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**Long-term prognosis for transplant-free survivors of
paracetamol-induced acute liver failure**

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Long-term prognosis for transplant-free survivors of paracetamol-induced acute liver failure

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Keywords: Fulminant liver failure; acetaminophen; hepatic encephalopathy; mortality; survival; epidemiology.

Abbreviations: CI = Confidence interval; ICD = International Classification of Diseases.

Summary

Background: The prognosis for transplant-free survivors of paracetamol-induced acute liver failure is unknown.

Aim: To examine whether paracetamol-induced acute liver failure increases long-term mortality.

Methods: We followed all transplant-free survivors of paracetamol-induced acute liver injury hospitalized in a Danish national referral center during 1984-2004. We compared age-specific mortality rates from one year post-discharge through 2008 between those in whom the liver injury led to an acute liver failure and those in whom it did not.

Results: We included 641 patients. On average, age-specific mortality rates were slightly higher for the 101 patients whose paracetamol-induced liver injury had caused an acute liver failure (adjusted mortality rate ratio = 1.70, 95% CI 1.02-2.85), but the association was age-dependent, and no survivors of acute liver failure died from liver disease, whereas suicides were frequent in both groups. These observations speak against long-term effects of acute liver failure. More likely, the elevated mortality rate ratio resulted from incomplete adjustment for the greater prevalence of substance abuse among survivors of acute liver failure.

Conclusions: Paracetamol-induced acute liver failure did not affect long-term mortality. Clinical follow-up may be justified by the cause of the liver failure, but not by the liver failure itself.

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Introduction

Acute liver failure is an immediately life-threatening condition that in Denmark and many other countries is caused primarily by paracetamol poisoning (1-3). The treatment strategy—securing patient survival until effective liver regeneration takes over and resorting to liver transplantation if this strategy fails—relies on the assumption that the liver is capable of complete regeneration leading to clinical recovery (4-6). The purpose of our study was to evaluate this assumption by studying long-term mortality among survivors of paracetamol-induced acute liver failure.

A recent case series suggested that non-paracetamol drug-induced liver injury with jaundice could play a role in the long-term risk of chronic liver disease, but without a comparison group a firm conclusion could not be reached (7). The choice of comparison group is critical because it is difficult to disentangle the long-term effects of the acute liver failure from the confounding effects of the other characteristics of patients who develop acute liver failure. Hence we restricted our study to patients at risk of acute liver failure, viz. patients with severe paracetamol-induced liver injury. Among them, we compared post-discharge mortality between those who had or had not experienced an acute liver failure. To corroborate the necessity of using restriction to reduce confounding, we also compared the mortality of patients with paracetamol-induced liver injury without acute liver failure with the mortality in the general population.

Materials and methods

Study population

According to national guidelines, Danish citizens hospitalized with severe paracetamol-induced liver injury (i.e. with the International Normalized Ratio [INR] above 1.7) must be considered for transfer to The Liver Unit at Rigshospitalet, Copenhagen, Denmark's only liver transplantation

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4 center. The decision to transfer patients is made by specialists at The Liver Unit on an individual
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6 basis. We identified all patients who were hospitalized for paracetamol-induced liver injury in The
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8 Liver Unit during 1984-2004, had an INR above 1.7 but survived without a liver transplant and
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10 were still alive one year after discharge. We had no data on other patients. Among the 656
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12 identified patients we excluded 15 who at the time of the paracetamol-induced liver injury had
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14 chronic liver disease, identified through the Danish National Patient Registry which has recorded
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16 hospital contacts in Denmark since 1977 (8). The registry data include admission and discharge
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18 dates and discharge diagnoses coded by physicians using the 8th revision of the International
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20 Classification of Diseases (ICD-8) through 1993 and the 10th revision (ICD-10) thereafter. Chronic
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22 liver disease was defined by a history of a diagnosis code for alcoholic cirrhosis (ICD-8: 571.09;
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24 ICD-10: K70.3), biliary cirrhosis (ICD-8: 571.90-91; ICD-10: K74.3-5), chronic hepatitis (ICD-8:
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26 571.93, 573.02; ICD-10: B18.x, K73.x), or unspecific cirrhosis (ICD-8: 571.92, 571.99; ICD-10:
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28 K74.0-2, K74.6). Simultaneous overdose of drugs other than paracetamol was not a criterion for in-
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30 or exclusion.
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39 *Patient data*

40 We used data from the patients' medical charts to ascertain the diagnosis of acute liver failure,
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42 defined by **coagulopathy**, **jaundice**, and hepatic encephalopathy grade 2-4 (9). We also obtained
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44 information on presence or absence of alcohol abuse; other substance abuse; schizophrenia or use of
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46 antipsychotic medication; affective disorder or use of antidepressants; borderline personality
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48 disorder; and eating disorder. We supplemented the chart data with discharge diagnoses of the same
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50 conditions in the National Patient Registry: alcohol abuse (ICD-8: 291.xx, 303.xx except 303.90;
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52 ICD-10: F10.2-9), other substance abuse (ICD-8: 294.30, 294.38, 304.xx; ICD-10: F11.x to F19.x),
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54 schizophrenia (ICD-8: 295.xx; ICD-10: F2x.x), affective disorder (ICD-8: 296.xx, 298.xx; ICD-10:
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56 F3x.x), borderline personality disorder (ICD-8: none; ICD-10: F60.3), and eating disorder (ICD-8:
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4 294.19; ICD-10: F50.x). If these conditions were noted in a patient's medical chart at admission for
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6 paracetamol-induced liver injury, they were considered present throughout the follow-up. If they
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8 were identified through the National Patient Registry, they were considered present from the date of
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10 the first hospital discharge with the diagnosis.
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14 We also obtained information on the following conditions, using only discharge diagnoses in the
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16 National Patient Registry: cancer (ICD-8: 140.xx to 195.xx; ICD-10: Cxx.x), chronic obstructive
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18 lung disease (ICD-8: 491.xx, 492.xx; ICD-10: J42.x, J43.x, J44.x), diabetes (ICD-8: 249.xx,
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20 250.xx; ICD-10: E10.x to E14.x), arterial hypertension (ICD-8: 40x.xx; ICD-10: I10.x to I15.x),
21
22 and ischemic heart disease (ICD-8: 41x.xx; ICD-10: I20.x to I25.x). These conditions were
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24 considered present from the date of the first hospital discharge with the diagnosis.
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29 30 *Mortality data*

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32 Dates of death were obtained from the Central Office of Civil Registration, where data are updated
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34 continuously with no loss to follow-up (10). Causes of death were ascertained from the Cause of
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36 Death Registry, which contains information on up to four events or medical conditions that led to
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38 death for each decedent. The data are supplied by the physician responsible for the patient's
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40 treatment at the time of death (11). We reviewed the registered data to define a single cause of death
41
42 for each patient; the investigators were blinded to patients' acute liver failure status.
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46 47 *Statistical analyses*

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49 Follow-up began one year after the date of discharge following paracetamol-induced liver injury
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51 and ended at death or on **31 December 2008**, whichever came first. The 1-year delay in follow-up
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53 was introduced to avoid bias due to early deaths related to the poisoning or its psychiatric cause
54
55 (e.g. risk of completed suicide is particularly high up to one year after a paracetamol poisoning)
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57 (12). **We used the Mann-Whitney test for the continuous variables, i.e. patient age and calendar**
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59 **time, and Pearson's chi-square test for the other variables to test the hypotheses that patients with or**
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4 without acute liver failure had similar characteristics at inclusion. We used a p-value below 0.05 to
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6 denote statistically significant non-similarity.
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10 We compared the mortality rate ratio (specifically, the hazard ratio) for patients with and without
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12 acute liver failure using Cox proportional hazards regression, and we adjusted for the effects of
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14 gender, calendar year, alcohol abuse, other substance abuse, schizophrenia or use of antipsychotics,
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16 affective disorder or use of antidepressants, borderline personality disorder, eating disorder, cancer,
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18 chronic obstructive lung disease, diabetes, arterial hypertension, and ischemic heart disease.
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21 Because we followed patients from a time point defined by *recovery* from acute paracetamol-
22
23 induced liver injury, we anticipated that patient age was a stronger predictor of death than time
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25 since hospital discharge, and therefore a more relevant time scale for our analyses (13). Using
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27 natural splines, we plotted the age-specific adjusted mortality rate ratios for acute liver failure (14).
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30 31 32 Comparison with population mortality

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34 Through the Central Office of Civil Registration we identified a control group from the general
35
36 population, the aim being to substantiate the excess mortality for patients hospitalized for
37
38 paracetamol-induced liver injury. We included 100 gender-, age-, and calendar time-matched
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40 Danish citizens per patient without acute liver failure, and they were drawn at random using risk set
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42 sampling (15). Using Cox regression and natural splines, as described above, we plotted the age-
43
44 specific mortality rate ratios for the general population sample vs. patients with paracetamol-
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46 induced liver injury without liver failure.
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50 51 52 **Results**

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54 We included 641 transplant-free survivors of paracetamol-induced liver injury, and 101 (16%) of
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56 these had acute liver failure. Among the patients with acute liver failure, 16% had hepatic
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58 encephalopathy of grade 2; 51% of grade 3; and 33% of grade 4. The median follow-up time was
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4 7.6 years, the maximum 23.2 years; 86 patients (13%) died during the follow-up, including 23
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6 patients in the acute liver failure group.
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10 Patients with acute liver failure were more likely than patients without acute liver failure to be
11 female, and they were older, and more likely to abuse alcohol and other substances (Table 1). Also
12 the age-specific prevalence of substance abuse was higher among patients with a history of acute
13 liver failure than among patients without such history. For example, at age 45 the prevalence of
14 alcohol abuse was 58% in the acute liver failure group (14 of 24 patients under observation)
15 compared with 29% in the group with milder liver injury (29 of 101 patients under observation)
16 (Table 2).
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27 On average, age-specific mortality rates were higher for patients with a history of acute liver failure
28 (adjusted mortality rate ratio = 1.70, 95% CI 1.02 to 2.85). However, the mortality rate ratio was
29 strongly age-dependent, so that 25-, 45-, or 75-year-old people who had more than one year
30 previously been hospitalized with paracetamol-induced acute liver failure had higher mortality than
31 equal-age people who had more than one year previously been hospitalized with paracetamol-
32 induced acute liver injury without liver failure, and vice versa among 35- or 60-year-old people
33 (Figure 1). However, the earlier temporary failure of liver function was not the cause of the excess
34 mortality: no patient with a history of acute liver failure was recorded to die from liver disease (data
35 on causes of death were unavailable for three decedents). By contrast, six patients without acute
36 liver failure died from acute or chronic liver disease. Suicides were very frequent in both groups (26
37 suicides = 37% of the 76 deaths with data on causes of death), as were accidents, cancer, and
38 cardiovascular disease (Table 3).
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56 Mortality before age 60 years was clearly higher for patients with a history of paracetamol-induced
57 liver injury without acute liver failure than for the general population sample (Figure 1). Hence, the
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4 mortality in the general population was not a relevant estimate of the expected mortality among the
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7 91% of our patients who were younger than 60 years old at discharge after paracetamol-induced
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9 liver injury.

10 11 12 13 **Discussion**

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15 We followed transplant-free survivors of paracetamol-induced liver injury and found that those who
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17 had suffered an acute liver failure had marginally higher mortality, but for causes not attributable to
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19 their earlier liver failure. We also showed that survivors of paracetamol-induced liver injury
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21 younger than 60 years of age had a markedly higher mortality than the general population, largely
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23 due to suicides and accidents.
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28 It is a long-standing and basic assumption that there is complete clinical recovery after a reversible
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30 loss of liver function. This assumption is rooted in the well-known regenerative capacity of the
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32 liver, but it has not previously been challenged by a long-term clinical follow-up study. Our data
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34 support the classical assumption. We found a marginal increase in mortality after acute liver failure,
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36 but it was age-dependent and not due to liver-related deaths. Rather, we expect the association to be
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38 an overestimate due to incomplete control of confounding by substance abuse, which was only
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40 crudely measured as absent or present.
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46 **The validity of the clinical diagnoses of acute liver failure is crucial because invalid diagnoses**
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48 **would have led us to underestimate the true effect of acute liver failure (16). However, we believe**
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50 **that the diagnoses were valid because they were made by specialists in a liver transplantation center**
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52 **and required clinically overt hepatic encephalopathy, i.e. grade 2-4.**

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56 The findings in our study accord with a recent follow-up study in which patients with and without
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58 hepatotoxic paracetamol overdose had parallel survival curves from one year after hospital
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4 discharge (17). In that study, however, at most only 15 deaths were observed more than one year
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6 after hospital discharge. Likewise, a study of post-discharge liver biopsies from patients with
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8 paracetamol-induced liver injury supplied histological evidence of reversibility (6), and complete
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10 regeneration has also been described after surgical liver injury in animals and humans (4, 5) and
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12 after severe toxic liver injury in rats (18).
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17 Our comparison with mortality in the general population is consistent with our previous findings
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19 that, for several years after hospitalization for paracetamol poisoning, the risks of being diagnosed
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21 with a psychiatric disease and/or completing suicide are greatly elevated (12, 19). Our analyses also
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23 demonstrate that a general population sample is not the proper comparison group for evaluating
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25 long-term effects of acute liver injury: those pre-existing patient characteristics that lead to
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27 experiencing an acute liver injury, *in casu* from paracetamol overdose, heavily influence prognosis.
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29 Therefore we conducted the study within a cohort of patients with a history of paracetamol-induced
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31 liver injury and excluded those who died within a year post-discharge. These design features
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33 minimized confounding from patient characteristics such as suicidal intent as opposed to therapeutic
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35 misadventure, because we can expect similar characteristics—82% with suicidal intent— in equal-
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37 age Danish patients with or without acute liver failure after paracetamol poisoning (20).
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44 In conclusion, paracetamol-induced acute liver failure did not increase long-term mortality, but
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46 many patients hospitalized for paracetamol-induced liver injury eventually completed suicide.
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48 Hence our findings reiterate that all patients hospitalized for paracetamol-induced liver injury
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50 should undergo psychiatric evaluation and follow-up, whereas follow-up by hepatologists is not
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52 indicated.
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Declaration of interests

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Figure legend

Figure 1. Mortality rates for patients with a history of paracetamol-induced acute liver failure (black) and for a random population sample (gray) relative to that for patients with a history of paracetamol-induced liver injury without liver failure (the dotted horizontal line). The thin lines show 95% confidence limits. Hence the black line shows that at age 45-50 years, primarily, mortality was higher for patients with a history of paracetamol-induced acute liver failure than for patients with a history of paracetamol-induced liver injury without acute liver failure. The gray line shows that mortality before age 60 years was much lower for the general population sample than for patients with a history of paracetamol-induced liver injury without acute liver failure. The horizontal boxplots illustrate the age distribution (median, quartiles, and extremes) at the time of paracetamol-induced liver injury with or without acute liver failure (ALF), and the superimposed black dots mark the ages at which deaths occurred.

Table 1. Characteristics of patients at inclusion. For the continuous variables, age and year of inclusion, the numbers shown are the median and 25th and 75th percentiles.

	Acute liver failure	No acute liver failure	p-value
Age	43 (33-55)	35 (24-47)	< 0.001
Women	73 (72%)	331 (61%)	0.05
Year of inclusion	1999 (1996-2003)	2001 (1996-2003)	0.50
<i>Substance abuse</i>			
Alcohol abuse	47 (47%)	145 (27%)	< 0.001
Other substance abuse	14 (14%)	34 (6.3%)	0.01
<i>Psychiatric disease</i>			
Schizophrenia or use of antipsychotics	16 (16%)	59 (11%)	0.21
Affective disorder or use of antidepressants	42 (42%)	207 (38%)	0.61
Borderline personality disorder	2 (2.0%)	12 (2.2%)	0.83
Eating disorder	0	8 (1.5%)	0.46
<i>Somatic disease</i>			
Cancer	1 (1.0%)	4 (0.74%)	0.72
Chronic obstructive lung disease	1 (1.0%)	6 (1.1%)	0.68
Diabetes	3 (3.0%)	15 (2.8%)	0.83
Arterial hypertension	4 (4.0%)	12 (2.2%)	0.50
Ischemic heart disease	2 (2.0%)	10 (1.9%)	0.75
Total	101 (100%)	540 (100%)	

Table 2. Characteristics of the 641 patients with paracetamol-induced liver injury, by current age. Columns show the number of patients in the cohort who are observed at a particular age and their characteristics. Patients are followed from 1 year after discharge after a paracetamol-induced liver injury, so a patient who was 33 years old at discharge and died at age 49 is under observation from age 34 to age 49.

	Current age (years)						
	20	30	40	45	50	60	70
<i>Number of patients under observation</i>							
Acute liver failure	8	11	20	24	19	20	2
No acute liver failure	76	113	112	101	82	55	24
<i>Women</i>							
Acute liver failure (%)	7 (88)	7 (64)	15 (75)	17 (71)	15 (79)	15 (75)	2 (100)
No acute liver failure (%)	68 (89)	63 (56)	59 (53)	62 (61)	48 (59)	35 (64)	16 (67)
<i>Alcohol abuse</i>							
Acute liver failure (%)	0	2 (18)	11 (55)	14 (58)	12 (63)	11 (55)	2 (100)
No acute liver failure (%)	3 (4)	10 (9)	24 (21)	29 (29)	34 (41)	22 (40)	13 (54)
<i>Other substance abuse</i>							
Acute liver failure (%)	0	4 (36)	2 (10)	3 (12)	3 (16)	2 (10)	1 (50)
No acute liver failure (%)	1 (1)	5 (4)	8 (7)	6 (6)	7 (9)	4 (7)	3 (12)
<i>Psychiatric disease*</i>							
Acute liver failure (%)	2 (25)	4 (36)	7 (35)	9 (38)	8 (42)	11 (55)	2 (100)
No acute liver failure (%)	15 (20)	36 (32)	39 (35)	43 (43)	37 (45)	31 (56)	16 (67)
<i>Somatic disease[#]</i>							
Acute liver failure (%)	0	0	2 (10)	3 (12)	5 (26)	5 (25)	1 (50)
No acute liver failure (%)	0	1 (1)	4 (4)	12 (12)	10 (12)	18 (33)	6 (25)

* Schizophrenia including use of antipsychotics, affective disorder including use of antidepressants, borderline personality disorder, or eating disorder.

[#] Cancer, chronic obstructive lung disease, diabetes, arterial hypertension, or ischemic heart disease.

Table 3. Causes of death. A total of 86 patients died during follow-up, but this table excludes the three patients with acute liver failure and seven patients without acute liver failure with no available data on cause of death.

Cause of death	Acute liver failure	No acute liver failure
Acute liver disease	0	1 (2%)
Chronic liver disease	0	5 (9%)
Alcoholism	0	5 (9%)
Cancer	4 (20%)	6 (11%)
Cardiovascular disease	3 (15%)	7 (13%)
Diabetes	1 (5%)	0
Pneumonia	0	2 (4%)
Respiratory disease	2 (10%)	0
Gastrointestinal bleeding	0	1 (2%)
Dementia	0	1 (2%)
Epilepsy	0	1 (2%)
Accident	2 (10%)	7 (13%)
Suicide	8 (40%)	20 (36%)
Total	20 (100%)	56 (100%)

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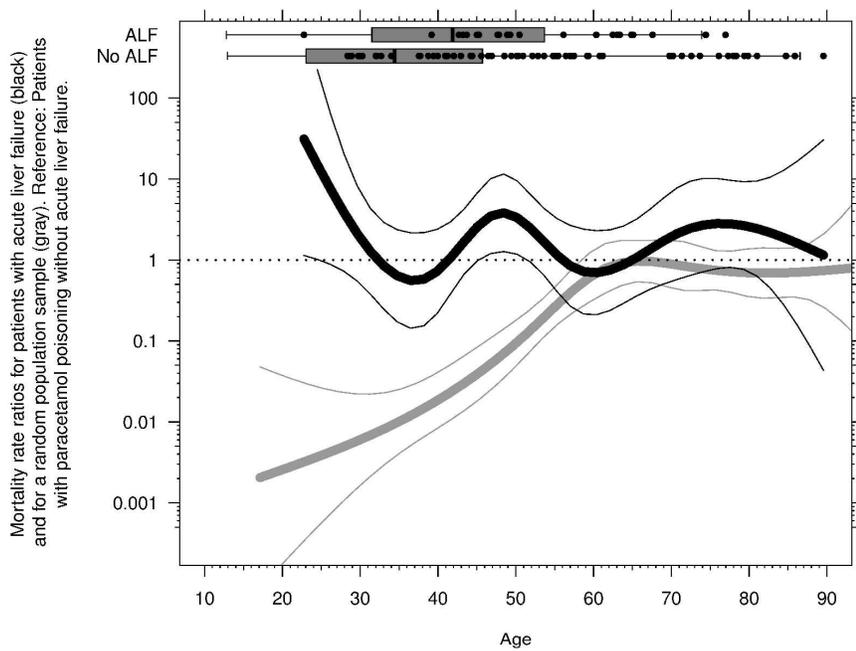


Figure 1. Mortality rates for patients with a history of paracetamol-induced acute liver failure (black) and for a random population sample (gray) relative to that for patients with a history of paracetamol-induced liver injury without liver failure (the dotted horizontal line). The thin lines show 95% confidence limits. Hence the black line shows that at age 45-50 years, primarily, mortality was higher for patients with a history of paracetamol-induced acute liver failure than for patients with a history of paracetamol-induced liver injury without acute liver failure. The gray line shows that mortality before age 60 years was much lower for the general population sample than for patients with a history of paracetamol-induced liver injury without acute liver failure. The horizontal boxplots illustrate the age distribution (median, quartiles, and extremes) at the time of paracetamol-induced liver injury with or without acute liver failure (ALF), and the superimposed black dots mark the ages at which deaths occurred.

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For Peer Review