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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Prediction models for carbapenem-resistant *Enterobacterales* carriage at liver transplantation: A multicenter retrospective study

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Abstract

Background: Carbapenem-resistant *Enterobacterales* (CRE) colonisation at liver transplantation (LT) increases the risk of CRE infection after LT, which impacts on recipients' survival. Colonization status usually becomes evident only near LT. Thus, predictive models can be useful to guide antibiotic prophylaxis in endemic centres.

Aims: This study aimed to identify risk factors for CRE colonisation at LT in order to build a predictive model.

Methods: Retrospective multicentre study including consecutive adult patients who underwent LT, from 2010 to 2019, at two large teaching hospitals. We excluded

patients who had CRE infections within 90 days before LT. CRE screening was performed in all patients on the day of LT. Exposure variables were considered within 90 days before LT and included cirrhosis complications, underlying disease, time on the waiting list, MELD and CLIF-SOFA scores, antibiotic use, intensive care unit and hospital stay, and infections. A machine learning model was trained to detect the probability of a patient being colonized with CRE at LT.

Results: A total of 1544 patients were analyzed, 116 (7.5%) patients were colonized by CRE at LT. The median time from CRE isolation to LT was 5 days. Use of antibiotics, hepato-renal syndrome, worst CLIF sofa score, and use of beta-lactam/beta-lactamase inhibitor increased the probability of a patient having pre-LT CRE. The proposed algorithm had a sensitivity of 66% and a specificity of 83% with a negative predictive value of 97%.

Conclusions: We created a model able to predict CRE colonization at LT based on easy-to-obtain features that could guide antibiotic prophylaxis

KEYWORDS
carbapenem-resistance, CLIF-SOFA score, machine learning, peritonitis prophylaxis, prediction model

1 | INTRODUCTION

Carbapenem-resistant *Enterobacterales* (CRE) is an emerging multidrug-resistant microorganism (MDRO) and has become a public health threat due to its worldwide dissemination and few available therapeutic options. Liver transplant (LT) recipients are at increased risk for CRE infections, and a high associated mortality rate has been described in this population. [1–3]

Among LT patients, the CRE infection incidence range from 2% to 26%, and pre-LT colonization is associated with a high risk for CRE infection after LT.[4,5] It has been estimated that about 37% of CRE colonized patients before LT will present a CRE infection after transplantation.[6,7]

A previous multicentric study described that 24% of LT recipients colonized by CRE acquired this MDRO before LT. Those patients had a higher incidence of severe presentation of CRE infection after LT and more frequently developed septic shock compared to patients who acquired CRE after LT. [8]

Therefore, the knowledge of CRE colonization status before LT is essential for the implementation of strategies that mitigate the risk of CRE infection after LT. However, the identification of CRE colonisation occurs usually closer to LT; a study that included 203 patients colonized by CRE pre-LT reported that the median time from CRE detection to LT was 6 days. CRE is commonly identified by surveillance cultures collected at the moment of LT, and the results are available only after transplantation.[8]

Therefore, a score able to identify patients with a high probability of being colonised by CRE at the moment of LT based on basic epidemiological information would be very useful for guiding prevention strategies in this high-risk population, such as adjustments in surgical prophylaxis.

The aims of this study are to analyze the risk factors for CRE colonization pre-LT and propose a risk score for pre-LT CRE colonization considering clinical and epidemiological information that can be applied immediately before LT.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a retrospective multicentric study including all consecutive adult patients that underwent LT, from 2010 to 2019, at two university hospitals in Brazil and Italy. All patients were followed from 90 days before LT until one year after the procedure. We excluded patients with CRE infection diagnosis within 90 days before LT. Infections in patients on the waiting list were identified through prospective active surveillance during the hospital stay. The criteria used to identify and classify infections were those outlined by the US National Healthcare Safety Network. [9]

Other data sources were clinical charts and hospital electronic records that were de-identified before entry into a standardized electronic case report form. Collected data were checked for accuracy, and queries for incongruent or missing data were submitted to investigators to ensure high quality and completeness. The study was first approved by the institutional review board (IRB) of the promoting center (n. 155/2019/Oss/AOUBo on March 20, 2019) and after that by the IRB of all participating centers.

2.2 | Setting

Two hospitals participated in the study; S. Orsola-Malpighi Hospital is a 1420-bed tertiary care University Hospital in Bologna (Northern Italy) with an average of 72 000 admissions per year and an active LT program, performing an average of 90 procedures per year. Hospital das Clinicas da Universidade de São Paulo is a 2400-bed university hospital with an average of 86 000 admissions per year and 100 LT performed per year during the study period. Both centers performed systematic screening of CRE carriage by rectal swab at inclusion in the waiting list, at LT, and weekly after LT until hospital discharge. Screening for CRE colonization at other sites was performed according to clinical judgment and local policy.

2.3 | Variables and definitions

The endpoint variable was CRE colonization at the time of LT, defined as any positive culture for CRE within the 30 days before LT.

The exposure variables were recorded within 90 days before LT and included age, aetiology of end-stage liver disease, presence of hepatocellular carcinoma, human immunodeficiency virus (HIV) infection, Charlson score, MELD score at waiting list inclusion and at transplantation, waiting time for liver transplant and transplantation type (combined or not); cirrhosis complications in the 90 days before LT as intensive care unit (ICU) admission, chronic liver failure sequential organ failure assessment (CLIF-SOFA) determination, acute on chronic liver failure (ACLF) occurrence, gastrointestinal bleeding, encephalopathy grades III or IV, hepatorenal syndrome, bacterial infection, infection by MDRO (see definition below), invasive Candida spp infection, *Clostridium difficile* infection and length of hospital stay before LT; antibiotic use to treat infections or prophylaxis for spontaneous bacterial peritonitis (SBP). Prophylaxis for SBP was indicated for 7 days during acute gastrointestinal bleeding and for long-term use in patients with a prior episode of SBP and patients with an ascitic fluid total protein less than 1.5g/dl with Child-Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, with either impaired renal function or hyponatremia, according to EASL and AASLD guidelines.[10]

ACLF was defined as decompensation of chronic liver disease or cirrhosis associated with extrahepatic organ failure, with acute and severe hepatic abnormalities resulting from different types of insults, according to EASL-CLIF definition.[11] The definitions of MDRO for clinical cultures were in accordance with the criteria established by the Center for Disease Control and Prevention and the European Centre for Disease Prevention and Control.[12]

2.4 | Microbiology

All CREs were initially identified and had their susceptibility pattern defined by an automated susceptibility testing system (VITEK or MALDI-TOF MS; bioMérieux, Marcy l'Étoile, France). Minimum inhibitory concentrations were interpreted according to the Clinical and Laboratory Standards Institute and EUCAST breakpoints. All carbapenem minimum inhibitory concentrations (MICs) were reviewed and reclassified according to the current breakpoints.[13,14]

2.5 | Statistical analysis

The sample size required for the clinical prediction was estimated using the Fleiss's Method. Considering an estimated prevalence of 7% of CRE colonisation before LT and an incidence in the high-risk group of 15%; we predicted that a total of 1150 patients would achieve a power of 90% and a two-sided confidence level of 95%.

2.6 | Missing data

A complete-case analysis was performed.

2.6.1 | Prediction score based on logistic regression

Continuous variables were transformed into dichotomous variables through cluster analysis, the ones with the lowest *p*-values being included in the analysis. In the statistical analysis, we used the chi-square test or Fisher's exact test, as indicated, for dichotomous variables, whereas the Mann–Whitney test was used for continuous variables. Variables showing a value of $p < .2$ in univariate analysis were included in a multivariate analysis performed by stepwise logistic regression. Variables that then reduced the −2 log-likelihood or showed a value of $p < .05$ were retained in the model. Multicollinearity was tested through the variance inflation factor. The regression coefficients of the final model were rescaled by dividing by the smallest final model coefficient and rounding considering multiples of 0.5. Patient scores were calculated by summing their respective points (risk score model). The risk score model discrimination was assessed with receiver operating characteristic (ROC) curves with the respective C statistics. The Hosmer-Lemeshow goodness-of-fit tests were used for the risk score model and logistic regression calibration. Data were processed and analyzed with the program R (http://www.R-project.org/).

2.6.2 | Prediction score based on machine learning algorithms

We tested the predictive performance of six popular machine learning algorithms: Catboost Classifier, Extra Trees Classifier, Gradient Boosting Classifier, K Nearest Neighbour, Light Gradient Boosting, and Random Forest [15–18]. Patients were randomly divided into 70% for training the algorithms and 30% for testing their predictive performance in new data. Due to the unbalanced nature of the outcome,

TABLE 1 Characteristics of the 1544 patients submitted to liver transplantation from January 2010 to December 2019

Variables	Number	Proportion
Male gender *N*	795	51.5%
Age in years (median, min-max)	54	12–76
Charlson score (median, min-max)	5	1–13
Cause of end-stage liver disease		
– Viral hepatitis	746	48.3%
– Alcoholic liver disease	372	24.1%
– Cholestatic diseases	127	8.2%
– Nonalcoholic Steatohepatitis	109	7.1%
– Fulminate hepatitis	105	6.8%
– Cryptogenic cirrhosis	83	5.4%
– Autoimmune hepatitis	53	3.4%
– Others	114	7.4%
Hepatocellular carcinoma	656	42.5%
Time on the waiting list in days (median, min-max)	178	0–4560
CLIF-SOFA before LT (median, min-max)	5	0-19
Bacterial infection within 90 days prior to LT	396	25.6%
SBP prophylaxis	493	31.9%
Meld score at LT	19	5–40
Length of hospital stay before LT in days (median, min-max)	1	0–289
Combined transplantation	66	4.3%

Abbreviations: LT, liver transplantation; SBP, spontaneous bacterial peritonitis.

we applied the Smoteenn balancing technique to the training set. [19] The optimization of the hyperparameters of the model was performed through cross-validation with 10 folds using Bayesian optimization (HyperOpt) for optimizing the area under the ROC curve (AUC).[20]

Model selection was made by analyzing the performance of the AUC. The performance of each model, always calculated on the test set, was also measured using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1 score. We also calculated the Shapley Value, which presents the contribution of each variable to the final predictive model. Density graphs were also added to visualize class discrimination. For the final analysis, we removed dichotomous variables with a positive value lower than 10%. All analyses were performed using the Python programming language, mostly the pandas and scikit-learn libraries. This study follows the Transparent Reporting of a multivariable prediction model for individual prognosis or diagnosis guide.[21]

3 | RESULTS

A total of 1582 patients underwent LT during the study period. Thirty-eight (2.4%) were excluded due to the occurrence of CRE infection up to 90 days before LT; therefore, 1544 patients were included in the study, 703 from the Italian centre (centre A) and 841 from the Brazilian centre (centre B) (Table 1).

The median age was 54 years (range from 12 to 76), and the most common aetiology of end-stage liver disease was viral hepatitis, 581 (37.6%) due to HCV, 152 (9.8%) due to HBV, and 13 (0.8%) due to HCV-HBV coinfection. Almost half of the patients (42.5%) had an hepatocellular carcinoma (HCC) diagnosis.

Two hundred thirty (14.9%) patients required ICU hospitalization before LT, 388 (25.1%) patients had ACLF within 90 days of LT, and the median CLIF-SOFA score was 5 (0–19). Infection within 90 days before LT occurred in 402 (26.0%) patients; 105 (26.1%) had more than one infection episode, 85 (21.1%) had an infection by MDRO other than CRE, and 19 (4.7%) had an invasive *Candida sp*. infection (Table 1).

CRE colonization was identified in 116 (7.5%) LT recipients, 43 (6.1%) in centre A and 73 (8.6%) in centre B. The median time from first CRE isolation to LT was 5 days (0-919).

The variables included in the final model of risk factors for CRE colonization at the time of LT were therapeutic antibiotic use within 90-days prior to LT ($p = .001$), carbapenem use within 90-days prior to LT ($p = .009$), infection in the previous 90-days of LT ($p = .04$), gastrointestinal bleeding ($p = .06$), worse CLIF-SOFA score ($p = .006$), fulminant hepatitis ($p = .13$), and prophylaxis for SBP ($p = .04$) (Tables 2 and 3). A risk score was created ranging from −4 to 21.5 with an AUC was 0.80 (CI 95% 0.78–0.82). Score ≥ 8 has a sensitivity of 77% and a specificity of 72% to estimate the risk of CRE colonization at the moment of LT (Figure 1) (Table 4). A sensitivity analysis was performed analysing only the patients whose CRE was identified 7 days before,

TABLE 2 Risk factors analysis for colonization by carbapenem-resistant Enterobacterales (CRE) at liver transplantation procedure

Variable	CRE colonisation at LT (*N* = 116)	Non-CRE colonisation at LT (*N* = 1428)	RR (CI95%)	*p*-Value
Age in years	54 (19–69)	55 (12–76)	-	.161
Female gender	52 (44.8%)	697 (48.8%)	0.99 (0.96–1.02)	.41
Baseline disease				
Cholestatic disease	13 (11.2%)	114 (8.0%)	1.03 (0.97–1.10)	.22
Autoimmune hepatitis	6 (5.2%)	47 (3.3%)	1.04 (0.95–1.15)	.29
Non-alcoholic steatohepatitis	9 (7.8%)	100 (7.0%)	1.01 (0.95–1.07)	.76
Alcoholic liver disease	29(25.0%)	343 (24.0%)	1.00 (0.97–1.04)	.81
Viral hepatitis	41 (35.3%)	705 (49.4%)	0.96 (0.93–0.99)	.004
Fulminant hepatitis	6 (5.2%)	99 (6.9%)	0.98 (0.93–1.03)	.47
Hepatocellular carcinoma	29 (25.0%)	627 (43.9%)	0.94 (0.92–0,97)	<.001
HIV infection	1 (0.9%)	12 (0.8%)	1.00 (0.86–1.17)	>.99
Meld at waiting list inclusion	18 (7-43)	15 (6-51)	-	<.001
Length of time on the waiting list	96 (1-1946)	180 (0-4560)	-	.01
ACLF before LT	58 (50.0%)	330 (23.1%)	1.12 (1.07–1.17)	<.001
ICU admission before LT	40 (34.5%)	190 (13.3%)	1.14 (1.07–1.21)	<.001
CLIF-SOFA score				
0–3	12 (10.3%)	477 (33.4%)		<.001
4–7	31 (26.7%)	540 (37.8%)		
8–12	52 (44.8%)	325 (22.8%)		
>12	21 (18.1%)	86 (6.0%)		
Grade III or IV ascites	63 (54.3%)	512 (35.9%)	1.06 (1.03–1.10)	<.001
Hepatorenal syndrome	52 (44.8%)	257 (18.0%)	1.14 (1.08–1.20)	<.001
Gastrointestinal bleeding	31 (26.7%)	124 (8.7%)	1.17 (1.08–1.27)	<.001
Grade III or IV hepatic encephalopathy	46 (39.7%)	323 (22.6%)	1.07 (1.03–1.12)	<.001
Infection in the 90 days before LT	74 (63.8%)	328 (23.0%)	1.18 (1.13–1.24)	<.001

(Continues)

TABLE 2 (Continued)

Variable	CRE colonisation at LT (*N* = 116)	Non-CRE colonisation at LT (*N* = 1428)	RR (CI95%)	*p*-Value
Number of bacterial Infection within 90 days before LT				<.001
0	42 (36.2%)	1100 (77.0%)		
1	46 (39.7%)	251 (17.6%)		
2	23 (19.8%)	61 (4.3%)		
3	5 (4.3%)	11 (0.8%)		
4	0	5 (0.4%)		
Invasive *Candida spp.* infection	2 (1.7%)	17 (1.2%)	1.03 (0.89–1.21)	.65
Other MDRO infection	21 (18.1%)	64 (4.5%)	1.24 (1.10–1.40)	<.001
Clostridium difficile infection	2 (1.7%)	5 (0.4%)	1.30 (0.81–2.07)	.09
Previous therapeutic antibiotic use	94 (81.0%)	542 (38.0%)	1.15 (1.11–1.19)	<.001
Previous β-lactam or β-lactamase inhibitor use	44 (37.9%)	242 (16.9%)	1.11 (1.06–1.17)	<0.001
Previous fluoroquinolone use	22 (19.0%)	129 (9.0%)	1.09 (1.02–1.17)	.001
Previous cephalosporin use	49 (42.2%)	289 (20.2%)	1.11 (1.06–1.16)	<.001
Previous carbapenem use	28 (24.1%)	70 (4.9%)	1.32 (1.16–1.49)	<.001
SBP prophylaxis	65 (56.0%)	428 (30.0%)	1.10 (1.06–1.14)	<.001
Norfloxacin prophylaxis	38 (32.8%)	185 (13.0%)	1.13 (1.07–1.21)	<.001
Hospital stays before LT in days	5.5 (0–75)	1 (0–289)	-	<.001
MELD score at transplantation			-	<.001
5–11	6 (5.2%)	334 (23.4%)		
12–18	17 (14.7%)	379 (26.5%)		
19–29	47 (40.5%)	453 (31.7%)		
>29	46 (39.7%)	262 (18.3%)		
Combined transplantation	4 (3.4%)	62 (4.3%)	0.98 (0.92–1.05)	.81

Abbreviations: ACLF, acute on chronic liver failure; ICU, intensive care unit; LT, liver transplantation; MDRO, multidrug-resistant microorganism; RR, relative risk; SBP, spontaneous bacterial peritonitis.

TABLE 3 Multivariate analysis of risk factors for carbapenem-resistant Enterobacterales (CRE) colonization at the moment of liver transplantation among 1544 patients

Variables	OR	CI 95%	*p*-Value
Fulminant hepatitis	0.49	0.19-1.25	.11
CLIF-SOFA score	1.47	1.12-1.94	.006
Number of bacterial infections	1.33	1.01-1.74	.04
Prophylaxis for SBP	1.57	1.03-2.41	.04
Therapeutic antibiotic use	2.78	1.53-5.06	.001
Carbapenem use	2.07	1.53-5.06	.009
Gastrointestinal bleeding	1.60	0.97-2.64	.06

Abbreviation: SBP, spontaneous bacterial peritonitis.

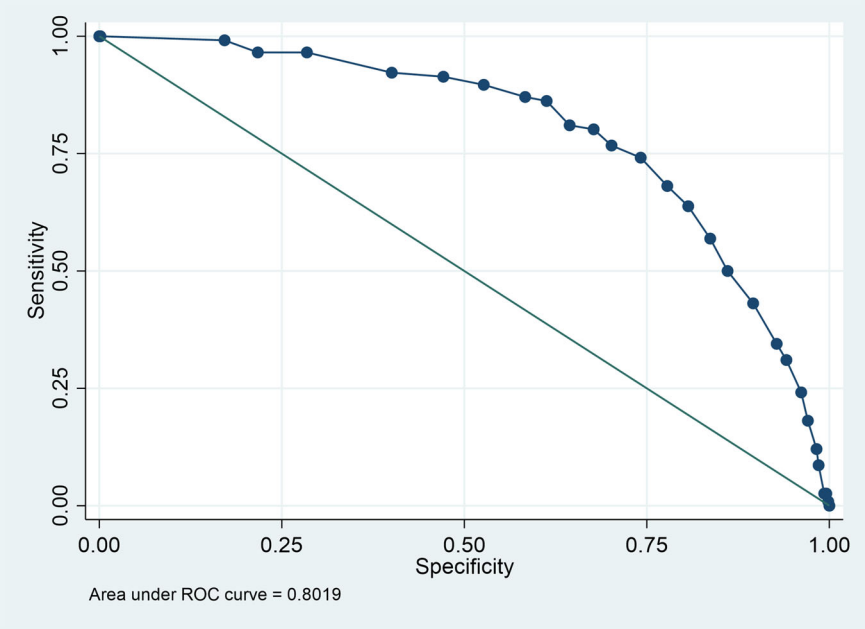

FIGURE 1 Receiver operating characteristic (ROC) curve for prediction score of carbapenem-resistant Enterobacterales (CRE) colonization before liver transplantation constructed through logistic regression analysis

in this model 64 CRE colonized and 1428 noncolonised patients were included; risk factors for CRE colonization identified in this analysis were prophylaxis for SBP ($p = .04$; OR 1.76 CI 95% 1.03–3.03), worse CLIF-SOFA score ($p < .01$; OR 1.96 CI 95% 1.40–2.75) and number of infections in the previous 90-days ($p < .001$; OR 1.87 CI 95% 1.40–2.49) (Table S1).

3.1 | Machine learning algorithms performance

Table 4 presents the predictive performance results of six popular machine learning algorithms. The random forest algorithm obtained the highest values for the AUC on the test set (0.83, 95% CI: 0.77–0.89), with a sensitivity of 0.66, and specificity of 0.83. Figure 2 presents the AUC of the random forests algorithm on the test data.

The five variables with the highest predictive importance to the model according to the Shapley value are shown in Figure 3; in this model, when in red, the positive result increases the probability of a patient having colonization by CRE. Therapeutic antibiotics use, hepatorenal syndrome, and high values of CLIF-SOFA score increased the probability of a patient having pre-liver transplant CRE. The predictive capacity of this algorithm is represented in Figure 4.

We also analyzed the total number of positive patients presented in the 20% highest predicted risk by the random forest algorithm and found that 62.9% of total positive patients were included in this group by the original model.

4 | DISCUSSION

This study proposes two types of scores to predict CRE colonisation before LT. Both scores use clinical and epidemiological information easily obtained at the time of transplantation. They have a similar accuracy; the logistic regression score has a higher sensitivity but lower specificity and the convenience of not using a computer to calculate the score. The machine learning score includes a lower number of variables

TABLE 4 Predictive performance of machine learning models on the test set

Algorithm	AUC (95% CI)	Sensibility	Specificity	PPV	NPV	F1
Extra trees classifier	0.79 (0.72–0.87)	0.51	0.86	0.23	0.96	0.32
Light gradient boosting machine	0.78 (0.70–0.85)	0.54	0.85	0.23	0.96	0.32
CatBoost classifier	0.78 (0.70–0.86)	0.57	0.86	0.25	0.96	0.34
K neighbors classifier	0.77 (0.69–0.84)	0.57	0.78	0.18	0.96	0.27
Random forest classifier	0.83 (0.77–0.89)	0.66	0.83	0.23	0.97	0.34
Gradient boosting classifier	0.65 (0.56–0.75)	0.40	0.89	0.21	0.88	0.28

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

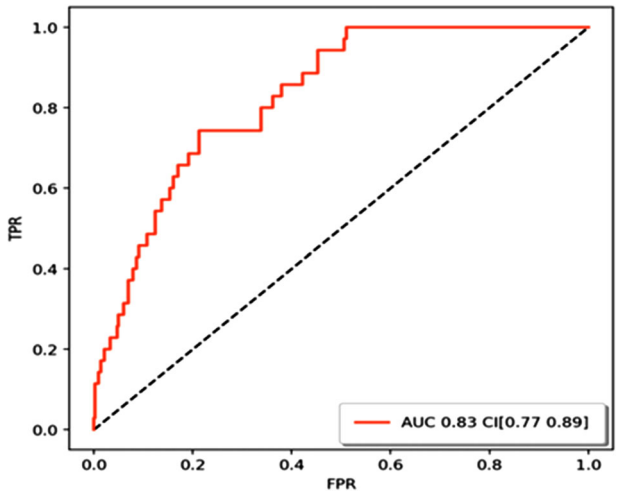

FIGURE 2 Receiver operating characteristic (ROC) curve for the test set of the random forest machine learning algorithm

and allows for the construction of a database that will be continually updated, improving the ability to identify CRE-colonised patients.

Machine learning has been increasingly used as a tool to predict MDRO infection. McGuire et al. developed extreme gradient boosting (Xgboost) algorithms to predict infections caused by CRE. A total of 68 472 patients met the inclusion criteria, with 1088 patients identified as having CR organisms, which is a much larger sample size than ours. The authors used about sixty-seven variables to develop the predictive model. In this study, the AUC was 0.85, with a sensitivity of 0.30, a PPV of 0.30, and an NPV of 0.99. [22] Overall, the results were similar to those presented in our study, but our sensitivity and specificity values were higher. It is also noteworthy that even with a smaller sample size compared with other studies, we found results consistent with the literature, offering a pragmatic model with few variables.

The construction of a score to predict CRE colonisation before LT is essential to implement preventive measures at the time of LT (i.e., targeted antibiotic prophylaxis). The logistics for CRE colonisation identification on waiting list patients is complex as in most hospital surveillance cultures are not performed on outpatients. Even if it were feasible, LT is not an elective surgery, and organ allocation depends on liver function and the patients' clinical conditions, with uncertainty of the LT date. In the present study, 49% of patients had the first positive CRE surveillance culture within 72 h before LT. Therefore, combining surveillance cultures with an individual risk stratification tool could be of help in promoting preventive strategies in centres where CRE is endemic.

Adjusting prophylaxis by MDR-Gram-negative bacteria colonisation is a controversial issue. Regarding ESBL-producing Enterobacteriaceae, several studies described that adjustment of prophylactic

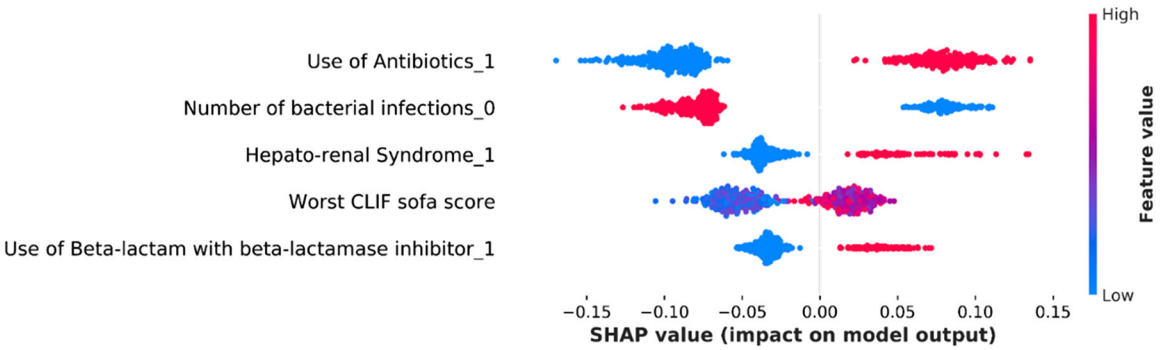

FIGURE 3 Top five feature contributions to predict carbapenem-resistant Enterobacterales (CRE) in the random forest models

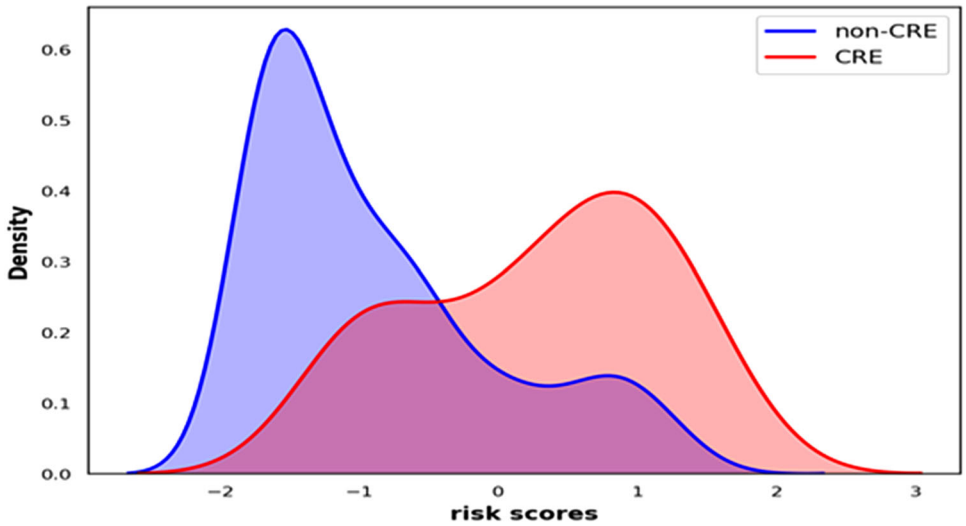

FIGURE 4 Probability density distributions for predicting carbapenem-resistant Enterobacterales (CRE) cases for the test set of the random forest machine learning algorithm. Figure 4 shows the distribution of the risk score indicating the class discrimination resulting from the model using the random forest algorithm. The distribution of probability densities shows in blue those who did not have CRE and red patients with CRE. It can be noticed that the random forest algorithm was able to definitively distinguish those who had or not have CRE colonization.

antibiotic was effective in reducing surgical site infection by this agent, although the impact on reducing overall surgical site infection (SSI) rate is less clear.[23,24] Few studies analyzed antibiotic prophylaxis adjusted for CRE-colonised patients, probably because this is a rarer condition, although it is an important issue for a specific group of surgeries such as LT. Two studies reported a reduction in SSI by CRE in kidney transplant recipients when aminoglycoside was included in surgical prophylaxis; however, one of them was performed during a CRE outbreak. [25,26] Among LT, we previously described a reduction of more than 60% of SSI by MDRO when amikacin was added to surgical prophylaxis for a group of risk for MDRO colonisation; nonetheless, the criteria used to define this group had low sensitivity and more than one-third of CRE colonised patients did not receive tailored prophylaxis.[27]

In the present study, we proposed a score with great sensitivity and specificity; we estimate that if we used this score to adjust surgical prophylaxis, almost 80% of the colonized patients would receive targeted prophylaxis, and a number needed to treat (NNT) of six patients to properly target a CRE carrier. This low NNT is reassuring in terms of the ecological impact of such an approach.

Our study identified that previous antibiotic treatment was a significant risk for CRE colonization, and it further increase of 4 points if a carbapenem was used. It is already well described that carbapenem increases the risk of CRE colonization through microbiota selection.[28] Additionally, antibiotic-promoting dysbiosis has a comprehensive role in sustaining CRE colonisation status.

The change in the gastrointestinal microbiota and the increased intestinal permeability leads to chronic stimulation of the immune system and overproduction of pro-inflammatory cytokines responsible for alterations in adaptive and innate response, leading to local and systemic immunodeficiency. [29,30] This chronic pro-inflammatory status also predisposes to ACLF episodes. On the other side, infection is the most frequent trigger of this condition, and ACLF, which is also a risk factor for MDRO infection, since patients in this condition frequently receive empirical antibiotic therapy, require prolonged ICU stays and are submitted to invasive devices and renal replacement therapy, all well-described risks factors for CRE.[28] A multicentric study including more than 1000 cirrhotic patients with infection reported 49% of infection-induced ACLF, and infection by MDRO was statistically associated with an increased risk of ACLF. [31] In our study, the graduation of CLIF-SOFA and MELD scores were related to the risk of CRE-colonization in both scores, demonstrating this multifactorial relationship between MDRO colonisation/infection and the degree of liver dysfunction.

Finally, although this is a multicentric study, these two new scores for the prediction of CRE colonization at the time of LT need to be validated in other settings, especially in centers with a low incidence of CRE. These scores presented a low PPVs, despite this is not a problem in centers with high CRE incidence, where the most important parameters are the sensitivity and NPV, in centres with low CRE prevalence the score accuracy may be compromised, and prevention strategies based on surveillance culture could be more cost-effective. Therefore, an external validation needs to be done in order to confirm the prediction parameters of these models. The main limitations of our study are its retrospective design and the methodology of CRE identification itself since no molecular method was used in addition to selective surveillance culture.

In conclusion, antibiotic use and liver dysfunction are the primary determinants for CRE colonisation at LT. Using machine learning algorithms, we developed prediction models for CRE colonization with high predictive performance, that are pragmatic for practical use to try to optimize measures to reduce the impact of CRE infection in the setting of LT.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

Study design: MPF, MG, and MB. *Machine learning analysis*: MF, TAO, and ADPCF. *Write the manuscript*: MPF, DRBT, and MG. *Collected clinical data*: NNM, GTL, DRBT, MR, ZP, and AM. *Analyzed and interpreted data*: ATWS and DRBT. *Manuscript critical revision*: MG, MR, EA, LACD, MC M, AS, MC, and CL.

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