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ORIGINAL ARTICLE

Pulmonary impairment independently determines mortality in critically ill patients with acute-on-chronic liver failure

Martin S. Schulz[1,2] | Jan Mengers[1] | Wenyi Gu[1,2] | Andreas Drolz[3] | Philip G. Ferstl[1] | Alex Amoros[4] | Frank E. Uschner[1,2] | Nora Ackermann[1] | Georg Guttenberg[1] | Alexander Queck[1] | Maximilian J. Brol[1,2] | Christiana Graf[1] | Philipp Stoffers[1] | Anna-Lena Laguna de la Vera[1] | Carla Cremonese[1] | Hans-Peter Erasmus[1] | Martin W. Welker[1] | Achim Grünewaldt[1] | Vincente Arroyo[4] | Jörg Bojunga[1] | Javier Fernandez[4,5] | Stefan Zeuzem[1] | Johannes Kluwe[3] | Kai-Hendrik Peiffer[1] | Christoph Welsch[1] | Valentin Fuhrmann[6] | Gernot Rohde[1] | Jonel Trebicka[1,2,4]

[1]Department of Internal Medicine I, Goethe University, Frankfurt, Germany

[2]Department of Internal Medicine B, University of Münster, Münster, Germany

[3]1st Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[4]European Foundation for Study of Chronic Liver Failure, EF-Clif, Barcelona, Spain

[5]Hospital Clinic of Barcelona, University of Barcelona, CIBEReHD, IDIBAPS, Barcelona, Spain

[6]Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Jonel Trebicka, Department of Internal Medicine B, Albert-Schweitzer-Campus 1, 48149, Münster, Germany.
Email: jonel.trebicka@ukmuenster.de

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Abstract

Background & Aims: In ACLF patients, an adequate risk stratification is essential, especially for liver transplant allocation, since ACLF is associated with high short-term mortality. The CLIF-C ACLF score is the best prognostic model to predict outcome in ACLF patients. While lung failure is generally regarded as signum malum in ICU care, this study aims to evaluate and quantify the role of pulmonary impairment on outcome in ACLF patients.

Methods: In this retrospective study, 498 patients with liver cirrhosis and admission to IMC/ICU were included. ACLF was defined according to EASL-CLIF criteria. Pulmonary impairment was classified into three groups: unimpaired ventilation, need for mechanical ventilation and defined pulmonary failure. These factors were analysed in different cohorts, including a propensity score-matched ACLF cohort.

Results: Mechanical ventilation and pulmonary failure were identified as independent risk factors for increased short-term mortality. In matched ACLF patients, the presence of pulmonary failure showed the highest 28-day mortality (83.7%), whereas mortality rates in ACLF with mechanical ventilation (67.3%) and ACLF without pulmonary impairment (38.8%) were considerably lower ($p < .001$). Especially in patients with pulmonary impairment, the CLIF-C ACLF score showed poor predictive accuracy.

Abbreviations: ACLF, acute-on-chronic liver failure; ACLF-MV, acute-on-chronic liver failure with the presence of mechanical ventilation; ACLF-noMV/noPF, acute-on-chronic liver failure with the absence of mechanical ventilation and pulmonary failure; ACLF-PF, acute-on-chronic liver failure with the presence of pulmonary failure; AD, acute decompensated liver cirrhosis; AUROC, area under receiver operating characteristic; CANONIC study, EASL-CLIF Acute oN chrONIC liver failure study; CLIF, chronic liver failure; CLIF-C ACLF score, CLIF-Consortium ACLF score; CLIF-C OFs, CLIF-Consortium Organ Failure score, CLIF-SOFA score CLIF-Sequential Organ Failure Assessment score; EASL, European Association for the Study of the Liver; FiO2, fraction of inspired oxygen; HE, hepatic encephalopathy; ICU, intensive care unit.; IMC, intermediate care unit.; INR, International normalized ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; MV, mechanical ventilation; PF, pulmonary failure; ROC, receiver operating characteristic.

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Adjusting the CLIF-C ACLF score for the grade of pulmonary impairment improved the prediction significantly.

Conclusions: This study highlights that not only pulmonary failure but also mechanical ventilation is associated with worse prognosis in ACLF patients. The grade of pulmonary impairment should be considered in the risk assessment in ACLF patients. The new score may be useful in the selection of patients for liver transplantation.

KEYWORDS

ACLF, acute-on-chronic liver failure, CLIF-C ACLF score, CLIF-C ACLF-R score, mechanical ventilation, pulmonary failure, respiratory failure

1 | INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a severe complication of cirrhosis and a frequent cause for admission to an intensive care unit (ICU). ACLF is associated with severe systemic inflammation and characterized by acute decompensation of pre-existing cirrhosis, accompanying organ failures and high short-term mortality.[1,2] ACLF patients constitute a heterogeneous group with respect to number and combination of organ failures, aetiology of underlying liver diseases and precipitating events.[1–3] The high short-term mortality and heterogeneity of ACLF patients underline the necessity to adequately stratify and identify patients at risk of further deterioration and death. In recent years, the CLIF-C ACLF score has been established as the superior prognostic model to predict short-term mortality in ACLF patients.[4–6] The CLIF-C ACLF score ranges from 0 to 100, whereby a threshold above 64 to 70 points is regarded as the futility of care.[4,7] In particular, patients presenting ACLF in combination with mechanical ventilation or pulmonary failure are often considered a vulnerable subgroup in an ICU setting, whose clinical condition can quickly deteriorate, ultimately resulting in death. These patients are frequently not considered for liver transplantation because of high short-term mortality.[9]

To date, however, studies have not discriminated between mechanical ventilation and pulmonary failure with sufficient detail. Also, the exact impact of pulmonary impairment on short-term mortality in ACLF patients remains to be determined. One reason may be that only a small percentage (10–16%) of ACLF patients presented with pulmonary failure.[10,11] The aims of this study are, first to evaluate the role of the need for mechanical ventilation and the presence of pulmonary failure as risk factors for short-term mortality in ACLF patients and secondly to calibrate the CLIF-C ACLF score for pulmonary impairment and thereby improve its predictive performance overall.

Highlights

- Mechanical ventilation and pulmonary failure constitute independent risk factors in ACLF.
- The CLIF-C ACLF score underestimates mortality in these patients.
- Adjusting for the presence of MV/PF improves the predictive accuracy of the CLIF-C ACLF score.

Lay Summary

Acute-on-chronic liver failure (ACLF) is one of the main causes of death in liver cirrhosis and is associated with a high short-term mortality. Currently, the CLIF-C ACLF score is the best model to predict mortality in ACLF patients. However, our data suggest that pulmonary complications are not adequately reflected in the CLIF-C ACLF score. This study introduces a calibration variable to adjust for pulmonary impairment. The resulting modified CLIF-C ACLF score seems to have significantly higher accuracy for the prediction of short-term mortality and may help clinical decision-making in the future.

2 | PATIENTS AND METHODS

2.1 | Study design and population

In this retrospective study, 498 patients were evaluated, who were admitted to our ICU/IMC ward between March 2015 and June 2019 with the diagnosis of liver cirrhosis and acute decompensation (AD) or ACLF. Including IMC/ICU readmissions until June 2019, these patients generated a total of 775 admissions. Routinely evaluated clinical data were aggregated for all patients including vital signs, medical history, medication, general clinical data, and laboratory parameters (see Table 1). Data were collected upon admission as well as on days 2, 7, 28, 90 and at 1-year follow-up. If patients left the outpatient care clinic, 1-year follow-up was assessed by telephone interview with the patient and/or the general practitioner to determine survival status. Patients were identified by using our computerized databases ORBIS (Agfa HealthCare) and MetaVision (iMDsoft). The ethical committee of the University Hospital Frankfurt approved the study (EK 20-707).

Diagnosis of liver cirrhosis was based on clinical data (i.e. laboratory results, sonography and/or other imaging, liver biopsies and endoscopy). ACLF was defined by hepatic and extrahepatic organ failures according to EASL CLIF criteria and ACLF grades were defined according to Moreau et al.[8] CLIF-C ACLF score was calculated according to the EF-CLIF formula.[12]

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TABLE 1 General characteristics of 498 cirrhotic patients admitted to IMC/ICU

Variables	Overall ($n = 498$)	Pulmonary failure (PF, $n = 68$)		Mechanical ventilation (MV, $n = 53$)		No Mechanical ventilation (noMV, $n = 377$)	p-values	STDs		
								PF vs. MV	MV vs. NoMV	PF vs. NoMV
Patient data										
Age, median (IQR)	60 (52–67)	58 (48–64)		60 (52–68)		61 (53–67)	.1	0.29	0.05	0.23
Female gender, patients (%)	141 (28.3%)	15 (22.1%)		12 (22.6%)		114 (30.2%)	.24	0.01	0.17	0.19
ICU-stay [days], median (IQR)	2,5 (1–7)	5 (2–14)	††	5 (2–13)	‡‡	2 (1–5)	**<.001**	0.04	0.36	0.38
Scores										
CLIF-C-ACLF, median (IQR)	42.6 (36.8–51.4)	55.2 (48–62.5)	††	51.7 (43.7–57.4)	‡‡	40.9 (35.8–48.1)	**<.001**	0.49	0.82	1.36
CLIF-C-AD, median (IQR)	58.2 (51.3–68.3)	65.4 (56.9–76.7)	††	61.9 (53.1–75.1)	‡	57.2 (50.6–66.4)	**<.001**	0.2	0.33	0.53
MELD, median (IQR)	18.5 (13.1–25.2)	24.6 (18.4–33.9)	††	21.2 (17.9–27.5)	‡‡	16.8 (12.2–22.7)	**<.001**	0.4	0.44	0.78
MELD-Na, median (IQR)	21.4 (14.9–29.1)	27.2 (18.6–35.1)	††	22.6 (16.9–31.4)		20.5 (14–27.9)	**<.001**	0.33	0.12	0.37
Mechanical venilation										
Mechnical ventilation at admission	79 (15.9%)	47 (69.1%)	††	32 (6.4%)	‡‡	0 (0.0%)	**<.001**	0.18	1.75	2.12
Horovitz-Index, mmHg, median (IQR)	331 (231–430)	176 (122–247)	§§/††	324 (279–458)		373 (310–454)	**<.001**	1.26	0.03	1.57
Respiratory rate, median (IQR)	20 (16–26)	21 (16–27)		21 (17–25)		20 (16–26)	.71	0.11	0.15	0.05
SpO2, %, median (IQR)	97 (95–99)	96 (94–98,8)	§§	100 (95–100)	‡‡	97 (95–99)	**<.001**	0.71	0.44	0.33
FiO2, median (IQR)	0,21 (0,21–0,30)	0,5 (0,4–0,6)	§§/††	0,33 (0,27–0,48)	‡‡	0,21 (0,21–0,24)	**<.001**	0.93	1.32	1.88
PaO2, mmHg, median (IQR)	90.6 (75.1–114)	84.3 (69.4–111.3)	§§	121 (89.1–157)		89.2 (74.3–108)	**<.001**	0.8	0.86	0.02
PvO2, mmHg, median (IQR)	41.4 (36.1–51.6)	44.3 (38.5–54.8)		38 (26.4–50.2)		41.2 (36.1–51.5)	.37	0.31	0.19	0.11
Vital parameters										
Heart rate, median (IQR)	82 (76–97)	97 (82–112)	§/††	86 (77–103)		80 (75–93)	**<.001**	0.47	0.2	0.72
MAP, median (IQR)	81 (71–91)	75 (65–84)	§/†	85 (75–95)		82 (72–91)	**.001**	0.39	0.02	0.37
Temperature, median (IQR)	36.5 (36–36.9)	36.3 (34,7–37)		36.1 (35.2–36.8)	‡‡	36.6 (36.2–36.9)	**<.001**	0.23	0.67	0.39
Liver cirrhosis related complications										
Ascites, patients (%)	365 (73.3%)	51 (75.0%)		42 (79.2%)		272 (72.1%)	.6	0.1	0.15	0.05
Portal vein trombosis, patients (%)	60 (12.0%)	6 (8.8%)		4 (7.5%)		50 (13.3%)	.33	0.06	0.19	0.14
HRS, patients (%)	136 (27.3%)	24 (35.3%)		17 (32.1%)		95 (25.2%)	.16	0.07	0.15	0.22
Active GI-Bleeding, patients (%)	133 (26.7%)	15 (22.1%)		18 (34.0%)		100 (26.5%)	.34	0.27	0.16	0.1
Transfusion requirement, patients (%)	191 (38.4%)	32 (47.1%)	†	35 (66.0%)	‡‡	124 (32.9%)	**<.001**	0.38	0.69	0.3
Esophageal varices, patients (%)	319 (64.1%)	37 (54.4%)	†	26 (49.1%)	‡	256 (67.9%)	**<.001**	0.24	0.4	0.3
Hepatic enzephalopathy, patients (%)	110 (22.1%)	20 (29.4%)	†	17 (32.1%)	‡	73 (19.4%)	**0**	0.25	0.29	0.36
TIPS, patients (%)	107 (21.5%)	5 (7.4%)	†	4 (7.5%)	‡	98 (26.0%)	**<.001**	0.01	0.51	0.52
Liver transplantation, patients (%)	14 (2.8%)	1 (1.5%)		3 (5.7%)		10 (2.7%)	.36	0.23	0.15	0.08

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TABLE 1 (Continued)

Variables	Overall ($n = 498$)	Pulmonary failure (PF, $n = 68$)		Mechanical ventilation (MV, $n = 53$)		No Mechanical ventilation (noMV, $n = 377$)	p-values	STDs		
								PF vs. MV	MV vs. NoMV	PF vs. NoMV
Laboratory results										
Sodium, mmol/L, median (IQR)	136 (131–140)	135 (130–141)		137 (130–142)		136 (131–140)	.63	0.05	0.11	0.06
Lactate, mg/dl, median (IQR)	17 (12–28)	33 (16–59)	††	27 (15.5–58)	‡‡	16 (11–24)	**<.001**	0.04	0.73	0.81
Serum Creatinine, mg/dl, median (IQR)	1.3 (0.9–2.4)	1.6 (1–2.9)	†	1.8 (1–2.6)	‡	1.2 (0.9–2.1)	**0**	0.11	0.31	0.23
Bilirubin, mg/dl, median (IQR)	2.1 (1.1–5.1)	4.8 (1.9–10.1)	§/††	2.2 (1.2–4.5)		1.9 (1–4.6)	**<.001**	0.41	0.05	0.47
CRP, mg/dl, median (IQR)	2.5 (0.74–5.5)	5.4 (2.8–10.4)		3.3 (0.5–6.9)		1.9 (0.7–4.5)	.21	0.28	0.07	0.07
Albumin, g/dl, median (IQR)	2.8 (2.3–3.3)	2.5 (2.1–2.9)	§/†	2.8 (2.3–3.6)		2.8 (2.4–3.3)	**.01**	0.51	0.1	0.48
INR, median (IQR)	1.5 (1.3–1.9)	1.9 (1.5–2.5)	††	1.7 (1.5–2.3)	‡	1.5 (1.3–1.8)	**<.001**	0.34	0.2	0.42
Leukocytes, 10^9/L, median (IQR)	8.2 (5.3–12.2)	11.4 (7.3–16.5)	††	10.2 (4.8–15.2)	‡	7.6 (5.2–11.2)	**<.001**	0.24	0.38	0.52
Hb, g/dl, median (IQR)	9.1 (7.7–11)	9.4 (8.1–11.1)	§	8.3 (6.9–9.7)	‡	9.2 (7.7–11)	**<.05**	0.39	0.25	0.14
Platelets, 10^9/L, median (IQR)	101 (62–152)	103 (62–158)		101 (55–152)		100 (64–151)	.85	0.04	0.07	0.03

p-values were obtained using chi-square test for non-metric variables or Kruskal–Wallis test for metric variables. For post-hoc-testing Mann–Whitney- U test was performed on metric variables applying Bonferroni correction. Post-hoc-significance is shown by symbols as follows:

PF vs MV: †$p < .05$; ††$p < .001$.

PF vs NoMV: §$p < .05$; §§$p < .001$.

MV vs NoMV: ‡$p < .05$; ‡‡$p < .001$.

p-values <0.05 are considered statistically significant and are formatted as bold. Balance of baseline covariables is assessed by standardized mean differences (STDs).

Abbreviations: ACLF, acute-on-chronic liver failure; Hb, hemoglobin; INR, international normalized ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; MV, mechanical ventilation; RF, respiratory failure; STDs, standardized mean differences; TIPS, transjugular intrahepatic portosystemic shunt.

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Predictors for short-term mortality were evaluated in the overall cohort of cirrhotic patients with first IMC/ICU admission ($n = 498$) and in an ACLF subcohort of 176 patients, who presented a defined ACLF at first admission (median CLIF-C ACLF 52.7, IQR 45.3–58.3). In order to evaluate whether mechanical ventilation and pulmonary failure constitute risk factors independent of associated ACLF severity, we performed 1:1:1 propensity score matching. ACLF patients were assigned to one of three groups: receiving high oxygenation therapy because of defined pulmonary failure (PF group), indication for mechanical ventilation in absence of manifest pulmonary failure (MV group) and control group without mechanical ventilation (noMV group). Since the CLIF-C ACLF score, which incorporates the degree of systemic inflammation, number of organ failures as well as age, has been unequivocally demonstrated in recent years to be the best predictor for short-term mortality in ACLF patients and being superior to any other prognostic model in capturing ACLF disease severity, we included the CLIF-C ACLF score as the major confounding covariate in our propensity score model. Moreover, we included sex as a possible confounder, since our unmatched cohort showed high deviation of sex distribution and since intersexually differing mortality rates have been described previously. In this 1:1:1 matched cohort ($n = 147$, median CLIF-C ACLF 54, IQR 49–59), 49 patients with ACLF-PF were matched to 49 patients with ACLF-MV and to 49 patients with ACLF-noMV, characteristics are displayed in Table 2. Table S1 shows standardized differences (STDs) to express degree of balance of baseline characteristics pre- and post-matching between the respective ACLF subgroups. The matched cohort was derived from ACLF patients at first IMC/ICU admission ($n = 176$) and was used as a test cohort to compute the calibration variable used for the CLIF-C ACLF-R score. To assess the validity of our results, we assigned patients with ACLF at IMC/ICU re-admission to a separate cohort for internal validation.

2.2 | Statistical analysis

Normally distributed data are expressed as mean and standard deviation. Non-parametric data are expressed as median and interquartile range. Non-parametric testing for unpaired comparisons was performed by Mann–Whitney *U* test for two groups and Kruskal-Wallis-test for >2 groups. Survival rates were analysed using the Kaplan–Meier method. Univariate and multivariate risk factor analyses were performed by Cox regression (backward step-wise likelihood quotient). Predictive performance of prognostic models was evaluated by ROC analysis and Harrel's C-index. The predicted 28-day mortality was calculated according to the formula proposed by the EASL- CLIF consortium.[12] A loess curve was constructed to assess the calibration. Standardized mean differences were calculated to assess the balance of covariates before and after propensity score matching. P-values <0.05 were considered statistically significant. Standardized differences were analysed by SAS V.9.4 (SAS Institute) to assess balance of baseline covariates before and after propensity score matching. Statistical analysis was performed by means of SPSS 25 for Windows (SPSS Inc. Chicago, IL, USA) and SAS V.9.4 (SAS Institute).

2.3 | Introduction of a calibration variable to adjust the CLIF-C ACLF score

We calculated for an easily realizable calibration variable (CV) to adjust for presence and absence of MV or PF and established the CV to be 1 for PF, 0.5 for MV, and −0.1 for noMV/noPF. The calibration variable was calculated within the matched cohort. The adjusted CLIF-C ACLF score, which we termed the CLIF-C ACLF-R score, is calculated as follows:

$$\text{CLIF} - \text{C ACLF} - \text{R} = \text{CLIF} - \text{C ACLF} + (20^{*}\text{CV}).$$

By factoring in the presence of PF with a CV of an additional 20 points to the CLIF-C-ACLF score, presence of MV with an additional 10 points and noMV/noPF with −2, we achieved a considerably improved predictive accuracy of short-term mortality in the first admission cohort (test cohort) and in the re-admission cohort (internal validation cohort).

3 | RESULTS

3.1 | General patient characteristics

The details on the general characteristics of enrolled patients are displayed in Table 1. The median age was 60 years, 357 patients (71.7%) were male and 141 (28.3%) were female. Aetiology of cirrhosis was alcohol in 262 patients (52.6%), viral hepatitis in 120 (24.1%), NASH in 40 (8.0%) and cryptogenic in 46 patients (9.2%). In 30 cases (6.0%), other causes, that is autoimmune liver diseases, drug-induced liver injury or hereditary liver diseases, were the underlying aetiology.

In total, 176 patients (35.3%) were admitted to ICU/IMC with a defined ACLF according to EASL-CLIF criteria. The most common organ failure in these ACLF patients was kidney failure (67.6%), followed by circulatory (54.5%), coagulation (26.7%), liver (26.1%), cerebral (19.3%) and pulmonary (19.3%) failure. Patients with ACLF at admission presented significantly more infectious complications compared to non-ACLF patients, that is SBP (20.8% vs. 4.6%, $p < .05$) and non-SBP infection (47.6% vs. 23.2%, $p < .01$). Different AD phenotypes were defined according to the PREDICT study.[13] Ninety patients (18.3%) developed ACLF within 90 days and were classified as pre-ACLF.

3.2 | Outcome and causes of death

Of our overall cohort of cirrhotic patients admitted to IMC/ICU ($n = 498$). 20.5% died during the index IMC/ICU admission, with

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TABLE 2 Characteristics of 147 matched ACLF patients (1:1:1 propensity score matching [PF:MV:noMV], covariables CLIF-C ACLF score and sex)

Variables	Overall ($n = 147$)	ACLF with pulmonary failure (PF, $n = 49$)	ACLF with mechanical ventilation (MV, $n = 49$)	ACLF without mechanical ventilation (noMV, $n = 49$)	Standardized differences (STDs)		
					PF vs. MV	MV vs. NoMV	PF vs. NoMV
Patient data							
Age, median (IQR)	59 (50–66)	59 (49–65)	59 (51–66)	62 (51–71)	**0.1**	0.11	0.2
Female gender, patients (%)	46 (31.3%)	17 (34.7%)	14 (28.6%)	15 (23.4%)	0.13	**0.05**	**0.09**
Scores							
CLIF-C-ACLF, median (IQR)	54 (49–59)	54 (49–59)	56 (48–60)	54 (48–58)	**0.03**	**0.1**	**0.08**
MELD, median (IQR)	27 (21–34)	25 (17–31)	27 (21–33)	31 (26–37)	0.23	**0.56**	**0.73**
MELD-Na, median (IQR)	30 (23–35)	29 (20–35)	29 (23–33)	34 (28–38)	**0.1**	**0.53**	**0.49**
Mechanical venilation							
Mechnical ventilation at admission	64 (43.5%)	33 (67.3%)	31 (63.3%)	0 (0.0%)	**0.09**	1.86	2.03
Horovitz-Index, mmHg, median (IQR)	293 (186–406)	148 (113–240)	323 (275–429)	405 (293–473)	1.47	0.27	1.76
Respiratory rate, median (IQR)	19 (16–24)	20 (15–27)	19 (15–22)	20 (16–27)	**0.02**	**0.01**	**0.05**
SpO2, %, median (IQR)	97 (95–100)	95 (93–99)	100 (95–100)	97 (95–99)	0.69	0.34	0.31
FiO2, median (IQR)	0.33 (0.21–0.50)	0.51 (0.40–0.62)	0.35 (0.23–0.46)	0.21 (0.21–0.28)	1.02	1.14	1.83
PaO2, mmHg, median (IQR)	95 (76–127)	83 (67–104)	118 (86–153)	91 (76–110)	0.94	0.83	0.24
PvO2, mmHg, median (IQR)	39.6 (31.3–49.8)	40.9 (33.5–51.9)	39.4 (26.4–48.2)	39.7 (31.7–50)	0.4	0.31	0.04
Vital parameters							
Heart rate, median (IQR)	86 (78–105)	96 (79–114)	80 (78–100)	79 (76–99)	0.38	0.12	**0.56**
MAP, median (IQR)	74 (63–86)	74 (66–84)	81 (63–91)	70 (59–85)	0.1	0.27	0.2
Temperature, median (IQR)	36.3 (35.3–36.9)	36.1 (34.5–37)	35.9 (34.9–36.6)	36.6 (36.2–36.9)	0.14	**0.67**	
Liver cirrhosis related complications							
Ascites, patients (%)	121 (82.3%)	40 (81.6%)	41 (83.7%)	40 (81.6%)	**0.05**	**0.05**	**0.001**
HRS, patients (%)	76 (51.7%)	22 (44.9%)	26 (53.1%)	28 (57.1%)	0.25	**0.08**	0.31
Active GI-Bleeding, patients (%)	40 (27.2%)	13 (26.5%)	14 (28.6%)	13 (26.5%)	**0.05**	**0.05**	**0.001**
Esophageal varices, patients (%)	87 (59.2%)	31 (63.3%)	30 (61.2%)	26 (53.1%)	0.21	0.17	0.28
Hepatic enzephalopathy, patients (%)	55 (37.4%)	13 (26.5%)	22 (44.9%)	20 (40.8%)	0.43	0.08	0.36
TIPS, patients (%)	24 (16.3%)	9 (18.4%)	9 (18.4%)	6 (12.2%)	**<0.001**	0.17	0.17
Laboratory results							
Sodium, mmol/l, median (IQR)	134 (129–139)	133 (129–139)	135 (129–141)	133 (127–137)	**0.05**	0.32	0.27

(Continues)

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TABLE 2 (Continued)

Variables	Overall (n = 147)	ACLF with pulmonary failure (PF, n = 49)	ACLF with mechanical ventilation (MV, n = 49)	ACLF without mechanical ventilation (noMV, n = 49)	Standardized differences (STDs)		
					PF vs. MV	MV vs. NoMV	PF vs. NoMV
Lactate, mg/dl, median (IQR)	27 (18–52)	33 (18–53)	33 (20–62)	22 (13–40)	0.12	**0.62**	**0.55**
Creatinine, mg/dl, median (IQR)	2.4 (1.6–3.9)	2.1 (1.1–3.1)	2.2 (1.6–4.1)	2.8 (2.3–4.6)	0.3	**0.39**	**0.67**
Bilirubin, mg/dl, median (IQR)	4.5 (1.8–11)	4.2 (1.8–7.6)	4 (1.7–8.2)	7.6 (1.8–24.3)	**0.05**	0.51	0.56
CRP, mg/dl, median (IQR)	3.9 (1.9–7.6)	5.2 (2.7–10.1)	3.7 (1.4–7.6)	2.8 (1.6–5)	0.18	0.2	0.4
Albumin, g/dl, median (IQR)	2.5 (2.2–3.2)	2.4 (2.1–3.1)	2.7 (2–3.2)	2.5 (2.3–3.1)	**0.06**	**0.09**	0.17
INR, median (IQR)	1.9 (1.5–2.6)	1.7 (1.5–2.2)	2.1 (1.5–2.8)	1.9 (1.5–2.7)	**0.06**	0.14	0.17
Leukocytes, 10^9/l, median (IQR)	10.1 (6.8–15.1)	10.8 (7.3–15.4)	10.1 (6.3–15.5)	9.2 (6.9–14.4)	**0.05**	**0.07**	**0.03**
Hb, g/dl, median (IQR)	8.4 (7.3–9.9)	9 (7.7–10.3)	8.2 (7.2–10.2)	8.3 (6.8–9.7)	0.28	0.13	0.43
Platelets, 10^9/l, median (IQR)	87 (46–137)	101 (53–146)	76 (46–126)	84 (41–132)	0.3	0.14	0.15

Notes: Balance of baseline covariables is assessed by standardized mean differences (STDs), STD values <10% are formatted as bold.

Abbreviations: ACLF, acute-on-chronic liver failure; Hb, hemoglobin; INR, 1 international normalized ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; MV, mechanical ventilation; RF, respiratory 2 failure; STDs, standardized mean differences; TIPS, transjugular intrahepatic portosystemic shunt.

overall 28-day mortality of 25.7%. Mortality rates are displayed in Table 3. At 1-year follow-up, 49.8% of all patients had died. The causes of death in the overall cohort were sepsis in 34.2%, ACLF in 19.3%, hemorrhagic shock in 14.4% (mostly because of gastrointestinal and variceal bleeding), cardiogenic shock in 4.1% and aspiration in 2.1% of cases. In 7.4% of cases, other reasons were reported (i.e. intestinal ischemia, intracerebral haemorrhage, status epilepticus or HCC), while in 13.5% of cases, cause of death could not be determined.

Of the patients with a defined ACLF, 45.7% died during index IMC/ICU admission, 28-day mortality was 54.3%. As expected, 28-day mortality in ACLF patients was strongly associated with ACLF grade (ACLF grade I: 37.3%; II: 52.4%; III: 76.5%), as shown in Figure 1A.

3.3 | Pulmonary impairment in ACLF

Mechanical ventilation at first IMC/ICU admission was required by 121/489 patients (24.3%). In 68 cases (56.2%), mechanical ventilation was initiated because of pulmonary failure (PF), and the remaining 53 patients (43.8%) required ventilation for airway protection in severe hepatic encephalopathy and gastrointestinal bleeding or upcoming surgery/intervention. This group will be referred to as the mechanical ventilation group (MV). Patients receiving mechanical ventilation with high oxygen support because of defined pulmonary failure will in future be referred to as the PF group. PF (n = 68) or MV (n = 53) were associated with significantly higher ICU mortality and higher 28-, 90-day and 1-year mortality compared to noMV/noPF patients (28-day mortality: 72.1% vs. 50.9% vs. 13.8%, p < .01, see Table 3). Patients with ACLF at admission showed a 28-day mortality of 43.5%, whereas ACLF-MV and ACLF-PF were associated with a 28-day mortality of 63.9% (p < .01) and 75.4% (p < .01) respectively. In the subgroup analysis, PF patients showed a higher presence of ACLF (83.8% vs. 67.1%) and higher ACLF grades (see Tables 1 and 3). In multivariate Cox regression, mechanical ventilation was associated with a hazard ratio of 2.45 (95% CI, 1.39–4.31 p = .002) and pulmonary failure with a hazard ratio of 4.90 (95% CI, 2.97–8.09, p < .001) in the ACLF cohort (n = 176), as shown in Table S2.

Since the presence of MV and PF are associated with a more advanced stage of ACLF (median CLIF-C ACLF score 51.7 and 55.2 respectively) compared to noMV/noPF (median CLIF-C ACLF 40.9), we performed 1:1:1 propensity score matching, as described in 'Methods'. Balance of baseline covariates pre- and post-matching was assessed by standardized mean differences (STDs, see Sup. Table 1). In the resulting 1:1:1 matched cohort (n = 147, median CLIF-C ACLF 54, IQR 49–59), all subgroups presented comparable age and gender distributions, similar ACLF grade distribution (STD <1%) and comparable CLIF-C ACLF scores (STD ≤10%, see Table 2). Of note, MELD and MELD-Na scores showed markedly higher STD values after matching compared to CLIF-C ACLF scores. We observed this to be an artificial shift in OF distribution towards

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TABLE 3 Mortality rates in different study cohorts stratified for presence and grade of pulmonary impairment

All first admissions	Overall $n = 498$		Pulmonary failure ($n = 68$, 13.7%)		Mechanical ventilation ($n = 53$, 10.6%)		No mechanical ventilation ($n = 377$, 75.7%)	
28-day mortality, patients (%)	128	(25.7%)	49	(72.1%)	27	(50.9%)	52	(13.8%)
90-day mortality, patients (%)	171	(34.3%)	50	(73.5%)	30	(56.6%)	91	(24.1%)
1-year mortality, patients (%)	225	(45.2%)	51	(75.0%)	31	(58.5%)	143	(37.9%)
ACLF at first admission	**Overall $n = 176$**		**Pulmonary failure ($n = 56$, 31.8%)**		**Mechanical ventilation ($n = 34$, 19.3%)**		**No mechanical ventilation ($n = 86$, 48.9%)**	
28-day mortality, patients (%)	88	(50.0%)	42	(75.0%)	23	(67.6%)	23	(26.7%)
90-day mortality, patients (%)	108	(61.4%)	45	(80.4%)	26	(76.5%)	37	(43.0%)
1-year mortality, patients (%)	122	(69.3%)	46	(82.1%)	26	(76.5%)	50	(58.1%)
1:1:1 matched ACLF cohort	**Overall $n = 147$**		**Pulmonary failure ($n = 49$, 33.3%)**		**Mechanical ventilation ($n = 49$, 33.3%)**		**No mechanical ventilation ($n = 49$, 33.3%)**	
28-day mortality, patients (%)	93	(63.3%)	41	(83.7%)	33	(67.3%)	19	(38.8%)
90-day mortality, patients (%)	98	(66.7%)	42	(85.7%)	34	(69.4%)	22	(44.9%)
1-year mortality, patients (%)	108	(73.5%)	43	(87.8%)	37	(75.5%)	28	(57.1%)
All readmissions	**Overall $n = 261$**		**Pulmonary failure ($n = 24$, 9.2%)**		**Mechanical ventilation ($n = 38$, 14.6%)**		**No mechanical ventilation ($n = 199$, 76.2%)**	
28-day mortality, patients (%)	81	(31.0%)	21	(87.5%)	21	(55.3%)	39	(19.6%)
90-day mortality, patients (%)	100	(38.3%)	21	(87.5%)	21	(55.3%)	58	(29.1%)
1-year mortality, patients (%)	140	(53.6%)	22	(91.7%)	26	(68.4%)	92	(46.2%)

MELD-captures OFs, which was dependent on patient grouping, but did not adequately reflect disease severity, as displayed by balance in CLIF-C ACLF scores. Inherently to the study design, parameters of mechanical ventilation largely show STD values >10%. Patients with ACLF-PF showed a higher 28-day, 90-day and 1-year mortality compared to matched ACLF-MV patients, and ACLF-MV showed a worse outcome than ACLF-noMV/noPF (28-day mortality: 83.7% vs. 67.3% vs. 38.8%), as shown in Figure 1B and Table 3. The median survival time of ACLF-PF patients was 11 days compared to 17 days in ACLF-MV and 148 days in ACLF-noMV patients, besides presenting a comparable severe ACLF setting. In multivariate Cox regression of all univariate significant variables, mechanical ventilation showed a hazard ratio of 1.65 (95% CI 1.03 to 2.67, $p = .039$) and pulmonary failure showed a hazard ratio of 3.03 (95% CI 1.64 to 5.58, $p < .001$), as shown in Table S3.

3.4 | Predictive performances of established scores in ACLF patients

To evaluate the predictive performances of different prognostic scores, we performed ROC analysis for 28-day and 90-day mortality. In our ACLF at first admission cohort ($n = 176$), the CLIF-C ACLF score outperformed all other scores tested for predicting 28-day mortality (AUROC 0.71, 95% CI 0.63–0.79, see Figure 2A). In order to analyse the predictive accuracy of the CLIF-C ACLF score in ACLF patients with pulmonary impairment, ROC analysis was performed separately in ACLF-MV and -PF as well as ACLF-noMV/noPF subgroups (see Figure 2). ROC analysis showed a good prediction of 28-day mortality in all ACLF and ACLF-noMV/noPF patients, with an AUROC of 0.71 and 0.75 respectively. In contrast, in ACLF-MV and ACLF-PF patients, the CLIF-C ACLF score was surprisingly outperformed by the other tested scores. Corresponding 11 C-Indices and 95% CIs are displayed in Sup. Table S7, displaying a comparable trend. An additional ROC analysis was performed to predict 28-day and 90-day mortality for each organ failure subgroup, such as liver, kidney, cerebral, coagulation, circulatory and pulmonary failure (see Figure S1). Data showed a fair to good prediction of short-term mortality for all organ failure subgroups (AUROC 0.69–0.85, Figures S1A–E) except for pulmonary failure. In an ACLF-PF setting, the CLIF-C ACLF score showed a poor prediction of 28-day mortality (AUROC 0.49, 95% CI 0.34–0.65) or 90-day (AUROC 0.52, 95% CI 0.36–0.68), as shown in Figure S1F.

3.5 | Predictive performance of the revised CLIF-C ACLF-R score and validation

Next, we assessed whether the prediction of short-term mortality provided by the CLIF-C ACLF score could be improved, since it fails to adequately reflect mortality in ACLF-PF and ACLF-MV patients. As described in 'Patients and Methods', we calculated an easily implantable calibration variable derived from a binary logistic regression model to factor in the grade of pulmonary impairment, resulting in our adjusted CLIF-C ACLF R score. In our main cohort of all cirrhotic patients at first admission ($n = 498$), the new CLIF-C ACLF-R score showed a superior prediction of 28-day mortality compared to the CLIF-C ACLF score in our first admission cohort (AUROC 0.87 vs. 0.81, see Figure 4A,B, Table S4). To illustrate the improved predictive accuracy of the CLIF-C ACLF-R score in ACLF and pre-ACLF patients,

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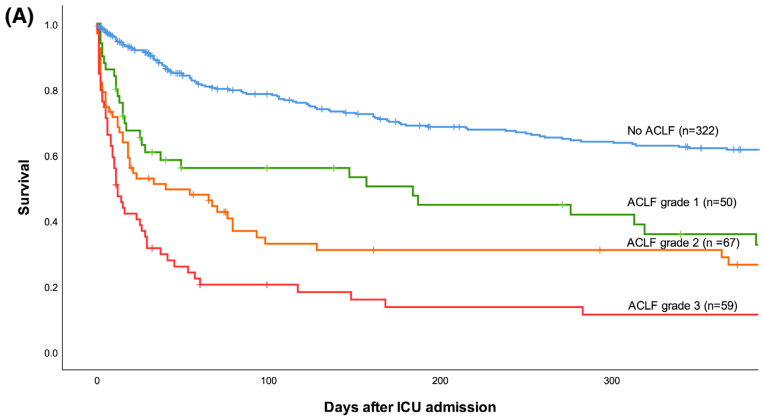
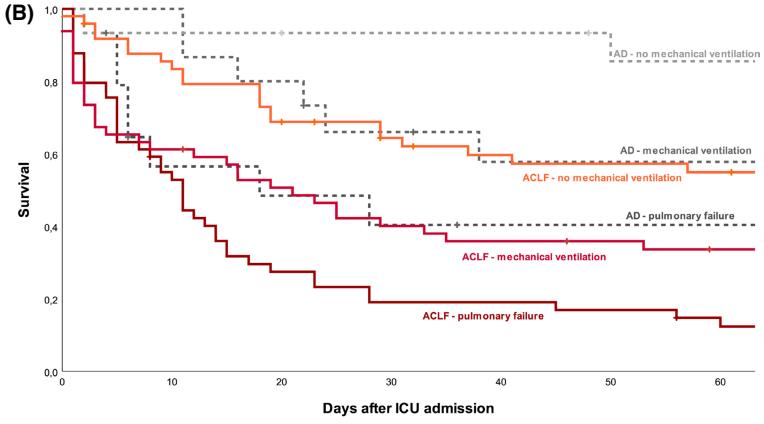
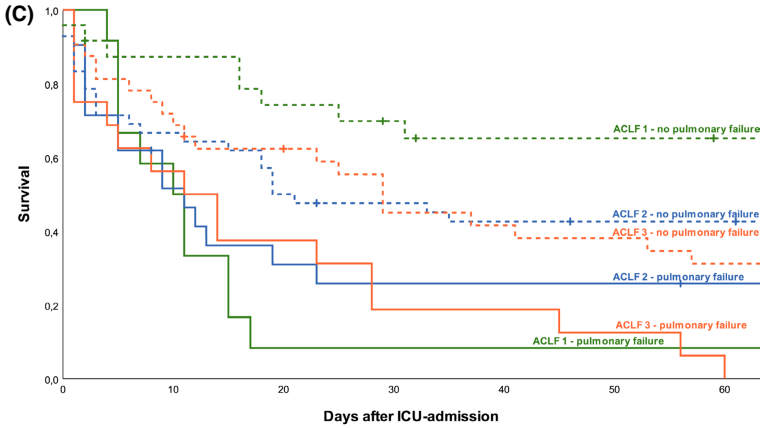


# at risk	Days	0	50	100	150	200	250	300	350
	No ACLF	322	231	206	188	171	165	158	151
	ACLF grade 1	50	22	21	19	16	16	14	11
	ACLF grade 2	67	30	17	16	15	15	14	14
	ACLF grade 3	59	14	9	7	6	6	5	5



# at risk	Days	0	10	20	30	40	50	60
	AD noMV	15	14	14	13	13	12	11
	AD MV	15	15	12	9	7	7	7
	AD PF	15	7	6	5	4	4	4
	ACLF noMV	49	41	33	28	25	24	23
	ACLF MV	49	30	24	19	17	16	14
	ACLF PF	49	26	13	9	9	8	6



# at risk	Days	0	10	20	30	40	50	60
	ACLF grade 1 - noPF	24	20	17	15	13	13	12
	ACLF grade 2 - noPF	42	28	21	19	17	16	16
	ACLF grade 3 - noPF	32	23	19	13	12	11	9
	ACLF grade 1 - PF	12	7	1	1	1	1	1
	ACLF grade 2 - PF	21	10	6	5	5	5	4
	ACLF grade 3 - PF	16	9	6	3	3	2	1

FIGURE 1 Survival after ICU admission depending on the presence of mechanical ventilation (MV) and pulmonary failure (PF). (A) Kaplan Meier plot of 1-year survival of 498 cirrhotic patients admitted to IMC/ICU depending on tge presence of ACLF and ACLF grade. (B) 60-day survival of 192 patients with ACLF and AD, cohort-matched by CLIF-C ACLF/AD and gender, depending on requirement for MV or presence of PF. (C) 60-day mortality of 1:1:1 matched ACLF (n = 147) patients, depending on ACLF grade and presence of PF.

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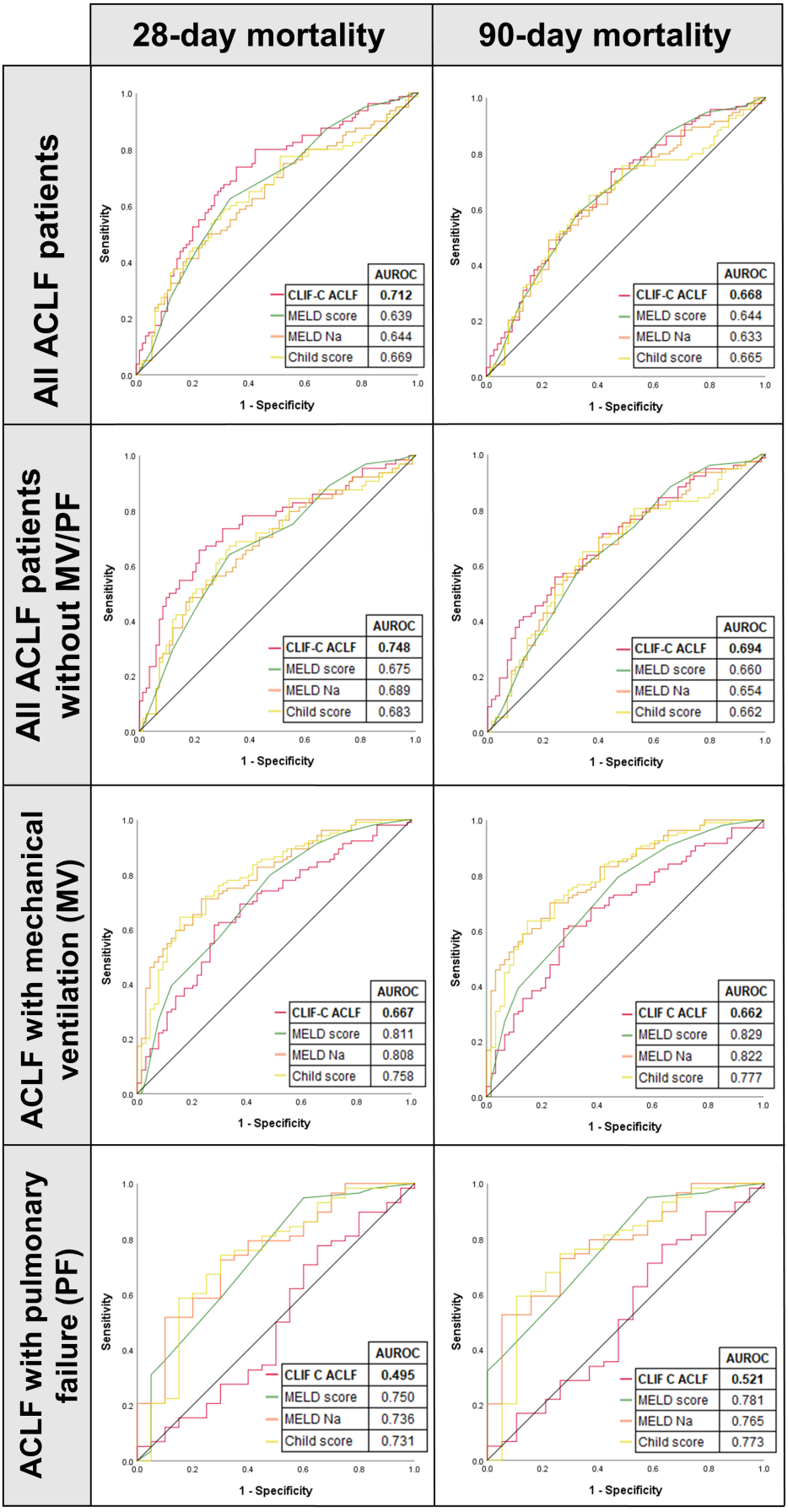

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FIGURE 2 Predictive accuracy of different prognostic scores for 28-day and 90-day mortality depending on presence/abscence of mechanical ventilation and pulmonary failure. ROC analysis performed for CLIF-C ACLF, Child-Pugh, MELD and MELD-Na score for prediction of 28- and 90-day mortality in the overall ACLF cohort ($n = 176$) and the ACLF-MV (AUROC 0.67/0.66), ACLF-PF (AUROC 0.49/0.52) and ACLFnoMV/noPF (AUROC 0.74/0.67) subgroups.

we contrasted the predicted and the observed 28-day mortality of the CLIF-C ACLF and CLIF-C ACLF-R score (see Figure 4). Data shows the CLIF-C ACLF score distinctly underestimating 28-day mortality in the mid-range between 41 and 69 score points (Figure 4A), whereas the CLIF-C ACLF-R score shows only a minimal overestimation in these patients (Figure 4B). Supplementary Figure S5 displays a loess-based calibration curve of the CLIF-C ACLF and the modified CLIF-C ACLF-R score, respectively. Shifts in scoring point distribution between the CLIF-C ACLF and the adjusted CLIF-C ACLF-R score, as a result of introducing the calibration variable, are displayed in Figure S2.

3.6 | Validation of the CLIF-C ACLF-R score

The calibration variable introduced in this study was calibrated in our 1:1:1 matched ACLF cohort ($n = 147$), consisting of ACLF patients at first IMC/ICU admission. To validate our findings, we designated the IMC/ICU re-admission cohort as the internal validation cohort to avoid double testing and to reduce confirmation bias. Figure S3 gives an overview of the assigned study groups. In all re-admitted patients ($n = 261$, AUROC 0.78 vs 0.70) and all re-admitted ACLF patients ($n = 148$, AUROC 0.74 vs. 0.64), the CLIF-C ACLF-R score showed a significantly higher predictive accuracy for 28-day mortality compared to the CLIF-C ACLF score (see Figure 3A,B respectively). In an external cohort, which was kindly provided by *Drolz* and colleagues,[21] the CLIF-C ACLF-R score showed a comparable but not superior predictive accuracy for 28-day mortality (see Table S4). In a subgroup analysis, the CLIF-C ACLF-R score showed a better prediction in ACLF grade 3 patients (AUROC 0.62 vs 0.60) and ACLF patients with extrahepatic organ failures (AUROC 0.62 vs 0.60). In addition, multivariate Cox regression in the external ICU cohort showed the new CLIF-C ACLF-R score to be predictive for 28-day mortality, independent of CLIF-C ACLF score, in ACLF grade 3 patients (Exp(B) 1.024, 95% CI 1.008–1.041, $p = .04$) as well as in patients with >4 organ failures (Exp(B) 1.065, 95% CI 1.065–1.116, $p = .009$).

The general characteristics of the main study cohorts and the external ICU cohort are displayed in Table S5. Results show distinct differences between patient populations with significant differences in CLIF-C ACLF score (CLIF-C $ACLF_{median}$ 42.6, IQR 36.8–51.4 vs. external 53.6, IQR 45.0–61.1, $p < .001$), MELD score ($MELD_{median}$ 18.5, IQR 13.1–25.2 vs external 20 IQR 14–29, $p = .006$) and distribution of ACLF grades ($p < .001$).

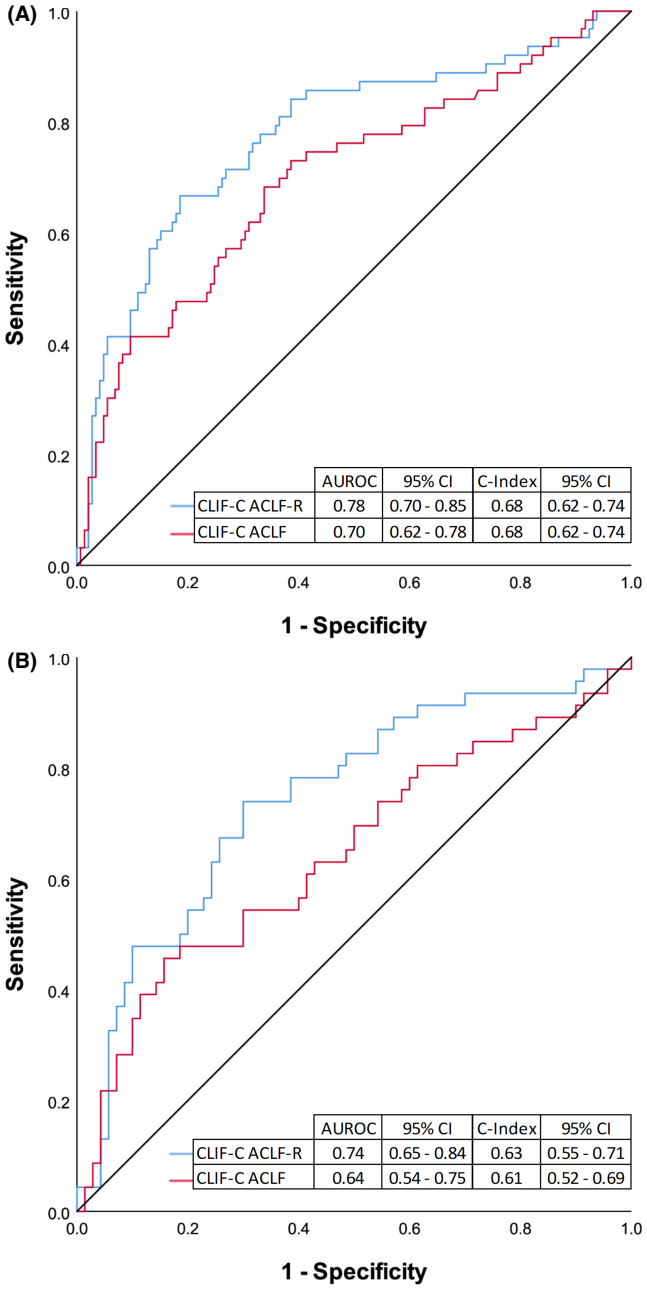

FIGURE 3 ROC analysis of the CLIF-C ACLF and adjusted CLIF-C ACLF-R score for 28-day mortality. ROC analysis for 28-day mortality performed in the designated internal validation cohort, consisting of (A) all cirrhotic patients with IMC/ICU re-admission ($n = 261$, $AUROC_{CLIF\text{-}C\text{-}ACLF\text{-}R}$ 0.78 vs. $AUROC_{CLIF\text{-}C\ ACLF}$ 0.70) and (B) all patients re-admitted with ACLF ($n = 148$, $AUROC_{CLIF\text{-}C\text{-}ACLF\text{-}R}$ 0.74 vs. $AUROC_{CLIF\text{-}C\ ACLF}$ 0.64).

4 | DISCUSSION

This study shows that pulmonary impairment, specifically classified according to mechanical ventilation and pulmonary failure, constitutes a distinct risk factor for increased 28-day mortality in ACLF patients, independent of ACLF severity. In our entire ACLF cohort, mechanical ventilation was associated with a 2.45-fold

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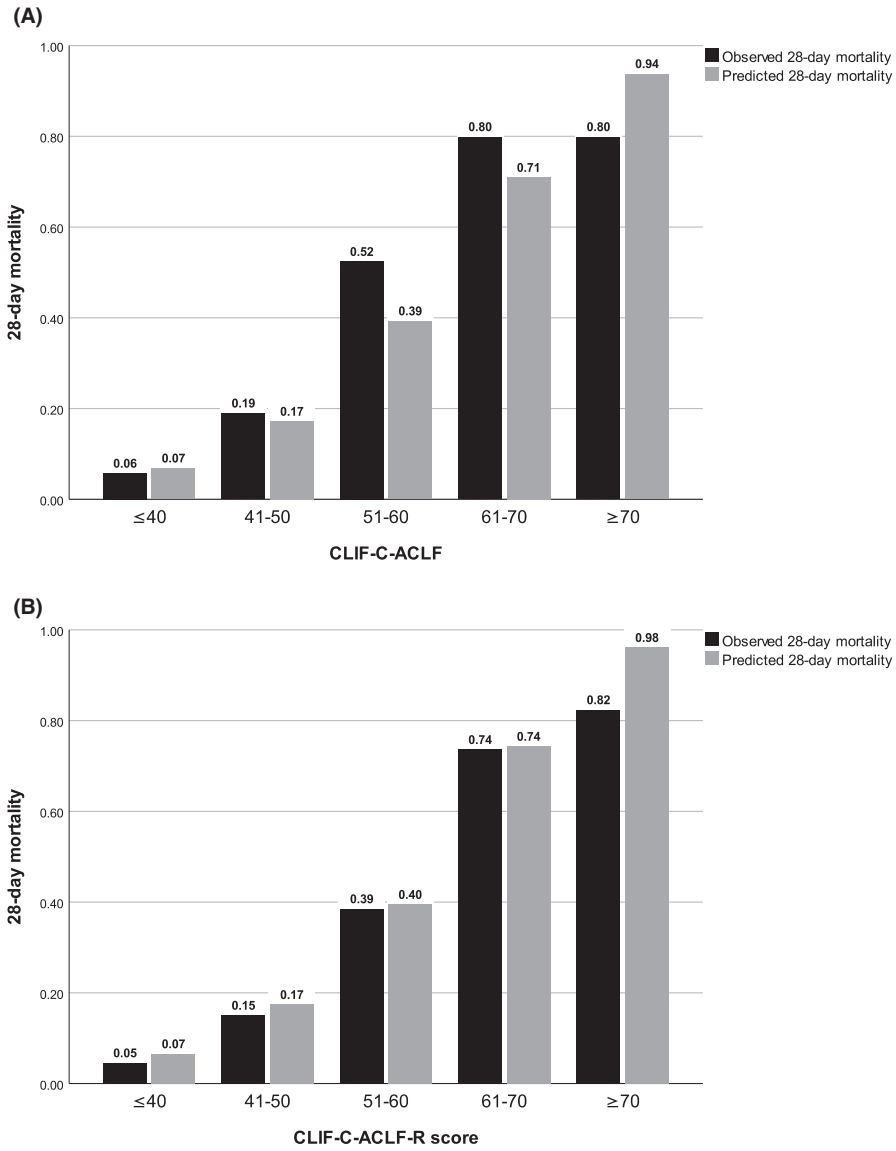

FIGURE 4 Observed and predicted 28-day mortality of the CLIF-C ACLF and CLIF-C ACLF-R scores. (A) Histogram of the predicted and observed 28-day mortality of the CLIF-C ACLF score. (B) Histogram of the predicted and observed 28-day mortality of the CLIF-C ACLF-R score.

increased risk of death and a 2.45-fold increased risk of pulmonary failure. In recent years, several studies have indicated that mechanical ventilation is associated with a worse outcome in cirrhotic patients.[11–14] Interestingly, in ACLF patients, pulmonary failure, defined by a Horovitz index (PaO2/FiO2) <200 mmHg according to the CLIF-OF score, has not yet been distinguished from mechanical ventilation.[11–15] This lack of distinction between both key clinical parameters is a limitation for interpretation of results. Moreover, pulmonary failure is defined by either mechanical ventilation as a surrogate for pulmonary failure or by the combined endpoint mechanical ventilation *and/or* PaO2/FiO2 < 200 mmHg (or SpO2/FiO2 < 214), according to the CANONIC study design.[16,17] In several studies, mechanical ventilation has been identified as a risk factor in cirrhotic and ACLF patients, associated with increased mortality.[11,18] As can be expected, the duration of mechanical ventilation and the time point of initiation are predictive of patient outcome, whereasearly mechanical ventilation discontinuation seems to be associated with better outcome.[11,16] However, the subgroup analyses in previous ACLF studies could neither dissect nor quantify the role of presence or severity of pulmonary failure as an independent risk factor of mechanical ventilation.[11–18]

To specifically analyse the role of mechanical ventilation and pulmonary failure, we adjusted for sex and severity of liver disease to eliminate possible confounders. Importantly, in this propensity-matched cohort, pulmonary failure almost doubled 28-day mortality compared to patients without pulmonary impairment. Patients with mechanical ventilation showed a more than 50% increase in 28-day mortality. These findings identify pulmonary impairment as a critical clinical marker for poor prognosis independent of ACLF severity.

The CLIF-C ACLF score was introduced in 2014 and it was derived from the CANONIC study.[12] It has since been established as the superior prognostic model to predict short-term mortality in ACLF patients.[3,6,19] Overall, we were able to confirm that the CLIF-C ACLF score is the best prognostic model for ACLF patients. However, the lack of precision regarding pulmonary impairment may render this score less suitable for critically ill patients requiring mechanical ventilation.[9] Thus, suboptimal risk stratification could decisively

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affect ICU decision-making, that is regarding transplant allocation. In our study, the CLIF-C ACLF score showed poor prediction of mortality for ACLF patients with pulmonary failure, similar to the flipping of a coin. In ACLF patients with mechanical ventilation but without defined pulmonary failure, the CLIF-C ACLF score performed better but was still outperformed by MELD, MELD-Na and Child-Pugh score. In order to improve the predictive accuracy for this specific patient population, we introduced a calibration variable adjusting for pulmonary impairment. This revised CLIF-C ACLF-R score improved overall predictive accuracy for mortality.

Notably, the investigations of the CANONIC study also demonstrated that the CLIF-C ACLF score underestimated mortality in patients with a score ranging up to 64 points.[12] We confirmed this in our dataset. However, the discrepancy was reduced after introducing the calibration variable. At least for our cohort, the underestimation of the CLIF-C ACLF score seems to be because of the lack of precision for mechanical ventilation or pulmonary failure.

To internally validate our results, we designated an ACLF cohort separate from the initial test and calibration cohort, which consisted of all IMC/ICU re-admitted patients. In this validation cohort, we were able to internally confirm the increased predictive accuracy of the new CLIF-C ACLF-R score. In addition, we validated our results externally in a large ICU cohort.[21] While the CLIF-C ACLF-R score showed comparable prediction for short-term mortality in the overall external cohort, subgroup analysis indicated that the prognosis of patients with a higher number of organ failures may be improved. However, sampling variability in our goodness-of-fit analysis shows that further evaluation and validation of the proposed CLIF-C ACLF-R score in other clinical cohorts is necessary.

This study has several limitations. First, as a result of the retrospective design results from this study could be affected by an inherent inadequacy of collected data. Nonetheless, we are confident that the data in this large retrospective cohort can be viewed as robust, since mortality rates, organ failure rates and complication rates are consistent with available data, that is as published in the CANONIC and PREDICT study.[3,13,17,20] By propensity score matching and adjusting for ACLF severity we aimed to effectively reduce selection bias in our cohort. Although data showed successful balancing for the selected confounding covariates in our propensity matched cohort, namely the CLIF-C ACLF score and sex, we acknowledge that balance of all baseline covariates (>30) was not fully achieved. Depending on the clinical data, reaching full balance among all baseline covariates can be difficult to obtain without substantially sacrificing sample size. Thus, we acknowledge that balancing can be seen as an inherent limitation to interpretation. Importantly, however, we found the MELD score STDs between our matched subgroups to remain >10% as an artificial effect of patient grouping, as was described earlier. Instead of adequately reflecting differences in disease severity between subgroups, to the authors this observation rather highlights the limited capability of the MELD/MELD-Na score to fully capture predicting factors of mortality in ACLF patients. This is underscored by the fact, that alignment of CLIF-C ACLF score and MELD score STDs in full balance rendered unfeasible in our cohort, when excluding a non-MELD-captured OF by patient subgrouping, regardless of PS condition. However, if this would be considered as a confounder, differences in MELD scores between matched subgroups would rather result in an underestimation of the observed effects on mortality. In regard to calibration, results of internal validation and the external ICU cohort should be considered with caution. To eliminate multiple testing and avoid confirmation bias, we designated a separate cohort for internal validation. However, an inherent bias in our internal validation cohort cannot be ruled out in a retrospective study of this nature. Furthermore, general characteristics of the patients included in our study differ from those of the external ICU cohort but are similar to the CANONIC study. This might contribute to the reason as to why we can validate our findings only in the most severe ACLF patients.

5 | CONCLUSION

In summary, we were able to identify and quantify the role of mechanical ventilation and pulmonary failure on mortality in ACLF patients. Subsequently, we modified the CLIF-C ACLF score in a way to render it more suitable for the prediction of mortality, including patients with pulmonary impairment. After further external validation, this simple modification may be used in clinical practice and may improve the stratification of patient care in most severe ACLF patients.

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The presented data in this manuscript is derived from original data.

ORCID

Martin S. Schulz https://orcid.org/0000-0002-5321-3056
Andreas Drolz https://orcid.org/0000-0002-2717-8517
Philip G. Ferstl https://orcid.org/0000-0002-0836-6643
Frank E. Uschner https://orcid.org/0000-0002-3760-2887

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Alexander Queck https://orcid.org/0000-0003-0553-2391
Philipp Stoffers https://orcid.org/0000-0001-6175-8315
Kai-Hendrik Peiffer https://orcid.org/0000-0002-3757-4476
Jonel Trebicka https://orcid.org/0000-0002-7028-3881

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