hol misuse, remained possible. These methodological considerations and limitations were explicated in our papers.[1,8]

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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Influenza virus infection as precipitating event of acute-on-chronic liver failure

To the Editor:

With great interest we have read the outstanding Grand Rounds article by Gustot *et al.* describing the current management of acute-on-chronic liver failure (ACLF),[1] which is a frequent and devastating complication of liver cirrhosis with mortality rates of up to 80% within 28 days. Specific hepatic and extrahepatic organ failures are the defining feature of ACLF and discriminate ACLF from classical decompensation of liver cirrhosis.[1]

While bacterial infection, reactivation of HBV and alcohol consumption are described as important precipitating events, in 44% no precipitating event could be identified. Systemic inflammation is a cardinal feature and – likely – driver of ACLF, which is, however, paralleled by a state of pronounced immunosuppression.[2] Still, apart from HBV reactivation,[3] little is known about the role of other viruses, such as respiratory viruses, as potential triggers of ACLF.

During winter 2017/2018, there was a serious outbreak of influenza virus infections in Germany. In order to locally control this outbreak and to manage patient flows, the wards of the Department of Gastroenterology and Hepatology of the University Hospital Essen were dedicated for cohorting patients with proven or suspected influenza infection, irrespective of the underlying medical condition of patients. In that given scenario, we aimed to characterize the association of the presence of liver cirrhosis with the risk of organ failures and the incidence of ACLF during influenza infection. From the end of January to

Table 1. Baseline characteristics and outcome of patients with influenza with and without liver cirrhosis.

	No liver disease	Liver cirrhosis	*p* value (no liver disease *vs.* cirrhosis)
Baseline characteristics	n = 34	n = 11	
Age, mean (SD)	54 (21)	57 (11)	n.s.
Male sex, n (%)	18 (53)	3 (27)	n.s.
Influenza type[1]			
A (non-H1N1), n (%)	4 (12)	2 (18)	n.s.
A (H1N1), n (%)	13 (38)	1 (9)	n.s.
B, n (%)	17 (50)	9 (82)	0.05
Viral load (ct value), mean (SD)	25 (6)	23 (5)	n.s.
Body mass index (kg/m^2), mean (SD)	27.2 (5.2)	23.6 (2.8)	0.04
Usage of immunosuppressive agents, n (%)	7 (21)	0 (0)	0.006
Charlson index (without liver disease), mean (SD)	1.8 (2.0)	1.0 (1.5)	n.s.
Charlson-Deyo score (without liver disease), mean (SD)	1.4 (1.6)	0.8 (1.3)	n.s.
Leukocytes (/nl), mean (SD)	8.6 (4.1)	8.4 (3.4)	n.s.
C-reactive protein (mg/dl), mean (SD)	5.1 (5.9)	7.1 (10)	n.s.
Platelets (/nl), mean (SD)	221 (76)	259 (102)	0.04
INR, mean (SD)	1.3 (0.8)	1.3 (0.3)	0.06
Bilirubin (mg/dl), mean (SD)	0.7 (0.5)	5.5 (9)	0.0001
Creatinine (mg/dl), mean (SD)	1.8 (1.7)	1.1 (0.4)	n.s.
ALT (U/ml), mean (SD)	353 (1850)	190 (276)	n.s.
Lactate (mmol/L), mean SD	1.2 (0.6)	1.9 (0.9)	0.09
Respiratory failure, n (%)	1 (3)	2 (18)	n.s.
Mean arterial pressure, mean (SD)	93.8 (17)	70.2 (22)	n.s.
Heart rate, mean (SD)	83 (18)	89 (32)	n.s.
ACLF (presence), n (%)	n.a.	2 (18)	n.a.
Grade 1, n (%)	n.a.	2 (18)	n.a.
Grade 2, n (%)	n.a.	0 (0)	n.a.
Grade 3, n (%)	n.a.	0 (0)	n.a.
CLIF-OF score, mean (SD)	n.a.	7.2 (1.6)	n.a.
MELD score, mean (SD)	n.a.	13.6 (6.7)	n.a.
Child-Pugh score, mean (SD)	n.a.	7.6 (1.8)	n.a.
Class A, n (%)	n.a.	2 (18)	n.a.
Class B, n (%)	n.a.	8 (73)	n.a.
Class C, n (%)	n.a.	1 (9)	n.a.
CLIF-SOFA score, mean (SD)	n.a.	4.1 (3.0)	n.a.
SOFA score, mean (SD)	1.3 (1.6)	3.7 (3.1)	0.01
Apache II score, mean (SD)	5.9 (4.2)	11.6 (5.9)	0.001
SAPS II score, mean (SD)	17.5 (8.8)	22.8 (9.6)	n.s.
Organ failure assessment, follow-up day 7	n = 17	n = 11	
Respiratory failure, n (%)	1 (6)	2 (18)	n.s.
Non-invasive ventilation, n (%)	1 (6)	0 (0)	n.s.
Invasive ventilation, n (%)	0 (0)	2 (18)	n.s.
Mean arterial pressure, mean (SD)	92 (23)	70 (23)	0.02
Heart rate, mean (SD)	77 (42)	89 (23)	n.s.
Use of vasopressors, n (%)	0 (0)	2 (18)	n.s.
ACLF (presence), n (%)	n.a.	5 (45)	n.a.
Grade 1, n (%)	n.a.	2 (18)	n.a.
Grade 2, n (%)	n.a.	2 (18)	n.a.
Grade 3, n (%)	n.a.	1 (9)	n.a.
CLIF-OF score, mean (SD)	n.a.	8.3 (2.8)	n.a.
MELD score, mean (SD)	n.a.	13.6 (2.8)	n.a.
CLIF-SOFA score, mean (SD)	n.a.	4.7 (3.8)	n.a.
SOFA score, mean (SD)	1.6 (1.4)	4.5 (3.2)	0.02
Apache II score, mean (SD)	8.1 (4.4)	11.3 (6.0)	n.s.
SAPS II score, mean (SD)	22.5 (12.0)	23.5 (8.7)	n.s.
Organ failure assessment, maximal scores during influenza infection	n = 34	n = 11	
Respiratory failure, n (%)	3 (9)	5 (45)	0.01
Non-invasive ventilation, n (%)	2 (6)	0 (0)	n.s.
Invasive ventilation, n (%)	1 (3)	5 (45)	0.02
Mean arterial pressure, mean (SD)	90 (22)	66 (25)	0.01
Heart rate, mean (SD)	87 (20)	71 (20)	0.004
Use of vasopressors, n (%)	2 (6)	4 (36)	0.08
Initiated renal replacement therapy, n (%)	1 (3)	2 (18)	n.s.

(*continued on next page*)

Table 1 (*continued*)

	No liver disease	Liver cirrhosis	*p* value (no liver disease *vs.* cirrhosis)
ACLF (presence), n (%)	n.a.	5 (45)	n.a.
Grade 1, n (%)	n.a.	1 (9)	n.a.
Grade 2, n (%)	n.a.	0 (0)	n.a.
Grade 3, n (%)	n.a.	4 (36)	n.a.
CLIF-OF score, mean (SD)	n.a.	9.0 (3.7)	n.a.
MELD score, mean (SD)	n.a.	16.1 (10.8)	n.a.
CLIF-SOFA score, mean (SD)	n.a.	6.6 (6.2)	n.a.
SOFA score, mean (SD)	1.9 (2.7)	6.9 (6.4)	0.03
Apache II score, mean (SD)	6.6 (5.0)	16.3 (10.6)	0.004
SAPS II score, mean (SD)	19.8 (10.1)	34 (18)	0.02
Clinical endpoints	n = 34	n = 11	
Days of hospitalization, mean (SD)	12.5 (16)	28 (35)	0.004
Need of intensive care therapy, n (%)	9 (26)	5 (45)	n.s.
Development of secondary bacterial pneumonia, n (%)	8 (24)	9 (82)	0.001
Death during follow-up, n (%)	1 (3)	2 (18)	n.s.

ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; CLIF, Chronic Liver Failure Consortium; INR, international normalized ratio; MELD, model for end-stage liver disease; OF, organ failure; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment. P values were calculated by means of chi-square contingency tables or Wilcoxon-Mann-Whitney-U-tests for dichotomous or continuous variables, respectively.
[1] One patient with liver cirrhosis was infected with both influenza virus type A (non-H1N1) and type B.

March 2018, 45 patients were admitted with proven influenza virus infection. Of those, 11 patients had liver cirrhosis and 34 patients had no liver disease. The baseline characteristics and outcomes of these patients are summarized in Table 1. By comparing patients' comorbidities using the Charlson comorbidity index[4] and Charlson-Deyo score,[5] without considering liver disease, there was no significant difference with respect to the number of comorbidities between both patient groups (Table 1). Furthermore, there were no significant differences in the distribution of influenza types and viral loads between both patient groups. Yet, patients with liver cirrhosis had significantly higher liver-specific and non-specific organ failure scores at the time influenza was diagnosed compared to patients without liver disease (Table 1). In addition, patients with liver cirrhosis experienced a more severe course of influenza than patients without liver disease, as evidenced by significantly higher maximal organ failure scores during follow-up, higher organ failure scores at day 7 of follow-up, and lower blood pressure levels (Table 1). Furthermore, organ failure scores of patients with liver cirrhosis increased (*i.e.* the mean maximum increase of sequential organ failure assessment score in patients with liver cirrhosis compared to baseline was 3.2 points ($p = 0.01$) *vs.* 0.6 points ($p = 0.05$) in patients without liver cirrhosis), and 5 out of 11 patients with liver cirrhosis developed ACLF during influenza infection. A numerically higher proportion of patients with liver cirrhosis died from influenza (2 deaths, 18%), compared to patients with no underlying liver disease (1 death, 3%). Finally, the risk of developing secondary bacterial infections during influenza was significantly higher in patients with liver cirrhosis compared to patients without liver disease (82% *vs.* 24%, $p = 0.001$).

Collectively, our observations indicate that patients with liver cirrhosis are at high risk of a severe course of influenza including the development of organ failures, secondary infections, and death. Influenza vaccination should be offered more stringently in particular to patients with liver cirrhosis.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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Supplementary data
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