ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2017 July 28; 23(28): 5041-5256

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 23 Number 28 July 28, 2017

EDITORIAL

5041 Colorectal cancer in young adults: A difficult challenge
Campos FG

5045 Precision medicine: In need of guidance and surveillance
Lin JZ, Long JY, Wang AQ, Zheng Y, Zhao HT

REVIEW

5051 Barrett's oesophagus: Current controversies
Amadi C, Gatenby P

5068 Gastrointestinal neuroendocrine peptides/amines in inflammatory bowel disease
El-Salhy M, Solomon T, Hausken T, Gilja OH, Hatlebakk JG

5086 Colorectal cancer screening: An updated review of the available options
Issa IA, Noureddine M

5097 Therapeutic potential of flavonoids in inflammatory bowel disease: A comprehensive review
Salaritabar A, Darvishi B, Hadjiakhoondi F, Manayi A, Sureda A, Nabavi SF, Fitzpatrick LR, Nabavi SM, Bishayee A

ORIGINAL ARTICLE

Basic Study

5115 Myo-inositol reduces β-catenin activation in colitis
Bradford EM, Thompson CA, Goretsky T, Yang GY, Rodriguez LM, Li L, Barrett TA

5127 Involvement of CRF2 signaling in enterocyte differentiation
Ducarouge B, Pelissier-Rota M, Powell R, Buisson A, Bonaz B, Jacquier-Sarlin M

5146 Bone marrow-derived monocyte infusion improves hepatic fibrosis by decreasing osteopontin, TGF-β1, IL-13 and oxidative stress
de Souza VCA, Pereira TA, Teixeira VW, Carvalho H, de Castro MCAB, D'assunção CG, de Barros AF, Carvalho CL, de Lorena VMB, Costa VMA, Teixeira AAC, Figueiredo RCBQ, de Oliveira SA

5158 Single amino acid mutation of SR-BI decreases infectivity of hepatitis C virus derived from cell culture in a cell culture model
Gao R, Gao W, Xu G, Xu J, Ren H

5167 Fibroblast-derived CXCL12/SDF-1α promotes CXCL6 secretion and co-operatively enhances metastatic potential through the PI3K/Akt/mTOR pathway in colon cancer
Ma JC, Sun XW, Su H, Chen Q, Guo TK, Li Y, Chen XC, Guo J, Gong ZQ, Zhao XD, Qi JB

Case Control Study

5179 Association between *CYP24A1* polymorphisms and the risk of colonic polyps and colon cancer in a Chinese population
Chen XQ, Mao JY, Li WB, Li J, Yang H, Qian JM, Li JN

Retrospective Cohort Study

5187 Clinical significance of glycemic parameters on venous thromboembolism risk prediction in gastrointestinal cancer
Guadagni F, Riondino S, Formica V, Del Monte G, Morelli AM, Lucchetti J, Spila A, D'Alessandro R, Della-Morte D, Ferroni P, Roselli M

5196 Sex-dependent difference in the effect of metformin on colorectal cancer-specific mortality of diabetic colorectal cancer patients
Park JW, Lee JH, Park YH, Park SJ, Cheon JH, Kim WH, Kim TI

Retrospective Study

5206 Sex-influenced association of non-alcoholic fatty liver disease with colorectal adenomatous and hyperplastic polyps
Chen QF, Zhou XD, Sun YJ, Fang DH, Zhao Q, Huang JH, Jin Y, Wu JS

Observational Study

5216 Development and validation of a simple and multifaceted instrument, GERD-TEST, for the clinical evaluation of gastroesophageal reflux and dyspeptic symptoms
Nakada K, Matsuhashi N, Iwakiri K, Oshio A, Joh T, Higuchi K, Haruma K

5229 Modified B-ultrasound method for measurement of antral section only to assess gastric function and guide enteral nutrition in critically ill patients
Liu Y, Gao YK, Yao L, Li L

Prospective Study

5237 Chronic liver failure-consortium acute-on-chronic liver failure and acute decompensation scores predict mortality in Brazilian cirrhotic patients
Picon RV, Bertol FS, Tovo CV, de Mattos ÂZ

CASE REPORT

5246 Refractory hepatic encephalopathy in a patient with hypothyroidism: Another element in ammonia metabolism
Díaz-Fontenla F, Castillo-Pradillo M, Díaz-Gómez A, Ibáñez-Samaniego L, Gancedo P, Guzmán-de-Villoria JA, Fernández-García P, Bañares-Cañizares R, García-Martínez R

5253 Endoscopic occlusion with silicone spigots for the closure of refractory esophago-bronchiole fistula after esophagectomy

Uesato M, Kono T, Akutsu Y, Murakami K, Kagaya A, Muto Y, Nakano A, Aikawa M, Tamachi T, Amagai H, Arasawa T, Muto Y, Matsubara H

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Edoardo G Giannini, FACG, MD, PhD, Assistant Professor, Department of Internal Medicine, University of Genoa, 16132 Genova, Italy

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports® cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

FLYLEAF **I-IX** Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Fen-Fen Zhang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*
Responsible Science Editor: *Yuan Qi*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

Stephen C Strom, PhD, Professor, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach, CA 90822, United States

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/1007-9327/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director
Yuan Qi, Vice Director
Ze-Mao Gong, Vice Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
July 28, 2017

COPYRIGHT
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: http://www.f6publishing.com

World J Gastroenterol 2017 July 28; 23(28): 5237-5245

DOI: 10.3748/wjg.v23.i28.5237

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Prospective Study

Chronic liver failure-consortium acute-on-chronic liver failure and acute decompensation scores predict mortality in Brazilian cirrhotic patients

Rafael Veiga Picon, Franciele Sabadin Bertol, Cristiane Valle Tovo, Ângelo Zambam de Mattos

Rafael Veiga Picon, Franciele Sabadin Bertol, Cristiane Valle Tovo, Gastroenterology and Hepatology Unit, Nossa Senhora da Conceição Hospital, Porto Alegre, Rio Grande do Sul 91350-200, Brazil

Cristiane Valle Tovo, Ângelo Zambam de Mattos, Gastroenterology and Hepatology Unit, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Rio Grande do Sul 90050-170, Brazil

Ângelo Zambam de Mattos, Gastroenterology and Hepatology Unit, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul 90619-900, Brazil

Author contributions: Picon RV and Bertol FS contributed for acquisition of data; Picon RV, Bertol FS, Tovo CV and de Mattos ÂZ contributed to analysis and interpretation of data; Picon RV and de Mattos ÂZ drafted the manuscript; Tovo CV and de Mattos ÂZ contributed for the study concept and design; critical revision of the manuscript for important intellectual content; all authors approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Nossa Senhora da Conceição Hospital Institutional Review Board.

Conflict-of-interest statement: None.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Ângelo Zambam de Mattos, MD, MSc, PhD, Professor of Medicine, Gastroenterology and Hepatology Unit, Federal University of Health Sciences of Porto Alegre, 154, Professor Annes Dias St., office 1103, Porto Alegre, Rio Grande do Sul 90050-170, Brazil. angmattos@hotmail.com
Telephone: +55-51-32269131
Fax: +55-51-32269131

Received: March 15, 2017
Peer-review started: March 18, 2017
First decision: May 12, 2017
Revised: May 30, 2017
Accepted: July 12, 2017
Article in press: July 12, 2017
Published online: July 28, 2017

Abstract

AIM

To validate prognostic scores for acute decompensation of cirrhosis and acute-on-chronic liver failure in Brazilian patients.

METHODS

This is a prospective cohort study designed to assess the prognostic performance of the chronic liver failure-consortium (CLIF-C) acute decompensation score (CLIF-C AD) and CLIF-C acute-on-chronic liver failure score (CLIF-C ACLF), regarding 28-d and 90-d mortality, as well as to compare them to other prognostic models, such as Model for End-Stage Liver Disease (MELD), MELD Sodium (MELD-Na), Child-Pugh (CP) score, and the CLIF-C Organ Failure score (CLIF-C OF). All participants were adults with acute decompensation of cirrhosis admitted to the Emergency Department of a tertiary hospital in southern Brazil. Prognostic performances were evaluated by means of the receiver operating characteristic (ROC) curves, area

under the curves (AUC) and 95%CI.

RESULTS

One hundred and thirteen cirrhotic patients were included. At admission, 18 patients had acute-on-chronic liver failure (ACLF) and 95 individuals had acute decompensation (AD) without ACLF, of which 24 eventually developed ACLF during the course of hospitalization (AD evolving to ACLF group). The AD group had significantly lower 28-d (9.0%) and 90-d (18.3%) mortality as compared to the AD evolving to ACLF group and to the ACLF group (both $P < 0.001$). On the other hand, 28-d and 90-d mortalities were not significantly different between AD evolving to ACLF group and ACLF group ($P = 0.542$ and $P = 0.708$, respectively). Among patients with ACLF, at 28 d from the diagnosis, CLIF-C ACLF was the only score able to predict mortality significantly better than the reference line, with an AUC (95%CI) of 0.71 (95%CI: 0.54-0.88, $P = 0.021$). Among patients with AD, all prognostic scores performed significantly better than the reference line regarding 28-d mortality, presenting with similar AUCs: CLIF-C AD score 0.75 (95%CI: 0.63-0.88), CP score 0.72 (95%CI: 0.59-0.85), MELD score 0.75 (95%CI: 0.61-0.90), MELD-Na score 0.76 (95%CI: 0.61-0.90), and CLIF-C OF score 0.74 (95%CI: 0.60-0.88). The same occurred concerning AUCs for 90-d mortality: CLIF-C AD score 0.70 (95%CI: 0.57-0.82), CP score 0.73 (95%CI: 0.62-0.84), MELD score 0.71 (95%CI: 0.59-0.83), MELD-Na score 0.73 (95%CI: 0.62-0.84), and CLIF-C OF score 0.65 (95%CI: 0.52-0.78).

CONCLUSION

This study demonstrated that CLIF-C ACLF is the best available score for the prediction of 28-d mortality among patients with ACLF. CLIF-C AD score is also useful for the prediction of mortality among cirrhotic patients with AD not fulfilling diagnostic criteria for ACLF, but it was not superior to other well-established prognostic scores.

Key words: Cirrhosis; Acute-on-chronic liver failure; Mortality; Prediction; Prognosis; Acute decompensation of cirrhosis

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The present study demonstrated that chronic liver failure-consortium (CLIF-C) acute-on-chronic liver failure score (ACLF) is the best available score for the prediction of 28-d mortality among patients with ACLF, but it was unable to determine the same regarding 90-d mortality. On the other hand, while this study also demonstrated that CLIF-C acute decompensation (AD) was useful for the prediction of 28-d and 90-d mortalities among patients with AD not fulfilling diagnostic criteria for ACLF, it failed to identify superiority when compared to other scores already routinely used worldwide.

Picon RV, Bertol FS, Tovo CV, de Mattos ÂZ. Chronic liver failure-consortium acute-on-chronic liver failure and acute decompensation scores predict mortality in Brazilian cirrhotic patients. *World J Gastroenterol* 2017; 23(28): 5237-5245 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i28/5237.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i28.5237

INTRODUCTION

Cirrhosis is a relevant disease worldwide, both because of its high prevalence and because of its high mortality. In addition, this disease is responsible for substantial use of health care resources[1]. In Brazil, for instance, liver diseases are the eighth leading cause of death, and cirrhosis is the major cause of hospital admissions and lethality among them. Moreover, the burden of cirrhosis in terms of hospital admissions and mortality rate is still increasing, despite considerable medical advances[2]. Most of cirrhosis-related admissions and deaths are related to its acute decompensations.

Recently, a redefinition of acute-on-chronic liver failure (ACLF), an especially severe form of cirrhosis decompensation based on the occurrence of organic dysfunctions, was proposed by the European Association for the Study of the Liver - Chronic liver failure (CLIF) consortium. ACLF represents a syndrome occurring in patients with chronic liver disease, which is characterized by acute deterioration of liver function and one or more extrahepatic organ failures, leading to increased short-term mortality[3]. In the United States, from 2001 to 2011, the proportion of patients discharged from hospitals with a diagnosis of cirrhosis increased from 0.4% to 4.0%, while the proportion of those discharged with a diagnosis of ACLF increased from 0.3% to 6.0%[1]. Similarly, a recent French study demonstrated that, between 2008 and 2013, the annual proportion of cirrhotic patients with ACLF undergoing orthotopic liver transplantation (OLT) increased from 32% to 51%[4].

Considering the need to better predict the prognosis of patients with acute decompensations of cirrhosis, the CLIF Consortium proposed the use of two scores: one for patients with ACLF and the other for patients with acute decompensation (AD), but not ACLF[5,6]. Considering the lack of evidence about the performance of these scores outside Europe and taking into account possible differences regarding the epidemiological aspects of liver diseases and the characteristics of health care systems, this study aimed at validating their use in a Brazilian population.

MATERIALS AND METHODS

Study design and setting

This was a prospective cohort study conducted with a convenience consecutive sample of patients admitted

to a tertiary hospital of Porto Alegre, southern Brazil. All participants were adults admitted to the Emergency Department of Nossa Senhora da Conceição Hospital with either acute decompensation of cirrhosis - AD group - or acute-on-chronic liver failure - ACLF group[3]. The AD group was further subdivided in two: (1) patients with AD that did not develop ACLF during hospital stay - hereafter AD group; and (2) patients admitted with AD that did develop ACLF at some point during the same hospitalization - henceforth AD evolving to ACLF group.

Outcome

The evaluated outcome was transplant-free survival according to the diagnosis of AD or ACLF.

Predictors

In order to evaluate the capacity of Chronic Liver Failure-Consortium Acute Decompensation (CLIF-C AD)[6] and Chronic Liver Failure-Consortium Acute-on-Chronic Liver Failure (CLIF-C ACLF) scores[5] in predicting death in 28 d and 90 d after the diagnosis, their sensitivity, specificity and positive and negative predictive values were calculated, and receiver operating characteristic (ROC) curves were developed. Several well-established severity scores employed for cirrhosis assessment were used as comparators: Model for End-Stage Liver Disease (MELD), MELD Sodium (MELD-Na), Child-Pugh (CP) score, and the Chronic Liver Failure-Consortium Organ Failure (CLIF-C OF) score[5-9].

Participants

Between January and September 2016, patients over 18 years-old admitted to the Emergency Department were screened by the International Classification of Diseases - 10th revision (ICD-10) codes and deemed eligible if codes K70 to K77 were stated at their hospital admission forms. Participants were cirrhotic patients undergoing a non-elective Emergency Department admission for acute decompensation - *i.e.,* ascites, encephalopathy, gastrointestinal hemorrhage, or bacterial infection according to criteria stated by Moreau *et al*[3]. Cirrhosis was diagnosed based on histology or on clinical grounds, laboratory tests, imaging and endoscopic findings. Exclusion criteria were (1) elective hospitalization; and (2) non-elective Emergency Department admission for reasons different from acute decompensation of cirrhosis. For patients undergoing more than one hospitalization during the studied period, only data regarding the first admission was considered for analysis. Participants were followed until the end of December 2016.

Data collection

Data were drawn from the electronic medical records of the patients. Data collection did not affect management of participants during hospital stay. Data extraction was carried-out on a pilot-tested Microsoft Excel™ spreadsheet by two authors (FSB and RVP).

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional Ethical Committee. Informed consent was waived by the Ethical Committee.

Statistical analysis

Qualitative data were described as proportions, and Pearson's χ^2 or Fisher's exact test was used for inferential analysis. Quantitative data were described as means ± SD, and analysis of variance (ANOVA) was used for comparison across three groups. Alpha was set at 0.05 and all comparisons were two-tailed.

OLT was regarded as a competing end-point, thus Kaplan-Meier survival analysis was undertaken assessing time to event as days from AD or ACLF diagnosis to death or OLT. Individuals who did not die nor were submitted to OLT were censored at the end of follow-up. Mantel-Cox log rank statistic was employed for inferential analysis across groups. Median survival times and their respective 95%CI according to group were obtained.

ROC curves, their corresponding areas under the curve (AUC) and respective AUC 95%CI were used to assess the performance of the CLIF-C AD score, CLIF-C ACLF score, CLIF-C OF score, MELD, MELD-Na, and CP score at 28 and 90 d from diagnosis. Patients lost to follow-up or with incomplete data were excluded from such analyses.

A univariate analysis was performed using all the scores and selected baseline clinical characteristics not embedded in the prediction scores as covariates and death at any point during the study as the dependent variable. Data analysis was performed using the Statistical Package for Social Sciences™ version 18.0.

RESULTS

One hundred seventeen patients were considered eligible for the study, and 113 individuals fulfilled all the inclusion criteria. At admission, 18 (15.9%) patients had ACLF and 95 (84.1%) individuals had AD without ACLF, of which 24 eventually develop ACLF during the course of hospitalization (AD evolving to ACLF group). Figure 1 shows the flowchart of patients through the study.

Tables 1 and 2 describe, respectively, baseline clinical characteristics and laboratory findings of patients according to group. Of note, none of the patients from the AD group was admitted for spontaneous bacterial peritonitis (SBP), while 3 (12.5%) patients from the AD evolving to ACLF group and 2 (11.1%) of those from the ACLF group were admitted for SBP (P = 0.035). Over 70.0% of patients who were diagnosed with ACLF had ACLF grade 1. Kidney failure was the single most frequent organic failure, being present in 66.7% of patients with ACLF at admission and in 75.0% of

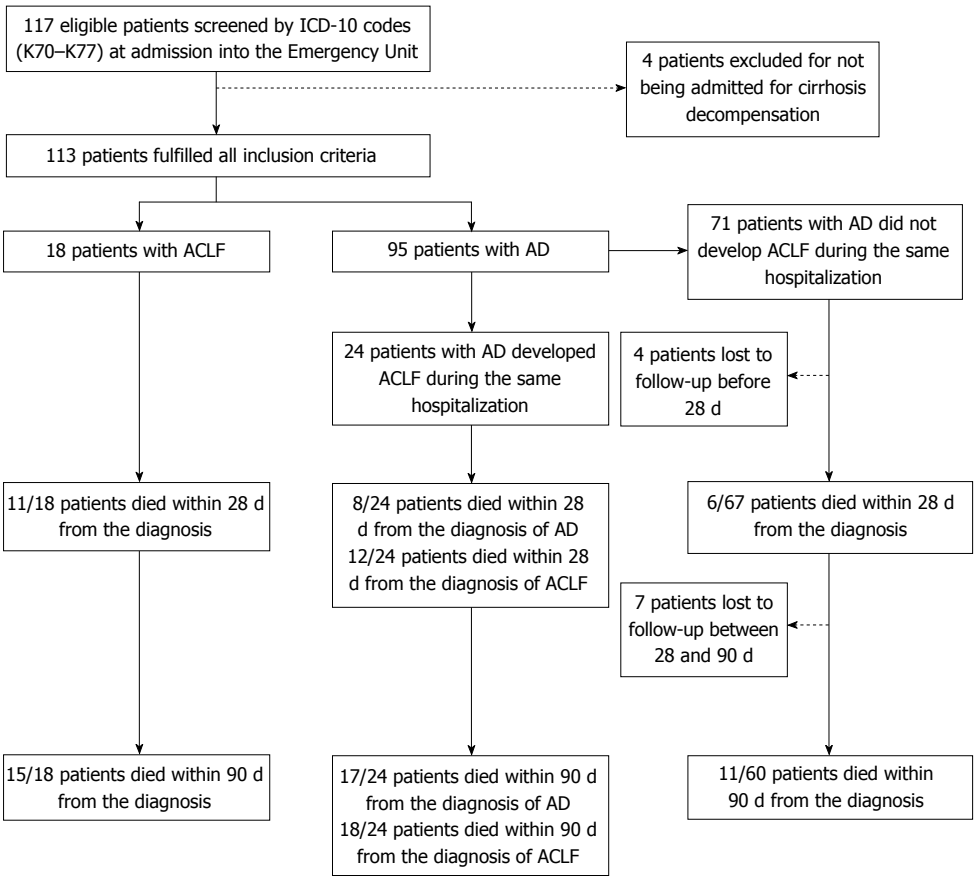

Figure 1 Flowchart of patients through the study. No patient was submitted to orthotopic liver transplantation. ICD-10: International Classification of Diseases, 10th revision; ACLF: Acute-on-chronic liver failure; AD: Acute decompensation of cirrhosis.

those with AD evolving to ACLF. Moreover, mean serum C-reactive protein was approximately three times higher in the ACLF group compared to the AD group (77.5 mg/dL *vs* 25.5 mg/dL, $P = 0.003$).

Median survival times for ACLF group (11.0 d) and AD evolving to ACLF group (32.0 d) did not differ significantly ($P = 0.247$). Merging the ACLF and the AD evolving to ACLF groups into a single cohort yielded a median survival time of 27.0 d (95%CI: 7.97-46.03; data not shown), which differed significantly from the median survival of 239 d of the AD group ($P < 0.001$). The AD group had significantly lower 28-d (9.0%) and 90-d (18.3%) mortality as compared to the AD evolving to ACLF group and to the ACLF group (both $P < 0.001$). The latter groups had comparable 28-d and 90-d mortalities ($P = 0.542$ and $P = 0.708$, respectively). At 28 d from the diagnosis of ACLF (either at admission or during hospitalization), 54.8% (23/42) of patients had died, whereas, at 90 d, 78.6% (33/42) of them had died. One patient from the ACLF group and seven others from the AD group died after 90 d of follow-up. Kaplan-Meier analysis revealed that patients with ACLF grades 1, 2, and 3 had significantly different survivals (Mantel-Cox $P = 0.031$), with median survival times of 29.0 d (95%CI: 4.3-53.7), 15.0 d (95%CI: 0.0-52.2), and 3.7 d (95%CI: 0.0-14.2) respectively (data not shown). No patient was submitted to OLT. Figure 2 depicts the Kaplan-Meier survival analysis, and Table 3 shows median survival times and mortalities according to group.

Figure 3 illustrates the ROC curves for mortality of several prognostic scores at 28 and 90 d from the diagnosis of either AD or ACLF. Since 24 patients developed ACLF during hospitalization, they contributed with data to both the CLIF-C AD and the CLIF-C ACLF ROC curves. One patient from the AD group did not have sufficient data to calculate CLIF-C AD score and was excluded from ROC curve analyses. Four patients from the AD group had follow-ups shorter than 28 d, hence they were also excluded from the 28-d and 90-d ROC curves. Furthermore, another seven individuals from the AD group were lost to follow-up between 28 and 90 d and were excluded from the 90-d ROC curve. Among patients with ACLF, at 28 d from the diagnosis, CLIF-C ACLF was the only score able to predict mortality significantly better than the reference line, with an AUC of 0.71 (95%CI: 0.54-0.88, $P = 0.021$). Considering a pretest probability of death at 28 d of 54.8% (23/42 patients with the diagnosis of ACLF at some point of the study), a CLIF-C ACLF score cut-off of 40 points yielded 100% sensitivity (Se), 37% specificity (Sp), 100% negative predictive value (NPV), and 65.8% positive predictive value (PPV), whereas a cut-off of 60 points yielded 4% Se, 100% Sp, 46.2%

Table 1 Baseline clinical characteristics and acute-on-chronic liver failure grade according to group

	AD (n = 71)		AD evolving to ACLF (n = 24)		ACLF (n = 18)		ANOVA/ pearson χ^2
	No. mean	% SD	No. mean	% SD	No. mean	% SD	*P* value
Sex							0.259
Male	48	67.6%	13	54.2%	14	77.8%	
Age (yr)	57.8	10.2	62.6	8.0	61.3	12.9	0.097
Primary etiology of cirrhosis							0.592
Alcohol	23	32.4%	11	45.8%	9	50.0%	
HBV	4	5.6%	0	0.0%	0	0.0%	
HCV	34	47.9%	9	37.5%	6	33.3%	
NASH	4	5.6%	1	4.2%	2	11.1%	
Other	6	8.5%	3	12.5%	1	5.6%	
Main cause of current hospital admission							0.035
SBP	0	0.0%	3	12.5%	2	11.1%	
Ascites - not SBP	20	28.2%	7	29.2%	1	5.6%	
Encephalopathy	15	21.1%	6	25.0%	5	27.8%	
Alcoholic hepatitis	2	2.8%	2	8.3%	1	5.6%	
Digestive bleeding	21	29.6%	2	8.3%	4	22.2%	
Sepsis	0	0.0%	0	0.0%	1	5.6%	
Other	13	18.3%	4	16.7%	4	22.2%	
No. of previous hospitalizations	2.4	4.7	2.5	3.4	2.2	3	0.972
Alcohol consumption in the past three months							0.683
Yes	10	14.1%	6	25.0%	3	16.7%	
West Haven HE grade at admission							0.005
No HE	54	76.1%	15	62.5%	7	38.9%	
Grades Ⅰ and Ⅱ	13	18.3%	9	37.5%	7	38.9%	
Grades Ⅲ and Ⅳ	4	5.6%	0	0.0%	4	22.2%	
Vasopressor at admission							0.070
Yes	0	0.0%	0	0.0%	1	5.6%	
Mechanical ventilation at admission							< 0.001
Yes	0	0.0%	0	0.0%	3	16.7%	
Mean arterial pressure (mmHg), n = 111	95.5	18.3	95.7	18.0	79.9	22.7	0.008
PaO_2/FiO_2 (mmHg), n = 17	476.0	173.5	380.0	No SD (n = 1)	352.4	152.5	0.341
SpO_2/FiO_2, n = 113	461.4	21.9	457.3	16.6	399.7	130.7	< 0.001
Child-Pugh score, n = 110	8.0	2.0	9.9	1.9	10.3	1.8	< 0.001
MELD score, n = 111	13.0	3.6	21.7	6.5	23.4	7.2	< 0.001
MELD-Na score, n = 111	14.0	4.6	23.8	5.8	23.9	8.9	< 0.001
CLIF-C OF score, n = 111	6.5	0.8	6.9	1.0	9.1	1.7	< 0.001
ACLF grade[1]							
ACLF grade 1	NA	NA	17	70.8%	13	72.2%	1.000
ACLF grade 2	NA	NA	2	8.3%	4	22.2%	0.375[2]
ACLF grade 3	NA	NA	5	20.8%	1	5.6%	0.214[2]

[1]For AD evolving to ACLF group, ACLF grade refers to classification at the time of ACLF diagnosis, not at the time of hospital admission; [2]Fisher's exact test. AD: Acute decompensation of cirrhosis; ACLF: Acute-on-chronic liver failure; ANOVA: Analysis of variance; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; SBP: Spontaneous bacterial peritonitis; HE: Hepatic encephalopathy; PaO_2: Arterial oxygen pressure; FiO_2: Inhaled oxygen fraction; SpO_2: Partial oxygen saturation; MELD: Model for End-Stage Liver Disease; MELD-Na: MELD sodium; CLIF-C OF: Chronic Liver Failure Consortium Organ Failure; NA: Not applicable.

NPV, and 100% PPV. The optimum cut-off value for the present study was 43.9 points, which returned 82.6% Se and 57.9% Sp. None of the several prognostic scores was superior to the reference line regarding 90-d mortality.

Regarding 28-d mortality among patients with AD, all the prognostic scores performed significantly better than the reference line and had similar AUCs when compared to each other: CLIF-C AD score 0.75 (95%CI: 0.63-0.88), CP score 0.72 (95%CI: 0.59-0.85), MELD score 0.75 (95%CI: 0.61-0.90), MELD-Na score 0.76 (95%CI: 0.61-0.90), and CLIF-C OF score 0.74 (95%CI: 0.60-0.88). At 90 d from the diagnosis, all prognostic scores also performed significantly better than the reference line, with comparable AUCs: CLIF-C AD score 0.70 (95%CI: 0.57-0.82), CP score 0.73 (95%CI: 0.62-0.84), MELD score 0.71 (95%CI: 0.59-0.83), MELD-Na score 0.73 (95%CI: 0.62-0.84), and CLIF-C OF score 0.65 (95%CI: 0.52-0.78). Considering a pretest probability of death at 90 d of 33.3% (28/84 patients; 95 patients with AD at admission minus 11 individuals lost to follow-up), a CLIF-C AD score cut-off of 45 points yielded 93% Se, 20% Sp, 85.1% NPV, and 36.7% PPV, while a cut-off of 60 points yielded 25% Se, 90.9% Sp, 70.8% NPV, and 57.8% PPV. The optimum cut-off value for this study was 53.4 points, which returned 65.5% Se and 72.2% Sp.

Univariate analysis for death at any given time

Table 2 Baseline laboratory findings according to group

	AD (n = 71)		AD evolving to ACLF (n = 24)		ACLF (n = 18)		ANOVA
	Mean	SD	Mean	SD	Mean	SD	*P* value
Total bilirubin (mg/dL), n = 112	2.1	2.2	5.1	5.3	5.7	7.2	< 0.001
Serum creatinine (mg/dL), n = 113	1.0	0.3	1.2	0.4	2.1	0.8	< 0.001
INR, n = 112	1.4	0.3	1.5	0.5	1.8	0.4	< 0.001
White-cell count (109 cells/L), n = 113	6.9	3.7	8.8	3.6	12.6	6.1	< 0.001
Serum sodium (mmol/L), n = 113	138.4	3.9	136.1	4.3	137.6	5.6	0.070
Serum albumin (g/dL), n = 112	3.0	0.6	2.7	0.5	2.7	0.5	0.006
Serum C-reactive protein (mg/L), n = 47	25.5	33.0	41.9	32.0	77.5	61.7	0.003

AD: Acute decompensation of cirrhosis; ACLF: Acute-on-chronic liver failure; ANOVA: Analysis of variance; INR: International normalized ratio.

Table 3 Survival time and mortality according to group

Group (group symbol)	Survival time[1]			Mortality[1]		
	Median (d)		Mantel-Cox	28-d mortality	90-d mortality	Death at any point during the study
	Estimate	(95%CI)	*P* value	n (%)	n (%)	n (%)
AD (A), n = 71	239	(166.4-311.6)	Reference group	6/67 (9.0)[2]	11/60 (18.3)[2]	18/60 (30.1)[2]
AD evolving to ACLF (B), n = 24	32	(0.0-64.4)	B *vs* A < 0.001; B *vs* C = 0.247	12/24 (50.0)[2,3]	18/24 (75.0)[2,3]	18/24 (75.0)[2,3]
ACLF (C), n = 18	11	(2.7-19.3)	C *vs* A < 0.001; B + C *vs* A < 0.001	11/18 (61.1)[2,3]	15/18 (83.3)[2,3]	16/18 (88.9)[2,3]
Overall, n = 113	165	(117.7-212.3)	Not applicable	29/109 (26.6)	44/102 (43.1)	52/102 (51.0)

[1]Survival time and mortality for group B regards to time elapsed from the diagnosis of ACLF; [2]Pearson's χ^2 *P* values < 0.001 for comparisons across all groups; [3]Fisher's exact test *P* values for comparisons between groups B and C were 0.542, 0.708, and 0.431 for 28-d mortality, 90-d mortality, and death at any point during the study, respectively. AD: Acute decompensation of cirrhosis; ACLF: Acute-on-chronic liver failure.

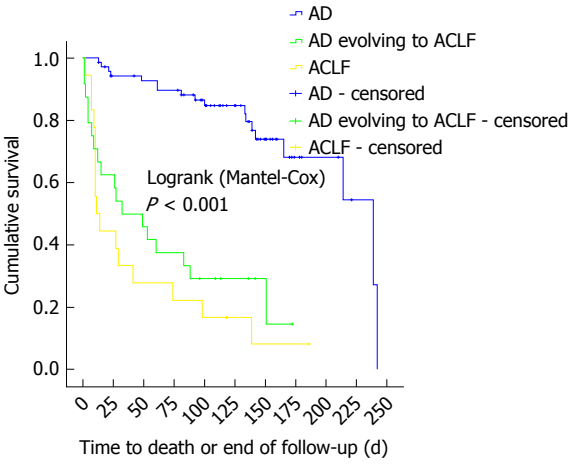

Figure 2 Kaplan-Meier survival analysis. AD: Acute decompensation; ACLF: Acute-on-chronic liver failure.

during the study was performed. The covariates evaluated were sex, alcohol ingestion three months prior to admission, alcohol-induced cirrhosis, digestive bleeding, SBP, history of any previous hospitalization, CLIF-C OF score, CLIF-C AD score, CLIF-C ACLF score, CP score, MELD, and MELD-Na. According to the univariate analysis, the only variable associated to death was CLIF-C ACLF score (P = 0.009). Considering that the univariate analysis identified only one variable associated to this outcome, a multivariate analysis was not performed.

DISCUSSION

Considering the high prevalence, mortality and impact on the healthcare systems associated to cirrhosis decompensations, it is of great importance to develop tools which could better predict outcomes of cirrhotic patients[1]. The present study demonstrated that CLIF-C ACLF is the best available score for the prediction of 28-d mortality among patients with ACLF, as previously suggested[5], but it was unable to demonstrate the same regarding 90-d mortality, probably because most of the deaths in this group of patients occurred early in their follow-up. On the other hand, while this study also demonstrated that CLIF-C AD was useful for the prediction of 28-d and 90-d mortalities among patients with AD not fulfilling diagnostic criteria for ACLF, it failed to identify superiority when compared to other scores, some of them already routinely used worldwide. This finding differs from that of the study that originally proposed CLIF-C AD score, in which it performed better than other scores, at least for the prediction of 90-d mortality[6]. This could be explained by our sample of patients with AD not being large enough in order to detect a difference between the performance of CLIF-C AD score and that of other prognostic scores. Nevertheless, it is important to remind that our sample was sufficiently large to demonstrate that CLIF-C AD score had an AUC significantly greater than that of the

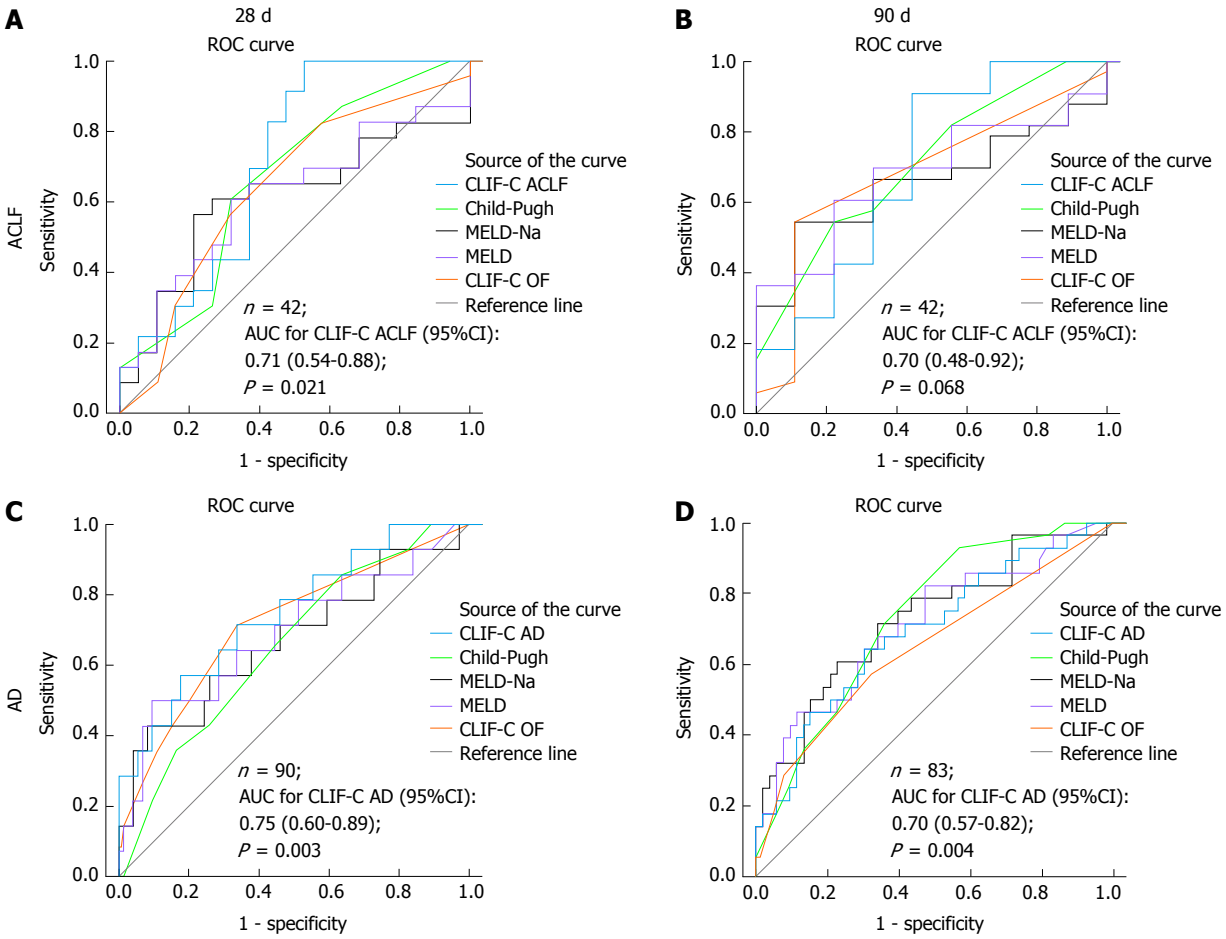

Figure 3 Receiver operating characteristic curves of prognostic scores regarding 28-d and 90-d mortality. A: Receiver operating characteristic (ROC) curves of several scores regarding 28-d mortality in patients diagnosed with acute-on-chronic liver failure (ACLF). B: ROC curves of several scores regarding 90-d mortality in patients diagnosed with ACLF. C: ROC curves of several scores regarding 28-d mortality in patients diagnosed with acute decompensation of cirrhosis (AD). D: ROC curves of several scores regarding 90-d mortality in patients diagnosed with AD. CLIF-C ACLF: Chronic liver failure-consortium acute-on-chronic liver failure score; CLIF-C AD: Chronic liver failure-consortium acute decompensation score; MELD: Model for End-Stage Liver Disease; MELD-Na: MELD sodium; CLIF-C OF: Chronic liver failure-consortium organ failure score; AUC: Area under the curve.

reference line.

In the present study, ACLF was diagnosed in 37% of patients with decompensated cirrhosis, which is similar to what was previously reported[10]. The group of patients that fulfilled the diagnostic criteria for ACLF had a median survival time of 27 d, which differed significantly from the median survival of 239 d of the AD group ($P < 0.001$), corroborating the idea that ACLF is a distinct syndrome with an elevated short-term mortality[3]. Moreover, as also previously described[3], the prognosis of patients diagnosed with ACLF at hospital admission was not significantly different from that of patients who developed ACLF during hospitalization. Therefore, patients should be managed similarly irrespective of the moment of the diagnosis of ACLF.

The poor prognosis of ACLF was also demonstrated in a North American population of infected cirrhotic patients. In that study, 30-d survival was 51.3% for patients with ACLF and 91.4% for those without ACLF[11], which is similar to what we found (28-d survival of 38.9% for patients with ACLF and 91% for those without ACLF). Nevertheless, it is important to highlight that the definition of ACLF used in that study is not the same as that suggested by the CLIF Consortium and used in the present study.

Using the CLIF Consortium definition of ACLF, Soares e Silva *et al*[12] also showed that ACLF was a strong predictor of short-term mortality in a Brazilian population. Similar findings were described as well in a recent Argentina study[13]. However, to the best of our knowledge, the present study is the first to validate CLIF-C AD and CLIF-C ACLF scores outside Europe.

Other interesting finding of our study is that patients with ACLF more frequently had alcohol-related cirrhosis and less frequently had hepatitis C virus. These results are similar to those reported in the CANONIC study[3] and also corroborate what Jeong *et al*[14] have shown in their paper.

ACLF differs from traditional decompensated cirrhosis, not only because of the presence of organ failure(s) and higher mortality rate, but also because it happens more frequently in younger patients and in those with an alcoholic etiology of cirrhosis, as

well as because it is associated to higher prevalences of some precipitating events (bacterial infections, active alcoholism, among others), and to a higher level of systemic inflammation[10]. As expected, in our study, we found that serum C-reactive protein and leukocyte count were significantly higher in the ACLF group compared to the AD group. This corroborates the systemic inflammation hypothesis[15], which suggests that ACLF is caused by an aggravation of systemic inflammation and by the associated systemic circulatory dysfunction already present in decompensated cirrhosis. According to this hypothesis, these processes would lead to organ failures as a consequence of hypoperfusion and the direct deleterious effects of inflammatory mediators on microcirculation and on cell physiology homeostasis[15]. The systemic inflammation hypothesis was based on the CANONIC study, in which it was observed a close relationship between blood leukocytes and C-reactive protein levels and the presence and severity of ACLF[3]. In this context, the association between the course of systemic inflammation and the course of ACLF was also recently demonstrated[16]. The relevance of the inflammatory state to the prognosis of cirrhotic patients is such that prognostic models incorporating C-reactive protein are also being studied[17,18].

Among the strengths of the present study, one must highlight its prospective character and the large sample of patients enrolled in a single centre. On the other hand, this study also presents limitations. One of the limitations, contradictorily, regards the fact that this was a single-center study, and its results might not reflect the reality elsewhere. For instance, despite being one of the largest hospitals in southern Brazil, our institution does not have a liver transplantation program, which does not preclude patients from being referred to others hospitals, but might explain why none of the studied patients was submitted to OLT. Nevertheless, we understand that the characteristics of our institution are similar to those of the majority of tertiary hospitals in Brazil and probably in Latin America and, therefore, we believe in the external validity of our findings.

Another limitation is the fact that we did not perform a sequential assessment of ACLF status and of the scores of the patients during hospitalization, which has recently been demonstrated useful[19,20]. This assessment was not planned prior to data collection, and we did not have sufficient data to perform it.

Yet another limitation of this study concerns missing data for some of the evaluated parameters, which is explained by the fact that authors did not interfere with the management of the patients. However, it should be noticed that the main analyses of this study were not affected by missing data.

In conclusion, in order to improve the quality of care of cirrhotic patients, it is of the utmost importance to be able to accurately predict the prognosis of decompensated cirrhosis. This study has shown that CLIF-C ACLF is the most accurate score to predict mortality of patients with ACLF in a Brazilian setting. Moreover, it has demonstrated that CLIF-C AD score is also useful for the prediction of mortality among cirrhotic patients with AD not fulfilling diagnostic criteria for ACLF, but it was not superior to other well-established prognostic scores.

COMMENTS

Background

Most of cirrhosis-related admissions and deaths are related to acute decompensations.

Research frontiers

Acute-on-chronic liver failure (ACLF) has a significantly higher mortality compared to other forms of acute decompensation (AD) of cirrhosis. Two recently developed scores - CLIF-C ACLF and CLIF-C AD - were proposed as tools for assessing prognosis of ACLF and AD. They were validated in European patients.

Innovations and breakthroughs

To the best of our knowledge, this is the first study to validate CLIF-C AD and CLIF-C ACLF scores outside Europe.

Applications

In order to aid clinical decision-making and to improve the quality of care of cirrhotic patients, it is of the utmost importance to accurately predict the prognosis of AD and ACLF. This study has shown that CLIF-C ACLF is the most accurate score to predict mortality of patients with ACLF in a Brazilian setting. Moreover, it has also shown that CLIF-C AD score is also useful to predict mortality among cirrhotic patients with AD not fulfilling diagnostic criteria for ACLF, but it was not superior to other well-established prognostic scores.

Terminology

ACLF: acute-on-chronic liver failure - *i.e.*, acute decompensation of cirrhosis with at leats two organ failures, or one organ failure plus renal dysfunction, or one organ failure plus mild encephalopathy, or isolated renal failure; AD: acute decompensation of cirrhosis - *i.e.*, digestive bleeding, large-volume ascites, hepatic encephalopathy, or bacterial infection.

Peer-review

The manuscript is novel one describing one of the most important issues in the diagnosis and mangement of decompensated and liver failure cases but some comments are to be considered: As the definition of ACLF it is a specific syndrome characterized by AD, organ failure and high short-term mortality.

REFERENCES

1 **Allen AM**, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. *Hepatology* 2016; **64**: 2165-2172 [PMID: 27696493 DOI: 10.1002/hep.28812]

2 **Nader LA**, de Mattos AA, Bastos GA. Burden of liver disease in Brazil. *Liver Int* 2014; **34**: 844-849 [PMID: 24422599 DOI: 10.1111/liv.12470]

3 **Moreau R**, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; **144**: 1426-1437, 1437.e1-1437.e9 [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]

4 **Levesque E**, Winter A, Noorah Z, Daurès JP, Landais P, Feray C,

Azoulay D. Impact of acute-on-chronic liver failure on 90-day mortality following a first liver transplantation. *Liver Int* 2017; **37**: 684-693 [PMID: 28052486 DOI: 10.1111/liv.13355]

5 **Jalan R**, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, Levesque E, Durand F, Angeli P, Caraceni P, Hopf C, Alessandria C, Rodriguez E, Solis-Muñoz P, Laleman W, Trebicka J, Zeuzem S, Gustot T, Mookerjee R, Elkrief L, Soriano G, Cordoba J, Morando F, Gerbes A, Agarwal B, Samuel D, Bernardi M, Arroyo V; CANONIC study investigators of the EASL-CLIF Consortium. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014; **61**: 1038-1047 [PMID: 24950482 DOI: 10.1016/j.jhep.2014.06.012]

6 **Jalan R**, Pavesi M, Saliba F, Amorós A, Fernandez J, Holland-Fischer P, Sawhney R, Mookerjee R, Caraceni P, Moreau R, Ginès P, Durand F, Angeli P, Alessandria C, Laleman W, Trebicka J, Samuel D, Zeuzem S, Gustot T, Gerbes AL, Wendon J, Bernardi M, Arroyo V; CANONIC Study Investigators; EASL-CLIF Consortium. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *J Hepatol* 2015; **62**: 831-840 [PMID: 25463539 DOI: 10.1016/j.jhep.2014.11.012]

7 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

8 **Kim WR**, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; **359**: 1018-1026 [PMID: 18768945 DOI: 10.1056/NEJMoa0801209]

9 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913]

10 **Moreau R**, Arroyo V. Acute-on-chronic liver failure: a new clinical entity. *Clin Gastroenterol Hepatol* 2015; **13**: 836-841 [PMID: 24583872 DOI: 10.1016/j.cgh.2014.02.027]

11 **Bajaj JS**, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, Fallon MB, Garcia-Tsao G, Maliakkal B, Malik R, Subramanian RM, Thacker LR, Kamath PS; North American Consortium For The Study Of End-Stage Liver Disease (NACSELD). Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014; **60**: 250-256 [PMID: 24677131 DOI: 10.1002/hep.27077]

12 **Silva PE**, Fayad L, Lazzarotto C, Ronsoni MF, Bazzo ML, Colombo BS, Dantas-Correa EB, Narciso-Schiavon JL, Schiavon LL. Single-centre validation of the EASL-CLIF consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis. *Liver Int* 2015; **35**: 1516-1523 [PMID: 24840673 DOI: 10.1111/liv.12597]

13 **Dominguez C**, Romero E, Graciano J, Fernandez JL, Viola L. Prevalence and risk factors of acute-on-chronic liver failure in a single center from Argentina. *World J Hepatol* 2016; **8**: 1529-1534 [PMID: 28008344 DOI: 10.4254/wjh.v8.i34.1529]

14 **Jeong JH**, Park IS, Kim DH, Kim SC, Kang C, Lee SH, Kim TY, Lee SB. CLIF-SOFA score and SIRS are independent prognostic factors in patients with hepatic encephalopathy due to alcoholic liver cirrhosis. *Medicine* (Baltimore) 2016; **95**: e3935 [PMID: 27367990 DOI: 10.1097/MD.0000000000003935]

15 **Bernardi M**, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015; **63**: 1272-1284 [PMID: 26192220 DOI: 10.1016/j.jhep.2015.07.004]

16 **Clària J**, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amorós À, Titos E, Alcaraz-Quiles J, Oettl K, Morales-Ruiz M, Angeli P, Domenicali M, Alessandria C, Gerbes A, Wendon J, Nevens F, Trebicka J, Laleman W, Saliba F, Welzel TM, Albillos A, Gustot T, Benten D, Durand F, Ginès P, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology* 2016; **64**: 1249-1264 [PMID: 27483394 DOI: 10.1002/hep.28740]

17 **Di Martino V**, Coutris C, Cervoni JP, Dritsas S, Weil D, Richou C, Vanlemmens C, Thevenot T. Prognostic value of C-reactive protein levels in patients with cirrhosis. *Liver Transpl* 2015; **21**: 753-760 [PMID: 25677965 DOI: 10.1002/lt.24088]

18 **Ruf AE**, Villamil FG. C-reactive protein and model for end-stage liver disease score: Have we found the fifth element? *Liver Transpl* 2015; **21**: 713-715 [PMID: 25846032 DOI: 10.1002/lt.24140]

19 **Gustot T**, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrief L, Hopf C, Solís-Munoz P, Saliba F, Zeuzem S, Albillos A, Benten D, Montero-Alvarez JL, Chivas MT, Concepción M, Córdoba J, McCormick A, Stauber R, Vogel W, de Gottardi A, Welzel TM, Domenicali M, Risso A, Wendon J, Deulofeu C, Angeli P, Durand F, Pavesi M, Gerbes A, Jalan R, Moreau R, Ginés P, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology* 2015; **62**: 243-252 [PMID: 25877702 DOI: 10.1002/hep.27849]

20 **Arroyo V**, Moreau R. Diagnosis and prognosis of acute on chronic liver failure (ACLF) in cirrhosis. *J Hepatol* 2017; **66**: 451-453 [PMID: 27989380 DOI: 10.1016/j.jhep.2016.10.012]

P- Reviewer: Arroyo V, El-Bendary MM, Jarcuska P, Lee HC
S- Editor: Gong ZM **L- Editor**: A **E- Editor**: Zhang FF

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

ISSN 1007-9327

© 2017 Baishideng Publishing Group Inc. All rights reserved.