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EPIDEMIOLOGY AND SURVEILLANCE

Clinical Predictive Model of Multidrug Resistance in Neutropenic Cancer Patients with Bloodstream Infection Due to *Pseudomonas aeruginosa*

C. Gudiol,[a,b,nn] A. Albasanz-Puig,[a,nn] J. Laporte-Amargós,[a] N. Pallarès,[c] A. Mussetti,[d] I. Ruiz-Camps,[e,nn] P. Puerta-Alcalde,[f,nn] E. Abdala,[g] C. Oltolini,[h] M. Akova,[i] M. Montejo,[j,nn] M. Mikulska,[k] P. Martín-Dávila,[l,nn] F. Herrera,[m] O. Gasch,[n,nn] L. Drgona,[o] H. Paz Morales,[p] A.-S. Brunel,[q] E. García,[r] B. Isler,[s] W. V. Kern,[t] I. Morales,[u,nn] G. Maestro-de la Calle,[v] M. Montero,[w,nn] S. S. Kanj,[x] O. R. Sipahi,[y] S. Calik,[z] I. Márquez-Gómez,[aa] J. I. Marin,[bb,cc] M. Z. R. Gomes,[dd] P. Hemmatti,[ee] R. Araos,[ff,gg] M. Peghin,[hh] J. L. del Pozo,[ii] L. Yáñez,[jj] R. Tilley,[kk] A. Manzur,[ll] A. Novo,[mm] J. Carratalà,[a,nn] for the IRONIC Study Group

[a]Infectious Diseases Department, Bellvitge University Hospital, IDIBELL, University of Barcelona, Barcelona, Spain
[b]Institut Català d'Oncologia (ICO)-Hospital Duran i Reynals, IDIBELL, Barcelona, Spain
[c]Statistics Advisory Service, Institute of Biomedical Research of Bellvitge, Barcelona, Spain
[d]Haematology Department, Institut Català d'Oncologia (ICO)-Hospital Duran i Reynals, IDIBELL, Barcelona, Spain
[e]Infectious Diseases Department, Vall d'Hebron University Hospital, Barcelona, Spain
[f]Infectious Diseases Department, Hospital Clínic i Provincial, Barcelona, Spain
[g]Instituto do Câncer do Estado de São Paulo, Faculty of Medicine, University of São Paulo, São Paulo, Brazil
[h]Unit of Infectious and Tropical Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy
[i]Department of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey
[j]Infectious Diseases Unit, Cruces University Hospital, Bilbao, Spain
[k]Division of Infectious Diseases, University of Genoa (DISSAL) and Ospedale Policlinico San Martino, Genoa, Italy
[l]Infectious Diseases Department, Ramon y Cajal Hospital, Madrid, Spain
[m]Infectious Diseases Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina
[n]Infectious Diseases Department, Parc Taulí University Hospital, Sabadell, Spain
[o]Oncohematology Department, Comenius University and National Cancer Institute, Bratislava, Slovakia
[p]Infectious Diseases Department, Hospital Erasto Gaertner, Curitiba, Brazil
[q]Infectious Diseases Department, Department of Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[r]Haematology Department, Reina Sofía University Hospital-IMIBIC-UCO, Córdoba, Spain
[s]Department of Infectious Diseases and Clinical Microbiology, Istanbul Education and Research Hospital, Istanbul, Turkey
[t]Division of Infectious Diseases, Department of Medicine II, University of Freiburg Medical Center and Faculty of Medicine, Freiburg, Germany
[u]Emergency Clinical Unit and Infectious Diseases Division, Hospital Universitario Virgen Macarena, Seville, Spain
[v]Infectious Diseases Unit, Instituto de Investigación Hospital 12 de Octubre (i+12), 12 de Octubre University Hospital, School of Medicine, Universidad Complutense, Madrid, Spain
[w]Infectious Diseases Service, Hospital del Mar, Infectious Pathology and Antimicrobials Research Group (IPAR), Institut Hospital del Mar d'Investigations Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB), CEXS-Universitat Pompeu Fabra, Barcelona, Spain
[x]Infectious Diseases Division, American University of Beirut Medical Center, Beirut, Lebanon
[y]Ege University Faculty of Medicine, Izmir, Turkey
[z]University of Health Science Izmir Bozyaka Training and Research Hospital, Izmir, Turkey
[aa]Infectious Diseases Department, Hospital Regional de Málaga, Málaga, Spain
[bb]Infectious Diseases and Clinical Microbiology Department, Clínica Maraya, Pereira, Colombia
[cc]Critical Care and Clinical Microbiology Department, Manizales, Colombia
[dd]Hospital Federal dos Servidores do Estado and Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Ministério da Saúde, Rio de Janeiro, Brazil
[ee]Department of Hematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann, Academic Teaching Hospital of Charité University Medical School, Berlin, Germany
[ff]Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana, Universidad del

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Address correspondence to C. Gudiol, cgudiol@iconcologia.net, or J. Carratalà, jcarratala@bellvitgehospital.cat.

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Desarrollo, Santiago de Chile, Chile
[gg]Millennium Initiative for Collaborative Research on Bacterial Resistance (MICROB-R), Santiago de Chile, Chile
[hh]Infectious Diseases Clinic, Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Integrata, Udine, Italy
[ii]Infectious Diseases and Microbiology Unit, Navarra University Clinic, Pamplona, Spain
[jj]Haematology Department, Marqués de Valdecilla University Hospital, Santander, Spain
[kk]Microbiology Department, University Hospitals Plymouth NHS Trust, Plymouth, United Kingdom
[ll]Infectious Diseases, Hospital Rawson, San Juan, Argentina
[mm]Haematology Department, Son Espases University Hospital, Palma de Mallorca, Spain
[nn]Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001), Instituto de Salud Carlos III, Madrid, Spain

ABSTRACT We aimed to assess the rate and predictive factors of bloodstream infection (BSI) due to multidrug-resistant (MDR) *Pseudomonas aeruginosa* in neutropenic cancer patients. We performed a multicenter, retrospective cohort study including oncohematological neutropenic patients with BSI due to *P. aeruginosa* 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 the multidrug resistance of the causative pathogens. Of a total of 1,217 episodes of BSI due to *P. aeruginosa*, 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 MDR *P. aeruginosa* BSI were prior therapy with piperacillin-tazobactam (odds ratio [OR], 3.48; 95% confidence interval [CI], 2.29 to 5.30), prior antipseudomonal carbapenem use (OR, 2.53; 95% CI, 1.65 to 3.87), fluoroquinolone prophylaxis (OR, 2.99; 95% CI, 1.92 to 4.64), underlying hematological disease (OR, 2.09; 95% CI, 1.26 to 3.44), and the presence of a urinary catheter (OR, 2.54; 95% CI, 1.65 to 3.91), whereas older age (OR, 0.98; 95% CI, 0.97 to 0.99) was found to be protective. Our prediction model achieves good discrimination and calibration, thereby identifying neutropenic patients at higher risk of BSI due to MDR *P. aeruginosa*. 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 broad-spectrum antibiotic coverage against MDR strains according to the local susceptibility patterns, thus avoiding the use of broad-spectrum antibiotics in patients at a low risk of resistance development.

KEYWORDS multidrug resistant, *Pseudomonas aeruginosa*, bacteremia, bloodstream infection, neutropenia, cancer, risk factors, predictive model

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

Pseudomonas aeruginosa has classically been one of the most important causes of severe sepsis and death among cancer patients with neutropenia (6–8). Recent data in patients with hematological malignancies show that BSI carries a poor prognosis and is associated with the highest mortality among different groups of patients with BSIs (9). In part, this may be due to multidrug-resistant (MDR) *P. aeruginosa*, which has been found at high rates in some series involving patients with hematological malignancies, particularly in Italy (10–15). Importantly, inadequate empirical antibiotic therapy is frequently administered in this scenario, which contributes to poor survival (10–12, 15).

The recent implementation of new treatment modalities, such as highly toxic myelosuppressive therapies, different types of hematopoietic stem cell transplants (HSCT), and the widespread use of other invasive procedures, may have had an impact on the risk of development of antibiotic resistance. Very few studies have examined the risk factors for MDR *P. aeruginosa* infections in patients with cancer under these new and evolving conditions or in the current era of widespread antimicrobial resistance (16, 17).

Identifying the risk factors for infections due to MDR *P. aeruginosa* in neutropenic

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

Country	No. of episodes included	Rate (%) of MDR[a] *P. aeruginosa*	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

[a]MDR, multidrug resistant.

cancer patients could help physicians more rapidly recognize patients at higher risk. Prompt administration of an empirical therapy active against MDR strains in these high-risk patients might benefit their outcomes. In this regard, estimating the probability of antibiotic resistance using a clinical prediction model could be useful for stratifying patients according to their risk. Along this line, Viasus et al. recently reported a score which identified hematological malignancy, nosocomial acquisition, prior treatment with antipseudomonal cephalosporins and quinolones, prior treatment with corticosteroids, and breakthrough BSI during treatment with quinolones and β-lactams other than ertapenem to be independent risk factors for MDR *P. aeruginosa* BSI in neutropenic patients (18). A limitation of that study was its single-center design, the relatively small number of BSI episodes, and the lack of performance of external validation. Also, the use of a clinical prediction model could help avoid the use of broad-spectrum antibiotics in patients with a low risk of resistance development and, therefore, improve antibiotic stewardship.

The aim of the present study was to assess the rate and evolution of multidrug resistance among *P. aeruginosa* isolates causing BSI in neutropenic cancer patients over recent 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.

RESULTS

Rate of multidrug resistance. Of a total of 1,217 episodes of BSI due to *P. aeruginosa* occurring in 1,177 patients, 309 episodes (25.4%) were caused by MDR strains, of which 234 (19.3%) were considered to be extensively drug resistant (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 *P. aeruginosa* isolates increased significantly over the study period ($P = 0.033$) (Fig. 1). The distribution of the rates of multidrug resistance according to the centers and the number of episodes included is shown in fig. S1 in the supplemental material.

Information regarding whether the *P. aeruginosa* strains were MDR or not was provided for all the isolates. A detailed susceptibility profile was available for 1,156 *P. aeruginosa* strains. Of them, 18.6% were resistant to cefepime, 21.9% were resistant to ceftazidime, 25.2% were resistant to piperacillin-tazobactam, 23% were resistant to meropenem, 25.4% were resistant to imipenem, 26.7% were resistant to ciprofloxacin, 9.4% were resistant to amikacin, 11.3% were resistant to tobramycin, and 1.2% were resistant to colistin. The activities of fosfomycin, ceftazidime-avibactam, and ceftolozane-tazobactam were tested against 312, 30, and 39 strains, respectively, and the rates of resistance were 10.4%, 0.7%, and 1%, respectively.

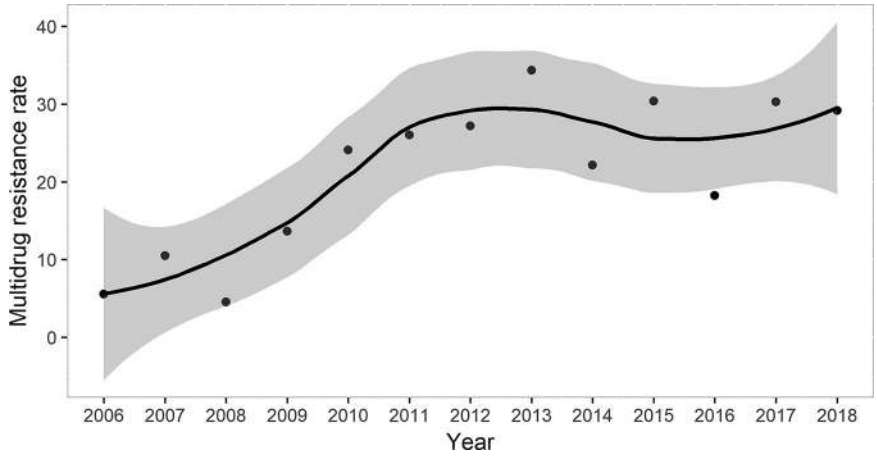

FIG 1 Evolution of multidrug resistance rates among *Pseudomonas aeruginosa* isolates from 2006 to 2018.

Clinical characteristics. The baseline and clinical characteristics of all 1,217 *P. aeruginosa* BSI episodes are reported in Table 2. The great majority of episodes occurred in patients with hematological malignancies (75.3%), with acute leukemia (44.7%) being the most frequent underlying disease. Lung cancer (29.6%) was the most common malignancy among patients with solid tumors. Profound neutropenia ($<0.1 \times 10^9$/liter) was present in 61.5% of the cases, and 23.8% of the cases were in HSCT recipients. An endogenous source (37.4%) and pneumonia (25.6%) were the most frequent sources of BSI. More than one-third of the 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 the patients' outcomes, we analyzed the rates of adequateness of empirical antibiotic therapy only in the 1,000 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 an MDR strain ($P < 0.001$). Also, the rates of persistent BSI (19.2% versus 7.4%, $P < 0.001$), early case fatality rates (38.6% versus % 22.8%, $P < 0.001$), and overall case fatality rates (56.2% versus 32.6%, $P < 0.001$) were significantly higher in patients infected with MDR strains than in those infected with susceptible strains.

Clinical prediction tool for multidrug resistance. The variables included in the final model were age (continuous variable), underlying disease (hematological malignancy versus solid tumor), fluoroquinolone prophylaxis, prior therapy with piperacillin-tazobactam, prior therapy with antipseudomonal carbapenems, the presence of a urinary catheter, and center (Fig. 2). The percentage of the time that each factor appeared in all the estimated models is shown in Table S1. 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 area under the receiver operating characteristic (ROC) curve (AUC) of 0.82 (95% confidence interval [CI], 0.79 to 0.85) (Fig. 3, left). 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

TABLE 2 Baseline and clinical characteristics of neutropenic cancer patients with *Pseudomonas aeruginosa* bloodstream infection[a]

Characteristic	Value for patients with:			
	Non-MDR *P. aeruginosa* infection (n = 908)	MDR *P. aeruginosa* (n = 309)	Study population (n = 1,217)	*P* value
Mean (SD) age (yr)	58.9 (16.2)	54.4 (15.5)	57.8 (16.2)	<0.001
No. (%) of male patients	577 (63.5)	174 (56.3)	751 (61.7)	0.028
No. (%) of patients with:				
Hematological disease	641 (70.6)	276 (89.3)	917 (75.3)	<0.001[b]
Acute leukemia/myelodysplastic syndrome	287 (31.6)	164 (53)	451 (37)	0.001
Lymphoma	235 (25.8)	71 (22.9)	306 (25.1)	0.336
Multiple myeloma/Waldenström disease	59 (6.4)	15 (4.8)	74 (6)	
Other	60 (6.6)	26 (8.4)	46 (3.7)	
HSCT	182 (26.6)	108 (35.0)	290 (23.8)	
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)	
Solid tumor	267 (29.4)	33 (10.6)	300 (24.6)	<0.001[b]
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 (<0.1 × 10^9/liter)	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 (within 1 mo)	456 (51.3)	176 (58.1)	632 (53)	0.048
Prior fluoroquinolone prophylaxis (within 1 mo)	98 (10.9)	97 (31.7)	195 (16.2)	<0.001
Prior antibiotic therapy (within 1 mo)	414 (46.5)	251 (81.8)	665 (55.6)	<0.001
Prior piperacillin-tazobactam therapy (within 1 mo)	98 (10.8)	101 (32.7)	199 (16.4)	<0.001
Prior antipseudomonal carbapenem therapy (within 1 mo)	98 (10.8)	103 (33.3)	201 (16.5)	<0.001
Prior antipseudomonal cephalosporin therapy (within 1 mo)	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 (within 3 mo)	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 temp of ≥38°C	797 (88.6)	285 (92.5)	1,082 (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				
Endogenous source	351 (38.7)	104 (33.7)	455 (37.4)	0.022
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[c]	27 (3.0)	12 (3.9)	39 (3.2)	

[a]MDR, multidrug resistant; HSCT, hematopoietic stem cell transplant; GVHD, graft-versus-host disease; MASCC, Multinational Association for Supportive Care in Cancer; ICU, intensive care unit.

[b]Comparison of solid tumor versus hematological disease.

[c]Other consists of mucositis, n = 24; odontogenic, n = 9; sinusitis, n = 4; otitis, n = 2.

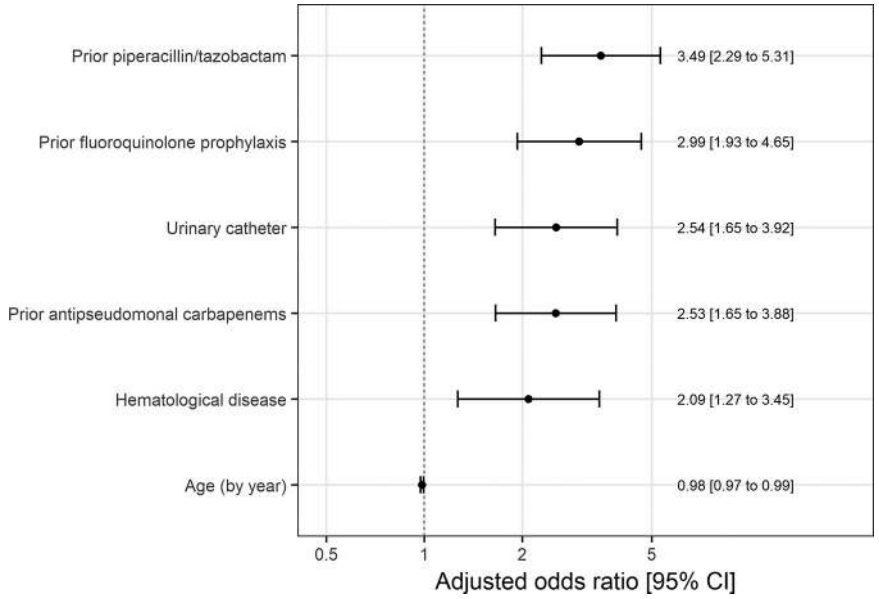

FIG 2 Odds ratio and 95% confidence intervals for multidrug resistance predictors included in the final model.

0 and a slope of 1 for the relation between observed and predicted multidrug resistance (Fig. 4, left).

Internal validation also showed a fair discrimination, with an AUC of 0.72 (95% CI, 0.63 to 0.80) (Fig. 3, right) and good agreement between prediction and observation (Fig. 4, right).

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 as an intervention to support treatment decisions should be evaluated externally and locally (19). The explanation of how to use the tool is provided in the supplemental material.

DISCUSSION

Using data from a large international cohort, we have developed a clinical predictive model that allows us to accurately identify neutropenic cancer patients at high risk of BSI due to MDR *P. aeruginosa*. 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.

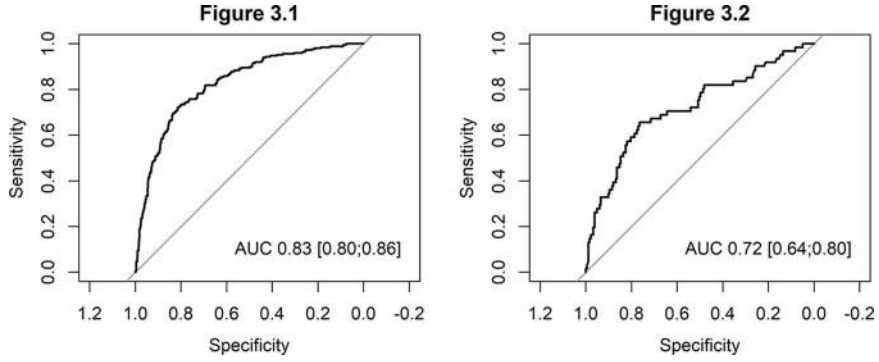

FIG 3 (Left) Area under the curve of the predictive model of multidrug resistance in patients with *Pseudomonas aeruginosa* bloodstream infection in the derivation cohort. (Right) Area under the curve of the predictive model of multidrug resistance in patients with *Pseudomonas aeruginosa* bloodstream infection in the validation cohort.

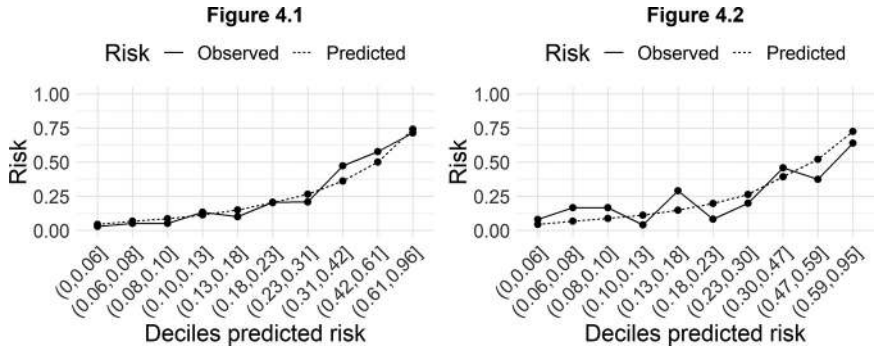

FIG 4 (Left) Observed versus predicted risk of multidrug-resistant *Pseudomonas aeruginosa* bloodstream infection, stratified by deciles of predicted risk, in the derivation cohort. (Right) Observed versus predicted multidrug-resistant *Pseudomonas aeruginosa* bloodstream infection, stratified by deciles of predicted risk, in the validation cohort.

Of particular concern, we found an overall high rate of multidrug resistance among *P. aeruginosa* isolates, and importantly, a significant increase was observed over time. These findings are in line with other reports that focused on patients with hematological malignancies (11–13, 15, 17), although most of those studies were conducted in the same geographical area. The emergence of resistance among *P. aeruginosa* isolates causing infection in neutropenic patients is worrisome, since the administration of inadequate empirical antibiotic therapy severely impairs patient outcomes (11, 12, 15). Indeed, we found significantly higher early and overall mortality rates in patients with MDR *P. aeruginosa* 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 MDR *P. aeruginosa* BSI (20). 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 the 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, in particular, 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 (21). 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, 22, 23). Hakki et al. recently reported the association between fluoroquinolone prophylaxis and breakthrough BSI with *P. aeruginosa* strains that are not susceptible to meropenem, probably due to mutations increasing efflux pump activity (16). In addition, fluoroquinolone exposure has been associated with an increased risk of *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* infection (24, 25). 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 (26).

The presence of a urinary catheter has previously been reported to be an independent risk factor for MDR GNB BSI in cancer patients (27). 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 that 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 have been decreased due to their neutropenia, therefore leading to a low number of urine cultures being 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 a 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 overfitting, and a validation process. Also, the center effect was addressed by including this variable in the model. However, there are some limitations that should be acknowledged. This was 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, 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 MDR *P. aeruginosa*, its clinical utility will be limited to patients who are found to have a BSI due to *P. aeruginosa* for which the susceptibility testing results are pending.

In conclusion, the prevalence of multidrug resistance among *P. aeruginosa* isolates causing BSI in neutropenic cancer patients is an alarming emerging problem. The reasonable use of broad-spectrum β-lactams and, in particular, 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 MDR *P. aeruginosa* 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 a low risk of resistance development.

MATERIALS AND METHODS

Study design, patients, and setting. This study is part of the IRONIC project, a multicenter, international, retrospective cohort study of adult (age, $\geq$18 years) neutropenic oncohematological patients, including hematopoietic stem cell transplant (HSCT) recipients, diagnosed with at least one episode of *P. aeruginosa* BSI from 1 January 2006 to 31 May 2018. Subsequent episodes caused by *P. aeruginosa* occurring in the same patient were included in the study if the interval between them was $>$1 month.

For this study, all episodes of *P. aeruginosa* BSI included in the IRONIC database were included. Patients were recruited retrospectively from 34 centers in 12 countries: Spain ($n = 14$ centers), Turkey ($n = 4$), Brazil ($n = 3$), Italy ($n = 3$), Argentina ($n = 2$), Germany ($n = 2$), Chile ($n = 1$), Colombia ($n = 1$), Lebanon ($n = 1$), Slovakia ($n = 1$), Switzerland ($n = 1$), and the United Kingdom ($n = 1$). The number of patients recruited at each center is provided in the supplemental material. The study was conducted in accordance with the STROBE recommendations, and the protocol has been published elsewhere (28).

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 of $<0.5 \times 10^9$/liter. The Multinational Association for Supportive Care in Cancer (MASCC) score was calculated as described elsewhere (29). A BSI was considered low risk when the infection originated in the urinary tract or was secondary to a vascular catheter infection or to gut translocation (endogenous source). Episodes of BSI originating from other sources were considered high-risk BSI (30). Antimicrobial therapy administered before susceptibility results were available was considered empirical therapy. Empirical antibiotic therapy was considered adequate when it included at least one antibiotic active *in vitro* against the *P. aeruginosa* strain causing the infection. A BSI was considered persistent if the blood cultures were positive after the first 48 h of adequate antibiotic therapy. An early case fatality was defined as death from any cause within

7 days of BSI onset. Overall 30-day case fatality was defined as death from any cause within 30 days of BSI onset.

Microbiological studies. Clinical samples were processed at the microbiology laboratory of each participating center in accordance with standard operating procedures. *P. aeruginosa* was identified using standard microbiological techniques at each center. *In vitro* susceptibility was determined according to the EUCAST recommendations in the great majority of centers (31). In the Lebanese center and in one center from Argentina, the CLSI cutoffs were used, and in the center from the United Kingdom, BSAC recommendations were used before 2016 (32). *P. aeruginosa* isolate phenotypes were stratified in accordance with recent standard definitions (33). We determined an isolate to be an MDR *P. aeruginosa* isolate when it 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 plus β-lactamase inhibitors, monobactams, fosfomycin, and polymyxins. Moreover, we determined an isolate to be an extensively drug resistant (XDR) *P. aeruginosa* isolate when it was not susceptible to at least one agent in all but two or fewer of these antimicrobial categories.

Statistical analysis. The original cohort was randomly split into a derivation cohort that included 80% of the patients and a validation cohort that consisted of the rest of the patients.

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

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

First, we performed a descriptive analysis of the factors assessed for the development of MDR infections. Multiple imputation with chained equations (MICE) was then used to minimize the impact of missing data for those variables for which data were missing (34). Ten data sets were created, using the Gaussian normal regression method to impute continuous variables (MASCC risk index score) and the binomial logistic regression method to impute categorical variables (high-risk BSI, high-risk MASCC index score, comorbidities, the presence of a urinary catheter, hypotension, corticosteroid use, severe mucositis, prior hospital admission, prior fluoroquinolone prophylaxis, orotracheal intubation, ICU admission, a prior episode of BSI during hospitalization, the presence of any venous catheter, and septic shock). Each imputed data set 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 (34, 35). 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 an 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 analyses performed with the derived sample were also repeated with the reserved sample for validation (36). The TRIPOD checklist for development and validation of predictive models is provided in the supplemental material.

All analyses were performed with a two-sided significance level of 0.05 and R software, version 3.5 (37).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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