AP&T Alimentary Pharmacology and Therapeutics

Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients

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Publication data
Submitted 30 January 2014
First decision 18 February 2014
Resubmitted 2 March 2014
Accepted 3 March 2014
EV Pub Online 24 March 2014

This article was accepted for publication after full peer-review.

This article is **dedicated to Andy Burroughs** for his continuous and valuable contribution to research in hepatology.

SUMMARY

Background
Morphological, haemodynamic and clinical stages of cirrhosis have been proposed, although no definite staging system is yet accepted for clinical practice.

Aim
To investigate whether clinical complications of cirrhosis may define different prognostic disease stages.

Methods
Analysis of the database from a prospective inception cohort of 494 patients. Decompensation was defined by ascites, bleeding, jaundice or encephalopathy. Explored potential prognostic stages: 1, compensated cirrhosis without oesophago-gastric varices; 2, compensated cirrhosis with varices; 3, bleeding without other complications; 4, first nonbleeding decompensation; 5, any second decompensating event. Patient flow across stages was assessed by a competing risks analysis.

Results
Major patient characteristics were: 199 females, 295 males, 404 HCV+, 377 compensated, 117 decompensated cirrhosis. The mean follow-up was 145 ± 109 months without dropouts. Major events: 380 deaths, 326 oesophago-gastric varices, 283 ascites, 158 bleeding, 146 encephalopathy, 113 jaundice, 126 hepatocellular carcinoma and 19 liver transplantation. Patients entering each prognostic stage along the disease course were: 202, stage 1; 216, stage 2; 75 stage 3; 206 stage 4; 213 stage 5. Five-year transition rate towards a different stage, for stages 1–4 was 34.5%, 42%, 65% and 78%, respectively ($P < 0.0001$); 5-year mortality for stages 1–5 was 1.5%, 10%, 20%, 30% and 88% respectively ($P < 0.0001$). An exploratory analysis showed that this patient stratification may configure a prognostic system independent of the Child–Pugh score, Model for End Stage Liver Disease and comorbidity.

Conclusion
The development of oesophago-gastric varices and decompensating events in cirrhosis identify five prognostic stages with significantly increasing mortality risks.

Aliment Pharmacol Ther 2014; **39:** 1180–1193

doi:10.1111/apt.12721

INTRODUCTION

The natural history of cirrhosis is characterised by a silent course until decompensation, when the progressive deterioration of liver function causes a rapid decline of life expectancy. The early stage of the disease is usually referred to as 'compensated cirrhosis', while the late one, defined by the appearance of ascites, bleeding, encephalopathy or jaundice, is termed 'decompensated cirrhosis'. Due to the strikingly different survival,[1, 2] compensated and decompensated cirrhosis are considered two distinct clinical entities.[3]

In recent years, a prognostic staging system of cirrhosis has been proposed, based on the observation that the patient outcome may be different according to the major clinical manifestations of the disease. Four stages have been proposed at the Baveno IV consensus conference:[4] stage 1, compensated cirrhosis without oesophageal varices; stage 2, compensated cirrhosis with varices; stage 3, ascites with or without varices; stage 4, bleeding with or without ascites. The four stages are characterised by a significant increase in the risk of death.[5] However, it has been shown that decompensated patients with ascites do have a significantly poorer outcome than those without ascites[6] and it has been therefore suggested that ascites should be a stratifying variable for decompensated patients. In agreement with this observation, a cohort study showed that 1-year death risk was significantly lower in patients with bleeding alone than in patients with ascites and that patients with ascites plus bleeding had the highest risk,[7] thus suggesting three stages for decompensated cirrhosis. A position paper of the American Association for the Study of Liver Disease has then reformulated the concept of cirrhosis from a static to a dynamic one with progression through biological, morphological and clinical stages and has encouraged clinical research in this sense.[3] Other studies have confirmed the concept of clinical[8, 9] and morphological[10] stages along with a correlation between morphological and clinical stages.[11, 12]

However, a definite staging system for cirrhosis, widely applicable in clinical practice is not yet available. We used the database from an inception cohort study[13, 14] to investigate whether a five-stage prognostic system based on development of oesophageal varices, bleeding, ascites and jaundice, allows classifying all the observed patients according to different survival probabilities within each stage. Competing risks of further clinical events and transitioning rates across stages were also investigated.

METHODS

To the aim of this study, we used a database drawn from a prospective inception cohort study, whose protocol was approved by the local ethics committee and based on the experience of a previous study of the natural history of cirrhosis performed at our Unit.[15] The major characteristics of the patient cohort are briefly summarised below.

From June 1981 to June 1984, all the consecutive in- or out-patients with newly diagnosed cirrhosis observed at our Unit were included in the study and those still alive are currently in follow-up. Patients were mostly referred directly from the family physicians to ascertain a suspected liver disease. The diagnosis of cirrhosis was biopsy proven in 342 patients without ascites or coagulopathy. In the remaining 152, diagnosis was based on typical ultrasonographic and laboratory findings with ascites (n = 78) or oesophageal varices (n = 56) or a firm liver and splenomegaly on physical examination (n = 18). Patients with Wilson disease (n = 4), haemocromatosis (N = 3), primary or secondary biliary cirrhosis (N = 5), or primary sclerosing cholangitis (N = 3) or autoimmune hepatitis (N = 6) were excluded. Six more patients were excluded because of incomplete cirrhosis on histology. Therefore, a total of 494 out of 521 patients were included.

HBsAg was determined by radioimmunoassay and a serum sample from all the included patients was stored at −80°C. Alcohol abuse was considered as a potential cause of cirrhosis when a habitual intake of >80 g/day for >5 years was admitted from the patient or his relatives. When commercial kits for serum anti-hepatitis C virus (HCV) were made available, all the stored sera were assessed with enzyme linked immunosorbent assay. Results are reported according to third generation assays.

After diagnosis of cirrhosis and informed consent to participate in the study, all the patients completed the initial study work-up including upper digestive endoscopy, liver ultrasonography and laboratory tests if not already performed in the diagnostic assessment. Follow-up started immediately after the informed consent and the initial study work-up was completed within 1 month. Endoscopy was then repeated every 2–3 years in patients without oesophageal varices, ultrasonography every 6–12 months, laboratory assessment every 6 months. Follow-up visits were repeated every 3–6 months or earlier according to the clinical condition. Loss to follow-up was prevented by recalling patients who did not present at each planned follow-up visit. The following clinical events were recorded: oesophageal varices, ascites, bleeding, encephalopathy, jaundice, hepato-

cellular carcinoma, comorbidity and death. The diagnosis of hepatocellular carcinoma was based on liver biopsy or on two imaging tests or one imaging test plus alpha-foetoprotein >400 UI/mL.[16]

No specific treatment was given to compensated patients free of varices. No patient received anti-viral treatment for HCV (not definitely recommended for cirrhotic patients along almost the entire study period),[17] while lamivudine was given according to evolving recommendations[18] in 10 HBsAg-positive patients. Treatments for variceal bleeding or its prophylaxis, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, portal systemic encephalopathy, were given according to guidelines or recommendations from consensus conferences available along the whole study period.[19–21] Only 19 patients were transplanted because no transplantation centre was available in Palermo before 1998, and only 12 were treated by trans-jugular intra-hepatic porto-systemic shunt (TIPS).

Compensated cirrhosis was defined by the absence of bleeding (any episode of haematemesis or melena), ascites on physical examination (confirmed by a tap), jaundice (serum bilirubin ≥3 mg/dL) or symptomatic encephalopathy[22] and decompensated cirrhosis by any of these complications.[1–3]

Prognostic stages were defined, according to major manifestations of decompensation of the disease, modifying The Baveno IV proposal[4] as follows: stage 1, compensated cirrhosis without varices; stage 2, compensated cirrhosis with varices; stage 3, bleeding without other disease complications; stage 4, first nonbleeding decompensating event; stage 5, any second decompensating event. Patients were considered within each stage until the occurrence of a new event, marking the transition towards a different stage. Hepatocellular carcinoma (HCC) was not considered as a separate stage as it may occur along the whole course of the disease and may be associated with compensated as well as decompensated cirrhosis.

Survival was assessed by the Kaplan–Meyer method[23] and differences between patient subgroups were assessed by the log-rank test. The cumulative incidence of major clinical events was assessed by a competing risks model,[24] where death was the competing event. Time zero for the analysis of outcome of each prognostic stage was the time a patient entered that stage. Therefore, patients leaving a stage, contributed to the assessment of the outcome of the next stage they entered, so that each patient may have contributed to the assessment of more than one stage.

An exploratory analysis by the proportional hazards Cox model[25] was performed to investigate whether the proposed stages may have an independent prognostic role for death, when adjusting for the most important death risk predictors already known.[5] Proportional-hazards assumption was tested by log-log plots inspection. A full model approach was used to select variables in multiple regression analyses to minimise the risk of overfitting.[26] Candidate predictors were set *a priori* among important and widely accepted prognostic indicators in cirrhosis:[5] age, gender, aetiology of cirrhosis, albumin, bilirubin, International Normalised Ratio of prothrombin activity, creatinine, platelet count, oesophago-gastric varices, ascites, porto-systemic encephalopathy, upper digestive bleeding, hepatocellular carcinoma, Child–Pugh score,[27] Model for End Stage Liver Disease (MELD)[28] and comorbidity.[29] Natural logarithm transformation was needed for INR to achieve normal distribution. Three models were performed to avoid the inclusion of potentially redundant variables in the same model: model 1 excluding Child–Pugh score and MELD; model 2 including Child–Pugh score and model 3 including MELD.

The aim of this prognostic analysis was purely exploratory. Therefore validation, or assessment of discrimination, calibration or comparison with previously known prognostic scores was not planned.

Statistical analyses were performed by STATA 11.0 (©Stata Corporation, College Station, TX, USA) and R 2.11.1 (© 2010 R free software foundation: http://www.r-project.org).

RESULTS

Overview of the cohort outcome

Patients' characteristics at inclusion and clinical events observed during the follow-up are reported in Tables 1–5: overall, 377 had compensated and 117 decompensated cirrhosis and aetiology was mostly from HCV. The mean follow-up was 145 ± 109 months without dropouts.

Survival was significantly better in patients with compensated than decompensated cirrhosis at diagnosis (Figure 1a). The competing risks analysis showed that decompensation occurred before death in 58% of patients with compensated cirrhosis, while only 10% died before decompensation and 4% died at the first decompensating event (Figure 1b). Patients dying at their first decompensating event likely presented acute on chronic liver failure (AoCLF), although available data in our database did not allow to classify these patients according to the recently proposed criteria for AoCLF.[30] The

Table 1 | Patient characteristics at inclusion: demographics, aetiology and biochemistry

Characteristics	Compensated (*N* = 377)	Decompensated (*N* = 117)	Total (*N* = 494)
Age	48.7 ± 12.9	58.2 ± 13.9	50.9 ± 13.7
Male/female	221/156	74/43	295/199
Aetiology			
Anti-HCV+	251	47	298
HBsAg+	18	4	22
Anti-HCV and HBsAg+	20	8	28
Alcohol	6	9	15
Alcohol and anti-HCV+	53	25	78
Alcohol and HBsAg+	10	6	16
Cryptogenic	19	18	37
Biochemistry			
Albumin, g/L*	37.8 ± 5.9	30.4 ± 5.7	36.02 ± 6.6
Bilirubin, mg/dL*,†	1.2 ± 0.5	2.9 ± 3.7	1.6 ± 2.0
Prothrombin%*	77 ± 15	57 ± 14	72 ± 17
INR*	1.36 ± 0.32	1.87 ± 0.48	1.47 ± 0.42
AST ×UNL, IU*	3.4 ± 2.4	3.1 ± 3.1	3.4 ± 2.6
ALT ×UNL, IU*	4.7 ± 3.8	2.4 ± 3.3	4.2 ± 3.8
Creatinine, mg/dL			
0–1	372	99	471
1.1–2	5	18	23
Haemoglobin, g/dL*	14.2 ± 2.3	11.9 ± 5	13.6 ± 3.3
Platelet count $\times 10^9$/L*	150 ± 66	130 ± 69	145 ± 67

* Mean ± standard deviation.

† Ordinal scale of values with steps of 1 mg/dL.

Table 2 | Patient characteristics at inclusion: clinical parameters

Characteristics	Compensated (*N* = 377)	Decompensated (*N* = 117)	Total (*N* = 494)
Child–Pugh class, A/B/C	290/84/3	8/60/49	298/144/52
Child–Pugh score*	5.9 ± 1.1	9.1 ± 1.8	6.6 ± 1.8
MELD*	10.1 ± 2.9	16.6 ± 5.1	11.7 ± 4.5
Oesophageal Varices	131	56	187
Small	98	19	117
Medium	21	17	38
Large	12	20	32
Gastric varices	5	3	8
Ascites	–	94	94
Bleeding	–	18	18
Encephalopathy	–	22	22
Jaundice	–	27	27
HCC	9	18	27

* Mean ± standard deviation.

cumulative incidence of the major *first* clinical event occurring in the 377 patients with compensated cirrhosis is shown in Figure 1c: ascites (33%), bleeding (10%) and HCC (9%) were the most frequent, while encephalopathy and jaundice occurred as the first clinical event in a minority of patients. Mortality before decompensation was mostly due to nonliver related causes, while after decompensation it was mostly due to liver-related causes (Table 5). Among the 109 patients who admitted alcohol abuse, 77 stopped it promptly after inclusion in the study, while 32 continued on intermittent moderate alcohol abuse before giving up. However, only five of 32 had purely alcoholic cirrhosis while the remaining had alcoholic plus viral aetiology, thus hampering a separate analysis of the effect of alcohol withdrawal on outcome in solely alcoholic cirrhosis.

Table 3 | Comorbidity at inclusion

Characteristics	Compensated (N = 377)	Decompensated (N = 117)	Total (N = 494)
Comorbidity*	216	69	285
Coronary heart disease	10	7	17
Other heart disease	4	0	4
Arterial hypertension	20	1	21
Chronic renal failure	3	1	4
Urolithiasis	11	0	11
Obstructive pulmonary disease	13	9	22
Diabetes	34	25	59
Other Endocrinological or Metabolic†	10	2	12
Cholelithiasis	32	11	43
Peptic ulcer	2	3	5
Other digestive‡	9	3	12
Haematological§	16	1	17
Immunological¶	10	3	13
Chronic infections**	10	0	10
Nonhepatic tumours	3	1	4
Neuro-psychiatric††	16	2	18
Other	13	0	13
None	161	48	209

* For patients with >1 comorbid conditions, the one considered most severe was recorded.

† Includes thyroid diseases, overweight, hyperlipidemia, osteoporosis, diabetes insipidus.

‡ Includes achalasia, oesophagitis, irritable bowel, colonic diverticular disease, pancreatitis, oesophageal stricture, early gastric cancer, previous intestinal surgery.

§ Includes thalassaemic diseases, spherocytosis, porfirias, polyglobulia, idiopatic thrombocytopoenia.

¶ Includes allergic disorders, psoriasis, sjogren, lupus erythematosus.

** Includes AIDS, tuberculosis, urinary or prostate infection, echinococcus.

†† Includes migraine, depression, psychosis, epilepsy.

Overall, 187 patients had oesophageal varices, eight gastric varices; 243 were free of varices at diagnosis while 56 did not undergo endoscopy (30 refused and 26 were not submitted to endoscopy because of advanced disease). New varices developed in 131 of 243 patients free of varices at diagnosis with a cumulative 10- and 20-year incidence of 44% and 53% respectively (Figure 1d). When varices were first detected either at diagnosis or during follow-up, (N = 326) their size[31] was small in 221, medium in 42 and large in 34. Progression of variceal size was observed in 96 of 292 patients with previously smaller varices. Cumulative 10- and 20-year survival after development of varices were 42% and 21% respectively (Figure 1e). By contrast, 10- and 20-year mortality before development of varices was 16% and 26% (Figure 1d).

Ten- and 20-year cumulative incidence of decompensation in the 377 patients with compensated cirrhosis at diagnosis were 42% and 62% respectively (including 4% who died at decompensation, Figure 1b), and were significantly higher in patients with than in those without varices (33% and 49% vs. 50% and 69%, respectively, $P < 0.0001$; Figure 1f). A total of 341 decompensated patients (117 at inclusion) were observed throughout the study: the first decompensating event was ascites in 202, bleeding in 75, ascites plus bleeding in 27, encephalopathy in 20 and jaundice in 19.

Overall, bleeding occurred in 158 patients and rebleeding in 57; the most frequent source was oesophageal varices either at first or recurrent bleeding (Table 4). The cumulative 20-year incidence of bleeding was 29% while 45% died before bleeding; 5- and 10-year mortality after bleeding was 70% and 82% (Figure 2a).

Ascites was present at diagnosis in 94 patients and occurred in further 189 during the follow-up with a 10- and 20-year cumulative incidence of 31% and 45% respectively (Figure 2b). Therefore, a total of 283 patients with ascites were observed during the study

Table 4 | Major outcome events during the whole follow-up (including clinical presentation), according to compensated or decompensated stage at diagnosis*

Clinical event	Compensated (*N* = 377) *N* (%)	Decompensated (*N* = 117) *N* (%)	Total (*N* = 494) *N* (%)
Oesophageal varices	224 (59)	76 (65)	300 (61)
Gastric varices	20 (5)	6 (5)	26 (5)
Ascites	174 (46)	109 (93)	283 (57)
Upper digestive bleeding	107 (28)	51 (43)	158 (32)
Source of bleeding†			
Oesophageal varices†	77 (72)	39 (76)	116 (73)
Gastric varices†	6 (6)	4 (8)	10 (6)
Portal hypertensive gastropathy†	7 (7)	3 (6)	10 (6)
Other†	10 (9)	2 (4)	12 (8)
Undefined†	7 (7)	3 (6)	10 (6)
Rebleeding	41 (11)	16 (14)	57 (12)
Source of rebleeding‡			
Oesophageal varices‡	21 (51)	9 (56)	30 (52)
Gastric varices‡	2 (5)	2 (13)	4 (7)
Portal hypertensive gastropathy‡	5 (12)	1 (6)	6 (10)
Other‡	7 (17)	1 (6)	8 (14)
Undefined‡	6 (15)	3 (19)	9 (16)
Encephalopathy	86 (23)	60 (51)	146 (30)
Jaundice	56 (15)	57 (49)	113 (2)
Hepatocellular carcinoma	94 (25)	32 (27)	126 (26)
Liver transplantation	17 (5)	2 (2)	19 (4)

* Numbers are the total of events observed across the whole study, including the events which defined patients as compensated or decompensated at inclusion.

† Percentage refers to the total of patients who bled.

‡ Percentage refers to the total of patients who rebled.

Table 5 | Causes of death according to compensated or decompensated stage at diagnosis

Clinical event	Compensated (*N* = 377)		Decompensated (*N* = 117)	Total (*N* = 494)
	N (% of deaths)			
Death*	While compensated*	After decompensation*	*N* (% of deaths)	*N* (% of deaths)
Total deaths	64	202	114	380
Liver failure	4 (6)	67 (33)	38 (33)	109 (27)
Variceal bleeding	7 (11)	33 (16)	25 (21)	65 (17)
Sepsis	4 (6)	7 (3)	7 (6)	18 (5)
Hepatocellular carcinoma	4 (6)	63 (31)	30 (26)	97 (26)
Neoplasia	10 (16)	7 (3)	2 (2)	15 (4)
Stroke	12 (19)	5 (2)	1 (1)	18 (5)
Myocardial infarction	5 (8)	2 (1)	0 (0)	7 (2)
Other nonliver related	13 (20)	10 (5)	7 (6)	29 (8)
Unknown	5 (8)	8 (4)	7 (6)	22 (6)

* For patients with compensated disease at inclusion in the study (*N* = 377), the number who died after decompensation (i.e. in the decompensated phase of the disease) or at a decompensating event, is reported in the separate sub-column.

(Table 4). Two- and 5-year cumulative mortality rates after occurrence of ascites, were 38% and 78% respectively (Figure 2b).

HCC developed overall in 126 patients (26%). The 20-year cumulative incidence was 18% (Figure 2c). Overall HCC developed before decompensation in 51 patients and after decompensation in 75. Two- and 5-year mortality after occurrence of HCC was respectively 74% and 91% (Figure 2c); corresponding figures when HCC developed in a compensated stage were 52% and 85%

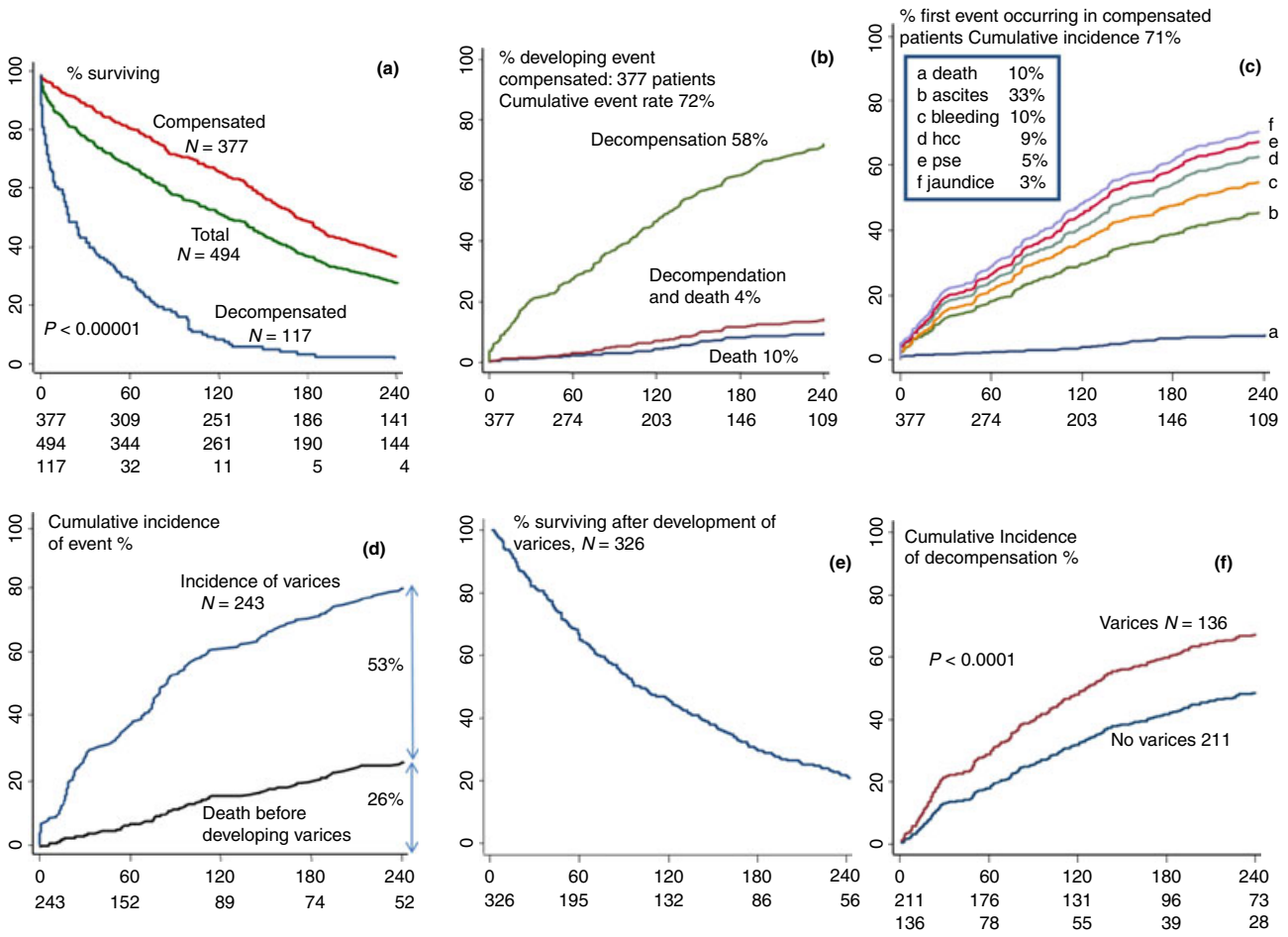

Figure 1 | Twenty-year survival and cumulative incidence of clinical events. Cumulative incidence is computed by competing risks analysis and each curve represents the probability of each specific outcome summed to the outcome probability represented in the next curve below. Survival curves are computed by the Kaplan–Meier method. The *x*-axis represents time in months and the numbers below the *x*-axis are patients at risk. (a) Survival of the whole series and, respectively, of compensated and decompensated patients at diagnosis. (b) Cumulative incidence of decompensation. Death and death at the time of first decompensation are shown as competing events. (c) Cumulative incidence of events presenting as a first event in 377 patients with compensated cirrhosis at the diagnosis. Twenty-year proportions of patients presenting each first event are reported in the box. (d) Cumulative incidence of oesophageal varices. Death is shown as a competing event. Arrows indicate the 20-year incidence of the two competing events. (e) Survival of patients after development of varices. (f) Cumulative incidence of decompensation in patients with and without varices at diagnosis.

and in a decompensated stage 90 and 97% ($P < 0.00001$) (Figure 2d).

The cumulative incidence of encephalopathy and of jaundice are shown in Figure 2e–f, together with mortality after the development of each.

Prognostic stages of cirrhosis

The number of patients entering each of the five prognostic stages (at diagnosis or during the follow-up) is reported in Figure 3 together with 20-year incidence of competing events per each stage. Five-year transitioning intensity and mortality per each prognostic stage is reported in Table 6.

There were 202 patients with compensated cirrhosis without oesophageal varices (*stage1)*. After 20 years, 163 had disease progression, while 39 were still in this stage. Fourteen patients bled in this stage: 10 bled from varices which were not present at previous endoscopy (1 to 3 years before); no varices were found in the remaining four patients in whom portal hypertensive gastropathy was the most likely source of bleeding, although there was no active bleeding at the time of endoscopy.

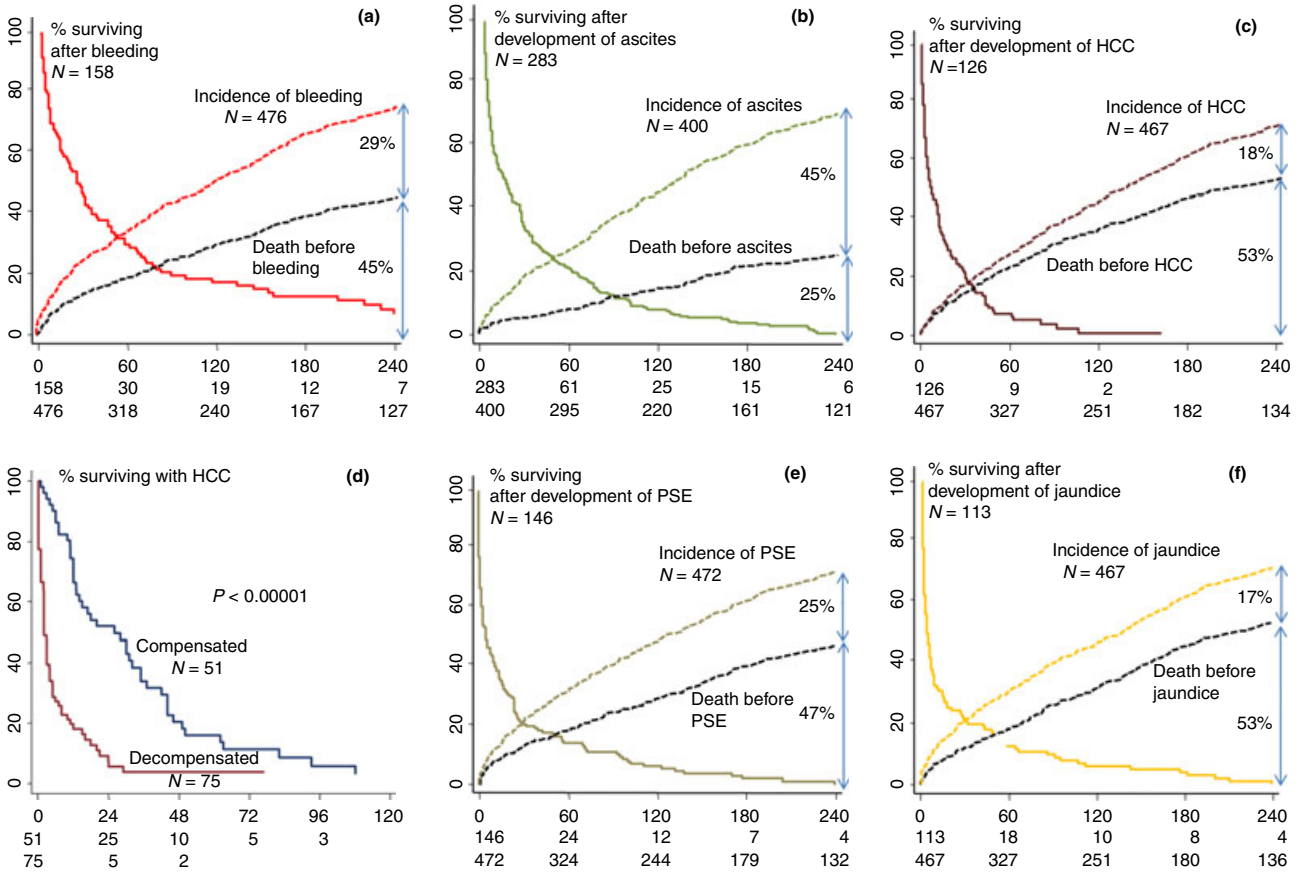

Figure 2 | Twenty-year cumulative incidence (competing risks plots) of events along the course of cirrhosis and survival (Kaplan–Meier plots) after each relevant event. Per each cumulative incidence curve death is the competing event. Arrows indicate the 20-year incidence of the competing events. In the panels, the *x*-axis represents the observation time in months and the numbers below the *x*-axis are the numbers of patients at risk. PSE = porto-systemic encephalopathy. (a) Upper digestive bleeding. (b) Ascites. (c) Incidence of hepatocellular carcinoma. (d) Survival after development of HCC in compensated and decompensated cirrhosis. (e) Portal systemic encephalopathy. (f) Jaundice.

Development of varices and ascites were the most frequent events occurring in this stage. After 20 years, mortality in the stage was 10%, while 20% of patients were still alive in the stage (Figure 3a).

Compensated cirrhosis with oesophageal varices (stage 2), was diagnosed in 137 patients at diagnosis and 79 (seven undetermined at diagnosis) developed varices before decompensation, during the follow-up. Therefore, overall 216 patients entered this stage. Major events in this stage were bleeding and ascites. After 20 years, mortality in the stage was 18%, while 19% of patients were still in the stage (Figure 3b).

Overall, 158 patients bled during the follow-up (18 at diagnosis of cirrhosis). Of them, 75 bled before the occurrence of any other decompensating event, thus entering in *stage 3*. The 20-year cumulative incidence of rebleeding was 19% (mean rebleeding time 28 ± 46 months). Five patients (6.5%) were still in this stage and did not rebleed at 20 years. Ascites was the most frequent event and 20-year mortality in the stage was 23% (Figure 3c).

There were 63 patients with one nonbleeding decompensating event at diagnosis and 143 developed one such event during follow-up. Therefore, 206 patients entered *stage 4*, 163 with ascites, 23 with jaundice and 21 with encephalopathy. Further events occurred overall in 196 patients, bleeding and encephalopathy being the most frequent; 20-year mortality in the stage was 39% (Figure 3d).

Overall, 213 patients developed a second decompensating event thus entering *stage 5*, mostly from stages 4 and 3, although 17 and 13 patients respectively, came from stage 2 and 1, presenting with two events at the

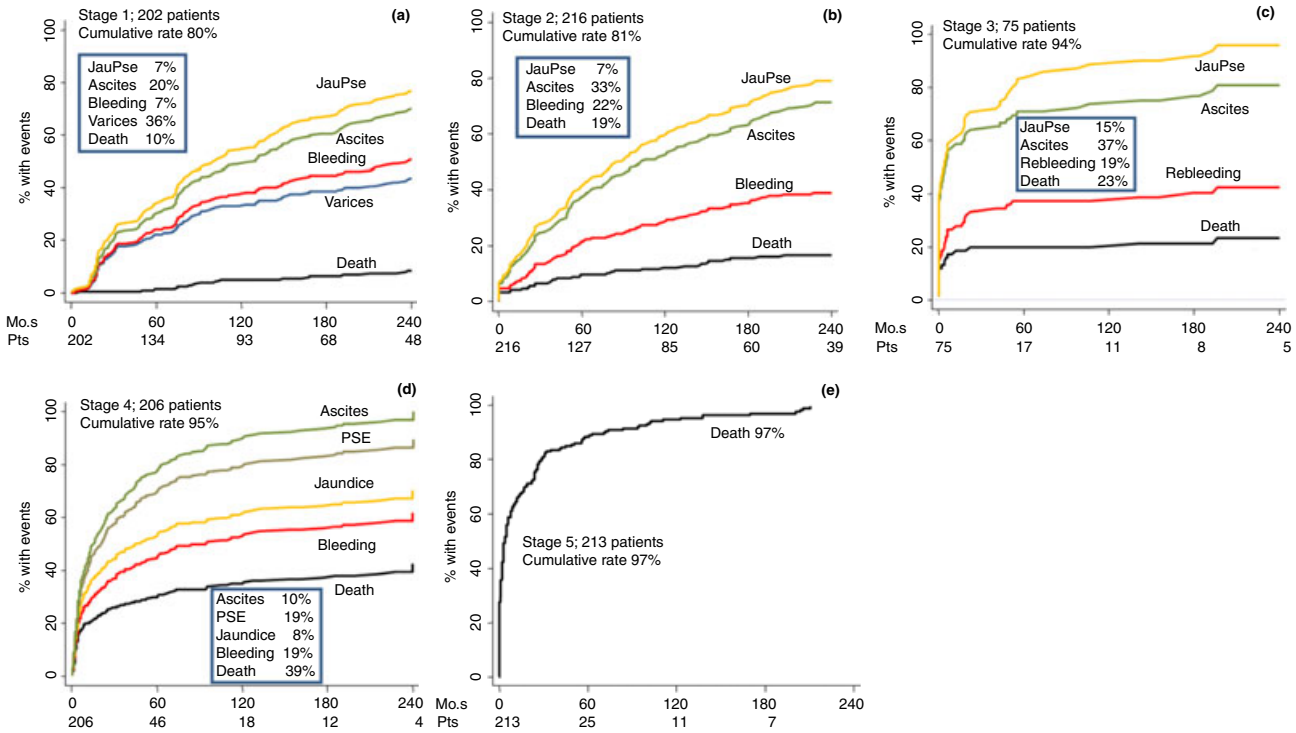

Figure 3 | Competing risk analysis of 20-year major outcomes from each of five assessed prognostic stages of cirrhosis. Each incidence curve represents the probability of each specific outcome summed to the outcome probability represented in the next curve below. In the panels, the *x*-axis represents the observation time in months and the numbers below the *x*-axis are the numbers of patients at risk. Boxes report 20-year occurrence rate of each outcome. JauPse, Jaundice and/or encephalopathy; PSE, porto-systemic encephalopathy. (a) Stage 1; (b) Stage 2; (c) stage 3; (d) stage 4; (e) stage 5.

Table 6 | Prognostic stages and outcome

Stage	Definition	No. of patients*	5-year transition rate (%)	5-year mortality rate (%)
1	Compensated cirrhosis without varices	202	34.5	1.5
2	Compensated cirrhosis with varices	216	42	10
3	Bleeding without other disease complications	75	65	20
4	First nonbleeding decompensating event	206	78	30
5	Any second decompensating event	213	–	88

* Total number of patients who entered in the stage during the study either at diagnosis or during follow-up.

same time. Overall, 206 patients (97%, Figure 3d) died in this stage (29% after a new clinical event: bleeding 6%, ascites 3%, jaundice 7%, encephalopathy 19%).

Five-year transition towards a different prognostic stage was respectively 34.5%, 42%, 65% and 78% in stages 1–4 (P for trend <0.0001) and 5-year mortality in stages 1–5 was respectively 1.5%, 10%, 20%, 30% and 88% (P for trend <0.0001) (Figure 4; Table 6).

Hepatocellular carcinoma occurred in stages 1–5 in 27, 28, 12, 30 and 29 patients respectively. All the patients who developed HCC in stages 1 or 2 developed one or more decompensating events before dying. The median survival time for patients developing HCC in a compensated stage was 15 months (range 2–96) and for patients developing HCC in a decompensated stage it was 3 months (range 1–35).

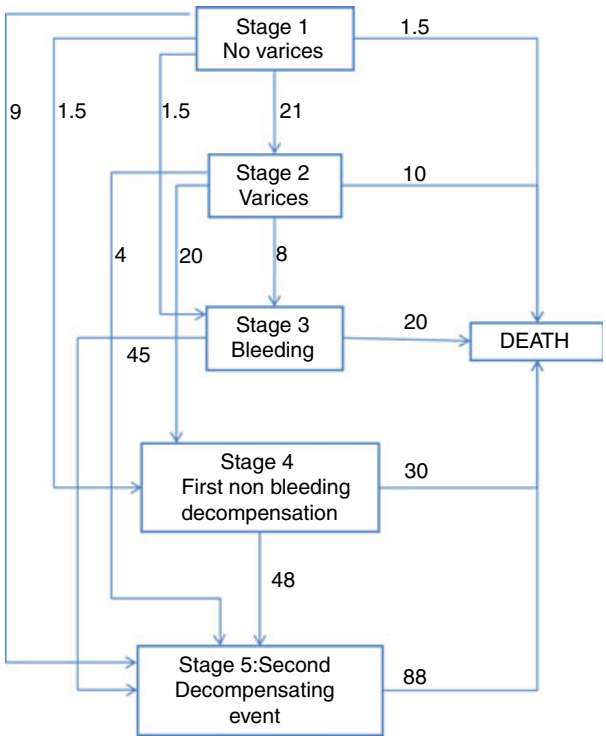

Figure 4 | Schematic representation of 5-year transitioning rate across stages and to death for the whole series of patients. Arrows represent transitions and the numbers close to each arrow are the relevant transition rates. A fairly steady increase in death rate was found across stages.

Exploratory prognostic analysis for mortality

Significant death risk predictors are shown in Table 7. As age was significantly correlated with comorbidity (mean ± standard deviation 47 ± 15 without and 53 ± 11 with comorbidity; $P < 0.00001$), it was withdrawn from the final model to assess the prognostic role of comorbidity. The variable *stages* showed an independent prognostic value even when adjusted for other important prognostic variables in cirrhosis including the Child–Pugh score, the MELD and comorbidity. Besides Child–Pugh score and the MELD, other significant variables were albumin, bilirubin, log transformation of INR, creatinine, hepatocellular carcinoma and comorbidity.

DISCUSSION

This study, based on a large cohort of cirrhotic patients with complete follow-up, showed that a prognostic staging system based on major clinical manifestations of the disease is suitable to classify patients according to significantly increasing risk of death, independently of Child–Pugh or Meld score or comorbidity.

An important finding of the study is the very low (14%) probability of death before decompensation for compensated patients. This finding underlines the appropriateness of considering the course of cirrhosis as the progression across different prognostic stages.[3] In fact, the probability of dying while in a compensated stage was markedly different from the probability shown by the Kaplan–Meier method for patients with compensated cirrhosis at diagnosis, without accounting for transition in a decompensated stage (Figures 1a,b). Importantly, while 10% of patients with compensated cirrhosis died before decompensation of nonliver-related causes, 4% died of their first decompensating event, suggesting that AoCLF[30] may have a major role in these critical events and potentially providing a measure of the impact of AoCLF on the course of cirrhosis. Unfortunately, complete data to characterise patients according to the criteria for AoCLF were not available in our database and therefore, we were not able to properly assess the role of this event in mortality of compensated patients.

By characterising patients according to the first occurrence of the major clinical manifestations of the disease, we assessed the disease progression from the time of appearance of each specific manifestation, by a competing risks analysis. Following this approach, we confirmed that the proposed stages allowed to classify all the patients with cirrhosis according to the major clinical patterns of the disease, and are fairly characterised by a steadily and significant increase in mortality.

The competing risks analysis also showed that major outcomes are appreciably different across stages. In fact, varices and ascites are the major outcomes for patients without varices at diagnosis, while bleeding and ascites are the most important after the development of varices, as rebleeding and ascites are for patients with a first bleeding without other complications. Ascites was by far the most frequent decompensating event and any second decompensating event was associated with mortality as high as 88% in 5 years. Patients presenting with upper digestive bleeding alone had a better survival than patients presenting with any other decompensating event; however, bleeding alone was observed in only approximately half of the total of patients who bled (75/158). In these patients, 5-year survival was 80% unless they developed other complications (Figure 3c). Hepatocellular carcinoma developed in 26% of patients and survival after its occurrence was significantly different according to whether it developed in a compensated or in a decompensated stage of cirrhosis (Figure 2d),

Table 7 | Exploratory prognostic analysis for death risk by the Cox model (494 patients)*

Variable†	Hazard ratio	Standard error	95% confidence interval	*P*
Model 1				
Albumin	0.97	0.009	0.96–0.99	0.005
Bilirubin	1.11	0.030	1.05–1.17	<0.0001
logINR	2.05	0.531	1.23–3.40	0.006
Creatinine	1.06	0.026	1.01–1.11	0.017
HCC	12.03	3.103	7.27–19.95	<0.0001
Comorbidity	1.44	0.157	1.16–1.79	0.001
Stage	1.44	0.082	1.23–1.61	<0.0001
Model 2				
HCC	13.35	3.343	8.17–21.81	<0.0001
Comorbidity	1.46	0.157	1.19–1.81	<0.0001
Child–Pugh score	1.28	0.058	1.17–1.40	<0.0001
Stage	1.37	0.087	1.21–1.55	<0.0001
Model 3				
Albumin	0.98	0.009	0.96–0.99	<0.0001
HCC	13.88	3.529	8.44–22.85	<0.0001
Comorbidity	1.49	0.161	1.20–1.84	<0.0001
MELD	1.09	0.017	1.06–1.12	<0.0001
Stage	1.41	0.079	1.27–1.58	<0.0001

HCC, hepatocellular carcinoma.

* Rating of variables included in the analyses was as follows: albumin, g/L (continuous values); bilirubin, mg/dL: ordinal values with 1 mg/dL steps (0–1 = 1, etc.); INR = log(INR); creatinine, mg/dL: 0–1 = 1; 1.1–2 = 2; Hepatocellular carcinoma, no = 0; yes = 1; comorbidity, no = 0, yes = 1; stage = 1–5 as reported in methods; Child–Pugh score = 5–15; MELD (model for end stage liver disease) = continuous values.

† Age was withdrawn from the final models because it was significantly correlated with comorbidity.

although it worsened prognosis either in compensated or in decompensated disease. The poor outcome after development of HCC may raise the question whether it should be included in the criteria of decompensation, although the increasing precocity of the diagnosis of HCC in the compensated stages will tend to increase the difference in survival of patients with HCC in compensated compared to decompensated cirrhosis.

The staging system here proposed is easily applicable in clinical practice and may have several favourable implications: first, it may allow to better define the disease outcomes so as to provide patients with more reliable information; second, it may allow to better classify patients and to achieve more homogeneous data from different centres or studies, particularly randomised clinical trials; third, it may allow to identify more accurate predictors of relevant outcomes, which in turn, may lead to improved patient selection for specific therapies including liver transplantation.

In an exploratory prognostic analysis, we sought to assess whether the prognostic stages we have defined may retain any prognostic value when adjusted for several important and widely used prognostic variables. The analysis showed that the variable *stages* is an independent and highly statistically significant predictor of death risk even when adjusted for comorbidity, Child–Pugh score and MELD. This suggests that, if validated in further studies, this prognostic staging system may provide an important incremental value to the most widely used prognostic scores. It is to note that, although comorbidity is usually not included in prognostic scores of cirrhosis, we included it in the analysis given its obvious prognostic value confirmed in a large population-based cohort study.[29] In fact, comorbidity was significant in all the three models we performed.

Besides the potential prognostic role of the staging system here proposed, the marked differences in the types and rates of outcomes observed across stages suggest that prognostic indicators should be separately assessed per each disease stage. It is in fact conceivable that prognostic indicators may be different or may have a different strength of association with the outcome, across different stages. As an example, 1 mg increase in serum bilirubin might have a different prognostic value in compensated and decompensated patients.

The observation that the type and rate of outcomes are different according to different prognostic stages has also been recently reported in a Danish cohort study assessing the clinical course of alcoholic cirrhosis:[7] although oesophageal varices were not considered as a stratifying variable for compensated cirrhosis, transitioning across stages was roughly similar to what observed in our study. In fact, the overall 5-year probability of developing a second decompensating event after bleeding alone or ascites alone was respectively 54% and 42%,[7] compared to 45% and 48% in our study and 5-year mortality was respectively 18% and 25%,[7] compared to 20% and 30% in our study. Similarly, the significantly higher decompensation rate of patients with oesophago-gastric varices compared to patients free of varices has also been previously reported[8, 9] and this observation is coherent with the increased risk of decompensation with hepatic vein pressure gradient >10 mmHg.[32] Also the different outcome of decompensated cirrhosis according to the major clinical characteristics, and particularly the better outcome of patients presenting with variceal bleeding compared to patients presenting with ascites, was previously reported[7] and recently confirmed in a cohort study of decompensated cirrhosis:[33] these findings, together with ours, support the appropriateness of considering bleeding alone as a separate prognostic stage in decompensated cirrhosis.

However, although several studies[6–12] have confirmed the rationale for a staging system in cirrhosis, a full independent and prospective validation of the system here proposed is needed before it may be applied in clinical practice. It is of note, in this respect, that preliminary results from a large multicentre study seem to validate this staging system.[34]

One limitation of the present study is that only alcohol, virus related and cryptogenic cirrhosis has been included and applicability of the proposed prognostic stages to other aetiologies remains to be assessed. However, as the prognostic stages here proposed represent major clinical manifestations of cirrhosis, it is conceivable that this staging system may also apply to other aetiologies. In fact, even if different outcome rates per each stage may be predicted according to aetiology, differences between stages may still be consistent across different aetiologies. Of course, this hypothesis has to be tested in further studies. It is of interest, in this respect, that the Laennec's histological stages of cirrhosis have been recently reported to be significantly related to the clinical stages and to clinically significant portal hypertension;[10–12] haemodynamic and biological correlation with clinical stages has been advocated too.[3]

Another limitation of this study is that, no treatment was given for HCV infection, for the reasons reported in the method section. However, in this respect, it may be worth to note that treatment with peginterferon-alpha and ribavirin is expected to achieve a sustained viral response (SVR) in approximately 22%[35] of cirrhotic patients; although the disease progression may be delayed in these patients, it is conceivable that their outcome will differ according to the development of major clinical events. Therefore, the prognostic stages here proposed, will be probably applicable even after anti-viral treatment. Similarly, anti-viral treatment for HBV cirrhosis may halt the progression of the disease, although it may be expected that even with anti-HBV treatment, the outcome of patients who have developed clinical manifestations of the disease will be worse than that of patients who have not. Yet, the role of fibrosis regression after sustained virological response either in HCV or in HBV infection,[36] in the clinical course of compensated cirrhosis remains to be assessed, particularly after the introduction of direct anti-viral agents for HCV,[37] which may significantly increase SVR even in patients with cirrhosis. However, until more definitive information on the long-term outcome of anti-viral treatments in cirrhosis either compensated or decompensated will be available, the prognostic staging system here proposed may help to improve outcome prediction in clinical practice.

In conclusion, this large prospective inception cohort study provides further insight in the clinical course of cirrhosis, suggesting a new perspective which better explains the different outcome of compensated and decompensated cirrhosis and shows that five prognostic stages may contribute to improve the disease outcome prediction, together with other important prognostic indicators. The marked difference in outcome across stages suggests that prognostic indicators should be assessed separately per each disease stage.

AUTHORSHIP

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Author contributions: Gennaro D'Amico: study concept, design, statistical analysis, interpretation of results, drafting and revising of manuscript for important intellectual content. Linda Pasta: study concept, design, interpretation of results, revising of manuscript. Alberto Morabito: statistical analysis, interpretation of results. Mario D'Amico: database updating, interpretation of results, acquisition of data. Maria Caltagirone: acquisition of data.

Giuseppe Malizia: acquisition of data, interpretation of results, revision of the manuscript for important intellectual content. Fabio Tinè: patient follow-up, acquisition of data. Gandolfo Giannuoli: patient follow-up, acquisition of data. Mario Traina: endoscopy, acquisition of data, patient follow-up. Giovanni Vizzini: database management, acquisition of data, patient follow-up. Flavia Politi: acquisition of data, patient follow-up. Angelo Luca: acquisition of data, patient follow-up. Roberto Virdone: ultrasonography, acquisition of data. Anna Licata: database updating, acquisition of data. Luigi Pagliaro: revising of manuscript for important intellectual content. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

1. Gines P, Quintero E, Arroyo V, *et al.* Compensated cirrhosis: natural history and prognosis. *Hepatology* 1987; **7**: 122–8.
2. Saunders JB, Walters JRF, Davies P, *et al.* A 20-year prospective study of cirrhosis. *Brit Med J* 1981; **282**: 263–36.
3. Garcia-Tsao G, Friedman S, Iredale J, *et al.* Now there are many stages where before there was one: in search of pathophysiological classification of cirrhosis. *Hepatology* 2010; **51**: 1445–9.
4. Garcia-Tsao G, D'Amico G, Abraldes JG, *et al.* Predictive models in portal hypertension. In: de Franchis R, ed. *Portal Hypertension*. Proceedings of the fourth international consensus workshop on methodology of diagnosis and treatment. Oxford: Blackwell Publishing, 2006; 47–100.
5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; **44**: 217–31.
6. Zipprich A, Garcia-Tsao G, Rogowsky S, *et al.* Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liv Int* 2012; **32**: 1407–14.
7. Jepsen P, Ott P, Andersen PK, *et al.* The clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; **51**: 1675–82.
8. Bruno S, Zuin M, Crosignani A, *et al.* Predicting mortality risk in patients with compensated HCV-induced cirrosi: a long term prospective study. *Am J Gastroenterol* 2009; **104**: 1147–58.
9. Vilar Gomez E, Sanchez Rodriguez Y, Calzadilla Bertot L, *et al.* The natural history of compensated HCV-related cirrhosis: a prospective long-term study. *J Hepatol* 2013; **58**: 434–44.
10. Kim SU, Oh HJ, Wanless IR, *et al.* The Laennec staging system for histological subclassification is useful for stratification of prognosis in patients with liver cirrhosis. *J Hepatol* 2012; **57**: 556–63.
11. Rastogi A, Maiwall R, Bihari C, *et al.* Cirrhosis histology and Laennec staging system correlate with high portal pressure. *Histopathology* 2013; **62**: 731–41.
12. Kim MY, Cho MY, Baik SK, *et al.* Histological subclassification of cirrhosis using the Laennec fibrosis scoring system correlates with clinical stage and grade of portal hypertension. *J Hepatol* 2011; **55**: 1004–9.
13. Pagliaro L, D'Amico G, Pasta L, *et al.* Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann RJ, eds. *Portal Hypertension. Pathophysiology and Treatment*. Oxford: Blackwell Scientific Publications, 1994; 72–92.
14. D'Amico G, Pasta L, Madonia S, *et al.* The incidence of esophageal varices in cirrosi. *Gastroenterology* 2001; **120** (Suppl.): A2.
15. D'Amico G, Morabito A, Pagliaro L, *et al.* Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci* 1986; **31**: 468–75.
16. Bruix J, Sherman M, Llovet JM, *et al.* Clinical management of hepatocellular carcinoma: conclusions of the Barcelona-2000 EASL Conference. *J Hepatol* 2001; **35**: 421–30.
17. Strader DB, Wright T, Thomas DL, *et al.* Diagnosis, management and treatment of Hepatitis C. AASLD practice guideline. *Hepatology* 2004; **39**: 1147–71.
18. Perrillo RP. Management of the patient with hepatitis B virus-related cirrhosis. *J Hepatol* 2003; **39**: S177–80.
19. de Franchls R, Pascal JP, Ancona E, *et al.* Definitions, methodology and therapeutic strategies m portal hypertension A consensus development workshop. *J Hepatol* 1992; **15**: 256–61.
20. Garcia-tsao G, Sanial A, Grace ND, *et al.* Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. AASLD practice guideline. *Hepatology* 2008; **46**: 922–38.
21. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397–417.
22. Ferenci P, Lockwood A, Mullen K, *et al.* Hepatic encephalopathy – definition, nomenclature, diagnosis and quantification: final report of the working party at11th world congresses of gastroenterology, Vienna 1998. *Hepatology* 2002; **35**: 716–21.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
24. Gooley TA, Leisenring W, Crowley J, *et al.* Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999; **18**: 695–706.
25. Cox DR. Regression models and life-tables (with discussion). *JR Stat Soc B* 1972; **34**: 187–220.
26. Royston P, Moons KGM, Altman DG, *et al.* Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009; **338**: b604.
27. Pugh RN, Murray-Lyon IM, Dawson JL, *et al.* Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646–6.
28. Kamath PS, Wiesner RH, Malinchoc M, *et al.* A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464–70.
29. Jepsen P, Vilstrup H. Lash TL development and validation of a comorbidity scoring system for patients with cirrhosis. *Gastroenterology* 2014 Jan; **146**: 147–56.
30. Moreau R, Jalan R, Gines P, *et al.* Acute on chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426–37.

31. The Italian Liver Cirrhosis Project. Reliability of endoscopy in the assessment of variceal features. *J Hepatol* 1987; **4**: 93–8.
32. Ripoll C, Groszmann R, Garcia-Tsao G, *et al.* Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; **133**: 481–8.
33. Bruno S, Saibeni S, Bagnardi V, *et al.* Mortality risks according to different clinical characteristics of first episode of liver decompensation in cirrhotic patients, a nationwide, prospective 3-year follow-up study in Italy. *Am J Gastroenterol* 2013; **108**: 1112–22.
34. D'Amico G, Villanueva C, Burroughs AK, *et al.* Clinical stages of cirrhosis a multicenter study of 1858 patients. *Hepatology* 2010; **52**(S1): 329A.
35. Van der Meer AJ, Veldt BJ, Feld JJ, *et al.* Association between sustained virological response and all cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584–93.
36. Elis EL, Mann DA. Clinical evidence for regression of liver fibrosis. *J Hepatol* 2012; **56**: 1171–80.
37. Liang TJ, Ghany MG. Current and future therapies for hepatitis c virus infection. *New Engl J Med* 2013; **368**: 1907–1317.