

**4η Ετήσια Επιστημονική Εκδήλωση  
Νεφρολογικού Τμήματος Γ.Ν "Παπαγεωργίου»**

**Περί θεραπευτικής αφαίρεσης**

**Αιμοπροσρόφηση :**

**Στις παθήσεις του ήπατος και τις δηλητηριάσεις**

**Πηνελόπη Χρ. Κούκη  
Ιπποκράτειο Γ. Ν. Αθηνών**

In accordance with the “Consensus Conference on Biocompatibility”, adsorption (and thus HP) is a method for removal of molecules from blood

**Poison:** A xenobiotic (exogenous chemical, including medication) or an endogenously found chemical (e.g., iron, copper, vitamins) resulting from exogenous exposure with the potential to cause toxicity

**Poisoning:** Exposure to a poison causing or capable of causing toxicity, regardless of intent. It includes intoxication, toxicity, and overdose.

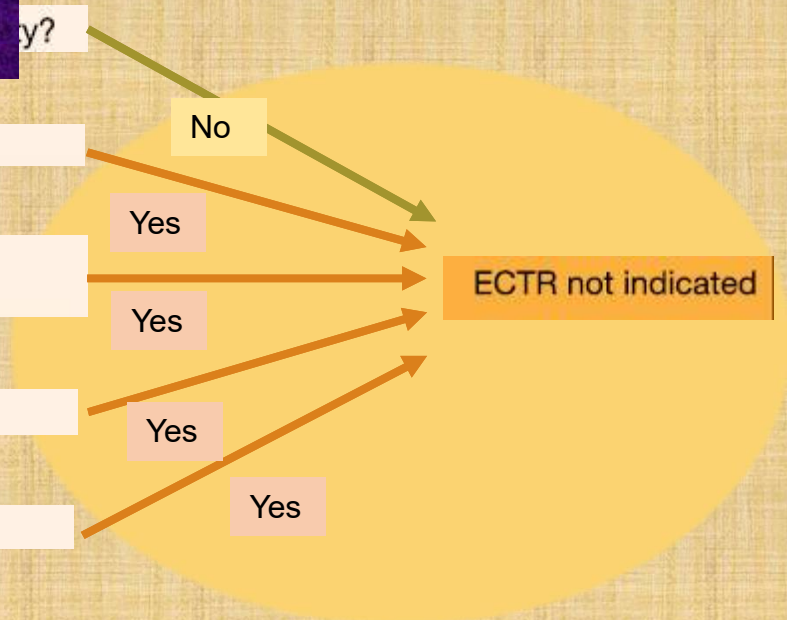
**Adverse outcome:** Significant clinical effect following poisoning. An adverse outcome can be critical (death or major end-organ damage, such as blindness in methanol poisoning) or non-critical (minor end-organ damage, such as tremors in lithium poisoning).

**Severe poisoning:** Exposure to a poison causing or having the potential to cause an adverse outcome.

stances that adsorb on its present in a fluid physical and chemical



Hydrophilic poisons distribute primarily in total body water, exhibit a smaller  $V_D$ , and are more readily removed by ECTR, whereas lipophilic poisons distribute throughout extravascular tissues, especially adipose tissue, leading to a large  $V_D$ . In general, poisons that are >80% protein bound are poorly removed by hemodialysis.



Is the poison's volume of distribution ( $V_D$ ) >1-2l/kg?

No

What percent of the poison is protein bound at the current concentration?

>95%

Therapeutic plasma exchange

<80%

80% to 95%

Hemoperfusion

What is the poison's molecular weight?

15,000 Da

High-flux Hemodialysis

15-25,000 Da

Hemofiltration

25-50,000 Da

HCO/MCO hemodialysis, hemoperfusion

>50,000 Da

Therapeutic plasma exchange

An overall clinical approach for the consideration of an extracorporeal treatment for the management of a generic poison. HCO, high-cutoff membrane; MCO, middle-cutoff membrane.

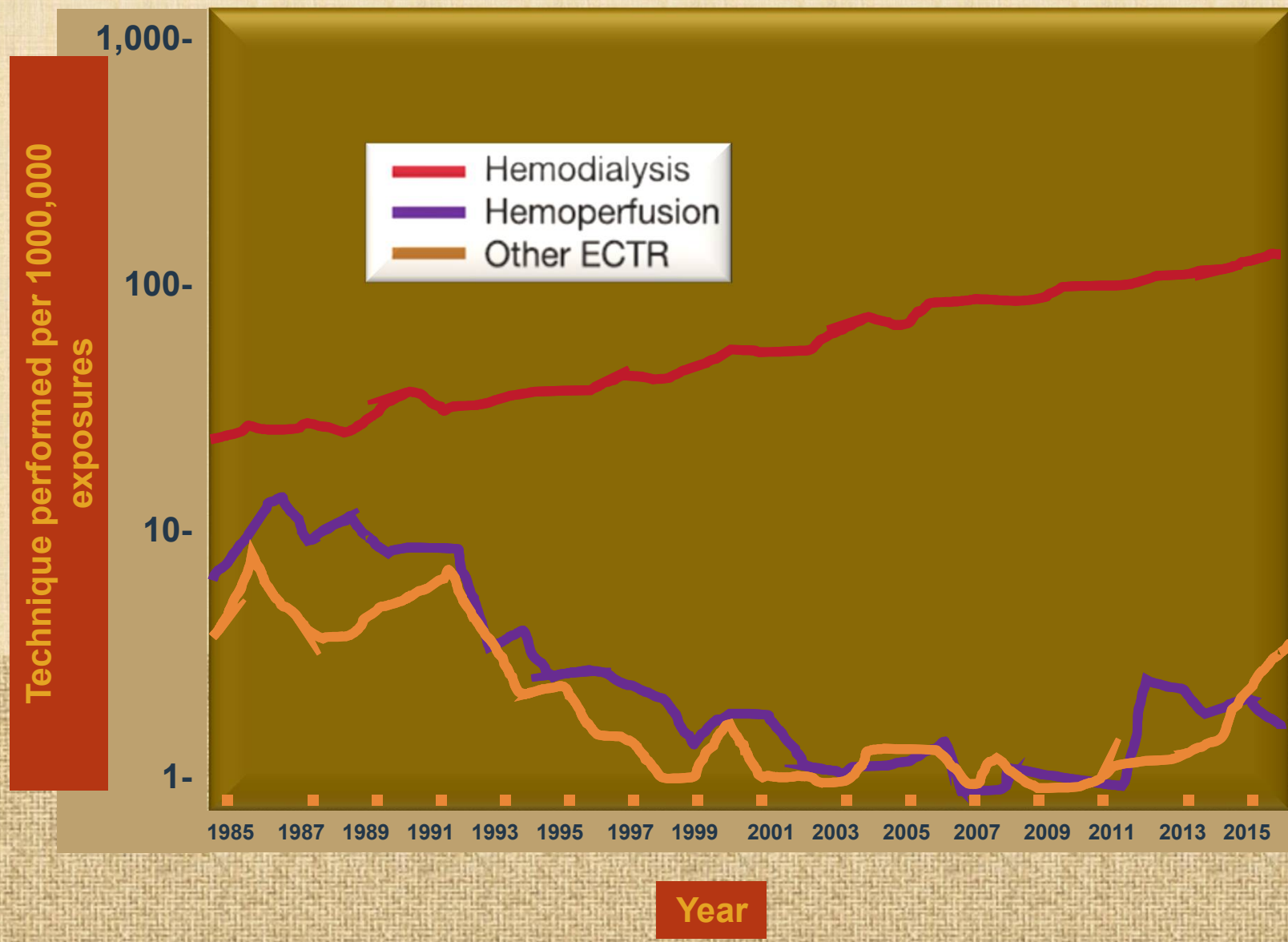
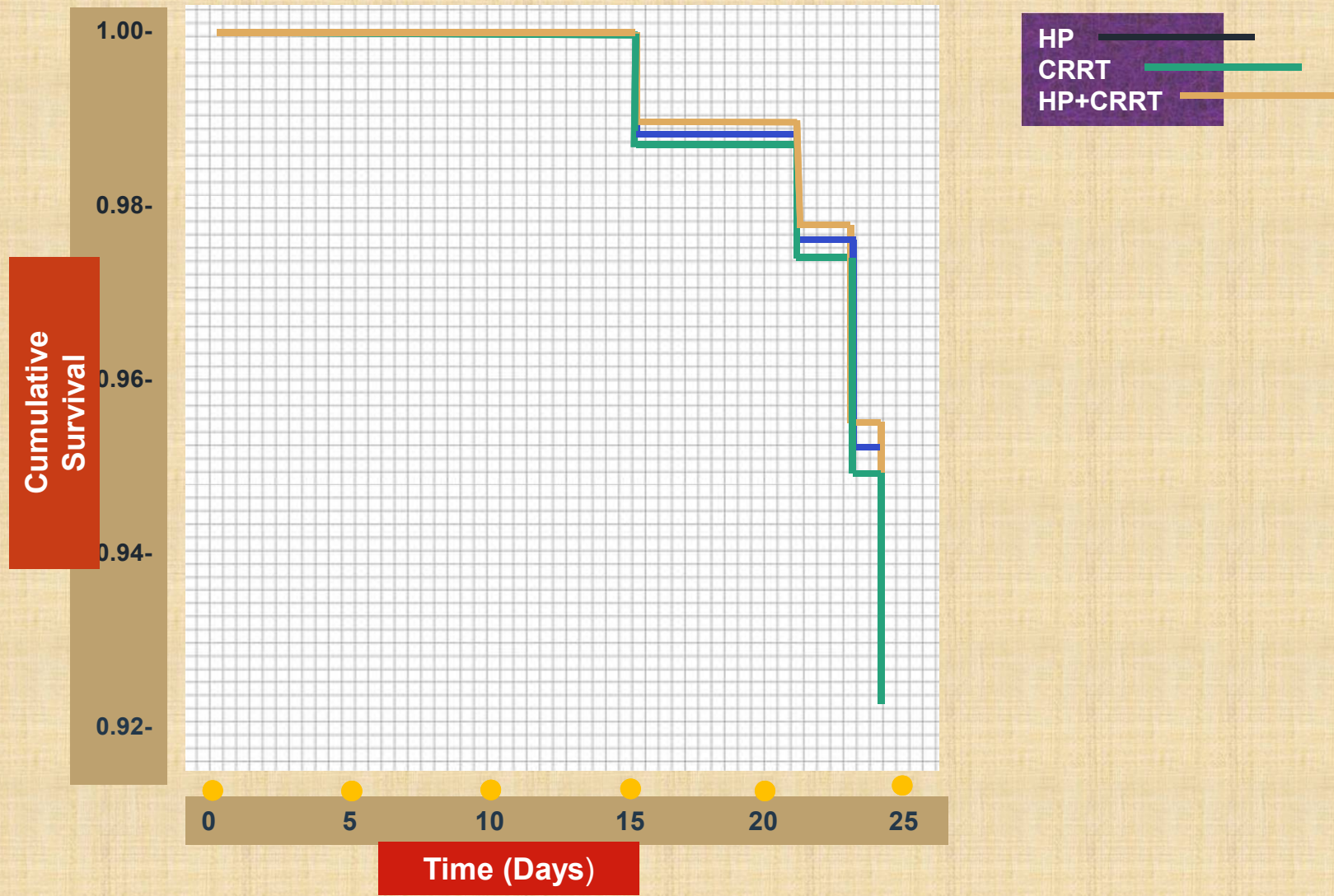


Figure 2 | US poison center trends in the use of hemodialysis, hemoperfusion, and other extracorporeal treatments.

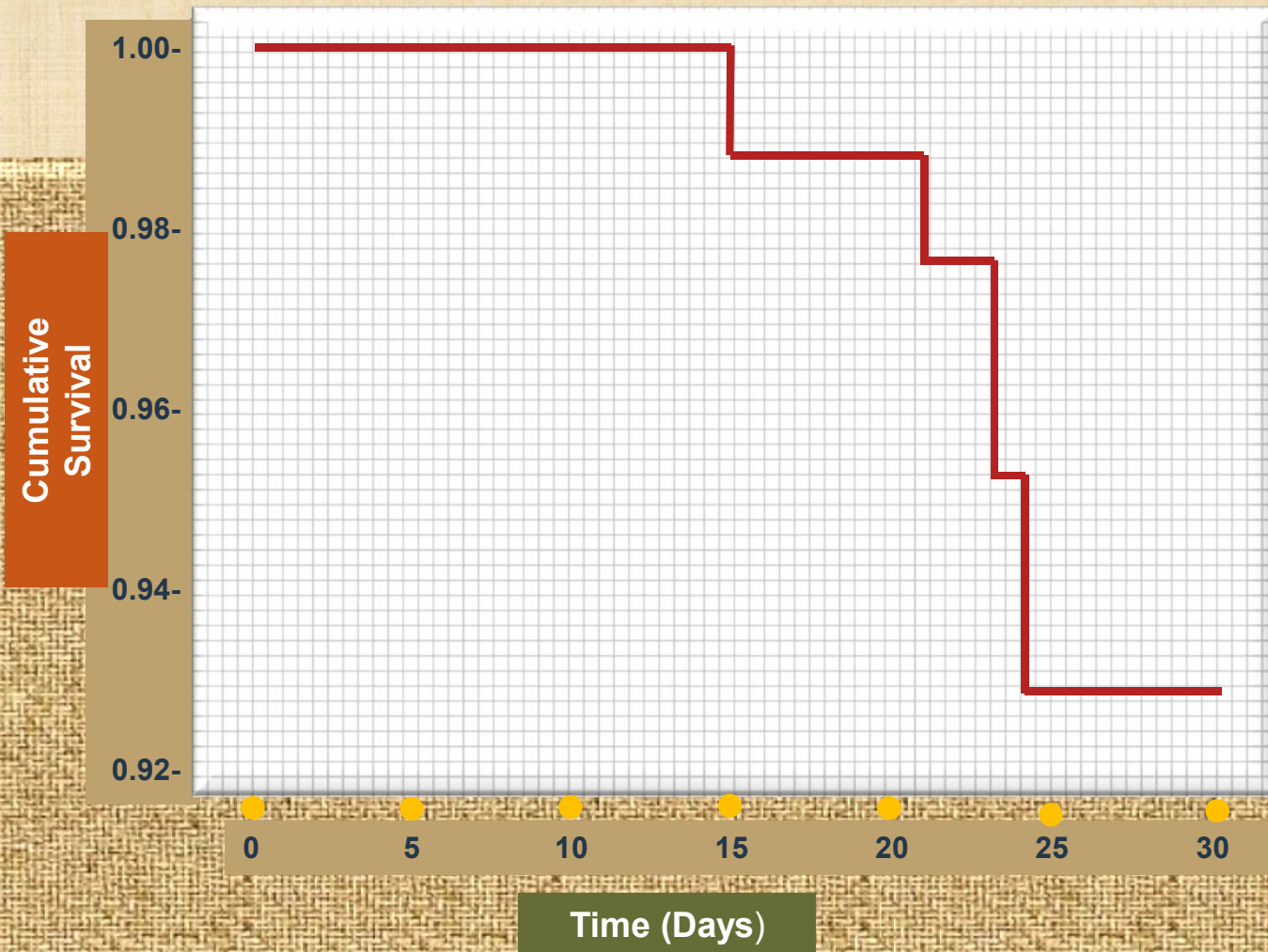
Effects of hemoperfusion and continuous renal replacement therapy on patient survival following paraquat poisoning. Wang Y et al. PLOS July 13,2017

Fatality times and rates of paraquat-poisoned patients with low plasma paraquat levels ( $50 \pm 1,000$  ng/mL, n = 83)

Treatment group	Death (<10 d)		Death (10±30 d)		Total Death	
	N	Fatality (%)	N	Fatality (%)	N	Fatality (%)
HP	0	0	2	7.1	2	7.1
CRRT	0	0	2	7.7	2	7.7
HP+CRRT	0	0	2	6.9	2	6.9



Comparison of survival curves for three treatments. Hemoperfusion (HP), continuous renal replacement therapy (CRRT), and combined treatment (HP+CRRT) in patients with plasma paraquat levels between 50 and 1,000 ng/mL. The chi-squared value between HP and CRRT was 1.056;  $p > 0.05$ . The chi-squared value between HP and HP+CRRT was 1.136;  $p > 0.05$ .

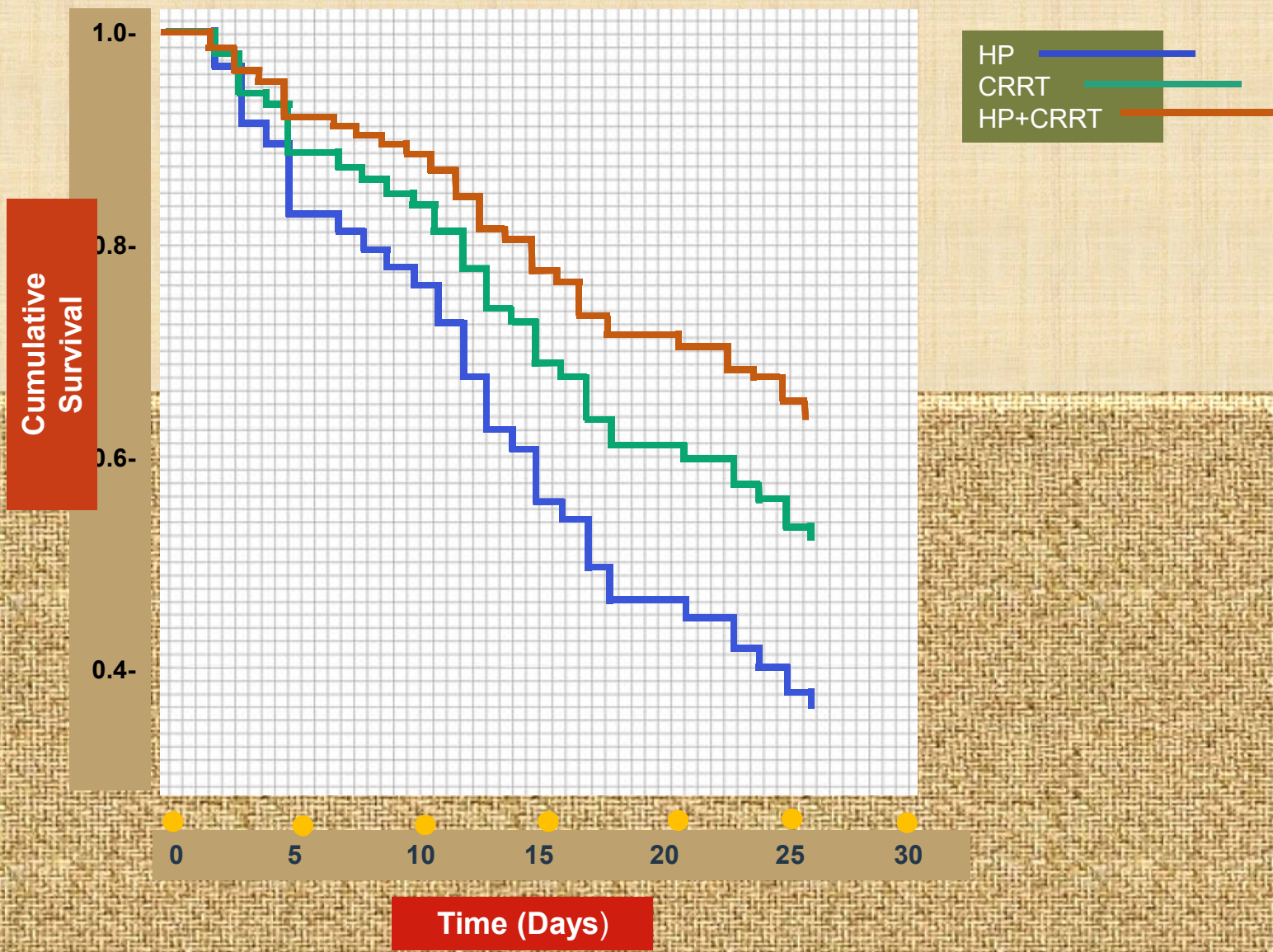


Survival time of 83 paraquat-poisoned patients (plasma paraquat levels:  $50 \pm 1,000$  ng/mL)

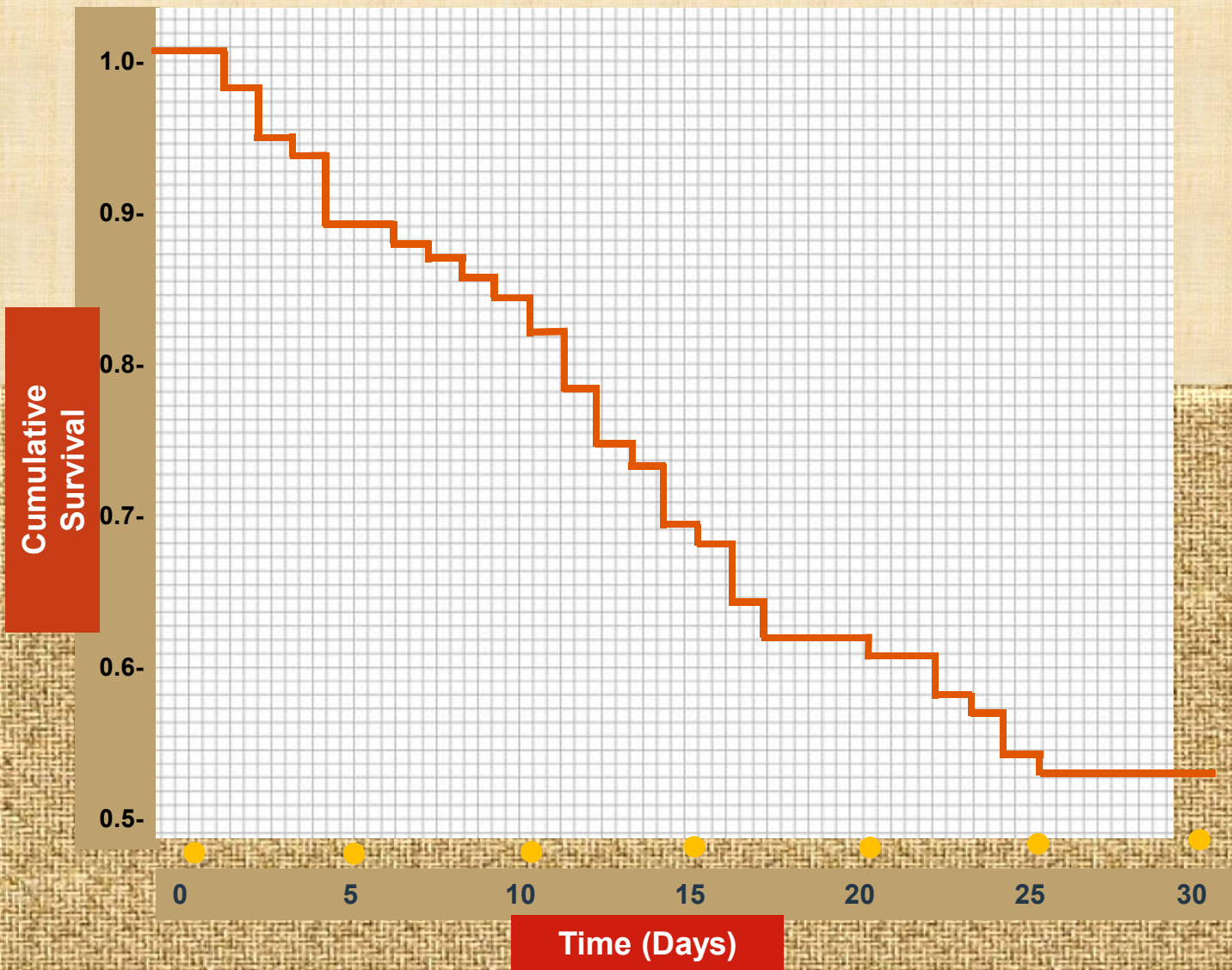
Fatality times and rates of paraquat-poisoned patients with high plasma paraquat levels (1,000±5,000 ng/mL, n = 81)

Treatment group	Death (<10 d)		Death (10±30 d)		Total Death	
	N	Fatality (%)	N	Fatality (%)	N	Fatality (%)
HP	7	25.9	9	33.3	19	<b>59.2</b>
CRRT	4	16	8	32	12	<b>48</b>
HP+CRRT	2	6.9	9	31	11	<b>37.9</b>





Survival time of 81 paraquat-poisoned patients (plasma paraquat levels:  $1,000 \pm 5,000$  ng/mL)



Survival time of 81 paraquat-poisoned patients (plasma paraquat levels:  $1,000 \pm 5,000$  ng/mL)

Prognostic comparison of goal-oriented hemoperfusion and routine hemoperfusion combined with continuous venovenous hemofiltration for paraquat poisoning. Zhao Xet al. J Inter Medic Res 2018, 46(3):1091-1102

139 patients were admitted with paraquat poisoning

Excluded (n=55)

- >24h from taking paraquat to admission (n=19)
- >24h from taking paraquat to HP (n=8)
- >75 years of age (n=2)
- Negative urinary paraquat (n=8)
- Combined with other poisons (n=7)
- History of sever diseases (n=4)
- Patients did not complete the conventional treatment (n=5)
- Loss to 28-day follow up (n=2)

84 patients were included

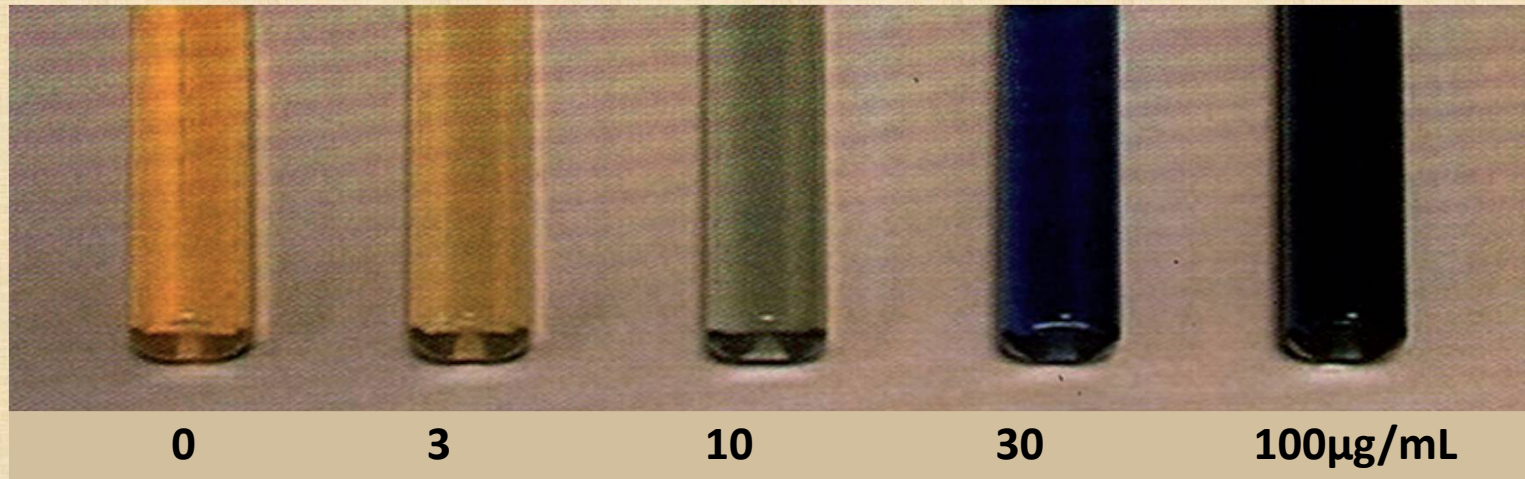
Control group (n=49)

Goal-oriented group (n=35)

- 28-day mortality of **69.4%** (n=34)  
Causes of death: 23 died from acute respiratory failure and 11 died from acute circulatory failure

- 28-day mortality of **51.4%** (n=18)  
Causes of death: 13 died from acute respiratory failure and 5 died from acute circulatory failure

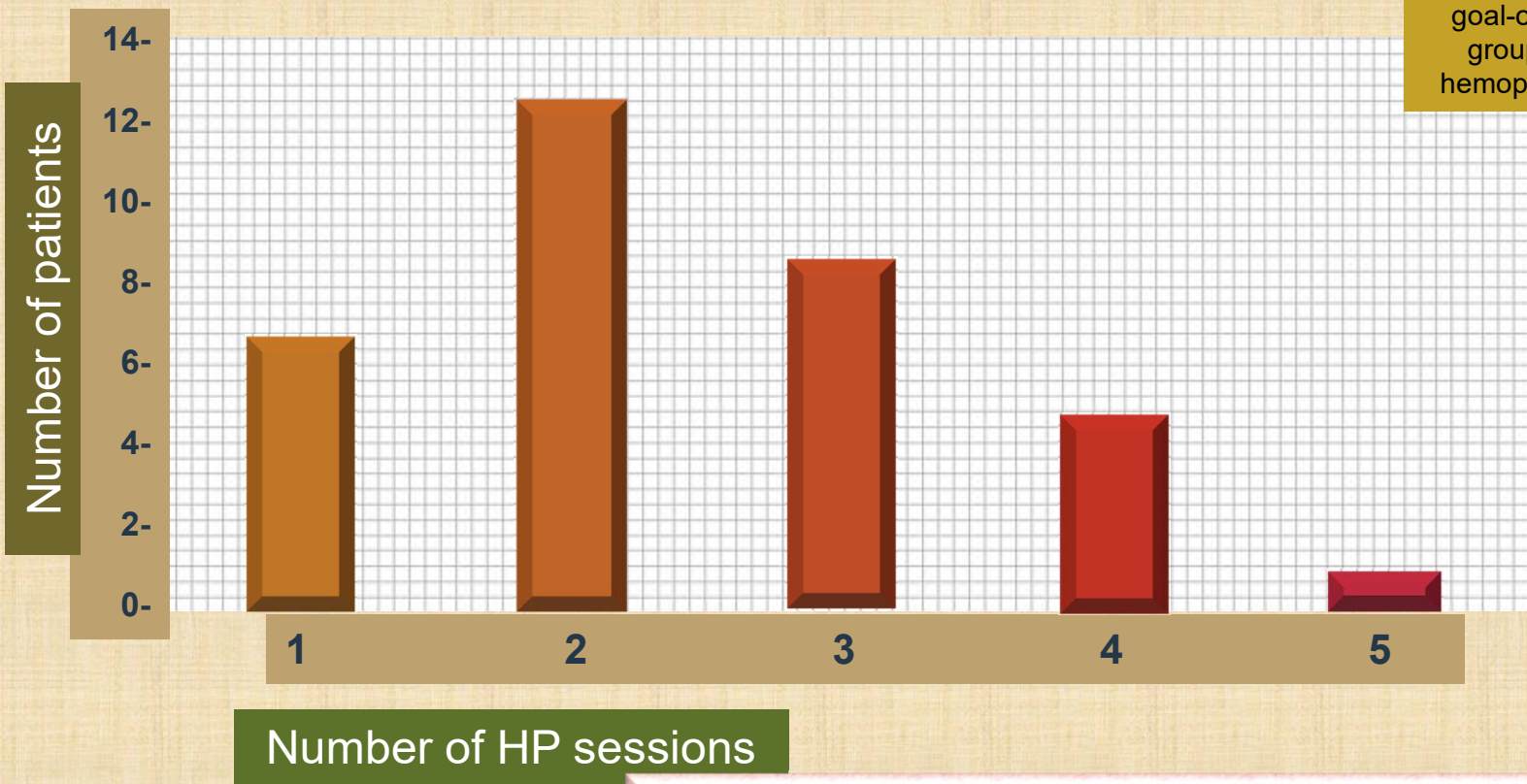
Flowchart of patients. HP, hemoperfusion



Color scale for semi-quantitative analysis of urine paraquat concentration.

**To investigate the impact of goal-oriented hemoperfusion (HP) with monitoring of the paraquat concentration on the prognosis of patients with acute paraquat poisoning.**

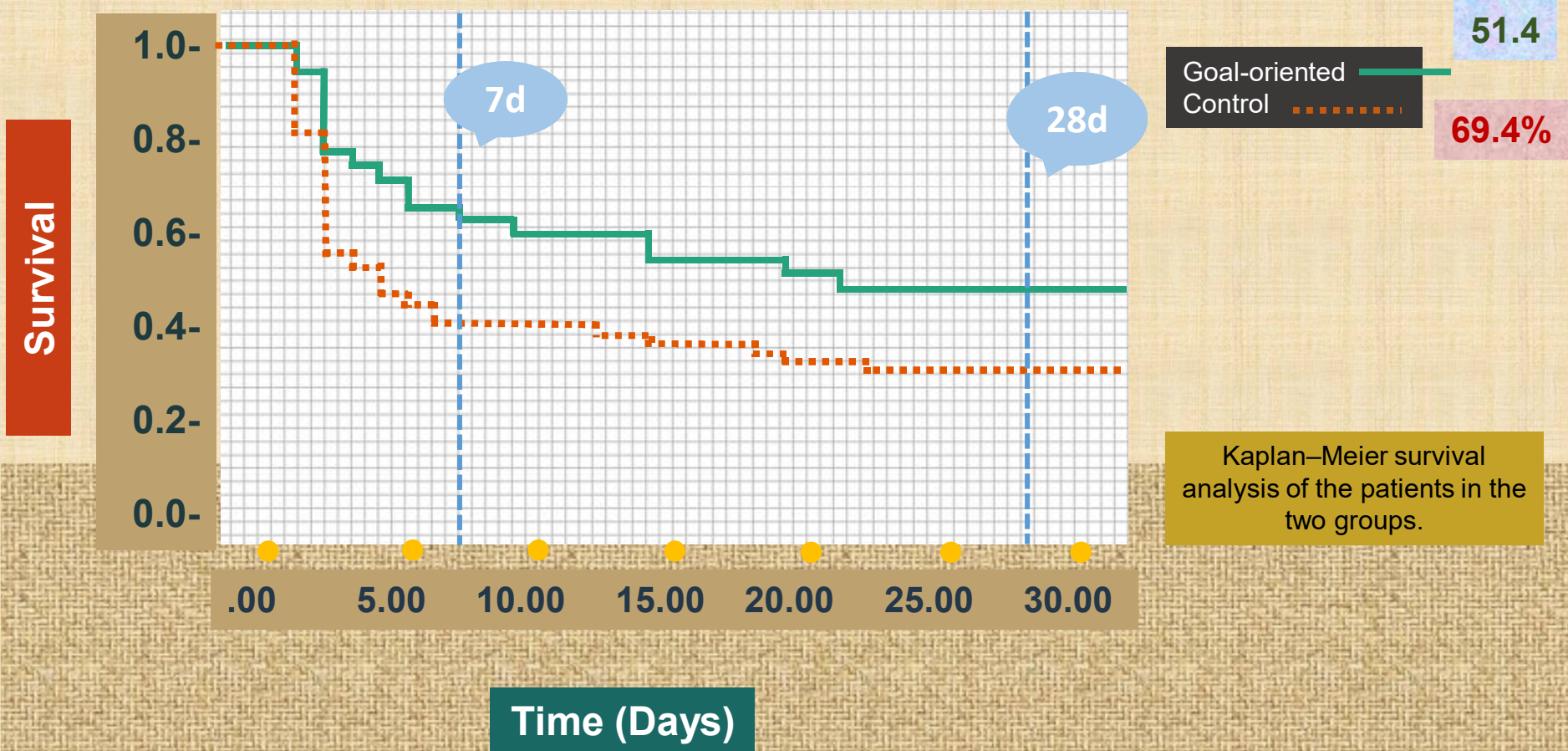
**The primary endpoint was 28-day mortality after poisoning. The secondary endpoints were the incidence of organ dysfunction within 7 days and 7-day mortality.**

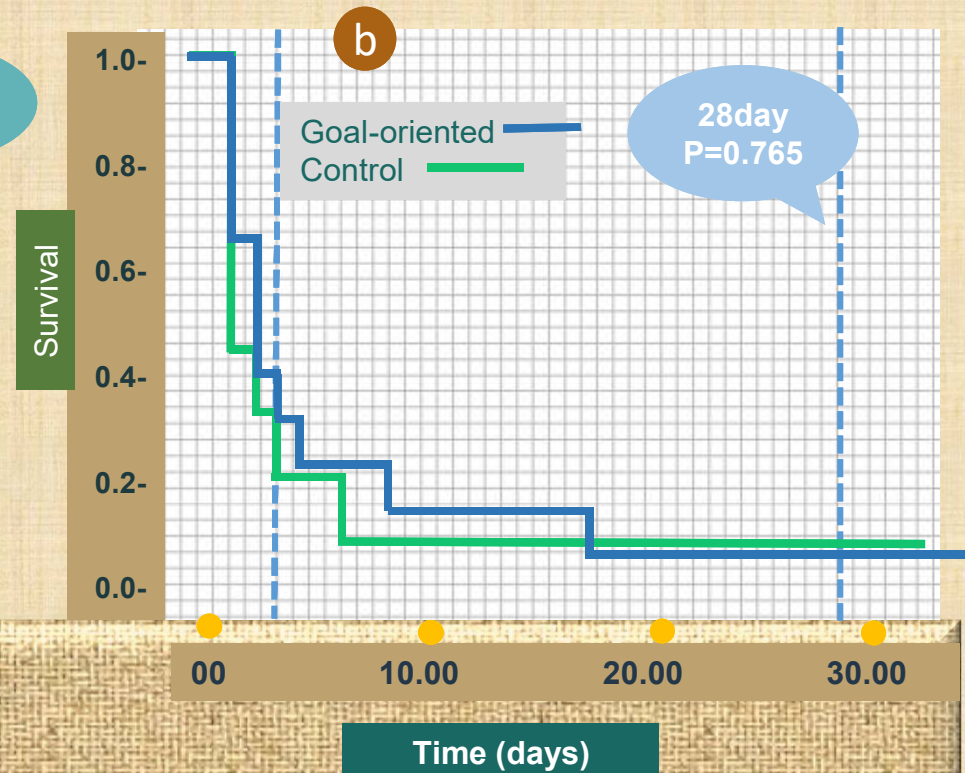
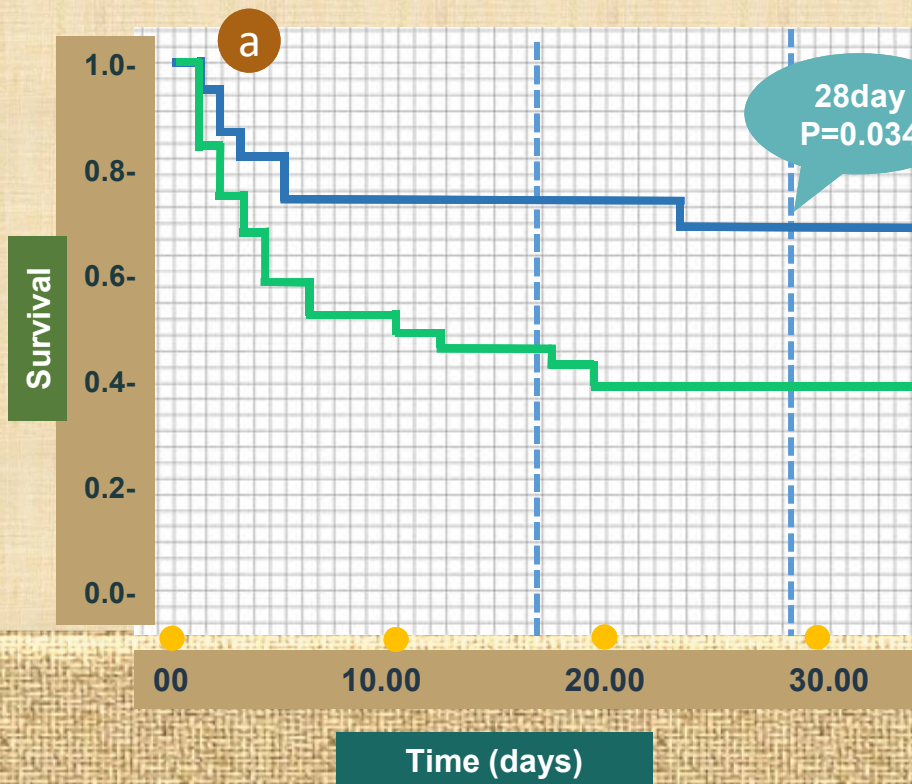


Number of hemoperfusion sessions in the goal-oriented group. HP, hemoperfusion

If the results suggested that the content was  $\geq 3 \mu\text{g/ml}$ , HP was continued until the urine detection turned negative.

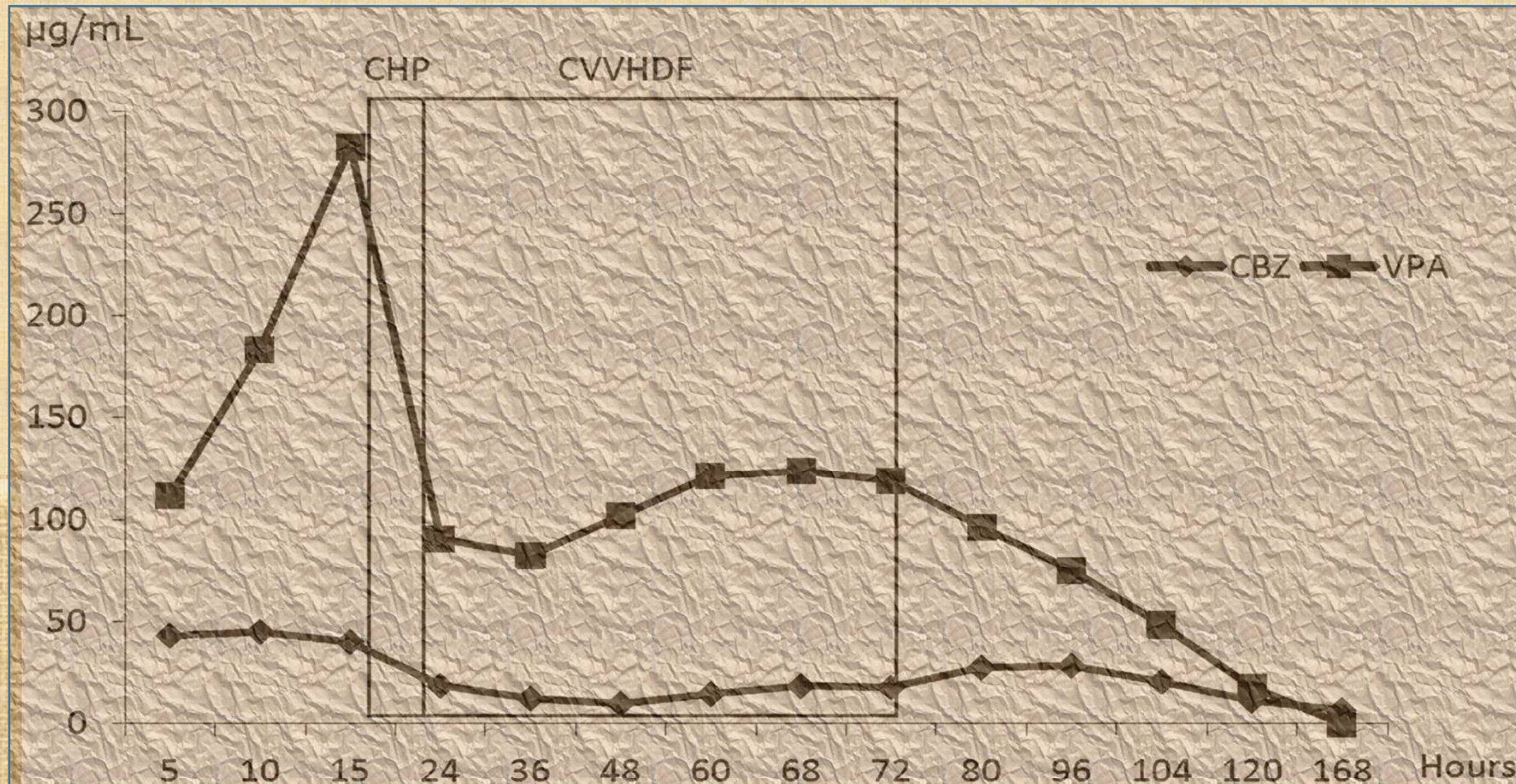
During subsequent 48 h, the urine paraquat concentration was detected every 6h, and if the concentration was again  $\geq 3 \mu\text{g/ml}$ , another HP session was performed. This protocol was repeated until negative urine detection was achieved as the standard of stopping HP. If the patients did not develop acute renal injury, sequential CVVH was not performed after HP.





Comparison of the 28-day mortality rate between the two groups after stratification based on the paraquat dose: (a) <50 ml, (b) >50 ml.

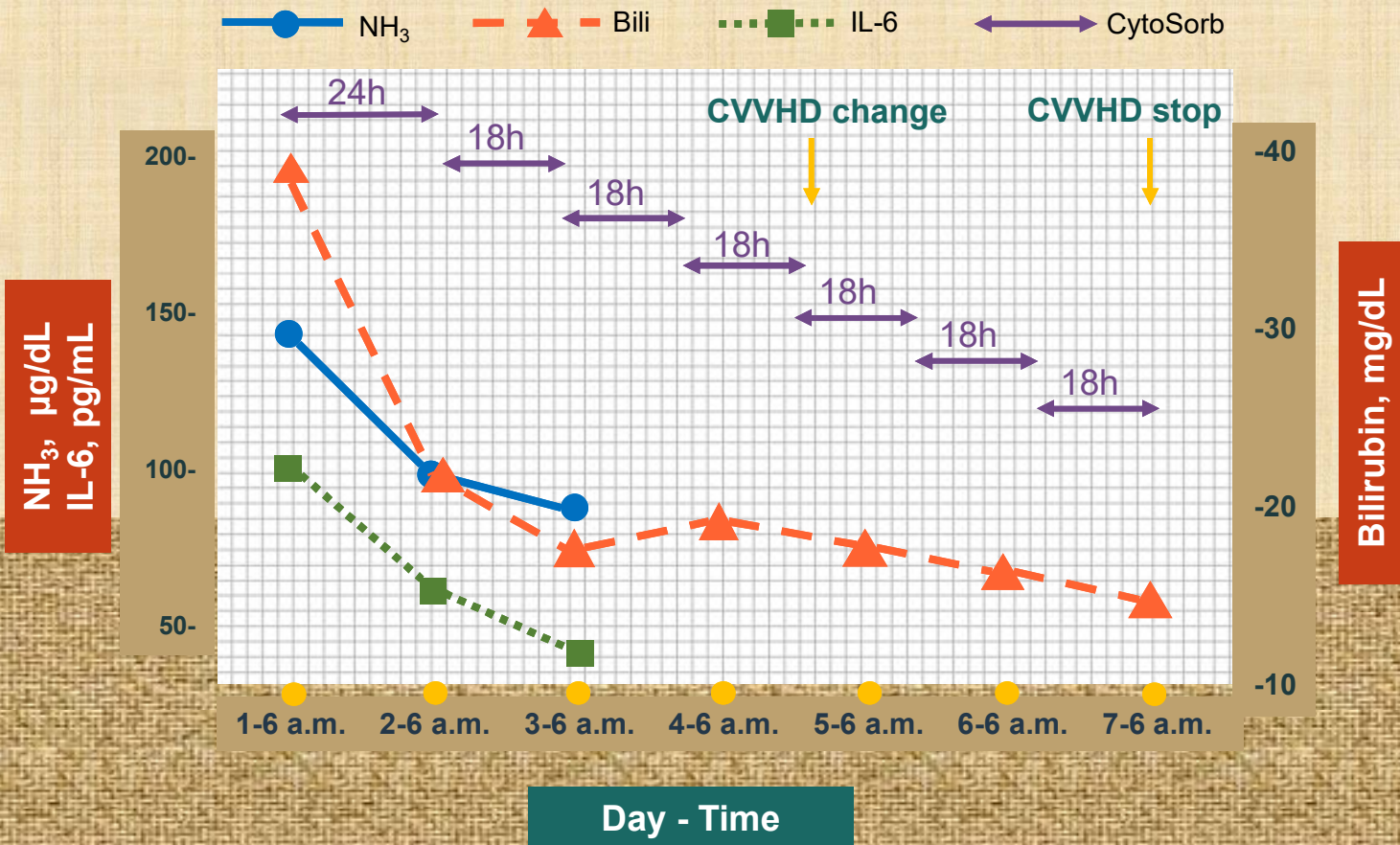
Overdose with antiepileptic drugs: the efficacy of extracorporeal removal techniques. Moinho R, et al. BMJ Case Rep 2014. doi:10.1136/bcr-2014-207761



Carbamazepine (CBZ) and valproic acid (VPA) serum concentration evolution before, during and after the treatment with **charcoal haemoperfusion (CHP)** and continuous venovenous hemodiafiltration (CVVHDF). Therapeutic levels of CBZ=4–12 µg/mL and of VPA=50–100 µg/mL.



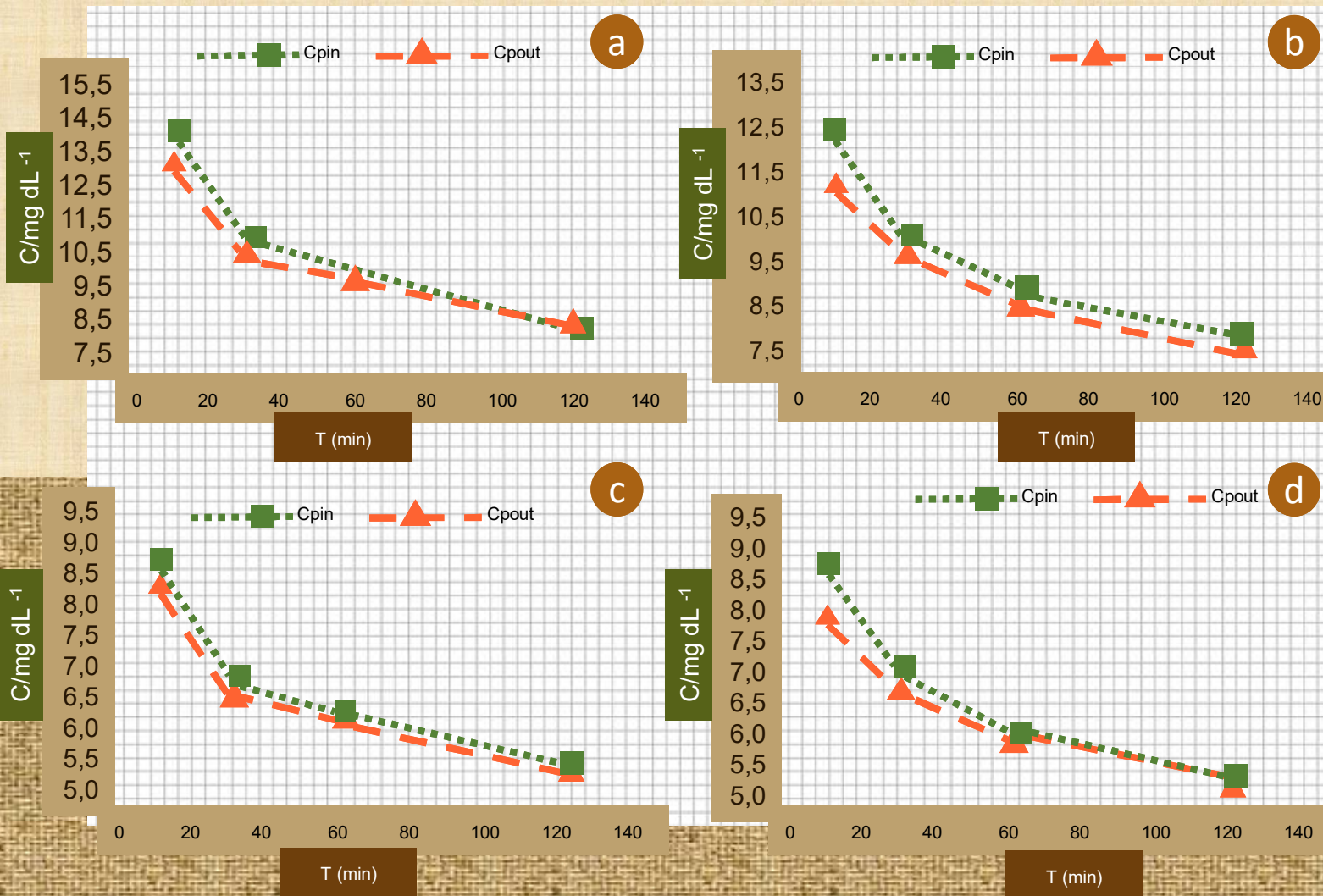
Use of Hemoabsorption in a Case of Severe Hepatic Failure and Hyperbilirubinemia. Andreas Falthauer and Frank Kullmann. Blood Purif 2017;44:98-99



Course of bilirubin, ammonia, and IL-6 during the hemoabsorption treatment over 7 days.

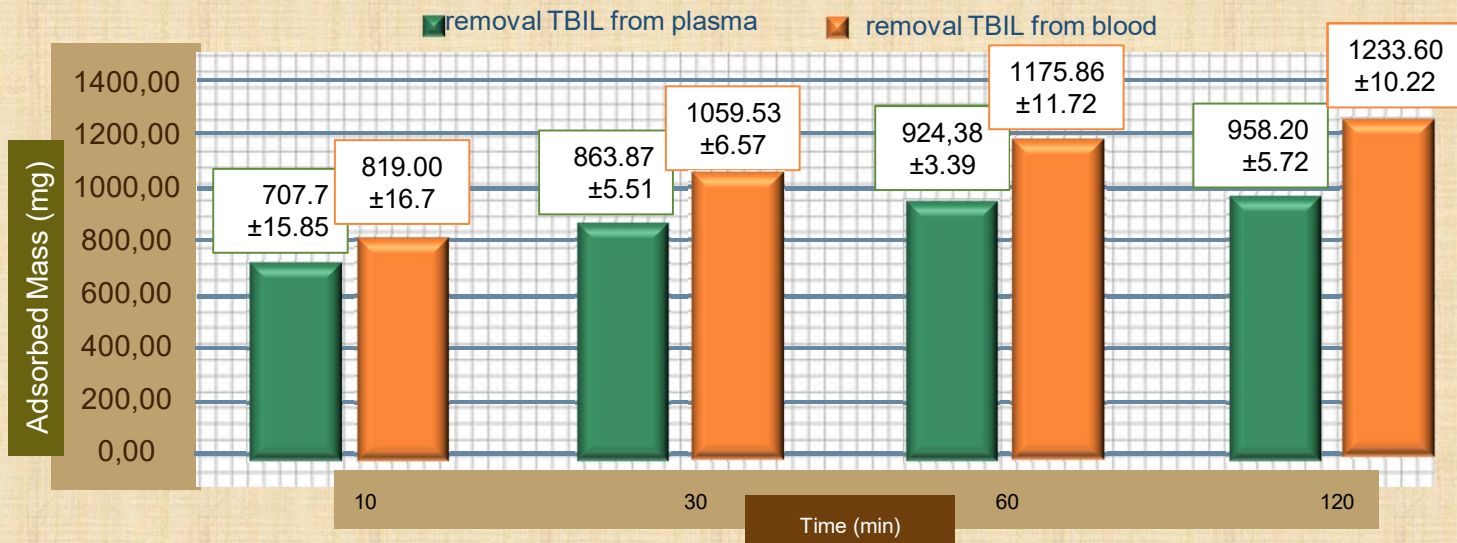


# New option for the treatment of hyperbilirubinemia: in vitro direct hemoperfusion with the Lixelle S-35. Santori et al. Int.J. Artif.Org 2014;37(11):815-823

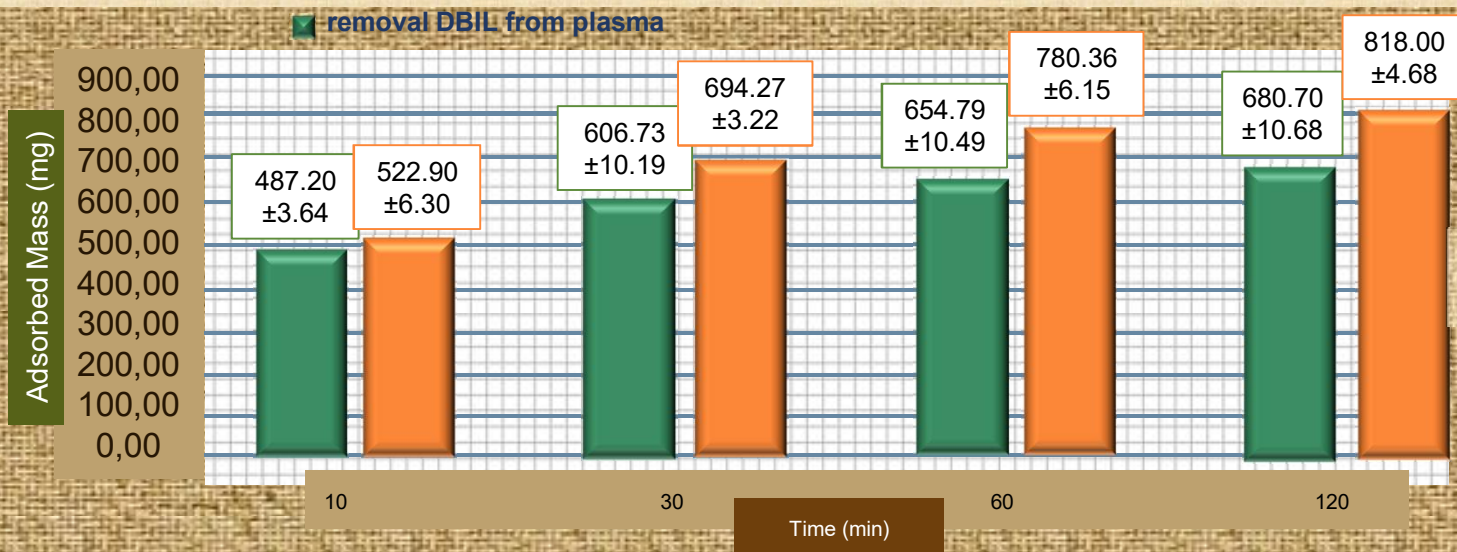


Change in arterial-venous concentrations during mock DHP: in a levels of total bilirubin in blood (baseline concentration  $23.10 \pm 0.47$  mg/dl); in b levels of total bilirubin in plasma (baseline concentration  $17.57 \pm 0.53$  mg/dl); in c levels of direct bilirubin in blood (baseline concentration  $15.37 \pm 0.24$  mg/dl); in d levels of direct bilirubin in plasma (baseline concentration  $12.57 \pm 0.23$  mg/dl).

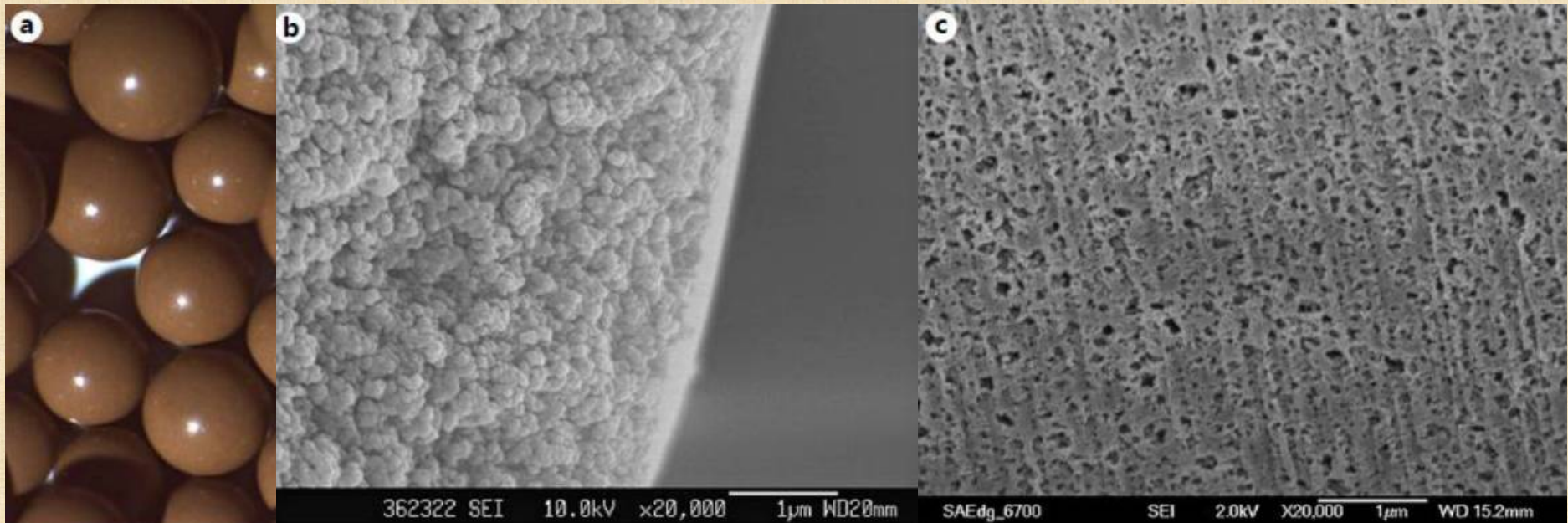
# New option for the treatment of hyperbilirubinemia: in vitro direct hemoperfusion with the Lixelle S-35



Mass Balance Analysis at 10, 30, 60 and 120 minutes. TBIL = total bilirubin; DBIL = direct bilirubin

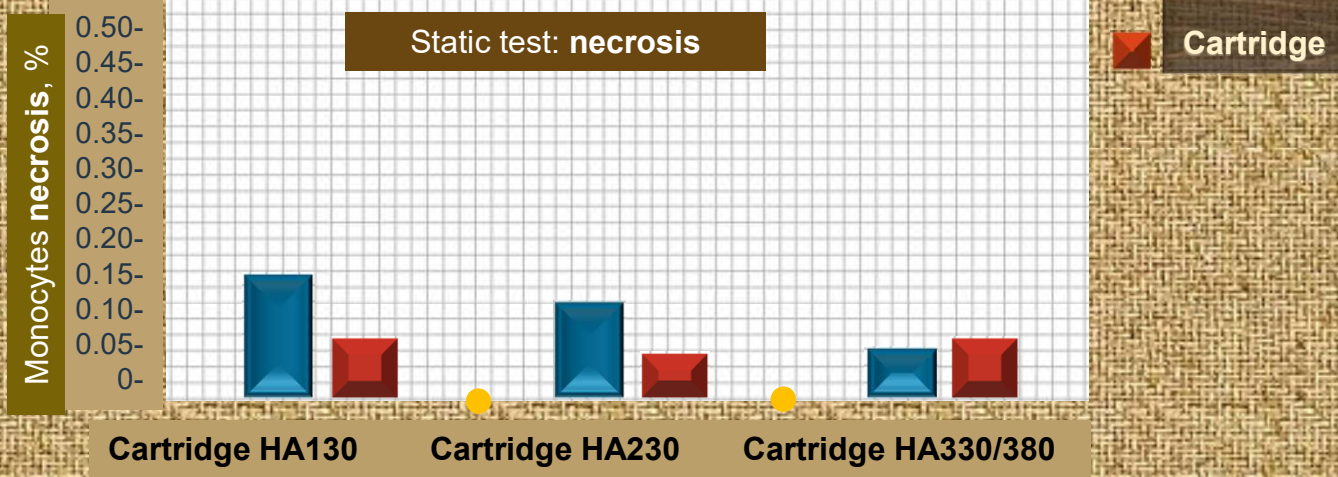
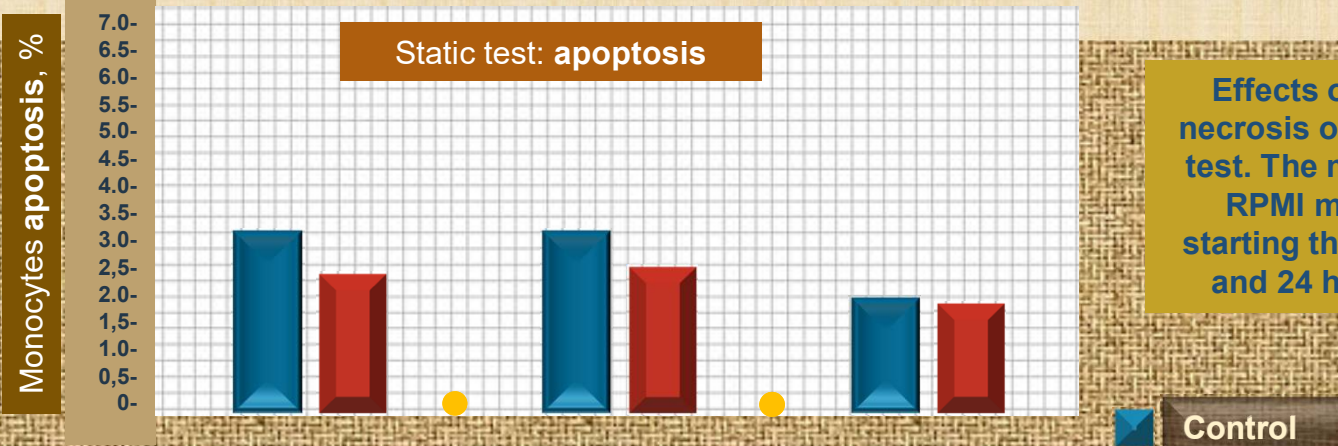
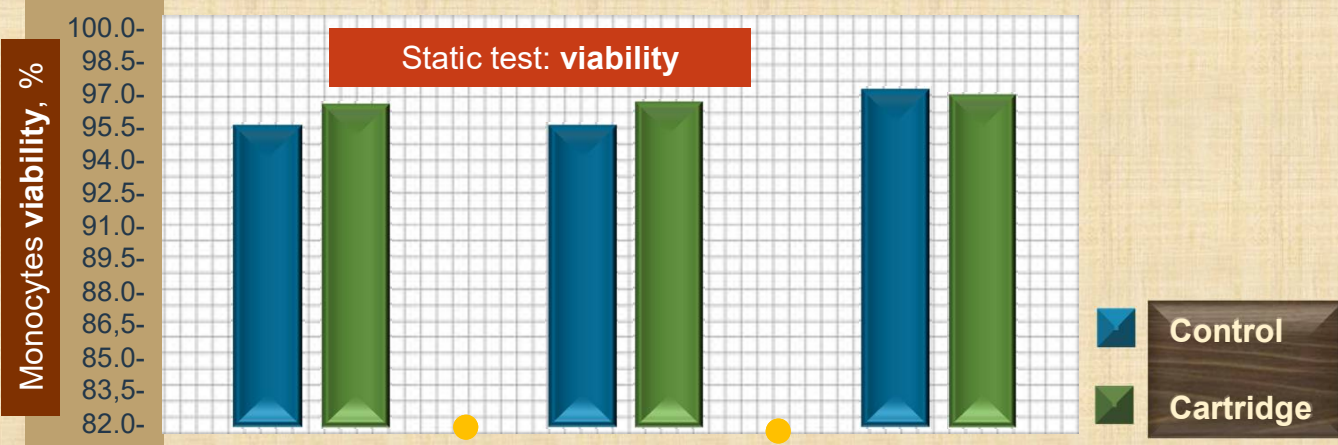


**Biocompatibility and Cytotoxic Evaluation of New Sorbent Cartridges for Blood Hemoperfusion. Montin DP et al. Blood Purif 2018;46:187-195**



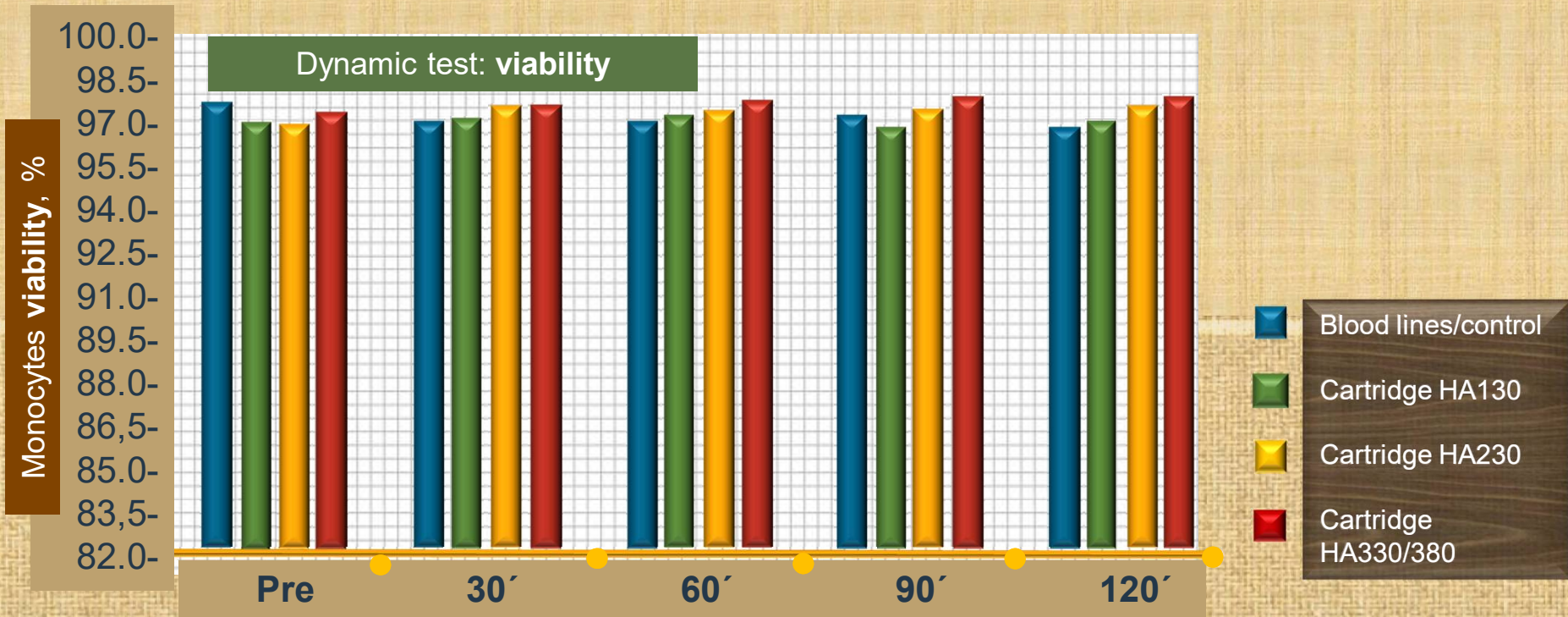
Neutro-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymer (a). In (b.c), pics made by transmission electron microscopy (TEM) of beads surface and section with the poor.

	HA130	HA230	HA330/380
Indications	Long term dialysis complications-itching renal osteodystrophy,hypertension, malnutrition	Intoxication poisoning of herbicide, rodenticide, pesticide,biotoxin, drug overdose	Critical ill patients suffered from cytokine storm-sepsis pancreatitis, trauma, cardiac surgery, inflammation
Toxins removal	Middle uremic toxins, protein-bound uremic toxins	Hydrophobic or protein-bound exogenous substances	Cytokines, complement ,free hemoglobin and so on
Molecules removed molecular range	5-30kDa	500Da-10kDa	10-60kDa
Resin pore size distribution	500Da-40kDa	200Da-10kDa	500Da-60kDa
Specificity Resin binding capacity	130	230	330/380
Structure Molecular adsorbent	110	145 Styrene divinylbenzene Copolymers	170/185
Material of housing Cartridge filter		PC Yes	
Sterilization method		Irradiation sterilization	

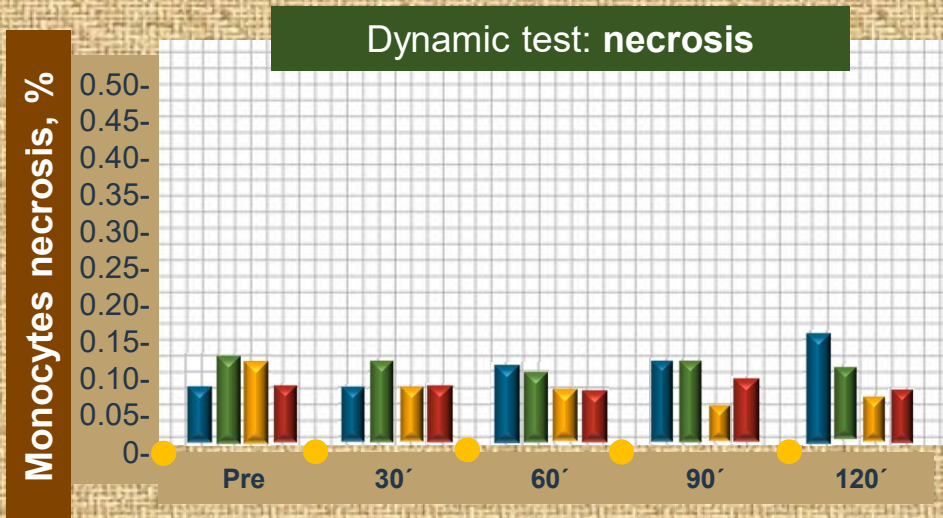
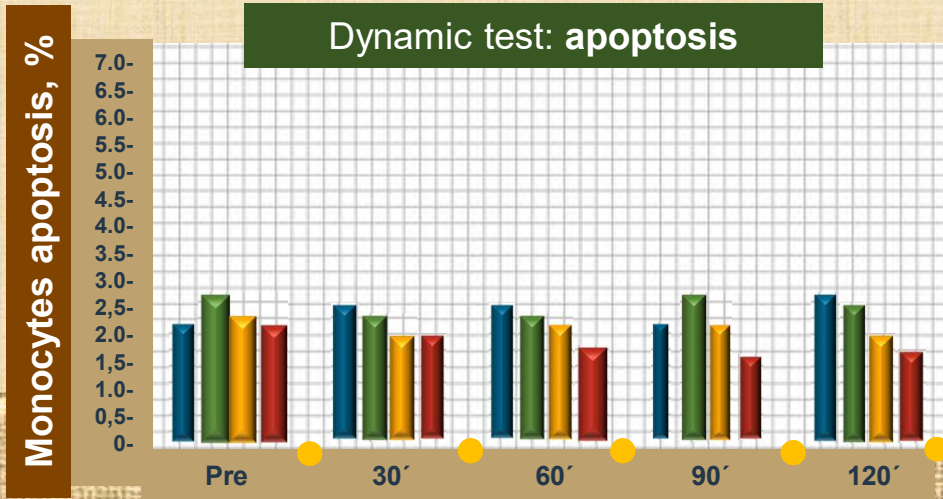


Effects on the viability, apoptosis and necrosis of U937 cell cultures in the static test. The monocytes were incubated with RPMI medium collected both before starting the experiment (negative control) and 24 h after storage into cartridges.

Percentage of viability, apoptosis, and necrosis of monocytes (U937 cell line) after 24 h of incubation for each cartridge type and controls, as negative control RPMI medium samples were collected before starting the experiment



Percentage of viability, apoptosis, and necrosis of monocytes (U937 cell line) after 24 h of incubation for each cartridge type and controls, as negative control RPMI medium samples were collected before starting the experiment

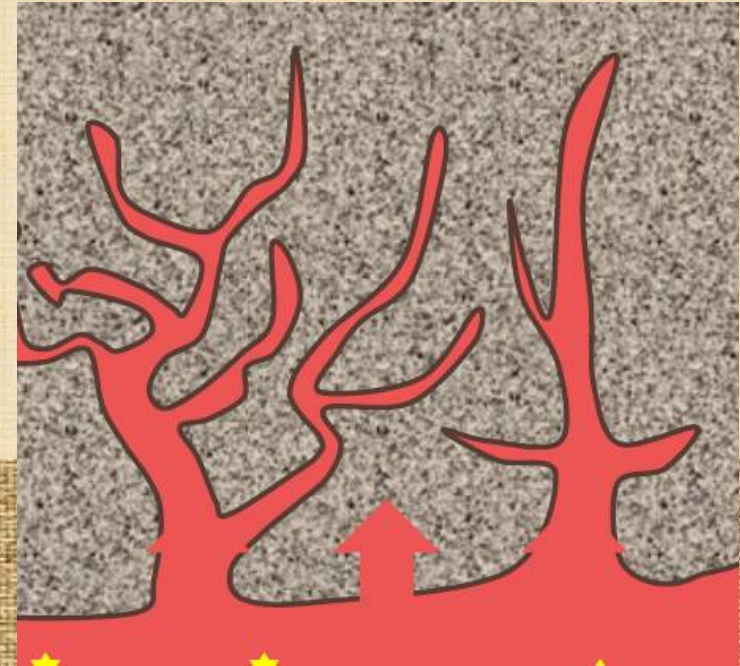
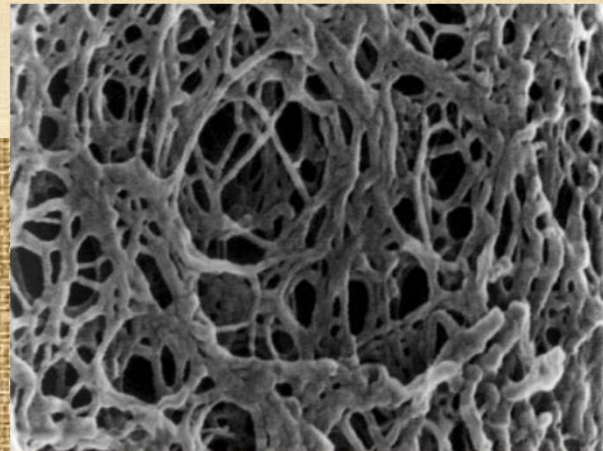


- Blood lines/control
- Cartridge HA130
- Cartridge HA230
- Cartridge HA330/380



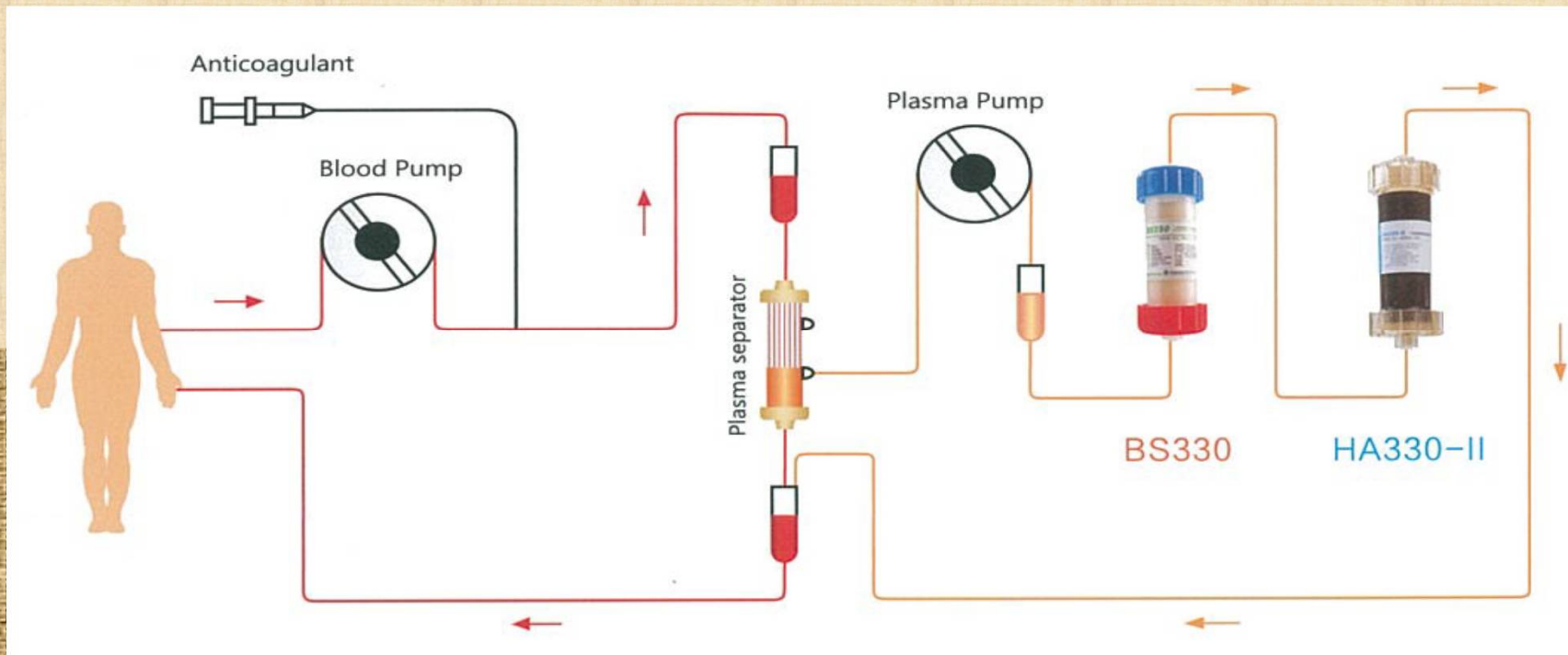
## HA230 HEMOPERFUSION CARTRIDGE

## HA230 for Poisoning



- Hydrophobicity
- Molecular Sieve
- Physical adsorption/Van der Waals
- Electrostatic interaction

# DPMAS – Efficient Liver Support System Double Plasma Molecular Adsorption System



BS330+HA330-II Plasma adsorption

BS330 specifically adsorbs bilirubin, bile acid and endotoxin



BS330 Disposable Plasma Bilirubin Adsorption Column



Anion-exchange resin

HA330-II broad-spectrum adsorbs toxins such as inflammatory mediators, ammonia, phenol mercaptan, etc

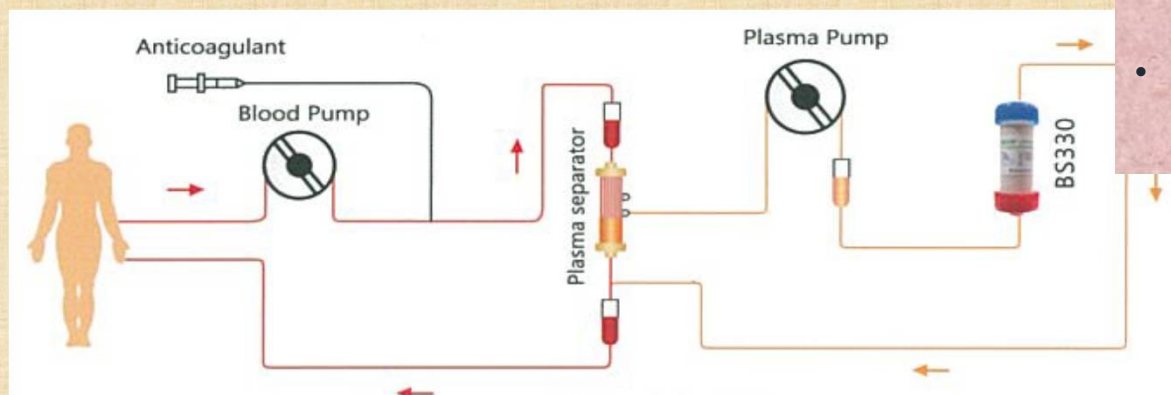


HA330-II Disposable Hemoperfusion Cartridge



Neutral-macroporous resin

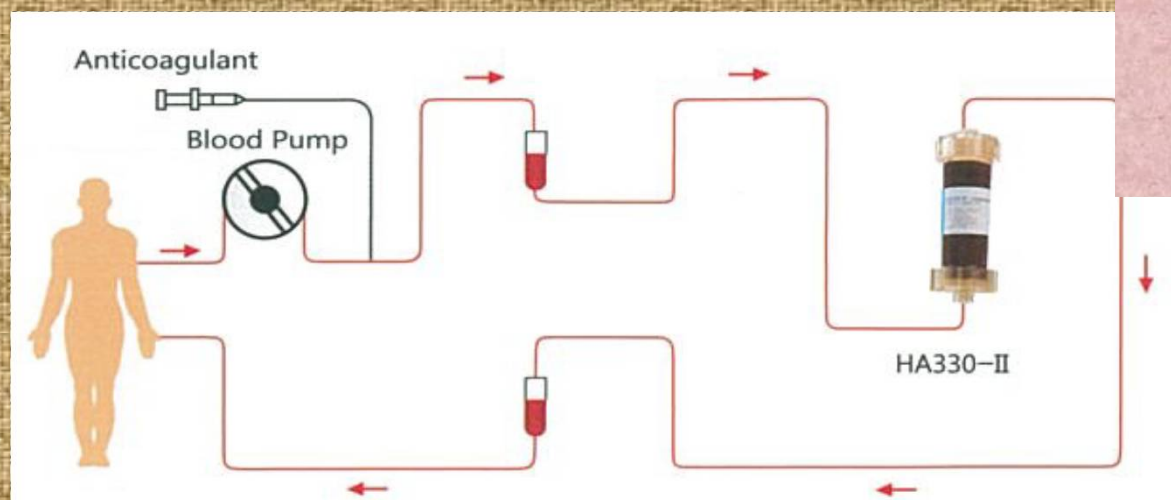
- BS330 plasma absorption



Plasma Adsorption

- For hyperbilirubinemia and hyperbileacidemia
- Effectively improve jaundice symptom

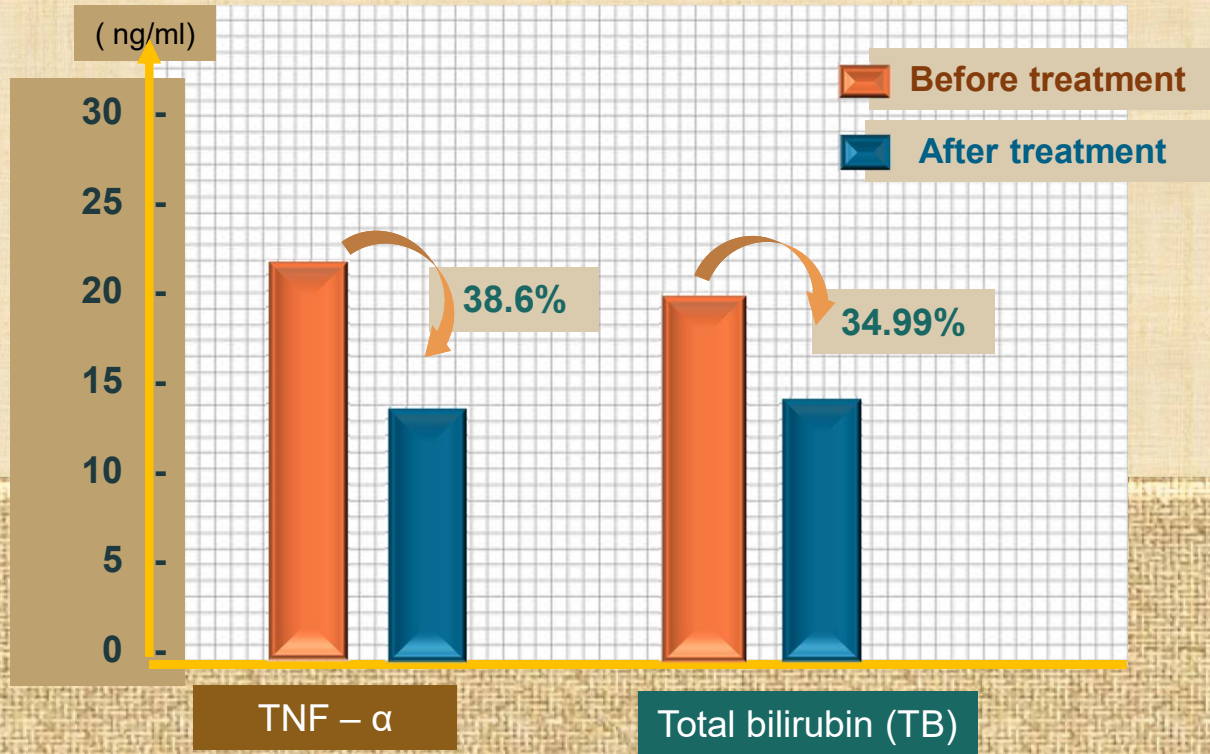
- HA330-II direct blood absorption



Direct Blood Perfusion

- For early hepatitis
- Extensively remove toxins induced by liver disorder such as inflammatory mediators, ammonia, phenol mercaptan, etc.

- Clinical Efficacy



**Conclusion:** DPMAS efficiently removes bilirubin while clearing inflammatory mediators

**Clinical emergency treatment of 68 critical patients with severe organophosphorus poisoning and prognosis analysis after rescue. Hui Dong et al. Medicine 2017;96(25)**

**The frequency of both groups having organ failure (n [%])**

Groups	Renal failure	Heart failure	Respiratory failure
Control group (n=34)	4 (11.76)	1 (2.94)	6 (17.65)
Treatment group (n=34)	1 (2.94)	3 (8.82)	6 (17.65)

**Comparison of rescue outcomes**

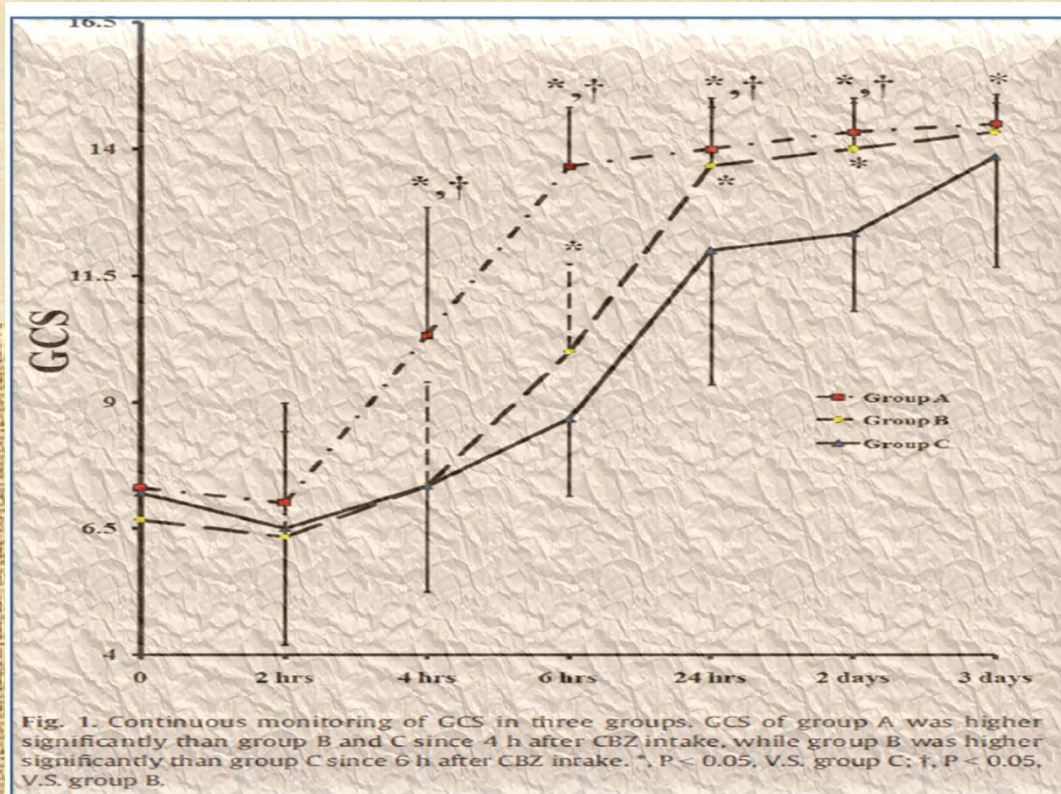
Groups	Renal failure	Heart failure	Respiratory failure
Control group (n=34)	<b>4 (11.76)</b>	<b>6 (17.65)</b>	<b>28 (82.35)</b>
Treatment group (n=34)	<b>1 (2.94)</b>	<b>1 (2.94)</b>	<b>33 (97.06)</b>
x <sup>2</sup>	5.712	11.715	11.715
P	<.05	<.05	<.05





Early hemoperfusion for emergency treatment of carbamazepine poisoning. Yang Xet al  
 .Am J Emerg Med 2018 Jun;36(6):926-930

104 patients with acute CBZ poisoning  
 Group (HP in Emergency Department)=51  
 Group (HP in the blood purification room)=34  
 Control group (No HP)=19



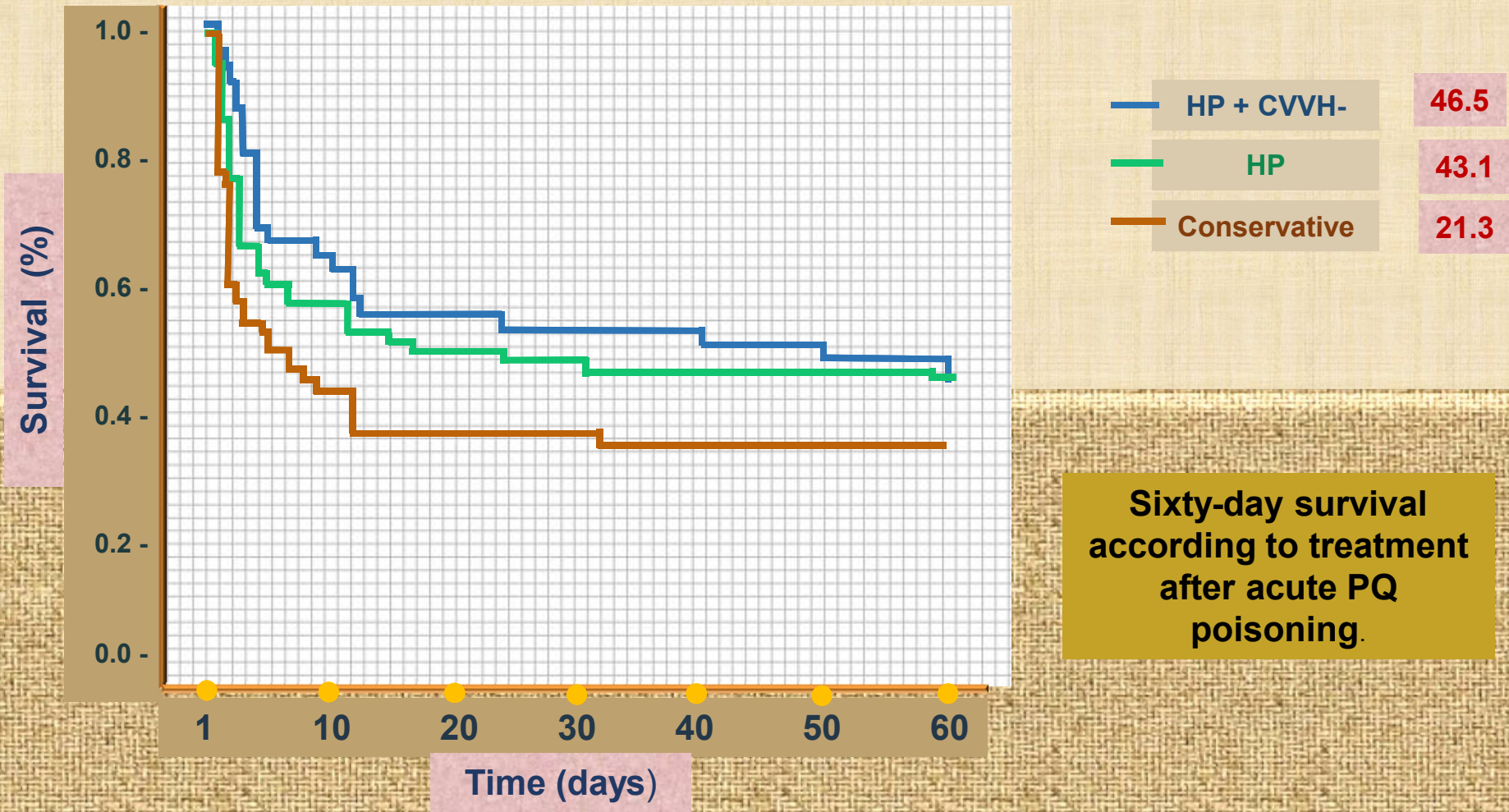
	HP IN EMERGENCY DEPARTMENT	HP IN BLOOD PURIFICATION ROOM	NO HP
<b>MORTALITY</b>	0	0	10.5 %
<b>HOSPITALIZATION DAYS</b>	3.12+/-0.98	4.16+/-0.74	5.85+/-1.32

Improve the consciousness recovery & survival and shorten the hospitalization



Early Stage Blood Purification for Paraquat Poisoning:  
A Multicenter Retrospective Study. An Li et al. Blood  
Purif 2016;42:93-99

HA330



Sixty-day survival according to treatment after acute PQ poisoning.

Early Stage Blood Purification for Paraquat Poisoning:  
A Multicenter Retrospective Study. An Li et al. Blood  
Purif 2016;42:93-99

Blood levels of PQ comparison at baseline and during treatment

Group	n	Baseline	24 h	48h	72h	p value
Conservative	75	21.56±11.17	16.71±8.35 <sup>a</sup>	10.33±6.67 <sup>a, b</sup>	6.02±3.29 <sup>a-c</sup>	<0.001
HP	65	22.95±10.41	7.84±3.63 <sup>*, a</sup>	4.54±2.58 <sup>*, a, b</sup>	2.50±1.34 <sup>a-c</sup>	<0.001
HP + CVVH	43	20.82±9.26	4.95±2.81 <sup>*, #, a</sup>	3.91±1.89 <sup>*, a, b</sup>	2.11±1.67 <sup>a-c</sup>	<0.001
p value	-	0.553	<0.001	<0.001	<0.001	

All data are presented as mean ± SD, µg/ml.

\* p < 0.05 vs. conservative treatment; # p < 0.05 vs. HP; a p < 0.05 vs. before baseline; b p < 0.05 vs. 24 h; c p < 0.05 vs. 48 h.

Therapeutic plasma exchange versus double plasma molecular absorption system in hepatitis B virus-infected acute-on-chronic liver failure treated by entercavir: A prospective study. Yue-Meng Wan et al. Journal of Clinical Apheresis

**Design** : A single center prospective controlled pilot study. Study

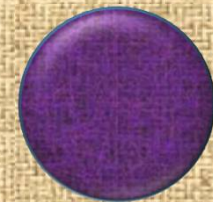
**Subject**: Acute-on-chronic liver failure (ACLF)

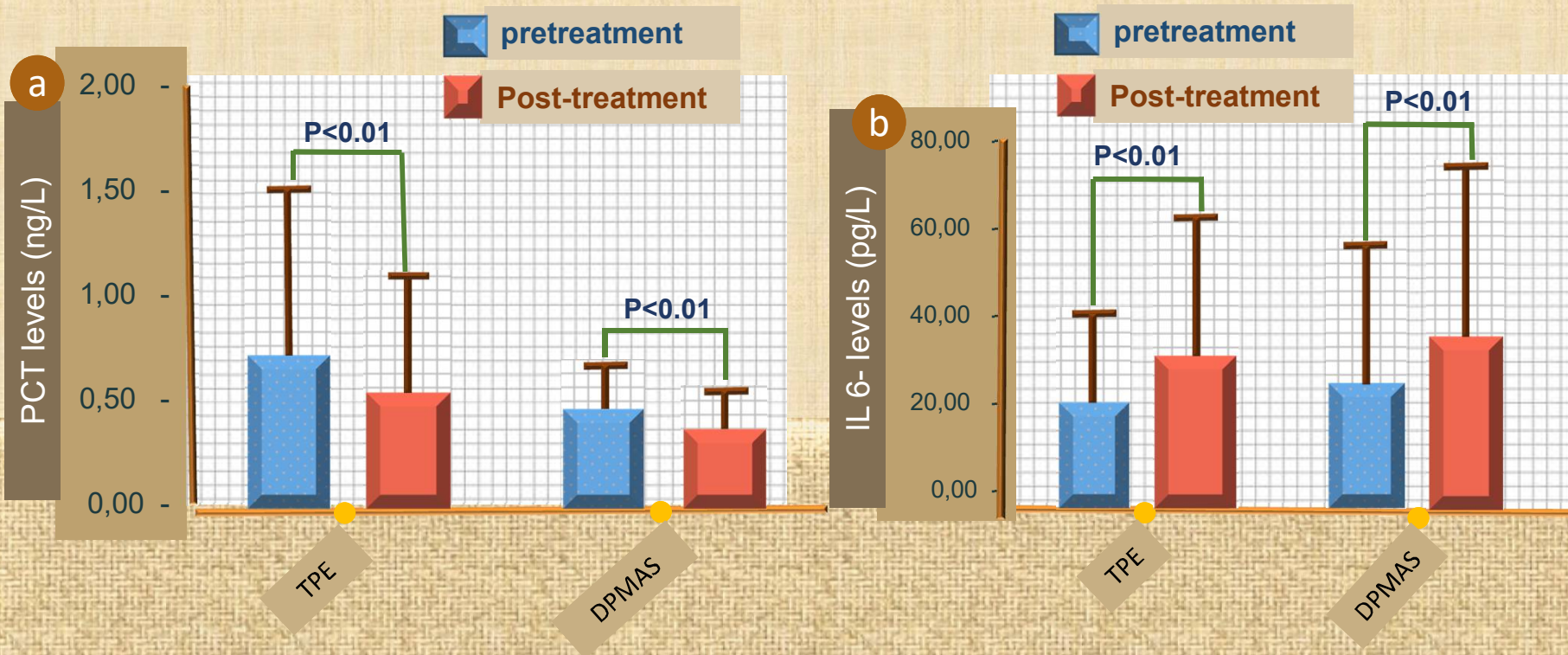
Regimens:

**TPE** Group (N=33): standard medical therapy + **TPE (2-3 times/week, 2-3h/session) plasma exchange rate: 20-30ml/min.**

**DPMAS** Group (N=27): standard medical therapy + **DPMAS (2-3 times/week, 2-3h/session) blood flow rate: 100-150ml/min, plasma flow rate: 25-50ml/min.**

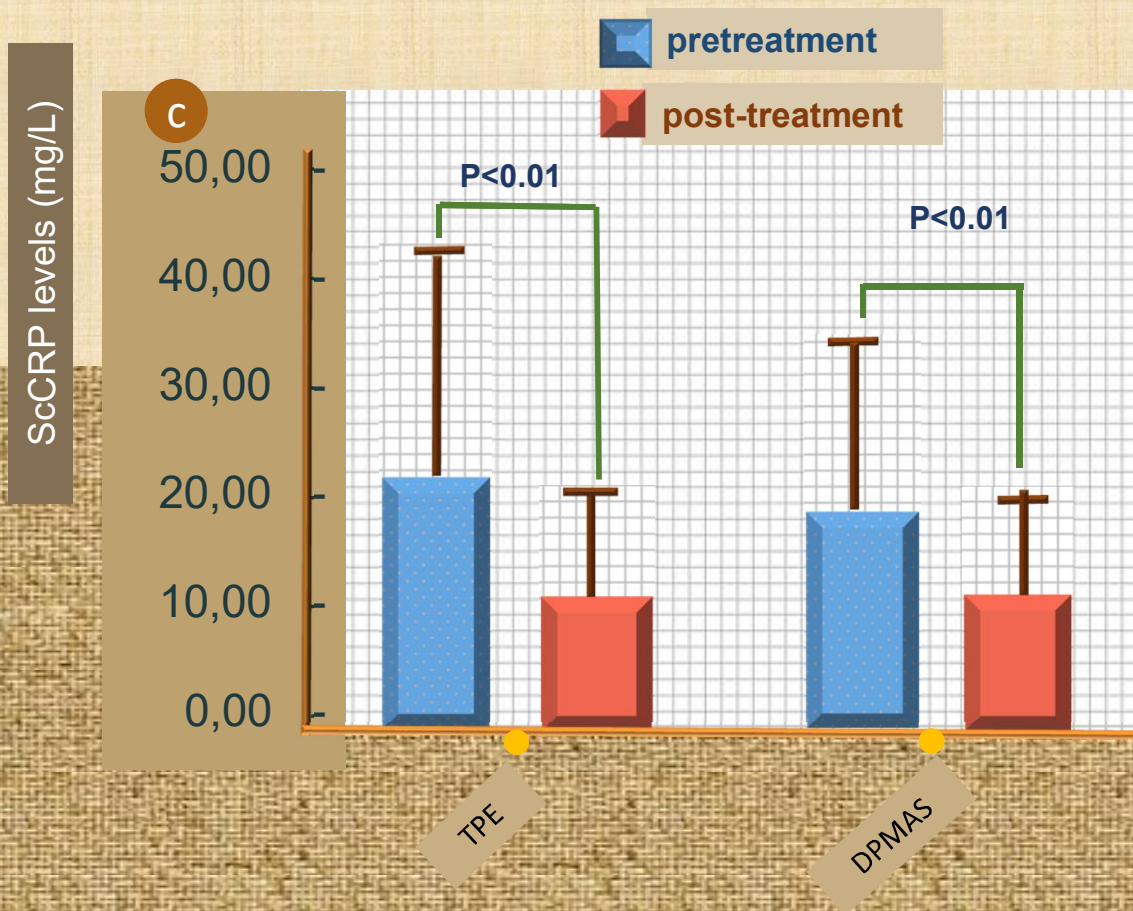
**Purpose**: compare the efficacy of TPE and DPMAS on acute on-chronic liver failure (ACLF) caused by hepatitis B virus (HBV-ACLF).





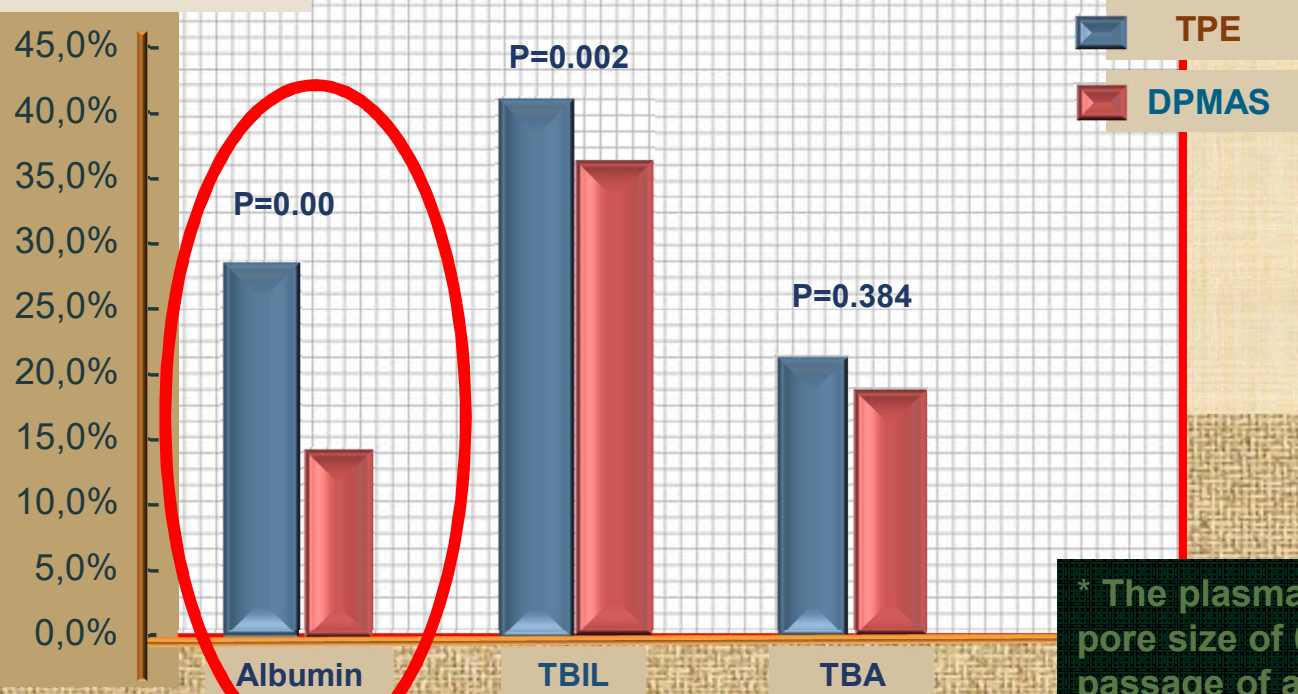
(A, B, C) Serum PCT, IL-6, hsCRP before and after TPE and DPMAS

IL-6 is usually considered a pro-inflammatory cytokine, but it is also a pleiotropic cytokine that induces many biological activities.

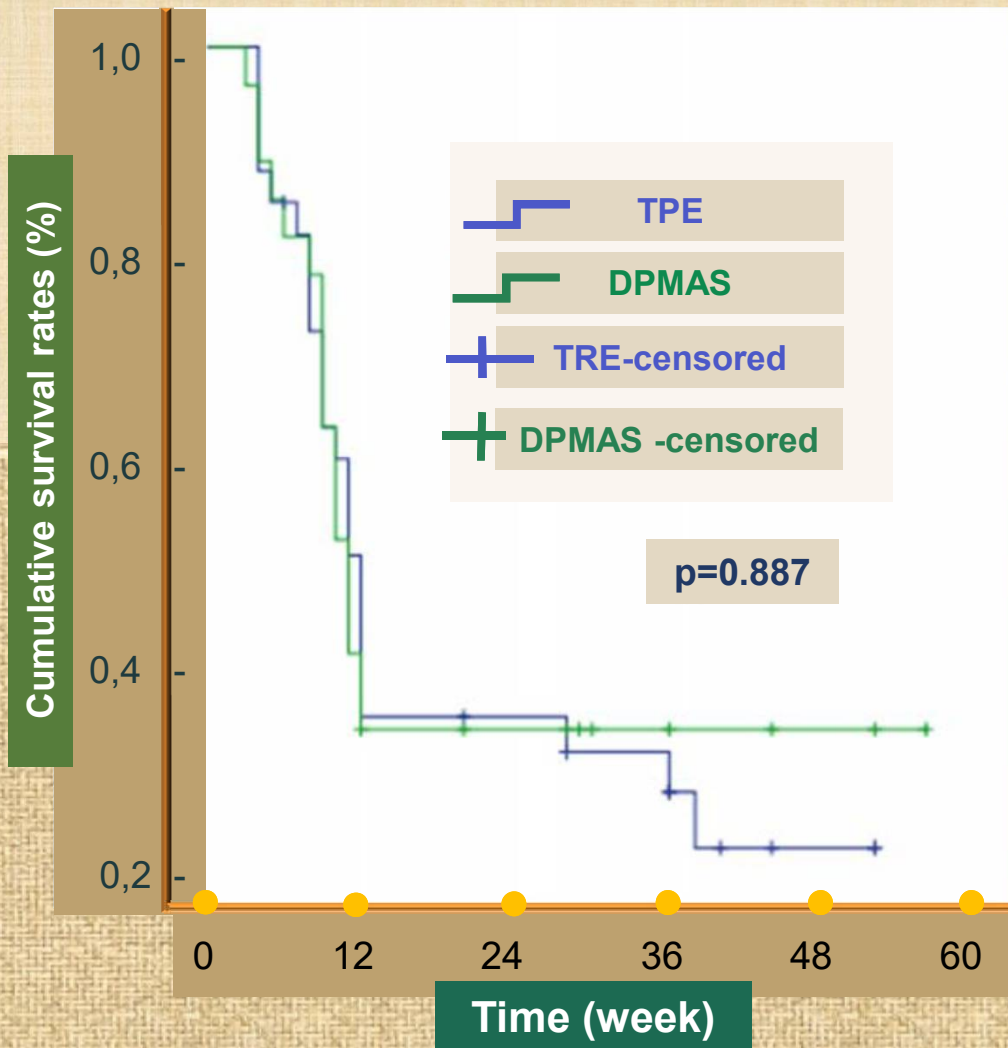


(A, B, C) SerumPCT, IL-6, hsCRP before and after TPE and DPMAS

## Removal Rate



\* The plasma separator with a pore size of 0.2-0.6 mm allows passage of all plasma constituents, including albumin, which will be either discarded in TPE or perfused over absorptive materials. The albumin then will be recycled into the patients in DPMAS.



Cumulative survival rates after treatment by TPE and DPMAS (P5.887, log-rank test)

High dynamic blood circulation is common in patients with liver failure, the circulation time is shortened, the ability to reserve the heart is diminished, **hypotension** is easy to occur.

The plasma adsorption column and extracorporeal circulation pipeline have a certain volume, After establishing the extracorporeal circulation, more blood is left in vitro, **the effective circulating blood volume is reduced.**



	<b>Drugs</b>	<b>HD</b>	<b>HP (NMR)</b>
<b>Sedative-hypnotics</b>	<b>Barbiturates</b> <b>Glutethimide</b> <b>Methaqualone</b> <b>diazepam</b>	<b>+~++</b> <b>-~+</b> <b>+/-~+++</b>	<b>+++</b> <b>++~+++</b> <b>++++</b> <b>++++</b>
<b>anodyne</b>	<b>salicylate</b>	<b>+++</b>	<b>++~++++</b>
<b>Cardiovascular drugs</b>	<b>digitoxin</b> <b>quinidine</b> <b>procainamide</b>	<b>+</b> <b>+/-~+</b> <b>+~+++</b>	<b>++~+++</b> <b>++</b> <b>++++</b>
<b>Organophosphorous pesticide</b>	<b>Dimethoate</b> <b>DDVP</b>	<b>++</b>	<b>+++</b> <b>++++</b>
<b>Other drugs</b>	<b>paraquat</b>		<b>+++</b>





	<b>Resin</b>	<b>Activated carbon</b>
<b>adsorbent</b>	Neutral microporous adsorption resin	Medical activated carbon
<b>Pore size</b>	Averaged 13-15mm	Not averaged
<b>Absorption spectrum</b>	Relative specific adsorption	Not selective
<b>adsorbate</b>	Middle and big molecular and high fat soluble substances	Middle and small molecular substances
<b>Application scope</b>	Detoxification, uremia, hepatology, critical illness and so on	detoxification
<b>safety</b>	<b>Produced by polymer material</b> <b>Uniform pore size, smooth surface</b> <b>Good blood compatibility</b>	Natural materials temperature firing Uneven surface  The damage of platelet