A clinical predictive model of multidrug resistance in neutropenic cancer patients with bloodstream infection due to *Pseudomonas aeruginosa* (IRONIC study)

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Abstract

Background: We aimed to assess the rate and predictive factors of bloodstream infection (BSI) due to multidrug-resistant (MDR) Pseudomonas aeruginosa (PA) in neutropenic cancer patients.

Methods: We performed a multicenter, retrospective cohort study including onco-hematological neutropenic patients with BSI due to PA conducted across 34 centers in 12 countries from January 2006 to May 2018. A mixed logistic regression model was used to estimate a model to predict multidrug resistance of the causative pathogens.

Results: Of a total of 1217 episodes of BSI due to PA, 309 episodes (25.4%) were caused by MDR strains. The rate of multidrug resistance increased significantly over the study period (p=0.033). Predictors of MDRPA BSI were prior therapy with piperacillin/tazobactam (odds ratio [OR], 3.48; 95% confidence interval [CI], 2.29-5.30), prior antipseudomonal carbapenem use (OR, 2.53; 95% CI, 1.65-3.87), fluoroquinolone prophylaxis (OR, 2.99; 95% CI, 1.92-4.64), underlying hematological disease (OR, 2.09 95% CI, 1.26-3.44) and the presence of a urinary catheter (OR, 2.54; 95% CI, 1.65-3.91), whereas older age (OR, 0.98; 95% CI, 0.97-0.99) was found to be protective.

Conclusions: Our prediction model achieves good discrimination and calibration, thereby identifying neutropenic patients at higher risk of BSI due to MDRPA. The application of this model using a web-based calculator may be a simple strategy to identify high-risk patients, who may benefit from the early administration of a broad-spectrum antibiotic coverage against MDR strains according to the local susceptibility patterns, thus avoiding the use of broad-spectrum antibiotics in patients at low risk of resistance.

Keywords: Multidrug-resistant, *Pseudomonas aeruginosa*, bacteremia, bloodstream infection, neutropenia, cancer, risk factors, predictive model.

144 **INTRODUCTION**

145 Bloodstream infection (BSI) is an important cause of morbidity and mortality in
146 neutropenic cancer patients. In recent years, an increase of BSI caused by Gram-
147 negative bacilli (GNB) has been reported in this population, as has the emergence of
148 antibiotic resistance [1-5].

149 *Pseudomonas aeruginosa* (PA) has classically been one of the most important
150 causes of severe sepsis and death among cancer patients with neutropenia [6-8].
151 Recent data in patients with hematologic malignancies show that it carries a poor
152 prognosis and is associated with the highest mortality among different BSIs [9]. In part,
153 this may be due to multidrug-resistant PA (MDRPA) that has been found at high rates
154 in some series involving hematologic patients, particularly in Italy [10-15]. Importantly,
155 inadequate empirical antibiotic therapy is frequently administered in this scenario,
156 which contributes to poor survival [10-12,15].

157 The recent implementation of new treatment modalities, such as highly toxic
158 myelosuppressive therapies, different types of hematopoietic stem cell transplants,
159 and the wide use of other invasive procedures, may have had an impact on the risk of
160 the development of antibiotic resistance. Very few studies have examined the risk
161 factors for MDRPA infections in patients with cancer under these new and evolving
162 conditions, or in the current era of widespread antimicrobial resistance [16,17].

163 Identifying the risk factors of infection due to MDRPA in neutropenic cancer
164 patients could help physicians recognize patients at higher risk more rapidly. Prompt
165 administration of an empirical therapy active against MDR strains in these high-risk
166 patients might benefit their outcomes. In this regard, estimating the probability of
167 antibiotic resistance using a clinical prediction model could be useful for stratifying

patients according to their risk. In this line, Viasus *et al*. recently reported a score which identified hematological malignancy, nosocomial acquisition, prior treatment with antipseudomonal cephalosporins and quinolones, corticosteroids, and breakthrough BSI during treatment with quinolones and β-lactams other than ertapenem as independent risk factors for MDRPA BSI in neutropenic patients [18]. A limitation of that study was its single center design, the relatively small number of BSI episodes, and that no external validation was performed. Also, the use of a clinical prediction model could help avoid the use of broad-spectrum antibiotics in patients with low risk of resistance, and therefore, improve the antibiotic stewardship.

The aim of the present study was to assess the rate and evolution of multidrug resistance among PA isolates causing BSI in neutropenic cancer patients over the last years, and to develop a clinical prediction model to estimate the probability of multidrug resistance acquisition in this population. To this end, we used data from a large multicenter, international cohort from 34 centers in 12 countries.

METHODS

Study Design, Patients and Setting

This study is part of the IRONIC project: a multicenter, international, retrospective cohort study of adult (≥ 18 years) neutropenic onco-hematological patients, including hematopoietic stem cell transplant (HSCT) recipients, diagnosed with at least one episode of PA BSI from January 1st 2006 to May 31st 2018. Subsequent episodes caused by PA occurring in the same patient were included in the study if the interval between them was >1 month.

For this study, all episodes of PA BSI included in the IRONIC database were included. Patients were recruited retrospectively from 34 centers in 12 countries: Spain (14), Turkey (4), Brazil (3), Italy (3), Argentina (2), Germany (2), Chile (1), Colombia (1), Lebanon (1), Slovakia (1), Switzerland (1) and the United Kingdom (1). The number of patients recruited at each center is provided in the Supplementary Material. The study was conducted in accordance with the STROBE recommendations, and the protocol has been published elsewhere [19].

The protocol of the study was approved by all the appropriate regulatory agencies and local Research Ethics Committees. The need for informed consent and information sheets was waived by the Ethics Committees because of the retrospective nature of the study.

Definitions

Neutropenia was defined as an absolute neutrophil count $<0.5 \times 10^9$/L. The Multinational Association for Supportive Care in Cancer (MASCC) score was calculated as described elsewhere [20]. Low-risk BSI was considered when the infection originated in the urinary tract, or was secondary to vascular catheter infection or to

gut translocation (endogenous source). Episodes of BSI originating from other sources were considered high-risk BSI [21]. Antimicrobial therapy administered before susceptibility results were available was considered as empirical therapy. Empirical antibiotic therapy was considered adequate when it included at least one *in vitro* antibiotic active against the PA strain causing the infection. BSI was considered to be persistent if the blood cultures were positive after the first 48 hours of adequate antibiotic therapy. Early case-fatality rate was defined as death from any cause within 7 days of BSI onset. Overall 30-day case-fatality rate was defined as death from any cause within 30 days of BSI onset.

Microbiological studies

Clinical samples were processed at the microbiology laboratories of each participating center in accordance with standard operating procedures. PA was identified using standard microbiological techniques at each centre. *In vitro* susceptibility was determined according to the EUCAST recommendations in the great majority of centers [22]. In the Lebanese center and in one center from Argentina the CLSI cut offs were used, and in the center from the United Kingdom, BSAC recommendations were used before 2016 [23]. PA isolate phenotypes were stratified in accordance with recent standard definitions [24]. We determined MDRPA when the isolate was not susceptible to at least one agent in three or more of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal cephalosporins, antipseudomonal penicillins + beta-lactamase-inhibitors, monobactams, fosfomycin, and polymyxins. Moreover, we determined extensively-resistant (XDR) PA when the isolate was not susceptible to at least one agent in all but two or fewer of these antimicrobial categories.

240 **Statistical analysis**

241 The original cohort was randomly split in a derivation cohort, including 80% of the
242 patients, and a validation cohort, consisting of the rest of patients.

243 The set of candidate risk factors to be included in the model was extracted from
244 the IRONIC case report form, and it mainly included socio-demographic variables,
245 underlying conditions (hematological malignancy vs solid tumor and comorbidities),
246 immunosuppressants and antibiotics administrated within the last 30 days, indwelling
247 catheters, prior hospitalization or intensive care unit (ICU) admission and infection-
248 related variables, including MASCC index score, shock, source of BSI, etc.

249 A mixed logistic regression model was used to estimate a predictive model for the
250 development of multidrug resistance based on the patient's medical history and
251 clinical findings. The decision to use a mixed model was based on analysis of the
252 variability in rates of MDR infection between centers using funnel plots. Such plots
253 allowed us to compare rates between centers/countries taking into account the
254 number of patients in each.

255 First, we performed a descriptive analysis of the factors assessed for the
256 development of MDR infections. Multiple imputation with chained equations (MICE)
257 was then used to minimize the impact of missing data, for those variables where data
258 was missing [25]. Ten datasets were created, using the Gaussian normal regression
259 method to impute continuous variables (MASCC risk index score) and the binomial
260 logistic regression method to impute categorical variables (high-risk BSI, high-risk
261 MASCC index score, comorbidities, urinary catheter, hypotension, corticosteroids,
262 severe mucositis, prior hospital admission, prior fluoroquinolone prophylaxis,
263 orotracheal intubation, ICU admission, prior episode of BSI during hospitalization, any

venous catheter and septic shock). Each imputed dataset was sampled by bootstrapping with replacement 100 times, totaling 1,000 samples. Models were fitted for each of the 1,000 samples using backwards elimination. Predictors retained in more than 80% of the 1,000 estimated models were considered for inclusion in the final model. A model including the predictors selected was then estimated using the 10 imputed samples and adjusting the coefficients and standard errors for the variability between imputations according to the Rubin rules [25,26]. Finally, discrimination was assessed by estimating the area under the ROC curve (AUC). This area indicates the probability that a patient with an infection due to a MDR strain had a higher predicted probability than a patient without one, for random pairs of patients with and without such an infection. To assess calibration, observed versus expected episodes of MDR BSI were compared graphically by deciles of predicted risk. All validation analysis performed in the derived sample were also repeated in the reserved sample for validation [27]. The TRIPOD checklist for development and validation of predictive models is provided in the Supplementary Material.

All analyss were performed with a two-sided significance level of 0.05 and using R software, version 3.5 [28].

RESULTS

Rate of multidrug resistance

Of a total of 1217 episodes of BSI due to PA occurring in 1177 patients, 309 episodes (25.4%) were caused by MDR strains, of which 234 (19.3%) were considered to be XDR. The rate of multidrug resistance by country is detailed in Table 1. It was found to be the highest in Colombia and Argentina, followed by Italy, and it presented the lowest rates in the United Kingdom and Switzerland. Notably, the rate of multidrug resistance among PA isolates increased significantly over the study period (p=0.033) (Figure 1). The distribution of the rates of multidrug resistance according to the centers and the number of episodes included is shown in the Supplementary material (Fig Suppl 1).

Information regarding whether the PA strains were MDR or not was provided for all the isolates. A detailed susceptibility profile was available for 1156 PA strains. Of them, 18.6% were resistant to cefepime, 21.9% to ceftazidime, 25.2% to piperacillin/tazobactam, 23% to meropenem, 25.4% to imipenem, 26.7% to ciprofloxacin, 9.4% to amikacin, 11.3% to tobramycin and 1.2% to colistin. Fosfomycin, ceftazidime/avibactam and ceftolozane/tazobactam were tested in 312, 30 and 39 strains, and the rate of resistance was 10.4%, 0.7% and 1%, respectively.

Clinical characteristics

Baseline and clinical characteristics of all 1217 PA BSI episodes are reported in Table 2. The great majority of episodes occurred in hematological patients (75.3%), with acute leukemia (49.1%) being the most frequent underlying disease. Lung cancer (29.6%) was the most common malignancy among patients with solid tumors. Profound

neutropenia (<0.1x10^9/L) was present in 61.5% of the cases, and 23.8% were HSCT recipients. An endogenous source (37.4%) and pneumonia (25.6%) were the most frequent sources of BSI. More than one third of patients (33.9%) presented with septic shock. More than 50% of the patients had received antibiotics in the previous month.

Antibiotic treatment and outcomes

The early and overall case-fatality rates for the entire cohort were 27.8% and 40.1%, respectively, and they were particularly high in patients with high-risk BSI (33.9% and 48.7%, respectively). To assess the impact of antimicrobial resistance on patients' outcomes, we analyzed the rates of adequateness of empirical antibiotic therapy only in the 1000 monomicrobial episodes. In this cohort, early and overall case-fatality rates were 28.0% and 40.4%, respectively. Overall, 187 patients (18.7%) received inadequate initial empirical antibiotic therapy, of which 131 (70.1%) had an infection due to a MDR strain (p<0.001). Also, persistent BSI (19.2% vs. 7.4%, p<0.001), early (38.6% vs % 22.8%, p<0.001) and overall case-fatality rates (56.2% vs. 32.6%, p<0.001) were significantly higher in patients infected by MDR strains.

Clinical prediction tool for multidrug resistance

The variables included in the final model were: age (continuous variable), underlying disease (hematological malignancy vs solid tumor), fluoroquinolone prophylaxis, prior therapy with piperacillin/tazobactam, prior antipseudomonal carbapenems, urinary catheter, and center (Figure 2). The percentage of times that each factor appeared in all the estimated models is shown in the Supplementary Material (Table Suppl 1). All the variables included in the model were found to be associated with multidrug resistance, except for older age, which was found to protect against multidrug resistance development.

The predictive model obtained in the derivation cohort had excellent discrimination, with an AUC of 0.82 (95% CI 0.79-0.85) (Figure 3.1). The observed probability corresponded well to the predicted probability, both on average and over the whole range of predictions. A linear regression model had an intercept at 0 and a slope of 1 for the relation between observed and predicted multidrug resistance (Figure 4.1).

Internal validation also showed a fair discrimination, with an AUC of 0.72 (95% CI 0.63-0.80) (Figure 3.2), and good agreement between prediction and observation (Figure 4.2).

We developed an intuitive online tool to calculate the risk of multidrug resistance using the clinical prediction model that we estimated (http://ubidi.shinyapps.io/ironic). Whether the tool is suitable for use to support treatment decisions should be evaluated externally and locally as an intervention [29]. The explanation of how to use the tool is provided in the Supplementary Material.

DISCUSSION

Using data from a large international cohort we have developed a clinical predictive model that allows us to accurately identifying neutropenic cancer patients at high risk of BSI due to MDRPA. This clinical tool may benefit these patients by improving the administration of adequate empirical antibiotic treatment, and it may also help optimize the efficacy of antibiotic stewardship programs.

Of particular concern, we found an overall high rate of multidrug resistance among PA isolates, and importantly, a significant increase was observed over time. These findings are in line with other reports that focused on hematological patients [11-13,15,17], although most of those studies were conducted in the same geographical area. The emergence of resistance among PA isolates causing infection in neutropenic patients is worrisome, since the administration of inadequate empirical antibiotic therapy severely impairs patients' outcomes [11,12,15]. Indeed, we found significantly higher early and overall mortality rates in patients with MDRPA BSI. In addition, in a recent study focused on patients with acute leukemia and BSI, inadequate empirical antibiotic therapy was the only modifiable risk factor independently associated with mortality in patients with MDRPA BSI [30]. Therefore, identifying patients at risk of infection due to resistant strains is imperative in order to administer broad-spectrum empirical antibiotics based on local susceptibility patterns, and improve patient outcomes. The development of a predictive model could be helpful in assessing and stratifying this risk, and the use of a straightforward web-based calculator would facilitate a prompt application of the predictive model in an easy way at the bedside.

The most important factors associated with the development of antibiotic resistance in our predictive model were exposure to β-lactam antibiotics, such as piperacillin/tazobactam and antipseudomonal carbapenems, and more importantly, the use of fluoroquinolone prophylaxis. The use of broad-spectrum antipseudomonal β-lactams is frequent in cancer patients, who may present repeated chemotherapy-induced episodes of febrile neutropenia. Nevertheless, these antibiotics, and particularly carbapenems, should be used reasonably, and the duration of empirical antibiotic treatments can be safely shortened, particularly in asymptomatic patients, regardless of their neutrophil count, as we recently demonstrated in a randomized clinical trial [31]. Other researchers have also suggested that exposure to fluoroquinolones is a risk factor for infection due to MDR Gram-negative bacilli in cancer patients [16,17,32-33]. Hakki *et al*. recently reported the association between fluoroquinolone prophylaxis and breakthrough BSI with PA strains that are not susceptible to meropenem, probably due to mutations increasing efflux pump activity [16]. In addition, fluoroquinolone exposure has been associated with increased risk of *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* infection [34, 35]. This is of special concern since the use of universal prophylaxis with fluoroquinolones in neutropenic patients is still routine practice in some institutions. In the absence of current evidence of its impact on mortality, this practice should be seriously reconsidered [36].

Urinary catheter has previously been reported as an independent risk factor for MDRGNB BSI in cancer patients [37]. This finding could be hypothetically explained by the association between the use of urinary catheters and the increased risk of urinary

tract infections. Even though the rate of BSI originated in the urinary tract in our study was found to be low, its diagnosis could have been limited in our patients whose inflammatory response and symptoms would be decreased due to their neutropenia, therefore leading to a low number of urine cultures performed.

The main strength of the present study is the large number of participating centers, from 12 countries around the world. This confers a clear advantage related to larger sample size and more generalizable results. Moreover, to estimate the clinical prediction model we used a robust methodology, including multiple imputations to account for missing data, bootstrapping to minimize over fitting and a validation process. Also, the center effect was addressed including this variable in the model. However, there are some limitations that should be acknowledged. This is a retrospective study, so the main limitation of the data is related to the potential effects of unmeasured variables and residual confounding. Also, different antimicrobial susceptibility testing methods and different interpretive criteria were used among the different centers, and breakpoints changed during the study period. In addition, the model was validated with data that, while not used to estimate the model, there were derived from the same sample, so real external validation is required and is anticipated in the near future. Finally, since this model is specific for MDRPA, it's clinical utility will be limited to patients who are found to hava BSI due to PA and the susceptibility testing results are pending.

In conclusion, the prevalence of multidrug resistance among PA isolates causing BSI in neutropenic cancer patients is an alarming emerging problem. Reasonable use of broad-spectrum β-lactams, and particularly carbapenems, is

strongly recommended in order to limit the development of resistance. In addition, the use of universal fluoroquinolone prophylaxis in neutropenic patients should be reconsidered in the current era of increasing antimicrobial resistance. Even though it needs external validation, the proposed prediction model achieves good discrimination and calibration allowing the risk of BSI due to MDRPA to be estimated in this high-risk population. The application of a predictive model using a web-based calculator would be a simple strategy to identify those patients at the highest risk of infection due to MDR strains, who may benefit from broad-spectrum antibiotic coverage, according to the local susceptibility patterns, and it could also help avoid the use of broad-spectrum antibiotics in patients with low risk of resistance.

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Transparency declarations

Nothing to declare

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698 **Figure legends**

699 Figure 1. Evolution of multidrug resistance rates among *Pseudomonas aeruginosa*
700 isolates from 2006 to 2018.

701 Figure 2. Odds Ratio and 95% confidence intervals for multidrug resistance predictors
702 included in the final model.

703 Figure 3.1 Area under the curve of the predictive model of multidrug resistance in
704 patients with *Pseudomonas aeruginosa* bloodstream infection in the derivation cohort.

705 Figure 3.2 Area under the curve of the predictive model of multidrug resistance in
706 patients with *Pseudomonas aeruginosa* bloodstream infection in the validation cohort.

707 Figure 4.1 Observed versus predicted risk of multidrug-resistant *Pseudomonas*
708 *aeruginosa* bloodstream infection, stratified by deciles of predicted risk, in the
709 derivation cohort.

710 Figure 4.2 Observed versus predicted multidrug-resistant *Pseudomonas aeruginosa*
711 bloodstream infection, stratified by deciles of predicted risk, in the validation cohort.

Table 1. Rates of multidrug resistance among *Pseudomonas aeruginosa* isolates by country.

Country	Number of included episodes	Rate of MDRPA	95% Confidence interval
Colombia	19	57.89	[33.50-79.74]
Argentina	47	46.81	[32.11-61.92]
Italy	123	40.65	[31.88-49.87]
Chile	13	30.77	[9.09-61.42]
Slovakia	32	25	[11.46-43.40]
Turkey	114	24.56	[16.98-33.50]
Spain	642	23.21	[19.99-26.67]
Brazil	125	19.2	[12.70-27.20]
Lebanon	22	18.18	[5.18-40.28]
Germany	41	12.2	[4.08-26.20]
Switzerland	28	10.71	[2.26-28.22]
United Kingdom	11	9.091	[0.23-41.27]

MDRPA: multidrug-resistant *Pseudomonas aeruginosa*

Table 2. Baseline and clinical characteristics of neutropenic cancer patients with *Pseudomonas aeruginosa* bloodstream infection.

Characteristic	Non-MDRPA N= 908 (%)	MDRPA N=309 (%)	Study population N = 1217 (%)	P value
Mean age in years (DS)	58.9 (16.2)	54.4 (15.5)	57.8 (16.2)	<0.001
Male sex	577 (63.5)	174 (56.3)	751 (61.7)	0.028
Hematological disease	641 (70.6)	276 (89.3)	917 (75.3)	<0.001**
Acute leukemia/Myelodysplastic syndrome	287 (31.6)	164 (53)	451 (37)	
Lymphoma	235 (25.8)	71 (22.9)	306 (25.1)	
Multiple myeloma/Waldenström disease	59 (6.4)	15 (4.8)	74 (6)	
Other	60 (6.6)	26 (8.4)	46 (3.7)	
Hematopoietic stem cell transplant (HSCT)	182 (26.6)	108 (35.0)	290 (23.8)	0.001
Allogeneic HSCT	97 (10.6)	80 (25.8)	177 (14.5)	
Autologous HSCT	85 (9.3)	28 (9)	113 (9.2)	
GVHD	49 (5.3)	29 (9.3)	78 (6.4)	0.336
Solid tumor	267 (29.4)	33 (10.6)	300 (24.6)	<0.001**
Lung cancer	79 (8.7)	10 (3.2)	89 (7.3)	
Lower gastrointestinal tract tumor	28 (3)	2 (0.6)	30 (2.4)	
Urinary tract cancer	24 (2.6)	5 (15.1)	29 (2.3)	
Breast cancer	28 (3)	0	28 (2.3)	
Head and neck tumor	22 (2.4)	4 (0.3)	26 (2.1)	
Other	86 (9.4)	12 (3.8)	98 (8.05)	
Comorbidities	453 (52.1)	133 (45.7)	586 (50.5)	0.067
Diabetes mellitus	75 (8.2)	11 (3.5)	86 (7)	0.009
Chronic heart disease	106 (11.6)	44 (14.2)	150 (12.3)	0.236
Chronic obstructive pulmonary disease	79 (8.7)	21 (6.7)	100 (8.2)	0.387
Chronic liver disease	25 (2.7)	11 (3.5)	36 (2.9)	0.566
Chronic renal disease	26 (2.8)	6 (1.9)	32 (2.6)	0.528
Profound neutropenia (<0.1x10^9/L)	526 (59.7)	202 (66.9)	728 (61.5)	0.032

High risk MASCC index score (<21 points)	551 (67.2)	213 (74.7)	764 (69.1)	<0.001
Grade III-IV mucositis	111 (12.4)	58 (19.1)	169 (14.1)	0.005
Previous corticosteroid therapy (1 month)	456 (51.3)	176 (58.1)	632 (53)	0.048
Prior fluoroquinolone prophylaxis (1 month)	98 (10.9)	97 (31.7)	195 (16.2)	<0.001
Prior antibiotic therapy (1 month)	414 (46.5)	251 (81.8)	665 (55.6)	<0.001
Prior piperacillin-tazobactam (1 month)	98 (10.8)	101 (32.7)	199 (16.4)	<0.001
Prior anti-pseudomonal carbapenem (1 month)	98 (10.8)	103 (33.3)	201 (16.5)	<0.001
Prior anti-pseudomonal cephalosporin (1 month)	72 (7.9)	26 (8.4)	98 (8.1)	0.80
Prior/current ICU admission	78 (8.6)	49 (15.9)	127 (10.5)	0.001
Previous hospitalization (3 months)	553 (61.5)	191 (62.6)	744 (61.8)	0.782
Nosocomial acquisition	177 (19.5)	40 (12.9)	694 (57.0%)	<0.001
Urinary catheter	122 (13.8)	84 (28.1)	206 (17.4)	<0.001
Intravascular catheter	626 (68.9)	282 (91.6)	908 (74.7)	<0.001
Central venous catheter	452 (49.7)	164 (53)	692 (56.8)	
Axillary temperature ≥ 38ºC	797 (88.6)	285 (92.5)	1082 (88.9)	0.062
Septic shock at presentation	271 (29.9)	140 (45.5)	411 (33.9)	<0.001
Ecthyma gangrenosum	33 (3.7)	18 (5.9)	51 (4.2)	0.135
Polymicrobial bloodstream infection	177 (19.5)	40 (12.9)	217 (17.8)	0.012
High-risk bloodstream infection	420 (52.2)	141 (48.5)	561 (51.2)	0.308
Source of bloodstream infection				0.022
Endogenous source	351 (38.7)	104 (33.7)	455 (37.4)	
Pneumonia	226 (24.9)	85 (27.5)	311 (25.6)	
Intravascular catheter infection	74 (8.2)	38 (12.3)	112 (9.2)	
Neutropenic enterocolitis	60 (6.6)	11 (3.5)	71 (5.8)	
Skin and soft tissue infection	46 (5.1)	24 (7.7)	70 (5.7)	
Other abdominal	50 (5.5)	8 (2.5)	58 (4.7)	
Urinary tract infection	37 (4.1)	14 (4.5)	51 (4.1)	
Perianal abscess	26 (2.8)	8 (2.5)	34 (2.8)	
Unknown	11 (1.2)	5 (1.6)	16 (1.3)	

Other*	27 (3.0)	12 (3.9)	39 (3.2)	

MDRPA: Multidrug-resistant *Pseudomonas aeruginosa*; MASCC: Multinational Association for Supportive Care in Cancer; ICU: Intensive care unit

*Other: mucositis 24, odontogenic 9, sinusitis 4, otitis 2; ** Comparison solid tumor vs hematological disease

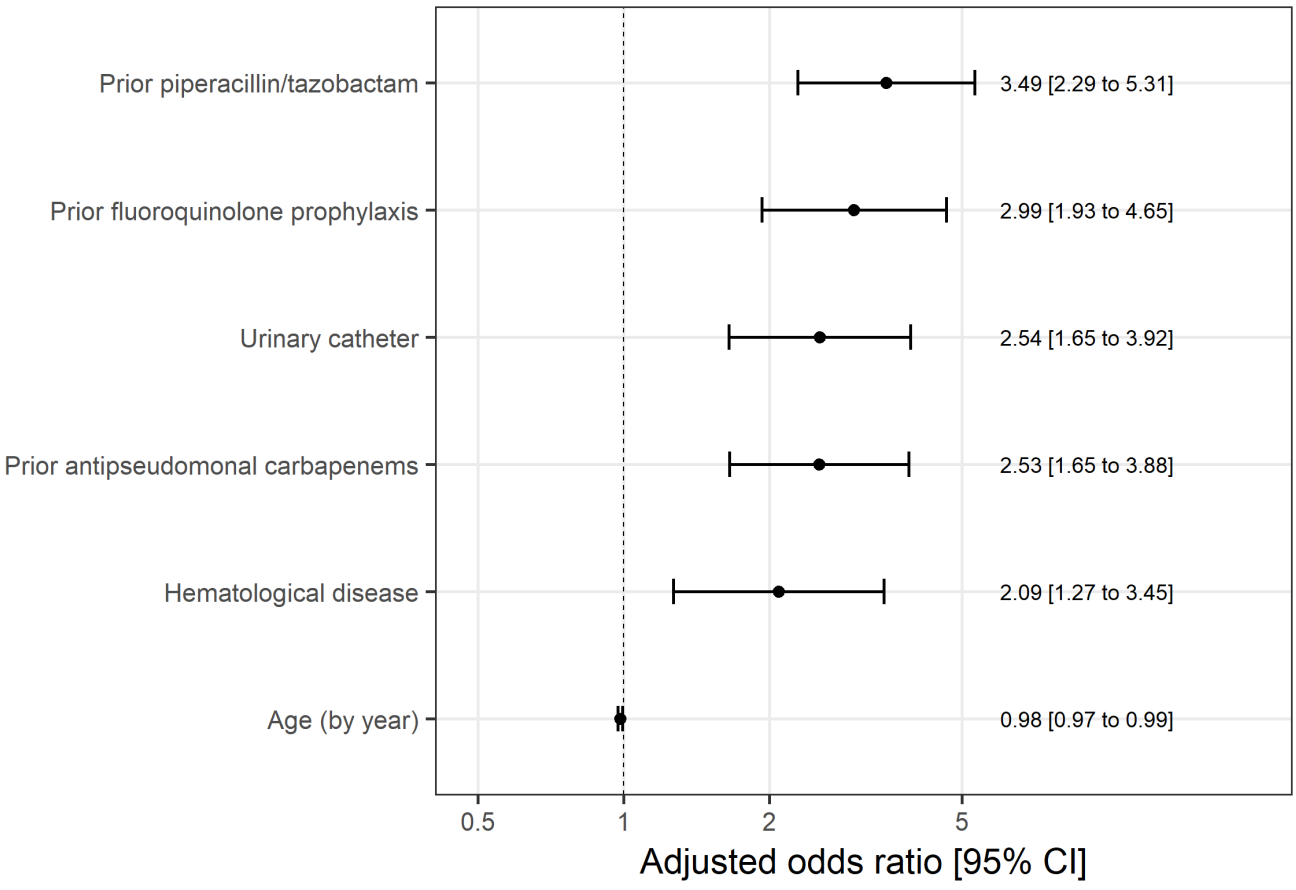

Figure 3.1

Figure 3.2

Figure 4.1

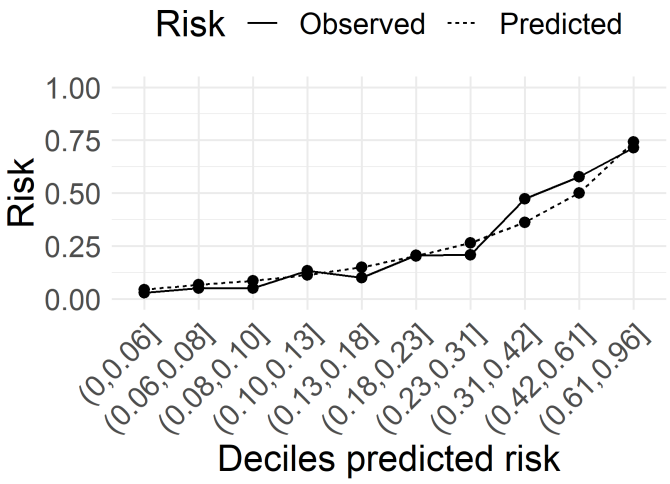

Figure 4.2