Title

New concepts on the clinical course and stratification of compensated and decompensated cirrhosis.

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Abstract

The clinical course of cirrhosis has been typically described by a compensated and a decompensated state based on the absence or, respectively, presence of any of bleeding, ascites, encephalopathy or jaundice. More recently, it has been recognized that increasing portal hypertension and several major clinical events are followed by a marked worsening in prognosis and disease states have been proposed accordingly in a multistate model. The development of multistate models implies the assessment of the probabilities of more than one possible outcome from each disease state. This requires the use of *competing risks analysis* which investigates the risk of several competing outcomes. In such a situation the Kaplan Meier risk estimates and the Cox regression may be not appropriate. Clinical states of cirrhosis presently considered as suitable for a comprehensive multistate model include, in *compensated cirrhosis*: early (mild) portal hypertension with hepatic venous pressure gradient (HVPG) >5 and <10 mmHg, clinically significant portal hypertension (HVPG ≥10 mmHg) without gastro-esophageal varices (GEV), and GEV; in *decompensated cirrhosis*: a first variceal bleeding without other decompensating events, any first non bleeding decompensation and any second decompensating event; in a *late decompensation* state, refractory ascites, sepsis, renal failure, recurrent encephalopathy, profound jaundice, acute on chronic liver failure, may occur, all predicting a very short survival.

In this review we illustrate how competing risks analysis and multistate models may be applied to cirrhosis.

Introduction

Growing evidence has emerged in the last years suggesting that the clinical course of cirrhosis may be described by a multi-state model. This evidence has been developed on the long-lasting knowledge that survival of patients with compensated cirrhosis (CC) is much longer than that of patients with decompensated cirrhosis, when decompensated cirrhosis is defined by the presence of any of bleeding, ascites, encephalopathy or jaundice. Moreover, patients with CC have an acceptable or at all good quality of life, do not usually experience symptoms and may remain in this disease state for many years, if not indefinitely. By contrast, patients with decompensated cirrhosis, not only have a significantly shorter survival, but also a worse quality of life marked by the presence of overt signs of decompensation. These marked clinical differences, have brought about the concept that compensated and decompensated cirrhosis are two different clinical states of the disease (1).

The typical representation of a disease outcome by Kaplan Meier survival curves (2), does not properly fit the real clinical course of the disease in a multistate setting. In fact, for example, patients with CC usually develop decompensation before dying. Therefore, they transition from a compensated to a decompensated state and their death risk is dramatically increased after this transitioning. By contrast, the risk of death of patients remaining in a compensated state is minimal and usually due to non liver related causes (3). The Kaplan-Meier survival analysis may not capture this change of clinical state because it has been developed to assess a simple two-state model, typically alive→dead. Instead, this is a *competing risks* situation, where death competes with decompensation to occur first, configuring a three-state model where compensated patients have two possible outcomes: death or decompensation. In such a situation the use of the Kaplan Meier estimator will result in overestimation of risks (4), while the appropriate analysis is the *competing risks analysis,* which using the Aalen-Johansen estimator provides the real incidence of two or more competing events (5).

In this review we will expand the concept of competing risks with practical examples from cirrhosis showing how competing risks and Kaplan Meier analyses provide different information and when it is appropriate to use each of them. A multistate model for cirrhosis is also shown.

Competing events

A competing event is an event whose occurrence either precludes the occurrence of another event or modifies the risk / probability that it occurs (figure 1a).

To illustrate this definition, suppose that a group of patients who survived a first variceal bleeding is followed to observe the occurrence of re-bleeding. If by the end of the observation period, each patient had re-bled or was still alive and free of re-bleeding, then one could conclude that re-bleeding occurs, earlier or later, without any competing event. This would imply that death would only occur after re-bleeding (figure 1b) and that the course of the disease after a first variceal bleeding could be assessed by two different 2-state models without competing risks. The first including the states of bleeding and re-bleeding, evaluating the risk of re-bleeding, the second including re-bleeding and death evaluating the risk of death after the occurrence of a re-bleeding. However, this does not occur in real life because several patient do die before re-bleeding. Therefore, in some patients death precludes the occurrence of re-bleeding (figure 1a). Moreover many patients die at or after re-bleeding. The real life model is therefore the 3-state model represented in figure 1c.

Recognizing competing risks is important because when assessing the risk of the event of interest in presence of competing risks, the Kaplan-Meier estimator (2), invariably results in upward biased estimates (4-5). In this situation, the competing risks analysis should be used. This analysis is based on the Cumulative Incidence Function (CIF) (5) which, by using a specific estimator, partitions the probability of each event, in such a way that the sum of the probabilities of each event ranges from 0 to 1. The essential difference between the two estimators is that while the

Kaplan-Meier censors or ignores the competing event, the competing risks analysis correctly counts each of the competing events.

Competing risks analysis.

To explain why to use competing risks analysis and how does it work, the example of the re-bleeding risk will be here expanded.

In a cohort study of the clinical course of cirrhosis (3), 158 patients experienced a first episode of variceal bleeding and, among them, 105 survived it. By the Kaplan-Meier estimator the 5-year cumulative risk of death without re-bleeding (the complement to Kaplan-Meier estimation, or 1-KM) was 0.53 and the corresponding risk of re-bleeding was 0.59 (figure 2, left panel), summing up to a total risk of 0.53+0.59 =1.12, which is clearly not credible because re-bleeding and mortality without re-bleeding are reciprocally excluding events and hence the sum of their probabilities may not yield values >1. Note that, when estimating the risk of death without re-bleeding the Kaplan-Meier estimator censors re-bleeding and when estimating the risk of re-bleeding it censors deaths, (hence the number of patients at risk per each observation period is identical for the two Kaplan-Meier estimates (figure 2, left panel)). By doing so, this estimator not only does not account for the competing event, but also it does not fulfill the well known requirements of censoring which has to be uninformative and independent of the outcome (6): this is clearly not the case when the censoring event is clinically relevant, like re-bleeding in cirrhosis and much more so when the censoring event is death.

However, it is possible to estimate the cumulative risk of any of the two events, death or re-bleeding whichever occurs first, by using the composite outcome (death or re-bleeding): in this way neither event is censored. By doing so the 3-state model has been reduced into a 2-state model ([no re-bleeding] →[re-bleeding or death]), and the Kaplan-Meier estimator may be safely applied, to estimate the cumulative incidence function (CIF) of the composite event. In this estimation, patients who do not experience any event (re-bleeding or death) are correctly right censored at the

end of the follow-up. This estimate in our cohort, is plotted in figure 2b (1-KM curve) and shows

that the cumulative 5-year risk, or CIF for the composite event (re-bleeding or death), was 0.82.

Assessing the cumulative incidence of the composite event however, is not usually

clinically helpful because clinical decisions may be different according to the specific risks of each

competing event. The competing risks analysis allows to partition the cumulative incidence of the

composite event in the cumulative incidence functions (CIFs) of each competing event. A specific

estimator is used to this aim, whose operating characteristics in the context of cirrhosis have been

illustrated elsewhere (4): it acts by applying the rate of the event of interest to the subjects still free

of any event (and not only to the ones free of the event of interest, as the Kaplan-Meier would do).

Thus, none of the competing events is censored; instead, all of them are considered as events and

patients experiencing any such events are no longer considered at risk of any event. The

partitioning characteristics of the CIF for competing risks may be seen in figure 2 (right panel)

where the CIFs for the two competing events (re-bleeding and death without re-bleeding) are

shown together with the 1-KM estimate for the composite event. As expected, the sum of the two

competing risks (0.82) was < 1 and corresponds to the CIF for the composite event of re-bleeding

or death (1-KM).

Several similar examples, where death is the competing event, are reported in table 1 from

the same prospective cohort study (3): competing risks analysis is reported for both the event of

interest and the competing one, together with the corresponding Kaplan Meier risk estimates (1-

KM) for comparison (competing event censored). It may be noted that the Kaplan Meier estimator

systematically overestimates the risks and that the overestimation is greater when the proportion of

patients experiencing the competing event is higher.

Incidence rate and risk

In table 1 the event rate, or incidence rate, is shown together with the cumulative risk. The

incidence rate is the ratio D/Y where D is the number of subjects developing the disease in a given

follow-up time and Y is the total amount of person-time at risk (i.e. the sum of the observation time of each subject up to the given follow-up time) (7). It is essentially an average measure of the speed of the occurrence of the event of interest, assuming a constant velocity or hazard of the event over time. Risk is typically defined as the ratio D/N, where D is the number of subjects who develop the disease over a given time and N is the number of subjects disease-free at the beginning of that time (7). Therefore, the rate differs from the risk because the denominator accounts also for the time of observation of each subject, thus it expresses the number of events occurring per unit of time. For example, from table 1 the rate of decompensation was 0.049 events per year (or an average of 4.9 events per 100 patients at risk observed for 1 year), while the 20-year cumulative risk of decompensation was 0.6, meaning that 60% of the patients decompensated during the 20 years of observation. It is to note that while the cumulative risk necessarily cannot decrease along the follow-up (because D either increases or is constant with time), the incidence rate may increase, stay roughly constant or decrease (supplementary figure 1).

In two state settings, there is a direct one to one correspondence between rate and risk, in that the number of subjects at risk and of events taken as basis for calculations is the same for rate and risk. In a multi-state setting (competing risks), the number of subjects at risk decreases at any time one of several competing events occurs (supplementary figure 2), and the interest is in the risk that the event of interest occurs as first (5). Therefore, in a multi-state setting the unique relationship between rate and risk (cumulative risk of the composite end-point) is lost because the overall risk depends on more than one rate of events. A simple and plane example of calculation of risks in a competing risks setting compared to a 2-state setting is reported in ref 4 table 3.

For this reason the Kaplan-Meier estimator may not be applied in the presence of competing risks (where the one to one relationship between rate and risk is lost), since it assumes that there is only one event of interest and that only this will contribute to reduce the number of patients at risk. In this situation, instead, the Aalen-Johansen estimator correctly estimates the risk

that the event of interest occurs as first, among several competing events, by the Cumulative Incidence Function or CIF.

Moreover, in the presence of competing events, the association of covariates with the rate may be different from their association with the risk, making it inappropriate the use of the Cox model (8), when looking for risks predictors (6).

Research areas where competing risks analysis is appropriate

Competing risks analysis should be used whenever several events may compete with each other to occur first and thus Kaplan Meier estimator is not appropriate. In fact, when assessing which, among several events, will occur first, all the assessed events are mutually exclusive and the sum of the probabilities of occurrence of all events has to range between 0 and 1. However, as already shown, when the Kaplan Meier estimator is used the sum of the probabilities may result higher than 1, because each event is considered separately, ignoring or censoring the competing events, and estimating the risk of event in a hypothetical population where the other events do not exist and do not modify the risk of the event of interest. As an example, in a cohort of cirrhosis patients (3), the 20-year probability of occurrence of ascites as the first event was correctly estimated as 0.33 using the competing risk methodology, and the same probabilities resulted 0.14 for death, 0.10 for bleeding, 0.09 for hepatocellular carcinoma, 0.05 for encephalopathy and 0.03 for jaundice, summing up to 0.74. In a similar study (9) where the Kaplan Meier model was used, 17-year probability was 0.55 for hepatocellular carcinoma, 0.35 ascites, 0.27 jaundice, 0.10 bleeding, 0.03 encephalopathy, summing up to a total probability of 1.3, which is of course impossible. One of the study conclusions was that the first clinical event was hepatocellular carcinoma, which cannot be inferred by such an analysis. The correct inference from the Kaplan Meier analysis presented in that study would be that hepatocellular carcinoma was the most frequently observed among the assessed complications of cirrhosis.

There are several other conditions, in specific subgroups of patients, for which a competing risks analysis would be appropriate. As an example, in patients with ascites, the risks of refractory ascites, spontaneous bacterial peritonitis, sepsis, hepatorenal syndrome, and renal failure should be reliably assessed by a competing risks approach where death is a competing event. The incidence of other major events in decompensated cirrhosis, like the development of esophageal varices, variceal bleeding, acute on chronic liver failure, acute kidney injury, should also be addressed considering death as a competing event. Also, for prognosis studies and for studies of the prevention of specific risks, competing risks analysis should be performed to identify the next relevant event to be prevented. Similarly, liver transplantation should also be considered a competing event when assessing the risk of death in patients with cirrhosis, and not censored or ignored as done in most published studies. It is in fact a very relevant event in the disease course and doesn't fulfill the major requirements of censoring (6): it is not uninformative and is not independent of the outcome in survival analysis.

Multistate approach and risk stratification in cirrhosis

Clinical states imply multistate models to describe the clinical course of the disease. In multistate models the progression of the disease is expressed by the probabilities of transitioning across disease states and these probabilities are assessed by competing risks analysis. In cirrhosis, the simplest multistate model consists of three states: compensated and decompensated cirrhosis and death. Patients with CC have a median survival of nearly 10-15 years and almost all develop decompensation before dying or die at the first decompensating event (3). By contrast, the median survival of patients with decompensated cirrhosis is in the order of 2-4 years (3;10). The Child-Turcotte-Pugh (CTP) (11) classification, widely used for risk stratification of cirrhosis, largely overlaps compensated and decompensated states, with almost 80% of compensated patients being in CTP class A and 93% of decompensated patients in classes B-C (10; unpublished data from ref 1). Compensated and decompensated cirrhosis have been further stratified according to their clinical characteristics and death risk in a 5-state model (figure 4, left), although progressing

knowledge of pathophysiology of both compensated (12) and decompensated (13) cirrhosis suggests a more comprehensive model potentially more adherent to the real disease course (figure 4, right) (14;15). In fact, growing evidence is accumulating that these proposed clinical states of cirrhosis are characterized by different risks of disease progression and mortality (table 2). In compensated cirrhosis two states were recognized based on the presence or absence of esophageal varices (3;16-17). More recently, it has been shown that in CC without GEV, *subclinical* or *mild* PH with hepatic venous pressure gradient (HVPG) >5 and <10 mmHg, indicates an earlier disease state with significantly better outcome compared to clinically significant portal hypertension (CSPH, defined by HVPG ≥10 mmHg or GEV), without GEV (12;15;18). Three states with increasing risk of death have been proposed for decompensated cirrhosis defined by the occurrence of a first variceal bleeding alone (without other decompensating events), any first non bleeding decompensating event (80% ascites), or any second decompensating event (3). However, in the last few years it is more and more recognized that beyond these states a more advanced or *late decompensation* state with a very short survival should be defined (14-15). This consideration comes from the observations that refractory ascites, infections, renal failure, acute on chronic liver failure are all associated with 1-year mortality risk of between 0.50 and 0.97 (table 2;10;14;19-21). Recurrent VH, recurrent encephalopathy and profound jaundice are also frequent manifestations of this late disease state.

The appropriateness of a multistate approach to the clinical course of cirrhosis is also supported by histopathological evidence. In fact, based on the thickness of fibrous septa and nodule size, the Metavir F4 fibrosis grade has been subdivided into 3 grades: 4A, 4B and 4C. In this sub-classification, 4A grade is characterized by thin septa and large nodules, 4C by thick septa and small nodules, and 4B by intermediate septa and nodules. Importantly, it has been shown that this histological sub-classification of cirrhosis is significantly related to HVPG and clinical states (22).

State occupation probability

State occupation probability is the probability that a patient will be in, or will occupy, a certain clinical state in the future. It is assessed by the Aalen-Johansen estimator, which is an extension of the Kaplan Meier estimator for multistate models (23). Statistical software for this kind of analysis are available in the R statistical package (*msSurv* or *mstate* routines).

To illustrate the type of information provided by the *state occupation probability* analysis we inspect here the clinical course of a cohort of patients with compensated cirrhosis (3). The cohort consisted of 377 patients. Kaplan-Meier survival analysis shows a 20-year death risk of 0.62 (figure 3, a); competing risks analysis finds that the 20-year risk of death before decompensation is 0.14 while the risk of decompensation before death is 0.52 (figure 3, b). The Kaplan-Meier estimate of survival after development of decompensation shows a 20-year death risk of 0.93 with a median survival time of 18 months (figure 3, c). Based on this analysis a three state model may be built including compensated, decompensated and death states. The relevant 5-years risks of transitioning from a state to the next, is assessed by the competing risks analysis (figure 3, d). However, we might also be interested in knowing the probabilities for compensated patients at time 0 to be alive compensated, alive decompensated, dead before decompensation or dead after decompensation along time. This information is provided by the state occupation probabilities estimates shown in figure 5 for patients compensated at diagnosis and performed by the *mstate* routine in the R statistical package. It may be seen that along the whole observation time, the probability of being alive in a decompensated state is low: in fact, patients who transition in the decompensated state have a very low survival time in that state. Similarly, the probability of being dead in the compensated state is low, because most patients develop decompensation before dying. At 20 years since diagnosis, 40% of the patients are dead after decompensation, while 35% are alive in a compensated state.

Competing risks and prognosis research

Prognosis research is aimed at assessing outcome probability and relevant predictors of outcome in a given time. Predictors may be patient characteristics or disease characteristics and

may play a causal role (causal factors) or just be associated to the outcome (predictive factors). When the interest is in causal factors (like in studies of the etiology of diseases), the analysis should identify any significant association between the candidate factors and the (instantaneous) hazard or rate of the event of interest, under the hypothesis that some biological or pathophysiological mechanism links the factor to the event of interest. Therefore, it is important to assess whether the event of interest occurs more rapidly or more slowly in patients presenting the candidate causal factor compared to those without. In this situation, the parameter to be compared is the rate, not the risk, and the proportional hazards Cox model (8) may be safely used because, by ignoring the competing events it focuses on the instantaneous rate of only the event of interest (cause specific hazard). It is to note, the interpretation of a causal effect relies on the assumption that all potential confounders are measured and adjusted for in the analysis.

On the other hand, when the interest is in risk prediction, the analysis is aimed at identifying factors associated with the risk that the event of interest will actually occur. In this condition it is essential to account also for competing events, which may modify the risk of the event of interest. Therefore, the Cox model is not appropriate because, with this model the competing events contribute only by passively removing individuals from the risk set and hence does not account for the fact that a competing event can preclude the occurrence of the event of interest (as first). similarly to the Kaplan Meier model, the prediction of the risk will be upwards biased.

A multiple regression proportional hazards model has been developed for competing risks, by Fine and Gray (24). This model focuses on a different quantity, the sub-(distribution) hazard and provides the sub(distribution)-hazard ratio (sHR), that measures the association between the factor and the risk of the outcome, due to both the association between the factor and the outcome and the possibly differential impact of the competing events in patients with and without the factor. By this model it is possible to predict the probability of the outcome of interest at a given time for individual patients.

To summarize, the Cox and the Fine and Gray models can be both applied in the presence of competing events to measure the association of the factor with the outcome, but with two

different aims. The Cox model is appropriate to study the etiology of the disease or causal factors of the outcome of interest; the Fine and Gray model is more appropriate for predicting the risk in individual patients.

To illustrate these concepts we performed a multiple regression analysis to investigate the role of esophageal varices in the risk of decompensation in patients with compensated cirrhosis, accounting for death as a competing risk. We also included in the analysis platelet count and the Child-Pugh score, to adjust for these two other important prognostic indicators in cirrhosis (1).

We had a dual aim in this analysis: a) to assess whether the presence of esophageal varices may disclose some causal mechanism; b) to assess whether, regardless of any causal mechanism, patients with esophageal varices are more likely to decompensate (i.e. whether the actual risk of decompensation is higher in patients with varices). We therefore used the Cox model for the first aim and the Fine and Gray model for the second one.

The number of patients at risk and the number of observed events together with 20-year decompensation rate are reported in table 1. Hazard ratios and sub-hazard ratios, respectively by the Cox (8) and by the Fine and Gray (24) models are reported with 95% confidence intervals in table 3. The Cox model showed a cause-specific hazard ratio of 1.51(95%CI 1.14-1.99) for patients with varices compared to patients without, indicating that the presence of varices is significantly associated with decompensation; the Fine and Gray model shows that patients with esophageal varices also have a significantly increased risk of decompensation compared to patients without varices in presence of death as a competing risk.

Conclusion

Competing risks are frequent in cirrhosis. The occurrence of each competing event modifies the probability for the outcome of interest to be the next relevant event. When this is not properly accounted for and the competing event is simply ignored or censored, incorrect estimates of risks are obtained with the consequence of inaccurate prognostication. This is particularly important in

presence of high risk of death as in decompensated cirrhosis, where death may frequently prevent the occurrence of the event of interest. Competing risks analysis accounts for each of the events of interest and provides an accurate risk assessment. Properly set multistate models may provide a more complete and realistic description of the patient flow across the most clinically relevant disease states and prognosis research should be modeled on competing risks to improve the performance of prognostic instruments.

Acknowledgment

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Table 1. Competing risks analysis and Kaplan Meier estimates for 20-year risk of several clinically relevant events. Death before the event of interest is the competing risk for all the examples. 1-Kaplan Meier estimate is reported for comparison (data from reference 3)

Event of interest	patients at risk (N)	observed events (D)	Person-years (Y)	Incidence rate (D/Y)	Risk (D/N)	Competing risks Cumulative Incidence Function estimate*		1-Kaplan Meier estimate **	
						Event of interest	Death before the event of interest	Event of interest	Death before the event of interest
Decompensation	377	227	4586	0.049	0.60	0.58	0.14	0.63	0.25
Varices	243	131	2462	0.053	0.54	0.53	0.25	0.61	0.46
Ascites	400	189	5033	0.037	0.47	0.45	0.25	0.53	0.37
Bleeding after development of varices	279	96	2697	0.036	0.34	0.37	0.43	0.48	0.60
Rebleeding	105	56	350	0.16	0.53	0.49	0.33	0.59	0.77
Hepatocellular carcinoma	467	99	5798	0.017	0.21	0.18	0.53	0.30	0.59
Encephalopathy	472	124	5624	0.022	0.26	0.25	0.47	0.35	0.58
Jaundice	467	86	5681	0.015	0.18	0.17	0.53	0.23	0.62

* by Aalen-Johansen estimator

**Competing events censored

Table 2. Two-year risk of new clinical events and death according to several disease states in compensated and decompensated cirrhosis

Clinical state		Characteristics	2 yrs risks		reference
			Clinical events	Death	
Compensated cirrhosis	No GEV, Subclinical PH	5<HVPG <10 mmhg	0.04	NA	18
	No GEV with CSPH	HVPG ≥10 mmHG	0.17	NA	18
	GEV (with CSPH, by definition)	HVPG ≥10 mmHG	0.09-0.19¶	0-0.05¶	3;16-17
Decompensated cirrhosis	Bleeding alone	Survivors of first variceal bleeding	0.50¶	0.20¶	3
	Any first non bleeding decompensation	Ascites 80% PSE 10% Jaundice 10%	0.41¶	0.24¶	3
	Any second decompensation	Ascites+bleeding 64%	NA	0.50-0.78	3
Late decompensation	End state	Refractory ascites Renal failure Infections ACLF	NA	0.50-0.97 Within 1 year	10; 14 ;19; 20; 21

¶ Competing risks analysis

Table 3. Cox proportional hazards model (8) and Fine and Gray (23) analyses of prognostic indicators of decompensation in a cohort of 377 patients with compensated cirrhosis

Candidate prognostic indicators and rating	Cox		Fine and Gray	
	Coefficient	Hazard ratio (95% CI)	Coefficient	Sub-distribuition hazard ratio (95% CI)
Esophageal varices (Yes versusNo)	0.412	1.51(1.14-1.99)	0.358	1.43(1.08-1.89)
Platelet count (>150000/ml versus ≤150000/ml)	-0.898	0.41(0.29-0.55)	-0.862	0.42(0.31-0.47)
Child-Pugh score Continuous values From 5 to 15	0.313	1.37(1.20-1.56)	0.255	1.29(1.12-1.48)

Figure legends

Figure 1

Schematic representation of competing risks and multistate disease models.

Panel a: death is shown as a competing event for disease progression.

Panel b: hypothetical model for the clinical course after variceal bleeding in cirrhosis in which no patient die before rebleeding: each of the two disease segments may then be assimilated to a two state disease model.

Panel c: the real life situation in which several patients may die before rebleeding and therefore a competing risks situation is configured in a three state model.

Figure 2

Left panel: 1-Kaplan-Meier estimates of the risk of death without rebleeding (rebleeding censored) and probability of rebleeding (death censored) in 105 patients with cirrhosis who survived a first episode of bleeding. The sum of the two risks is higher than 1 (0.53+0.59=1.12).

Right panel: risk of death and risk of rebleeding assessed by the competing risks analysis (Cumulative Incidence Function, CIF). The 1-Kaplan Meier estimate of the composite endpoint (death or rebleeding) is also plotted to show as the CIF partitions the risk of any event in the risks of each event (.33+.49=.82)

In both panels, the abscissa denotes the number of months of observation and the numbers below the abscissa are the number of patients at risk per each observation period. Note that the number of patients at risk per each observation period for the two Kaplan-Meier plots in the left panel is the same because when estimating the risk of death without re-bleeding the Kaplan-Meier estimator censors re-bleeding and when estimating the risk of re-bleeding it censors deaths. Therefore per each observation period the number of patients at risk is the number at risk at the beginning of the previous observation period – (N rebleding + N death + N of censored observation) for both curves.

For the same reason, the number of patients at risk in the competitive risks analysis and in the 1-KM plot in the right side of the figure are the same as those in the plots of the left side.

Figure 3

Panel a: 20-year survival curve plotted by the Kaplan-Meier estimator for a cohort of 377 patients with compensated cirrhosis at the diagnosis. The 20-year risk of death from diagnosis is 1-survival probability or 1-0.38=0.62.

Panel b: cumulative risk of decompensation and of death before or at decompensation of the same 377 patients as in panel a, computed by the competing risks analysis. The 20-year competing risks are 0.58 for decompensation and 0.14 for death. The cumulative incidence of the composite event (death or decompensation) is also shown as 1-KM

Panel c: survival probability of 224 patients, after development of decompensation (time zero= first appearance of decompensation). The 20-year probability of being alive after decompensation is 0.07 and the corresponding death risk is 0.93.

Panel d: schematic representation of the 5-year probability of transition across the three disease states of compensated and decompensated cirrhosis and death

In panels a, b, c the abscissa denotes the observation time in months and the numbers below the abscissa are the number of patients at risk per each observation period.

Figure 4

Representation of proposed multistate models for the clinical course of cirrhosis. Left side: multistate model proposed by a prospective cohort study. Right side more comprehensive model including earlier and later disease states.

Figure 5

State occupation probability for 377 patients with compensated cirrhosis along the follow-up. The disease states considered are compensated, decompensated and death (model reported in Figure 2 panel d). The probability of being dead after decompensation or before decompensation are exploited to allow a more complete prognostic assessment. The abscissa denotes the observation time in months.
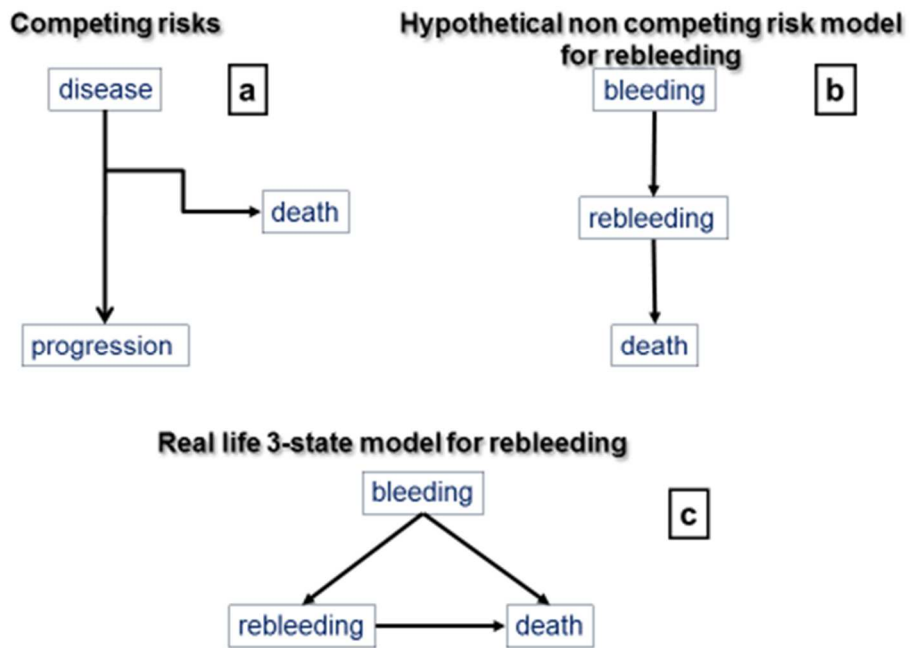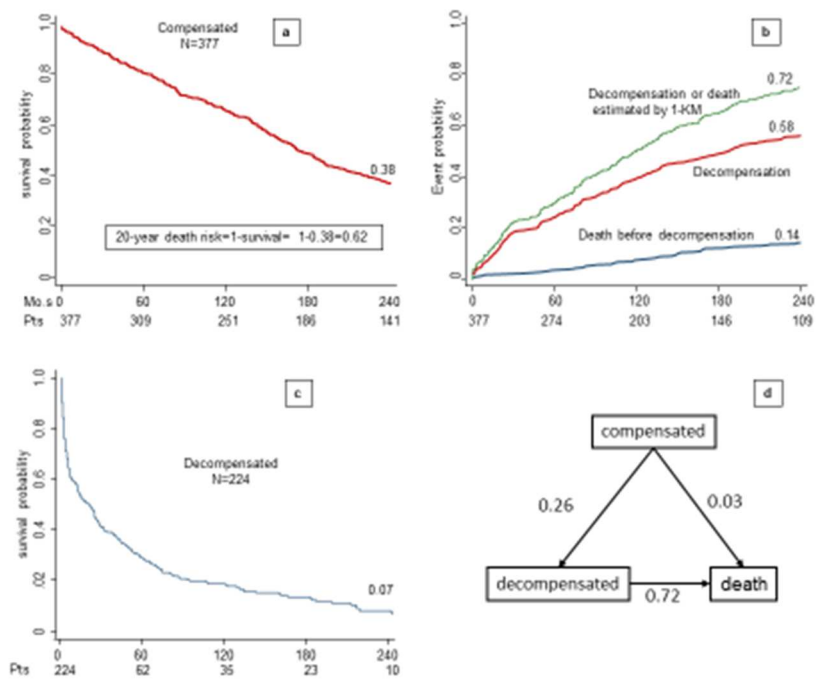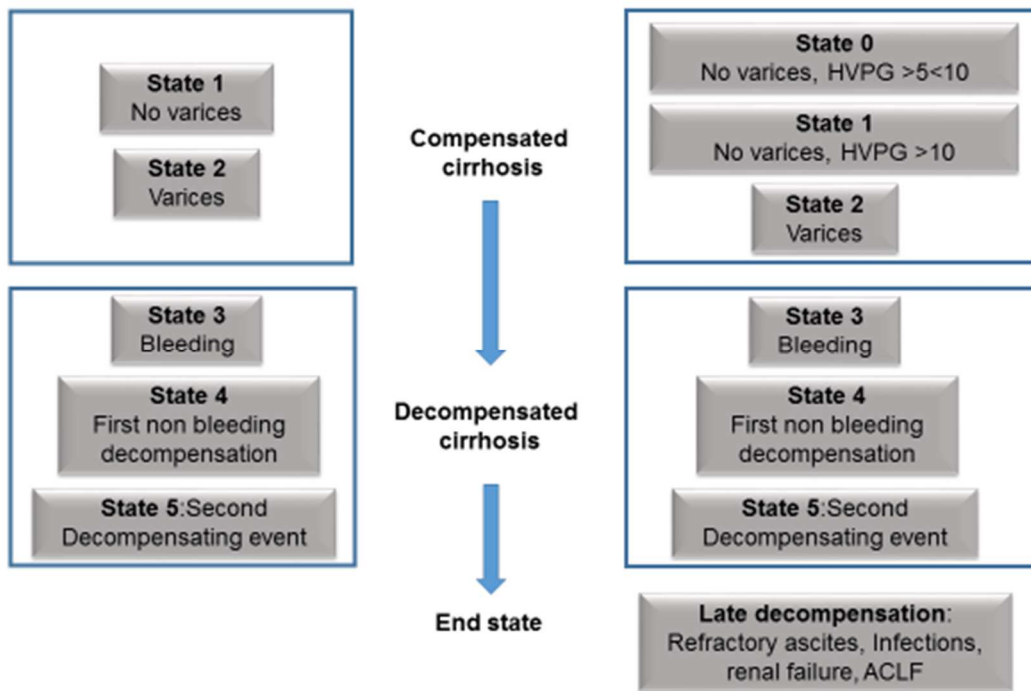
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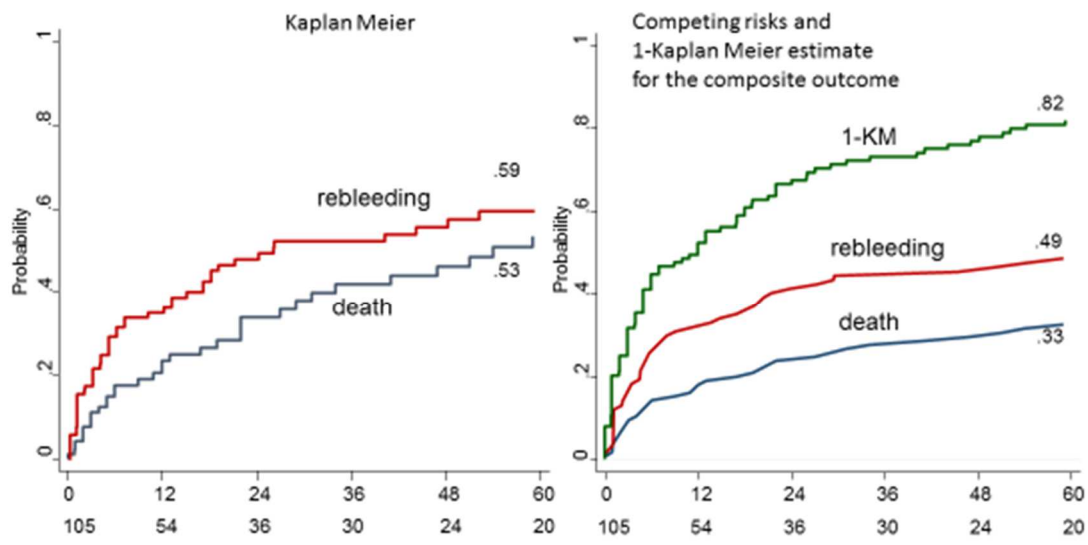
Figure 2

Figure 3

Figure 4

Figure 5