Infections increase the risk of decompensation and death in patients with early alcohol-related liver disease

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Table S1. Independent prognostic factors associated with death.

	Multivariable analysis aHR (95% CI)	p
Infection, yes	5.57 (3.03-10.23)	<0.001
Age	1.00 (0.98-1.03)	0.720
Gender	0.98 (0.55-1.77)	0.953
Kleiner fibrosis stage	1.40 (1.09-1.78)	0.008
MELD score	1.06 (0.94-1.21)	0.323

Table S2. 30-day mortality rates for infections according to baseline fibrosis stage and infection site.

	Fibrosis stage F0-2* (n = 366)		**Fibrosis stage F3-4*** (n = 93)	
Site of infection	**Infections**	**30-day mortality**	**Infections**	**30-day mortality**
All infections, n	182	20 (11%)	125	14 (11%)
Pulmonary, n	70 (38%)	12 (17%)	33 (26%)	5 (15%)
Urinary tract, n	29 (16%)	2 (7%)	28 (22%)	2 (7%)
Skin, n	23 (13%)	1 (4%)	4 (3%)	0
Sepsis, n	14 (8%)	3 (21%)	11 (9%)	4 (36%)
Gastrointestinal tract, n	11 (6%)	0	11 (9%)	1 (9%)
SBP, n	2 (1%)	1 (9%)	9 (7%)	2 (22%)
Other, n	24 (17%)	0	21 (17%)	0
Unknown, n	9 (1%)	1 (11%)	8 (6%)	0

Table S3. Independent prognostic factors associated with decompensation.

	Multivariable analysis aHR (95% CI)	p
Infection, yes	2.60 (1.18-5.73)	0.018
Age	0.98 (0.95-1.01)	0.234
Gender	0.90 (0.47-1.74)	0.762
Kleiner fibrosis stage	2.52 (1.91-3.34)	<0.001
MELD score	1.11 (0.95-1.30)	0.179

Table S4. Factors associated with developing severe infections assessed by univariable and multivariable competing risk regression analysis.

	Univariate analysis sHR (95% CI)	p-value	Multivariate analysis sHR (95% CI)	p-value
Age ≥50, yes	1.23 (0.74-2.04)	0.419	0.87 (0.47-1.62)	0.669
Gender, male	1.00 (0.62-1.60)	0.992	1.10 (0.67-1.80)	0.711
Alcohol overuse at baseline, yes	1.52 (0.98-2.35)	0.061	1.11 (0.66-1.84)	0.701
Alcohol overuse during follow-up, yes	**2.21 (1.31-3.71)**	**0.003**	**2.24 (1.19-4.21)**	**0.012**
Smoking ≥ 30 pack years	**1.87 (1.20-2.91)**	**0.005**	**1.87 (1.11-3.16)**	**0.019**
BMI≥30, yes	0.65 (0.39-1.07)	0.089	0.58 (0.29-1.16)	0.126
Type 2 diabetes	**1.81 (1.02-3.22)**	**0.042**	1.30 (0.57-2.96)	0.526
HOMA-IR≥2.5, yes	1.03 (0.68-1.56)	0.894	0.65 (0.39-1.08)	0.096
Leukocytes ≥ 8.8	1.31 (0.85-2.00)	0.218	1.36 (0.82-2.23)	0.233
CRP ≥ 6	1.21 (0.79-1.87)	0.381	0.99 (0.60-1.63)	0.977
MELD score ≥ 9	**2.68 (1.52-4.73)**	**0.001**	1.51 (0.74-3.06)	0.259
Transient elastography				
≤10 kPa	1	-	1	-
>10 - ≤15 kPa	**3.61 (1.89-6.93)**	**<0.001**	**2.29 (1.02-5.10)**	**0.044**
>15 kPa	**4.77 (2.96-7.69)**	**<0.001**	**2.84 (1.13-7.12)**	**0.026**
TE at follow-up	1	-	1	-
≤10 kPa				
>10 - ≤15 kPa	**3.50 (1.75-7.00**)	**<0.001**	1.89 (0.80-4.49)	0.148
>15 kPa	**4.35 (2.78-6.79)**	**<0.001**	1.75 (0.74-4.13)	0.201
Progression of TE during follow-up, yes	1.20 (0.75-1.92)	0.441	1.11 (0.61-2.01)	0.740

Table S5. Characteristics of patients with fibrosis stage F0-2 at baseline.

Fibrosis stage F0-2 (n = 366)		
	No infection N= 285	**Infection** N= 81
Patients with repeated TE during FU	217	81
Baseline TE (kPa) • ≥10 kPa • ≥15 kPa	5.5 (4.4-7.9) 33 (12%) 14 (5%)	6.8 (5.2-10.4) 23 (28%) 7 (9%)
Repeated TE (kPa) • ≥10 kPa • ≥15 kPa	5.3 (4.2-7.1) 18 (%) 20 (%)	6.5 (5.1-10.0) 12 (%) 13 (%)
Months between TE at baseline and follow up	37 (14-58)	43 (13-68)
Events during follow-up		
Decompensation	11 (4%)	7 (9%)
Death	13 (5%)	23 (28%)
Alcohol history		
Abstinent at inclusion	115 (40%)	31 (38%)
Duration of excess drinking (years)	16 (8-26)	16 (8-26)
Drinks in the week leading up to inclusion, for ongoing drinkers (units)	21 (8-30)	15 (7-35)
Evidence of excessive alcohol intake during follow-up	138 (48%)	64 (79%)
Summary data reported as median with IQR or counts with proportions.		

Table S6. Characteristics of infections stratified by baseline fibrosis stage.

	Fibrosis stage F0-2* (n = 366)	Fibrosis stage F3-4* (n = 93)
All infections	182	125
Severe infections	99 (54%)	82 (66%)
Patients with min. 1 infection	81 (22%)	51 (55%)
Site of infection		
Pulmonary, n	70 (38%)	33 (26%)
Urinary tract, n	29 (16%)	28 (22%)
Skin, n	23 (13%)	4 (3%)
Sepsis, n	14 (8%)	11 (9%)
Gastrointestinal tract, n	11 (6%)	11 (9%)
SBP, n	2 (1%)	9 (7%)
Other, n	24 (17%)	21 (17%)
Unknown, n	9 (1%)	8 (6%)
Type of infection		
Bacterial	62 (34%)	65 (52%)
Viral	7 (4%)	2 (2%)
Fungal	2 (1%)	4 (3%)
Unknown (not cultured)	120 (66%)	54 (43%)
Treatment		
No treatment	6 (3%)	2 (2%)
Intravenous treatment	96 (53%)	86 (69%)
Peroral treatment	79 (43%)	37 (30%)
Infection when hospitalized, yes	133 (73%)	108 (86%)

* Fibrosis stage is missing in 99 patients: we refrained from a biopsy in patients with TE<6 kPa (n=97) from 2016, 1 with an inconclusive biopsy, and 1 technically not possible. The two patients with no biopsy and TE >6 kPa developed a total of five infections, which is not reported in this table.
The group ‘Fibrosis stage F0-2’ includes biopsied patients with fibrosis stage F0-2 and patients with transient elastography <6 kPa.

STROBE Statement - Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract p. 5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract p. 5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction p. 8
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction p. 8-9
Methods			
Study design	4	Present key elements of study design early in the paper	'Study design' section p. 10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	'Patients' section p. 10 and 'Patients and infection characteristics' p. 15
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	'Patients' p. 10 and 'Follow-up data' p. 11-12
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	'Follow-up data' p. 11-12 and 'Infections' p. 12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	'Investigations' p. 10-11, 'Follow-up data' p. 11-12 and 'Infections' p. 12
Bias	9	Describe any efforts to address potential sources of bias	Not reported
Study size	10	Explain how the study size was arrived at	All consecutive patients with an available follow-up were used.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	'Statistical analysis' p. 13-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	'Statistical analysis' p. 13-14
		(*b*) Describe any methods used to examine subgroups and interactions	'Statistical analysis' p. 13-14
		(*c*) Explain how missing data were addressed	'Statistical analysis' p. 13-14
		(*d*) If applicable, explain how loss to follow-up was addressed	'Statistical analysis' p. 13-14
		(*e*) Describe any sensitivity analyses	'Statistical analysis' p. 13-14

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	'Patients and infection characteristics' p. 12
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Not reported
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	'Patients and infection characteristics' p. 15 and table 1
		(b) Indicate number of participants with missing data for each variable of interest	Reported when applicable in table 1, figure 3A+3B
		(c) Summarize follow-up time (e.g., average and total amount)	'Patients and infection characteristics' p. 15
Outcome data	15*	Report numbers of outcome events or summary measures over time	'Patients and infection characteristics' p. 15 and table 1+2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	'Predictors associated with development of infections' p. 17-18 and table 3 and supplementary table S4
		(*b*) Report category boundaries when continuous variables were categorized	Not reported
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not reported
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	'Predictors associated with development of infections' p. 17-18 and figure 1B+3A+3B and supplementary table S4
Discussion			
Key results	18	Summarize key results with reference to study objectives	Discussion p. 19-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion p. 22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion p. 19-23
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion p. 19-23
Other information			

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page p. 2

*Give information separately for exposed and unexposed groups.