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1 **Quantifying risk of disease due to extended-spectrum β -lactamase producing**
2 **Enterobacteriaceae in patients who are colonized at ICU admission**

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29
30
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1 **Abstract (248 words)**

2

3 **Background:** The prevalence of extended-spectrum beta-lactamase-producing
4 Enterobacteriaceae (ESBL-PE) has globally increased and spread to the community. No
5 clinical score is available to select carriers in whom these organisms can be empirically
6 targeted at ICU admission.

7

8 **Methods:** We prospectively assessed between 2009 and 2017 the prevalence of ESBL-PE
9 infection in carriers at ICU admission. A logistic regression was used to determine
10 independent risk factors associated with ESBL-PE infection, and to build a clinical risk score.

11

12 **Results:** Of the 8,061 admissions over the study 7-year period, 745 (9%) patients were ESBL-
13 PE carriers at admission, of whom 395 had infections at ICU admission including 59 (15%)
14 who had culture-proven ESBL-PE related infection. By multivariable analysis, age >60 years,
15 cirrhosis, being on broad-spectrum antibiotics within the past three months, urinary or intra-
16 abdominal source of infection, and the absence of chronic pulmonary disease, were the five
17 independent factors associated with ESBL-PE infection in carriers. A clinical risk score
18 ranging from 0 to 7 was built based on these variables, with an area under the receiver
19 operating characteristic curve (ROC) of 0.82 (95% CI 0.78-0.86); $p < 0.001$. The prevalence of
20 ESBL-PE infection for clinical risk scores of 0-1, 2-3, 4-5, or 6-7 was 0%, 4%, 26%, and
21 49%, respectively. The negative predictive value when Mondor ESBL risk score is <4 was
22 97%.

23

24 **Conclusion.** ESBL-PE related infection was not common in carriers at ICU admission. A
25 clinical risk score may spare ESBL-PE carriers with lower risk of ESBL-PE infection at ICU
26 admission unnecessary empiric carbapenem therapy.

27

28 **Key words:** ESBL-PE infection, risk factors, ESBL-PE colonization, ICU, score

29

30

31

1 **INTRODUCTION**

2

3 Since the beginning of the century, the prevalence of infection with extended-spectrum β -
4 lactamase-producing Enterobacteriaceae (ESBL-PE) has been steadily growing [1,2]. The
5 number of ESBL-PE carriers has also dramatically increased worldwide and spread to the
6 community [3–5]. ESBL-PE infections are associated with prolonged hospital stay and high
7 healthcare costs, albeit their effect on mortality remains controversial [1,6–8]. Such outcomes
8 are attributed, at least in part, to improper treatment. Carbapenems are the empirical drugs of
9 choice for sepsis in patients with suspected ESBL-PE infections [9].

10

11 In many Intensive Care Units (ICUs), as well as in other hospital wards, screening for ESBL-
12 PE carriage is routinely conducted, primarily for the implementation of isolation protocols
13 and cases documentation [10]. This helps inform intensivists about prior ESBL-PE carriage at
14 admission especially when a significant proportion of ESBL-PE carriers remain colonized for
15 up to one year. ESBL-PE carriage is associated with a high risk of ESBL-PE infection [11].
16 The colonization status is understandably seen as a decision tool to optimize the potential use
17 of adequate empirical therapy in patients with suspected sepsis. For such, intensivists may use
18 carbapenem as first-line therapy to better target these organisms when infection is suspected
19 at admission of known carriers. With time, carbapenem consumption has accrued in patients
20 with ESBL-PE infection, as well as in ESBL-PE carriers without related infection [12] thus
21 fostering carbapenem-resistant bacteria (CRB) colonization and CRB-acquired infection in
22 ICU patients [13,14].

23

24 Broader knowledge of the prevalence of ESBL-PE related infections and their associated
25 factors would help physicians refine their therapeutic approach. For this purpose, a clinical

1 score assessing the risk of ESBL-PE infection in carriers would facilitate the selection of
2 patients who require carbapenem as empirical therapy at ICU admission. Two previous
3 scoring models [15,16] were published and used to identify patients who are likely to have
4 ESBL-PE infection based on information collected at hospital admission. The applicability of
5 these models in intensive care or on colonized patients has not been tested.

6

7 The primary aim of our study was to determine, in ESBL-PE carriers, the prevalence of
8 ESBL-PE infection and its associated factors at ICU admission. The secondary aim was to set
9 up a clinical risk score specifically designed to predict ESBL-PE infection in this bacteria
10 carriers, named the Mondor ESBL risk score (after Henri Mondor hospital cohort).

11

12

13 **METHODS**

14

15 *Setting and patients*

16 From May 2009 to January 2017, we conducted a prospective monocentric study in the 24-
17 bed medical ICU of a university hospital. Patients were routinely screened for ESBL-PE
18 carriage using rectal swab samples collected within 24 h of ICU admission. Rectal swabs
19 were examined on chromogenic agar (Oxoid Ltd, Cambridge, UK; Biomérieux, Courtaboeuf,
20 France). ESBL production was confirmed by the double-disk diffusion method using
21 ceftazidime or cefotaxime and clavulanic acid. Patients were included if they were diagnosed
22 with infections at ICU admission and tested positive for ESBL-PE carriage at the same time.
23 Patients diagnosed with ESBL-PE related infection at ICU admission but tested negative on
24 rectal swab examination, or if no rectal swab was performed for them at then, were also
25 included and classified as positive for ESBL-PE rectal carriage (n=4). Data of all patients

1 with ESBL-PE carriage at admission were prospectively collected. Patients transferred from
2 other ICUs were excluded in order to avoid the enrolment of ICU-acquired infection.

3

4 *Ethical issues*

5 This observational study was approved by the Ethical Review Board of the French Intensive
6 Care Society (FICS), and informed consent was waived in compliance with the French law.

7

8 *Data collection*

9 For all patients, the following data were prospectively collected from ICU patient's medical
10 file: demographic variables (age, gender), Simplified Acute Physiology Score (SAPSII) [17],
11 comorbidities and Charlson comorbidity index [18], recent hospital admission or surgery,
12 presence of indwelling device for more than 24 hours before ICU admission, past history of
13 urinary tract disease or urinary catheterization during the 30 days preceding ICU admission,
14 administration of antibiotics in the previous year (stratified into received within 3 months of
15 admission, or earlier), and past history of ESBL-PE infection. Urinary tract disease was
16 defined as more than two episodes of urinary tract infections per year or having abnormal
17 urinary tract. Information regarding infection at admission (source of infection, bacteraemia,
18 shock, culture, and susceptibility results), antibiotic therapy at admission (use of carbapenem
19 therapy in the 24 hours following admission, adequacy of empiric antibiotic therapy),
20 infection-related events (mechanical ventilation, ICU mortality) were also recorded. Broad-
21 spectrum antibiotics included β -lactam/ β -lactamase inhibitor combinations, fluoroquinolone,
22 third generation cephalosporin, carbapenem, and aminoglycoside. Community-acquired
23 infection was defined as infection detected within less than 48 hours of hospital admission in
24 patients without previous contact with a healthcare facility. Hospital-acquired infection was
25 defined as infection present 48 hours or more after hospital admission and not incubating at

1 admission time. Healthcare-associated infection was defined as an infection present at
2 hospital admission or within 48 hours of admission in patients who fulfilled any of the
3 following criteria: received intravenous therapy at home, wound care, or specialized nursing
4 care in the previous 30 days; attended a hospital or hemodialysis clinic or received
5 intravenous chemotherapy in the previous 30 days; were hospitalized in an acute care hospital
6 for ≥ 2 days in the previous 90 days, resided in a nursing home or long-term care facility.

7
8
9

10 *Statistics*

11 The data were analysed using SPSS Base 24.0 statistical software package (IBM Corp.,
12 Armonk, NY) and MEDCALC software for AUC comparison. Continuous data were
13 expressed as median [25th –75th percentiles] and compared using Mann–Whitney test.
14 Categorical variables, expressed as numbers and percentages, were evaluated using chi-square
15 or Fisher’s exact tests. To identify patients’ characteristics associated with ESBL-PE
16 infection, we used multivariable logistic regression with a backward procedure. The selection
17 process was guided by availability at ICU admission, non-redundancy, and maximal
18 imbalances between groups (as estimated by absolute standardized differences, which are
19 independent of the sample size and variable unit) (22). Coefficients were computed by the
20 method of maximum likelihood. Calibration of models was assessed by Hosmer-Lemeshow
21 goodness-of-fit statistic (good fit was defined as p value >0.05) and discrimination was
22 assessed by the area under the receiver operating characteristics curve (ROC-AUC). Variables
23 with p values <0.05 in multivariable logistic regression were retained for inclusion in the
24 Mondor ESBL risk score. Beta coefficients of independent risk factors for ESBL-PE infection
25 were used to build the score. Individual patient scores were generated and tested by assessing

1 model calibration and discrimination using Hosmer–Lemeshow goodness-of-fit statistic and
2 ROC-AUC, respectively. Sensitivity (Se), specificity (Sp), negative predictive value (NPV),
3 and positive predictive value (PPV) were determined for each threshold. All tests were two-
4 tailed, and p values of 0.05 were considered to be statistically significant. The accuracy of
5 Mondor risk score was compared with that of the Italian model (Tumbarello et al.[16]) and of
6 Duke model (Johnson et al [15]) using ROC analysis as proposed by DeLong [19].

7

8

1 **RESULTS**

2

3 Of the 8,061 admissions examined over the 7-year study period, 745 (9%) patients were
4 ESBL-PE carriers at admission, of whom 395 patients had infections at admission, thus
5 included in the study (Figure 1). Infection due to ESBL-PE was present in 59 patients (15%)
6 at ICU admission and was mainly urinary tract infection (UTI, 39%). Community/healthcare
7 associated pneumonia was less common (n=5, 4%) (Table E1, online supplement). Most
8 ESBL-PE infections were hospital-acquired (n=35, 59%) (Table E2, online supplement). The
9 causative agent of ESBL-PE infection was identical to that of carriage in the vast majority of
10 cases (n= 49, 83%). History of ESBL-PE carriage within the previous year was known in only
11 57 patients (14%). No causative agent was found in 130 patients, mostly in those with
12 pneumonia (n=101, 78%).

13

14 ***Factors associated with ESBL-PE infection in carriers***

15 Variables associated with ESBL-PE infection detected in carriers at admission are shown in
16 the univariate analysis (Table E2, online supplement). As shown by the multivariable
17 analysis, age >60 years [OR=2.4 (1.2-4.9), p=0.01], absence of chronic pulmonary disease
18 [OR=6.9 (1.6-31), p=0.01], cirrhosis [OR=3.1 (1.2-8.0), p=0.02], being on broad-spectrum
19 antibiotics (β -lactam/ β -lactamase inhibitor combinations, fluoroquinolone, 3GC, carbapenem,
20 aminoglycoside) within the past three months [OR=3.2 (1.7-6.2), P<0.001], and a urinary or
21 intra-abdominal source of infection [OR 5.4 (2.9-10.2), p<0.001] were the five independent
22 factors associated with ESBL-PE infection in carriers (Table 1).

23 ***Mondor ESBL risk score***

24 To build the Mondor ESBL risk score, a weighted score was attributed to each risk factor
25 found to be independently associated with ESBL-PE infection as follows: two points for

1 urinary or abdominal infections and for absence of chronic pulmonary disease (since their
2 ORs were twice as high as the others), and one point for each of the remaining variables, age
3 > 60 years, cirrhosis, and broad spectrum antibiotics within the three preceding months (Table
4 2). The individual scores were added together to produce an overall score ranging from 0 to 7
5 points. The prevalence of ESBL-PE infection for Mondor risk scores of 0-1, 2-3, 4-5, or 6-7
6 was 0%, 4%, 26%, and 49%, respectively (Figure 2). The cut-off value corresponding to the
7 maximal Youden's index ($J = 0.55$) was a risk score ≥ 4 associated with a sensitivity,
8 specificity, positive and negative predictive values of 86%, 68%, 32%, and 97%, respectively.
9 The prediction of ESBL-PE infection at ICU admission according to Mondor risk score is
10 described in Figure 2 and Table 3. Given the high negative predictive value of 97%, the
11 empiric use of carbapenem could be avoided when Mondor ESBL risk score is <4 (Figure 2).
12 The latter risk score demonstrated a good calibration ($\chi^2 = 4.1$, $p = 0.40$, for Hosmer–
13 Lemeshow goodness-of-fit test) and good discrimination (with an area under the ROC of
14 0.82; 95 % CI 0.78–0.86, $p < 0.001$). The area under the ROC curve of Mondor risk score was
15 significantly higher than that of the Italian score [0.68 (95% CI, 0.63–0.72); $p < 0.001$] and of
16 Duke score [0.67 (95% CI, 0.62–0.72); $p < 0.001$] (Figure 3).

17

18 **Outcome**

19 As compared with their counterparts, carriers with an ESBL-PE infection had higher values of
20 SAPSII scores, more bacteraemia, more shock events, and more often get inadequate initial
21 antibiotic therapy despite the higher use of carbapenem (Table E4, online supplement);
22 however, ICU mortality was similar between groups.

23

24

25 **DISCUSSION**

1 We herein report a 15% prevalence of ESBL-PE infection in ESBL-PE carriers who were
2 diagnosed with infections at ICU admission. While as many as 9.2% of patients admitted to
3 the ICU had ESBL-PE carriage, only 0.7% of all patients admitted to ICU (not those
4 transferred from other ICUs) had infections caused by ESBL-PE at admission (Fig. 1). A
5 clinical risk score based on five variables readily available on admission has a good
6 discrimination and calibration to help diagnose ESBL-PE in case the bacterial carriers are
7 admitted to ICU with infections.

8
9 The published ESBL-PE colonisation rates of ICU patients range from 2.2% to 49.0% with
10 big geographical differences [20]. Data on ESBL-PE infection rates at ICU admission in
11 colonised patients are scarce and highly variable. These marked fluctuations of carriage and
12 infection prevalence at ICU admission influence the pre-test probability upon assessing the
13 likelihood of ESBL-PE infection at admission. For example, the Italian score may not be
14 suitable for the identification of ESBL-PE infection at admission to a Dutch hospital where
15 the prevalence of ESBL-PE carriage and infection is very low. The risk of ESBL-PE infection
16 in carriers is less influenced by local epidemiology [11, 23]. However, our results are
17 consistent with those of other studies (prevalence ~10%) [12,21].

18
19 We showed that old age (>60 years), cirrhosis, broad spectrum antibiotics within the three
20 preceding months, and a urinary or abdominal site of infection are the independent factors
21 associated with ESBL-PE infection in carriers. Most of these factors have been previously
22 reported [3, 24–32]. Intriguingly, chronic pulmonary disease was negatively associated with
23 ESBL-PE infection in carriers, indicating that this disease was dominated by other organisms
24 than ESBL-PE, mostly *Streptococcus pneumoniae* or non-fermenting gram-negative bacilli
25 [31,32]. Good knowledge of risk factors associated with infection caused by ESBL-PE is

1 necessary to help physicians identify the population at risk in whom carbapenem might be
2 warranted, and in consequence lessen the proportion of inappropriate treatment. Our score is,
3 to the best of our knowledge, the first one that specifically identifies ESBL-PE infection in
4 ESBL-PE carriers at ICU admission. The score is simple to calculate and relies on variables
5 that are readily available at the time of ICU admission. Carbapenems are more than ever
6 considered as the gold standard treatment of ESBL-PE-related infections [9,33]. Empiric
7 therapy with carbapenem should thus be considered if Mondor risk score is ≥ 4 and appears
8 warranted if the score is ≥ 6 ; conversely, carbapenem could be spared if the score is < 4 (Figure
9 2).

10

11 The impact of ESBL-PE infections on the outcome of ICU infected patients is equivocal. In
12 the current study, no association between ESBL-PE infection and mortality was found despite
13 the inadequate initial antibiotic therapy in some (Table E4). The higher SAPS II at admission
14 of patients with ESBL-PE related infections could be explained by their older age. As
15 previously shown [22,34], urinary infection was the predominant ESBL-PE infection [22,34]
16 (which could probably explain the higher prevalence of bacteraemia associated with ESBL-
17 PE infections). On the other hand, ESBL-PE infection was less common in community-
18 acquired pneumonia patients. A previous study showed that patients with urinary tract
19 infections have a better prognosis than if have other site infection [35].

20

21 On a short-term basis, rapid diagnostic tools performed on clinical samples (based on
22 chromogenic assays that rapidly detect 3GC-hydrolyzing enzymes, or molecular assays
23 allowing the detection of ESBL-encoding genes), may help customize the empirical regimen
24 of ICU patients [20]. The Surviving Sepsis Campaign recommends initiating antimicrobials as
25 soon as possible and within one hour of sepsis onset [36]. Thus, these tools might be limited

1 when it comes to choose empirical antibiotic therapy for sepsis. Moreover, pneumonia is the
2 most common infection at ICU admission with often no clinical samples available for
3 examinations. Mondor ESBL risk score, which is simple and readily available, may therefore
4 prove useful in these settings. However, it can only be used in patients with a known ESBL-
5 PE rectal carriage or who have a clinical sample positive for ESBL-PE (e.g. urine) before ICU
6 admission.

7 Our study has several limitations. First, it was conducted in France and its monocentric design
8 limits its external validity. Before implementation of these prediction rules, a prospective
9 external validation is required. Second, we focused on infection at ICU admission in carriers.
10 However, ESBL-PE carriage status is often known 48-72 h after admission which may hinder
11 the immediate implementation of our score. ESBL-PE carriage within the previous year was
12 known in only 57 patients. Known ESBL-PE carriers before ICU admission have different
13 characteristics than unknown carriers (Table E5). However, known ESBL-PE colonisation or
14 infection within the previous year was not associated with ESBL-PE infection in the
15 multivariable analysis. Tumbarello and Johnson score aimed at identifying risk factors for
16 ESBL isolation (either colonization or infection). One hundred and thirty patients who had
17 unidentified agents were considered as non ESBL-PE infection, a fact that may have led to a
18 statistical bias. Among those patients, 120 didn't receive carbapenem treatment and had a
19 favorable outcome.

20

21 **CONCLUSION**

22 The prevalence of ESBL-PE infection in carriers admitted to ICU with infections was not
23 negligible (15%). Urinary tract infections represented almost half of all ESBL-PE infections.
24 We herein propose a risk score which could help select patients warranting empiric ESBL-

1 targeted antimicrobial drug therapy. Further studies are needed to validate this score as a
2 guide for prescribing empirical antibiotic therapy in this setting.

3

4 **ACKNOWLEDGMENTS**

5 **Author Contributions** KR, JR, and AD had full access to the entire database of the study and
6 take responsibility for the integrity of these data and the accuracy of their analyses. KR, JR,
7 and AMD contributed to the initial study design, analysis, interpretation of data, drafting of
8 the submitted manuscript, critical revisions for intellectual content, and providing approval for
9 the final version to be published. ADP, JWD, PLW, NdP, CBB, and GC contributed to the
10 study design and analysis, interpretation of data, drafting of the submitted manuscript, critical
11 revisions for intellectual content, and providing approval for the final version to be published.
12 All authors read and approved the final manuscript.

13 **Potential conflicts of interests.**

14 All authors report no conflict of interest relevant to this study.

15 **Ethical approval**

16 This study was approved by the Ethical Review Board of the French Intensive Care Society
17 (FICS), and informed consent was obtained in accordance with the French law. Written and
18 oral information about the study was given to the patients or their families.

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21 **Consent for publication**

22 Not applicable

23 **Availability of data and materials**

24 The datasets generated and/or analysed during the current study are not publicly available as
25 consent for publication of raw data was not obtained from study participants, but could be
26 provided by the corresponding author on reasonable request.

1 **Abbreviations**

2 ESBL-PE: Extended-spectrum beta-lactamase-producing Enterobacteriaceae

3 **Figure titles**

4 *Fig1.* Flow chart of the study.

5 *Fig. 2* Prevalence of ESBL-PE sepsis in carriers according to Mondor ESBL risk score, n =
6 number of patients having the score.

7

8 *Fig 3.* Receiving operating characteristic (ROC) curves for ESBL-PE infection in carriers
9 according to Mondor ESBL risk score, Italian model, and Duke model.

10

11

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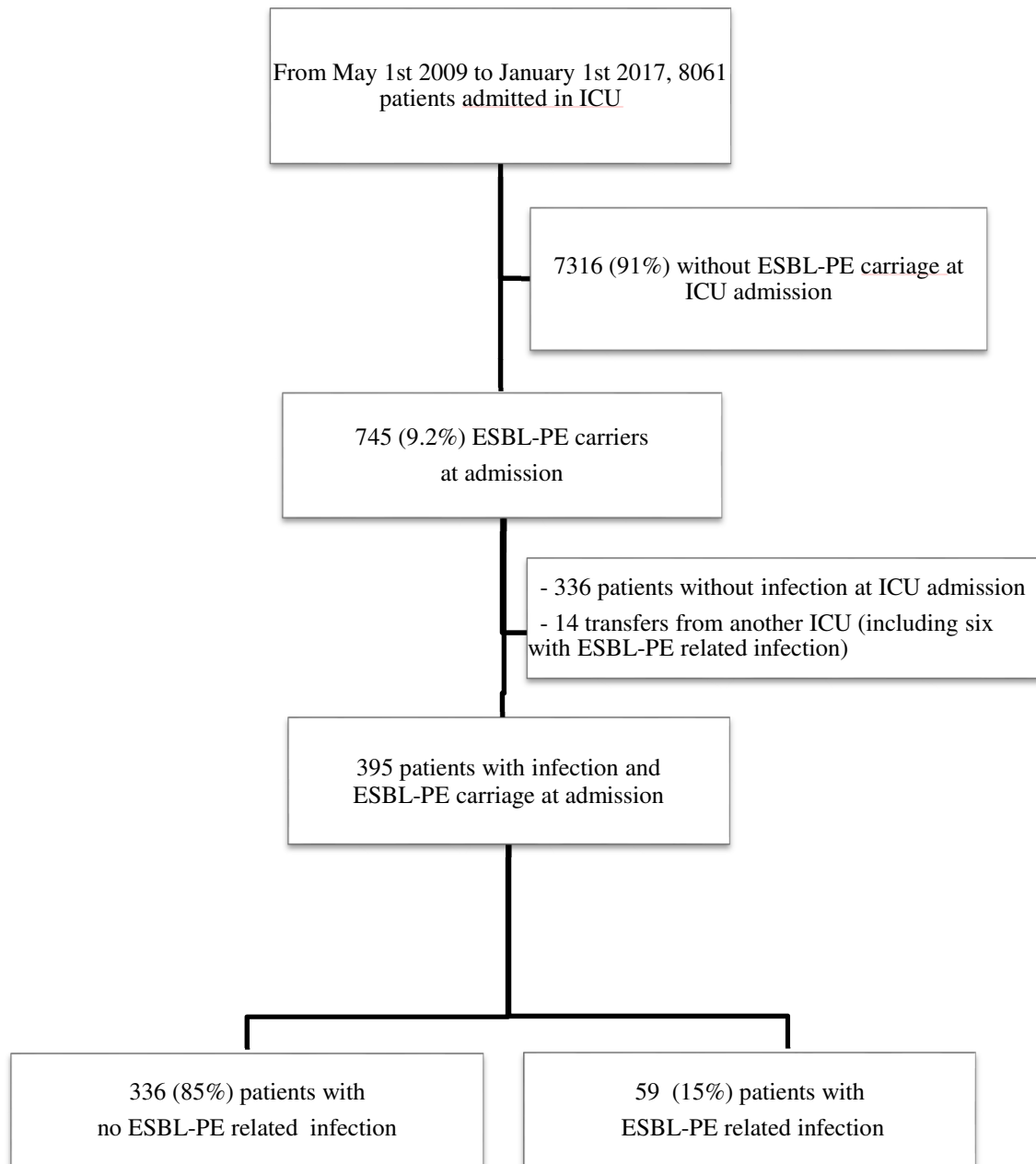
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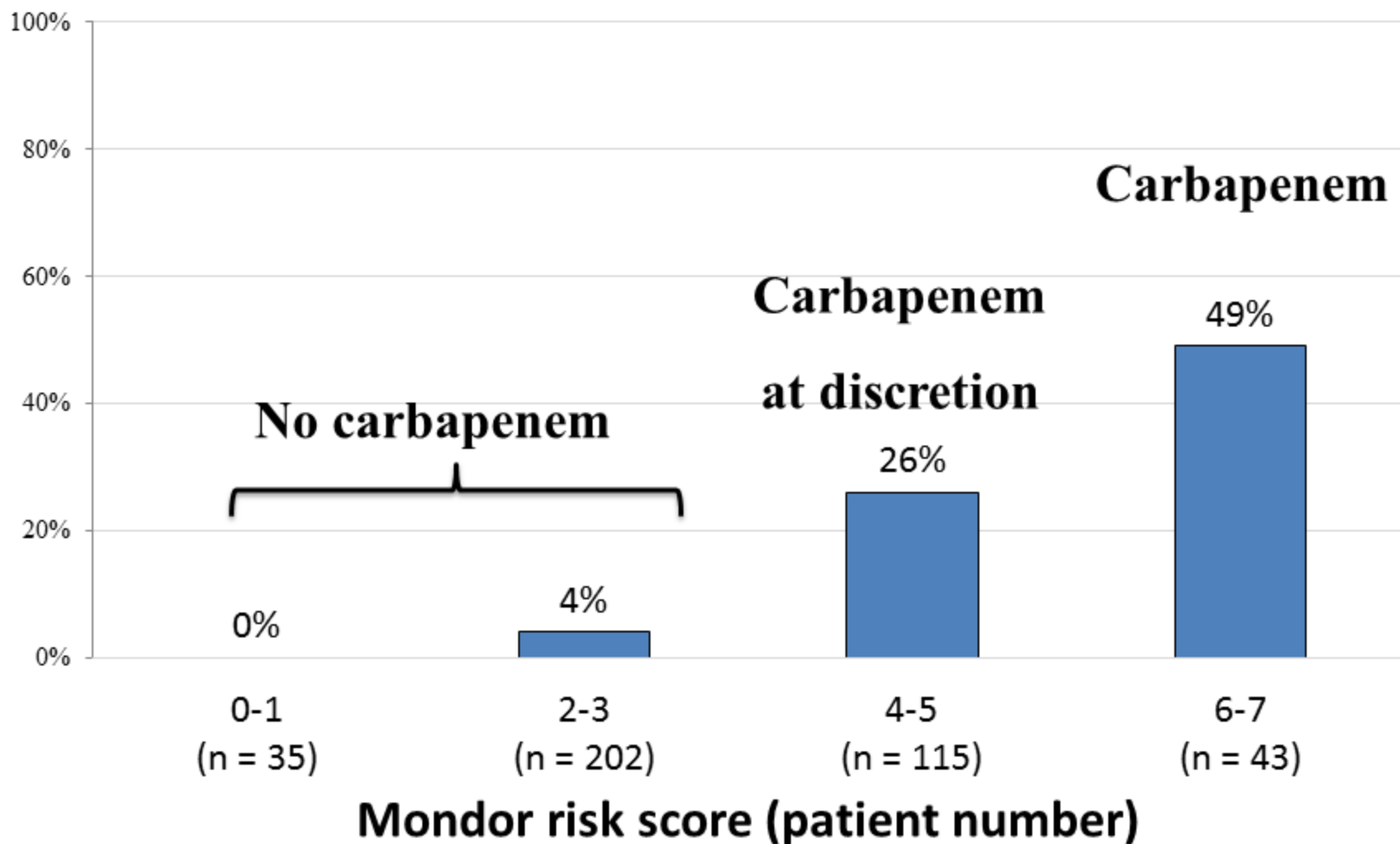
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Fig. 1 Flow chart of the study.



Prevalence of ESBL-PE infection



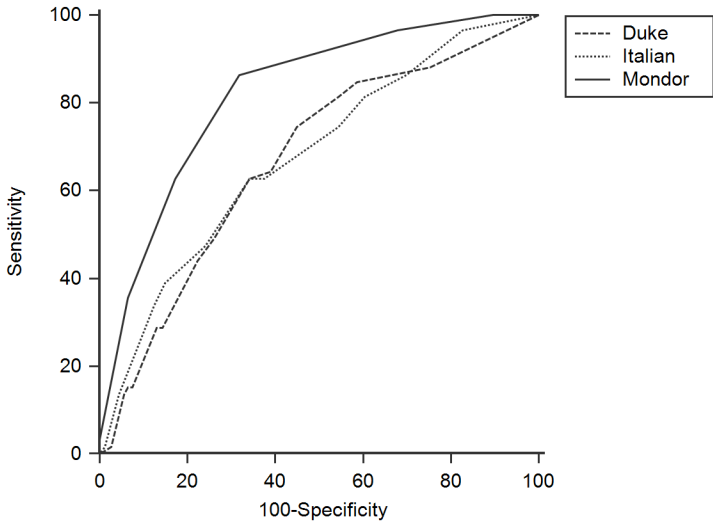


Table 1. Multivariable analysis of variables associated with extended-spectrum β -lactamase producing Enterobacteriaceae related infections in carriers (n= 395) at ICU admission. .

<i>Parameter</i>	<i>Missing values, n</i>	<i>Absolute Standardized differences</i>	Odds ratio (95% CI), p value by logistic regression	
			Univariate	Multivariable
Age > 60 years old (yes vs. no)	0	34	2.0 (1.1-3.8), p=0.02	2.4 (1.2-4.9), p=0.01
Hospital-acquired sepsis (yes vs. no)	0	47	2.5 (1.4-4.4), p=0.002	I/NR
No chronic pulmonary disease (yes vs. no)	0	51	6.3 (1.5-26.6), p=0.01	6.9 (1.6-31), p=0.01
Cirrhosis (yes vs. no)	0	35	3.4 (1.5-7.8), P=0.004	3.1 (1.2-8.0), p=0.02
Urinary tract disease* (yes vs. no)	0	48	4.0 (2.0-8.4), P<0.001	I/NR
Broad-spectrum Antibiotics <3 months (yes vs. no)	0	63	3.3 (1.8-5.8), P<0.001	3.2 (1.7-6.2), P<0.001
Urinary or intra-abdominal source of infection (yes vs. no)	0	100	7.0 (3.8-12.7), p<0.001	5.4 (2.9-10.2), p<0.001
Known ESBL-PE infection <1 year (yes vs. no)	0	43	4.2 (1.9-9.3), p<0.001	I/NR

Abbreviations; CI=confidence interval; ESBL-PE=extended-spectrum β -lactamase producing Enterobacteriaceae. NI=not included; I/NR=included, but not retained by the final model. Broad-spectrum antibiotics included β -lactam/ β -lactamase inhibitor combinations, fluoroquinolone, third generation cephalosporin, carbapenem, and aminoglycoside.

Table 2 Mondor ESBL risk score for extended-spectrum β -lactamase producing Enterobacteriaceae related infection at ICU admission in carriers.

Items	Number of points
Age > 60 years	1
Cirrhosis	1
No chronic pulmonary disease	2
Broad spectrum antibiotics < 3 months	1
Urinary or abdominal infection	2

As shown by the multivariable analysis, “No chronic pulmonary disease” and “Urinary or intra-abdominal source of infection” had their odd ratios almost twice as high as the other significant variables. Therefore, they were attributed two points in the score whereas the other significant variables were given one point each.

Table 3 Sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) for extended-spectrum β -lactamase producing Enterobacteriaceae related infection in carriers according to Mondor ESBL risk score, in 395 patients.

Score	Se	Sp	PPV	NPV
≥ 0 point	100	0	15	
≥ 1 point	100	3	15	100
≥ 2 points	100	10	16	100
≥ 3 points	97	32	20	98
≥ 4 points	86	68	32	97
≥ 5 points	62	83	39	93
≥ 6 points	36	93	49	89
≥ 7 points	3	100	100	86