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Death rates and causes of death in cohorts of serum hepatitis patients followed up for more than 20 years

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SUMMARY

A cohort of 214 drug addicts with serum hepatitis and a cohort of 193 hepatitis patients without drug addiction were examined in respect of death rates, causes of death and a number of risk factors for reduced survival. The death rate was significantly higher among the drug addicts than among non-addicts. The annual mortality rate was 1·5% in the drug addict group and 0·7% in the non-addict group. The highest relative risk of death was 860 for female drug addicts in age group 15–24 compared to females of the same age in the general population. The most prevalent cause of death in the drug addict group was drug overdose (53%), whereas in the other group 66% died from various somatic diseases. Hepatitis or complications of viral hepatitis played no role as cause of death among the drug addicts, and infections as a whole were also responsible for very few deaths. For male drug addicts, imprisonment before admission and leaving hospital without the doctors' permission were risk factors for early death.

INTRODUCTION

From the late 1960s drug addiction increased markedly in Norway [1, 2], a phenomenon also reported from other countries [1]. The increase coincided with the introduction of illegally imported drugs such as heroin, which resulted in a new group of addicts that was younger than previous addicted groups and often involved in various criminal activities [1, 3, 4].

Along with the increased problem of addiction and the change in the drug addict population, there was an increase in the incidence of serum hepatitis in Norway. This epidemic was, to a large extent, due to spread of hepatitis virus through the habit of sharing needles and syringes when injecting illegal drugs intravenously.

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Many of the drug addicts with acute hepatitis were admitted to Ullevål University Hospital in Oslo, which was the only hospital with a department of infectious disease in the area. There they shared wards with non-addicted patients with acute hepatitis.

Medical records and laboratory results have been kept for all hospitalized patients. Hence, the hospital has a unique archive of records from all the hospitalized serum hepatitis cases occurring in Oslo and its suburban area, that is a population of over 500000 people.

In the present study we have examined the death rate and the causes of death, including risk factors for death, in patients with serum hepatitis and drug addiction, hospitalized in the years 1972–6. The follow-up period was more than 20 years. We have compared these data with the findings in a non-addict

group of serum hepatitis patients hospitalized during the same period. Finally we have also compared the data for these two patient groups with mortality causes and death rates in the general Norwegian population.

METHODS

Study population

The total study population consisted of 407 consecutive patients discharged with a diagnosis of serum hepatitis (defined below) from Ullevål University Hospital, Department of Infectious Diseases, during the period January 1972 to December 1976. Of these 407 patients, 214 suffered from drug addiction, which was defined as periodical or continuous use of opiates and/or amphetamine (or similar drugs) intravenously. This group is classified as intravenous drug users (IVDU). The duration of drug injection ranged from 2 months to 8 years (mean 2·6) and started at age 14–17 (mean 15) years.

The hospital records of the remaining 193 patients gave no indication of drug addiction, and this group is classified as non intravenous drug users (NIVDU).

More information about the two patient groups, with emphasis on the occurrence of some possible risk factors, is shown in Table 1, which also shows the number of patients admitted each year during the 5 years period. Although, in some respects, the two patient groups were rather similar, there was more than 10 years difference in mean age, and also marked differences with regard to employment status, habitation and previous imprisonment. Patients who were readmitted to the hospital with the same diagnosis, were only counted once (37 subjects).

Serum hepatitis – definition

Serum hepatitis was defined as hepatitis B and/or non-A–non-B hepatitis. Patients fulfilling the clinical and biochemical criteria of acute hepatitis with presence of HBsAg or increasing titre of anti-HBs in the blood were classified as having acute hepatitis B. A few had clinical and laboratory findings indicating chronic hepatitis B. At the time of the admissions the terms Australia antigen and antibody were used [5], but in this presentation the current terms HBsAg and anti-HBs are used.

The non-A–non-B patient group consisted of patients with hepatitis in whom, in addition to hepatitis B virus, causes like hepatitis A virus, cytomegalovirus, Epstein–Barr virus, alcohol and drugs were excluded by clinical judgement and the laboratory methods available. Later we have found antibodies against hepatitis C virus in stored sera from a few of the patients, and we consider it likely that a majority of the non-A–non-B patients had hepatitis C. Furthermore there is evidence that some patients were infected with both hepatitis B virus and hepatitis C virus at the time of hospitalization, but due to lack of stored sera and incomplete follow-up after discharge from hospital, it has not been possible to examine this fully.

Data collection

Data on the 407 patients were obtained from their medical records. In addition to information relevant to the actual hepatic disease, we collected the available data on drug abuse, mental and physical health and sociodemographic variables. Specific data on the type of drug abuse were found for 187 of the 214 drug addicts. In 182 of the 214 subjects information on the duration of intravenous drug use prior to study entry was obtained.

The causes and date of death were obtained from the National Cause of Death Registry. Diagnoses were classified according to ICD-8 from 1972 to 1985 and ICD-9 from 1986 [6]. The code for suicide and self-inflicted injury was based on rubrics E 950–959.

Follow-up

The observation period was from the date of the admission to Ullevål University Hospital, Department of Infectious Diseases until death or 31 December 1998. The median follow-up was 23·51 years (lower quartile: 22·25 and upper quartile: 25·12). The data file was linked with the National Death Registry at the end of December 1998 on the basis of the 11-digit person identification number. Fourteen patients had emigrated. Dates of death were included along with ICD-codes for the causes of death. Information on mortality and causes of death were compared with figures for the total Norwegian population given by official statistics for the period 1972–98 [7, 8].

Statistical methods

Mortality rates were calculated by dividing the number of deaths in each group with the amount of

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Table 1. *Patient profile at hospital admission time and number of admitted serum hepatitis patients according to year and subgroup*

	Serum hepatitis and drug addiction		Serum hepatitis and no drug addiction		
Gender	Male	Female	Male	Female	Total
Number (%)	130 (60%)	84 (40%)	118 (61%)	75 (39%)	407
Unmarried	107 (88%)	72 (89%)	76 (66%)	43 (60%)	
Drug injection among close family members	11 (10%)	7 (9%)	6 (5%)	9 (13%)	
Alcohol abuse among close family members	17 (15%)	11 (15%)	2 (2%)	5 (7%)	
Without permanent habitation	38 (29%)	31 (38%)	9 (8%)	2 (3%)	
Imprison prior to hospital admission	56 (57%)	12 (19%)	5 (5%)	0	
9–10 years school education or less	100 (88%)	68 (85%)	43 (54%)	37 (71%)	
Unemployment	85 (70%)	56 (69%)	5 (4%)	5 (7%)	
Mean age	21·54	19·24	31·01	31·08	
Year of study entry					
1972	50		26		76
1973	40		31		71
1974	21		36		57
1975	66		48		114
1976	37		52		89
Total	214		193		407

person-years in the observation period. Relative risk in each age group was found by dividing the mortality rates by age specific rates given in the Norwegian official statistics [7]. Odds ratios with 95% confidence intervals were calculated by a method described by Altman [9]. A comparison on age at admission among the sexes was examined by independent *T* test samples [10].

Survival analysis was done by the Kaplan–Meier method [11]. Difference between two survival curves was estimated by Gehan and log rank test [12].

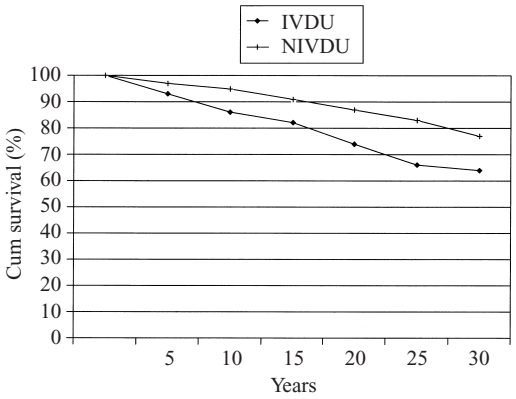

Fig. 1. Probability of survival for 214 intravenous drug users (IVDU) and 193 non-intravenous drug users (NIVDU) in a life table analysis plot (Gehan test: $P = 0{\cdot}0004$).

RESULTS

Death rates

In the 214 drug addicts (IVDU) there were 68 deaths during the observation period, versus 32 deaths in the 193 non-drug addicts (NIVDU). No deaths occurred in the acute phase of the hepatitis disease, but patients died every year during the observation period. In Figure 1 the probability of survival during the follow-up period is shown for the IVDU and NIVDU patients. There was a highly significant difference in survival between the two groups (Gehan test: $P = 0{\cdot}0004$ and log rank test: $P = 0{\cdot}0005$).

The mortality rate in the IVDU group was 1·5% (1·1% for females and 1·9% for males) per year. The overall mean age at death in this group was about 33 years; 31·83 years in women and 34·29 years in men. However, the females were significantly younger at admission (Table 1). If the drug addicts were divided into two subgroups, hepatitis B and hepatitis non-

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Table 2. *Number of deaths, number of person-years and observed mortality rates per 1000 person-years for 407 hepatitis patients according to age, gender and use of intravenous drugs (IVDU) compared to the general Norwegian population matched by age and gender*

Age	No. deaths according to age at death	No. of person-years	Observed mortality rates for patients	Observed mortality rates for the general pop.	Rate ratio of death (95% confidence interval)
IVDU					
Females					
15–24	8	31·59	253	0·3	843 (350–2027)*
25–34	3	39·21	77	0·5	154 (48–490)*
35–44	8	1364·99	6	1·0	6 (1–39)
45–54	1	395·71	2·5	2·7	0·9 (0·08–9·51)
Total	20	1831·50	11		
Males					
15–24	12	39·04	307	1·0	307 (155–609)*
25–34	13	132·81	98	1·0	98 (38–252)*
35–44	15	1150·81	13	2·0	6·5 (2–24)*
45–54	6	1167·84	5·1	5·3	0·9 (0·36–3)
55–64	1	73·56	13·6	14·3	0·9 (0·44–2)
65–74	1	22·99	43	37·9	1·1 (0·70–2)
Total	48	2587·05	18		
Not IVDU					
Females					
15–24	0				
25–34	0				
35–44	2	654·14	3	1·0	3 (0·35–26)
45–54	2	559·67	3·5	2·7	1·3 (0·26–6)
55–64	2	153·52	13	6·7	1·9 (0·77–5)
65–74	4	140·52	28	19·0	1·5 (0·82–3)
75–86	5	138·29	36	81·5	0·4 (0·29–0·65)†
Total	15	1646·15	9		
Males					
15–24	0				
25–34	3	49·90	60	1·0	60 (20–177)*
35–44	5	350·38	14	2·0	7·0 (2–26)*
45–54	2	1243·61	1·6	5·3	0·3 (0·03–3)
55–64	2	615·67	3·3	14·3	0·2 (0·07–0·69)†
65–74	2	300·63	6·7	37·9	0·1 (0·08–0·36)†
75–86	3	104·13	29	113	0·2 (0·17–0·37)†
Total	17	2664·32	6·4		
Total	100	8729·02	11		

* P values $< 0{\cdot}05$ for higher mortality rates.
† P values $< 0{\cdot}05$ for lower mortality rates.

A–non-B, there was no difference in mortality rate between the subgroups.

In the NIVDU group the mortality rate was 0·7% (0·9% for females and 0·6% for males) per year, and the overall mean age at death was about 58 years (66·09 for women and 52·09 for men). In this group men and women had a similar mean age at admission (Table 1).

Odds ratio for death among the category of IVDU versus NIVDU, was 2·34 (95% CI: 1·45–3·77). Rate ratio of death in the two groups compared was 1·9 (95% CI: 1·32–2·78). At the time of hospital admission the NIVDU patients were significantly older than the IVDU group.

The numbers of deaths according to age and gender for the two groups of hepatitis patients compared to the general Norwegian population matched by age and gender are shown in Table 2. Mortality rates for

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Table 3. *Number and causes of death during the observation period in hepatitis patients with (IVDU) and without (NIVDU) drug addiction background. The percentages of the deaths are given in parentheses*

	Intravenous drug user (IVDU)	Not IVDU
Alive	146 (68·2)	161 (80·1)
Dead	68 (31·8)	32 (19·9)
Total	214	193
Causes of death		
Drug overdose	38 (55·8)	2 (6·3)
Suicide by drug overdose	11 (16·2)	1 (3·1)
Suicide by other means than overdose	5 (7·4)	0
Accidents	4 (5·8)	2 (6·3)
Chronic liver disease	3 (4·4)	3 (9·4)
AIDS	1 (1·5)*	3 (9·4)
Other diseases	5 (7·4)	18 (56·3)
Unknown	1 (1·5)	3 (9·4)

* In addition, two patients who died from drug overdose suffered from HIV infection.

female IVDUs were significantly higher for age groups up to 35 years compared to the general population. Among the males the mortality rate was significantly higher for all groups up to 45 years. The highest relative risk of death in comparison to the general population was found in females aged 15–24 years.

In the NIVDU group there was not a significantly higher death rate in any of the female age groups, but male age groups 25–34 and 35–44 had higher mortality rates compared to the general population. However, as seen from Table 2, some NIVDU age groups had a lower death rate than the general population.

Causes of death

The causes of death in the two groups of hepatitis patients are given in Table 3. In the IVDU group most of the deaths were related to drug abuse, as 49 of the 68 patients died from either drug overdose or suicide by drug overdose: 85% of the females and 67% of the males died from these causes. Of the overdoses, 35 were with opiates, whereas 14 were with other analgesics, antidepressants and sedatives.

Suicide by means other than overdose was the cause of death in 5 patients; 2 by hanging, 2 by shooting and 1 by carbon monoxide poisoning. Four of the remaining deaths were due to accidents, 3 male patients in car accidents and 1 female by drowning. Of all the death diagnoses, 61 (90%) were from autopsies and of the drug-related deaths, 100% were examined *post mortem*. Among the remainder, there were 1 suicide by shooting, 4 accidents and 2 pneumonias.

Three of the patients in the group died from chronic liver disease with a likely alcoholic aetiology. These three patients all had acute hepatitis B that resolved during the stay at hospital. However, based on liver biopsy one year before death, one of the patients had chronic hepatitis non-A–non-B in addition to alcoholic liver disease at the time of death. The remaining deaths were as follows: 2 from bronchopneumonia, 2 from coronary heart disease, 1 from AIDS and 1 from alcohol intoxication.

In the NIVDU group two patients died from opiate drug overdose and one from suicide with alcohol and sedative drugs in combination. These represented 6% of the deaths among the females and 11% among the males. Two male patients in this group died from accidents; by drowning and an accidental fall respectively.

The 24 deaths from somatic diseases (75% of the deaths in this group), were 9 from cancer (9 different neoplasm types), 3 from AIDS, 3 from liver cirrhosis, 2 from coronary heart diseases, 4 from other diseases of the circulatory system and 3 from respiratory disease. Of the 3 patients who died from liver disease, 2 died from liver cirrhoses related to chronic hepatitis B infection, and 1 from alcoholic liver cirrhosis. This last patient had at the hospital admission an acute hepatitis B.

In the NIVDU group, 22 of the 32 death diagnoses were identified by biopsies and autopsies, and among the remaining there were 2 AIDS patients, 2 pneumonias, 1 cancer, 1 myocardial infarction and 1 drowning, diagnosed clinically.

According to the death certificates, a majority (49/68) in the IVDU group were classified as having drug dependence and one as having alcohol dependence, as an underlying cause of death, in contrast to the other group which, at the time of death, included only 2 with drug dependence and 2 alcoholics.

Risk factors for early death

In the IVDU group the survival was significantly lower among men than among women (Table 4). Furthermore imprisonment before the episode of acute hepatitis was highly associated with shortened

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Table 4. *Risk factors of total mortality using survival curves for 214 intravenous drug users*

Variables	Level	*n*	25 years cum. survival	*P* value Gehan test	*P* value log rank test
Sex	Female	84	74·6 ± 4·9	0·064	0·0411
	Male	130	57·1 ± 5·7		
Age at admission	< 21	146	69·1 ± 3·9	0·591	0·298
	⩾ 21	68	51·6 ± 9·7		
Dropout from hospital	Yes	100	58·3 ± 5·2	0·019	0·019
	No	102	71·3 ± 6·1		
Education	< 9–10 years	168	63·7 ± 4·3	0·116	0·103
	> 9–10 years	26	82·3 ± 8·2		
Without perm. habitation	Yes	143	64·1 ± 6·2	0·788	0·934
	No	69	65·5 ± 4·9		
Unemployment	Yes	141	62·2 ± 4·9	0·685	0·523
	No	62	70·4 ± 6·1		
Imprisonment	Yes	68	61·9 ± 6·2	0·00001	0·00001
	No	94	86·8 ± 5·5		
Drug abuse in family	Yes	18	54·5 ± 11	0·089	0·109
	No	175	69·2 ± 4·4		
Alcohol abuse in family	Yes	25	64·5 ± 10	0·597	0·599
	No	163	69·9 ± 4·5		
No. years IV-drug abuse	< 3	100	60·6 ± 5·9	0·524	0·540
	⩾ 3	114	68·2 ± 4·7		

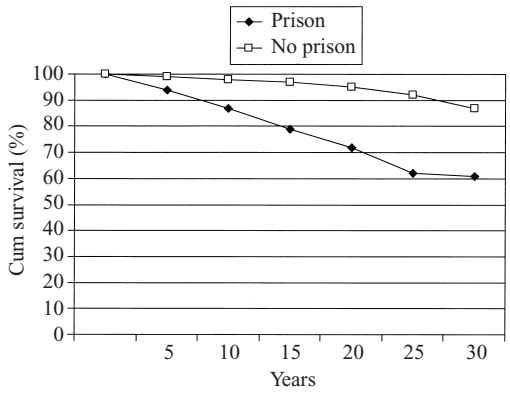

Fig. 2. Probability of survival for 214 intravenous drug users according to imprisonment prior to admission in a life table analysis plot (Gehan test: $P = 0{\cdot}00001$).

survival (Fig. 2). As can be seen from Table 4 other possible risk factors such as length of education and employment status did not significantly influence length of survival. The impact of dropout, defined as leaving without the doctors permission from hospital, as a risk factor on survival, was significant (log rank test: $P = 0{\cdot}01$). In addition, if the IVDU and NIVDU groups were considered together, both low educational level, unemployment and drug abuse in the family were significant risk factors for reduced survival.

When examining the NIVDU group for the risk factors listed in Table 4, none of the factors seemed to be of significance for reduced survival.

DISCUSSION

In this follow-up study of a cohort of hepatitis patients with and without drug addiction we found that mortality rates during a period of more than 20 years were approximately twice as high in drug-addicted patients as compared to non-addicts. Mean age at admission was about 11 years higher in the latter group, and the difference in annual mortality rate would probably have been even larger if age at admission to hospital had been equal in the two groups.

Increased mortality for drug addicts compared to the general population as seen in this study, was not an unexpected finding. Results from similar studies done in Scandinavian countries [13–18] show mortality of the same magnitude or slightly higher. Data from cohort studies from various European countries estimate annual lethality of drug addicts to about 1–3% [17, 19]. The mean observation time of more than 20 years in the present study is longer than for other studies published. It is possible that some IVDU managed to stop taking drugs during the observation period, and this may be one of many possible factors

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that might have contributed to a slightly lower mortality rate in our study. We are, at present studying this question, by examining surviving patients. Possibly our patient group was a selection of drug addicts who sought help more often than those who were not hospitalized, thereby contributing to a better survival. It is not likely that the slightly lower yearly mortality rate can be explained by a considerable number of unnoted deaths in the group, as the National Death Registry includes deaths reported both from Norway and abroad. A number of other factors not looked for in our study may have had an impact on mortality in this cohort, such as the methadone treatment project in Oslo (although very few of our patients were participants in this programme). A needle exchange programme seems to have had little effect on mortality among drug addicts in Oslo [1].

In the IVDU group, mortality rates for men for all age groups were higher than for women (Table 2). Compared to the general population the youngest age groups both of males and females had the highest death rates. In the general population there is a gender difference with a higher mortality rate for males than females at the same given age [7]. In the present study we confirmed the findings by others [14], that this difference is present but reduced in the drug addict group. It is interesting to note that the highest risk of mortality in comparison to a similar group in the general population was definitely found among females younger than 24 years. The results obtained thus indicate that the younger groups of drug addicts are at special risk of early death and are in special need of care and closer follow-up.

The higher mortality rates in the male NIVDU groups aged 25–44 years may partially be explained by three deaths from AIDS in these groups, and it is also likely that the NIVDU group contained drug abusers and people with other types of risky behaviour. The lower mortality found among NIVDU of older age compared to the general population is difficult to explain and to discuss in a meaningful way since the number of death in these groups was small.

Compared to official statistics on causes of death in the general population, there was a different distribution of diagnoses in the IVDU group. The main cause of death was drug overdose and suicide by drug overdose. Among the overdose victims 34% were women, which is higher than seen in another Norwegian study on overdose deaths in drug addicts [20]. However, this proportion of women among the overdose victims almost equals the amount of females in the study group (39%) and among the dead (30%). The prevalent use of opiates for overdosing is in accordance with what is seen in other settings [21–23]. The overdose deaths occurred in all three decades of the observation period. Thus there were 11 overdose deaths during the years 1972–80, and 14 and 13 deaths respectively during the periods 1981–90 and 1991–8.

Infections contributed directly only to 3 of the 68 deaths in the IVDU group. In none of the patients was acute or chronic viral hepatitis the main cause of death, although chronic (non-A–non-B) hepatitis may have contributed to death in one of the patients. An unknown number of those who died may have had a non-registered chronic viral hepatitis at the time of death, but we did not have any opportunity to analyse this. Preliminary results from testing IVDU patients that are still alive, shows however that infections with hepatitis C virus are widespread in the surviving group. Only one patient in the IVDU group died from AIDS (lymphoma), reflecting that HIV infection has not been a major problem among drug addicts in the Oslo area.

The distribution of causes of death in the NIVDU group differed also from the general population. The reason for this discrepancy is not obvious, but hospitalized patients with serum hepatitis may in several aspects be a selected group. There were fewer patients in this group than expected dying from coronary heart diseases. In fact, there were more cases dying from cancer, AIDS and liver diseases. It is noteworthy that some drug addicts of course may have been included in this group, a suggestion which may be supported by the fact that there were patients in this group that died from drug overdose. The three patients dying from AIDS were all homosexuals, who died from common AIDS complications. The two patients who died from hepatitis B, with liver cirrhosis, were women who were 87 and 59 years respectively at the time of death. There was no suspicion of drug or alcohol abuse in these two patients.

Major differences were found in this follow-up study between hepatitis patients with drug addiction and hepatitis patients without. Mortality rates were significantly different and also causes of death differed markedly. In both groups interesting observation were also made in comparison with the general population. Younger drug addicts seem to be at special risk of death, and special attention should be paid to these groups. The higher mortality among those who left hospital without permission, suggest

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that the hospital should try to make more effort in following up these patients. This may reflect the problem of treating patients with a strong need for narcotics in hospital without giving them any substitutes for the illegal drugs to which they are addicted. Studies of the drug addicts hospitalized with hepatitis in the 1970s and still alive are in progress.

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