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

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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

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

Shashidhar Venkatesh Murthy,

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.

The natural course of liver disease in chronic hepatitis C
(age by exposure 20–25 years)

Spontaneous clearance 25–30%

Chronic hepatitis C 70–75%

HCV RNA+ → Anti-HCV+/HCV RNA−

ESLD, HCC, liver-tx, liver death

F0-F1

F2

F3

F4

Acute hepatitis C

HCV exposure

Years since HCV exposure
Factors which may increase or reduce fibrosis progression

<table>
<thead>
<tr>
<th>Host factors</th>
<th>External factors</th>
<th>Viral factors</th>
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</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Alcohol</td>
<td>Genotype 3</td>
</tr>
<tr>
<td>High age at exposure</td>
<td>(Tobacco)</td>
<td>Genetic variability</td>
</tr>
<tr>
<td>Untreated co-infection HIV</td>
<td>(Cannabis)</td>
<td></td>
</tr>
<tr>
<td>Untreated co-infection HBV</td>
<td>Coffee (reduced fibrosis?)</td>
<td></td>
</tr>
<tr>
<td>Overweight/steatosis/NASH</td>
<td>Chocolate (reduced fibrosis?)</td>
<td></td>
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<tr>
<td>Insulin resistance/metabolic</td>
<td></td>
<td></td>
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<tr>
<td>syndrome/DM2</td>
<td></td>
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<tr>
<td>Genetic and other factors</td>
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</tbody>
</table>
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%
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

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%

Mean age 50 years

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

Log rank test: p = 0.16

Number of patients at risk

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<th>0</th>
<th>10</th>
<th>20</th>
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<tr>
<td>HCVRNA−</td>
<td>195</td>
<td>161</td>
<td>122</td>
<td>77</td>
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<tr>
<td>HCVRNA+</td>
<td>328</td>
<td>283</td>
<td>237</td>
<td>154</td>
<td>11</td>
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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

Number of patients at risk

- HCV RNA−: 195, 169, 130, 89, 5
- HCV RNA+: 328, 292, 246, 177, 15

Cum Survival

- HCV RNA−
- HCV RNA+

Years since HCV exposure

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

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

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Mean age 50 years

CumSurvival

Number of patients at risk

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

- **Spontaneous clearance**: 25–30%
- **Chronic hepatitis C**: 70–75%
- **ESLD, HCC, liver-tx, liver death**
Natural course of chronic hepatitis C in PWID
(age by exposure 20–25 years)

- Spontaneous clearance 25–30%
- Chronic hepatitis C 70–75%
- Deaths by other causes than liver disease

Liver deaths
- F0-F1
- F2
- F3
- F4
- ESLD, HCC, liver-tx
Estimated situation for anti-HCV positive PWID at age 50–60 years – about 30–35 years after HCV exposure

Among all HCV-exposed PWID:
- Dead by other causes than liver disease: 45–50%
- Dead by liver disease
  - Spontaneous clearance: 15%
  - F0–F1: 30–35%
  - F2: 10%
  - F3: 10%
  - F4: 12%
  - ESLD, HCC, liver-tx: 8%

Among surviving HCV-exposed PWID:
- May be fewer because of re-infections
- Spontaneous clearance: 25–30%
  - F0–F1: 30–35%
  - F2: 10%
  - F3: 10%
  - F4: 12%
  - ESLD, HCC, liver-tx: 8%

May be strongly influenced by antiviral treatment
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

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?


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

- **Spontaneous clearance 30%**
- **Chronic hepatitis C 70%**
- **Deaths from other causes than liver disease**
- **Liver deaths**

F0-F1, F2, F3, F4, ESLD, HCC, liver-tx

Years since HCV exposure

HCV exposure

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

- **Spontaneous clearance 30%**
- **Chronic hepatitis C 70%**
- **Clearance (SVR) after treatment**
- **Deaths from other causes than liver disease**

![Graph showing the natural course of chronic hepatitis C](image)

- **HCV exposure**
- **Years since HCV exposure**

- **Chronic hepatitis C**
- **F0-F1**
- **F2**
- **Deaths from other causes than liver disease**

- **Spontaneous clearance 30%**
- **Chronic hepatitis C 70%**
- **Clearance (SVR) after treatment**

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

- Spontaneous clearance 30%
- Chronic hepatitis C
- Clearance (SVR) after treatment
- Deaths from other causes than liver disease
Conclusions

• 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.

- Unknown
- Other diseases
- Respiratory disease
- Cardiovascular disease
- Cancer
- Endocarditis
- Liver disease
- HIV
- Intoxication possible suicide
- Accidents
- Homicide
- Suicide
- Alcohol dependence
- Drug dependence
- Other intoxication
- Intoxication alcohol
- Intoxication opioids