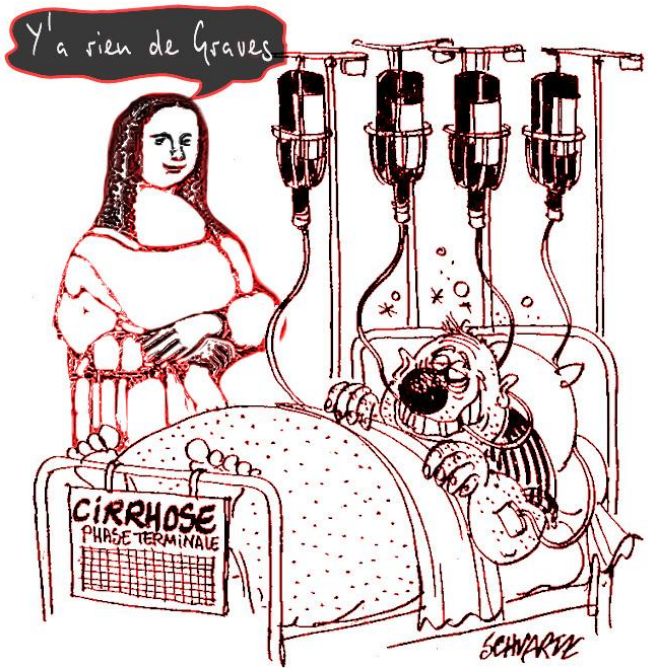
# Insuffisance rénale aigue et maladie hépatique

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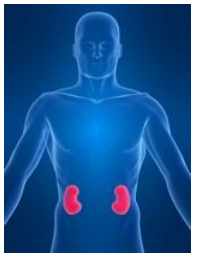
# Introduction



La dysfonction rénale est un facteur pronostic majeur dans la cirrhose

5ème cause d'hospitalisation lors de cirrhose

Majorité des patients (75%) développent une insuffisance rénale lors de maladie hépatique

Facteurs +: Ascite, PBS et Aminoglycosides

Gines P. NEJM 2009
Hampel H. Am J Gasto 2001
Eckardt K. Int Care Med 1999

# Nouvelles définitions IRA

| Classification stage | Criteria according to baseline creatinine | Criteria according to diuresis |
|---|---|---|
| **RIFLE** | | |
| Risk | ↑ creat 1.5x *or* ↓ GFR > 25% | Diuresis < 0.5ml/kg/h x 6H |
| Injury | ↑ creat 2x *or* ↓ GFR > 50% | Diuresis < 0.5ml/kg/h x 12H |
| Failure | ↑ creat 3x *or* ↓ GFR > 75%<br>*Or* ↑ creat 44µmol/l if creat ≥354 µmol/l | Diuresis < 0.3ml/kg/h x 24H<br>*Or* anuria x12H |
| Loss | Complete loss of renal function > 4 weeks | |
| End stage renal failure | Dialysis dependent for at least 3 months | |
| **AKIN** | | |
| 1 | ↑ creat ≥ 26.4µmol/l *or* ↑ creat ≥ 1.5-2x | Cf RIFLE criteria |
| 2 | ↑ creat ≥ 2-3x | |
| 3 | ↑ creat >3x<br>*Or* ↑ creat ≥ 44µmol/l if creat ≥354 µmol/l<br>*Or* dialysis necessary | |

# Nouvelles définitions dans la cirrhose

| Diagnosis | Definition |
|---|---|
| Acute kidney injury | Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h<br>HRS type 1 is a specific form of acute kidney injury |
| Chronic kidney disease | Glomerular filtration rate of <60 ml/min for >3 months calculated using MDRD6 formula<br>HRS type 2 is a specific form of chronic kidney disease |
| Acute-on-chronic kidney disease | Rise in serum creatinine of ≥50% from baseline or a rise of serum creatinine by ≥26.4 μmol/l (≥0.3 mg/dl) in <48 h in a patient with cirrhosis whose glomerular filtration rate is <60 ml/min for >3 months calculated using MDRD6 formula |

Wong.Gut 2011

# Syndrome hépatorénal (SHR)

**New diagnostic hepatorenal syndrome criteria in cirrhosis**

- Cirrhosis with ascites.
- Serum creatinine >133 μmol/l (1.5 mg/dl).
- No improvement of serum creatinine (decrease to a level of ⩽133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

# Définitions SHR

- Classification en 2 types :
  - **Type I**: **IR sévère et d'installation rapide**.
    ↑créatinine > 220 umol/l (↑100%) en moins de 15 j
    Clinique: IRA, hypotension, atteinte multiorganique
    Facteur déclenchant dans 50-70% des cas.

  - **Type II**: **IR d'installation lente**, modérée et stabilisée entre 132 et 220 umol/l
    Clinique: ascite réfractaire aux diurétiques.
    Rarement un facteur déclenchant.

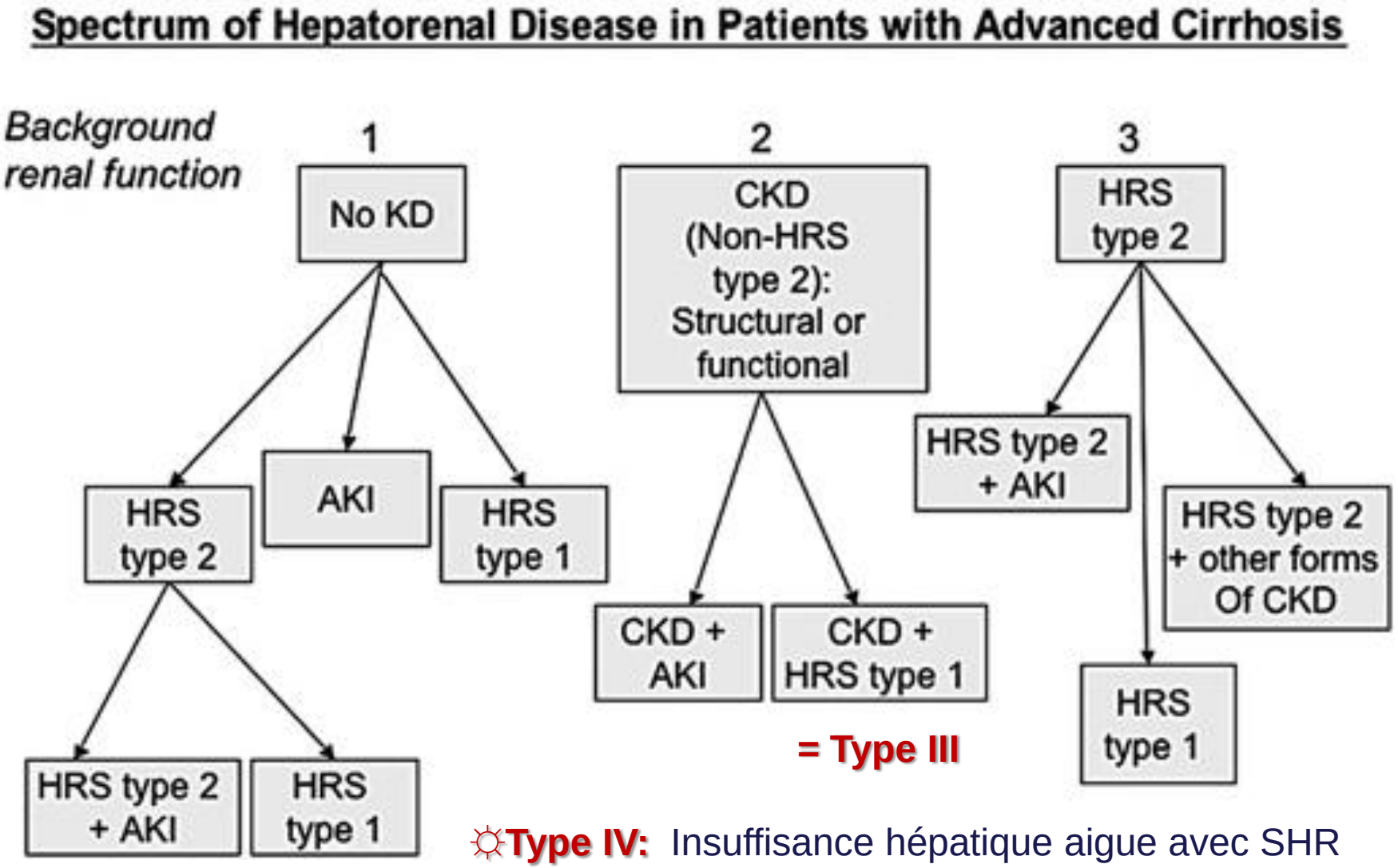
Salerno. Gut 2007
EASL guidelines: J Hepatology 2010

# Définition ascite réfractaire

| | |
|---|---|
| Diuretic-resistant ascites | Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment |
| Diuretic-intractable ascites | Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage |
| Requisites | |
| 1. Treatment duration | Patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a salt-restricted diet of less than 90 mmol/day |
| 2. Lack of response | Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake |
| 3. Early ascites recurrence | Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization |
| 4. Diuretic-induced complications | Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor<br>Diuretic-induced renal impairment is an increase of serum creatinine by >100% to a value >2 mg/dl (177 μmol/L) in patients with ascites responding to treatment<br>Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L<br>Diuretic-induced hypo- or hyperkalemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures |

EASL group J Hepatology 2010

# Spectre SHR




☼**Type IV:** Insuffisance hépatique aigue avec SHR

Wong. Gut 2012

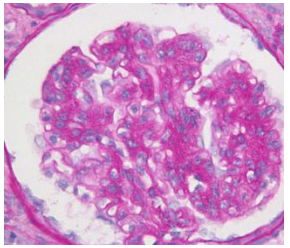
# Causes IRA – maladie hépatique

1. Infections
   a. Spontaneous bacterial peritonitis
   b. Spontaneous bacteremia
   c. Urinary tract infection, pneumonia, skin infections
2. Hypovolemia-induced renal failure
   a. Vomiting, diarrhea
   b. Gastrointestinal bleeding (with or without shock)
   c. Diuretic-induced
3. Hepatorenal syndrome
4. Intrinsic renal diseases
   a. Glomerulopathies – IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis, polyarteritis nodosa, cryoglobulinemia due to viral hepatitis, or alcohol.
   b. Chronic kidney diseases due to diabetes, hypertension or other causes.
5. Drug induced renal failure
   a. Hemodynamically induced—Nonsteroidal anti-inflammatory agents, ACE Inhibitors, Angiotensin receptor blockers
   b. Acute tubular necrosis- Aminoglycosides, Amphotericin B, Tenofovir, Adefovir
   c. Acute interstitial nephritis- penicillin, rifampin and sulfonamides

Drug-induced hepato-nephrotoxicity (acetaminophen, aspirin, NSAIDs)
Granulomatous diseases (e.g., sarcoidosis, leptospirosis)
Storage diseases (e.g., amyloidosis)
Systemic autoimmune diseases (e.g., lupus erythematosus)
Non-alcoholic fatty liver disease and diabetic nephropathy
Autosomal dominant polycystic kidney disease
Wilson's disease
Pregnancy-induced liver diseases (pre-eclampsia /HELLP syndrome)
Shock (cardiac failure, sepsis, hemorrhage, dehydration)
Alpha1-antitrypsin deficiency

Gines P. The Kidney. Chap 79.
Hartleb. WJC 2012

# Biopsie rénale



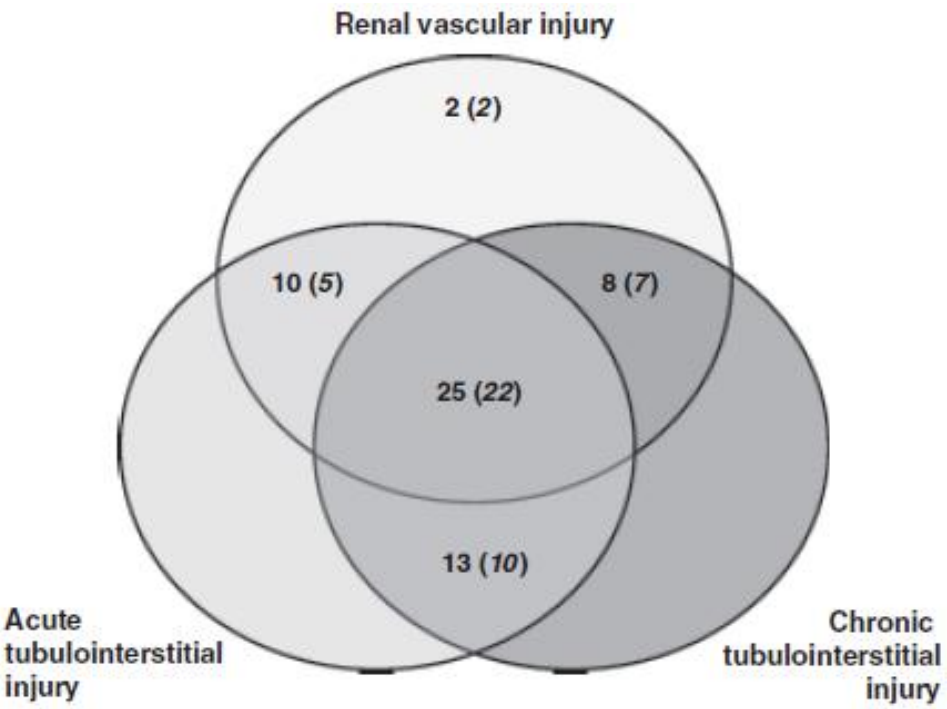



**Table 2:** Kidney biopsy findings in 44 liver transplant candidates with renal failure

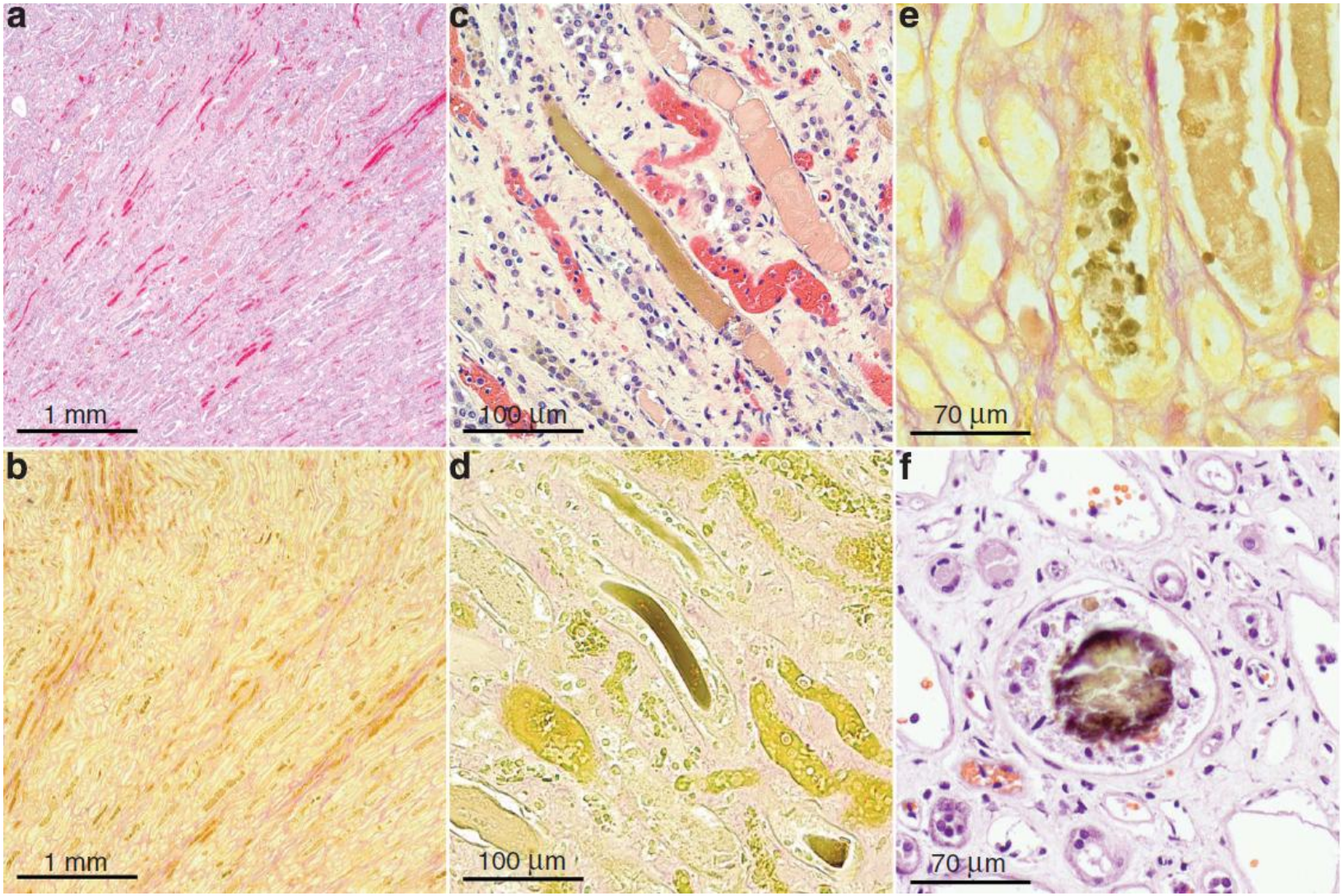
| Histological finding[1] | Number (%) |
|---|---|
| Glomerulonephritis | 31 (71) |
| IgAN | 20 (45) |
| MPGN | 6 (14) |
| Diabetic nephropathy | 5 (11) |
| FSGS | 4 (9) |
| ATN/injury | 18 (41) |
| Advanced IF | 12 (27) |
| Advanced gGS | 7 (16) |

IgAN = IgA nephropathy; MPGN = membranoproliferative glomerulonephritis; FSGS = focal segmental glomerulosclerosis.
[1]More than one finding was present in 28 patients.

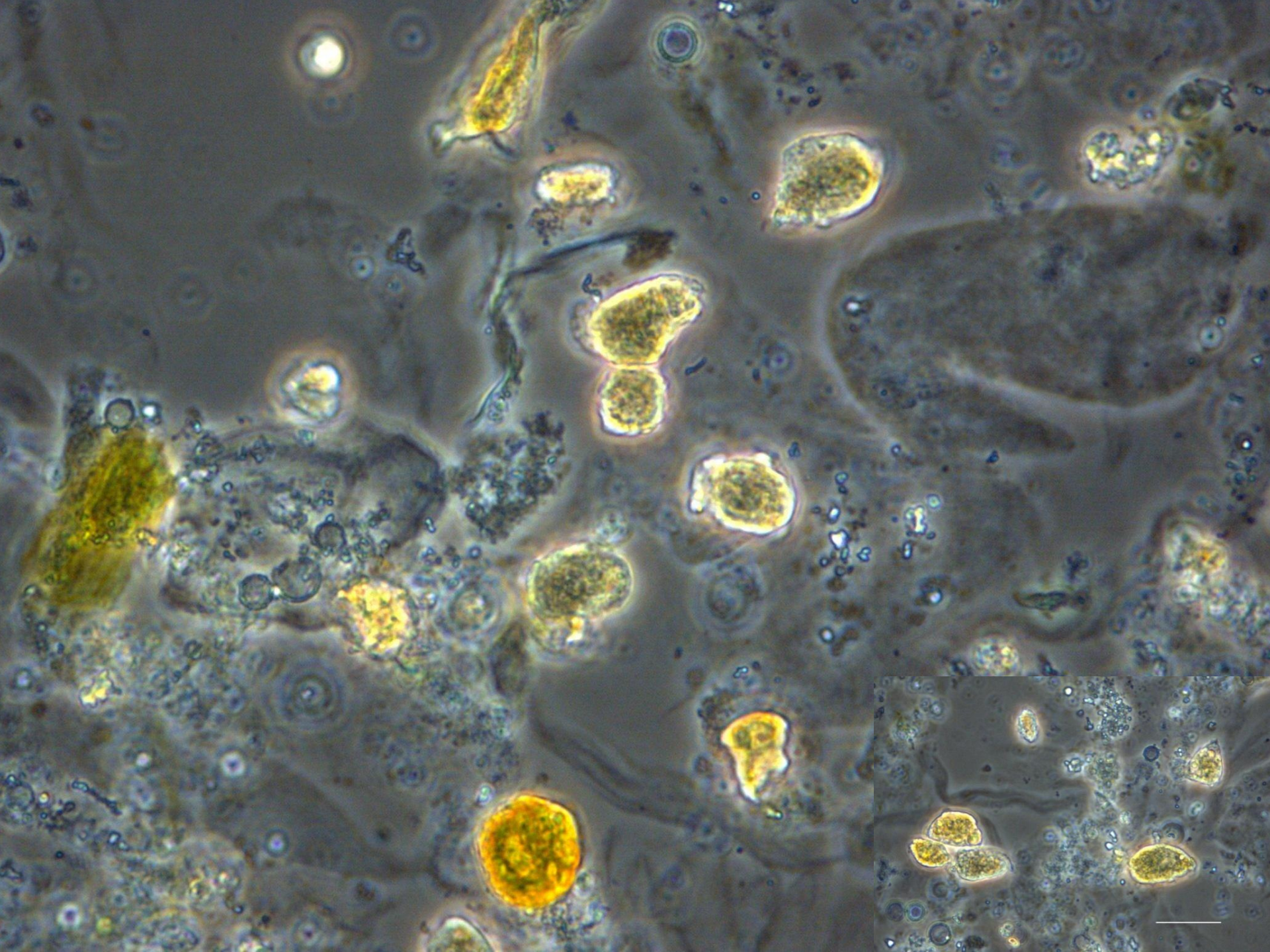
N=65 avec anomalies urinaires ou élévation créat

Wadei et al Am J Transpl 2008
Trawale. Liv International 2009

# « Bilirubin cast nephropathy




Van Slambrouck.KInt. 2013

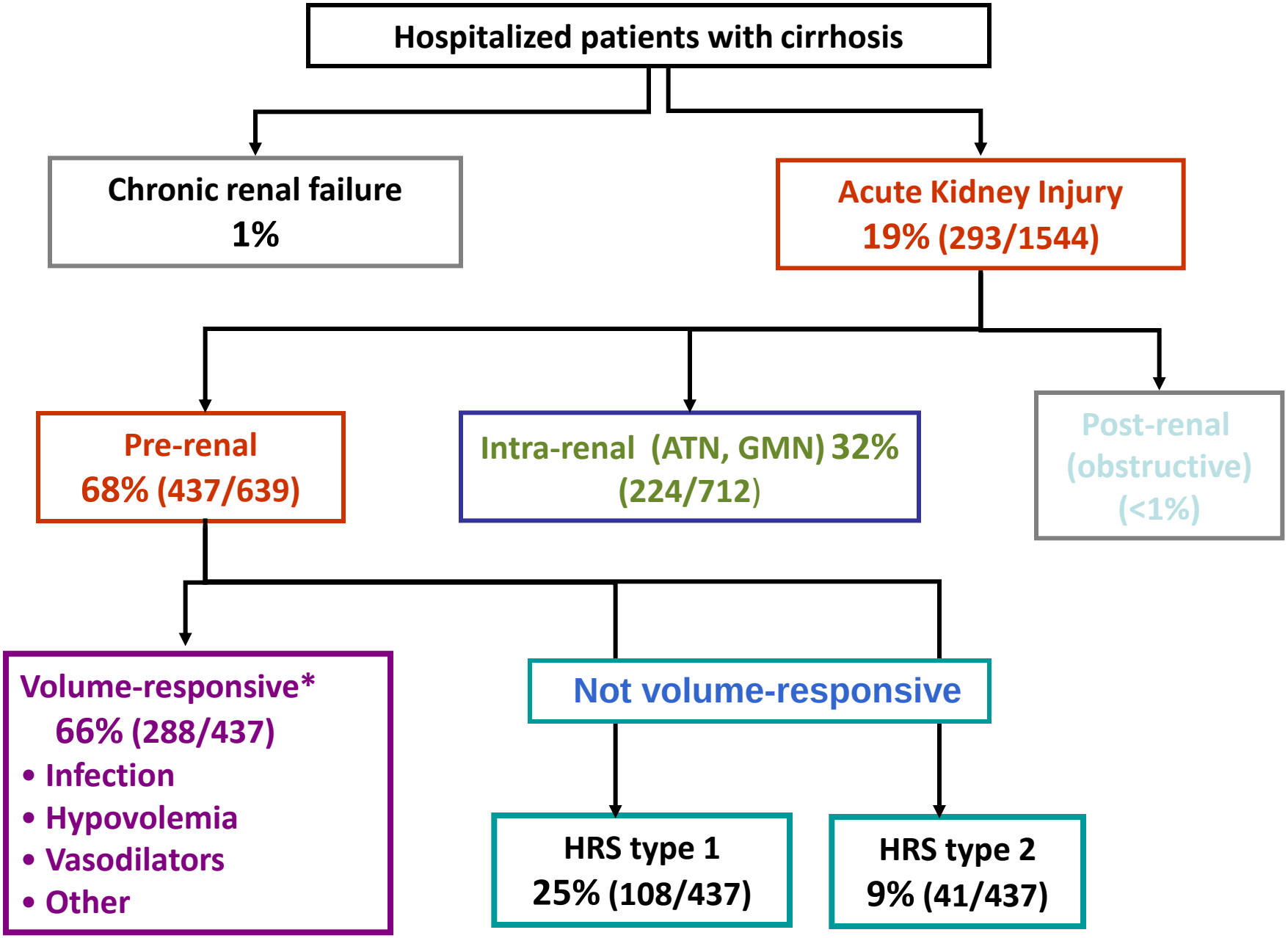


# Epidémiologie: prévalence IRA

Varie selon les situations cliniques:

| | |
|---|---|
| ✓ Hospitalisés: | 20% admissions<br>70% durant hosp<br>17% IRA sur IRC durant hosp |
| ✓ Post transplantation hépatique: | 12-70%<br>→ 71% nécessitent dialyse |
| ✓ Soins intensifs (RIFLE): | 49% pendant séjour<br>→ 22% stade R, 19% F |
| ✓ Infection cutanée: | 21% |
| ✓ Peritonite bactérienne spontanée: | 41-56% |
| ✓ Post TIPS: | 5.5% |

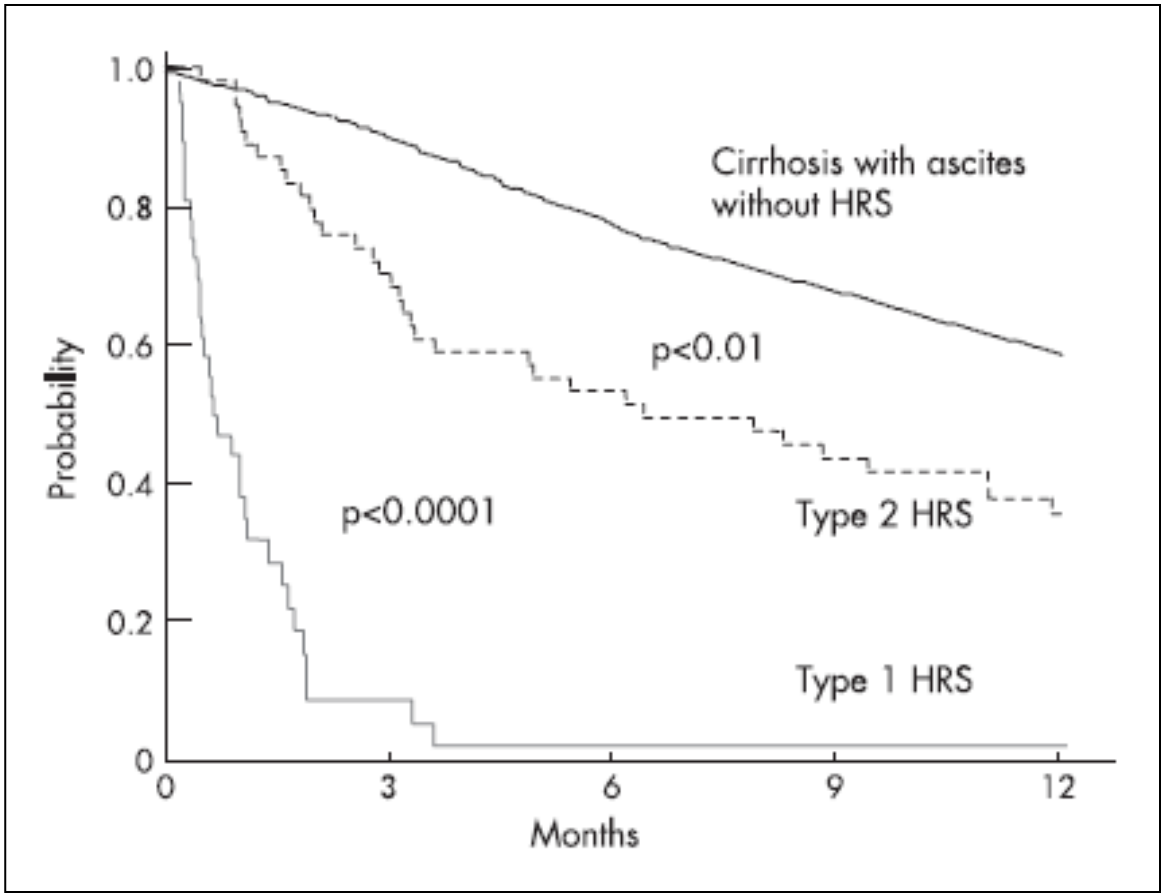
Mucino-Bermejo.Annals of hepathology 2012




Garcia-Tsao: Hepatology 2008

# Pronostic IRA

Survie globale lors d'atteinte rénale: 50% à 1 mois et 20% à 6 mois.
20% développent SHR à 1 an → 50% à 3-5 ans




**Type II:**
Survie médiane 6 mois

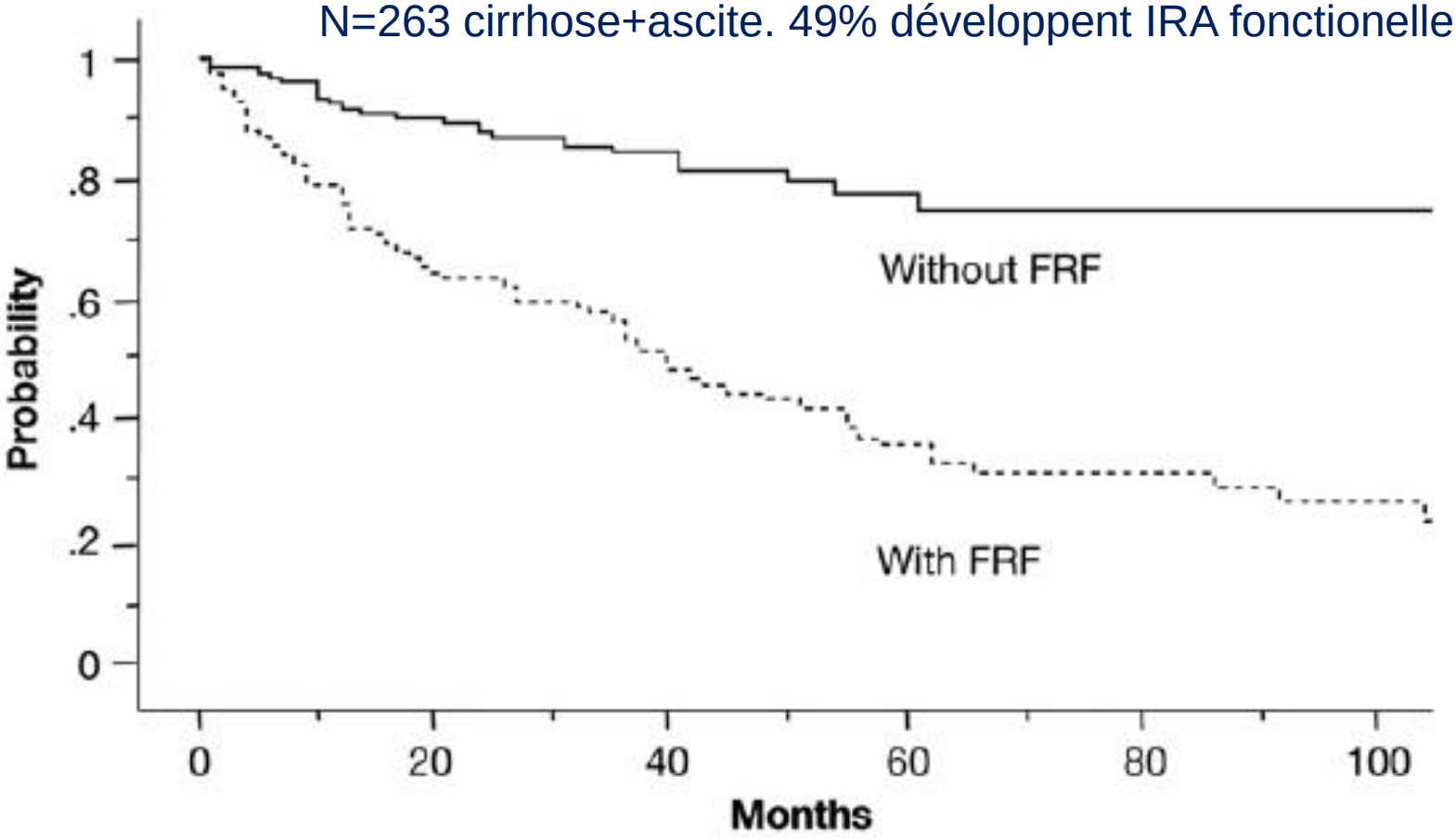
**Type I:**
Survie médiane 11-14j
10% de survie à 90j

Cholongitas E. Eur J Gatroenterol Hepatol 2009
D'Amico G. J Hepatology 2006

# Pronostic IRA

## IRA fonctionnelle de moins bon pronostic qu'IRA « organique »

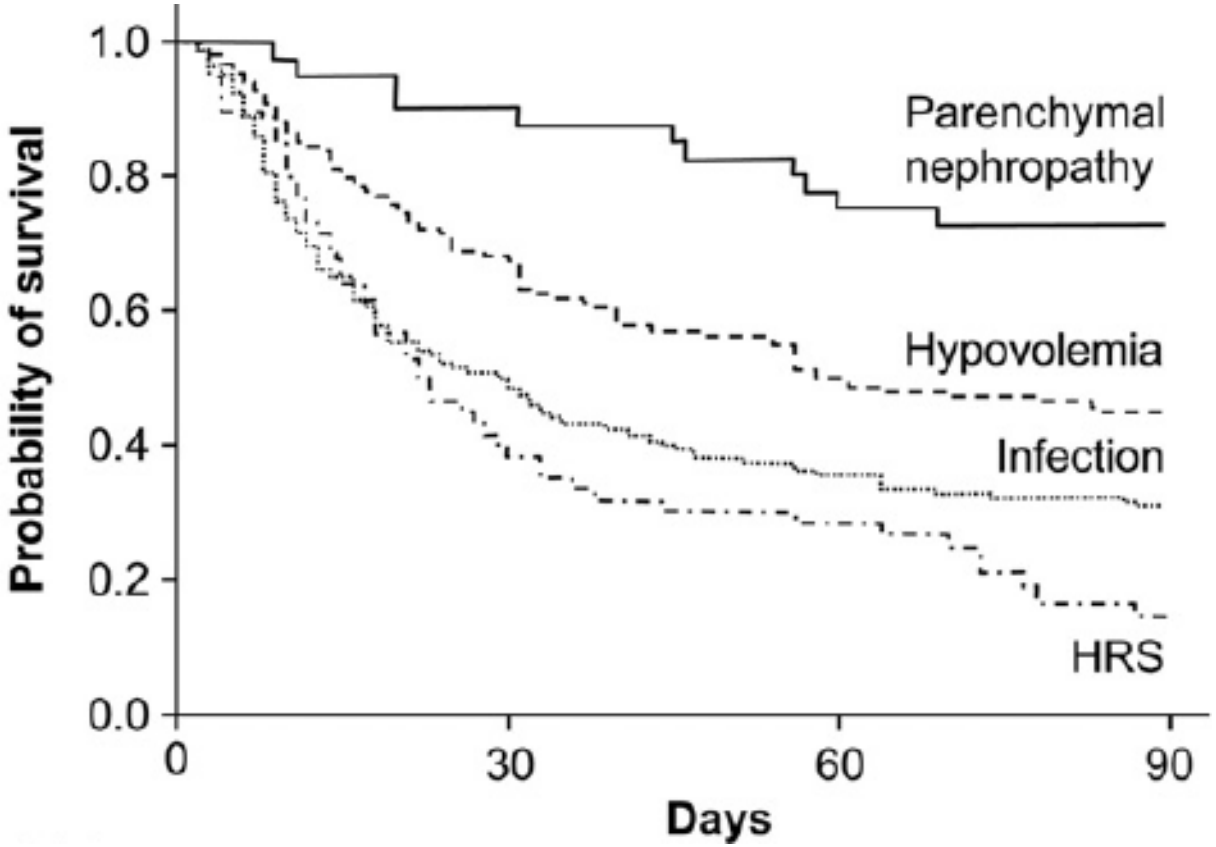
N=263 cirrhose+ascite. 49% développent IRA fonctionelle




Monoliu.ClinGastroHepathol 2010

# Pronostic IRA

## La cause de l'IRA dans la cirrhose influence le pronostic

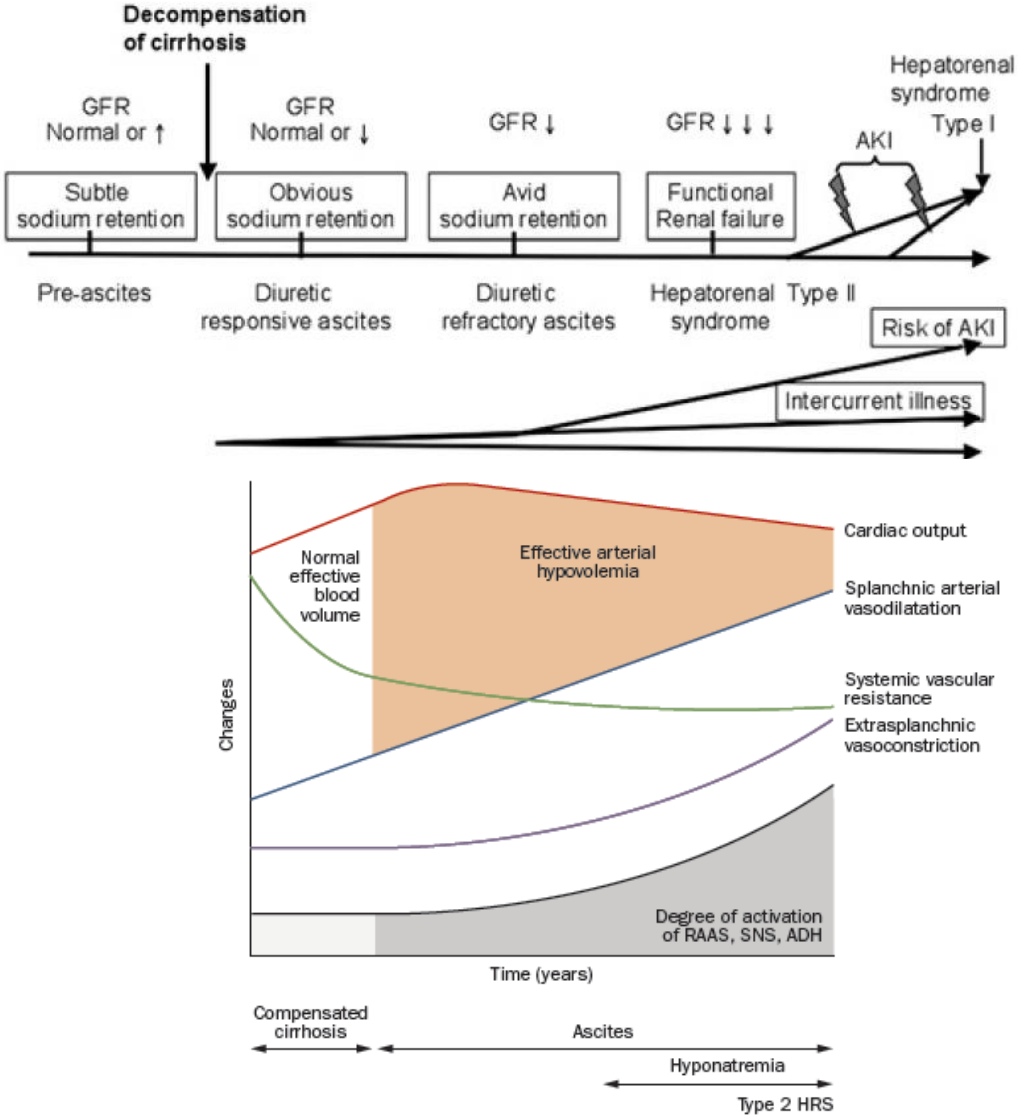


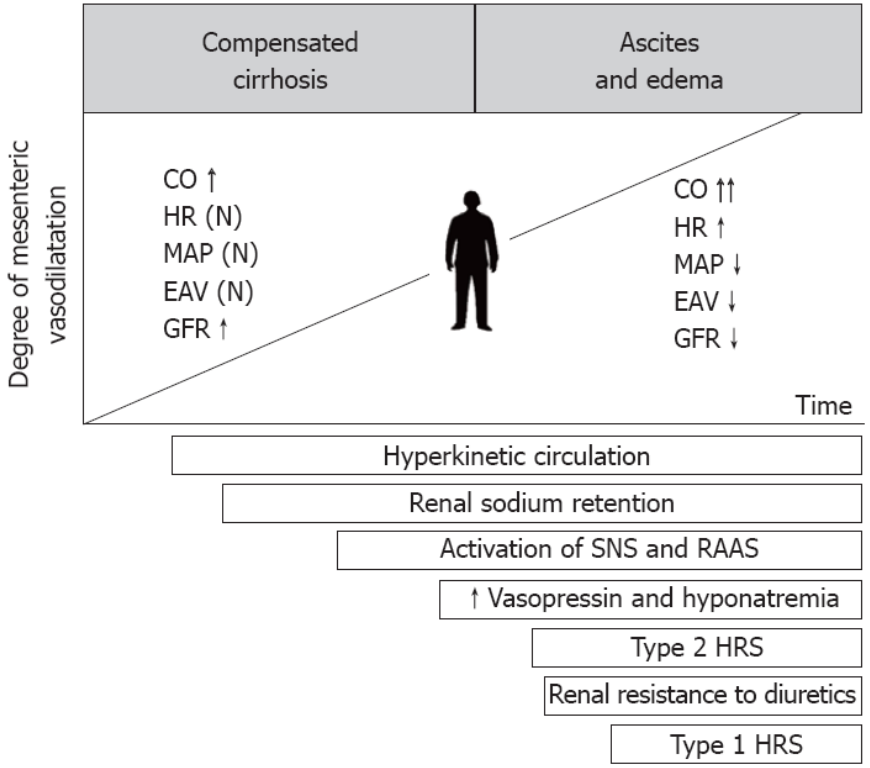

Etiologies - 4catégories:
46% infection
32% hypovolémie
13% SHR
9% parenchyme

OR selon étiologie:
2.62 infection
2.32 hypovolemie
6.88 SHR

Martin-Llahi M. Gastroenterology 2011

# Histoire naturelle



# Classification AKIN

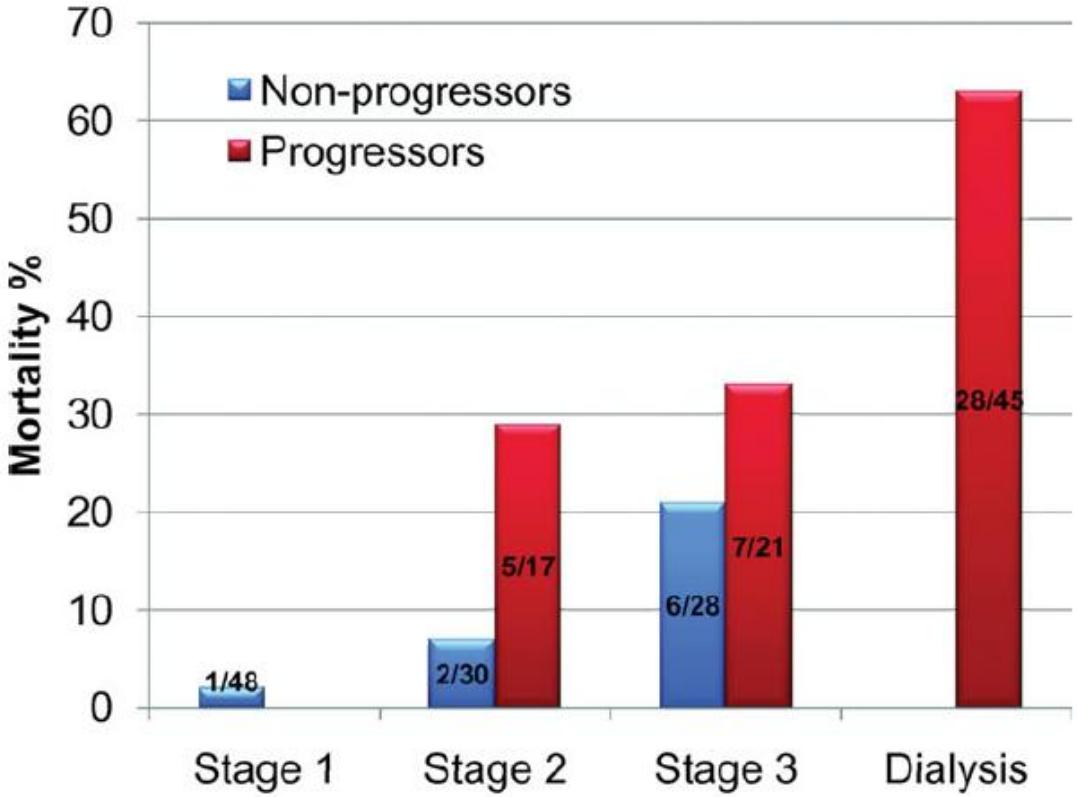
IRA mininime (↑0.3mg/dl) influence pronostic

Tsien. Gut 2013

Classification AKIN prédit mortalité  hospitalière

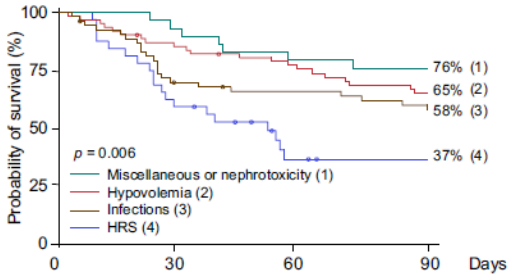
Ribero Carbalho.Jclin Gastro 2012

Progression AKI détermine pronostic:



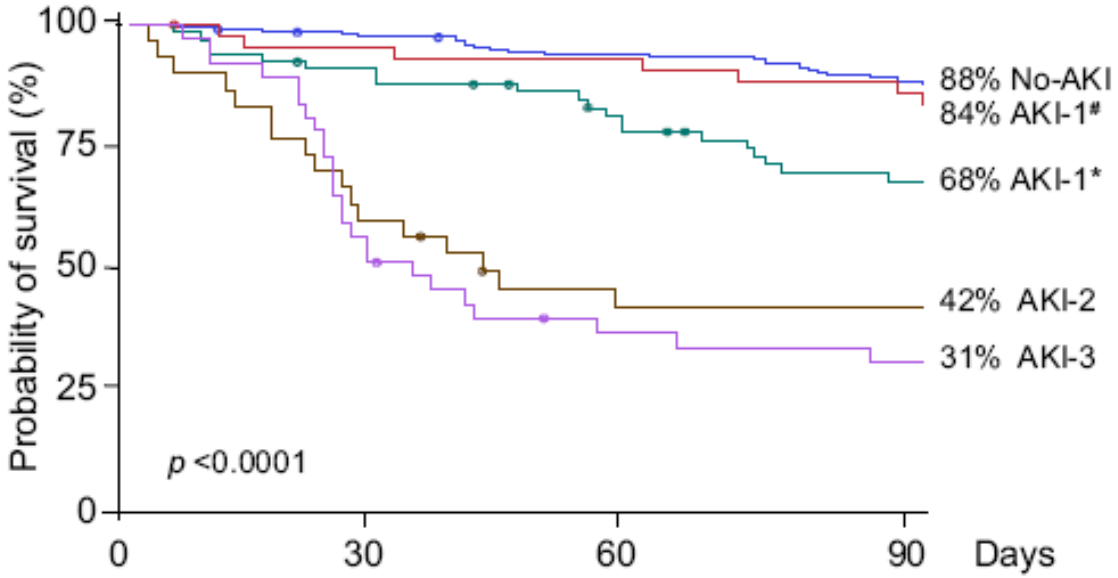

Belher.Hepathology 2013.

# AKIN + créat




N=375 dont 177 AKI

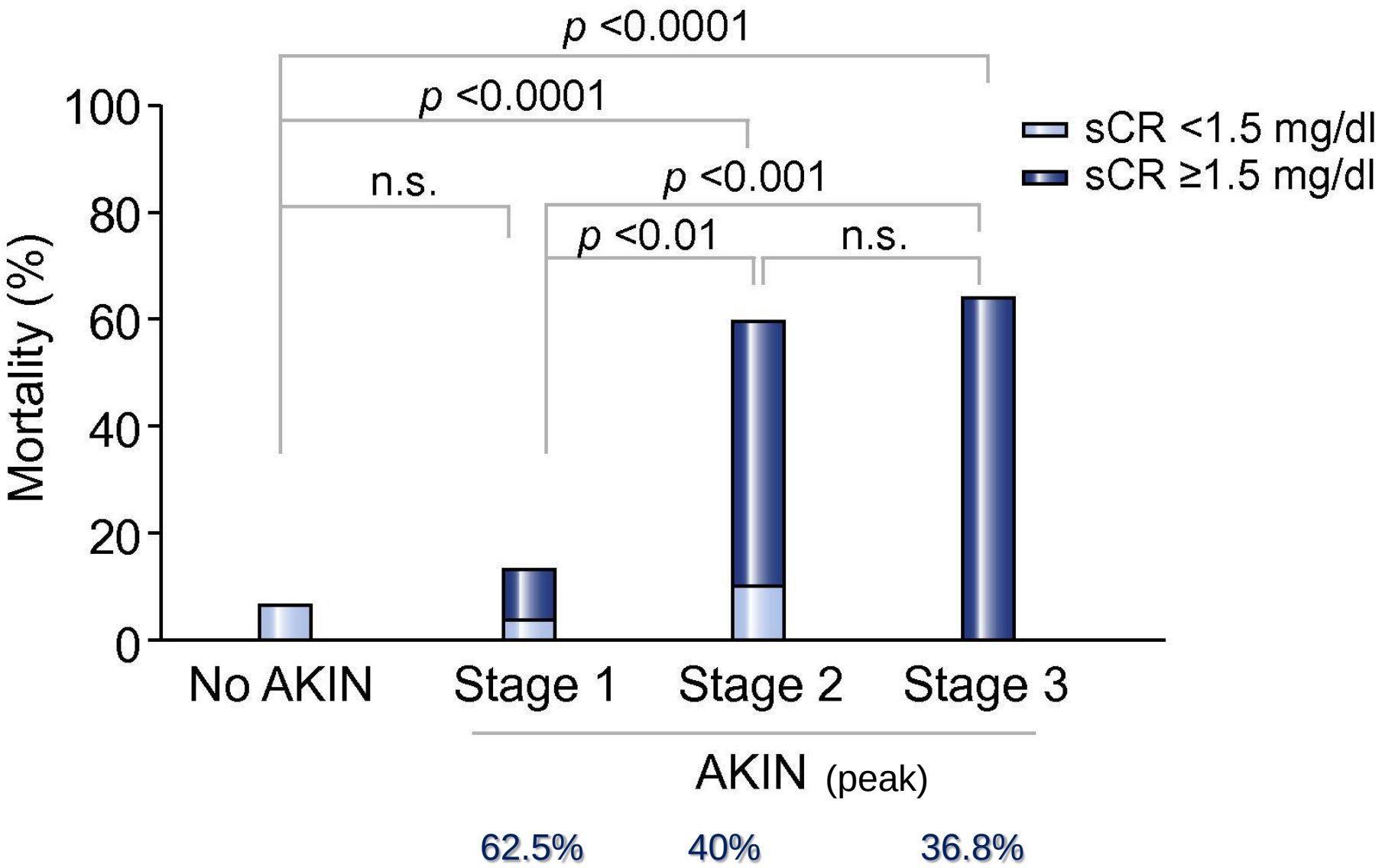
Survie différente pour stade 1 si créat >1.5mg/dl




| | | | |
|---|---|---|---|
| No AKI (n = 198) | 191 | 182 | 172 |
| AKI-1#(n = 44) | 41 | 39 | 37 |
| AKI-1*(n = 66) | 57 | 48 | 40 |
| AKI-2 (n = 30) | 18 | 11 | 11 |
| AKI-3 (n = 37) | 18 | 12 | 10 |

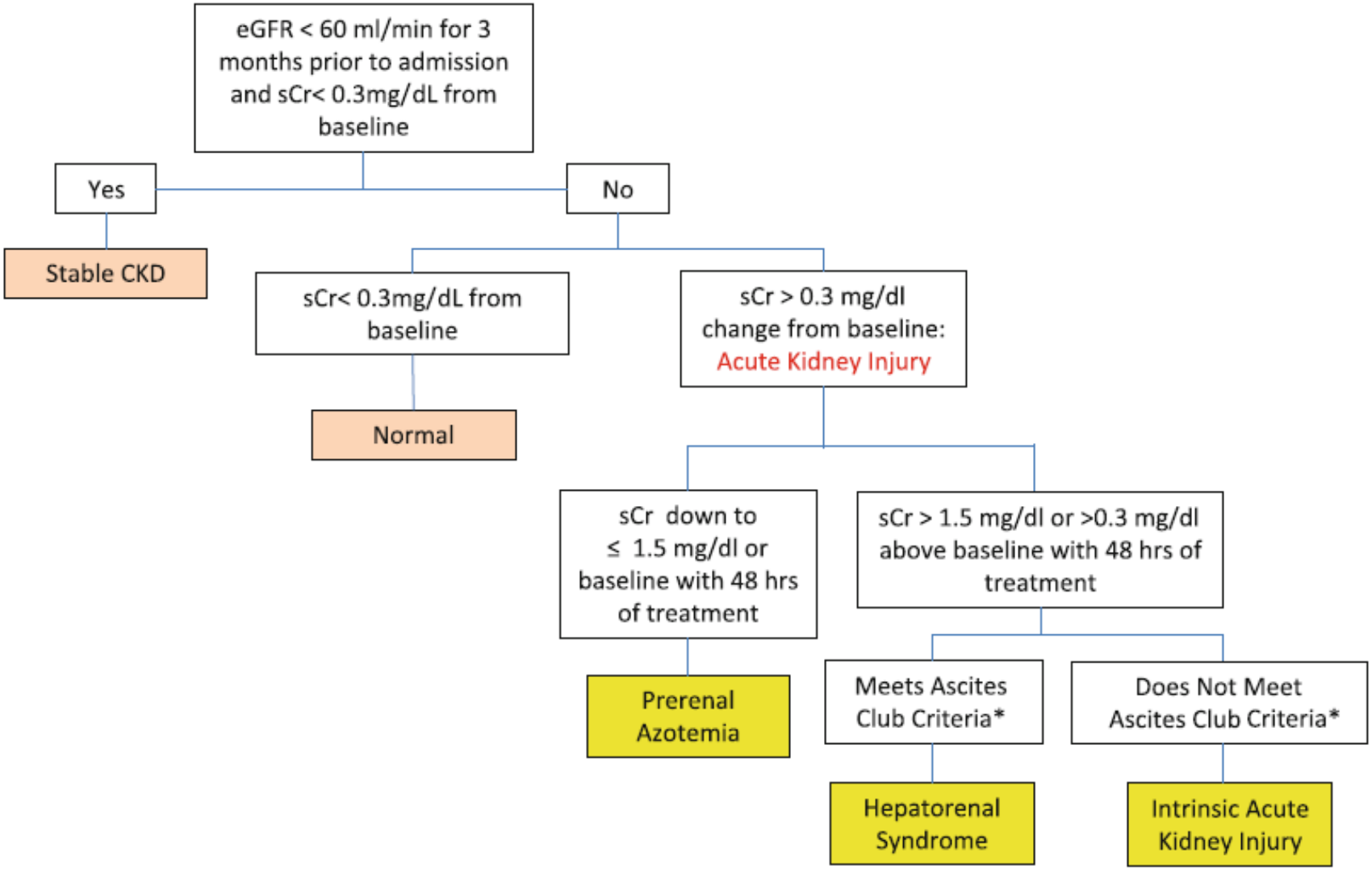
Fagundes. J Hepathol 2013

N=233 cirrhose + ascite→ 25%AKI

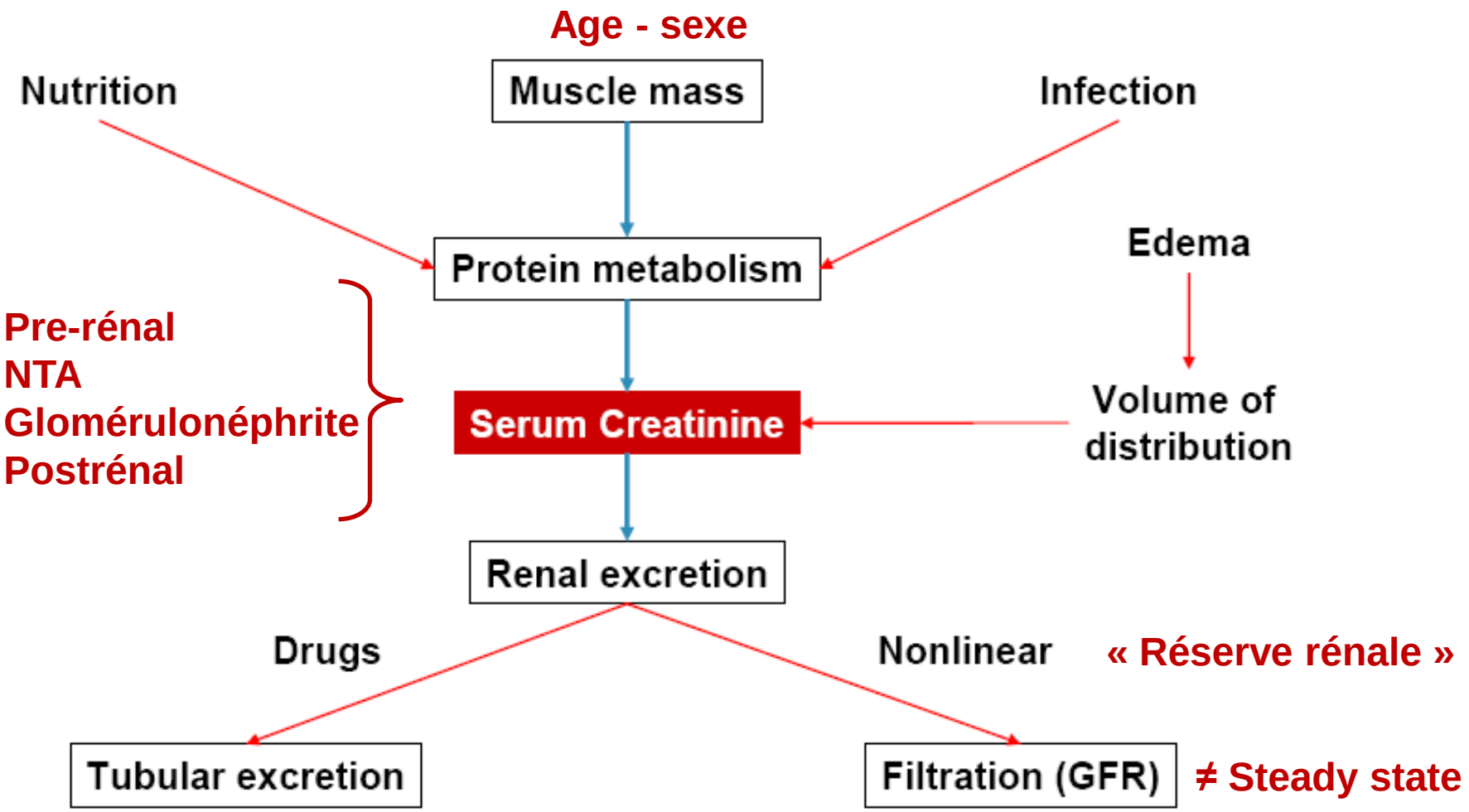



Piano et al, J Hepatol 2013

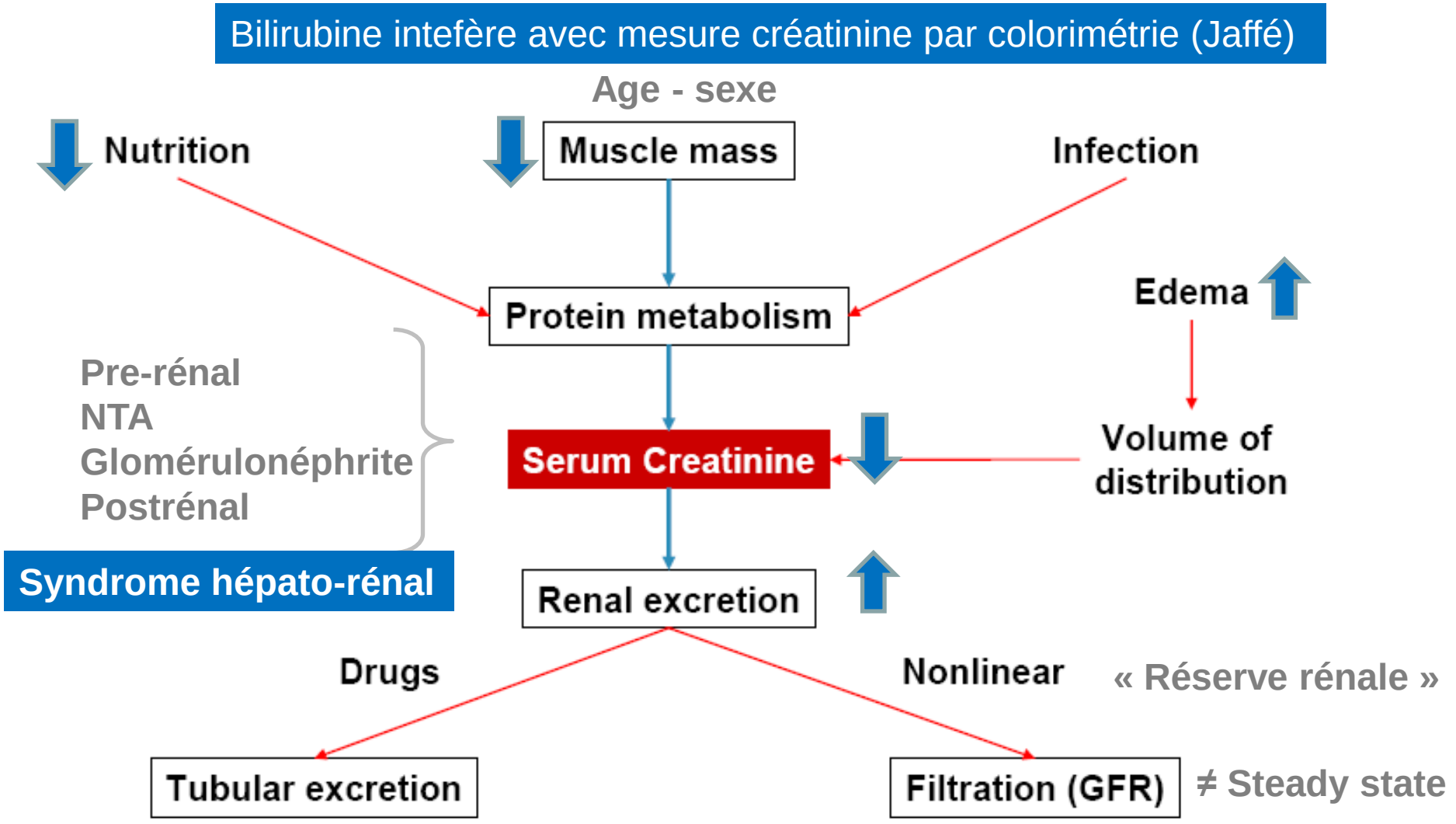
# Diagnostic différentiel



# Limitations de la Créatinine



# Limitations de la créatinine: cirrhose



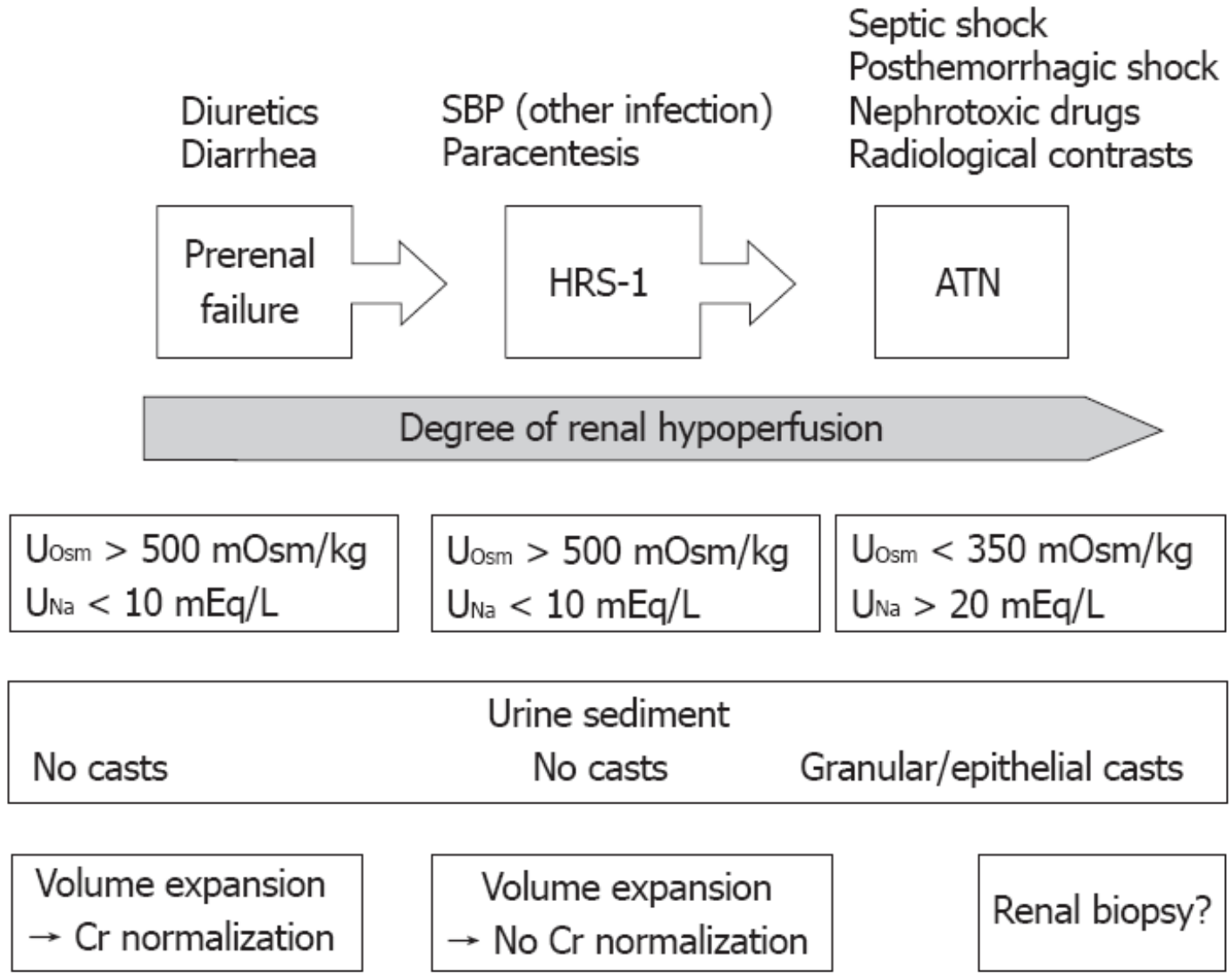
# Diagnostic différentiel

**Pre Renal Acute Kidney Injury**

- **Volume Response 66%**
  - **Most common causes**
    - •Sepsis
    - •GI hemorrhage
    - •Diarrhea
    - •Aggressive use of diuretics
    - •NSAIDs
    - •Contrast dye
- **Volume Non Response 34%**
  - **HRS Type I 25%**
  - **HRS Type II 9%**

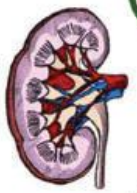
| | HRS | ATN | GN |
|---|---|---|---|
| Urine Na | <20 mEq | >40 mEq | >20 mEq |
| Fx Na Excretion | <1% | >2% | >2% |
| Osmolarity | >500 | <350 | ----- |
| Urine Sediment | Bland | Epithelial casts | RBC casts, oval fat bodies – Proteinuria |
| Other markers | | B-2 microglobulin | |

# Problématique: continuum?



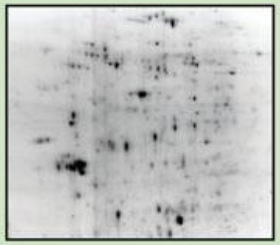

Hartleb. WJG. 2012

Kidney and Urine

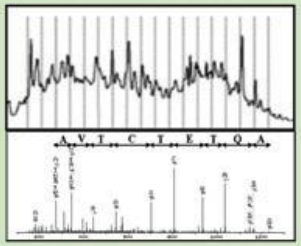


Sample preparation
& protein extraction

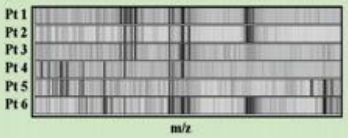
Proteomic Analysis



2-D PAGE

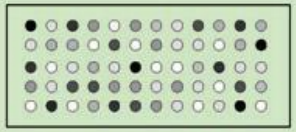


LC-MS/MS




SELDI-TOF-MS


CE-MS



Microarrays

Validation

Diagnostic & prognostic biomarkers

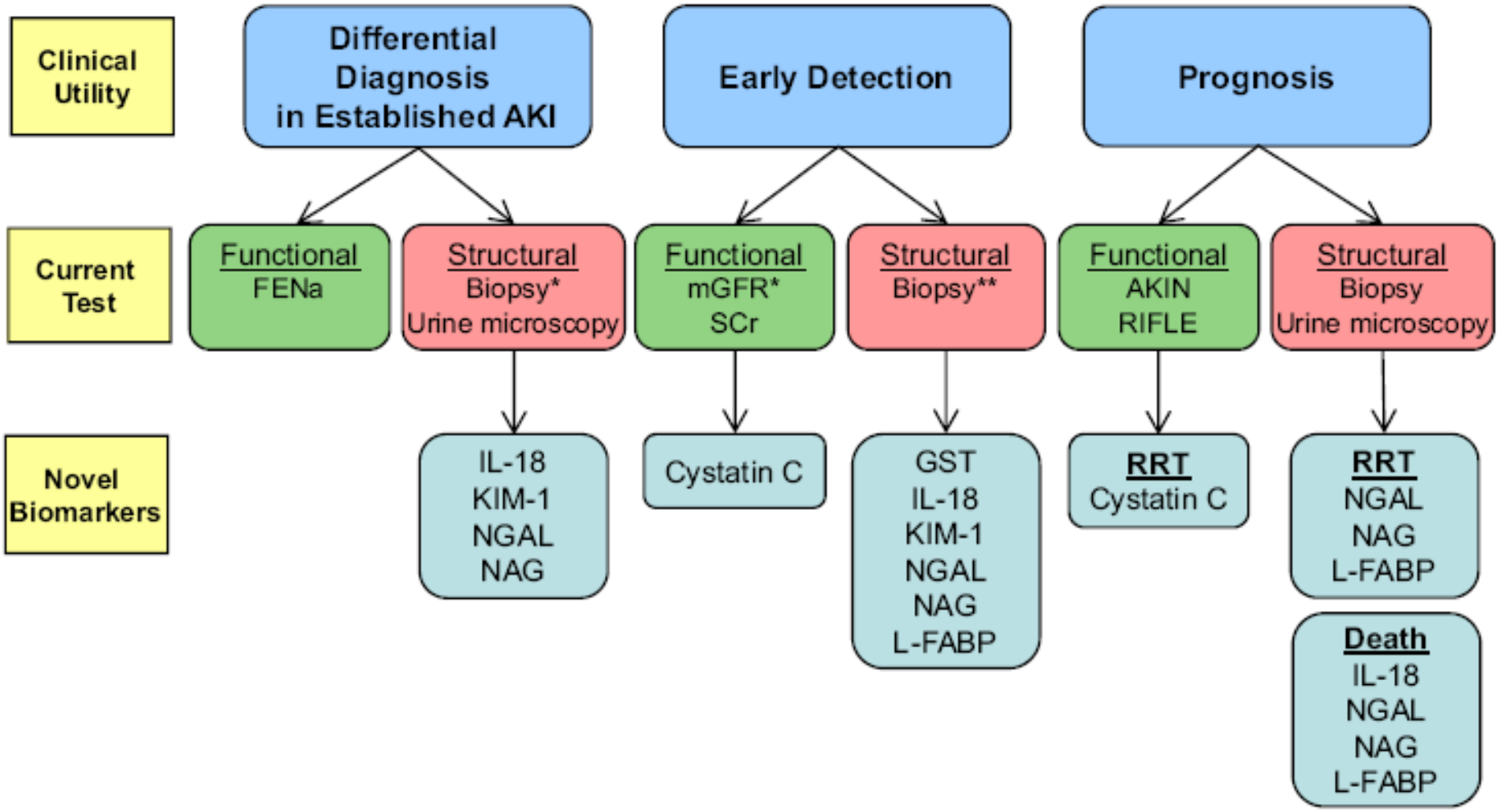
Functional Study

Better understanding of biology & physiology

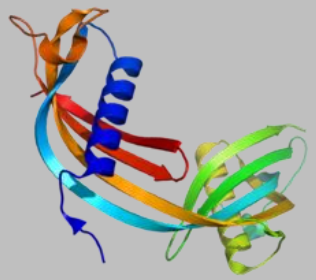
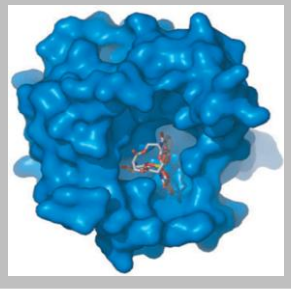
New therapeutic targets, drugs & treatments

Pathogenic mechanisms & pathophysiology

# Marqueurs de lésions rénales




Belcher. AJKD 2011.

| Marqueur | caractéristiques | Rein | Délai | confondants |
|---|---|---|---|---|
| **Cystatine C**<br>Sang +urine<br>Néphélométrie<br>  | 13kda<br>Inhibe Cysteine protease<br>Produite par cellules nuclées à taux constant<br>Non influencé par sexe, muscle, hydratation | Librement filtré<br>Réabsorbé par TP<br>Pas de sécrétion tubulaire<br>**Marqueur de filtration glomérulaire** | **12-24h** | Inflammation<br>Néoplasie<br>Mal thyroïde<br>Corticoïdes<br>Tabac |
| **NGAL**<br>Sang+urine<br>ELISA<br>  | 25kda<br>Lipocaline-2<br>Liée à gelatinase neutrophiles<br>Présente dans tissus ou induite par lésions épithéliales | Librement filtrée<br>Réabsorption complète par cellules tubulaires proximales<br>Produite par segments distaux | **2-4h** | Sepsis<br>Néoplasie<br>IRC<br>Pancréatite<br>Infection urine |

# Cystatine c - MELD

**Table 1.** Demographic, clinical and biochemical features of the study cohort

| | Study cohort ($n$ = 429) |
|---|---|
| Demographic | |
| Mean age (year) (SD) | 57.2 (12.0) |
| Sex (f/m) | 136/293 |
| Cause of cirrhosis (%) | |
| ALD/NASH | 58.7 |
| Viral hepatitis | 25.6 |
| Cryptogenic | 5.8 |
| Other | 9.8 |
| Biochemical (median, IQR) | |
| Serum bilirubin (mg/dL) | 1.6 (0.9–3.3) |
| Serum creatinine (mg/dL) | 0.9 (0.7–1.2) |
| Cystatin C (g/L) | 1.2 (1.0–1.7) |
| INR | 1.2 (1.1–1.5) |
| Median MELD (IQR) | 12 (9–17) |
| Median follow-up (year) (IQR) | 1.3 (0.6–3.5) |
| Deaths/liver transplantation ($n$) | 83/50 |
| 75‰ transplant free survival time (year) | 4.2 |

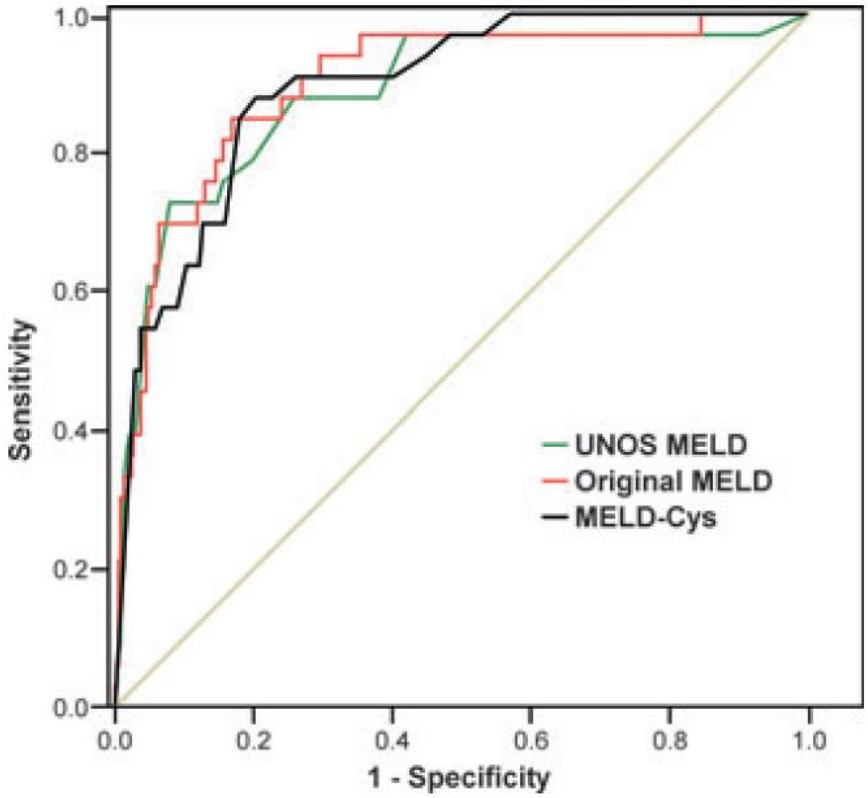
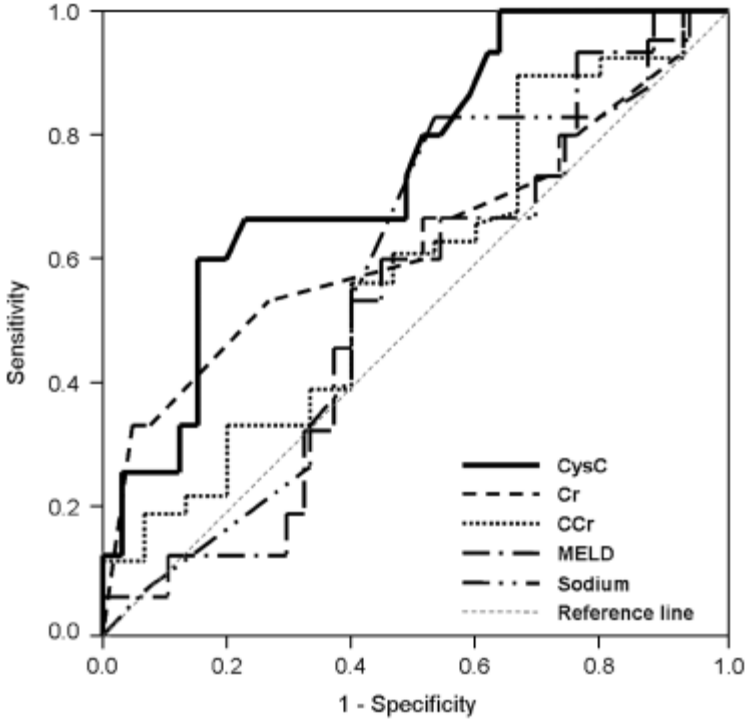



**Table 3.** Discriminative performance and thresholds for 90-day mortality of the three models

| | Cut-off value | AUC (95% CI) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| Original MELD | ≥ 16 | 0.90 (0.84–0.96) | 85 | 83 |
| UNOS MELD | ≥ 21 | 0.88 (0.82–0.95) | 73 | 92 |
| MELD-Cys | ≥ 26 | 0.89 (0.84–0.94) | 88 | 80 |

# Cystatine c prédit SHR



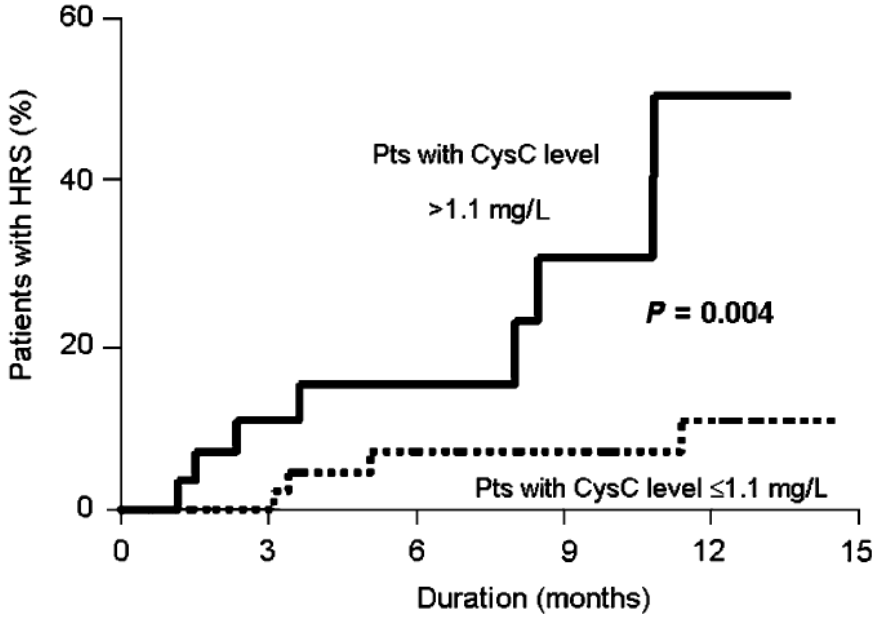
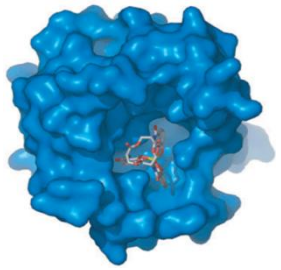




**Table 4.** Area under the receiver operating characteristic curve and cutoff value for predicting the development of hepatorenal syndrome within 12 months

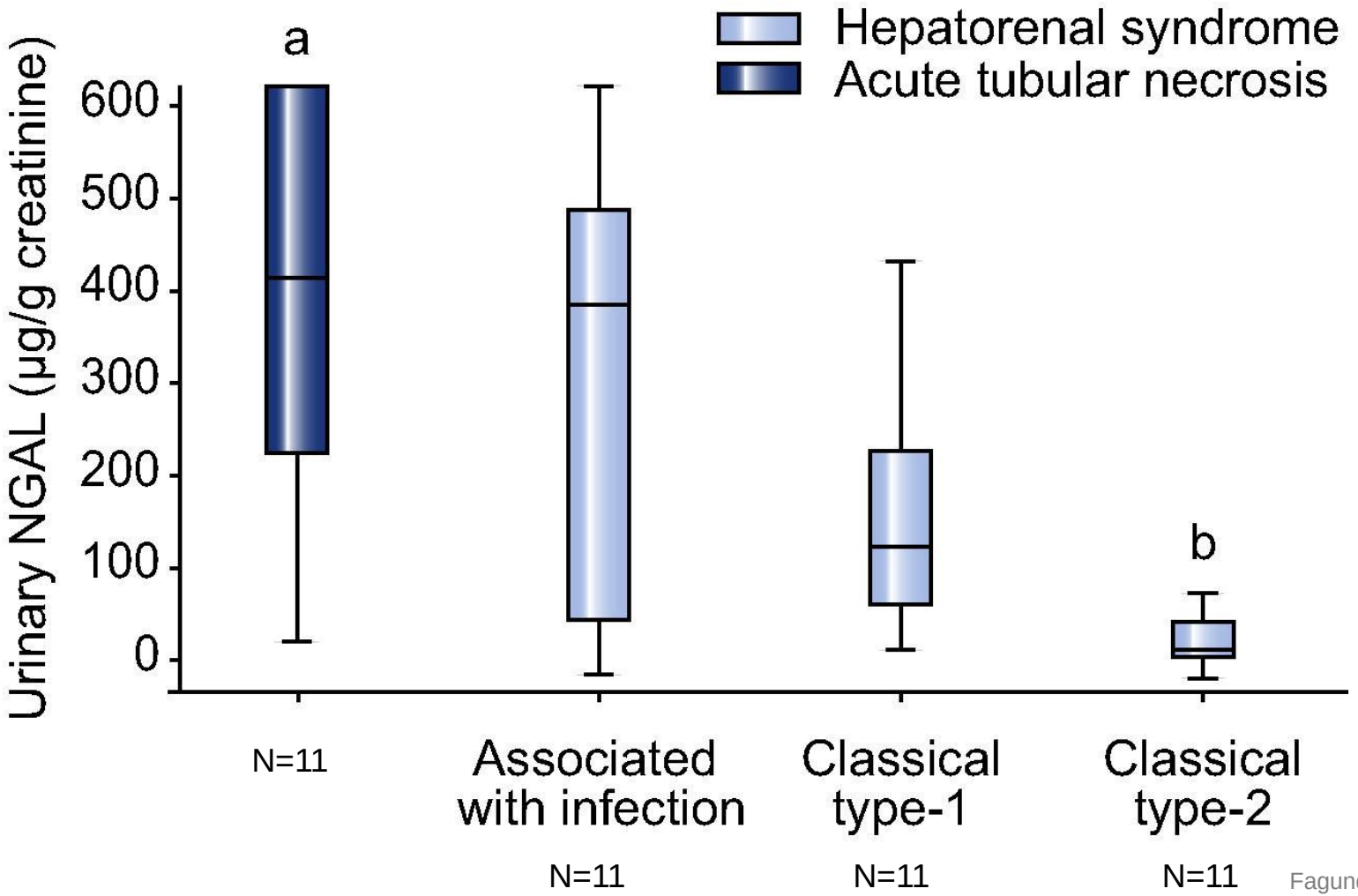
| | Cutoff value | AUC (95% CI) | Sensitivity (%) | Specificity (%) | Likelihood ratio | *P* |
|---|---|---|---|---|---|---|
| CysC | 1.105 | 0.750 (0.610–0.891) | 66.7 | 78 | 9.492 | 0.004 |
| Cr | 0.995 | 0.633 (0.449–0.817) | 33.3 | 95.1 | 7.120 | 0.132 |
| CCr | 84.55 | 0.583 (0.411–0.755) | 60 | 39 | 0.004 | 0.345 |
| MELD score | 10.498 | 0.538 (0.376–0.701) | 93.3 | 24.4 | 2.584 | 0.664 |
| Sodium | 139.5 | 0.572 (0.386–0.759) | 66.7 | 26.8 | 0.223 | 0.410 |

Seo Y. Liv Int 2009

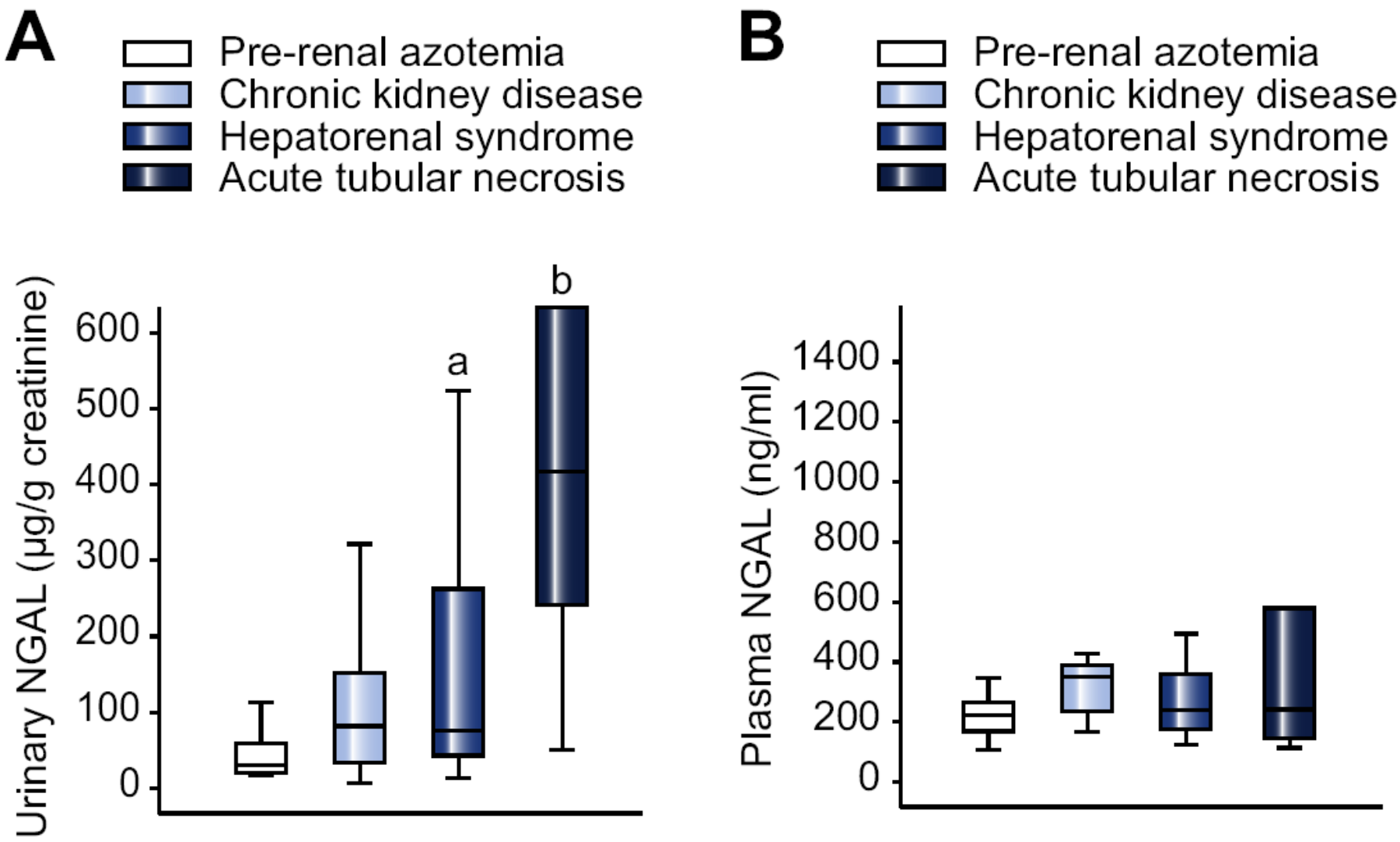
# Neutrophil Gelatinase Associated Lipocalin



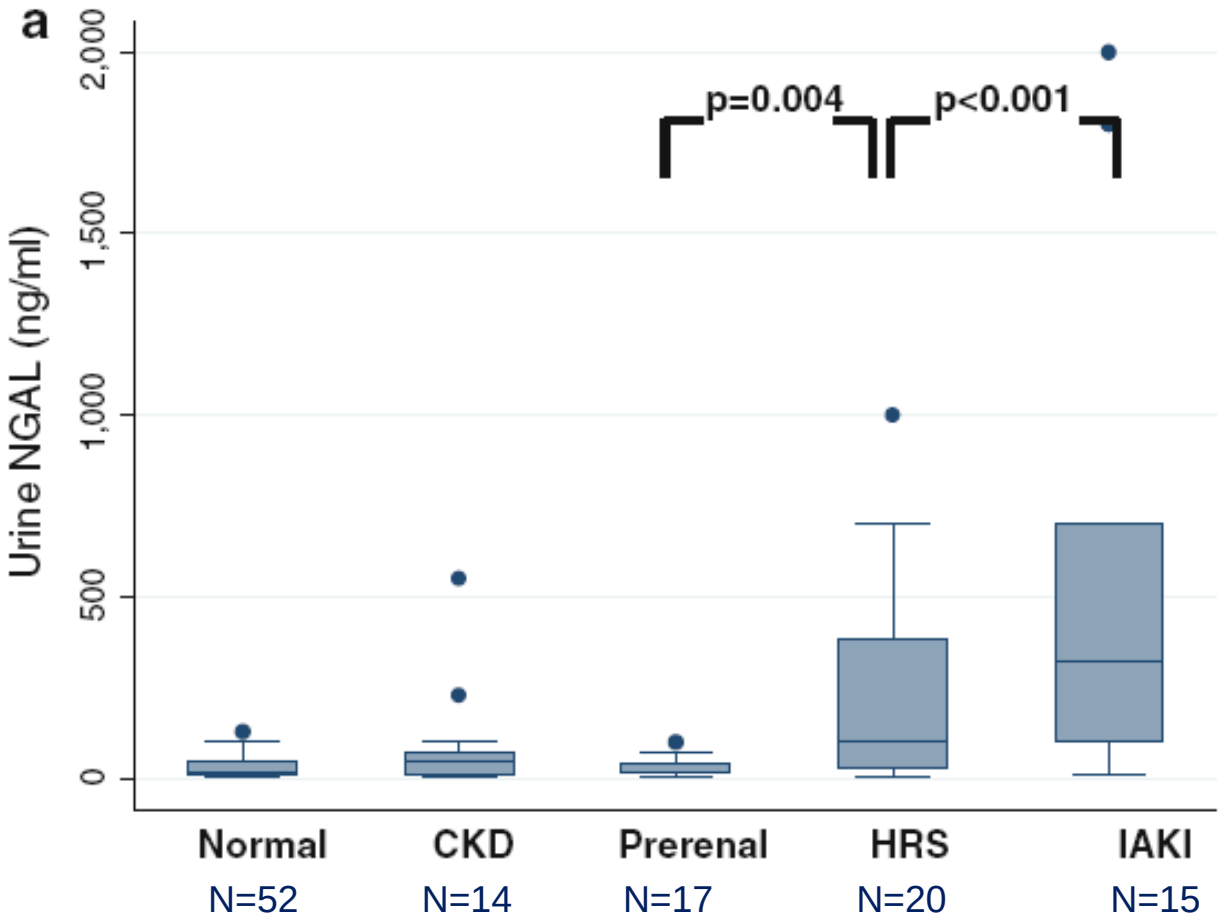
N=241 (72 sans ascite, 85 + ascite, 84 avec irc)



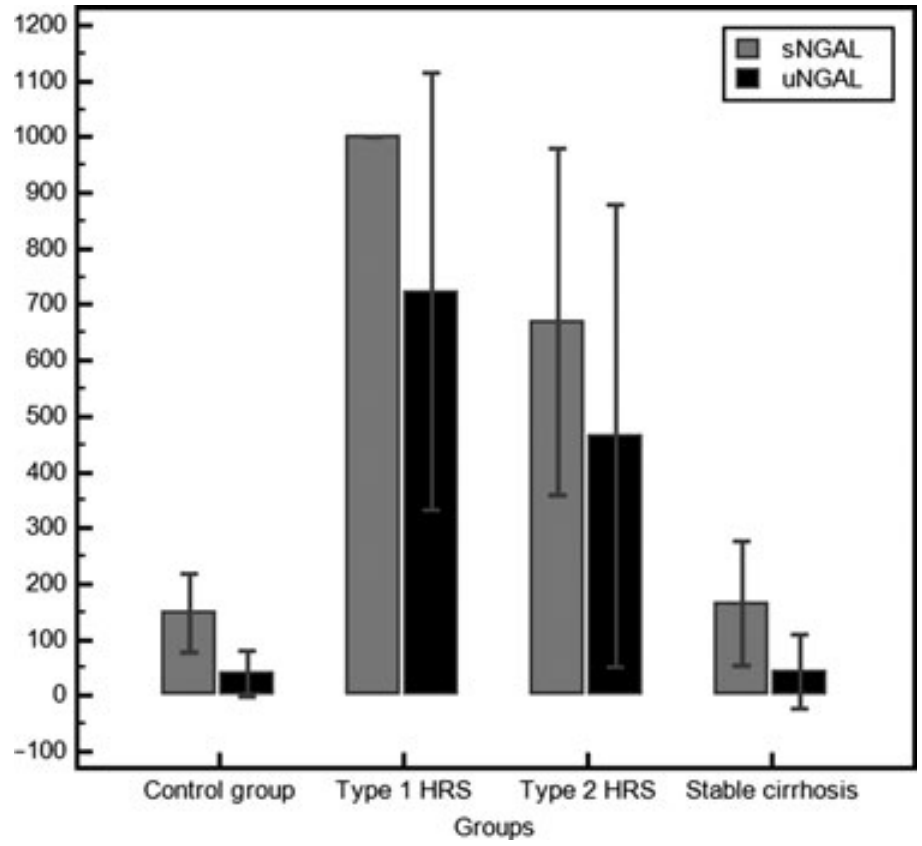

Fagundes. J Hepatol 2012




Fagundes. J Hepatol 2012




| Biomarker | OR (95 % confidence interval) | | | | |
|---|---|---|---|---|---|
| | Mortality $n = 15$ | Mortality or liver transplant $n = 22$ | Dialysis $n = 13$ | Mortality or dialysis $n = 18$ | Intensive care unit $n = 26$ |
| uNGAL (per ng/mL) | 2.00 (1.36–2.94) | 2.01 (1.42–2.85) | 1.66 (1.14–2.41) | 1.91 (1.34–2.74) | 1.58 (1.17–2.12) |
| sCr (per mg/dL) | 2.95 (1.68–5.61) | 3.69 (2.04–6.68) | 2.50 (1.47–4.26) | 3.65 (2.00–6.67) | 2.11 (1.33–3.34) |
| MELD | 1.51 (1.07–1.24) | 1.18 (1.10–1.28) | 1.10 (1.04–1.17) | 1.16 (1.08–1.25) | 1.08 (1.02–1.13) |
| FENa (%) | 0.32 (0.07–1.48) | 1.07 (0.92–1.25) | 1.13 (0.95–1.34) | 1.10 (0.94–1.29) | 1.05 (0.90–1.22) |



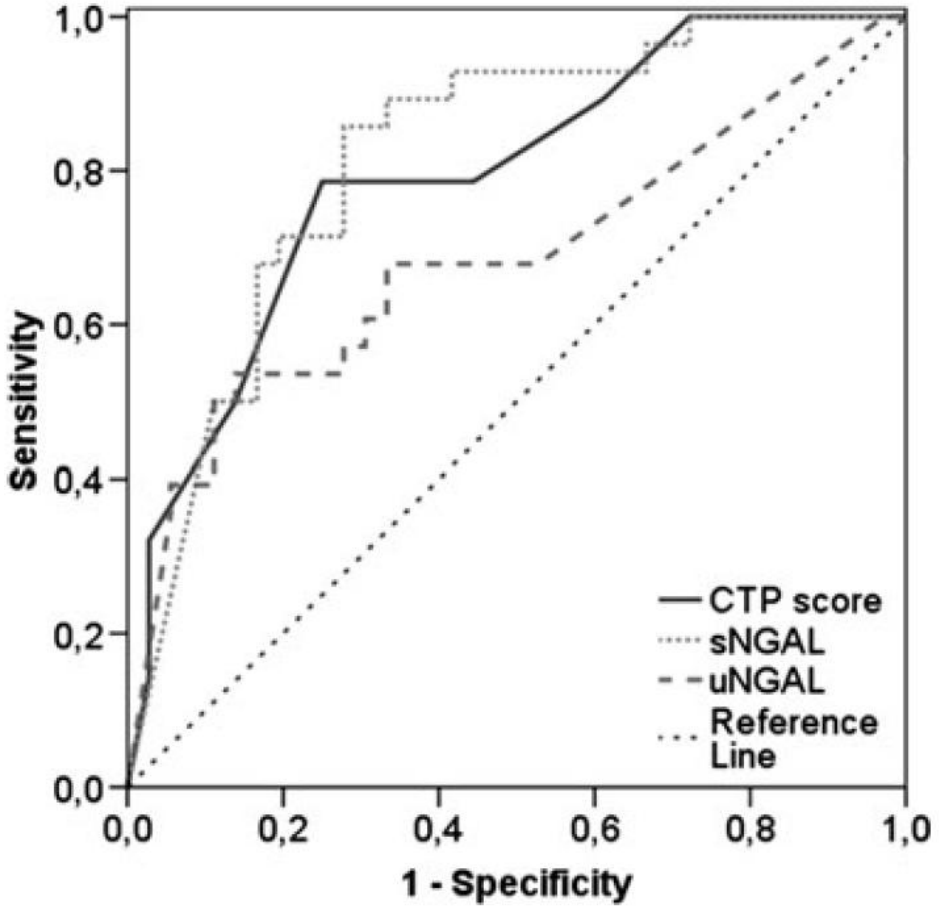
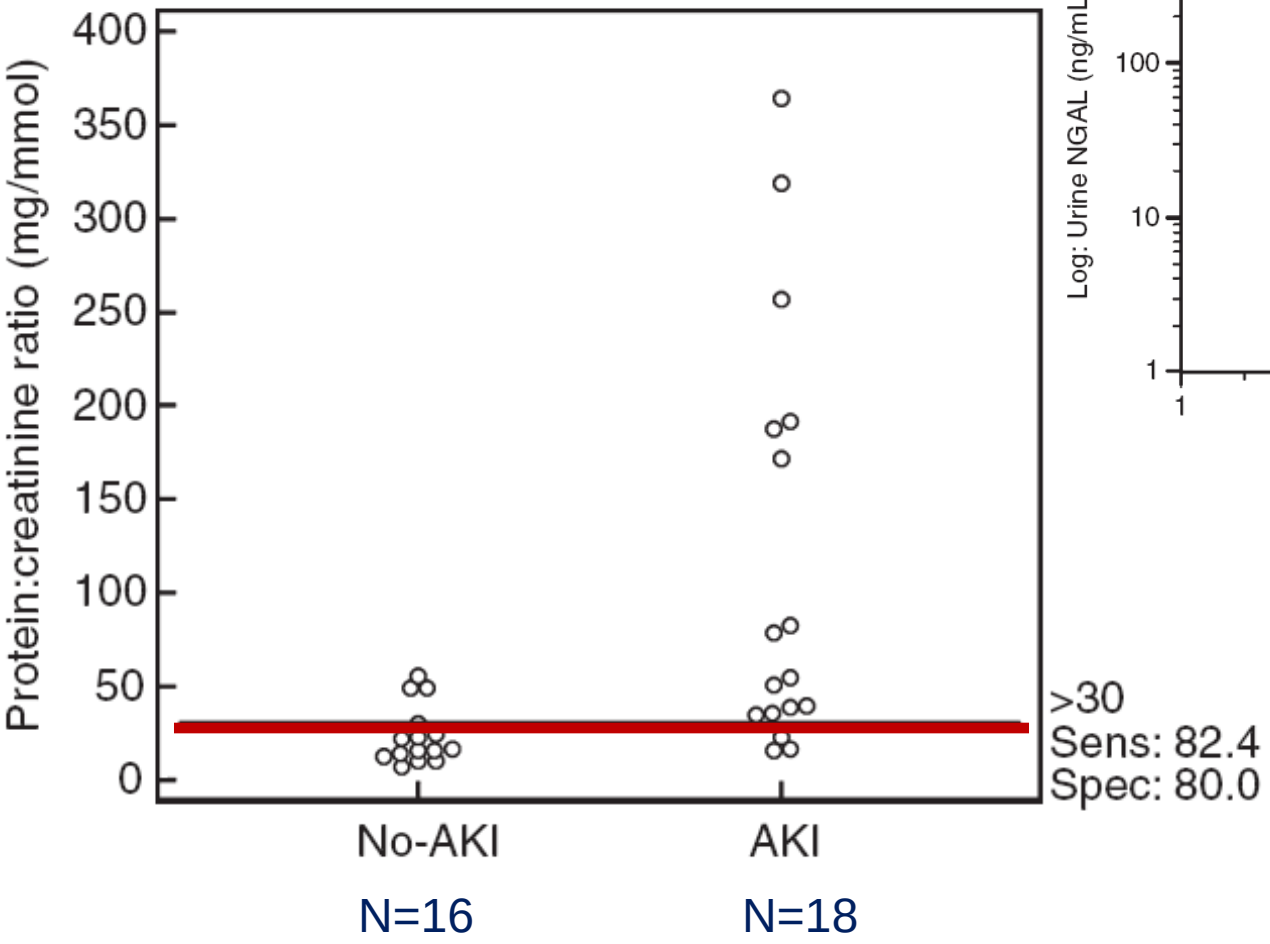
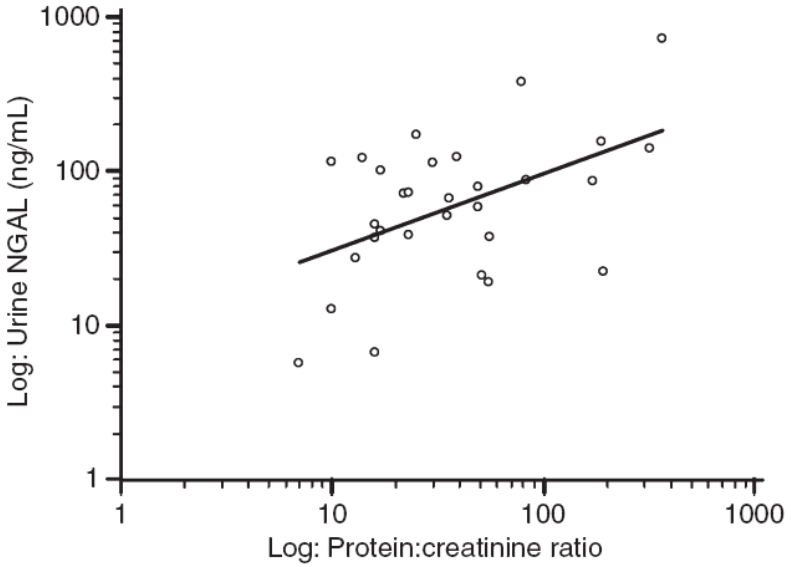




**Table 5.** Comparison of ROC curves among CTP, MELD-Na scores and urine and plasma NGAL in prediction of mortality

| | Cut-off | AUC (95% CI) | Sens.% | Spec.% | PPV.% | NPV.% | *P* value* |
|---|---|---|---|---|---|---|---|
| CTP score | >10 | 0.795 (0.675–0.885) | 78.6 | 75.0 | 71 | 81.8 | <0.0001 |
| MELD-Na | >19.5 | 0.807 (0.689–0.895) | 82.1 | 68.4 | 69.7 | 83.9 | <0.0001 |
| uNGAL (μg/L) | >225.2 | 0.686 (0.557–0.796) | 51.3 | 86.1 | 75.0 | 70.5 | 0.0068 |
| pNGAL (μg/L) | >289.6 | 0.819 (0.703–0.904) | 83.7 | 72.2 | 70.6 | 86.7 | <0.0001 |

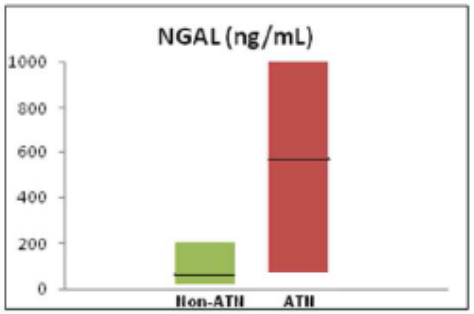
# Protéinurie

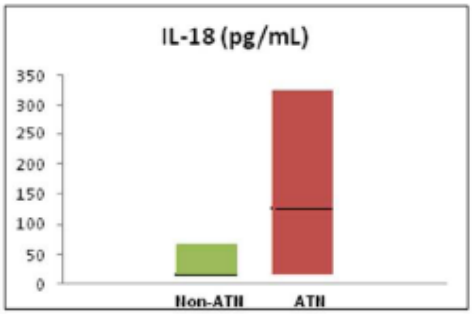


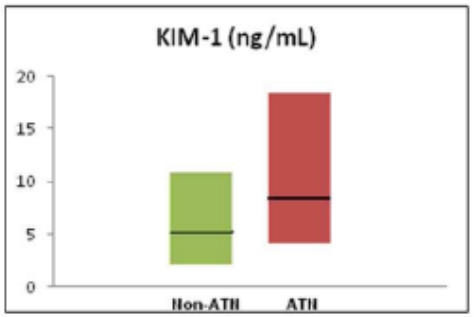



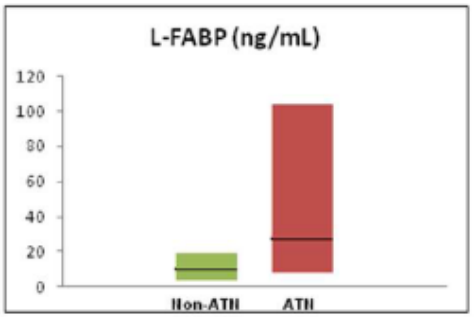
# Multiples biomarkers?

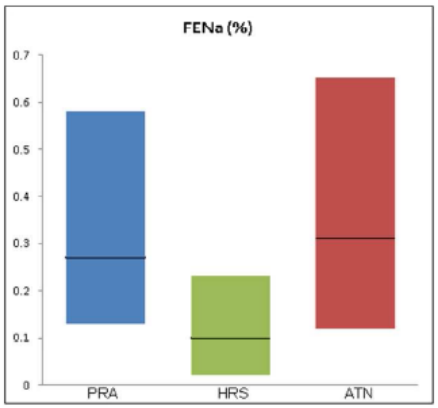
N=188 AKI
NTA=39
SHR=16
Non NTA=71

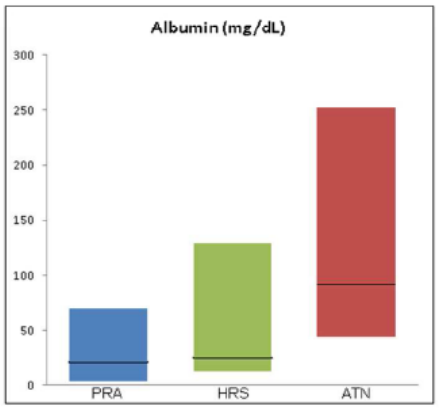


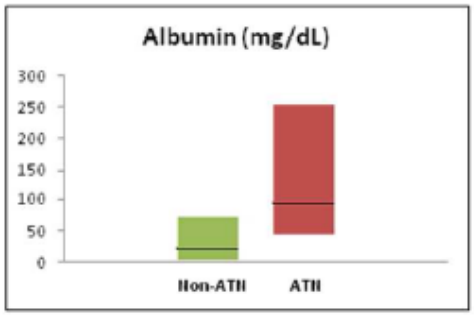

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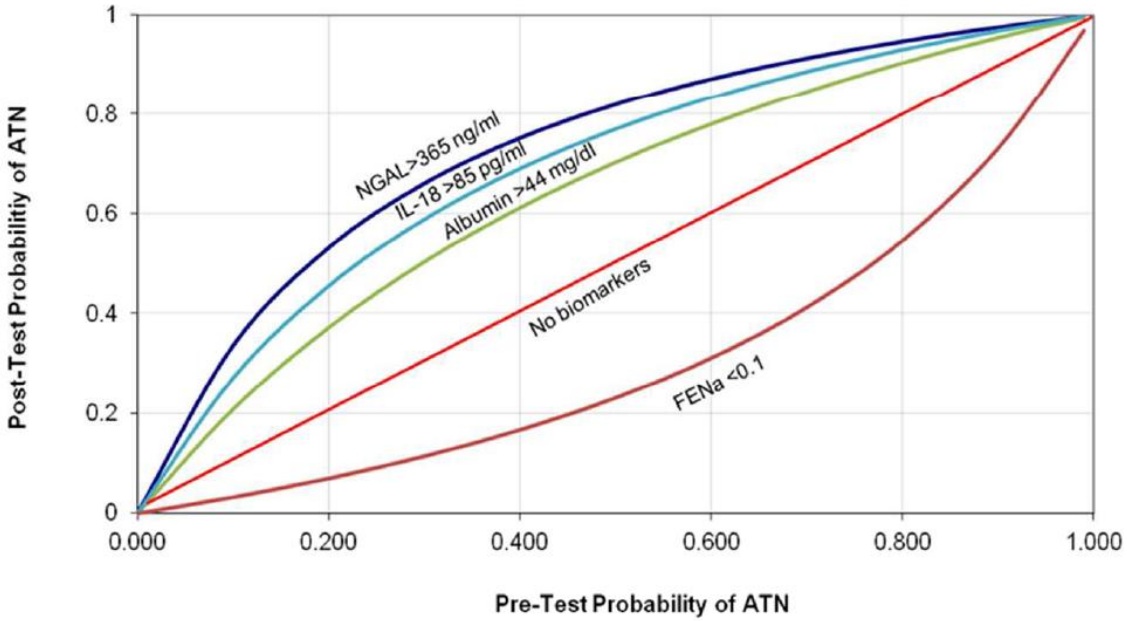
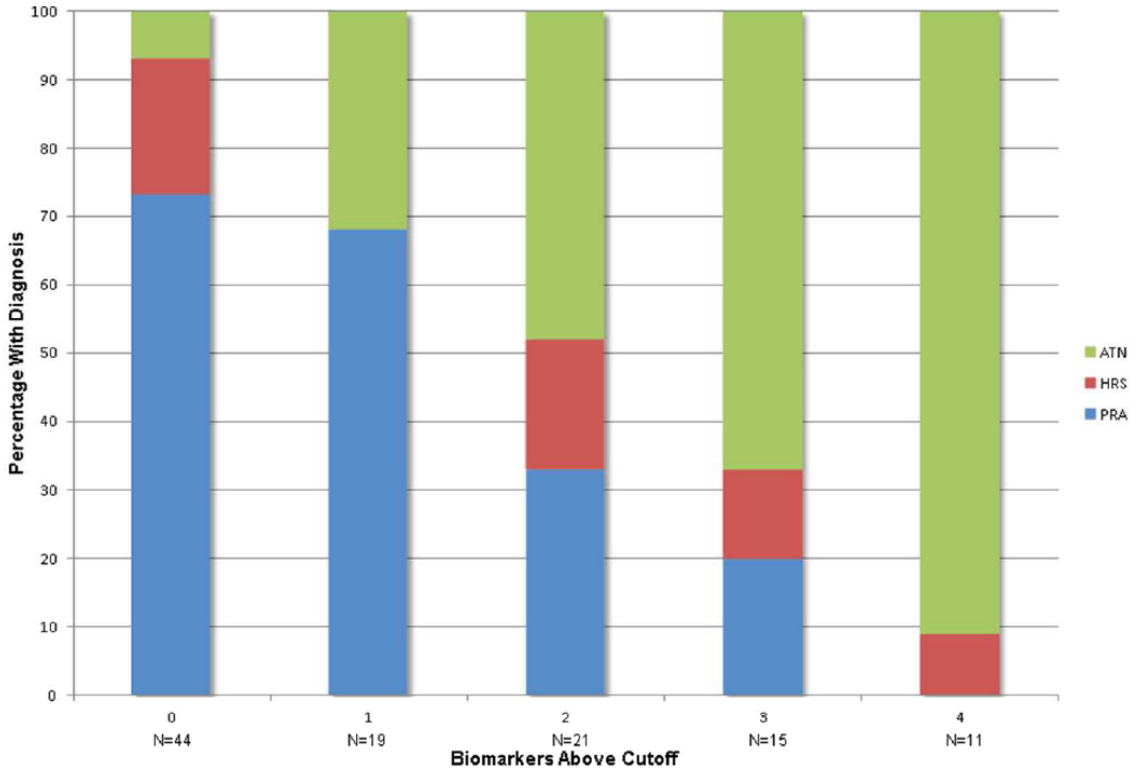
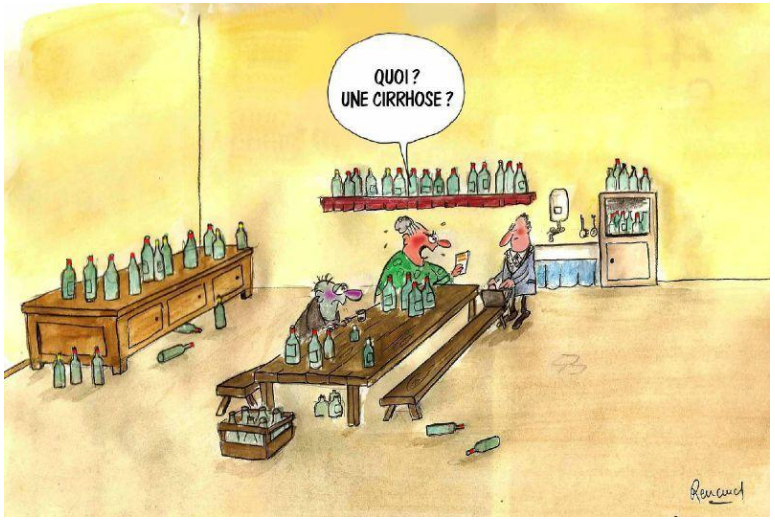

Post-Test Probabilitiy of ATN
1
0.8
0.6
0.4
0.2
0
0.000
0.200
0.400
0.600
0.800
1.000
NGAL>365 ng/ml
IL-18 >85 pg/ml
Albumin >44 mg/dl
No biomarkers
FENa <0.1
Pre-Test Probability of ATN

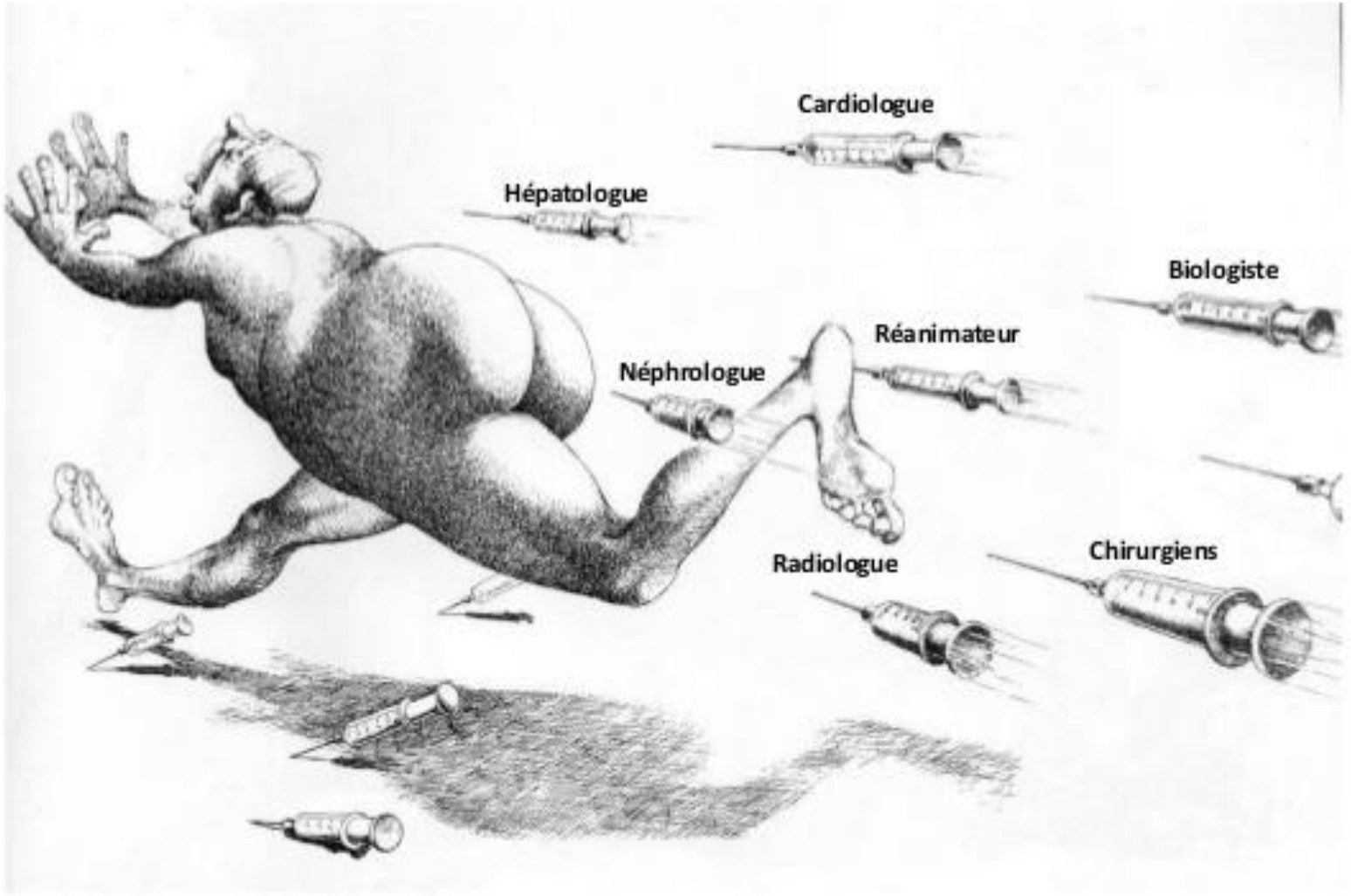
AUC: 0.56-0.79


Percentage With Diagnosis
100
90
80
70
60
50
40
30
20
10
0
0
N=44
1
N=19
2
N=21
3
N=15
4
N=11
Biomarkers Above Cutoff
ATN
HRS
PRA

# Conclusions

- L'IRA est une complication fréquente de la cirrhose
- L'étiologie est un facteur pronostic important
- La sévérité de l'ira détermine aussi le pronostic
- Les nouvelles définitions des KDIGO pour l'ira doivent être mises en place aussi pour la cirrhose
- Nécessité de détecter précocemment ira dans cirrhose
- Nouveaux biomarqueurs en cours d'étude  mais peu d'évidence pour l'instant



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