Risk factors for drug-resistant pathogens in community-acquired pneumonia: systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
This review identified 11 risk factors for drug-resistant pathogens in CAP. Unlike prior reviews, we clearly distinguished all-patient and culture-positive pneumonia cohorts. Developing a new predictive score based on these findings would be desirable. https://bit.ly/42lVenq

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Abstract

Introduction Community-acquired pneumonia (CAP) is a leading cause of death worldwide. Reducing inappropriate and excessive use of extended-spectrum antibiotics is essential for treating CAP effectively. Evaluating the risk of drug-resistant pathogens (DRPs) is crucial for determining initial antibiotic therapy in clinical settings.

Methods This systematic review and meta-analysis assessed the risk factors for DRPs in patients with CAP. CAP-DRPs were defined as pathogens resistant to commonly used antibiotics for CAP, including nonpseudomonal β-lactams such as ceftriaxone or sulbactam-ampicillin, macrolides and respiratory fluoroquinolones. The studies included were divided into two cohorts, namely an all-patient cohort, comprising both culture-positive and culture-negative patients, and a culture-positive pneumonia cohort, comprising patients with identified causative pathogens. The primary objective of this study was to evaluate the risk factors for CAP-DRPs in the all-patient cohort.

Results 24 articles were included with 11 categorised into the all-patient cohort. The meta-analysis identified 11 significant risk factors for CAP-DRPs, namely prior DRP infection/colonisation, tracheostomy, severe respiratory failure requiring early induction of mechanical ventilation, prior use of antibiotics, chronic lung disease, COPD, wound care, neurological disorders, prior hospitalisation, nursing home residence and low activities of daily living.

Conclusion To our knowledge, this is the first systematic review focused on CAP-DRP. Unlike previous reviews, the all-patient and culture-positive pneumonia cohorts were analysed separately. Findings from the all-patient cohort are particularly relevant for guiding initial antimicrobial selection in clinical practice. Furthermore, the abovementioned factors should be considered when developing prediction models for CAP-DRPs.

Introduction

Community-acquired pneumonia (CAP) remains a leading cause of mortality worldwide [1–3]. Infections caused by drug-resistant pathogens (DRPs), such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, have become substantial concerns in CAP cases [4–6]. The number of patients with CAP affected by DRPs has been increasing [4, 7, 8]. Consequently, clinicians should carefully select the initial antibiotics at the time of CAP diagnosis, considering the potential involvement

of DRPs and the importance of antibiotic stewardship to avoid overtreatment. Inadequate initial antibiotic therapy is associated with unfavourable clinical outcomes [9–11]. Thus, appropriate evaluation of the causative organism is crucial for determining the initial treatment.

The 2019 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommend extended-spectrum antibiotic therapy for patients with risk factors for DRPs [12]. Similarly, the recent European and Latin American guidelines for severe CAP suggest that assessing the risk of DRPs may reduce inappropriate antibiotic use and improve patient outcomes [13]. Based on numerous observational studies attempting to identify clinical characteristics related to DRPs and develop predictive models, the guidelines cite prior DRP isolation, prior hospitalisation and prior antibiotics use as risk factors for DRPs. Other risk factors, considered weakly associated with DRPs, are described as locally validated risk factors and are not specified [12]. To enhance the usability of the 2019 ATS/IDSA guidelines, clarifying these risk factors would be helpful to physicians.

There are two issues regarding previous reports on DRPs in CAP. First, to our knowledge, systematic reviews focusing on DRPs in CAP are scarce. The relevant review articles lack a clear description of systematic literature searches [12, 14–24]. Chen *et al*. [25] performed a systematic review and meta-analysis of risk factors for DRPs in lower respiratory tract infections, including CAP, hospital-acquired pneumonia and ventilator-associated pneumonia. However, they conducted a subgroup analysis of CAP studies focusing only on the risk of prior antibiotic treatment for DRPs. Second, most previous studies mainly analysed pneumonia cases with identified causative pathogens. However, causative pathogens remain unidentified in approximately half of CAP cases in clinical practice [1, 26–28]. Physicians must select initial antibiotics for patients with pneumonia at diagnosis, leading to a discrepancy between the target population assessed for DRP risk in clinical practice and previous reports.

Here, we performed a systematic review and meta-analysis to identify the risk factors for DRPs in patients with CAP. This study was conducted as part of an effort to revise the clinical practice guidelines for pneumonia published by the Japanese Respiratory Society.

Materials and methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (table S1) [29, 30]. The study protocol was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000049116).

Search strategy and study selection process

The study participants were adult patients with CAP, as defined in the 2019 ATS/IDSA guidelines [12]. CAP-DRPs refer to pathogens not susceptible to antibiotics commonly used for CAP, such as nonpseudomonal β-lactams, macrolides and respiratory fluoroquinolones. The eligibility criteria included studies assessing the risk factors for CAP-DRPs, randomised control trials, prospective observational trials or retrospective observational trials written in English or Japanese. Studies were excluded if they used unadjusted analyses to assess CAP-DRP risks or were meeting abstracts. In this study, clinical characteristics obtained at the diagnosis of pneumonia were regarded as candidate risk factors for CAP-DRP. Scores incorporating multiple clinical factors, such as the Pneumonia Severity Index, were excluded from the candidate risk factors.

We searched three databases (PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and Ichushi-Web) on 16 February 2024. The details of the search formula are provided in table S2. Two reviewers independently screened the titles and abstracts of all the identified studies and reviewed the full texts of the articles. Studies cited in related review articles were also assessed for eligibility. Any disagreements were discussed between the reviewers and, if a consensus could not be reached, a third author was consulted.

Data collection

Two reviewers independently extracted data on study characteristics, patient characteristics and odds ratios of all reported risk factors after adjustment for confounding factors. When risk factors for specific pathogens were evaluated separately without assessing the risk factors for all types of DRPs, the odds ratio for each risk factor was calculated based on the bacteria with the highest detection rates among all DRPs. If data were insufficient, we attempted to contact the corresponding authors *via* email.

Studies meeting the eligibility criteria were divided into two groups based on the study population, namely an all-patient cohort and a culture-positive pneumonia cohort. The all-patient cohort included patients with a clinical diagnosis of CAP regardless of culture test results (including both culture-positive and culture-negative patients). The culture-negative patients were treated as non-DRP cases. The culture-positive pneumonia cohort included only CAP patients with positive culture test results. The primary end-points were the risk factors for CAP-DRPs in the all-patient cohort. Secondary end-points included the risk factors for CAP-DRPs in the culture-positive pneumonia cohort and the risk factors for MRSA, Gram-negative rods (GNRs) of CAP-DRPs or multidrug-resistant pathogens (MDRs) in each cohort. MDR was defined according to the definitions used in each original study.

Risk of bias assessment in each study

Two investigators independently evaluated the risk of bias using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) [31]. Each reviewer used the same set of decision rules to score each study and a consensus was reached through discussion.

Data synthesis and statistical analysis

Risk factors for DRPs estimated in two or more studies were synthesised using a general inverse variance method with the DerSimonian and Laird random-effects model. Subgroup analyses were conducted according to specific pathogen strains (MRSA, GNR and MDR). Heterogeneity between studies was quantified using I^2 statistics. Publication bias was assessed by visual inspection of funnel plots. A fixed-effects model was used for sensitivity analysis to assess design bias. All analyses were performed using Review Manager 5.4 (Cochrane Collaboration, London, UK).

Results

Study characteristics

We identified 3870 articles through electronic searches and the full texts of 85 articles were screened. Finally, 24 references were included in the systematic review and meta-analyses (figure 1) [3, 26, 32–53].

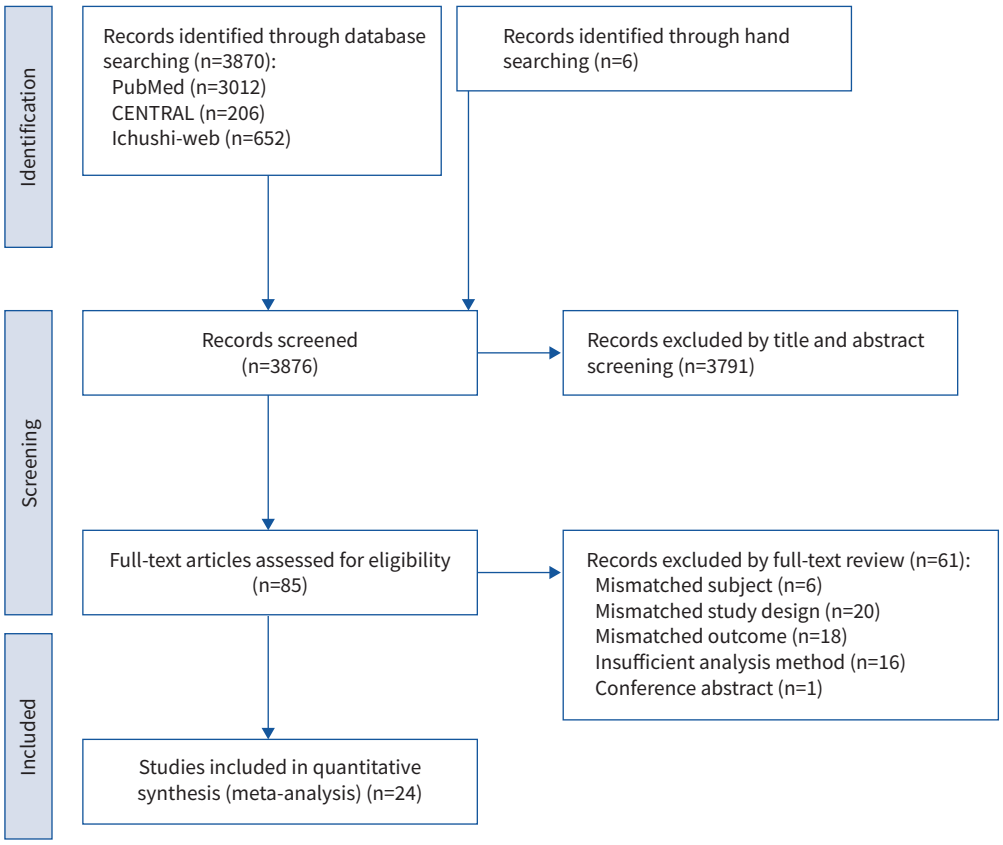

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram. CENTRAL: Cochrane Central Register of Controlled Trials.

The characteristics of the included studies are summarised in table 1. 11 articles [3, 26, 32–40] evaluated the all-patient cohort, whereas 14 [3, 41–53] focused on the culture-positive pneumonia cohort (one article assessed both cohorts). All the included studies were observational and conducted before the coronavirus disease 2019 (COVID-19) pandemic. Eight studies were conducted in Asia, nine in the US, five in Europe and two globally. Sample sizes ranged between 46 and 272 337, with almost all patients admitted in an inpatient setting. The definition of DRPs varied slightly between studies, with some only including MRSA or GNR. The DRP detection rate in the all-patient cohort ranged between 0.4–50.0%. The risk of bias in each study was generally low (figure S1).

Risk factors for CAP-DRPs in all-patient cohort

Figure 2 presents the meta-analyses of risk factors in the all-patient cohort. Of 24 candidates, 11 clinical factors were significantly correlated with CAP-DRPs, namely prior DRP infection/colonisation (OR 5.58, 95% CI 2.15–14.49; I^2=93%, p<0.01), tracheostomy (OR 3.53, 95% CI 1.03–12.15; I^2=70%, p=0.045), severe respiratory failure requiring early induction of mechanical ventilation (OR 3.03, 95% CI 1.87–4.92; I^2=96%, p<0.01), prior use of antibiotics (OR 2.14, 95% CI 1.13–4.05; I^2=80%, p=0.02), chronic lung disease (OR 1.87, 95% CI 1.43–2.45; I^2=89%, p<0.01), COPD (OR 1.68, 95% CI 1.18–2.39; I^2=81%, p<0.01), wound care (OR 1.62, 95% CI 1.08–2.43; I^2=95%, p=0.02), neurologic disorders (OR 1.60, 95% CI 1.44–1.77; I^2=0%, p<0.01), prior hospitalisation (OR 1.51, 95% CI 1.33–1.70; I^2=79%, p<0.01), nursing home residence (OR 1.38, 95% CI 1.13–1.68; I^2=80%, p<0.01) and low activities of daily living (OR 1.29, 95% CI 1.06–1.57; I^2=91%, p=0.01). Despite high heterogeneity, the meta-analysis results for these significant risk factors were generally consistent. Additionally, four risk factors evaluated in only one study each were significantly correlated with CAP-DRPs, namely prior influenza virus infection, vasopressor administration on the day of admission, low body mass index and inhaled corticosteroids (table 2). In total, 15 clinical factors were identified as the primary outcomes of our study (table 3).

Subgroup analyses of the risk factors for specific pathogens are presented in table 3 and figures S2–S4. All the original studies reporting GNR subgroup results defined GNR as *P. aeruginosa*. These results, based on 1–4 studies for each clinical factor, showed trends consistent with those of overall DRPs. Notably, the risk factors for diabetes mellitus differed between assessments of MRSA and *P. aeruginosa*.

Risk factors for CAP-DRPs in culture-positive pneumonia cohort

Significant risk factors for DRPs, MRSA, GNR and MDR subgroups in the culture-positive pneumonia cohort are summarised in table 4. The results of the meta-analyses are shown in figures S5–S7. Prior use of antibiotics (OR 2.50, 95% CI 1.93–3.24; I^2=29%, p<0.01) was significantly associated with CAP-DRPs, based on the meta-analysis of nine studies with low heterogeneity, narrow confidence interval and consistent results between the included studies. Male sex was identified as a significant risk factor for CAP-DRPs in this cohort but was not assessed in the all-patient cohort articles. Again, the number of studies available for subgroup analyses was limited. However, in the subgroup analysis of the culture-positive cohort, the findings corroborated the results of the DRP analysis within the same group, specifically regarding prior DRP infection/colonisation, prior hospitalisation and prior antibiotic use.

Discussion

Main findings

In this systematic review and meta-analysis, 11 clinical factors were significantly associated with the identification of DRPs in patients clinically diagnosed with CAP, namely prior DRP infection/colonisation, tracheostomy, severe respiratory failure requiring early induction of mechanical ventilation, prior use of antibiotics, chronic lung disease, COPD, wound care, neurological disorders, prior hospitalisation, nursing home residence and low activities of daily living. The studies included in this review were divided into two groups, namely all-patient and culture-positive pneumonia cohorts. To our knowledge, few previous reviews have systematically examined the risk factors for CAP-DRPs in an all-patient cohort, including both culture-positive and culture-negative groups. Generally, physicians must determine the initial antibiotics without culture test results, which take several days to reveal. Therefore, the risk factors for CAP-DRPs in the all-patient cohort are more clinically relevant than those in the culture-positive pneumonia cohort.

Differences between all-patient and culture-positive pneumonia cohorts

In the all-patient cohort, the odds ratio was calculated assuming that patients with CAP and culture-negative results have no DRPs. Reports comparing new, sensitive examinations with culture tests suggest that culture-negative results generally indicate the absence of DRPs; several studies revealed that *P. aeruginosa* was detected in only 0–2.5% of cases by 16S rRNA or the FilmArray Pneumonia Panel

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TABLE 1 Characteristics of included studies

First author, reference, year	Country	Study design	Definition of DRP	Number of total patients	Number of culture-positive patients (%)	Number of DRP, MRSA, *P. aeruginosa* and MDR patients (%)
All-patient cohort						
Aliberti [3] 2016	54 countries	Retrospective Multicentre	MRSA	3193	1173 (36.7)	MRSA 188 (5.8)
von Baum [26] 2010	Germany	Prospective Multicentre	*P. aeruginosa*	5130	2102 (40.9)	*P. aeruginosa* 22 (0.4)
Lewis [32] 2021	USA	Retrospective Multicentre	MRSA, *P. aeruginosa*	10 723	Not described	MRSA 356 (3.3), *P. aeruginosa* 250 (2.3)
Metersky [33] 2016	USA	Retrospective Multicentre	MRSA, *P. aeruginosa*	61 651	Not described	*P. aeruginosa* 1156 (1.8), MRSA 641 (1.0)
Minejima [34] 2014	USA	Retrospective Multicentre	MRSA	268	162 (60.4)	MRSA 134 (50)
Restrepo [35] 2018	54 counties	Retrospective Multicentre	*P. aeruginosa*	3193	1173 (36.7)	*P. aeruginosa* 133 (4.1)
Rhodes [36] 2023	USA	Retrospective Multicentre	MRSA	1823	Not described	MRSA 21 (1.2%)
Rothberg [37] 2023	USA	Retrospective Multicentre	Any organism resistant to either a quinolone or the combination of a third-generation cephalosporin and a macrolide was considered resistant to CAP therapy	111 013	Not described	DRP 4127 (3.7)
Soedarsono [38] 2021	Indonesia	Retrospective Single centre	MRSA and all pathogens which are resistant to ⩾1 agent in ⩾3 antimicrobial categories	1364	790 (57.9)	MDR 294 (21.6), *P. aeruginosa* 91 (6.6)
Ukai [39] 2023	Japan	Retrospective Multicentre	MRSA and *P. aeruginosa*	272 337	Not described	MRSA 5141 (1.9) *P. aeruginosa* 3497 (1.3)
Wu [40] 2013	Taiwan	Retrospective Multicentre	*Pseudomonas* spp., *Acinetobacter* spp., MRSA, cefotaxime- or ceftazidime-resistant *Enterbacteriaceae*	1646	824 (50.0)	Not described
Culture-positive pneumonia cohort						
Aliberti [41] 2012	Italy	Prospective Single centre	MRSA, *P. aeruginosa* resistant to antipseudomonal penicillins, cephalosporins, carbapenems and quinolones, *S. maltophilia*, vancomycin-resistant *Enterococcus*, *A. baumannii*, ESBL-producing *Enterobacteriaceae*, other nonfermenting Gram-negative bacilli	935	170 (18.1)	MRSA 16 (9.4), *P. aeruginosa* 12 (7.0), MDR 33 (3.5)
Aliberti [3] 2016	54 countries	Retrospective Multicentre	MRSA	3193	1173 (36.7)	MRSA 188 (5.8)
Barreto [42] 2022	Portugal	Prospective Single centre	*P. aeruginosa*, ESBL-producing *Enterobacteriaceae* or MRSA, nonfermenting Gram-negative bacteria, *A. baumannii*, *S. maltophilia*, *Burkholderia cepacia*, *Ralstonia picketii*	197	197 (100)	DRP 37 (18.7)
Cillóniz [43] 2016	Spain	Prospective Single centre	*P. aeruginosa*	2023	2023 (100)	*P. aeruginosa* 77 (3.8)
Covington [44] 2023	USA	Retrospective Single centre	MRSA, *P. aeruginosa*, ESBL-producing organisms, *Acinetobacter* spp. and *S. maltophilia*.	46	46 (100)	DRP 19 (41.3), MRSA 12 (26.0), *P. aeruginosa* 7 (15.2)

Continued

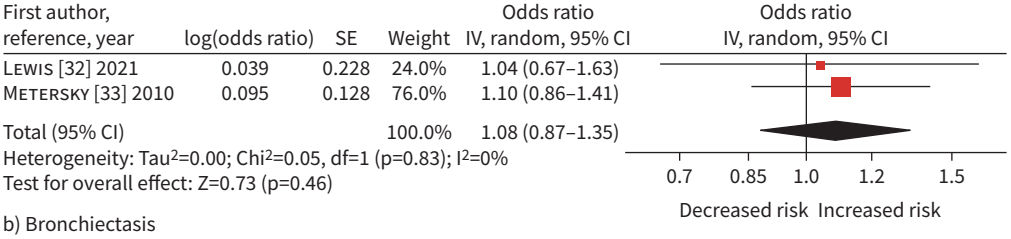
TABLE 1 Continued

First author, reference, year	Country	Study design	Definition of DRP	Number of total patients	Number of culture-positive patients (%)	Number of DRP, MRSA, *P. aeruginosa* and MDR patients (%)
Jeong [45] 2014	South Korea	Retrospective Single centre	MRSA, *P. aeruginosa*, *Acinetobacter* spp., *S. maltophilia* and ESBL-producing *Enterobacteriaceae*	315	315 (100)	DRP 47 (14.9), *P. aeruginosa* 36 (11.4), MRSA 23 (7.3)
Jung [46] 2013	South Korea	Retrospective Single centre	MRSA	943	943 (100)	MRSA 78 (8.2)
Park [47] 2012	South Korea	Retrospective Single centre	MRSA, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, ESBL-producing *Enterobacteriaceae*	339	339 (100)	DRP 122 (36.0)
Park [48] 2013	South Korea	Retrospective Single centre	MRSA, *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, ESBL-producing *Enterobacteriaceae*	580	580 (100)	DRP 227 (39.1)
Prina [49] 2015	Spain	Prospective Single centre	MRSA, *P. aeruginosa*, ESBL-producing *Enterobacteriaceae*	1597	1597 (100)	DRP 94 (6), *P. aeruginosa* 72 (4)
Schreiber [50] 2010	USA	Retrospective Single centre	MRSA, *P. aeruginosa*, ESBL-producing *Enterobacteriaceae*	190	190 (100)	DRP 60 (31.6)
Shindo [51] 2013	Japan	Prospective Multicentre	Not susceptible to beta-lactams (ceftriaxone or ampicillin-sulbactam), macrolides (azithromycin or clarithromycin) and fluoroquinolones (moxifloxacin, levofloxacin or garenoxacin)	1413	795 (56.2)	DRP 119 (8.4), MDR 119 (8.4)
Shorr [52] 2008	USA	Retrospective Single centre	MRSA, *P. aeruginosa*, ESBL-producing *Klebsiella* spp., and other nonfermenting Gram-negative rods	639	639 (100)	DRP 289 (45.2)
Webb [53] 2016	USA	Retrospective Multicentre	Resistant to either ceftriaxone plus azithromycin or levofloxacin	200	200 (100)	Not described

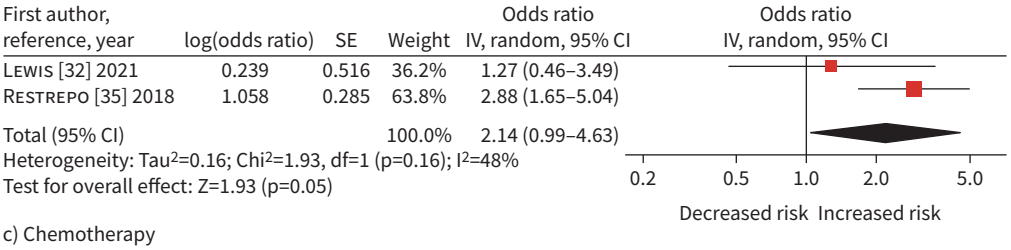
A.: *Acinetobacter*; CAP: community-acquired pneumonia; DRP: drug-resistant pathogen; ESBL: extended-spectrum β-lactamase; MDR: multidrug resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; *P.*: *Pseudomonas*; *S.*: *Stenotrophomonas.*

https://doi.org/10.1183/16000617.0183-2024

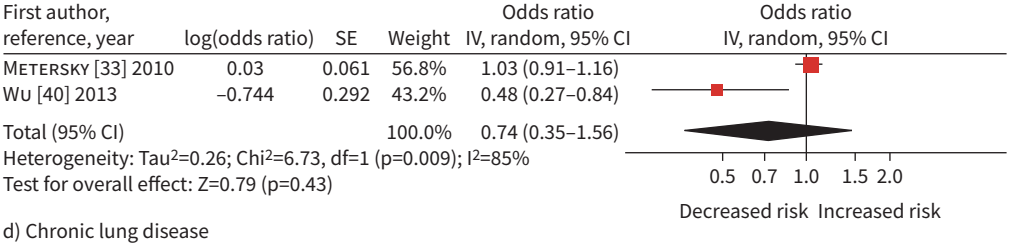
a) Alcohol use



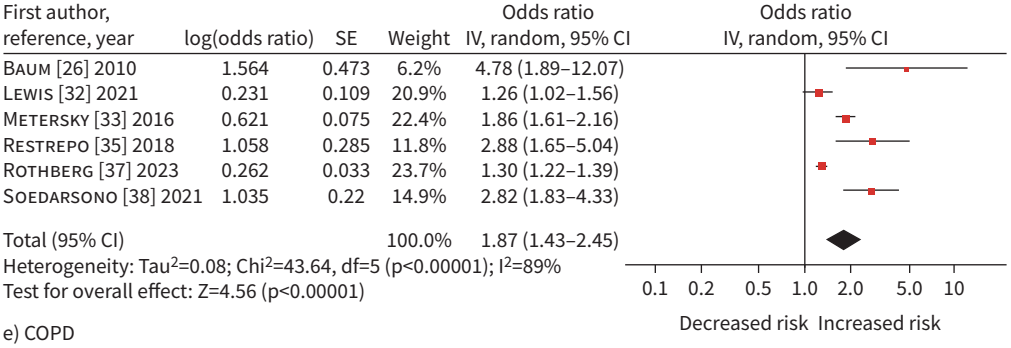
b) Bronchiectasis



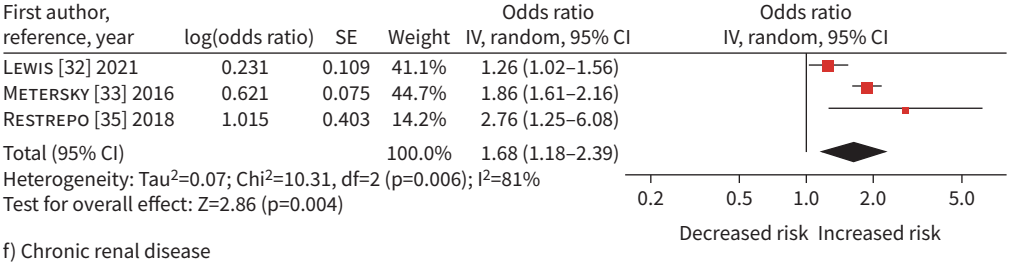
c) Chemotherapy



d) Chronic lung disease



e) COPD



f) Chronic renal disease

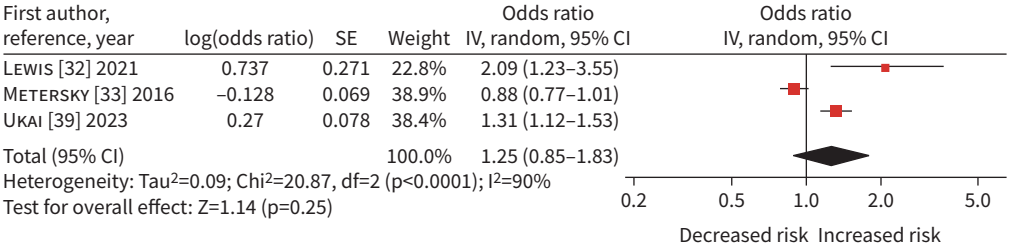
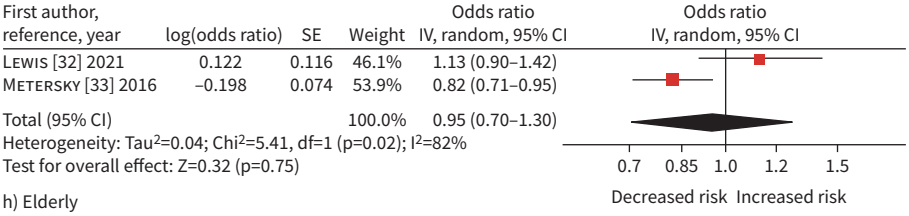
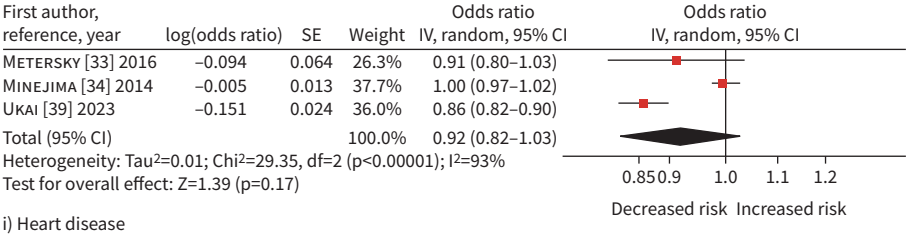


FIGURE 2 Results of meta-analysis of risk factors for community-acquired pneumonia (CAP)-drug-resistant pathogens (DRPs) (all-patient cohort). #: Based on the Z-test, p=0.045. However, Review Manager 5.4 shows p=0.05 due to rounding. ADL: activities of daily living; IV: inverse variance.

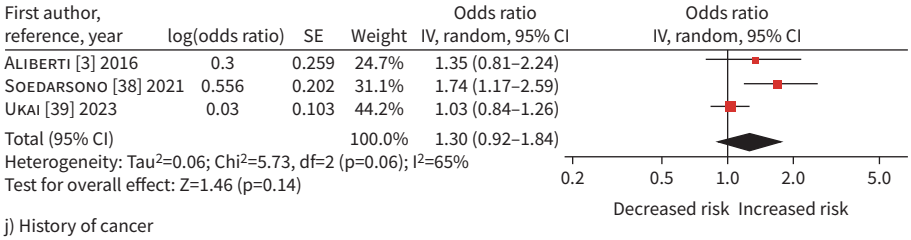
g) Diabetes mellitus



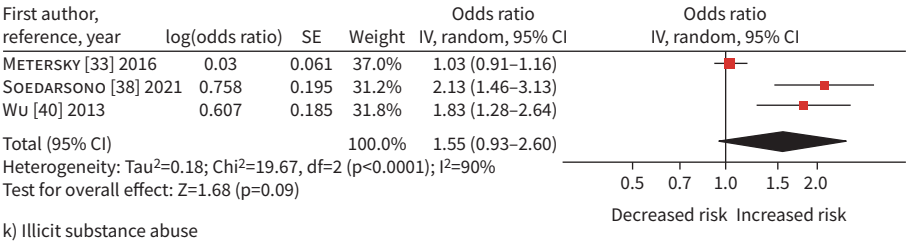
h) Elderly



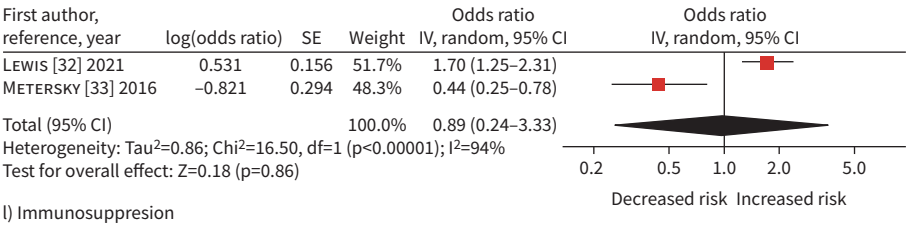
i) Heart disease



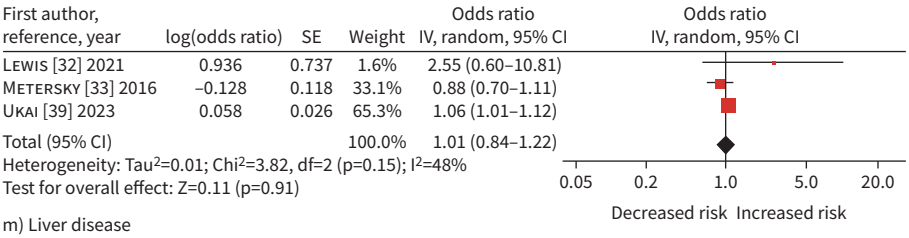
j) History of cancer



k) Illicit substance abuse



l) Immunosuppresion



m) Liver disease

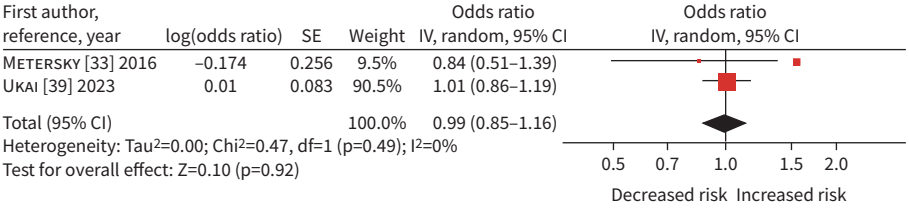
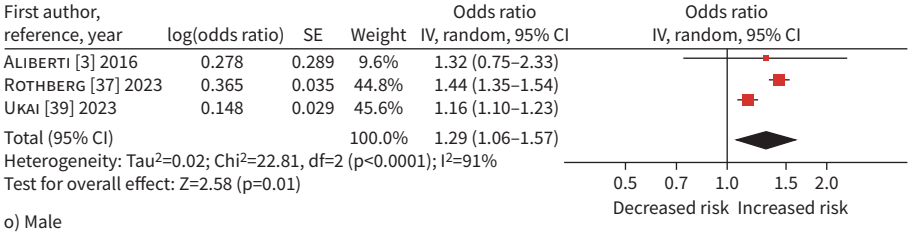
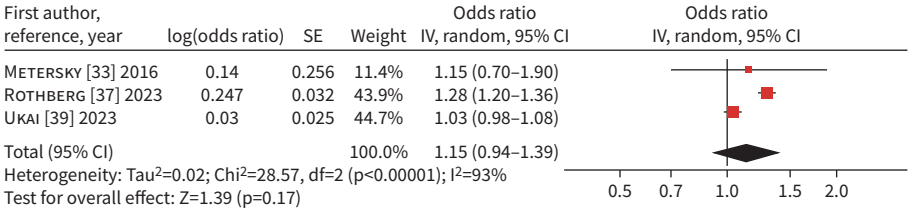


FIGURE 2 Continued.

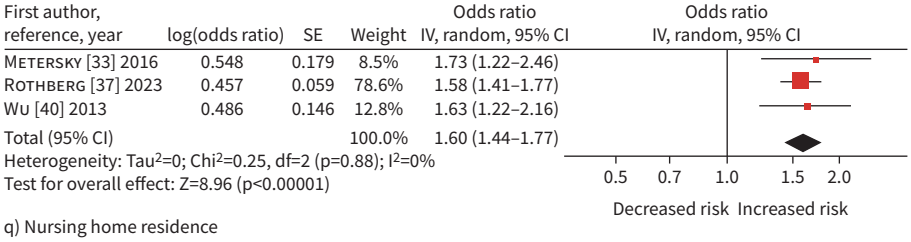
n) Low ADL



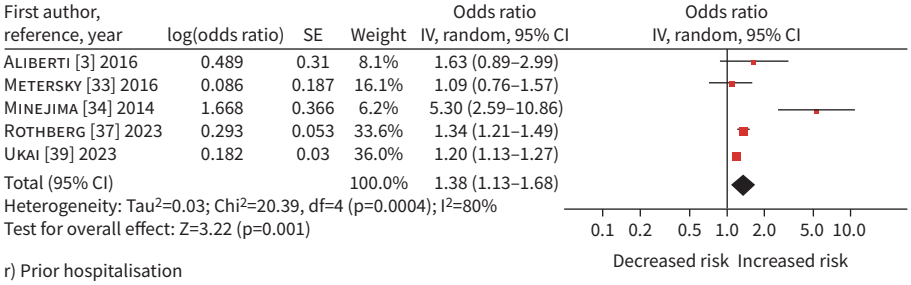
o) Male



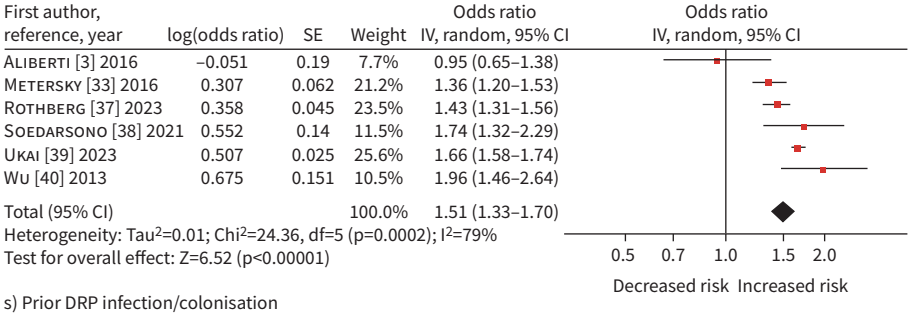
p) Neurological disorders



q) Nursing home residence



r) Prior hospitalisation



s) Prior DRP infection/colonisation

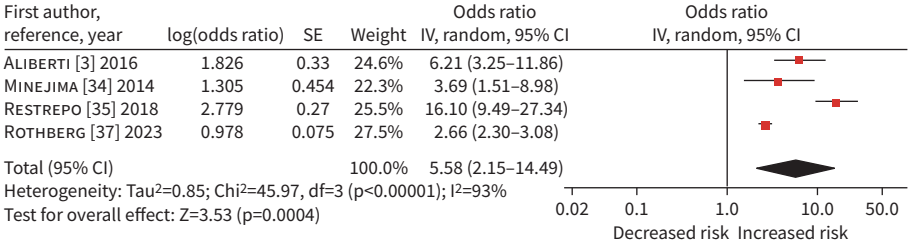
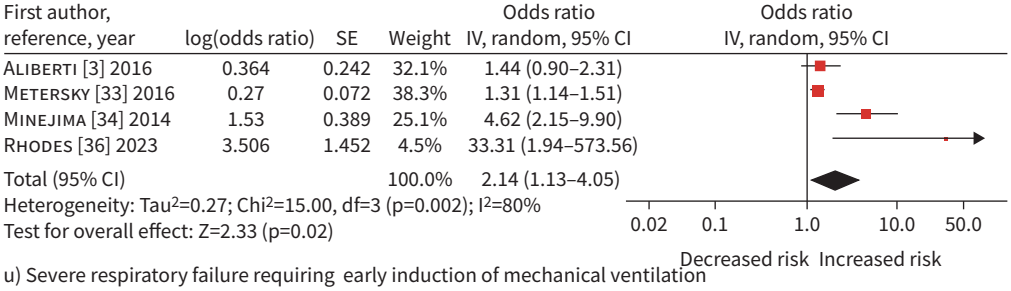
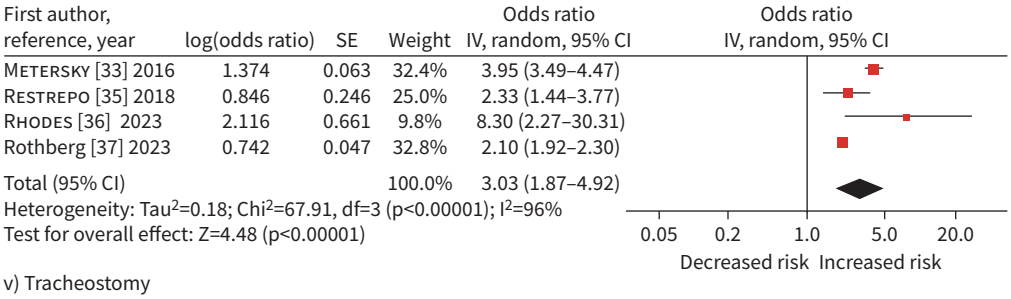


FIGURE 2 Continued.

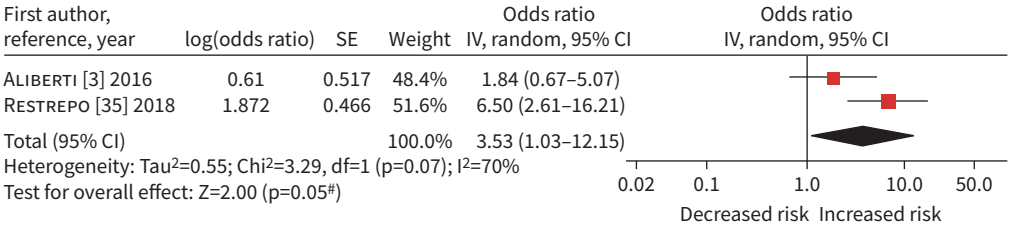
t) Prior use of antibiotics



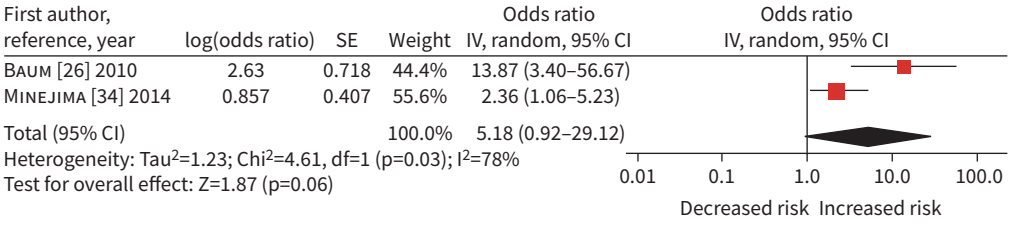
u) Severe respiratory failure requiring early induction of mechanical ventilation



v) Tracheostomy



w) Tube feeding



x) Wound care

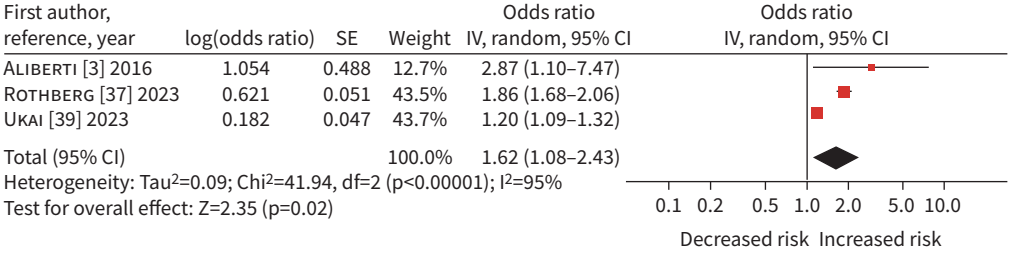


FIGURE 2 Continued.

when not cultured in sputum samples [54–56]. Based on this low prevalence, culture-negative patients were considered to have no DRPs, although this assumption warrants further discussion.

Comparing the all-patient cohort to the culture-positive pneumonia cohort, the risk factors for CAP-DRPs were largely similar between these two groups and the findings aligned with previous reports. The culture-positive cohort may effectively capture the selective pressure by prior antibiotic use. In contrast, the all-patient cohort reflects the full spectrum of patients routinely encountered in clinical practice, offering a comprehensive perspective for guiding clinical decisions. Additionally, the reduced odds ratio of prior

TABLE 2 Risk factors for community-acquired pneumonia drug-resistant pathogens analysed in a single study (all-patient cohort)

Risk factors	Odds ratio (95% CI)
Current smoker	0.77 (0.71–0.85)
Inhaled corticosteroid	1.40 (1.23–1.61)
Low body mass index	1.58 (1.51–1.66)
More than two comorbid conditions	1.95 (0.98–3.89)
Prior influenza virus infection	2.34 (1.18–4.67)
Vasopressor administration on the administration day	1.63 (1.47–1.80)

antibiotic use observed in the all-patient cohort suggests that it is a significant risk factor; however, its impact may vary depending on the patient population and the presence of culture-negative cases. These differences highlight the importance of evaluating risk factors across diverse cohorts. Further investigation is required to assess the effect of prior antibiotic use especially in the all-patient cohort.

Identified risk factors

Regarding the integrated odds ratio, prior DRP infection/colonisation had a large magnitude of effect according to GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) guidelines [57]. In contrast, other factors significantly associated with DRPs in this study had relatively small effects [12, 53]. Current consensus suggests that extended-spectrum antibiotics should be administered to patients with a history of DRP infection/colonisation or multiple risk factors for DRP other than DRP infection/colonisation history [12, 53, 58]. Therefore, our findings in our study support that this consensus regarding the strategy of extended-spectrum antibiotic use may be acceptable.

Explaining the mechanism of why severe respiratory failure requiring early induction of mechanical ventilation is associated with CAP caused by DRPs may be difficult. Many previous studies have not found the severity of illness as a risk factor for DRPs. Conversely, SANDO *et al*. [59] reported that pneumonia caused by *P. aeruginosa*, which is one of the representative DRPs, had a high mortality compared with non-*P. aeruginosa* pneumonia, implying the association between severity and pneumonia due to DRP. However, further investigation is needed.

Chronic lung diseases were not subcategorised in many of the primary studies; however, we conducted meta-analyses on three categories of pre-existing pulmonary disease, namely bronchiectasis, chronic lung disease and COPD. Chronic lung disease encompassed the other two diseases. Figure 2 and table 3 show similar results across these categories, except for a higher odds ratio for *P. aeruginosa* infection in bronchiectasis patients. These results suggest that bronchiectasis should be differentiated from other chronic lung diseases in future studies about CAP-DRP risk assessments.

We also analysed the risk factors for MRSA and GNR. While many factors were compatible with previous reports [15, 18, 19, 23, 24, 60, 61], illicit substance use and the need for vasopressors or invasive mechanical ventilation were newly identified risk factors for MRSA, whereas tracheostomy and inhaled corticosteroids were identified as risk factors for GNR. Further verification is required due to the limited number of studies in these subgroup analyses.

Implications for clinical practice and future research

Developing a scoring system with high predictive accuracy for patients with CAP is a remarkable future challenge. Several studies have proposed methods and scoring systems to predict DRPs based on clinical factors at CAP diagnosis [12, 51, 53, 62, 63]. Most methods have high negative predictive values and low positive predictive values [53, 64]. The discussion of how the threshold should be set is one crucial issue that needs addressing to avoid both inadequate antibiotic treatment and overuse of extended-spectrum antibiotics. Ideally, such a system should be designed considering ideas of which patients can be treated with narrow-spectrum antibiotics (*e.g.*, nonpseudomonal β-lactams, macrolides and respiratory fluoroquinolones) and those who need extended-spectrum antibiotics. Moreover, these extended-spectrum antibiotics should be separately considered for MRSA and antibiotic-resistant GNR. However, currently available data for each subgroup (MRSA and GNR, including *P. aeruginosa*) are limited. The factors identified in this study, especially those with large magnitudes, should be considered as candidate variables for developing future scoring systems and may provide a more accurate approach to physicians in making

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TABLE 3 Summary of significant risk factors for drug-resistant pathogen (DRPs) revealed by meta-analyses for the all-patient cohort

Significant risk factors	CAP-DRPs		MRSA		*P. aeruginosa*		MDR	
	Number of studies	Odds ratio (95% CI)	Number of studies	Odds ratio (lower–upper)	Number of studies	Odds ratio (95% CI)	Number of studies	Odds ratio (95% CI)
Bronchiectasis	–	–	–	–	2	4.16 (1.99–8.72)	–	–
Chronic lung disease	6	1.87 (1.43–2.45)	2	1.22 (1.06–1.40)	4	2.09 (1.64–2.66)	2	2.78 (1.89–4.10)
COPD	3	1.68 (1.18–2.39)	2	1.22 (1.06–1.40)	3	1.88 (1.65–2.13)	1	2.69 (1.10–6.55)
Diabetes mellitus	–	–	2	1.16 (1.01–1.33)	2	0.73 (0.55–0.97)	–	–
Heart disease	–	–	–	–	–	–	1	1.74 (1.17–2.59)
History of cancer	–	–	–	–	–	–	1	2.13 (1.46–3.13)
Illicit substance abuse	–	–	2	1.62 (1.25–2.10)	–	–	–	–
Immunosuppression	–	–	3	1.12 (1.04–1.20)	–	–	–	–
Inhaled corticosteroid	1	1.40 (1.23–1.61)	–	–	1	1.40 (1.23–1.61)	–	–
Low ADL	3	1.29 (1.06–1.57)	2	1.38 (1.29–1.48)	–	–	–	–
Low BMI	1	1.58 (1.51–1.66)	1	1.29 (1.22–1.36)	1	2.09 (1.95–2.23)	–	–
Neurological disorders	3	1.60 (1.44–1.77)	–	–	1	1.73 (1.22–2.46)	–	–
Nursing home residence	5	1.38 (1.13–1.68)	4	2.00 (1.26–3.16)	–	–	–	–
Prior hospitalisation	6	1.51 (1.33–1.70)	3	1.33 (1.09–1.64)	2	1.74 (1.08–2.83)	1	1.74 (1.32–2.29)
Prior infection/colonisation of DRP	4	5.58 (2.15–14.49)	2	5.19 (3.07–8.75)	1	16.1 (9.48–27.35)	1	12.34 (5.05–30.14)
Prior influenza virus infection	1	2.34 (1.18–4.67)	1	2.34 (1.18–4.67)	–	–	–	–
Prior use of antibiotics	4	2.14 (1.13–4.05)	–	–	1	1.31 (1.14–1.51)	–	–
Severe respiratory failure requiring early induction of mechanical ventilation	4	3.03 (1.87–4.92)	2	4.27 (2.48–7.36)	2	3.20 (1.93–5.31)	1	3.42 (1.47–7.97)
Tracheostomy	2	3.53 (1.03–12.15)	–	–	1	6.50 (2.61–16.19)	–	–
Tube feeding	–	–	1	2.36 (1.06–5.23)	1	13.87 (3.40–56.67)	–	–
Vasopressor administration on the administration day	1	1.63 (1.47–1.80)	–	–	–	–	–	–
Wound care	3	1.62 (1.08–2.43)	–	–	–	–	–	–

–: no studies/not applicable; ADL: activities of daily living; BMI: body mass index; CAP: community-acquired pneumonia; MDR: multidrug resistance; MRSA: methicillin-resistant *Staphylococcus aureus*; *P.*: *Pseudomonas*.

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TABLE 4 Summary of significant risk factors for drug-resistant pathogen (DRPs) revealed by meta-analyses for the culture-positive pneumonia cohort

Significant risk factor	CAP-DRPs		MRSA		GNR		MDR	
	Number of studies	Odds ratio (95% CI)	Number of studies	Odds ratio (95% CI)	Number of studies	Odds ratio (95% CI)	Number of studies	Odds ratio (95% CI)
Chronic lung disease	6	1.89 (1.45–2.47)	–	–	3	3.00 (2.03–4.44)	–	–
Chronic renal disease	5	2.11 (1.41–3.16)	–	–	–	–	–	–
Heart disease	2	1.63 (1.07–2.50)	–	–	–	–	–	–
Immunosuppression	4	2.08 (1.19–3.63)	–	–	–	–	–	–
Inhaled corticosteroid	–	–	–	–	1	3.47 (1.97–6.09)	–	–
Low ADL status	4	2.54 (1.61–3.99)	–	–	–	–	–	–
Male	2	2.56 (1.47–4.46)	–	–	1	3.71 (1.65–8.35)	–	–
Nursing home residence	11	2.09 (1.54–2.84])	4	1.94 (1.29–2.92)	–	–	1	3.55 (1.12–11.24)
Prior hospitalisation	9	2.46 (1.72–3.52)	3	1.64 (1.02–2.66)	–	–	1	4.87 (1.90–12.40)
Prior infection/colonisation of DRP	4	5.60 (3.05–10.26)	2	5.56 (3.37–9.16)	1	5.24 (1.56–17.66)	–	–
Prior influenza virus infection	–	–	–	–	1	0.39 (0.21–0.72)	–	–
Prior use of antibiotics	9	2.50 (1.93–3.24)	2	1.75 (1.19–2.59)	2	2.99 (1.29–7.11)	1	3.32 (1.07–10.31)
Respiratory failure	–	–	–	–	1	2.36 (1.28–4.36)	–	–
Tube feeding	5	4.56 (1.53–13.59)	–	–	1	12.93 (2.28–73.37)	–	–
Use of gastric acid suppressive agents	1	2.22 (1.39–3.57)	–	–	–	–	–	–
Wound care	3	2.15 (1.04–4.46)	2	3.61 (1.59–8.18)	–	–	–	–

–: no studies/not applicable; ADL: activities of daily living; BMI: body mass index; CAP: community-acquired pneumonia; GNR: Gram-negative rods; MDR: multidrug resistance; MRSA: methicillin-resistant *Staphylococcus aureus*.

clinical decisions for initial appropriate antibiotic use. Furthermore, consideration for co-dependence and interaction between the risk factors would enable the development of improved scoring systems.

Limitations

Our study had some limitations. First, the prevalence of DRPs and associated risk factors can vary between regions [12, 64]. Therefore, integrating the results of studies conducted in different regions would be inappropriate, which is a major flaw in systematic reviews in nature. Among the most risk factors identified in this study, however, little heterogeneity was found in the fact that the risk was elevated, although there was heterogeneity in the degree of risk increase. This finding suggests that these factors universally increase the likelihood of DRPs regardless of the region. High I^2 statistics scores can partly result from large sample sizes and undermine the reliability of the meta-analysis results. Nonetheless, it remains crucial to consider locally validated risk factors for DRPs. Second, some studies defined DRPs as specific pathogens, such as MRSA or *P. aeruginosa*. In studies assessing risk factors for MRSA, patients with CAP caused by *P. aeruginosa* might have been classified into the non-DRP group, although in many other studies, patients with *P. aeruginosa* were included in the DRP group. These slight differences in DRP definitions between the included studies could have affected the meta-analysis results for CAP-DRPs. Third, determining whether the culture results from sputum samples indicate the true causative bacteria is difficult. However, it is often clinically determined to be the causative bacteria if the sputum is of good quality. Furthermore, most of the included studies made their assessment on this basis. Therefore, our results are clinically relevant. Fourth, many of the studies included in this systematic review did not specify how risk factors were selected for multivariate analysis nor describe the odds ratio for nonsignificant variables. This raises concerns regarding the publication bias, meaning the odds ratios presented here could be exaggerated. Finally, all the included studies were conducted before the COVID-19 pandemic. Patients with COVID-19 were reported to have different bacterial microbiota [65] and trends in invasive bacterial diseases changed slightly during the first 2 years of the pandemic [66]. Therefore, the prevalence of DRPs may have shifted before and after the COVID-19 pandemic.

Conclusion

We identified risk factors for CAP-DRPs. In the all-patient cohort, significant risk factors included prior DRP infection/colonisation, tracheostomy, severe respiratory failure requiring early induction of mechanical ventilation, prior use of antibiotics, chronic lung disease, COPD, wound care, neurological disorders, prior hospitalisation, nursing home residence and poor activities of daily living. These factors should be considered when determining initial antibiotics for clinicians and when developing prediction models for CAP-DRPs for researchers. The prediction models should be ideally designed based on antibiotic prescription patterns. In addition, it would be useful if the model can classify patients with pneumonia into those who can be treated with the following specific antibiotics: narrow-spectrum antibiotics that are commonly used for CAP and extended-spectrum antibiotics, including anti-MRSA and antipseudomonal antibiotics.

Points for clinical practice

This systematic review is the first to focus on the risk factors for CAP-DRPs. We identified several clinical characteristics that were significant risk factors for CAP-DRPs. The important future challenge is to develop a prediction model for CAP-DRPs with high predictive accuracy so that physicians can select appropriate initial antibiotics for patients with CAP. The identified factors can be candidates for component factors of the prediction model.

A distinguishing feature of our study, compared with previous reviews, is that we carefully analysed the included studies by separately considering all-patient and culture-positive pneumonia cohorts. This distinction had not been adequately addressed in prior research. Given the low culture-positive rate among patients with pneumonia, the data from the all-patient cohort is more relevant for clinical application. Our findings suggest that further validation is necessary, particularly in the all-patient cohort.

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Availability of data and materials: The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Author contributions: N. Nakagawa, M. Katsurada, Y. Fukuda and S. Noguchi collected and analysed the data. N. Nakagawa, M. Katsurada, Y. Fukuda and Y. Shindo interpreted the data and drafted the manuscript. N. Horita, a specialist in statistics, supervised statistics-related matters. M. Miki, H. Tsukada, K. Senda, Y. Shindo and H. Mukae reviewed and revised the manuscript. All the authors have read and approved the final version of this manuscript.

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