Patient-reported outcome measures in the recovery of adults hospitalised with community-acquired pneumonia: a systematic review

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Patients report substantial morbidity in CAP recovery; the commonest symptom is fatigue (45–73%), followed by cough (35–70%) and dyspnoea (34–67%). Methodological consistency is weak across studies. A core set of PROMs is suggested. http://ow.ly/d6N430nhdIq

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

Comprehensive searches in accordance with the PRISMA statement were conducted to March 2017. Eligible studies included adults discharged from hospital following confirmed CAP and reporting PROMs.

15 studies (n=5644 patients) were included; most were 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 (45.0–72.6% of patients, three studies), followed by cough (35.3–69.7%) and dyspnoea (34.2–67.1%); corresponding values from studies restricted by age <65 years (two studies) were lower: fatigue 12.1–25.7%, cough 19.9–31.9% and dyspnoea 16.8–27.5%. Functional impairment 4 weeks post-discharge was reported in 18–51% of patients (two studies), while median time to return to normal activities was between 15 and 28 days (three 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 ~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 UK healthcare costs are GBP441 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 guidance on drug development in CAP recommends incorporation of PROMs as trial end-points [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 PRISMA statement [11]. The review protocol was prospectively registered in the PROSPERO database (identifier CRD42017059799).

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), Allied and Complementary Medicine Database (AMED; 1985 to March 2017), and Web of Science (1985 to March 2017). The search strategy included subject headings and key words related to CAP, 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 given in the supplementary material. 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 from 2014 to 2017 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 nonrandomised studies in adults attending secondary care facilities with a presenting diagnosis of CAP and assessing at least one of the predefined 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 radiography. 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 (H.J.P and T.M.M.) conducted a 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 (W.S.L.) as necessary.

Outcome measures

Primary outcomes of interest measured within 6 weeks following hospital discharge were: 1) patient-reported symptoms, 2) return to work and/or usual activities of daily living (ADLs), and 3) healthcare utilisation. Secondary outcomes of interest measured within 6 weeks following discharge were: 1) proportion with physician-determined clinical cure in studies reporting symptomatic and functional recovery, and 2) change in quality of life scores. (The time-point of 6 weeks after discharge was chosen for outcomes 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 (H.J.P. and T.M.M.) using a pre-designed form that was initially piloted on five studies; any disparities were resolved by discussion and consensus, including a third reviewer (W.S.L.) as required. Where data were represented graphically within studies, Digitizelt

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 Downs and Black Quality Assessment Tool [12, 13]. Each study was assessed for details pertaining to study period and location, participant selection, and outcome measure, with a final total score out of 6 points (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, College Station, TX, USA). 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 the eligibility criteria and were included in the systematic review (see study flow diagram in figure 1) [6, 14–27].

Characteristics of included studies

The characteristics of the 15 included studies are summarised in table 1. Briefly, eligible studies included two RCTs, eight prospective cohort studies, one retrospective cohort study and four studies with cohort
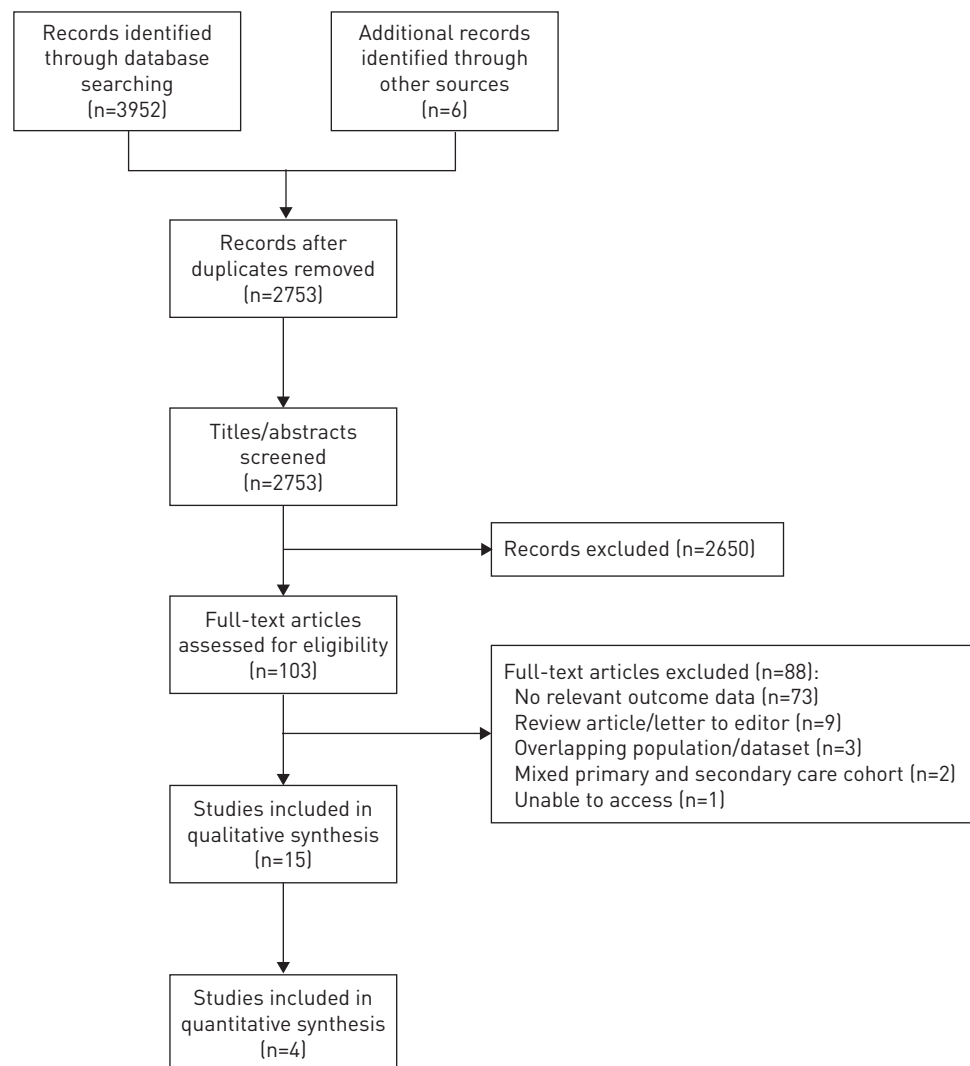

FIGURE 1 Study flow diagram.

TABLE 1 Summary of included studies

First author [ref.]	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 [6]	The Netherlands	November 2000–July 2003	Multicentre prospective cohort	119 adults with CAP. CAP aetiology: *S. pneumoniae* 27.7%. Selection criteria: age: unselected (mean±SD age 56.6±17.8 years); severity: low severity, PSI <110 (mean±SD PSI 65.5±22.1); comorbid disease: unselected; immune status: unselected	Normalisation of CAP score at day 10: 32.0%; physician-rated clinical cure at day 28: 88.9%
Carratala [16]	Spain	October 2000–October 2002	Cohort from multicentre RCT	224 adults with CAP: 101 patients in hospitalised cohort. CAP aetiology: *S. pneumoniae* 14.0%, *L. pneumophila* 4.4%, *H. influenzae* 2.6%, "atypical" 2.6%. Selection criteria: age: unselected (mean±SD age: outpatient group 67.5±11.8 years; inpatient group 64.9±13.4 years); severity: low severity, PSI classes II and III (mean±SD PSI: outpatient group 70±11.6; inpatient group 66.9±12.5); comorbid disease: excluded if pregnant, breastfeeding, 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"
Daniel [17]	UK	February 2015–April 2016	Multicentre prospective cohort	108 adults with CAP (male 48.2%). CAP aetiology: *S. pneumoniae* 16.7%. Selection criteria: age: 18–65 years only (median (IQR) age 50 (38.3–57.8) years); severity: unselected (CURB-65 0–1: 88.9%; CURB-65 2: 9.3%; CURB-65 ⩾3: 1.8%); comorbid disease: unselected; immune status: unselected	Proportion of patients reporting prevalence of symptoms and functional impairment at 28 days following discharge: cough 31.9%, dyspnoea 27.5%, chest pain 16.5%, sputum 11.0%, fatigue 12.1%, ⩾1 symptom 58.2%, not returned to ADLs 51.1%, not returned to work 34.3%; reconsultation within 28 days: ED attendance 12.0%, primary care 59.2%
El Moussaoui [18]	The Netherlands	November 2000–July 2003	Cohort from multicentre RCT	91 adults with CAP (male 58.8%). CAP aetiology: *S. pneumoniae* 23.8%. Selection criteria: age: unselected (median (IQR) age 65 (48–72) years); severity: low severity, PSI <110 (mean±SD PSI 71±23); comorbid disease: excluded if pregnant, severe underlying disease, preceding antibiotic treatment for >24 h prior to admission, concurrent comorbid disease likely to interfere with course of pneumonia, respiratory failure; immune status: unselected; other: excluded if amoxicillin allergy	Median (IQR) CAP scores: 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 [20]	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 (IQR) age 66 (48–77) years); severity: low severity, PSI classes I–III (PSI I: 16.0%; PSI II: 41.0%; PSI III: 43.0%); comorbid disease: excluded if pulmonary tuberculosis, alcoholism and evidence of end-organ damage, social problems incompatible with recruitment, illicit drug use 30 days; immune status: immunocompetent only (excluded if HIV, immunosuppression)	Median (IQR) time for return to ADLs: workers 22 (11–29) days, nonworkers 20 (9–29) days; median (IQR) time return to work 14 (8–29) days
Metlay [22]	USA	April 1996–February 1997	Single-centre prospective cohort	126 adults with CAP (male 54.8%). CAP aetiology: not reported. Selection criteria: age: 18–64 years; severity: low severity, PSI classes I–III (mean PSI 55.2); comorbid disease: excluded if pregnancy, severe neuromuscular disease; immune status: immunocompetent only (excluded if chronic immunosuppression, HIV); other: nursing home residence, psychological or social problems compromising follow-up	Proportion of patients reporting prevalence of symptoms at 28 days following discharge: cough 19.9%, dyspnoea 16.8%, fatigue 25.7%, fever 3.5%, ⩾1 symptom 35.0%
Studies where participants were unselected for severity or age (n=9 studies, n=4427 individual participants)					
Adamuz [14]	Spain	January 2007–December 2009	Single-centre prospective cohort	828 adults with CAP (male 65.8%). CAP aetiology: *S. pneumoniae* 44.1%, *L. pneumophila* 3.0%, *H. influenzae* 4.4%, anaerobes 5.6%. Selection criteria: age: unselected (median (IQR) age 71 (55–79) years); severity: unselected (PSI >90 in 62.2%); comorbid disease: unselected; immune status: immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy equivalent to prednisolone >20 mg 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 30 days: primary care (n=149): respiratory symptoms 75.2%, general symptoms 22.8%; ED (n=177): worsening pneumonia symptoms 47.5%
Adamuz [15]	Spain	January 2011–October 2014	Multicentre RCT	207 adults with CAP (male 59.9%). CAP aetiology: *S. pneumoniae* 24.6%, *H. influenzae* 5.4%, influenzae A 3.4%. Selection criteria: age: unselected (21–49 years: 20.2%; 50–69 years: 30.5%; >70 years: 49.3%); severity: unselected (CURB-65 0–1: 49.3%; CURB-65 2: 34.3%; CURB-65 ⩾3: 16.4%); comorbid	Healthcare utilisation at 30 days: primary care 20.3%, ED 18.4%; median (IQR) time off work: intervention group 30 (15–66.5) days, usual care group 26 (12.5–37) days

TABLE 1 Continued

First author [ref.]	Country	Study period	Study type	Study population	Outcome
				disease: excluded cognitive impairment; immune status: immunocompetent only (excluded HIV, splenectomy, immunosuppressive therapy, corticosteroid therapy equivalent to prednisolone >20 mg daily, neutropenia, Ig deficiency, solid organ transplant); other: excluded if nursing home resident or long-term care facility, language barrier	
FINE [19]	USA/Canada	October 1991–March 1994	Multicentre prospective cohort	1343 adults with CAP (male 52.4%) CAP aetiology: *S. pneumoniae* 9.1%, *H. influenzae* 4.8%, "atypical" 2.1%, *Enterobacter* sp. 2.8%, *P. aeruginosa* 0.9% Selection criteria: age >65 years 58.7%; severity: unselected (PSI I: 13.8%; PSI II: 17.4%; PSI III: 18.9%; PSI IV: 33.2%; PSI V: 16.7%); comorbid disease: unselected; immune status: excluded if HIV	Proportion of patients reporting prevalence of symptoms and functional impairment at 30 days following discharge: cough 47.1%, dyspnoea 46.5%, sputum 42.3%, fatigue 72.6%, ≥1 symptom 68.5%; not returned to ADLs: workers 18% (median 15 days), nonworkers 42.8% (median 24 days); not returned to work 31.9%
MARRIE [21]	Canada	January 1998–July 1998	Multicentre prospective cohort	535 adults with CAP (male 52.3%) CAP aetiology: not reported Selection criteria: age: unselected (mean±SD age 61.6±19.1 years); severity: unselected (mean±SD PSI 76.2±32.8); comorbid disease: unselected; immune status: unselected	Proportion of patients reporting prevalence of symptoms/functional impairment at 14/42 days 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 symptom 85.6%/64.3%
NICKLER [23]	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 (IQR) age 72 (52–82) years); severity: unselected (PSI I: 10.0%; PSI II: 19.7%); comorbid disease: excluded if terminal illness; immune status: immunocompetent only (excluded if long-term immunosuppression); other: excluded if language impairment precluding written consent, *i.v.* drug abuse	EQ-5D index: decline in ADLs in 29% at day 30
SHARMA [24]	USA	March 1995–March 1998	Single-centre prospective cohort	79 adults with CAP (male 35%) CAP aetiology: not reported Selection criteria: age: unselected (mean±SD age 79.9±6.1 years); severity: unselected (mean±SD PSI 106.2±23.9); comorbid disease: excluded if terminal illness; immune status: unselected; other: excluded if coma, intensive care admission, unable to participate in interview	Proportion with decline in ADLs score of >1 point 28% at day 30
URANGA [25]	Spain	January 2012–August 2013	Multicentre RCT	312 adults with CAP (male 62.8%) CAP aetiology: *S. pneumoniae* 16.0%, *L. pneumophila* 3.5%, *H. influenzae* 0.3% Selection criteria: age: unselected (mean±SD age 62.2±6.07 and 64.7±18.7 years in the control and intervention groups, respectively); severity: unselected (mean±SD PSI 83.7±33.7 and 81.8±33.8, in the control and intervention groups, respectively); comorbid disease: unselected; immune status: immunocompetent only (excluded if HIV, immunosuppression for solid organ transplantation, splenectomy, receiving ≥10 mg·day^{-1} prednisone equivalent for >30 days, taking other immunosuppressive agents, neutropenia); other: excluded if care home resident, antibiotics within preceding 30 days, intercostal chest drain, extrapulmonary manifestations, death or ICU admission prior to randomisation	Mean±SD CAP-symptom score at 5 days 24.7±11.4 to 27.2±12.5; mean±SD CAP-symptom score at 10 days 18.6±9.0 to 17.9±7.6; median (IQR) time for return to normal activity 15 (10–21) to 18 (9–25) days
WOOTTON [26]	UK	February 2011–March 2013	Multicentre prospective cohort	169 adults with CAP (male 52%) CAP aetiology: not reported Selection criteria: age: unselected (mean±SD age 68 (range 16–98) years); severity: unselected (CURB-65 0–1: 46.7%; CURB-65 2: 29.6%; CURB-65 ≥3: 23.7%); comorbid 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 patients reporting prevalence of symptoms at 28 days following discharge: cough 13.6%, dyspnoea 67.1%, chest pain 31.2%, fatigue 57.0%, ≥1 symptom 96.4%
WYRWICH [27]	USA	Unknown	Multicentre retrospective cohort	201 adults with CAP (male 45%) CAP aetiology: not reported Selection criteria: age: ≥50 years; severity: unselected; comorbid disease: unselected; immune status: unselected; other: respondent to e-mail survey, excluded if nursing home resident	Mean (median (IQR)) time to symptom resolution: cough 13.6 (7 (2–14)) days, dyspnoea 25.1 (14 (7–43)) days, chest pain 12.9 (7 (2–14)) days, sputum 14.8 (7 (7–14)) days, fatigue 25 (20 (7–24)) days, fever 2.7 (2 (1–2)) days; median time for return to work 14 days

CAP: community-acquired pneumonia; RCT: randomised controlled trial; *S. pneumoniae*: *Streptococcus pneumoniae*; PSI: Pneumonia Severity Index; *L. pneumophila*: *Legionella pneumophila*; *H. influenzae*: *Haemophilus influenzae*; SF-36: Short Form-36 health survey; IQR: interquartile range; CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate ≥30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ≤60 mmHg (diastolic), age ≥65 years; *P. aeruginosa*: *Pseudomonas aeruginosa*; ICU: intensive care unit; ADLs: activities of daily living; ED: emergency department; EQ-5D: EuroQoL health-related quality of life questionnaire.

data for participants originally enrolled in RCTs. Six studies were restricted to patients with low/moderate severity CAP (Pneumonia Severity Index (PSI) classes I–III, PSI score <110 or CURB-65 (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years) score 0–2) [6, 16–18, 20, 22] or age <65 years [17, 22]. One study did not assess disease severity [27] 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 [14, 15, 19, 21, 23–26]. 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
The median (interquartile range (IQR)) quality score across all included studies was 4.5 (4–5). Three studies scored full marks at quality assessment (supplementary table S1) [15, 16, 25]. 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 (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 [14, 17, 19, 21, 22, 26].

Four studies reported prevalence of symptoms for participants unselected for age or disease severity [14, 19, 21, 26]. At 28–42 days post-discharge, the commonest symptom reported was fatigue (range 45.0–72.6% of patients), followed by cough (range 35.3–69.7%) and dyspnoea (range 34.2–67.1%) (figure 2) [19, 21, 26]. 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 [14]. Restricting the population to working adults, two studies reported symptom prevalence at 4 weeks following discharge and found one 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% [17, 22]. Chest pain (16.5%) and sputum production (11%) were reported by participants in one of these studies [17].

Finally, in an e-mail survey investigating average time for resolution of symptoms following CAP in adults aged ⩾50 years (n=500), median (IQR) time for resolution of cough was 7 (2–14) days, dyspnoea 14 (7–43) days, chest pain 7 (2–14) days, sputum production 7 (7–14) days, fever 2 (1–2) days and fatigue 20 (7–24) days [27].

Quantitative synthesis
Random effects meta-analysis was performed on amenable data from four studies (n=1715) reporting outcomes at 4 weeks [17, 19, 22, 26]. High levels of heterogeneity were evident. The summary estimate of the proportion of patients reporting one or more symptoms was 70% (95% CI 53–86%; I^2=98.6%), cough 42% (95% CI 24–60%; I^2=97.1%), dyspnoea 39% (95% CI 21–58%; I^2=97.5%) and fatigue 42% (95% CI 10–74%; I^2=99.2%) (figure 3a–d).

CAP-specific symptom scores
Four studies included data derived from pneumonia symptom scores [6, 18, 25, 26].

Two studies (n=91 and n=95) used the CAP score (higher score signifying fewer symptoms). The median (IQR) CAP scores reported by EL MOUSSAOUI et al. [18] at days 3, 7, 10, 14 and 28 following admission were 56 (38–69), 60 (37–75), 65 (37–86), 77 (61–88) and 75 (58–93), respectively. BRUNS et al. [6] 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.

Two studies (n=169 and n=312) used the CAP-symptom score (lower score signifying fewer symptoms). WOOTTON et al. [26] observed the average CAP-symptom score at day 2 from admission was 23.8 and at day 28 was 13.6. URANGA et al. [25], in an interventional trial of short-course antibiotics, reported that the average CAP-symptom score in the control group at day 5 from admission was 24.7±11.4 and at day 10 was 18.6±9.0, with corresponding values in the intervention group of 27.2±12.5 and 17.9±7.6.

Return to functional activity
Five studies included data for time to return to normal activities [15, 17, 19, 20, 25].

TABLE 2 Summary of methodology of included studies

First author [ref.]	Destination after initial review		Severity		Outcome measure										Timing of assessment of outcome measure				
					Assessment of symptoms			Health status		Assessment of function (return to)		Clinical cure	Healthcare utilisation						
	IP	OP	CURB-65	PSI	Prevalence	CAP score	CAP-symptom score	SF-36	EQ-5D	ADLs	Occupation		Primary care	ED	Average time to ...	≤14 days	28 days	30 days	42 days
Studies with participants selected for low/moderate severity CAP or age <65 years (n=6 studies, n=1217 individual participants)																			
Bruns [6]	✓			✓		✓						✓				✓	✓		
Carratala [16]	✓	✓		✓				✓											✓
Daniel [17]	✓		✓		✓					✓	✓		✓	✓			✓		
El Moussaoui [18]	✓			✓		✓										✓	✓		
Laberere [20]	✓	✓		✓						✓	✓				✓				
Metlay [22]		✓		✓	✓												✓		
Studies where participants were unselected for severity or age (n=9 studies, n=4427 individual participants)																			
Adamuz [14]	✓			✓	✓								✓	✓				✓	
Adamuz [15]	✓		✓								✓		✓	✓	✓			✓	
Fine [19]	✓	✓		✓	✓					✓	✓							✓	
Marrie [21]	✓	✓		✓	✓										✓				✓
Nickler [23]	✓			✓					✓									✓	
Sharma [24]	✓			✓						✓								✓	
Uranga [25]	✓			✓			✓			✓					✓	✓			
Wootton [26]	✓		✓		✓		✓								✓		✓		
Wyrwich [27]	✓	✓			✓						✓				✓				

IP: inpatient; OP: outpatient; CURB-65: confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years; PSI: Pneumonia Severity Index; CAP: community-acquired pneumonia; SF-36: Short Form-36 health survey; EQ-5D: EuroQoL health-related quality of life questionnaire; ADLs: activities of daily living; ED: emergency department.

First author [ref.]: ● MARRIE [21] ▲ METLAY [22] ✕ DANIEL [17] ■ WOOTTON [26] ◆ FINE [19]
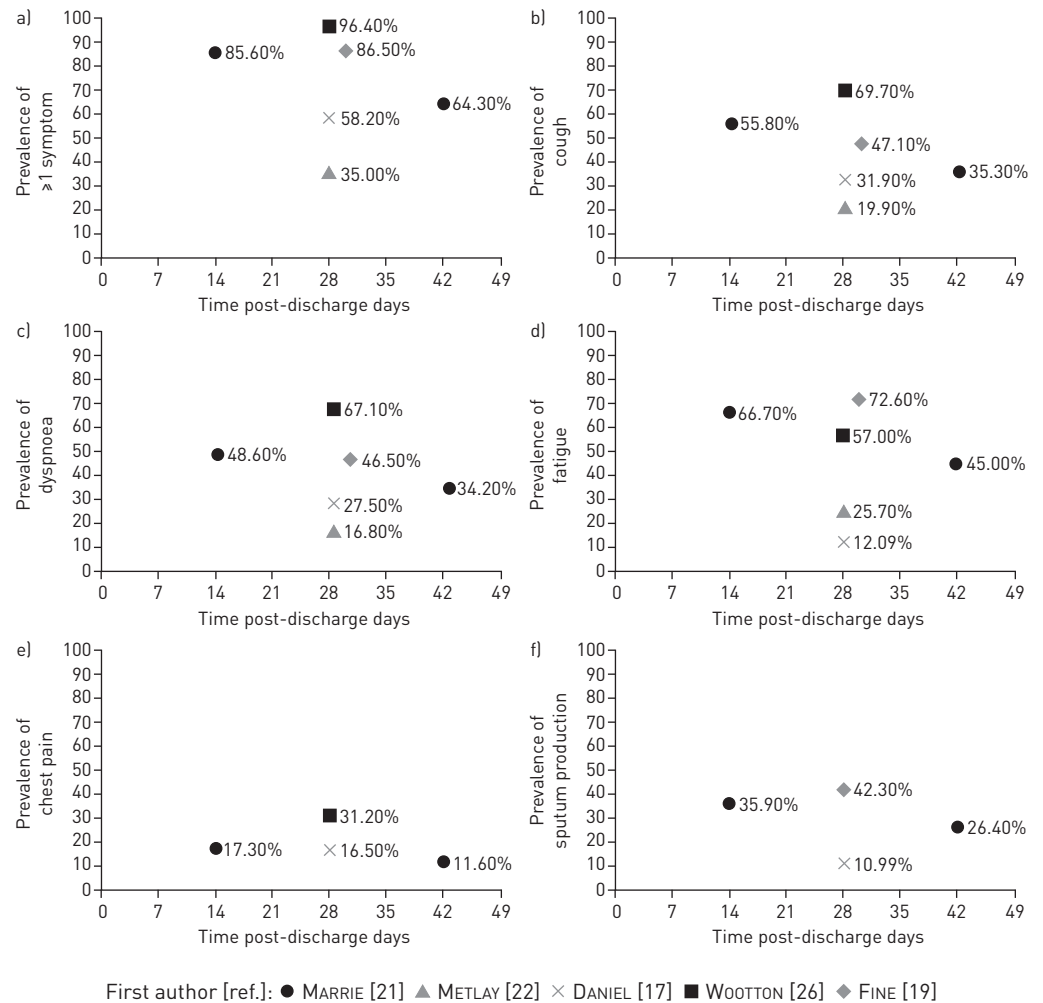
FIGURE 2 Prevalence of symptoms in recovery following community-acquired pneumonia (CAP): a) one or more symptom, b) cough, c) dyspnoea, d) fatigue, e) chest pain and f) sputum production. METLAY et al. [22] and DANIEL et al. [17] are studies of patient cohorts restricted to either low/moderate severity CAP (Pneumonia Severity Index classes I–III or CURB-65 (confusion, urea >7 mmol·L^{-1}, respiratory rate ≥30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ≤60 mmHg (diastolic), age ≥65 years) score 0–2) or age <65 years, by design. In the study by MARRIE et al. [21], symptom prevalence was assessed twice during the follow-up period (at 14 and 42 days); the other studies reported symptom prevalence once in the defined follow-up period.

DANIEL et al. [17] found that 51.1% of adults aged <65 years had not resumed baseline ADLs at 4 weeks. In contrast, FINE et al. [19] found that 18.0% of workers had not resumed baseline ADLs at 4 weeks compared with 42.8% of nonworkers.

The median (IQR) time for return to normal activity reported by URANGA et al. [25] was 18 (9–25) days in the control group and 15 (10–21) days in the intervention group. FINE et al. [19] found the median time for return to ADLs in workers was 15 days and in nonworkers was 24 days, whereas LABARERE et al. [20] found little difference in the median (IQR) time for return to ADLs between workers (22 (11–29) days) and nonworkers (20 (9–29) days).

Of two studies with relevant data, 34.3% [17] and 31.9% [19] of participants had not returned to work at 4 weeks. Median time for return to work following discharge was 14 days [20, 27]. ADAMUZ et al. [15] reported that the median (IQR) time taken off work by participants in the control group was 26 (12.5–37) days compared with 30 (15–66.5) days in the intervention group.

Healthcare utilisation

In addition to PROMs, three studies reported rates of primary care consultation and/or emergency department attendance within 4–6 weeks following hospital discharge [14, 15, 17].
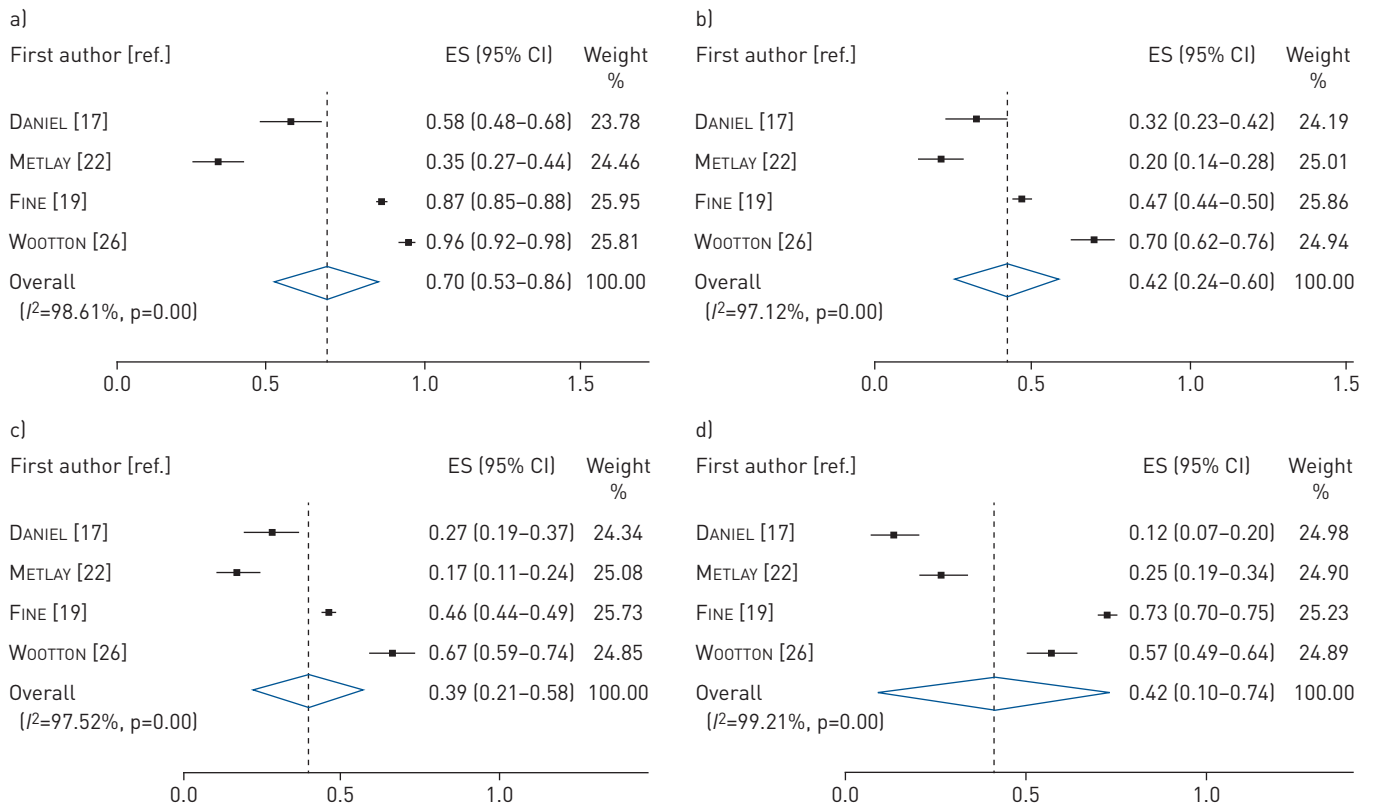
FIGURE 3 Random effects meta-analysis of prevalence of symptoms at 4 weeks following discharge from hospital with community-acquired pneumonia (CAP): a) one or more symptom, b) cough, c) dyspnoea and d) fatigue. ES: effect size. METLAY et al. [22] and DANIEL et al. [17] are studies of patient cohorts restricted to either low/moderate severity CAP (Pneumonia Severity Index classes I–III or CURB-65 (confusion, urea >7 mmol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg (systolic) or ⩽60 mmHg (diastolic), age ⩾65 years) score 0–2) or age <65 years, by design.

DANIEL et al. [17] found that 59.2% had consulted primary care and 12.0% had attended emergency departments within 4 weeks. This compares with 18.0% and 20.3% attending primary care and 18.4% and 21.4% attending emergency departments in the two studies from ADAMUZ et al. [14, 15]. Of those reconsulting a general practitioner, ongoing or new respiratory symptoms were reported by 68.8–75.2% of patients. The reported reason for emergency department attendance was pneumonia-related symptoms or signs in 47.5–84.6% of patients [15, 17].

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 [16]. Using the EuroQoL EQ-5D health-related quality of life questionnaire, NICKLER et al. [23] 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.

Physician-assessed clinical cure was noted by BRUNS et al. [6] in 88.9% of participants 28 days after discharge, although only 41.7% of patients reported normalisation of symptoms and function (based on the CAP score) at the same time-point. 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" (e.g. 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 varies across studies in accordance with the 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 measuring 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, 18, 21, 26]. 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 [28]. Quantitatively, the CAP-symptom score captures the degree of fatigue on a scale of 0–5 [29]. 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, multidimensional tools have been developed to better quantify and assess fatigue [30, 31].

Return to functional activity, measured as return to "normal activities" or ADLs, was consistently reported as taking a median of 15–25 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 [32]. 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 [33]. Experience from patients recovering from exacerbations of chronic obstructive pulmonary disease, where impaired lung function, exercise capacity and quality of life persists despite apparent symptomatic resolution, provides further support for this view [34–36].

We identified only two relatively small studies that attempted to describe the correlation between PROMs and healthcare reconsultation [14, 17]. These studies suggest that persistence of pneumonia-related symptoms is a major factor in general practitioner reconsultations, while new or worsening comorbid illnesses increase in prominence in relation to emergency department reattendances. An episode of pneumonia may be a marker for frailty or increased susceptibility to illness from non-pneumonia-related factors [37]. A better understanding of the association between PROMs, long-term complications and healthcare reconsultations is necessary if appropriate interventions are to be developed.

Strengths and limitations

To the best of our knowledge, 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 with the large burden of disease. Existing studies are disparate in their study populations (age, comorbid 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 outpatient 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. [9] previously defined core outcomes sets for CAP research, including recommending the CAP-symptom score for use in studies of recovery. Ideally, the CAP-symptom score should be externally validated for hospitalised patients and a multidimensional 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 reconsultation 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.

Conclusions

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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