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Terlipressin therapy is associated with increased risk of colonisation with multidrug-resistant bacteria in patients with decompensated cirrhosis

Marcus M. Mücke[1] | María Hernández-Tejero[2] | Wenyi Gu[1,3] | Michael Kuhn[4] | Malte Janz[1] | Marisa I. Keller[4] | Anthony Fullam[4] | Laura Altepeter[1] | Victoria T. Mücke[1] | Fabian Finkelmeier[1] | Katharina M. Schwarzkopf[1] | Carla Cremonese[1] | Peter-Merton Hunyady[1] | Myriam W. Heilani[1] | Frank Erhard Uschner[1,3] | Robert Schierwagen[1,3] | Maximilian J. Brol[1,3] | Julia Fischer[3] | Sabine Klein[1,3] | Kai-Henrik Peiffer[1,3] | Michael Hogardt[5,6] | Saeed Shoaie[7,8] | Minneke J. Coenraad[9] | Jörg Bojunga[1] | Vicente Arroyo[10] | Stefan Zeuzem[1] | Volkhard A. J. Kempf[5,6] | Christoph Welsch[1] | Wim Laleman[3,11] | Peer Bork[4] | Javier Fernandez[2,10] | Jonel Trebicka[1,3,10] | on behalf of MICROB-PREDICT and PREDICT Study Group of the EASL-CLIF Consortium

[1]Medical Clinic 1, University Hospital, Goethe-University Frankfurt, Frankfurt am Main, Germany

[2]Liver ICU, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS and CIBERehd, Barcelona, Spain

[3]Department of Internal Medicine B, Muenster University Clinic, University of Münster, Münster, Germany

[4]Structural and Computational Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany

[5]Institute of Medical Microbiology and Infection Control, Goethe University Frankfurt, Germany University Center for Infectious Diseases, University Hospital Frankfurt, Frankfurt, Germany

[6]University Center of Competence for Infection Control, State of Hesse, Germany

[7]Centre for Host-Microbiome Interactions, Dental Institute, King's College London, London, UK

[8]Science for Life Laboratory, KTH—Royal Institute of Technology, Stockholm, Sweden

[9]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

[10]European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain

[11]Department of Gastroenterology & Hepatology, Section of Liver and Biliopancreatic Disorders, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Correspondence
Jonel Trebicka, Medicine Clinic B, University Hospital Muenster, Albert-Schweitzer-Campus 1, A1, Muenster, Germany.
Email: jonel.trebicka@ukmuenster.de

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Summary

Background: Patients with cirrhosis are susceptible to develop bacterial infections that trigger acute decompensation (AD) and acute-on-chronic liver failure (ACLF). Infections with multidrug-resistant organisms (MDRO) are associated with deleterious outcome. MDRO colonisation frequently proceeds MDRO infections and antibiotic therapy has been associated with MDRO colonisation.

Marcus M. Mücke, María Hernández-Tejero, Javier Fernandez and Jonel Trebicka contributed equally to this study.

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Aim: The aim of the study was to assess the influence of non-antibiotic medication contributing to MDRO colonisation.

Methods: Three hundred twenty-four patients with AD and ACLF admitted to the ICU of Frankfurt University Hospital with MDRO screening were included. Regression models were performed to identify drugs associated with MDRO colonisation. Another cohort ($n=129$) from Barcelona was included to validate. A third multicentre cohort ($n=203$) with metagenomic sequencing data of stool was included to detect antibiotic resistance genes.

Results: A total of 97 patients (30%) were identified to have MDRO colonisation and 35 of them (11%) developed MDRO infection. Patients with MDRO colonisation had significantly higher risk of MDRO infection than those without ($p=0.0098$). Apart from antibiotic therapy (odds ratio (OR) 2.91, 95%-confidence interval (CI) 1.82–4.93, $p<0.0001$), terlipressin therapy in the previous 14 days was the only independent covariate associated with MDRO colonisation in both cohorts, the overall (OR 9.47, 95%-CI 2.96–30.23, $p<0.0001$) and after propensity score matching (OR 5.30, 95%-CI 1.22–23.03, $p=0.011$). In the second cohort, prior terlipressin therapy was a risk factor for MDRO colonisation (OR 2.49, 95% CI 0.911–6.823, $p=0.075$) and associated with risk of MDRO infection during follow-up ($p=0.017$). The validation cohort demonstrated that antibiotic inactivation genes were significantly associated with terlipressin administration ($p=0.001$).

Conclusions: Our study reports an increased risk of MDRO colonisation in patients with AD or ACLF, who recently received terlipressin therapy, while other commonly prescribed non-antibiotic co-medications had negligible influence. Future prospective trials are needed to confirm these results.

1 | INTRODUCTION

Patients with liver cirrhosis are at an increased risk of bacterial infections. Indeed, bacterial infection is the most often occurring precipitant of acute decompensation (AD) or (pre-) acute-on-chronic liver failure (ACLF), which is associated with dramatically high short and long-term mortality.[1–4] Patients with AD and ACLF with accompanying infections and those where infections trigger AD/ACLF, have been reported to have worse outcomes than patients without these conditions.[2,4] Infections with multidrug-resistant organisms (MDRO) in patients with liver disease have especially high mortality rates.[3,5,6]

Several prospectively conducted cohort studies have identified an increasing number of infections by MDRO in patients with liver cirrhosis who were hospitalised with AD or ACLF. In Europe, the prevalence of MDRO infections increased from 29% in 2011 to 38% in 2017–2018.[5] A similar study globally assessing MDRO prevalence among hospitalised patients with liver cirrhosis estimated that more than one third of all infections were caused by MDRO.[7] Therefore, early administration of broad-spectrum antibiotic therapy has been advocated in critically ill patients with liver cirrhosis and suspected infections, which could thus prevent ACLF and improve outcome, in line with current sepsis guidelines.[4,8–10]

MDRO colonisation is an established risk factor for MDRO infections and MDRO screenings have been implemented in critical care in the last decades.[11] Recently, general application of MDRO screening in patients with (decompensated) liver disease has been debated, as intestinal colonisation with resistant bacteria has been linked to important clinical outcomes, such as mortality, development of MDRO infections or failure of antibiotic prophylaxis to prevent spontaneous bacterial peritonitis (SBP).[12–14]

Several risk factors for MDRO colonisation and infections have been reported and used in daily clinical routine to identify susceptible patients. Recent antibiotic therapy, nosocomial/health care-associated infections, recent hospitalisation or recent intensive care unit (ICU) admission are known to be associated with an increased risk of MDRO infections. New data indicated that also non-antibiotic drugs may have a selective effect on the composition of the human gut microbiota (e.g., metformin), inducing antibiotic resistance and thereby promoting MDRO colonisation or selection.[15] Therefore, our study analysed, in an unbiased approach, the contribution of prior non-antibiotic drug administration to MDRO colonisation.

2 | PATIENTS AND METHODS

2.1 | Study design

In this retrospective study, consecutive adult patients with liver cirrhosis admitted to ICU at the Department of Internal Medicine I, University Hospital Frankfurt, Germany, from 2008 to 2018 were eligible for inclusion. For the identification of eligible candidates, the patient chart database of the University Hospital Frankfurt was systematically reviewed. Decompensated cirrhotic patients with AD or ACLF (diagnosed according to current guidelines[9]) and regular MDRO screening upon ICU admission with available data on medication intake were enrolled. All medications taken or administered during that the last 14 days prior ICU admission were evaluated. Medications were grouped according to their class for statistical reason based on the number of patients receiving the medication: The following pharmaceutical (sub)groups were assessed: (non)selective beta blockers, diuretics (loop diuretics, thiazides, antimineralcorticoids), statins, antihypertensive drugs (ACE inhibitors, calcium channel blockers, angiotensin II inhibitors), novel oral anticoagulants, antiplatelet therapy (mainly aspirin), opioids, nonsteroidal antirheumatic drugs, metamizole, antidiabetic drugs (insulins, metformin, inhibitors of dipeptidyl peptidase 4), l-thyroxine, uricosurics, neuroleptic drugs (no class differentiation), antidepressants (no class differentiation), inhalation medications (short/long acting beta-2 adrenergic agonists, short/long acting muscarinic antagonists), proton pump inhibitors (mainly pantoprazole), albumin, terlipressin and other vasopressors (including mainly noradrenalin, dobutamine and argipressin), lactulose and antibiotic therapy.

The diagnosis of cirrhosis was based on histology from liver biopsy (if available) or by a combination of clinical, imaging and laboratory findings.[9]

Patients were excluded if they were aged below 18 years, pregnant, had received solid organ transplantation or were receiving immunosuppressive therapy. The local ethics committee approved this study (no. 20-707). More details on initial data collection, microbiological studies, metagenomic analyses and definition of microbiological resistance can be found in the Methods S1.

Data from a second cohort of patients from Spain with liver cirrhosis and AD or ACLF were included. The cohort prospectively included all critically ill cirrhotic patients consecutively admitted to the liver abdominal ICU of the Hospital Clinic in Barcelona, Spain from October 2015 to September 2016. Details of comedications administered 14 days before the MDRO colonisation diagnosis during follow-up (if an event occurred, if not, those administered during the first 14 days of admission) were retrospectively collected and analysed. Features of the study population, initial study design and microbiological examinations can be found elsewhere.[16]

An external validation cohort of STOOL-PREDICT from the prospective multi-centre European PREDICT study with 203 decompensated cirrhosis patients was included. Stool samples were collected at inclusion and during hospitalisation. Details of the study can be found elsewhere.[3] An overview of the three different cohorts included in this study is depicted in Figure S1.

2.2 | Statistical analysis

For statistical analysis, BiAS, version 11.03 and SPSS, version 19, SAS 9.4 and R were used. Group differences were assessed by the Mann–Whitney *U*-test and Fisher's exact test for continuous or categorical variables, respectively. Univariable statistical analysis of the association between each baseline characteristic (demographics, medical history, treatments, etc.) and MDRO colonisation on the one hand and terlipressin administration on the other hand was carried out to assess potential confounders of the effects of terlipressin on colonisation. Odds ratio (OR) estimates (with 95% confidence intervals [CIs]) were obtained for each characteristic by fitting binary logistic regression (LR) models, and the selected potential confounders (significant in univariable analysis) were then used to adjust treatment effects in the final LR model. Multivariable LR analysis was performed to analyse factors associated with de novo MDRO colonisation and a $p \geq 0.05$ for removal from the model.

To account for factors possibly influencing MDRO colonisation and mortality, propensity score matching (1:3) of the Frankfurt cohort receiving terlipressin with patients not receiving terlipressin was performed adjusted for age, sex, MELD score, mechanical ventilation and prior antibiotic therapy.

For mortality outcome time-to-event was estimated with the Kaplan–Meier method and differences were compared with the log-rank test. Cumulative incidence function for death (competing for MDRO infections) were performed, and differences between curves were compared using Gray's test.

Two-sided *p*-values <0.05 were considered to be statistically significant.

To account for potential confounders in the analysis of relation between clinical factors and the fraction of genes for antibiotic inactivation, we checked the effect of a patient's MELD score, CLIF-AD score, concurrent antibiotic treatment, and whether they had been hospitalised in the previous 3 months, using type II ANOVA in the external validation cohort of STOOL-PREDICT.

3 | RESULTS

3.1 | Patient characteristics

In the Frankfurt cohort, 324 patients with liver cirrhosis hospitalised with AD or ACLF with valid MDRO screening and who matched the described inclusion criteria were included. Detailed patient characteristics are depicted in Table 1. Briefly, the majority of patients were male (69%) with a mean age of 60 years (range 29–91) and alcohol (42%) and viral hepatitis (28%) as the main causes of liver cirrhosis. ACLF was present in 42% of patients (mean CLIF-C ACLF score 44.0 ± 9.9) upon

TABLE 1 Patient characteristics of the overall cohort and the subgroup of patients with and without terlipressin therapy.

Characteristics	All patients ($n = 324$)	Patients with terlipressin therapy ($n = 24$)	Patients without terlipressin therapy ($n = 300$)	p-value
Age (years) mean (range)	60 (29–91)	59 (42–82)	61 (29–91)	0.373
Male sex, *n* (%)	224 (69.1)	18 (75.0)	206 (68.7)	0.648
MAP (mm Hg), mean (SD)	79.7 (15.7)	79.5 (15.4)	79.8 (15.8)	0.950
Aetiology of cirrhosis, *n* (%)				
Alcohol	137 (42.3)	12 (50.0)	125 (41.7)	0.521
Viral hepatitis	89 (27.5)	7 (29.2)	82 (27.3)	0.816
NAFLD	30 (9.3)	4 (16.7)	26 (8.7)	0.259
Cryptogenic	35 (10.8)	1 (4.2)	34 (11.3)	0.492
Other	33 (10.5)	0 (0)	33 (11.0)	0.151
Diabetes mellitus, *n* (%)	118 (36.4)	6 (25.0)	112 (37.3)	0.275
Acute-on-chronic liver failure				
ACLF present at admission, *n* (%)	137 (42.3)	11 (45.8)	126 (42.0)	0.831
CLIF OF score, mean (SD)	8.2 (±2.2)	8.4 (±2.2)	8.2 (±2.2)	0.463
CLIF-C ACLF score, mean (SD)	44.0 (±9.9)	44.5 (±10.2)	43.9 (±9.9)	0.854
Reason for ICU admission, *n* (%)				
Surgery	12 (3.7)	0 (0)	12 (4.0)	1.000
GI-bleeding	78 (24.1)	5 (20.8)	73 (24.3)	0.808
Infection	67 (20.7)	5 (20.8)	62 (20.7)	1.000
HRS[a]	74 (25.4)	14 (58.3)	60 (22.5)	<0.001
Other	162 (50.0)	14 (58.3)	148 (49.3)	0.525
Other vasopressors[a], *n* (%)	69 (23.7)	8 (33.3)	61 (22.8)	0.314
Noradrenaline	64 (22)	5 (20.8)	59 (22.1)	1.000
Vasopressin	8 (2.7)	2 (8.3)	6 (2.2)	0.134
Argipressin	6 (2.1)	2 (8.3)	4 (1.5)	0.080
Dobutamine	2 (0.7)	0 (0.0)	2 (0.7)	1.000
Risk factors for MDRO, *n* (%)				
Prior hospitalisation	248 (76.5)	21 (85.7)	227 (75.7)	0.221
Prior ICU admission	41 (12.7)	3 (12.5)	38 (12.7)	1.000
Prior systemic antibiotics	116 (35.8)	13 (54.2)	103 (34.3)	0.075
Norfloxacin prophylaxis	17 (5.2)	0 (0)	17 (5.7)	0.625
Prior MDRO infections	14 (4.3)	2 (8.3)	12 (4.0)	0.278
Laboratory results, mean (SD)				
MELD score	20 (±10)	21 (±10)	19 (±10)	0.290
Serum sodium (mmol/L)	135 (±7)	135 (±9)	135 (±7)	0.374
Bilirubin (mg/dL)	4.9 (±6.9)	5.5 (±8.4)	4.8 (±6.8)	0.621
Creatinine (mg/dL)	2.0 (±1.7)	2.4 (±2.2)	1.9 (±1.7)	0.166
International normalised ratio	1.8 (±1.4)	1.7 (±0.5)	1.8 (±1.5)	0.452
Albumin (g/dL)[b]	2.8 (±0.6)	3.2 (±0.5)	2.8 (±0.6)	0.028
Platelets (/nL)	120 (±77)	139 (±69)	118 (±78)	0.052
MDRO data upon ICU admission, *n* (%)				
Colonisation since initial screening	97 (29.9)	20 (83.3)	77 (25.7)	<0.0001
Infection during hospital stay	35 (10.8)	2 (8.3)	33 (11.0)	1.000
Outcome, transplant or death, *n* (%)				
30 days	89 (27.5)	7 (29.2)	82 (27.3)	0.816

TABLE 1 (Continued)

Characteristics	All patients ($n=324$)	Patients with terlipressin therapy ($n=24$)	Patients without terlipressin therapy ($n=300$)	p-value
90 days	122 (37.7)	12 (50.0)	110 (36.7)	0.198
365 days	149 (46.0)	14 (58.3)	135 (45.0)	0.287

Abbreviations: ACLF, acute-on-chronic liver failure; GI, gastrointestinal; HRS, hepatorenal syndrome; ICU, intensive care unit; MAP, mean arterial pressure; MDRO, multidrug-resistant organism; MELD, Model for End-Stage Liver Disease; NAFLD, non-alcoholic fatty liver disease.

[a]Data are missing in 33 patients.

[b]Data are missing in 39 patients.

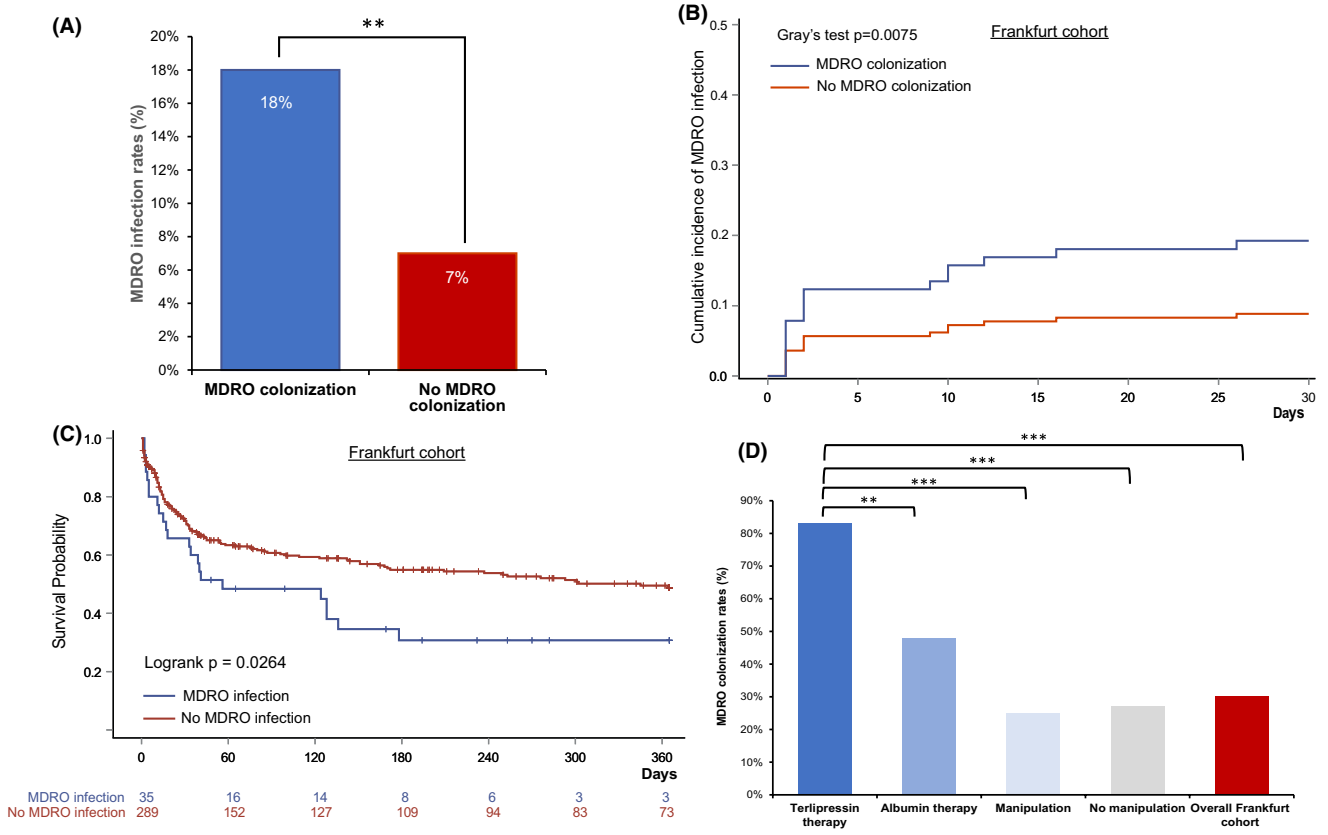

FIGURE 1 Clinical impact of MDRO colonisation. (A) MDRO infections rates during hospital stay, in patients with and without colonisation at screening; (B) cumulative incidence function for MDRO infections (death as competing risk) in the first 30 days, compared patients with and without MDRO colonisation. (C) Kaplan–Meier curve depicting survival of patients with and without MDRO infection. (D) Rate of MDRO colonisation in patients with different subgroups. Patients with previous terlipressin treatment had significantly higher rates than any other subgroup cohort or the overall cohort. Manipulation = group of patients with periodic interactions with HCW on a regular basis. $^{**}p=0.01$; $^{***}p<0.0001$. MDR, multidrug-resistant, MDRO multidrug-resistant organism.

ICU admission. 97 patients (30%) were identified with MDRO colonisation at ICU admission, and 35 patients (11%) developed MDRO infection during their hospital stay. Bacteria detected in rectal swabs upon ICU admission screening (colonisation) and from microbiological cultures during follow-up (infection) are depicted in Table S1. Patients with MDRO colonisation had a significantly higher risk of MDRO infections than patients without ($p=0.0098$, Figure 1A). Cumulative incidence for MDRO infections (death as competing risk) over time was significantly higher in patients with MDRO colonisation ($p=0.0075$, Gray's test, Figure 1B). Patients with MDRO infections had a significantly increased mortality compared to patients without MDRO infection ($p=0.026$, log-rank test, Figure 1C). MDRO risk factors in these patients included prior hospitalisation (76.5%), prior ICU admission (12.7%), prior systemic antibiotic therapy (35.8%) and MDRO infection in the last 3 months (4.3%). Overall mortality after 30, 90 and 365 days was 27.5%, 37.7% and 46.0%, respectively.

TABLE 2 Uni- and multivariable analysis of different medications impacting MDRO colonisation.

	Univariable analysis		Multivariable analysis	
All patients	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Serum creatinine	0.94 (0.83–1.08)	0.399		
HRS	2.17 (1.26–3.75)	0.005	1.62 (0.87–3.01)	0.131
MELD Score	0.99 (0.97–1.02)	0.671		
Accepted risk factors for MDRO				
Prior hospitalisations	2.17 (1.14–4.12)	0.017		
Systemic antibiotics	2.95 (1.79–4.85)	<0.0001	2.91 (1.82–4.93)	<0.0001
Medications				
Beta blockers	0.62 (0.38–1.00)	0.052		
Loop diuretics	0.64 (0.39–1.04)	0.073		
Thiazides	0.34 (0.10–1.17)	0.086		
Metamizole	2.61 (1.16–5.88)	0.021	2.09 (0.83–5.27)	0.120
Oral diabetics	0.43 (0.16–1.16)	0.095		
Antidepressants	1.38 (0.59–3.25)	0.461		
Opioids	2.00 (0.76–5.24)	0.161		
L-thyroxine	0.54 (0.28–1.03)	0.062		
Lactulose	1.91 (1.17–3.12)	0.009	1.47 (0.84–2.57)	0.179
Terlipressin	13.93 (3.58–42.3)	<0.0001	9.47 (2.96–30.23)	<0.0001
Other vasopressors	1.46 (0.83–2.55)	0.190		
Matched cohort				
Age	0.98 (0.94–1.02)	0.320		
MELD score	0.96 (0.92–1.01)	0.100		
Albumin therapy	0.18 (0.07–0.47)	<0.0001	1.69 (0.47–6.07)	0.418
HRS	3.56 (1.43–8.87)	0.006	2.38 (0.87–6.51)	0.091
Terlipressin therapy	10.0 (3.07–32.54)	<0.0001	5.30 (1.22–23.03)	0.026

Note: Serum creatinine (as a possible confounder for terlipressin therapy), MELD score (as possible confounder for severity of liver disease), age and medications significant in subgroup analyses were included into the model. Depicted are only medications with $p < 0.1$ in univariable analysis.

Abbreviations: CI, confidence interval; HRS, hepatorenal syndrome; MDRO, multidrug-resistant organism; MELD, model for end-stage liver disease.

3.2 | Factors impacting de novo MDRO colonisation

Next, we used uni- and multivariable LR model to identify risk factors for MDRO development in patient medications prior to de novo MDRO colonisation (Table 2 and Table S2). Interestingly, severity of liver disease (represented by MELD score) was not associated with de novo colonisation in this cohort ($p = 0.67$). Although HRS as an indication of terlipressin treatment, was significantly associated with risk of MDRO colonisation in the univariable model, it was not statistically significant in the multivariable model. As expected, prior antibiotic therapy was independently associated with de novo MDRO colonisation (OR 2.92, 95% CI 1.62–5.26, $p < 0.0001$). Of all remaining reviewed medication, terlipressin therapy in the last 14 days was the only other independent variable predicting de novo MDRO colonisation (OR 9.45, 95% CI 2.95–30.25, $p < 0.0001$). A second model was created for all patients with prior antibiotic therapy in the last 3 months and a third model for all patients without it (Table S3). Again, terlipressin was an independent predictor for de novo MDRO colonisation in both models (OR 8.07, $p = 0.015$ and OR 23.25, $p = 0.0001$).

3.3 | Investigating possible confounders of terlipressin therapy

Next, to identify possible confounders in the terlipressin group, we examined patients with and without terlipressin therapy in more detail (Table 1). Terlipressin was administered as bolus infusion (1 mg in 50 mL NaCl 0.9%) in the majority of patients ($n = 23$) to treat hepatorenal syndrome with a median dose of 4 mg/day and a median duration of 4 days (±3 days). In case of bleeding, the initial bolus was 2 mg. Interestingly, no differences were observed between groups except for a higher MDRO colonisation rate ($p < 0.0001$) and higher serum albumin levels upon ICU admission ($p = 0.028$) in the terlipressin group (the latter likely due to concomitant albumin treatment in case of hepatorenal syndrome).

As terlipressin was administered at the normal ward via bolus infusion every 4–6 h, inappropriate antimicrobial exposure (IAE) due to periodic interactions between patients and healthcare workers (HCW) on a regular basis could present another possible confounder. Therefore, further analysis investigating this phenomenon was performed (IAE due to HCW defined as periodic infusion therapy or subcutaneous injections several times/day). Additionally, patients with albumin monotherapy were compared to patients with terlipressin and albumin therapy to identify possible confounders due to albumin therapy.

Results are shown in Tables S4 and S5. In the albumin group, patients were comparable in all aspects except that they were older (63 years vs. 58 years, $p = 0.028$) and had lower rates of MDRO colonisation (48.5% vs. 85.7%, $p = 0.009$). When comparing patients with terlipressin to patients without terlipressin but with possible IAE due to periodic HCW exposure and patients without terlipressin and without possible IAE, again patients were comparable in all characteristics except for the following two aspects: rates of MDRO colonisation were higher in the terlipressin group ($p < 0.001$) and patients were older in the possible IAE group ($p < 0.001$). As subcutaneous insulin injections were considered as one possible IAE, more patients had NASH cirrhosis ($p = 0.023$) and diabetes mellitus ($p < 0.001$) and less had alcoholic cirrhosis ($p = 0.012$) in the group of patients without terlipressin but possible IAE.

Rates of MDRO colonisation in the different subgroups and the overall cohort are depicted in Figure 1D. Here, the terlipressin group had significantly higher MDRO colonisation rates than any other subgroup or the overall cohort.

To better adjust our calculation and to match for group differences, we performed propensity score matching for patients who received terlipressin and patients who did not in a 1:3 ratio, adjusting for severity of liver disease (MELD score), age, sex, mechanical ventilation (a higher rate was observed in the terlipressin group) and prior antibiotic therapy. All other risk factors for MDRO and all previous medications were well-distributed among both groups, except for administration of loop diuretics which were significantly more often used ($p < 0.001$) in the non-terlipressin group (in patients requiring terlipressin due to oesophageal bleeding or hepatorenal syndrome, loop diuretics are usually discontinued). Results from the two cohorts (terlipressin $n = 24$ with matched patients $n = 72$) are depicted in Table S6. When comparing all accountable factors in these two groups, again previous terlipressin therapy remained the only

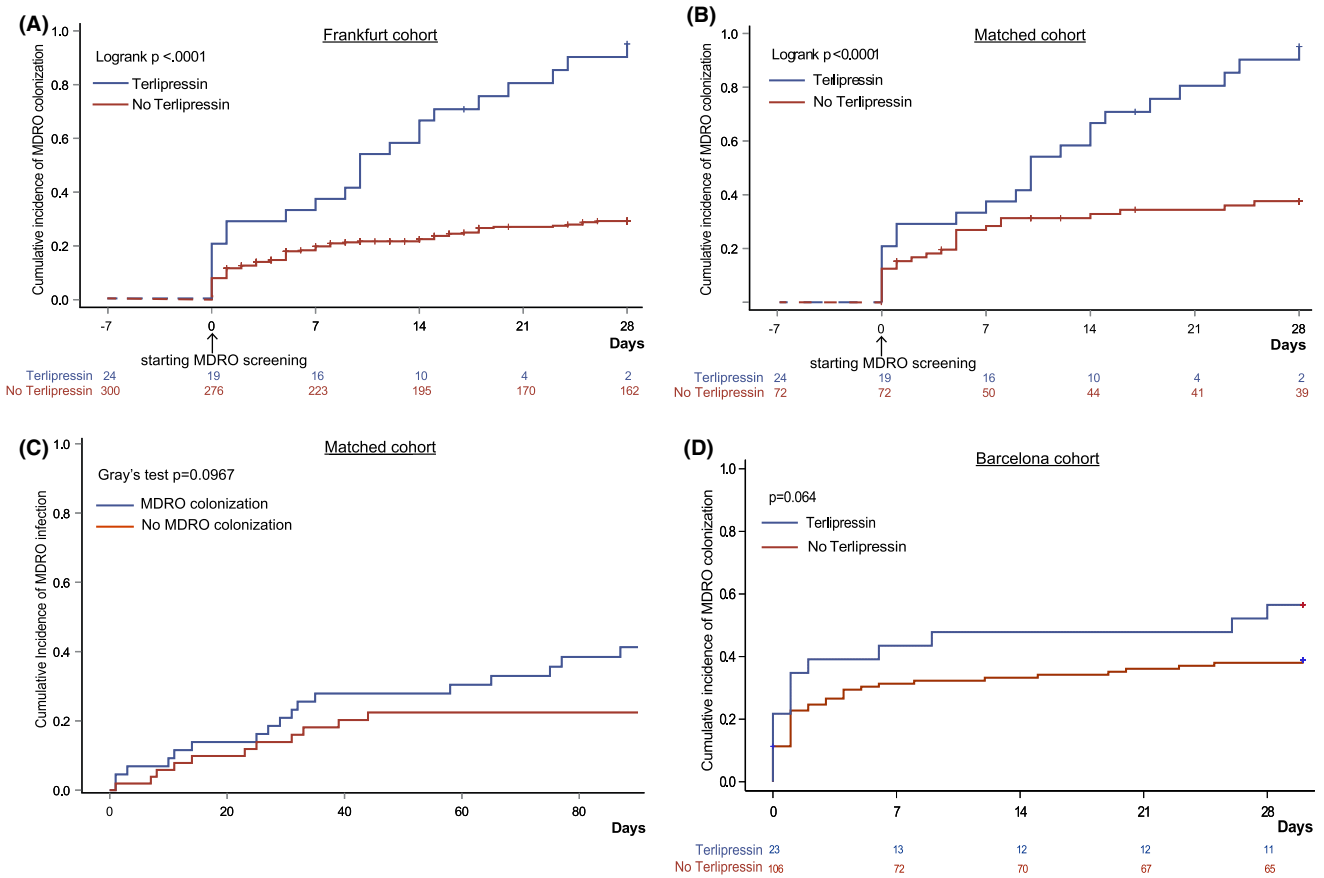

FIGURE 2 Incidence of MDRO colonisation in patients with and without prior terlipressin treatment in the (A) overall Frankfurt cohort and (B) matched cohort. MDRO screening started upon ICU admission, some patients were admitted to ICU at baseline. (C) Cumulative Incidence function of infection (death as competing risk) in the matched cohort in accordance with MDRO colonisation for 90 days (Frankfurt). (D) Cumulative incidence of MDRO colonisation during follow-up in patients with and without prior terlipressin treatment in the validation cohort. *p*-value was adjusted by MELD score and antibiotic treatment (Barcelona).

independent risk factor for MDRO colonisation at baseline (univariate analysis: OR 10.0, 95% CI 3.07–32.55, $p<0.0001$; multivariate analysis: OR 5.30, 95% CI 1.22–23.03, $p=0.011$). While the rate of MDRO detection was higher in the albumin cohort when comparing it with the non-matched overall cohort, in the matched cohort, albumin therapy was associated with a decreased risk for MDRO detection in univariate analysis (OR 0.18, 95% CI 0.07–0.47, $p<0.0001$) but not in multivariate analysis ($p=0.329$, Table 2).

Figure 2 depicts Kaplan–Meier incidence curves of MDRO colonisation between patients with and without terlipressin treatment for the overall cohort (A) and the matched cohort (B). Patients with prior terlipressin treatment had a significantly increased risk of MDRO colonisation up to baseline MDRO screening (overall cohort: HR 2.30, 95% CI 1.53–3.44, $p<0.0001$, 3A; matched cohort HR 2.97, 95% CI 1.69–5.23, $p<0.0001$, 3B). When considering the overall hospitalisation period, MDRO colonisation, again, was increased in the terlipressin group (overall cohort: HR 2.09, 95% CI 1.38–3.12, $p<0.0001$; matched cohort HR 2.44, 95% CI 1.46–4.08, $p<0.0001$).

Cumulative incidence function for MDRO infection (mortality as a competing risk) of the matched cohort according to MDRO colonisation is depicted in Figure 2C. Here, we observed a trend towards better survival in patients without MDRO colonisation, although significance was not reached in this cohort ($p=0.0967$ after 90 days, and $p=0.086$ after 180 days).

3.4 | Validation cohort

A cohort of 129 patients with liver cirrhosis and AD or ACLF admitted to the ICU from a previously published cohort was included to validate the results.[16] The data were retrospectively analysed for risk factors (in medications) that might impact MDRO colonisation. Details on patient characteristics can be found in Table S7. The majority of patients were male (72.1%) with a median age of 60 (range 51–68) years. The leading aetiology of cirrhosis was alcoholic liver disease (49%) followed by viral hepatitis (31%). ACLF was present in 41 patients upon admission with a mean CLIF-C-ACLF score of 54 (±14). Further details on the prevalence of rectal MDRO colonisation and type of recovered resistant MDRO have been published recently.[16]

Patients who received terlipressin prior to follow-up MDRO colonisation were comparable in terms of baseline features with the group of patients who did not receive terlipressin, including risk factors for MDRO colonisation, for example prior hospitalisation, prior ICU admission, prior systemic antibiotics or MDRO infections. Similarly, patients with prior terlipressin therapy had a higher rate of MDRO colonisation than patients without (22% vs. 14%), but without reaching statistical significance. However, a significantly higher risk of MDRO infection during the follow-up (26% vs. 9%; $p=0.017$) and an increased 1-, 3- and 12-months mortality (39%, 48% and 41% vs. 20%, 27% and 32%; $p=0.047$, 0.054 and 0.034, respectively) was revealed in the terlipressin group. These findings support the previously described non-significant trend towards a higher colonisation rate in the terlipressin group. Lack of statistical significance was likely due to the low number of patients treated with terlipressin in the cohort (only 18% of the patients received terlipressin).

After adjusting for the potential confounding factors selected in univariate analyses (Table 3), the multivariable LR model showed that administration of terlipressin was found to be associated with MDRO colonisation during follow-up. The corresponding OR estimate was 2.493 (95%-CI 0.911–6.823; $p=0.0754$), which was close to statistical significance. Other expected factors revealed to be associated with MDRO colonisation were MELD score and prior treatment with antibiotics for at least 5 days (Table 3).

When comparing patients who received albumin monotherapy with patients who underwent dual terlipressin and albumin treatment,

TABLE 3 Uni- and multivariable analysis for risk factors for MDRO colonisation (Barcelona cohort).

	Univariable analysis		Multivariable analysis[a]	
Variables	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Serum creatinine	1.05 (0.77–1.43)	0.781		
MELD score	1.04 (1.00–1.08)	0.074	1.05 (1.00–1.1)	**0.038**
Accepted risk factors for MDRO				
Prior hospitalisations	2.55 (1.23–5.26)	**0.012**		
Any previous systemic antibiotics	3.01 (1.45–6.26)	**0.003**		
Antibiotics >5 days				
Any antibiotic	4.00 (1.82–8.78)	**<0.001**	5.07 (2.17–11.88)	**<0.001**
Beta-lactams	0.383 (0.15–0.98)	**0.046**		
Albumin	0.630 (0.30–1.31)	0.214		
Terlipressin	2.061 (0.83–5.13)	0.120	2.49 (0.91–6.82)	**0.075**
Albumin + terlipressin	0.989 (0.35–2.80)	0.984		

[a]The multivariable LR model was fitted to estimate the effect of terlipressin administration on the follow-up colonisation adjusting by the potential confounders found in univariable analysis.

Abbreviations: CI, confidence interval; MDRO, multidrug-resistant organism; MELD, model for end-stage liver disease.

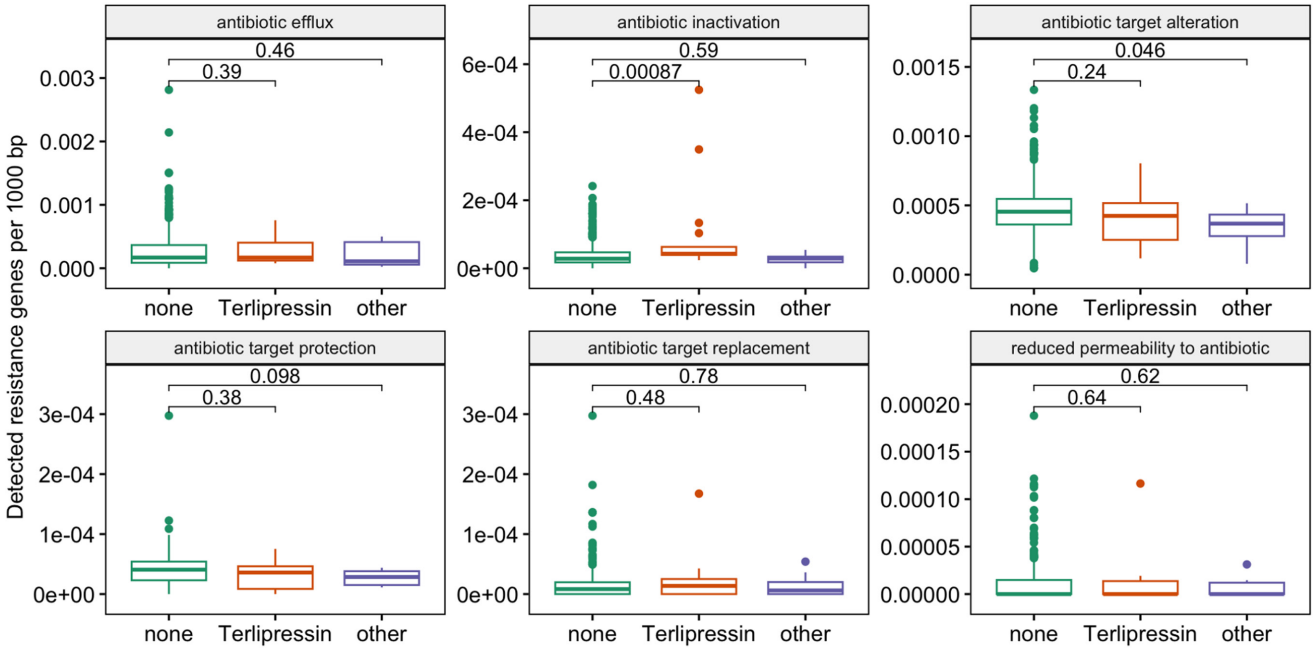

FIGURE 3 Fraction of antibiotic resistance genes per 1000 base pairs of metagenomic sequencing data in STOOL-PREDICT cohort. Samples are separated by vasopressor treatment (no treatment, terlipressin, or another vasopressor). Only antibiotic inactivation was strongly influenced by terlipressin treatment. *p*-values were calculated using Wilcoxon rank sum exact tests.

again, a higher rate of MDRO infection during follow-up in the terlipressin group (7% vs. 29%; $p=0.017$) could be observed (Table S8).

The incidence of MDRO colonisation during follow-up in the Barcelona cohort is depicted in Figure 2D. Here, it seems that administration of terlipressin has a potential impact on colonisation during follow-up ($p=0.064$).

3.5 | External validation

Of the 203 patients of the STOOL-PREDICT cohort, 16 received terlipressin, eight received another vasoconstrictor and 179 received neither. The number of samples was 17, 8, and 363, respectively. The baseline clinical characteristics are summarised in Table S9. Patients were mainly male (70%) with a mean age of 59. Three quarters of the patients presented with alcohol-related liver cirrhosis. However, no significant differences were found between patients with terlipressin or without terlipressin regarding aetiology, decompensation or disease severity. Only 5% of patients had MDRO infection during hospital stay.

Interestingly, of the six different resistance mechanisms in the metagenomics sequencing data analyses of the antibiotic resistance genes, antibiotic inactivation showed a significant increase between samples from patients with terlipressin administered compared to patients ($p=0.00087$; Figure 3).

In the following, we focus only on antibiotic inactivation. To account for potential confounders, we assessed the effect of the patient's MELD score, CLIF-AD score, concurrent antibiotic treatment, and whether they had been hospitalised in the previous 3 months. Of these, the CLIF-AD score and concurrent antibiotic treatment were not significant. In a combined model of terlipressin treatment, the MELD score and prior hospitalisations, terlipressin treatment was the most significant factor ($p<0.0001$; Table 4).

In 10 patients, samples taken prior to terlipressin and during terlipressin were available. While the median increase in the fraction of antibiotic inactivation genes was 83%, the Wilcoxon matched-pairs signed-rank revealed no significant difference ($p=0.28$). In seven patients, samples taken during and after terlipressin treatment were available (median follow-up time 29 days). In that time, the fraction decreased slightly by 9% ($p=0.69$).

4 | DISCUSSION

In our retrospective study, we observed a significantly increased risk for MDRO colonisation in patients who had received terlipressin therapy. Importantly, apart from administration of antibiotics, terlipressin was the only independent risk factor among all other drugs administered in the preceding time period. Similar results were obtained when a propensity score matched cohort and a second external validation cohort were analysed. Finally, we could confirm the same results in an external multi-centre cohort, and in addition, elucidate the mechanism, namely an increase of inaction genes for antibiotics in the microbiome in these patients.

Infections by MDRO constitutes a present and growing problem in patients with liver cirrhosis. Two independent large-scale studies, one conducted in Europe, the other globally, reported that one third of culture-positive infections in patients with liver cirrhosis are

Terlipressin	MELD score	CLIF-C AD score	Antibiotic treatment	Any hospitalisation previous 3 months
1.6e-07	–	–	–	–
–	2.7e-05	–	–	–
–	–	0.97	-	–
–	–	–	0.7	–
–	–	–	–	0.008
9.6e-07	0.00061	–	–	–
1.6e-05	0.047	–	–	0.087

TABLE 4 Type II ANOVA *p*-values for the relation between clinical factors and the fraction of genes for antibiotic inactivation.

Abbreviations: CLIF-C AD, CLIF consortium acute decompensation; MELD, model for end-stage liver disease.

caused by MDRO.[5,7] An increased mortality was reported in patients with MDRO infections in these cohorts and in our study. Recently, we showed that patients with known MDRO colonisation or infection were more likely to experience prophylaxis failure when taking quinolone antibiotics to prevent SBP.[12] Additionally, a reduced efficacy of norfloxacin to prevent SBP was observed in recent decades.[17] In a Spanish cohort of decompensated cirrhotic patients who were admitted and weekly screened for MDRO colonisation, Hernandez-Tejero and colleagues reported MDRO colonisation to be an independent risk factor for MDRO infection during hospitalisation. Importantly, these patients were significantly more often infected by the same MDRO that colonised them.[14] Similarly, MDRO infections occurred significantly more often in our cohort in patients previously identified as 'MDRO carriers'.

As expected, prior systemic antibiotic use was independently associated with MDRO colonisation in both cohorts. However, the use of norfloxacin prophylaxis was not associated with increased MDRO colonisation.

Interestingly, the use of non-antibiotic drugs may also have an impact on the development of MDRO colonisation, as shown by the increased risk in hospitalised patients. Vila et al. investigated the impact of commonly used drugs on the composition and metabolic function of the gut microbiota, observing that 19 out of 41 studied drugs could be linked to changes in microbial feature. Proton pump inhibitors, metformin and laxatives—besides antibiotics—showed the strongest associations when controlling for multiple medications.[18] In our overall cohort, metformin, lactulose, beta blockers and metamizole showed a trend in univariate analysis, while not independently associated with MDRO colonisation in multivariate analysis. Interestingly, disease severity—represented by the MELD score—was not associated with increased MDRO colonisation in both the overall cohort and the propensity score matched cohort. However, in the validation cohort, the MELD score was associated with MDRO colonisation, but as in the derivation cohort, patients with prior terlipressin therapy had a higher rate of MDRO colonisation than patients without and a significantly higher risk of MDRO infection during follow-up.

While we are unable to provide a mechanistic explanation for the influence of terlipressin on MDRO colonisation in this study, we could rule out several confounders. Terlipressin was administered as bolus infusion on the ward. Despite a numerical trend towards a higher rate of MDRO colonisation in the albumin cohort compared with the overall cohort, this effect was not seen in the validation cohort and in the propensity score matched group, albumin therapy was in fact associated with a decreased risk of MDRO colonisation in univariate analysis. A similar trend was seen in the validation cohort. Whether this is due to a protective effect of albumin remains speculative.

IAE due to periodic interactions between patients and HCWs on a regular basis could present another possible confounder as terlipressin was administered at least four times daily. However, we could not observe an increased risk in patients with increased contact to HCWs for other therapies than terlipressin (e.g., insulin, heparin). Moreover, the number of MRSA colonisation or *Clostridioides difficile* infections remained comparable in both groups as a marker of our effective mandatory hygiene infection control protocols.

Terlipressin is a prohormone of lysine vasopressin which is cleaved by endothelial peptidases resulting in a prolonged release of lysine vasopressin. It has affinity for V1 and V2 receptors causing splanchnic and extrarenal vasoconstriction via V1 receptors.[16,17] If no other mechanism of MDRO selection can be identified, one could speculate that splanchnic vasoconstriction may lead to an altered (possibly hypoxic) intestinal milieu which then results in the alteration of gut microbiota and the selections of MDRO. Another possible explanation is that terlipressin is directly responsible for inducing—due to yet unknown mechanisms—resistance in gram-negative bacteria that were formerly non-MDRO. However, this has not been described in the literature to date and could not be investigated in this study due to its retrospective design. Nevertheless, we could confirm our results in a third external validation cohort from a multi-centre prospective study. The results from the metagenomic sequencing data showed that a potential mechanism of terlipressin induces antibiotic inactive genes of the microbiome in the patients, which was independent from the severity of disease and antibiotics treatment.

Interestingly, while MDRO infection was associated with increased mortality, MDRO colonisation was not. This might be explained by the fact that not all patients with MDRO colonisation later develop infections. An alternative and complementary explanation would be that, since the study population was regularly screened for MDRO, the treating physicians conducted a guided antibiotic treatment covering colonising germs when needed.

A major limitation of our study is its retrospective design and that only a minority of study patients received terlipressin (10.4% of patients). Data were retrieved from clinical charts and only patients with complete lists of all prior medication intake were included. Additionally, as routine screenings for MDRO were performed systematically at ICU admission, there is, to some extent, a risk of selection bias as not all patients with decompensated liver disease were included in this analysis. It has to be emphasised that because of these limitations there still exists a relevant possibility of confounding (besides our attempts to compensate for this), especially with regards to the disease severity of patients: Despite matching, sicker patients may have been more likely to have received terlipressin and are at higher risk of MDRO colonisation and infection. The low cohort size receiving terlipressin and the retrospective design makes it particularly difficult to draw strong conclusion. Nevertheless, this is the first large-scale study assessing risks of non-antibiotic medication influencing MDRO colonisation, not only at baseline, but also during follow-up. Future prospective trials are needed to further investigate the observed phenomenon.

In conclusion, our study reports an increased risk of colonisation with MDRO in patients with AD or ACLF admitted to the ICU who had recently received terlipressin therapy. Other commonly prescribed comedication—besides antibiotic therapy—were not associated with MDRO colonisation. Patients with MDRO colonisation were more likely to develop MDRO infections which were associated with increased mortality. Our study suggests that close MDRO monitoring may be even more important in patients with AD or ACLF who receive terlipressin. Future prospective trials need to confirm our results and then adapting antibiotic treatment may be warranted in these patients.

AUTHOR CONTRIBUTIONS

Wenyi Gu: Methodology; software; data curation; investigation; validation; formal analysis; visualization; writing – review and editing. **Marcus M. Mücke:** Methodology; software; data curation; conceptualization; investigation; validation; formal analysis; supervision; visualization; project administration; resources; writing – original draft; writing – review and editing. **María Hernández-Tejero:** Methodology; software; data curation; investigation; validation; visualization; writing – original draft; writing – review and editing. **Michael Kuhn:** Methodology; software; validation; formal analysis; visualization. **Malte Janz:** Methodology; data curation. **Marisa I. Keller:** Methodology; validation; formal analysis. **Anthony Fullam:** Methodology; validation; formal analysis. **Laura Altepeter:** Data curation. **Victoria T. Mücke:** Data curation. **Fabian Finkelmeier:** Data curation. **Katharina M. Schwarzkopf:** Data curation. **Carla Cremonese:** Data curation. **Peter-Merton Hunyady:** Data curation. **Myriam W. Heilani:** Data curation. **Frank Erhard Uschner:** Data curation. **Robert Schierwagen:** Data curation; investigation. **Maximilian J. Brol:** Data curation. **Julia Fischer:** Writing – review and editing. **Sabine Klein:** Data curation. **Kai-Henrik Peiffer:** Data curation; methodology. **Michael Hogardt:** Data curation. **Saeed Shoaie:** Writing – review and editing. **Minneke J. Coenraad:** Writing – review and editing. **Jörg Bojunga:** Data curation. **Vicente Arroyo:** Investigation; supervision. **Stefan Zeuzem:** Data curation. **Volkhard A. J. Kempf:** Data curation; writing – review and editing. **Christoph Welsch:** Data curation. **Wim Laleman:** Data curation; writing – review and editing. **Peer Bork:** Investigation; validation; supervision. **Javier Fernandez:** Data curation; supervision; methodology; conceptualization; investigation; validation; funding acquisition; project administration; writing – original draft; writing – review and editing. **Jonel Trebicka:** Conceptualization; methodology; data curation; supervision; validation; investigation; funding acquisition; project administration; resources; writing – original draft; writing – review and editing.

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AUTHORSHIP

Guarantor of the article: Marcus M. Mücke.

ORCID

Fabian Finkelmeier https://orcid.org/0000-0001-8559-9910

Jonel Trebicka https://orcid.org/0000-0002-7028-3881

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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