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Title

Patient Reported Outcome Measures in the recovery of adults hospitalised with community-acquired pneumonia: a systematic review

Authors

Harry J Pick[1], Charlotte E Bolton[2], Wei Shen Lim[1,2], Tricia M McKeever[3]

Institutions

[1] Department of Respiratory Medicine, Nottingham University Hospital NHS Trust, Nottingham NG5 1PB, UK;

[2] NIHR Nottingham BRC Respiratory Theme, School of Medicine, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK;

[3] Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK.

Corresponding author:

Dr HJ Pick

Department of Respiratory Medicine, Room B02, Clinical Sciences Building

Nottingham City Hospital Campus, Nottingham University Hospitals NHS Trust

Hucknall Road, Nottingham NG5 1PB

Email; harry.pick@nuh.nhs.uk

Tel; +44(0)1159691169

Key Words;

Systematic review, Community acquired pneumonia, Functional status, Symptoms, Patient Reported Outcome Measures (PROMs), Quality of life (QoL), Activities of daily living (ADL), meta-analysis, Re-consultation, fatigue

ABSTRACT;

Symptomatic and functional recovery are important patient-reported outcome measures (PROMs) in community-acquired pneumonia (CAP) that are increasingly used as trial endpoints. This systematic review summarises the literature on PROMs in CAP.

Comprehensive searches in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement were conducted to March 2017. Eligible studies included adults discharged from hospital following confirmed CAP and reporting PROMs.

Fifteen studies (n=5644 patients) were included; most of moderate quality. Studies used a wide range of PROMs and assessment tools. At 4-6 weeks' post-discharge, the commonest symptom reported was fatigue (45% to 72.6% of patients, 3 studies), followed by cough (35.3% to 69.7%) and dyspnoea (34.2% to 67.1%), corresponding values from studies restricted by age <65 years (2 studies) were lower; fatigue 12.1% to 25.7%, cough 19.9% to 31.9%, dyspnoea 16.8% to 27.5%. Functional impairment 4 weeks post-discharge was reported in 18% to 51% of patients (2 studies) while median time to return to normal activities was between 15 to 28 days (3 studies).

Substantial morbidity is reported by patients up to 6 weeks post-discharge. There is weak methodological consistency across existing studies. A core set of PROMs for use in future studies is suggested.

INTRODUCTION

Community-acquired pneumonia (CAP) affects approximately 1% of the UK adult population each year, accounting for over 100,000 hospital admissions.[1] The average length of stay is 6 days and estimated direct healthcare costs are £441 million.[2,3] Most patients survive their inpatient admission and are discharged to recuperate.[4,5] In clinical practice, a patient is deemed to have recovered from CAP based on the clinical assessment of a physician, often in association with radiological improvement. In one study 78% of patients were deemed clinically cured at 4 weeks following discharge from hospital,[6] while corresponding rates of radiological resolution vary between 53% and 67%[6-8]

However, there is discordance between physician rated clinical cure and radiographic resolution versus patient-reported symptoms and functional impairment.[6] Patient-reported outcome measures (PROMs) are increasingly recognised as providing a more robust indication of patient experienced morbidity during recovery.[9] As a reflection of this, recent US Food and Drug Administration (FDA) guidance on drug development in CAP recommends incorporation of PROMs as trial endpoints.[10] The aim of this study was to systematically gather and summarise the available literature regarding PROMs following a hospital admission episode for CAP in order to inform future research in this area.

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[11] The review protocol was prospectively registered in the PROSPERO database (CRD42017059799).[12]

Search Strategy

Comprehensive searches of biomedical electronic databases were conducted: Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 3), MEDLINE (1946 to March week 3, 2017), EMBASE (1980 to March 2017), CINAHL (1981 to March 2017), AMED (1985 to March 2017), Web of Science (1985 to March 2017). The search strategy included subject headings and key words related to community-acquired pneumonia, symptom recovery, functional activity, healthcare utilisation and treatment outcome. The searches were not subject to any language restrictions. Details of the search strategy for each database are found in Online Supplement - Appendix 1. An additional grey literature search was conducted using Google Scholar to identify unpublished data of potential

significance to the review. Reference lists of included studies were reviewed to identify potentially relevant articles. The full texts of identified articles were reviewed and assessed against eligibility criteria. Conference proceedings of the last 3 years for the American Thoracic Society Conference, British Thoracic Society Winter Meeting and European Respiratory Society Congress were reviewed to identify potentially eligible articles.

Study selection

Randomised controlled trials (RCTs), quasi-experimental, and non-randomised studies in adults attending secondary care facilities with a presenting diagnosis of CAP and assessing at least one of the pre-defined patient-reported markers of recovery were included. A diagnosis of CAP was defined as: symptoms and signs consistent with an acute lower respiratory tract infection associated with radiological confirmation of pneumonia on chest x-ray. Attendance at a secondary care facility was defined as any patient receiving their initial review and all or part of their treatment for CAP at an acute hospital facility, including Emergency department visits, with or without subsequent admission.

Two study authors conducted sequential review of identified studies independently, proceeding from title to abstract to full-texts, with exclusions at each stage if studies did not fulfil eligibility criteria. Disagreement was resolved by discussion and consensus, involving a third review author as necessary.

Outcome measures

Primary outcomes of interest measured within 6 weeks following hospital discharge were a) patient reported symptoms, b) return to work and/or usual activities of daily living, and c) healthcare utilisation. Secondary outcomes of interest measured within 6 weeks following discharge were a) proportion with physician determined clinical cure in studies reporting symptomatic and functional recovery, and b) change in quality of life scores. (Outcomes occurring within six weeks of discharge was chosen as the time-point for assessment because we anticipated most studies would report outcomes at that time-point, and it coincides with the time-point at which other outcomes are commonly measured in studies of CAP.)

Data extraction

All data were independently extracted by two authors (HP, TM) using a pre-designed form that was initially piloted on five studies; any disparities were resolved by discussion and consensus, including a third reviewer as required. Where data were represented graphically within studies, DigitizeIt©

software (Version 2.3.3, www.digitizeit.de) was used to derive estimated values. Information on study population, outcome, and study design were collected.

Assessment of risk of bias

A specific quality assessment tool was created combining relevant aspects from the Newcastle-Ottawa scale and the Down's and Black Quality Assessment Tool.[13,14] Each study was assessed for details pertaining to study period and location, participant selection, and outcome measure with a final total score out of six (with 0 representing low quality and 6 representing the highest possible quality rating.)

Data synthesis

Extracted results were reviewed to assess if adequate similarity existed with respect to outcomes to conduct a random effects meta-analysis using Stata © version 15 (StataCorp. 2017.) The I^2 statistic was used to assist with assessment of heterogeneity between studies.

RESULTS

The search strategy identified 3958 articles of which 15 articles fulfilled eligibility criteria and were included in the systematic review. (See study flow diagram, Figure 1.)[6,15-28]

Characteristics of included studies

The characteristics of the 15 included studies are summarised in Table 1. Briefly, eligible studies included 2 RCTs, 8 prospective cohort studies, 1 retrospective cohort studies and 4 studies with cohort data for participants originally enrolled in RCTs. Six studies were restricted to patients with low and moderate severity CAP (Pneumonia Severity Index (PSI) classes I to III, PSI score <110, or CURB65 score 0-2)[6,17-19,21,23] or age < 65 years.[18,23] One study did not assess disease severity,[28] and the remaining studies included patients of all disease severities with mean PSI across studies ranging from 76.2 (±32.8) to 106.2 (±23.9).[15,16,20,22,24-27] Outcome measures of interest varied substantially between the included studies, with variable choice of outcome, tool for assessment, and timing of measurement. Individual study methodology is summarised in Table 2.

Risk of bias in included studies

Across all included studies the median quality score was 4.5 (IQR 4-5.) Three studies scored full marks at quality assessment.[16,17,26] (see Online supplement - Table 1) All included studies defined

their follow-up period, with all but a single study adequately defining study population and study period. The study populations were often restricted by selection criteria, such as age, severity of disease, level of dependency or residential status, see Table 1, but these selection criteria were deemed appropriate when study design and outcomes of interest were considered. Included studies rarely reported loss to follow-up.

Patient reported symptoms

Six studies included data for patient-reported prevalence of symptoms within 6 weeks of discharge.[15,18,20,22,23,27]

Four studies reported prevalence of symptoms for participants unselected for age or disease severity.[15,20,22,27] At 28–42 days post-discharge, the commonest symptom reported was fatigue (range: 45% to 72.6% of patients), followed by cough (range: 35.3% to 69.7%) and dyspnoea (range: 34.2% to 67.1%)(Figure 2).[22 20,27] One study of patients attending for healthcare review within 30-days of discharge observed that respiratory symptoms were reported in 75.2% of those attending primary care and 47.5% of those attending emergency departments.[15] Restricting the population to working adults, two studies reported symptom prevalence at 4 weeks following discharge and found 1 or more symptom was reported by 35.0% and 58.2% of participants, cough by 19.9% and 31.9%, dyspnoea by 16.8% and 27.5%, and fatigue by 12.1% and 25.7%.[18,23] Chest pain (16.5%) and sputum production (11%) were reported by participants respectively in one of these studies.[18]

Finally, in an email survey investigating average time for resolution of symptoms following CAP in adults aged ≥50 years (n=500), median time for resolution of cough was 7 days (IQR 2-14), dyspnoea 14 days (IQR 7-43), chest pain 7 days (IQR 2-14), sputum production 7 days (IQR 7-14), fever 2 days (IQR 1-2), and fatigue 20 days (IQR 7-24).[28]

Quantitative synthesis

Random effects meta-analysis was performed on amenable data from 4 studies (n=1715) reporting outcomes at 4 weeks. [18,20,23,27] High levels of heterogeneity were evident. Summary estimates of the proportion of patients reporting 1 or more symptoms was 70% (95% CI 53% to 86%, I^2=98.6%); cough 42% (95% CI 24% to 60%, I^2=97.1%), dyspnoea 39% (95% CI 21% to 58%, I^2=97.5%), and fatigue 42% (95% CI 10 % to 74%, I^2=99.2%) (Figure 3 a - d.)

CAP specific symptom scores

Four studies included data derived from pneumonia symptom scores.[6,19,26,27] Two studies (n=91 and n=95) used the CAP score (higher score signifying fewer symptoms); The median CAP scores reported by El Moussaoui *et al* at days 3, 7, 10, 14 and 28 following admission were 56 (IQR 38-69), 60 (IQR 37-75), 65 (IQR 37-86), 77 (IQR 61-88) and 75 (IQR 58-93), and Bruns *et al* reported that normalisation of CAP score, relative to retrospectively assessed baseline scores 6 weeks prior to admission, occurred in 32% of patients at 10 days following hospital admission, and 41.8% of patients at 28 days.[6]

Two studies (n=169 and n=312) used the CAP-symptom score (*lower* score signifying fewer symptoms); Wootton *et al* observed the average CAP-symptom score at day 2 from admission was 23.8 and at day 28 was 13.6, [27] Uranga *et* al, in an interventional trial of short course antibiotics, reported that average CAP-symptom score in the control group on Day 5 from admission was 24.7 (±11.4) and on Day 10 was 18.6 (±9.0) with corresponding values in the intervention group of 27.2 (±12.5) and 17.9 (±7.6).[26]

Return to functional activity

Five studies included data for time to return to normal activities[16,18,20,21,26]. Daniel *et al* found that 51.1% of adults aged below 65 years had not resumed baseline ADLs at 4 weeks.[18] In contrast, Fine *et al* found that 18.0% of 'workers' had not resumed baseline ADLs at 4 weeks compared to 42.8% of 'non-workers'.[20]

The median time for return to normal activity reported by Uranga *et al* was 18 days (IQR 9-25) in the control group and 15 days (IQR 10-21) in the intervention group.[26] Fine *et al* found the median time for return to ADLs in workers was 15 days and in non-workers was 24 days[20] whereas Labarere *et al* found little difference in the median time for return to ADLs between workers (22 days (IQR 11-29)) and non-workers (20 days (IQR 9-29)).[21]

Of two studies with relevant data, 34.3%[18] and 31.9%[20] of participants had not returned to work at 4 weeks. Median time for return to work following discharge was 14 days.[21,28] Adamuz *et al* reported that the median time taken off work by participants in the control group was 26 days (IQR 12.5-37) compared to 30 days (IQR 15-66.5) in the intervention group.[16]

Healthcare utilisation

In addition to PROMs, three studies reported rates of Primary Care consultation and/or Emergency Department (ED) attendance within 4 to 6 weeks following hospital discharge.[15,16,18] Daniel *et* al

found that 59.2% had consulted primary care and 12.0% had attended EDs within 4 weeks.[18] This compares with 18.0% and 20.3% attending primary care, and 18.4% and 21.4% attending EDs in the two studies from Adamuz *et al*.[15,16] Of those re-consulting a GP, on-going or new respiratory symptoms were reported by 68.8% to 75.2% of patients. Pneumonia-related symptoms or signs was the reported reason for ED attendance in 47.5% to 84.6% of patients.[16,18]

Other outcomes

In relation to quality of life measures, a single Spanish study commented that "*SF-36 score at 30 days following hospital discharge remained abnormal when compared to the reference scores for the Spanish population*," but no data were reported.[17] Using the EQ-5D index, Nickler et al noted that 29% of participants exhibited a decline in ADLs at 30 days and that the decline was associated with levels of pro-adrenomedullin and pro-atrial natriuretic peptide.[24]

Physician assessed clinical cure was noted by Bruns et al in 88.9% of participants 28-days after discharge though only 41.7% of patients reported normalisation of symptoms and function (based on the CAP score) at the same time point.[6] No data were provided on any correlation between clinical cure and CAP score.

DISCUSSION

This systematic review confirms that a high proportion of patients report substantial symptomatic and functional impairments during the first 6 weeks of recovery following hospitalisation with CAP. These are accompanied by adverse impacts on the performance of 'normal activities', such as return to work, and healthcare utilisation. Fatigue, cough, and dyspnoea are the commonest symptoms reported. The prevalence of symptoms over the first 6 weeks of recovery vary across studies in accordance with severity of CAP and age of study cohorts.

The majority of studies assessed the prevalence of symptoms and functional impairment at specific times (most commonly 4 weeks post-discharge) without reference to baseline prevalence. Given the high proportion of patients with chronic cardiac and respiratory conditions within study cohorts, this approach likely overestimates the contribution of acute pneumonia to the prevalence of patients' symptoms during recovery. That said, studies that measured PROMs at multiple time points during recovery all reported a declining trend in the prevalence of symptoms over time, up to 42 days post-discharge.[6,19,22,27] These findings suggest that many patients continue to have symptoms related to the acute pneumonia episode even at 6 weeks post-discharge.

Fatigue is the commonest symptom to be reported during recovery. The importance of fatigue as a contribution towards reduced functional recovery in CAP has not been widely examined. In a qualitative study of patients with low-severity CAP, both extreme tiredness and need for sleep were reported as prominent symptoms during recovery.[29] Quantitatively, the CAP-symptom score captures the degree of fatigue on a scale of 0-5.[30] However, these assessments do not adequately reflect the complexity of fatigue as a symptom, nor its impact on functional recovery. In other conditions where fatigue is a prominent symptom, validated disease-specific, multi-dimensional tools have been developed to better quantify and assess fatigue.[31,32]

Return to functional activity, measured as return to 'normal activities' or ADLs, was consistently reported as taking a median of 15 to 25 days in included studies. This measure is set alongside other included studies that consistently reported a large proportion of patients failing to resume normal activities within 4 weeks post-discharge. One study, not included in this review, found that at 6 weeks post-discharge, 12% of elderly persons had required a change of residence indicating a greater level of dependency.[33] Overall, these studies suggest that the full burden of adverse health outcomes following an episode of CAP is likely to be higher than reflected in measures of symptom resolution alone.[34] Experience from patients recovering from exacerbations of COPD where impaired lung function, exercise capacity, and quality of life persists despite apparent symptomatic resolution provides further support for this view.[35-37]

We identified only two relatively small studies that attempted to describe the correlation between PROMs and healthcare re-consultation.[15,18] These studies suggest that persistence of pneumonia related symptoms is a major factor in GP re-consultations, while new or worsening comorbid illnesses increase in prominence in relation to ED re-attendances. An episode of pneumonia may be a marker for frailty or increased susceptibility to illness from non-pneumonia related factors.[38] A better understanding of the association between PROMs, long-term complications and healthcare re-consultations is necessary if appropriate interventions are to be developed.

Strengths and limitations

As far as we know, this is the first systematic review of studies assessing PROMs in recovery from CAP. This review was conducted in accordance with PRISMA guidelines. Eligibility criteria were designed to focus the review on studies of patients with CAP and not on cohorts with hospital-acquired pneumonia or aspiration pneumonia.

We found only a small number of high quality research studies in this field compared to the large burden of disease. Existing studies are disparate in their study populations (age, co-morbid illness, and disease severity) and outcome measures (Table 2). Importantly, there is a lack of consistency across studies in the choice and application of measurement tools to assess PROMs. The CAP-symptom score is the only available PROM psychometrically validated using a recognised approach, albeit only in an out-patient setting. These variations in outcome measures precluded many studies from the planned meta-analysis; the resulting meta-analysis retained high study heterogeneity. Most notably, the meta-analysis illustrates how, at a given time-point, the severity of CAP and / or age of the study cohort greatly affects estimates of symptom prevalence.

Implications

There is an important need for researchers to develop *and* agree on appropriate tools and methodology in the assessment of PROMs during recovery from CAP. Barlow et al previously defined core outcomes sets for CAP research, including recommending the CAP-symptom score for use in studies of recovery. [9] Ideally, the CAP-symptom score should be externally validated for hospitalised patients and a multi-dimensional CAP-specific tool for assessing fatigue developed

In the meantime, considering the available evidence, we suggest the CAP-symptom score remains the most appropriate tool for the measurement of symptoms, . As the prevalence of symptoms remains high for 2 – 4 weeks post-discharge, and healthcare re-consultation is concentrated to

within the same time period, we suggest that PROMs should be assessed, at a minimum, twice post-discharge, at around 2 weeks and again at 4 or 6 weeks. To enable analysis of the degree of recovery at these time-points, an assessment at the time of hospital discharge is necessary, together with an assessment of 'pre-pneumonia baseline'; accepting that the latter is inevitably subject to recall bias. In addition to symptom reporting, we recommend measuring functional recovery, both in terms of quality of life (EQ-5D) and return to normal activities. Ideally, the time needed to return to 'baseline' health status within different domains should be measured. These interim suggestions should be refined as new, stronger evidence emerges and our understanding of recovery from CAP increases.

Conclusion

Morbidity from CAP continues for a sizeable proportion of patients up to at least 6 weeks post-discharge from hospital. There is a large relative lack of high-quality research in this field.

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* Senior Fellow in Respiratory Infection, Institute of Infection and Global Health, University of Liverpool

$ Honorary Consultant Respiratory Physician, Aintree University Hospitals NHS Foundation Trust

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Table 1. Summary of Included Studies

First Author	Country	Study Period	Study Type	Study Population	Outcome
Studies with participants selected for low-moderate severity CAP or Age <65 years (n=6 studies, n=1217 individual participants)					
Bruns 2010[6]	Netherlands	November 2000 - July 2003	Multicentre prospective cohort	119 adults with CAP CAP Aetiology: • Streptococcus pneumoniae 27.7% Selection criteria; • Age – unselected (mean age 56.6 (±17.8) • Severity – low severity, PSI<110 (mean PSI 65.5 (±22.1)) • Co-morbid disease – unselected • Immune status – unselected	Normalisation CAP score at day 10 – 32.0% Physician rated clinical cure at day 28 - 88.9%
Carratala 2005[17]	Spain	October 2000 - October 2002	Cohort from Multicentre RCT	224 adults with CAP – 101 patients in hospitalised cohort CAP Aetiology: • Streptococcus pneumoniae - 14.0% • Legionella pneumophila - 4.4% • Haemophilus influenzae - 2.6% • "Atypical" - 2.6% Selection criteria; • Age – unselected (mean age; outpatient group 67.5 (±11.8), inpatient group 64.9 (±13.4)) • Severity – low severity, PSI classes II & III (Mean PSI outpatient group 70 (±11.6), inpatient group 66.9 (±12.5)) • Co-morbid disease – excluded if pregnant, breast feeding, respiratory failure, concomitant unstable comorbid conditions necessitating hospitalisation, complicated pleural effusion, lung abscess, shock, metastatic infection, severe social problems, cognitive impairment, psychiatric disease. • Immune status – immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy, neutropenia, solid organ transplant) • Other – excluded if quinolone allergy or quinolone therapy in preceding 3 months	SF-36 score; "At 30-day follow-up SF-36 scores remained abnormal, but had returned towards baseline for Spanish population"

First Author	Country	Study Period	Study Type	Study Population	Outcome
Daniel 2018[18]	UK	February 2015 - April 2016	Multicentre prospective cohort	108 adults with CAP Male – 48.2% CAP Aetiology: • Streptococcus pneumoniae – 16.7% Selection criteria; • Age – 18-65 years only (median age 50 (IQR 38.3-57.8)) • Severity – unselected (CURB65 0-1 = 88.9%, CURB65 2 = 9.3%, CURB65 ≥ 3 = 1.8%) • Co-morbid disease – unselected • Immune status – unselected	Proportion of patient reporting prevalence of symptoms and functional impairment at 28days following discharge; Cough – 31.9% Dyspnoea – 27.5% Chest pain – 16.5% Sputum – 11.0% Fatigue – 12.1% 1 or more symptom – 58.2% Not returned to ADLs – 51.1% No to returned to Work 34.3% Re-consultation within 28 days ED attendance – 12.0% Primary care – 59.2%
El Moussaoui 2006[19]	Netherlands	November 2000 - July 2003	Cohort from Multicentre RCT	91 adults with CAP Male 58.8% CAP Aetiology: • Streptococcus pneumoniae – 23.8% Selection criteria; • Age – unselected (median age 65 (IQR 48-72)) • Severity – low severity, PSI <110 (mean PSI 71 (±23) • Co-morbid disease – excluded if pregnant, severe underlying disease, preceding antibiotic treatment for >24 hours prior to admission, concurrent co-morbid disease likely to interfere with course of pneumonia, respiratory failure • Immune status – unselected Other – excluded if amoxicillin allergy	Median CAP scores (IQR) Day 3 – 56 (38-69) Day 7 – 60 (37-75) Day 10 – 65 (37-86) Day 14 – 77 (61-88) Day 28 - 75 (58-93)
Laberere 2007[21]	USA / Canada	January 2001 - December 2001	Cohort from Multicentre RCT	549 adults with CAP Male 44% CAP Aetiology: Not reported Selection criteria; • Age – unselected (median age 66 (IQR 48-77) • Severity – low severity, PSI classes I-III (PSI I – 16.0%, PSI II – 41.0%, PSI III – 43.0% • Co-morbid disease – excluded if pulmonary tuberculosis, alcoholism &evidence of end-organ damage, social problems incompatible with recruitment, illicit drug use 30days Immune status – immunocompetent only (excluded if HIV, immunosuppression)	Median time for return to ADLs Workers - 22 days (11-29) Non-workers - 20 days (9-29) Median time return to work - 14 days (8-29)

First Author	Country	Study Period	Study Type	Study Population	Outcome
Metlay 1998[23]	USA	April 1996 - February 1997	Single centre prospective cohort	126 adults with CAP Male – 54.8% CAP Aetiology: Not reported Selection criteria; • Age – 18 to 64 years • Severity – low severity, PSI classes I-III (mean PSI 55.2) • Co-morbid disease – excluded if pregnancy, severe neuromuscular disease • Immune status – immunocompetent only (excluded if chronic immunosuppression or HIV.) Other – nursing home residence, psychological or social problems compromising follow-up	Proportion of patient reporting prevalence of symptoms at 28days following discharge; Cough – 19.9% Dyspnoea – 16.8% Fatigue – 25.7% Fever – 3.5% 1 or more symptom – 35.0%

First Author	Country	Study Period	Study Type	Study Population	Outcome
<u>Studies where participants were unselected for severity or age (n=9 studies, n=4427 individual participants);</u>					
Adamuz 2011[15]	Spain	January 2007 - December 2009	Single centre prospective cohort	828 adults with CAP Male – 65.8% CAP Aetiology: • Streptococcus pneumoniae – 44.1% • Legionella pneumophila – 3.0% • Haemophilus influenzae – 4.4% • Anaerobes – 5.6% Selection criteria; • Age – unselected (median age 71 (IQR 55-79)) • Severity – unselected (PSI>90 IN 62.2%) • Co-morbid disease – unselected • Immune status – immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy equivalent to prednisolone >20mg daily, neutropenia, Ig deficiency, solid organ transplant) • Other – excluded if inpatient death	Healthcare utilisation at 30 days ED – 21.4% Primary Care – 18.0% Symptoms reported in participants reconsulting within 30days Primary care (n=149) Respiratory symptoms – 75.2% General symptoms – 22.8% ED (n=177) Worsening pneumonia symptoms – 47.5%
Adamuz 2015[16]	Spain	January 2011 - October 2014	Multicentre RCT	207 adults with CAP Male – 59.9% CAP Aetiology: • Streptococcus pneumoniae – 24.6% • Haemophilus influenzae – 5.4% • Influenzae A – 3.4% Selection criteria; • Age – unselected (21-49 = 20.2%, 50-69 = 30.5%, >70 = 49.3%) • Severity – unselected (CURB65 0-1 = 49.3%, CURB65 2 = 34.3%, CURB65 ≥ 3 = 16.4%) • Co-morbid disease – Excluded cognitive impairment • Immune status – immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy equivalent to prednisolone >20mg daily, neutropenia, Ig deficiency, solid organ transplant) • Other – excluded if nursing home resident or long-term care facility, language barrier	Healthcare utilisation at 30daysPrimary care – 20.3% ED – 18.4% Median time off work; Intervention group – 30 days (IQR 15-66.5) Usual care group – 26 days (IQR 12.5-37)

First Author	Country	Study Period	Study Type	Study Population	Outcome
Fine 1999[20]	USA / Canada	October 1991 - March 1994	Multicentre prospective cohort	1343 adults with CAP Male 52.4% CAP Aetiology: • Streptococcus pneumoniae – 9.1% • Haemophilus influenzae 4.8% • "Atypical" – 2.1% • Enterobacter sp. – 2.8% • Pseudomonas aeruginosa – 0.9% Selection criteria; • Age > 65years 58.7% • Severity – unselected (PSI I – 13.8%, PSI II – 17.4%, PSI III – 18.9%, PSI IV – 33.2%, PSI V – 16.7%) • Co-morbid disease - unselected • Immune status – excluded if HIV	Proportion of patient reporting prevalence of symptoms and functional impairment at 30days following discharge; Cough – 47.1% Dyspnoea – 46.5% Sputum – 42.3% Fatigue – 72.6% 1 or more symptom – 68.5% Not returned to ADLs; Workers – 18% (median 15days) Non-workers – 42.8% (median 24 days) Not returned to Work 31.9%
Marrie 2000[22]	Canada	January 1998 - July 1998	Multicentre prospective cohort	535 adults with CAP Male – 52.3% CAP Aetiology: Not reported Selection criteria; • Age – unselected (mean age 61.6 (±19.1) • Severity – unselected (mean PSI 76.2 (±32.8) • Co-morbid disease - unselected • Immune status – unselected	Proportion of patient reporting prevalence of symptoms and functional impairment at 14days and 42days following discharge; Cough – 55.8%, 35.3% Dyspnoea – 48.6%, 34.2% Chest pain – 17.3%, 11.6% Sputum – 35.9%, 26.4% Fatigue – 66.7%, 45.0% Fever – 8.4%, 4.7% 1 or more symptom – 85.6%, 64.3%
Nickler 2016[24]	Switzerland	October 2006 - March 2008	Cohort from Multicentre RCT	753 adults with CAP Male 58.8% CAP Aetiology: Not reported Selection criteria; • Age – unselected (median age 72 (IQR 52-82) • Severity – unselected (PSI I – 10.0%, PSI II – 19.7%, • Co-morbid disease – excluded if terminal illness • Immune status – immunocompetent only (excluded if long-term immunosuppression) • Other – excluded if language impairment precluding written consent, intravenous drug abuse.	EQ-5D index – decline in ADLs in 29% at day 30

First Author	Country	Study Period	Study Type	Study Population	Outcome
Sharma 2006[25]	USA	March 1995 - March 1998	Single centre prospective cohort	79 adults with CAP Male – 35% CAP Aetiology: Not reported Severity criteria; • Age – unselected (mean age 79.9 (±6.1) • Severity – unselected (mean PSI 106.2 (±23.9) • Co-morbid disease – excluded if terminal illness • Immune status – unselected • Other – excluded if coma, intensive care admission, unable to participate in interview	Proportion with decline in ADL score of greater than 1 point - 22/79 (28%) at day 30
Uranga 2016[26]	Spain	January 2012 - August 2013	Multicentre Randomised Control Trial	312 adults with CAP Male 62.8% CAP Aetiology: • Streptococcus pneumoniae – 16.0% • Legionella pneumophila – 3.5% • Haemophilus influenzae – 0.3% Selection criteria; • Age – unselected (mean age 62.2 (±6.07) and 64.7 (±18.7)) • Severity – unselected (mean PSI 83.7 (±33.7) and 81.8 (±33.8)) • Co-morbid disease – unselected • Immune status – immunocompetent only (excluded if HIV, immunosuppression for solid organ transplantation, splenectomy, receiving ≥10mg/d of prednisone or the equivalent for >30 days, taking other immunosuppressive agents, or neutropenia) • Other – excluded if care home resident, antibiotics within preceding 30 days, intercostal chest drain, extra-pulmonary manifestations, death or ICU admission prior to randomisation	Mean CAP symptom score at 5 days 24.7(±11.4) to 27.2(±12.5) Mean CAP symptom score at 10 days 18.6(±9.0) to 17.9(±7.6) Median time for return to normal activity 15days (IQR 10-21) to 18days (IQR 9-25)

First Author	Country	Study Period	Study Type	Study Population	Outcome
Wootton 2017[27]	UK	February 2011 - March 2013	Multicentre prospective cohort	169 adults with CAP Male 52% CAP Aetiology: Not reported Selection criteria • Age – unselected (mean age 68 (range 16-98) • Severity – unselected (CURB65 0-1 = 46.7%, CURB65 2 = 29.6%, CURB65 ≥3 = 23.7%) • Co-morbid disease – excluded if bronchiectasis, cystic fibrosis, advanced malignancy • Immune status – unselected • Other – excluded if palliative treatment, invasive ventilation	Average CAP symptom score - 23.8 at day 2 Average CAP symptom score - 13.6 at day 28 Proportion of patient reporting prevalence of symptoms at 28days following discharge; Cough – 13.6% Dyspnoea – 67.1% Chest pain – 31.2% Fatigue – 57.0% 1 or more symptom – 96.4%
Wyrwich 2015[28]	USA	Unknown	Multicentre retrospective cohort	201 adults with CAP Male – 45% CAP Aetiology: Not reported Selection criteria; Age – ≥50 years Severity – unselected Co-morbid disease – unselected Immune status – unselected Other – respondent to email survey, excluded in nursing home resident	Average time to symptom resolution, in days; Cough; mean 13.6 median 7 (2-14) Dyspnoea; mean 25.1 median 14 (7-43) Chest pain; mean 12.9 Median 7 (2-14) Sputum; mean 14.8 Median 7 (7-14) Fatigue; mean 25 Median 20 (7-24) Fever; mean 2.7 Median 2 (1-2) Median time for return to work – 14 days

Table 2. Summary of methodology of included studies

Study	Destination after initial review		Severity		Outcome Measure										Timing of assessment of outcome measure (days)				
					Assessment of Symptoms			Health Status		Assessment of function (return to)		Clinical Cure	Healthcare utilisation						
	I/P	O/P	CURB65	PSI	Prevalence Symptoms	CAP Score	CAP-symptom score	SF-36	EQ-5D	ADLs	Occupation		Primary Care	ED	Average time to X	≤14	28	30	42
Studies with participants selected for low-moderate severity CAP or Age <65 years (n=6 studies, n=1217 individual participants)																			
Bruns 2010[6]	X			X		X						X				X	X		
Carratala 2005[17]	X	X		X				X										X	
Daniel 2018[18]	X		X		X					X	X		X	X			X		
El Moussaoui 2006[19]	X			X		X										X	X		
Laberere 2007[21]	X	X		X						X	X				x				
Metlay 1998[23]		X		X	X												X		
Studies where participants were unselected for severity or age (n=9 studies, n=4427 individual participants);																			
Adamuz 2011[15]	X			X	X								X	X				X	
Adamuz 2015[16]	X		X								X		X	X	X			X	
Fine 1999[20]	X	X		X	X					X	X							X	
Marrie 2000[22]	X	X		X	X											X			X
Nickler 2016[24]	X			X					X									X	
Sharma 2006[25]	X			X						X								X	
Uranga 2016[26]	X			X			X			X					X	X			
Wootton 2017[27]	X		X		X		X								X		X		
Wyrwich 2015[28]	X	X			X						X				X				

Abbreviations; I/P – inpatient, O/P – outpatient, CURB65 – confusion, urea, blood pressure, age>65 years, PSI – Pneumonia severity index, CAP – community-acquired pneumonia, SF-36 – short-form health survey, EQ-5D – EuroQoL health-related quality of life questionnaire, ADLs – activities of daily living, ED – emergency department.

Appendix 1 - Details of search strategies

MEDLINE (Ovid)

1. exp Pneumonia/
2. exp Community-Acquired Infections/
3. “community-acquired pneumonia.tw.
4. exp “Outcome Assessment (Health Care)”/
5. exp “Recovery of Function”/
6. exp “Activities of Daily Living”/
7. exp Symptom Assessment
8. exp Treatment Outcome/
9. exp Patient Readmission/
10. symptom recovery.tw.
11. symptomatic recovery.tw.
12. functional recovery.tw.
13. 1 and 2
14. 3 or 13
15. OR/ 4-12
16. 14 and 15

EMBASE (OVID)

1. exp pneumonia/

2. exp community acquired infection/

3. community acquired pneumonia*.tw.

4. community-acquired pneumonia*.tw.

5. 1 and 2

6. OR/ 3-5

7. exp outcome assessment/

8. recovery of function*.mp. or exp convalescence/

9. exp daily life activity/

10. exp symptom assessment/

11. exp treatment outcome/

12. exp hospital readmission/

13. symptom recovery*.tw.

14. symptomatic recovery*.tw.

15. OR/ 7-14

16. 6 and 15

AMED (OVID)

1. exp Pneumonia/

2. community-acquired infection*.mp.

3. community-acquired pneumonia*.mp.

4. community acquired pneumonia*.mp.

5. OR/ 1-4

6. exp "recovery of function"/

7. exp "Activities of daily living"/

8. exp Symptoms/

9. exp Treatment outcome/

10. exp Rehabilitation/

11. patient readmission*.mp.

12. functional recovery*.mp.

13. OR/ 6-12

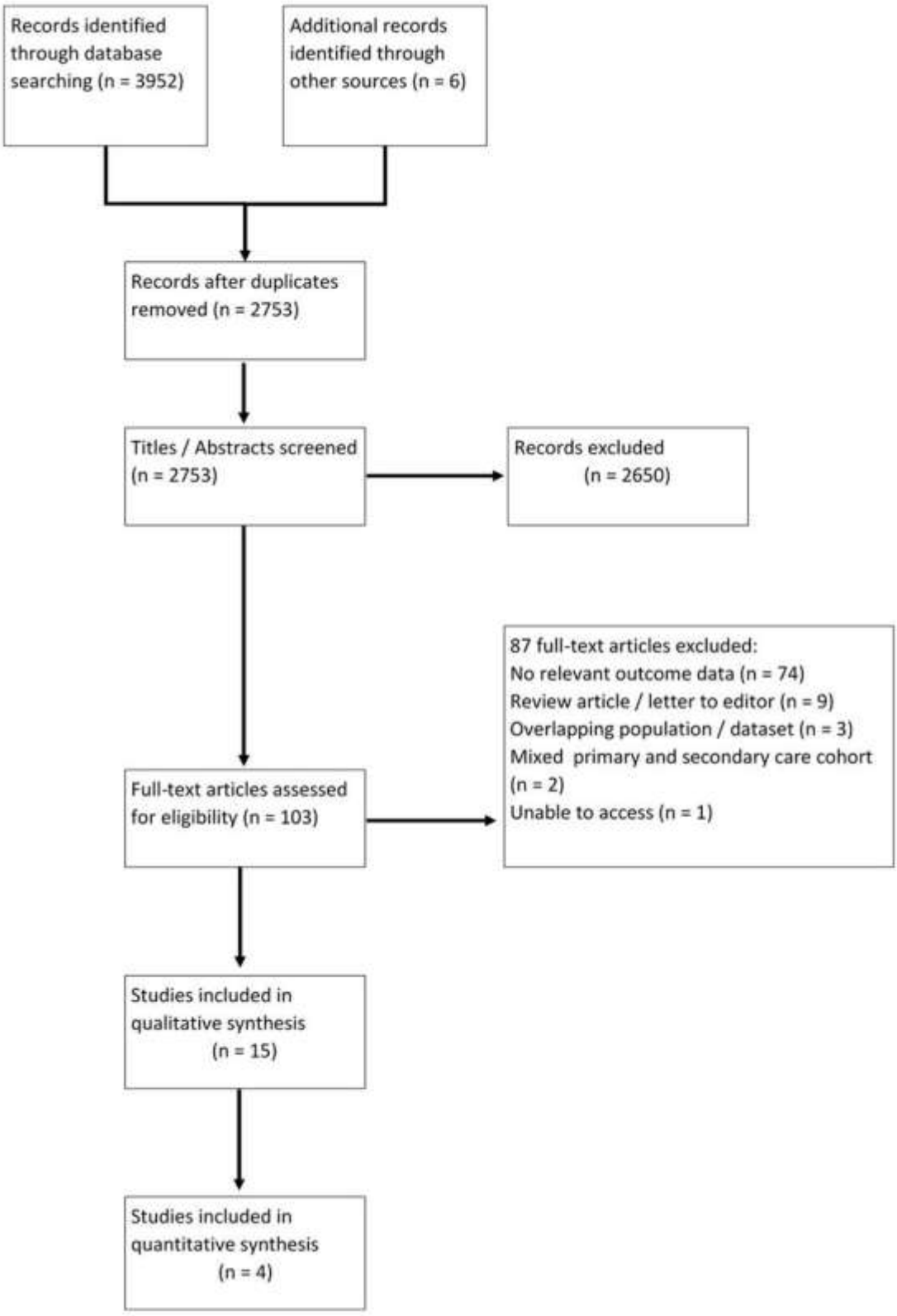
14. 5 and 13

Appendix 2; Online supplementary material; Table 1; Risk of bias in included studies

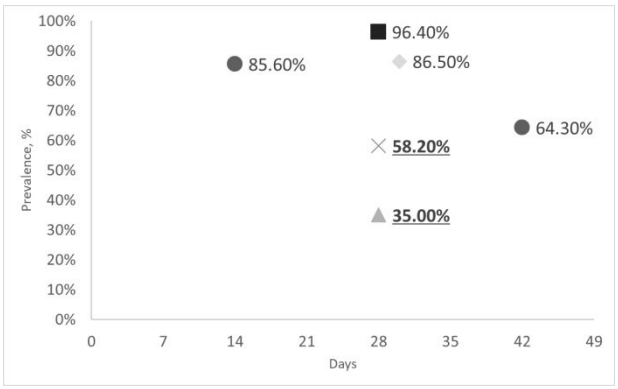
First Author	Primary Outcome	Selection Domain (max 3)	Outcome Domain (max 3)	Comments
Adamuz 2011	Additional healthcare utilisation within 30days of discharge	3	2	Outcome measure not clearly defined or justified
Adamuz 2015	Additional healthcare utilisation within 30days of discharge	3	3	
Bruns 2010	Rate of radiographic resolution	2	2	20.1% loss to follow-up
Carratala 2005	Successful outcome' - composite of 7 predefined criteria	3	3	Low severity CAP (PSI classes II and III only)
Daniel 2018	Healthcare re-consultation within 4 weeks of discharge	2	3	Working age adults, low severity CAP
El Moussaoui 2006	Pneumonia related symptoms during follow-up	2	2	Low severity CAP
Fine 1999	Not defined - process of care and outcome of outpatients and hospitalised patients with CAP	2	2	
Labarere 2007	30 day mortality rate	2	3	Low severity CAP
Marrie 2000	Proportion of patients with symptom resolution at 6 weeks	2	2	No details regarding loss to follow-up
Metlay 1998	Proportion of patients with symptom resolution at 4 weeks	2	2	
Nickler 2016	Decline in QoL from hospital admission (baseline) to day 30 and after 6 years.	2	2	Not representative sample excluded elderly, dementia, significant co-morbid

				disease
Sharma 2006	Decline in ADL score by at least 1 point, comparing baseline prehospitalization ADL to 1 and 6 months post discharge.	2	2	Not representative sample, from cohort study of delirium in elderly, no details on loss to follow-up
Uranaga 2016	Clinical success rate at day 10 and day 30 since admission	3	3	
Wootoon 2017	Time for symptomatic recovery to baseline	2	2	Excluded patients with cognitive impairment, no loss to follow-up information
Wyrwich 2015	Time for symptom resolution	0	2	

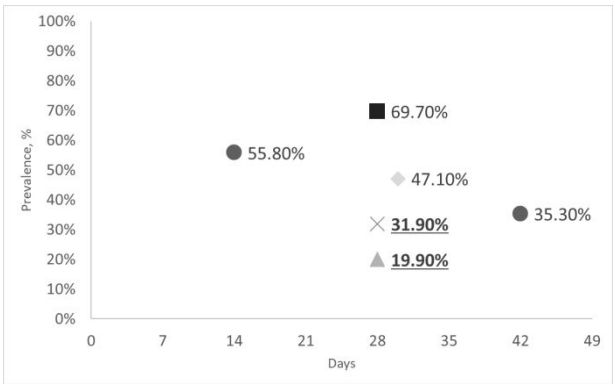
Figure 1. Study flow diagram



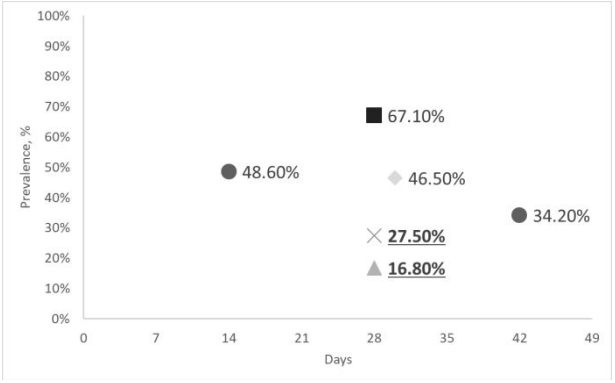
2 (a) Prevalence of 1 or more symptom in CAP recovery



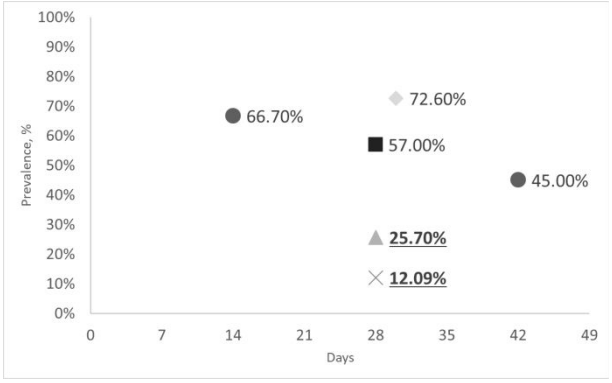
2 (b) Prevalence of cough in CAP recovery



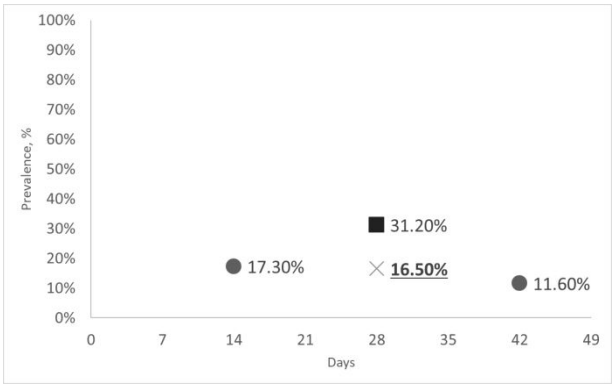
2 (c) Prevalence of dyspnoea in CAP recovery



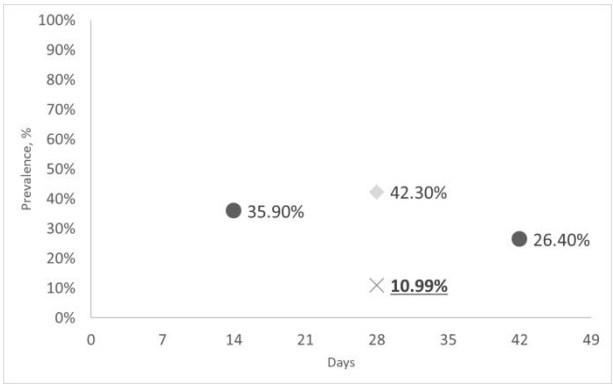
2 (d) Prevalence of fatigue in CAP recovery



2 (e) Prevalence of chest pain in CAP recovery



2 (f) Prevalence of sputum production in CAP recovery

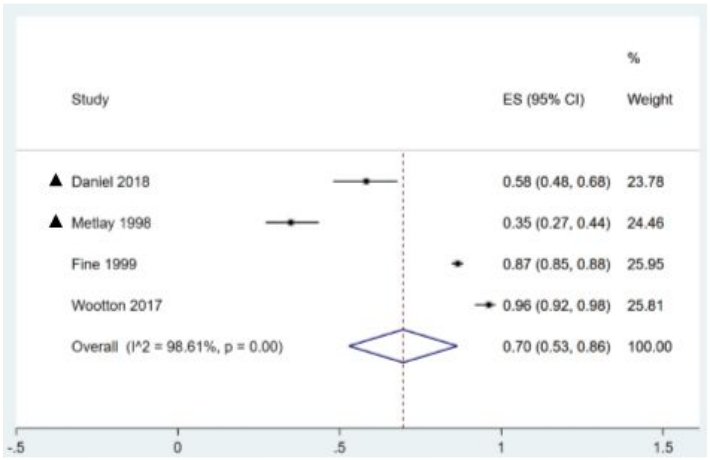


● Marrie 2000 ▲ Metlay 1998 × Daniel 2018 ■ Wootton 2017 ◆ Fine 1999

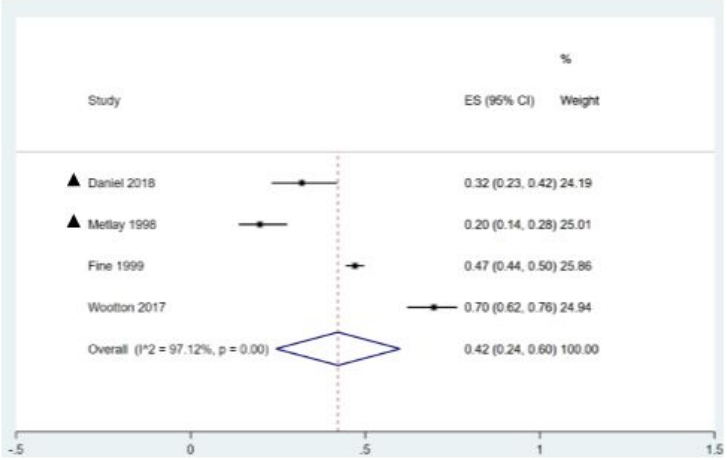
* Studies in bold and underlined are from studies of patient cohorts restricted to either low-moderate severity CAP (PSI Class III or less, CURB65 0-2) or age < 65 years, by design. Marrie et al measured symptom prevalence twice (14days and 42 days), all other studies measured symptom prevalence once.

Figure 3 (a) to (d); Random effects meta-analysis of prevalence of symptoms at 4 weeks following discharge from hospital with community-acquired pneumonia.

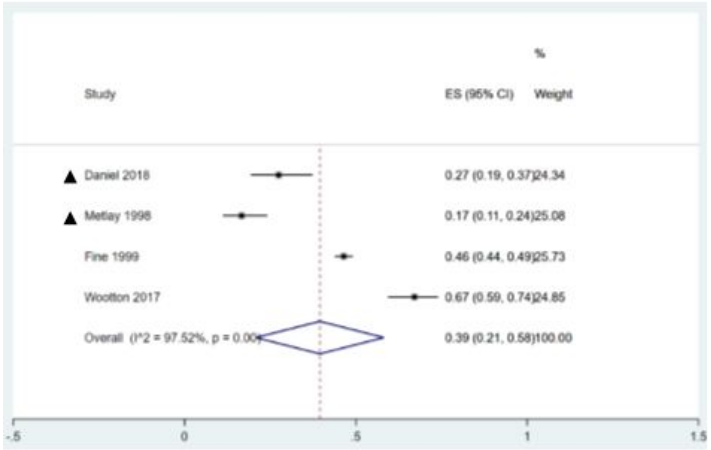
3 (a) Prevalence of 1 or more symptom at 4 weeks



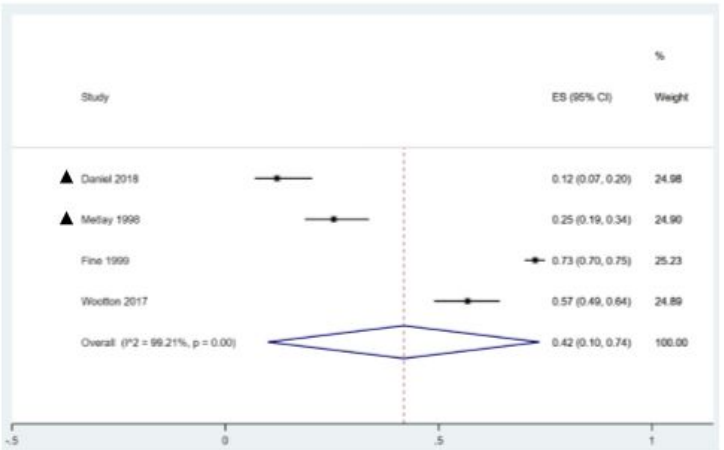
3 (b) Prevalence of cough at 4 weeks



3 (c) Prevalence of dyspnoea at 4 weeks



3 (d) Prevalence of fatigue at 4 weeks



▲ = Studies that selected patients with low-moderate severity CAP or age <65 years