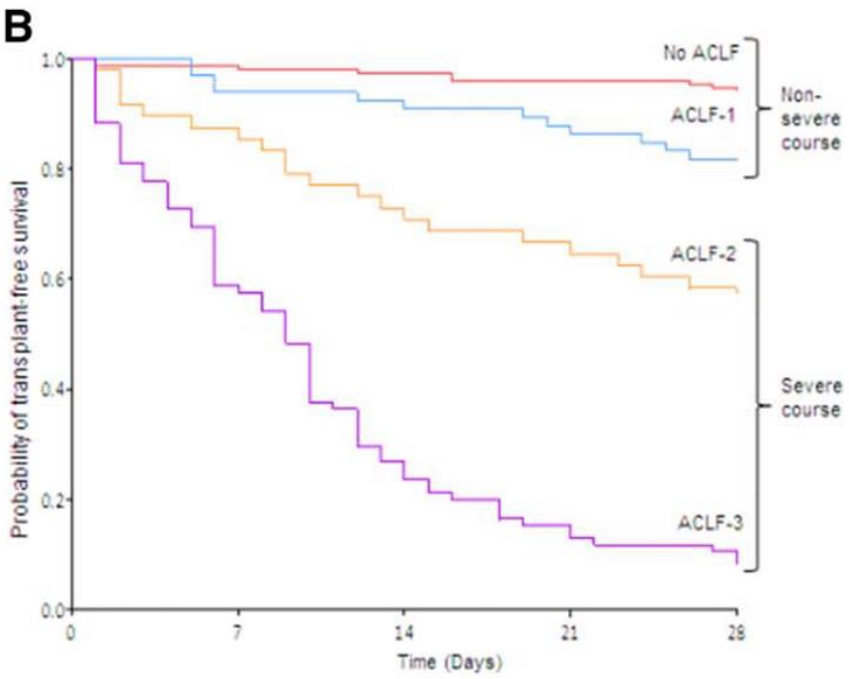
Histolojik patern prognozu belirler



Mortalite riski organ yetmezliği ile ilişkilidir

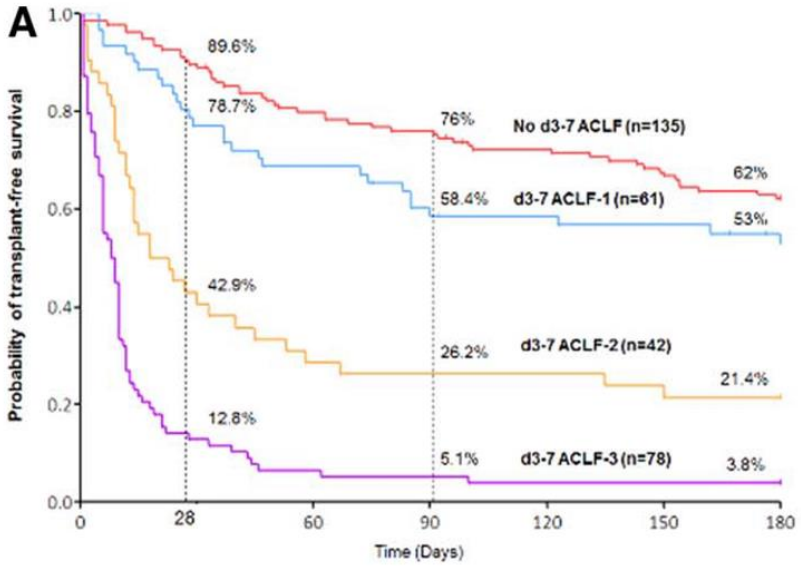


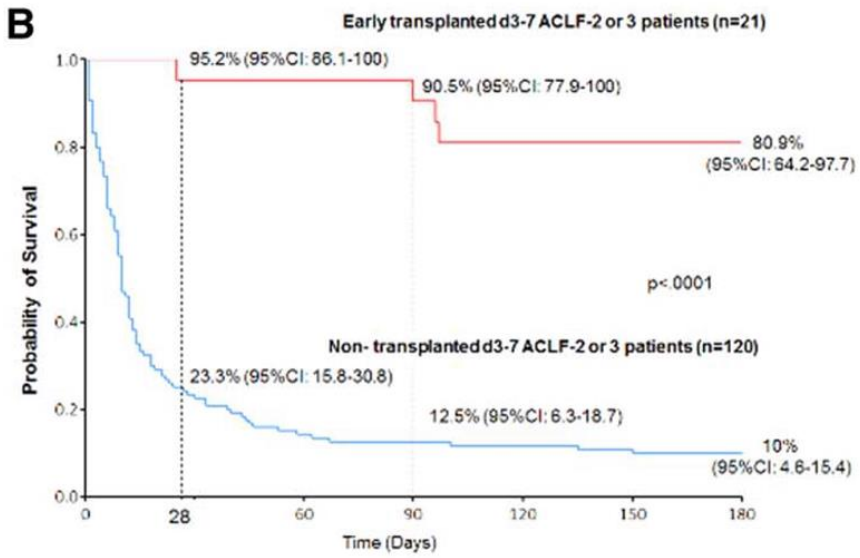
Zamana göre hastalık seyri



Gustot T, et al. Hepatology 2015

Karaciğer nakli hayat kurtarıcıdır





Gustot T, et al. Hepatology 2015

Salvage Karaciğer Nakli

- Genç hasta grubunda görülmekte
- Yüksek mortaliteye sahip
- %33 hastanın daha önce tanısı yok
- %25 presipite edici olay aktif alkol alımı
  - 6 ay alkol kesilme
- Hekim kaygılı

Putignano A, et al. Liver Transpl 2017

Salvage Karaciğer Nakli

- Bekleme listesi mortalite oranı yüksek
  - >%50 vs %15
- KC nakli sonrası sürvi net bilinmiyor
  - >%50/5yıllık sürvi
- Nakil sonrası yaşam kalitesi
  - Renal yetmezlik
  - Diğer organ yetmezlikleri
  - Mortalite
    - İrreversibl organ yetmezliği ve sepsis

Putignano A, et al. Liver Transpl 2017

Önemli noktalar,

- YB öncesi hastanın medikal durumu
  - Yaş
  - Frailty
  - KVR
- Presipite eden faktör
  - Sepsis/enfeksiyon,
    - En sık mortalite nedeni
  - Aktif alkol alımı
    - Aile desteği
- Organ yetmezlik durumu: Heterojen
  - Sayısı
  - Tipi

Karvellas CJ, et al. Transplantation 2021

Önemli noktalar,

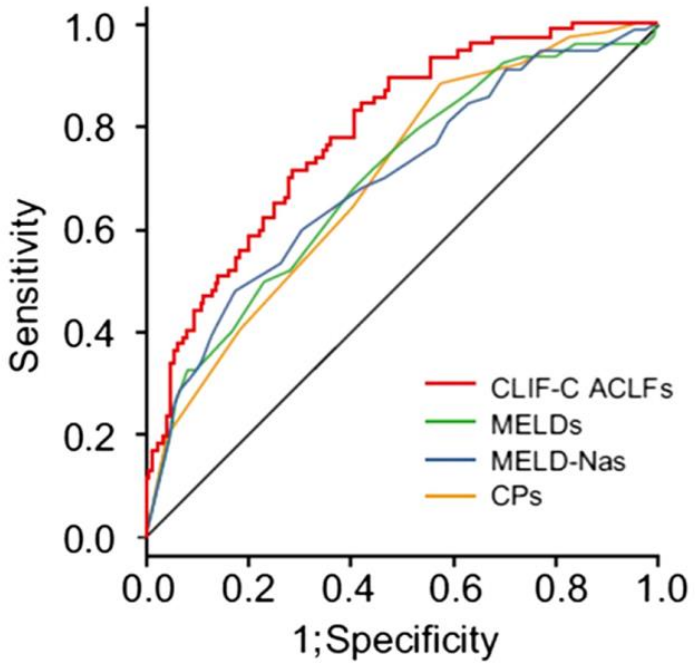
- Organ yetmezlik durumu: Heterojen
  - Tip
    - Hepatik, Nörolojik, Koagülasyon
    - Pulmoner, Dolaşım ve Renal
  - Mekanik ventilasyon
    - P/F < 100
  - Vazopressor ihtiyacı

Karvellas CJ, et al. Transplantation 2021

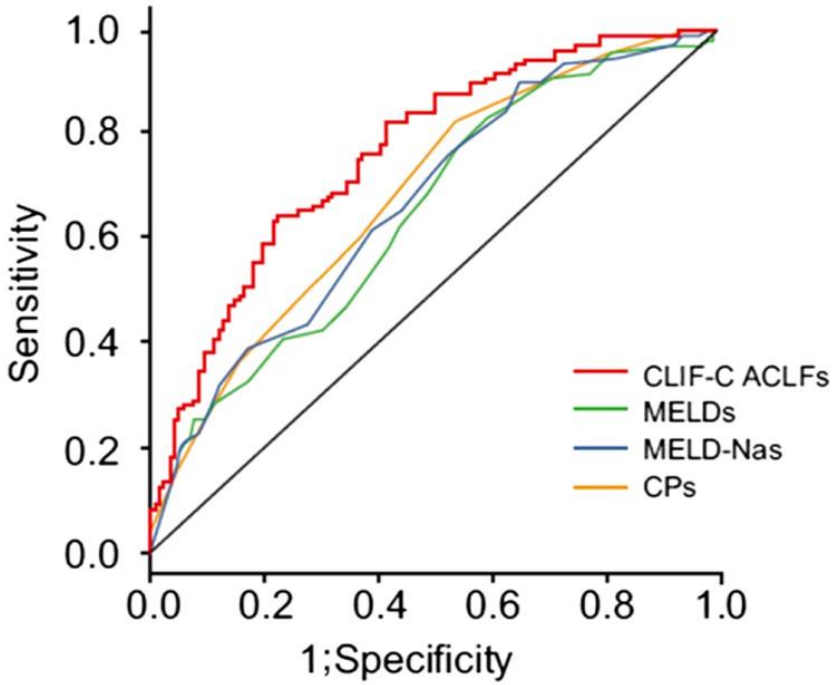
Öncelikli hastayı belirlemede MELD skor yeterli mi?

- MELD skor
- MELD-Na skor
- The CLIF-OF skor
- CLIF-SOFA skor
- CLIF-C Organ Failure skor
  - CLIF Consortuim Web site

Hastalık seyrini belirleme

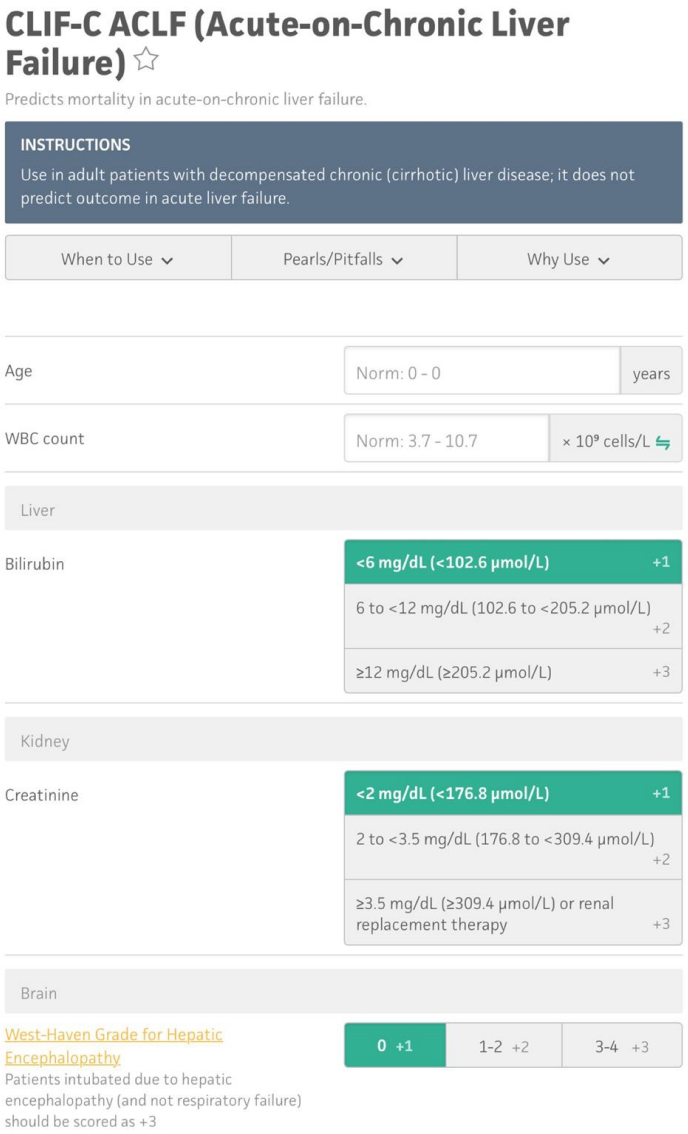


		AUROC (95% CI)	*p* value; *vs*; CLIF-C ACLF
—	CLIF-C ACLFs	0.79 (0.73–0.85)	
—	MELDs	0.70 (0.62–0.77)	0.0089
—	MELD-Nas	0.70 (0.62–0.77)	0.0097
—	CPs	0.70 (0.63–0.77)	0.0075



		AUROC (95% CI)	*p* value; *vs*; CLIF-C ACLF
—	CLIF-C ACLFs	0.76 (0.70–0.83)	
—	MELDs	0.65 (0.58–0.72)	0.0014
—	MELD-Nas	0.67 (0.60–0.74)	0.0082
—	CPs	0.69 (0.62–0.75)	0.0301

CLIF-C ACLF skorlaması



CLIF-C ACLF (Acute-on-Chronic Liver Failure) ☆

Predicts mortality in acute-on-chronic liver failure.

INSTRUCTIONS

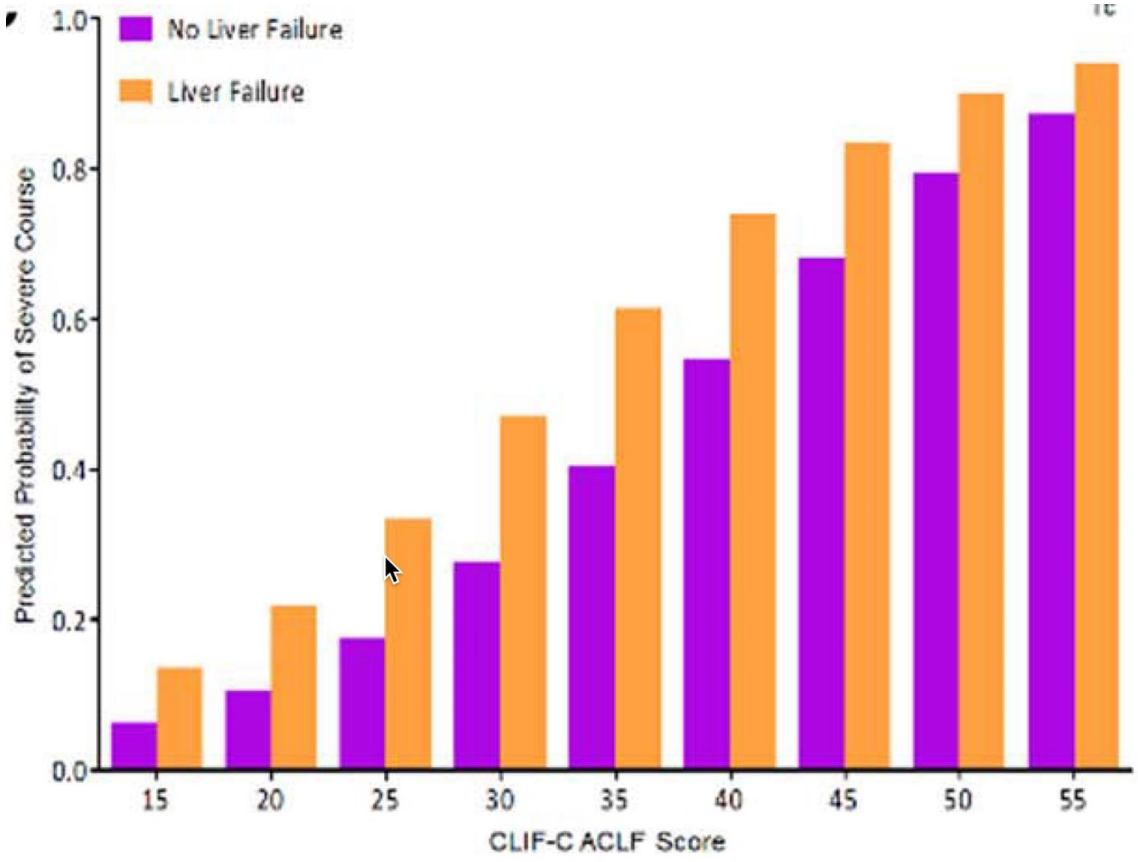
Use in adult patients with decompensated chronic (cirrhotic) liver disease; it does not predict outcome in acute liver failure.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Age	Norm: 0 - 0	years
WBC count	Norm: 3.7 - 10.7	× 10^9 cells/L ⇋
Liver		
Bilirubin	**<6 mg/dL (<102.6 µmol/L)**	**+1**
	6 to <12 mg/dL (102.6 to <205.2 µmol/L)	+2
	≥12 mg/dL (≥205.2 µmol/L)	+3
Kidney		
Creatinine	**<2 mg/dL (<176.8 µmol/L)**	**+1**
	2 to <3.5 mg/dL (176.8 to <309.4 µmol/L)	+2
	≥3.5 mg/dL (≥309.4 µmol/L) or renal replacement therapy	+3
Brain		
West-Haven Grade for Hepatic Encephalopathy	**0 +1**	1-2 +2 / 3-4 +3

Patients intubated due to hepatic encephalopathy (and not respiratory failure) should be scored as +3

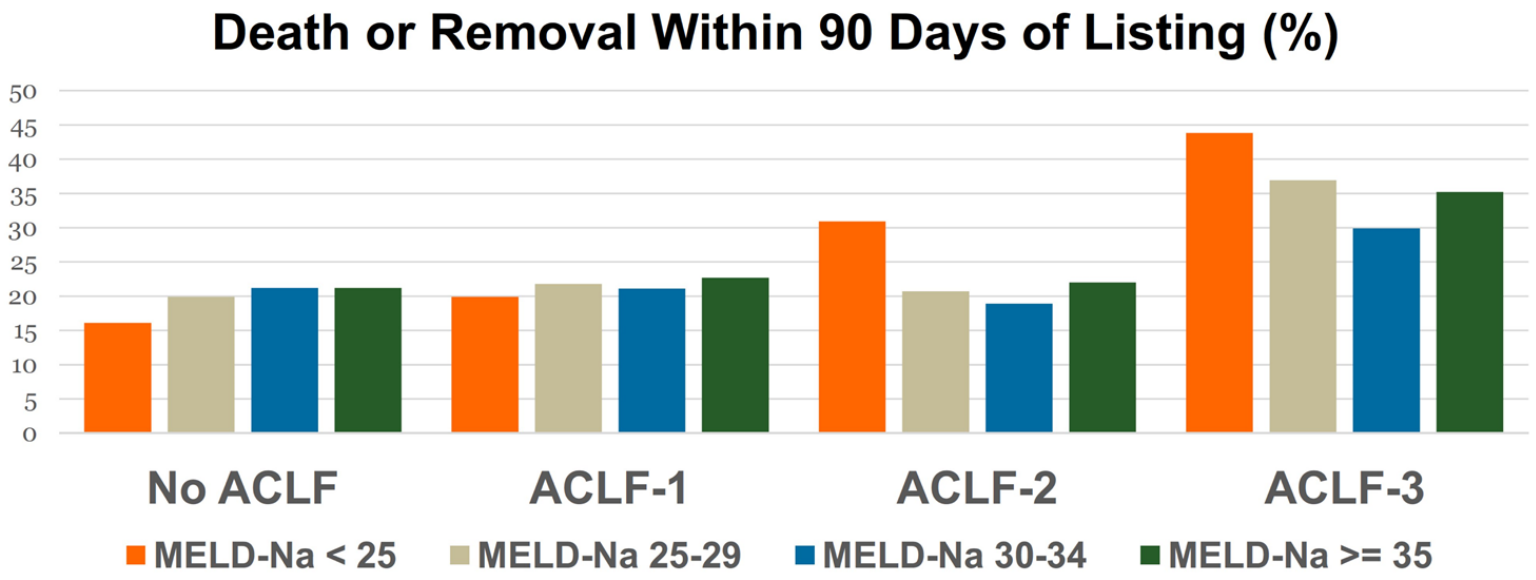
CLIF-C ACLF skorlaması



Gustot T, et al. Hepatology 2015

Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation

Vinay Sundaram,[1,*] **Rajiv Jalan**,[2,*] Tiffany Wu,[3] Michael L. Volk,[4] Sumeet K. Asrani,[5] Andrew S. Klein,[6] and Robert J. Wong[7]



Gastroenterology

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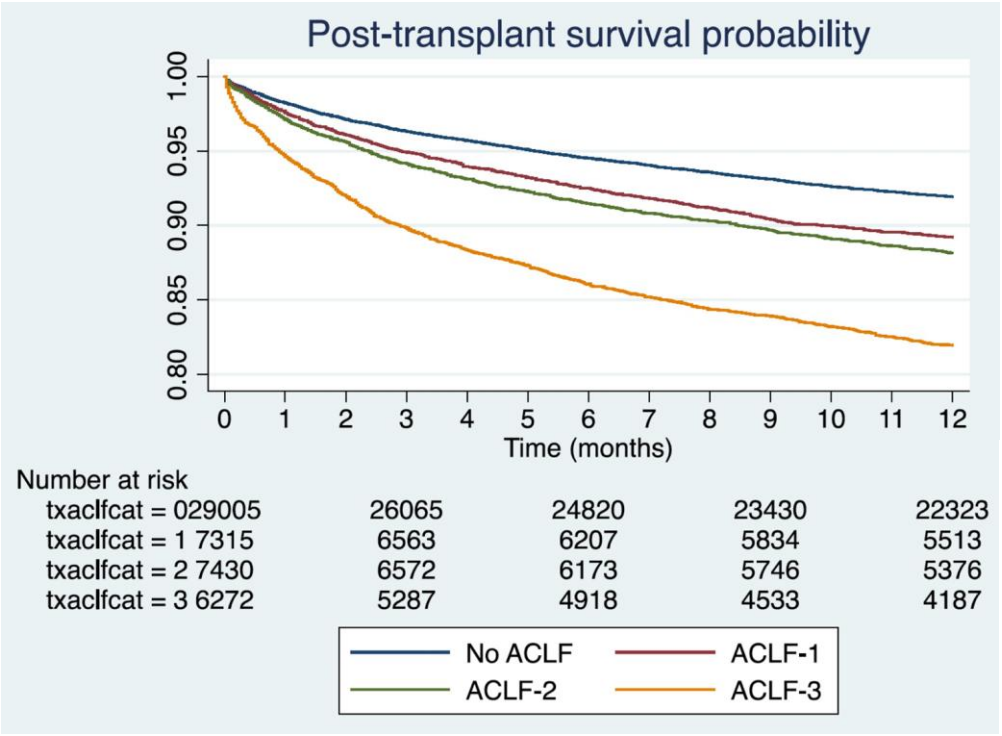


UNOS veri sistemi
2005-2016,
100,594 non-ACLF vs
50,552 ACLF
EASL ACLF kriterlerine göre

	Univariable analysis HR (95% CI)	Multivariable analysis[a] HR (95% CI)
Renal failure	1.25 (1.13–1.41)	1.38 (1.19–1.60)
Mechanical ventilation	2.07 (1.67–2.57)	2.01 (1.46–2.76)
Circulatory failure	1.62 (1.39–1.90)	1.31 (1.04–1.64)
Neurologic failure	1.22 (1.08–1.37)	1.09 (0.99–1.19)
Coagulation failure	0.71 (0.65–0.79)	1.03 (0.88–1.21)
Liver failure	0.68 (0.61–0.76)	0.98 (0.85–1.11)

Gastroenterology 2019

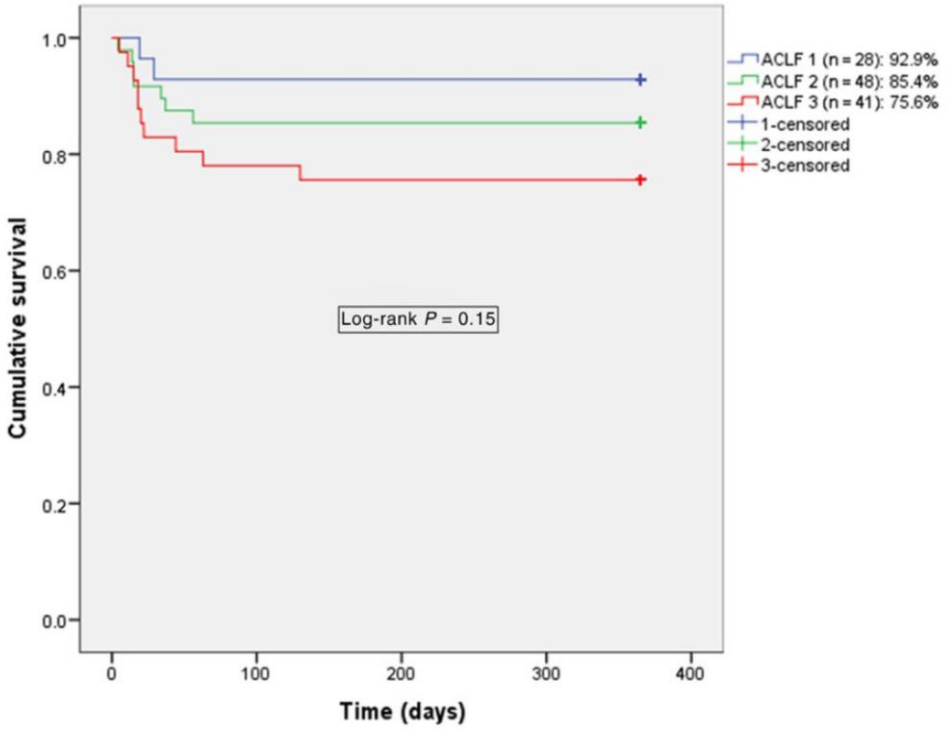
Donor Organ: En iyi donor-en iyi alıcı

- DRI indeks
  - >1.7
- Canlı donör
- Split, DCD donor graft

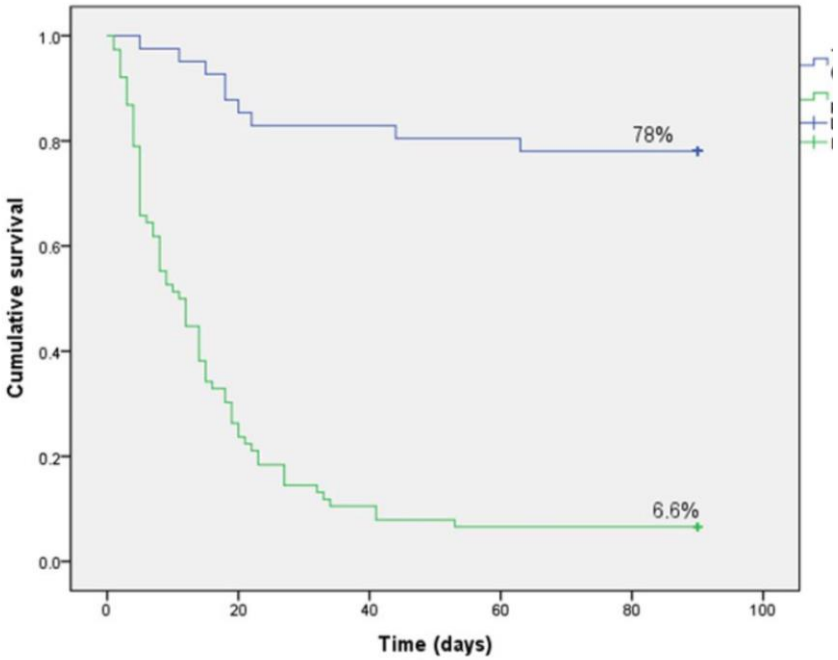
Kribben A, et al. Gastroenterology 2012
Banares R, et al. Hepatology 2013
Alshamsi F, et al. Intensive Care Med 2020

Living Donor Liver Transplantation for Acute-on-Chronic Liver Failure

Sanjay Kumar Yadav, Neeraj Saraf, Narendra S. Choudhary, Jayant Kumar Sah, Sujeet Kumar Sah, Amit Rastogi, Prashant Bhangui, Sanjiv Saigal, and Arvinder Singh Soin



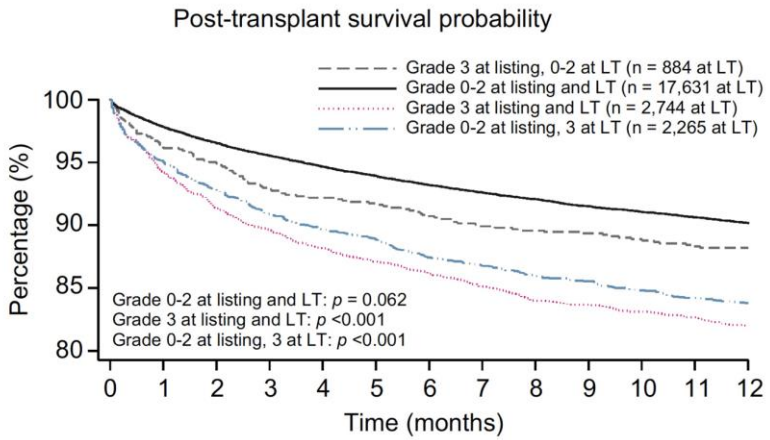
- 218 ACLF hastası (EASL)
- 42.9 yaş
- Sepsis
- 117 hasta nakil olmuş



Liver Transpl 2019

Effect of the clinical course of acute-on-chronic liver failure prior to liver transplantation on post-transplant survival☆

Vinay Sundaram[1,*], Shannon Kogachi[1], Robert J. Wong[2], Constantine J. Karvellas[3], Brett E. Fortune[4], Nadim Mahmud[5], Josh Levitsky[6], Robert S. Rahimi[7], Rajiv Jalan[8]

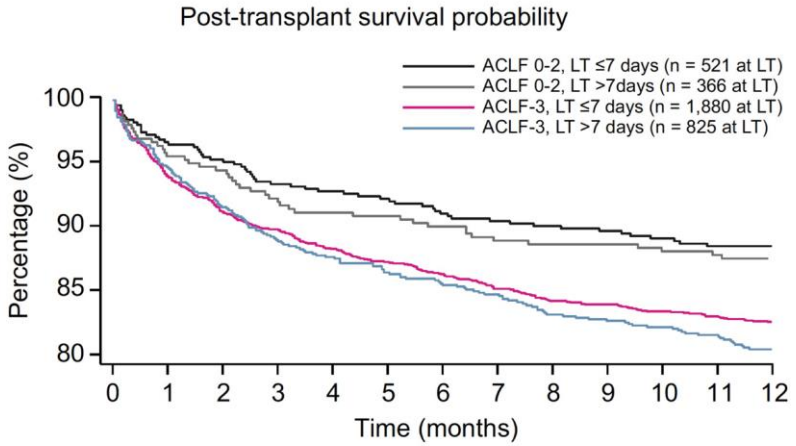


	1 month	3 months	6 months	12 months
ACLF-3 at listing, ACLF 0-2 at LT	0.962 (n = 851)	0.929 (n = 821)	0.907 (n = 799)	0.882 (n = 735)
ACLF 0-2 at listing and LT	0.978 (n = 17,243)	0.955 (n = 16,837)	0.932 (n = 16,183)	0.902 (n = 15,903)
ACLF-3 at listing and LT	0.942 (n = 2,584)	0.896 (n = 2,458)	0.861 (n = 2,362)	0.820 (n = 2,250)
ACLF 0-2 at listing, ACLF-3 at LT	0.949 (n = 2,149)	0.909 (n = 2,058)	0.874 (n = 1,979)	0.838 (n = 1,898)

J Hepatology 2020

KC nakli için listelenen 3636 ACLF-3 hastası

- %25 iyileşme
- %75 nakil olmuş



	1 month	3 months	6 months	12 months
ACLF 0-2 at transplant, LT ≤7 days	0.965 (n = 502)	0.935 (n = 486)	0.911 (n = 472)	0.886 (n = 432)
ACLF 0-2 at transplant, LT >7 days	0.956 (n = 350)	0.921 (n = 336)	0.901 (n = 329)	0.876 (n = 304)
ACLF-3 at transplant, LT ≤7 days	0.939 (n = 1,765)	0.898 (n = 821)	0.864 (n = 799)	0.827 (n = 735)
ACLF-3 at transplant, LT >7 days	0.947 (n = 781)	0.889 (n = 733)	0.856 (n = 703)	0.805 (n = 640)

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	Reference	Hazard ratio, 95% CI*	Hazard ratio, 95% CI**	Hazard ratio, 95% CI***	Hazard ratio, 95% CI****	Hazard ratio, 95% CI†
ACLF grade 0–2 at LT	ACLF grade 3 at LT	0.74 (0.63–0.88)	0.65 (0.53–0.78)	0.65 (0.54–0.79)	0.67 (0.55–0.81)	0.63 (0.52–0.78)
Age 40–60	Age <40	1.14 (0.92–1.42)	1.13 (0.91 –1.42)		1.13 (0.89–1.43)	1.12 (0.88 –1.43)
Age >60		1.70 (1.33–2.16)	1.68 (1.31–2.18)		1.74 (1.33–2.27)	1.74 (1.32–2.28)
Age		1.02 (1.01–1.02)		1.01 (1.00–1.02)		
MELD–Na score		1.01 (1.01–1.02)	0.97 (0.96–1.00)	0.98 (0.97–1.00)	0.97 (0.98–1.00)	0.97 (0.96–1.01)
ALD	NASH	0.91 (0.78–1.05)				
Diabetic	Non-diabetic	1.26 (1.07–1.48)	1.18 (1.00–1.39)	1.18 (1.00–1.39)	1.10 (0.92 –1.33)	1.17 (0.98–1.42)
DRI ≥1.7	DRI <1.7	1.24 (1.05 –1.46)	1.22 (1.03 –1.45)	1.22 (1.03–1.45)	1.18 (0.98 –1.42)	1.14 (0.94 –1.39)
Time to LT (days)		1.00 (0.99–1.01)				
Years 2012–2017	Years 2004–2011	0.88 (0.77–1.02)				

J Hepatology 2020

Karaciğer Destek sistemleri

- Biyokimyasal düzelme
- Hepatik komada iyileşme
- Mortaliteye etkisi gösterilememiştir.
- Bridge???

Kribben A, et al. Gastroenterology 2012
Banares R, et al. Hepatology 2013
Alshamsi F, et al. Intensive Care Med 2020

Perioperatif yaklaşımlar bireyselleştirilmelidir

- Renal replasman tedavileri
- Antimikrobiyal proflaksi
- İmmunsüpresif tedavi

Karvellas CJ, et al. Transplantation 2021

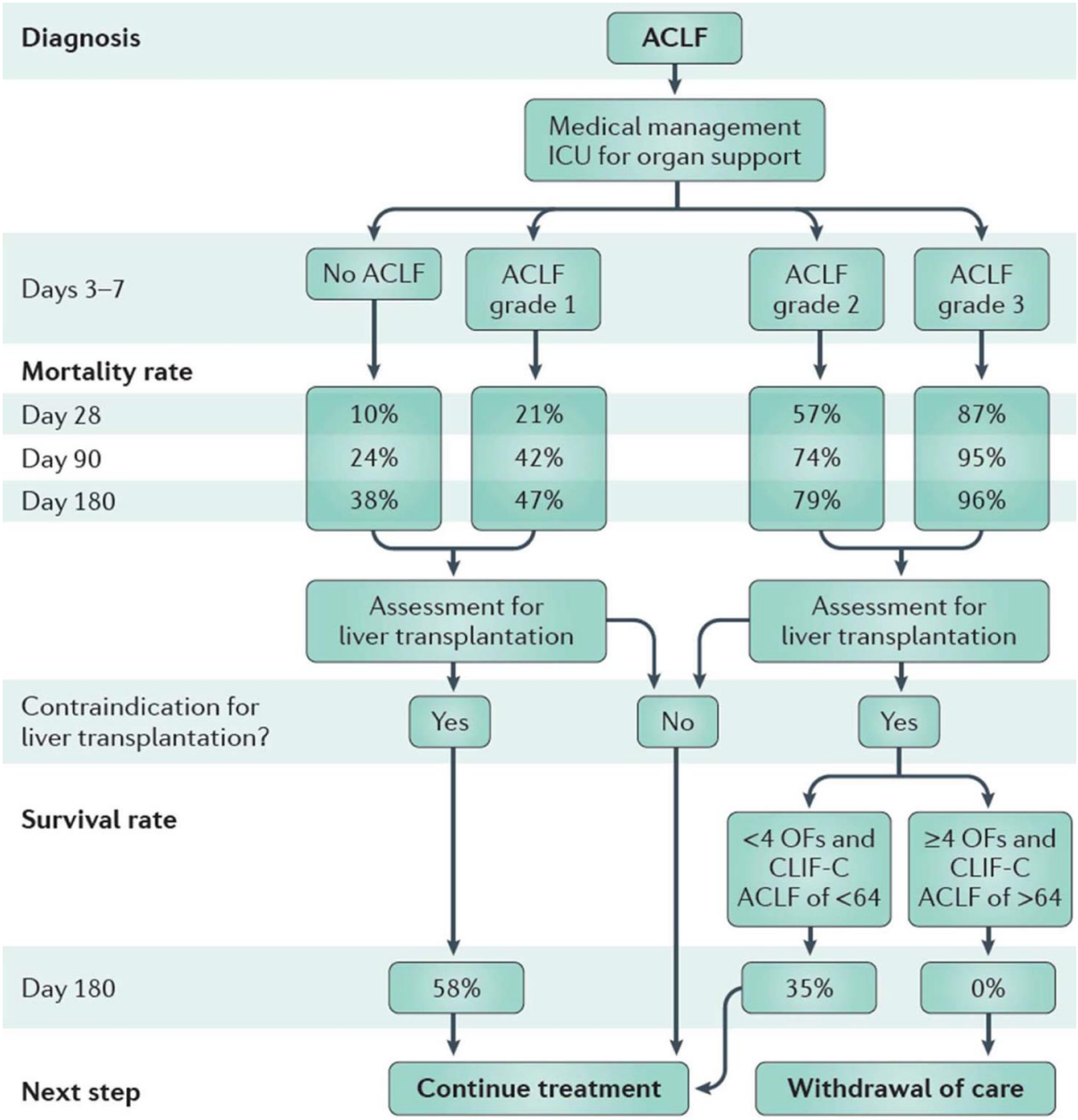
Çözülmesi gerekenler...

- Hızlı pretransplant hazırlama protokolleri
  - Canlı donör veya kadavra
- Öncelik kurallarının ortaya konulması
- Transplantasyon için ideal zaman
  - Köprü tedavilerin tanımlanması
- Liste dışı bırakma kriterlerinin tanımlanması

Putignano A, et al. Liver Transpl 2017

Sonuç olarak,

- Karaciğer fonksiyon kaybı ve organ yetmezliği
  - Mortalitesi yüksek
- ACLF tanı ve yaklaşım prensipleri netleşmeli
- Karaciğer nakli tek küratif tedavi yaklaşımı
  - Seçme (puan), öncelik (puan), hazırlama ve liste dışı bırakma kriterleri netlik kazanmalı
  - Nakil sonrası yakın takip


Diagnosis
ACLF
Medical management
ICU for organ support
Days 3–7
No ACLF
ACLF grade 1
ACLF grade 2
ACLF grade 3
Mortality rate
Day 28
10%
21%
57%
87%
Day 90
24%
42%
74%
95%
Day 180
38%
47%
79%
96%
Assessment for liver transplantation
Assessment for liver transplantation
Contraindication for liver transplantation?
Yes
No
Yes
Survival rate
<4 OFs and CLIF-C ACLF of <64
≥4 OFs and CLIF-C ACLF of >64
Day 180
58%
35%
0%
Next step
Continue treatment
Withdrawal of care