Evidence-based medicine
ตามเกณฑ์ความรู้แพทยสภาเพื่อสอบใบอนุญาตฯ

1.2.9.1 asking focused questions: translation of uncertainty to an answerable question

1.2.9.2 finding the evidence: systematic retrieval of best evidence available

1.2.9.3 critical appraisal: testing evidence for validity, clinical relevance, and applicability

1.2.9.4 making a decision: application of results in practice

1.2.9.5 evaluating performance: auditing evidence-based decisions.

1.2.9.1 asking focused questions: translation of uncertainty to an answerable question

ตั้งคำถามแบบ EBM หรือ P I C O

1. ปัญหา หรือ ผู้ป่วย (***P***roblem or ***P***atient) เช่น ลักษณะทางคลินิกของผู้ป่วย
2. สิ่งที่จะให้แก่ผู้ป่วย (***I***ntervention) เช่น การให้ยาใหม่ หรือการใช้วิธีการวินิจฉัยแบบใหม่
3. สิ่งที่เป็นตัวเปรียบเทียบ (***C***omparison intervention) เช่น การให้ placebo หรือให้ยาเดิม
4. ผลที่ต้องการ (***O***utcome) เช่น ประสิทธิผลที่เกิดขึ้น หรือความแตกต่างที่ต้องการ

1.2.9.1 asking focused questions: translation of uncertainty to an answerable question

	Patient or Problem	**Intervention** (a cause, prognostic factor, treatment, etc.)	**Comparison Intervention** (if necessary)	**Outcomes**
Tips for Building	Starting with your patient, ask "How would I describe a group of patients similar to mine?" Balance precision with brevity.	Ask "Which main intervention am I considering?" Be specific.	Ask "What is the main alternative to compare with the intervention?" Again, be specific.	Ask "What can I hope to accomplish?" or "What could this exposure really affect?" Again, be specific.
Example	"In patients with heart failure from dilated cardiomyopathy who are in sinus rhythm ..."	"... would adding anticoagulation with warfarin to standard heart failure therapy ..."	"... when compared with standard therapy alone ..."	"... lead to lower mortality or morbidity from thromboembolism. Is this enough to be worth the increased risk of bleeding?"

1.2.9.2 finding the evidence: systematic retrieval of best evidence available

1. Search for Primary Sources
   -Use methodological filters to target the right type of study. For instance, PubMED filters for therapy, diagnosis, prognosis, etiology

2. Look for Secondary Sources
   -Guidelines: UK National Library for Health, NICE, SIGN; US National Guidelines Clearinghouse; Canadian Medical Association; New Zealand Guidelines Group.
   -Evidence-Based Summaries: Bandolier, Clinical Evidence
   -Systematic Reviews: Cochrane Library
   -To search several of the databases simultaneously you can use: www.tripdatabase.com

1.2.9.3 critical appraisal: testing evidence for validity, clinical relevance, and applicability

1. การศึกษามีความถูกต้อง (valid) หรือไม่
   -ถูกต้องตามระเบียบวิธีวิจัยหรือไม่ ปราศจากอคติ

2. ผลการศึกษามีความสำคัญ (*importance*) หรือไม่
   -ขนาด (magnitude) และความแม่นยำ (precision)

3. นำไปใช้ในผู้ป่วยของเรา (applicability) ได้หรือไม่
   -ความคล้ายคลึง การยอมรับ และทรัพยากร

1.2.9.4 making a decision: application of results in practice

Figure 1. Three targets for making decisions

1.2.9.5 evaluating performance: auditing evidence-based decisions

You might consider one of the following:

- Reading an evidence-based abstraction journal,
- Keeping a log book of your own clinical questions, or
- Running a case based discussion journal club around questions you have recorded and selected.

EBM Keywords for Prognosis

Survival (time-to-event) analysis
5-year survival , Median survival & Relative survival
Censoring
Kaplan-Meier (survival) curve
Log rank test
Cox regression (Cox proportional hazard model)
Hazard ratio

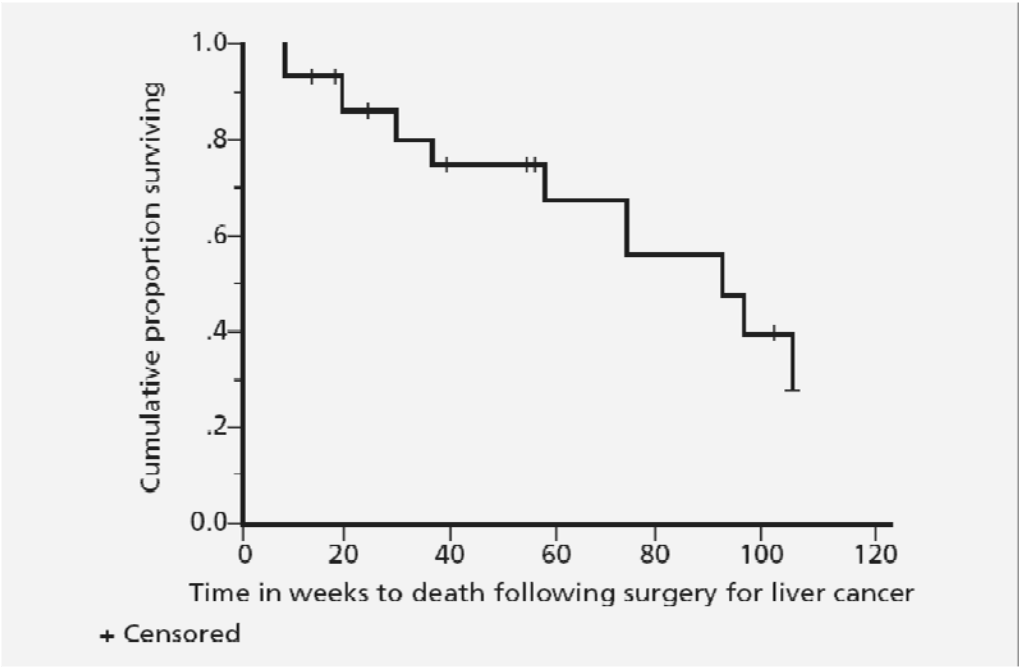
Survival & Censoring

- 5-year survival rate หมายถึงร้อยละของผู้ป่วยที่ไม่เกิดเหตุการณ์ (เช่น การตาย) อย่างน้อย 5 ปีนับแต่เริ่มศึกษา
- Median survival หมายถึงระยะเวลาที่จำนวนผู้ป่วยร้อยละ 50 ยังไม่เกิดเหตุการณ์ (เช่น ยังไม่ตาย)
- Relative survival หมายถึงอัตราส่วนของ 5-year survival rates ระหว่างกลุ่มที่สนใจกับประชากรทั่วไปในวัยเดียวกัน
- Censoring หมายถึงผู้ป่วยที่ไม่เกิดเหตุการณ์ (เช่น การตาย) เมื่อสิ้นสุดการศึกษา หรือ lost follow-up ระหว่างศึกษา

Table 1. Calculation of Kaplan–Meier estimate of the survivor function

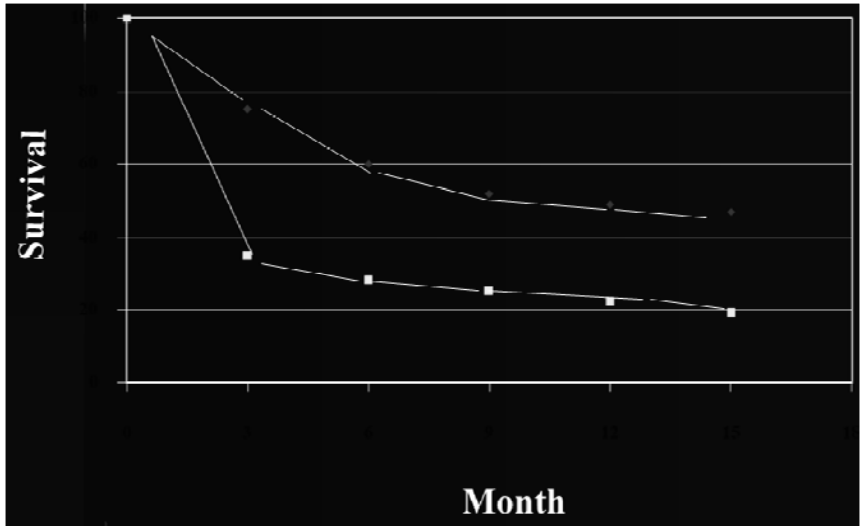
A	B	C	D	E	F
Time (weeks)	Number at risk at start of study	Number of deaths	Number censored	Proportion surviving until end of week	Cumulative proportion surviving
10	18	1	0	1 – 1/18 = 0.9444	0.9444
13*	17	0	1	1 – 0/17 = 1.0000	0.9444
18*	16	0	1	1 – 0/16 = 1.0000	0.9444
19	15	1	0	1 – 1/15 = 0.9333	0.8815
23*	14	0	0	1 – 0/17 = 1.0000	0.8815
30	13	1	0	1 – 1/13 = 0.9230	0.8137
36	12	1	0	1 – 1/12 = 0.9167	0.7459
38*	11	0	1	1 – 0/17 = 1.0000	0.7459
54*	10	0	1	1 – 0/17 = 1.0000	0.7459
56*	9	0	1	1 – 0/17 = 1.0000	0.7459
59	8	1	0	1 – 1/8 = 0.8750	0.6526
75	7	1	0	1 – 1/7 = 0.8571	0.5594
93	6	1	0	1 – 1/6 = 0.8300	0.4662
97	5	1	0	1 – 1/5 = 0.8000	0.3729
104*	4	0	1	1 – 0/4 = 1.0000	0.3729
107	3	1	0	1 – 1/3 = 0.6667	0.2486
107*/107*	2	0	2	1 – 0/2 = 1.0000	0.2486

Kaplan-Meier (survival) curve



Log rank test

- เป็นวิธีการสถิติที่ใช้เปรียบเทียบ Kaplan-Meier curves ว่า แตกต่างกันอย่างมีนัยสำคัญทางสถิติหรือไม่ เช่น เปรียบเทียบกลุ่มเพศชายกับกลุ่มเพศหญิง



Cox regression

The Cox Regression Equation

The equation for a basic Cox regression model is:

$$ln_{incidence}(t) = \beta_0(t) + \beta_1 x_i$$

This equation tells us that the incidence rate for individual *i* at time *t* is the product of two quantities:

- $\beta_0(t)$ → the baseline hazard function (which can be interpreted as a sort of intercept)
- $\beta_1 x_i$ → linear function of covariate(s) which is exponentiated

Assumption for Cox Regression

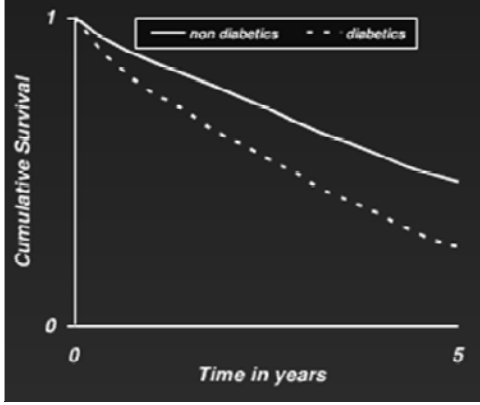
1. Non-informative censoring : censoring of individual subjects are not related to prognosis (the probability of an event occurring)

2. Proportional hazards : survival curves must have hazard functions that are proportional over time (i.e. constant relative hazard or hazard ratio)

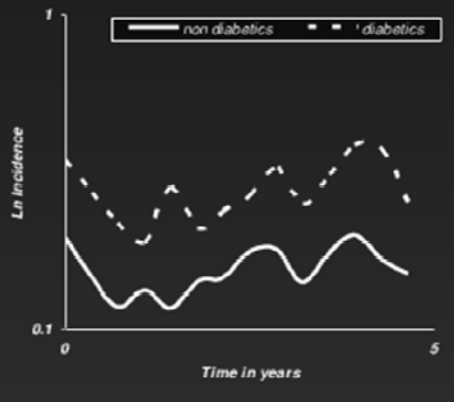
Example

Comparing the survival of patients with and patients without diabetes

Comparison of the cumulative survival curves:

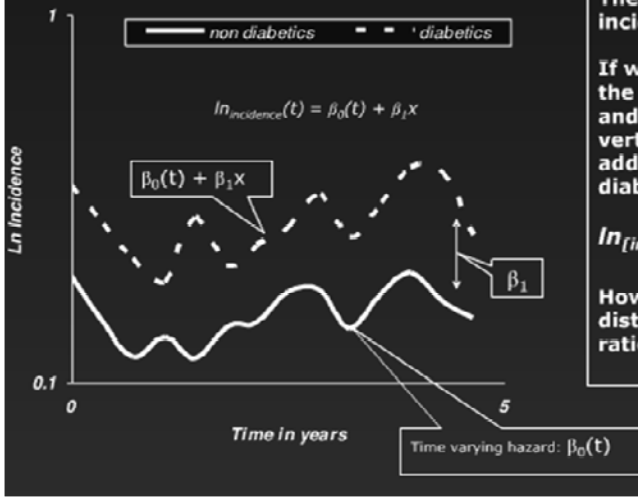


Comparison of the $Ln_{incidence\ rates}$:



Example

Comparing the survival of patients with and patients without diabetes



The graph shows that the incidence rate varies over time

If we compare the logarithm of the incidence rate of diabetics and non diabetics then, the vertical distance (β_1) is the additional risk for patients with diabetes

$$ln_{[inc\ diab]} - ln_{[inc\ nondiab]} = \beta_1$$

How can we convert this vertical distance β_1 into a RR type of ratio. ***See next slide***

From Beta to Hazard Ratio

If both sides of the equation:

$ln_{[inc\ 1]} - ln_{[inc\ 0]} = \beta_1$ *(where 1=diab, 0= nondiab)*

are exponentiated:

$e^{(ln[inc_1] - ln[inc_0])} = e^{\beta_1}$

we obtain a ratio of the incidence of both groups:

$[inc_1] / [inc_0] = e^{\beta_1}$ → which is the hazard ratio (HR)

The hazard ratio (HR) quantifies the impact of diabetes on outcome and can be interpreted as a relative risk type of ratio

Typical Output of a Cox Regression Model

The Diabetes Example

Estimates						
Variable	Beta	Standard Error	P value	Hazard Ratio exp(Beta)	95% confidence interval	
Diabetes (yes/no)	0.537	0.068	<.0001	1.711	1.498	1.954

- Diabetes was coded as a binary variable (1=yes/ 0=no)
- In this case the beta is positive (0.54) which means that the log of the incidence rate for death in diabetics is higher than in non diabetic patients
- Thus, the hazard ratio (HR) for diabetics compared to non diabetics is $e^{0.54} = 1.71$
- The 95% confidence interval for the hazard ratio is [1.498-1.954]

Conclusion: the mortality of patients with diabetes is higher than in patients without diabetics

OR should we account for known ***confounders*** (e.g. age) before drawing any conclusions

Typical Output of a Cox Regression Model

The Diabetes Example, Adjustment for Age

Estimates						
Variable	Beta	Standard Error	P value	Hazard Ratio exp(Beta)	95% confidence interval	
Age (continuous)	0.047	0.002	<.0001	1.048	1.043	1.053
Diabetes (yes/no)	0.662	0.068	<.0001	**1.939**	**1.696**	**2.216**

- Cox regression is the tool to account for confounding effects when performing survival analysis
- The output of this multiple Cox regression model shows an effect of both age and diabetes
- The hazard ratio for diabetes increased from 1.711 (see previous slide) to 1.939. This change shows that after accounting for the confounding effect of age, the impact of diabetes on survival is even stronger
- Our previous conclusion: "the mortality of patients with diabetes is higher than in patients without diabetics" is still valid. Moreover, age is indeed an important confounder in the diabetes-mortality relationship

- ผู้ป่วยชายไทยอายุ 60 ปี admit ด้วย GI bleeding มีประวัติดื่มเหล้าและสูบบุหรี่มากว่า 30 ปี ได้รับการวินิจฉัยว่าเป็น liver cirrhosis
- ผู้ป่วยถามแพทย์ว่าเขาจะมีชีวิตยืนยาวเท่าใด และควรปฏิบัติตัวอย่างไรเพื่อให้มีชีวิตยืนยาวที่สุด

P : In elderly male with liver cirrhosis

I : smoking cessation and alcohol abstinence

C : do nothing

O : improve survival (live longer)

พิมพ์ Search terms ใน PubMed Clinical Queries ดังนี้

5-year survival cirrhosis alcohol smoking

เลือก Category Prognosis พบ 5 บทความ

เลือกบทความของ Pessione et al: Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int. 2003 Feb;23(1):45-53.

Prognosis Checklists for Validity

- Was the defined representative sample of patients assembled at a common (usually early) point in the course of their disease?
- Was patient follow-up sufficiently long and complete?
- Were outcome criteria either objective or applied in a 'blind' fashion?
- If subgroups with different prognoses are identified, did adjustment for important prognostic factors take place?

Prognosis Checklists for Results

What are the results?

- How likely are the outcomes over time?
  - Survival curves (Kaplan-Meier)?
- How precise are the prognostic estimated?
  - Confidence intervals?

Prognosis Checklists for Applicability

- Can I apply this valid, important evidence about prognosis to my patient?

- Is my patient so different to those in the study that the results cannot apply?

- Will this evidence make a clinically important impact on my conclusions about what to offer to tell my patients

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Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence

Pessione F, Ramond M-J, Peters L, Pham B-N, Batel P, Rueff B, Valla D-C. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver International 2003: 23: 45–53. © Blackwell Munksgaard, 2003

Abstract: *Aim:* To evaluate 5-year survival predictive factors in hospitalised patients with excessive alcohol intake and cirrhosis, including in a multivariate analysis the severity of the liver disease, gastrointestinal bleeding, concomitant viral B or C infection, smoking status, presence of alcoholic hepatitis at inclusion and abstinence from alcohol during follow-up. *Methods:* In a non-concurrent cohort study, 122 patients with excessive alcohol intake and cirrhosis were followed up at least five years or till death. Two patients were lost to follow-up. *Results:* The 5-year survival rates were 43% in the 122 patients and 66%, 50% and 25% in Child–Pugh class A, B and C patients, respectively. In multivariate analysis, age ($P = 0.01$), Child–Pugh score ($P = 0.0001$), gastrointestinal bleeding ($P = 0.01$), presence of HBs Ag and/or anti-HCV ($P = 0.03$), smoking ($P = 0.01$), absence of histologically proven alcoholic hepatitis ($P = 0.05$) and persistent alcohol intake ($P = 0.002$) were associated with significantly increased risk ratios of death. *Conclusions:* In hospitalised patients with excessive alcohol intake and cirrhosis: (1) age, liver failure, gastrointestinal bleeding, concomitant viral B or C infection and persistent alcohol intake are independent poor prognostic markers, (2) smoking may contribute to the aggravation of cirrhosis, and (3) alcoholic hepatitis, being a potentially reversible cause of liver failure, has a favourable prognostic significance.

F. Pessione[1], M-J. Ramond[1], L. Peters[1], B-N. Pham[2], P. Batel[1], B. Rueff[1] and D-C. Valla[1]

[1]Fédération d'Hépato-Gastroentérologie and [2]Laboratoire d'Hématologie et Immunologie, Hôpital Beaujon, Clichy, France

Key words: alcoholic cirrhosis – alcoholic hepatitis – prognosis – survival – tobacco

Dr F. Pessione, Utama, Hôpital Beaujon, 100 bd du Général Leclerc, 92110 Clichy, France.
Tel: 33 1 44 67 59 46.
Fax: 33 1 44 67 59 30.
e-mail: fpessione001@efg.rss.fr

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Cirrhosis in patients with excessive alcohol intake is one of the main indications for liver transplantation so that interest for long-term prognostic factors has been recently growing. In most studies, the severity of liver disease was the best survival predictor, and predictive indices including different factors, mainly related to hepatocellular function, have been proposed (1–6) but none has been widely accepted until now. Alcohol withdrawal has been related with increased survival in four studies (7–10), but not in a fifth one (11) including 146 patients. Gastrointestinal bleeding is a well-recognized short-term prognostic factor in cirrhotic patients, but whether it could be a long-term prognostic factor is not established. Alcoholic hepatitis has been associated with increased long-term mortality in patients with cirrhosis (12, 13) but, since the publication of these papers, it has been shown that, in the severe forms of the disease, mortality could be significantly reduced by corticosteroid therapy (14). Concomitant chronic viral B or C infection and smoking, which are important prognostic factors in the general population, have seldom been studied in long-term survival analyses of patients with excessive alcohol intake and cirrhosis. Multivariate analyses evaluating the independent effects of all these factors have not been performed and the follow-up did not exceed two years in most studies.

The aim of this study was to evaluate the 5-year survival prognostic factors in hospitalised patients with excessive alcohol intake and cirrhosis,

including a multivariate analysis of the severity of the liver disease, gastro-intestinal bleeding at entry, concomitant viral B or C infection, smoking status, presence of alcoholic hepatitis during the index hospitalisation and alcohol withdrawal during follow-up.

Subjects and methods

The records of all patients admitted consecutively, on the liver unit at Beaujon Hospital, near Paris, between January and December 1991 with the diagnosis of excessive alcohol intake and cirrhosis were analysed. Twenty-six patients with hepatocellular carcinoma and three patients with a transplanted liver at inclusion were not included. One hundred and twenty two patients were included in the study. Cirrhosis was present on percutaneous or transvenous liver biopsy in 109 patients. In the other 13 patients, the diagnosis of cirrhosis was made on clinical and biochemical criteria. Less frequent forms of liver cirrhosis such as hereditary haemochromatosis, Wilson's disease, primary biliary cirrhosis, autoimmune hepatitis, etc. were excluded on the basis of the absence of biochemical, serological and histological hallmarks. Patients with HBs Ag and/or anti-HCV were included only if their alcohol intake had been heavy. Alcohol intake was evaluated by interrogation of the patient, general practitioners and family members. There was evidence of past or present heavy alcohol intake (more than 80 g/day during ten or more years) in all included patients (patients with moderate or dubious alcohol intake were excluded).

The end-point of the study was death or a follow-up of at least five years. The status 'dead or alive' and the date of death were obtained from medical consultations and civil registration. Seven baseline characteristics were recorded: age, gender, smoking status, presence of HBs Ag and/or hepatitis C virus antibodies (anti-HCV), Child–Pugh score (15) and gastrointestinal bleeding at entry, histologically proved alcoholic hepatitis during the index hospitalisation. The Child–Pugh score, which takes into account encephalopathy, ascites, prothrombin time, serum albumin and bilirubin, is the most widely used and recognized score evaluating the severity of hepatic disease. An episode of bleeding was defined as one in which there was haematemesis, melena or blood in a gastric aspirate and a decrease in haemoglobin levels > 2 g/dL. The 28 patients with gastrointestinal bleeding at entry underwent an endoscopic examination: oesophageal varices were present in 26 and a variceal rupture was diagnosed in 18 patients. An anti-HCV Elisa test had been performed in 1991 in most patients; however, these results were not considered since sensitivity and specificity of first-generation tests are low (16). Frozen serum was available for 87 of the 122 patients and was tested in 1998 using two third-generation Elisa tests (HCV 3.0 AXSYM (Abbott) and anti-HCV PLUS MONOLISA (Sanofi Pasteur). For patients who survived more than two months, the evolution of alcohol intake was evaluated from in-hospital consultations and from the general practitioner. Three groups of patients were considered according to alcohol intake at the end of follow-up: patients with long-lasting abstinence (whose alcohol intake was less than 20 g/day for more than one year), non-abstinent patients and unknown drinking status (intermittent abstinence or information not available).

Survival rates were estimated by the Kaplan–Meier method in univariate analysis, and the differences were tested by the log-rank test. The Cox proportional–hazard regression analysis was performed to estimate adjusted risk ratios in a multivariate analysis. One set of analysis was based on 122 patients including the baseline characteristics, and a second included the 102 patients that survived more than two months, including all the baseline variables and the evolution of alcohol intake. Abstinence was treated as a fixed covariate, and not as a time-dependent one because abstinence is not always a discrete process. Age and Child–Pugh score were fitted as continuous variables because their relationship with mortality was approximately linear. Lost to follow-up patients and patients with a liver transplantation during follow-up were censored alive. Liver transplantation was considered as a competing risk for mortality rather than time-dependent prognostic variable because of the risk of over adjustment with the other prognostic variables. All reported *P*-values are two-tailed. Analyses were performed using SAS software (SAS Institute Inc. Cary, NC, USA).

Results

One hundred and twenty-two patients were included. The baseline and follow-up characteristics are presented in Table 1, according to Child–Pugh class. It has been shown that the presence of morphologically defined alcoholic hepatitis is poorly correlated with the clinical syndrome usually attributed to alcoholic hepatitis (17), and that, even in severe forms of the disease, the clinico-biological diagnosis was not histologically confirmed in up to 15% of patients (18). In the present study, 32 patients had biopsy-proved alcoholic hepatitis (22 class C, 7 class B and 3 class A).

Table 1. Characteristics of 122 drinkers with cirrhosis according to Child–Pugh class

Characteristics	All		Child–Pugh class		
	$N=122$ %	N	A ($n=32$) %	B ($n=33$) %	C ($n=57$) %
Gender					
Male	61.5	75	65.6	63.2	57.9
Female	38.5	47			
Age (years): mean (SD)	52.1 (10)		48.2 (9)	53.5 (10)	53.5 (10)
Gastrointestinal bleeding					
Yes	23.0	28	22.0	21.2	24.6
No	77.0	94			
Variceal bleeding	14.7	18	12.5	15.1	15.8
HBs Ag and/or anti-HCV					
Positive	10.6	13	15.6	6.0	10.5
Negative	60.7	74	59.4	57.6	63.2
Unknown	28.7	35	25.0	36.4	26.3
Acute alcoholic hepatitis					
Yes	26.2	32	9.4	21.2	38.6
No	41.0	50	59.4	33.3	35.1
No biopsy	32.8	40	31.2	45.5	26.3
Smoking status					
Current or former smoker	60.7	74	62.5	54.5	63.2
Non smoker	32.8	40	34.4	39.4	28.1
Unknown	6.6	8	3.1	6.1	8.7
	All $N=102$		A ($n=32$)	B ($n=32$)	C ($n=38$)
Long-lasting abstinence at the end of follow-up in patients who survived more than two months					
Yes	57.0	58	47.0	50.0	71.0
No	27.4	28	25.0	37.5	21.0
Unknown	15.7	16	28.1	12.5	7.9

SD: standard deviation.

Seventeen of these 32 patients (15 class C and 2 class B) had severe alcoholic hepatitis, as previously defined (Maddrey's discriminant function above 32), and were treated with prednisolone (40 mg/day during 28 days) during the index hospitalisation, as it is routinely the case in our unit since the results of our double blind trial (18). Two patients were lost to follow-up after 1 and 28 months, respectively, and were censored alive. The 120 other patients were followed up till death or at least five years. Two patients with liver transplantation after the index hospitalisation were censored alive at the time of transplantation (after a follow-up of 2 and 28 months).

Sixty-eight patients died during the 5-years' follow-up. The median survival time was 48 months (95% confidence interval, 35–64). The five-year survival rates were 43% in the 122 patients, and 66%, 50% and 25% in Child–Pugh class A, B and C patients, respectively (Fig. 1). Nineteen class C and one class B patients died during the first two months after entry. In the 102 patients who survived more than two months, the five-year survival rate was 51% in all patients and 66%, 52% and 38% in class A, B and C patients, respectively. The cause of death was known in 46 patients and was mainly related to liver disease: 13 patients died of gastrointestinal bleeding, 18 of liver failure, two of hepatocellular carcinoma, six of sepsis and five of causes other than cirrhosis. Five of the 17 patients who received corticosteroids for severe alcoholic hepatitis died during the first two months.

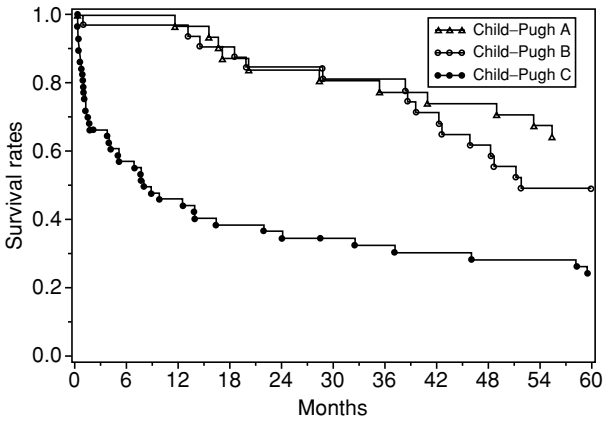

Fig. 1. Five-year survival curves of 122 patients with excessive alcohol intake and cirrhosis, according to Child–Pugh class at inclusion.

In univariate as well as multivariate analyses, older age and higher Child–Pugh score were related with decreased survival, whereas gender was not related to survival (Table 2). Survival curves of class A (Child–Pugh score from 5 to 6) and B (Child–Pugh score from 7 to 9) patients were not significantly different (adjusted risk ratio = 1.7, $P = 0.2$ in model 2), but the two curves differed after a 3-years' follow-up (Fig. 1). The survival curve of class C (Child–Pugh score from 10 to 15) patients was significantly different from that of the pooled group of class A and B patients (adjusted risk ratio = 5.0, $P < 0.001$ in model 2) (Fig. 1).

Gastrointestinal bleeding at inclusion was related with decreased survival in univariate and first multivariate analyses (Table 2). The five-year survival rates were 23% and 49% respectively, in patients with and without gastrointestinal bleeding (Fig. 2A). In the group of 102 patients who survived more than two months, the risk ratio was slightly reduced (1.7 *vs* 2) and the *P*-value was not significant ($P = 0.09$) (Table 2). In this group of 102 patients, the survival curves according to gastrointestinal bleeding at inclusion were similar till 12 months but seemed to differ afterwards (Fig. 2B). The interaction between time and gastrointestinal bleeding was not statistically significant in multivariate analysis ($P = 0.9$). In the subgroups of patients who survived more than 6, 12 and 24 months, gastrointestinal bleeding at inclusion was significantly related to the risk of death (adjusted RR = 1.9 ($P = 0.04$), RR = 2.0 ($P = 0.07$), RR = 2.7 ($P = 0.02$), respectively). This suggests that gastrointestinal bleeding could be both a very short-term and a delayed long-term prognostic factor. Esophagogastric varices were the source of bleeding in 18 out of 28 patients. If variceal bleeding instead of gastrointestinal bleeding had been included in the multivariate analyses, the difference would not have been statistically significant (RR = 1.4, $P = 0.25$).

In patients with and without HBs Ag and/or anti-HCV, the five-year survival rates were 38 and 44%, respectively, and were not significantly different in univariate analysis. In multivariate analysis, positive viral serology was related with decreased survival, the statistical test being significant in the first model (RR = 2.4, $P = 0.03$) but not in the second (RR = 2.5, $P = 0.08$) (Table 2). Baseline variables in patients with and without available frozen serum were similar (data not shown),

Table 2. Univariate and multivariate survival analysis in drinkers with cirrhosis

Variables	Univariate analysis		Multivariate analysis Model 1 ($n = 122$)			Multivariate analysis Model 2 ($n = 102$)		
	Risk ratio of death	*P*	Risk ratio of death	$CI_{95\%}$[a]	*P*	Risk ratio of death	$CI_{95\%}$[a]	*P*
Gender								
Female ($n = 47$)	1		1			1		
Male ($n = 75$)	1.22	0.4	1.1	0.8–2.0	0.4	1.0	0.5–1.9	0.9
Child–Pugh score (point)	1.2	0.001	1.4	1.3–1.6	0.0001	1.3	1.1–1.6	0.01
Age (year)	1.045	0.0002	1.04	1.01–1.06	0.01	1.07	1.04–1.1	0.0001
Gastrointestinal bleeding								
No ($n = 94$)	1		1			1		
Yes ($n = 28$)	2.3	0.0005	2.0	1.1–3.3	0.01	1.7	0.9–3.2	0.09
HBs Ag and/or anti-HCV								
Negative ($n = 74$)	1		1			1		
Positive ($n = 13$)	1.2	0.5	2.4	1.1–5.2	0.03	2.5	0.9–7	0.08
Unknown ($n = 35$)	1.1	0.6	1.6	0.9–2.7	0.1	0.8	0.4–1.7	0.5
Acute alcoholic hepatitis								
No ($n = 50$)	1		1			1		
Yes ($n = 32$)	0.8	0.4	0.5	0.3–1.0	0.05	0.3	0.1–0.7	0.01
No biopsy ($n = 40$)	1.1	0.7	1.2	0.7–2.1	0.5	1.0	0.5–1.9	0.9
Smoking status								
Never smoker ($n = 40$)	1		1			1		
Current or former smoker ($n = 74$)	1.6	0.08	2.0	1.2–3.6	0.01	2.8	1.4–5.5	0.004
Unknown ($n = 8$)	1.1	0.8	0.6	0.2–1.9	0.4	0.1	0.01–1.07	0.05
Abstinence								
Yes ($n = 58$)	1		–		–	1		
No ($n = 28$)	1.6	0.1				3.1	1.5–6.4	0.002
Unknown ($n = 16$)	0.8	0.5				1.3	0.5–3.3	0.6

Model 1 Includes baseline variables in 122 patients and Model 2 includes baseline and follow-up variables in 102 patients who survived more than two months after entry. [a]Ninety-five percent confidence interval.

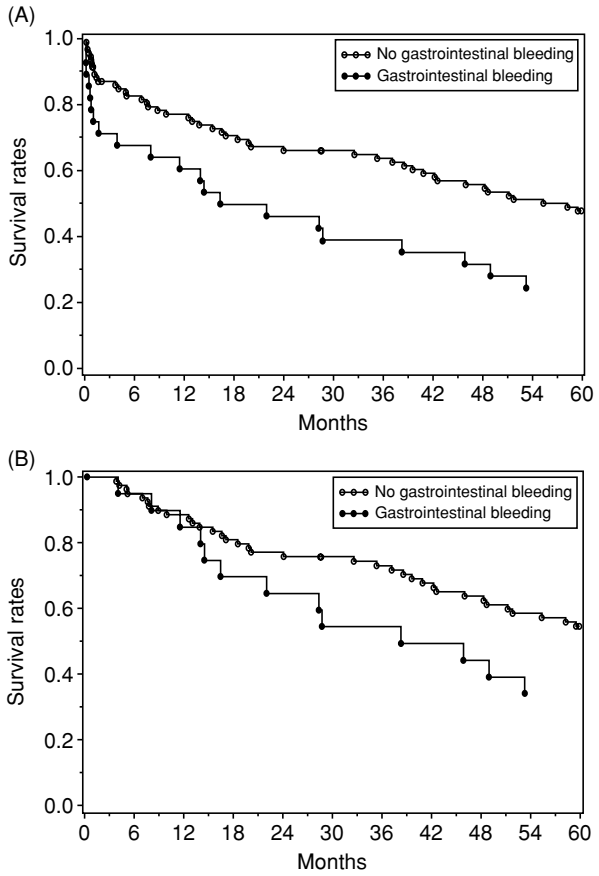

Fig. 2. (A) Five-year survival curves of 122 patients with excessive alcohol intake and cirrhosis with and without gastrointestinal bleeding at entry. (B) Five-year survival curves of 102 patients with excessive alcohol intake and cirrhosis living more than two months, with and without gastrointestinal bleeding at entry.

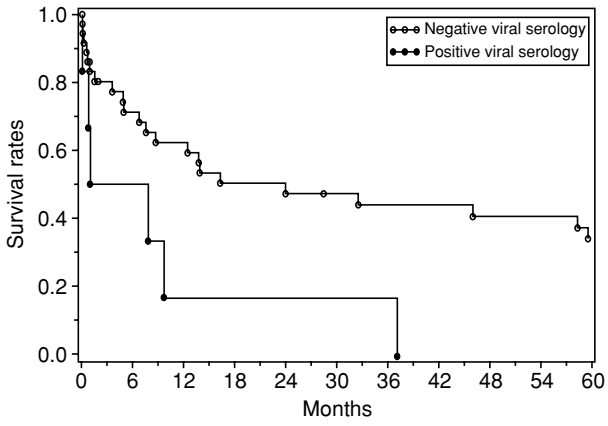

Fig. 3. Five-year survival curves of Child–Pugh class C patients with excessive alcohol intake and cirrhosis with and without HBs Ag and/or anti-HCV.

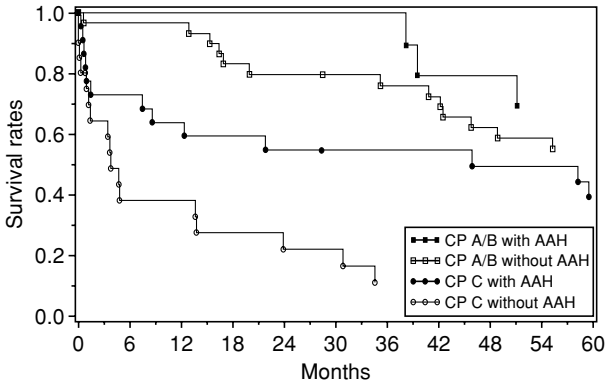

Fig. 4. Five-year survival curves of patients with excessive alcohol intake and cirrhosis with and without biopsy-proved acute alcoholic hepatitis, according to Child–Pugh class.

so that it can be hypothesised that availability of frozen serum was randomly distributed. The survival curves of patients with and without positive viral serology were drawn in Child–Pugh C patients only (Fig. 3), as the number of events (two deaths) was too small in Child–Pugh A/B patients.

The presence of acute alcoholic hepatitis at inclusion was not related to survival in univariate analysis, but was related with increased survival in the two multivariate analyses ($P = 0.05$ and $P = 0.01$, respectively) (Table 2), whereas the presence of alcoholic hepatitis was related, with an increased Child–Pugh score ($P = 0.01$) (Table 1). The 5-year survival rates were 70% and 56% in class A/B patients, and 40% and 11% respectively in class C patients with and without histologically proven acute alcoholic hepatitis (Fig. 4). The mortality rates of patients without biopsy and without alcoholic hepatitis on biopsy were similar (RR = 1 and 1.2, $P = 0.5$ and 0.9 in the two multivariate analyses, respectively) (Table 2).

Smoking was not related to survival in univariate analysis, but was related with decreased survival in the two multivariate analyses ($P = 0.01$ and $P = 0.004$) (Table 2). Smokers were younger than non-smokers (49.5 *vs* 54.4 years, $P = 0.01$) at inclusion. The 5-year survival rates in smokers and non-smokers were 42% and 73% in patients younger than 55 years, and 17% and 43% in patients older than 55 years. Smokers became less frequently abstinent than non-smokers, but smoking was significantly related to mortality whatever the evolution of alcohol intake ($P = 0.004$ in the second multivariate analysis).

Fifty-eight of the 102 patients (57%) were abstinent at the end of the follow-up (30% were totally abstinent and 27% drank less than 20 g/day), 28 patients remained non-abstinent and 16 patients could not be classified as abstinent or non-abstinent (Table 1). Abstinent patients were older (53 *vs* 48 years, $P = 0.03$), less frequent smokers (53% *vs* 75%, $P = 0.05$) and had a more severe

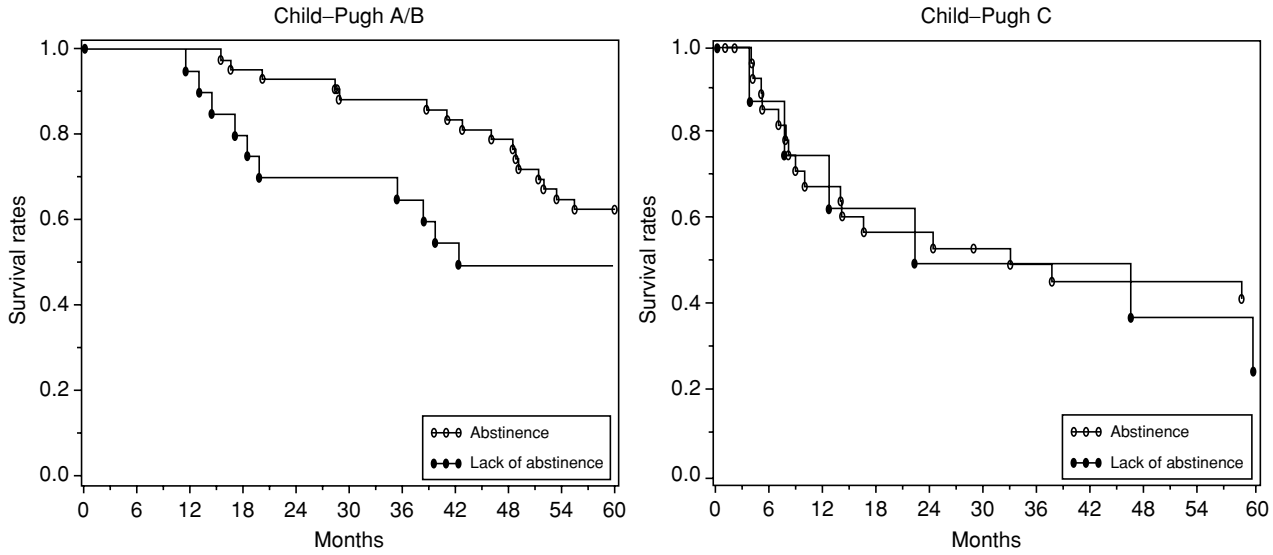

Fig. 5. Five-year survival curves of patients with excessive alcohol intake and cirrhosis with and without abstinence, according to Child–Pugh class. In this bi-variable analysis a difference appears only in class A and B, whereas in multivariable analysis the differences are significant in class A and B ($P = 0.002$) and C ($P = 0.04$) patients.

liver disease (46% *vs* 28% Child–Pugh class C patients, $P = 0.08$) than non-abstinent patients. Thirty of the 38 class C patients who survived more than two months after entry became abstinent. Among class C patients, seven out of eight (87%) non-abstinent and 19 out of 30 (63%) abstinent patients died. Abstinence after hospitalisation was not significantly related to survival in univariate analysis, with the 5-year survival rates being 43% and 55% in abstinent and non-abstinent patients respectively. However, lack of abstinence was related with increased risk of mortality in multivariate analysis (RR = 3.1, $P = 0.002$) (Table 2). In a bivariate description, i.e. survival according to abstinence and Child–Pugh class, the survival curves of abstinent and non-abstinent patients differed significantly in Child–Pugh class A/B but not in class C patients (Fig. 5). If multivariate analyses were performed separately in class A/B and C patients, alcohol withdrawal would have been related with an increased survival, not only in class A/B patients (adjusted RR = 5.6, $P = 0.002$), but also in class C patients (adjusted RR = 4.8, $P = 0.04$). Information about abstinence was not available in 16 patients. In the multivariate analysis, the mortality rate of these patients was similar to that of abstinent patients (RR = 1.3) (Table 2). Two situations were simulated: (a) if all these 16 patients were abstinent, the non-abstinence adjusted risk ratio was not modified (RR = 2.7, $P = 0.006$), (b) if they were all non-abstinent, the non-abstinence adjusted risk ratio remained statistically significant (RR = 2.0, $P = 0.04$).

Discussion

The survival rates of hospitalised patients with excessive alcohol intake and cirrhosis were estimated in a cohort of 122 patients with only two patients lost to follow-up after five years. Only three variables were significantly related to survival in univariate analysis, i.e. age, Child–Pugh score and gastrointestinal bleeding. When all variables were included in the multivariate analyses, four other important factors appeared to be significantly related to survival, i.e. presence of alcoholic hepatitis, absence of HBs Ag and/or anti-HCV, non-smoking and abstinence. This is due to complex and opposite relationships between prognostic factors and survival. If related factors have opposite effects on survival, the univariate effect of each factor is highly confounded (19). For example, presence of acute alcoholic hepatitis is related with increased Child–Pugh score, so that, in univariate analysis, the positive survival effect of alcoholic hepatitis is confounded by the negative effect of Child–Pugh score, and the univariate test is not significant.

Gastrointestinal bleeding was strongly related to mortality whatever the Child–Pugh score and the other factors tested in the first multivariate analysis; the-non-significant effect of variceal bleeding in multivariate analysis could be due to a loss of power. It should be noticed that, in spite of the development of effective endoscopic and pharmacologic treatments, which were routinely used in our unit in 1991, gastrointestinal bleeding remains highly predictive of death. Although the risk of

bleeding has been reported to be higher in Child–Pugh class C patients in prospective studies (20, 21), the percentage of bleeding class A, B and C patients was the same in our study (Table 1). This could be explained by the high and early mortality rates of bleeding class C patients (22), with a number of such patients dying before hospitalisation in a specialised unit. In the group of patients remaining alive after two months, the risk ratio of death in patients with gastrointestinal bleeding at inclusion was slightly reduced in multivariate analysis. However, the survival curves of patients still alive after two months with and without gastrointestinal bleeding at inclusion (Fig. 2B) suggest a late mortality effect, which was confirmed by the subgroup analyses of patients who survived more than 6, 12 and 24 months respectively. Whether this late effect could be due to re-bleeding or to other factors, cannot be inferred from our study. Variceal bleeding in patients with cirrhosis has been reported to increase only early mortality, with survival curves being similar after 6–12 weeks of follow-up in patients with and without haemorrhage (23, 24). However, this was inferred from a follow-up of only 12 and 20 months (25, 26), and subgroup analyses of patients surviving more than 6, 12 and 24 months were not performed, and thereby the early and late effects were not differentiated.

HBs Ag was present in five out of 120 patients (4%) and anti-HCV antibodies were present in eight out of 87 patients (9%) whose serum could be tested in 1998. Positive viral serology was related with decreased survival in the first multivariate analysis. A lack of power could explain the negative result of the second multivariate analysis since the risk ratio was unchanged (2.4 *vs* 2.5) (Table 2). It is noticeable that, although our patients were heavy drinkers, with frequent alcoholic hepatitis, a concomitant chronic viral infection keeps a prognostic significance. To our knowledge, long-term survival rates of patients with excessive alcohol intake and cirrhosis with and without anti-HCV antibodies have been compared in only three studies. The results of the first two ones cannot be taken into consideration since first-generation anti-HCV tests were used (27, 28). In the third study, 35 patients with alcoholic cirrhosis were followed up during 2–6 years; anti-HCV second generation tests were positive in 21 patients; cumulative survival rates were significantly higher in patients without than in patients with anti-HCV antibodies ($P = 0.01$), with the difference being apparent on the curves after four years of follow-up; however, a multivariate analysis was not performed (29).

In our study, presence of acute alcoholic hepatitis was paradoxically associated with increased survival. It should be outlined that this effect was not observed in univariate analysis but only in the multivariate analysis after adjustment on the Child–Pugh score (Fig. 4). If biopsy had been systematically performed in patients with mild hepatitis and omitted in patients with severe hepatitis, its performance could have introduced a bias in our study. On the contrary, transjugular biopsy was systematically performed in alcoholic patients with liver failure since corticosteroids were administered only in patients with severe histologically proven alcoholic hepatitis. Survival was improved in patients with moderate as well as severe liver failure (Fig. 4), so that corticosteroid therapy could not have introduced a bias in our results. Alcoholic hepatitis in patients with cirrhosis is a severe disease, which is frequently associated with liver failure, and therefore alcoholic hepatitis has been associated with increased mortality in patients with cirrhosis in previous studies (12, 13). However, in these studies, patients with severe forms of alcoholic hepatitis were not systematically treated with corticosteroids and multivariate analyses were not performed. In the severe forms of the disease, mortality has been significantly reduced by corticosteroid therapy (14), and a critical point is that alcoholic hepatitis is an acute disease, which improves with abstinence if patients do survive. In patients with cirrhosis who recover from alcoholic hepatitis, the improvement of liver function tests is more frequent, rapid and marked than in cirrhotic patients without alcoholic hepatitis, which could explain why the presence of alcoholic hepatitis was associated with improved survival in our patients. However, since alcoholic hepatitis worsens hepatocellular function, the positive prognostic effect of alcoholic hepatitis cannot appear if the severity of the disease is not taken into account in multivariate analyses.

Although smoking is associated with increased mortality in the general population (30), till now it had never been studied as a prognostic factor in patients with liver disease. This could be explained by the fact that ① most patients with cirrhosis die of liver-related causes ②, and cardio-vascular mortality, which is highly related to smoking and is low in patients with cirrhosis, whereas it is high in the general population and ③ that the possible hepatotoxicity of smoking has been suggested only recently. In the present study, smoking was associated with decreased survival in the two multivariate analyses. This relationship could be explained: ① by the same effect as in general population ② by a relationship between smoking and the level of alcohol intake, and/or ③ by a negative

effect of smoking on liver disease. In smoking alcoholic patients, the amount of smoked tobacco has been reported to be correlated with the amount of consumed alcohol (31), but in our study, the prognostic effect of smoking was not modified if the amount of alcohol consumed at inclusion was included in the multivariate analyses (data not shown). It has been recently reported that smoking, whatever the alcohol intake, was associated with an increased risk of cirrhosis in alcoholic patients (32, 33) and in asymptomatic chronic hepatitis B virus carriers (34). In the liver of rats exposed to cigarette smoke, damage to mitochondrial DNA has been reported and could be prevented by N-acetylcysteine (35). In another study, significant alterations of biochemical oxidative parameters with a synergistic effect of ethanol were documented in the liver of rats, which had been exposed to nicotine (36). These data suggest that tobacco could worsen liver disease per se.

One half of patients surviving after two months were abstinent at the end of the follow-up. In multivariate analysis, abstinence was significantly related to survival in Child–Pugh A/B and C patients. In our analysis, abstinence was treated as a fixed covariate, which meant that patients stopped alcohol consumption immediately after the index hospitalisation. However, it was not true for all patients, some of them becoming abstinent later, so that the prognostic effect of abstinence could have been underevaluated in this study. The relationship between abstinence and survival was not apparent in the univariate analysis, because of complex relationships between different factors, i.e. the frequency of alcohol abstinence was higher in class C than in class A/B patients. These confounding effects can explain the negative results of one published study (11) and could lead to wrong clinical judgement. To our knowledge, a positive long-term prognostic effect of abstinence was shown in four studies previously published (7–10), but multivariate analyses including other important prognostic factors have not been performed till now.

In conclusion, ① it should be outlined that these prognostic factors were identified in hospitalised patients with excessive alcohol intake and cirrhosis. ② Multivariate analysis is mandatory when prognostic factors are studied and all the variables should be included in the analysis in order to avoid false negative results due to complex relationships between different factors. ③ We confirm the prognostic importance of abstinence whatever the severity of liver disease, and we first report that non-smoking and presence of alcoholic hepatitis are independent good prognostic markers.

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DOES THE STUDY ADDRESS A CLEAR QUESTION?

1. Is there a clearly focussed question? Consider • Patients • Disease/Condition • Outcome	**Yes**	**Can't tell**	**No**

ARE THE RESULTS VALID?

2. Was a defined, representative sample of patients assembled at a common (usually early) point in the course of their disease?	**Yes**	**Can't tell**	**No**
3. Was the follow-up of these patients sufficiently long and complete?			
4. Were objective and unbiased outcome criteria used? Consider: • Did the individual assessing the outcome criteria know whether or not the patient had a potential prognostic factor, i.e. were they blinded?			
5. Was there adjustment for important prognostic factors? Consider: • Was there standardisation for potentially important prognostic factors e.g. age? • Were different sub-groups compared? • Was there validation in an independent group of patients?			

WHAT ARE THE RESULTS?

6. How likely are the outcome event(s) over a specified period of time?	
7. How precise are the estimates of this likelihood? Consider: • Are the results presented with confidence intervals?	

WILL THE RESULTS HELP ME WITH THIS PATIENT?

8. Were the study patients similar to this patient?	**Yes**	**Can't tell**	**No**
9. Will the results lead directly to selecting or avoiding a treatment?			
10. Are the results useful for reassuring or counselling my patient? Consider: • Will the evidence make a clinically important impact on your conclusions about what to offer or tell this patient?			