CLINICAL COURSE OF CIRRHOSIS: PHASES

1. Compensated cirrhosis (CC). Slow (>10-15y) progression of fibrosis and portal hypertension

2. Acute decompensation (AD): 70% of patients admitted to hospital with cirrhosis. Acute development of ascites, gastrointestinal hemorrhage, hepatic encephalopathy and/or acute bacterial infection (mean survival <3 y)

3. Acute-on-Chronic Liver Failure (ACLF): 32% of patients admitted to hospital (22% present ACLF at admision; 10% develop ACLF during hospitalization). Characteristics: a). AD; b). Organ failure(s) (Liver, Kidney, Brain, Coagulation, Respiration, Circulation) and c). High short-term mortality (main cause of death in cirrhosis)

DIAGNOSTIC CRITERIA OF ACLF: ORGAN FAILURES. CLIF-CONSORTIUM ORGAN FAILURE SCORE.(CANONIC STUDY)

Organ / System	Score = 1	Score = 2	Score = 3
Liver (mg/dl)	Bilirubin < 6	6 ≤ Bilirubin ≤ 12	Bilirubin >12
Kidney (mg/dl)	Creatinine <2	Creatinine ≥2 <3.5	Creatinine ≥3.5 or renal replacement
Brain (West-Haven)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR < 2.0	2.0 ≤ INR < 2.5	INR ≥ 2.5
Circulation	MAP ≥70 mm/Hg	MAP <70 mm/Hg	Vasopressors

Values at study enrolment. Highlighted area reflects the definition of each organ failure.

OTHER IMPORTANT DIAGNOSTIC CRITERIA OF ACLF.

1.High short-term mortality rate: 28-day mortality rate > 15%*.

2.Cerebral Dysfunction: Grade 1-2 (West Haven) hepatic encephalopathy.

3.Renal Dysfunction: Serum creatinine 1.5- 1.9 mg/dl

* 50% mortality rate of septic shock

DIAGNOSIS AND GRADES OF ACLF. (CANONIC Study)

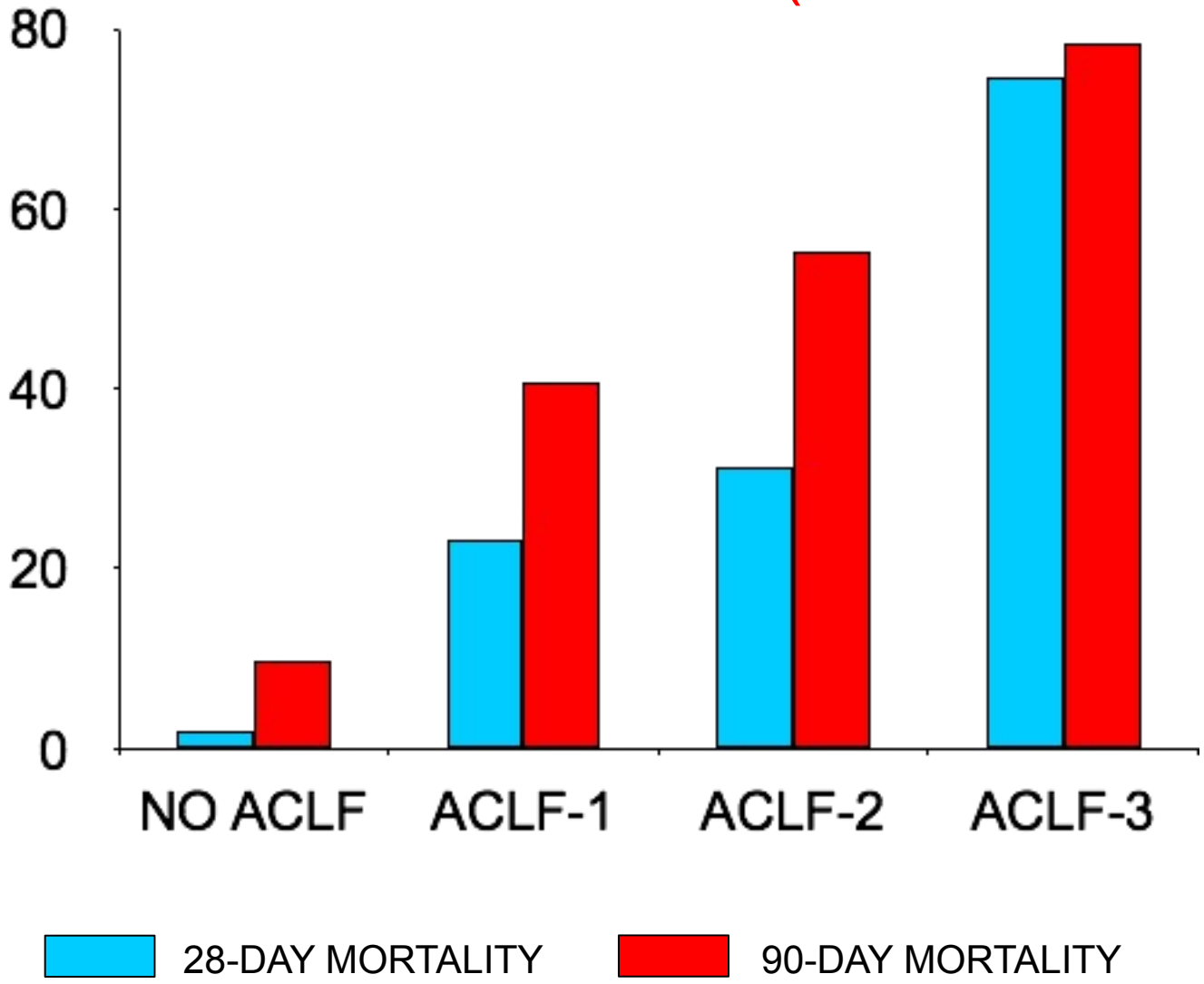
	TX-FREE PATIENTS (N =1287)	28-DAY DEATH RATE	ACLF grades
No OF	879 (68.3%)	39/879 (4.4%)	→ No ACLF
Single non renal OF, creatinine <1.5 mg/dl, no HE	128 (9.9%)	8/128 (6.3%)	
Single renal failure	86 (6.68%)	16/86 (18.6%)	→ ACLF-1
Single non-renal OF, creatinine 1.5-1.9 mg/dL and/or grade 1-2 HE.	54 (4.1%)	15/54 (27.7%)	
2 OF	97 (7.5%)	31/97 (32.0%)	→ ACLF-2
3 OF	25 (1.9%)	17/25 (68.0%)	→ACLF-3
4-6 OF	18 (1,4%)	12/18 (88.9%)	

CLINICAL CHARACTERISTICS OF ACLF. CANONIC Study.

1. Prevalence of ACLF: 415/1343: (32%; 22% at admission; 10% during hospitalization)
2. Grade frequency: ACLF-1: 51%; ACLF-2: 35%; ACLF-3: 14%.
3. Age : 56 y.
4. Etiology of cirrhosis: alcoholic 56%, hepatitis C 15%, alcohol + hepatitis C 9%.
5. Time from first decompensation: No prior decompensation 26.5%; <3 months 15.5%.
6. Precipitating events*: Bacterial infections 31%, acute alcoholic liver injury 23%, other 8%; No identifiable precipitating event (45.6%).

*GI bleeding was less frequent in patients with ACLF

28-DAY AND 90-DAY MORTALITY RATES ASSOCIATED TO ACLF (Canonic Study)

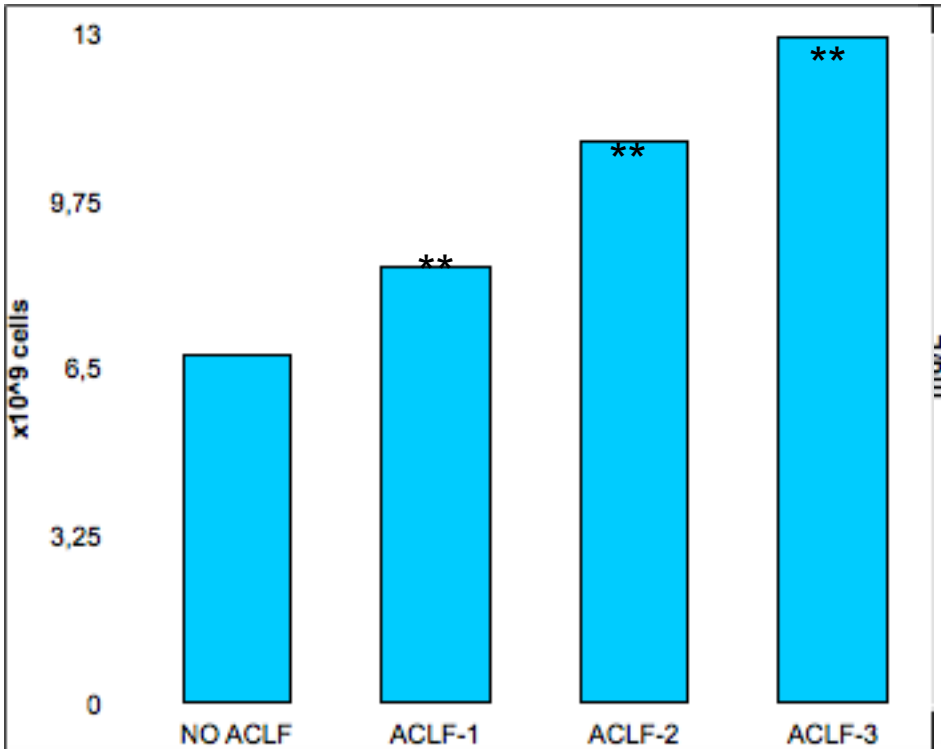


CLINICAL COURSE OF PATIENTS WITH ACLF (Canonic Study)

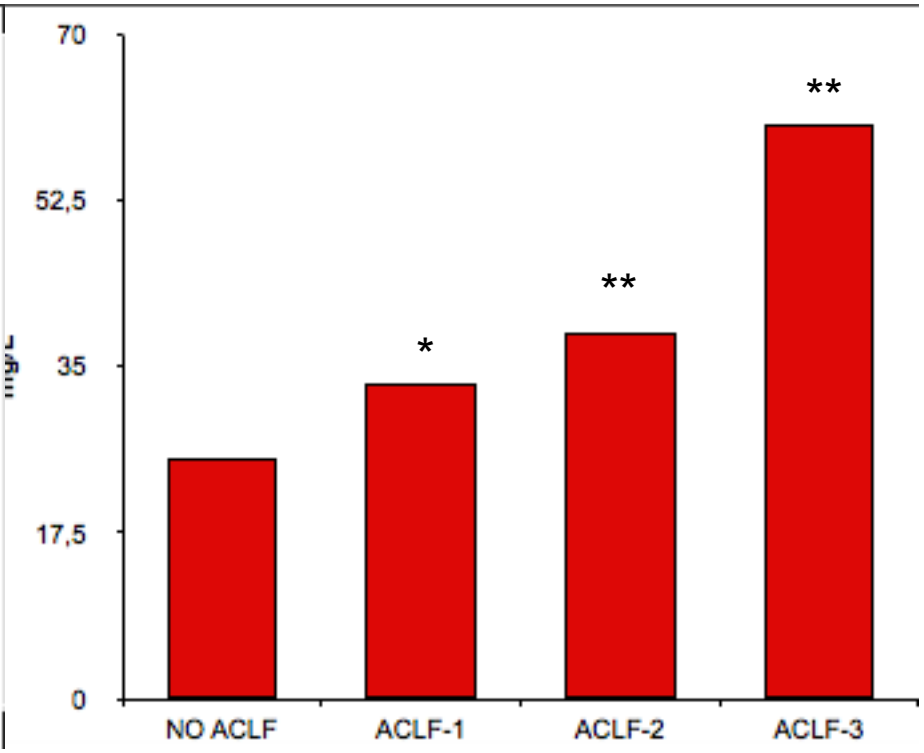
Initial Grade	Final Grade			
	No-ACLF	ACLF-1	ACLF-2	ACLF-3
ACLF-1 (202)	55%	24%	9%	12%
ACLF-2 (136)	34%	14%	25%	25%
ACLF-3 (50)	16%	4%	12%	68%

INFLAMMATORY MARKERS AND DEVELOPMENT OF ACLF AT ENROLLMENT OR DURING HOSPITALIZATION (Canonic Study)

Leucocyte count



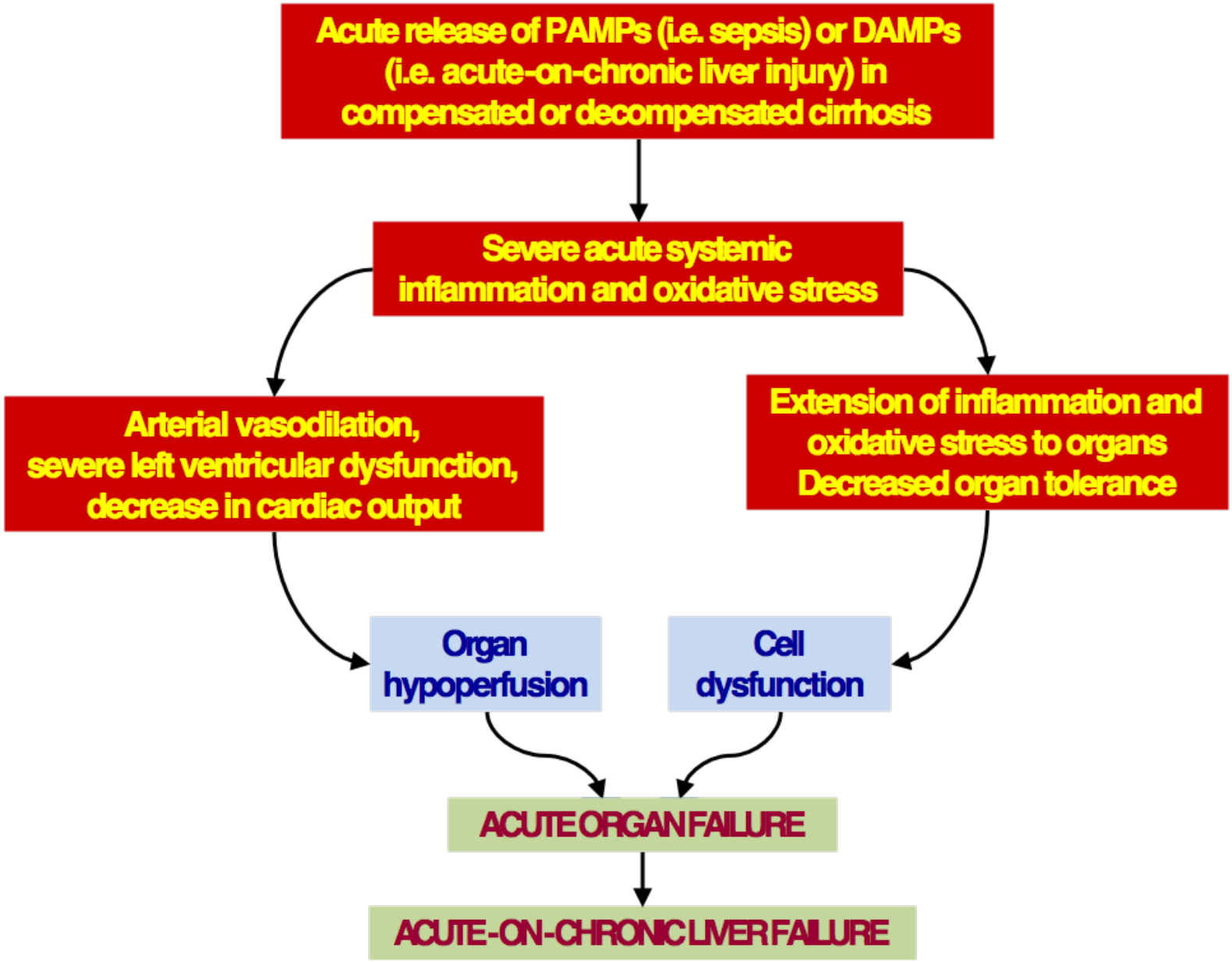
C-reactive Protein



* p<0.05 with respect to No ACLF

** p<0.001 with respect to No ACLF

ACUTE-ON-CHRONIC LIVER FAILURE



SUMMARY

- ACLF is a distinct syndrome in cirrhosis characterized by acute decompensation, organ failure and high short-term mortality. It may occur at any time during the course of the disease (from compensated to decompensated)
- It is related to an acute systemic inflammatory reaction due to bacterial infections (PAMPs), acute liver injury (DAMPs) or to as yet an unidentified mechanism (translocation of bacterial products?). Prognosis of ACLF depends on the severity of systemic inflammation and number of organ failures (not on the precipitating event).
- ACLF is very common in patients alcoholic cirrhosis and in untreated patients with cirrhosis due to HBV infection. The frequency of ACLF in untreated patients with cirrhosis due to HCV infection is lower. There are specific differences in ACLF related to cirrhosis etiology.