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Original Contribution

Prognosis of cirrhotic patients admitted to Emergency Departments: A multicenter study

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ABSTRACT

Objectives: Life threatening complications can occur at any stage of cirrhosis progression. There are few studies on the prognosis of cirrhotic patients managed in an Emergency Department (ED) although management of patients will occur in the ED. The objective of our study was to determine the risk factors for mortality in cirrhotic patients who visited to the ED.

Methods: All cirrhotic patients attending ED in three different university hospitals of Assistance Publique - Hôpitaux de Paris between January 2014 and June 2015 were identified by a retrospective analysis of digital records and included in the study. The primary end-point was 30-day mortality in all cirrhotic patients who visited the ED.

Results: A total of 609 ED visits were analyzed among 224 patients: 115 (51%) presented a cirrhosis of alcoholic origin, 43 (19%) were caused by Hepatitis C, 28 (13%) of mixed origin (viral and alcoholic), 17 (8%) were caused by Hepatitis B and 21 (9%) of other origins. Fifty-five (25%) of these patients died within 30 days of their initial presentation to the ED. In multivariate analysis, the age (Odds Ratio: 1.04 [1.01–1.07]), cirrhosis associated with hepatocellular carcinoma (OR: 3.07 [1.37–6.91]), serum creatinine at admission (OR: 1.01 [1.01–1.02]), serum bilirubin at admission (OR: 1.01 [1.01–1.02]) and health impairment (OR: 2.57 [1.28–5.16]) were associated with mortality.

Conclusions: The mortality rate of cirrhotic patients attending an ED was high. The prognosis of cirrhotic patients admitted to the ED depended on the severity of the liver and other organ dysfunction. The presence of a hepatocellular carcinoma on admission was also a risk factor for death.

1. Introduction

The prevalence for cirrhosis in France is estimated to be between 2000 and 3300 cases per million inhabitants. Alcoholic cirrhosis occurs in between 1500 and 2500 cases per million inhabitants. [1] Alcohol Related Liver Disease, hepatitis C, and nonalcoholic fatty liver disease are the three most common causes of cirrhosis in France. The other causes of cirrhosis are rare. [1]

Complications, occurring during the course of cirrhosis, can be life threatening. They may be related to cirrhosis in patients with decompensated cirrhosis: ascites, gastrointestinal bleeding, hepatorenal syndrome and hepatic encephalopathy. They include also other acute diseases unrelated to cirrhosis, especially sepsis. [2-5] These complications need rapid management and the Emergency Department (ED) often offers the first opportunity to make a rapid accurate diagnosis and start an appropriate treatment. In a retrospective study, fifty-nine (43%) of 138 cirrhotic patients admitted to the intensive care unit (ICU) were initially admitted to the ED. [6] Eighty-three (33%) of 253 patients who admitted to the ED for a gastrointestinal bleeding had a cirrhosis, according to another recent prospective study. [7]

The prognosis of cirrhotic patients admitted to the ICU is perfectible. The mortality rate of cirrhotic patients in the ICU was respectively 31%, 35% and 43% with an in-hospital mortality rate of 54%, 43% and 53% in three recent studies. [6,8,9] The liver disease-specific scores (Child-Pugh, Model for End- Stage Liver Disease score (MELD score)) and the

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organ failure-specific scores used in ICU (Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score (SAPS II) were tested as predictive tools of mortality for cirrhotic patients admitted to ICU. In these studies, the SOFA score had the highest discriminant factor for predicting the mortality of cirrhotic patients admitted to ICU. [6,8,9] The necessity of mechanical ventilation, the use of catecholamines, the presence of an infection as well as hepatic failure at admission, had a significant prognostic value in the most recent prospective study. [8] In a study by Das, [6] the mortality among patients needing catecholamines and mechanical ventilation was of 80% and 67% respectively.

In a recent meta-analysis, the prognostic performance of general ICU scores was found to decrease over time, unlike the Child-Pugh and MELD-scores, which were found to be useful even when used in the context of organ failure. [10] Infection-related parameters had a short-term impact, whereas liver and renal failure had a sustained impact on mortality. [10] Even though cirrhotic patients are frequent attenders to the ED, very few studies on the prognosis of cirrhotic patients admitted through the ED exists. [11] Hence, the objective of our study is to determine the independent predictive factors associated with 30 day-mortality in cirrhotic patients attending the ED.

2. Patients and methods

2.1. Design and setting

This retrospective observational study included all patients with liver cirrhosis who visited the EDs of three Parisian Academic Public Hospitals (Jean Verdier in Bondy, Louis Mourier in Colombes and Saint -Antoine in Paris 11e) between January 2014 and June 2015. All three hospitals are teaching hospitals with ED, hepatology unit and ICU. The study included only adult patients with a confirmed diagnosis of cirrhosis (histologically and/or clinically).

Our study complied with Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies. The protocol was approved by the local ethics committee (Comité de Protection des Personnes d'Ile de France 10). According to French legislation, no written informed consent was required because of the observational nature of the study.

2.2. Participant inclusion and exclusion criteria

The study inclusion criteria were: diagnosis of cirrhosis in an adult (over 18 years old) patient who presented to the ED. The diagnosis of cirrhosis was made either histologically and/or clinically (portal hypertension with ascites, esophageal varices or encephalopathy) and was already known prior to admission. The diagnosis of cirrhosis was confirmed by an expert hepatologist. The only exclusion criterion was a diagnosis of hepatic transplantation and the lack of a confirmed diagnosis of cirrhosis. The patients were identified by retrospective analysis of the ED electronic medical records database.

2.3. Data collection

A medical records abstractor trained in the diagnosis of cirrhosis was in charge of the patients 'enrollment. The data abstractor has been trained on 10 records prior to the study period. He collected the data, not knowing about the aim of the study. We reviewed all cirrhotic patient records. For each emergency visit, the emergency physician collected the following data on standardized forms: (1) demographical: age, sex, cause of cirrhosis, association with hepatocellular carcinoma; (2) clinical: presenting complaint and diagnosis in the ED, including gastrointestinal bleeding, encephalopathy, ascites, hepatorenal syndrome, sepsis, alcohol intoxication, pain, acute fatigue, convulsion and trauma; (3) biological (serum sodium, serum creatinine and serum bilirubin) and (4) severity: SOFA score at admission to determine the severity of the pathology leading to the ED, as well as the Child-Pugh score at admission to determine the severity of the liver disease. Collection and data were blind to the tested hypothesis. The data abstractor and the principal investigator met monthly to resolve disagreement. The principal investigator (NJ) double checked the database.

2.4. Definitions

Organ failure-specific scores (Sequential Organ Failure Assessment [SOFA] and the number of organ failures) were calculated at admission to ED. The SOFA score is a mortality prediction score based on the degree of dysfunction of six organ systems (respiratory, cardiovascular, hepatic, renal, coagulation and neurological) graded from 0 to 4, with 0 meaning normal organ function while an organ failure was defined with a SOFA score of 3 or 4 for the concerned organ (need for vasopressor, mechanical ventilation with PaO2/FiO2 ratio of <200, Glasgow Coma Scale score of <9, serum bilirubin of >100 μmol/L, serum creatinine of >300 μmol/L or oliguria lasting for 24 h or the need for renal replacement therapy, or platelet count of <50,000/mm3). [12]

Liver disease severity was assessed at ED admission with a liver disease-specific score (Child-Pugh). The Child-Pugh score was calculated from five parameters (degree of encephalopathy, degree of ascites, serum bilirubin, albumin, and prothrombin time). Each score is graduated from 1 to 3 according to the level of dysfunction. Stage A is defined by 5 to 6 points, stage B by 7 to 9 points and stage C by 10 to 15 points. [13]

Isolated encephalopathy was defined as flapping tremor, confusion, or an unexplained coma with exclusion of other causes and no aggravating factor (gastrointestinal bleeding, infection, drug or metabolic disorder). Infection on admission was diagnosed by the emergency physician using standard criteria (clinical symptoms, imaging techniques, biological and microbiological examinations). In microbiologically undocumented cases, infection could be clinically documented (spontaneous bacterial peritonitis: polymorphonuclear cells count >250 per cubic millimeter in ascites with negative culture; pneumonia using standard criteria). Acute fatigue was defined as a diagnosis of exclusion when no encephalopathy, nor aggravating factor that could explain asthenia reported by patient was found.

2.5. Statistical analysis

Quantitative variables are presented as medians with interquartile ranges (IQR) and qualitative data as numbers with percentages. Associations between mortality at 30 days and risk factors were identified using a mixed logistic regression model with random effects because each patient could have experienced more than one visit to the ED. The model was conducted using an independent correlation structure. We built GEE models to study the quasi-likelihood under the independence model criterion (QIC) for selecting a working correlation structure. All factors with a p-value <0.10 in univariate analysis were included in multivariate model. Prognostic scores were not included in this multivariate model as this study aimed to establish individual risk factors. A forward stepwise variable selection was performed using a stopping rule based on a p-value cut-off of 0.05. All tests were 2-sided. A p-value <0.05 was considered significant. We used R statistical software version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Six hundred and nine visits to the ED by 224 patients (Fig. 1) were screened and analyzed. Most patients (71%) were males and had a median age of 60 (52–69) years (Table 1). The liver disease identified was most frequently alcohol-related (in over 50% of cases). Cirrhosis was

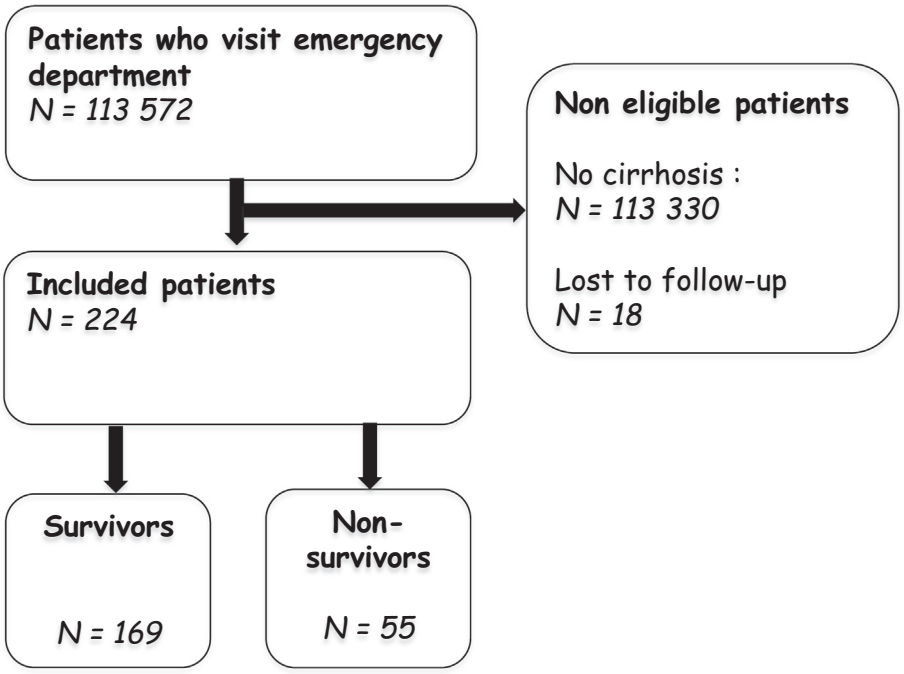

Fig. 1. Flow chart of patients.

Hepatitis C related in almost 1/5 of patients. The cirrhosis was of mixed etiology (viral and alcoholic), Hepatitis B related or linked to a nonalcoholic fatty liver disease in the remaining patients. Cirrhosis was associated with hepatocellular carcinoma in almost one quarter of the cases. Fifteen (7%) patients were co-infected by HIV and 49 (22%) had active alcohol consumption.

3.2. Visits to the emergency department

Values for clinical and biological characteristics defining severity and principal diagnoses at ED admission are shown in Table 2. The most common primary diagnoses for ED visit were: ascites (in almost 1/4 of the cases), hepatic encephalopathy (15%), severe infection (13%), gastrointestinal bleeding (11%) and acute alcohol intoxication (11%). Other more generalized systemic symptoms (asthenia, anorexia, weight loss) were found in 54 (9%) cases. At ED admission, patients presented with a median SOFA score of 3 (2–5) and a median Child-Pugh score of 7 (6–8).

Table 1
Patient characteristics.

Characteristics	Patients n = 224
Male patients, no. (%)	159 (71)
Age (yr), median (IQR)	60 (52–69)
Cirrhosis cause, no. (%)	
Alcohol	115 (51)
Hepatitis C	43 (19)
Alcohol + viral	28 (13)
Hepatitis B	17 (8)
Nonalcoholic fatty liver disease	21 (9)
Coexisting conditions, no. (%)	
Hepatocellular carcinoma	54 (24)
Active alcohol consumption	49 (22)
HIV	15 (7)

IQR denotes interquartile range, ICU intensive care unit and ED emergency department.

3.3. Factors associated with mortality

The cumulative incidence of mortality was 24% (55 out 224 patients were non-survivors within 30 days of their last presentation to the ED). The majority of deaths (41; 18%) occurred in an hepatology unit. The other deaths occurred in ICU (12; 5%) and in the ED (2; 1%).

The results of the univariate analysis performed on all 609 visits to the ED by 224 cirrhotic patients are presented in Table 3, in order to determine predictive factors of hospital mortality after 30 days of follow-up. There was no significant differences in gender, cause of cirrhosis and primary diagnosis at admission between the survivor and non-survivor groups.

The biological parameters, prognostic scores, age, presence of hepatocellular carcinoma, acute fatigue and active alcohol consumption

Table 2
Characteristics of visits to the emergency department.

Visits to the emergency department	n = 609
Prognostic scores, median (IQR)	
Child-Pugh	7 (6–8)
SOFA	3 (2–5)
MELD	14.6 (10.9–19.4)
Biological parameters, median (IQR)	
Serum sodium (mmol/L)	134 (133–138)
Serum creatinine (μmol/L)	89 (64–98)
Serum bilirubin (μmol/L)	43 (32–54)
Final diagnosis, no. (%)	
Linked to cirrhosis	
Ascites	139 (23)
Hepatic encephalopathy	91 (15)
Gastrointestinal bleeding	70 (11)
Spontaneous bacterial peritonitis	19 (3)
Hepato-renal syndrome	1 (−)
Not linked to cirrhosis	
Sepsis	78 (13)
Alcohol intoxication	68 (11)
Pain	62 (10)
Acute fatigue	54 (9)
Convulsion	10 (2)
Trauma	17 (3)

IQR denotes interquartile range, SOFA Sequential Organ Failure Assessment.

Table 3
Predictive factors of mortality determined by univariate analysis in 609 ED visits of 224 cirrhosis patients.

Variables	Odds ratio (OR) (95% CI)	p
Age	1.05 (1.03–1.16)	<0.0001
Male	0.61 (0.25–1.5)	0.28
Cause of cirrhosis		
Alcohol	1.0	–
Hepatitis C	1.08 (0.39–1.24)	0.89
Alcohol + viral	0.55 (0.15–0.17)	0.36
Hepatitis B	3.52 (0.87–41.38)	0.08
Nonalcoholic fatty liver disease	1.44 (0.39–2.96)	0.58
Active alcohol consumption		
Hepatocellular carcinoma	0.2 (0.07–0.57)	0.003
Prognostic scores	4.7 (2.0–97.39)	0.0004
Child-Pugh	1.66 (1.3–4.49)	<0.0001
SOFA	1.54 (1.29–1.83)	<0.0001
MELD	1.20 (1.14–1.26)	<0.0001
Biological parameters		
Serum sodium	0.97 (0.94–0.99)	0.040
Serum creatinine	1.05 (1.04–1.14)	<0.0001
Serum bilirubin	1.05 (1.02–1.15)	<0.0001
Final diagnosis		
Linked to cirrhosis		
Ascites	1.04 (0.46–1.12)	0.93
Hepatic encephalopathy	1 (0.38–1.01)	1.00
Gastrointestinal bleeding	0.41 (0.1–1.6)	0.20
Spontaneous bacterial peritonitis	4.09 (0.8–64.82)	0.090
Hepatorenal syndrome	–	–
Not linked to cirrhosis		
Sepsis	0.64 (0.21–2.0)	0.44
Alcohol intoxication	0.65 (0.15–2.84)	0.57
Pain	0.15 (0.02–0.90)	0.080
Acute fatigue	4.23 (1.67–71.3)	0.002
Convulsion	–	–
Trauma	1.22 (0.09–1.79)	0.88

SOFA denotes Sequential Organ Failure Assessment, OR Odds Ratio and CI confidence interval.

differed significantly between the two groups. Patients admitted with younger age or active alcohol consumption had better prognosis for survival, whereas patients admitted for acute fatigue or with a cirrhosis associated with hepatocellular carcinoma had a poorer prognosis. Non-survivors patients displayed older age, more biological abnormalities (lower serum sodium, higher serum creatinine and bilirubin) and significantly higher values on prognostic scores (SOFA, MELD and Child-Pugh) at admission values compared to survivors patients.

A multivariate logistic regression analysis with mortality as the end-point was performed using categorical and/or continuous variables. Prognostic scores at admission were excluded from this analysis to prevent any risk of collinearity. Table 4 shows that age, serum creatinine or serum bilirubin at admission, cirrhosis associated with hepatocellular carcinoma at admission and diagnosis of acute fatigue were independently related to mortality. Active alcohol consumption was independently associated with better a prognosis for 30-day survival.

Table 4
Factors independently associated with mortality (within 30 days of their last visit) in 609 visits of 224 patients admitted to the ED – multiregression model.

	OR [95% CI]	p
Age	1.04 [1.01–1.07]	0.005
Active alcohol consumption	0.3 [0.1–0.94]	0.03
Hepatocellular carcinoma	3.07 [1.37–6.91]	0.008
Serum creatinine	1.01 [1.01–1.02]	<0.0001
Serum bilirubin	1.01 [1.01–1.02]	<0.0001
Acute fatigue	2.57 [1.28–5.16]	0.007

OR denotes Odds Ratio and CI confidence interval.

3.4. Comparison of discrimination ability of different scores to predict mortality

Receiving Operating Characteristic curves were used to evaluate the power of the scores (Fig. 2). SOFA and Child-Pugh scores at admission were found to be reliable systems relative to survival, with Area Under the Receiver Operating Characteristic Curve (AUROC) values of 0.89 [0.84–0.93] and 0.88 [0.85–0.91], respectively. The AUROC of the linear predictor derived from the multivariate logistic regression was 0.85 [0.80–0.91], which was not significantly lower than the AUROC of the SOFA and Child-Pugh scores.

4. Discussion

This first multi-centric cohort study has evaluated the mortality risk factors in 224 cirrhotic patients admitted to general ED and reports three main results: (1) the overall prognosis was poor; (2) the most important independent risk factors for mortality at day 30 were older age, cirrhosis associated with hepatocellular carcinoma at admission, primary diagnosis of acute fatigue, as well as higher serum creatinine and bilirubin, and lower serum sodium. Active alcohol consumption was associated with a better prognosis with a significantly higher rate of survival at day 30; (3) the Organ failure-specific score (SOFA), the liver disease-specific score (Child-Pugh) and our score (derived from multivariate logistic regression) had a similar capacity to predict mortality.

In our study, the overall 30-day mortality of cirrhotic patients after a visit to the ED was around 25% and was close to the Ximenes study [11]. Indeed, in this single-center retrospective study of 277 ED admissions from 149 patients with decompensated cirrhosis (mainly due to alcoholic cirrhosis [53%]), 36 (24%) died during hospital stay. In this study, variables independently associated with mortality were creatinine >132 μmol/L and INR >1.65 [11]. Other recent studies have evaluated the mortality among cirrhotic patients admitted to ICU. [6,8-10] Despite a lower mortality rates in the more recent ICU-studies, 28-day mortality rates were generally higher than the rate we found for the ED, with ranges from 43% to 54% in three studies. [6,8,9] A recent meta-analysis, on the prognosis of cirrhotic patients admitted to ICU, confirms that in-ICU survival was significantly better in patients admitted after 2004. [10] The discrepancies are the consequence of varying severity

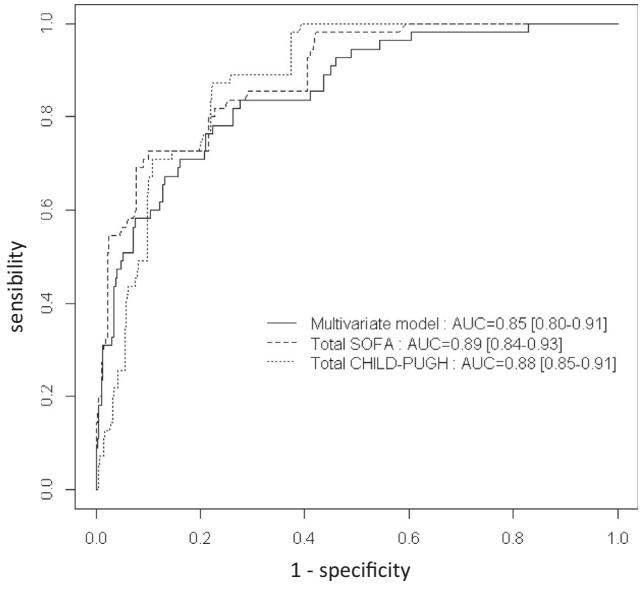

Fig. 2. Receiver Operating Characteristic (ROC) curves for scores predicting mortality in 609 admissions among 224 patients to the ED. SOFA (Sequential Organ Failure Assessment).

of patients at admission. Higher SOFA scores were found to be a good predictive factor of ICU-mortality, as reflected in our study, with the caveat that SOFA score is an ICU, rather than an ED, score. In 110 (18%) admissions to the ED in our series, patients had at least one organ failure, compared to 270 (71%) patients in ICU-studies. [6,8-10] Moreover, liver disease severity, assessed by the Child-Pugh score, was greater in ICU-studies than in our study. [6,8-10]

In our study, cirrhosis associated with hepatocellular carcinoma was an independent predictive factor for 30-day mortality. This risk factor is not highlighted in ICU-studies. The main hypothesis that may explain this observation is a stricter selection of patients by intensivists for ICU admission. Indeed, only 6 patients had hepatocellular carcinoma in one recent ICU-study [9] and cirrhosis was associated with hepatocellular carcinoma in only 11.7% of cases in one recent meta-analysis (less than half that what we found in our study). [10] Hepatocellular carcinoma, which develops within an established background of chronic liver disease (70–90% of all patients), is the leading cause of death among patients with cirrhosis. [14] The 5-year survival rate has remained below 12% which partly explains our high mortality rate. [15]

Acute fatigue is an independent risk factor of death in the patients of our study. This diagnosis was not discussed in the ICU-series, where complications of cirrhosis (gastrointestinal bleeding, hepatic encephalopathy and hepatorenal syndrome), as well as of sepsis, were the main reasons for ICU admission. [6,8-10] Acute fatigue remains a frequent cause of hospitalization and is associated with a mortality rate of 16% and 42% at 3 and 6 months in two retrospective studies. [16,17] Advanced age, high serum creatinine and bilirubin are independent predictive factors of 30-day mortality in our series, in agreement with the referenced ICU studies. [6,8-10]

Finally, active alcohol consumption was positively associated with 30-day survival in our study. Cirrhotic patients in our study had particularities; most patients had alcoholic cirrhosis and some of them were still drinking. The low number of admissions for organ failure and the moderate liver disease severity explains probably the fact that active alcohol consumption was associated with survival in contrast to ICU-studies and other studies. [18,19]

5. Limits

Our study had several limitations. This was a retrospective and observational study. Even though data collection was standardized with objective primary outcome, certain factors, such as received treatment, were not documented. One particular possible source of bias of selection that could have occurred in our study is the use of the electronic medical record database to identify patients. Nevertheless, the high number of included patients and admissions to the ED makes the result of the study powerful.

6. Conclusion

In conclusion, the mortality of cirrhotic patients attending general ED was high. Our multi-centric study shows that the prognosis of cirrhotic patients admitted to the ED, depends on the severity of the hepatic dysfunction and the association of an extra-hepatic organ failure. The primary diagnosis on presentation to the ED and the associated presence of hepatocellular carcinoma are risk factors associated with 30-days mortality and may be interesting indicators for when start palliative care. Knowledge of these risk factors and their early treatment in the ED are both important both for the appropriate management of cirrhotic patients and for their early referral to ICU with the aim of improving prognosis.

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Authors' COI

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