


How and why to measure renal function in patients with liver disease?

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Agenda

- How to measure renal function?
  - How to measure glomerular function (GFR)?
  - How to measure tubular damage/function?
- Why to measure renal function?

S. Piano et al. Liver Int. 2017 ; 37 (Suppl 1) : 116-122

Definition of renal failure in cirrhosis

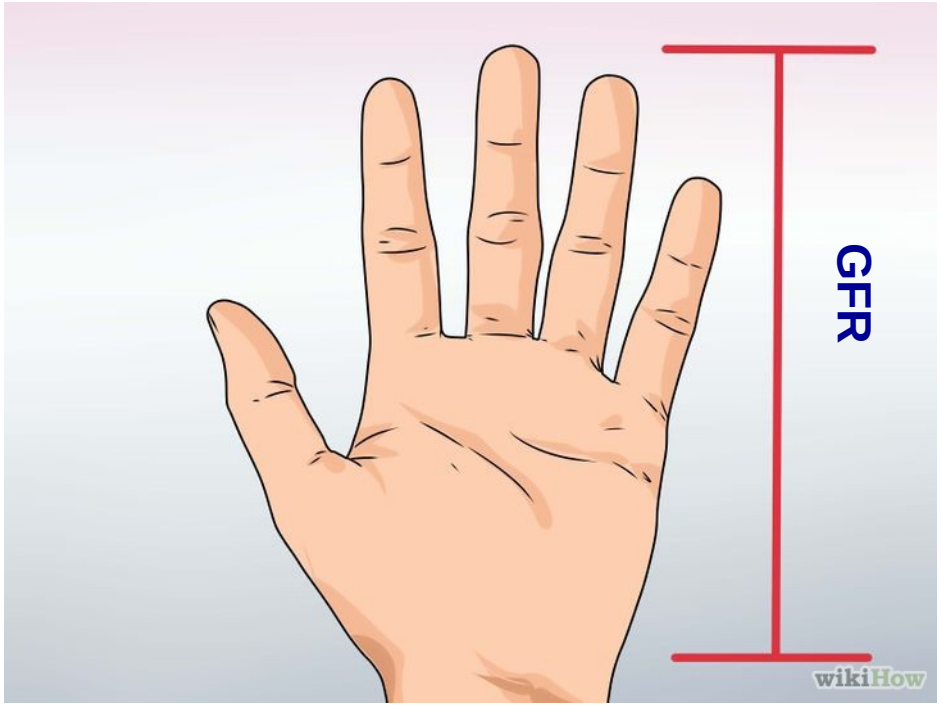
- The traditional diagnostic criteria of renal failure in cirrhosis were proposed 20 years ago and have been improved in subsequent years.

- It is based on the presence of a serum creatinine ≥ 1.5 mg/dl which represents a GFR below 40 ml/min.

V. Arroyo et al. Hepatology 1996 ; 23 : 164-176.

Salerno F. et al. Gut 2007 ; 56 : 1310-1318.

The use of serum creatinine (sCr) as a marker of glomerular filtration rate (GFR)



Pittfalls related to the use of serum creatinine (sCr) as a marker of glomerular filtration rate (GFR)

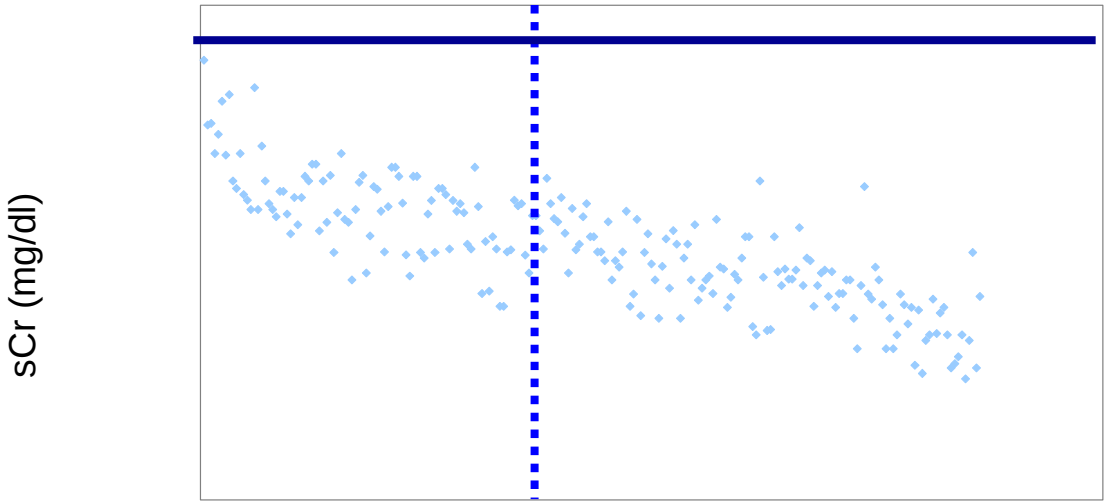
- Creatine is synthesized in the liver before being stored in muscles where it is phosphorylated as creatinine (Cr). This small compound is freely filtered by the kidney but it can also be secreted by the proximal tubule. The ratio between Cr secreted by the tubule to the amount of Cr filtered by the glomerulus increases as GFR decreases.

- In the general population sCr is influenced by age, gender and ethnicity.

- Several reasons make that in patients with liver disease, serum Cr (sCr0 can further overestimate GFR:
  - Impaired liver function results in decreased Cr production.
  - Protein-calorie malnutrition and muscle wasting which are common during cirrhosis also contribute to decreased Cr production.
  - An high ratio between Cr secreted by the proximal tubule and sCr filtered by the glomerulus can develop.

D. Thanacoody et al. J Hepatol. 2010; 52 : 605-613.

Relationship between GFR (ml/min 1.73 m2) measured by inulin clearance (mGFR) serum creatinine (sCr)



S. Rosi et al. Liver Int. 2015 ; 35 : 2108-2014

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  - How to measure glomerular function (GFR)?

- Why to measure renal function?
  - For diagnostic asessment

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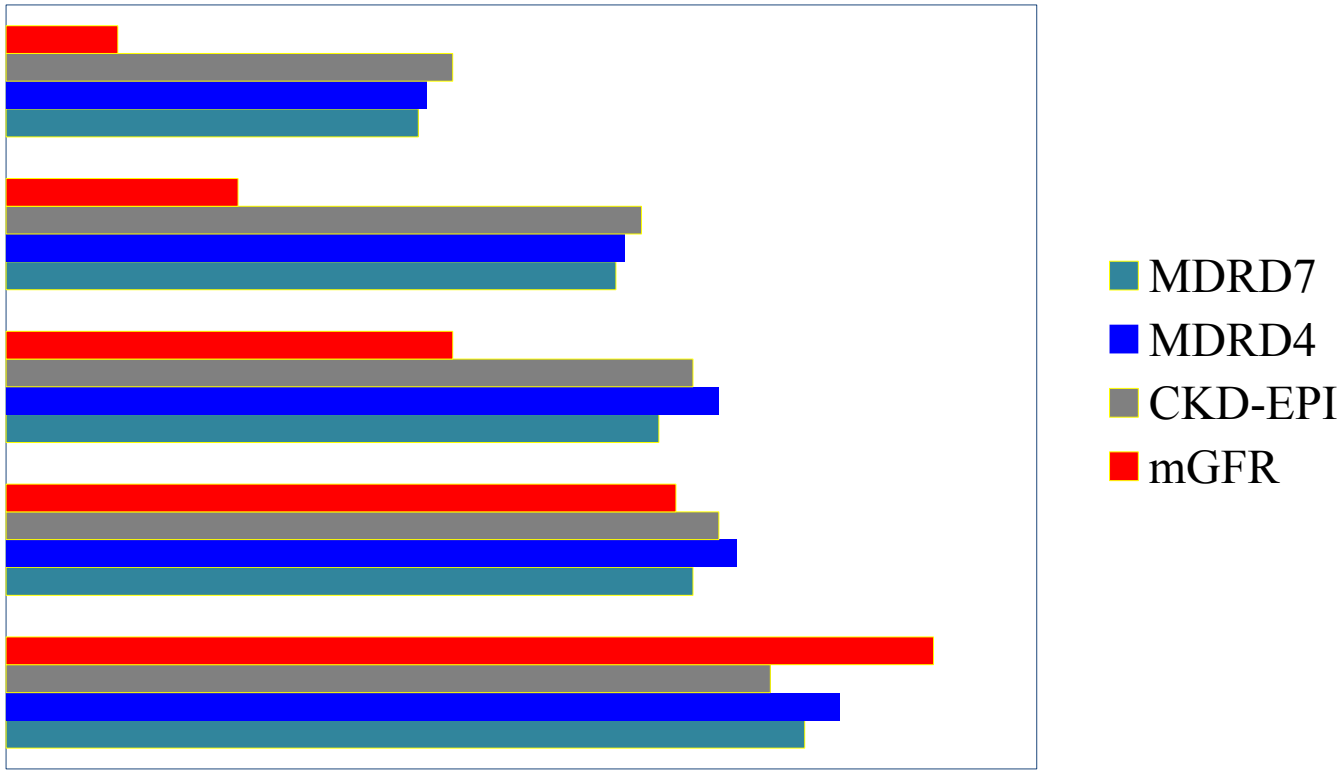
	Decrease in GFR ≥ 35% or increase in sCr ≥ 50 % for < 3 months	
CKD	GFR < 60 ml/min per 1.73 m2 for > 3 months	Kidney damage for ≥ 3 months

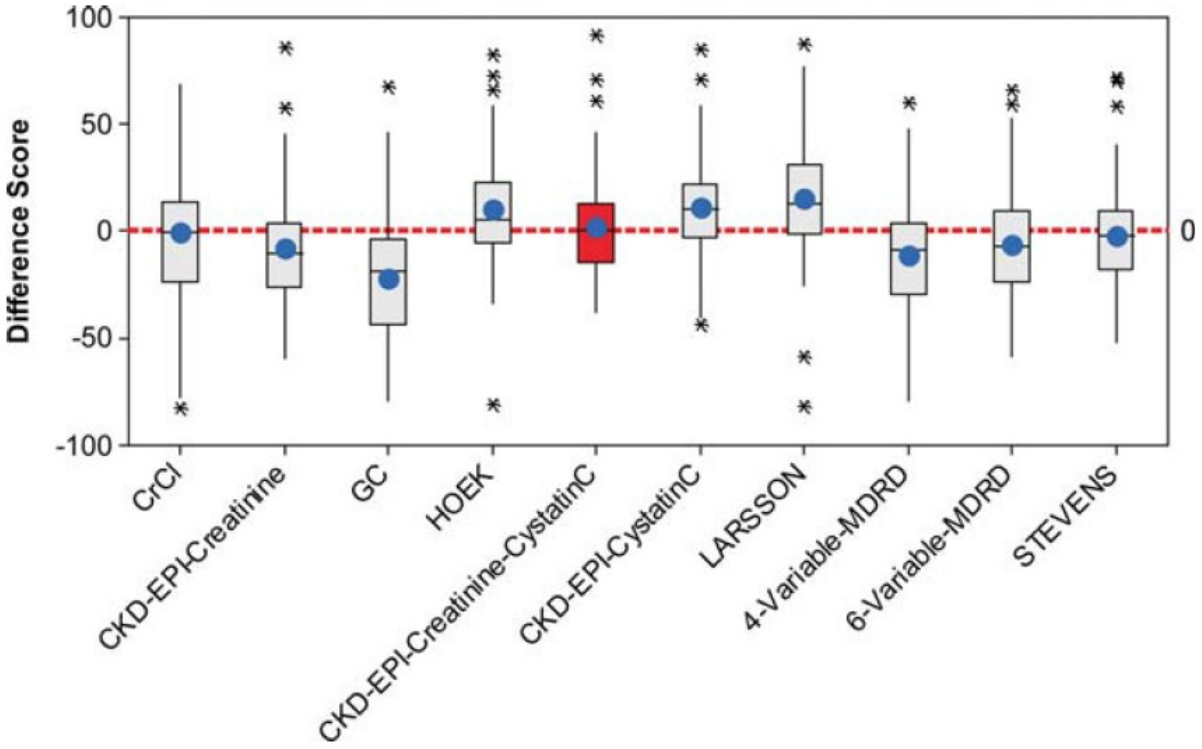
KDIGO AKI Work Group Kidney Int. Suppl. 2012 ; 2 : 1-138

Estimated Glomerular Filtration Rate (GFR) by serum creatinine-based equations versus measured GFR



S. Rosi et al. Liver Int. 2015 ; 35 : 2108-2014

Definition of CKD in patients with cirrhosis



AL Mindikoglu et al. Hepatology 2014 ; 59 : 1352-1542

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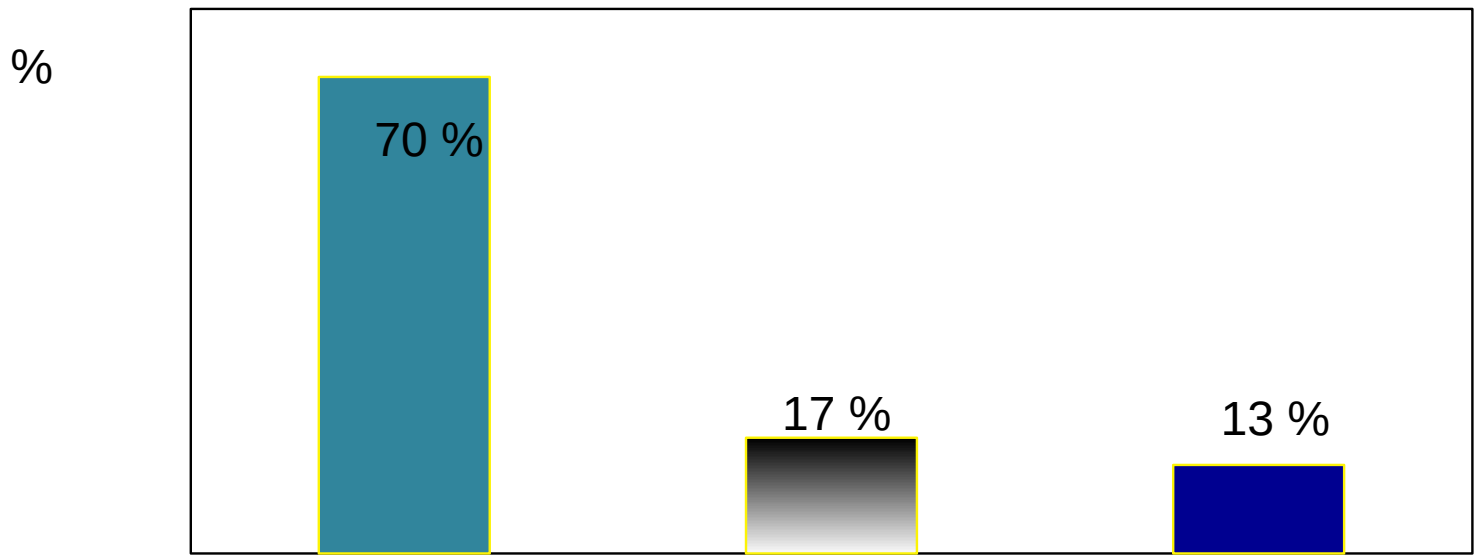
Prevalence of AKI and CKD in patients with cirrhosis and serum creatinine > 1.5 mg/dl admitted to the hospital



N.S. Warner et al. J. Investig. Med. 2011 ; 59 : 1244-1251.

Definition and of acute renal failure in cirrhosis

Conventional criteria = a rapid reduction in kidney function currently defined as a percentage increase in serum creatinine of more or equal to 50 % (1.5-fold from baseline) to a final value equal or higher than 1.5 mg/dl.

P. Ginès at al. N Engl J Med 1991;325:829-835.

P. Sort et al. N Engl J Med 1999;341:403-409.

A. Ginès et al. Gastroenterology. 1996;111:1002-1010.

P. Angeli et al. Gut 2010;59:98-104.

Definition and staging of Acute Kidney Injury (AKI)

KDIGO criteria = an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (26.4 µmol/l), or a percentage increase in serum creatinine of more or equal to 50 % (1.5-fold from baseline) in less than 7 days.

Stage	Serum creatinine criteria
1°	Increase in serum creatinine of more than or equal to 0.3 mg/dl (26.4 µmol/l) or a percentage increase in serum creatinine of more or equal to 50 % (< 2 fold from baseline).
2°	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline
3°	Increase in serum creatinine to more than 300 % (> 3-fold) from baseline or serum creatinine of more or equal to 4.0 mg/dl (354 µmol/l) with an acute increase of at least 0.5 mg/dl (44 µmol/l) or need for renal replacement therapy

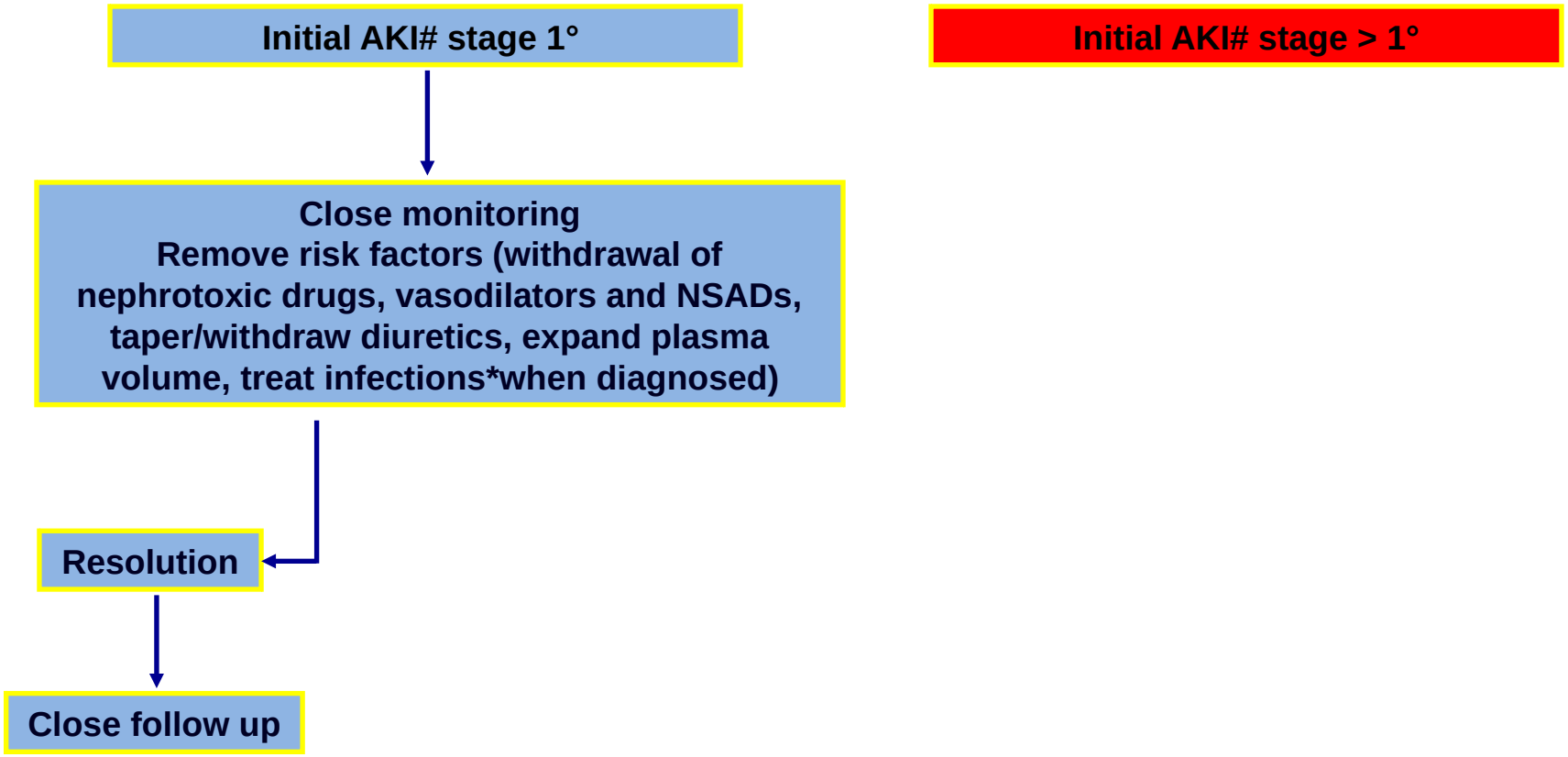
KDIGO AKI Work Group Kidney Int. Suppl. 2012 ; 2 : 1-138

Accuracy of conventional criterion vs KDIGO criteria in the prediction of in-hospital mortality in a series of 233 patients with cirrhosis and ascites

Criteria	Sensibility 95 % CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	LR+ 95% CI	LR- 95% CI
Conventional criteria	0.5152 (0.33 - 0.69)	0.9450 (0.90 - 0.97)	0.6071 (0.40 - 0.78)	0.9220 (0.87 - 0.95)	9.3664 (4.8 - 18.17)	0.5131 (0.36 - 0.73)
KDIGO criteria	0.6667 (0.48 - 0.82)	0.8100 (0.74 - 0.86)	0.3667 (0.24 - 0.50)	0.9364 (0.88 - 0.96)	3.5088 (2.41 - 5.10)	0.4115 (0.25 - 0.66)
KDIGO with Progression	0.5455 (0.36 - 0.71)	0.9450 (0.90 - 0.97)	0.6207 (0.42 - 0.79)	0.9265 (0.88 - 0.95)	9.9174 (5.15 - 19.06)	0.4810 (0.33 - 0.70)

S. Piano et al. J. Hepatol. 2013 ; 59 : 482-489

Algorithm for AKI management in patients with cirrhosis



#= AKI at the first fulfilling of KDIGO criteria

P. Angeli et al. J. Hepatol. 2015 ; 62 : 968-974

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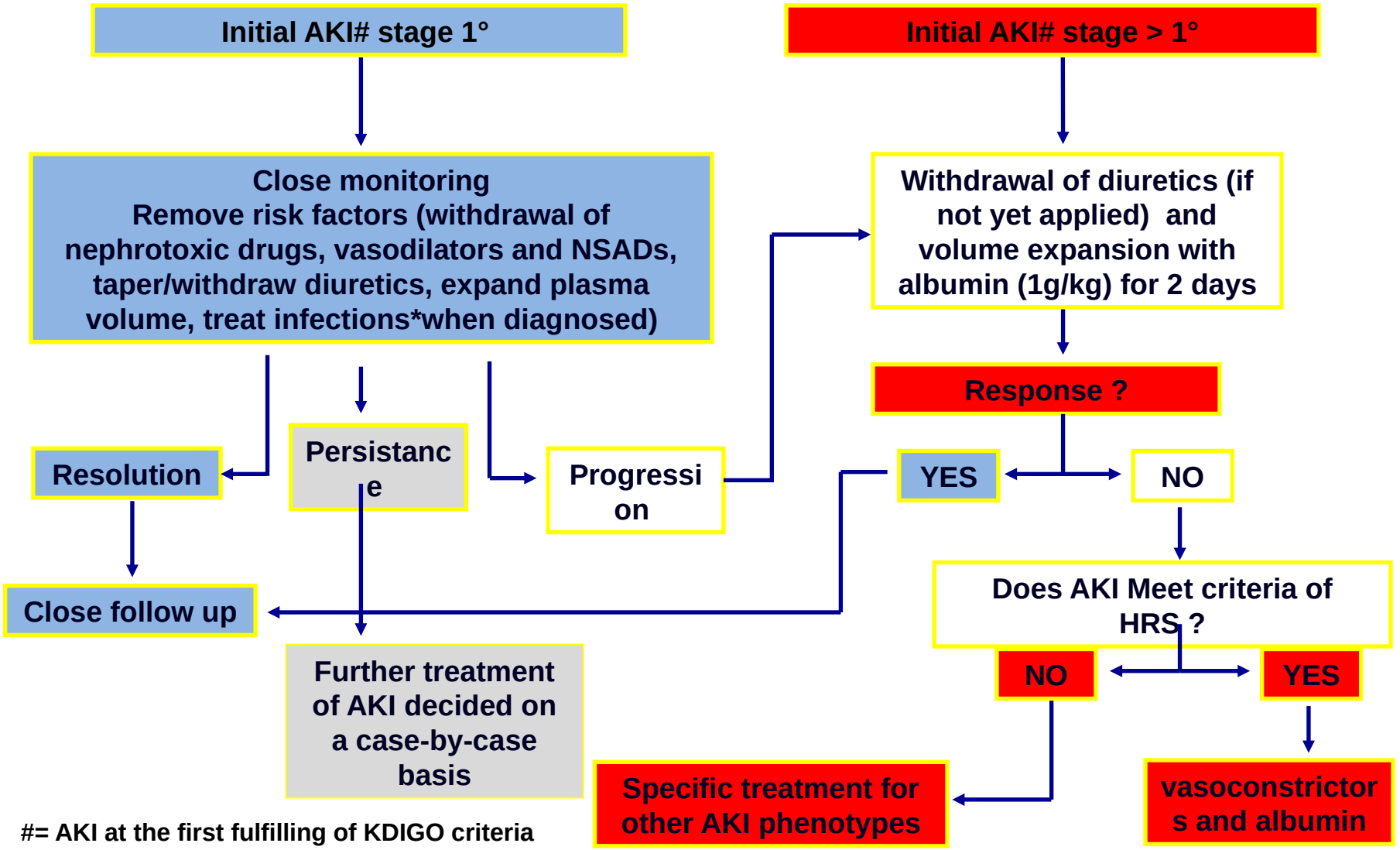

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The problem of the baseline serum creatinine in the KDIGO criteria

- The KDIGO guidelines suggest that patients should be assumed to have a baseline eGFR of 75 ml/min/1.73 m2 in cases where there is no history of CKD and baseline kidney function is unknown.

- The KDIGO guidelines suggest to use an inverse application of MDRD equation assuming that baseline glomerular filtration rate is 75 ml/min per 1.73 m2 to calculate an imputed baseline creatinine.

A. Khwaja et al. Nephron Clin. Pract. 2012 : 120 : 179-184

Definition and defining criteria of AKI in cirrhosis

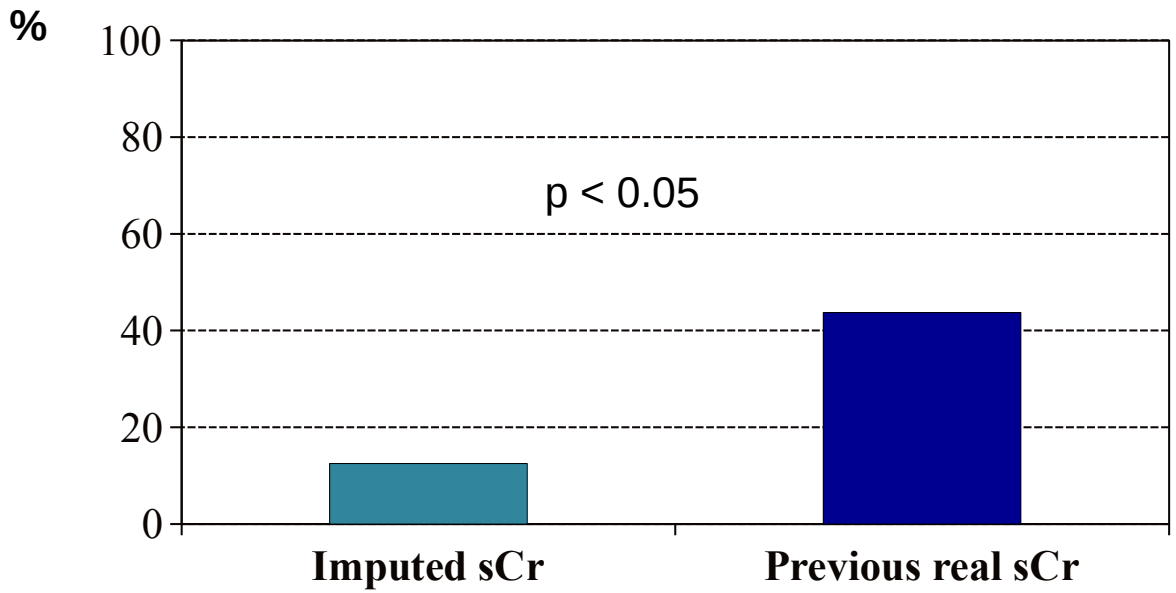
Table 2. International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis.

Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	• Increase in sCr ≥0.3 mg/dl (≥26.5 μmol/L) within 48 hours; or, • A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days		
Staging of AKI	• **Stage 1**: increase in sCr ≥0.3 mg/dl (26.5 μmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline • **Stage 2**: increase in sCr >2-fold to 3-fold from baseline • **Stage 3**: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 μmol/L) with an acute increase ≥0.3 mg/dl (26.5 μmol/L) or initiation of renal replacement therapy		
Progression of AKI	**Progression** Progression of AKI to a higher stage and/or need for RRT	**Regression** Regression of AKI to a lower stage	
Response to treatment	**No response** No regression of AKI	**Partial response** Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 μmol/L) above the baseline value	**Full response** Return of sCr to a value within 0.3 mg/dl (26.5 μmol/L) of the baseline value

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.

P. Angeli et al. Gut 2015 ; 64 : 531-537

Prevalence of AKI on admission using an imputed value or a previous value of serum creatinine (sCr)



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KDIGO AKI Work Group Kidney Int. Suppl. 2012 ; 2 : 1-138

National Kidney Foundation Kidney Disease Outcome Quality Initiative: Classification of CKD

Chronic kidney disease is defined as either kidney damage or decreased kidney function (decreased GFR) for 3 or more months

	With kidney damage	Without kidney damage
GFR (ml/min/1.73m2)	Stage	Stage
>/= 90	1	Normal
60-89	2	Decreased GFR*
30-59	3	3
15-29	4	4
< 15	5	5

* may be normal for age

Levey AS et al. Ann. Intern. Med. 2003 ; 139 : 137-147.

Phenotypes of AKI in patients with cirrhosis and ascites

- Acute tubular necrosis (ATN-AKI) (41.7%)
- Prerenal failure (Prenal-AKI) (38%)
- Hepatorenal syndrome (HRS-AKI) (20%)
- Postrenal failure (Postrenal AKI) (0.3%)

R. Moreau et al. Hepatology 2003 ; 37 : 233-243.

Current diagnostic criteria of HRS

1. Cirrhosis with ascites;

Deleted

3. No sustained improvement of serum creatinine (decrease to a level of 133 µmol/l or less) after at least two days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day;
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs;
6. Absence of parenchimal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

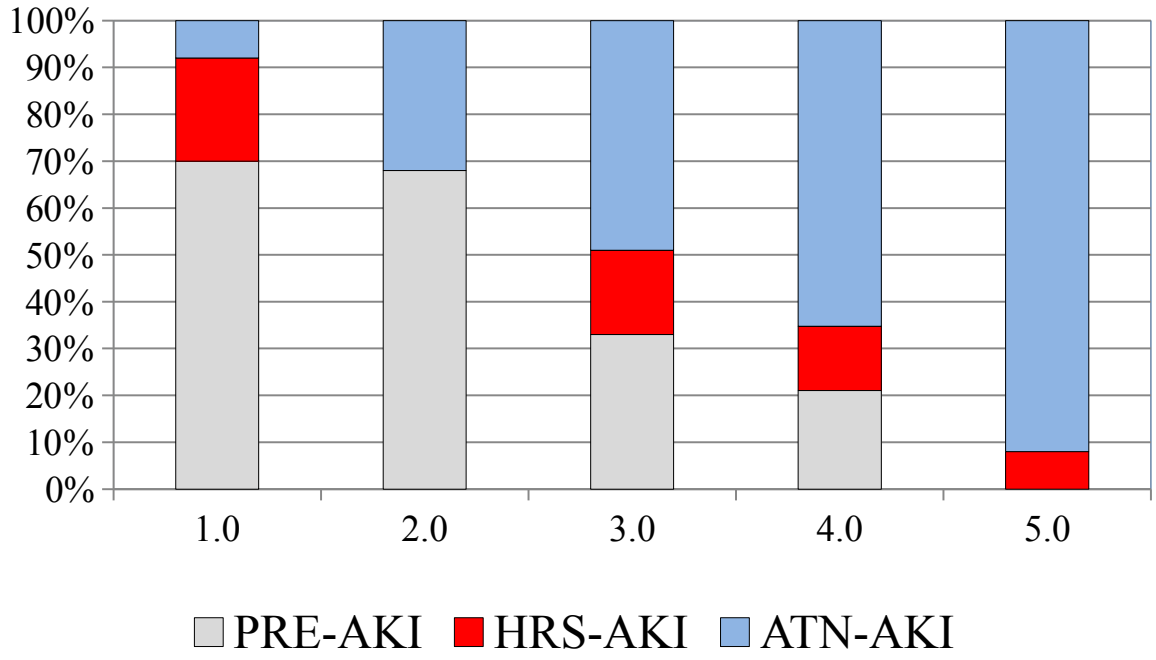
F. Salerno, et al. Gut 2007 ; 56 : 1310-1318.

Values of urinary biomarkers in patients categorized according to the absence or presence of AKI and phenotype of AKI

Biomarkers	No AKI	Prerenal AKI	HRS-AKI	ATN-AKI	P
NGAL (µg/g sCr)	30 (17-41)	36 (26-125)	104 (58-208)	1807 (494-3716)	<0.0001
IL-18 (ng/g sCr)	21 (16-35)	16 (14-36)	18 (10-29)	150 (58-259)	<0.0001
Albumin (mg/g sCr)	3 (1-7)	9 (1-77)	16 (8-46)	324 (53-380)	<0.0001
TFF-3 (µg/g sCr)	582 (367-1665)	2300 (323-2720)	1893 (840-2715)	5810 (4019-14466)	< 0.0001
MCP-1 (µg/g sCr)	0.2 (0.1-1.4)	0.9 (0.2-2.5)	3 (1-6)	4 (1-14)	<0.0001
Ostepontin (µg/g sCr)	1456 (715-3210)	2914 (1847-8382)	5471 (2959-11983)	83337 (4019-14466)	< 0.0001
Calbindin (µg/g sCr)	71 (26-150)	5 (2-34)	25 (8-58)	118 (37-324)	0.010
GST-TT (µg/g sCr)	3 (1-16)	3 (1-7)	4 (2-21)	50 (9-169)	0.012
KIM-1 (µg/g sCr)	0.5 (0.3-1.4)	0.5 (0.1-1.1)	1.2 (0.5-2.8)	1.7 (0.9-5.1)	0.015
Cistatin C (µg/g sCr)	24 (12-435)	21 (15-53)	27 (10-47)	115 (39-1552)	0.023

X. Ariza et al. Plos One 2015 ; 10 [Epub ahead of print]

Percentage of patients with prerenal- (PRE-), hepatorenal syndrome (HRS-), and acute tubular necrosis- (ATN-) AKI by the number of biomarkers of structural injury above their optimal cutoff for the diagnosis of ATN



JM. Belcher et al. Hepatology 2014 ; 60 : 622-632

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  - For prescription of drug therapy
    - for tailoring the dose of drug
    - for specific treatment of renal dysfunction

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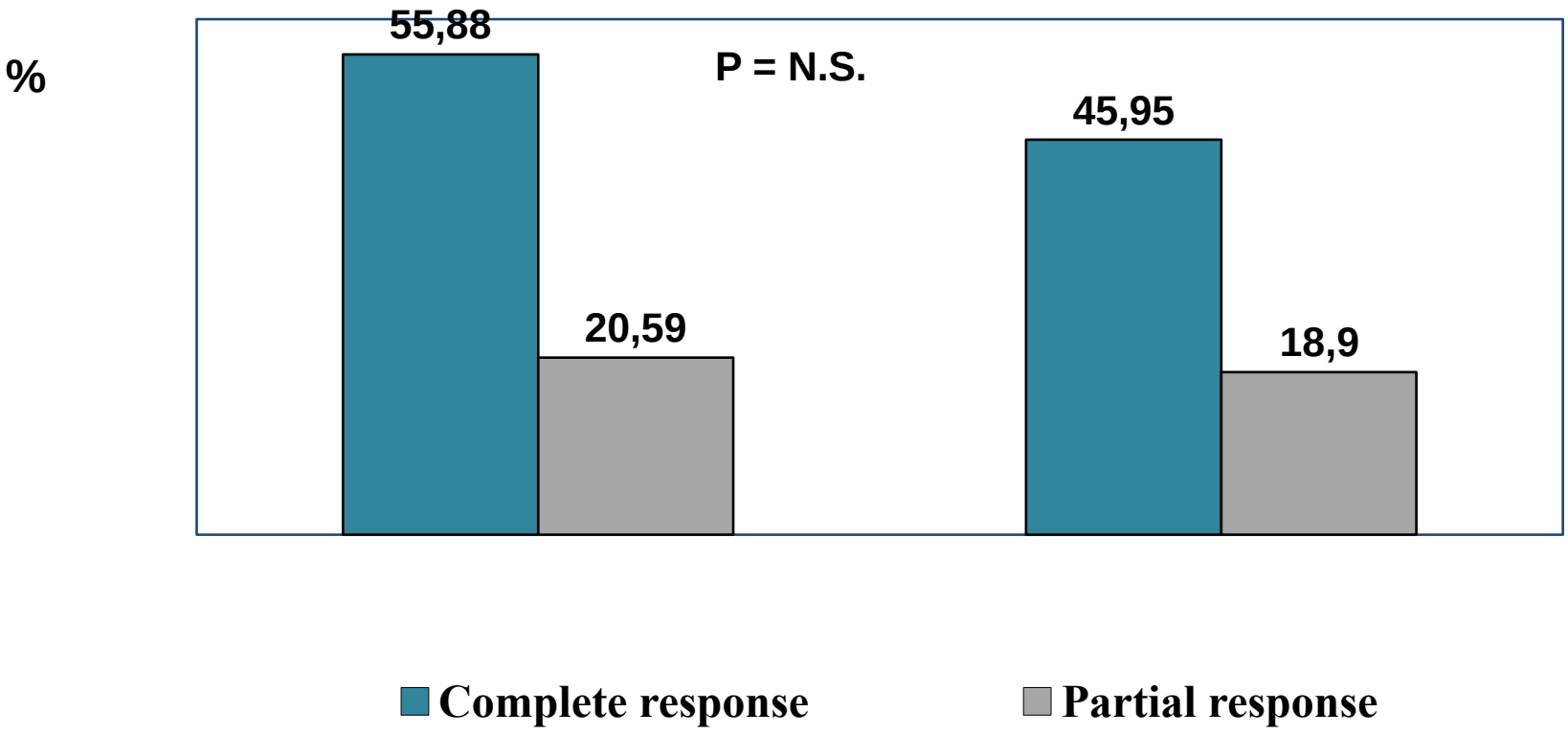
Pharmacologic therapy for HRS

- Albumin (20-40 g/day intravenously)
- Terlipressin (0.5-2 mg/4-6hr intravenously)

J. Uriz et al. J. Hepatol. 2000 ; 33 : 43-48.

Rate of response in patients with type 1 HRS according to the schedule of i.v. administration of terlipressin



M. Cavallin et. al. 2016 ; 63 : 983-992

Clinical types

Type 1 HRS : rapidly progressive reduction of renal function as defined by a doubling of the initial serum creatinine to a level > 226 µmol/l or 2.5 mg/dl in less than two weeks. It may occurs spontaneously, but it can also follow a precipitating event.

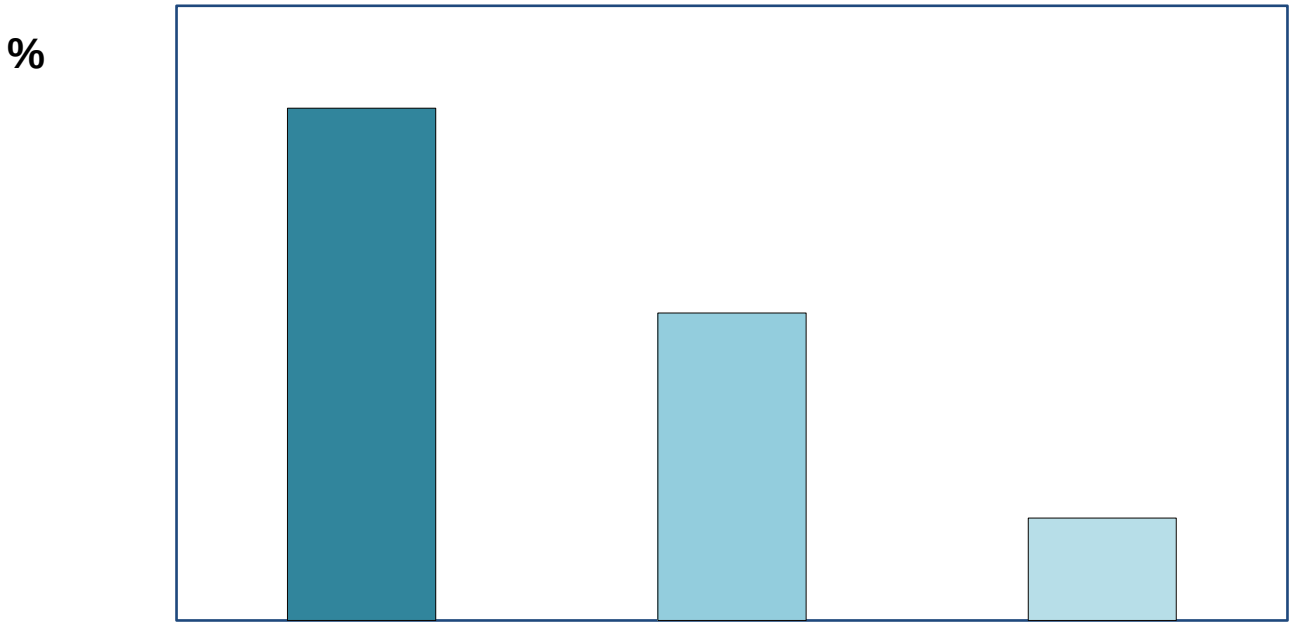
Clinical pattern: acute renal failure

Type 2 HRS: is characterized by moderate renal failure (serum creatinine from 133 to 226 µmol/l or 1.5 to 2.5 mg/dl) with a steady or slowly progressive course.

Clinical pattern: refractory ascites

F. Salerno, et al. Gut 2007 ; 56 : 1310-1318.

Response to treatment according to the baseline serum creatinine value



T.D. Boyer et al. J. Hepatol. 2011 ; 55 ; 315-321.

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HRS-AKI

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    - for specific treatment of renal dysfunction
  - For prognostic evaluation

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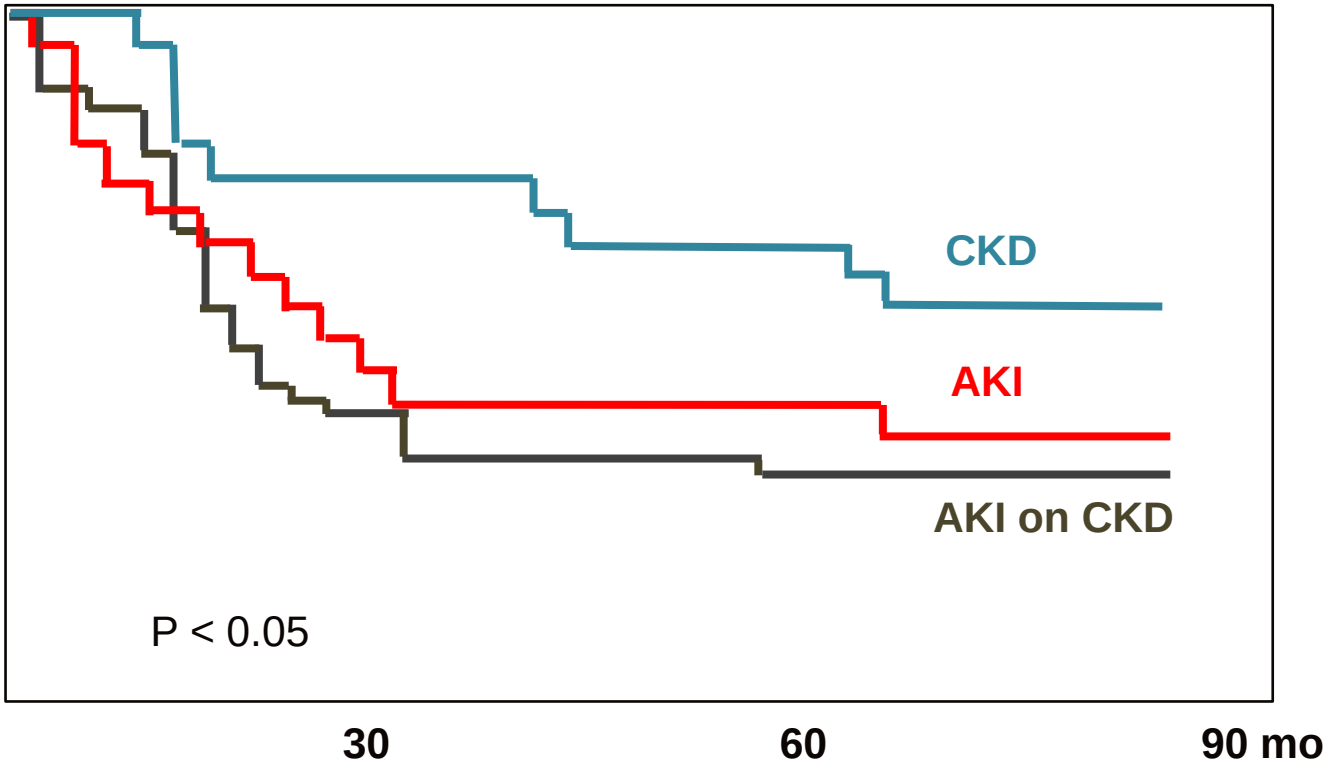
Ninety day mortality as a function of the presence of AKI or CKD in hospitalized patients with cirrhosis



M. Martin–Llahi et al. Gastroenterology. 2011 ; 140 : 488-496

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  - For the definition of the transplant strategy

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Chronic Kidney Disease

1. The candidate has begun regularly administered dialysis as an end-stage renal disease (ESRD) patient in a hospital based, independent non-hospital based, or home setting.
2. The candidate's most recent measured or calculated creatinine clearance (CrCl) or glomerular filtration rate (GFR) is less than or equal to 35 mL/min at the time of registration on the kidney waiting list.

OPT/UNOS Kidney Transplnatation Committee: Public Comment Period: August–October, 2015

Sustained acute kidney injury (AKI)

1. That the candidate has been on dialysis for at least 6 consecutive weeks.
2. That the candidate has a measured or calculated CrCl or GFR less than or equal to 25 mL/min for at least 6 consecutive weeks and this is documented in the candidate's medical record every 7 days beginning with the date of the first test with this value.
3. That the candidate has any combination of #1 and #2 above for six consecutive weeks.

OPT/UNOS Kidney Transplatation Committee: Public Comment Period: August–October, 2015

Summary

- Patients with advanced liver disease frequently show an impairment of renal function
- The evaluation of renal function guides diagnostic and therapeutic management, prognostic evaluation and indication to LT or SLK
- Serum creatinine and serum creatinine-based equations lead to an overestimation of GFR in these patients.
- The differential diagnosis between HRS-AKI and ATN-AKI is complex.
- New biomarkers of glomerular filtration rate and parenchymal kidney damage are promising tools in refining the evaluation of renal function in these patients.

S. Piano et al. Liver Int. 2017 ; 37 (Suppl 1) : 116-122