Risk Factors for Community-Acquired Pneumonia in Adults: A Systematic Review of Observational Studies

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Keywords

Community-acquired pneumonia · Risk factors · Adults · Systematic review · Observational studies

Abstract

We performed a systematic review of the literature to establish conclusive evidence of risk factors for community-acquired pneumonia (CAP). Observational studies (cross-sectional, case-control, and cohort studies) the primary outcome of which was to assess risk factors for CAP in both hospitalized and ambulatory adult patients with radiologically confirmed pneumonia were selected. The Newcastle-Ottawa Scale specific for cohort and case-control designs was used for quality assessment. Twenty-nine studies (20 case-control, 8 cohort, and 1 cross-sectional) were selected, with 44.8% of them focused on elderly subjects ≥ 65 years of age and 34.5% on mixed populations (participants' age > 14 years). The median quality score was 7.44 (range 5–9). Age, smoking, environmental exposures, malnutrition, previous CAP, chronic bronchitis/chronic obstructive pulmonary disease, asthma, functional impairment, poor dental health, im-

munosuppressive therapy, oral steroids, and treatment with gastric acid-suppressive drugs were definitive risk factors for CAP. Some of these factors are modifiable. Regarding other factors (e.g., gender, overweight, alcohol use, recent respiratory tract infections, pneumococcal and influenza vaccination, inhalation therapy, swallowing disorders, renal and liver dysfunction, diabetes, and cancer) no definitive conclusion could be established. Prompt assessment and correction of modifiable risk factors could reduce morbidity and mortality among adult CAP patients, particularly among the elderly.

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Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in industrialized countries. In the general adult population, the annual incidence of CAP ranges between 1.6 and 13.4 cases per 1,000 inhabitants, 22–51% of whom require inpatient care, with a lethality of 3–24%. The mortality rate varies

between 0.1 and 0.7 per 1,000 persons each year [1]. Despite considerable research, great improvement in medical care, and advances in antimicrobial therapy with the availability of active antibiotics against the known causative pathogens, mortality from CAP has not improved during the last decades. Targeted risk reduction interventions based on understanding and recognizing risk factors for CAP are of primary importance in reducing CAP-related death rates [2].

So far, only 1 systematic review analyzing risk factors for CAP has been published in the literature [3]. This study, however, was published in German and the search was limited to the MEDLINE database, including articles published between 1996 and December 2003. In the last years, new data have been published, sometimes corroborating previous evidence, sometimes with controversial results and in other occasions suggesting new possible risk factors that need to be further studied. These studies have different designs, methodological quality, and populations, have measured different risk factors, or have assessed the same risk factors in different ways. Therefore, they not always report conclusive and concordant results.

Because of this heterogeneity, there is a need to update all the evidence to reach a more definitive conclusion for the studied factors. Our systematic review not only updates the earlier review of Kohlhammer et al. [3] published in 2005, but also summarizes the scientific evidence from observational studies about risk factors for CAP in adults.

Methods

Study Selection

Observational studies in which the primary outcome was to assess risk factors for CAP in both hospitalized and ambulatory adult patients with radiologically confirmed pneumonia were selected for the study. Observational studies included cross-sectional, case-control, and cohort study designs. Exclusion criteria were as follows: (a) studies addressing other aspects of CAP, such as bacteraemia, health care-acquired pneumonia, hospital-acquired pneumonia, and CAP caused by antibiotic-resistant pathogens; (b) studies focused on prognostic or treatment-related factors for CAP; and (c) studies of CAP carried out in specific populations, such as patients with diabetes mellitus, chronic obstructive pulmonary disease (COPD), or HIV infection.

The search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [4]. The electronic databases PubMed MEDLINE (US National Library of Medicine, Bethesda, MD, USA) and EMBASE Elsevier were systematically searched until June 30, 2015. The search strategy is detailed in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000479089). Reports published in English, Spanish, and French were consid-

ered. Potentially relevant articles were screened for eligibility independently in an unblinded standardized manner by the two reviewers (J.A. and V.B.), initially by abstract and then by full text if necessary, to determine whether they met the inclusion criteria. Disagreement between the reviewers was resolved by discussion with the rest of the researchers. The reference lists of the identified articles were manually searched for additional studies that may have been overlooked using the computer-assisted search strategy.

Data Extraction

We developed a data extraction sheet, pilot-tested it on 3 randomly selected included studies, and refined it accordingly. One author (J.A.) extracted the data from the included studies and a second author (M.S.-P.) checked the extracted data. Disagreements were resolved by discussion between the two review authors. The following information was extracted from each included paper: authors and year of publication; study design; characteristics of study participants (number, mean age, and gender); and risk factors for CAP. In order to reinforce the confidence of the predictive effect of risk factors for CAP, only those factors that were individually analyzed in at least 3 studies were considered. The number of at least 3 studies was arbitrarily decided on, because of the possibility of disagreement between only 2 studies. Risk factors were grouped into the broad categories of sociodemographic and lifestyle factors, comorbidities or clinical conditions, and therapeutic factors.

Quality Assessment

The quality of all included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for nonrandomized studies. The NOS specific for cohort and case-control designs was used [5], with an overall quality score ranging from 0 (minimum) to 9 (maximum) stars. Discrepancies in quality assessment were discussed and resolved by three authors (J.A., I.B., and V.B.).

Data Synthesis and Analysis

The quality and concordance of the evidence was used to develop standardized statements for each risk factor. For each analysis in each individual study, the resulting effect of the risk factors was categorized as “significant risk factor,” “significant protective factor,” or “nonsignificant risk factor.” Only the results of multivariate adjusted models were taken into account. If a given category (significant risk factor, significant protective factor, or nonsignificant risk factor) was present in >66% of the studies and the other categories in ≤34% of the studies, and the given category had no clearly lower methodological quality, then standardized statements of “clear risk factor,” “clear protective factor,” or “no effect” were established; otherwise, a statement of “no definitive conclusion” was considered (Table 1). No clearly lower methodological quality was considered if the difference in median NOS scores between categories was <1 point.

Whenever a factor was analyzed more than once in a study (e.g., it was included in ≥2 predictive models for CAP), it was counted in all the categories that applied. In these cases, the percentages of the “risk/protection/no effect” categories added up to >100%, and the standardized statement was extended as follows: if two categories had >66% of the studies and one category had a higher methodological quality than the other, then the statement was “possible risk factor/possible protective factor/possible no effect.” Each factor was classified according to its predictive profile (risk factor,

Table 1. Standardized definitions of the confidence of the predictive effect of risk factors for CAP

Categories of effect of risk factors	Percentage of studies favoring the effect	NOS quality versus other categories of effect	Standardized definition
Significant risk factor	>66%	Higher Lower	Clear risk factor No definitive conclusion
Significant protective factor	>66%	Higher Lower	Clear protective factor No definitive conclusion
Nonsignificant risk factor	>66%	Higher Lower	No effect No definitive conclusion
Significant risk factor	≤66%	Not applicable	No definitive conclusion
Significant protective factor	≤66%	Not applicable	
Nonsignificant risk factor	≤66%	Not applicable	

CAP, community-acquired pneumonia; NOS, Newcastle-Ottawa Scale.

protective factor, or no effect) and to the standardized consideration of the confidence that could be placed on that profile (clear, possible, or no definitive conclusion). To analyze and synthesize the evidence, for each risk factor we present the number of publications and the number of analyses in the three possible categories of effect, specifying the number of publications on elderly patients. We also present the median score (range) on the NOS, and, for those that are clearly risk or protective factors, the estimated effect independent from the multivariate models. It is expressed as the median (range) of all the adjusted odds ratios (OR), from the categories of clear risk/protective, and from those publications that presented risk factors in a homogeneous way to allow its synthesis (i.e., similar cutoff points or categorization and similar measure of the risk factor).

Results

Search Results

The electronic search strategy identified a total of 2,731 records from electronic databases, 114 of which were retrieved for full paper evaluation. Of these 114 full papers, 36 met the eligibility criteria and were subjected to data extraction [2, 6, 7–40]. However, these 36 articles referred to only 29 studies, since in 5 cases the same study or different aspects of the same study were published in more than 1 article [2, 7, 8, 10–12, 24, 25, 32, 33, 39, 40]. Therefore, a total of 29 studies were included for qualitative synthesis (Fig. 1).

Characteristics of the Studies

Twenty studies (70%) had a case-control design, 8 (27.6%) had a cohort design, and 1 (3.4%) had a cross-

sectional design (Table 2). The case-control and cross-sectional studies included 29,018 participants. The cohort studies were prospective in 6 cases and retrospective in 2, and overall they included more than 140,000 participants. The cohort studies were published between 1994 and 2015, with the longest follow-up being 16 years and 11 months. Most studies focused on elderly subjects ≥65 years of age (44.8%) or mixed populations where the participants' age was >14 years (34.5%), and a few studies (13.8%) considered only the age range between 18 and 60 years. The definitions used for cases and controls, as well as exposed and nonexposed subjects, in each of the included studies are detailed in online supplementary Table 2.

Quality Assessment

The median quality score of the studies was 7.44 (range 5–9). The median quality score of the case-control and cross-sectional studies was 7.42, which was very similar to that of the cohort studies (7.5).

Evidence Synthesis

Sociodemographic and Lifestyle Factors

Clear risk factors for CAP were age, smoking, poor nutritional status, and environmental exposures to different substances (metals, dust, fumes, etc.) (Table 3). No definitive conclusions were drawn for the effect of male gender and alcohol use. No effect was demonstrated for overweight and passive smoking in the overall adult population.

Fig. 1. Flowchart of the studies included in this review. CAP, community-acquired pneumonia.

Comorbidities or Clinical Conditions

As shown in Table 4, functional impairment, COPD/chronic bronchitis, asthma, a history of CAP, and orodental and/or periodontal diseases were clear risk factors for CAP. Recent upper respiratory tract infections showed to be a possible risk factor. Chronic heart disease, dysphagia, cancer, chronic liver disease, and diabetes allowed no definitive conclusion, while chronic renal disease showed no effect.

Therapeutic Factors

Immunosuppressive treatment, use of oral steroids, and proton pump inhibitors or H₂ blockers were classified as clear risk factors for CAP (Table 5). Treatment with antibiotics for any reason prior to admission for CAP and influenza vaccines had no effect, whereas the role of inhaled drugs remained in the “no definitive conclusion” category. Pneumococcal vaccination (polysaccharide 23V) was classified in the “possibly no effect” category.

The results of other, less studied factors (i.e., individually analyzed in <3 studies) are detailed in Table 6.

Discussion

This study shows conclusive evidence of age, smoking habit, environmental exposures, poor nutritional status, functional impairment, chronic bronchitis/COPD, asthma, previous CAP (in the past 1 or 2 years), poor oral health, immunosuppressive therapy, oral steroids, and

treatment with proton pump inhibitors or H₂ antagonists as risk factors for CAP in adults. No effect was found for other factors, including overweight, passive smoking, influenza vaccine, use of antibiotics before CAP, and chronic renal disease. Also, the role of male gender, alcohol use, passive smoking in the older age subgroup, heart disease, dysphagia, cancer, chronic liver disease, diabetes, use of inhalers, and pneumococcal vaccine remained inconclusive. A large number of other potential risk factors for CAP (detailed in Table 6) need to be further studied.

Age is a well-known risk factor for CAP, especially in older people. In 2 studies carried out on subjects of all ages, significant results were only found for the oldest segment of the population [14, 20], whereas in 1 study on young people [14], age was not a significant factor. These findings may suggest a nonlinear effect, with older age as a risk factor for CAP. Age may also modify or interact with other factors in elderly people. Active smoking has a direct and independent effect on the risk of pneumonia, but it may also act indirectly, causing COPD, which is a well-recognized risk factor for CAP. In relation to gender, the results of the studies are conflicting. In our systematic review, male gender was a significant risk factor in 4 analyses and a nonsignificant factor in 3 studies. Women are often less represented than men in COPD populations, and typically smoke substantially less than men. Only 3 studies [2, 21, 30] assessed the effect of passive smoking, 2 of which showed no significant effect [2, 21]. However, the third study [30], of somewhat greater quality, observed a significant effect in elderly subjects, in whom the lung defense mechanisms might be insufficient

Table 2. General characteristics of the 29 studies included in the systematic review of risk factors for CAP

First author, country	Year [Ref.]	Design	Number of participants	Age and representativeness	NOS quality score
Almirall, Spain	1999 [6]	Case-control	Cases, <i>n</i> = 205; controls, <i>n</i> = 475	>14 years; outpatients and hospitalized pneumonia cases, population controls	7
Almirall, Spain	2008 [2] 2015 [7] 2010 [8]	Case-control	Cases, <i>n</i> = 1,336; controls, <i>n</i> = 1,326 Cases, <i>n</i> = 437; controls, <i>n</i> = 235	>14 years; outpatients and hospitalized pneumonia cases, population controls	7
Almirall, Spain	2013 [9]	Case-control	Cases, <i>n</i> = 36; controls, <i>n</i> = 72	≥70 years; hospitalized cases consecutively included in the study, population controls	9
Alperovich, USA Neuman, USA Neuman, USA	2007 [10] 2007 [11] 2010 [12]	Cohort	Nurses' Health Study (NHS) II; cohort, <i>n</i> = 83,165 women; 925 cases observed for 650,377 person-years	Women aged 27–44 years; outpatients and hospitalized pneumonia cases (follow-up 10 years)	6
Atsumi, Japan	2009 [13]	Cross-sectional	Total, <i>n</i> = 4,666 patients; with CAP, <i>n</i> = 313; without CAP, <i>n</i> = 4,353	Adults; hospitalized from a department with a respiratory unit, an infectious unit, and a digestive unit	7
Baik, UK	2000 [14]	Nested case-control	HPFS cohort of 26,429 men (cases, <i>n</i> = 290) and NHS II cohort of 83,165 women (cases, <i>n</i> = 305)	Health professionals (40–75 years) and nurses (27–44 years); cases and controls from the HPFS and NHS II cohorts	6
Dang, Canada	2014 [15]	Cohort	Cohort, <i>n</i> = 2,709; cases, <i>n</i> = 245; controls, <i>n</i> = 2,464	>17 years; cases and controls, survivors of a hospitalized CAP and free of pneumonia for ≥3 months	9
de Melo Neto, Brazil	2013 [16]	Case-control	Cases, <i>n</i> = 70; controls, <i>n</i> = 70	≥18 years; hospitalized cases and controls	8
Doshi, USA	2011 [17]	Case-control	Cases, <i>n</i> = 347; controls, <i>n</i> = 694	Adults; hospitalized	8
Eurich, Canada	2010 [18]	Nested case-control	Cohort, <i>n</i> = 3,415; cases, <i>n</i> = 248; controls, <i>n</i> = 2,476	Population-based cohort of patients >17 years of age admitted with CAP; cases were patients aged ≥65 years hospitalized for recurrent pneumonia; matched controls were free of pneumonia	8
Eurich, Canada	2013 [19]	Nested case-control	Cohort, <i>n</i> = 6,874; cases, <i>n</i> = 653; controls, <i>n</i> = 6,244	Population-based cohort of patients >17 years of age admitted with CAP; cases were patients aged ≥65 years hospitalized for recurrent pneumonia; matched controls free of pneumonia	9
Farr, UK	2000 [20]	Case-control	Cases, <i>n</i> = 66; controls, <i>n</i> = 489	15–79 years; community-diagnosed pneumonia, population controls	6
Farr, UK	2000 [21]	Case-control	Cases, <i>n</i> = 178; controls, <i>n</i> = 385	18–75 years; hospitalized cases having survived a previous primary pneumonia, population controls	6
Fernández-Solá, Spain	1995 [22]	Case-control	Cases, <i>n</i> = 50; controls, <i>n</i> = 50	18–60 years; hospitalized cases and controls	7
Gau, USA	2010 [23]	Case-control	Cases, <i>n</i> = 194; controls, <i>n</i> = 952	≥65 years; hospitalized cases and controls	7
Jackson, USA	2003 [24] 2004 [25]	Retrospective cohort (3 years)	Cohort of 47,365 persons; 3,061 cases observed for 127,180 person-years	≥65-year-old members of a health maintenance organization; outpatient pneumonia cases	8
Jovanovich, USA	2014 [26]	Retrospective cohort (3–15 months)	Cases, <i>n</i> = 66; controls, <i>n</i> = 66	Community-living adult individuals hospitalized with CAP or sepsis	7

Table 2 (continued)

First author, country	Year [Ref.]	Design	Number of participants	Age and representativeness	NOS quality score
Juthani-Mehta, USA	2013 [27]	Cohort	Cohort of 1,441 participants; cases, <i>n</i> = 193	70–79 years; hospitalized pneumonia cases, community-dwelling adults with dental examination (follow-up 10 years)	8
Kang, Korea	2008 [28]	Case-control	Cases, <i>n</i> = 255; controls, <i>n</i> = 255	Only male soldiers 18–23 years old; hospitalized cases and controls	6
Koivula, Finland	1994 [29]	Cohort	Cohort of 4,175 participants; cases, <i>n</i> = 185	≥60 years; all inhabitants of Varkaus (population cohort) (follow-up 3 years)	9
Loeb, Canada	2009 [30]	Case-control	Cases, <i>n</i> = 717; controls, <i>n</i> = 867	≥65 years; population controls, cases presented to emergency departments, controls from the same catchment area	7
Meijvis, The Netherlands	2011 [31]	Case-control	Cases, <i>n</i> = 430; controls, <i>n</i> = 1,720	Adults, age ranges not stated; hospitalized cases, population controls	9
Merchant, USA	2004 [32] 2005 [33]	Cohort	HPFS cohort of 38,378 men, 446 cases observed for 145,878 person-years	Only health professionals 40–75 years; men	5
Neupane, Canada	2010 [34]	Case-control	Cases, <i>n</i> = 365; controls, <i>n</i> = 494	≥65 years; hospitalized cases, population controls	8
Palmer, UK	2003 [35]	Case-control	Cases, <i>n</i> = 525; controls, <i>n</i> = 1,122	Only men 20–64 years of age; hospitalized cases and controls	6
Paul, USA	2015 [36]	Nested case-control	Cases, <i>n</i> = 1,039; controls, <i>n</i> = 2,022	Community-dwelling immunocompetent adults 65–94 years of age	8
Piednoir, France	2003 [37]	Case-control	Cases, <i>n</i> = 101; control, <i>n</i> = 101	≥80 years; hospitalized cases and controls	8
Riquelme, Spain	1996 [38]	Case-control	Cases, <i>n</i> = 101; control, <i>n</i> = 101	>65 years; hospitalized cases and controls	8
Vila-Córcoles, Spain	2005 [39] 2009 [40]	Cohort	Cohort of 11,241 subjects; 117 cases observed for 11,025 person-years	≥65 years; outpatient pneumonia cases in a population-based cohort (follow-up 1 year)	9

CAP, community-acquired pneumonia; NOS, Newcastle-Ottawa Scale; HPFS, Health Professionals Follow-Up Study.

to counteract the aggressive invasion of other people's cigarette smoke.

Poor nutritional status, which in the different studies encompassed hypoalbuminemia, hypoproteinemia, malnourishment, or a low nutritional score, was a strong predictor of CAP. Despite the lack of a standardized definition to identify frail older adults, functional impairment assessed according to different criteria was a clear risk factor for CAP.

Environmental substances are known to be involved in the pathogenesis of lung diseases (bronchitis, bronchiolitis, asthma, COPD, and lung cancer) and this review shows their effect on CAP. However, this effect may vary according to the different substances (metals, dust, fumes, etc.), settings (home, occupational environment), extent, and definitions of environmental exposures. The transmission, control, and treatment of pneumonias acquired

at the workplace represent intriguing and challenging areas of concern to epidemiologists and clinicians.

We also found that chronic bronchitis, COPD, and asthma were definitive risk factors for CAP. In some studies [8, 23], an effect of inhaled drugs on the risk of CAP was observed in COPD and asthma patients after adjusting for the effect of other respiratory diseases (and their concomitant treatments) and other nonrespiratory risk factors for CAP, including vaccines [8]. There are 8 studies assessing the effect of inhalation therapy on the risk of CAP. Four of them showed a significant effect of inhalers as a risk factor for CAP, while the other 4 studies, of similar methodological quality, obtained no significant and conclusive results. The lack of consistency among the studies may be due to differences in study design, type of the drug inhaled, number of puffs per day, or severity of the underlying disease (asthma or COPD) or differences

Table 3. Selected sociodemographic and lifestyle factors

Risk factor	Category of effect	Studies, <i>n</i>		elderly (≥65 years) [Ref.]	Quality score		Standardized definition	Adjusted odds ratio
		all [Ref.]			individual studies	total		
Age	Significant risk factor	10 [14, 15, 20, 21, 24, 29, 30, 34, 37, 39]		6 [24, 29, 30, 34, 37, 39]	8.0 (6.0–9.0)		Clear risk factor	1.07 (1.01–1.19) ^a per year of increase
	Nonsignificant risk factor	4 [13, 10, 23, 27]		2 [23, 27]	7.0 (6.0–7.0)	7.5 (6.0–9.0)		
Male gender	Significant risk factor	4 [24, 27, 34, 39]		4 [24, 27, 34, 39]	8.0 (8.0–9.0)		No definitive conclusion	Not applicable
	Significant protective factor	1 [13]			7.0 (7.0–7.0)	8.0 (7.0–9.0)		
	Nonsignificant risk factor	3 [15, 23, 29]		2 [23, 29]	9.0 (7.0–9.0)			
Alcohol use	Significant risk factor	3 [22, 29, 30]		2 [29, 30]	7.0 (7.0–9.0)		No definitive conclusion	Not applicable
	Nonsignificant risk factor	3 [2, 10, 14]			6.0 (6.0–7.0)	7.0 (6.0–9.0)		
Smoking	Significant risk factor	11 [2, 6, 10, 14, 21, 23, 24, 27, 30, 34, 37]		6 [23, 24, 27, 30, 34, 37]	7.0 (6.0–8.0)		Clear risk factor	1.57 (1.12–2.77) vs. never smokers
	Nonsignificant risk factor	3 [6, 22, 39]		1 [39]	7.0 (7.0–9.0)	7.0 (6.0–9.0)		
Passive smoking	Significant risk factor	1 [30]		1 [30]	7.0 (7.0–7.0)		No effect	Not applicable
	Nonsignificant risk factor	2 [2, 21]			6.5 (6.0–7.0)	7.0 (6.0–7.0)		
Environmental exposures	Significant risk factor	5 [7, 21, 30, 34, 35]		2 [30, 34]	6.5 (6.0–8.0)		Clear risk factor	Not applicable
	Nonsignificant risk factor	3 [2, 34, 35] ^b		1 [34]	7.0 (6.0–8.0)	7.0 (6.0–8.0)		
Overweight	Significant risk factor	1 [10]			6.0 (6.0–6.0)		No effect	Not applicable
	Nonsignificant risk factor	4 [2, 6, 14, 28]			7.0 (7.0–7.0)	7.0 (6.0–7.0)		
Poor nutritional status	Significant risk factor	4 [23, 28, 30, 38]		3 [23, 30, 38]	7.0 (7.0–8.0)		Clear risk factor	6.14 (0.65–11.58)
	Nonsignificant risk factor	2 [21, 38]		1 [38]	7.5 (7.0–8.0)	7.0 (7.0–8.0)		

Quality scores and adjusted odds ratios are given as median (range). “Smoking” includes current smokers and ex-smokers, as well as a history of pack-years and different thresholds for the number of cigarettes per day. “Environmental exposures” (home, occupational, and environment) includes a large variety of substances (e.g. gases, dust, fumes, chemicals, solvents, oil mists, gasoline, ferrous metal, and asbestos). “Overweight” was defined above different body mass index ranges. “Poor nutritional status” includes low total plasma protein levels, hypoalbuminemia, and low nutritional scores. ^a In 2 studies, a risk equivalent to 1 year was calculated. ^b Factors considered in more than 1 model in the same study.

Table 4. Comorbidities or clinical conditions as risk factors for CAP

Risk factor	Category of effect	Studies, <i>n</i>		elderly (≥65years) [Ref.]	Quality score		Standardized definition	Adjusted odds ratio
		all [Ref.]			individual studies	total		
Functional impairment	Significant risk factor	5 [9, 15, 27, 30, 37]		4 [9, 27, 30, 37]	8.0 (7.0–9.0)		Clear risk factor	2.13 (0.50–7.94)
	Nonsignificant risk factor	1 [38]		1 [38]	8.0 (8.0–8.0)	7.5 (6.0–9.0)		
Chronic bronchitis/COPD	Significant risk factor	11 [2, 6, 9, 13, 20, 21, 23, 24, 29, 30, 39]		6 [9, 23, 24, 29, 30, 39]	7.0 (6.0–9.0)		Clear risk factor	1.99 (0.67–13.53)
	Nonsignificant risk factor	2 [22, 37]		1 [37]	7.5 (7.0–8.0)	7.0 (6.0–9.0)		
Asthma	Significant risk factor	4 [2, 21, 24, 29]		2 [24, 29]	7.5 (6.0–9.0)		Clear risk factor	1.71 (1.00–4.20)
	Nonsignificant risk factor	2 [2, 6]			7.0 (7.0–7.0)	7.0 (6.0–9.0)		
Previous CAP and/or childhood pneumonia	Significant risk factor	5 [2, 21, 24, 27, 39]		3 [24, 27, 39]	8.0 (6.0–9.0)		Clear risk factor	1.86 (1.53–3.81)
	Nonsignificant risk factor	1 [6]			7.0 (7.0–7.0)	7.5 (6.0–9.0)		
Recent upper respiratory tract infection	Significant risk factor	3 [2, 6, 21]			7.0 (6.0–7.0)		Possibly risk	
	Nonsignificant risk factor	2 [2, 21]			6.5 (6.0–7.0)	7.0 (6.0–7.0)		
Chronic heart disease	Significant risk factor	6 [21, 23, 24, 29, 30, 39]		5 [23, 24, 29, 30, 39]	7.5 (6.0–9.0)		No definitive conclusion	
	Nonsignificant risk factor	6 [2, 9, 22, 23, 24, 37] ^a		4 [9, 23, 24, 37]	7.5 (7.0–9.0)	7.5 (6.0–9.0)		
Dysphagia or swallowing disorders	Significant risk factor	2 [9, 30]		2 [9, 30]	8.0 (7.0–9.0)		No definitive conclusion	
	Nonsignificant risk factor	2 [37, 38]		2 [37, 38]	8.0 (8.0–8.0)	8.0 (7.0–9.0)		
Chronic renal disease	Significant risk factor	1 [30]		1 [30]	7.0 (7.0–7.0)		No effect	Not applicable
	Nonsignificant risk factor	4 [21, 24, 29, 39]		3 [24, 29, 39]	8.5 (6.0–9.0)	8.0 (6.0–9.0)		
Cancer	Significant risk factor	2 [24, 39]		2 [24, 39]	8.0 (8.0–9.0)		No definitive conclusion	Not applicable
	Nonsignificant risk factor	4 [2, 21, 24, 29] ^a		2 [24, 29]	7.0 (6.0–9.0)	8.0 (6.0–9.0)		
Chronic liver disease	Significant risk factor	1 [39]		1 [39]	9.0 (9.0–9.0)		No definitive conclusion	Not applicable
	Nonsignificant risk factor	2 [6, 22]			7.0 (7.0–7.0)	7.0 (7.0–9.0)		
Diabetes	Significant risk factor	1 [24]		1 [24]	8.0 (8.0–8.0)		No definitive conclusion	
	Nonsignificant risk factor	7 [2, 6, 21, 22, 29, 37, 39]		3 [29, 37, 39]	7.0 (6.0–9.0)	7.5 (6.0–9.0)		
Orodonal and/or periodontal diseases	Significant risk factor	4 [9, 16, 27, 37]		2 [27, 37]	8.0 (8.0–8.0)		Clear risk factor	2.78 (1.60–4.40)
	Significant protective factor	1 [2]			7.0 (7.0–7.0)			
	Nonsignificant risk factor	1 [2]			7.0 (7.0–7.0)	8.0 (7.0–8.0)		

Quality scores and adjusted odds ratios are given as median (range). “Functional impairment”: low and intermediate levels of dependence defined as a Barthel index <100, incontinence, mobility limitations, and being bedridden. “Chronic renal disease” includes chronic pyelonephritis. “Chronic liver disease” includes cirrhosis and alcoholic hepatitis. “Orodonal and/or periodontal diseases” include dental dysesthesia, gingivitis, dental prostheses, dental plaque, periodontitis, and visits to the dentist in the previous month. CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease. ^a Factors considered in more than 1 model in the same study.

Table 5. Therapeutic risk factors for CAP

Risk factor	Category of effect	Studies, <i>n</i>		elderly (≥65 years) [Ref.]	Quality score		Standardized definition	Adjusted odds ratio
		all [Ref.]			individual studies	total		
Antibiotics prior to admission	Significant risk factor	1 [23]		1 [23]	7.0 (7.0–7.0)	7.0 (7.0–8.0)	No effect	Not applicable
	Nonsignificant risk factor	2 [2, 38]		1 [38]	7.5 (7.0–8.0)			
Immunosuppressive therapy	Significant risk factor	2 [29, 30]		2 [29, 30]	8.0 (7.0–9.0)	8.0 (7.0–9.0)	Clear risk factor	3.1 (1.27–15.13)
	Nonsignificant risk factor	1 [24]		1 [24]	8.0 (8.0–8.0)			
Steroids (oral)	Significant risk factor	3 [21, 24, 39]		2 [24, 39]	8.0 (6.0–9.0)	7.5 (6.0–9.0)	Clear risk factor	1.87 (1.30–4.05)
	Nonsignificant risk factor	1 [2]			7.0 (7.0–7.0)			
Proton pump inhibitors or H ₂ antagonists	Significant risk factor	2 [18, 31]			8.5 (8.0–9.0)		Clear risk factor	1.51 (1.18–1.60)
	Nonsignificant risk factor	1 [23]		1 [23]	7.0 (7.0–7.0)	8.0 (7.0–9.0)		
Inhalers	Significant risk factor	4 [2, 19, 21, 23]		2 [19, 23]	7.0 (6.0–9.0)	7.0 (6.0–9.0)	No definitive conclusion	Not applicable
	Nonsignificant risk factor	4 [2, 6, 15, 23] ^a		1 [23]	7.0 (7.0–7.0)			
Pneumococcal vaccine	Significant protective factor	2 [2, 39]		1 [39]	7.0 (7.0–9.0)	8.0 (7.0–9.0)	Possibly no effect	Not applicable
	Nonsignificant risk factor	2 [24, 39] ^a		2 [24, 39]	8.5 (8.0–9.0)			
Influenza vaccine	Significant protective factor	1 [2]			7.0 (7.0–7.0)	8.0 (7.0–7.0)	No effect	Not applicable
	Nonsignificant risk factor	3 [2, 24, 39] ^a		2 [24, 39]	8.0 (7.0–9.0)			

Quality scores and adjusted odds ratios are given as median (range). “Immunosuppressive therapy” includes immunosuppressant drugs, radiotherapy, and chemotherapy. “Inhalers”: with and without spacers (steroids, anticholinergics, and β_2 agonists). CAP, community-acquired pneumonia. ^a Factors considered in more than 1 model in the same study.

Table 6. Other, less studied potential risk factors for CAP

Factors	Significant risk factor		Nonsignificant risk factor		Significant protective factor	
	studies, <i>n</i> [Ref.]	quality score	studies, <i>n</i> [Ref.]	quality score	studies, <i>n</i> [Ref.]	quality score
<i>Sociodemographic and lifestyle</i>						
Ethnicity/race (Caucasian)	1 [27]	8.0 (8.0–8.0)				
Civil status ^a	1 [2]	7.0 (7.0–7.0)			1 [30]	7.0 (7.0–7.0)
Education level	1 [34]	8.0 (8.0–8.0)	1 [2]	7.0 (7.0–7.0)		
Living at home					1 [30]	7.0 (7.0–7.0)
Usual contact with children			1 [2]	7.0 (7.0–7.0)		
Physical activity (MET hour score)			2 [10, 14]	6.0 (6.0–6.0)	1 [10]	6.0 (6.0–6.0)
Military trainee	1 [28]	7.0 (7.0–7.0)				
Deficient social support	2 [21, 30]	6.5 (6.0–7.0)				
Sudden temperature changes at work	1 [2]	7.0 (7.0–7.0)				
Poor quality of life			1 [38]	8.0 (8.0–8.0)		
Contact with pets			1 [2]	7.0 (7.0–7.0)		
Season (Winter)	1 [37]	8.0 (8.0–8.0)				
<i>Comorbidities or clinical conditions</i>						
Outpatient visits in previous 1 or 2 years	1 [24]	8.0 (8.0–8.0)				
Hospital admission in previous 5 years	1 [2]	7.0 (7.0–7.0)				
HTLV-1 positive	1 [13]	7.0 (7.0–7.0)				
Total cholesterol <100 mg/dL					1 [28]	7.0 (7.0–7.0)
Any fatty acid intake	1 [10]	6.0 (6.0–6.0)	2 [10, 32]	5.5 (5.0–6.0)	1 [32]	5.0 (5.0–5.0)
Epilepsy	1 [2]	7.0 (7.0–7.0)				
HIV infection			1 [2]	7.0 (7.0–7.0)		
Stroke	1 [24]	8.0 (8.0–8.0)	1 [37]	8.0 (8.0–8.0)		
Thyroid dysfunction			1 [29]	9.0 (9.0–9.0)		
Connective tissue diseases	1 [13]	7.0 (7.0–7.0)	1 [29]	9.0 (9.0–9.0)		
Pulmonary tuberculosis			2 [2, 6]	7.0 (7.0–7.0)		
Anemia			1 [17]	8.0 (8.0–8.0)		
Depression			1 [2]	7.0 (7.0–7.0)		
Dementia	1 [24]	7.0 (7.0–7.0)	1 [2]	7.0 (7.0–7.0)		
Psychiatric disorders			1 [2]	7.0 (7.0–7.0)		
Vitamin D deficiency	1 [26]	7.0 (7.0–7.0)				
FEV ₁	1 [27]	8.0 (8.0–8.0)				
Gastroesophageal reflux disease			1 [37]	8.0 (8.0–8.0)		
Interventions on the upper respiratory tract in previous month			1 [2]	7.0 (7.0–7.0)		
<i>Therapeutic risk factors</i>						
Amiodarone	1 [2]	8.0 (8.0–8.0)				
Benzodiazepines					1 [6]	7.0 (7.0–7.0)
N-acetylcysteine	1 [2]	7.0 (7.0–7.0)	1 [2]	7.0 (7.0–7.0)		
Atypical antipsychotics	1 [23]	7.0 (7.0–7.0)				
Aminophylline/xanthines	2 [2, 6]	7.0 (7.0–7.0)				
Plastic pear spacers			1 [6]	7.0 (7.0–7.0)		
Medication with 5 different drugs per day	1 [37]	8.0 (8.0–8.0)				
Iron supplement			1 [23]	7.0 (7.0–7.0)		
Narcotics			1 [23]	7.0 (7.0–7.0)		
Nonsteroidal anti-inflammatory drugs			1 [23]	7.0 (7.0–7.0)		
Any vitamin intake			2 [10, 32]	5.5 (5.0–6.0)	1 [10]	6.0 (6.0–6.0)
Digoxin			1 [2]	7.0 (7.0–7.0)		
Diuretics			1 [2]	7.0 (7.0–7.0)		
Oxygen therapy	2 [2, 24]	7.0 (7.0–7.0)				
Anticholinergics (oral)	1 [36]	8.0 (8.0–8.0)				

Quality scores are given as median (range). CAP, community-acquired pneumonia; MET, metabolic equivalents; HTLV-1, human T-lymphotropic virus 1; FEV₁, forced expiratory volume in 1 s (severe vs. mild/normal). ^a Married or living with a partner vs. widowed/divorced/living alone.

in the use of spacers. Thus, a definitive conclusion regarding inhalation therapy has not yet been reached, and further research is required.

Likewise, in the observational studies, “possibly no effect” or “no effect” was obtained for the role of 23-valent pneumococcal polysaccharide and influenza vaccination, respectively, as a protective factor against CAP. The protective effect of vaccination should be better assessed in randomized clinical trials. The results of this systematic review agree with those of a meta-analysis of the efficacy of pneumococcal vaccination in adults, which also concluded that vaccination does not appear to be effective in preventing pneumonia [41, 42]. However, meta-analyses have produced conflicting results for the efficacy of 23-valent pneumococcal polysaccharide vaccine [43, 44]. A 13-valent pneumococcal conjugate vaccine (PCV13) is now available for the prevention of pneumonia and invasive pneumococcal disease caused by PCV13 serotypes in adults. In a randomized, double-blind, placebo-controlled trial involving 84,496 adults ≥ 65 years of age, PCV13 was effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic CAP and vaccine-type invasive pneumococcal disease, but not in preventing CAP from any cause [45]. The role of influenza vaccination as a protective factor against CAP is also unclear [46, 47].

On the other hand, it has been argued that inappropriate antibiotic use increases bacterial resistance to common antibiotics and also alters the normal bacterial flora of the host [48]. Nonetheless, only 1 out of 3 reviewed studies found an association between a recent history of taking antibiotics and CAP [23]. Hence, the few available studies and their lower quality lead us to conclude that previous consumption of antibiotics has no effect on the risk of CAP. Ideally, it would be desirable to have more studies to answer this important question.

It has been reported that the use of gastric acid-suppressive therapy (proton pump inhibitors and H_2 receptor antagonists) increases the risk of CAP [49], particularly if treatment has been recently started [18, 31]. It has been suggested that a reduction of gastric acid secretion facilitates pathogen colonization of the upper gastrointestinal tract and oral infections [49]. However, other studies do not support a pharmacological effect of gastric acid suppressors on the risk of CAP [2, 50]. This review concludes that treatment with gastric acid-suppressive drugs is a risk factor for CAP. This finding is clinically relevant because acid-suppressive drugs are commonly prescribed for complaints of dyspepsia and gastroesophageal reflux disease and their effectiveness in the treatment of upper gastrointestinal symptoms is excellent. However, the use of

these drugs may be reconsidered for patients with other risk factors for CAP, such as elderly subjects, persons with COPD or asthma, and immunocompromised persons.

Use of oral steroids and immunosuppressive therapy were also clear risk factors for CAP. The increased risk of infectious complications is an important safety concern when prescribing immunosuppressive therapy. Prevention of infection is a key management strategy, to which early recognition of other associated risk factors for CAP should be added.

Interestingly, poor oral health and orodental diseases increased the risk of CAP both in elderly subjects and in the general population. Dental plaque and dental prostheses favor colonization and may constitute a reservoir for respiratory pathogens [51]. Prevention of the accumulation of plaque and bacterial colonization, particularly in subjects with dental prostheses, dental caries, and periodontal disease, is an important practical consequence of our findings. Regular dental examinations and good oral hygiene should be recommended.

Other comorbidities, such as chronic heart disease, renal dysfunction, liver disease, diabetes, cancer, and dysphagia or swallowing disorders, had no effect, or no definitive conclusions could be drawn. Moreover, the effect of other potential risk factors for CAP identified in the present review should be confirmed in further studies. These include a large number of factors, such as the role of civil status, ethnicity, usual contact with children, deficient social support, sudden temperature changes at the workplace, impaired quality of life, physical activity, previous outpatient visits and hospital admissions, HTLV-1 (human T-lymphotropic virus 1) and HIV infections, epilepsy, stroke, thyroid dysfunction, connective tissue diseases, pulmonary tuberculosis, anemia, depression, dementia, and oxygen therapy, as well as treatment with amiodarone, benzodiazepines, N-acetylcysteine, atypical antipsychotics, aminophylline, narcotics, nonsteroidal anti-inflammatory drugs, motility agents, iron supplementation, vitamins, digoxin, and diuretics. All these factors have been inconsistently assessed in a few individual studies, and no definitive conclusions could be reached.

Observational studies are vulnerable to various sources of bias, and the evidence obtained by them is less robust than evidence derived from experimental studies. The present findings should be interpreted taking into account this limitation, but the clinical questions posed in this review could only be answered reasonably through observational designs. One of the main difficulties of this systematic review lies in the unavoidable heterogeneity of studies in terms of populations, risk factors analyzed, lengths of

follow-up, and statistical methods, including differences in adjusting for confounding variables and covariates both within and between studies. By contrast, strengths of the present systematic review include the comprehensive literature search, the use of sound methodological review techniques, the use of a well-established tool (NOS) for quality assessment of the individual studies, the high quality scores obtained for the included studies, and the weighted conclusions based on the quality of the evidence.

The present results provide robust current evidence of the importance of age, smoking, malnutrition, environmental exposures, previous CAP, chronic bronchitis/COPD, asthma, functional impairment, poor dental health, immunosuppressive therapy, oral steroids, and gastric acid-suppressive drugs as definitive risk factors for CAP. Clinicians should be aware of these risk factors, because some of them are modifiable and amenable to effective interventions. Special attention should be devoted to oral hygiene, antacid drug reduction, functional impairment monitoring, and rehabilitation protocols. Implementation of the findings of the present systematic review into daily practice is clinically relevant, since early recognition and adequate management of those factors that are modifiable may reduce CAP-associated morbidity and mortality among adults, particularly elderly individuals.

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Author Contributions

J.A. participated in the study design, selection of studies for inclusion in the review, assessment of the quality of articles, interpretation of the analysis, and writing of the manuscript. M.S.-P. carried out the search of the literature, selection of studies for inclusion in the review, selection of criteria for the analysis, assessment of the quality of articles, statistical analysis, interpretation of the data, and writing of the manuscript. I.B. participated in the study design, methodological assessment, selection of criteria for the analysis, assessment of the quality of articles, and writing of the manuscript. V.B. was involved in the methodological assessment, assessment of the quality of articles, analysis of the data, synthesis of the results, and critical review of the content of the manuscript. All authors read and approved the final manuscript.

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