Received: 6 December 2022 | Revised: 20 January 2023 | Accepted: 27 January 2023

DOI: 10.1111/tid.14036

TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

# Validation of the INCREMENT-SOT-CPE score in a large cohort of liver transplant recipients with carbapenem-resistant Enterobacterales infection

Matteo Rinaldi[1,2] | Cecilia Bonazzetti[1,2] | Mena Gallo[2] | Giuseppe Ferraro[1,2] | Maristela Freire[3] | Débora Raquel Benedita Terrabuio[4] | Francesco Tandoi[5] | Renato Romagnoli[5] | Francesco Giuseppe De Rosa[6] | Alessandra Mularoni[7] | Alberto Ferrarese[8] | Patrizia Burra[8] | Marcia Halpern[9] | Elizabeth Balbi[9] | Jacques Simkins[10] | Lilian Abbo[11] | Ignacio Morrás[12] | Mireia Cantero[13] | Laura Alagna[14] | Alessandra Bandera[14,15] | Wanessa Trinidade Clemente[16] | Maricela Valerio[17] | Ainhoa Fernández[18] | Patricia Muñoz[17] | Liran Statlender[19] | Dafna Yahav[20] | Luis Fernando Aranha Camargo[21] | Evelyne Santana Girão[22] | Paolo Grossi[23] | Pierluigi Viale[1,2] | Stefania Curti[2] | Maddalena Giannella[1,2] | CRECOOLT study group[#]

**Correspondence**
Maddalena Giannella, Infectious Disease Unit, IRCCS Policlinico S. Orsola-Malpighi, Via Massarenti 11, 40138 Bologna, Italy.
Email: maddalena.giannella@unibo.it

## Abstract

**Background:** Management of infections due to carbapenemase-resistant Enterobacterales (CRE) in solid organ transplant (SOT) recipients remains a difficult challenge. The INCREMENT-SOT-CPE score has been specifically developed from SOT recipients to stratify mortality risk, but an external validation is lacking.

**Methods:** Multicenter retrospective cohort study of liver transplant (LT) recipients colonized with CRE infection who developed infection after transplant over 7-year period. Primary endpoint was all-cause 30-day mortality from infection onset. A comparison between INCREMENT-SOT-CPE and other selected scores was performed. A two-level mixed effects logistic regression model with random effects for the center was fitted. Performance characteristics at optimal cut-point were calculated. Multivariable Cox regression analysis of risk factors for all-cause 30-day mortality was carried out.

**Results:** Overall, 250 CRE carriers developed infection after LT and were analyzed. The median age was 55 years (interquartile range [IQR]: 46–62) and 157 were males (62.8%). All-cause 30-day mortality was 35.6%. A sequential organ failure

**Abbreviations:** BSI, bloodstream infection; CMV, *Cytomegalovirus*; CRE, carbapenem-resistant Enterobacterales; ICS, INCREMENT-CPE score; ICU, intensive care unit; LT, liver transplant; MELD, model for end-stage liver disease; NPV, negative predictive value; PPV, positive predictive value; SOFA, sequential organ failure assessment; SOT, solid organ transplant.

[#]CRECOOLT study group details are available in appendix section.

assessment (SOFA) score ≥ 11 showed a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 69.7%, 76.4%, 62.0%, 82.0%, and 74.0%, respectively. An INCREMENT-SOT-CPE ≥ 11 reported a sensitivity, specificity, PPV, NPV, and accuracy of 73.0%, 62.1%, 51.6%, 80.6% and 66.0%, respectively. At multivariable analysis acute renal failure, prolonged mechanical ventilation, INCREMENT-SOT-CPE score ≥ 11 and SOFA score ≥ 11 were independently associated with all-cause 30-day mortality, while a tigecycline-based targeted regimen was found to be protective.

**Conclusions:** Both INCREMENT-SOT-CPE ≥ 11 and SOFA ≥ 11 were identified as strong predictors of all-cause 30-day mortality in a large cohort of CRE carriers developing infection after LT.

**KEYWORDS**
CRE infection, INCREMENT-SOT-CPE score, liver transplantation, SOT

## 1 | INTRODUCTION

Infections due to carbapenem-resistant Enterobacterales (CRE) are increasing worldwide and remain a major issue in endemic centers.[1] Solid organ transplant (SOT) recipients have an increased risk for CRE colonization and subsequent infection, with high risk of death, attesting between 30% and 50%.[2,3] These high mortality rates justify the efforts to recognize specific risk factors, preemptive strategies, and risk stratification tools in order to better address available interventions.[4] Recently, the INCREMENT-CPE score (ICS) was developed and externally validated in a large cohort of intensive care unit (ICU) patients with CRE bacteraemia, exhibiting a predictive accuracy comparable to sequential organ failure assessment (SOFA) and Pitt scores.[5] Furthermore, such score was validated in patients with colistin-resistant pathogens[6] and in patients treated with ceftazidime/avibactam,[7] showing similar results. However, these studies were not focused on SOT recipients. Therefore, a new score (INCREMENT-SOT-CPE) was derived in a retrospective cohort of SOT recipients, showing an area under the curve (AUROC) of 0.82 (95% confidence interval [CI]: 0.76–0.88) on predicting 30-day mortality.[8] However, such score was not validated in an external cohort. The aim of our study was to evaluate the accuracy of the INCREMENT-SOT-CPE score and other main scores on predicting mortality in a large international multicenter cohort of liver transplant (LT) recipients colonized with CRE who developed CRE infection after transplant.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

Multicenter multinational retrospective cohort study was performed between January 2010 and December 2017. Data were gathered from clinical charts and hospital electronic records, de-identified before entry into a standardized electronic case report form (eCRF), and managed using REDCap electronic data capture tool, hosted by Alma Mater University of Bologna[9,10] from July 2021 to October 2021. The accuracy of data was checked by an investigator of the coordinating center (Matteo Rinaldi). Queries for incongruous or missing data were submitted to investigators to ensure high quality and completeness. CRE-infected patients were extracted from a previous multicenter cohort of LT carriers.[4] The study was first approved by Institutional Review Board (IRB) of the promoting center (n. 155/2019/Oss/AOUBo on March 20, 2019), then by IRB of all participating centers.

### 2.2 | Setting

Fourteen hospitals performing LT participated in the study: five from Italy (Bologna, Turin, Padua, Palermo, and Milan); five from Brazil (two in São Paulo, one in Fortaleza, one in Belo Horizonte, and one in Rio de Janeiro); two from Spain (Madrid and Majadahonda); one from the United States (Miami); and one from Israel (Petah-Tikva). In each center, an active surveillance screening for CRE colonization is in force.

### 2.3 | Study population

All consecutive adult (≥18 years) patients colonized with CRE prior or post LT who developed a CRE infection within 180 days after LT were analyzed. Only the first CRE infection was considered with a minimum follow-up of 30 days after infection onset. CRE was defined as any Enterobacterales displaying in vitro non-susceptibility to any of the carbapenems according to the criteria (CLSI or EUCAST) adopted at the participating center during the study period. The colonization status was defined as isolation of CRE from rectal swabs or other samples other than blood cultures or sterile fluids (e.g., urine, respiratory samples, superficial skin samples) in absence of symptoms and signs

of infection. CRE infection was defined accordingly with Centers for Disease Control and Prevention (CDC) criteria.[11] The assessment of CRE infection was established by the local investigator and revised by an investigator of the promoting center (Matteo Rinaldi); in case of no agreement, a third blinded investigator of the promoting center (Maddalena Giannella) was asked to revise the case for establishing the final diagnosis.

## 2.4 | Validation of the INCREMENT-SOT-CPE score and other scores

The primary objective was to validate in our cohort, the prognostic performance of the INCREMENT-SOT-CPE score in predicting 30-day mortality. The accuracy of such score was further compared with other main prognostic scores: SOFA score, PITT score, qPITT score, and ICS.[12–15]

Study variables included demographic data (age and sex), comorbidities according to Charlson index, underlying liver disease, and severity of liver disease according to model for end-stage liver disease (MELD) at inclusion in waiting list and at LT. Complications occurring from LT to the diagnosis of CRE infection were recorded and included: re-intervention, acute kidney injury (AKI) according to KDIGO criteria,[16] renal replacement therapy (RRT), prolonged (≥48 h) mechanical ventilation (MV), graft dysfunction (primary or secondary), biopsy-proven rejection, re-transplantation, and *Cytomegalovirus* (CMV) DNAemia greatere than 100 000 copies/mL.[17] Data regarding empirical and targeted anti-CRE treatments were collected. Finally, variables included in INCREMENT-SOT-CPE, ICS, SOFA, PITT, and qPITT scores were also collected at CRE infection onset.

## 2.5 | Missing data

A complete case analysis was performed.

## 2.6 | Statistical analysis methods

Categorical variables were reported as counts and percentages. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if non-normally distributed.

For the comparison between survivors and non-survivors, categorical variables were compared using $\chi^2$ test or Fisher's exact test as appropriate, whereas continuous variables were compared using Student's *t*-test or Mann–Whitney *U* test depending on whether normally distributed or not.

A comparison between INCREMENT-SOT-CPE and other selected scores (i.e., ICS, PITT, qPITT, and SOFA) was performed by calculating the area under the receiver operating characteristic (ROC) curve for observed data. Each score was assessed as a binary variable on the basis of the optimal cut-off according to Youden's criterion.[18] We used a two-level mixed effects logistic regression model, where the center identifies the group structure for the random effects at that level (i.e., data clustered within centers).[19–21] A likelihood-ratio test was used to compare this model with ordinary logistic regression. Performance characteristics at cut-point (i.e., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy) were calculated along with their 95% CI. Given that the INCREMENT-SOT-CPE score was developed exclusively for patients with bloodstream infection (BSI), subgroup analyses among patients with and without BSI were performed (see Tables S1–S4 and Figures S1 and S2). In addition to that, considering that SOFA is especially aimed at critical patients, subgroup analyses among patients admitted or not to the ICU at time of developing the infection were carried out (see Tables S5 and S6 and Figures S3 and S4).

Multivariable Cox regression analysis for all-cause 30-day mortality was performed considering patients from the day of infection diagnosis until death or 30 days, whichever occurred first. We used a Cox model with gamma-distributed frailty, where the center defines the group over which frailties are shared.[22] A likelihood-ratio test was used to verify if correlation within centers cannot be ignored. The covariates to be included in the multivariable Cox regression model were selected through a backward stepwise selection strategy (*p*-value for inclusion ≤.1, *p*-value for exclusion >.2). Variables were primarily entered according to clinical relevance and lack of collinearity. The full model included the following variables: gender, acute renal failure, prolonged mechanical ventilation, targeted polymyxin-based regimen, targeted aminoglycoside-based regimen, targeted tigecycline-based regimen, INCREMENT-SOT-CPE, and SOFA score. These scores were entered as binary variables according to optimal cut-offs based on Youden's criterion. The reduced model finally retained: acute renal failure, prolonged mechanical ventilation, targeted tigecycline-based regimen, INCREMENT-SOT-CPE, and SOFA score. The proportional hazards assumption was checked by plotting a log–log graph of survival curves along with statistical tests and graphical diagnostics based on Schoenfeld residuals (see Figures S5 and S6). If proportional hazard assumption was violated for a variable, that is, for that variable the hazard changed over time, the variable was included in the model assuming that has time-dependent coefficients through the use of a step function reporting different coefficients, and thus also different hazard ratios, over different time intervals. Time intervals selection was based on visual analysis of the log–log plot of survival curves (Figure S6).[23] A final Cox model with shared frailty that included a time-dependent covariate for SOFA was fitted.

All the analyses were carried out using Stata 16.1 (Stata Corp., College Station, TX, USA). All statistical tests were two-sided and an alpha error of .05 was accepted.

# 3 | RESULTS

Overall, 250 out of 840 CRE carriers developed infection after LT recipients and were analyzed. The distribution of events across participating centers is shown in Table S1. The principal characteristics of study

population are shown in Table 1. Briefly, the median age was 55 years (IQR 46–62) and the proportion of men was 62.8% ($n = 157$). The mean Charlson index was 5.5 (SD 2.0), the primary indication for LT was viral hepatitis in 114/250 subjects (45.6%), followed by alcoholic cirrhosis (49/250, 19.6%). Hepatocellular carcinoma (HCC) was diagnosed in almost one third of patients (71/250, 28.4%). MELD at inclusion in waiting list and at LT was 19 (IQR 14–27) and 25 (IQR 16–32), respectively. Among post-LT complications, acute renal failure occurred in 176/250 cases (70.4%), followed by prolonged mechanical ventilation (132/250, 52.8%) and needing of a surgical re-intervention (123/250, 49.2%). CMV infection was diagnosed in 70/250 cases (28%), 146/250 patients (58.4%) had an infection other than CRE. One-quarter of LT recipients were found to be colonized with CRE prior LT (63/250, 25.7%). KPC genotype was the most common mechanism of resistance (183/250, 73.2%).

CRE infection episodes included 91 BSI (36.4%), of which 38.5% were classified as primary; 59 lower respiratory tract infections (23.6%), 52 intra-abdominal infections (20.8%), and 65 surgical site infections (26%). The median time from LT to CRE infection was 19 days (IQR 9–42). Vasopressors were administered in 49/250 cases (39.6%), 114/250 patients (45.6%) required mechanical ventilation. In vitro active empirical therapy was started in 147 patients (58.8%). Among targeted treatments, polymyxin-based regimen was administered in 114 cases (60%), followed by aminoglycoside-based (39, 20.5%), and tigecycline-based regimens (33, 17.4%; of these 30/33 had intra-abdominal infection and 10/33 presented with septic shock). Only four patients (2.1%) received ceftazidime/avibactam. The all-cause 30-day mortality was 35.6%. Among scores calculated at CRE infection onset, median INCREMENT-SOT-CPE, ICS, PITT, qPITT, and SOFA score were 10 (IQR 7–13), 8 (IQR 6–14), 3 (IQR 1–6), 2 (IQR 0–3), and 8 (IQR 5–13), respectively. The comparison between survivors and non-survivors with CRE infection is shown in Table 1.

The likelihood-ratio test comparing two-level mixed effects logistic regression model with ordinary logistic regression for each score showed that the former is the most accurate model (Table S2). Sensitivity, specificity, PPV, NPV, and accuracy for each selected score are shown in Table 2. In particular, a SOFA score ≥ 11 showed a sensitivity, specificity, PPV, NPV, and accuracy of 69.7% (95% CI: 59.0%–79.0%), 76.4% (95% CI: 69.1%–82.7%), 62.0% (95% CI: 51.7%–71.5%), 82.0% (95% CI: 74.9%–87.8%), and 74.0% (95% CI: 68.6%–79.4%), respectively. An INCREMENT-SOT-CPE ≥ 11 reported a sensitivity, specificity, PPV, NPV, and accuracy of 73.0% (95% CI: 62.6%–81.9%), 62.1% (95% CI: 54.1%–69.6%), 51.6% (95% CI: 42.5%–60.6%), 80.6% (95% CI: 72.6%–87.2%), and 66.0% (95% CI: 60.1%–71.9%), respectively. The ROC curves for each selected score are shown in Figure 1. Of note, the diagnostic characteristics for each selected score along with ROC curves analysis among those patients with and without BSI were similar to the main analysis on all infection sites (see Tables S3 and S4, and. Figures S1 and S2). In addition, subgroup analyses among patients admitted or not to the ICU at the time of developing the infection are reported in Tables S5 and Table S6, and Figures S3 and S4.

At multivariable Cox regression analysis, we found a significant frailty effect, meaning that the correlation within centers cannot be ignored ($p = .043$). The independent risk factors for all-cause 30-day mortality were acute renal failure, prolonged mechanical ventilation, INCREMENT-SOT-CPE score ≥ 11, and SOFA score ≥ 11, while tigecycline-based regimen was associated to a lower risk (Table 3). Of note, the assumption of proportional hazard was violated for the SOFA score ($p = .039$) (Figures S5 and S6). The visual analysis suggested a greater effect for SOFA ≥ 11 in the first week (i.e., 0–7 day time interval) compared to 8–30 day time interval. The final Cox model with shared frailty included a time-dependent covariate for SOFA showing a higher risk for SOFA ≥ 11 in 0–7 day time interval (Table 3).

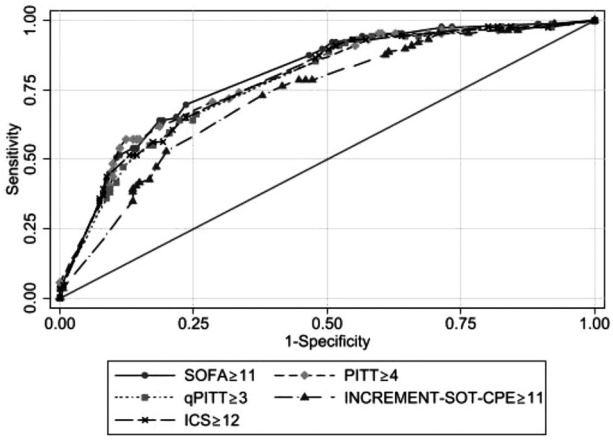


**FIGURE 1** Receiver operating characteristic (ROC) curve for each selected score.

## 4 | DISCUSSION

We performed an external validation of the INCREMENT-SOT-CPE score compared to other selected prognostic scores in a large, multicenter, international cohort of LT recipients colonized with CRE and who developed CRE infection after transplantation. Although an INCREMENT-SOT-CPE score ≥ 11 was independently associated with a higher mortality risk, SOFA score was more accurate in the setting of liver transplantation, with a greater effect for SOFA ≥ 11 in the first week.

The INCREMENT-SOT-CPE score was first derived from a mixed cohort of SOT recipients, in which LT recipients accounted for 56%. Some variables included in the INCREMENT-SOT-CPE score, such as lymphopenia and CMV infection after transplantation, are related to the net state of immunosuppression of the recipient.[24,25] Generally, these complications occurred more frequently in non-LT recipients due to the more intensive immunosuppression regimens used in those patients.[26] This issue may partially explain the difference in accuracy of INCREMENT-SOT-CPE to predict mortality in patients with CRE infection between our cohort of LT recipients and that of the derivation study. Furthermore, INCREMENT-SOT-CPE score was developed considering only BSI, excluding other types of nonbacteremic infections, while we analyzed all types of CRE infections diagnosed in colonized patients including BSI (36.4%), lower respiratory tract (24%), and

**TABLE 1** Univariable analysis between survivors and non-survivors LT recipients with CRE infection.

| | Survivors N = 161 | Non-survivors N = 89 | Total N = 250 | *p*-Value |
|---|---|---|---|---|
| **Demographic data** | | | | |
| Age (years), median (IQR) | 55 (47–62) | 56 (44–63) | 55 (46–62) | .953 |
| Sex, male | 97 (60.3) | 60 (67.4) | 157 (62.8) | .262 |
| **Comorbidities** | | | | |
| Myocardial infarction | 5 (3.1) | 1 (1.1) | 6 (2.4) | .426 |
| Congestive heart failure | 8 (5.0) | 2 (2.3) | 10 (4.0) | .502 |
| Peripheral vascular disease | 4 (2.5) | 2 (2.3) | 6 (2.4) | 1.000 |
| Cerebrovascular disease | 4 (2.5) | 2 (2.3) | 6 (2.4) | 1.000 |
| COPD | 6 (3.7) | 10 (11.2) | 16 (6.4) | .020 |
| Diabetes without organ damage | 27 (16.8) | 15 (16.9) | 42 (16.8) | .986 |
| Moderate/severe renal disease | 19 (11.8) | 17 (19.1) | 36 (14.4) | .115 |
| Diabetes with organ damage | 15 (9.3) | 6 (6.7) | 21 (8.4) | .482 |
| Any tumor within 5 years | 61 (37.9) | 16 (18.0) | 77 (30.8) | .001 |
| Charlson index, mean (SD) | 5.6 (2.0) | 5.3 (1.9) | 5.5 (2.0) | .147 |
| **Underlying liver disease** | | | | |
| Viral hepatitis | 80 (49.7) | 34 (38.2) | 114 (45.6) | .081 |
| Alcohol | 34 (21.1) | 15 (16.9) | 49 (19.6) | .416 |
| Metabolic disease | 16 (9.9) | 5 (5.6) | 21 (8.4) | .238 |
| Autoimmune disease | 9 (5.6) | 2 (2.3) | 11 (4.4) | .337 |
| Fulminant hepatitis | 6 (3.7) | 10 (11.2) | 16 (6.4) | .020 |
| Hepatocellular carcinoma | 55 (34.2) | 16 (18) | 71 (28.4) | .007 |
| Prior transplant | 7 (4.3) | 7 (7.9) | 14 (5.6) | .262 |
| MELD at inclusion in waiting list, median (IQR) | 19 (14–25) | 19 (15–31) | 19 (14–27) | .257 |
| MELD at LT, median (IQR) | 24 (16–30) | 29 (18–37) | 25 (16–32) | .004 |
| **CRE carriage management** | | | | |
| Targeted peri-operative prophylaxis | 10 (6.2) | 3 (3.4) | 13 (5.2) | .390 |
| Selective decolonization | 4 (2.5) | 0 (0) | 4 (1.6) | .300 |
| **Postoperative complications** | | | | |
| Acute renal failure | 96 (59.6) | 80 (89.9) | 176 (70.4) | <.001 |
| Renal replacement therapy | 63 (39.1) | 65 (73.0) | 128 (51.2) | <.001 |
| Mechanical ventilation >48 h | 70 (43.5) | 62 (69.7) | 132 (52.8) | <.001 |
| PGNF | 23 (14.3) | 31 (34.8) | 54 (21.6) | <.001 |
| Re-intervention | 81 (50.3) | 42 (47.2) | 123 (49.2) | .637 |
| Re-transplantation | 25 (15.5) | 12 (13.5) | 37 (14.8) | .663 |
| Rejection | 29 (18.0) | 21 (23.6) | 50 (20.0) | .291 |
| CMV infection | 50 (31.1) | 20 (22.5) | 70 (28.0) | .148 |
| Infections other than CRE | 89 (55.3) | 57 (64.0) | 146 (58.4) | .178 |
| **CRE carriage** | | | | |
| CRE acquisition pre LT | 38 (24.4) | 25 (28.1) | 63 (25.7) | .520 |
| CRE acquisition post LT | 118 (75.6) | 64 (71.9) | 182 (74.3) | .520 |
| **Genotype of the strain** | | | | |
| KPC | 121 (75.2) | 62 (69.7) | 183 (73.2) | .348 |
| VIM | 1 (0.6) | 2 (2.3) | 3 (1.2) | .289 |
| OXA-48 | 3 (1.9) | 3 (3.4) | 6 (2.4) | .669 |

(Continues)

**TABLE 1** (Continued)

| | Survivors N = 161 | Non-survivors N = 89 | Total N = 250 | p-Value |
|---|---|---|---|---|
| **Infection site** | | | | |
| BSI | 58 (36.0) | 33 (37.1) | 91 (36.4) | .868 |
| Primary | 21/58 (36.2) | 14/33 (42.4) | 35/91 (38.5) | |
| Secondary | 24/58 (41.4) | 13/33 (39.4) | 37/91 (40.7) | |
| CVC device related | 13/58 (22.4) | 6/33 (18.2) | 19/91 (20.9) | |
| Lower respiratory tract | 32 (19.9) | 27 (30.3) | 59 (23.6) | .062 |
| Intra-abdominal | 34 (21.1) | 18 (20.2) | 52 (20.8) | .868 |
| Urinary tract | 20 (12.4) | 3 (3.4) | 23 (9.2) | .021 |
| Surgical site | 39 (24.2) | 26 (29.2) | 65 (26.0) | .389 |
| **Infection severity** | | | | |
| SOFA score, median (IQR) | 5 (4–9) | 13 (6–16) | 8 (5–13) | <.001 |
| qPITT score, median (IQR) | 1 (0–2) | 3 (2–3) | 2 (0–3) | <.001 |
| PITT score, median (IQR) | 2 (0–5) | 6 (3–9) | 3 (1–6) | <.001 |
| INCREMENT-CPE, median (IQR) | 6 (5–11) | 12 (7–15) | 8 (6–14) | <.001 |
| INCREMENT-SOT-CPE, median (IQR) | 10 (4–12) | 12 (8–14) | 10 (7–13) | .002 |
| Septic shock | 40 (24.8) | 55 (61.8) | 95 (38.0) | <.001 |
| **Antibiotic treatment** | | | | |
| In vitro active empirical treatment | 94 (58.4) | 53 (59.6) | 147 (58.8) | .858 |
| **Targeted treatment** | | | | .918 |
| Combination therapy vs. monotherapy | 134 (86.5) | 60 (87.0) | 194 (86.6) | |
| **Targeted regimens** | | | | .024 |
| Polymyxin based | 72 (54.5) | 42 (72.4) | 114 (60.0) | |
| Aminoglycoside based | 27 (20.5) | 12 (20.7) | 39 (20.5) | |
| Tigecycline based | 29 (22.0) | 4 (6.9) | 33 (17.4) | |
| CZA based | 4 (3.0) | 0 (0.0) | 4 (2.1) | |

*Note*: All values given are *n* (%) unless otherwise stated.
Abbreviations: BSI, bloodstream infection; CMV, *Cytomegalovirus*; COPD, chronic obstructive pulmonary disease; CRE, carbapenem-resistant Enterobacterales; CVC, central venous catheter; CZA, ceftazidime/avibactam; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease; PGNF, primary graft non-function; SD, standard deviation.

**TABLE 2** Diagnostic characteristics for INCREMENT-SOT-CPE score along with other selected scores

| Score | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) | Accuracy (95% CI) |
|---|---|---|---|---|---|
| SOFA ≥ 11 | 69.7% (59.0%–79.0%) | 76.4% (69.1%–82.7%) | 62.0% (51.7%–71.5%) | 82.0% (74.9%–87.8%) | 74.0% (68.6%–79.4%) |
| PITT ≥ 4 | 70.8% (60.2%–79.9%) | 71.4% (63.8%–78.3%) | 57.8% (48.0%–67.2%) | 81.6% (74.2%–87.6%) | 71.2% (65.6%–76.8%) |
| qPITT ≥ 3 | 64.0% (53.2%–73.9%) | 77.6% (70.4%–83.8%) | 61.3% (50.6%–71.2%) | 79.6% (72.5%–85.6%) | 72.8% (67.3%–78.3%) |
| INCREMENT-SOT-CPE ≥ 11 | 73.0% (62.6%–81.9%) | 62.1% (54.1%–69.6%) | 51.6% (42.5%–60.6%) | 80.6% (72.6%–87.2%) | 66.0% (60.1%–71.9%) |
| ICS ≥ 12 | 65.2% (54.3%–75.0%) | 76.4% (69.1%–82.7%) | 60.4% (49.9%–70.3%) | 79.9% (72.7%–85.9%) | 72.4% (66.9%–77.9%) |

Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

**TABLE 3** Multivariable Cox regression analysis for all-cause 30-day mortality from infection

| Variable | HR (95% CI)[a] | *p*-Value |
|---|---|---|
| Acute renal failure | 2.79 (1.23–6.32) | .014 |
| Mechanical ventilation ≥48 h | 1.90 (1.09–3.30) | .024 |
| Tigecycline-based regimen | 0.25 (0.09–0.70) | .009 |
| INCREMENT-SOT-CPE ≥ 11 | 1.83 (1.09–3.07) | .023 |
| SOFA ≥ 11 | | |
| 0–7 days | 4.13 (1.47–11.59) | .007 |
| 8–30 days | 2.49 (1.37–4.50) | .003 |

[a]A Cox model with shared frailty that included a time-dependent covariate for SOFA ≥ 11 was fitted (see Statistical Methods).

intra-abdominal (21%) infections. However, despite BSI accounted for only one-third of cases in our cohort, the 30-day mortality rate (35.6%) was similar to that observed in the derivation cohort (36.6%). In addition, in the study by Perez-Nadales et al., an INCREMENT-SOT-CPE score ≥ 12 identifies the "very high-risk" group. Similarly, in our cohort, a score ≥ 11 was associated with an almost two-fold risk of short-term death.

SOFA score showed the best accuracy in predicting 30-day mortality. As a significant rate of CRE infections accounted in ICU, these results are expected considering the high accuracy of such score in this specific setting. A recent case–control study performed in ICU highlighted the importance of SOFA score as an independent risk factor for short-term mortality in critically ill patients with CPE bacteremia.[27] Although our cohort was composed of SOT recipients, at multivariable analysis a SOFA score ≥ 11 was confirmed as an independent risk factor for 30-day mortality. Such issue was already underlined in a small cohort of kidney transplant recipients infected with CPE, in which at multivariable analysis an elevated SOFA score was the only risk factor associated with mortality.[28]

Other variables retained in the multivariable analysis, such as acute renal failure and prolonged mechanical ventilation, are well-known postoperative complications strictly associated with CRE colonization, infection, and burdened by high mortality rates.[29,30]

Considering targeted therapies, a trend toward increased mortality in patients treated with a polymyxin-based regimen was observed, on the other hand no differences were reported among aminoglycoside-based regimen. Of interest, a tigecycline-based regimen was found to have a protective impact on 30-day mortality. Such finding could be explained by the almost exclusive use in abdominal infections (91%) where the pharmacokinetic/pharmacodynamic behavior of tigecycline is favorable.[31,32] However, other confounding bias influencing this feature cannot be excluded. The potential role of a combination therapy based on tigecycline was already mentioned in a retrospective cohort of abdominal SOT recipients infected with carbapenem-resistant gram-negative pathogens, even if an increasing rate of resistance over the study period was recorded.[33]

Despite the limitation of retrospective studies, we applied strict definitions and performed several revisions of data with local investigators to solve concerns about missing or incongruous data, as well as multivariable analyses to ensure high quality of data and minimization of potential confounding bias. The limited use of new anti-CRE drugs in our cohort could be seen as another limitation. On this regard, it is worth noting that accessibility to such new drugs is still limited in several world areas. However, we recognize that the impact of the new drugs in mortality rates and in the management of CRE colonization/infection in SOT recipients is a key issue deserving further investigations. Finally, our cohort was burdened by a high prevalence of KPC-producing Enterobacterales, with a very low number of other resistance mechanisms detected. In addition, all patients enrolled in our cohort were CRE carriers, of these three-quarters acquired colonization after LT. Such issue could have created a selection bias.

In conclusion, in colonized LT recipients with CRE infection, SOFA score showed the highest accuracy in predicting 30-day mortality risk, suggesting a greater effect for SOFA ≥ 11 in the first week within infection onset. However, an INCREMENT-SOT-CPE score ≥ 11 was confirmed as a strong predictor of mortality. Compared to other "old" anti-CRE treatments, a tigecycline-based regimen was found to be protective on 30-day mortality.

## AUTHOR CONTRIBUTIONS

Matteo Rinaldi: interpretation of data and paper drafting. Cecilia Bonazzetti, Giuseppe Ferraro, Débora Raquel Benedita Terrabuio, Alberto Ferrarese, Elizabeth Balbi, Lilian Abbo, Mireia Cantero, Laura Alagna, Wanessa Trinidade Clemente, Maricela Valerio, and Liran Statlender: data acquisition. Mena Gallo: data analysis. Maristela Freire: work design. Francesco Tandoi, Renato Romagnoli, Francesco Giuseppe De Rosa, Patrizia Burra, Marcia Halpern, Jacques Simkins, Ignacio Morrás, Alessandra Bandera, Ainhoa Fernández, Patricia Muñoz, Dafna Yahav, Luis Fernando Aranha Camargo, Evelyne Santana Girão, and Paolo Grossi: draft revision. Alessandra Mularoni: data acquisition and draft revision. Pierluigi Viale: final approval and draft revision. Stefania Curti: data analysis and final revision. Maddalena Giannella: conceptualization, draft revision, and final approval.

## AFFILIATIONS

[1]Infectious Diseases Unit, IRCCS Sant'Orsola Hospital, Bologna, Italy

[2]Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

[3]Working Committee for Hospital Epidemiology and Infection Control, Hospital das Clinicas, Universidade de São Paulo, São Paulo, Brazil

[4]Infectious Diseases Department, Hospital das Clinicas, Universidade de São Paulo, São Paulo, Brazil

[5]Department of Surgical Sciences, Liver Transplant Center, General Surgery Unit, AOU Città della Salute e della Scienza, Molinette Hospital, University of Turin, Turin, Italy

[6]University Infectious Diseases, University of Turin, Turin, Piemonte, Italy

[7]Infectious Diseases, ISMETT IRCCS, Palermo, Italy

[8]Department of Surgery Oncology and Gastroenterology, Multivisceral Transplant Unit (Gastroenterology), Surgical and Gastroenterological Sciences, Padua University Hospital, Padua, Italy

[9]Liver Transplant Unit, Quinta D'Or Hospital, Rio de Janeiro, Brazil

[10]Transplant Infectious Diseases and Immunocompromised Host Service, Division of Infectious Diseases, University of Miami/Miami Transplant Institute, Miami, Florida, USA

[11]Department of Medicine, Division of Infectious Diseases, University of Miami, Miami, Florida, USA

[12]Servicio de Medicina Interna, HU Puerta de Hierro-Majadahonda, Madrid, Spain

[13]Servicio de Medicina Preventiva, HU Puerta de Hierro-Majadahonda, Madrid, Spain

[14]Infectious Diseases Unit, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[15]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

[16]Transplant Unit and Infection Control Commission, Hospital das Clínicas - Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

[17]Department of Clinical Microbiology and Infectious Diseases, Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[18]Department of Gastroenterology, Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Marañón, Madrid, Spain

[19]Intensive Care Unit, Rabin Medical Center, Petah Tikva, Israel

[20]Infectious Disease Unit, Beilinson Hospital, Petah Tikva, Israel

[21]Infectious Diseases Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil

[22]Infectious Diseases Unit and Liver Transplant Unit of Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, Fortaleza, Brazil

[23]Infectious Disease Unit, Department of Medicine and Surgery, University of Insubria, Varese, Italy

## ACKNOWLEDGMENTS

Open Access Funding provided by Universita degli Studi di Bologna within the CRUI-CARE Agreement.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to the present study.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*Matteo Rinaldi* https://orcid.org/0000-0002-3568-5973
*Maristela Freire* https://orcid.org/0000-0002-9691-192X
*Alessandra Mularoni* https://orcid.org/0000-0001-8612-5581
*Jacques Simkins* https://orcid.org/0000-0001-9626-0760
*Lilian Abbo* https://orcid.org/0000-0003-1974-4547
*Maricela Valerio* https://orcid.org/0000-0001-6394-2861
*Patricia Muñoz* https://orcid.org/0000-0002-0697-3992
*Dafna Yahav* https://orcid.org/0000-0003-3181-9791
*Maddalena Giannella* https://orcid.org/0000-0001-8273-7601

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Rinaldi M, Bonazzetti C, Gallo M, et al. Validation of the INCREMENT-SOT-CPE score in a large cohort of liver transplant recipients with carbapenem-resistant Enterobacterales infection. *Transpl Infect Dis*. 2023;25:e14036. https://doi.org/10.1111/tid.14036

## APPENDIX: CRECOOLT study group

Italy:
Bologna, IRCCS Policlinico di Sant'Orsola, Michele Bartoletti, Renato Pascale, Caterina Campoli, Simona Coladonato, Francesco Cristini, Fabio Tumietto, Antonio Siniscalchi, Cristiana Laici, Simone Ambretti.
Torino, AOU Città della Salute e della Scienza di Torino, Renato Romagnoli, Francesco Giuseppe De Rosa.
Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Antonio Muscatello, Davide Mangioni, Andrea Gori, Barbara Antonelli, Daniele Dondossola, Giorgio Rossi, Federica Invernizzi.
Udine, Azienda Sanitaria Universitaria Integrata di Udine, Maddalena Peghin.
Padova, Azienda Ospedale Università di Padova, Umberto Cillo.
Modena, Azienda Ospedaliero - Universitaria di Modena, Cristina Mussini, Fabrizio Di Benedetto.
Palermo, ISMETT IRCCS.

Brazil:

São Paulo, Hospital das Clinicas, Universidade de São Paulo, Débora Raquel Benedita Terrabuio.
São Paulo, Hospital Israelita Albert Einstein, Carolina D Bittante, Alexandra do Rosário Toniolo.
Rio de Janeiro, Quinta D'Or Hospital, Elizabeth Balbi. Fortaleza, Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, José Huygens Parente Garcia.

Spain:
Majadahonda, Puerta de Hierro-Majadahonda University Hospital, Angel Asensio, Ignacio Morrás, Antonio Ramos.
Madrid: Hospital General Universitario Gregorio Marañón, Magdalena Salcedo.

Israel:
Petah-Tikva, Beilinson Hospital.
US:
Miami, University of Miami/Miami Transplant Institute.