TANNOUS, E., LIPMAN, S., TONNA, A., HECTOR, E., HUSSEIN, Z., STEIN, M., and REISFELD, S. 2020. Time above the MIC of piperacillin/tazobactam as a predictor of outcome in pseudomonas aeruginosa bacteraemia. *Antimicrobial agents and chemotherapy* [online], 64(8), article ID e02571-19. Available from: https://doi.org/10.1128/aac.02571-19

Time above the MIC of piperacillin/tazobactam as a predictor of outcome in pseudomonas aeruginosa bacteraemia.

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2020

Time above the minimum inhibitory concentration of piperacillin/tazobactam as a predictor of outcome in *Pseudomonas aeruginosa* bacteraemia

Abstract

Pseudomonas aeruginosa bacteraemia is an infection associated with high mortality rate. Piperacillin + Tazobactam is a β-lactam β-lactamase inhibitor combination that is frequently used for the management of *Pseudomonas aeruginosa* . The pharmacokinetic-pharmacodynamic index associated with in-vitro maximal bacterial killing for Piperacillin + Tazobactam is the percentage of time at which the free fraction concentration is above the minimum inhibitory concentration (%fT>MIC). However, the precise %fT>MIC target associated with improved clinical outcomes is unknown.

The aim of this study was to investigate the correlation between survival of patients with *Pseudomonas aeruginosa* bacteraemia and the threshold of Piperacillin + Tazobactam %fT>MIC. This retrospective study included all adult patients hospitalized over an 82 month period with *Pseudomonas aeruginosa* bacteraemia, and treated with Piperacillin + Tazobactam . Patients with a polymicrobial infection or those who died within 72 hours of culture, were excluded. The %fT>MIC of Piperacillin + Tazobactam associated with in-hospital survival was derived using Classification and Regression Tree analysis. After screening 270 patients, 78 were eligible for inclusion in the study; 18% died during hospitalization. Classification and Regression Tree analysis identified %fT>MIC >60.68% as associated with improved survival, and this remained statistically significant after controlling for clinical covariates (OR= 7.74, 95% CI 1.32-45.2). In conclusion, the findings recommend dosing of Piperacillin + Tazobactam with the aim of achieving a pharmacodynamic target of at least 60% fT>MIC in these patients.

Introduction

Pseudomonas aeruginosa (PA) bacteraemia is a common hospital-acquired infection (1), associated with increased mortality, ranging between 18-61% (2). Early appropriate antimicrobial therapy is associated with improved survival (3–8).

Piperacillin and the combination of piperacillin and tazobactam (TZP) are extensively used in the treatment of infectious diseases in critically ill patients; specifically, when PA is the causative pathogen (8). Protein binding for piperacillin ranges between 20-30% and for tazobactam it is approximately 30% (9, 10). Various population pharmacokinetic studies have suggested that the main covariates influencing the volume of distribution and clearance of TZP were weight and creatinine clearance, respectively (11–16). The usual dose of TZP is 4.5g three times daily for most infections and may be increased to 4.5g four times daily in severe health-care acquired infections (17), and in PA infections, as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI). Dose adjustments for renal impairment vary widely between sources (9, 17, 18). There is no sufficient data regarding dosing regimens that will achieve pharmacokinetic and pharmacodynamic (PK-PD) targets that are correlated with improved clinical outcomes.

Piperacillin, like other β-lactams, exhibits a time-dependent bactericidal activity. *In-vitro* and animal studies suggest that the PK-PD parameter for β-lactams that is most predictive of microbiological efficacy, is the percentage of time between doses at which the free fraction concentration remains above the minimum inhibitory concentration (%fT>MIC) (19). For piperacillin, a PK-PD target of 50% fT>MIC is often cited based on studies on other penicillins (20), for example ticarcillin (21, 22).

There is only one study that reported a relationship between bacterial kill and %fT>MIC with significant thresholds of 27% for bacteriostasis and 75% for bactericidal activity (23).

Very few studies have tried to correlate %fT>MIC with clinical outcomes. Among them is the DALI trial, a prospective multinational study that included 361 critically ill patients who were treated with a β-lactam (24). This study concluded that for all β-lactams a %fT>MIC >50% is associated with better outcomes. Other studies dealt specifically with Meropenem and neutropenic patients (25), and cephalosporins (26, 27).

Moreover, the need for a clinically driven %fT>MIC target is augmented by the fact that β-lactams display indirect antimicrobial properties. These properties cannot be identified by the standard *in-vivo* susceptibility testing and include synergy with cationic host defence peptides and action as immune-adjuvants (28). The use of an *in-vitro* derived PK-PD target for any antimicrobial without clinical validation is highly problematic (29). This observation is especially true in the case of β- lactams.

The aim of this study was to investigate the correlation between the concentration/time profile of TZP and clinical outcomes in patients with PA bacteraemia. Additionally the study aimed to find if there is a threshold of %fT>MIC that is associated with improved survival at 30 days.

Results

A total of 270 patients with PA bacteraemia were screened for this retrospective study during January 2012- October 2018, and 78 fulfilled the inclusion criteria for the study. (Figure 1)

Baseline patients' characteristics are described in Table 1. Included patients had a mean (SD) age of 65 years (±17.95), 37.1% were female and mean (SD) modified APACHE II score on culture day was 11.5 (±5.46). Patients had a median (IQR) creatinine clearance of 53.5 mL/min (23.25-97), and 16 patients (20.5%) had an acute kidney injury (AKI). The most common source of bacteremia was respiratory (28.2%) and 7 (9%) patients were treated in the intensive care unit (ICU). Median MIC was 8 mcg/mL and was similar among patients who survived and patients who died.

The primary outcome of in-hospital survival occurred in 64 (82%) of included patients. Patients who survived had a lower APACHE II score, fewer cases of AKI, and were less frequently hospitalized in the ICU than patients who died (10.8 vs 14.5, p=0.022, 14% vs 50%, p=0.003, 4.7% vs 28.6%, p=0.005, respectively).

The estimated median volume of distribution of piperacillin was 23.19 L (IQR= 18.47-30.19) and the estimated median elimination rate constant was 0.56 h^{-1} (IQR= 0.36-0.86). The mean %fT>MIC calculated from the pharmacokinetic model and estimated parameters was 63% (IQR= 47-85). Table 2 presents median %fT>MIC by different creatinine clearance groups. Patients with creatinine clearance less than 20mL/min had a higher median %fT>MIC as compared to patients with creatinine clearance above 20mL/min (82% and 59%, respectively).

Classification and Regression Tree analysis (CART) identified a %fT>MIC threshold of 60.68%, as associated with improved in-hospital survival, adjusting for creatinine clearance (Figure 2).

The final logistic regression model included AKI, modified APACHE II score ≥ 14, and an interaction term between them as independent variables, in addition to the

CART derived %fT>MIC threshold. fT>MIC > 60.68% was entered in the final model as a categorical variable. The adjusted odds ratio of achieving the threshold of fT>MIC > 60.68% was 7.74, 95% CI 1.32-45.2. (Table 3) Comparison between the final model and competing models is summarized in table 1 in the supplementary material.

Goodness of fit and regression diagnostics of the final model are summarized in tables 2-4 in the supplementary material. Internal validation with bootstrap analysis is summarized in tables 5 and 6 in the supplementary material. Moreover, other %fT>MIC thresholds were tested adjusting for the same covariates, as shown in Table 4. %fT>MIC> 40% and %fT>MIC> 50%, as well as %fT>MIC> 70% and %fT>MIC> 80% were not significant predictors of in-hospital survival.

Eleven patients received concomitant treatment with other antimicrobial agents: Ciprofloxacin (n=9), Levofloxacin (n=1) and Gentamicin (n=1). In univariable analysis for 30 day survival the OR of concomitant treatment was 0.3 (p= 0.0984). In the multivariable logistic regression adding this variable did not increase the explanatory power of the model (AIC=64.41, -2Loglik = 52.41) compared to the final model.

Discussion

The key finding of this study is the fact that the CART derived threshold of %fT>MIC> 60.68% of TZP was found to be a significant predictor of in-hospital survival in patients with PA bacteremia, adjusting for covariates. Lower thresholds (%fT>MIC > 40% and %fT>MIC > 50%), as well as higher thresholds (%fT>MIC > 70% and %fT>MIC > 80%) were not significant predictors of in-hospital survival. To

122 the best of our knowledge, this is the first study to report a %fT>MIC threshold of
123 TZP that is associated with improved survival.

124 The results of this study are consistent with other clinical studies concerning the
125 effects of %fT>MIC of β-lactams on clinical outcomes. In the DALI study, achieving a
126 %fT>MIC >50% and %fT>MIC >100% was associated with improved clinical
127 outcomes (24). This cohort had a relatively lower mean modified APACHE II score
128 compared to the DALI study (11.5 and 18, respectively). Interestingly, in the DALI
129 study, the adjusted odds ratio of %fT>MIC >50% and %fT>MIC >100% for improved
130 clinical outcome were similar among patients who did not receive renal replacement
131 therapy (1.03 [95%CI 1.01-1.04] and 1.02 [95%CI 1.01-1.05], respectively). This
132 latter finding is consistent with the threshold of %fT>MIC >60% reported in this
133 study.

134 Ariano *et al* studied the influence of %fT>MIC of meropenem in neutropenic patients
135 with bacteraemia and found an average of 83% fT>MIC among 42 clinical
136 responders compared with 59% fT>MIC for the 18 non-responders (p = 0.04), but in
137 their study no adjustment for severity of illness was performed (25). Rhodes *et al*
138 reported two % fT>MIC thresholds for Cefepime (68% and 74%) that were
139 associated with improved survival (adjusted OR 7.12 [95% CI 1.9-26.7] and 6.48
140 [95% CI 1.9-22.1], respectively) (27), similar to our results, although our patient
141 population had a lower mean modified APACHE II score (11.5 and 14.6,
142 respectively), and a lower median creatinine clearance (59.5 mL/min in patients who
143 survived and 53.5 mL/min among patients who died in our study, compared to 74.9
144 mL/min and 83 mL/min, respectively, in the study by Rhodes *et al*)(27).

145 The EUCAST rational document for TZP states that a piperacillin %fT>MIC of 30-
146 35% is needed for stasis against PA, and a 40% fT>MIC is required for a 2 log drop

in viable organisms in animal models. This statement is based on limited data (30). Yet, a higher dose of 4.5g four times daily is recommended. This higher dose, according to EUCAST, renders all wild type PA susceptible to TZP and allows a clinical MIC breakpoint of 16mg/L. The former conclusion was based on a Monte-Carlo simulation of varying dosing regimens. It did not consider special populations such as critically ill patients, who usually have higher piperacillin volume of distribution and patients with augmented renal clearance, whose piperacillin clearance is significantly increased. Indeed, Udy *et al* demonstrated that patients with augmented renal clearance had increased clearance of piperacillin. They concluded that when considering the MIC distribution of PA, the 4.5g four times daily regimen administered as a 30-minute infusion is not expected to achieve 50% fT>MIC in a significant portion of critically ill patients (31). The cohort in this study was too small to analyze the optimal dosing regimen.

There are some limitations to this study. First, this was a retrospective, single-centre study with the limitations resulting from the study design. Still, results contribute to evidence in an area where there is limited literature available. Second, the small sample size may have affected the estimation of the adjusted odds ratio of %fT>MIC > 60% of TZP on in-hospital survival, as reflected by large confidence intervals in some of the results. Third, TZP concentrations were not measured in any patient and former studies have shown substantial variability in TZP concentrations in hospitalized patients (24). Nevertheless, piperacillin volume of distribution and elimination rate constant was estimated for each patient using a highly qualified population model. Moreover, across various population pharmacokinetics studies, weight and creatinine clearance were identified as the main covariates affecting piperacillin`s volume of distribution and clearance, respectively. Concentrations were

predicted for each patient controlling for weight and creatinine clearance. Therefore, concentration prediction and imputation represented the best available strategy to study the influence of %fT>MIC on in-hospital survival in our patient cohort.

This study has several strengths. First, data was extracted and reviewed by two health care professionals reviewing all medical records. Second, exact dosing times were used to calculate %fT>MIC and symmetric dosing intervals were not assumed; an assumption that is mostly inaccurate in the hospital setting (31). Third, creatinine clearance was estimated using three different methods, to account for patients with unstable serum creatinine and patients whose weight was 30% higher than their ideal body weight. Fourth, the logistic regression model utilised purposeful variable selection as a model building strategy that includes testing for interactions between selected variables. Fifth, the final logistic model was tested for goodness of fit and rigorous regression diagnostics were performed and the final model was internally validated with bootstrap analysis.

Additionally, the findings of the present study support dose individualization of TZP with the aim of achieving a threshold of 60% fT>MIC. In settings where therapeutic drug monitoring of TZP is available, concentration monitoring is recommended for critically ill patients with PA bacteraemia in order to achieve the pharmacodynamic target of 60% fT>MIC.

In conclusion, we have found that achieving a 60% fT>MIC of TZP was associated with improved in-hospital survival in patients with PA bacteraemia. Until more data is available, it is prudent to recommend dosing TZP with the aim of achieving the pharmacodynamic target of at least 60% fT>MIC in patients with PA bacteraemia.

Methods

This retrospective study was conducted at a secondary university affiliated hospital with 495 beds. Study methods were approved by the ethics committees at Hillel Yaffe Medical Center, Hadera, Israel, and Robert Gordon University, Aberdeen, Scotland. Patients above 18 years old, with a positive blood culture for PA and who were hospitalized in our medical center between January 2012 and October 2018, were reviewed for inclusion. Patients not treated with TZP, or for whom treatment was delayed >96 hours of indexed blood culture or having polymicrobial blood culture or cases where the MIC of TZP was not reported, were excluded. Moreover, patients who had died in less than 72 hours of obtaining a blood culture were excluded. If a patient had two episodes of PA positive blood cultures in less than three months, only the first episode was included.

Information was extracted from paper-based and electronic patient records. PA blood cultures were extracted from the microbiology laboratory data base, as well as MICs for TZP. Extracted data included: age, gender, comorbidities, modified APACHE II score (32, 33), Glasgow coma scale, absolute neutrophil count, weight, serum creatinine, TZP dose and dosing interval. In cases of patients with stable serum creatinine (defined as a difference less than 0.3mg/dl between two consecutive serum creatinine levels), creatinine clearance was estimated using the Cockroft and Gault equation for patients whose actual body weight was no more than 30% greater than their ideal body weight, and otherwise the Salazar-Corcoran equation was used. In patients with unstable serum creatinine the Jelliffe equation was used.

Pharmacokinetic analysis:

To estimate %fT>MIC of piperacillin, we utilized a population pharmacokinetics 1-compartment model published by Chen et al. (15). This model was selected because it best fitted the population in our study, reported inter-subject variability, was qualified by visual predictive checks and was validated using non-parametric bootstrap analysis. Using NONMEM 7.4 the volume of distribution and clearance were estimated for each patient. Subsequently, for each patient, the free fraction piperacillin concentration was generated every 15 minutes for the first 48 hours of TZP treatment, assuming a mean protein binding of 25%. The cumulative time above MIC was calculated and divided by 48 giving the estimated %fT>MIC of piperacillin. MIC was determined using Vitek 2 (Vitek 2®, bioMérieux).

The primary outcome was in-hospital survival.

Statistical analysis

Statistical analysis was performed by SPSS 25 and R. The %fT>MIC threshold associated with improved survival was derived by using the classification and regression tree (CART) analysis function in SPSS 25, using %fT>MIC and creatinine clearance as continuous independent variables.

To test the influence of the CART derived %fT>MIC threshold on in-hospital survival adjusting for significant covariates, a logistic regression model was utilized. Variable selection was performed using purposeful variable selection (34).In brief, candidate variables at a univariate level of significance of $P<0.25$ were assessed as possible predictors of in-hospital survival. The importance of each variable was tested using the likelihood ratio test with one degree of freedom. Variables were retained in the model if there deletion resulted in a change of > 3.84 in the likelihood ratio. (47) Moreover, the presence of interactions among retained variables was explored and

245 significant interactions were added into the final model (34). Goodness of fit was
246 assessed using the Hosmer and Lemeshow test in SPSS 25, and regression
247 diagnostics were performed using the "car" package in R (35). (See supplementary
248 material). Internal validation of the final model was performed with bootstrap analysis
249 using the "boot" package in R. (20,000 replications, confidence intervals were
250 calculated using the percentile method; See supplementary material)

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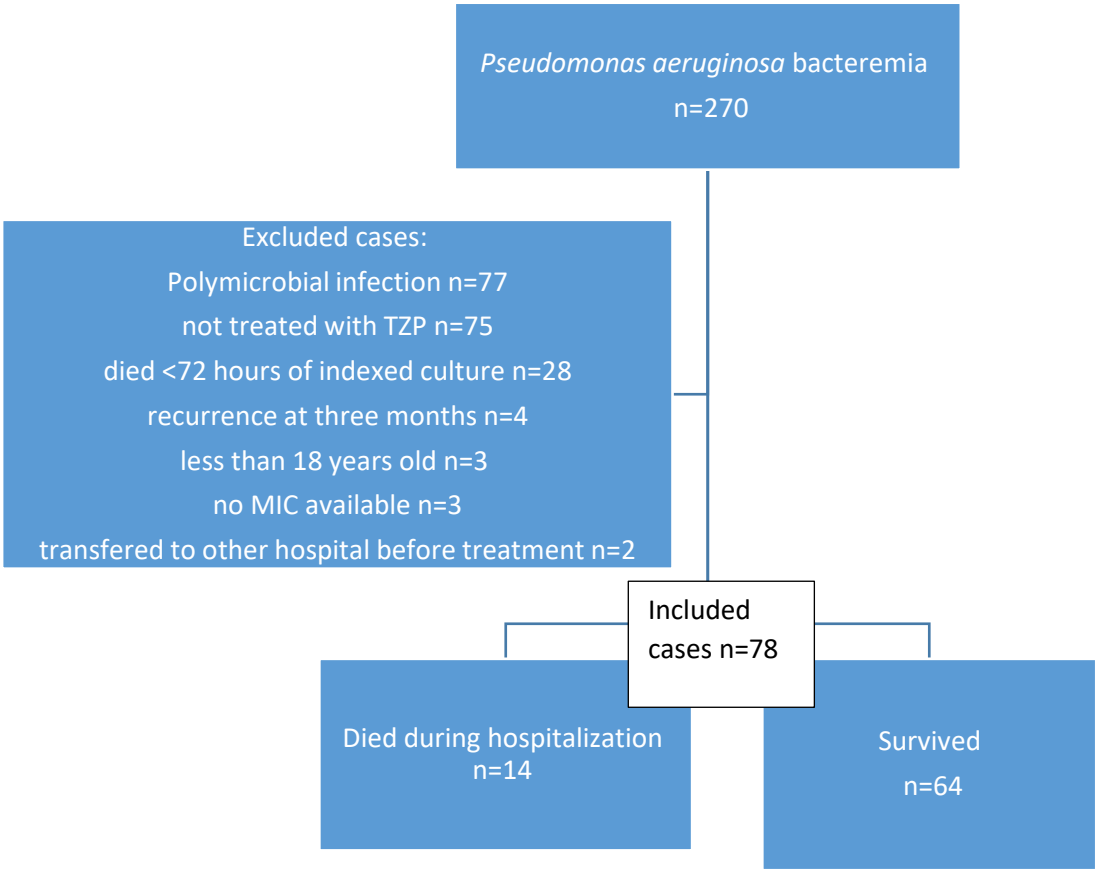
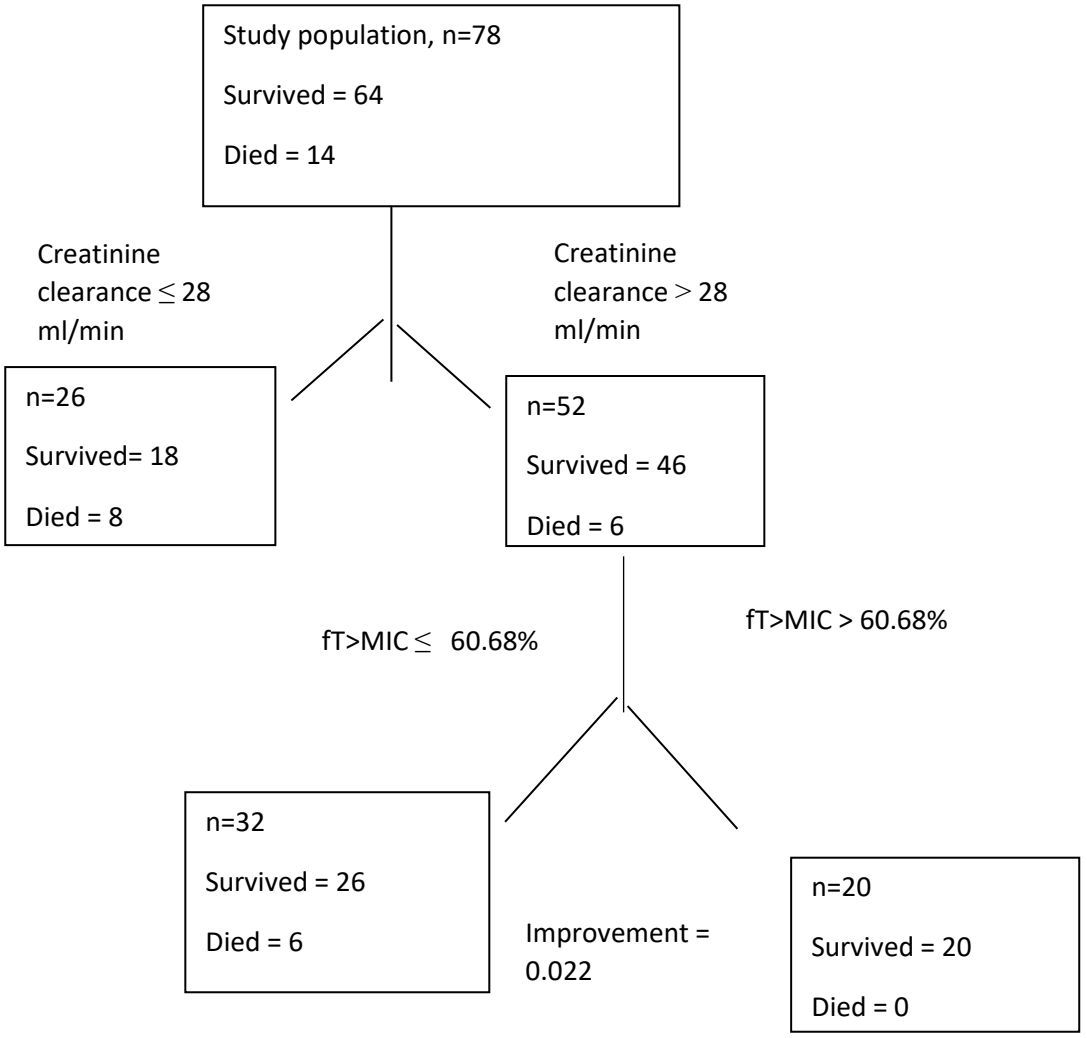
371 Figure 1- Study flow chart



372

Figure 2: CART derived %fT>MIC threshold



389 Table 1: Baseline characteristics of 78 patients with PA bacteremia

	Total cohort	Survived in-hospital	Died	P-value
Total number of patients (%)	78	64 (82%)	14 (18%)	
Age, years, mean (SD)	65 (17.95)	65 (18.27)	68 (16.82)	0.568
Female n, (%)	29(37.1)	24 (37.5)	5 (35.7)	0.900
Weight kg, median (IQR)	73.9 (80.75,62.25)	74 (84.25, 62.75)	71 (74, 61.75)	0.108
Modified APACHE II score on culture day, mean (SD)	11.5 (5.46)	10.8 (5.61)	14.5 (3.48)	0.022
Source, n (%)				
Respiratory	22 (28.2)	14 (21.8)	8 (57)	0.011
Intra-abdominal	7 (8.9)	7 (10.9)	0 (0)	0.991
Urinary	14 (17.9)	13 (20.3)	1 (7.1)	0.269
Skin and wound	11 (14.1)	10 (15.6)	1 (7.1)	0.442
Central line	9 (11.5)	9 (14)	0 (0)	0.994
Unknown	15 (19.2)	11 (17.2)	4 (28.6)	0.333
Medical history, n (%)				

Hypertension	39 (50)	32 (50)	7 (50)	1
Type 2 diabetes	29 (37.2)	23 (35.9)	6 (42.8)	0.627
IHD	12 (15.4)	10 (15.6)	2 (14.3)	0.900
Heart Failure	17 (21.8)	11 (17.2)	6 (42.8)	0.035
Hyperlipidaemia	28 (35.9)	23 (35.9)	5 (35.7)	0.987
Dementia	9 (11.5)	8 (12.5)	1 (7.1)	0.57
CKD	25 (32)	18 (28.1)	7 (50)	0.112
COPD	9 (11.5)	5 (7.8)	4 (28.5)	0.025
Recipient of immunosuppression (90 days)	12 (15.4)	7 (10.9)	5 (35.7)	0.02
Creatinine Clearance (mL/min)*, median (IQR)	53.5 (97,23.25)	59.5 (98.5, 26.95)	26.5 (78.25, 13.525)	0.214
AKI, n (%)	16 (20.5)	9 (14)	7 (50)	0.003
Solid tumours, n (%)	18 (23)	12 (20.3)	5 (37.5)	0.22
Hematological malignancies, n (%)	4 (5.1)	2 (3.1)	2 (14.1)	0.117
Duration of hospitalization until	1 (7,0)	1 (7,0)	0 (9.5,0)	0.952

indexed culture, days, median (IQR)				
Time until appropriate antipseudomonal therapy, days, median (IQR)	1 (2,0)	1 (2,0)	1 (2.75,1)	0.603
Treated in ICU, days, mean (SD)	7 (9)	3 (4.7)	4 (28.6)	0.005
IQR, interquartile range; IHD, ischemic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury; ICU, intensive care unit.				

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392 Table 2: %fT>MIC by different creatinine clearance groups

Creatinine clearance mL/min	%fT>MIC, median	%fT>MIC, IQR
0-20 (n=19)	82	69-89
21-40 (n=19)	65	45-85
41-60 (n=5)	47	43-90
61-80 (n=5)	69	55-99
81-100 (n=11)	53	40-70
101-120 (n=6)	54	50-60
>120 (n=13)	56	35-75

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395 Table 3: Logistic regression model of in-hospital survival

	Adjusted OR for in-hospital survival	P-value	95% CI
%fT>MIC > 60%	7.74	0.023	1.32-45.2
AKI	0.14	0.003	0.001-0.234
Modified APACHE II ≥ 14	0.113	0.018	0.019-0.685
AKI * Modified APACHE II ≥ 14	20.65	0.05	1.99-420.8

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398 Table 4: Different %fT>MIC thresholds effect on in-hospital survival

	Adjusted OR for in-hospital survival	P-value	95% CI
%fT>MIC > 40%	3.70	0.151	0.62-22
%fT>MIC > 50%	3.76	0.100	0.77-18.18
%fT>MIC > 60%	7.74	0.023	1.32-45.2
%fT>MIC > 70%	2.55	0.199	0.61-10.65
%fT>MIC > 80%	2.25	0.280	0.52-9.82

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