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THE STATE UNIVERSITY OF NEW JERSEY

Role of Plasmapheresis in Acute and Acute-On-Chronic Liver Failure

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Disclosures

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- Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are two distinct classifications of severe hepatic dysfunction associated with secondary multi-organ failures (MOFs), both of which effect significant morbidity and mortality.
- The exact mechanisms by which MOFs are mediated have not been definitively established but are thought to be driven by
  - excessive systemic inflammation
  - dysregulated immune activation
    - triggered by both microbial and non-microbial factors, and less so by the primary insult to the liver

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- Besides treating the underlying etiologies and supportive therapy, OLTx is the only definitive therapy for those with advanced disease.

» BUT

- Grafts are not readily available
- The availability of donor organ limits the availability of the patients that can be saved.
- In addition OLTx is not available worldwide

The pathogenesis of MOFs in ALF in a nutshell!

- Release of damage- associated molecular patterns (DAMPs)
  - from injured hepatic cells and
  - microbial pathogen-associated molecular patterns (PAMPs)
  - in the presence of superimposed **infection** or bacterial **translocation**
- The innate immune cells activated by PAMPs and DAMPs produce **proinflammatory cytokines**
  - [interleukin (IL)-6, IL-1ß, IL-8, tumor necrosis factor-alpha (TNF-α)]
    - that mediate **systemic inflammation** and further hepatocyte injury
    - In support of this hypothesis, levels of TNF-α and IL-6 have been shown to be significantly higher in patients with acute liver failure when compared to patients with acute liver injury.

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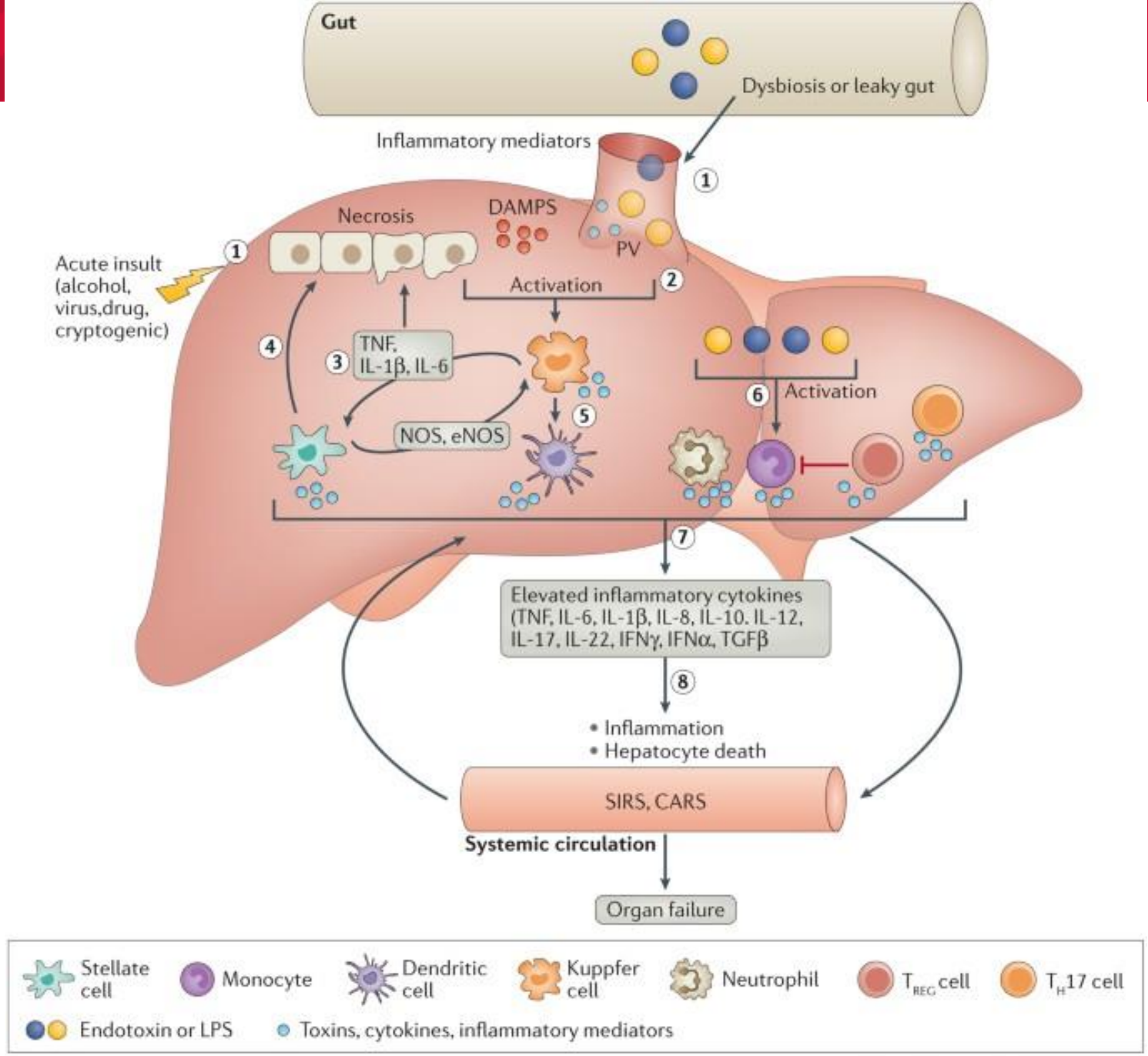
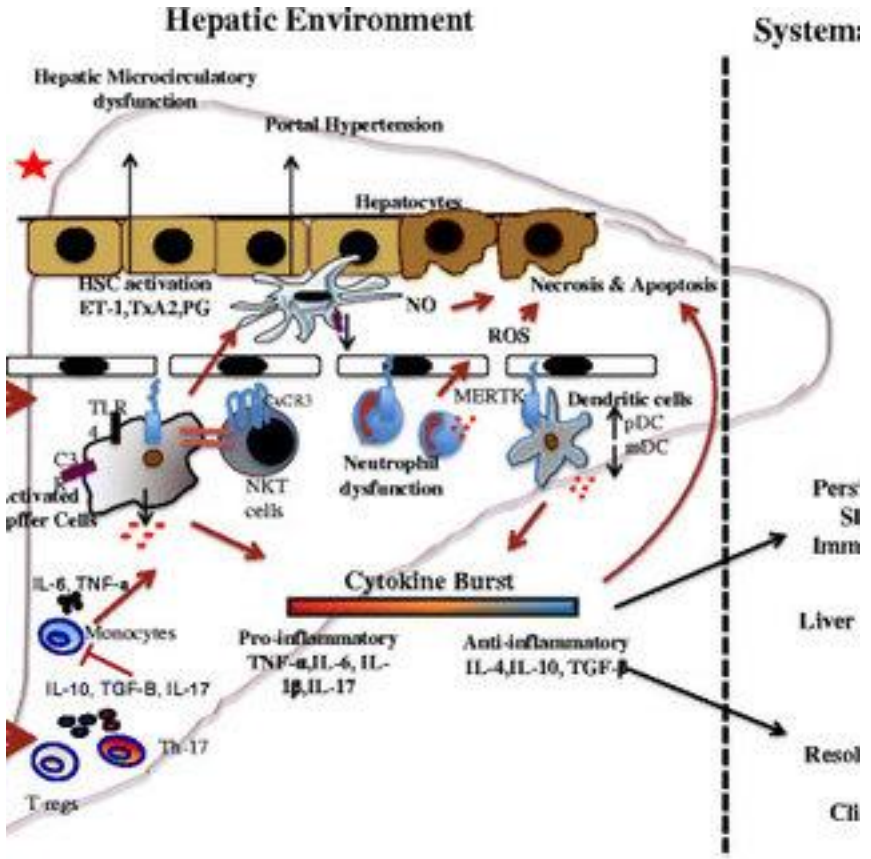
- The hallmark of the ACLF clinical syndrome is excessive systemic inflammation and bacterial translocation mediated by PAMPs and DAMPs
- ACLF patients have been shown to manifest elevated levels of pro- and anti-inflammatory cytokines, as well as white blood cell count and C reactive protein.
- Moreover, there is a proven correlation between cytokine levels and number of organ failures in ACLF


Gut
Dysbiosis or leaky gut
Inflammatory mediators
1
Necrosis
DAMPS
PV
Acute insult
(alcohol,
virus,drug,
cryptogenic)
1
Activation
2
4
3
TNF,
IL-1β, IL-6
6
Activation
5
NOS, eNOS
7
Elevated inflammatory cytokines
(TNF, IL-6, IL-1β, IL-8, IL-10, IL-12,
IL-17, IL-22, IFNγ, IFNα, TGFβ
8
• Inflammation
• Hepatocyte death
SIRS, CARS
Systemic circulation
Organ failure
Stellate cell
Monocyte
Dendritic cell
Kuppfer cell
Neutrophil
T_REG cell
T_H17 cell
Endotoxin or LPS
Toxins, cytokines, inflammatory mediators


Hepatic Environment
Hepatic Microcirculatory dysfunction
Portal Hypertension
Hepatocytes
HSC activation
ET-1,TxA2,PG
NO
Necrosis & Apoptosis
ROS
MERTK
Dendritic cells
pDC
mDC
Neutrophil dysfunction
NKT cells
Cytokine Burst
IL-6, TNF-a
Monocytes
IL-10, TGF-B, IL-17
Pro-inflammatory TNF-a,IL-6, IL-1β,IL-17
Anti-inflammatory IL-4,IL-10, TGF-β
Th-17
T regs
Liver

In other words

- Expanded treatment options are needed to:
  - Bridge critically ill patients to LT
  - or to preserve liver function when LT is either contra-indicated or unavailable

What is Plasmapheresis?

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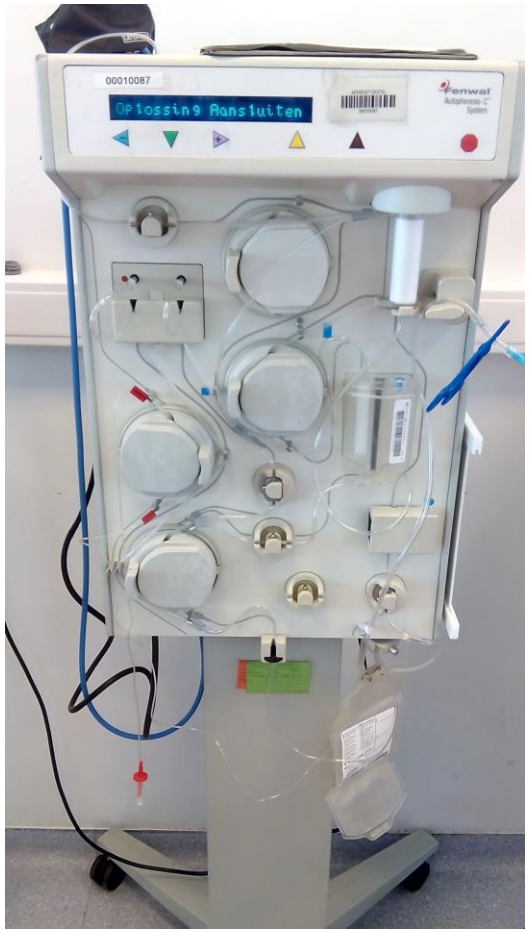
- Plasmapheresis is a process in which the plasma is separated from the blood either by centrifugation or membrane filtration.
- Plasmapheresis was originally described by doctors Vadim A. Yurevick and Nicolay Rosenberg of Imperial Medical and Surgical Academy of Saint Petersburg, Russia, in 1913.
- Moreover, Michael Rubinstein was the first to use plasmapheresis to treat an immune-related disorder when he saved the life of an adolescent boy with thrombotic thrombocytopenic purpura (TTP) at Cedar of Lebanon Hospital in Los Angeles, USA, in 1959.
- The modern plasmapheresis procedure originated at USA National Cancer Institute between 1963 and 1968.



What is Plasma Exchange?

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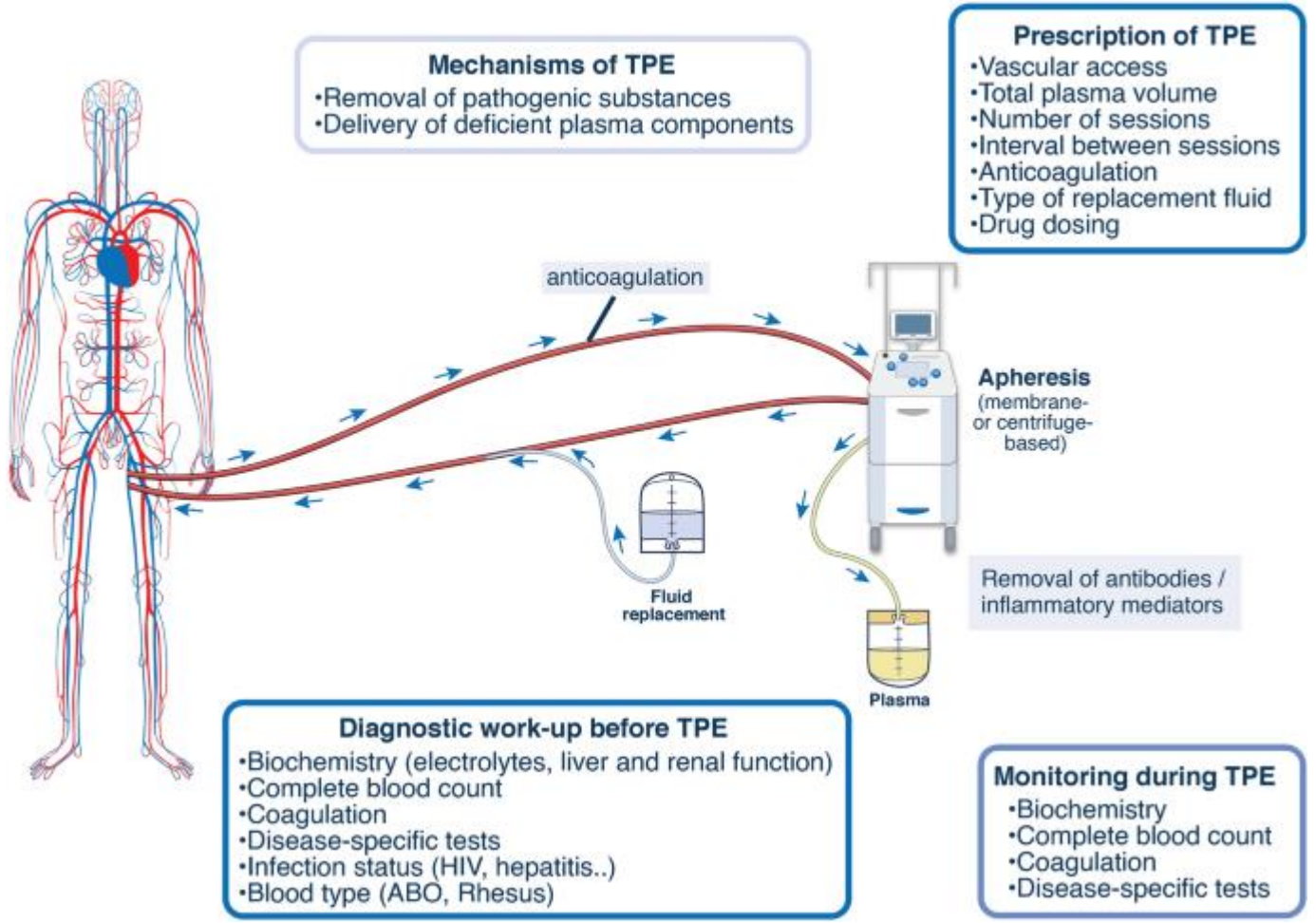
- Plasma exchange is the technique of discarding the plasma totally and substituting it with replacement fluid.
- It involves the removal of the liquid portion of blood to remove harmful substances and replace it with a replacement solution. Then the removed plasma is discarded, and the patient receives the replacement donor plasma, albumin, or a combination of albumin and saline (normally 70% albumin and 30% saline).
- Therapeutic apheresis or plasma exchange is performed in such a way as to remove toxic elements from the bloodstream.



Bottomline….

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Plasmapheresis

is an apheresis procedure that separates and removes the plasma component from a patient.

Plasma exchange is when plasmapheresis is followed by replacement with fresh frozen plasma infusion

Therapeutic plasma exchange

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- The practice of exchange transfusion in patients with cirrhosis dates back to the **1960s** when **exchange blood transfusion** was employed for the treatment of hepatic coma .
- Therapies were later modified to TPE as apheresis equipment became more widely available and as a means to reduce the risks associated with whole blood transfusion.
- Historically, TPE in liver failure has been primarily described in case series and cohort studies.
- The first randomized control trial (RCT) describing the utility of TPE in ALF patients was reported in 2016 by Larsen *et al*.

PLASMAPHERESIS IN HEPATIC COMA

SIR,—Plasmapheresis has been successful in treating coma in patients with cirrhosis [1] and heroin intoxication.[2] We briefly report here 4 cases of hepatic coma due to viral hepatitis treated by plasmapheresis.

The 4 patients were women, 54, 21, 17, and 22 years old. Virus-A infection seems evident for cases 1, 3, and 4, and virus B for case 2. Clinical, biochemical, and electroencephalographic signs of impending coma were found on the fourth day after onset of jaundice in the 1st case, on the seventh day in the 2nd, the eighth day in the 3rd, and the third day in the 4th. Corticosteroids, high doses in 3 cases and small doses in 1, were given at the same time as plasmapheresis. Plasma exchange was started from the first signs of encephalopathy in cases 2, 3, and 4, and from the third day of coma in the 1st case, and was repeatedly applied in every case. The total plasma-exchange was 4·75 litres over three days in the 1st case, 6 litres over two days in the 2nd, 8 litres over three days in the 3rd, and 17 litres over six days in the 4th.

The 1st patient recovered consciousness at the end of the first 2·25 litre exchange. At the end of the next day she was again in deep coma and, despite a further exchange of 2·5 litres, she did not recover and died fourteen hours later with bulbar syndrome and with hæmorraghic features.

The 2nd patient recovered consciousness shortly after a first exchange of 3 litres of plasma. The signs of encephalopathy rapidly subsided and the clinical state significantly improved. After a second exchange next day, she was able to speak and write correctly and no signs of alteration of consciousness persisted. Later on, the biochemical disturbances (including transaminases and bilirubin) improved too. Three days after the episode of coma she felt very well, and the only

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L. DEMEULENAERE
F. BARBIER
P. VERMEIRE.

Article | 1 January 1968

Treatment of Hepatic Coma in Cirrhosis by Plasmapheresis and Plasma Infusion (Plasma Exchange)

STANLEY SABIN, M.D., JOHN A. MERRITT, M.D.

Author, Article, and Disclosure Information

https://doi.org/10.7326/0003-4819-68-1-1

Abstract

Abstract

Three patients with proved active fatty nutritional cirrhosis were treated with plasma exchange after at least 72 hr of refractory hepatic coma. In each case coma cleared after this treatment. The role of plasma exchange in hepatic coma is discussed.

- TPE in liver failure requires the extracorporeal removal of large compounds from the blood, including:
  - albumin-bound and
  - water-soluble toxins and
  - replacement with plasma and/or albumin.

Toxins need to be removed

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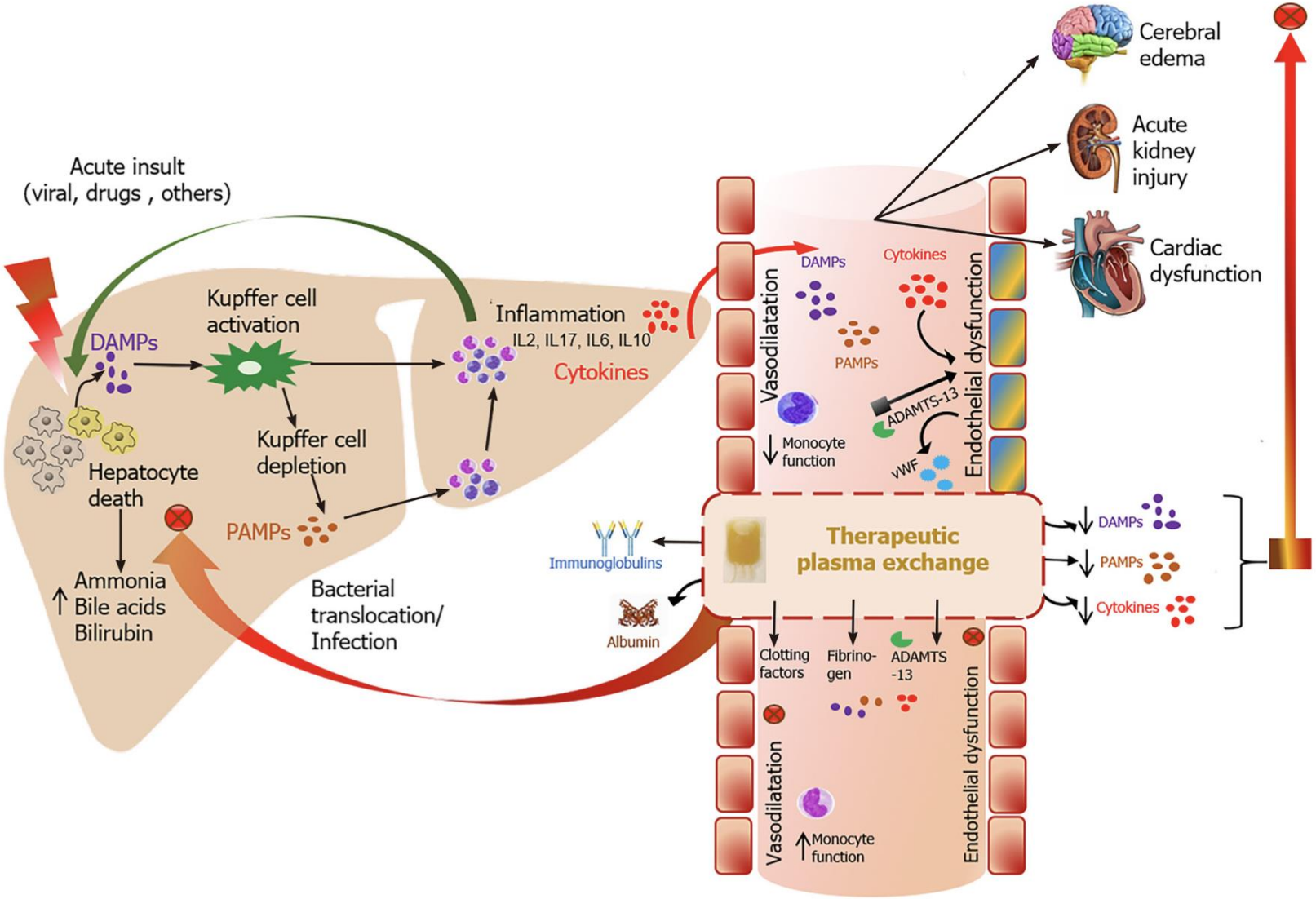
- Inflammatory cytokines,
- endotoxins,
- bilirubin,
- bile acids,
- ammonia,
- aromatic amino acids


Acute insult
(viral, drugs , others)
DAMPs
Kupffer cell activation
Inflammation
IL2, IL17, IL6, IL10
Cytokines
Kupffer cell depletion
Hepatocyte death
PAMPs
Ammonia
Bile acids
Bilirubin
Bacterial translocation/ Infection
Cerebral edema
Acute kidney injury
Cardiac dysfunction
DAMPs
Cytokines
PAMPs
Vasodilatation
Monocyte function
ADAMTS-13
vWF
Endothelial dysfunction
Immunoglobulins
Albumin
Therapeutic plasma exchange
DAMPs
PAMPs
Cytokines
Clotting factors
Fibrino-gen
ADAMTS -13
Vasodilatation
Monocyte function
Endothelial dysfunction

Research Article

EASL | JOURNAL OF HEPATOLOGY

High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial

Fin Stolze Larsen[1,*], Lars Ebbe Schmidt[1], Christine Bernsmeier[2], Allan Rasmussen[3], Helena Isoniemi[4], Vishal C. Patel[2], Evangelos Triantafyllou[2], William Bernal[2], Georg Auzinger[2], Debbie Shawcross[2], Martin Eefsen[1], Peter Nissen Bjerring[1], Jens Otto Clemmesen[1], Krister Hockerstedt[4], Hans-Jørgen Frederiksen[5], Bent Adel Hansen[1], Charalambos G. Antoniades[2,6,†], Julia Wendon[2,†]

[1]*Department of Hepatology, Rigshospitalet, Copenhagen, Denmark;* [2]*Institute of Liver Studies, King's College Hospital, London, United Kingdom;* [3]*Department of Surgery and Liver Transplantation C, Rigshospitalet, Copenhagen, Denmark;* [4]*Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Finland;* [5]*Department of Anaestesia AN-2041, Rigshospitalet, Copenhagen, Denmark;* [6]*Section of Hepatology, St. Mary's Hospital, Imperial College London, London, UK*

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- High-volume plasma exchange (HVP), defined as exchange of 8–12 or 15% of ideal body weight with fresh frozen plasma in case series improves systemic, cerebral and splanchnic parameters.
- Prospective, randomized, controlled, multicenter trial
- 182 patient randomly assigned s with ALF to receive either standard medical therapy (SMT; 90 patients) or SMT plus HVP for three days (92 patients).
- The primary endpoint was liver transplantation-free survival during hospital stay.
- Secondary endpoints included survival after liver transplantation with or without HVP with intention-to-treat analysis.
- A proof-of- principle study evaluating the effect of HVP on the immune cell function was also undertaken.

Table 1. Clinical characteristics of the two groups studied at the time of randomization.

	SMT (n = 90)	HVP (n = 92)	*p* value
Gender (females)	57 (63.3%)	66 (71.7%)	0.23
Age (years)	45 (36-56)	46 (33-56)	0.84
Weight (kg)	70 (61-81)	67 (60-75)	0.19
Height (cm)	170 (165-180)	169 (161-175)	0.24
Hyper/Acute/Subacute	69/13/8	65/22/5	0.16
Etiology*	58/5/17/6/2/2	50/6/22/11/0/3	0.39
HE grade (2/3/4)	6/26/58	7/28/55	0.49
Mechanical ventilated	66 (77.7%)	77 (86.5%)	0.13
Episodes with systolic BP <80 mmHg	23 (27.1%)	25 (28.1%)	0.88
Need for vasopressors	51 (60.7%)	45 (51.1%)	0.23
Oliguria	43 (51.2%)	52 (59.8%)	0.11
Oozing	14 (16.9%)	14 (16.1%)	0.89
Hyperthermia (>38.0 °C)	6 (7.2%)	13 (14.8%)	0.12
Suspected infection	26 (30.1%)	29 (33.0%)	0.78

SMT, standard medical therapy; HVP, plasma exchange; ICP, intracranial pressure, HE, hepatic encephalopathy. *Given as ALF induced by: paracetamol/acute viral hepatitis/unknown aetiology/toxic hepatitis/acute Budd-Chiari/various.

- All patients received at least one treatment session with HVP apart from one patient who was transplanted before HVP could be initiated.
- All the 182 enrolled patients were included in the ITT analysis.
- The mean number of HVP treatments per patient was 2.4 ± 0.8.
- The mean plasma volume exchanged during the first session was 9.3±1.3L, 9.2±1.2L for session 2 and 9.0±1.2L session 3.
- The mean administered dose was 0.33 ± 0.12 L/kg of actual body weight per treatment.

Comparison of HVP and SMT group

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- Mean length of hospital stay was 21.9 ± 28.3 days in the HVP group, compared to 41.8 ± 27.9 days in the SMT group (p = 0.98).
- Forty-six (50%) of the patients in the HVP group and 44 (49%) in the control group were listed for liver transplantation.
- 24 (26.1%) patients in the HVP group underwent transplantation as compared to 32 (35.6%) patients in the control group (p = 0.17).
- The mean time to transplantation following listing was 4.6 ± 0.6 days in the HVP treated group and 3.7 ± 1.5 in the SMT group (p = 0.75).

- Survival to hospital discharge was 58.7% for patients treated with HVP vs. 47.8% for the control group (HR for high-volume HVP vs. SMT with stratification for liver transplantation: 0.56; 95% CI 0.36 to 0.86; p = 0.0083) at hospital discharge

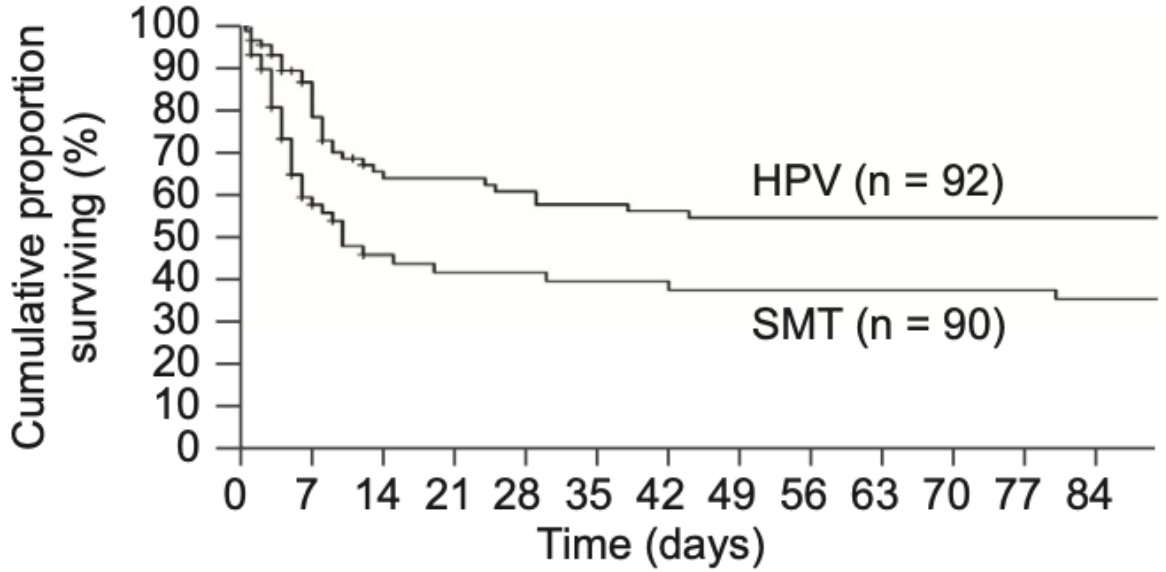


Fig. 1. Main results of the intention-to-treat analysis survival data in the standard medical treated group (SMT) compared to the high-volume plasma exchange (HVP) treated group (LogRank: $p = 0.0058$).

- In patients who were transplanted, HVP prior to transplantation did not improve survival compared with patients who received SMT alone

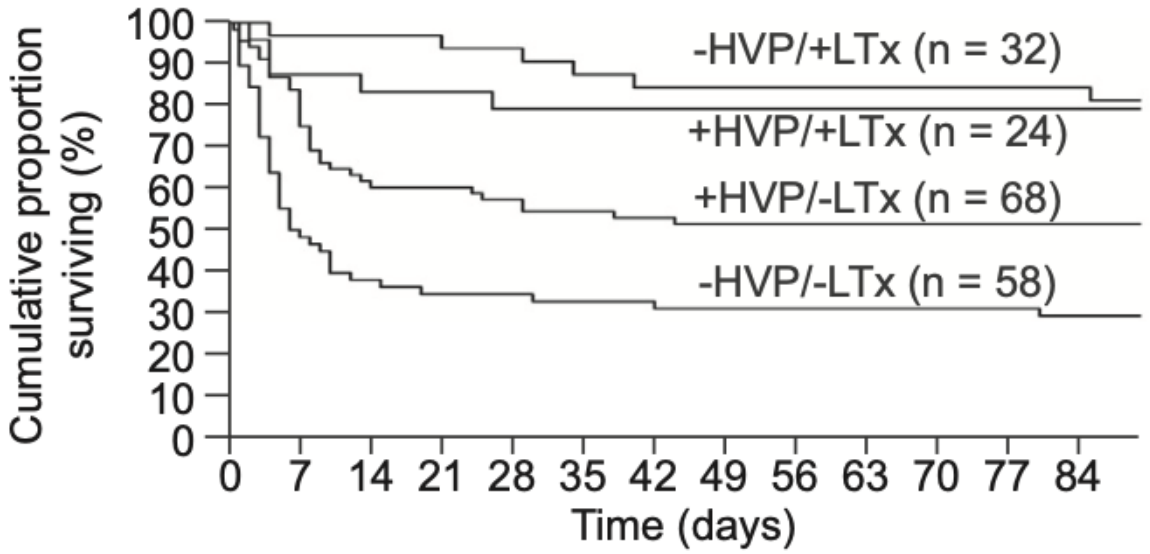
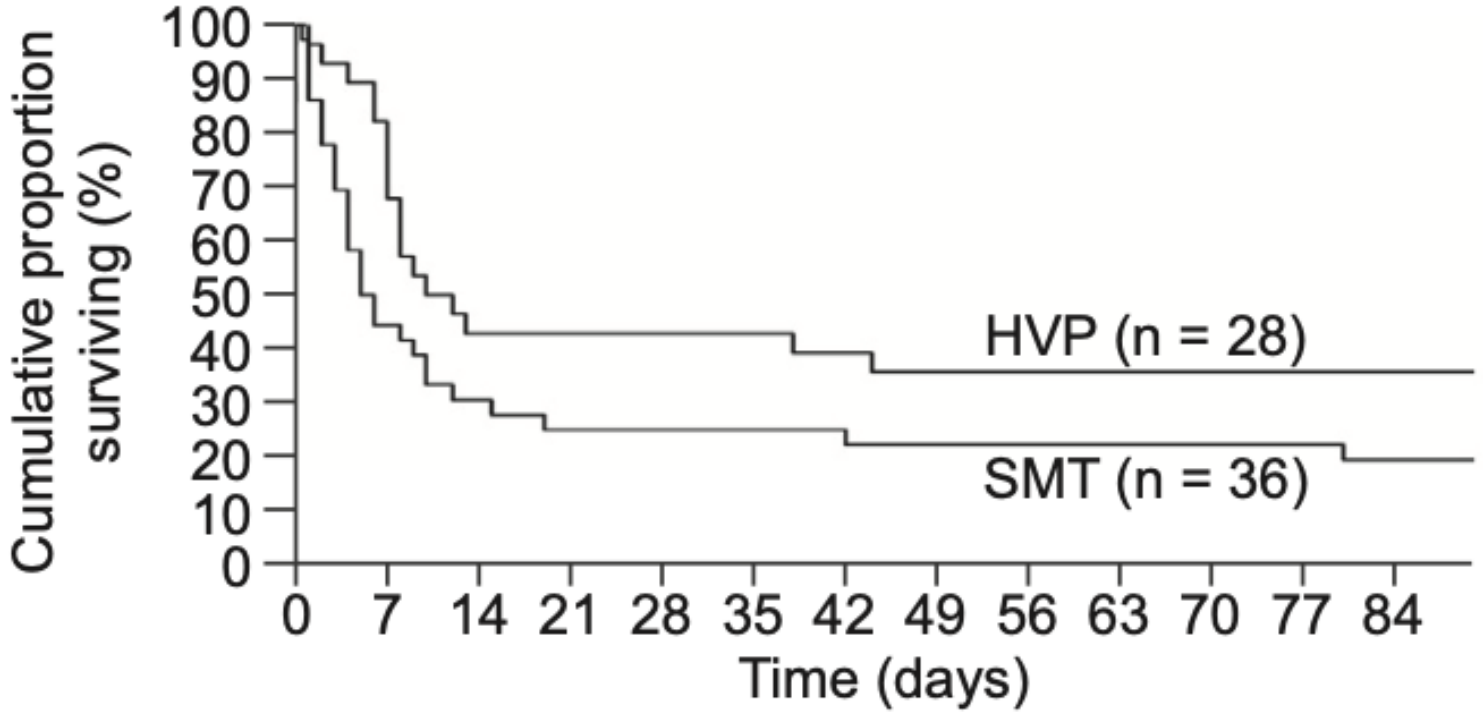


Fig. 2. Survival in the groups, in the two groups receiving SMT (standard medical treated group) with and without emergency transplantation (–HVP +LTx *vs.* +HVP–LTx) and the two group receiving SMT with and without emergency transplantation (–HVP–LTx *vs.* +HVP–LTx) (LogRank: $p = 0.0058$) and Cox proportional hazard: LTx: $p < 0.0001$; HVP: $p = 0.0076$).

- The survival of those patients who fulfilled poor prognostic criteria but were not listed for transplantation due to contraindications (such as severe psychiatric disease or medical comorbidity) was significantly higher in those who received SMT plus HVP (n = 28) as compared to those in receipt of SMT alone (n = 36)



- There was a non-significant trend in those listed for transplantation but not offered a graft (due to development of contraindications or an improved clinical condition such that de-listing occurred) to have improved outcome in the group of patients treated with HVP (n = 22) compared to SMT (n = 12) (Cox: p = 0.13).

Clinical variables

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- INR, bilirubin, ALT and arterial ammonia concentration, but not lactate, all decreased significantly during the first 7 days in the HVP group compared to the SMT group.
- There were significantly fewer patients in the HVP group who required renal replacement therapy from day 1–7 compared to the control group (47% vs. 68%), OR 0.42 (CI 0.23–076: p <0.0045); despite similar creatinine at enrolment. Plasma creatinine was unchanged from day 0 to day 7 in the HVP group (192 ± 153 to 150 ± 48 mmol/L) but increased from 226 ± 181 to 286 ± 230 lmol/L in the SMT group (p <0.0001).
- Mean arterial pressure increased significantly in the HVP group compared to the control group alongside a significant decrease in vasopressor requirement .
- Other physiological parameters were unchanged.
- ICP was measured in 16 patients in the HVP group and 16 in the control group during the first 7 days of the study; there were no differences in measured ICP or sustained increases in ICP between the two groups in this study period

SIRS and SOFA scores

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- SIRS score decreased in the HVP group from day 2 when compared to baseline and in comparison to the SMT group .
- The SOFA and CLIF-SOFA also decreased significantly from baseline in the HVP group and in comparison with the SMT group.
- SIRS, SOFA and CLIF-SOFA scores did not change significantly over time in the SMT group

		SMT (n = 90)		HVP (n = 92)		
	Day	Median	IQR	Median	IQR	*p* value
SOFA-score	0	14	[11-18]	13	[11-18]	0.59
	1	15*	[13-19]	12#	[10-16]	<0.01
	2	16#	[14-19]	13	[10-16]	<0.001
	3	16#	[14-19]	13	[11-16]	<0.0001
	7	17	[14-19]	13	[11-17]	0.05
CLIF-score	0	17	[14-20]	16	[14-19]	0.67
	1	18#	[15-20]	13**	[12-17]	<0.0001
	2	18#	[15-20]	13**	[12-16]	<0.0001
	3	18	[15-21]	13*	[12-16]	<0.0001
	7	18	[15-21]	13#	[12-18]	0.01
SIRS-score	0	2	[1-3]	2	[2-3]	0.13
	1	2	[1-2]	1**	[1-2]	0.24
	2	2	[1-3]	1**	[0-2]	<0.001
	3	2	[1-3]	1*	[1-2]	0.01
	7	2	[1-3]	1*	[1-2]	0.06

Adverse events

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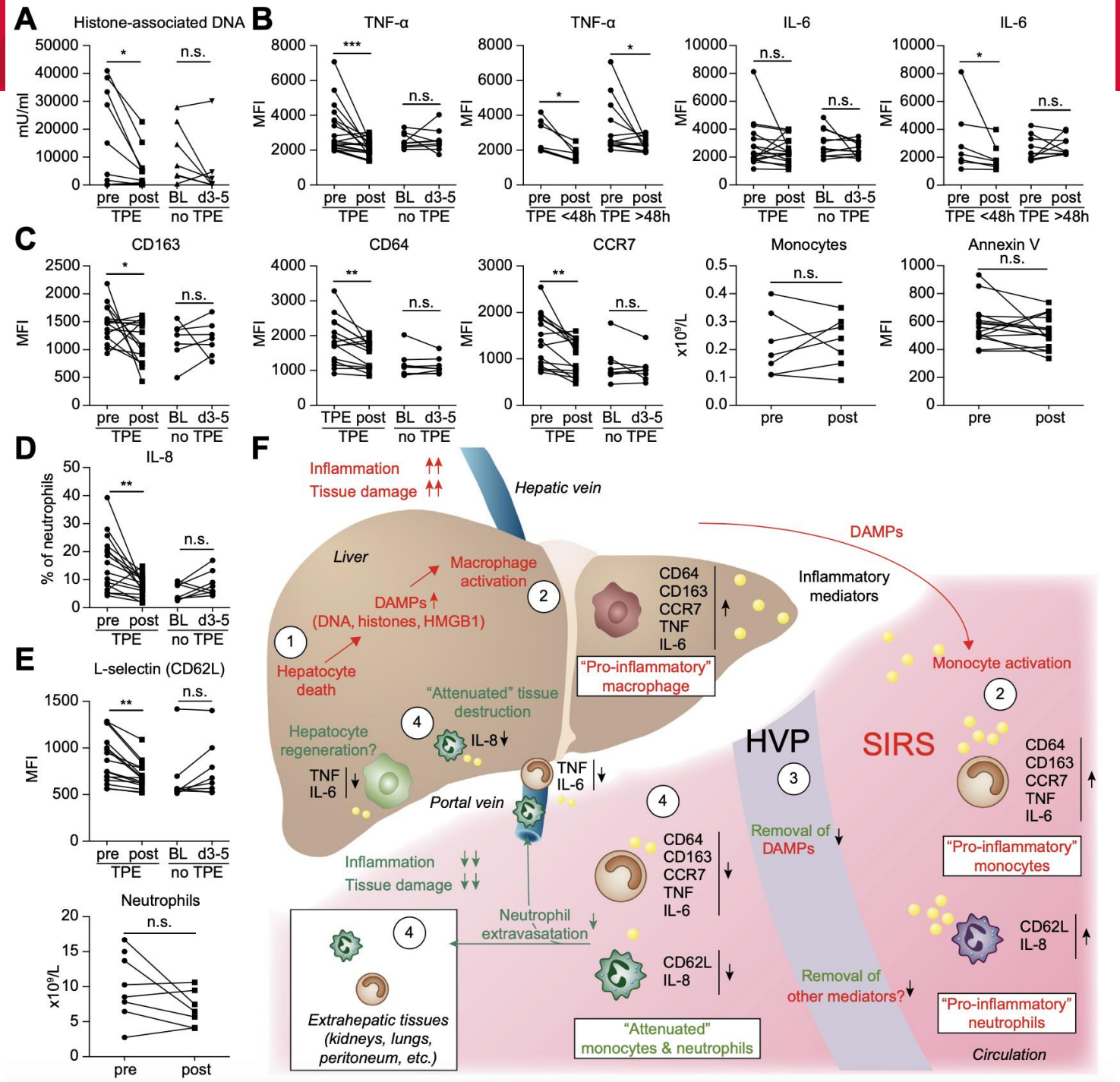
- Cardiac arrhythmia, pancreatitis, worsening gas exchange, ARDS, or transfusion-related acute lung injury, culture positive infection or hemorrhage were **not statistically significant different between the two groups**


A
Histone-associated DNA
mU/ml
pre post TPE
BL d3-5 no TPE
B
TNF-α
TNF-α
IL-6
IL-6
MFI
TPE <48h
TPE >48h
C
CD163
CD64
CCR7
Monocytes
Annexin V
x10⁹/L
D
IL-8
% of neutrophils
E
L-selectin (CD62L)
Neutrophils
F
Inflammation
Tissue damage
Hepatic vein
Liver
Macrophage activation
DAMPs
(DNA, histones, HMGB1)
Hepatocyte death
Hepatocyte regeneration?
"Attenuated" tissue destruction
IL-8
TNF
IL-6
Portal vein
CD64
CD163
CCR7
"Pro-inflammatory" macrophage
DAMPs
Inflammatory mediators
Monocyte activation
HVP
SIRS
Removal of DAMPs
"Pro-inflammatory" monocytes
CD62L
"Pro-inflammatory" neutrophils
Neutrophil extravasation
Extrahepatic tissues (kidneys, lungs, peritoneum, etc.)
"Attenuated" monocytes & neutrophils
Removal of other mediators?
Circulation

- This study shows, for the first time in patients with ALF an **improved transplant free survival** by using a rather primitive form of extracorporeal liver support utilizing HVP.
- This provides rationale for further comparative studies between HVP and other liver support systems to explore the immunological effects of these therapies.
- In addition, further work may be required to determine the optimal dosing and timing of HVP. However, there are limitations for undertaking further studies.
- As reported in the sub-analysis in this latter study we also show that the effect of HVP was primarily found in patients that were not transplant candidates/ not transplanted.

Editorial

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High volume plasma exchange in acute liver failure: Dampening the inflammatory cascade?

Constantine J. Karvellas[1,*], R. Todd Stravitz[2]

[1]*Divisions of Hepatology and Critical Care Medicine, University of Alberta, Edmonton, Alberta, Canada;* [2]*Section of Hepatology, Hume-Lee Transplant Center of Virginia Commonwealth University, Richmond, VA, USA*

Despite limitations, this study remains the only randomized, controlled study in patients with ALF to demonstrate a conclusive improvement in transplant-free survival as the primary end-point of the study, and consistent improvements in biochemical, immunological, and clinical features. Furthermore, a major strength of the approach described by Larsen *et al.*, is the wide-spread availability of administering HVP without specialized equipment or cultured hepatocytes. Based on the immunological findings of this study, future studies in extracorporeal liver support might target acetaminophen-ALF, given the rapid early up regulation of SIRS and the high potential for recovery if end-organ complications such as cerebral edema are mitigated.

Standard-Volume Plasma Exchange Improves Outcomes in Patients With Acute Liver Failure: A Randomized Controlled Trial

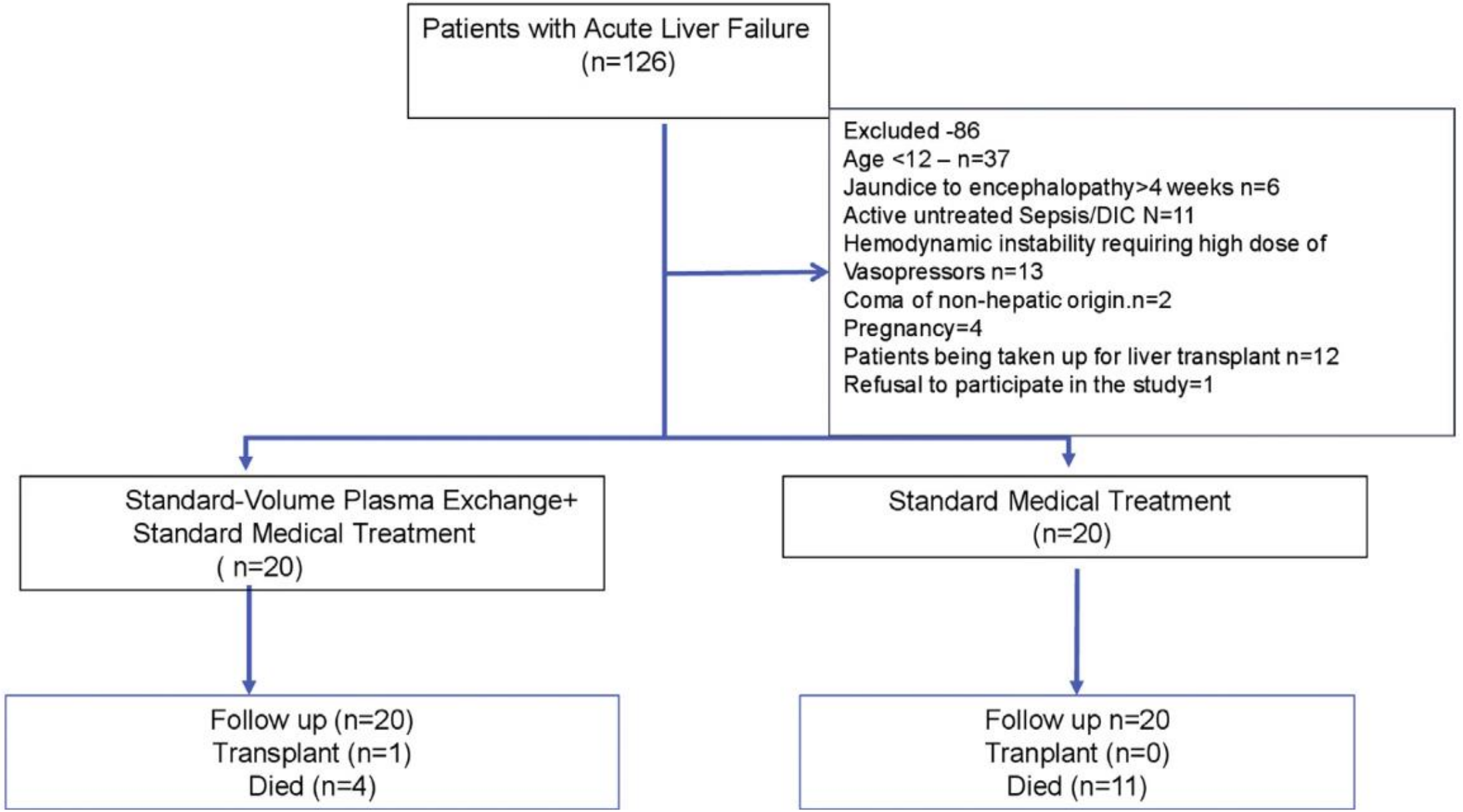
Rakhi Maiwall,[*] Meenu Bajpai,[‡] Akanksha Singh,[*] Tanvi Agarwal,[§] Guresh Kumar,[‖] Ankit Bharadwaj,[‖] Nidhi Nautiyal,[§] Harsh Tevethia,[*] Rakesh Kumar Jagdish,[*] Rajan Vijayaraghavan,[*] Ashok Choudhury,[*] Rajendra Prasad Mathur,[¶] Ashini Hidam,[§] Nirupama Trehan Pati,[§] Manoj Kumar Sharma,[*] Anupam Kumar,[§] and Shiv Kumar Sarin[*]

Clinical Gastroenterology and Hepatology 2022;20:e831–e854

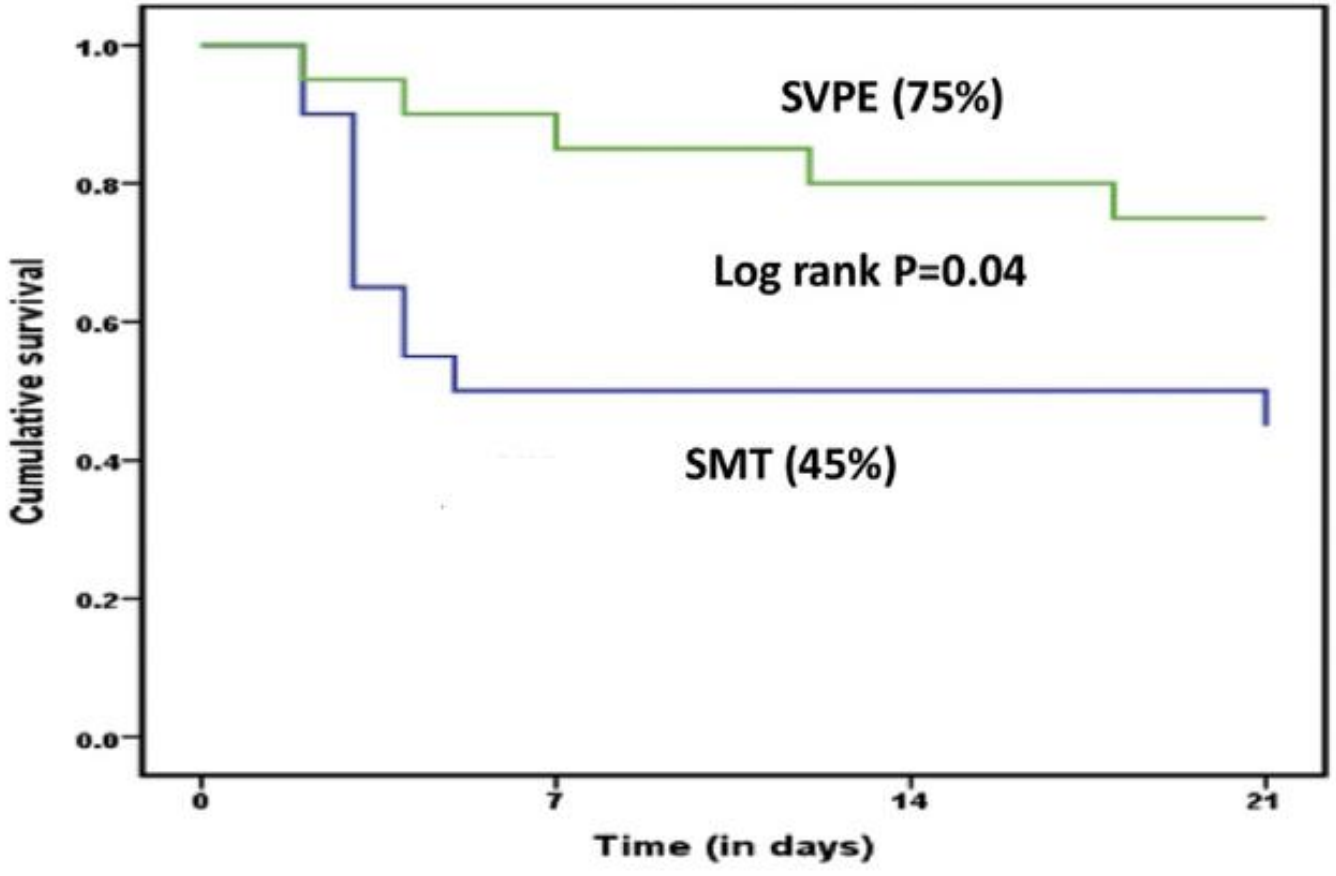
- Open-label randomized controlled trial,
- 40 consecutive patients of ALF were randomized 1:1 to either standard medical treatment (SMT) or SMT with standard-volume plasma-exchange (SVPE).
- SVPE was performed using centrifugal apheresis [target volume of 1.5 to 2.0 plasma volumes per session] until desired response was achieved.
- Cerebral edema was assessed by brain imaging.
- Results were analyzed in an intention-to-treat analysis.
- Primary outcome was 21-day transplant-free survival.
- The levels of cytokines, damage-associated molecular patterns (DAMPs) and endotoxins were analyzed at baseline and day 5.

- ALF patients aged 31.5 – 12.2 years, 60% male,
- 78% viral, 83% hyperacute,
- 70% with SIRS were included.
- At day 5, SVPE [mean sessions 2.15 – 1.42, median plasma volume replaced 5.049 L] compared to SMT alone, resulted in :
  - higher lactate clearance (p [.02),
  - amelioration of SIRS (84% vs. 26%; P [.02),
  - reduction in ammonia levels [(221.5 – 96.9) vs.(439 – 385.6) mg/ dl, P [.02)
  - SOFA scores [9.9(–3.3) vs. 14.6(–4.8); P [.001].
- There were no treatment related deaths.
- SVPE was associated with a higher 21-day transplant free-survival [75% vs. 45%; P [.04, HR 0.30, 95%CI 0.01-0.88]
- A significant decrease in levels of pro-inflammatory cytokines and an increase in anti-inflammatory cytokines alon with a decrease in endotoxin and DAMPs was seen with SVPE.

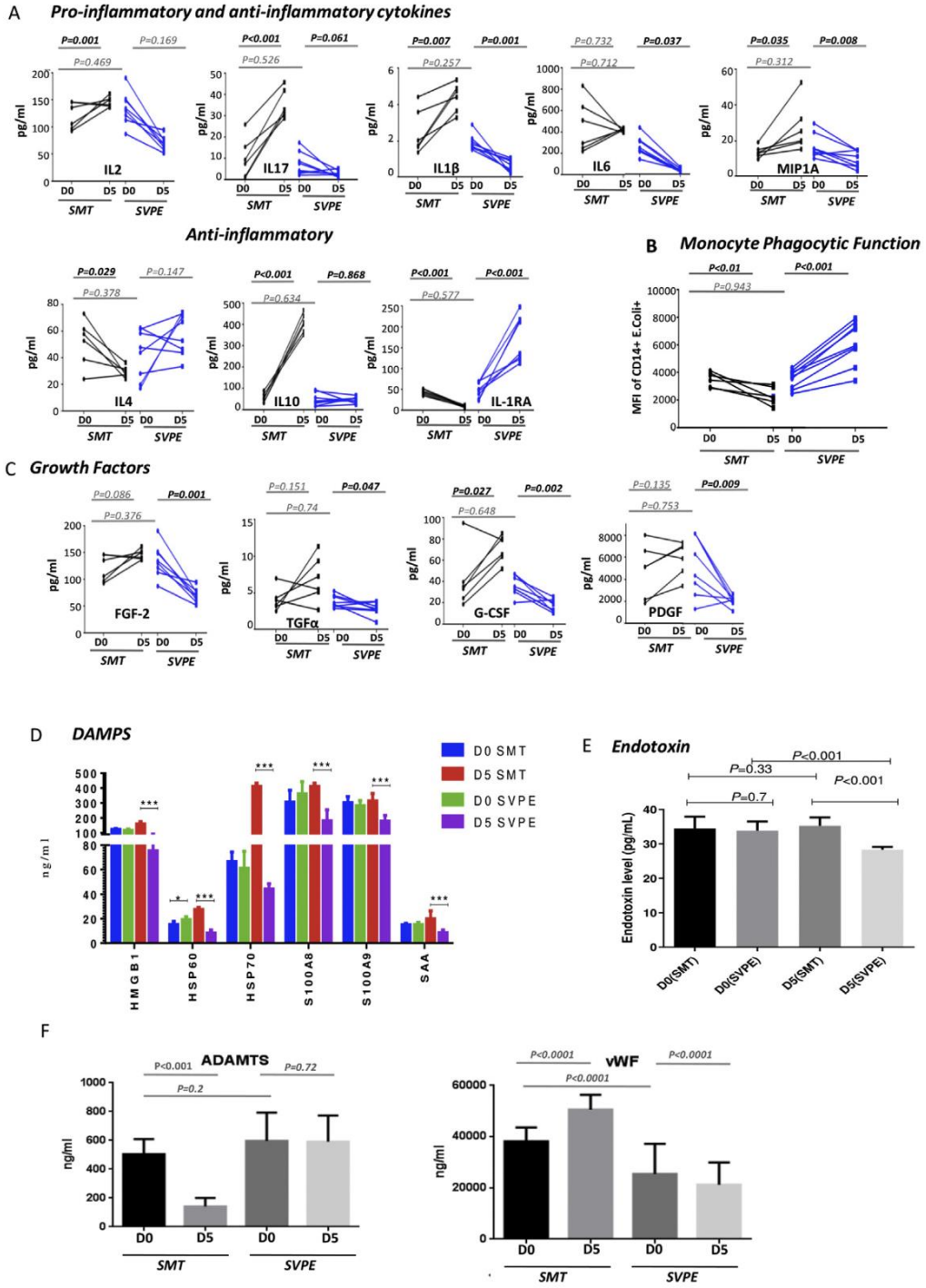
- In ALF patients with cerebral edema, SVPE is safe and effective and improves survival possibly by a reduction in cytokine storm and ammonia


Patients with Acute Liver Failure
(n=126)
Excluded -86
Age <12 – n=37
Jaundice to encephalopathy>4 weeks n=6
Active untreated Sepsis/DIC N=11
Hemodynamic instability requiring high dose of
Vasopressors n=13
Coma of non-hepatic origin.n=2
Pregnancy=4
Patients being taken up for liver transplant n=12
Refusal to participate in the study=1
Standard-Volume Plasma Exchange+
Standard Medical Treatment
(n=20)
Standard Medical Treatment
(n=20)
Follow up (n=20)
Transplant (n=1)
Died (n=4)
Follow up n=20
Tranplant (n=0)
Died (n=11)

21-day transplant-free survival between standard-volume plasma-exchange and standard medical treatment



Days		0	7	14	21
SMT	At risk	20	10	10	9
	Died	0	10	10	11
SVPE	At risk	20	17	16	15
	Died	0	3	4	5


A Pro-inflammatory and anti-inflammatory cytokines
IL2
IL17
IL1β
IL6
MIP1A
Anti-inflammatory
IL4
IL10
IL-1RA
B Monocyte Phagocytic Function
MFI of CD14+ E.Coli+
C Growth Factors
FGF-2
TGFα
G-CSF
PDGF
D DAMPS
D0 SMT
D5 SMT
D0 SVPE
D5 SVPE
ng/ml
HMGB1
HSP60
HSP70
S100A8
S100A9
SAA
E Endotoxin
Endotoxin level (pg/mL)
D0(SMT)
D0(SVPE)
D5(SMT)
D5(SVPE)
F
ADAMTS
vWF
ng/ml
D0
D5
SMT
SVPE

Plasma exchange in patients with acute and acute-on-chronic liver failure: A systematic review

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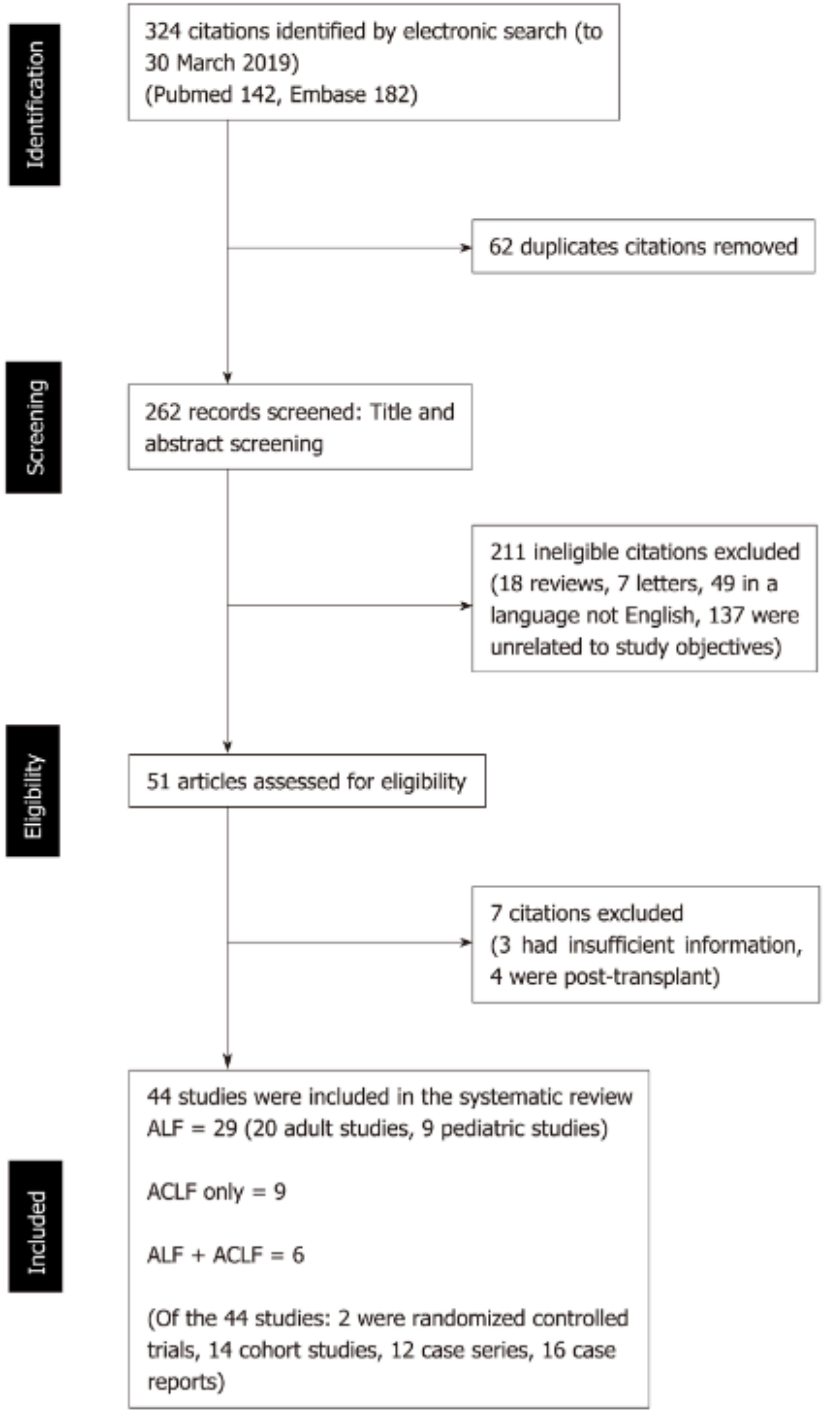
Table 1 Participants, interventions, comparisons, outcomes and study design criteria used to define the research question for this systematic review

Variable	Description
Population	Humans diagnosed with liver failure (ALF/ACLF)
Intervention	Plasma exchange with or without other alternative liver support systems; no restrictions on dose, duration and type of plasma exchange
Comparator	Randomized controlled trials/Cohort studies: Standard medical treatment Case series/case reports: Nil
Outcome	All-cause mortality, changes in liver biochemistry, and survival in non-transplanted patients
Study design	Randomized Controlled Trials, Cohort studies, Case series, Case reports
Research question	Does plasmapheresis have an effect on all-cause mortality, changes in liver biochemistry, and survival in non-transplanted patients with ALF/ACLF, compared to standard medical treatment?


Identification
324 citations identified by electronic search (to 30 March 2019)
(Pubmed 142, Embase 182)
62 duplicates citations removed
Screening
262 records screened: Title and abstract screening
211 ineligible citations excluded (18 reviews, 7 letters, 49 in a language not English, 137 were unrelated to study objectives)
Eligibility
51 articles assessed for eligibility
7 citations excluded
(3 had insufficient information, 4 were post-transplant)
Included
44 studies were included in the systematic review
ALF = 29 (20 adult studies, 9 pediatric studies)
ACLF only = 9
ALF + ACLF = 6
(Of the 44 studies: 2 were randomized controlled trials, 14 cohort studies, 12 case series, 16 case reports)

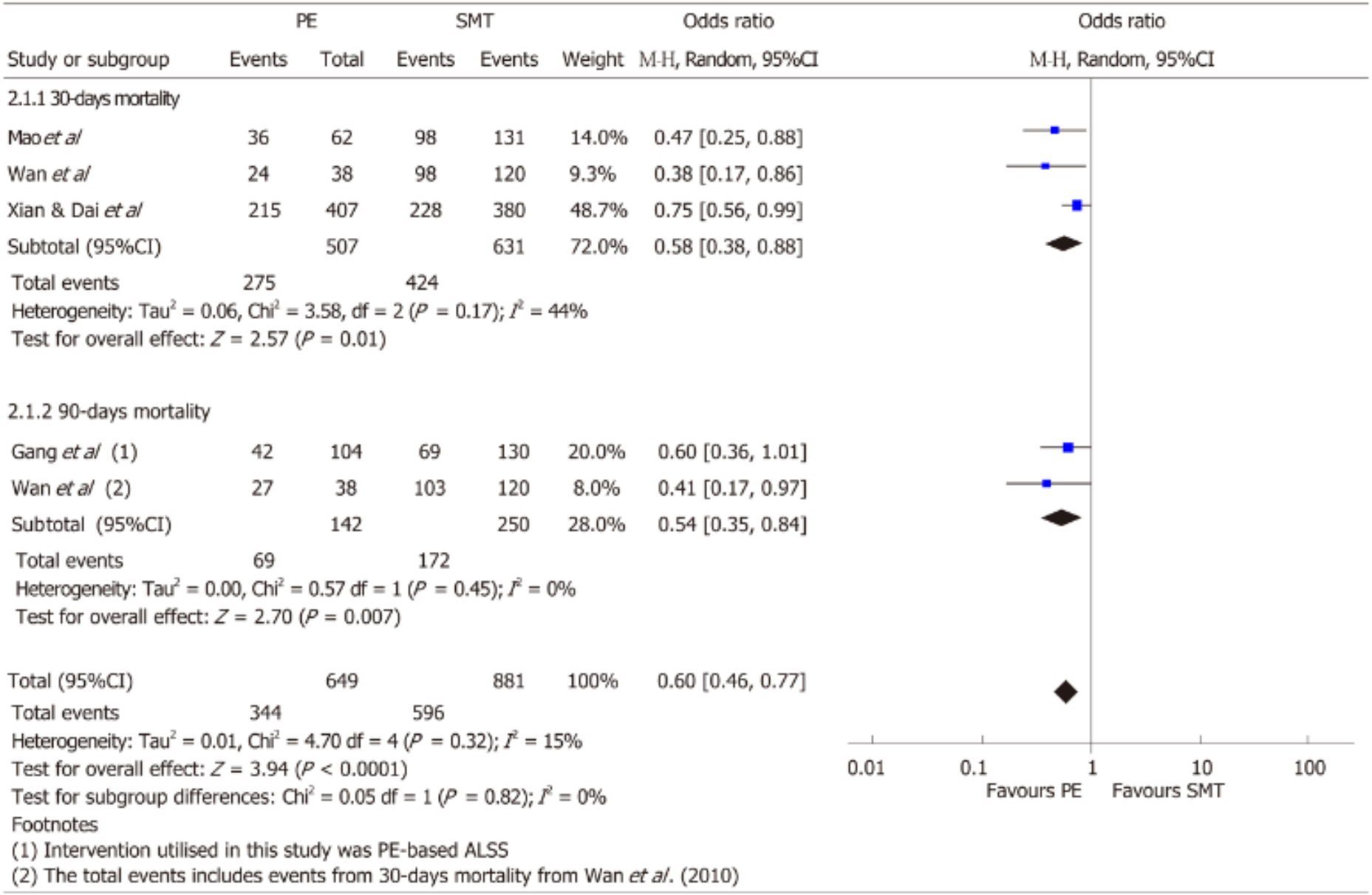


Figure 2 Forest plot for 30- and 90- d mortality in acute-on-chronic liver patients undergoing plasma exchange-based interventions or standard medical treatment. PE: Plasma exchange; SMT: Standard medical treatment.

Plasma exchange in ALF

RUTGERS

- A total of 35 studies included patients with ALF
- Of this, 24 were studies in adults and 11 in the pediatric population
  In the studies that included adult subjects, 4 also included patients with ACLF.
- Of the 24 studies in adults, there was 1 randomized controlled trial, 4 cohort studies, 9 case series and 10 case reports.
- Of the 11 studies with pediatric subjects, there was 1 cohort
  study, 4 case series and 6 case reports; and 2 of the 11 studies included patients with both ALF and ACLF.

Biochemical improvement

- All studies that assessed biochemical improvement pre- and post-plasma exchange, found an improvement in biochemical parameters such as coagulopathy, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase or ammonia.
- However, biochemical improvement did not directly relate to mortality outcome. Even in the patients who did not survive, there was also biochemical improvement post- plasma exchange

Standard vs high volume plasma exchange

RUTGERS

- There is heterogeneity in the amount of plasma exchange a patient gets in ALF amongst the various studies.
- Two studies used plasma exchange at least 15% ideal body weight removal at 1-2 L per hour while in Buckner et al case series, plasma exchange with 10 L of donor plasma regardless of weight was used.
- Similar to Buckner et al, Damsgaard et al in a case report used 8-9 L of plasma per session for plasma exchange for a patient with ALF from Wilson's disease, who survived without need for liver transplant.
- In contrast, in case series by Akdogan et al, only one plasma volume was being exchanged daily till patient expired or improved.
- Majority of studies used approximately 2-4 L of fresh frozen plasma at each plasma exchange

FFP vs albumin

RUTGERS

- Most studies used 100% **FFP** for plasma exchange with the exception of few where plasma substitutes or albumin were used in conjunction with plasma.
- In a case series by Liu et al seven liters of fluid was used for plasma exchange, but the first 4.7 L was composed of fresh frozen plasma, while the rest comprised of plasma consisting of 25% human albumin, 0.9% saline and Ringer's solution.
- There are by far no studies that use pure albumin as replacement fluid for plasma exchange in ALF.
- However, Collins et al has described in their case report, a patient with fulminant hepatitis from Wilson's disease who underwent single-pass albumin dialysis (SPAD) with improvements in bilirubin. Although of note, the same patient underwent plasma exchange after stopping SPAD in view of serum copper rebound

- Only few studies used a strict consecutive daily or every other day 3-d therapy plasma exchange regime as in the open-RCT by Larsen et al.
- Instead, most studies continued plasma exchange till patient dies, or improves clinically, or receives a liver transplant at a range of intervals from every other day to intermittent (as and when necessary).
- Buckner et al reported an interesting finding in their case series where a patient with halothane toxicity and acute liver failure received plasma exchange with 5-10 L of plasma almost daily for 37 d before she recovered from coma.
- Few studies did not include detailed information on the frequency of plasma exchange

Etiology specific outcome

RUTGERS

- Not all studies assessed included etiology of liver failure
- In larger cohort studies, predominant causes of ALF include paracetamol, followed by unknown cause
- In a Chinese cohort study comparing the efficacy of plasma exchange + hemoperfusion + CVVHDF to plasma exchange + CVVHDF and hemoperfusion + CVVHDF, treatment of the 61 patients using the artificial liver support system yielded a combined survival rate of 62.3% (38/61). When subdivided into viral versus non- viral groups, the viral group survival rate was 35.0% (7/20) while the non-viral group survival rate was 75.6% (31/41).

Plasma exchange in ACLF

RUTGERS

- A total of 15 studies of patients with ACLF were included of which 6 studies included patients with both ACLF and ALF
- 2 of the studies, which included both ACLF and ALF, were in pediatric patients.
- The rest of the 13 studies included adult patients only. Of the 13, 1 is a randomized controlled trial, 10 are cohort studies, 2 are case series.

Mortality

RUTGERS

- An open-label randomized control study by Qin et al recruited 234 patients with HBV-related ACLF not suitable for liver transplant and randomized patients to SMT vs plasma exchange centered ALSS plus SMT.
- In this study, survival rates in plasma exchange-based ALSS were significantly higher: 60% vs 47% in the control group.
- In Yue-Meng et al, patients with ACLF who had plasma exchange+SMT had increased rate of survival compared to patients who had SMT only: 4-wk mortality was 82% vs 63%, $P = 0.001$; 12-wk mortality 86% vs 71%, $P = 0.001$).
- Mao et al reported increased 30-day survival in patients with HBV related ACLF where survival rates were 41.9% and 25.2% for plasma exchange and medical therapy respectively ($P < 0.05$).

- a range of 2000-4500 mL of plasma exchange per session was adopted
- Most studies used FFP for plasma exchange or plasma exchange-based ALSS
- In addition, Mao et al used additional albumin during plasma exchange.
- Albumin dialysis was not compared with plasma exchange in this review

Three-day therapy vs intermittent or response guided

RUTGERS

- All studies included for review extended plasma exchange beyond three days wherever relevant based on clinical necessity
- In addition, most studies do not use daily plasma exchange,
  and instead, this was performed 2-3 times per week and were response guided,
  where plasma exchange often was continued till clinical improvement, transplant, or death

Etiology specific outcome

RUTGERS

- Of the 13 included studies for plasma exchange in ACLF in adult patients, all were being conducted in Asia where hepatitis B is endemic.
  - Thus, the majority of the patients assessed have HBV related ACLF.
- In comparison to non- viral causes, ACLF in the presence of viral causes tends to have a poorer survival rate.

  Cheng et al reported a 24% survival in hepatitis B related ACLF vs 67% in alcohol-related ACLF in their retrospective cohort study of 45 ACLF and 10 ALF patients.
- Furthermore, where there were more than two causes for chronic liver injury e.g., HCV and alcohol, HBV and alcohol or in autoimmune hepatitis, mortality was high at 100%.
- However, this will need to be interpreted with caution as degree fibrosis or severity of cirrhosis of each patient was not available in the published study

- "The best way to predict the future is to invent it."

Short-term Survival of Subjects With Acute-on-Chronic Liver Failure After Plasma Exchange With Human Serum Albumin 5% (APACHE)

RUTGERS

- Phase 3, multicenter, randomized, controlled, parallel-group, open-label study to evaluate the effects of plasma exchange using human serum albumin 5% (PE-A 5%) in acute-on-chronic liver failure (ACLF) subjects.
- The study involve approximately 40 study centers in the United States, Canada, and Europe with expertise in the management of subjects with ACLF.
- Subjects with ACLF at a high risk of hospital mortality will be enrolled.
- The study consist of a Screening Period during which subjects will be randomized (1:1) to receive either standard medical treatment (SMT) + PE-A 5% (treatment group) or SMT only (control group), followed by a Treatment Period, and a Follow-up Period.
- The Treatment Period for subjects in the SMT+ PE-A 5% treatment group will be between 7 and 17 days, depending on ACLF evolution.
- The Treatment Period for subjects in the SMT control group is a minimum of 7 days for all subjects and up to 17 days depending on the ACLF evolution. Subjects in this group will receive SMT according to the institution's standards.
- The Follow-up Period for subjects in both groups is 90 days.

- Approximately 380 subjects with cirrhosis, ACLF, and high risk of hospital mortality (ACLF-1b, ACLF-2, or ACLF-3a) will be included in this study after obtaining written informed consent. In case of hepatic encephalopathy (HE), written informed consent will be obtained from a relative or a legally authorized representative (surrogate).
- Randomization of subjects will be stratified by region (European Union [EU] or North America [NA]) and the 3 ACLF grades (ACLF-1b, ACLF-2, or ACLF-3a). Within each stratum (ie, each unique combination of region and ACLF grade), subjects will be randomized in a 1:1 ratio into 2 treatment groups below:
  - SMT+PE-A 5% (treatment group)
  - SMT (control group)

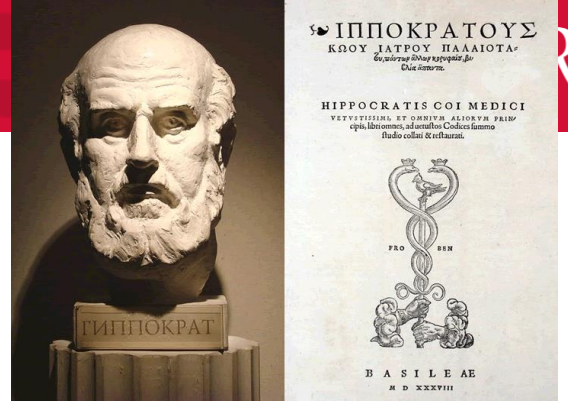
- SMT + PE-A 5% Treatment Group:
- PE-A 5% will be performed using 5% albumin as the main replacement fluid administered intravenously. Fresh frozen plasma (FFP) will be given after each PE-A 5% session to prevent coagulopathy.
- The exact number of sessions will be determined by the pattern of response (achieving complete response or no improvement/deterioration of ACLF) to PE-A 5% therapy.
- IVIGs will be administered to prevent the development of hypogammaglobulinemia and infection.

- SMT Control Group:
- The Treatment Period will be 7 days for all subjects and will be prolonged depending on subject's ACLF evolution to up to 17 days.
- Subjects in both the SMT+ PE-A 5% treatment group and the SMT control group will be followed for 90 days after randomization. During the entire study, the safety of both groups will be monitored by a Data Safety Monitoring Board.

- Primary Outcome Measures :
  - Time to death through Day 90 [Time Frame: Day 1 to Day 90]Time to death through Day 90 after randomization of SMT+PE-A 5% versus SMT alone
- Secondary Outcome Measures :
  - Time to transplant or death through Day 90 [Time Frame: Day 1 to Day 90]Time to transplant or death through Day 90 after randomization of SMT+PE-A 5% versus SMT alone
  - Time to death through Day 28 [Time Frame: Day 1 to Day 28]Time to death through Day 28 after randomization of SMT+PE-A 5% versus SMT alone

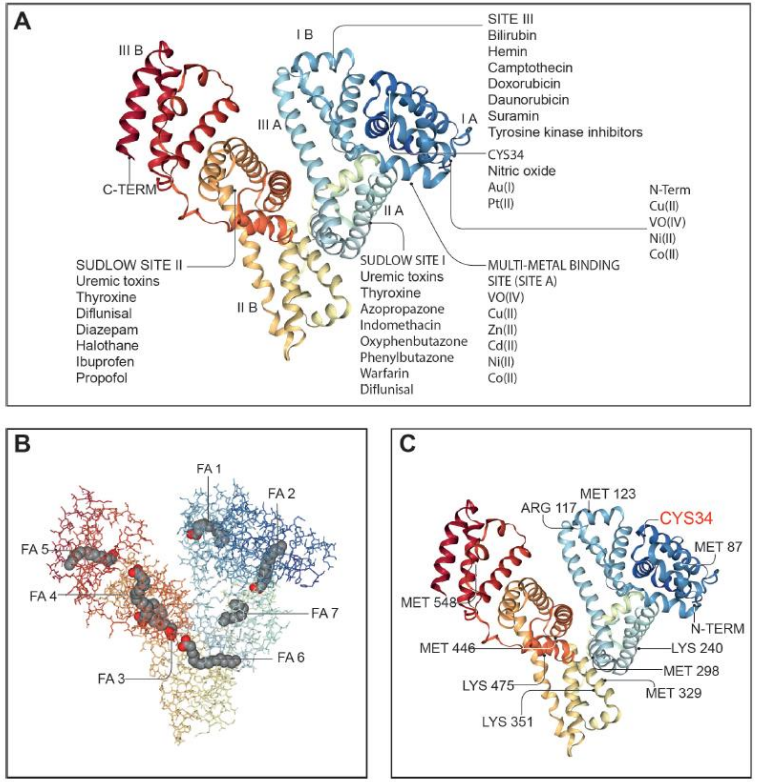
- Why albumin?

Human Serum Albumin



- Human serum albumin (**HSA**) is the most abundant plasma protein of the body
- HSA modulates plasma oncotic pressure and fluid distribution between body compartments
- Many of the physiological functions of HSA rely on its ability to reversibly bind to an extremely wide range of ligands

Endogenous and Exogenous Binding Sites in the Albumin Molecule



Bhattacharya AA et al. *J Mol Biol*. 2000;303:721–32; Bernardi M et al. *Gut*. 2020:1127-1138; Jagdish RK et al. *Hepatology.* 2021;74:2848-2862.

Multiple functions (faces)

ABC of Actions of Albumin

Anti-oxidant effects:

Free radical scavenger, metal ion chelation, buffering action, pH

Anti-coagulant/ anti-thrombotic effects:

NO binding at cys-34, Anti-inflammatory

Cardiac and positive inotropic effects

Binding and transport:

Drugs, ions, fatty acid, bile acids, bilirubin, gases, ligands, hormones, Ca^{++}, etc.

Capillary integrity:

Interstitial matric binding, capillary permeability and endothelial stabilization

Corrects immune dysfunctions, binds endotoxins, PG

Colloidal osmotic pressure, intravascular fluid movement

As a nutrient

Bernardi M et al. *Gut*. 2020:1127-1138; Jagdish RK et al. *Hepatology*. 2021;74:2848-2862;
Campos Munoz A et al. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
Available from: https://www.ncbi.nlm.nih.gov/books/NBK534241/?report=classic.

HMA
reduced form

HNA
oxidized form

HNA1

HNA2

HSA — reversible ⇄ HSA — irreversible → HSA

Cys^{34}-SH

Cys^{34}-S-S-**R**

Cys^{34}-SOH, $-SO_2H$, $-SO_3H$

R: cysteine > homocysteine > glutathione
(Cystein is a major conjugate.)

Healthy condition

Disease condition
- ✓ Chronic liver disease
- ✓ Chronic kidney disease
- ✓ Diabetes mellitus etc.

Posttranslational modification

HSA ⇄ (Disease progression / Complication; Therapeutic intervention) HSA

Glycation, Carbamylation, Truncation, Dimerization

Cys^{34}-SH

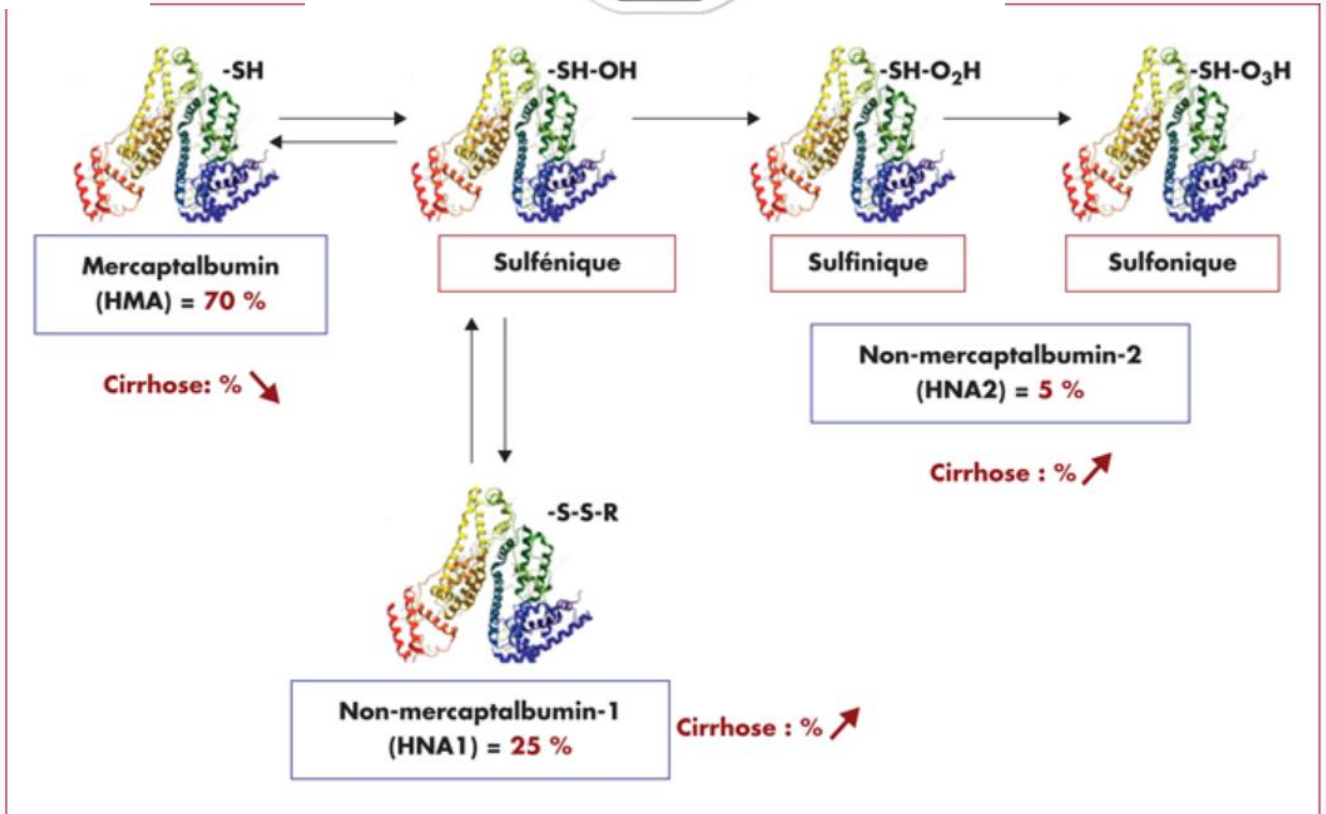
Functional albumin

Cys^{34}-S-S-**R**

Oxidation
Cysteinylation

Dysfunctional albumin
Ligand binding ability ↓
Anti-oxidative capacity ↓

"Diagnostic tool for disease progression or therapeutic effect"

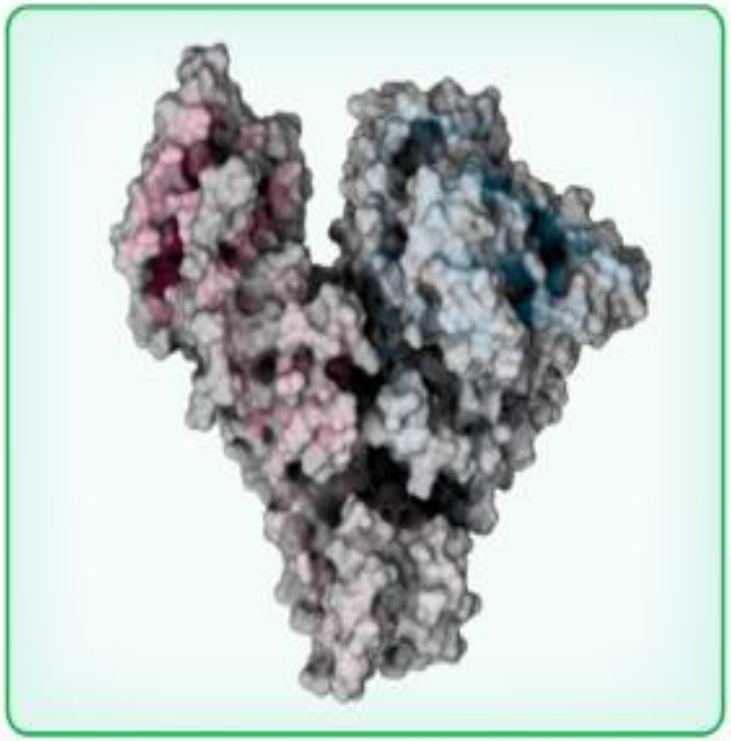


Albumin in healthy individuals

Oncotic — Properties — Non-oncotic

Regulation of fluid distribution

Negative net charge
High molecular weight
High plasma concentration



Most abundant circulating protein
(50-60% of the total proteins)
Reference lab range: 3.5-5.0 g/dl

Binding, transport, detoxification

Many endogenous and exogenous compounds including drugs

Antioxidant activity

Free radical and metal ion scavenging

Endothelial stabilisation

Haemostatic effect

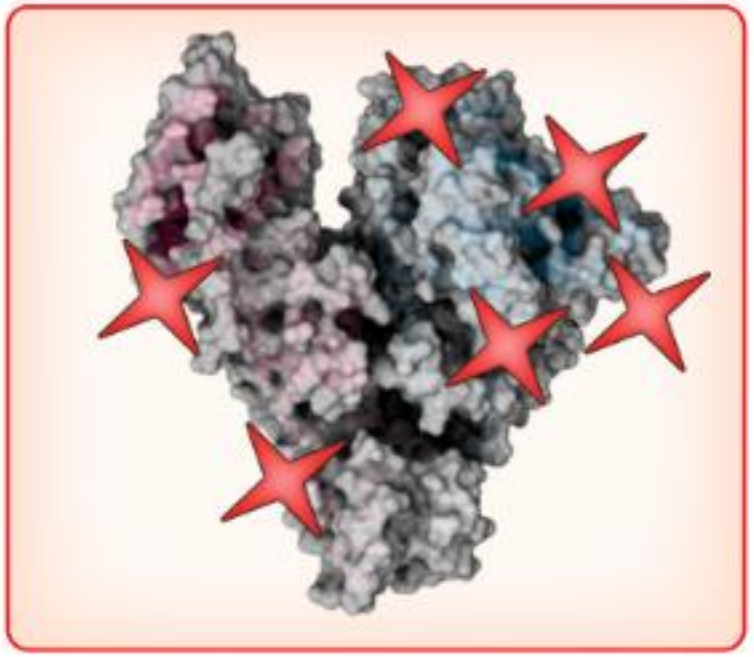
Immune/inflammatory response modulation

LPS binding, activation of pro-inflammatory genes, modulation of intracellular redox state, PGE_2 binding

Albumin in patients with decompensated cirrhosis

Structural damage

Reversible and irreversible oxidation
Glycation
N- and C-terminal truncation
Dimerisation



Reduced plasma concentration

Reduced synthesis

Impaired functions

Reduced antioxidant activity
Reduced binding/detoxification capacities
Reduced anti-inflammatory activity
Others?

Clinical Practice Guidelines

CrossMark

EASL JOURNAL OF HEPATOLOGY

RUTGERS

EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure☆

European Association for the Study of the Liver*

- Liver support systems (biological or adsorbent) should only be used in the context of RCT (**evidence level II-1, grade of recommendation 1**).
- Plasma exchange in RCT, has been shown to improve transplant-free survival in patients with ALF, and to modulate immune dysfunction (**evidence level I, grade of recommendation 1**).
- Plasma exchange may be of greater benefit in patients who are treated early and who will not ultimately undergo LTx (**evidence level I, grade of recommendation 2**).


That's all Folks!


Thank you