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The International Community-Acquired Pneumonia (CAP) Collaboration Cohort (ICCC) study: rationale, design and description of study cohorts and patients

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ABSTRACT

Objective: To improve the understanding of the determinants of prognosis and accurate risk stratification in community-acquired pneumonia (CAP).

Design: Multicentre collaboration of prospective cohorts.

Setting: 6 cohorts from the USA, Canada, Hong Kong and Spain.

Participants: From a published meta-analysis of risk stratification studies in CAP, the authors identified and pooled individual patient-level data from six prospective cohort studies of CAP (three from the USA, one each from Canada, Hong Kong and Spain) to create the International CAP Collaboration Cohort. Initial essential inclusion criteria of meta-analysis were (1) prospective design, (2) in English language, (3) reported 30-day mortality and transfer to an intensive or high dependency care and (4) minimum 1000 participants. Common baseline patient characteristics included demographics, history and physical examination findings, comorbidities and laboratory and radiographic findings.

Primary and secondary outcome measures: This paper reports the rationale, hypotheses and analytical framework and also describes study cohorts and patients. The authors aim to (1) compare the prognostic accuracy of existing CAP risk stratification tools, (2) assess patient-level determinants of prognosis, (3) improve risk stratification by combined use of scoring systems and (4) understand prognostic factors for specific patient groups.

Results: The six cohorts assembled from 1991 to 2007 included 13 784 patients (median age 71 years, 54% men). Aside from one randomised controlled study, the remaining five were cohort studies, but all had similar inclusion criteria. Overall, there was 0%–6% missing data. A total of 6159 (44%) had severe pneumonia by Pneumonia Severity Index class IV/V. Mortality at 30 days was 8% (1036). Admission to intensive care or high dependency unit was also 8% (1059).

Conclusions: International CAP Collaboration Cohort provides a pooled multicentre data set of patients with CAP, which will help us to better understand the prognosis of CAP.

ARTICLE SUMMARY

Article focus

This paper reports the rationale, hypotheses and analytical framework and also describes study cohorts and patients. We aim to

- compare the prognostic accuracy of existing CAP risk stratification tools;
- assess patient-level determinants of prognosis;
- improve risk stratification by combined use of scoring systems;
- understand prognostic factors for specific patient groups.

Key messages

- The International CAP Collaboration Cohort (ICCC) as described in this report will be able to provide better understanding of determinants of outcomes in CAP. Examples of such development include comparison of commonly and less commonly known CAP severity scoring systems and identification of characteristics of CAP patients with poor outcome (30-day mortality) despite non-severe status of severity score.
- In view of the large sample size, the ICCC cohort will be able to provide the determinants of outcomes in patient groups with specific conditions such as cardiovascular and respiratory diseases taking into account case mix and individual prognostic indicators.
- The ICCC cohort will be of benefit to the CAP research community and help define a future agenda for research, as well as helping clinicians make better clinical decisions for patients with CAP.

ARTICLE SUMMARY

Strengths and limitations of this study

- The ICCC is a multicentre/multiethnic cohort where all collaborating groups defined pneumonia based on clinical features and the presence of CXR evidence of pneumonia. The major strengths of ICCC are prospective study design, inclusion of CAP patients spanning across wide age range, ethnicity, different healthcare settings and large sample size. Potential areas of improvement in assessment of CAP might be identification of at-risk patients with pneumonia who have been initially assessed as non-severe CAP. With large sample size, ICCC may provide an opportunity to identify characteristics of such individuals. Based on this work, risk assessment may be applied at more than one point in time in order to observe temporal trends in recovery or deterioration in future CAP research and clinical practice.
- There were multiple observers and data collections across several centres. However, all cohorts followed the strict criteria in data collection as described in table 1. Furthermore, the data collected were objective measures such as age and urea level, thereby ruling out potential observer bias. The process of care between hospitals may be variable. There may be a variation in clinical management between different hospitals and in different healthcare setting between the various countries such as there may be important variations in antibiotic use, patterns of infective micro-organisms, care protocols and treatment guidelines. Other limitations to consider are biomarkers, healthcare provider and site characteristics. The patients were enrolled into the study at different time periods. However, this presents an opportunity to compare and contrast different healthcare systems to better understand the variation in healthcare setting and outcomes. Since all six studies used the Pneumonia Severity Index (PSI) for risk stratification, this can have implications, for example, patients who scored non-severe at initial assessment (low PSI) but might have had worse outcome are under-represented if such patients were sent home. This could contribute to attenuation of estimates in low PSI group. Nevertheless, it is possible that these patients would have presented again to the medical centre if/when deterioration occurred. Cohorts that only had data on CURB-related variables and cohorts with smaller sample sizes were not included in the ICCC, and this may introduce some degree of selection bias. Nevertheless, this should not have any effect on the internal relationship between the predictors and outcomes of interest.

BACKGROUND

Community-acquired pneumonia (CAP) is a common medical condition, with an incidence of 11.6/1000 adults per year.[1] It is one of the leading infectious causes of death worldwide[2–4] and accounts for substantial use of healthcare resources.[5] About 30% of patients with CAP require hospital admission[6] and up to one-fifth require intensive care admission.[7–9] The estimated costs for treating pneumonia exceeded $9 billion per year in the mid-1990s in the USA and exceed £441 million per year in the UK.[10 11]

The management of CAP is challenging as the outcome depends on multiple factors, such as patient characteristics, care setting, type and virulence of the infective agent, appropriate assessment and nature of healthcare intervention, such as antibiotic administration, and intensive care support, and so on. Thus, clinical determinants of outcomes in CAP have been the subject of considerable research focus over the past few decades.[12–15] Several severity scores have been developed and validated widely, with the aim of guiding the initial site of treatment (eg, home vs hospital; hospital ward vs intensive care unit (ICU)) and appropriate level of intervention, including choice and route of administration of antibiotics.[14–19] Better understanding of determinants of patient outcomes in CAP may help clinicians make better clinical decisions in future.

To date, there is no uniform agreement on the optimal severity assessment tool or an agreed definition of the term severe pneumonia.[20] Pneumonia Severity Index (PSI) was derived to identify patients with pneumonia who are at low risk for short-term mortality and potential candidates for outpatient care[14] and widely used. The British Thoracic Society endorses the use of CURB-65, which is an extensively validated score since the publication of Lim *et al*'s[15] work in stratifying risk of CAP mortality using simple criteria. Its derivative, CRB-65, has the advantage that it is simple and can be implemented without laboratory investigations.[21]

Other scores that have since been developed include SMART-COP,[18] ADROP,[22] CORB,[23] SCAP,[16] CURSI and CURASI,[24] and CURB-age,[25] among others. SMART-COP is a tool derived from an Australian study[18]; it uses systolic blood pressure, multilobar involvement, albumin levels, respiratory rate adjusted for age, heart rate, confusion, oxygen level adjusted for age and arterial pH to risk stratify for the need for intensive respiratory or vasopressor support.[18] The Japanese Respiratory Society proposed the score ADROP to risk stratify, which has been shown to yield similar results as CURB-65. ADROP uses similar parameters as CURB-65, but there are different cut-off values for age (>70 years for men, >75 years for women), dehydration (blood urea nitrogen (BUN) >210 mg/l), respiratory failure (SaO_2 <90% or PaO_2 <60 mm Hg), orientation disturbance (confusion) and low blood pressure (systolic <90 mm Hg or diastolic <60 mm Hg).[22] SCAP was developed in Spain, which suggested arterial pH <7.30, systolic blood pressure <90 mm Hg, respiratory rate >30/min, altered mental status, BUN >30 mg/dl, oxygen arterial pressure <250 mm Hg, age >80 years and multilobar/bilateral involvement to predict severe pneumonia.[16] CURSI/CURASI and CURB-age are modified versions of CURB-65 and developed in the UK where shock index (pulse rate divided by systolic blood pressure with or without consideration of temperature) is used instead of blood pressure and age in CURSI/CURASI,[24] and CURB-age used two cut-off points for urea (>7 and >11 mmol/l) and age (65 and 85 years).[25]

Several studies have also directly compared different pneumonia severity scales. Man *et al*[26] directly compared

the PSI, CURB-65 and CRB-65 in a cohort of CAP patients in Hong Kong and found that PSI and CURB-65 has similar performance at predicting 30-day mortality. Capelastegui *et al*[27] compared CURB-65 and CRB-65 in a Spanish cohort; they also found similar results using the two scales. Espana *et al*[16] tested the SCAP prediction rule in a Spanish cohort and found that it was comparable in predictive value as both the CURB-65 and PSI. Shindo *et al*[22] compared the use of ADROP and CURB-65 and found similar results. In the derivation study of SMART-COP, the new score was compared against CURB-65 and PSI and SMART-COP had higher area under the receiver operator curve in predicting need for intensive respiratory or vasopressor support.[18]

While PSI and CURB indices were widely validated, newly derived and less well-known CAP severity indices have not been validated in a large sample. We created the International CAP Collaboration Cohort (ICCC) to assess patient-level determinants of prognosis and compare the prognostic accuracy of existing pneumonia risk stratification tools for patients hospitalised with CAP. In this paper, we describe the six prospective CAP cohorts from Asia, Europe and the North America collaborating in ICCC.[14 26–30] We also provide the rationale, hypotheses and objectives of the study and describe the characteristics of the combined cohort. Finally, we discuss implications and the future direction of research using this data set.

Rationale

While there have been some recent attempts to address existing uncertainties through meta-analysis of severity assessment tools,[31 32] somewhat conflicting results arose from the quality of studies included in these meta-analyses. Loke *et al*[31] included prospective studies only, and Chalmers *et al*[32] included both prospective and retrospective studies. Another limitation of these reviews is that they had to rely on study-level aggregated data, rather than individual patient data. Furthermore, it has also been well recognised that severity measures do not capture specific patient groups. For example, there has been increasing concern with regard to suitability of CURB-65 in both older and younger patients with CAP.[33 34] A recent comprehensive review by Singanayagam *et al*[20] and a study by Aliberti *et al*[35] also highlighted the limitations of current established CAP severity assessment criteria. Therefore, it is important to better understand the determinants and outcomes of CAP in a heterogeneous patient population to improve the identification of patients with higher risk of poor outcomes, taking into account of other important factors, such as ethnicity, and healthcare systems. The rationale of ICCC is to address the specific objectives based on the hypotheses set out below by creating a CAP cohort with large sample size with adequate power. This paper aims to describe this ICCC cohort, which will test the hypotheses and describe the pooled outcomes across studies of different world regions.

Hypotheses and objectives

The hypotheses are as follows:

1. Different severity assessment tools for CAP have different advantages and disadvantages.
2. It is possible to identify patients with CAP who have been initially classified as having non-severe CAP by one scoring system but who are at risk of death.
3. It is possible to apply more than one scoring system sequentially to better identify CAP patients at high risk of mortality.
4. There are patient characteristics, which can be identified, which is associated with increased risk of death in specific patient groups.

The main objectives of the ICCC, therefore, are to:

1. compare the accuracy (sensitivity, specificity, predictive values and likelihood ratios) and discrimination (receiver operating characteristics analyses) of existing severity tools in predicting 30-day mortality and/or ICU admission;
2. explore the characteristics of patients with pneumonia with poor outcome despite who scored non-severe at initial assessment to identify relatively high-risk group of patients;
3. examine whether using sequential assessment with two separate rules (eg, one deployed as a triage test in primary care or emergency department, followed by a more specific test to guide inpatient management) would improve predictive ability;
4. evaluate risk factors for prognosis and compare the performance of existing severity rules in distinct patient subgroups, for example, Nursing Home Acquired Pneumonia, in those with chronic obstructive pulmonary disease (COPD) and people who are immunocompromised.

METHODS

Our patient population was derived from previously reported prospective CAP cohorts that were included in a meta-analysis comparing the PSI and CURB-65.[31] The published CAP literature was reviewed as described in Loke *et al*,[31] and the largest cohorts (n>1000) meeting the required standard of the review were invited to participate.[14 26–30] Each individual studies had prior respective institutional research ethics approval for their original data collection, and ICCC study was approved by the Faculty of Medicine and Health Sciences Research Ethics Committee, University of East Anglia, UK (Ref, 2011/2012-29).

The main inclusion criteria at individual patient level were adults with diagnosis of pneumonia based on the combination of clinical symptoms and signs of pneumonia (cough, sputum and fever) and radiological findings of an opacity (or opacities) on chest radiograph consistent with pneumonia. The coordinating centre (CC) from the UK prepared a standardised data sheet, and it was distributed to all collaborating centres for data entry. The variables listed in the appendix 1 were requested to all centres. The data were based on all the variables needed to calculate the PSI score as well as the

CURB-65 score, which also cover most of the variables included in less well-known criteria. Therefore, those who only reported CURB indices were not considered for inclusion into the ICCC. We identified five research groups who had relevant data on six cohorts, and all five groups replied positively to the request. Additional baseline information collected included patient comorbidities, patient residence, antibiotic treatment they received and the route of administration of antibiotics. Outcomes such as admission to ICU with or without ventilation and high dependency unit (HDU) were collected along with the main outcome of 30-day mortality.

Anonymised patient data were entered by the participating centres and returned to the CC. Data were checked and compiled by the research team at CC. Data standardisation (eg, converting to same SI units) and quality checking were centrally conducted. First, all the data were combined into a single data file with the same coding and units for each variable. Most dichotomous variables values were coded as numbers (0=no, 1=yes) and blanks for missing values. In particular, urea values were converted to BUN by multiplying by a factor of 2.8. For each variable, the values were checked for errors by considering the maximum and minimum values or values that are beyond the expected/plausible range. Finally, some variables were combined to generate new variables, including any ICU variable (ICU with ventilation and ICU without ventilation combined) and any ICU/HDU variable (any ICU and HDU admission combined).

Analytical approach

Data are presented descriptively for individual cohorts as well as the ICCC (combined cohort) for the purposes of the current report. We pooled the cohorts by simple aggregation of individual patient data rather than using any form of weighting or meta-analytic techniques to combine the study and explore the heterogeneity. We present median (IQR) values for non-normally distributed data and mean (SD) for normally distributed continuous data and numbers (percentages) for categorical data. We analysed the data using STATA V.10.0 (2009, StataCorp).

At present, we have simply pooled the data and describe the cohort in this rationale paper, but expect to use meta-analytic techniques and individual patient data approaches to better explore between cohort heterogeneity, such as ethnicity and healthcare setting, and how it may relate to outcomes. Furthermore, we should be able to explore more general issues such as how best to deal with missing data in large clinical samples (ie, complete case, dummy variables for missing data, imputation).

Overview of study designs and methods

Overall, five research teams responsible for assembling six potentially eligible cohorts were invited to participate. In all six cohorts, CAP was defined based on the presence of clinical symptoms and signs of pneumonia, and the presence of radiographic pulmonary opacity/opacities consistent with CAP, as interpreted by either the treating physician or by a staff radiologist. Patients recruited were those with CAP first presenting to an outpatient department (cohort 3) or the emergency departments (all other cohorts) (see table 1). In general, all cohorts used similar inclusion criteria with similar reliable methods to diagnose pneumonia combing both clinical evidence and radiological features of pneumonia. The ascertainment of survival at 30 days varied from telephone interviews to record linkage using administrative healthcare databases. Four of six cohorts recruited participants from multiple centres, while two (Hong Kong and Spain) involved only a single centre.

Baseline patient characteristics

Table 2 shows the patient-related sample characteristics. The median ages of cohorts ranged between 59 and 76 years at the time of enrolment (median age in this pooled data set is 71 years; IQR 52−80 years), of which 54% were men. Data on race and ethnicity were available in four cohorts. Data on smoking and alcohol use were available for 54% and 74%, respectively, of the patients. Only 1% of the ICCC patient population has missing data for whether they were admitted from nursing home facility or elsewhere.

Table 3 shows the prevalence of comorbid conditions. The most commonly captured comorbid conditions were COPD, coronary artery disease and stroke/cerebrovascular disease. Five cohorts have available data on background dementia (total n=832 of 12 021, 0.07%), and all have information on presence or absence of malignant disease (total n=912 of 13 744, 0.07%).

Table 4 shows clinical and laboratory characteristics. There were no material differences in key clinical characteristics among cohorts, except for prevalence of confusion, which was relatively lower in cohort 1, and mean systolic blood pressure that was notably higher in cohort 5 where the median age of the cohort was relatively higher than other cohorts. All six studies used the PSI for risk stratification, and two cohorts (cohorts 2 and 5) also used the CURB-65. Overall, as defined within each cohort, 6159 (44%) patients had severe pneumonia by PSI class IV/V.

All cohorts had complete data on 30-day mortality outcome but recorded ICU and HDU admission in various format/coding. Generally, all cohorts have complete data for ICU and/or HDU outcome (only 1 with missing data). The 30-day mortality ranged between 4% and 11%, with an overall ICCC 30-day mortality of 8% (n=1036). Admission to intensive care or HDU was also 8% (1059).

Missing data and data that were not recorded

Overall, across all cohorts, there were 12.2% of data that were requested from each cohort that were not recorded and maximum of 6% of data were missing (see appendix 2).

DISCUSSION

The ICCC is a multicentre/multiethnic cohort where all collaborating groups defined pneumonia based on clinical features and the presence of CXR evidence of

Table 1 Overview of study designs and methods

	Year of establishment/ location	Type of healthcare setting	Inclusion/exclusion criteria	CAP definition	Outcome ascertainment methods
Cohort 1	GenIMS cohort, November 2001–2003, 28 hospitals in southwestern Pennsylvania, Connecticut, southern Michigan and western Tennessee, USA	Hospital emergency departments	Age >18 years with CAP. Excluded were those transferred from another hospital, discharged from hospital within previous 10 days, receiving chronic mechanical ventilation, with cystic fibrosis, active tuberculosis, admitted for palliative care, previous enrolled in GenIMS study, incarcerated or pregnant	Clinical and radiological diagnosis (one or more symptoms suggestive of pneumonia and radiographic evidence of pneumonia within 24 h of presentation)	Data were collected by structured patient or proxy interviews, bedside assessment, medical records abstraction and telephone call and National Death Index search for those discharged
Cohort 2	January 2001–December 2007, a single hospital in Galdakao, Spain	Hospital emergency department	Age >18 years with CAP. Excluded were those who were HIV positive, immunosuppressed or had been hospitalised for previous 14 days	New pulmonary infiltrate on chest radiograph and symptoms consistent with pneumonia, including cough, dyspnoea, fever and/or pleuritic chest pain	Data were recorded from medical records and follow-up was conducted either by medical examination at hospital or by telephone call
Cohort 3	PORT cohort, October 1991–March 1994, five medical institutions in Pittsburgh and Boston, USA and Halifax, Nova Scotia, Canada	Outpatients and inpatients	Age >18 years with CAP, informed consent for baseline and follow-up interviews. Excluded were those discharged from an acute care hospital within 10 days before presentation with pneumonia or those who are HIV-positive	One or more symptoms of suggestive of pneumonia with radiographic evidence of pneumonia. Screened ~13 000	Data collected by patient or proxy interview by clinical research assistants
Cohort 4	November 2000–November 2002, at all six sites in Edmonton, Alberta, Canada (population-based)	Six emergency departments and affiliated hospitals: two tertiary, two secondary and two smaller community hospitals	Patients with CAP including nursing home patients. Excluded were those directly admitted to intensive care units, hospitalised previous 10–14 days, tuberculosis, cystic fibrosis, pregnant, nursing mothers and immunosuppression, including HIV infection. Patients treated according to a previously validated clinical pathway	Two or more symptoms of pneumonia (cough, pleuritic chest pain, shortness of breath, temperature >38°C, crackles or bronchial breathing) and radiographic evidence as interpreted by the treating physicians	Prospective data collection including telephone interviews, ward visits, chart reviews and 5-year follow-up using administrative linked healthcare databases

Continued

Table 1 Continued

	Year of establishment/ location	Type of healthcare setting	Inclusion/exclusion criteria	CAP definition	Outcome ascertainment methods
Cohort 5	January 2004–June 2005, a single hospital in Hong Kong	Hospital emergency department	Age >17 years with CAP. Excluded were immunosuppressed, pulmonary tuberculosis and patients admitted to hospital within the previous 14 days	Symptoms of acute infection and acute infiltrate on a chest radiograph in a patient not hospitalised for more than 14 days before onset of symptoms	Data recorded by standard questionnaire by a trained research nurse
Cohort 6	ED-CAP cohort, January 2001–December 2001, 32 hospitals in Connecticut and Pennsylvania, USA	Hospital emergency departments	Age >18 years with CAP. Excluded were patients who had hospital-acquired pneumonia, cystic fibrosis, pulmonary tuberculosis or were immunosuppressed, incarcerated, homeless, pregnant, previously enrolled or had psychosocial conditions or substance abuse problems that were incompatible with treatment, enrolment and follow-up	Clinical diagnosis of pneumonia and new pulmonary infiltrate identified on radiography	Research staff collected data with structured review of patient's medical records and telephone interviews

CAP, community-acquired pneumonia.

Table 2 Patient-related characteristics of individual collaborating cohorts and the combined cohort (ICCC)

Variables	Cohort 1 (n=1847)	Cohort 2 (n=2110)	Cohort 3 (n=2287)	Cohort 4 (n=3415)	Cohort 5 (n=1014)	Cohort 6 (n=3201)	ICCC (n=13 874)
Age (years)	65 (47–83)	71 (54–87)	56 (35–77)	69 (51–87)	74 (62–86)	63 (43–83)	65 (46–85)
Sex							
Men	950 (51.4%)	1376 (65.2%)	1144 (50.0%)	1803 (52.8%)	645 (63.6%)	1554 (48.5%)	7472 (53.9%)
Women	897 (48.6%)	734 (34.8%)	1143 (50.0%)	1612 (47.2%)	369 (36.4%)	1647 (51.4%)	6402 (46.1%)
Ethnicity							
White	1456 (78.8%)	–	1949 (85.2%)	0 (0%)	0 (0%)	2791 (87.9%)	6196 (44.7%)
Black	305 (16.5%)	–	292 (12.7%)	0 (0%)	0 (0%)	309 (9.1%)	906 (6.5%)
Asian	5 (0%)	–	16 (0.7%)	0 (0%)	1014 (100%)	81 (2.4%)	1116 (8.0%)
Hispanic	58 (2.7%)	–	0 (0%)	0 (0%)	0 (0%)	8 (0.2%)	66 (0.5%)
Non-aboriginal	0 (0%)	–	0 (0%)	3293 (96.4%)	0 (0%)	0 (0%)	3293 (23.7%)
Aboriginal	0 (0%)	–	0 (0%)	122 (3.6%)	0 (0%)	0 (0%)	122 (0.9%)
Other	23 (1.2%)	–	30 (1.3%)	0 (0%)	0 (0%)	11 (0.3%)	64 (0.5%)
Missing/NA	0 (0%)	2110 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)	2111 (15.2%)
Smoking status*							
Non-smoker	92 (5.0%)	246 (11.7%)	1664 (72.8%)	1454 (42.6%)	885 (87.3%)	–	4340 (31.3%)
Ex-smoker	–	168 (8.0%)	–	939 (27.5%)	–	–	1107 (8.0%)
Smoker	–	89 (4.2%)	–	1023 (29.9%)	–	–	1112 (8.0%)
Smoking history	232 (12.6%)	–	604 (26.4%)	–	129 (12.7%)	–	965 (7.0%)
Missing/NA	1523 (82.5%)	1607 (76.2%)	19 (0.8%)	0 (0%)	0 (0%)	3201 (100%)	6350 (45.8%)
Alcohol use							
Yes	1186 (64.2%)	107 (5.1%)	357 (15.6%)	245 (7.2%)	9 (0.9%)	–	1904 (13.7%)
No	642 (34.8%)	1983 (94.0%)	1562 (68.3%)	3170 (92.8%)	999 (98.5%)	–	8356 (60.2%)
Missing/NA	19 (1.0%)	20 (0.9%)	368 (16.1%)	0 (0%)	6 (0.6%)	3201 (100%)	3614 (26.0%)
Nursing home							
Yes	81 (4.3%)	173 (8.2%)	195 (8.5%)	637 (21.9%)	0 (0%)	130 (4.1%)	1216 (8.8%)
No	1628 (88.1%)	1937 (91.8%)	2092 (91.5%)	2778 (78.1%)	1014 (100%)	3071 (95.9%)	12 520 (90.2%)
Missing	138 (7.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	138 (1.0%)

Values presented are median (IQR) for normally distributed and non-normally distributed continuous data (other continuous variables) and number (%) for all categorical data. Percentages may not sum to 100% due to rounding.
*Some cohorts (cohorts 1, 3 and 5 recorded smoking history without differentiating between ex- and current smokers).
ICCC, International Community-Acquired Pneumonia (CAP) Collaboration Cohort; NA, not available.

Table 3 Distribution of selected comorbid conditions in individual collaborating cohorts and the combined cohort

Comorbidities	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	ICCC
COPD							
Yes	–	569 (27.0)	588 (25.7)	638 (18.7)	10 (1.0)	1034 (32.3)	2839 (20.5)
No	–	1541 (73.0)	1687 (73.8)	2777 (81.3)	1004 (99.0)	2167 (67.7)	9176 (66.1)
Missing/NA	1847 (100)	0 (0)	12 (0.5)	0 (0)	0 (0)	0 (0)	1859 (13.4)
Asthma							
Yes	–	–	–	440 (12.9)	1 (0.01)	–	441 (3.2)
No	–	–	–	2975 (87.1)	1013 (99.9)	–	3988 (28.7)
Missing/NA	1847 (100)	2110 (100)	2287 (100)	0 (0)	0 (0)	3201 (100)	9445 (68.1)
Pleural effusion							
Yes	201 (10.9)	219 (10.4)	204 (8.9)	745 (21.8)	112 (11.0)	461 (14.4)	1942 (14.0)
No	1523 (82.5)	1891 (89.6)	1976 (86.4)	2670 (78.2)	902 (89.0)	2715 (84.8)	11 677 (84.2)
Missing/NA	123 (6.7)	0 (0)	107 (4.7)	0 (0)	0 (0)	25 (0.8)	255 (1.8)
Heart failure							
Yes	294 (15.9)	163 (7.7)	253 (11.1)	727 (21.3)	121 (11.9)	427 (13.3)	1985 (14.3)
No	1429 (77.4)	1947 (92.3)	2030 (88.8)	2688 (78.7)	893 (88.1)	2774 (86.7)	11 761 (84.8)
Missing/NA	124 (6.7)	0 (0)	4 (0.2)	0 (0)	0 (0)	0 (0)	128 (0.9)
Coronary artery disease							
Yes	–	215 (10.2)	406 (17.8)	910 (26.6)	–	667 (20.8)	2198 (15.8)
No	–	1895 (89.8)	1880 (82.2)	2505 (73.4)	–	2534 (79.2)	8814 (63.5)
Missing/NA	1847 (100)	0 (0)	1 (<0.1)	0 (0)	1014 (100)	0 (0)	2862 (20.6)
Cerebrovascular disease							
Yes	150 (8.1)	200 (9.5)	210 (9.2)	306 (9.0)	143 (14.1)	267 (8.3)	1276 (9.2)
No	1574 (85.2)	1910 (90.5)	2076 (90.8)	3109 (91.0)	871 (85.9)	2934 (91.7)	12 474 (89.9)
Missing	123 (6.7)	0 (0)	1 (<0.1)	0 (0)	0 (0)	0 (0)	124 (0.9)
Liver disease							
Yes	34 (1.8)	76 (3.6)	33 (1.4)	117 (3.4)	17 (1.7)	28 (0.9)	305 (2.2)
No	1690 (91.5)	2034 (96.4)	2251 (98.6)	3298 (96.6)	997 (98.3)	3173 (99.1)	13 443 (96.9)
Missing	123 (6.7)	0 (0)	3 (0)	0 (0)	0 (0)	0 (0)	126 (0.9)
Renal disease							
Yes	89 (4.8)	160 (7.6)	153 (6.7)	490 (14.3)	106 (10.5)	108 (3.4)	1106 (8.0)
No	1635 (88.5)	1950 (92.4)	2131 (93.2)	2925 (85.7)	908 (89.5)	3093 (96.6)	12 642 (91.1)
Missing	123 (6.7)	0 (0)	3 (0.1)	0 (0)	0 (0)	0 (0)	126 (0.9)
Cancer							
Yes	87 (4.7)	131 (6.2)	109 (4.8)	499 (14.6)	1 (0.1)	85 (2.7)	912 (6.6)
No	1637 (88.6)	1979 (93.8)	2171 (94.9)	2916 (85.4)	1013 (99.9)	3116 (97.3)	12 832 (92.5)
Missing	123 (6.7)	0 (0)	7 (0.3)	0 (0)	0 (0)	0 (0)	130 (0.9)
Diabetes							
Yes	–	309 (14.6)	235 (10.3)	190 (5.6)	–	625 (19.5)	1359 (9.8)
No	–	1801 (85.4)	2052 (89.7)	3225 (94.4)	–	2576 (80.5)	9654 (69.6)
Missing/NA	1847 (100)	0 (0)	0 (0)	0 (0)	1014 (100)	0 (0)	2861 (20.6)
Dementia							
Yes	–	276 (13.1)	141 (6.2)	265 (7.8)	22 (2.2)	128 (4.0)	832 (6.0)
No	–	1834 (86.9)	2141 (93.6)	3150 (92.2)	992 (97.8)	3072 (96.0)	11 189 (80.6)
Missing/NA	1847 (100)	0 (0)	5 (0.2)	0 (0)	0 (0)	1 (<0.1)	1853 (13.4)
Seizure							
Yes	–	–	91 (4.0)	151 (4.4)	2 (0.2)	–	244 (1.8)
No	–	–	2196 (96.0)	3264 (95.6)	1012 (99.8)	–	6272 (45.9)
Missing/NA	1847 (100)	2110 (100)	0 (0)	0 (0)	0 (0)	3201 (100)	7158 (52.3)

Values presented are number (%). Percentages may not sum to 100% due to rounding.
COPD, chronic obstructive pulmonary disease; ICCC, International Community-Acquired Pneumonia (CAP) Collaboration Cohort; NA, not available.

pneumonia. The major strengths of ICCC are prospective study design, inclusion of CAP patients spanning across wide age range, ethnicity, different healthcare settings and large sample size. Potential areas of improvement in assessment of CAP might be identification of at-risk patients with pneumonia who have been initially assessed as non-severe CAP. With large sample size, ICCC may provide an opportunity to identify characteristics of such individuals. Based on this work, risk assessment may be applied at more than one point in time in order to observe temporal trends in recovery or deterioration in future CAP research and clinical practice.

Furthermore, despite there being some degree of missing data, the large sample size of ICCC enables us to examine the CAP outcome in patient populations with specific characteristics of interest. Examples of such

Table 4 Selected clinical and laboratory characteristics of individual collaborating cohorts and the combined cohort

Variable	Cohort 1 (n=1847)	Cohort 2 (n=2110)	Cohort 3 (n=2287)	Cohort 4 (n=3415)	Cohort 5 (n=1014)	Cohort 6 (n=3201)	ICCC (n=13 874)
Confusion							
Yes	57 (3.1)	269 (12.7)	238 (10.4)	701 (20.5)	92 (9.1)	121 (3.8)	1478 (10.7)
No	1689 (91.4)	1841 (87.3)	2047 (89.5)	2714 (79.5)	922 (90.9)	3080 (96.2)	12 293 (88.6)
Missing	101 (5.5)	0 (0)	2 (<0.1)	0 (0)	0 (0)	0 (0)	103 (0.7)
BUN							
Continuous	–	28 (12–43) (n=2110)	23 (5–41) (n=1500)	26 (5–47) (n=2930)	23 (7–39) (n=1014)	21 (7–36) (n=2518)	–
Categorical							
≥30 (mg/dl)	264 (14.3)	660 (31.3)	326 (14.3)	748 (21.8)	198 (19.5)	430 (13.4)	2626 (18.8)
<30 (mg/dl)	1456 (78.8)	1450 (68.7)	1174 (51.3)	2185 (64.1)	816 (80.5)	2088 (65.2)	9169 (66.1)
Missing	127 (6.9)	0 (0)	787 (34.4)	482 (14.1)	0 (0)	683 (21.3)	2079 (15.0)
Urea (mmol/l)	–	9.9 (4.4–15.5) (n=2110)	8.2 (1.8–14.6) (n=1500)	9.3 (1.9–16.7) (n=2930)	8.3 (2.4–14.1) (n=1014)	7.7 (2.4–12.8) (n=2518)	–
Respiratory rate/min							
Continuous	–	23 (16–30) (n=2110)	24 (15–33) (n=1805)	26 (18–34) (n=3294)	24 (19–30) (n=1014)	23 (17–28) (n=3201)	–
Respiratory rate high	24 (20–28)	–	–	–	–	–	–
Respiratory rate low	20 (18–20)	–	–	–	–	–	–
Categorical							
>30 (/min)	0 ()	275 (13.0)	269 (11.8)	787 (23.1)	125 (12.3)	287 (9.0)	1743 (12.6)
≤30 (/min)	0 (0)	1835 (87.0)	1525 (67.0)	2504 (73.4)	889 (87.7)	2896 (90.5)	9649 (69.6)
Missing/NA	1847 (100)	0 (0)	482 (21.2)	121 (3.5)	0 (0)	18 (0.6)	2468 (17.8)
Systolic BP (mm Hg)							
Continuous	–	132 (27) (n=2106)	134 (28) (n=2020)	134 (27) (n=3371)	145 (28) (n=1014)	138 (26) (n=3192)	– (n=13 874)
Categorical							
≥90 mm Hg	1650 (89.3)	1999 (94.9)	1971 (86.2)	3282 (96.2)	1002 (98.8)	3140 (98.1)	13 044 (94.1)
<90 mm Hg	68 (3.7)	107 (5.1)	49 (2.1)	89 (2.6)	12 (1.2)	52 (1.6)	377 (2.7)
Missing	129 (7.0)	0 (0)	267 (11.7)	41 (1.2)	0 (0)	9 (0.3)	446 (3.2)
Diastolic BP (mm Hg)	–	72 (15) (n=2074)	76 (15) (n=1936)	75 (16) (n=3365)	73 (16) (n=1014)	75 (15) (n=3156)	–
Diastolic BP high	77 (62–92)	–	–	–	–	–	–
Diastolic BP low	63 (49–79)	–	–	–	–	–	–
Temperature (°C)	–	37.5 (1.0) (n=2110)	37.6 (1.1) (n=2018)	37.3 (1.2) (n=3369)	37.9 (1.1) (n=1014)	37.6 (1.1) (n=3168)	–
Heart rate (beats per minute)	–	98 (21) (n=2110)	99 (20) (n=1971)	101 (22) (n=3401)	102 (20) (n=1014)	99 (20) (n=3197)	–
Heart rate high	104 (84–125)	–	–	–	–	–	–
Heart rate low	85 (68–102)	–	–	–	–	–	–

Continued

Table 4 Continued

Variable	Cohort 1 (n=1847)	Cohort 2 (n=2110)	Cohort 3 (n=2287)	Cohort 4 (n=3415)	Cohort 5 (n=1014)	Cohort 6 (n=3201)	ICCC (n=13 874)
PaO_2 (mm Hg)	–	61 (47–75) (n=2050)	70 (41–100) (n=959)	68 (37–100) (n=2278)	93 (64–122) (n=1013)	74 (37–112) (n=593)	–
pH	–	7.45 (7.38–751) (n=2052)	7.45 (7.37–7.51) (n=959)	7.43 (7.33–7.50) (n=2248)	7.41 (7.32–7.49) (n=1014)	7.42 (7.35–7.49) (n=593)	–
Glucose (mg/dl)	–	151 (81–220) (n=2108)	141 (72–209) (n=1459)	142 (76–209) (n=2987)	137 (84–191) (n=1014)	123 (74–214) (n=2510)	–
Glucose high	147 (67–227)	–	–	–	–	–	–
Glucose low	135 (75–196)	–	–	–	–	–	–
Sodium (mmol/l)	–	136 (131–141) (n=2110)	137 (132–142) (n=1495)	137 (132–143) (n=3272)	136 (131–140) (n=1013)	137 (133–141) (n=2524)	–
Sodium high	137 (132–142)	–	–	–	–	–	–
Sodium low	137 (132–142)	–	–	–	–	–	–

Values presented are mean (SD) for normally distributed (systolic BP, diastolic BP, temperature and heart rate) and median (IQR) for non-normally distributed continuous data (other continuous variables) and number (%) for all categorical data. Percentages may not sum to 100% due to rounding.
BP, blood pressure; BUN, blood urea nitrogen; ICCC, International Community-Acquired Pneumonia (CAP) Collaboration Cohort; NA, not available.

groups include those with COPD and cancer and patients admitted from nursing homes. Another important aspect in estimating prognosis in patients with CAP is with regard to older people whose mortality outcome is substantially higher. The ICCC provides a large prospective cohort of older people aged 65 years and older and subset of extremely old patients (aged 85 + years). The usefulness of different assessment scores and impact of co-existing comorbidities can be further examined to enhance the understanding of prognosis in this growing patient population due to current and expected demographics.

In addition, there have been studies that evaluate mortality risk scores in specific patient populations with CAP. The elderly represent a distinct population group, and the SOAR score has been developed specifically to predict mortality.[36] The MELD-CAP score has been show to outperform CURB-65 and PSI in patients with cirrhosis.[37] For patients admitted to the ICUs, the PIRO score has been developed.[19] There have also been other studies, which look at predictive value of pneumonia severity scores in other populations, including patients with H1N1 infection,[38] HIV infection[39] and chronic kidney disease.[40] Therefore, ICCC also provides a large cohort, which may be able to address the value of different pneumonia severity scores in specific populations.

Our study has limitations. There were multiple observers and data collections across several centres. However, all cohorts followed the strict criteria in data collection as described in table 1. Furthermore, the data collected were objective measures such as age and urea level, thereby ruling out potential observer bias. The process of care between hospitals may be variable. There may be a variation in clinical management between different hospitals and in different healthcare setting between the various countries such as there may be important variations in antibiotic use, patterns of infective micro-organisms, care protocols and treatment guidelines. Other limitations to consider are biomarkers, healthcare provider and site characteristics. The patients were enrolled into the study at different time periods. However, this presents an opportunity to compare and contrast different healthcare systems to better understand the variation in healthcare setting and outcomes. Since all six studies used the PSI for risk stratification, this can have implications, for example, patients who scored non-severe at initial assessment (low PSI) but might have had worse outcome are under-represented if such patients were sent home. This could contribute to attenuation of estimates in low PSI group. Nevertheless, it is possible that these patients would have presented again to the medical centre if/when deterioration occurred. Cohorts that only had data on CURB-related variables and cohorts with smaller sample sizes were not included in the ICCC, and this may introduce some degree of selection bias. Nevertheless, this should not have any effect on the internal relationship between the predictors and outcomes of interest.

In summary, the ICCC as described in this report will be able to provide better understanding of determinants of outcomes in CAP. Examples of such development include comparison of commonly and less commonly known CAP severity scoring systems and identification of characteristics of CAP patients with poor outcome (30-day mortality) despite non-severe status of severity score. In view of the large sample size, the ICCC cohort will be able to provide the determinants of outcomes in patient groups with specific conditions such as cardiovascular and respiratory diseases taking into account case mix and individual prognostic indicators. The ICCC cohort will be of benefit to the CAP research community and help define a future agenda for research, as well as helping clinicians make better clinical decisions for patients with CAP.

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APPENDIX 1

Variables requested from each collaborating cohort

- Age (continuous)
- Gender (male/female)
- BMI
- Race
- Smoking
- Alcohol
- Illicit drug use
- Altered mental status (yes/no)
- Altered mental status (abbreviated mental test score if measured as continuous)
- Urea or BUN levels (continuous)
- BUN category (as per PSI using cut-off point of 30; ≤30 vs >30)
- Respiratory rate (continuous)
- Respiratory rate (categorical as per PSI using cut-off point of 30; <30 vs ≥30)
- Systolic blood pressure (continuous)
- Systolic blood pressure (categorical as per PSI using cut-off point of 90; <90 vs ≥90)
- Diastolic blood pressure (continuous) (for CURB-65/CRB calculation)
- Pneumonia Severity Index score (sum)

Other parameters in Pneumonia Severity Index

- Residence (categorical data with coding)
- Nursing home residence (yes/no)
- Renal disease (yes/no)
- Liver disease (yes/no)
- CHF (yes/no)
- Cerebrovascular disease (yes/no)
- Neoplasia (yes/no)
- Temperature (continuous)
- Temperature (categorical as per PSI; <35 or ≥40 vs 35–40)
- Heart rate (continuous)
- Heart rate (categorical as per PSI; <125 vs ≥125)
- pH (continuous)
- pH (categorical as per PSI; <7.35 vs ≥7.35)
- PO2 (continuous)
- PO2 (categorical as per PSI; <60 vs ≥60)
- Saturation (continuous)
- Saturation (categorical as per PSI using cut-off point of 90; <90 vs ≥90)
- Sodium (Na) (continuous)
- Sodium (categorical as per PSI using cut-off point of 130; <130 vs ≥130)
- Haematocrit (continuous)
- Haematocrit (categorical as per PSI using cut-off point of 30; <30 vs ≥30)
- Glucose (continuous)
- Glucose (categorical as per PSI using cut-off point of 250; ≤250 vs >250)
- Pleural effusion (yes/no)
- Comorbidities (others)
- Antibiotic use (in text)
- Route (IV/oral)
- Whether they completed the study (lost to follow-up) (yes/no)
- Whether they died during the 30-day follow-up (yes/no)
- Whether they died during admission (in hospital death) (yes/no)
- Date of death (dd/mm/yyyy format)
- Death within 30 days (yes/no)
- Whether they were admitted to intensive care unit (for ventilation) (yes/no)
- Whether they were admitted to high dependency unit (yes/no)
- Whether they were admitted to ICU without ventilatory support (yes/no)

APPENDIX 2
Data not recorded or missing

Variable	Cohort 1 (n=1847)		Cohort 2 (n=2110)		Cohort 3 (n=2287)		Cohort 4 (n=3415)		Cohort 5 (n=1014)		Cohort 6 (n=3201)	
	Not recorded	Missing	Not recorded	Missing	Not recorded	Missing	Not recorded	Missing	Not recorded	Missing	Not recorded	Missing
Age	N	0	N	0	N	0	N	0	N	0	N	0
Sex	N	0	N	0	N	0	N	0	N	0	N	0
Ethnicity	N	0	Y	NA	N	0	N	0	N	0	N	1
Smoking	N	1523	N	1607	N	19	N	0	N	0	Y	NA
Alcohol	N	19	N	20	N	368	N	0	N	6	Y	NA
Nursing home	N	138	N	0	N	0	N	0	N	0	N	0
COPD	Y	NA	N	0	N	12	N	0	N	0	N	0
Asthma	Y	NA	Y	NA	Y	NA	N	0	N	0	Y	NA
Pleural effusion	N	123	N	0	N	107	N	0	N	0	N	25
Heart failure	N	124	N	0	N	4	N	0	N	0	N	0
CAD	Y	NA	N	0	N	1	N	0	Y	NA	N	0
CVD	N	123	N	0	N	1	N	0	N	0	N	0
Liver disease	N	123	N	0	N	3	N	0	N	0	N	0
Renal disease	N	123	N	0	N	3	N	0	N	0	N	0
Cancer	N	123	N	0	N	7	N	0	N	0	N	0
Diabetes	Y	NA	N	0	N	0	N	0	Y	NA	N	0
Dementia	Y	NA	N	0	N	5	N	0	N	0	N	1
Seizure	Y	NA	Y	NA	N	0	N	0	N	0	N	0
Confusion	N	101	N	0	N	2	N	0	N	0	N	0
BUN	N	127	N	0	N	787	N	482	N	0	N	683
Urea	Y	NA	N	0	N	787	N	485	N	0	N	683
Resp	N	8	N	0	N	482	N	121	N	0	N	683
sBP	N	129	N	0	N	267	N	41	N	0	N	9
dBP	N	4	N	46	N	351	N	50	N	0	N	45
Temp	Y	NA	N	0	N	269	N	46	N	0	N	33
HR	N	1	N	0	N	316	N	14	N	0	N	4
PaO_2	N	123	N	60	N	1328	N	1137	N	1	N	2608
pH	Y	NA	N	58	N	1328	N	1167	N	0	N	2608
Glucose	N	190	N	2	N	828	N	428	N	0	N	691
Na	N	171	N	0	N	792	N	143	N	1	N	677
ICU/vent	Y	NA	N	0	N	0	N	0	N	0	Y	NA
ICU/any	N	0	N	0	N	0	N	0	N	0	N	9
HDU	Y	NA	N	0	Y	NA	Y	NA	N	1	Y	NA
ICU/HDU	N	0	N	0	N	0	N	0	N	0	N	0
Death	N	0	N	0	N	0	N	0	N	0	N	56

BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; dBP, diastolic blood pressure; HDU, high dependency unit; HR, heart rate; ICU, intensive care unit; N, no; NA, not applicable; sBP, systolic blood pressure; Y, yes.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	7-8
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	10-13
Objectives	3	State specific objectives, including any prespecified hypotheses	14
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 Table 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	15-16
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Appendix Tables
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	16-17
Bias	9	Describe any efforts to address potential sources of bias	19, Appendix 2
Study size	10	Explain how the study size was arrived at	17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	16-17
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Appendix 2
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	17-18
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1, 2 and 3
		(b) Indicate number of participants with missing data for each variable of interest	Appendix 2
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8, 18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	20-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for exposed and unexposed groups.