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Liver disease mortality among drug users, competing causes of deaths and age differences

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EMCDDA, September 30, Lisboa

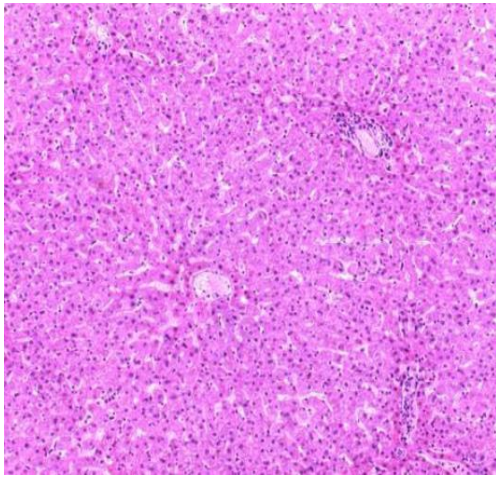
Disclosures

- K.B. Kielland has given sponsored lectures for MSD and AbbVie

Classification of the progression of liver fibrosis in hepatitis C

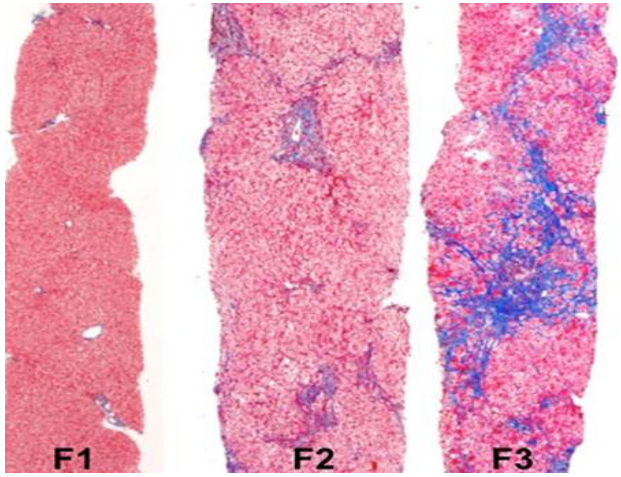
Biopsies: Metavir stages F0–F4

Normal liver
F0

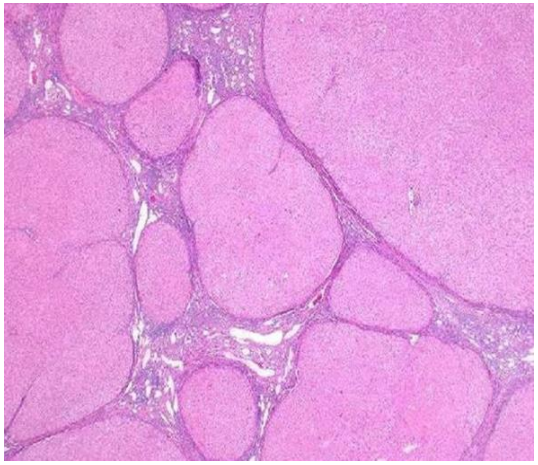


Amar Paul Dhillon, UCL Medical School Royal Free Campus, London

F1 F2 F3



Cirrhosis
F4



Shashidhar Venkatesh Murthy,

F1 = portal fibrosis without septa
F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis (septal or bridging fibrosis)

Elastography

Mean duration of Metavir stages

A meta-analysis concluded with the following mean progression time through the Metavir stages

- F0–F1: 9 years
- F1–F2: 12 years
- F2–F3: 12 years
- F3–F4: 8 years
- F0–F4: 40 years

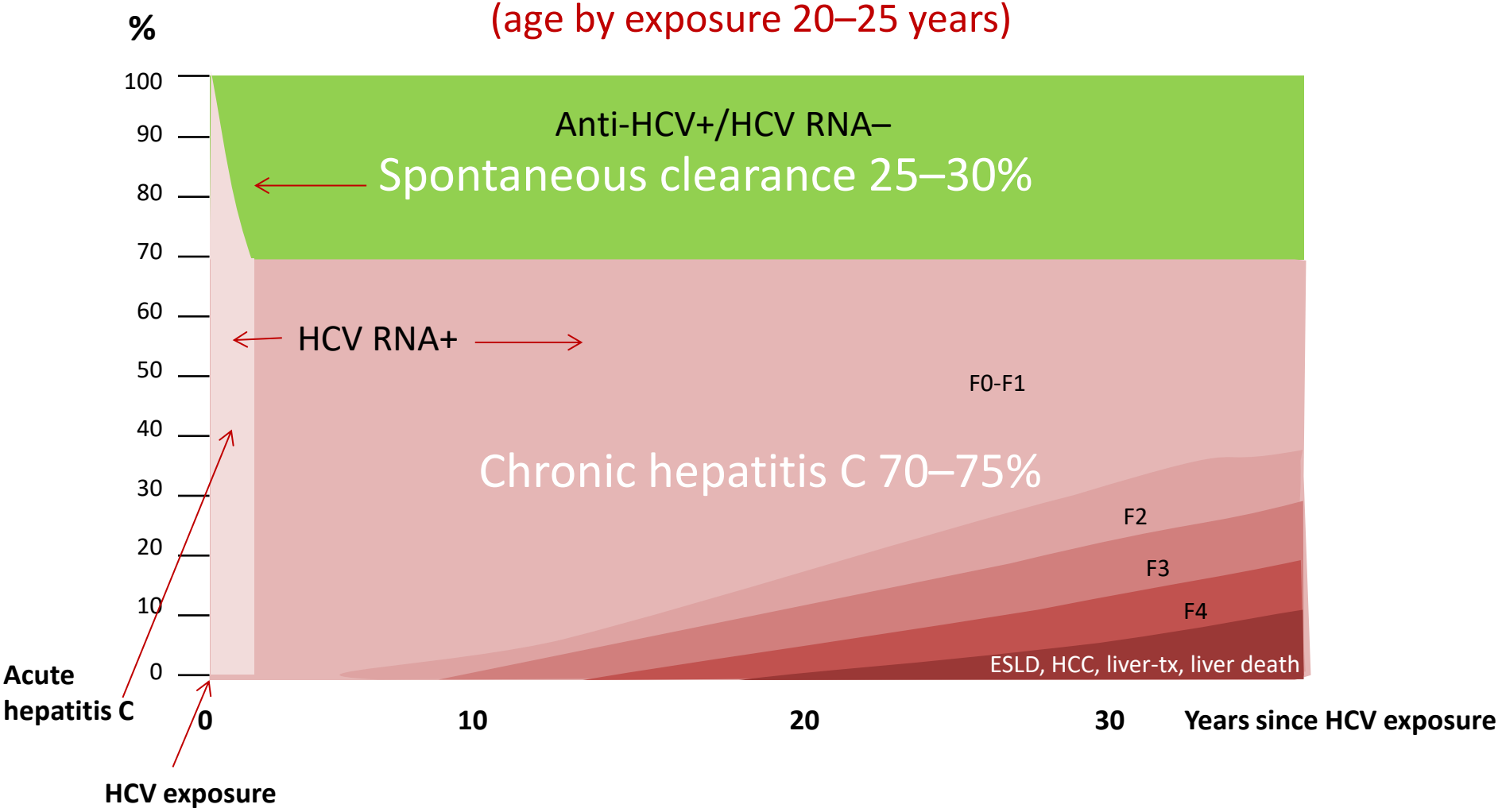
Conclusions:

- For probable more than half the patients the progression is very slow (“non-fibrosing”)
- For at least 1/3 it is much more rapid.

Thein HH, Yi Q, Dore GJ, Krahn MD. *Hepatology* 2008; 48(2):418-431.

The natural course of liver disease in chronic hepatitis C

(age by exposure 20–25 years)



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Factors which may increase or reduce fibrosis progression

Host factors

Male gender
High age at exposure

Untreated co-infection HIV
Untreated co-infection HBV

Overweight/steatosis/NASH
Insulin resistence/
metabolic syndrome/DM2

Genetic and other factors

External factors

Alcohol
(Tobacco)
(Cannabis)
Coffee (reduced fibrosis?)
Chocolate (reduced fibrosis?)

Viral factors

Genotype 3
Genetic variability

Cirrhosis

- Cirrhosis:
  - Annual risk of liver cancer (HCC):1–5%
  - Annual risk of hepatic failure (decompensation): 3–6% (variceal hemorrhage, ascites, encephalopathy)

- Decompensated cirrhosis:
  - Risk of death the following year 15–20%

Westbrook RH, Dusheiko G.. J Hepatol. 2014 Nov;61(1 Suppl):S58-68.

Thein HH, Yi Q, Dore GJ, Krahn MD. Hepatology 2008;48:418–431.

Natural course of drug use

Meta-analyses of mortality:

- People who inject drugs:
  - ✓ Mortality rate: 2.3/100PY.
  - ✓ Standard mortality rate: 15
  - ✓ Main causes of deaths: Overdose and HIV

Mathers. Bull World Health Organ 2013

- Dependent users of heroin/other opioids:
  - ✓ Mortality rate: 2.1/100PY
  - ✓ Standard mortality rate: 15
  - ✓ Main cause of death: Overdose

Degenhardt. Addiction 2011

All-cause mortality among 523 anti-HCV positive PWID admitted for drug abuse treatment 1970–84 in Norway, followed up until 2012

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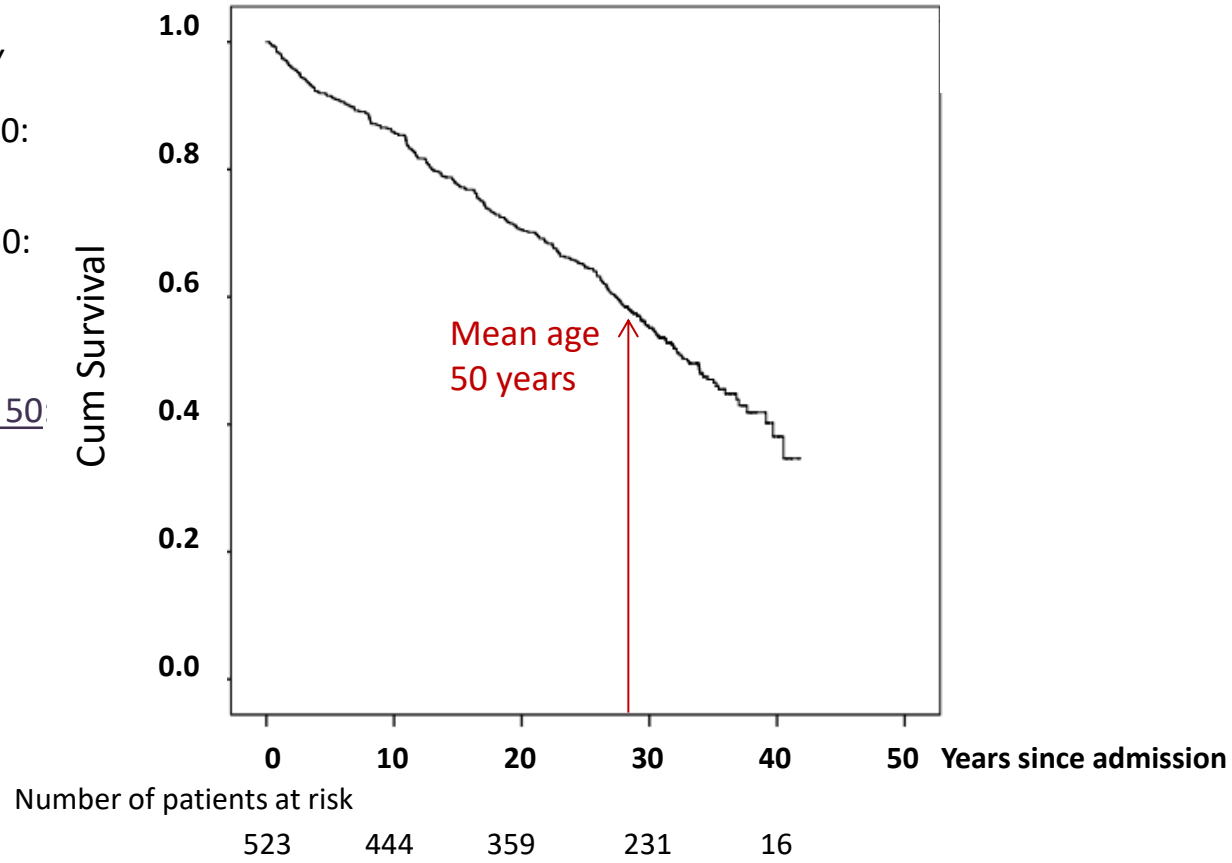
CMR: 2.0/100PY

CMR until age 50: 1.8/100PY

CMR after age 50: 3.6/100PY

Still alive at age 50:
Males: 56%
Females: 65%

All: 59%



Kielland KB, unpublished data

All-cause mortality according to HCVRNA among anti-HCV positive PWID admitted for drug abuse treatment 1970–84 in Norway followed up until 2012

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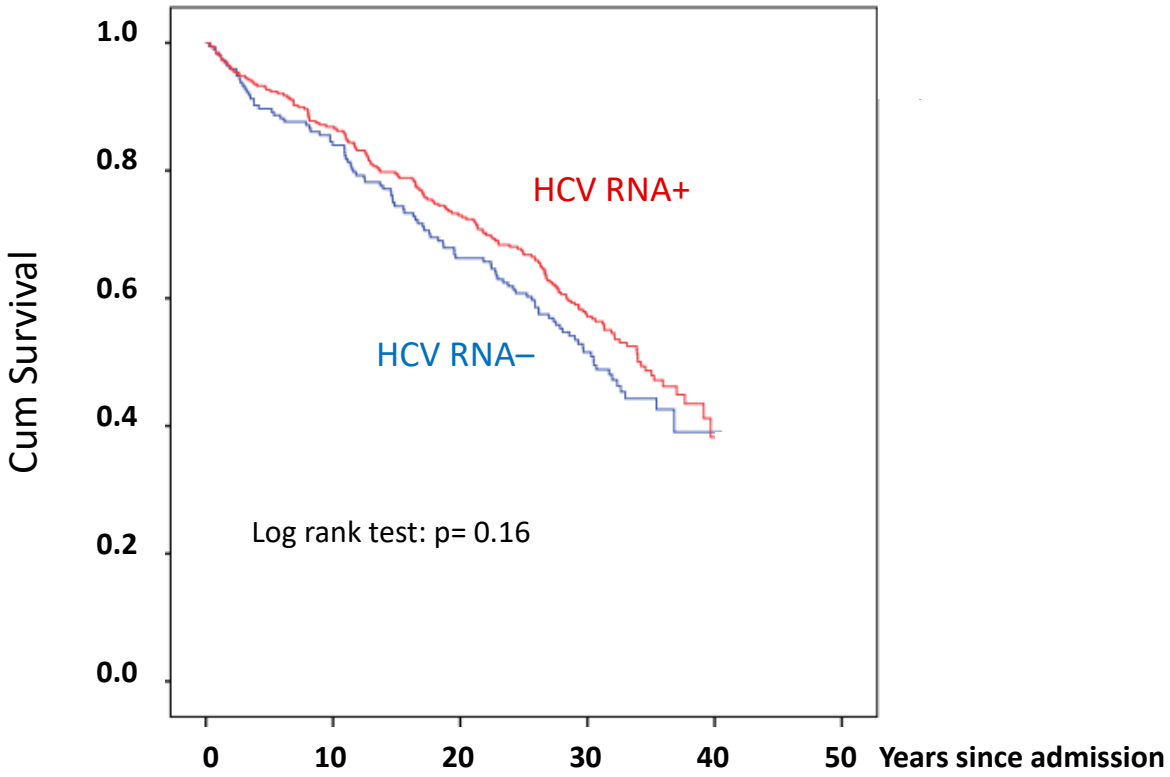
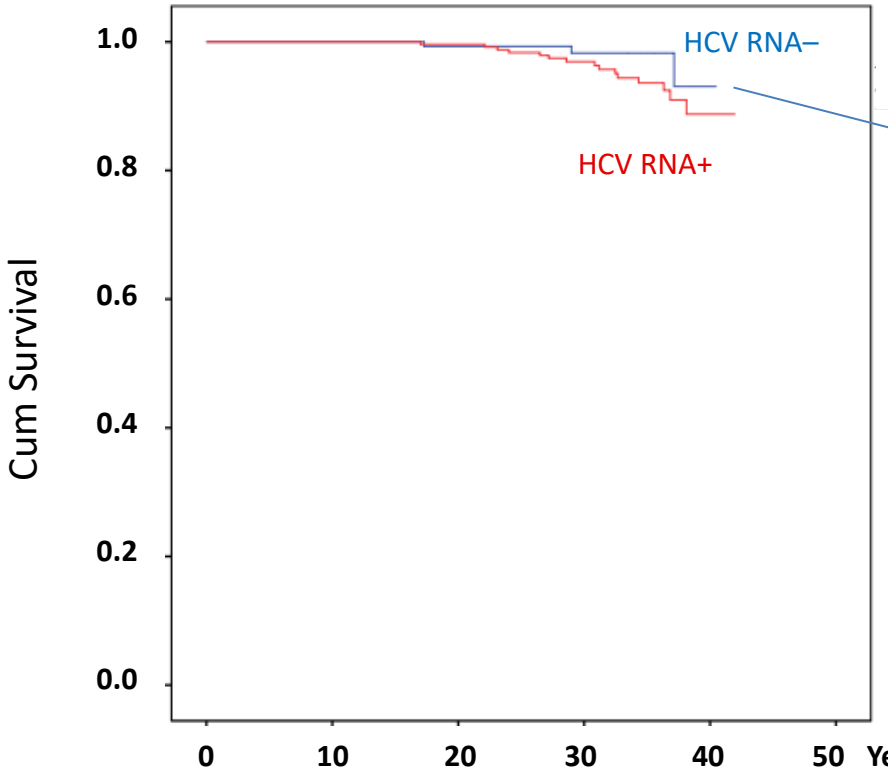


Number of patients at risk

HCVRNA–	195	161	122	77	5
HCVRNA+	328	283	237	154	11

Kielland KB, unpublished data

Liver-related mortality according to HCV RNA among anti-HCV positive PWID admitted for drug abuse treatment 1970–84 in Norway, followed up until 2012



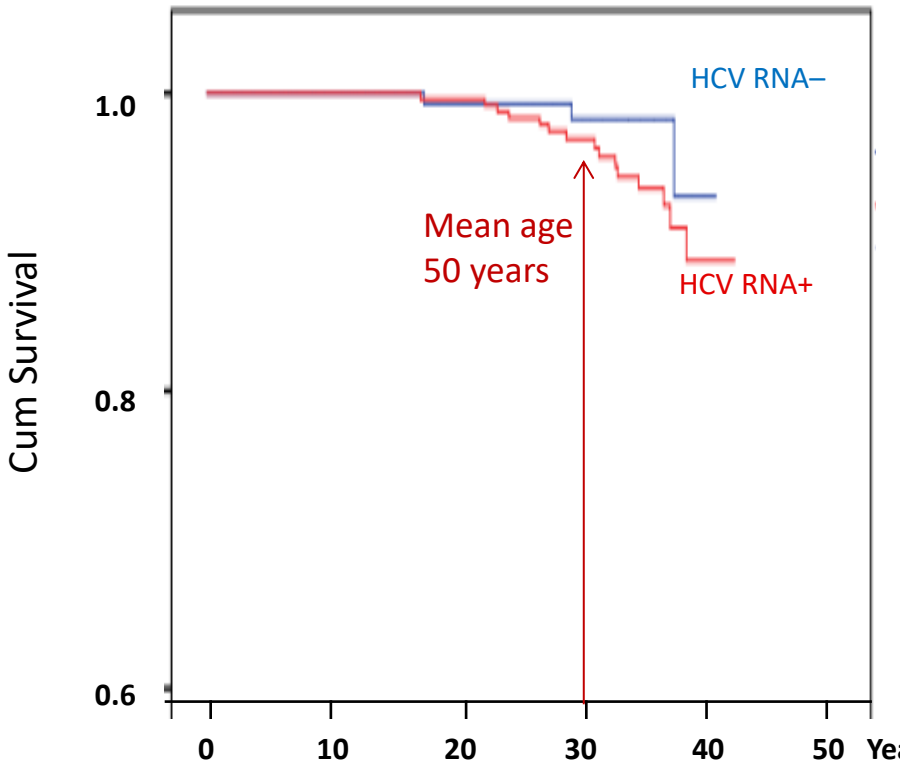
Hepatitis B (two cases)
Alcoholic liver disease (one case)

Number of patients at risk

HCV RNA–	195	169	130	89	5
HCV RNA+	328	292	246	177	15

Kielland KB, unpublished data

Liver-related mortality according to HCV RNA among anti-HCV positive PWID admitted for drug abuse treatment 1970–84 in Norway, followed up until 2012



Kielland KB, unpublished data

Number of patients at risk

HCV RNA–	195	169	130	89	5
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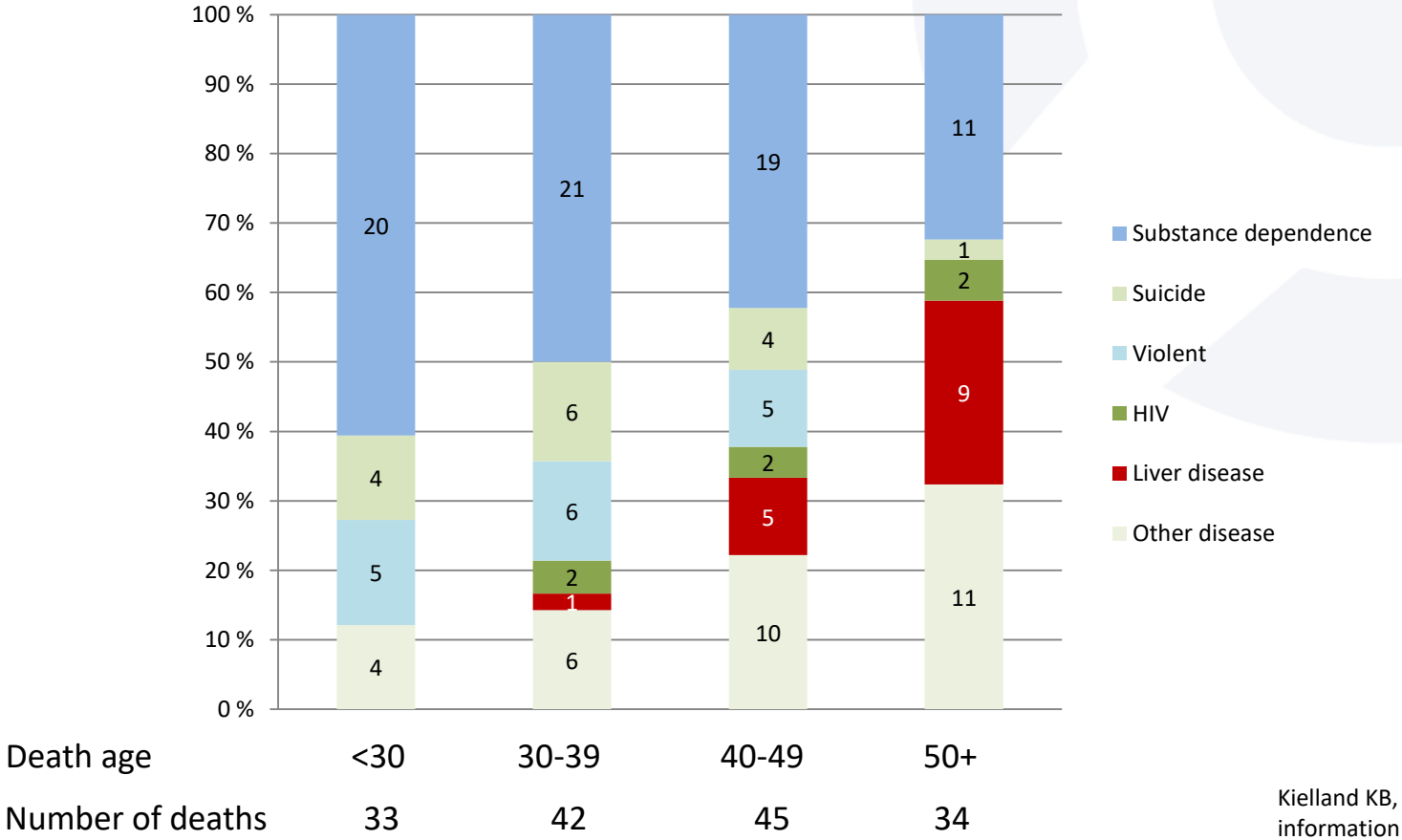
Causes of death among PWID with chronic hepatitis C according to death age

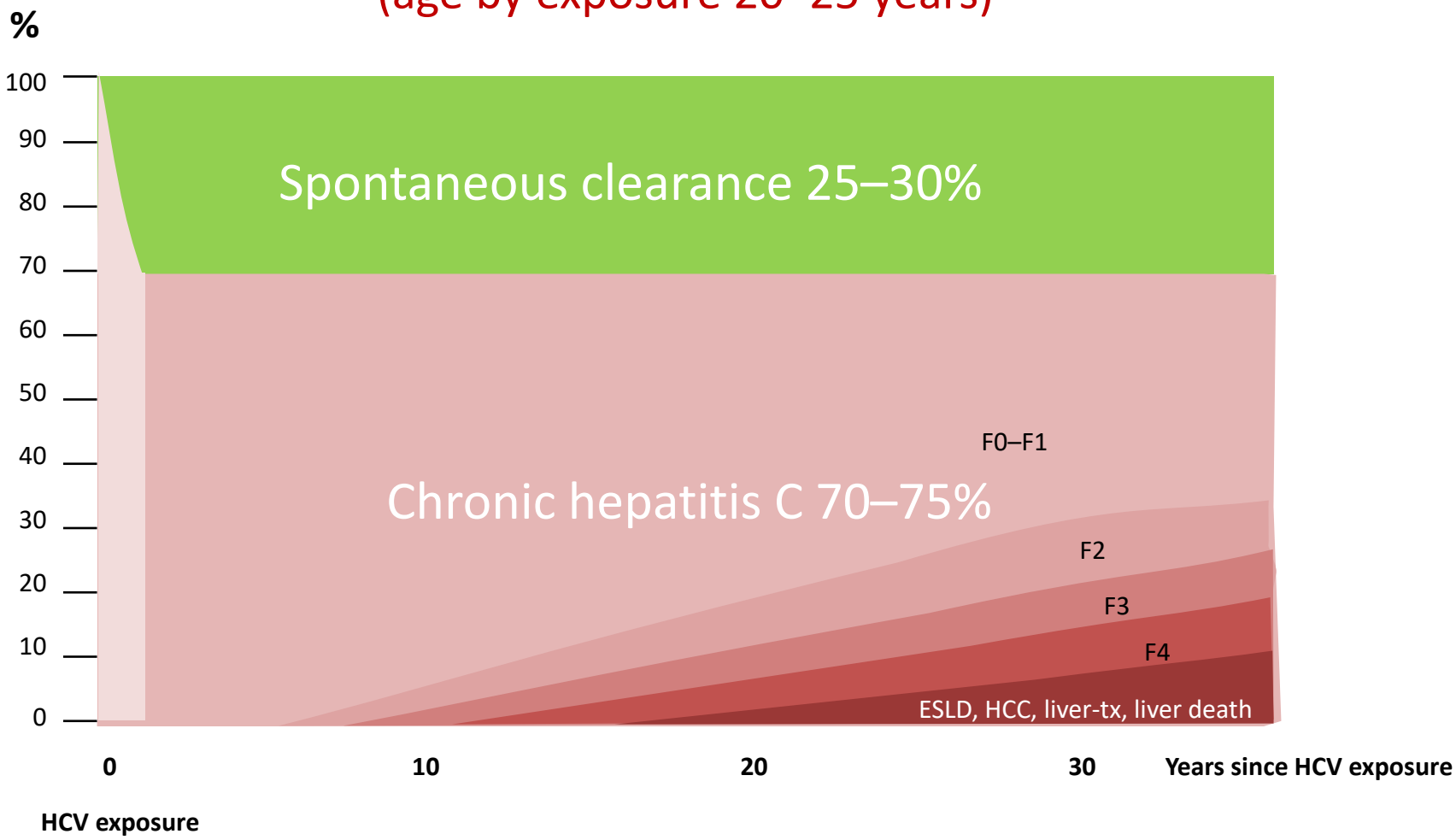


Death age	<30	30-39	40-49	50+
Number of deaths	33	42	45	34

Kielland KB, unpublished information

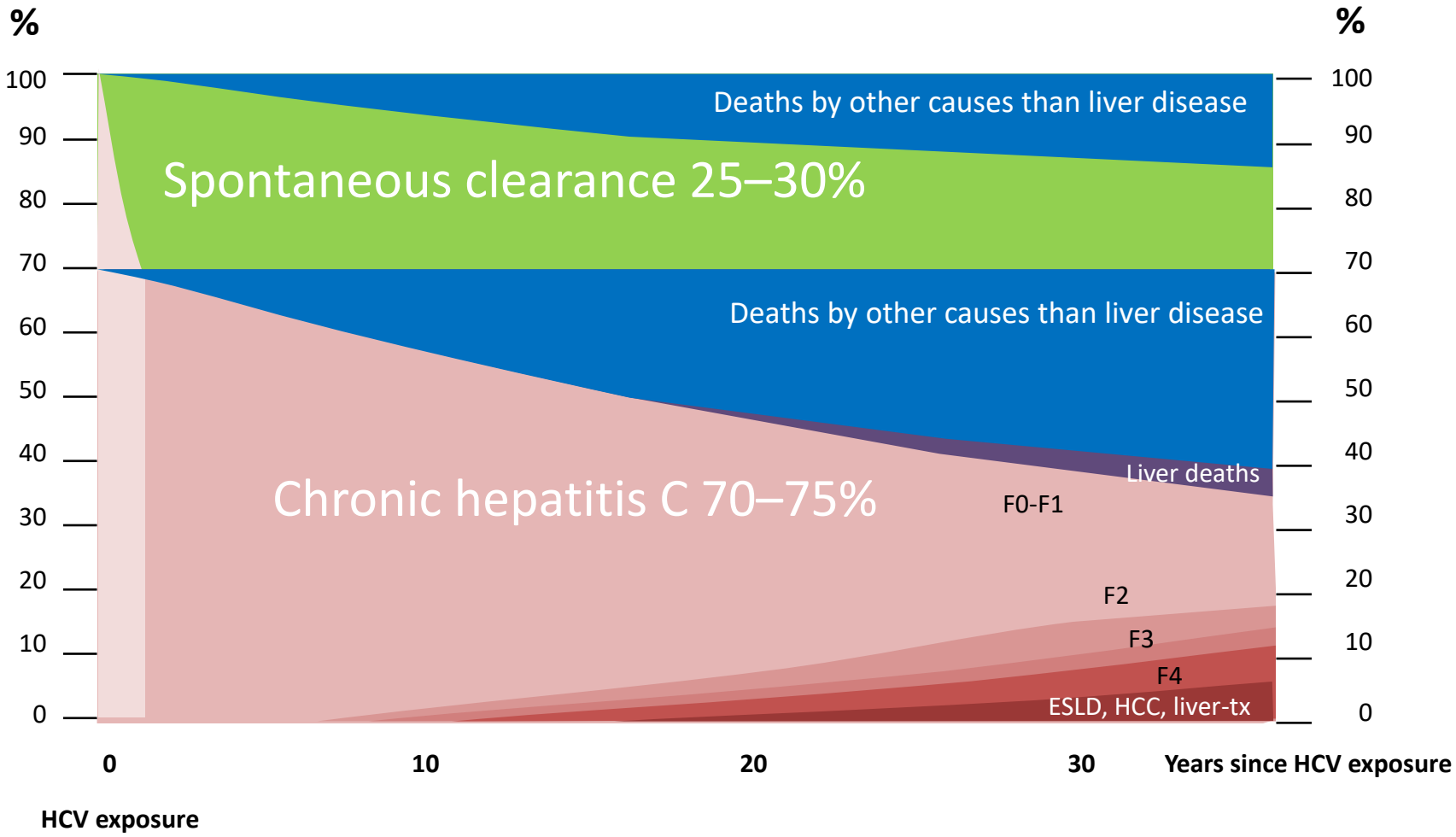
Natural course of chronic hepatitis C

(age by exposure 20–25 years)

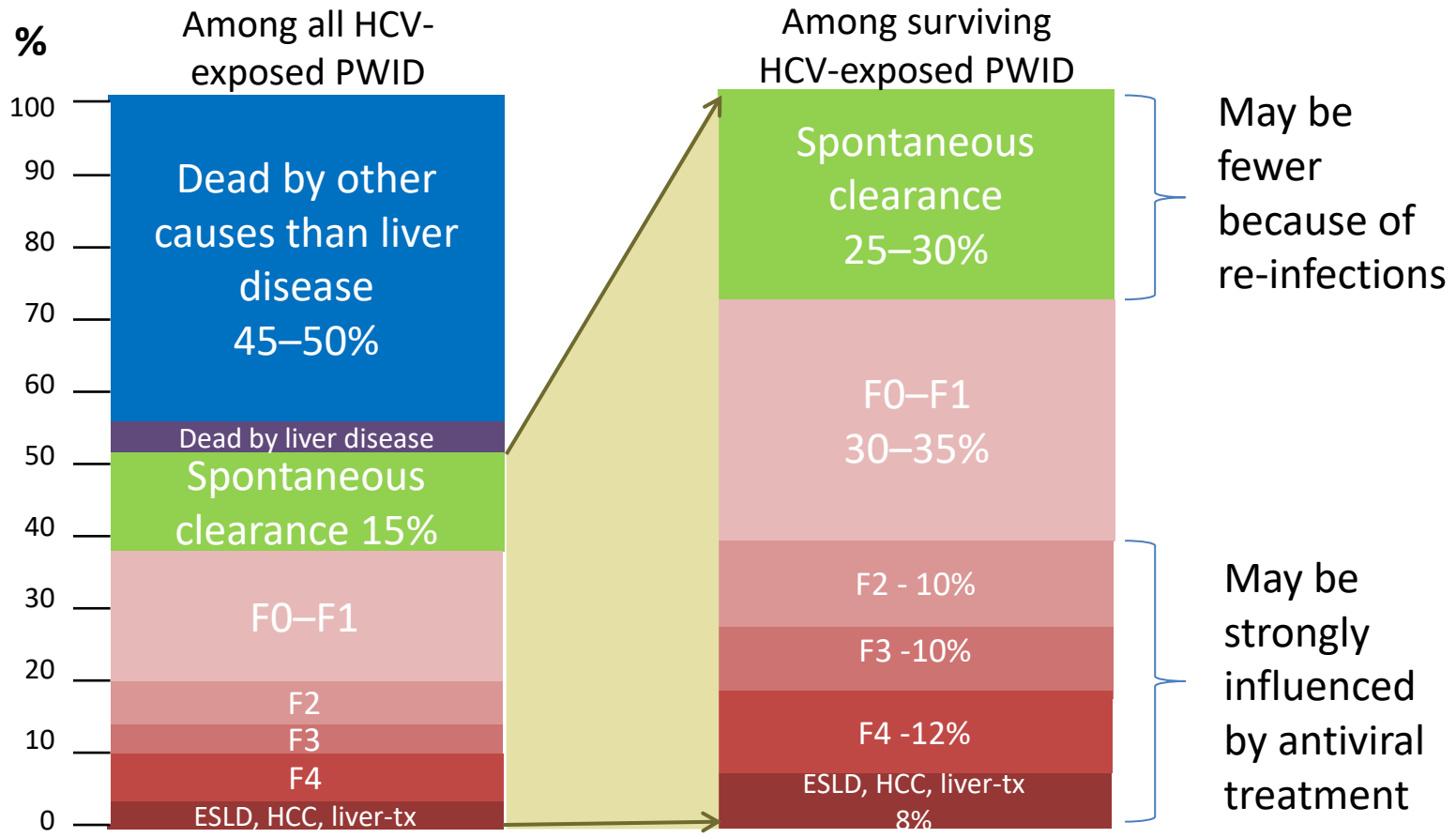


Natural course of chronic hepatitis C in PWID

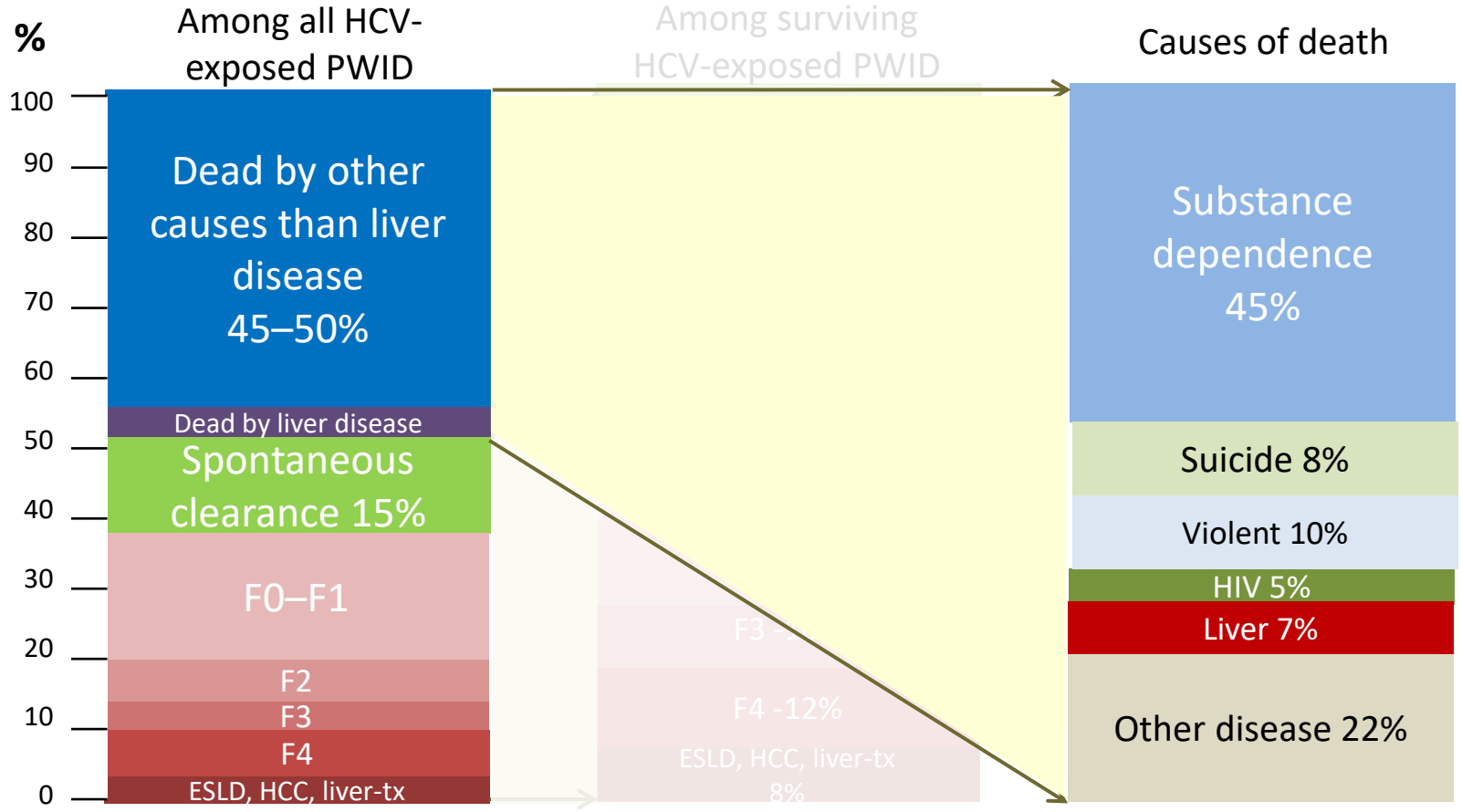
(age by exposure 20–25 years)



Estimated situation for anti-HCV positive PWID at age 50–60 years – about 30–35 years after HCV exposure



Cumulated causes of death among Norwegian PWID in 2012 in a cohort admitted for drug abuse treatment 1970-1984 at mean age 22 years



Extrahepatic manifestations

Certain associations with HCV:

- Cryoglobulinemia
  - >50% (mostly low levels without clinical consequences)
  - Prevalence increases with age, and in Europe higher in the south than in the north
  - Skin disease (<5%)
  - Kidney disease (glomerulonephritis)
  - Peripheral neuropathy
- Non-Hodgkin lymphoma, relative risk 2.0-2.5

Jan Peveling-Oberhag, Luca Arcaini, Martin-Leo Hansmann, Stefan Zeuzem. Journal of Hepatology 2013 vol. 59 j 169–177

Extrahepatic manifestations

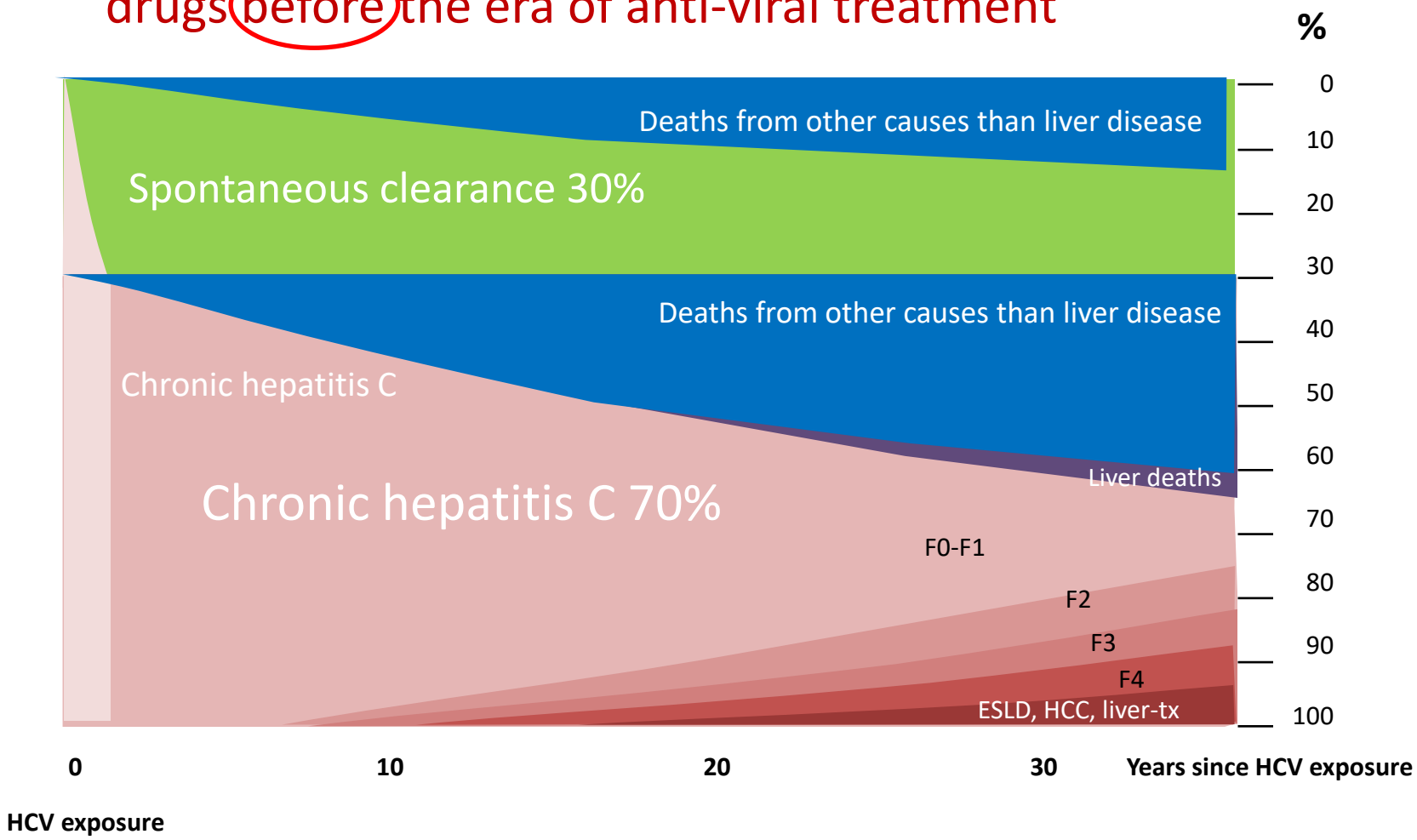
Possibly or probably associated with HCV:

- Diabetes mellitus type 2
- Some autoimmune diseases
- Fatigue, depression secondary to the chronic inflammation
- Vascular disease?
- Brain affection directly associated with virus replication in the brain?
  - Impaired cognitive function? Depression? Fatigue?

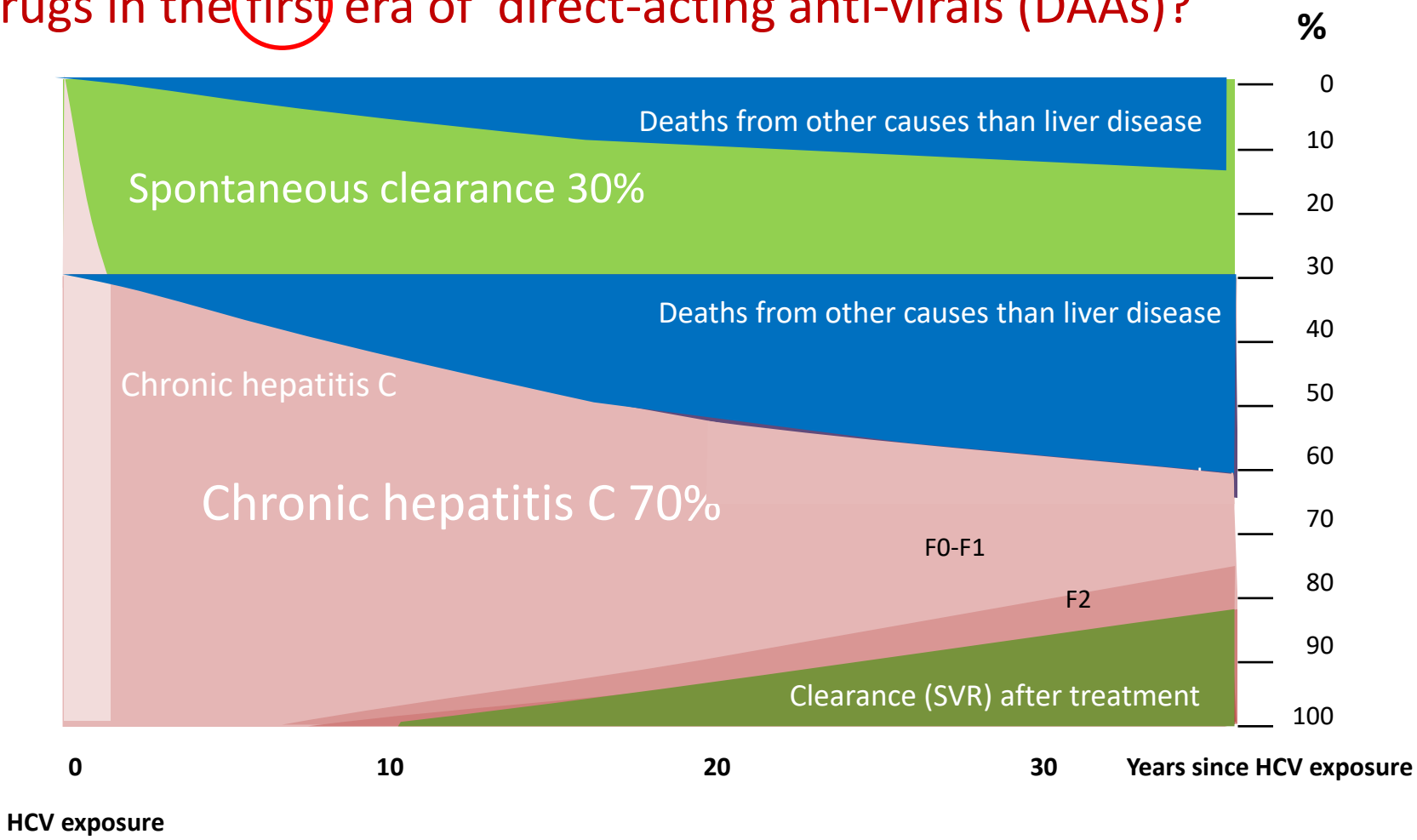
Tang et al. Infectious Agents and Cancer (2016) 11:29

Ruhl CE, Menke A, Cowie CC, Everhart JE. Hepatology. 2014 Oct; 60(4): 1139–1149.

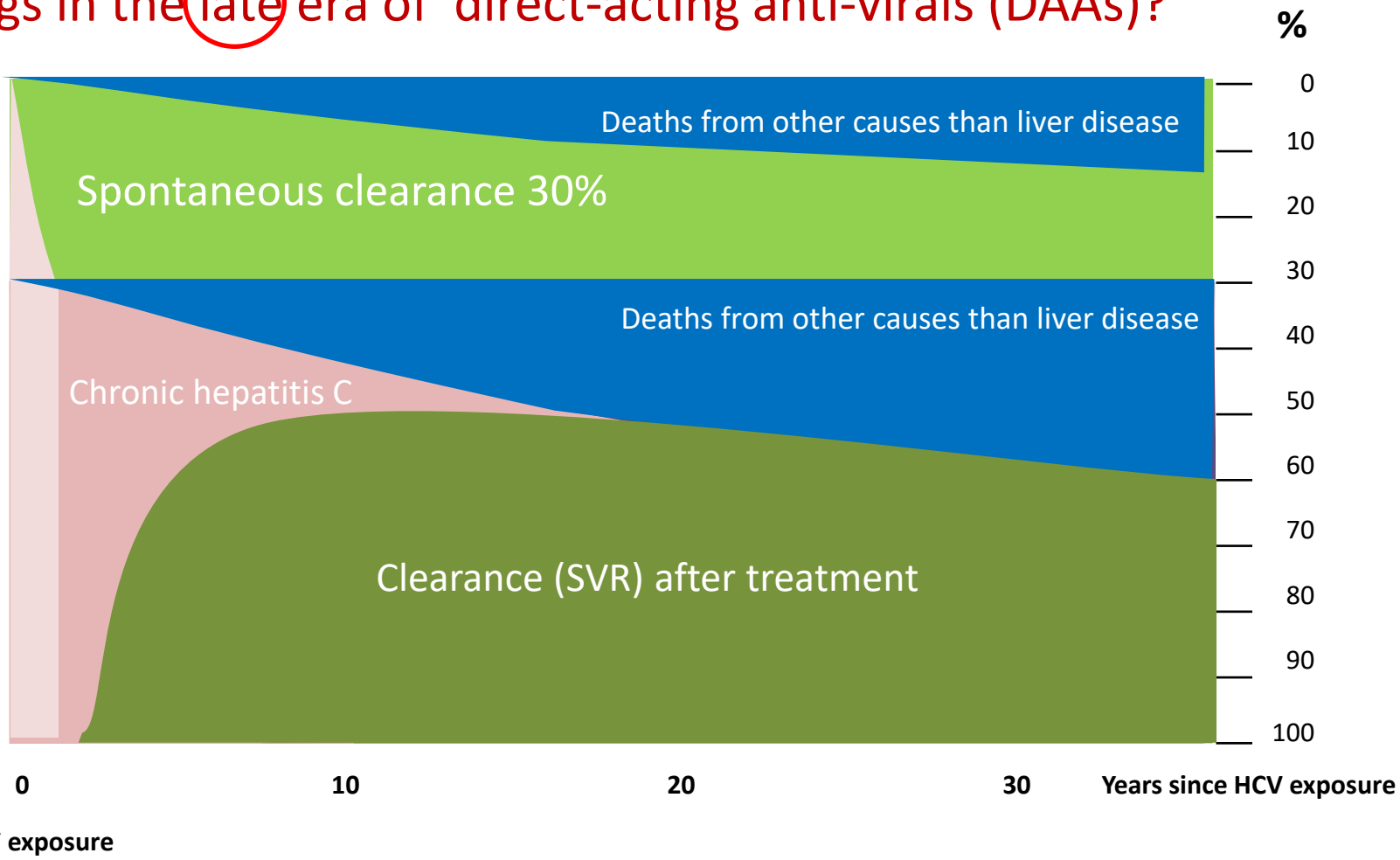
Natural course of chronic hepatitis C in people who inject drugs before the era of anti-viral treatment



Natural course of chronic hepatitis C in people who inject drugs in the first era of direct-acting anti-virals (DAAs)?



Natural course of chronic hepatitis C in people who inject drugs in the late era of direct-acting anti-virals (DAAs)?



Conclusions

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- 30–40% of PWID with CHC will develop advanced liver fibrosis/cirrhosis within 25–40 years
- After age 40–50 years, liver disease becomes an increasingly important cause of death
- Among PWID under 40–50 years of age, other causes of death dominate, mainly drug related
- Direct-acting antivirals may eliminate both the burden of liver disease and liver-related mortality

Causes of death in cohort of Norwegian PWID 30-40 years after admission to drug abuse treatment 1970-1984, mean age at that time was 22 years