Early screening of risk for multi-drug resistant organisms in the emergency department in patients with pneumonia and early septic shock: single-center, retrospective cohort study

Wen-Lin Su
Taipei Tzu Chi Hospital
I-Shiang Tzeng
Taipei Tzu Chi Hospital
Hao-Ai Shui
National Defense Medical Center
Meng-Yu Wu
Taipei Tzu Chi Hospital
Ming-Yieh Peng
Taipei Tzu Chi Hospital
Chih-Yu Chan
Taipei Tzu Chi Hospital
Edward D. Chan
National Jewish Health
Yao-Kuang Wu
Taipei Tzu Chi Hospital
Chou-Chin Lan
Taipei Tzu Chi Hospital
Mei-Chen Yang
Taipei Tzu Chi Hospital
Kuo-Liang Huang
Taipei Tzu Chi Hospital
Chih-Wei Wu
Taipei Tzu Chi Hospital
Chia-Hui Chang
Taipei Tzu Chi Hospital
Giou-Teng Yiang (gtyiang@gmail.com)
Taipei Tzu Chi Hospital https://orcid.org/0000-0001-8473-3591

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Abstract

Background Pneumonia is the fourth leading cause of death globally, with rapid progression during septic shock. Multidrug-resistant organisms (MDROs) are becoming more common with some healthcare-associated pneumonia events. Early detection of MDRO risk may improve the outcomes; however, the risk of MDROs in patients with pneumonia and septic shock is unknown and may need broad spectrum multidrug antibiotic therapy. This study investigated the disease outcomes and multidrug antibiotic therapy of pneumonia with early septic shock in patients admitted in the emergency department (ED), a population with a high prevalence of MDROs, after early screening of MDROs risk. Methods In this retrospective cohort study, patients with pneumonia and sepsis (n=533) admitted to the ED at the Taipei Tzu Chi Hospital from 2013 to 2019 were enrolled. The study population was divided into the high-risk and low-risk groups (patients from the communities or long-term care facilities with high and low prevalence of MDROs) and further divided into four subgroups to those whose screening procedure completed within 1 or 6 h of admission (high-risk within 1 h, high-risk within 6 h, low-risk within 1 h, and low risk within 6 h groups). The ICU mortality and multidrug antibiotic therapy were compared. Results The high-risk MDROs groups had higher percentage of P. aeruginosa than the low-risk group. Furthermore, the appropriate ED first antibiotics were higher in the “within 1 h” than in the “within 6 h” subgroup of the high-risk MDROs group. In multivariate analysis, the “within 6 h” high-risk MDROs subgroup had an adjusted odds ratio of 7.191 (95% CI: 2.911–17.767, p <0.001) and 2.917 (95% CI:1.456–5.847, p=0.003) for the ICU mortality and multidrug therapy in the ICU, respectively, after adjusting for other confounding factors. Conclusions Delayed MDRO screening in the high risk group had significant higher ICU mortality and multidrug antibiotic therapy in patients with pneumonia and early septic shock in the ED, especially in areas with a high prevalence of MDROs.

Background

Pneumonia is the fourth leading cause of death in Taiwan and worldwide [1–5]. In 2016, the new U.S. guidelines for hospital acquired pneumonia were published, but they excluded healthcare-associated pneumonia (HCAP) because it had less-resistant pathogens [4]. However, in Taiwan 25.1–32% of HCAP cases were caused by virulent and drug-resistant pathogens, such as Pseudomonas aeruginosa [6–8]. As the national health insurance system in Taiwan is unique, HCAP was further divided into the respiratory care wards (RCW), hemodialysis-associated (HDAP), and nursing-home-associated pneumonia (NHAP), among patients in communities and long-term care facilities [3].

Several of the risk factors associated with infection with multidrug-resistant organisms (MDROs) were also elucidated in the guidelines for HCAP [9, 10]. Previous antibiotic exposure that exerts a selection pressure on bacteria is an important risk factor for MDROs and HCAP [11–13] Infections by MDROs are associated with initial inappropriate antibiotic therapy, increased length-of-stay in the hospital, and mortality [14, 15]. In Taiwan, the detection rate of MDROs in the long-term care facilities is 27.9–44.7% [16, 17], while the readmission rate within 1 month is 23.6% [18]. Thus, it is difficult for the emergency department (ED) physicians to choose the appropriate antibiotics for pneumonia immediately.

Sepsis is defined as a life-threatening organ dysfunction induced by systemic infection. Septic shock, which has a high mortality of approximately 38.5–51.7%, corresponds to sepsis with persisting hypotension requiring vasopressors and abnormal lactate levels despite adequate volume resuscitation [19, 20]. Therefore, broad spectrum antibiotics should be administered within 1 h when patients are suspected of having sepsis [21, 22]. Pneumonia with sepsis still had higher in-hospital mortality than other infections [23]. Therefore, broad spectrum antibiotics should be administered to patients with pneumonia-induced septic shock within 1 h in the ED.

The current 1-h sepsis bundles [24] and early antibiotics for pneumonia [25] increase the potential adverse effects associated with noncompliance, which can place a burden on the ED and the intensive care unit (ICU) critical care. There is still a lack of evidence for the net benefits of following the treatment for septic shock and pneumonia with these regimens [24–26] In contrast, antibiotic multidrug or combination therapy was recommended to increase survival for patients with septic shock and mechanical ventilation by the Surviving Sepsis Campaign guidelines [21, 27–29] The impact of pneumonia with septic shock requiring broad spectrum antibiotics within 1 h of admission on ICU mortality and multidrug therapy remains unknown. We hypothesized that the prevalence of MDROs would be higher among patients with HCAP and septic shock than among those with community-acquired pneumonia (CAP). Early MDRO screening during ED admission may lead to the initial use of appropriate antibiotics and increase in the survival of patients with pneumonia with septic shock.

Materials And Methods

Study design and setting

This single-center, retrospective cohort study was approved by the Institutional Review Board of the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation on August 20, 2019 (Protocol No.: 08-X-068) and was conducted in accordance with the guidelines of the amended Declaration of Helsinki. Waiver of informed consent was reviewed and approved by the Institutional Review Board, and patients' data anonymity was protected. The study was performed in a facility settled within a 1000-bed tertiary referral hospital containing 45 medical intensive care unit (MICU) beds. The nurse-to-patient and respiratory therapist-to-patient ratios in the MICU were 1:2 and 1:10, respectively. Experienced physicians served all patients with pulmonary and critical care medicine issues, and in-hospital night coverage was provided by resident physicians. Consultation services were provided mostly by medical and surgical physicians.

Selection of Participants

This study enrolled patients with pneumonia and suspected septic shock, who were treated at the MICU of the Taipei Tzu Chi Hospital from July 1, 2013 to June 30, 2019. The ED electronic medical records were screened. Especially, the first three codes of the international classification of diseases (ICD)-9-CM codes 785.52, 995.91, 995.92, and the ICD-10-CM codes A41, R65.20, R65.21 were screened for sepsis and septic shock. Additionally, the ICD-9-CM codes 481 to 483, 485, 486, and the ICD-10-CM codes J13 to J18 were screened for pneumonia.

Pneumonia classifications were based on risks of MDROs. HCAP was defined based on the patients' medical history of hospitalization for ≥2 days within 90 days prior to the diagnosis of infection or showing any of the following events within 30 days prior to the diagnosis of infection: attending to a healthcare institution, living in a nursing home (nursing home-associated pneumonia [NHAP]), or receiving medical treatments (wound care, chemotherapy, intravenous injections, or hemodialysis [HDAP]) [3, 30, 31]. CAP was defined based on the patients' history of not meeting any of the HCAP criteria. NHAP was further divided into the high-risk and low-risk groups (patients from the long-term care facilities with high and low prevalence of MDROs).

Screening of risks for the MDROs started from the time of the ED visit during the study periods. According to the MDROs risk phenotype classifications, pneumonia was further divided into the high-risk (high-risk HCAP and NHAP, and HDAP) and low-risk (low-risk NHAP and CAP) groups for the MDROs (Table 1) [9].

On July 1, 2016, the ED in the Taipei Tzu Chi Hospital advocated early screening of the MDROs and healthcare classifications for patients who were suspected of having sepsis, and changed the time of screening from 6 h to 1 h before taking the decision to administer antibiotics for the first time. Patients with MDROs whose screening was completed within 6 h from July 1, 2013 to June 30, 2016 and those whose screening was completed within 1 h from July 1, 2016 to June 30, 2019, were enrolled. The “within 6 h” group was treated according to the 2005 US pneumonia treatment, 2007 Taiwan, and 2012 Surviving Sepsis Campaign (SSC) guidelines (Table 2) [27,32,33] In contrast, the “within 1 h group” was treated based on the 2016 US, 2018 Taiwan, and 2016 SSC guidelines [3,4,21,34]

The study population was divided to four subgroups according to the MDROs risk phenotype, and the screening completion time within 1 or 6 h. The clinical outcomes were compared between these four groups (low-risk within 6 h, low-risk within 1 h, high-risk within 6 h, and high-risk within 1 h groups).

The inclusion criteria were symptoms of pneumonia and early sepsis encountered at the ED. Pneumonia was defined as early onset of fever, cough, or phlegm, and infiltrations or patches in chest X ray. Patient had suspected septic shock and an ED physician decided whether fluid resuscitation or inotropes should be applied to keep the mean arterial pressure ≥ 65mmHg [19].

Patients who had infection (tuberculosis, viral, or fungal infections only), transferred from the RCW with nosocomial infections, could not admit to the ICU within 24 h, or those for whom hospice palliative care was decided were excluded from the study.

Measurements

Disease severity indexes of sepsis and pneumonia were collected from the ED or MICU including the pneumonia severity (CURB-65), acute physiology and chronic health evaluation II (APACHE II) [35], quick sequential organ failure assessment (qSOFA), and SOFA scores, and the mechanical ventilation and lactate levels. CURB-65 and qSOFA scores were measured as previously described [36]. Additionally, underlying comorbidities in patients were recorded and used to derive the Charlson comorbidity index

(CCI) [37]. Previous antibiotic exposure was defined as at least one course of antibiotic therapy within 90 days before the current ED admission. Previous cultures were collected within 90 days of ED admission, where available.

CURB-65 was measured based on confusion (newly disoriented in person, place, or time), blood urea nitrogen (BUN) >20 mg/dl, respiratory rate ≥30 breaths/min, blood pressure (systolic [SBP]) <90 mmHg, or diastolic blood pressure ≤60 mmHg), and age ≥65 years [36] Additionally, underlying comorbidities (disabling neurologic conditions, chronic obstructive or restrictive lung disease, coronary atherosclerotic disease, congestive heart failure, liver cirrhosis, end-stage renal disease, diabetes, metastatic cancer, and acquired immunodeficiency syndrome) in patients were recorded. The comorbidities were used to derive the CCI [37]. The qSOFA score was calculated by adding one point for any of the following criteria: altered mental status (Glasgow coma scale <15), high respiratory rate (≥22/min), or low blood pressure (SBP ≤100 mmHg).

Sputum cultures were collected within 3 days of admission to the ED by expectoration, secretion suction, or endotracheal suction. The sputum quality was determined by the presence of squamous epithelial cells on Gram stain (≤10/low power field), and the first collection specimen with positive result and good quality was chosen.

Antimicrobial susceptibility test was performed according to the Clinical and Laboratory Standards Institute guidelines [13]. α- and β-*streptococcus,* and *Haemophilus influenzae* were subjected to the BBL™ Sensi-Disc™ susceptibility tests (Becton Dickinson and Company, Franklin Lakes, NJ, USA), and other bacteria were subjected to the minimum inhibitory concentration tests by using the VITEK®2 automated system (bioMérieux, Lyon, France). Antibiotic resistance was manually examined by the BBL Sensi-Disc test or automatically determined by the VITEK®2 automated system. Infection with polymicrobial pathogens in the sputum and more than two infection sources other than those developed in the lung, were recorded. MDROs were defined as vancomycin-resistant *Enterococci*, oxacillin-resistant *Staphylococcus aureus*, or multidrug-resistant Gram-negative bacilli (GNB), with acquired non-susceptibility to at least one agent in three or more antimicrobial categories [38]

The appropriate antibiotic treatment was defined as the final cultured microorganisms that were susceptible to the antibiotics used. Multidrug therapy was defined as a combined therapy of more than one antibiotic to broaden the antimicrobial coverage or accelerate pathogen clearance; this included combination therapies [21].

Outcomes

The clinical primary outcomes examined were the ICU and in-hospital mortality rates, length-of-stay in the ICU, and ventilator-use days. The secondary outcomes were the rates of the appropriate antibiotic treatment within 1 h and the rates of multidrug therapy in the ED and the ICU.

The initial admission time since the ED admission was measured. The ICU mortality was determined as the number of patients who died during the ICU admission divided by the total number of patients hospitalized. In-hospital mortality was determined as the number of patients who died during this admission divided by the total number of patients hospitalized. The length of the ICU stay was measured as the time from the ED admission to the end of the ICU care. Ventilator-use days were measured as the total number of days from the ED admission until the patient was weaned off the ventilators (including the non-invasive positive airway pressure and invasive mechanical ventilators).

Statistical Analysis

Continuous data are expressed as the mean ± standard deviation. Categorical data are expressed as frequencies and percentages. The demographic and clinical characteristics were compared using the Student's t-test between the "within 1 h" and "within 6 h" groups. The analysis of variance (ANOVA) was used for comparisons among the four subgroups. The chi-square test was used for comparing categorical variables between the subgroups. Additionally, we performed post-hoc analysis for continuous variables that showed significant differences. The Kaplan-Meier survival curve was used to examine mortality among different levels of risk for the MDROs. Multivariate analysis using the Cox regression analysis was performed to determine the factors associated with ICU mortality after adjusting for other confounding factors and those associated with multidrug therapy in the ICU. The data were analyzed using SPSS version 24.0 (IBM Corp, Armonk, NY, US) and a p-value of <0.05 was considered statistically significant.

Results

Characteristics of study participants

A total of 1,105 and 786 patients had initial shock only and pneumonia with shock, respectively, according to the ICD screening. According to the inclusion criteria of definite pneumonia with suspected initial septic shock by ED chart reviewed, a total of 542 patients participated. After the exclusion of nine patients who could not admit to the ICU within 24 h or had poor sputum quality, there were 533 patients were finally enrolled in this study. All patients were intubated with mechanical ventilation within 3 days from the ED admission. The total culture positive rate was 491/533 (92.1%) for the culture collected within 3 days from the initial ED admission with at least one culture availed by endotracheal suction, and 42/533 (7.9%) had mixed normal flora with good sputum quality. Of the 533 patients enrolled, 254 (48%) and 279 (52%) patients were screened within 1 h and 6 h for the risk of MDROs, respectively. The real MDROs protocol completion times that were retrospectively estimated for the "within 1 h" and "within 6 h" groups were 1.3±0.8 and 3.5±2.0 h, respectively ($p<0.001$) (Table 2). There was no difference in the protocol completion time between the low-risk and high-risk MDROs groups.

The baseline characteristics, underlying comorbidity, disease severity index, pneumonia classifications, previous infection experiences, and current infection events are shown in Table 2.

There were no significant differences in sex, age, underlying comorbidity, SOFA score, APACHE II score, lactate levels, ED mechanical ventilation, and infection experiences between the two groups. However, there was a higher disease severity with a qSOFA score of 3 (31.1% vs. 21.9%, p=0.018) and CURB-65 of 5 (29.1% vs. 20.1%, p=0.016), higher percentage of septic shock (40.6% vs. 29.0%, p=0.006), and higher percentage of polymicrobial infections (30.7% vs. 19.4%, p=0.003) in the “within 1 h” than in the “within 6 h” group.

Laboratory data

Comparisons of previous exposure to pathogens and antibiotic resistant phenotypes in the four subgroups stratified by the MDROs risks and the protocol completion time are shown in Table 3. Previous infection experiences and current infection events were significantly different between the four subgroups (p <0.001) apart from *K. pneumoniae,* the resistance phenotypes (aminoglycoside and ciprofloxacin), penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus*. The culture positive rates were higher in the high than in the low MDROs risk subgroup especially those of *P. aeruginosa*, *A. baumanni*, and *S. aureus* (Table 3). *P. aeruginosa* (16.4% vs 18.9%), *K. pneumoniae* (12.3% vs 18.0%), *A. baumanni* (12.3% vs 18.0%), multidrug-resistant (MDR) GNB (30.5% vs 38.5%), and methicillin-resistant *S. aureus* (MRSA) (10.7% vs 10.9%) were more prevalent in the high-risk than in the low-risk groups (Table 3). After merging the data for the within 1 h and 6 h subgroups, the high-risk group had higher culture positive rates than the low-risk group for *P. aeruginosa* (25.6% vs. 9.5%, relative risk [RR] with confidence interval [CI]: 2.683 (1.769–4.069), p <0.001); *A. baumanni* (18.0% vs. 6.0%, RR (CI): 2.996 (1.761–5.098), p <0.001); and *S. aureus* (18.8% vs. 8.8%, RR (CI): 7.641 (2.711–21.536), p=0.001, Fisher’s exact test). Additionally, the drug-resistant phenotypes were significantly higher in the high-risk than in the low-risk subgroups including resistance to piperacillin/tazobactam, cefepime, carbapenem, MDR GNB, MRSA, and MDROs (Table 3). After merging the data for the “within 1 h” and “within 6 h” groups, the high-risk group had significantly higher drug resistance phenotypes than the low-risk groups for piperacillin/tazobactam (10.8% vs. 2.5%, RR (CI): 4.366 (1.935–9.851), p <0.001); cefepime (9.2% vs. 1.8%, RR (CI): 5.207 (2.010–13.492), p <0.001); carbapenem (11.2% vs. 2.8%, RR (CI): 3.962 (1.840–8.532), p <0.001); MDR GNB (34.4% vs. 0%, RR (CI): infinity, p <0.001); MRSA (10.8% vs. 1.4%, RR (CI): 7.641 (2.711–21.536), p <0.001); and MDROs (47.2% vs. 1.8%, RR (CI): 26.715 (11.097–64.316), p <0.001).

The MDRO prevalence was significantly higher in the groups at high-risk of MDROs (50.8% and 43.8% for the “within 1 h” and “within 6 h” subgroups, respectively) than in the groups at low risk (1.5% and 2.0% for the within 1 h and 6 h groups, respectively) (p <0.001). Moreover, the prevalence of previous antibiotic exposure was significantly higher in the high-risk groups (60.7% and 74.2% for the “within 1 h” and “within 6 h” subgroups, respectively) than in the low-risk subgroups (0%).

Clinical outcomes data

A total of 126 patients (23.6%) died in the ICU. Patients in the high-risk group had higher ICU and in-hospital mortalities than those in the low-risk group (Figure 1a and supplemental Figure 1). In the four

subgroup comparisons, the RR (CI) of the ICU mortality in the “high-risk within 6 h,” “high-risk within 1 h,” and “low-risk within 6 h” groups compared with the “low-risk within 1 h” group, used as the reference group, were 3.094 (1.924–4.974), 2.359 (1.586–3.511), and 1.906 (1.291–2.815), respectively. For in-hospital mortality, the RR (CI) was 3.094 (2.013–4.755), 2.397 (1.673–3.436), and 1.937 (1.363–2.752), respectively. The patients in the “high-risk within 6 h” group had a longer length-of-stay in the ICU (14.4±13.1 vs. 10.9±8.9, p=0.008) and more ventilator use days (12.5±13.5 vs. 7.4±8.2, p<0.001) than those in the “low-risk within 1 h” group (Figure 1b). Antibiotic treatment was compared among the four groups. The patients in the high-risk group had a lower rate of appropriate antibiotic treatment in the ED (46.9% to 65.6% vs. 80.1% to 84.8%) and antibiotic checking in the ICU (65.6% to 67.2% vs. 82.8% to 84.8%) than those in the low-risk group (Figure 1c). Moreover, in the high-risk group, the rate of the appropriate antibiotic treatment in the ED was significantly lower in the “within 6 h” than in the “within 1 h” subgroup (6 h vs. 1 h: 46.9% vs. 65.6%, p=0.003).

The patients in the high-risk group had a higher percentage of multidrug therapy in the ED (10.9% to 15.6% vs. 0% to 11.3%) and ICU (23.8% to 41.4% vs. 11.4% to 17.9%) than those in the low-risk group. In the high-risk group, the multidrug therapy use was higher in the “within 1 h” than in the “within 6 h” group in the ED (15.6% vs. 10.9%, p=0.351 by Fisher’s exact test, Figure 1d), but significantly lower in the “within 1 h” than in the “within 6 h” subgroup in the ICU (23.8% vs. 41.4%, p=0.003 by Fisher’s exact test, Figure 1d).

Risk factors for the ICU mortality in pneumonia with sepsis at different screening time of MDROs

The survival probabilities of the time from ED admission for the four subgroups are presented as Kaplan-Meier survival curves (Figure 2). The four subgroups had different levels of risks for MDROs on the day of ED admission (p <0.001). The screening time (1 h vs. 6 h) had insignificant (p=0.434) and significant (p=0.002) effects on the survival curve in the low-risk and high-risk groups, respectively (Figure 2).

In the multivariable Cox regression analysis (Table 4), we found that patients in high-risk for MDROs (adjusted HR [aHR]=2.000, 95% CI: 1.153–3.470, p=0.014; CCI [aHR=1.325, 95% CI 1.231–1.428, p <0.001]; APACHE II [aHR=1.142, 95% CI: 1.106–1.180, p <0.001]; lactate levels [aHR=1.080, 95% CI: 1.023–1.139, p=0.005]; and septic shock [aHR=1.556, 95% CI: 1.065–2.272, p=0.022]) within 6 h of screening, had increased hazards of ICU mortality.

In the multivariate analysis adjusted for all the variables that had a p <0.05 in the univariate analysis (Table 5), the clinical features that were significantly associated with the ICU multidrug therapy included high-risk for MDROs within 6 h of screening (aOR=2.917, 95% CI: 1.456–5.847, p=0.003); CCI [aOR=1.126, 95% CI: 1.026–1.236, p=0.013]; APACHE II [aOR=1.065, 95% CI: 1.016–1.117, p=0.009]; and two sources of infection [aOR=2.411, 95% CI: 1.365–4.260, p=0.002]).

Discussion

Our study demonstrated that early screening (within 1 h) of the risk of MDROs increased the appropriateness of the ED first antibiotic use in patients with pneumonia and septic shock, and later, decreased the multidrug therapy in the ICU, and lowered the ICU mortality. The MDRO prevalence and previous antibiotic exposure were significantly higher in high-risk than in the low-risk groups of MDRO infection. Thus, MDROs persisted that records of previous cultures and hospitalization were important [39, 40] Screening for the HCAP criteria was beneficial in predicting drug-resistant pathogens, especially in patients with more than three HCAP risk factors [9]. Previous studies have reported that patients who were readmitted with previous antibiotic exposure within 90 days had multiple pathogens and drug-resistant bacteria at admission in Taiwan [41, 42] and worldwide [12, 43, 44]. There was a high prevalence of HCAP in Taiwan that required rapid differentiation for the selection of the appropriate antibiotics [6–8, 13] Here, especially in patients with pneumonia and sepsis, the prevalence rate of HCAP was 61.6–66.1% (Table 2). Furthermore, low-risk NHAP without previous antibiotic exposure emerged together with CAP as “low-risk for MDROs groups” and had very low MDROs and zero MDR GNB (Table 3). Therefore, MDROs risk screening is necessary and appropriate in areas with a high prevalence rate of HCAP.

In the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) conference in 2016, HCAP was excluded from the hospital-acquired pneumonia/ventilator-associated pneumonia guidelines [4] because the HCAP criteria had low discriminatory ability for the MDROs [45–47] Furthermore, the clinical outcomes in HCAP were similar in severity as that in CAP, despite the initial inappropriate antibiotic therapy, in some studies [45, 48] In contrast, MDROs risk screening including previous antibiotic exposure or admissions within 90 days in nursing homes, with high prevalence of MDROs, was more important than the HCAP criteria, which only determine the possibility of MDROs pathogens, such as the drug-resistant P. aeruginosa and MRSA [9, 11, 46]. P. aeruginosa, K. pneumoniae, A. baumanni, MDR GNB, and MRSA were more prevalent in the high-risk than in the low-risk groups. Therefore, multidrug therapy was necessary and appropriate, as mentioned in the new guideline for pneumonia [3, 4]. In 2019, the ATS/IDSA guidelines recommended that the HCAP category should no longer be used [5]. However, the guideline emphasized the relevance of the local epidemiology and validated the risk factors including recent hospitalization and prior respiratory isolation to determine the need for MRSA and P. aeruginosa coverage. Here, the high-risk groups were classified with previous antibiotic exposure (60.7–74.2%) and culture results (64.8–77.3%) (Table 3). Moreover, the high-risk groups had 30.5–38.5% MDR GNB and 10.7–10.9% MRSA. This suggests that the MDROs risk screening is suitable for drug-resistant classification in patients with pneumonia and sepsis and could ensure that they received immediate and appropriate antibiotic therapy in the ED (Fig. 1c).

Unidentified pneumonia with sepsis at the ED delays the appropriate antibiotic therapy [49]. Initial inappropriate antibiotic treatment increases mortality and delays the resolution of pneumonia [50, 51]. Furthermore, the timing of appropriate antibiotics is important for the treatment of sepsis and septic shock and improves the length of the ICU stay and in-hospital mortality [52–54]. Broad-spectrum empiric antibiotic treatment within 1 h is the standard procedure for patients with suspected sepsis at the ED triage [22, 55]. In the groups at high risk of infection with MDROs, the proportion of patients who received appropriate antibiotics in the ED was significantly higher in the “within 1 h” than in the “within 6 h” group,

but there was no significant difference between the “within 1 h and 6 h” groups in the proportion who received appropriate antibiotics in the ICU. This suggests that early MDRO-risk screening is important because it provides immediate information on the probability of infection with MDROs.

Late administration of the appropriate antibiotics in the ED occurs due to undetermined infection. For each hour of delay of antibiotic administration, there is a 12% reduction in survival of patients with sepsis [52]. Furthermore, an increase in the time for the appropriate antibiotic therapy prolongs the ICU stay [54]. High prevalence of MDROs often occurs in the long-term care facilities due to repeated admissions in the Taiwan hospital systems [16, 18] Here, in the high-risk for MDROs group, there was lower appropriate initial antibiotics use in the ED in the “within 6 h” than in the “within 1 h” screening subgroup (46.9% vs. 65.6%, p = 0.003, Fig. 1d). Especially the “within 6 h” screening subgroup had the longest length of ICU stay (14.4 days) and ventilator use days (12.5 days) (Fig. 1d). After adjusting for other confounding factors, high-risk for the MDROs within 6 h screening was an independent risk factor for ICU mortality (aHR = 2.000, p = 0.014, Table 4).

Multidrug (combination) therapy is necessary for severe in-patient pneumonia according to the 2019 ATS/IDSA CAP guidelines and includes beta-lactams combined with macrolide or fluoroquinolone [5]. In the groups at low-risk of infections with MDROs, those in the “within 1 h and 6 h” subgroups had similar probability of receiving multidrug therapy in the ICU (Fig. 1d). This suggests that early screening for MDROs does not increase the probability of multidrug therapy in the low-risk groups in the ICU. Furthermore, at the high risk for MDROs group, the multidrug therapy was lower in the “within 1 h” than in the “within 6 h” subgroup (Fig. 1d). In the logistic regression model, the high-risk for MDROs within 6 h screening subgroup had significantly higher correlation with multidrug therapy than with other groups in the ICU (p = 0.003, Table 5). Thus, we concluded that the 1 h protocol completion would not increase the multidrug therapy use in the ICU antibiotic selection. Global awareness of sepsis and antimicrobial stewardship should be considered as a two-sided coin [56, 57]. ED and critical care physicians who use broad spectrum and multidrug therapy within 1 h are committed to survival of patients with sepsis and are undertaking the global responsibility to prevent rapid antimicrobial resistance. Early MDROs screening within 1 h for patients with pneumonia and sepsis may ensure appropriate selection of broad-spectrum multidrug therapy in the ED and later, and possible decrease the multidrug therapy use in the ICU in our study.

Although multidrug (combination) therapy is recommended especially in patients with septic shock, early discontinuation was suggested when culture results become available and/or clinical outcomes are stabilized to prevent the development of drug-resistant pathogens due to selection pressure [21]. Here, in the high-risk for MDROs groups, the antibiotic multidrug therapy was higher in the “within 1 h” than in the “within 6 h” subgroup in the ED, but significantly lower in the ICU. We conclude that the initial use of multidrug therapy in the ED guided by MDROs risk screening did not further increase the applied multidrug therapy in the ICU. Furthermore, ED multidrug therapy use did not affect ICU mortality (Table 4 and Table 5). These results suggest that early MDROs risk screening is suitable for practical application.

In conclusion, MDROs screening within 6 h in patients with pneumonia and early septic shock in high-risk for MDROs is an independent risk factor for ICU mortality since it is related to inappropriate initial antibiotics use in the ED and higher rate of multidrug therapy in the ICU. However, further prospective studies are needed to be performed with randomized comparisons of MDROs screening within 1 and 6 h of ED admission, especially in areas with a high prevalence of MDROs.

Limitations

There were some study limitations. This was a retrospective study with two MDRO risk screening policies in the ED. The 1-h completion policy might have increased the appropriate antibiotic use in the ED and later lower the ICU mortality in the high risk MDRO subgroups, but this study design still involves selection bias. There were two reasons as follows: first, as the MDRO risk screening policy regarding the sepsis definition was changed in July 2016, the pneumonia treatment guidelines were also changed and the good clinical outcomes may be related to the changes in MDRO screening and treatment improvements; second, shock status and lactate level data collected for making a diagnosis of pneumonia with septic shock were not easy to be complete in the within 1 h screening. These biases could mean that the conclusion only applied to the early onset of pneumonia with septic shock. The data of late onset of pneumonia with septic shock, which were confirmed after 1 h of ED admission, were still missed in this study.

Abbreviations

HCAP, healthcare-associated pneumonia; RCW, respiratory care wards; HDAP, hemodialysis-associated pneumonia; NHAP, nursing-home-associated pneumonia; MDROs, multidrug-resistant organisms; ED, emergency department; ICU, intensive care unit; CAP, community-acquired pneumonia; MICU, medical intensive care unit; SSC, Surviving Sepsis Campaign; APACHE II, acute physiology and chronic health evaluation II; qSOFA, quick sequential organ failure assessment; CCI, Charlson comorbidity index; BUN, blood urea nitrogen; MDR, multidrug-resistant, GNB, gram-negative bacilli; MRSA, methicillin-resistant *S. aureus*; RR, relative risk; CI, confidence interval; IDSA, Infectious Diseases Society of America

Declarations

Ethics approval and consent to participate

This single-center, retrospective cohort study was approved by the Institutional Review Board of the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, and New Taipei City, Taiwan on August 20, 2019 (Protocol No.: 08-X-068) and was conducted in accordance with the guidelines of the amended Declaration of Helsinki.

Consent for publication

For this retrospective cohort study, the informed consent waiver was received from IRB and the patient privacy rights including any individual person's data in any form (including individual details, images or videos) are observed. This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (approval number 08-X-068) and conducted in accordance with the amended Declaration of Helsinki.

Availability of data and materials

The data that support the findings of this study are available from Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

WLS, GTY conceived the study, designed the trial, and obtained research funding. WLS, HAS, MYP supervised the conduct of the trial, data collection, and critical revision. WLS, IST, HAS, MYW provided statistical advice on study design and analyzed the data; MYW, CYC, EDC, YKW, CCL, MCY, KLH, CWW, CHC provided data analysis, data interpretation, and manuscript preparation. WLS, GTY chaired the data oversight committee. WLS drafted the manuscript, and all authors contributed substantially to its revision. GTY takes responsibility for the paper as a whole.

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Tables

Table 1. Screening and antibiotic treatment of risk for MDROs for pneumonia with septic shock

Screening of risk for MDROs	Antibiotic treatment
High risk	As HAP/VAP
A. Recent hospitalization for more than 48 h within 90 days	A. Consider multidrug therapy for methicillin resistant *Staphylococcus aureus* and drug resistant *Pseudomonas aeruginosa*
B. Received intravenous antibiotics or chemotherapy or large wound care within 90 days	B. Consider atypical pathogens such as Legionella
C. Resident in nursing home or long-term care facility with high prevalence of MDROs	C. Cover anaerobic pathogens for considering aspiration pneumonia
D. Risk of aspiration and previous sputum culture of MDROs within 90 days	
E. Long-term outpatient hemodialysis	
Low risk	As CAP
A. The patients' history of not meeting any of the HCAP criteria	A. Favor single broad spectrum antibiotic
B. Resident in nursing home or long-term care facility with low prevalence of MDROs	B. Cover atypical pathogens such as Legionella
C. Resident in nursing home or long-term care facility without recent hospitalization within 90 days	C. Cover anaerobic pathogens for considering aspiration pneumonia
	D. Cover *Pseudomonas aeruginosa* for NHAP

MDROs, multidrug-resistant organisms; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; HCAP, healthcare-associated pneumonia;

Table 2: Demographic characteristics of patients stratified by the protocol completion time

	Within 1 h (N=254)	Within 6 h (N=279)	p-value
Estimated time, h (Mean ± SD)	1.3 ± 0.8 (1)	3.5 ± 2.0 (3)	<0.001*
Low risk for MDROs	1.3 ± 0.8 (1)	3.5 ± 2.0 (3)	<0.001*
High risk for MDROs	1.4 ± 0.8 (1)	3.6 ± 2.1 (3)	<0.001*
Sex			0.334
Female	100 (39.4%)	122 (43.7%)	
Male	154 (60.6%)	157 (56.3%)	
Ages	76.3 ± 12.3	76.0 ± 13.5	0.747
Charlson comorbidity index	6.8 ± 2.8	6.5 ± 3.0	0.334
Disease severity index			
qSOFA			0.018*
2	175 (68.9%)	218 (78.1%)	
3	79 (31.1%)	61 (21.9%)	
CURB-65			0.016*
4	180 (70.9%)	223 (79.9%)	
5	74 (29.1%)	56 (20.1%)	
SOFA score	9.3 ± 2.7	9.4 ± 3.2	0.637
APACHE II	27.2 ± 5.8	26.4 ± 6.1	0.117
Lactate (mmol/l)	2.8 ± 2.6	2.4 ± 2.5	0.067
Mechanical ventilation	165 (65.0%)	190 (68.1%)	0.463
ED Oxygenation (ventilation)			0.462
Non-rebreathing mask	89 (31.9%)	89 (31.9%)	
Noninvasive ventilation	32 (12.6%)	45 (16.1%)	
Invasive ventilation	133 (52.4%)	145(52.0%)	
Pneumonia classification			
CAP	86 (33.9%)	107 (38.4%)	0.112
Low risk NHAP	46 (18.1%)	44 (15.8%)	
HDAP	24 (9.4%)	32 (11.5%)	
High risk NHAP	36 (14.2%)	21 (7.5%)	
High risk HCAP	62 (24.4%)	75 (26.9%)	
MDRO risk phenotype			0.664
Low risk MDRO	132 (52.0%)	151 (54.1%)	
High risk MDRO	122 (48.0%)	128 (45.9%)	

Previous infection experience			
Previous antibiotic exposure	74 (29.1%)	95 (34.1%)	0.227
Previous culture available	79 (31.1%)	99 (35.5%)	0.312
Infection events			
Polymicrobial infection	78 (30.7%)	54 (19.4%)	0.003*
More than 2 infection sources	66 (26.0%)	65 (23.3%)	0.482
MDROs	64 (25.2%)	59 (21.1%)	0.303

qSOFA, quick Sepsis-related Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; MDRO, multidrug-resistant organisms; HCAP, healthcare-associated pneumonia; CAP, community-acquired pneumonia; NHAP, nursing home associated pneumonia; HDAP, hemodialysis associated pneumonia; SD, standard deviation.

(*) Statistical significant ($p < 0.05$)

Table 3: Comparison of previous exposure to pathogens and antibiotic-resistant phenotypes in the four subgroups stratified by the MDROs risks and protocol completion time

MDROs risks	Low risk	Low risk	High risk	High risk	p-value
Protocol completion time	within 1 h	within 6 h	within 1 h	within 6 h	
	(N=132)	(N=151)	(N=122)	(N=128)	
Previous infection experience					
Previous antibiotics	0 (0%)	0 (0%)	74 (60.7%)	95 (74.2%)	<0.001*
Previous cultures	0 (0%)	0 (0%)	79 (64.8%)	99 (77.3%)	<0.001*
Infection events					
Polymicrobial	18 (13.6%)	10 (6.6%)	60 (49.2%)	44 (34.4%)	<0.001*
More than 2 sources	28 (21.2%)	18 (11.9%)	38 (31.1%)	47 (36.7%)	<0.001*
Pathogens					
P. aeruginosa	12 (9.1%)	15 (9.9%)	34 (27.9%)	30 (23.4%)	<0.001*
K. pneumoniae	18 (13.6%)	21 (13.9%)	28 (23.0%)	28 (21.9%)	0.79
A. baumanni	9 (6.8%)	8 (5.3%)	22 (18.0%)	23 (18.0%)	<0.001*
S. aureus	13 (9.8%)	12 (8.0%)	23 (18.8%)	24 (18.7%)	0.009
S. pneumoniae	19 (14.4%)	25 (16.6%)	4(3.3%)	3(2.3%)	<0.001*
Resistance phenotype					
Piperacillin/Tazobactam	3 (2.3%)	4 (2.6%)	14 (11.5%)	13 (10.2%)	0.001*
Cefepime	2 (1.5%)	3 (2.0%)	11 (9.0%)	12 (9.4%)	0.001*
Carbapenem	5 (3.8%)	3 (2.0%)	12 (9.8%)	16 (12.5%)	0.001*
Aminoglycoside	8 (6.1%)	3 (2.0%)	8 (6.6%)	9 (7.0%)	0.20
Ciprofloxacin	12 (9.1%)	14 (9.3%)	16 (13.1%)	17 (13.3%)	0.537
MDR GNB	0 (0.0%)	0 (0.0%)	47 (38.5%)	39 (30.5%)	<0.001*
MRSA	2 (1.5%)	2 (1.3%)	13 (10.7%)	14 (10.9%)	<0.001*
PRSP	2 (1.5%)	1 (0.7%)	4 (3.3%)	3 (2.3%)	0.431
VRE	0 (0.0%)	1 (0.7%)	2 (1.6%)	3 (2.3%)	0.285

MDRO	2 (1.5%)	3 (2.0%)	62 (50.8%)	56 (43.8%)	<0.001*

VRE, Vancomycin-resistant *Enterococcus*; GNB, Gram-negative bacilli; PRSP, Penicillin-resistant *Streptococcus pneumoniae*; MDR, Multidrug-resistant; MRSA, Methicillin-resistant *S. aureus*; MDRO, multidrug-resistant organisms; Pathogens, the most popular five pathogens were selected.

(*) Statistical significant ($p < 0.05$)

Table 4: Cox regression model after adjusting for other confounding factors

	Bivariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Protocol MDROs	Ref:1(1 h low)	<0.001*		0.013*
2 (6 h low)	1.300 (0.716–2.361)	0.389	1.609 (0.883–2.933)	0.120
3 (1 h high)	1.589 (0.875–2.885)	0.128	1.037 (0.567–1.899)	0.905
4 (6 h high)	3.234 (1.896–5.516)	<0.001*	2.000 (1.153–3.470)	0.014*
Age	1.007 (0.993–1.022)	0.318		
Sex	0.958 (0.672–1.366)	0.812		
CCI	1.293 (1.217–1.374)	<0.001*	1.325 (1.231–1.428)	<0.001*
qSOFA	1.893 (1.328–2.698)	<0.001*		0.258
CURB65	1.920 (1.343–2.746)	<0.001*		0.201
SOFA score	1.168 (1.105–1.234)	<0.001*		0.211
APACHE II	1.167 (1.133–1.202)	<0.001*	1.142 (1.106–1.180)	<0.001*
Lactate	1.109 (1.058–1.163)	<0.001*	1.080 (1.023–1.139)	0.005*
Ventilator use	2.118 (1.310–3.424)	0.002*		0.222
Previous culture	1.844 (1.300–2.616)	0.001*		0.444
Polymicrobial	1.650 (1.148–2.371)	0.007*		0.643
Two sources of infection	1.549 (1.072–2.239)	0.020*		0.283
MDRO	1.377 (0.943–2.011)	0.097		
ED first antibiotics	2.564 (1.807–3.639)	<0.001*		0.155
ED broad spectrum	1.194 (0.658–2.167)	0.560		

Events: ICU mortality, time: days since ED admission to discharge or in-hospital mortality

Selection: stepwise

HR, hazard ratio; CI, confidence interval; MDROs, multidrug-resistant organisms; CCI, Charlson comorbidity index; qSOFA, quick sepsis-related organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; ED, emergency department.

(*) Statistical significant (p <0.05)

Table 5: Logistic regression model after adjusting for other confounding factors

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Protocol MDRO	Ref:1(1 h low)	<0.001*		<0.001*
2 (6 h low)	1.698 (0.861–3.352)	0.127	0.789 (0.332–1.875)	0.591
3 (1 h high)	2.432 (1.232–4.802)	0.010*	0.619 (0.258–1.484)	0.282
4 (6 h high)	5.512 (2.900–10.478)	<0.001*	2.917 (1.456–5.847)	0.003*
Sex	0.985 (0.655–1.480)	0.942		
Age	1.009 (0.993–1.025)	0.277		
CCI	1.118 (1.043–1.199)	0.002*	1.126 (1.026–1.236)	0.013*
qSOFA	1.547 (0.999–2.395)	0.051		
CURB-65	1.445 (0.922–2.264)	0.108		
SOFA score	1.143 (1.069–1.223)	<0.001*		0.330
APACHE II	1.099 (1.061–1.139)	<0.001*	1.065 (1.016–1.117)	0.009*
Lactate	1.020 (0.946–1.099)	0.608		
Ventilator use	1.178 (0.764–1.816)	0.459		
Previous culture	2.025 (1.341–3.058)	0.001*		0.395
Polymicrobial	2.327 (1.507–3.592)	<0.001*		0.160
Two sources of infection	2.139 (1.383–3.310)	0.001*	2.411 (1.365–4.260)	0.002*
MDRO	2.958 (1.906–4.589)	<0.001*		0.947
ED antibiotics	1.754 (1.151–2.672)	0.009*		0.103
ED broad spectrum		0.997		

Dependent variable: ICU multidrug therapy

OR, odds ratio; CI, confidence interval; MDROs, multi-drug resistant organisms; CCI, Charlson comorbidity index; qSOFA, quick sepsis-related organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; ED, emergency department.

(*) Statistical significant ($p < 0.05$)

Supplemental Information Note

The supplemental figure mentioned on page 14 was omitted by the authors in this version of the paper.

Figures

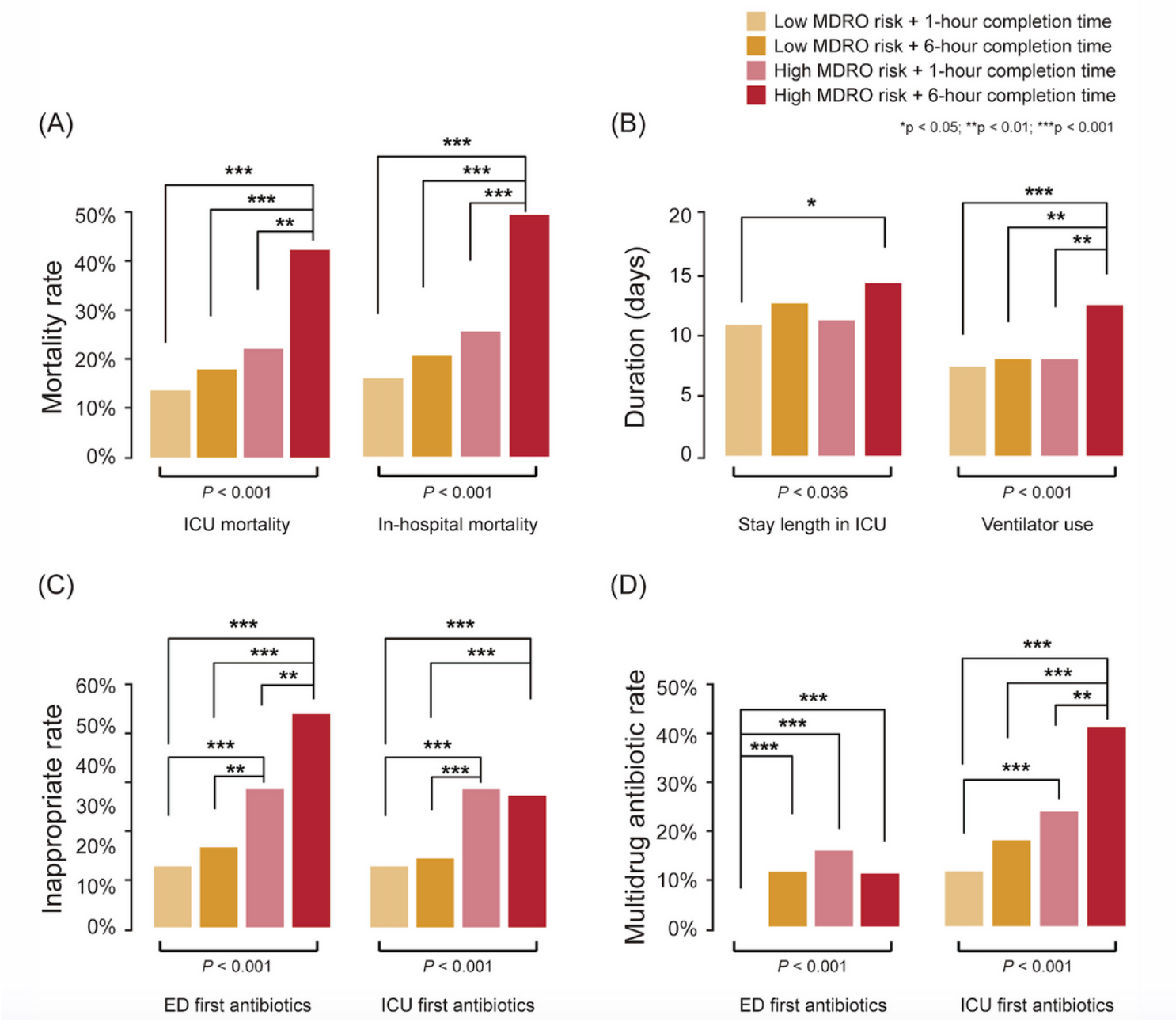

Figure 1

Bar charts showing the significant differences. The proportions of (a) mortality, (b) stay length in ICU and ventilator use days, (n) inappropriate rate of antibiotics, and (d) multidrug antibiotic rate between four

subgroups stratified by the MDROs risks and protocol completion times are presented. The overall probability values (p values) calculated by the Chi square or Fisher's exact test are shown at the top of charts. The stay length in the ICU and the ventilator use days were calculated by the one-way ANOVA and Post hoc pairwise least significant difference tests. (*), (**), and (***) indicate p <0.05, <0.01, and <0.001 for significance difference of the paired bars, respectively. MDROs, multidrug-resistant organisms; ICU, intensive care unit; ED, emergency department.

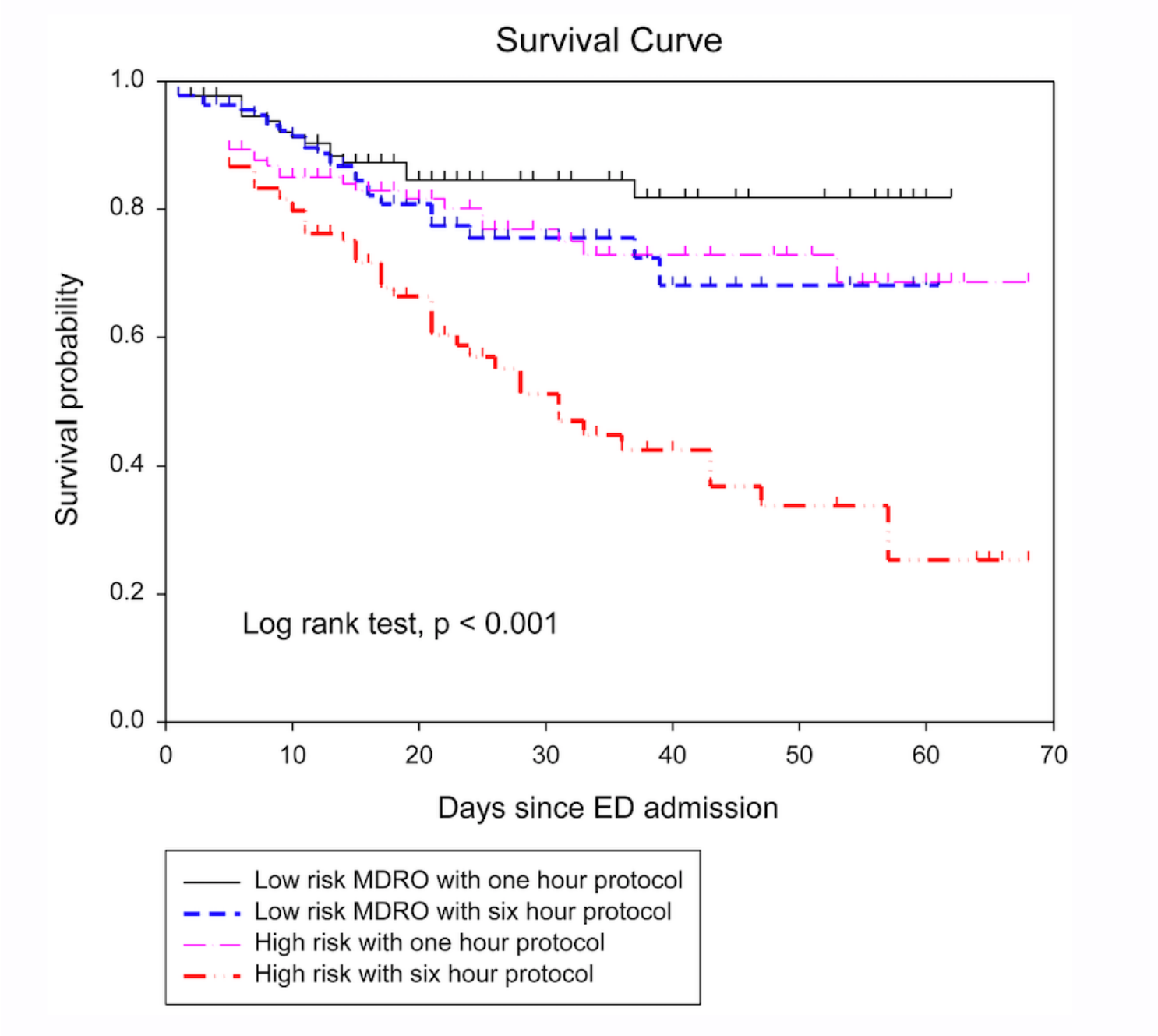

Figure 2

Survival curves according to different risks for MDROs, and protocol completion times (four groups). The Kaplan-Meier survival analysis was undertaken in the data of patients with (a) low-risk for MDROs within 1 h of screening, (b) low-risk for MDROs within 6 h of screening, (c) high-risk for MDROs within 1 h of

screening, and (d) high-risk for MDROs within 6 h of screening during their entire hospital stay. Log-rank test: p <0.001; low risk for MDROs: 6 h vs. 1 h, p=0.434; high risk for MDROs: 6 h vs. 1 h, p=0.002 MDROs, multidrug-resistant organisms.

Supplementary Files

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- GraphicalAbstract.pdf