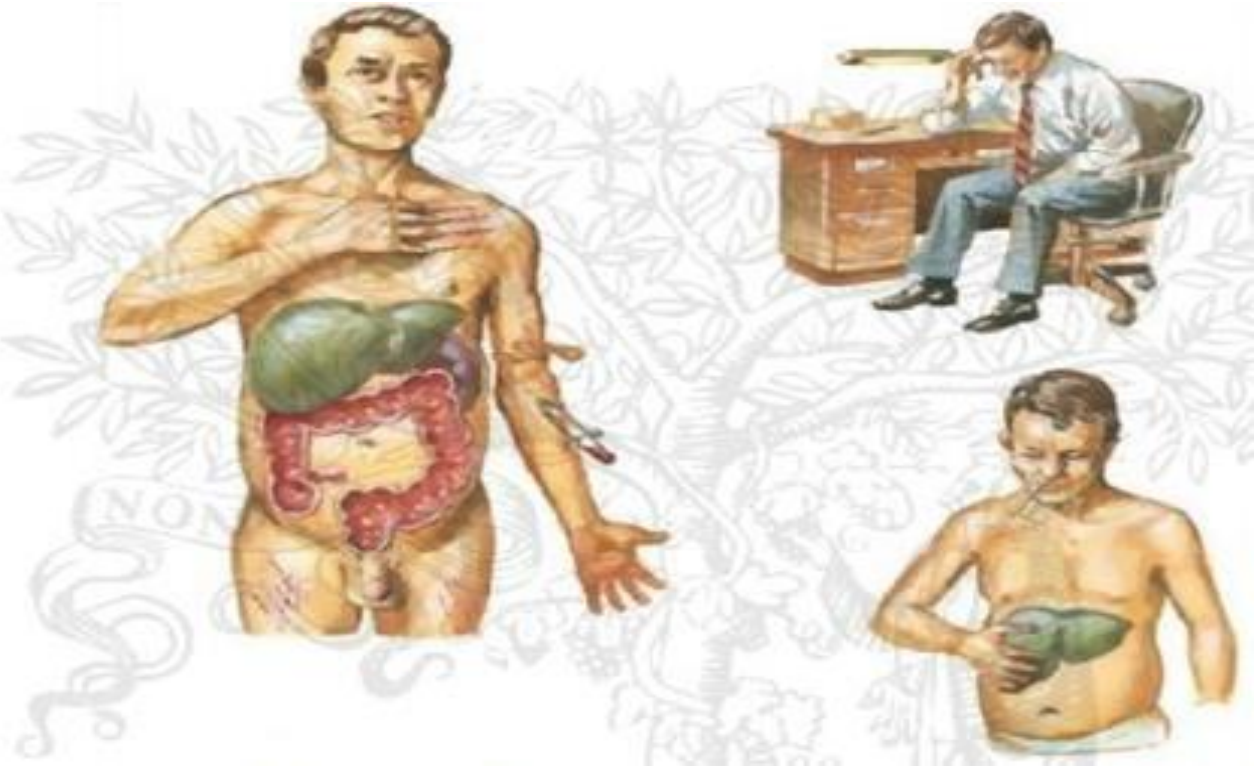
NAFLD ve Karaciğer Nakli

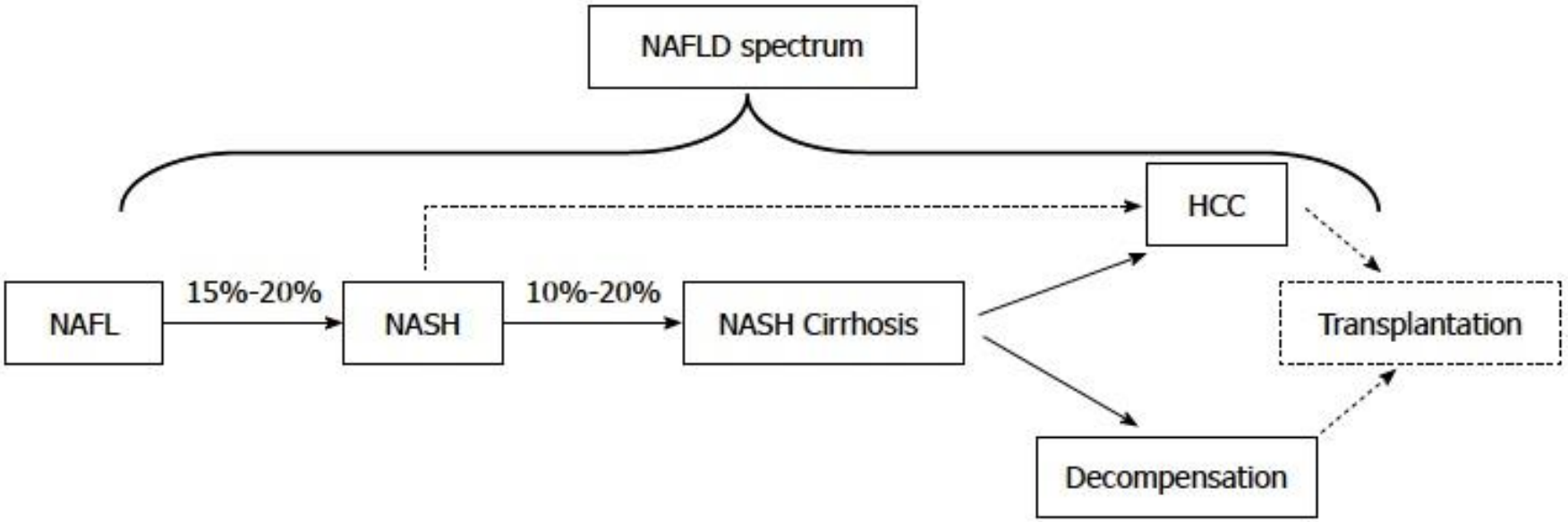


Prof.Dr.Murat AKYILDIZ

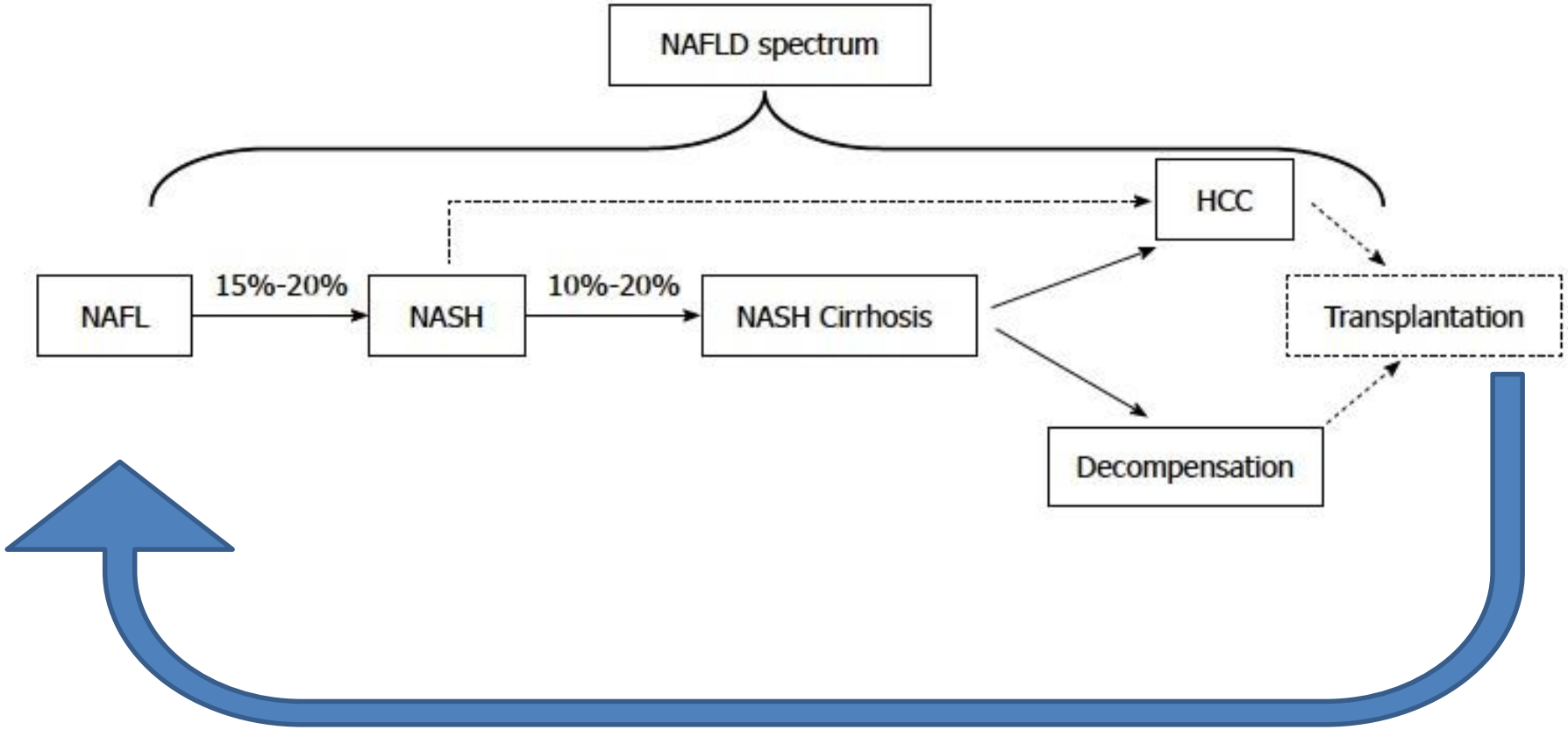
Ataşehir Memorial Hastanesi

Gastroenteroloji Bölümü& Organ Nakli Merkezi

Giriş


NAFLD spectrum
HCC
NAFL
15%-20%
NASH
10%-20%
NASH Cirrhosis
Transplantation
Decompensation

AYNI SENARYO……..



Summary of the main diseases (excluding neoplasms) that are thought to recur following liver transplantation.

Recurrent Disease	Frequency (%)	Histological Features (in biopsies >12 months post-transplant)	Comments
Primary sclerosing cholangitis (PSC)	20-30	Fibrous cholangitis (rarely seen in liver biopsies). Diagnosis more often based on findings of chronic cholestasis, ductopenia, ductular reaction and a "biliary pattern" of fibrosis. Approximately 25% have bridging fibrosis or cirrhosis by 5 years post-transplant.	More frequently clinically symptomatic than recurrent PBC. Approximately 10% progress to graft failure. Histological and radiological features difficult to distinguish from ischaemic cholangiopathy. Diagnosis therefore requires exclusion of other causes of biliary tract disease.
Autoimmune hepatitis (AIH)	20-30	Portal tract plasma cell-rich inflammatory infiltrate associated with interface hepatitis. Lobular inflammation frequently present - severe cases include foci of confluent/bridging necrosis. Lobular inflammatory changes may resemble "central perivenulitis" and can occur as the first manifestation of recurrent disease.	Most cases occur as a result of suboptimal immunosuppression and respond to immunosuppressive therapy. Diagnosis based on a combination of biochemical, serological, and histological findings.
Alcoholic liver disease (ALD)	10-30	Fatty change common (>60% of cases) Steatohepatitis and fibrosis less common. Progression to cirrhosis rare.	Recurrent alcohol consumption common, but serious graft complications are rare.
Non-alcoholic Fatty Liver Disease (NAFLD)	20-40	Fatty change common (60-100% of cases). 10-40% progress to steatohepatitis and up to 12% become cirrhotic.	Risk factors for NAFLD often persist and may be exacerbated by immunosuppressive drugs and other transplant-related factors. Many people with recurrent NAFLD have normal LFTs.

Journal of Hepatology 2011;55: 702–717

NAFLD ve KC Nakli

- NAFLD ilişkili karaciğer nakil bekleme listesi 2004-2013 arasında ABD de %170 artmıştır,
- NASH ilişkili HCC 2002 yılına göre 2012 de 4 kat artış göstermekte
- NAFLD li olgular
  - Daha yaşlı
  - Diyabetik
  - Obez
  - Kardiyovasküler komplikasyonlar daha fazla
  - Perioperatif morbidite ve mortalite daha yüksek
- Sağkalım NASH vs non-NASH benzer

- Siddigui and Charlton. Gastroenterology 2016

Gastroenterology 2015;148:547–555

CLINICAL—LIVER

Nonalcoholic Steatohepatitis Is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the United States

Robert J. Wong,[1] Maria Aguilar,[1] Ramsey Cheung,[2,3] Ryan B. Perumpail,[2] Stephen A. Harrison,[4] Zobair M. Younossi,[5,6] and Aijaz Ahmed[2]

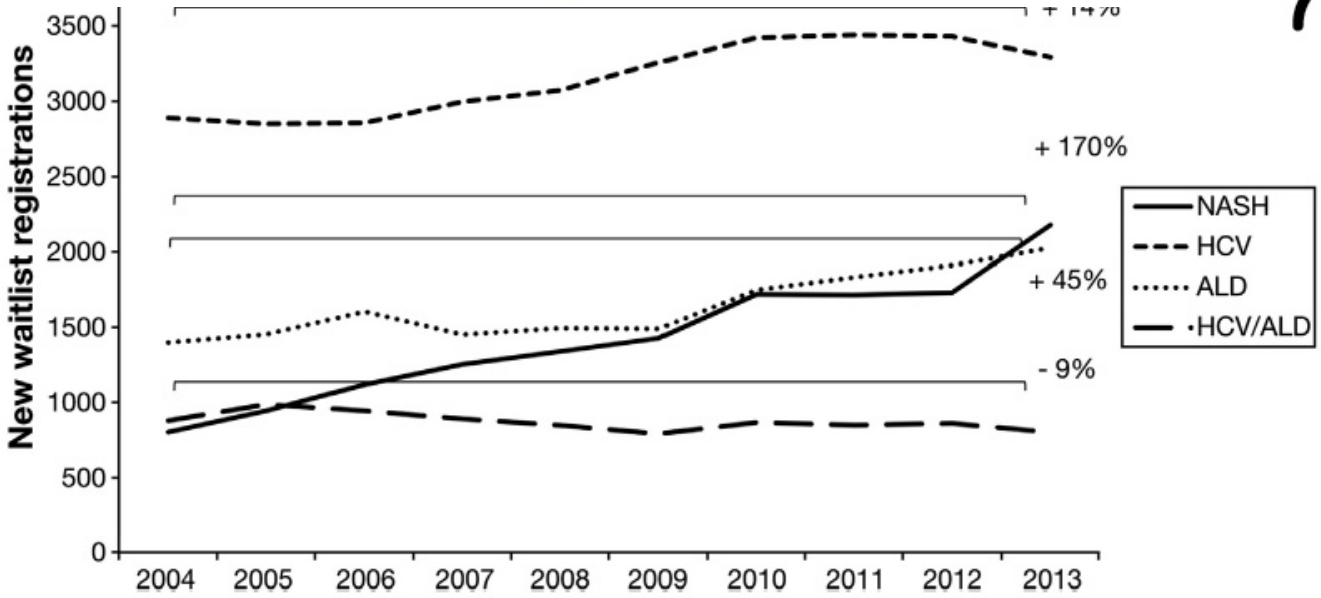


Figure 1. Annual trends in new liver transplant waitlist registrations.

Etyolojik Dağılım

- HCV ve ALD ile karşılaştırıldığında NASH giderek artıyor
  - Kompanse siroz
  - Kronik karaciğer yetmezliği (NASH'de x3 artış)
  - HCC
- HCC nedeniyle Tx yapılan olgularda etyoloji;
  - HCV 2x artarken
  - NASH 4x artmış

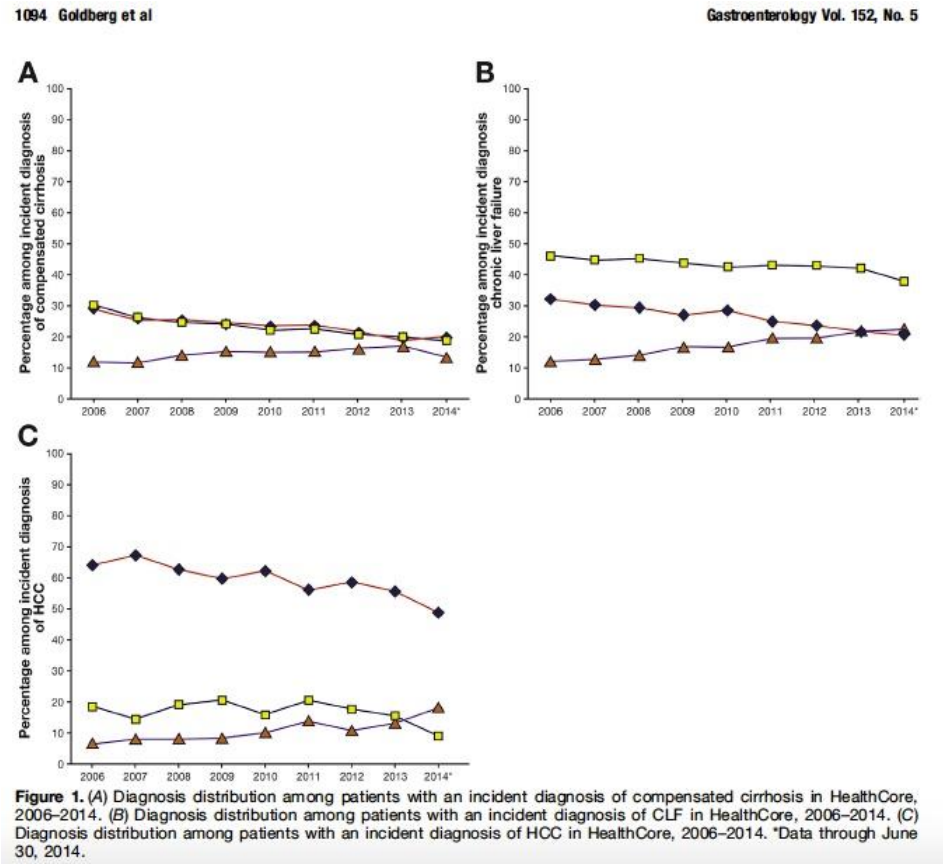


Figure 1. (*A*) Diagnosis distribution among patients with an incident diagnosis of compensated cirrhosis in HealthCore, 2006–2014. (*B*) Diagnosis distribution among patients with an incident diagnosis of CLF in HealthCore, 2006–2014. (*C*) Diagnosis distribution among patients with an incident diagnosis of HCC in HealthCore, 2006–2014. *Data through June 30, 2014.

Wong, Hepatology, 2014

Nonalcoholic Fatty Liver Disease Incidence and Impact on Metabolic Burden and Death: a 20 Year-Community Study

Alina M. Allen, MD[1], Terry M. Therneau, PhD[2], Joseph J. Larson[2], Alexandra Coward[1], Virend K. Somers, MD, PhD[3], Patrick S. Kamath, MD[1]

Characteristics		NAFLD N= 3,869	Controls N= 15,209	P value
Age – median (IQR)		53 (42-63)	53 (43-64)	0.02
Female (%)		2,032 (52%)	7,973 (52%)	0.91
BMI – median (IQR) kg/m^2		33 (29-38)	28 (24-32)	<0.0001
Diabetes mellitus	at baseline	1,254 (32%)	1,614 (11%)	<0.0001
	after 10 years	1,532 (40%)	2,086 (14%)	<0.0001
Hypertension	at baseline	1,963 (51%)	4,164 (27%)	<0.0001
	after 10 years	2,334 (60%)	5,170 (34%)	<0.0001
Dyslipidemia	at baseline	2,914 (75%)	7,174 (47%)	<0.0001
	after 10 years	3,084 (80%)	7,979 (52%)	<0.0001
Cardiovascular disease	at baseline	1,102 (28%)	2,754 (18%)	<0.0001
	after 10 years	1,303 (34%)	3,304 (22%)	<0.0001

Hepatology 2017 in press

Nonalcoholic Fatty Liver Disease Incidence and Impact on Metabolic Burden and Death: a 20 Year-Community Study

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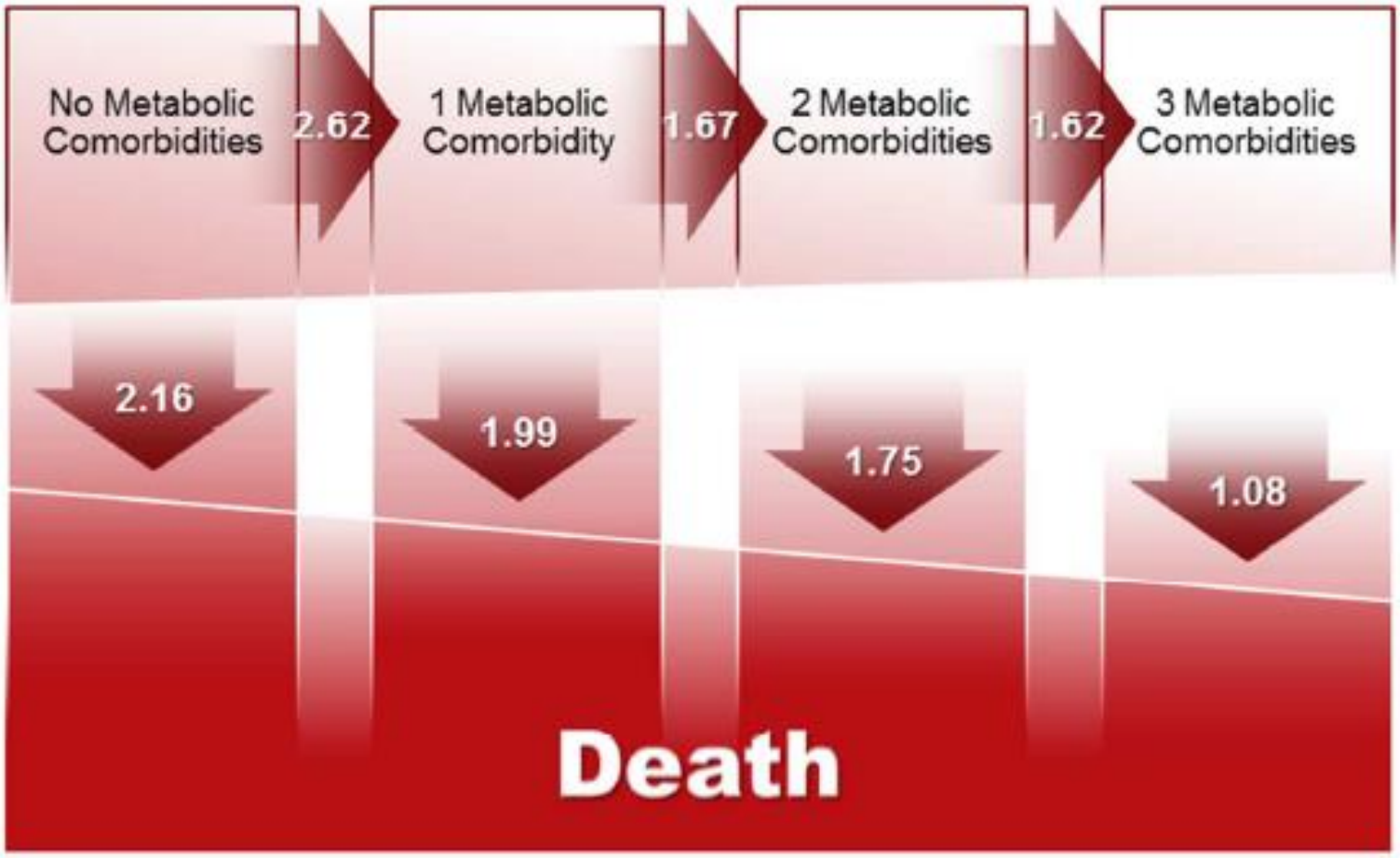
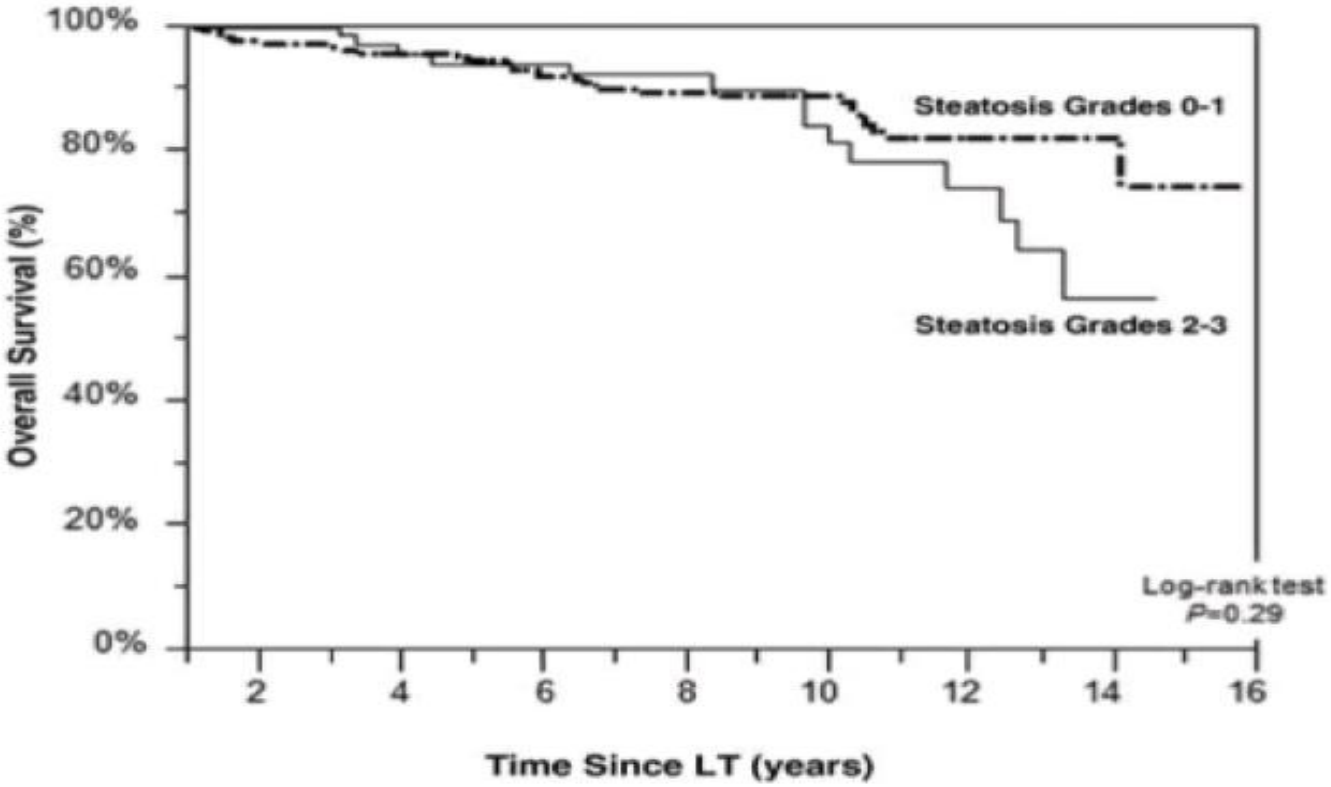


Hepatology 2017 in press

Fatty Allograft and Cardiovascular Outcomes after Liver Transplantation

Rahima A. Bhanji[1], M.D. and Kymberly D. Watt[1], M.D.

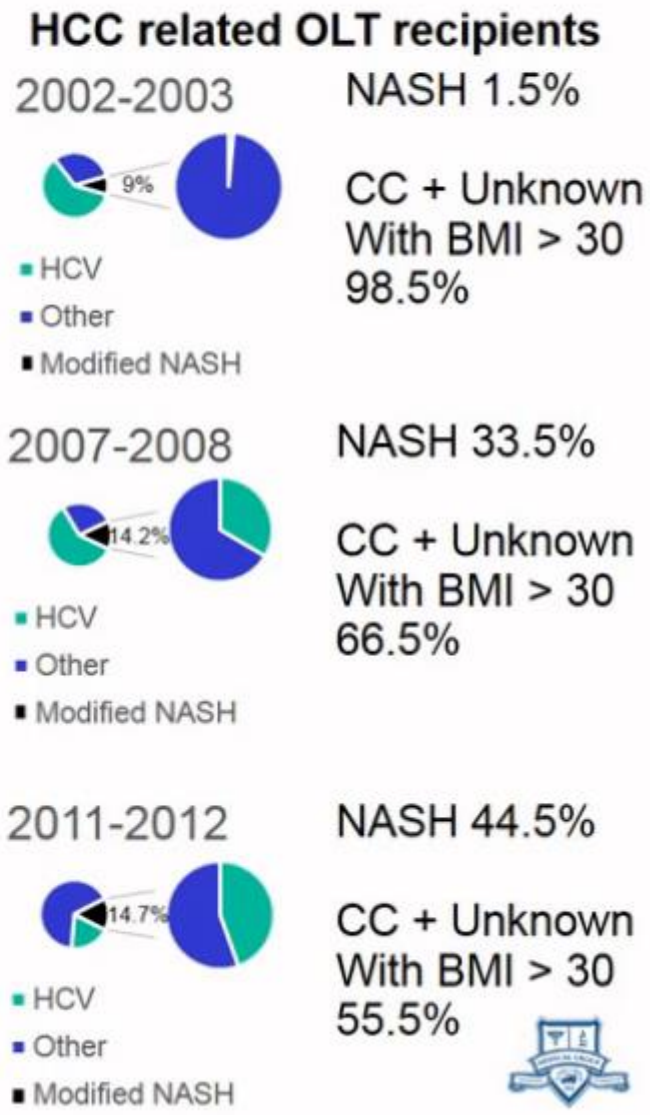
[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN.



Years since LT	1	2	4	6	8	10	12	14	15
Patients at risk (n); Steatosis grades 0-1	416	376	284	194	139	88	39	13	4
Patients at risk (n); Steatosis grades 2-3	91	88	61	54	43	29	19	3	1

ABD de HCC Nedeniyle KC TX Yapılanlarda NASH En Hızlı Artış Gösteren Etyoloji

- 2002-2012 61,868 LT with 10,061 HCC
- HCC-related LT increased 2.2% 1995 to 23.3% 2012
- NASH-HCC increased 0% 2002 to 6% 2012
- Modified NASH-HCC increased 8.3% 2002 to 13.5% 2012 (364% increase)
- Patients with NASH-HCC were more often older, higher BMI, higher rate of DM



Adapted from Wong et al, Hepatology 2014;59(6):2188-95

NAFLD grubu:
daha yaşlı,
daha kilolu,
daha çok renal ve metabolik problem
HCC

Table 1. Characteristics of New Liver Transplant Waitlist Registrants in the United States, 2004–2013

Characteristics	NASH	HCV	ALD	HCV/ALD	*P* value
Male, n (%)	7631 (54.9)	21,620 (69.8)	12,338 (76.5)	7111 (83.1)	<.01
Age, *y*, mean ± SD	58.0 ± 8.7	55.0 ± 7.1	54.2 ± 8.7	53.0 ± 6.2	<.001
BMI, *kg/m²*, median (range)	31.6 (18.7–47.7)	28.0 (18.5–43.9)	27.6 (17.6–44.1)	28.1 (18.4–43.3)	<.001
Race/ethnicity, n (%)					<.001
Non-Hispanic white	10,796 (78.5)	21,221 (69.1)	12,501 (78.5)	6131 (72.4)	
Black	460 (3.3)	3598 (11.7)	528 (3.3)	735 (8.7)	
Hispanic	2070 (15.0)	4803 (15.7)	2674 (16.8)	1542 (18.2)	
Asian	433 (3.2)	1,06 (93.5)	229 (1.4)	56 (0.7)	
HCC, n (%)	2925 (21.0)	7632 (24.6)	1212 (7.5)	1128 (13.2)	<.001
MELD, mean ± SD	16.5 ± 7.8	15.7 ± 7.6	19.1 ± 8.4	17.3 ± 8.1	<.001
Albumin, *g/dL*, mean ± SD	3.1 ± 0.7	3.0 ± 0.7	3.1 ± 0.7	2.9 ± 0.7	<.001
Bilirubin, *mg/dL*, median (range)	2.1 (1.0–38.0)	2.0 (1.0–38.4)	2.9 (1.0–40.4)	2.4 (1.0–40.8)	<.01
INR, mean ± SD	1.52 ± 0.80	1.51 ± 0.85	1.69 ± 0.69	1.63 ± 0.68	<.01
Creatinine, *mg/dL*, mean ± SD	1.45 ± 0.90	1.38 ± 0.86	1.55 ± 1.03	1.42 ± 0.90	<.01
GFR, *mL/min/1.73 m²*, mean ± SD	55.2 ± 20.0	61.6 ± 19.9	57.3 ± 21.6	62.7 ± 20.5	<.02
Ascites, n (%)	10,585 (76.1)	22,338 (72.1)	13,903 (86.2)	7114 (83.1)	<.001
Hepatic encephalopathy, n (%)	8490 (61.1)	18,004 (58.2)	11,533 (71.5)	6160 (72.0)	<.001
Diabetes, n (%)	6032 (46.3)	6307 (21.3)	3008 (19.5)	8211 (17.7)	<.001

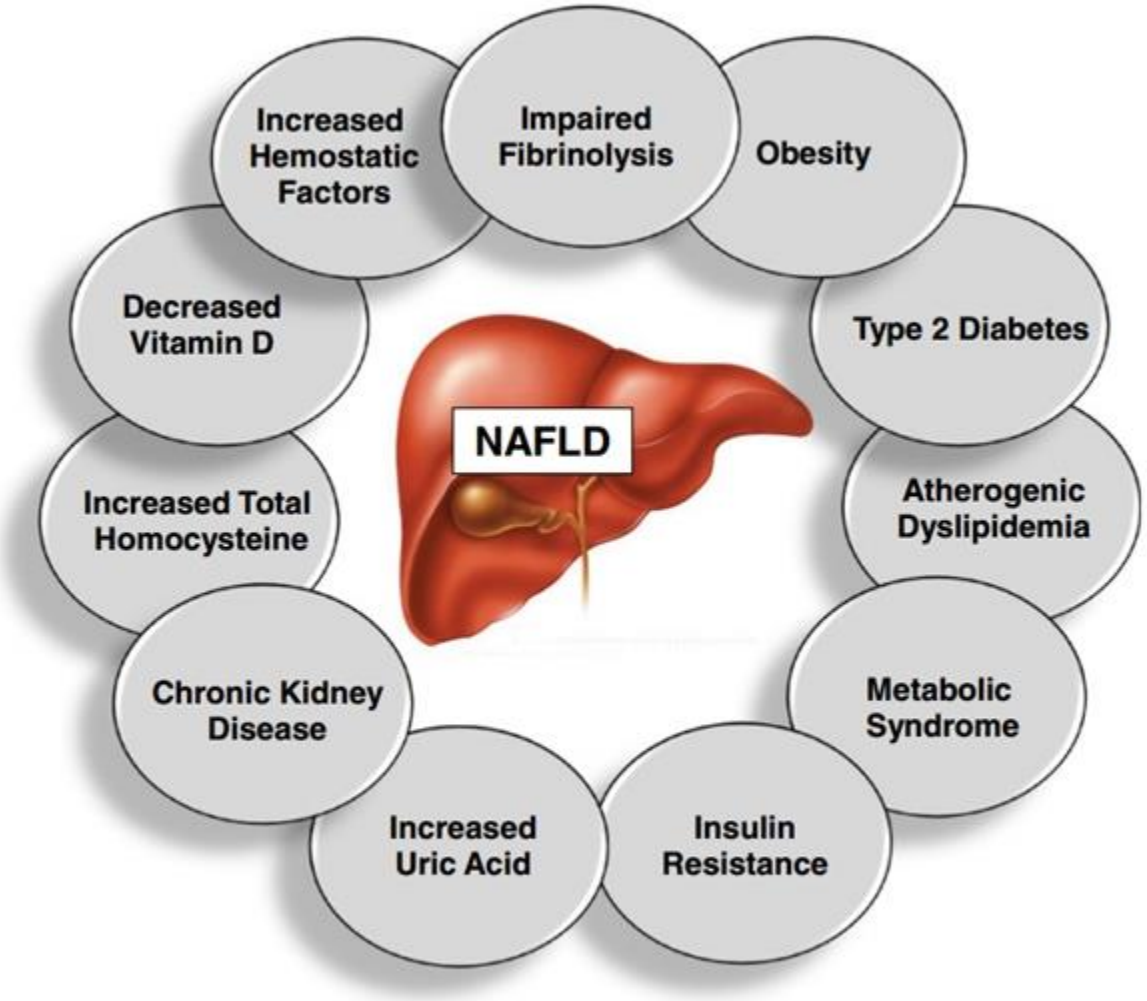
GFR, glomerular filtration rate; calculated using Modification of Diet in Renal Disease Study calculations; INR, international normalized ratio.

Wong, Gastroenterology, 2015

NASH Kardiyovasküler Risk - Patofizyoloji

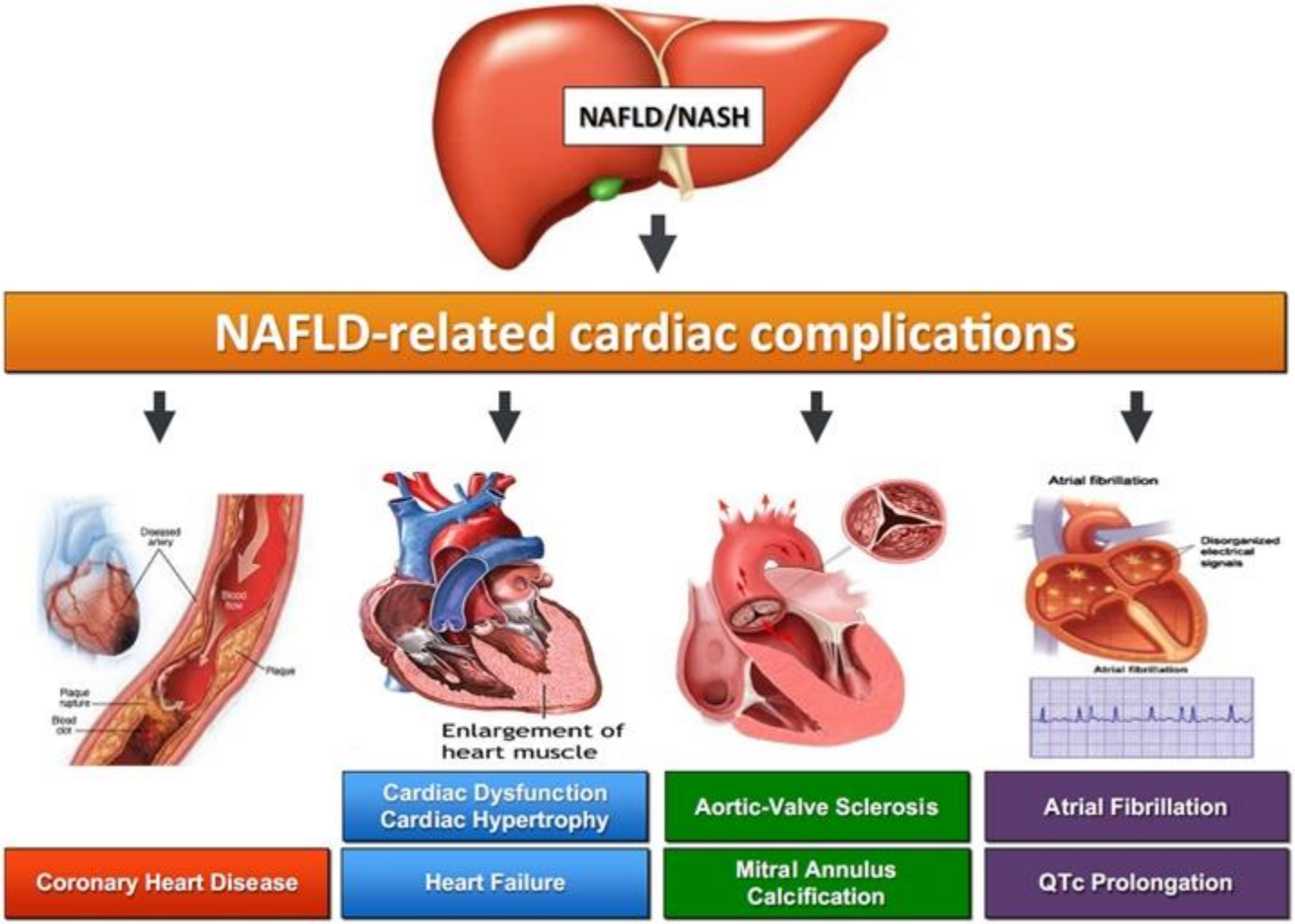
- Bozulmuş endotel Tx
- Riskli plak prevelansında artış
- Pro-aterojenik lipid profili
- Carotis IM kalınlığı ve koroner kalsifikasyonlar fazla
- Subklinik myokard disfx→ semptomatik diastolik disfx fazla
- NASH tüm bu risklerden bağımsız olarak da KVH için risk faktörü
- x4 kat KV olay riski

VanWagner, Liver Int, 2015



LONARDO *et al,* Metabolism 2016;65:1136-50

NAFLD ve KV Komplikasyonlar



MANTOVANI *et al,* Dig Dis Sci 2016;61:1246–1267

Kardiyovasküler Risk Değerlendirmesi

Accuracy of noninvasive methods for assessment of coronary artery disease in the general population

Imaging Modality	Sensitivity (%)	Specificity (%)
Exercise electrocardiogram	45–50	85–90
Exercise stress echocardiogram	80–85	80–88
Exercise SPECT	73–92	63–87
Dobutamine stress echocardiogram	79–83	82–86
Dobutamine stress cardiac MRI	79–88	81–91
Adenosine SPECT	90–91	75–84
CT coronary angiography	95–99	64–83
Adenosine PET	81–97	74–91

Based on 2013 ESC guidelines on the management of stable coronary artery disease (12). SPECT, single-photon emission computed tomography; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography.

Malhi, Curr Opin Organ Transplant, 2016

NAFLD VE KARDİYOVASKÜLER HASTALIK

Author [ref]	N	Follow-up (yrs)	Proportion due to CVD (%)	Findings
Angulo [1]	619	12.6 (median)	**38.3**	CVD most common COD Extent of fibrosis Independent assoc c death
Söderberg [2]	118	24 (median)	**30**	↑Death in those w NASH, CVD most common COD
Ekstedt [3]	129	13.7±1.3 (mean)	**16**	↑CVD death NASH not SS CVD most common COD
Dam-Larsen[4]	170	20.4 (median)	**38**	No difference between SS and control
Rafiq [5]	173	18.5 (median)	**12.7**	CVD death NAFLD=NASH

[1] Angulo et al. Gastroenterology 2015; [2] Söderberg et al., *Hepatology* 2010; [3] Ekstedt et al., *Hepatology* 2006; [3] Dam-Larsen et al., *Scand J of Gastroenterol* 2009; [5] Rafiq et al. *Clin Gastro Hep* 2009

Zamanla Tx Alıcılarında Yaş Dağılımı Değişiyor

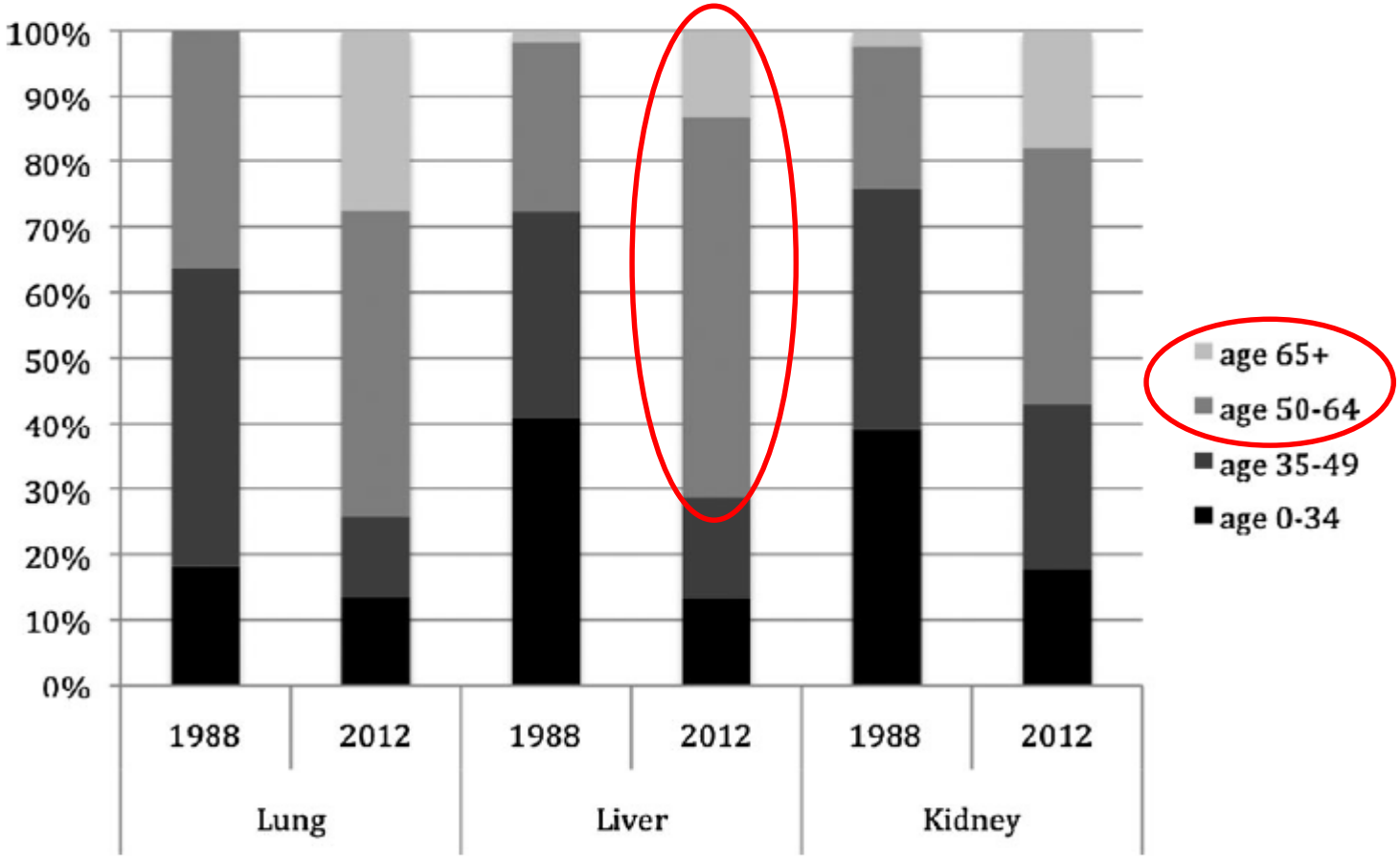


Figure 1: Difference in age distribution of transplant recipients—1988 versus 2012.

American Journal of Transplantation 2014; 14: 2228–2234

Karaciğer Tx Adaylarında Koroner Arter Hastalık Prevalansı

Study	Number of Patients	Prevalence of Coronary Artery Disease*	Definition of Significant Coronary Artery Disease
Carey et al.[8] (1995)	37	28% (15.2-43.1)	>70% stenosis
Morris et al.[9] (1995)	608	5.7% (4.0-7.7)	Criteria not described
Donovan et al.[10] (1996)	165	2.9% (0.7-6.3)	>50% stenosis
Plotkin et al.[11] (1998)	40	7.1% (0.5-17.4)	>70% stenosis
Tiukinhoy-Laing et al.[12] (2006)	161	20.3% (14.4-26.8)	>70% stenosis
Blei et al.[3] (2007)	161	24.5% (18.2-31.4)	>70% stenosis
Fili et al.[13] (2009)	627	3.0% (1.8-4.5)	>50% stenosis

LIVER TRANSPLANTATION 16:550-557, 2010

KAH için risk faktörleri pre-op değerlendirmede önemli

- Yaş
- Sigara
- Cinsiyet
- Lipid profili
- İnsülin direnci ve tip 2 DM
- Aile öyküsü
- Daha önce KAH öyküsü
- Obezite
- Hipertansiyon
- Etyoloji. NAFLD
- Pre-Tx renal hastalık
- …..

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doi:10.1016/j.jacc.2011.03.026

STATE-OF-THE-ART PAPER

Cardiovascular Risk Assessment of the Liver Transplant Candidate

Zankhana Raval, MD,* Matthew E. Harinstein, MD,† Anton I. Skaro, MD, PHD,‡ Ata Erdogan, MD,* Andre M. DeWolf, MD,§ Sanjiv J. Shah, MD,* Oren K. Fix, MD, MSC,‖ Nina Kay, RN,‡ Michael I. Abecassis, MD, MBA,‡ Mihai Gheorghiade, MD,*¶ James D. Flaherty, MD*

Chicago, Illinois; Pittsburgh, Pennsylvania; and San Francisco, California

Liver transplantation (LT) candidates today are increasingly older, have greater medical acuity, and have more cardiovascular comorbidities than ever before. Steadily rising model for end-stage liver disease (MELD) scores at the time of transplant, resulting from high organ demand, reflect the escalating risk profiles of LT candidates. In addition to advanced age and the presence of comorbidities, there are specific cardiovascular responses in cirrhosis that can be detrimental to the LT candidate. Patients with cirrhosis requiring LT usually demonstrate increased cardiac output and a compromised ventricular response to stress, a condition termed cirrhotic cardiomyopathy. These cardiac disturbances are likely mediated by decreased beta-agonist transduction, increased circulating inflammatory mediators with cardiodepressant properties, and repolarization changes. Low systemic vascular resistance and bradycardia are also commonly seen in cirrhosis and can be aggravated by beta-blocker use. These physiologic changes all contribute to the potential for cardiovascular complications, particularly with the altered hemodynamic stresses that LT patients face in the immediate post-operative period. Post-transplant reperfusion may result in cardiac death due to a multitude of causes, including arrhythmia, acute heart failure, and myocardial infarction. Recognizing the hemodynamic challenges encountered by LT patients in the perioperative period and how these responses can be exacerbated by underlying cardiac pathology is critical in developing recommendations for the pre-operative risk assessment and management of these patients. The following provides a review of the cardiovascular challenges in LT candidates, as well as evidence-based recommendations for their evaluation and management. (J Am Coll Cardiol 2011;58:223–31) © 2011 by the American College of Cardiology Foundation

Non-invaziv Yöntemler KAH saptamada Yeterli Değil!!

- DSE nun negatif prediktif değeri %75-%85 ancak pozitif prediktif değeri düşük %27
- SPECT-(single-photon emission CT) düşük poiztif prediktif değeri var ve yanlış pozitiflik
- MPS duyarlılığı düşük
- Korone kalsiyum skoru tek başına kıstlı değeri var ancak diğer risk faktörleriyle birlikte daha anlamlı olabilir. Kalsiyum skoru sıfır ise <%50 koroner darlık, daha çok negatif prediktif değeri var

- Bu nedenlerle 2 veya daha fazla risk faktörü varsa veya DM varsa önerilen koroner anjiyografi
  - Kanama
  - Akut börek hasarı
  - Transradyal yaklaşım
  - İlaçlı stentler tercih edilmez: ikili antiagregan verildiği için

Appraising cardiac dysfunction in liver transplantation: an ongoing challenge

Liver Intern 2014

Non-invaziv Yöntemler KAH saptamada Yeterli Değil!!

Non-invaziv Yöntemlerin Duyarlılığı		
	MPS	DSE
Kidney	29–92%	44–89%
Lung	43%	Unknown
Liver	Unknown	Unknown

DSE, dobutamine stress echocardiography; MPS, myocardial perfusion scanning.

American Journal of Transplantation 2014; 14: 2228–2234

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AASLD PRACTICE GUIDELINE

Evaluation for Liver Transplantation in Adults: 2013 Practice Guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation

Paul Martin,[1] Andrea DiMartini,[2] Sandy Feng,[3] Robert Brown, Jr.,[4] and Michael Fallon[5]

Recommendations:

6. Cardiac evaluation needs to include assessment of cardiac risk factors with stress echocardiography as an initial screening test with cardiac catheterization as clinically indicated (1-B).

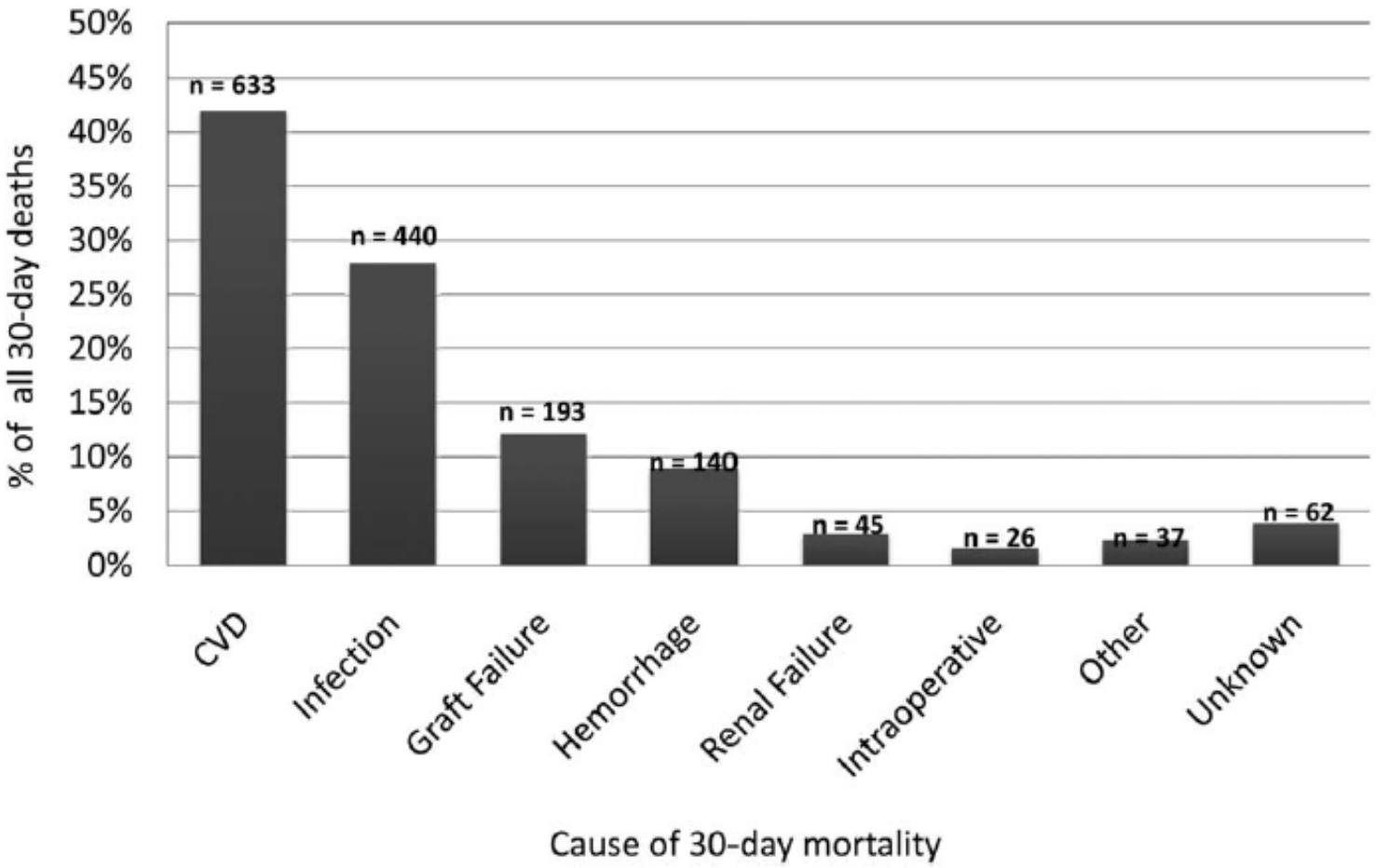
7. Cardiac revascularization should be considered in LT candidates with significant coronary artery stenosis prior to transplant (2-C).

High Early Cardiovascular Mortality After Liver Transplantation

- 2002-2012 arası Tx yapılmış 56.914 hasta OPTN(organ procurementand transplantation network) verisinden değerlendirilmiş
  - 2217'si değerlendirme dışı; AKY, eş zamanlı kalp-barsak-AC-pankreas TX
- Kardiyovasküler hastalık nedenli ölüm
  - Aritmi
  - Kalp yetmezliği
  - AMİ
  - Primer kardiyak arrest
  - İnme/trombembolik olay

LIVER TRANSPLANTATION 20:1306–1316, 2014

High Early Cardiovascular Mortality After Liver Transplantation



LIVER TRANSPLANTATION 20:1306–1316, 2014

Kardiyak Olay prediktörleri

Multivariable predictors of 30 and 90-day MACE after liver transplantation

	30-day MACE		90-day MACE	
	Incidence rate ratio (IRR)	95% confidence interval	Incidence rate ratio (IRR)	95% confidence interval
Recipient female sex	1.0	.82–1.1	1.0	.84–1.3
Recipient age				
<45	Ref	Ref	Ref	Ref
45–64	1.8	1.2–2.7	2.0	1.4–2.8
65+	2.8	1.8–4.4	2.9	1.9–4.3
Atrial fibrillation pretransplant	6.9	5.0–9.6	6.1	4.5–8.3
Stroke pretransplant	6.3	1.6–25.4	4.8	1.2–19.2
Alcohol-induced cirrhosis	1.6	1.2–2.2	1.5	1.2–2.0
Nonalcoholic steatohepatitis	1.6	1.1–2.4	1.7	1.2–2.4
Creatinine, at transplant (per dL)	1.1	1.04–1.2	1.1	1.03–1.14

* Multivariate Poisson regression analysis

Pre-Tx AF, altta yatan sirotik kardiyomyopatinin potansiyel belirtecidir ve erken MACE ile ilişkilidir.

Van Wagner, Am J Transplant, 2016

Obesitenin Post-Tx Komplikasyonlara Etkisi

Table 4. Overall hospital characteristics.

Characteristic	BMI ≥ 40 (n = 416)	BMI < 40 (n = 12 029)	P-value
Center volume			
LV-C	137 (33)	3997 (33.3)	0.083
MV-C	122 (29.4)	4062 (33.8)	
HV-C	156 (37.6)	3955 (32.9)	
LOS			
Total LOS	11 (10)	9 (8)	<0.0001
ICU LOS	3 (6)	3 (4)	0.0002
Mortality	20 (4.8)	488 (4.1)	0.45
Routine discharge home	305 (77)	9911 (85.9)	<0.0001
Direct cost (LT-to-discharge)	$98 541 ($60 976)	$100 469 ($60 721)	0.73
Readmission (30 days)	156 (39.4)	4367 (37.8)	0.53

BMI, body mass index; LV-C, low-volume center; MV-C, medium-volume center; HV-C, high-volume center; LT, liver transplantation; LOS, length of stay; ICU, intensive care unit.
Categorical variables are presented as numbers and percentages; continuous variables are presented as medians and interquartile range.

Additional sensitivity analyses were performed to assess the effect of diabetes and MELD on BMI. Both analyses showed results similar to the overall dataset that the in-hospital outcomes and short-term survival were not different with and without diabetes or by different gradations of MELD score.

Survival analysis

With a median follow-up of 2 years, there was no statistically significant difference for overall patient and graft survivals between the two groups (Figs 1 and 2). Also, subset analyses using a data set including patients only with higher MELD scores (≥20) or diabetes did not show any signifi-

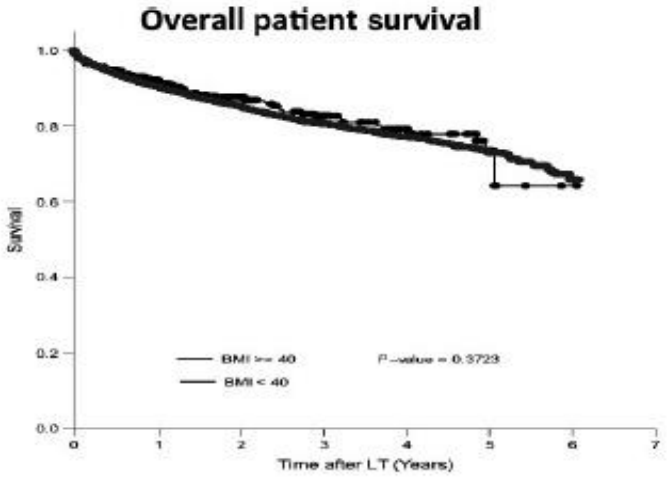


Figure 1 Morbidly obese recipients have equivalent patient survival following liver transplantation when compared with all other recipients (log-rank $P = 0.37$).

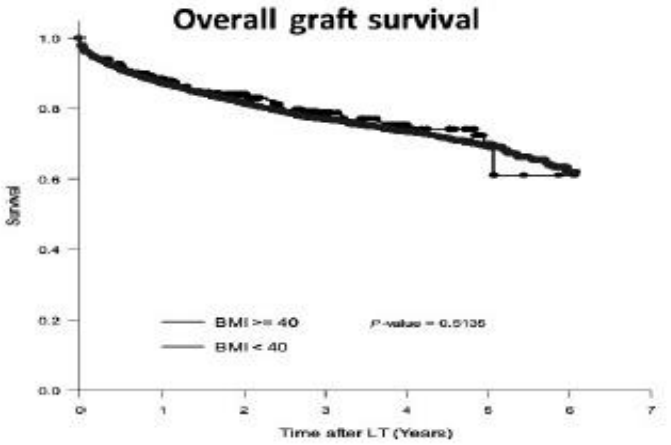


Figure 2 Morbidly obese recipients have equivalent graft survival following liver transplantation when compared with all other recipients (log-rank $P = 0.51$).

Singhal, Transplant Int, 2014

Obes vs Non-obes sağkalım benzer
Komplikasyonlar artar; infeksiyon, YBÜ kalış, transfüzyon,

TABLE 1. Summary of Studies Related to Effect of Obesity on Complications Following LT

Author	Year	N	BMI Cohort	Findings	Notes
Fujikawa et al., 2006[14]	1990-2005, U.S. center	700	<25 25-30 >30	No difference in cost, LOS, reoperation, surgical complications, graft or patient	Only n = 37 patients with BMI >35
Nair et al., 2009[15]	2005-2007, U.S. center	193	<30.0 30.0-34.9 35.0-39.9 >39.9	No differences in resource utilization, surgical complications, patient, or graft	Scoring system combining diabetes, obesity and prior abdominal surgery
Schaeffer et al. 2009[16]	1999-2003, Canadian	167	<30.0 30.0-34.9 ≥35.0	Increased wound complications, longer LOS	Small numbers
LaMattina et al., 2012[17]	1997-2008, U.S. center	813	<25.1 25.1-30.0 30.1-35.0 35.1-40.0 >40.0	Increased operating time, LOS, infection, transfusion, infection, operative complication	Patient and graft survival outcome similar
Agopian et al., 2012[18]	1993-2011, U.S. center	1235	<18.5 18.5-20.0 20.1-25.0 25.1-30.0 30.1-35.0 35.1-40.0 >40.0	Increased operative time, hospital stay, and blood loss	Patient and graft outcome similar
Hakeem et al., 2013[19]	1994-2009, U.K. center	1325	<18.5 18.5-20.0 20.1-25.0 25.1-30.0 30.1-35,0 >35,0	Longer hospital and ICU stay, increased infection	Patient and graft outcomes similar

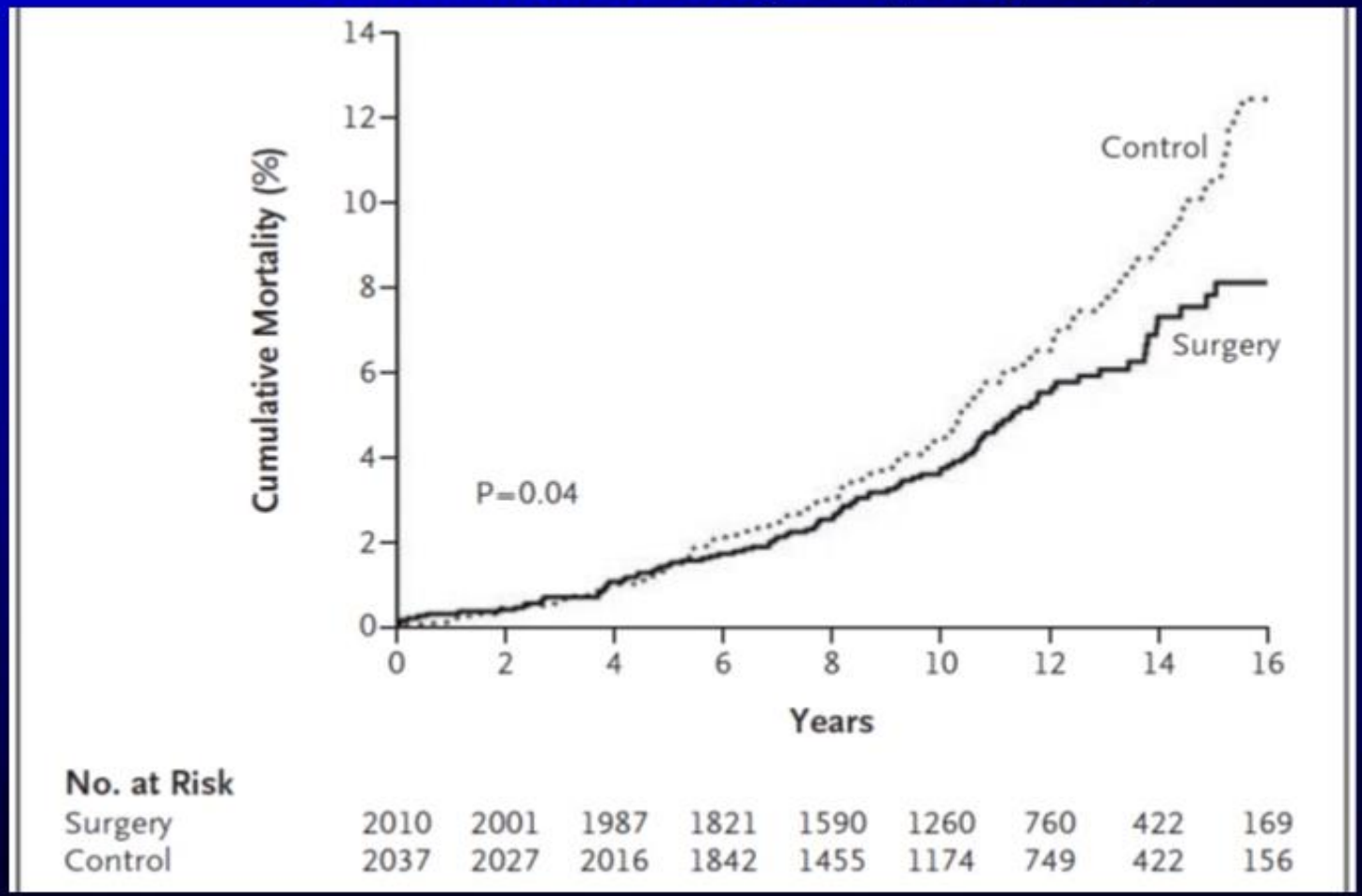
Heimbach, Liver Transplantation, 2014

NASH ve Bariatrik cerrahi

- Gastrik bypass; IS tedavi doz ayarlamasında problemlere neden olan malabzorbsiyona neden olduğu için Sleeve Gastrektomi tercih edilmelidir
- İdeal zaman: Pre-Tx (Eş zamanlı da yapanlar var)
- İdeal hasta: Child A, BMI<35, Nüks NASH – ReTx, Greftte ilerleyici fibrozis varlğında post-Tx
- Dikkat:
  - Adhezyonlar (Laparoskopik daha iyi olabilir)
  - Hızlı kilo vermeye bağlı yağlanma!

Reino, WJH 2015
Newsome, Gut 2102

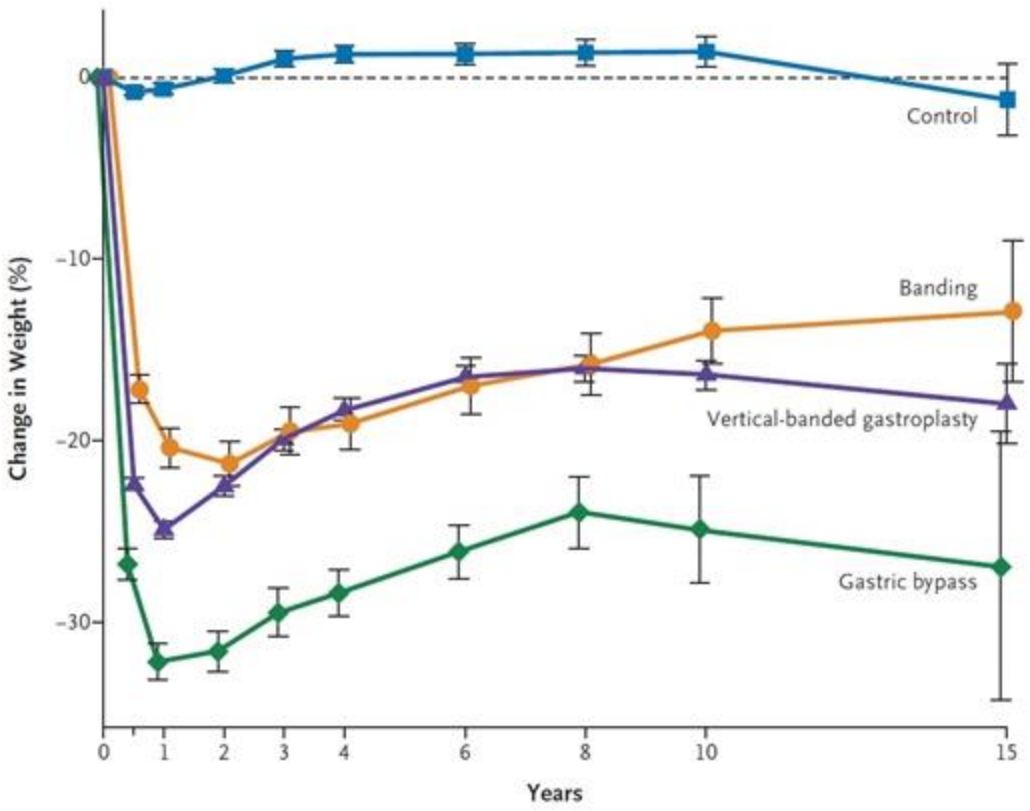
BARİATRİK CERRAHİ SAĞKALIMI ARTIRMAKTA



Sjöström L, N Egnl J Med 2007

Adams TD, N Egnl J Med 2007

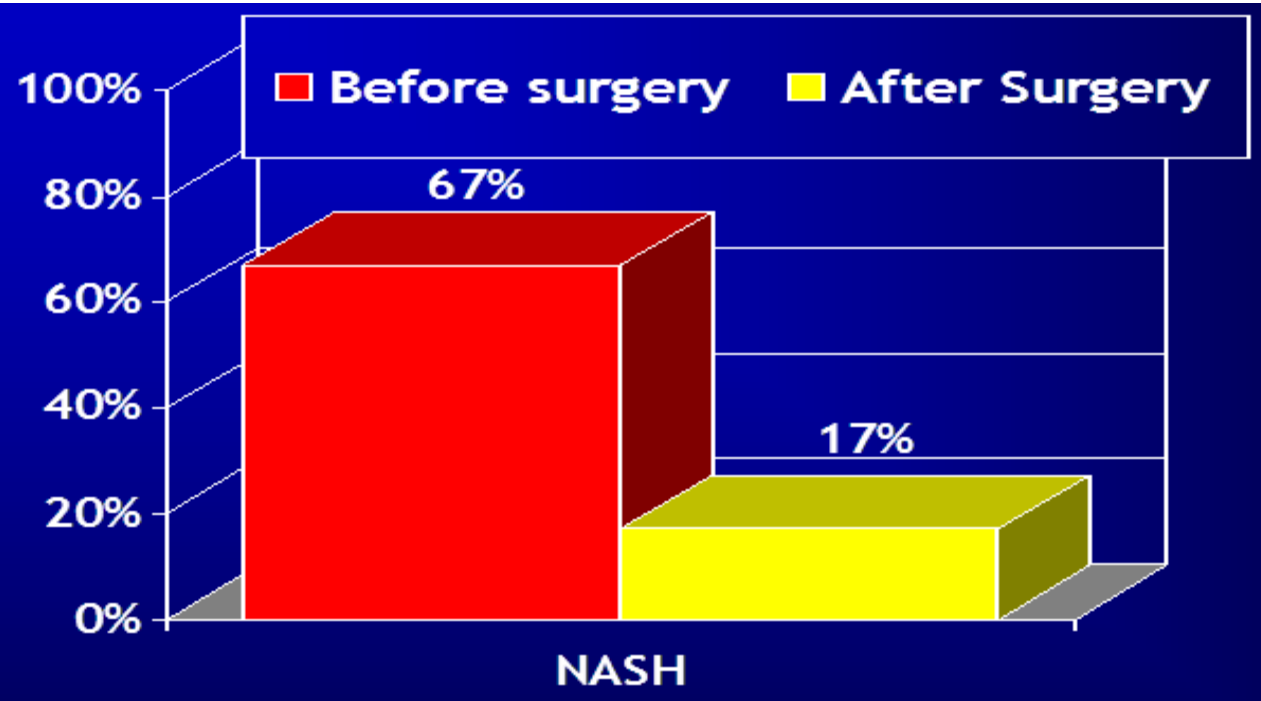
BARİATRİK CERRAHİ KİLO KONTROLÜNÜ SAĞLAMAKTA



No. Examined									
Control	2037	1768	1660	1553	1490	1281	982	886	190
Banding	376	363	357	328	333	298	267	237	52
Vertical-banded gastroplasty	1369	1298	1244	1121	1086	1004	899	746	108
Gastric bypass	265	245	245	211	209	166	92	58	10

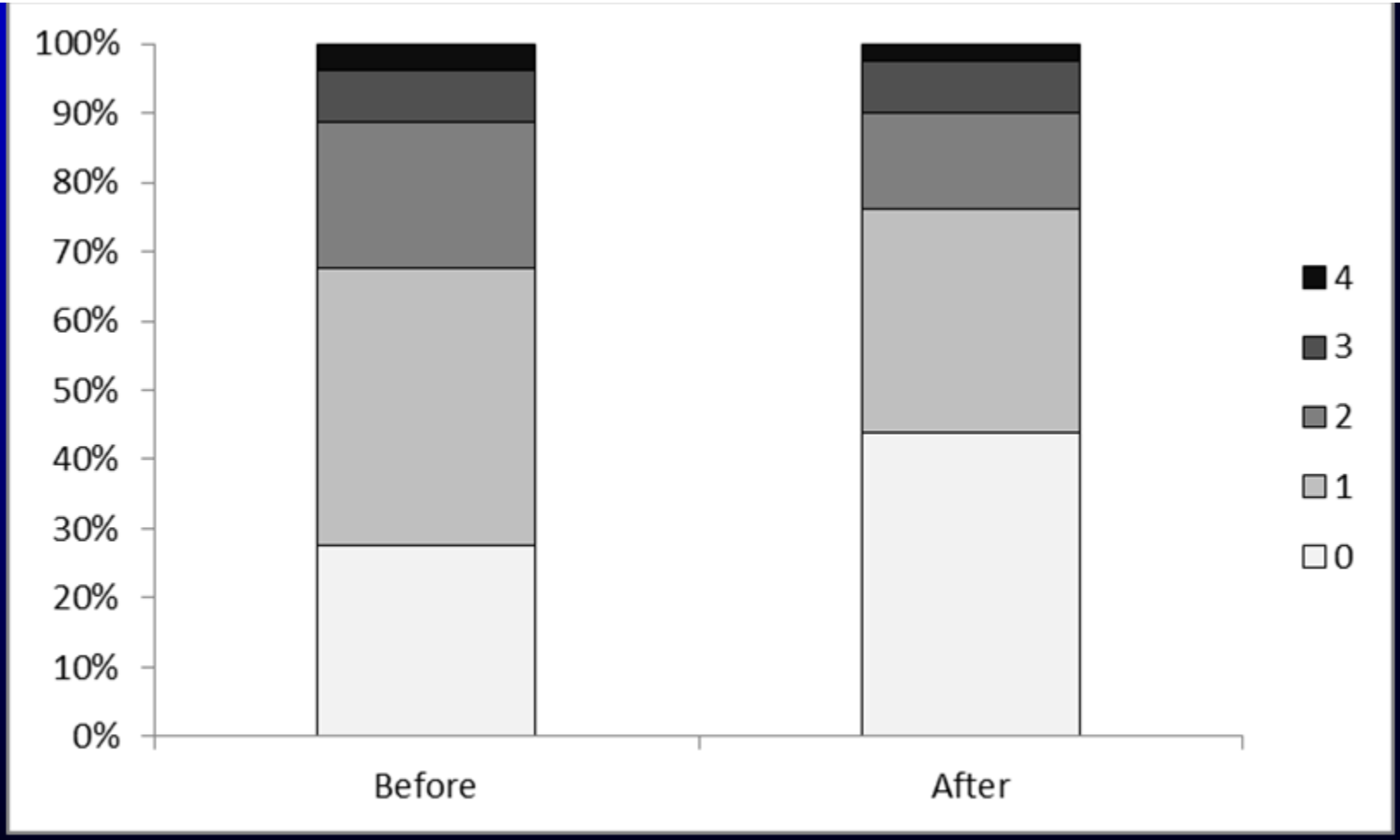
Sjöström L, N Egnl J Med 2007

BARİATRİK CERRAHİ VE NASH



Dixon Hepatology 2004

BARİATRİK CERRAHİ VE FİBROZİS PROGRESYONU



Lassailly G, Gastroenterogloy 2015

Outcome of liver transplantation in patients with prior bariatric surgery

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Keywords: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, body mass index, postoperative complications

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ABSTRACT

Non-alcoholic fatty liver disease is becoming the leading cause of disease resulting in liver transplantation (LT). As a result of this trend, more liver transplant candidates are presenting with prior history of bariatric surgery (BS). Over the last decade, 960 patients underwent LT at our institution; 11 (1.1%) had prior BS. Most common type of BS was Roux-en-Y gastric bypass (n=9) with 1 sleeve gastrectomy and 1 jejunoileal bypass. Nine patients underwent LT alone and 2 underwent simultaneous liver-kidney transplantation. Most common indication for LT was non-alcoholic steatohepatitis (n=10) with 5 having additional diagnosis of alcoholic liver disease. Thirty-day reoperation rate was 36.4% (n=4); indications were bile duct repair (n=3) and wound repair (n=1). In first 6 months after LT, biliary complications were seen in 54.5% (n=6) of the patients. Both patient and graft survival rates at 1 and 2 years were 81.8% (n=9) and 72.7% (n=8), respectively. Eight patients (72.7%) had indications for liver biopsy post-LT; significant macro-vesicular steatosis was found in 2 (18.2%). In patients with history of alcohol consumption, 2 (40.0%) relapsed post-LT. Two patients (18.2%) had history of diet-controlled diabetes pre-LT; 1 of these patients became insulin dependent post-LT. Mean body mass index at LT was 31.0±5.7. Mean body mass index at 1, 6, and 12 months post LT was 28.3±5.8, 28.0±3.2 and 31.0±6.6, respectively. Mean preoperative albumin was 2.6±0.6 mg/dl. Patients showed improvement in albumin post-LT, with mean albumin of 2.7±0.6 and 3.2±0.5 mg/dl, at 1 and 3 months, respectively. Liver profile was stable post-LT, with mean AST of 32.9±18.4 and 26.6±19.8 IU/L and ALT of 28.0±17.5 and 30.2±17.0 IU/L at 6 and 12 months, respectively. In conclusion, outcomes of LT patients with prior BS are comparable to other transplant recipients with regards to patient and graft survival, and post-LT complication rates.

ABSTRACT

Non-alcoholic fatty liver disease is becoming the leading cause of disease resulting in liver transplantation (LT). As a result of this trend, more liver transplant candidates are presenting with prior history of bariatric surgery (BS). Over the last decade, 960 patients underwent LT at our institution; 11 (1.1%) had prior BS. Most common type of BS was Roux-en-Y gastric bypass (n=9) with 1 sleeve gastrectomy and 1 jejunoileal bypass. Nine patients underwent LT alone and 2 underwent simultaneous liver-kidney transplantation. Most common

Pre-TX BS yapılan 11 hasta (10 u NAFLD)
9 u gastrik by-pass
Post-Tx 1. ayda re-op %36
Sağkalım ve komplikasyon oranları benzer
Uzun dönemde nüks NASH açısından BS vs non-BS olanlarla ilgili çalışmaya gereksinim var

Patients showed improvement in albumin post-LT, with mean albumin of 2.7±0.6 and 3.2±0.5 mg/dl, at 1 and 3 months, respectively. Liver profile was stable post-LT, with mean AST of 32.9±18.4 and 26.6±19.8 IU/L and ALT of 28.0±17.5 and 30.2±17.0 IU/L at 6 and 12 months, respectively. In conclusion, outcomes of LT patients with prior BS are comparable to other transplant recipients with regards to patient and graft survival, and post-LT complication rates.

Donör Karaciğerde NAYK

- İskemi reperfüzyon hasarı nedeniyle HS'li donörlerde greft yemezliği ve fonksiyon bozukluğu fazla
- >%60 takılmıyor
- %30 – 60 sonuçlar daha kötü (1y greft yetmezliği için bağımsız risk faktörü)
- Canlı donör >%10 – 15 HS kötü
  - Diyet – zayıflatma
- Kadavra: Ischemic preconditioning(tartışmalı sonuçlar)
  - Sevofluran
  - CS
  - Antioksidanlar

KC Nakli Sonrası NAFLD Nüksü

- KC nakli sonrası NAFLD nüksü 5 yılda %100
  - Contos et al , Liver Transp 2001
- Kriptojenik siroz nedenli KC tx li olgularda NAFLD
  - 1 yıl %8
  - 3 yıl %13.6
  - 5 yıl %24.9
  - 10 yıl %32.9
  - İleri fibrozis gelişimi düşük;
    - 5 yılda %5
    - 10 yılda %10
  - Tx öncesi NASH olanlarda
    - daha ileri fibrozis;
    - 5 yılda %27
    - 10 yılda %31
    - Yalamanchili et al. Liver Transp 2010
    - Dureja et al. Transplantation 2011

Summary of the main diseases (excluding neoplasms) that are thought to recur following liver transplantation.

Recurrent Disease	Frequency (%)	Histological Features (in biopsies >12 months post-transplant)	Comments
Primary sclerosing cholangitis (PSC)	20-30	Fibrous cholangitis (rarely seen in liver biopsies). Diagnosis more often based on findings of chronic cholestasis, ductopenia, ductular reaction and a "biliary pattern" of fibrosis. Approximately 25% have bridging fibrosis or cirrhosis by 5 years post-transplant.	More frequently clinically symptomatic than recurrent PBC. Approximately 10% progress to graft failure. Histological and radiological features difficult to distinguish from ischaemic cholangiopathy. Diagnosis therefore requires exclusion of other causes of biliary tract disease.
Autoimmune hepatitis (AIH)	20-30	Portal tract plasma cell-rich inflammatory infiltrate associated with interface hepatitis. Lobular inflammation frequently present - severe cases include foci of confluent/bridging necrosis. Lobular inflammatory changes may resemble "central perivenulitis" and can occur as the first manifestation of recurrent disease.	Most cases occur as a result of suboptimal immunosuppression and respond to immunosuppressive therapy. Diagnosis based on a combination of biochemical, serological, and histological findings.
Alcoholic liver disease (ALD)	10-30	Fatty change common (>60% of cases) Steatohepatitis and fibrosis less common. Progression to cirrhosis rare.	Recurrent alcohol consumption common, but serious graft complications are rare.
Non-alcoholic Fatty Liver Disease (NAFLD)	20-40	Fatty change common (60-100% of cases). 10-40% progress to steatohepatitis and up to 12% become cirrhotic.	Risk factors for NAFLD often persist and may be exacerbated by immunosuppressive drugs and other transplant-related factors. Many people with recurrent NAFLD have normal LFTs.

Journal of Hepatology 2011;55: 702–717

TABLE 1. Summary of the Recurrence Rates for Steatosis, Steatohepatitis, and Advanced Disease (Bridging Fibrosis or Cirrhosis) in the Posttransplant Setting From Studies Performing Histological Reviews

Study	Patients (n)	<1 Year	1 Year	2 Years	3 Years	>4 Years
Steatosis						
Kim et al.[22] (1996)	8	5/8 (63%) in 4 months		1/8 (13%)		
Contos et al.[23] (2001)	30	4/27 (15%) in 6 months				14/27 (52%)
Charlton et al.[25] (2001)	31	9/15 (60%) in 4 months				
Ayata et al.[26] (2002)	9	Not reported				
Malik et al.[27] (2009)	98	36/79 (45%) in a mean of 260 days				
Bhagat et al.[28] (2009)	71 (32 with biopsy- or ultrasound-proven NASH)	Not reported				
Yalamanchili et al.[29] (2010)	227		8.2%*	13.6%*	24.9% in 5 years and 32.9% in 10 years*	
Steatohepatitis						
Kim et al.[22] (1996)	8	1/8 (13%) in 6 weeks	—	1/8 (13%) in 2 years	1/8 (13%) in 2.5 years	
Contos et al.[23] (2001)	30	0	1/27 (4%)	—	2/27 (7%)	3/27 (11%)
Charlton et al.[25] (2001)	31	2/15 (13%) in 4 months	4/15 (27%)	5/15 (33%)		
Ayata et al.[26] (2002)	9			2/9 (22%) in 1.5 and 2 years		
Malik et al.[27] (2009)	98	19/79 (24.1%) in 461 days				
Bhagat et al.[28] (2009)	71 (32 with biopsy- or ultrasound-proven NASH)	21/64 (33%) in >6 months				
Yalamanchili et al.[29] (2010)	227				13/227 (6%) in 20 years	
Bridging Fibrosis or Cirrhosis						
Kim et al.[22] (1996)	8			No cirrhosis within a mean follow-up period of 15 months		
Contos et al.[23] (2001)	30	1/30 (3%), time not stated				
Charlton et al.[25] (2001)	31	3/15 (20%), ≥stage 2				5/15 (33%)
Ayata et al.[26] (2002)	9	Not reported				
Malik et al.[27] (2009)	98				14/79 (18%) in 461 days	
Bhagat et al.[28] (2009)	71 (32 with biopsy- or ultrasound-proven NASH)			No cirrhosis within a median follow-up period of 1517 days		
Yalamanchili et al.[29] (2010)	227				5% in 5 years and 10% in 10 years	

De-novo Alkol Dışı Yağlı KC Hastalığı (NAFLD)

- Nüks ya da de-novo NAFLD arasındaki ayrım sıklıkla zordur.

- Risk faktörleri
  - diyabetes mellitus ve insulin direnci
  - Kilo alımı,
  - Hipertansiyon ve hiperlipidemi
  - Yağlı donör karaciğeri
  - HCV

- Kriptojenik siroz ve/veya transplantasyon öncesi metabolik sendrom risk faktörlerini barındıran hastalarda gelişen NAFLD de daha çok nüks NAFLD düşünülmelidir .

- Histolojik özellikler
  - Yağlanma nüks hastalıktan bağmsız olarak trasnplant sonrası protokol biyopsilerinin %18-40 da izlenmektedir
  - Steatoz başlıca makrovezikülerdir ve genellikle ılımlı derecededir.
  - Steatohepatitin özellikleri, tipik olarak ılımlı olmakla birlikte, %1-13 vakada izlenmektedir.

LIVER TRANSPLANTATION 20:1064-1071, 2014

ORIGINAL ARTICLE

Recurrent or De Novo Nonalcoholic Fatty Liver Disease After Liver Transplantation: Natural History Based on Liver Biopsy Analysis

Mélanie Vallin,[1] Olivier Guillaud,[1] Olivier Boillot,[1,3] Valérie Hervieu,[2,3] Jean-Yves Scoazec,[2,3] and Jérôme Dumortier[1,3]

[1]*Hospices Civils de Lyon, Edouard Herriot Hospital, Department of Digestive Diseases;* [2]*University Claude Bernard Lyon 1; and* [3]*Hospices Civils de Lyon, Edouard Herriot Hospital, Department of Pathology, Lyon, France*

Nonalcoholic fatty liver disease (NAFLD) is a potential long-term complication after liver transplantation (LT) and can occur as recurrent disease in patients undergoing transplantation for NAFLD or as de novo NAFLD in others. The aim of this study was to compare these 2 different entities. From a cohort of adult patients undergoing transplantation between 2000 and 2010, we selected all patients with a diagnosis of NAFLD made during liver biopsy examinations during post-LT follow-up; clinical, biological, and histological features of patients with recurrent NAFLD and patients with de novo NAFLD were compared. The diagnosis of post-LT NAFLD was made for 91 patients during the study period: 11 cases were classified as recurrent NAFLD, and 80 cases were classified as de novo NAFLD. The groups were not statistically different with respect to the sex ratio, age, prevalence of hypercholesterolemia, prevalence of obesity, or prevalence of hypertension. The prevalence of diabetes mellitus was higher in patients with recurrent NAFLD (100% versus 37.5%, $p < 0.01$). At 5 years, severe fibrosis (stage 3 or 4) and steatohepatitis were more frequent in patients with recurrent NAFLD versus patients with de novo NAFLD [71.4% versus 12.5% ($P < 0.01$) and 71.4% versus 17.2% ($P < 0.01$), respectively]. NAFLD was already present in 67% of the patients with de novo NAFLD and in 100% of the patients with recurrent NAFLD after 1 year. According to successive liver biopsies, steatosis disappeared in 18 patients (22.5%) with de novo NAFLD and in none of the patients with recurrent NAFLD. In conclusion, our results strongly suggest that recurrent NAFLD and de novo NAFLD after LT are different entities; recurrent NAFLD appears to be a more severe and irreversible disease with an earlier onset. *Liver Transpl 20:1064-1071, 2014.* © 2014 AASLD.

Received February 10, 2014; accepted May 28, 2014.

In the last decades, nonalcoholic fatty liver disease (NAFLD) has been increasingly recognized as the most common liver disease in Western countries, and it possibly affects up to 30% of individuals.[1] NAFLD is associated with a potential risk of progression to liver fibrosis, cirrhosis, and eventually liver failure and hepatocellular carcinoma.[2] Liver transplantation (LT) is the accepted treatment of end-stage liver disease. The short-term results of this procedure have dramatically improved, whereas long-term outcomes are compromised by an increased risk of cancer and by the adverse effects of immunosuppressive treatment.[3] NAFLD after LT can occur in 2 different settings. First, it can be the recurrence of the initial disease in patients undergoing transplantation for complications of NAFLD (mainly liver failure or hepatocellular carcinoma).[4] In addition, because LT recipients accumulate several risk factors for NAFLD,[5] they can develop

Abbreviations: LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NS, not significant.

Potential conflict of interest: Nothing to report.

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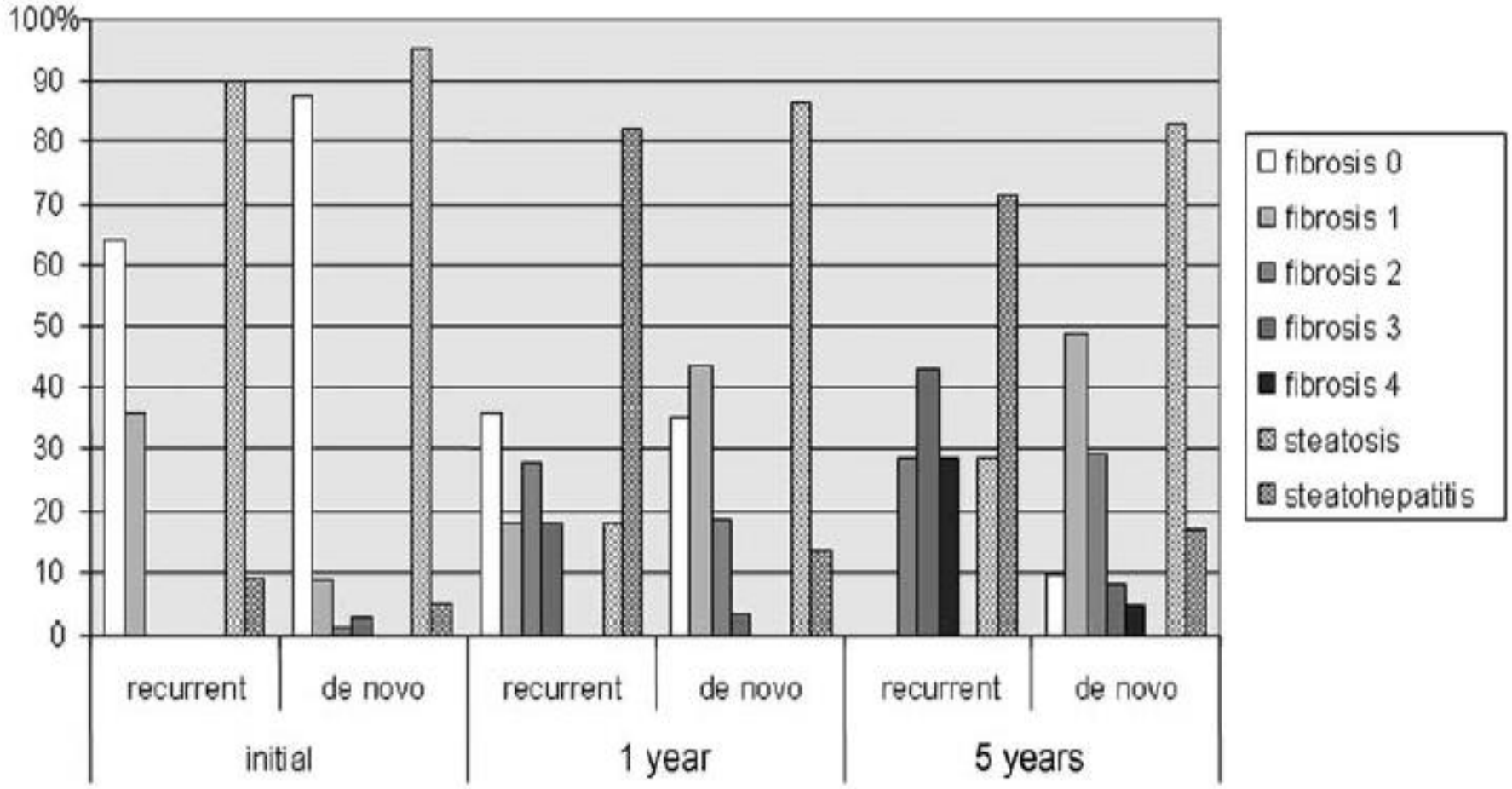
Characteristic	Recurrent NAFLD (n = 11)	De Novo NAFLD (n = 80)	*P* Value
At the time of LT			
Age (years)*	56 ± 10	52 ± 7	NS
Recipient sex ratio: male/female	2.7 (8/3)	2.2 (55/25)	NS
Indication for LT [n (%)]			Not relevant
Alcohol	0 (0)	62 (77.5)	
Hepatitis B virus	0 (0)	6 (7.5)	
Hepatitis C virus	0 (0)	2 (2.5)	
NAFLD	11 (100)	0 (0)	
Other	0 (0)	10 (12.5)	
Mean recipient body mass index (kg/m^2)	24 ± 4	23 ± 4	NS
Initial graft steatosis [n (%)]	8 (72.3)	46 (57.5)	NS
Mean cold ischemia time (minutes)	624 ± 170	631 ± 177	NS
After LT†			
Liver biopsies per patient after LT*	4.1 ± 0.5	4.5 ± 0.8	NS
Mean weight gain since LT (kg)	13 ± 15	14 ± 15	NS
Mean body mass index (kg/m^2)	28 ± 6	28 ± 6	NS
Immunosuppressive regimen [n (%)]‡			
Steroids	0 (0)	8 (10)	NS
Cyclosporine A	1 (9)	16 (20)	NS
Tacrolimus	10 (91)	64 (80)	NS
Mycophenolate mofetil	9 (82)	60 (75)	NS
Diabetes mellitus [n (%)]	11 (100)	30 (37.5)	<0.001
Diabetes mellitus treated with insulin [n (%)]	4 (36.4)	14 (46.7)	NS
Hypercholesterolemia [n (%)]	5 (45.4)	34 (42.5)	NS
Obesity [n (%)]	9 (82)	50 (62.5)	NS
Hypertension [n (%)]	6 (54.5)	42 (52.5)	NS

Nüks NAFLD grubunda NASH ve ileri fibrozis daha progresif seyrederken;
De-novo grupta yağlanma ve düşük dereceli fibrozis görülüyor



Valin et al. Liver Transplant 2014

NAFLD nedeniyle KC Nakli Olan Hastaların Sağkalımı

	Patient Survival (Years)				
Study	1	3	5	10	20
Kim et al.[22] (1996)	100% at a mean interval of 15 months (6 weeks to 4 years)				
Contos et al.[23] (2001)			90% at a median interval of 3.5 years		
Charlton et al.[25] (2001)		81.2%			
Ayata et al.[26] (2002)			78% at a mean interval of 1285 days		
Malik et al.[27] (2009)			83%		
Bhagat et al.[28] (2009)			73% at a median interval of 4 years		
Yalamanchili et al.[29] (2010)	85.6%		71.4%	56.5%	12.6%

İleri dönemde sağkalımı genellikle kardiyovasküler hastalıklar belirlemekte

Long-term Outcomes in Patients Undergoing Liver Transplantation for Nonalcoholic Steatohepatitis-Related Cirrhosis

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Background. Nonalcoholic steatohepatitis (NASH), a clinically aggressive variant of nonalcoholic fatty liver disease (NAFLD), is becoming an increasingly common indication for liver transplantation (LT); however, relatively little is known regarding its clinical course post-LT. The aim of the current study is to describe disease recurrence and clinical course after LT. **Methods.** All surviving patients transplanted for NASH at the authors' institution had transient elastography (TE) to evaluate hepatic steatosis and fibrosis. The charts of deceased patients were reviewed for liver biopsy to evaluate for disease recurrence. Finally, causes of mortality in these patients were evaluated. **Results.** Of the 103 patients who met criteria, 56 had TE, whereas 34 had a liver biopsy. Steatosis was detected in 49 (87.5%) of the patients who had a TE and were defined to have recurrent NAFLD. Most patients had liver stiffness measurements consistent with no fibrosis (42.9%) or F1-F2 fibrosis (30.4%). Advanced fibrosis was noted in 26.8%, whereas 5.4% had cirrhosis but were clinically compensated. In patients with liver biopsy, 88.2% had recurrent NAFLD, whereas 41.2% had recurrent NASH. Bridging fibrosis was noted in 20.6% of patients but no patients had cirrhosis. Within the cohort, 32 patients died with the leading cause of mortality cancer (25%), infectious complications (25%), and cardiovascular disease (21.9%). Only 9% of deaths were attributable to graft cirrhosis. **Conclusions.** Recurrent NAFLD is common post-LT occurring in nearly 88% of all patients, whereas nearly a quarter of patients were noted to have advanced fibrosis.

(*Transplantation* 2017;101: 1867–1874)

Nonalcoholic fatty liver disease (NAFLD) accounts for nearly 75% of chronic liver diseases in the United States[1] and is closely linked with features of metabolic syndrome, particularly insulin resistance.[2,3] NAFLD exists in predominantly 2 main histological subtypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH).[4] NAFL is characterized by presence of greater than 5% hepatic steatosis in the absence of cytological ballooning, and significant inflammation or fibrosis. In contrast, presence of cytological ballooning and lobular inflammation along with hepatic steatosis is the minimum histological criteria necessary to diagnose NASH.

NAFLD affects nearly 30% of the U.S. population, and its prevalence is higher in patients with diabetes and obesity.[5] Although a rare cause of cirrhosis in the 1990s, NASH is now the fastest-growing listing indication for liver transplantation (LT) among new waitlist registrants.[6] Additionally, the number of patients receiving LT for NASH continues to increase and NASH is the only indication for LT that appears to be rising.[7] Despite the increase in frequency in LT for NASH, there is paucity of data regarding recurrence of NAFLD post-LT and factors associated with disease progression.[8] The only study to systematically evaluate NAFLD post-LT reported universal recurrence of NAFLD after LT.[9] In the largest study published on patients transplanted for cryptogenic or NASH-related cirrhosis, only 7% of the cohort consisted of patients who had LT for NASH.[10] The published literature is thus limited by inconsistent definition of patients with NASH cirrhosis, detailed histological description on postliver transplant biopsies, lack of long-term

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C.B., A.J.S., C.D., R.T.S., S.M., P.P., A.S., A.C., M.L., R.S., V.L., H.L., and M.S.S. participated in project design. M.O. participated in histology. C.B., M.S.S., S.M., R.T.S., C.D., and H.G. participated in patient enrollment. M.R., D.R.K., C.B., and M.S.S. participated in data collection. C.B. and M.S.S. participated in data analysis. C.B. and M.S.S. participated in article preparation. C.B., M.O., A.J.S., M. R., C.D., R.T.S., D.R.K., S.M., P.P., H.G., A.S., A.C., M.L., R.S., V.L., H.L., and M. S.S. participated in article review.

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Long-term Outcomes in Patients Undergoing Liver Transplantation for Nonalcoholic Steatohepatitis-Related Cirrhosis

	Histology	Transient elastrography
Demographics		
N	34	56
Age, y	61.5 ± 9.7	63 ± 9.2
Sex (% male)	47.1	55.4
BMI, kg/m^2	33.3 ± 5.3	31.7 ± 5.3
DM (% of cohort)	65.6	72.3
HTN (% of cohort)	90.3	95.2
Hyperlipidemia (% of cohort)	78.6	86.3
ALT, IU/L	39.1 ± 26.4	26.3 ± 14
AST, IU/L	31.716.6	25.4 ± 13.4
Median time from LT to follow-up, mo	47 (23-95)	75 (40-146)
NAFLD Recurrence (% of cohort)	88.2	—
NASH	41.2	—
Steatosis (% of cohort):		
Grade 0	4 (11.8)	7 (12.5%)
Grade 1	17 (50.0))	49 (87.5%)
Grade 2	7 (20.6)	40 (71.4%)
Grade 3	6 (17.6)	28 (50%)

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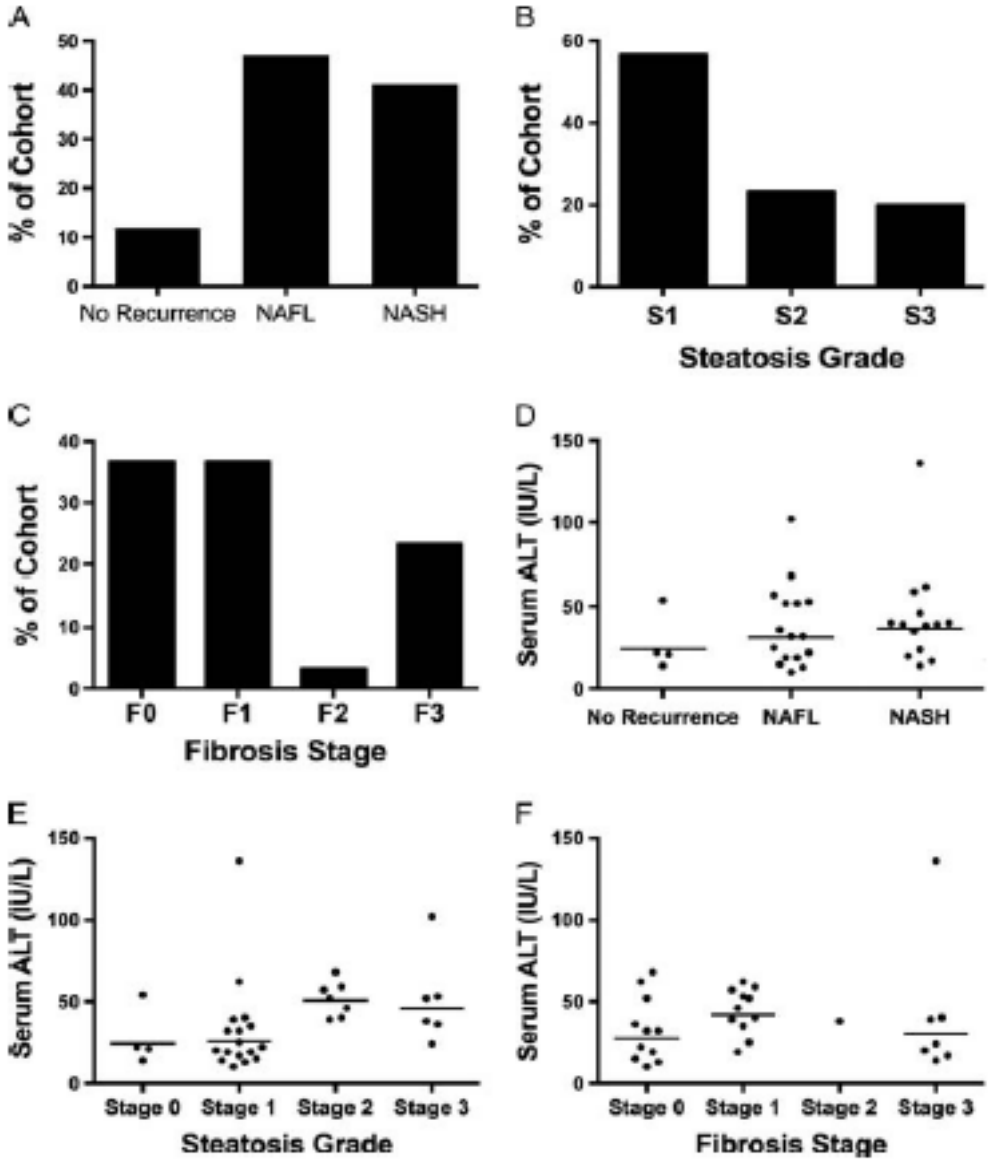

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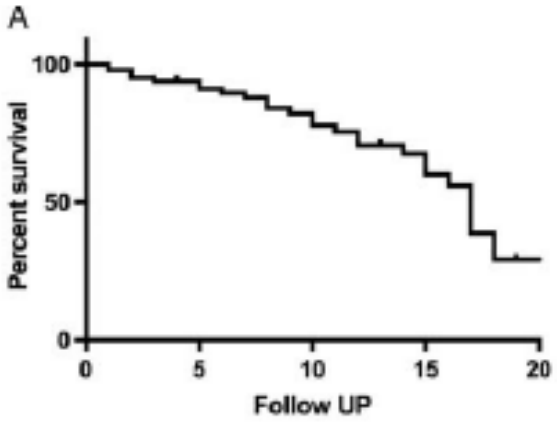
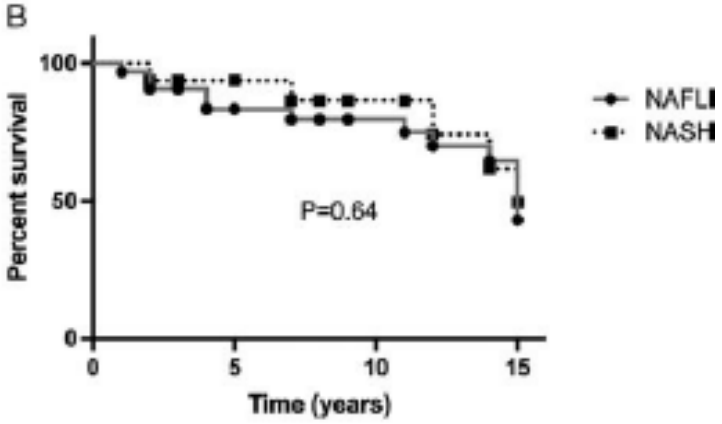
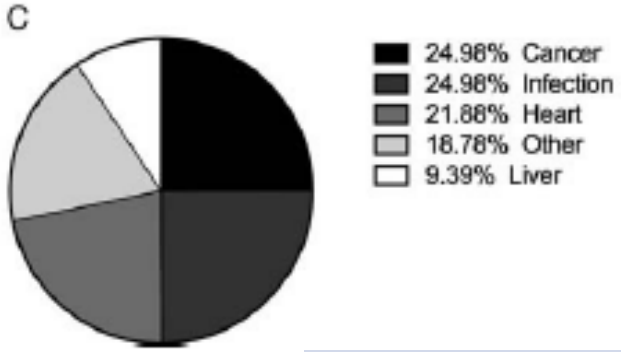






Cause of mortality	N (%)
Cancer	8 (25%)
Gynecological cancer	2
Hepatocellular cancer*	2
Breast cancer	1
Pancreatic cancer	1
Melanoma	1
Lung cancer	1
Infections	
Sepsis	8 (25%)
CVD	7 (21%)
CVA	4
Myocardial infarction	2
Heart failure	1
Liver	
Recurrent graft cirrhosis	3 (9%)
Others	6 (19%)
Perioperative death	3
Motor vehicle accident	1
Kidney failure	1
Unknown	1

* All cases were recurrent HCC.

Transplantation 2017;101: 1867–1874

İMMUNSUPRESİF İLAÇLAR

GENETİK FAKTÖRLER

İNSÜLİN DİRENCİ

OBEZİTE

HİPERLİPİDEMİ

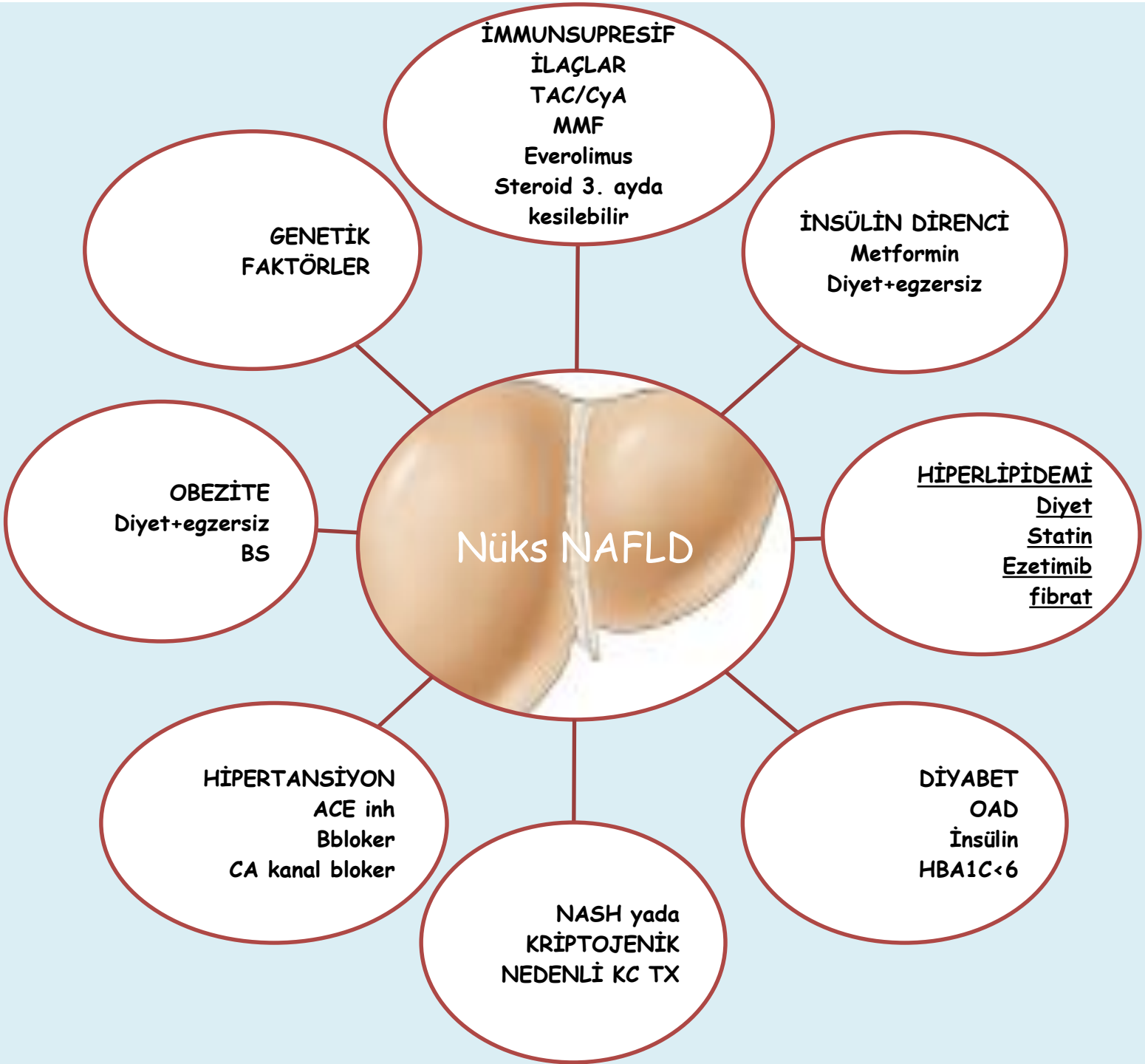
HİPERTANSİYON

NASH yada KRİPTOJENİK NEDENLİ KC TX

DİYABET

NAFLD Rekürrensinde Yaklaşım

- Pre-TX dönemle benzer
- ACE inhibitörleirinin olumlu etkisi mevcut
- Vitamin E, thiazolidonlar ve pentoksifilinin yararı tartışmalı
- Eşlik eden metabolik bozukluğa uygun tedavi
- Hipopituitarism varsa GH replasmanı
- Obeziteyle mücadele
  - Yaşam şekli değişikliği
  - Egzersiz+beslenme programı
  - Obezite cerrahisi
    - Roux-N-Y gastrik by pass sonrası greft disfonksionuna yol açan NASH nüksü bildirilmiş
    - Gastrik by-pass cerrahisi teknik olarak daha zor
    - Bu konuda yeterli çalışma yok
- Mortalite kardiyovasküler ve metabolik sendrom komplikasyonlarıyla birlikte de-novo maligniteler


İMMUNSUPRESİF İLAÇLAR
TAC/CyA
MMF
Everolimus
Steroid 3. ayda kesilebilir
GENETİK FAKTÖRLER
İNSÜLİN DİRENCİ
Metformin
Diyet+egzersiz
OBEZİTE
Diyet+egzersiz
BS
Nüks NAFLD
HİPERLİPİDEMİ
Diyet
Statin
Ezetimib
fibrat
HİPERTANSİYON
ACE inh
Bbloker
CA kanal bloker
NASH yada KRİPTOJENİK NEDENLİ KC TX
DİYABET
OAD
İnsülin
HBA1C<6

Sonuç

- NASH önümüzdeki dönemde en sık nakil nedeni olarak karşımıza gelecek
- Obezite cerrahisi histolojik iyileşme sağlıyor
- Tx yapılan hastalarda sağkalım diğer nedenlerle benzer
- Nüks NAFLD'de daha hızlı fibrozis vs de-novo NAFLD
- Tedavi yaklaşımı benzer
- Tx sonrası metabolik problemler ve kardiyovasküler olaylar sağkalımı belirliyor!!!
- Multidisipliner yaklaşım şart