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Research paper

Benefits of pharmacist intervention in the critical care patients with infectious diseases: A propensity score matching retrospective cohort study

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ABSTRACT

Background: The importance of optimising antimicrobial therapy is highlighted in the hospital intensive care unit (ICU) patients. But roles of ICU pharmacists are still in its infancy in China.
Objectives: This study's objective was to evaluate the values of clinical pharmacist interventions in the antimicrobial stewardship (AMS) on ICU patients with infections.
Aim: The aim of this study was to evaluate the value of clinical pharmacist interventions in the antimicrobial stewardship (AMS) in critically ill patients with infections.
Methods: From 2017 to 2019, a propensity score matching retrospective cohort research was conducted on critically ill patients with infectious illnesses. The trial was split into groups that received pharmacist assistance and those who did not. Baseline demographics, pharmacist actions, and clinical results were compared between the two groups. Factors influencing mortality were demonstrated using univariate analysis and bivariate logistic regression. The State Administration of Foreign Exchange in China monitored the exchange rate between the RMB and the US dollar and also gathered the charges of the agents as an economic indicator.
Results: Out of the 1523 patients who were evaluated, 102 critically ill patients with infectious diseases were included in each group after matching. The top five prescription regimens adjusted were settled by sickness progression, microbiological results, de-escalation, drug withdrawal, and therapeutic drug monitoring suggestions. The pharmacist exposure group's antibiotic use density (AUD) decreased significantly ($p = 0.018$) compared to the control group, going from 241.91 to 176.64 defined daily doses/100 bed days. Following pharmacist interventions, the AUD proportion for carbapenems dropped from 23.7 to 14.43%, while for tetracyclines, it dropped from 11.5 to 6.26%. In the group exposed to the pharmacist, the median cost of antibiotics decreased significantly from $836.3 to $362.15 per patient stay ($p < 0.001$), and the median cost of all medications dropped from $2868.18 to $1941.5 per patient stay ($p = 0.06$). RMB was converted into US dollars according to the current exchange rate. According to univariate analyses, pharmacist interventions did not differ between the groups that survived and died ($p = 0.288$).
Conclusions: This study showed that antimicrobial stewardship had a significant financial return on investment without raising the mortality rate.

1. Introduction

Antibiotics are the most frequently administered medications in the intensive care unit (ICU), where infections affect patients

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most frequently.[1,2] Compared to the general wards, ICUs frequently have to deal with complications related to prolonged immobilisation and recumbent positioning, limited physiological reserve, haemodynamic instability, and a variety of complications related to changes in the parameters of pharmacokinetics and pharmacodynamics (PK/PD) of administered drugs.[3,4] The importance of optimising antimicrobial therapy is further highlighted by variations in the pharmaco-therapeutic efficacy and safety in critically ill patients, including the best drug dose, frequency, route of delivery, duration of antibiotics, or rates of adverse drug reaction (ADR) for antibiotics.[4,5] For both doctors and pharmacists to provide optimum antibiotic therapy, it is essential to understand these obstacles at the ICU.

In recent years, clinical pharmacists have received increased attention globally , particularly during the COVID 19 pandemic and are vital members of the ICU patient care team where their role is to promote optimal medication utilisation and consequently improve patient outcomes. Studies have demonstrated the beneficial effects of clinical pharmacists in the treatment of patients with chronic illnesses such diabetes, atrial fibrillation, and cardiovascular disorders.[6–8] Care of the critically ill patient is a multidisciplinary endeavour.[9] One systematic review and meta-analysis showed critical care pharmacists including in the multidisciplinary ICU team could improve patient outcomes including mortality, ICU length of stay (LOS) in mixed ICUs, and preventable/nonpreventable adverse drug events.[10] Antimicrobial stewardship (AMS) programs have been developed for optimising the regimens of infections and reducing infection-related morbidity and mortality.[11,12] The critical care pharmacist in the ICU team could identify prescription errors, monitor or modify the dosage and identify adverse effects associated with the co-administration of numerous medicines, optimise antibiotics adoptions,[13] and enhance the clinical and financial outcomes.[9,14–16]

Compared with the pharmacists in other speciality areas, the role of the ICU pharmacist are still in their infancy in China[17] Therefore, we aimed to investigate the benefits of clinical pharmacy services for critically ill patients in this study. Our goal was to assess the efficiency and financial effects of the clinical ICU pharmacist on the treatment of critically ill infected patients.

2. Methods

2.1. Study design, setting, and ethics

The investigation was carried out in a medical-surgical ICU ward with 20 beds at a university-affiliated tertiary hospital in China that has 1100 beds. This was a single-centre, retrospective cohort study. The study was divided into two groups: the control group, which received no pharmacy intervention from January 1, 2017, to December 31, 2017, and the pharmacy-exposed group, which received pharmacy intervention from January 1, 2019, to December 31, 2019. All of the patients were over the age of 65 years. Patients were excluded if (i) the inpatient department or admission department was not an ICU; (ii) information about documented discharges was missing; (iii) information about antibiotic use in the ICU was missing; and/or (iv) they have extreme outliers with laboratory tests such as alanine aminotransferase or aspartate aminotransferase >1000 and ICU LOS $\leq$1 or $\geq$30 days. This study was approved by the Scientific Ethics Committee, Beijing Shijitan Hospital Affiliated to Capital Medical University [Ethics approval No: sjtky11-1x-2022(038)]. Due retrospective and deidentified data collection, the need for informed consent was waived.

2.2. Pharmacist-initiated AMS programs

To ensure the consistency and calibre of the interventions, the clinical pharmacist, who completed the specialised training and had more than 10 years of expereince as a hospital pharmacist, was assigned to the ICU ward.

The ICU pharmacist spent at least 20 h per week with the ICU doctors attending daily unit rounds during the observation period. The pharmacist would concentrate on optimising anti-infectious pharmacotherapy, including agents of usage and dosage, curative effect, ADR, and treatment course in accordance with professional guidelines or standards such as published by Chinese Medical Association or other authoritative academic institutes from China, Infectious Diseases Society of America (IDSA), American Thoracic Society (ATS), National Institute for Health and Clinical Excellence (NICE), European Respiratory Society (ERS), and so on. The AMS programs would be triggered if the pharmacist had different opinions after revisions. The adjustment proposal would be given to the senior physician and an ICU expert. If necessary, the microbiologist would participate in the discussion. A thorough discussion may have resulted in changes to the current prescription. The details are displayed in Supplement 1. As part of routine duties in the ICU, pharmacist consultation services on basic pharmacological information or interpretations of pharmacokinetic parameters were also accessible.

2.3. Covariates

Antimicrobial use and the covariates were collected for all patients admitted to the ICUs during the study periods. As a starting point, demographic data on age, sex, and race were gathered. The baseline clinical characteristics were the Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, white blood cell, neutrophil percentage, C-reactive protein, procalcitonin, and diagnoses of infections with ICD 10 code within 48 h of patient admission. The ICU pharmacist's daily records were used to gather information about pharmaceutical services. The accepted rate by the ICU physician was defined as the percentage of recommendations agreed upon by the ICU physicians and the ICU pharmacist during the exposure period.

2.4. Outcomes and measurement

The main outcome measure was ICU mortality. The secondary outcome parameters were antibiotic use density (AUD) proportion and AUD descender (%), LOS, antibiotic costs, and total drug costs. Regular antibiotics used in the ICU setting include carbapenems (meropenem, imipenem, and cilastatin sodium), broad-spectrum penicillin (piperacillin sodium and tazobactam sodium), third-generation cephalosporins, monocyclic lactams (ceftazidime, and cefoperazone sodium and sulbactam sodium), fluoroquinolones, aminoglycosides, tetracyclines (minocycline and tigecycline), glycopeptides and oxazolidine, and systemic antifungal agents. The World Health Organization (WHO) used the antibiotic Anatomical Therapeutic Chemical (ATC) classification as a guide.[18]

The defined daily doses, the number of days spent in bed, and the AUD were utilised to determine the antibiotic availability. On the WHO website, the standard defined daily doses for antibiotics was confirmed.[19] As one of the antimicrobial medication management metrics in China, the density of antibiotic use defined daily doses/100 bed days (AUD) was computed.[20] The methodology was supported by the WHO.[20] The influence of ICU clinicians' prescription tendency of certain kinds of antibiotics were measured by

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the AUD proportion or AUD descender. The calculations used the following formulas: AUD = accumulated drug use (g)/defined daily doses/number of days spent in bed (day) × 100. AUD proportion (%) = AUD of specific antibiotic types in the control or pharmacist-exposed group/total AUD of all antibiotic types in the corresponding control or pharmacist-exposed group × 100%. The AUD descender (%) = (AUD in the control group − AUD in the pharmacist-exposed group)/AUD in the control group × 100%.

In terms of economic indicators, the costs utilised in this study were the sums paid in whole by the patient prior to Medicare reimbursement. Total costs per hospital admission and antimicrobial use were collected for each study subject. The State Administration of Foreign Exchange in China monitored the exchange rate between the RMB and the US dollar as well as the prices of antibiotics or all agents as another economic indicator. On May 11, 2021, the currency rate was US $100 = RBM 643.61 Yuan.

2.5. Statistical analysis

We used 1:1 propensity score matching (PSM) to control for potential confounders, which were measured age, baseline APACHE-II score, procalcitonin, and CCI. The pharmacist-exposed and control groups were split in a 1:1 ratio using PSM. The setting for the caliper was 0.25.

Descriptive statistics were used to characterise the study group. The mean and standard deviation, medians (interquartile range, IQR), and number (percentage) were used to depict normally distributed data, non-normally distributed continuous data, and categorical data, respectively. The median value of the responses from the other participants were used to fill in the missing values of the laboratory parameters. Additionally, the primary infectious illnesses identified in this study group were included along with their matching ICD-10 codes. According to the application's requirements, the recorded data were compared using the Pearson chi-square test, Fisher exact test, or Student's t-test for categorical variables or the Mann−Whitney U test for quantitative variables. Univariate analysis and bivariate logistic regression were used to illustrate the influencing factors on the mortality outcome.

IBM SPSS Statistics for Windows (version 25.0, IBM Corp; Armony, NY) was used to analyse all data. All statistical tests were two-tailed, and a significance level of p 0.05 was regarded as statistically significant.

3. Results

3.1. Demographic characteristics

According to the exclusion criteria, a total of 561 cases were enrolled after the deletion of 553 abnormal data and 409 medical records with missing information on discharge expenses or antimicrobial use. The initial analysis was 270 in the control group and 291 in the pharmacist-exposed group. Fig. 1 and Table 1 show a comparison of baseline characteristics between the control group and the pharmacist-exposed group before and after PSM, as well as a brief overview of the main infectious diseases types diagnosed. After PSM matching, basic demographic characteristics in both groups are similar, including age, gender, APACHE-II score, race and baselines of APACHE-II score, CCI score, and lab examination results. Following PSM, the median age of the patients in this study was 85 years in the control group and 84 years in the pharmacist-exposed group. The gender ratio is close to 1:1 in both two groups. The median baseline APACHE-II score was 24 in the control group and 22 in the pharmacist-exposed group. The median value of baseline CCI was 5 in both groups. We also found that most common infectious diseases diagnosed during the study period were bacterial pneumonia (29.85%), sepsis (23.79%), urinary infection (13.59%), and septic shock (11.17%), followed by fungal pneumonia (5.83%) and fungal urinary infection (1.84%). There were no significant differences in the types of infectious diseases between the control and pharmacist intervention groups.

3.2. Activities of clinical pharmacist and AMS programs

A total of 862 pharmacist recommendations were identified, with 833 (96.64%) reaching agreement between the pharmacist and the ICU physicians. The top five actions, which were mostly carried out by the ICU pharmacist, were select the appropriate antibiotic agents based on diseases factors (180/862, 20.88%) with 95.00% accepted rate (171/180), select the appropriate antibiotic agents based on microbial results (170/862, 19.72%) with 95.88% accepted rate (163/170), recommend appropriate duration of treatment (114/862, 13.23%) with 96.49% accepted rate (110/114), suggest therapeutic drug monitoring (103/862, 11.95%) with 98.06% accepted rate (101/103), and deescalate in time for treatment (75/862, 8.70%) with 100.00% accepted rate (75/75). The details are shown in Table 2.

3.3. The trend for drug selection on ICU clinicians

We are interested in the impact of pharmacist intervention on antibiotic use in ICU patients. In a summary, the intervention reduced the AUD of all antibiotics used in the ICU from 241.91 defined daily dose/100 bed days to 176.64 defined daily dose/100 bed days ($p = 0.018$). According to the agent, AUD proportions were observed to decline with carbapenems (23.07% vs 14.43%), triazole, and other antimycotics for systemic use (16.98% vs 18.53%), glycopeptides and linezolid (15.32% vs 14.83%), tetracyclines (11.56% vs 6.26%), and third-generation cephalosporins (6.91% vs 4.57%). The descender was 48.59%, 10.27%, 20.44%, 55.52%, or 45.61%, respectively. While the proportion of AUD increased for aminoglycosides (from 9.41% to 11.77%), monobactams (from 4.76% to 9.47%), penicillin-beta-lactamase inhibitor combos (from 3.71% to 10.65%), and fluoroquinolones (from 2.42% to 0.91%), the descender was −2.77%, −63.68%, −135.65%, and −14.92%, respectively. The corresponding results are shown in Fig. 2.

3.4. Clinical and economic outcomes with and without ICU pharmacists

As shown in Table 3, there was no statistically significant difference in ICU mortality ($p = 0.607$) or length of stay ($p = 0.163$) with or without pharmacist exposure. A pharmacist's intervention considerably reduced the median costs of antibiotics from $836.3 (IQR, 426.88, 1682.09) to $362.15 (IQR, 148.23, 1034.4) per patient stay ($p < 0.001$). Correspondingly, total median costs of all medications were reduced from $2868.18 (IQR, $1268.44, $5059.00) to $1941.5 (IQR, $1092.89, $3538.97) per patient stay ($p = 0.016$).

3.5. The relationship between mortality and pharmacist interventions

Univariate analyses showed that there was no statistically difference in pharmacist intervention between the groups of survivors and deaths ($p = 0.288$), but there was a difference in age ($p = 0.001$), baseline APACHE-II score ($p = 0.029$), baseline CCI score ($p = 0.032$), admissions ($p = 0.001$), numbers of antibacterial drugs adoptions ($p = 0.007$), numbers of antibacterial drugs combinations ($p = 0.005$), discharge diagnostic items ($p < 0.001$), total number of bacteria detected ($p = 0.001$), numbers of gram-positive cocci detected ($p = 0.038$), and number of fungi detected

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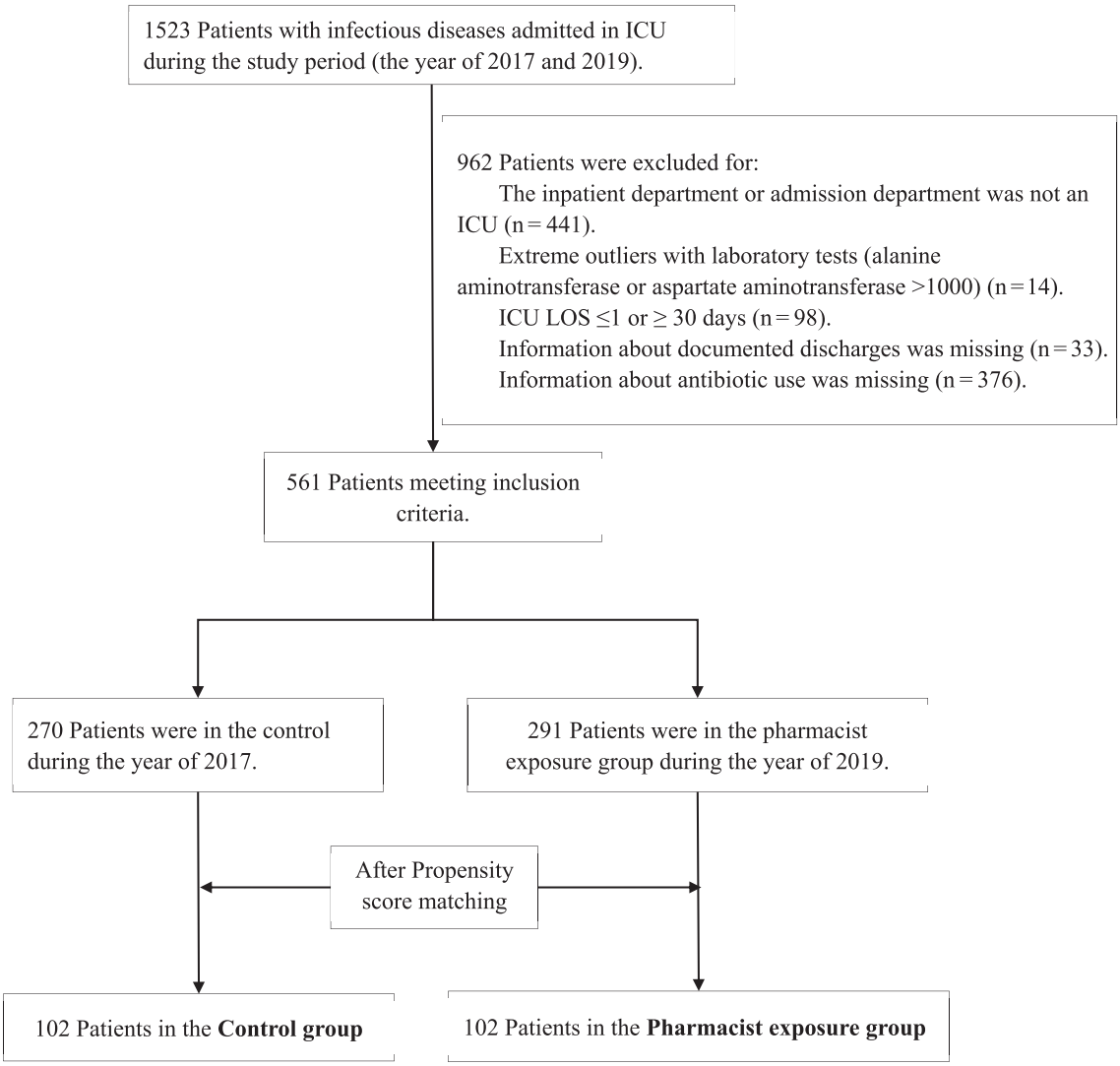

Fig. 1. Flowchart of patient screening and inclusion.

(p = 0.002) which were significant variables affecting the morality. Bivariate logistic regression analysis revealed that the mortality outcome was related to the patients' numbers of admissions (odds ratio [OR] = 1.095, 95% confidence interval [CI] = 1.028−1.165), discharge diagnostic items (OR = 1.109, 95% CI = 1.054−1.166), and numbers of gram-positive cocci detected (OR = 3.392, 95% CI = 1.348−8.531). The details are shown in Supplement 2 and 3.

4. Discussions

The United States of America (USA) Centre for Disease Control advised the implementation of an Antimicrobial Stewardship Programs (ASP) in all acute hospitals in the USA in 2014. Other countries including Australia, the United Kingdom, and Japan also established government-led guidelines.[21] The National Health Commission of China also issued the harshest antibacterial medicine regulation in its history in 2011 since the number of antibiotic-resistant bacteria was currently on the rise as a serious problem in China.[22] However, none of the aforementioned rules provided direction for using APS. Therefore, we describe the successful integration of a clinical pharmacist into the ICU and provide an overview of the pharmacist's main responsibilities within the ICU AMS team and outcomes related to cost avoidance.

The three existing models of pharmacist attendance to the clinician collaboration are pharmacist−clinician cooperation, pharmacist-driven, and independent pharmacy work. A multidisciplinary approach would be ideal in the ICU due to patient complexity, the severity of the condition, and the variety of drug use.[23] During this study, the pharmacist worked in the ICU, reviewed the prescriptions of the infectious patients, and discussed with the physician as needed about any treatment problems. The pharmacist and the AMS team engaged in a lengthy debate and exchange of views. In the majority of cases the recommendations made by the pharmacist were accepted . Ultimately, the pharmacist promoted treatment options for infected patients that could be optimised in accordance with professional guidance or treatment standards. Therefore, in our investigation, we assured that pharmacist-initiated AMS in the ICU could be useful.

Additionally, after including the pharmacist in the AMS team, there was a 50% reduction in the AUD of tetracyclines and carbapenems. The usage of beta-lactamase inhibitors, monobactams, and penicillins in combination therapy, on the other hand, was obviously growing, indicating that following the pharmacist's recommendation, more patients were receiving antibiotics with a narrower spectrum than carbapenems. The results indicated that clinical pharmacists play a guiding role on the rational use of broad-

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Table 1
Baseline characteristics of study patients before and after PSM.

	Before PSM			After PSM		
	The control group (N = 270)	The pharmacist-exposed group (N = 291)	p-Value	The control group (N = 102)	The pharmacist-exposed group (N = 102)	p-Value
Age (median year, IQR)	85.5 (79.0, 90.0)	83.0 (74.0, 88.0)	0.002[a]	85.00 (77.00, 89.00)	84.00 (74.00, 89.00)	0.716
65–84 y, n (%)	96.0 (35.56%)	144.0 (49.48%)		36.0 (35.29%)	49.0 (48.04%)	
≥85 y, n (%)	146.0 (54.07%)	121.0 (41.58%)		54.0 (52.94%)	46.0 (45.10%)	
Male, n (%)	149.0 (55.19%)	148.0 (50.86%)	0.305	47.0 (46.08%)	49.0 (48.04%)	0.780
Race/ethnic Han, n (%)	264.0 (97.78%)	281.0 (96.56%)	0.388	101.0 (99.02%)	97.0 (95.1%)	0.098
Baseline APECH-II score (median, IQR)	26.5 (23.0, 28.0)	17.0 (13.0, 22.0)	<0.001[a]	24.0 (19.0, 26.5)	22.0 (19.0, 27.0)	0.901
Baseline CCI, median (IQR)	5 (4, 6)	6 (5, 8)	<0.001[a]	5 (4, 6)	5 (4, 7)	0.662
Baseline lab examinations						
CRP, median (IQR)	44.42 (10.05, 99.65)	50.96 (10.36, 118.20)	0.541	32.84 (6.41, 81.90)	43.23 (8.95, 100.66)	0.300
PCT, median (IQR)	0.26 (0.10, 1.33)	0.20 (0.07, 0.92)	0.018	0.24 (0.09, 1.33)	0.24 (0.06, 0.92)	0.236
WBC, median (IQR)	9.07 (6.73, 13.61)	9.45 (6.72, 13.17)	0.950	9.01 (6.76, 13.60)	9.94 (6.90, 13.17)	0.621
NE%, median (IQR)	85.15 (77.00, 90.10)	84.40 (75.60, 90.40)	0.752	85.45 (75.30, 90.00)	82.65 (74.70, 89.30)	0.203
Main infectious diseases, n	927	1006	0.317	399	412	0.317
Bacterial pneumonia (J15.901[a]), n (%)	249 (26.86%)	323 (32.11%)		109 (27.32%)	123 (29.85%)	
Sepsis (A41.902[a]), n (%)	232 (25.03%)	245 (24.35%)		100 (25.06%)	98 (23.79%)	
Urinary infection (N39.001[a]), n (%)	133 (14.35%)	132 (13.12%)		58 (14.54%)	56 (13.59%)	
Septic shock (A41.903[a]), n (%)	107 (11.54%)	93 (9.24%)		43 (10.78%)	46 (11.17%)	
Fungal pneumonia (B49xx20[a]), n (%)	54 (5.83%)	58 (5.77%)		21 (5.26%)	24 (5.83%)	
Fungal urinary infection (B49xx04[a]), n (%)	28 (3.02%)	22 (2.19%)		11 (2.76%)	8 (1.94%)	

IQR, interquartile range; PSM, propensity score matching; APECH-II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; NE, neutrophil percentage.
[a] ICD 10 code.

Table 2
The top five pharmacist actions and the ICU clinicians' acceptance.

No.	Contents	No.	Proportion (%)	Consensus No. with ICU physicians	Acceptance (%)
1	Select the appropriate antibiotic agents based on diseases factors	180	20.88%	171	95.00%
2	Select the appropriate antibiotic agents based on the microbial results	170	19.72%	163	95.88%
3	Recommend appropriate duration of treatment	114	13.23%	110	96.49%
4	Suggest for TDM	103	11.95%	101	98.06%
5	Deescalate in time for treatment	75	8.70%	75	100.00%

ICU, intensive care unit; TDM, therapeutic drug monitoring.

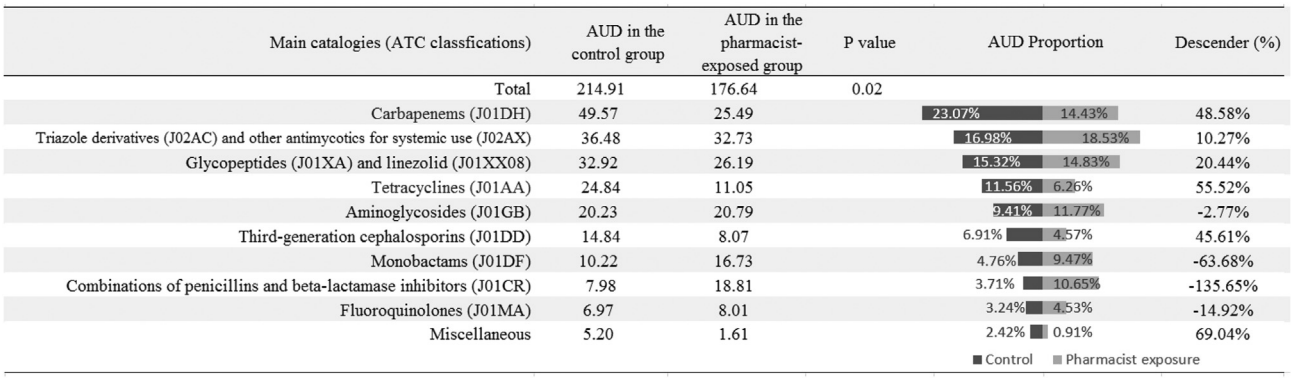

Fig. 2. AUD influence of the ICU clinicians on drug selection tendency. AUD proportion (%) = AUD of specific antibiotic types in the control or pharmacist-exposed group/total AUD of all antibiotic types in the corresponding control or pharmacist-exposed group × 100%; descender (%) = (AUD in the control group − AUD in the pharmacist-exposed group)/AUD in the control group × 100%.

spectrum antimicrobial drugs, which was consistent with other research results.[24]

Numerous studies have demonstrated the contributions that pharmacists make to patient care.[25–29] According to Lee et al., the inclusion of the crticial care pharmacist in the multidisciplinary ICU team improved patient outcomes in terms of mortality, ICU LOS, and preventable/nonpreventable adverse medication events.[10] In our study, the rate of antimicrobial agent usage in the patients who were discharged dropped following the pharmacist's presence, and patient antibiotic charges, including the total cost of drugs, were reduced per stay. ICU mortality did not increase throughout this time. After pharmacist intervention, there was no statistically

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Table 3
Clinical and financial outcomes of critically patients with infectious diseases in the control and pharmacist-exposed groups.

Clinical and economic outcomes	The control group	The pharmacist-exposed group	p-Value
Mortality, No (%)	20.00 (19.61%)	23.00 (22.55%)	0.607
LOS, median (IQR)	8.00 (5.00, 13.00)	6.90 (4.50, 12.15)	0.163
Antibiotic charges per stay ($/case), median (IQR)	836.3 (426.88, 1682.09)	362.15 (148.23, 1034.4)	<0.001
Drug charges per stay ($/case), median (IQR)	2868.18 (1268.44, 5059.00)	1941.5 (1092.89, 3538.97)	0.016

IQR, interquartile range; LOS, length of stay.

significant difference between the groups of survivors and fatalities, according to the results of the univariate analysis. As a result, it might be rigorously managed separately. Economic data show that the pharmacist's influence on antibiotic consumptions was evident in the reduction of the median cost of antibiotics per stay for an infectious patient in the ICU ward by 56.70% and the reduction of the cost of all medications per stay by 32.31%.

This study has several limitations. First, this intervention study was designed without involving a simultaneous control ICU group since the ICU ward in this study was the only general ICU in the hospital and it was difficult to find the parallel control group from another ward at the same study time to be compared. So, the results in this study may be probably influenced by the different time periods during which data were collected. Second, this was a single-centre study. Every medical setting has different cooperation patterns between clinical pharmacists and ICU physicians, as well as different work priorities, and then leading to different roles. Therefore, our results might not be generalised to other ICU settings. Third, about the observed period, the clinical pharmacist joined the ICU in 2018. In that year, the pharmacist mainly adapted to the working environment of the ward and focused on exploring the clinical pharmaceutical work, and this time period was identified as a transitional stage. So, we did not enrol the annual data of 2018 as the observed period. Finally, because the drugs used in ICUs were too complex to obtain the precise data retrospectively that are needed for analysis, the median reduction in the length of antimicrobial therapy was not taken into account this time. Hence, more rigourous studies are needed to confirm the role of ICU clinical pharmacists.

5. Conclusions

In conclusion, this study showed that antimicrobial stewardship had a significant financial return on investment without raising the mortality rate. These results need to be validated with further studies and the specific activities associated with the greatest benefit determined.

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CRediT authorship contribution statement

Hongyan Gu: Writing - Original Draft, Project administration, Funding acquisition. Lulu Sun: Methodology, Supervision. Bo Sheng: Investigation, Resources. Xuyun Gu and Suozhu Wang: Investigations: Bin Dai: Validation and Funding acquisition. Lei Liu: Formal analysis, Data Curation. Wei Chen: Conceptualisation, Writing - Review & Editing.

Conflict of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2022.12.011.

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