

Liver Transplantation: The End of the Road in Chronic Hepatitis C Infection



Disclosure

I have no actual or potential conflict of interest in relation to this program/presentation.

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May 22 2012





Liver
Transplant

HCV

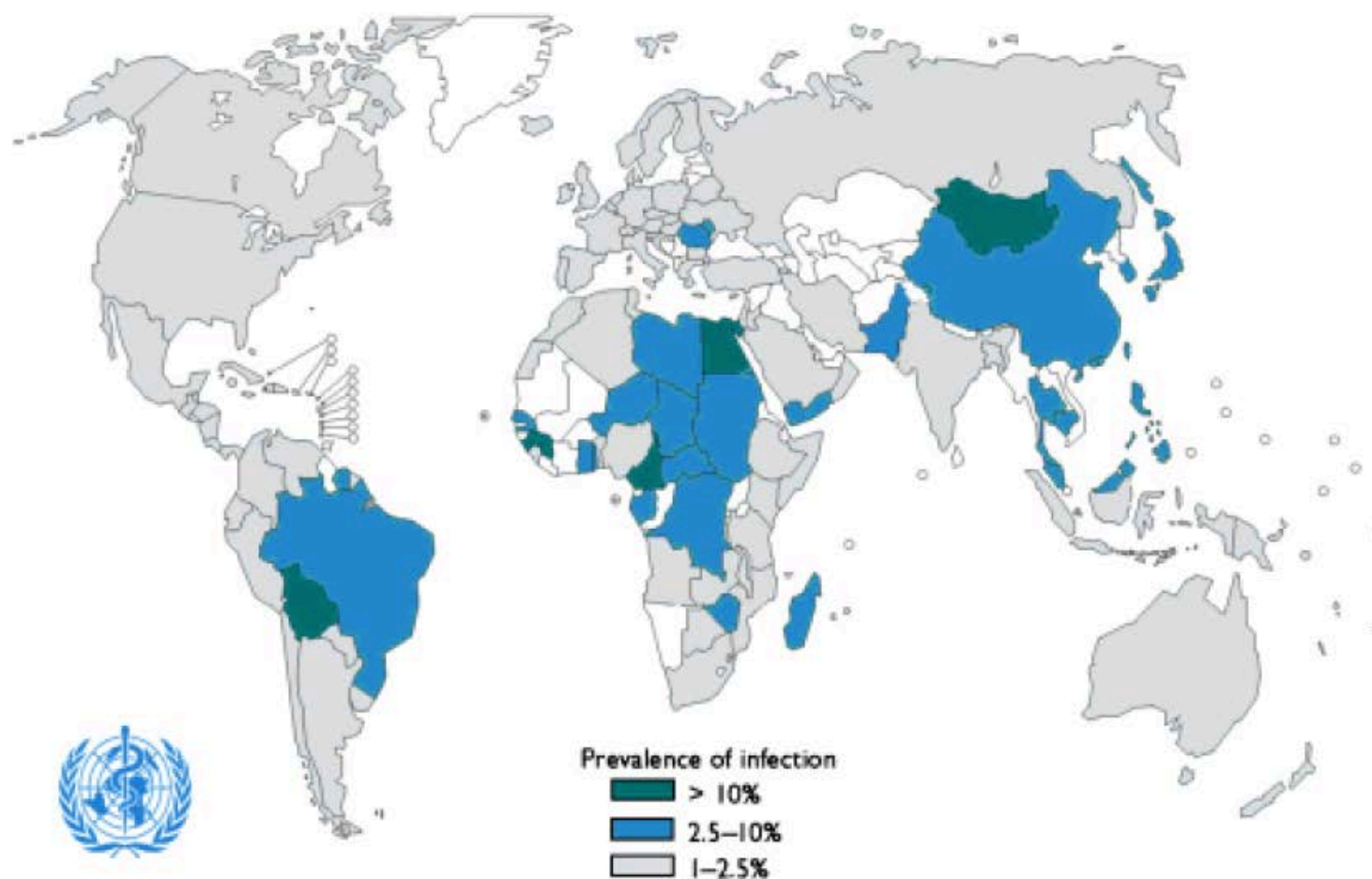
Magnitude of the problem

- 170 million people world wide affected by HCV
- About 1 to 2 % of the population in industrial countries is infected with HCV.
- Number one cause of liver failure requiring liver transplant

The global burden of hepatitis C

Liver International 2009; 29(s1): 74–81

Hepatitis C, 2004



Global prevalence of hepatitis C.

Natural history of HCV infection

- 20% of acutely infected patients spontaneously clear the virus
- 75% to 85% progress to chronic infection
- Rate of chronic infection varies by age, sex, race, and immune system status
- 20% of chronically infected individuals will develop cirrhosis over a 20- to 25-year period
- 3%–4% will develop HCC per year

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18 May 2012 Last updated at 22:02 ET

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US baby boomers urged to take hepatitis C blood test

US baby boomers have been advised by health officials for the first time to get tested for the liver-destroying virus hepatitis C.

Those born between 1945-1965 are most likely to be infected but it is thought only a quarter of this generation has been tested for the virus.

The US Centers for Disease Control (CDC) believes its campaign could save more than 120,000 lives.

The CDC estimates some 17,000 hepatitis C infections currently occur each year.

Health officials believe hundreds of thousands of infections occurred each year in the 1970s and '80s, when baby boomers would have been



The CDC is recommending a one-time blood test to check for the virus

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CDC considering recommending Hepatitis C test for boomers

It's a "silent epidemic," an "unrecognized health crisis," according to the Centers for Disease Control and Prevention. And it's affecting 2.1 million baby boomers in the United States.

The CDC announced Friday that it is considering recommending Hepatitis C testing for everyone born between 1945 and 1965. Currently the CDC recommends this testing only for those who are at-risk - people who participated in intravenous drug use or had a blood transfusion before 1992, when screening was implemented.

In 2007, approximately 17,000 new Hepatitis C virus infections were diagnosed in the United States. The CDC estimates that 3.2 million Americans have chronic Hepatitis C and more than 75% don't know it because they aren't experiencing any symptoms. Baby boomers represent the majority of cases - more than 75%, and are five times more likely to be infected than other adults.

"It's causing more deaths than AIDS, the costs are expected to quadruple and cure rates are at 80 to 90%," Ryan says. "[This recommendation] just kind of makes sense."

Characteristics of adult liver transplant recipients, SRTR 2009

Primary cause of disease	Acute hep. necrosis	246	4.3
	HCV	1,470	25.6
	Alcoholic liver dis.	999	17.4
	Cholestatic dis.	455	7.9
	Metab. liver dis.	143	2.5
	Malignancy	1,077	18.7
	All others	1,358	23.6

Primary cause of disease

— Acute hepatic necrosis

— HCV

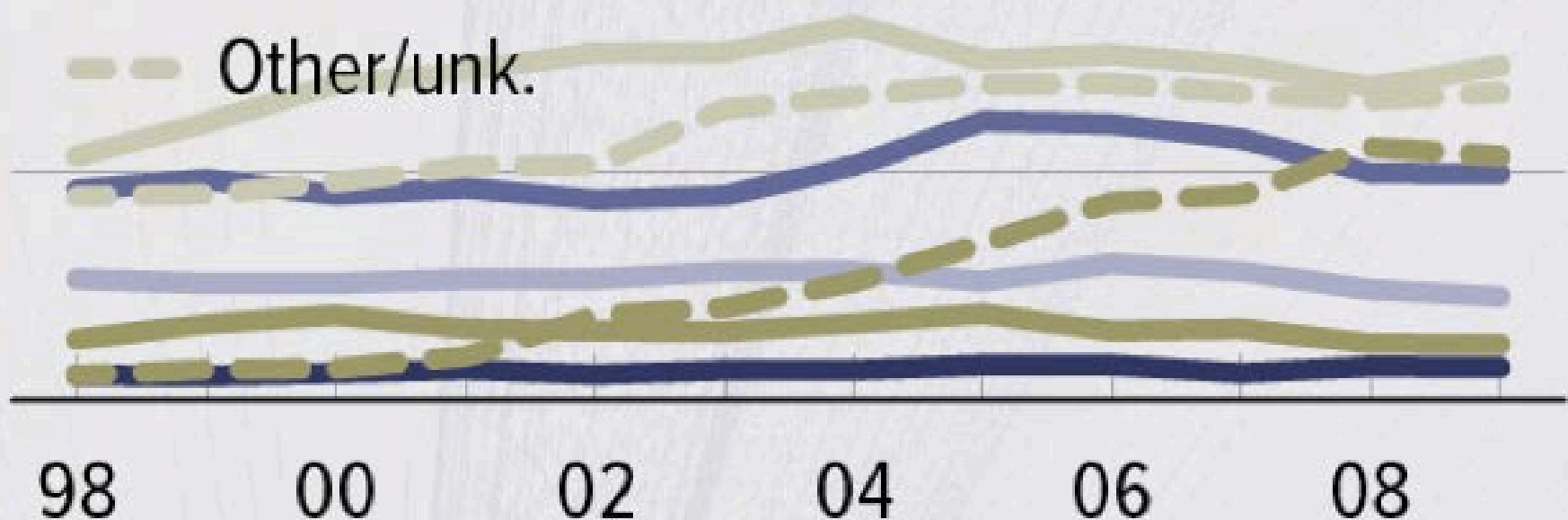
— Alcoholic liver disease

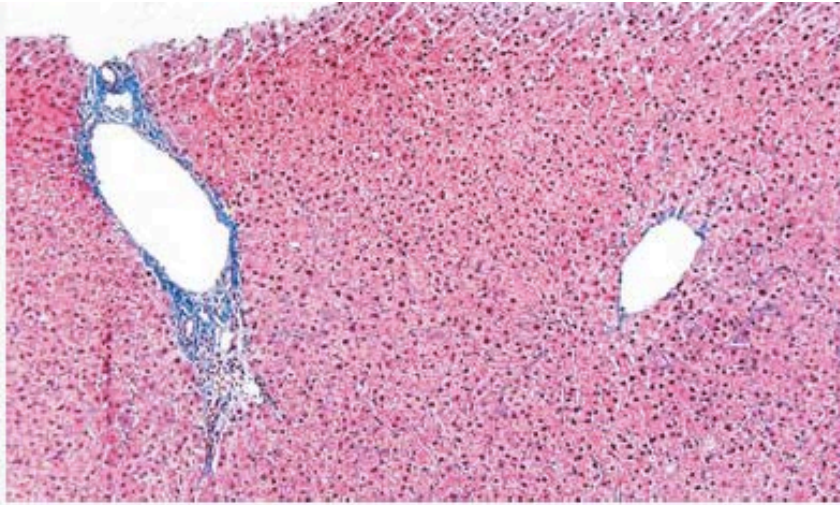
— Cholestatic disease

— Metabolic liver disease

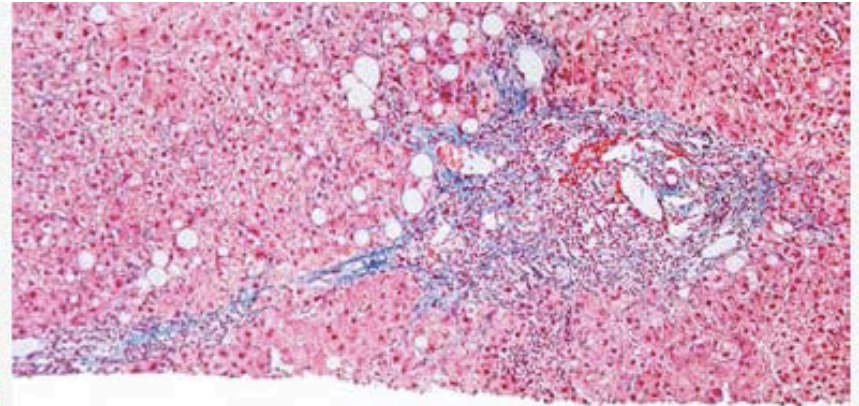
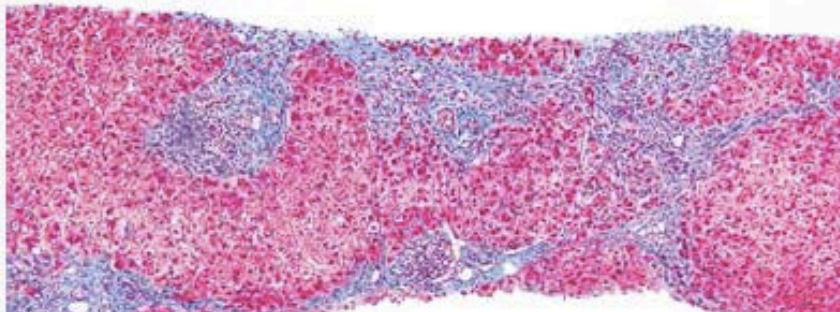
- - Malignancy

- - Other/unk.

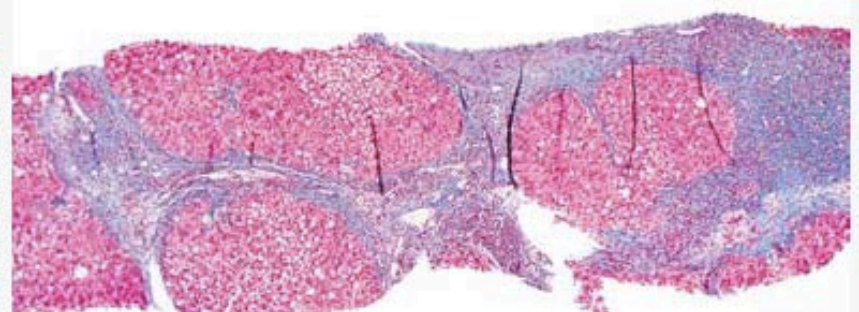


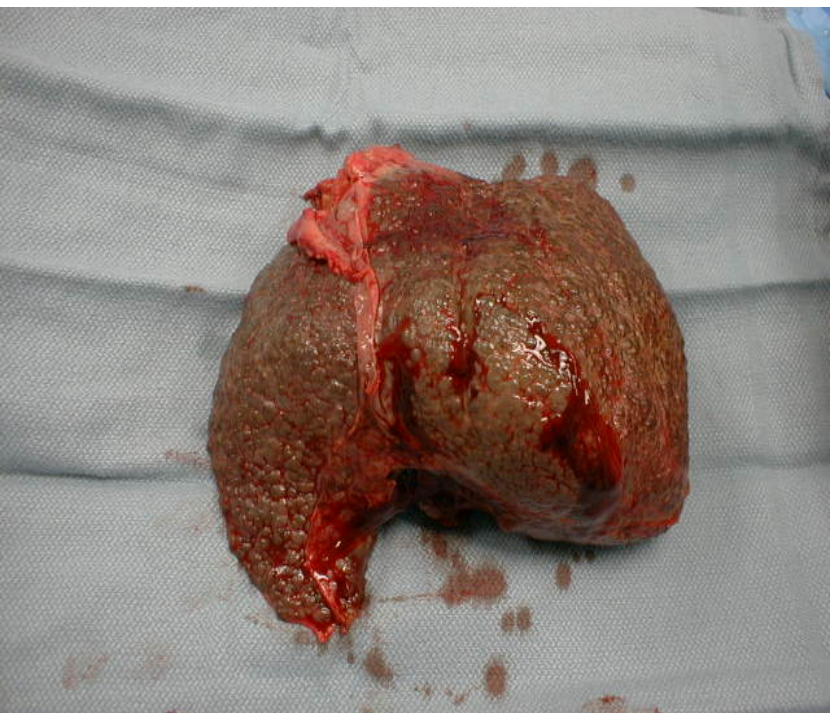
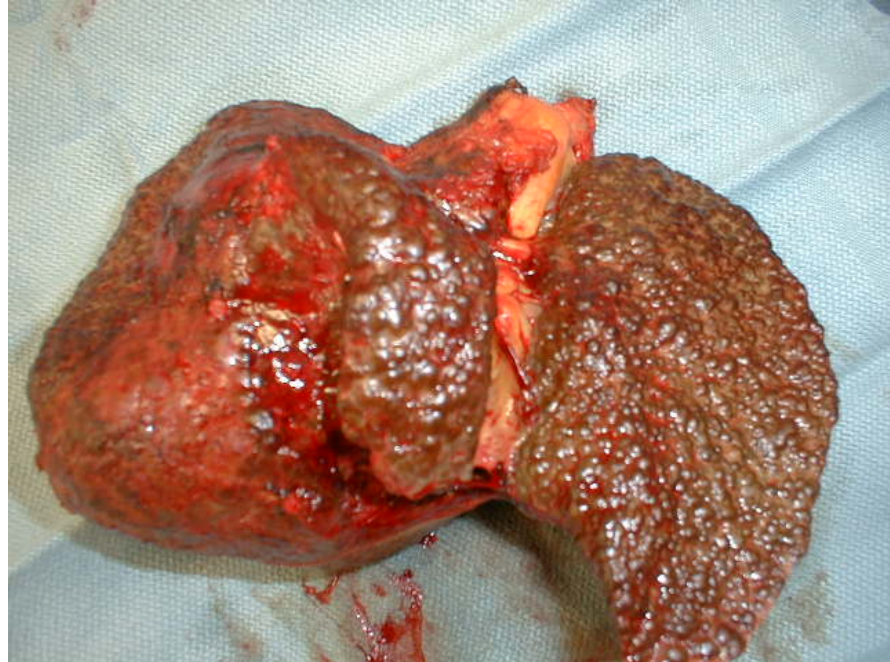


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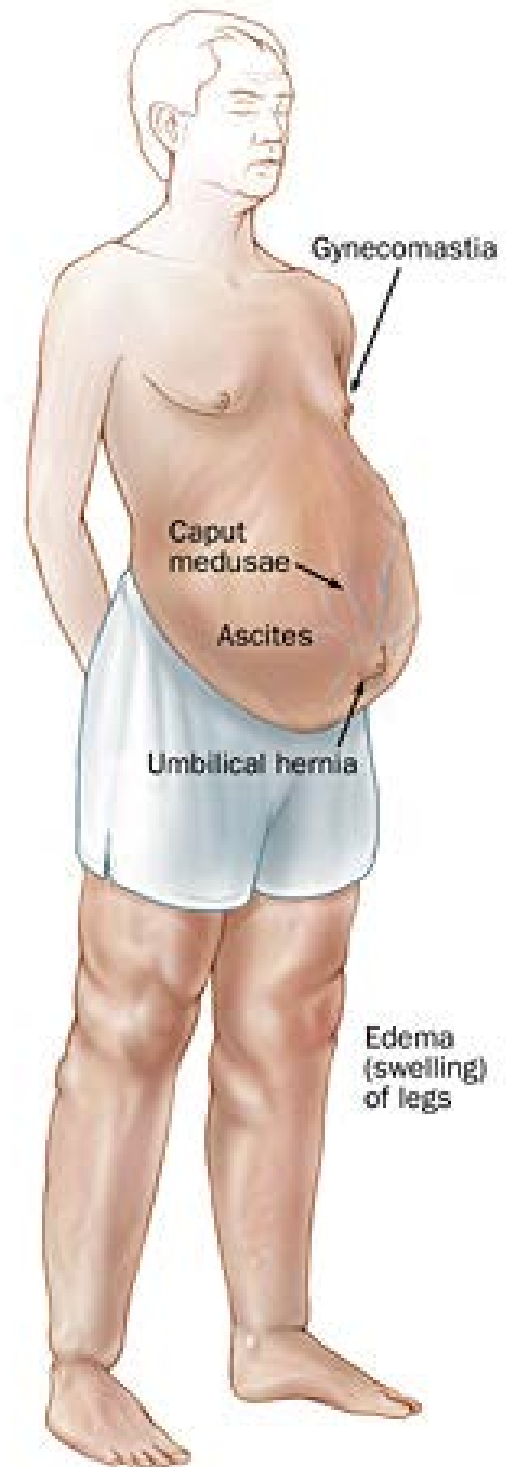
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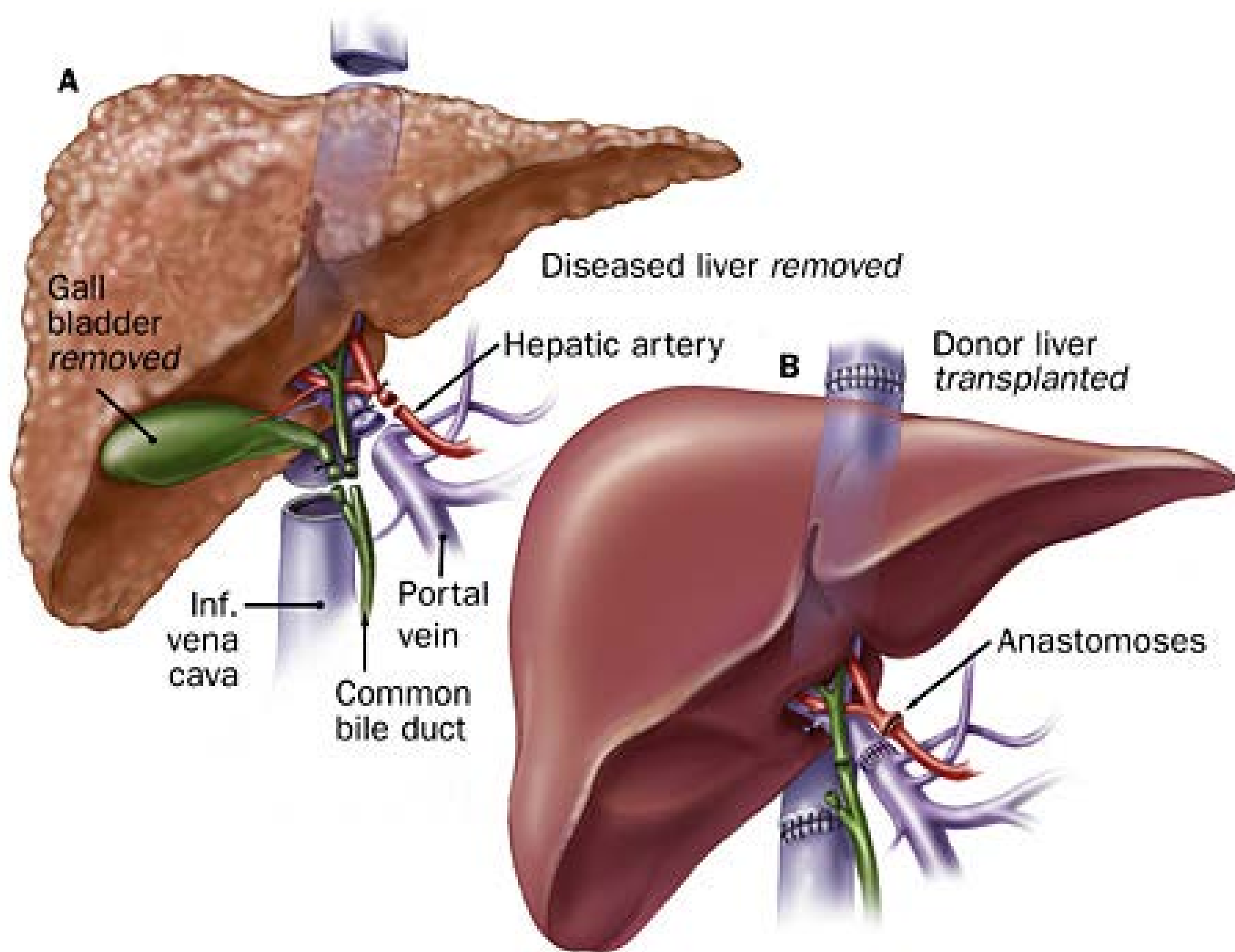
Decompensated Cirrhosis

- Portal Hypertension
 - Esophageal variceal bleeding
 - Ascites
- SBP
- Encephalopathy
- Hepatorenal Syndrome
- Hepatopulmonary Syndrome
- Portopulmonary Hypertension
- Coagulopathy
- Jaundice
- Pruritus
- Sleep wake cycle disturbances



Liver Transplant

- Allocation of Organ based on MELD
- Predictor of 3 month wait list mortality



HCV

Post Transplant Course

- Graft reinfection with HCV is universal
- Fibrosis progression is accelerated , compared to immunocompetent patients .
- Patients have a 23% increased rate of mortality and a 30% increased rate of graft loss at 5 years post-transplantation as compared to patients transplanted for other indications
- Cirrhosis is reported in up to 30% of recipients within 5 years
- Once cirrhosis is established, patients are at high risk for complications, with up to 42% developing liver decompensation within 1 year
- Retransplantation, is controversial in patients with HCV, as their survival is inferior compared to patients with non-HCV indications

Forman LM, Lewis JD, Berlin JA, et al. *The association between hepatitis C infection and survival after orthotopic liver transplantation.*

Gastroenterology.

2002;122:889–896.

- Retrospective cohort study of 11,036 patients (4439 HCV-positive and 6597 HCV-negative).
- Patients transplanted for HCV-related cirrhosis had an increased rate of death and allograft failure compared with patients transplanted for causes other than HCV.
- There was a 23% increased mortality rate and 30% increased allograft failure rate associated with HCV infection.



Natural History of Post-Liver Transplantation Hepatitis C: A Review of Factors That May Influence Its Course

Juan F. Gallegos-Orozco,*¹ Amir Yosephy,^{2*} Brie Noble,² Bashar A. Aqel,² Thomas J. Byrne,² Elizabeth J. Carey,² David D. Douglas,² David Mulligan,³ Adyr Moss,³ Giovanni de Petris,⁴ James W. Williams,⁴ Jorge Rakela,² and Hugo E. Vargas²

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Our aim was to assess long-term survival in patients transplanted for HCV-related end-stage liver disease (ESLD) and evaluate potentially modifiable predictors of survival. We performed a retrospective analysis of adult liver transplants (LT) at our institution for HCV-related ESLD since the program's inception. Pertinent demographic, clinical, and biochemical information

Factors negatively affecting post transplant outcome

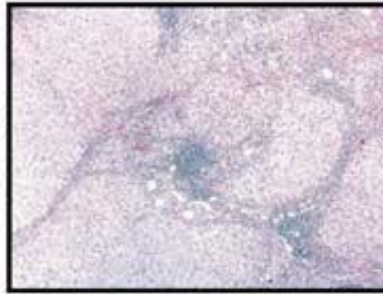
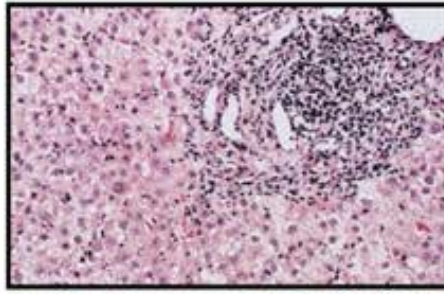
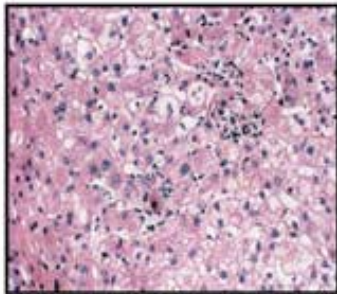
- Clinically significant histological recurrence within the first year of transplantation
- Advanced fibrosis stage at the 1 year protocol liver biopsy (fibrosis stage 2)
- Acute cellular rejection within the first 3 months of LT
- Donor age
- History of pretransplant HCC (regardless of prior therapy)

Donor factors (suboptimal donor quality)

Age, sex, steatosis, genetics, donation after cardiac death ...

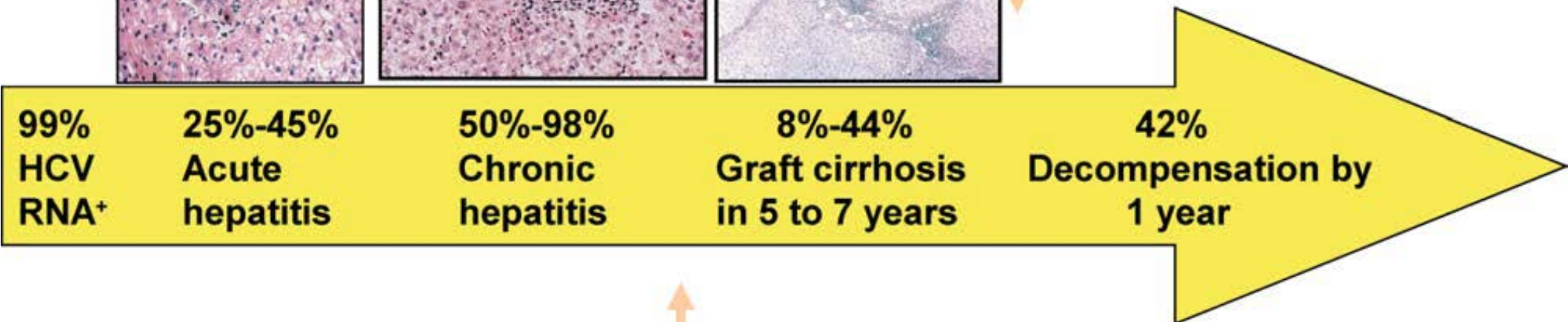
Surgical factors (complicated surgery)

Ischemia time, living donor liver transplantation, preservation injury, biliary complications ...



Viral factors

Viral load
Genotype
Quasispecies



99%	25%-45%	50%-98%	8%-44%	42%
HCV RNA ⁺	Acute hepatitis	Chronic hepatitis	Graft cirrhosis in 5 to 7 years	Decompensation by 1 year

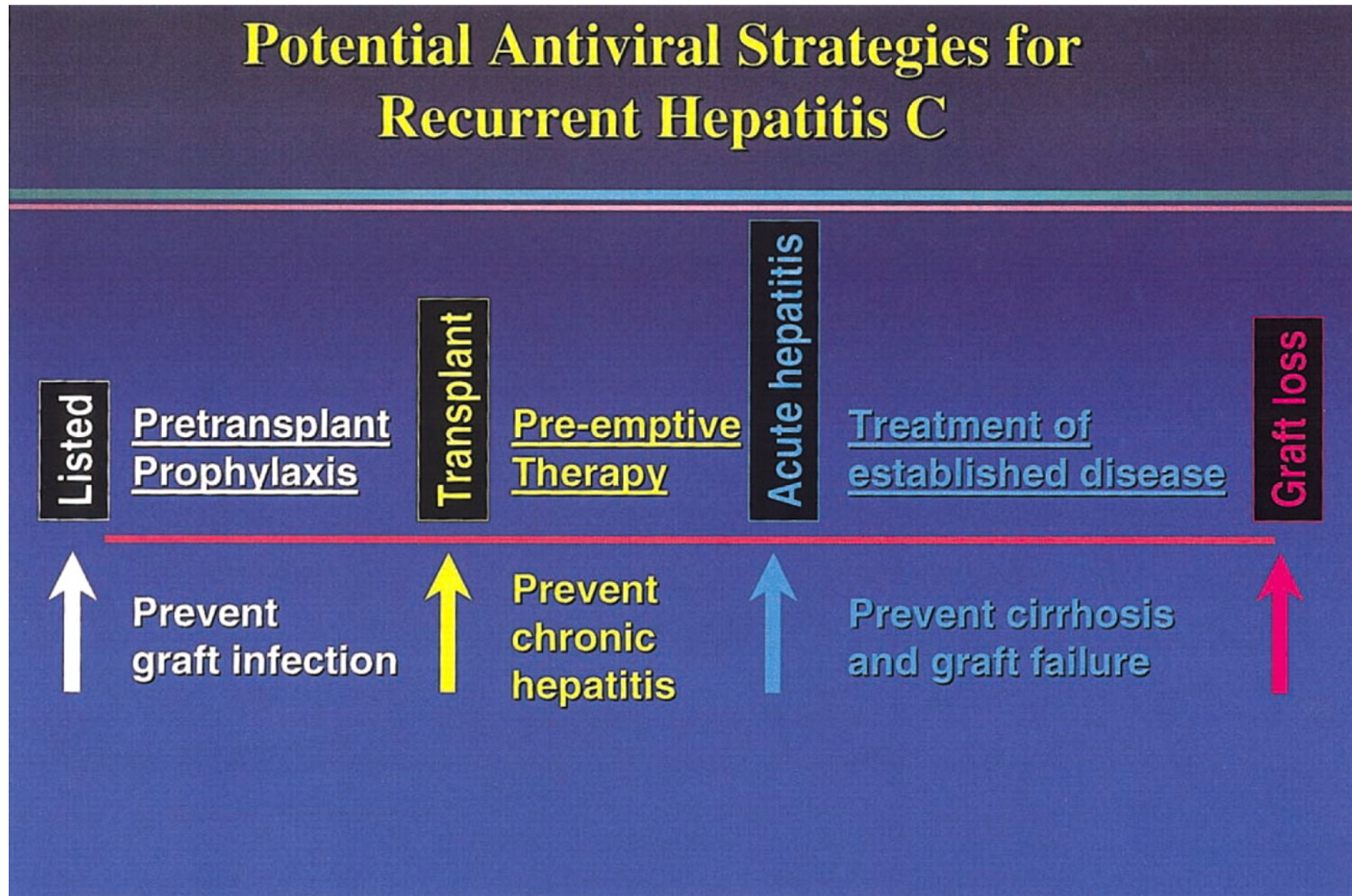
Host factors

Human leukocyte antigen, race, sex, age, immunogenetic background, immune system, obesity, diabetes, metabolic syndrome

External factors

Immunosuppression, alcohol, viral coinfection, antiviral therapy

Potential antiviral strategies for treatment of recurrent hepatitis C. Courtesy of Dr. Ed Gane.



Snydman D R et al. Clin Infect Dis. 2003;37:807-812

When to treat HEP C

Pre transplant

Martinez-Bauer E, Carrion JA, Ramirez S, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent hepatitis C recurrence after liver transplantation. J Hepatol 2006;44: S64.A150.

- 50 cirrhotic patients with HCV on the LT waiting list.
- The baseline model for end-stage liver disease (MELD) score was 12
- pegylated interferon and ribavirin

Martinez-Bauer E, Carrion JA, Ramirez S, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent hepatitis C recurrence after liver transplantation. J Hepatol 2006;44: S64.A150

- 46% of patients became HCV-RNA negative before transplantation
 - Post-LT SVR of 71%
 - Relapse rate of 29%.
 - *20% of genotype 1 patients maintained post-LT SVR.*
- Side effects included
 - Life-threatening complications :
 - Hepatic decompensation and infection (32%)
 - Neutropenia (20%)
 - 2 deaths on therapy (spontaneous bacterial peritonitis)

Immunosuppression

Cyclosporin VS Tacrolimus

Firpi RJ, Zhu H, Morelli G, et al. Cyclosporine suppresses hepatitis C virus in vitro and increases the chance of a sustained virological response after liver transplantation. Liver Transpl 2006;12:51–57.

- Patients treated with cyclosporine
- 46% were more likely to achieve SVR vs patients treated with tacrolimus (27%)
- There was no statistically significant difference in patient survival between the 2 groups
- cyclosporine treated patients had a lower baseline HCV RNA
- More episodes of acute cellular rejection requiring steroid treatment.

O'Grady JG, Hardy P, Burroughs AK, et al. UK and Ireland Liver Transplant Study Group. Randomized controlled trial of tacrolimus versus microemulsified cyclosporin (TMC) in liver transplantation: post-study surveillance to 3 years. Am J Transplant 2007; 7:137–141.

- No difference in outcomes in cyclosporine- vs tacrolimus-treated HCV patients at 3 years

Risks and Benefits of Antiviral Therapy for Recurrent HCV

Benefits

- Only medications shown to eradicate recurrent HCV
- Virus eradication would substantially improve outcome

Risks

- Frequently ineffective in genotype 1
- Optimal time for treatment initiation unclear
- Duration of treatment for fibrosing cholestatic HCV unknown
- Numerous side effects that can be serious and often lead to treatment discontinuation
- Expensive
- Progressive fibrosis with decompensation reported despite SVR

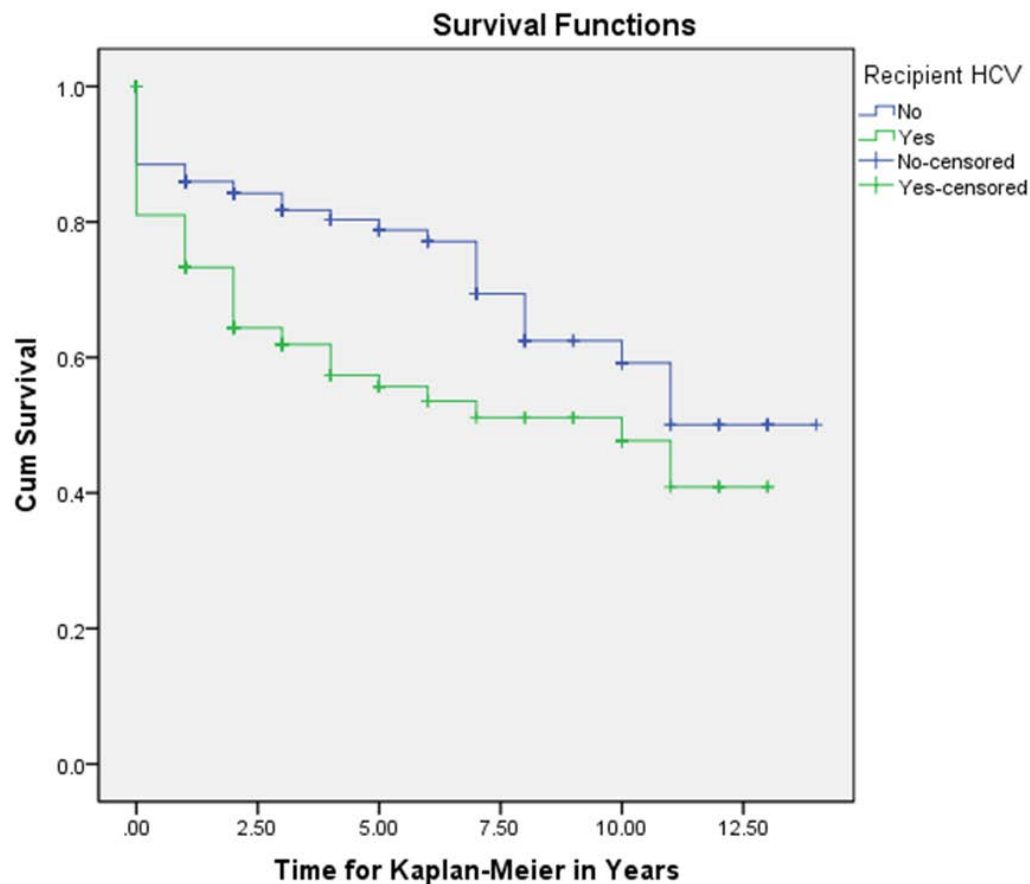


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- 1998 To Present
- 350 consecutive Liver Transplants
- 158 cases of HCV + Recipients (45%)
- 192 cases of HCV – Recipients (55 %)

	Hcv – N = 192	HCV+ N = 158	P
Age	56	54	0.6
MELD	18.9	18.7	0.4
Male	107	124	NS
Female	85	34	0.000
White	151	110	NS
AA	4	5	NS
Other	37	43	NS
Import	59	33	0.01
Donor Age	55.5	48.5	0.000
DRI	2.12	1.81	0.001

UMass HCV+ Patients vs. HCV- Patients



Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	9.932	1	.002
Breslow (Generalized Wilcoxon)	10.062	1	.002
Tarone-Ware	11.030	1	.001

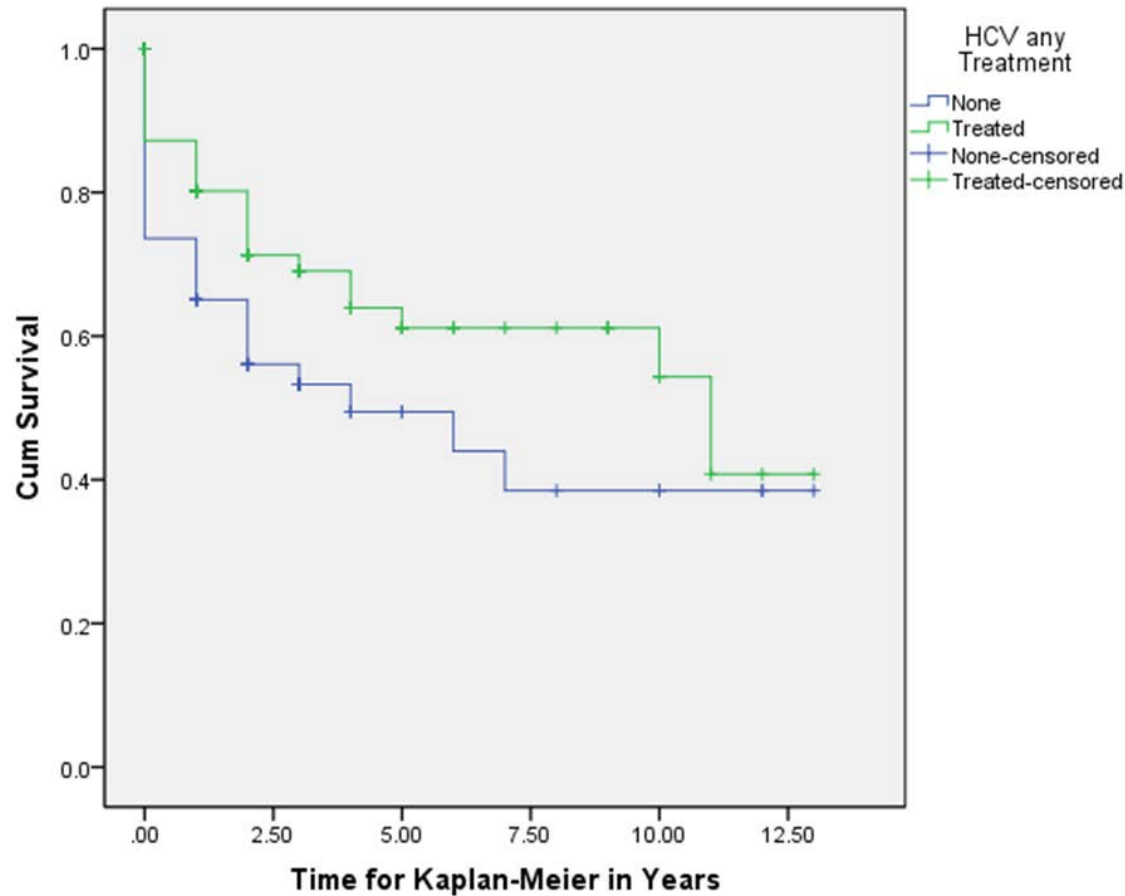
Case Processing Summary				
Recipient HCV	Total N	N of Events	Censored	
			N	Percent
No	191	43	148	.8
Yes	158	59	99	.6
Overall	349	102	247	.7

158 HCV + recipients

	Treatment (--) N=72	Treatment (+) N=86	P
Age	54	54	NS
MELD	19.6	17.75	0.49
Female	19	15	NS
Male	53	71	NS
White	50	60	NS
AA	2	3	NS
Other	20	23	NS
Import	15	18	0.99
Donor Age	52	45	0.36
Donor sex (F)	15	23	NS
Donor sex (M)	34	36	NS
DRI	1.86	1.74	0.95

UMass HCV+ Patients Treated vs. Non-Treated

Survival Functions



Overall Comparisons

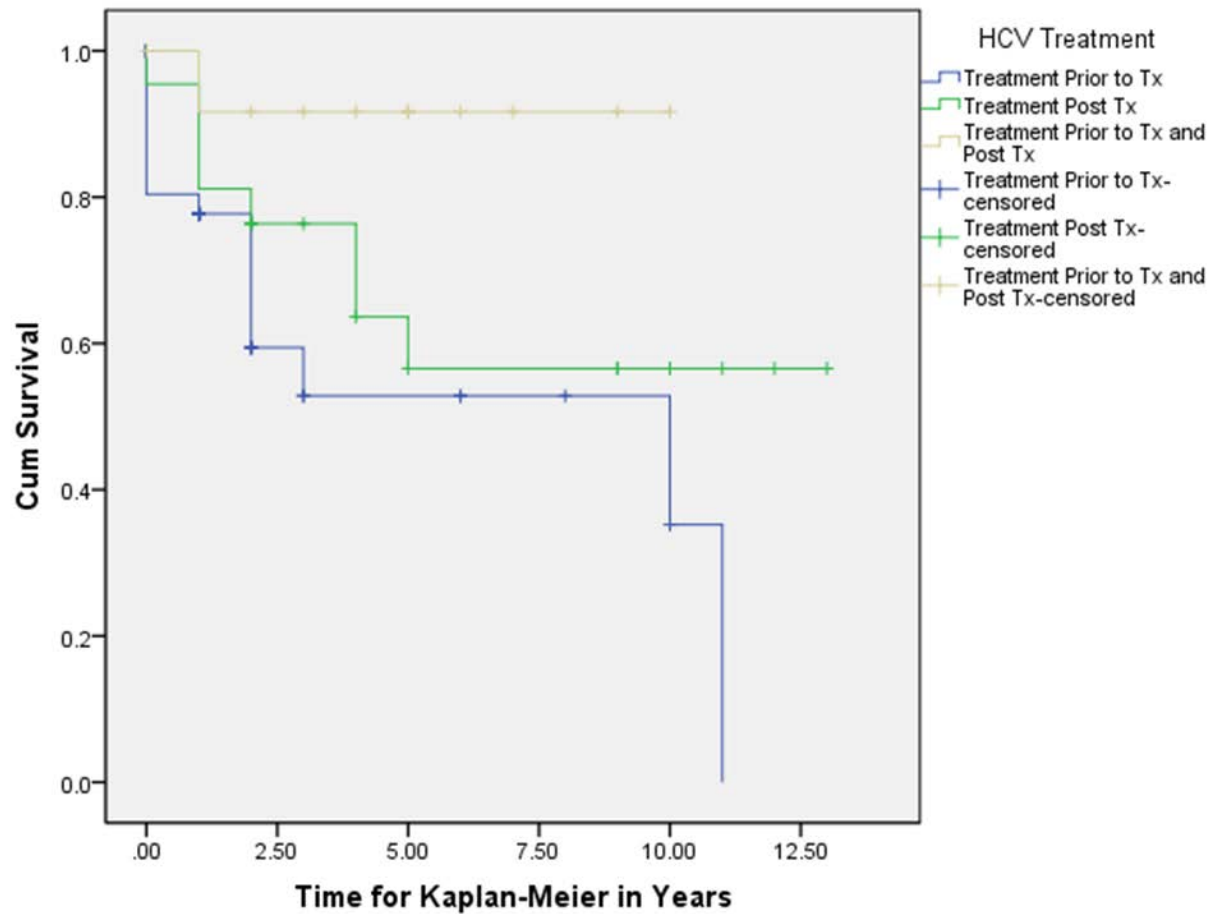
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.993	1	.046
Breslow (Generalized Wilcoxon)	5.223	1	.022
Tarone-Ware	4.969	1	.026

Case Processing Summary

HCV any Treatment	Total N	N of Events	Censored	
			N	Percent
None	72	32	40	.6
Treated	86	27	59	.7
Overall	158	59	99	.6

UMass HCV+ Patients Treated vs. Non-Treated

Survival Functions



Overall Comparisons

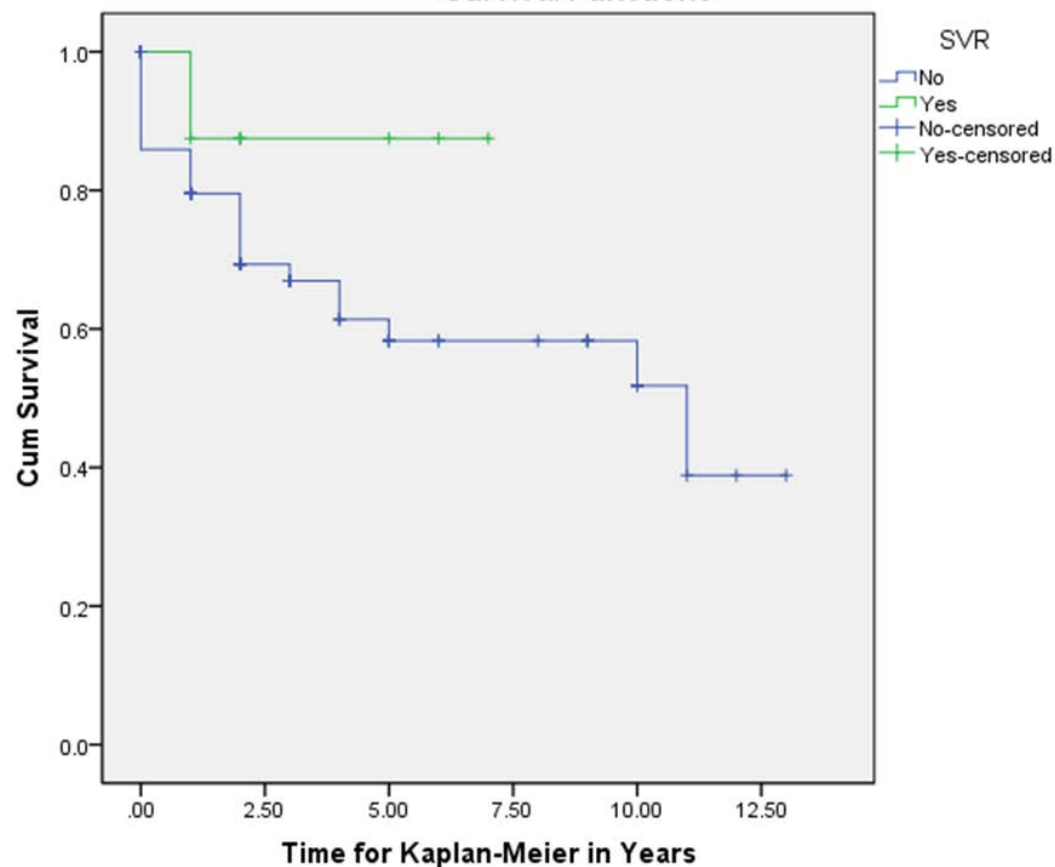
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	7.157	2	.028
Breslow (Generalized Wilcoxon)	5.340	2	.069
Tarone-Ware	5.976	2	.050

Case Processing Summary

HCV Treatment	Total N	N of Events	Censored	
			N	Percent
Treatment Prior to Tx	51	18	33	.6
Treatment Post Tx	22	8	14	.6
Treatment Prior to Tx and Post Tx	13	1	12	.9
Overall	86	27	59	.7

UMass HCV+ Patients SVR vs. Non-SVR

Survival Functions



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.406	1	.236
Breslow (Generalized Wilcoxon)	1.238	1	.266
Tarone-Ware	1.325	1	.250

Case Processing Summary

SVR	Total N	N of Events	Censored	
			N	Percent
No	78	26	52	.7
Yes	8	1	7	.9
Overall	86	27	59	.7