Post-DDW
Post-EASL
Update

End Stage Liver Disease

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Acute on Chronic Liver Failure (ACLF)

- Definitions (latest – still in evolution)
  - Liver (bilirubin>12mg/dL)
  - Coagulation (INR>2.5)
  - Circulatory (pressor)
  - Renal (sCR>2mg/dl, RRT)
  - Cerebral (HE grade ¾)
  - Respiratory (hypoxia)

	28-d mortality rate	ACLF grades
No organ failure	39/879 (4.4%)	→ No ACLF
Single nonrenal failure, creatinine < 1.5 mg/dL, no HE	8/128 (6.3%)	
Single renal failure	16/86 (18.6%)	→ ACLF-1
Single nonrenal failure, creatinine 1.5–1.9 mg/dL and/or HE	15/54 (27.7%)	
2 organ failures	31/97 (32.0%)	→ ACLF-2
3 organ failures	17/25 (68.0%)	→ ACLF-3
4–6 organ failures	12/18 (88.9%)	

Arroyo. Semin Liver Dis 2016; 36(02): 109-116

Epidemiology of Acute on chronic liver failure (ACLF)

"Time Trends in the Healthcare Burden and Mortality of Acute on Chronic Liver Failure (ACLF) in the United States" Allen et al.

- ACLF- acute deterioration of liver function and one or more extrahepatic organ failures: High short-term mortality despite highly resource-intensive care
- Paucity of epidemiological data in the US
- Nationwide Inpatient Sample (NIS) database
  - Largest inpatient database
  - More than 1,000 hospitals
  - 8 million individual discharge records/year
- Time-frame: 2001-2011

Allen. DDW 2016 Abstract 265

ACLF definition: cirrhosis + 2 failed organs
ICD-9 codes of the following diagnoses

CARDIOVASCULAR

Septic shock
Severe sepsis
Arterial line
Pulmonary artery/wedge pressure
Central venous pressure

RESPIRATORY

Mechanical ventilation

CIRRHOSIS

Alcoholic cirrhosis
Cirrhosis without alcohol
Portal hypertension
Hepatorenal syndrome
Esophageal varices
Hepatic encephalopathy
Spontaneous bacterial peritonitis

RENAL

Hemodialysis
Acute kidney failure

CEREBRAL

Hepatic coma

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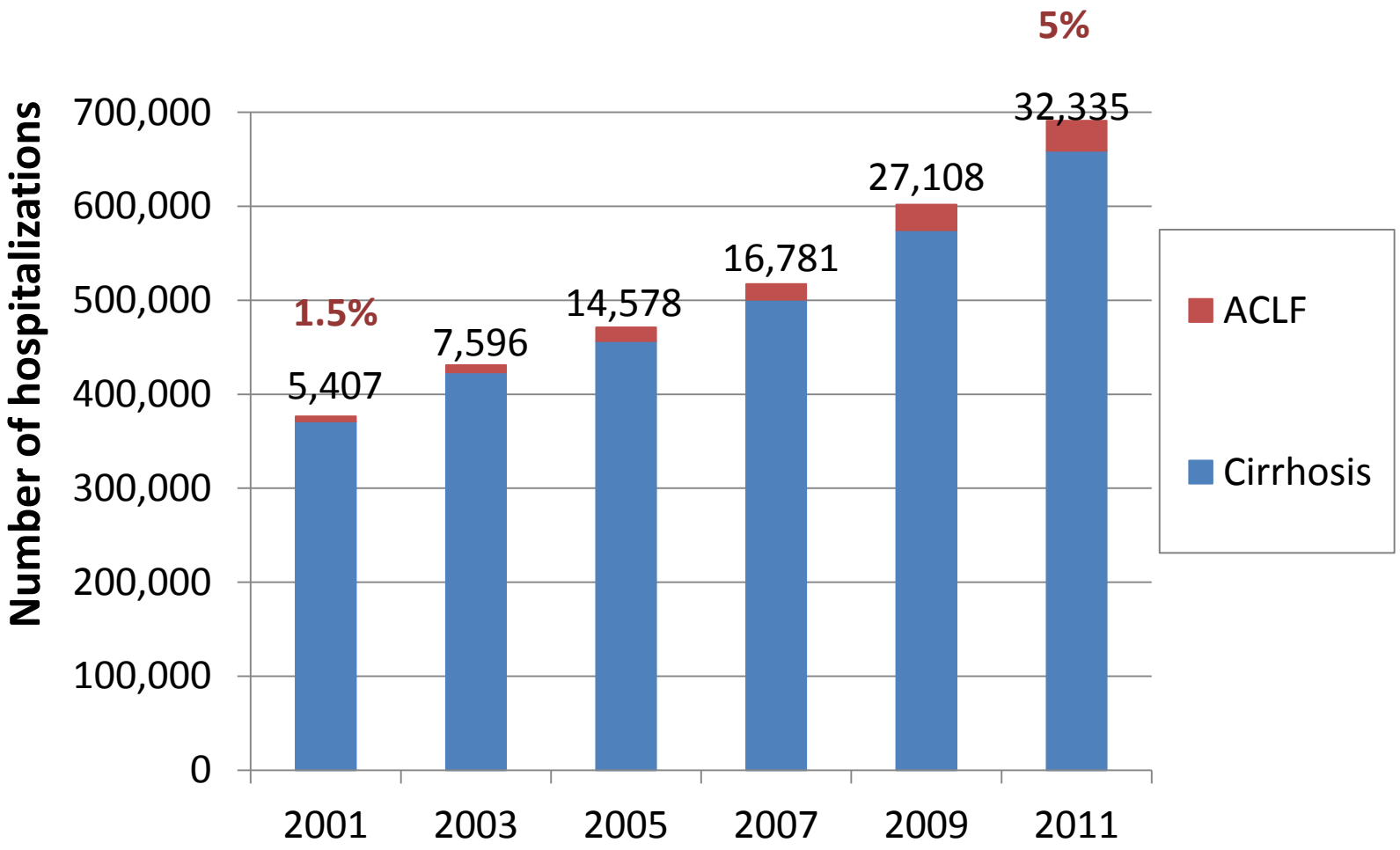
Increasing number of hospitalizations for ACLF and cirrhosis



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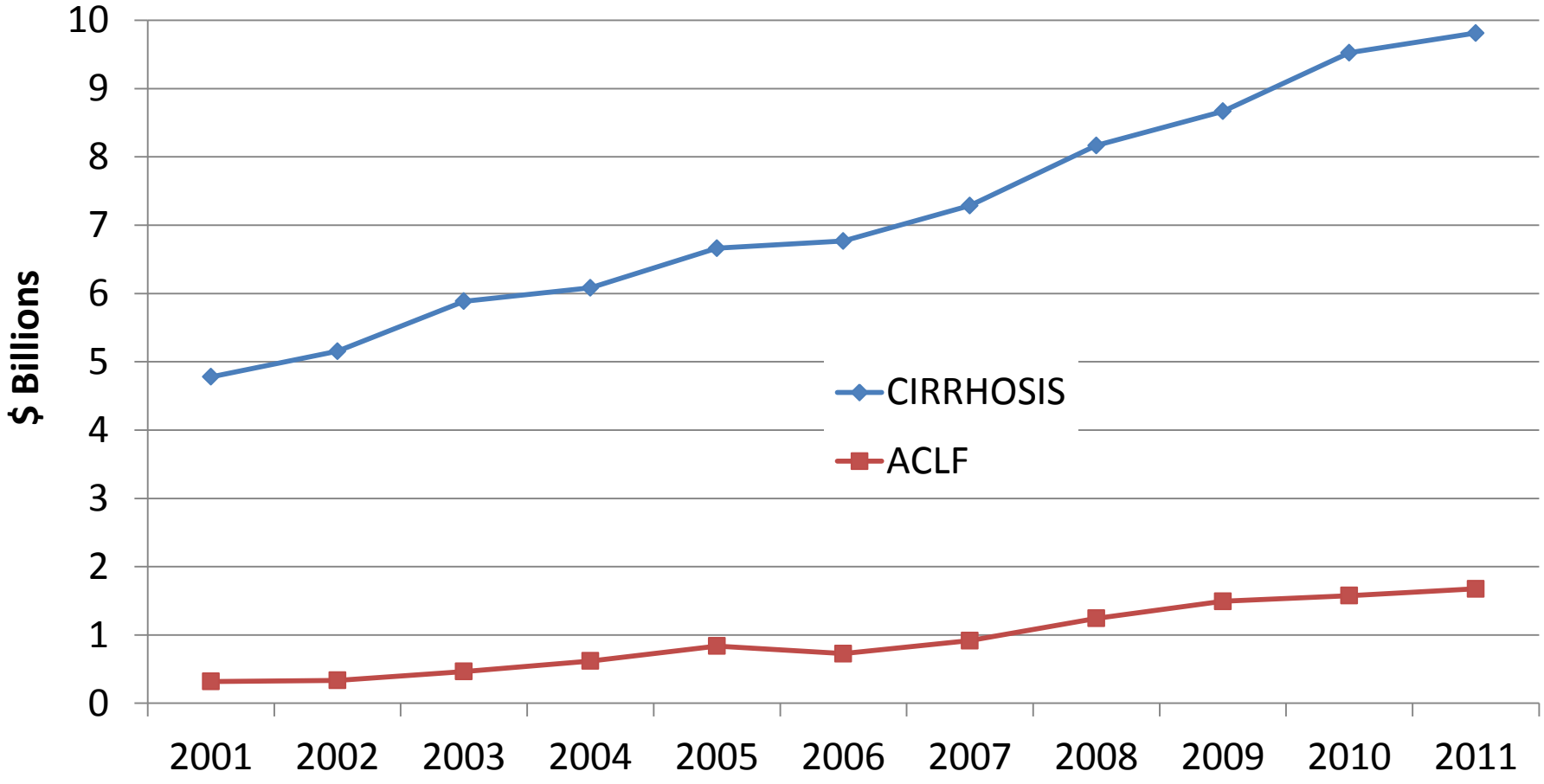
Estimated costs of hospitalization per year



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Time-trends in All cirrhotics (including ACLF)

		2001-04	2005-08	2009-11
Age (mean)		58	58	58
Female (%)		39	38	39
Race/ethnicity (%)	White	65	65	65
	Black	12	11	12
	Hispanic	17	18	17
	API	2	2	2
Etiology (%)	Viral	18	16	15
	Alcohol	37	36	34
	Other	45	48	50
Length of stay (days)		7	7	7

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Time-trends in ACLF

		2001-04	2005-08	2009-11
Rates of ACLF organ failures (%)	Respiratory	91	86	82
	Renal	51	41	41
	Cardiovascular	49	74	74
	Cerebral	21	21	29
Length of stay (days)		17	16	16

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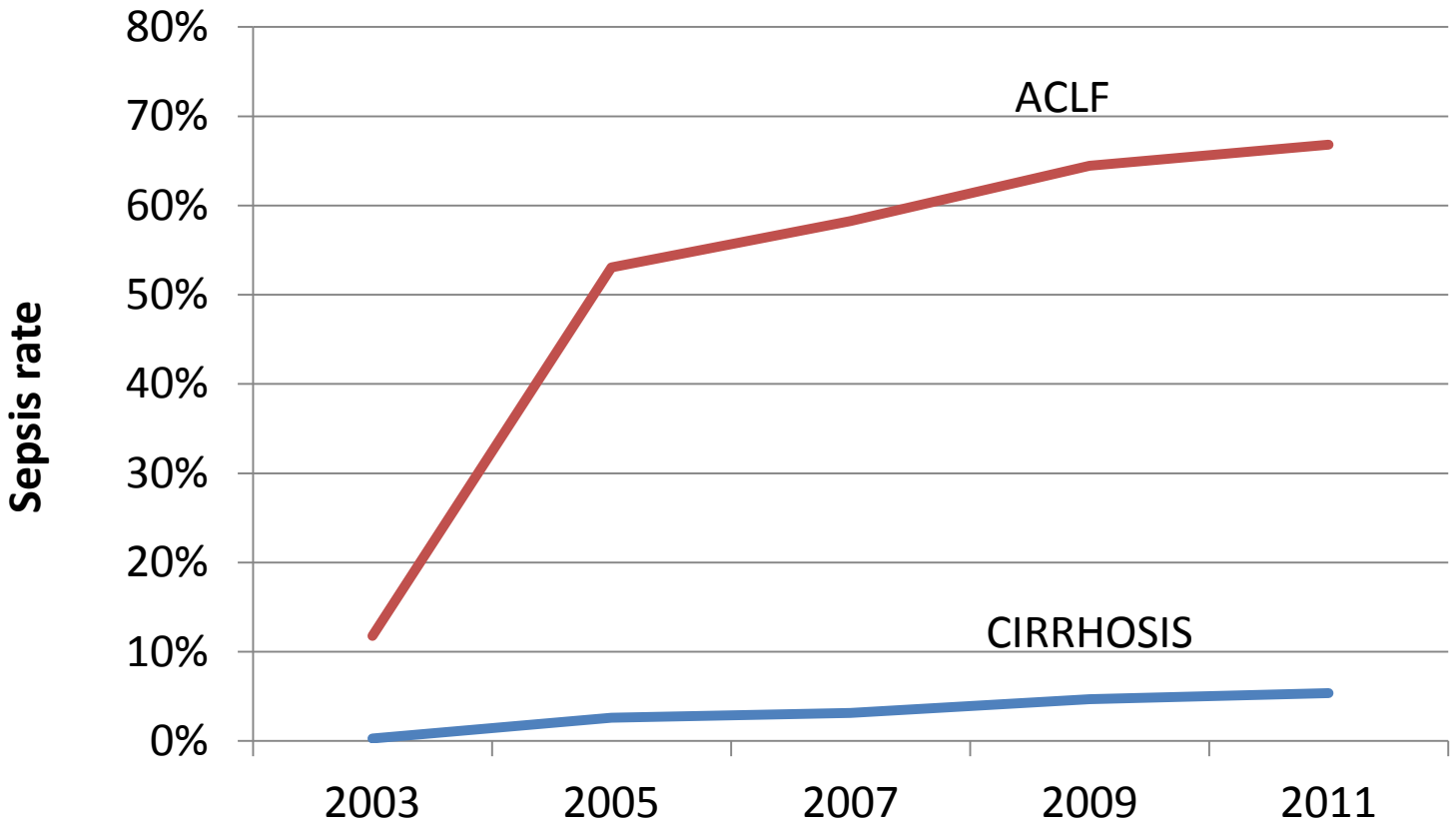
Increasing rates of documented sepsis



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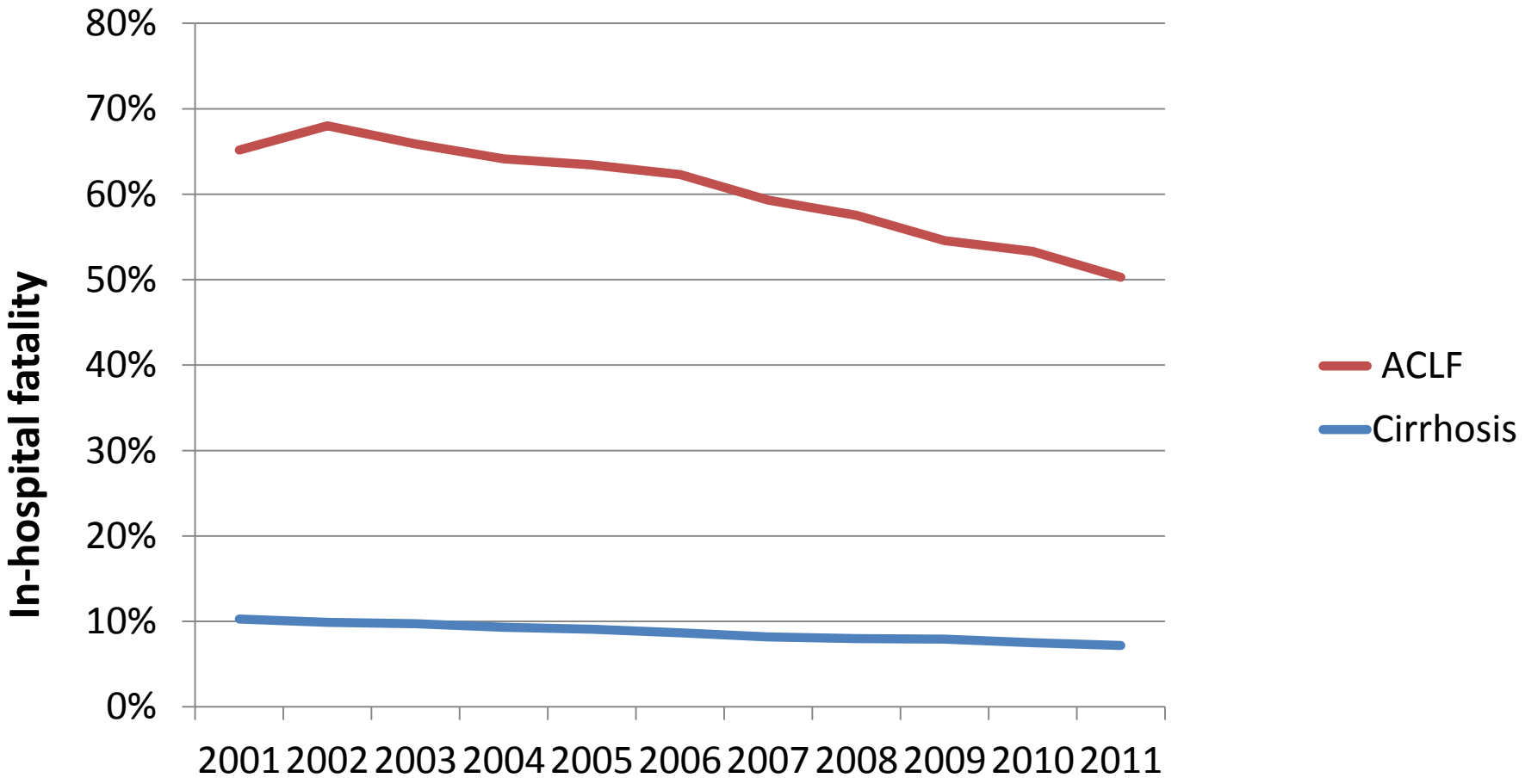
Mortality trends



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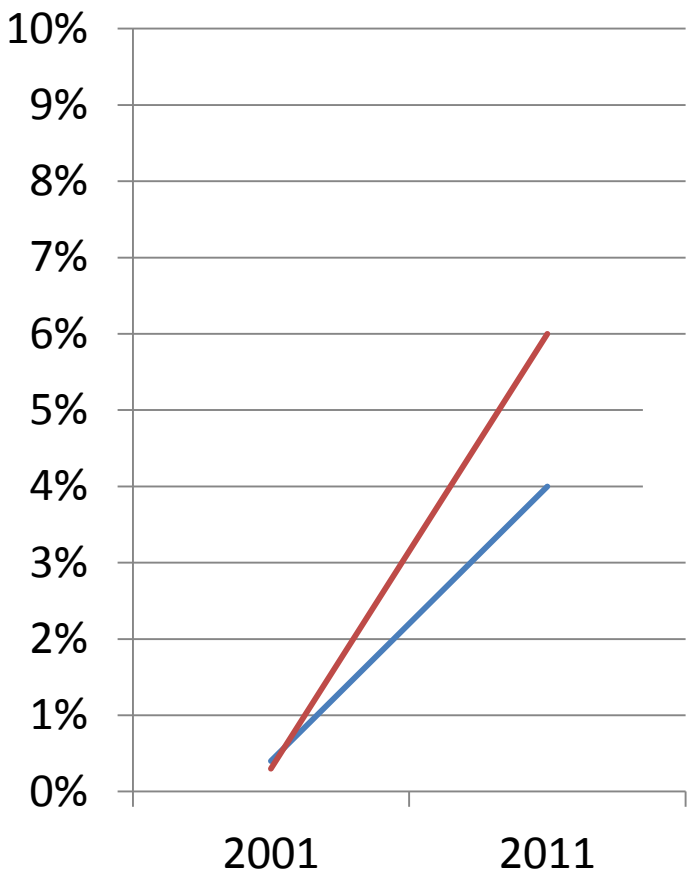
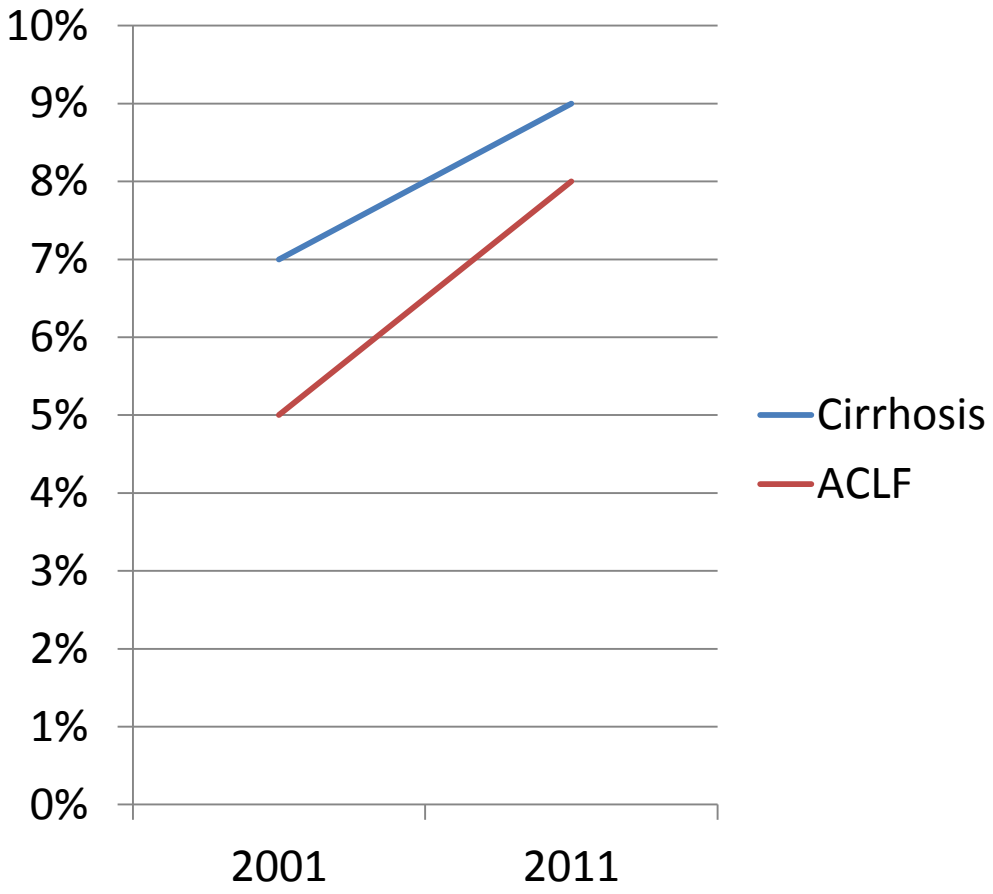
Discharge Status

Discharges to hospice



Discharges to skilled nursing facilities



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Determinants of in-hospital mortality in ACLF

		Adjusted OR*	p
Age (per decade >20)		1.27	<0.01
Male		1.12	<0.01
Race/ethnicity (reference white)	Black	1.13	<0.01
	Hispanic	0.86	<0.01
	Asian	1.16	<0.01
Organ failure			
Cirrhosis or 1 organ failure		reference	--
2 organ-failure	Respiratory + cardiovascular	30.73	<0.01
	Respiratory + renal	21.87	<0.01
	Respiratory + cerebral	9.61	<0.01
	Cardiovascular + renal	10.0	<0.01
	Cardiovascular + cerebral	8.88	<0.01
	Renal + cerebral	2.02	<0.01
3 organ-failure		43.1	<0.01

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*Adjusted for insurance status and income quartiles

Spontaneous Bacterial Peritonitis

- Patients with ascitic fluid PMN counts $\geq$ 250 cells/mm^3 in a community-acquired setting in the absence of recent *B*-lactam antibiotic exposure should receive empiric antibiotic therapy, e.g., an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours. (Class I, Level A)
- Patients with ascitic fluid PMN counts $\geq$ 250 cells/mm^3 in a nosocomial setting and/or in the presence of recent *B*-lactam antibiotic exposure should receive empiric antibiotic therapy based on local susceptibility testing of bacteria in patients with cirrhosis. (Class IIa, Level B)
- Oral ofloxacin (400 mg twice per day) can be considered a substitute for intravenous cefotaxime in inpatients without prior exposure to quinolones, vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL. (Class IIa, Level B)

Runyon. AASLD Guideline

Spontaneous Bacterial Peritonitis

- Patients with ascitic fluid PMN counts $\geq$ 250 cells/mm^3 and clinical suspicion of spontaneous bacterial peritonitis, who also have a serum creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL should receive 1.5 g albumin per kg body weight within 6 hours of detection and 1.0 g/kg on day 3. (Class IIa, Level B)
- Patients who have survived an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with daily norfloxacin (or trimethoprim/ sulfamethoxazole). (Class I, Level A)
- In patients with cirrhosis and ascites, longterm use of norfloxacin (or trimethoprim/ sulfamethasoxazole) can be justified if the ascitic fluid protein <1.5 g/dL along with impaired renal function (creatinine ≥1.2, BUN ≥25 or serum Na ≤130) or liver failure (Child score ≥9 and bilirubin ≥3. (Class I, Level A)

Runyon. AASLD Guideline

Large Volume Paracentesis in SBP

The safety of diagnostic larger volume paracentesis in patients with spontaneous bacterial peritonitis

- Question:
  - SBP: Hemodynamic and renal dysfunction secondary to relative hypovolemia
  - In patients requiring LVP, presence of SBP is not known at the time of the tap.
- Retrospective study of patients with SBP (n=104): 2007-14
  - Mean MELD=16
  - Group A (LVP): >4 L removed (n=27)
  - Group B: <4 L (n=77)
- SBP management
  - Albumin days 1 and 3
  - Abx

Sandhu et al. DDW 2016. Abst. Sa1595

Safety of Large Volume Paracentesis in SBP Patients

- End points:
  - HR increase by > 20 BPM or SBP drop by > 20 mmHg
  - Renal injury (sCr increase by > 0.3 mg/dL)

	Group A	Group B
Increase in Heart Rate	11.11%	12.99%
Decrease in Systolic Blood Pressure	48.15%	41.56%
Acute Kidney Injury	25.93%	33.77%

Significant decrease in Systolic Blood Pressure

Time from paracentesis	Group A	Group B
0-24 hours	48.15%	41.56%
24-48 hours	48.15%	29.87%
48-72 hours	33.33%	24.68%

- 1 year survival: 41% (Group A) versus 35% (Group B)

Authors' conclusion

- LVP coincident to SBP diagnosis is as safe as smaller volume tap.
- Early administration of albumin and abx

Sandhu et al. DDW 2016. Abst. Sa1595

Norfloxacin versus Bactrim for SBP Prophylaxis

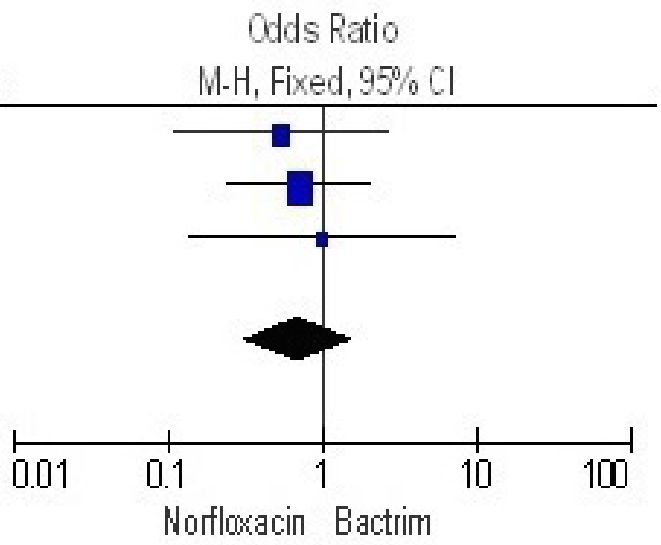
Norfloxacin versus Trimethprim-Sulfamethoxazole in Prevention of Spontaneous Bacterial Peritonitis: A meta-analysis

Development of SBP:

Study or Subgroup	Norfloxacin Events	Norfloxacin Total	Bactrim Events	Bactrim Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alvarez 2005	3	32	4	25	30.1%	0.54 [0.11, 2.69]
Lontos 2008	8	37	9	32	56.9%	0.70 [0.24, 2.11]
Lontos 2014	2	40	2	40	14.0%	1.00 [0.13, 7.47]
Total (95% CI)		109		97	100.0%	0.70 [0.31, 1.59]
Total events	13		15			

Heterogeneity: $Chi^2 = 0.22$, $df = 2$ ($P = 0.90$); $I^2 = 0\%$

Test for overall effect: $Z = 0.86$ ($P = 0.39$)

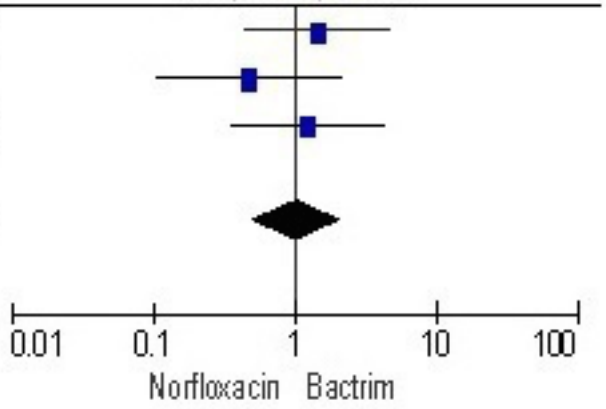


Hamdeh. DDW 2016. Abst Su1488

Extraperitoneal infections:

Study or Subgroup	Norfloxacin Events	Total	Bactrim Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alvarez 2005	10	32	6	25	33.5%	1.44 [0.44, 4.70]
Lontos 2008	3	37	5	32	35.7%	0.48 [0.10, 2.17]
Lontos 2014	6	40	5	40	30.8%	1.24 [0.34, 4.43]
Total (95% CI)		109		97	100.0%	1.03 [0.49, 2.17]
Total events	19		16			

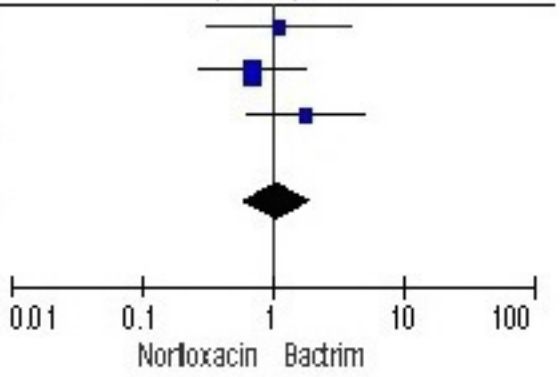
Heterogeneity: $Chi^2 = 1.38$, $df = 2$ ($P = 0.50$); $I^2 = 0\%$
Test for overall effect: $Z = 0.09$ ($P = 0.93$)



Mortality:

Study or Subgroup	Norfloxacin Events	Total	Bactrim Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alvarez 2005	7	32	5	25	22.8%	1.12 [0.31, 4.07]
Lontos 2008	13	37	14	32	50.7%	0.70 [0.26, 1.84]
Lontos 2014	11	40	7	40	26.4%	1.79 [0.61, 5.22]
Total (95% CI)		109		97	100.0%	1.08 [0.58, 2.01]
Total events	31		26			

Heterogeneity: $Chi^2 = 1.64$, $df = 2$ ($P = 0.44$); $I^2 = 0\%$
Test for overall effect: $Z = 0.25$ ($P = 0.80$)



Hamdeh. DDW 2016. Abst Su1488

Daily Norfloxacin versus Weekly Ciprofloxacin

Comparison of Daily Norfloxacin versus Weekly Ciprofloxacin for the Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients: A Randomized Controlled Trial

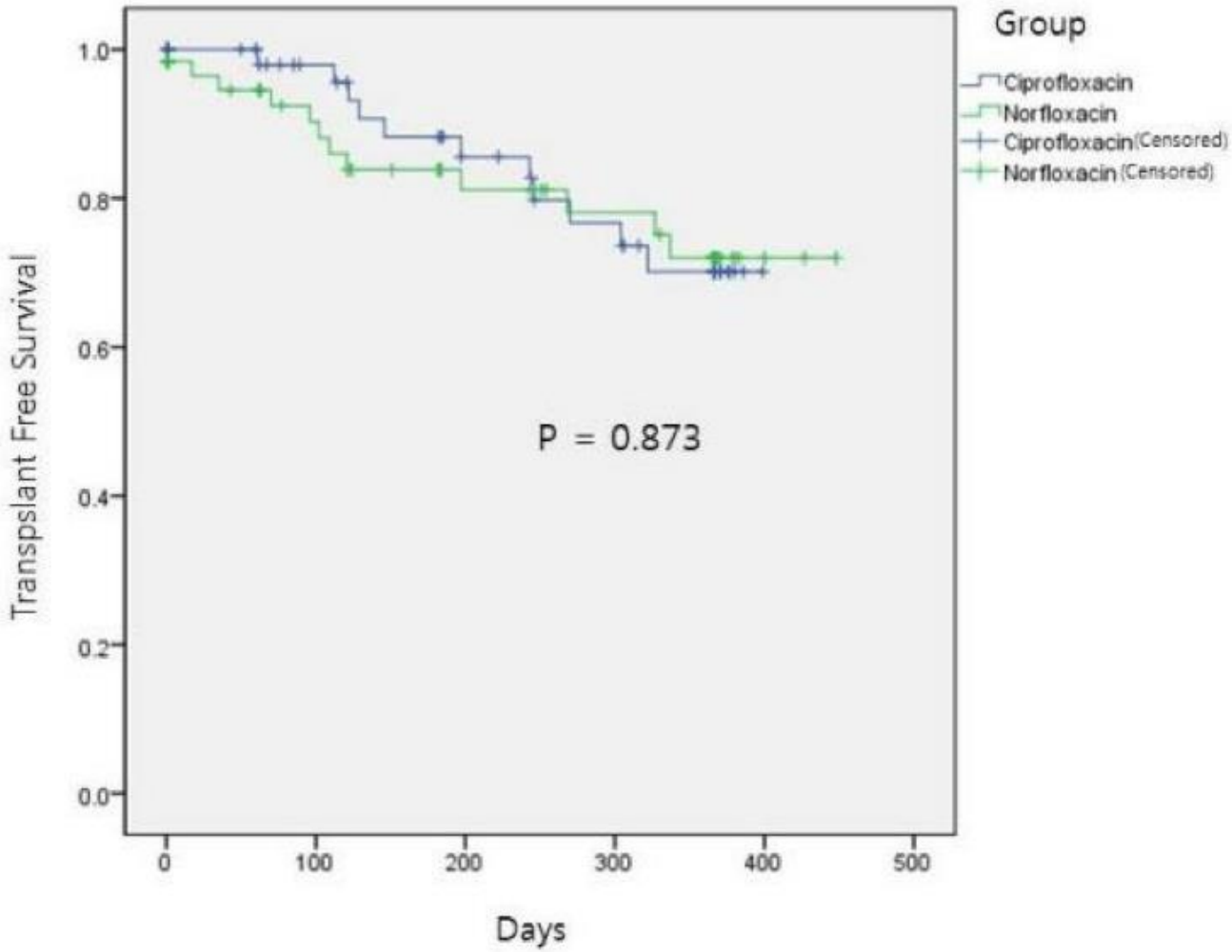
- Randomized trial for 12 months (n=124)
  - Ciprofloxacin 750mg weekly
  - Norfloxacin 400mg daily

- **Inclusion criteria:** patients with cirrhosis and ascites between 20 and 75 years old were screened, and enrolled in this RCT if: 1) ascitic polymorphonucleated cell count <250/ mm^3, 2) ascitic protein is equal or less than 1.5 g/dL, or 3) the presence of history of SBP
- **Exclusion criteria** include: a) hypersensitivity or intolerability with quinolones, b) hepatocellular carcinoma beyond Milan Criteria,c) hepatic encephalopathy > grade 2 and d) history of treatment with antibiotics within 2 weeks of enrollment.

Im. EASL 2016. PS017

Results

- SBP developed in one patient of ciprofloxacin group, and in 2 patients of norfloxacin group (p=1.0).



Im. EASL 2016. PS017

Use of FFP for LVP

Correction of Coagulopathy prior to Paracentesis is Associated with Excessive Albumin Administration and No Apparent Clinical Benefit

- 243 LVP done in 107 hospitalized patients
- 112 (46%) LVPs were preceded by FFP transfusions to correct INR in 40 patients (30 males and 10 females)

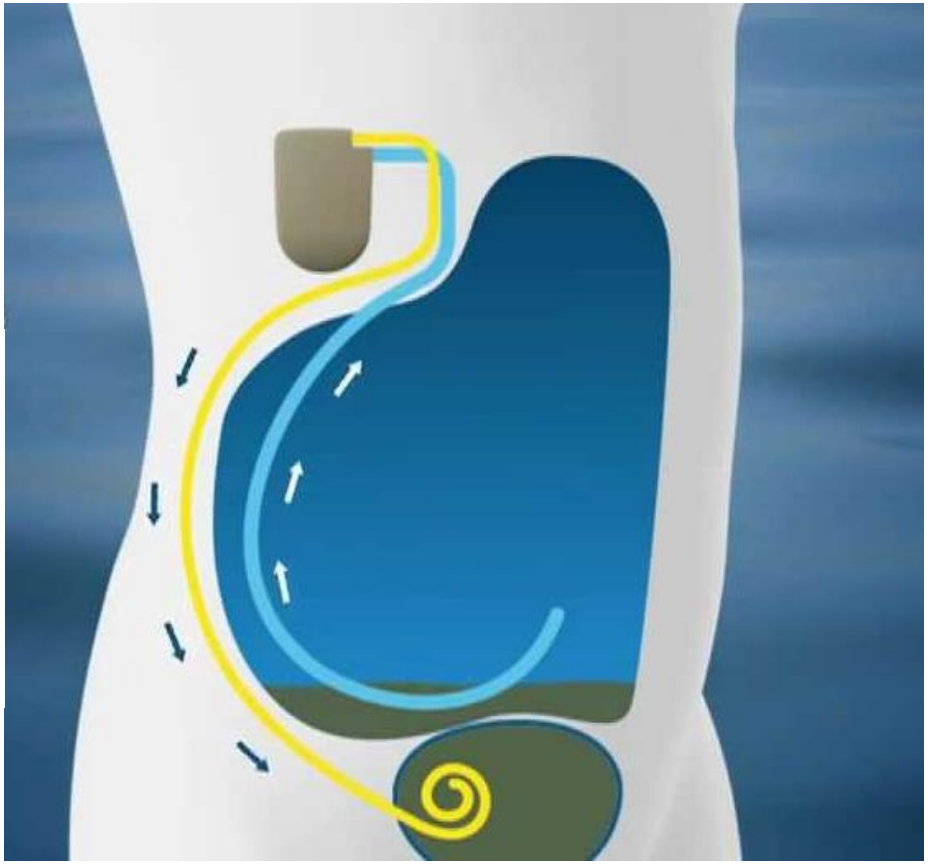
	Mean	Range
Ascites Volume Removed (L)	6.8 ± 0.2	2.0 - 13.1
FFP transfused prior to LVP (u/pt)	4.0 ± 0.2	1 - 11
Albumin Content in FFP (g/dL)	3.6 ± 0.05	3.4 - 3.7

- Total excess cost of $ 404.27 per paracentesis
- In 6 months, for the 112 LVPs corrected with FFP, we spent an excess of $ 45,278 with no associated clinical benefit or worsening regarding renal function.

Manickavasagan. DDW 2016. Abst Sa1641

Alternative to LVP

Alfapump system versus large volume paracentesis in the treatment of refractory ascites: Results from a multicenter randomized controlled study



Adebayo EASL 2016 RS 2598

Alfapump versus LVP

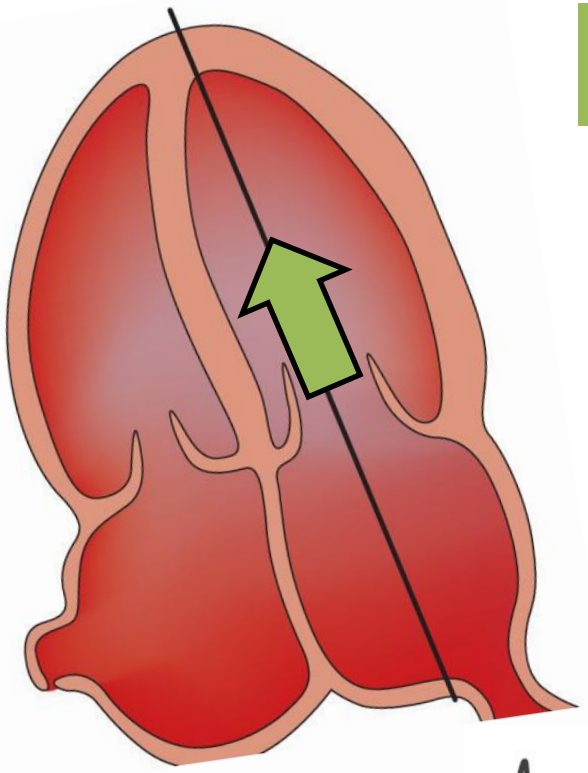
	ALFA (n=24)	LVP (n=25)
MELD at baseline	12.6	11.7
Median # of LVP	0.2/mo	1.4/mo
6 month survival	0.84	0.83
Infection	9/9	12/9
AKI	8/5	2/2
Encephalopathy	3/3	2/2
Device SAE	Catheter blockage 3 peritoneal 3 bladder	
Albumin (6mo)*	3.28	3.10

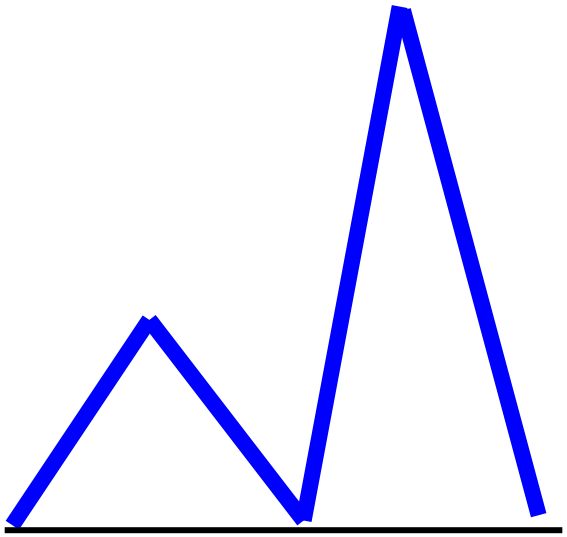
* No change in other liver biochemistry
Nutrition improved with Alfapump

Adebayo EASL 2016 RS 2598

Diastolic Dysfunction in Liver Transplant Candidates

- Mitral Inflow



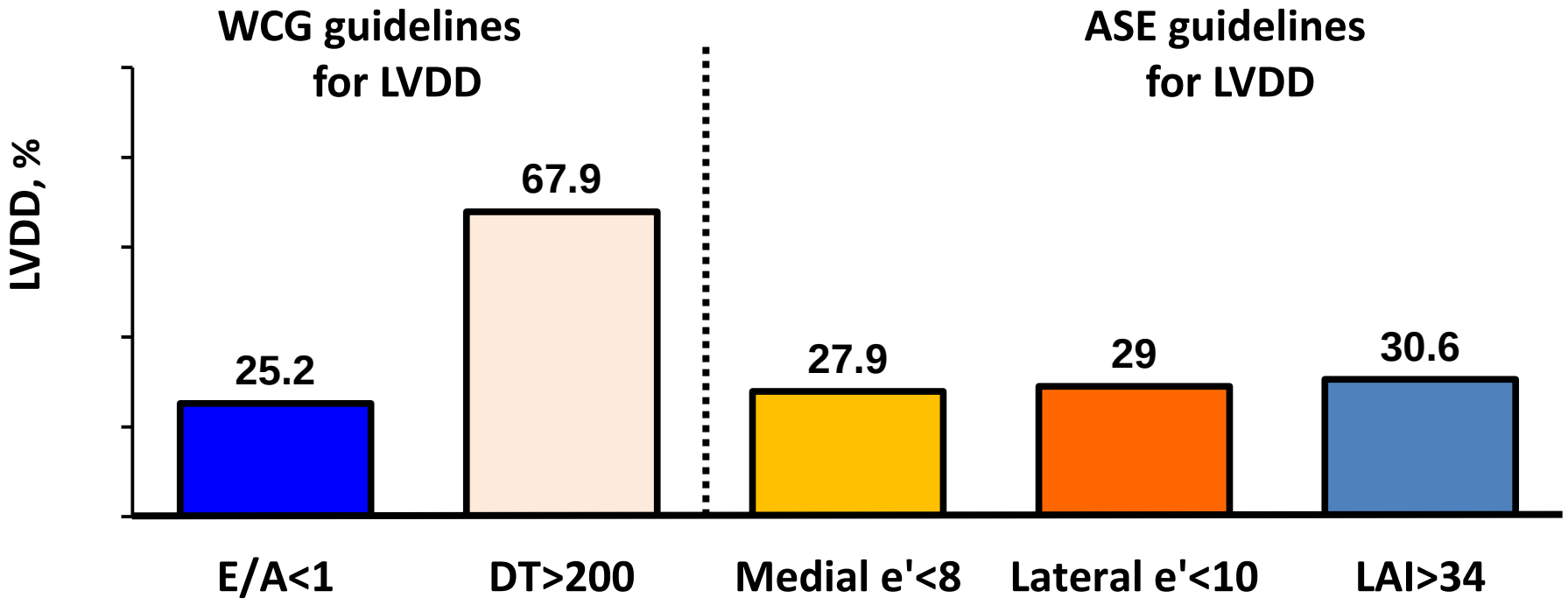


Moller et al. Gut 2008;57:268-278

Peeraphatdit. DDW 2016. Abst 426

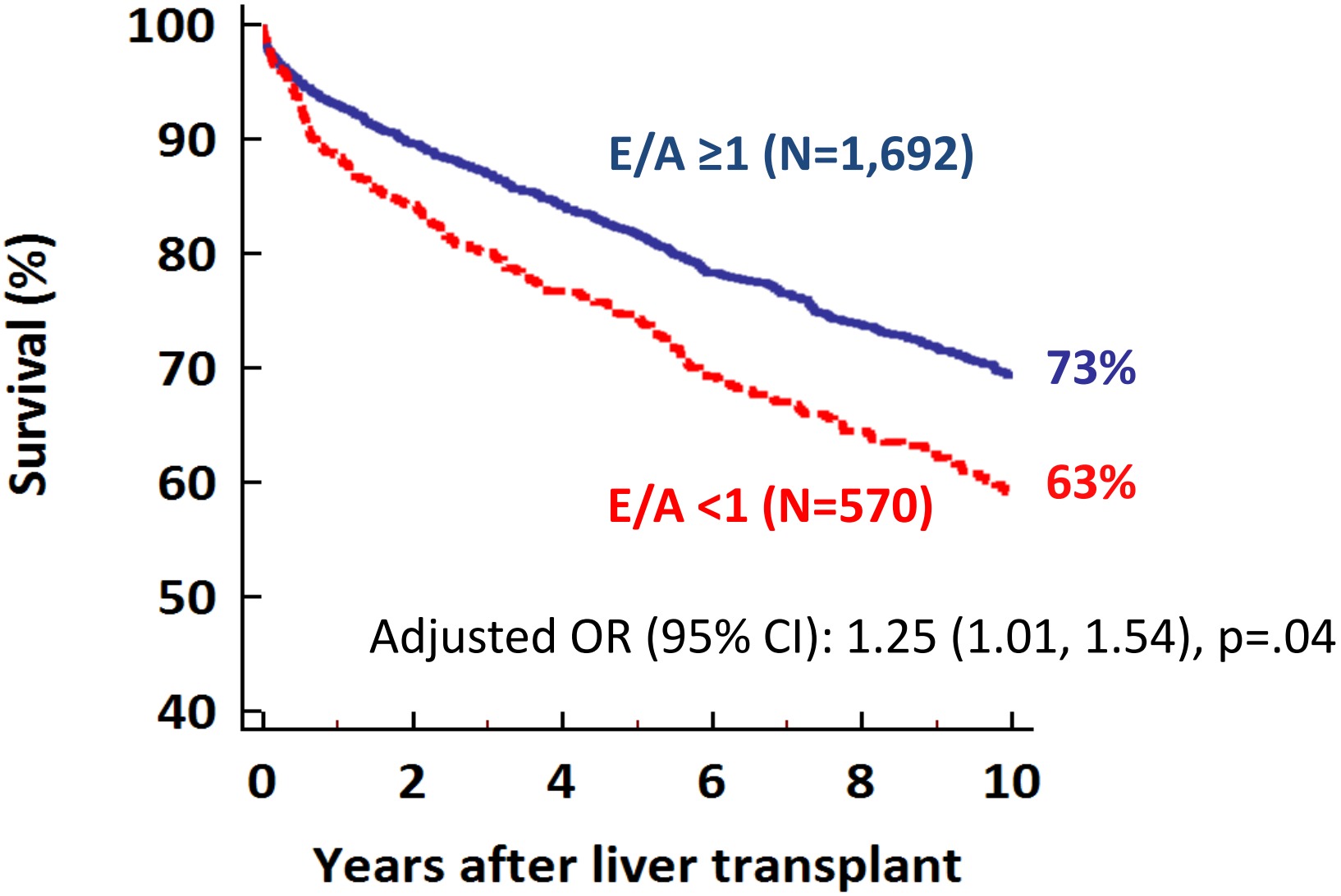
Prevalence of LVDD

The rate of LVDD diagnosis varied from 25-68% according to each echocardiographic parameter



Peeraphatdit. DDW 2016. Abst 426

Post-Transplant Survival



Peeraphatdit. DDW 2016. Abst 426

Cirrhotic Cardiomyopathy and NSBB

Prevalence of Cardiomyopathy and Impact of the Use of Non-Selective Beta Blockers in End Stage Liver Disease

- Retrospective study of liver transplant candidates (n=526)

  77% male, mean age 53 years old

  49% Alcohol, 27% HCV and 12% HBV

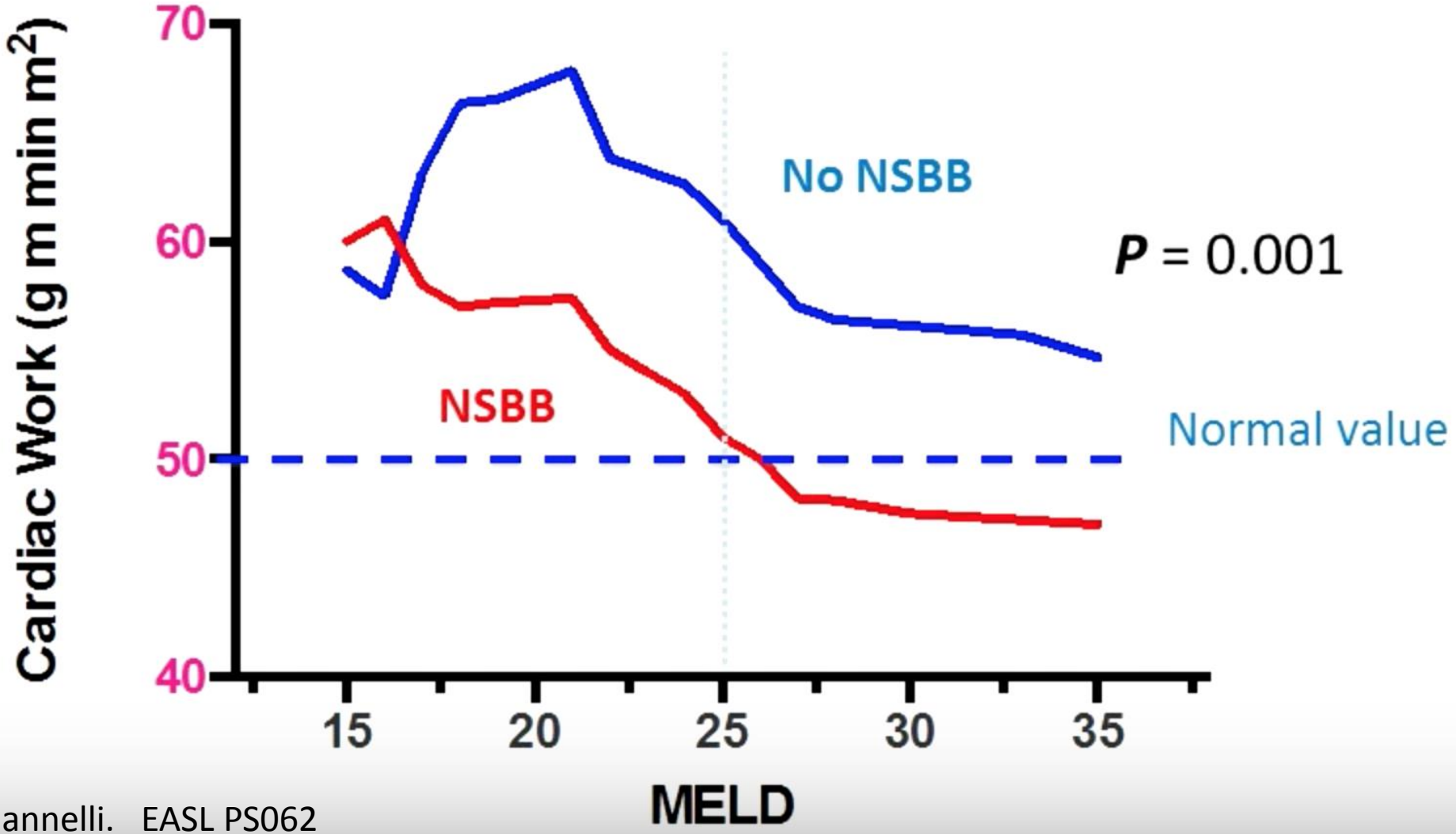
MELD Category	n	NSBB	Myocardial Dysfunction
MELD <15	246	47%	32%
MELD 16-25	215	58%	35%
MELD >25	60	50%	37%

- Severity of cardiomyopathy measured by

  Left ventricular stroke work index (LVSWI): Normal > 50

Giannelli. EASL PS062

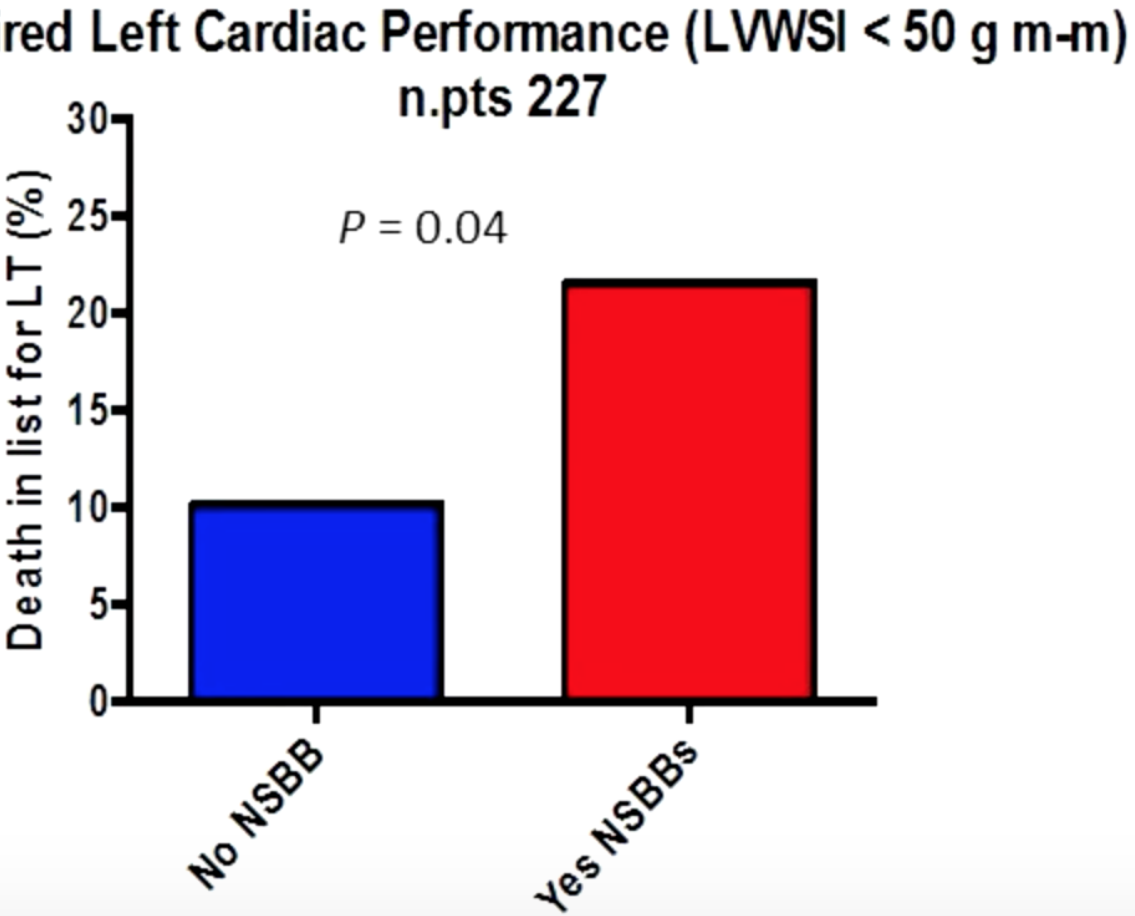
Negative Impact of NSBB on Cardiac Function



Giannelli. EASL PS062

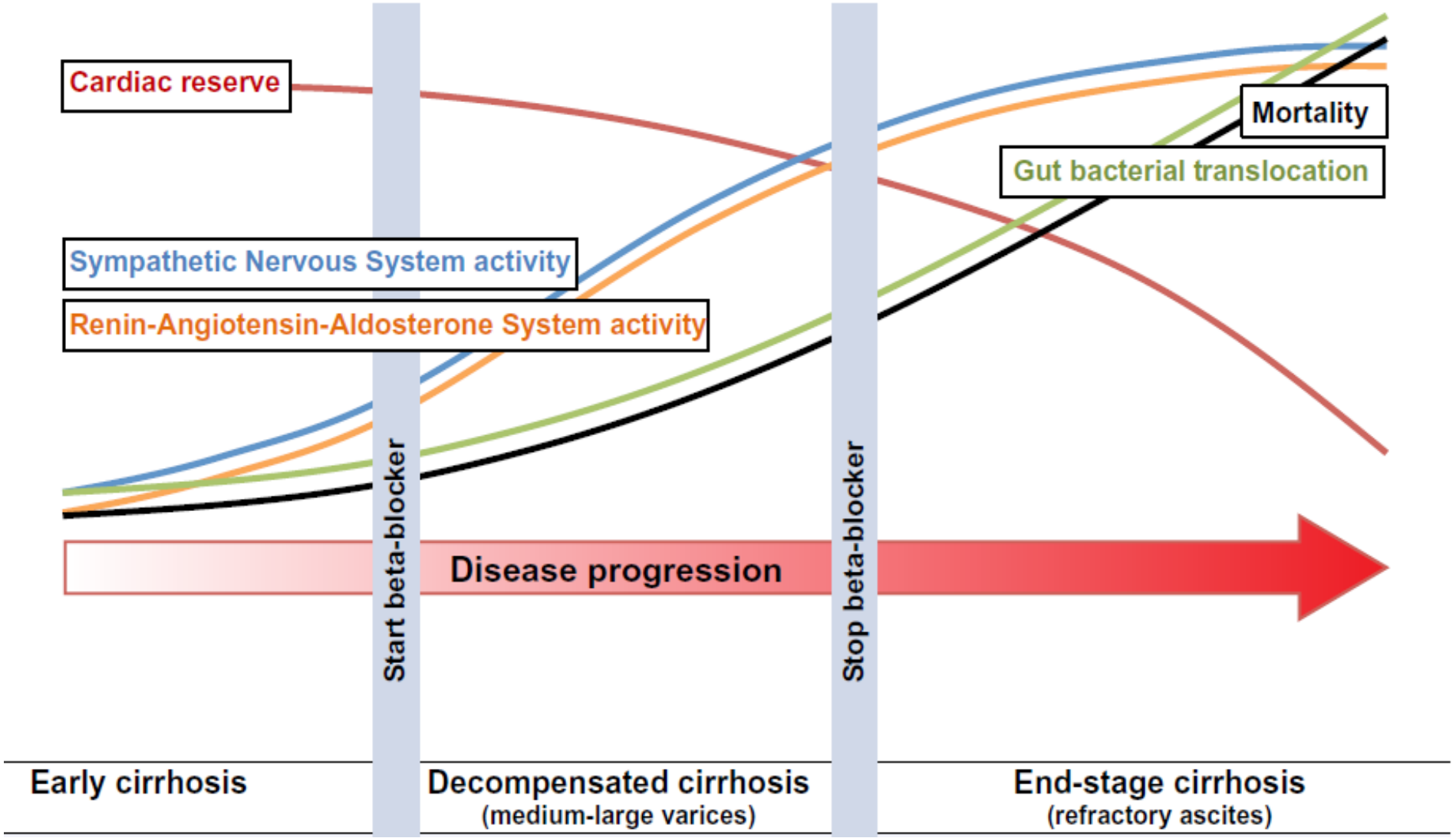
Impact on Mortality

Mortality among Patients with LVSWI < 50



Giannelli. EASL PS062

Window Theory



Am J Gastroenterol 2012; 107:418–427