Infection (2019) 47:617–627
https://doi.org/10.1007/s15010-019-01299-1

ORIGINAL PAPER

Utility of predictive tools for risk stratification of elderly individuals with all-cause acute respiratory infection

Allison S. Bloom[1] · Sunil Suchindran[2] · Julie Steinbrink[3] · Micah T. McClain[2,3,4]

Received: 7 September 2018 / Accepted: 18 March 2019 / Published online: 30 March 2019

Abstract

Purpose A number of scoring tools have been developed to predict illness severity and patient outcome for proven pneumonia, however, less is known about the utility of clinical prediction scores for all-cause acute respiratory infection (ARI), especially in elderly subjects who are at increased risk of poor outcomes.

Methods We retrospectively analyzed risk factors and outcomes of individuals ≥ 60 years of age presenting to the emergency department with a clinical diagnosis of ARI.

Results Of 276 individuals in the study, 40 had proven viral infection and 52 proven bacterial infection, but 184 patients with clinically adjudicated ARI (67%) remained without a proven microbial etiology despite extensive clinical (and expanded research) workup. Patients who were older, had multiple comorbidities, or who had proven bacterial infection were more likely to require hospital and ICU admission. We identified a novel model based on 11 demographic and clinical variables that were significant risk factors for ICU admission or mortality in elderly subjects with all-cause ARI. As comparators, a modified PORT score was found to correlate more closely with all-cause ARI severity than a modified CURB-65 score (r, 0.54, 0.39). Interestingly, modified Jackson symptom scores were found to inversely correlate with severity (r, −0.34) but show potential for differentiating viral and bacterial etiologies.

Conclusions Modified PORT, CURB-65, Jackson symptom scores, and a novel ARI scoring tool presented herein all offer predictive ability for all-cause ARI in elderly subjects. Such broadly applicable scoring metrics have the potential to assist in treatment and triage decisions at the point of care.

Keywords Aging · Respiratory infection · Viral infection · Pneumonia

Introduction

Respiratory infections are widespread throughout the United States and account for a large percentage of outpatient and hospital visits annually. In 2017, influenza alone was one of the leading causes of mortality in the United States, accounting for over 79,000 total deaths [1]. The burden of these infections and corresponding complications is particularly high among adults 65 years and older, who face increased disease susceptibility and higher hospitalization and mortality rates following respiratory illnesses [2–8]. This burden of disease increases with age, with individuals 85 years and older being 16–32 times more likely to die of an influenza-associated illness compared to individuals age 65–69 [4]. This trend towards more severe disease in the elderly is consistent across both viral and bacterial etiologies of ARI.

Distinct causes of respiratory infection are difficult to differentiate based on clinical presentation alone, which can

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s15010-019-01299-1) contains supplementary material, which is available to authorized users.

✉ Allison S. Bloom
allisonsbloom@gmail.com

✉ Micah T. McClain
micah.mcclain@duke.edu

[1] Duke University School of Medicine, Durham, NC, USA

[2] Center for Applied Genomics and Precision Medicine, Department of Medicine, Duke University, Durham, NC, USA

[3] Division of Infectious Diseases, Duke University Medical Center, Durham, NC, USA

[4] Durham Veteran's Affairs Medical Center, Durham, NC, USA

lead to a time and cost-consuming clinical workup. Of individuals requiring hospitalization for community-acquired pneumonia, it has been estimated that as few as 30% of those with radiographic evidence of pneumonia and specimens available for testing have a pathogen detected despite modern diagnostic tests [3, 5, 9, 10]. Furthermore, even when an etiologic agent is identified predicting clinical progression and outcomes for appropriate patient disposition, allocation of resources, and antibiotic stewardship continues to remain problematic [11]. These challenges often lead to delays in patient care, inappropriate antibiotic usage, and poor patient outcomes [12].

To aid in clinical decision making, several widely used metrics have been developed to predict illness severity and patient outcomes [13–19]. However, many of these prognostic scoring tools are intended for use in patients presenting with syndromes specifically suggestive of community-acquired pneumonia, including the British Thoracic Society (BTS)-recommended CURB-65 score [14, 16, 18], and the Pneumonia Severity index (PSI), developed by the Pneumonia Outcome Research Team (PORT) [9, 17]. When focused on the performance of decision tools with advancing age, CURB-65 and CORB, a decision tool for use in the emergency department, were found to perform well among elderly individuals (median age of 83) with suspected pneumonia, but little has been done to assess their utility in the broader clinical syndrome of ARI [19, 20].

Although the focus has historically been on pneumonia, research into predictive metrics for elderly individuals with all causes of respiratory illness is essential due to the potential for overlapping clinical syndromes. Development of a broadly applicable outcome prediction tool from commonly assessed characteristics and laboratory values would assist with antibiotic stewardship, patient triage, and overall patient outcome among a high-risk population.

The present study aimed to characterize elderly individuals presenting to the emergency department with symptoms consistent with an acute respiratory illness and compare the utility of risk stratification tools developed for individuals with community-acquired pneumonia to a novel metric for all causes of acute respiratory illness.

Methods

Patient selection

Patients were identified from those previously enrolled in the Emergency Departments of Duke University Medical Center (Durham, NC), the Durham VA Medical Center (Durham, NC), UNC Health Care (Chapel Hill, NC) or Henry Ford Hospital (Detroit, MI) as part of the Community-Acquired Pneumonia and Sepsis Outcome Diagnostics (CAPSOD) study or the Duke Emergency Department study from 2006 to 2014 [21–25]. All studies were reviewed and approved by appropriate Institutional Review Boards and in accordance with the Declaration of Helsinki. All patients, or a legally authorized representative, provided written informed consent prior to enrollment. Patients were eligible for enrollment in the parent studies if they had a known or suspected infection and the presence of at least two SIRS criteria (temperature ≤ 36 °C or ≥ 38 °C, heart rate ≥ 90 bpm, respiratory rate ≥ 20 breaths/min or $PaCO_2 < 32$ mmHg, and white blood cell count $\geq 12{,}000$ or ≤ 4000 cells/mm^3 or $> 10\%$ neutrophil bands forms) or clinician diagnosed respiratory infection [21–26]. For the current analysis, we selected all patients 60 years of age and above with adjudication of known or suspected viral or bacterial acute respiratory infection. Patients were excluded for evidence of non-respiratory co-infection.

Data collection

Patient demographics, past medical history and physical examination were recorded at the time of enrollment for all individuals. Collection of modified Jackson symptom score, based on the scoring criteria developed by Jackson et al. [27], at time of enrollment was limited to a single study [22]. Eight patient symptoms: nasal discharge, nasal congestion, sneezing, cough, malaise, throat discomfort, fever and or chills, and headache, were used in the calculation of the modified Jackson symptom score. Patient outcome data was gathered at least 28 days after enrollment. Patients with initial hospital stay extending to or beyond the time of follow up had length of stay documented as 28 days. 28-day mortality was documented if the patient died during the hospitalization or within the follow-up period. Patients were categorized into one of four outcome categories based on severity of illness. The categories include: (1) outpatient treatment, (2) inpatient treatment with length of hospital stay of 1–2 days (mild), (3) inpatient treatment with length of hospital stay of 3 or more days (moderate), (4) inpatient treatment with ICU requirement and/or 28-day mortality (severe). Modified PORT scores were calculated for each patient at time of presentation using the prediction rule developed by Fine et al. [17]. Four variables included in the PORT score calculation: nursing home resident, altered mental status, $pH < 7.35$ and $pO_2 < 60$ mmHg, were excluded due to lack of collection or missing data. Modified CURB-65 scores were calculated at time of presentation using the metric developed by Lim et al. [18]. Confusion was not included in our calculation due to inability to reliably capture it retrospectively from our electronic medical record.

Clinical adjudication

As a retrospective study, diagnostic workup and treatment plans for all subjects were determined by primary medical teams in accordance with standard of care. There were no study-specific additional diagnostic workup or management criteria [21, 22]. A panel of infectious disease and pulmonary/critical care specialists developed consensus diagnoses based on available clinical and microbiological data from the electronic medical record that was acquired through the application of standard care diagnostic and treatment practices. This results in variable inter-subject data collection and, therefore, a panel of infectious disease and pulmonary/critical care specialists was utilized to adjudicate the most likely etiology of the acute illness in each clinical case, as previously described [22]. This resulted in three possible outcomes: viral infection, bacterial infection, and unknown etiology.

Statistical analyses

The statistical significance of categorical variables was determined by the Chi-square test and the statistical significance of continuous variables was determined by the Wilcoxon rank-sum. Pearson's correlation coefficient was used to assess association between two variables.

A score identifying patients most likely to suffer from severe outcomes was generated using the R environment for statistical computing [28]. Severe outcome was defined as need for ICU admission and/or mortality within 28 days of enrollment. The novel model was developed from demographic and clinical variables including age, gender, patient comorbidities (hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, chronic lung disease, cancer, heart failure, cerebrovascular disease, chronic kidney disease), physical examination findings (highest temperature, highest respiratory rate, highest heart rate, lowest systolic and lowest diastolic blood pressure) and laboratory findings (white blood cell count, blood urea nitrogen, serum sodium, serum glucose, hematocrit) at time of enrollment. Liver disease was not included in the analysis due to low variability among our patient population. Neutrophil, lymphocyte, and monocyte percentage were not included in the analysis due to a high degree of missingness. Temperature and serum glucose were log transformed. Multivariable analysis was performed using regularized regression implemented in the glmnet R package [29, 30]. Measures of predictive accuracy were generated using nested cross-validation.

Results

Overview of the study population

Over the study period, 276 individuals were enrolled from the emergency department with symptoms consistent with acute respiratory infection and 246 (89%) of these individuals were admitted to the hospital for further care (Table 1). Half (50%) of all patients were male (Table 1). The median age of patients was 69 years (range 60–92 years) with 53% between 60 and 69 years of age, 26% between 70 and 79 years old and 21% 80 years old and above (Table 1). 60% of patients identified as Caucasian and 37% identified as African American (Table 1). The majority of patients (73%) were residing at home prior to emergency department presentation (Table 1). Hypertension (71%) and chronic lung disease (50%) were the most common comorbidities among patients in the study (Table 1).

Clinical manifestations differ between subjects requiring admission and those treated as outpatients

Patients requiring admission tended to be older than patients treated in the outpatient setting (70 vs 63 years, $p < 0.001$), with patients requiring inpatient treatment more likely to have two or more comorbidities (hypertension, hyperlipidemia, diabetes mellitus, chronic liver disease, cancer, chronic kidney disease, heart failure, coronary artery disease, chronic lung disease or cerebrovascular disease) compared to those treated in the outpatient setting (80% vs 63%, $p = 0.037$) (Table 1). Patients requiring inpatient treatment were also more likely to have tachycardia (103 vs 94 beats per min, $p = 0.028$) and tachypnea (24 vs 20 breaths per min, $p < 0.001$) as compared to those treated in the outpatient setting (Table 2). Systolic (119 vs 136 mmHg, $p = 0.011$) and diastolic blood pressure (64 vs 71 mmHg, $p = 0.002$) were consistently lower among patients requiring hospital admission (Table 2). Interestingly, average temperature did not differ by level of patient care (37.7 vs 37.0 degrees Celsius, $p = 0.187$) (Table 2). Both an elevated total white blood cell count and a neutrophilic predominance were associated with inpatient treatment (Table 2). Elevated blood urea nitrogen (BUN) (20 vs 15 mg/dL, $p < 0.001$) and serum glucose (126 vs 110 mg/dL, $p = 0.015$) were also more common among patients treated in the inpatient setting (Table 2).

Table 1 Patient demographics

	All ($n = 276$)	Outpatient ($n = 30$)	Inpatient ($n = 246$)	P Value
Age	69.0 [63.0–78.0] (276)	63.0 [62.0–68.8] (30)	70.0 [64.0–79.0] (246)	<0.001
60–69 years, %	52.5 (145)	83.3 (25)	48.8 (120)	0.002
70–79 years	26.1 (72)	10.0 (3)	28.0 (69)	
≥ 80 years	21.4 (59)	6.7 (2)	23.2 (57)	
Male, %	50.0 (138)	43.3 (13)	50.8 (125)	0.439
Race, %				0.391
Caucasian	60.1 (166)	70.0 (21)	58.9 (145)	
African American	37.3 (103)	30.0 (9)	38.2 (94)	
Other/unknown	2.5 (7)	0 (0)	2.9 (7)	
Ethnicity, %				0.004
Non-hispanic, non-latino	90.9 (251)	76.7 (23)	92.7 (228)	
Other/unknown	9.1 (25)	23.3 (7)	7.3 (18)	
BMI	26.7 [23.0–33.0] (214)	30.0 [26.0–36.0] (29)	26.0 [23.0–33.0] (185)	0.064
Comorbidities, %				
Hypertension (276)	71.4 (197)	66.7 (20)	72.0 (177)	0.546
Hyperlipidemia (276)	35.1 (97)	50.0 (15)	33.3 (82)	0.071
Diabetes mellitus (276)	37.0 (102)	26.7 (8)	38.2 (94)	0.216
Liver disease (271)	1.1 (3)	0 (0)	1.2 (3)	0.539
Cancer (276)	17.4 (48)	3.3 (1)	19.1 (47)	0.031
Chronic kidney disease (275)	16.0 (44)	3.3 (1)	17.6 (43)	0.045
Heart failure (271)	17.7 (48)	0 (0)	19.9 (48)	0.007
Coronary artery disease (276)	27.9 (77)	26.7 (8)	28.0 (69)	0.873
Chronic lung disease (275)	49.8 (137)	33.3 (10)	51.8 (127)	0.056
Cerebrovascular disease (276)	11.2 (31)	6.7 (2)	11.8 (29)	0.402
≥ 2 Comorbidities (275)	78.2 (215)	63.3 (19)	80.0 (196)	0.037
Location prior to admission, %				0.023
Home	72.5 (200)	93.3 (28)	69.9 (172)	
Skilled nursing facility	7.2 (20)	0 (0)	8.1 (20)	
Other/unknown	20.3 (56)	6.7 (2)	22.0 (54)	

Values presented for age and BMI are medians, with IQR in brackets []. The number of individuals with each variable recorded or data available is shown in parenthesis (*n*)

Despite modern diagnostics a definitive etiology for ARI is rarely obtained

Following workup considered clinically appropriate by the health care providers, 52 individuals (19%) were found to have a proven bacterial infection and 40 (14%) proven viral infection (Table 3 and Suppl Table 1). Interestingly, 67% of individuals thought to have an infectious process, based on thorough clinical adjudication, had no specific pathogen identified as the cause of their illness (Table 3). 97% of individuals presenting with symptoms of acute respiratory infection had chest imaging performed and 72% had evidence of infection as determined by the radiologist or clinical adjudicator. While 90% of those with bacterial infection had radiographic evidence of lung infection, only 47% with a viral etiology and 73% of those with an undefined etiology had infectious findings. Thus, while there are clear differences between etiologies, radiographic evidence alone did not reliably differentiate between the various etiologies.

Clinical presentation and outcomes differ between underlying etiology of ARI

Individuals with bacterial infections were more likely to have increased heart (114 vs 98 beats per minute, $p = 0.044$) and respiratory rate (26 vs 21 breaths per minute, $p < 0.001$) and decreased systolic blood pressure (112 vs 124 mmHg, $p = 0.013$) when compared to individuals with viral infections (Table 3). Individuals with bacterial infection also had higher white blood cell count (13.3 vs 9.4×10^9/L, $p = 0.006$) (Table 3).

Table 2 Clinical variables associated with treatment location

Vital signs and laboratory values at presentation	All	Outpatient	Inpatient	*p* value
Age, years	69.0 [63.0–78.0] (276)	63.0 [62.0–68.8] (30)	70.0 [64.0–79.0] (246)	<0.001
Temperature, °C	37.6 [36.7–38.6] (268)	37.0 [36.3–38.7] (30)	37.7 [36.7–38.6] (238)	0.187
Heart rate, beats per minute	102.0 [90.0–118.0] (276)	93.5 [81.5–113.8] (30)	103.0 [90.0–119.0] (246)	0.028
Respiratory rate, breaths per minute	24.0 [20.0–28.0] (276)	20.0 [18.0–21.5] (30)	24.0 [20.0–28.0] (246)	<0.001
Systolic blood pressure, mmHg	119.0 [104.5–140.0] (275)	135.5 [112.3–149.8] (30)	119.0 [104.0–135.0] (245)	0.011
Diastolic blood pressure, mmHg	65.0 [56.0–75.0] (275)	70.5 [65.5–80.0] (30)	64.0 [55.0–73.0] (245)	0.002
White blood cell count, $\times 10^9$/L	12.3 [8.7–16.2] (272)	10.0 [6.6–12.7] (27)	12.8 [8.8–16.9] (245)	0.017
Neutrophils, %	83.3 [72.8–89.3] (252)	75.1 [66.6–77.8] (22)	84.0 [77.2–89.9] (230)	<0.001
Lymphocytes, %	8.0 [4.3–12.4] (250)	13.9 [10.7–17.5] (22)	7.7 [4.2–12.0] (228)	<0.001
Monocytes, %	5.6 [3.1–8.0] (252)	7.0 [4.8–11.0] (22)	5.2 [3.0–8.0] (230)	0.017
Blood urea nitrogen, mg/dL	19.0 [14.0–27.3] (272)	15.0 [11.5–17.0] (27)	20.0 [14.0–28.0] (245)	<0.001
Serum sodium, mmol/L	138.0 [135.0–140.0] (272)	138.0 [136.0–140.5] (27)	137.0 [134.0–140.0] (245)	0.293
Serum glucose, mg/dL	123.0 [104.5–170.0] (271)	110.0 [100.0–120.5] (27)	125.5 [105.0–172.0] (244)	0.015
Serum hematocrit, %	37.0 [33.0–41.0] (271)	39.0 [36.8–41.0] (27)	36.9 [32.7–41.0] (244)	0.072

Values presented are medians, with IQR in brackets []. The number of individuals with each variable recorded or data available is shown in parenthesis (*n*)

Values for temperature, heart rate and respiratory rate are highest value recorded on day of presentation. Systolic and diastolic blood pressure are lowest value recorded on day of presentation

The rate of hospital admission was highest among individuals with bacterial infection (100%), followed by individuals with unknown etiology (91%) and viral infection (65%) (Table 3). Of all patients requiring hospital admission, the median length of hospital stay was 4 days, with length of stay differing by infectious etiology, 3 days for viral infection, 4 days for indeterminate and 7.5 days for bacterial infections (Table 3). 70 of the 246 (28%) individuals requiring hospital admission were admitted to the ICU during their hospital stay, with individuals with bacterial infection having the highest ICU admission requirement followed by those with unknown etiology and those with viral infection (Table 3). 23 of the 245 (9.4%) hospitalized patients with mortality data available died within 28 days of presentation compared to none of the non-admitted patients (Table 3). The 28-day mortality rate was 13.5% among all individuals with bacterial etiology, 8.2% among all individuals with unproven etiology and 2.5% among all individuals with viral etiology (Table 3).

Development of a novel scoring predictor for all-cause ARI in the elderly

Multivariable logistic regression analysis was performed to identify demographic and clinic variables predictive of severe clinical outcome, as defined by ICU admission or 28-day mortality, among our study cohort. The multivariable logistic regression analysis indicated that 11 of 21 variables were associated with severe clinical outcome (Tables 4, 5). Four demographic variables: gender, cancer, chronic lung disease and hyperlipidemia, and seven clinical variables: temperature (°C), systolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), blood urea nitrogen (mg/

Table 3 Differences in clinical course by infectious etiology

Presenting characteristics	Unknown etiology	Bacterial	Viral	*p* value
Age, years	69.0 [63.0–78.0] (184)	70.5 [63.8–79.3] (52)	67.5 [62.0–75.3] (40)	0.166
Temperature, °C	37.4 [36.6–38.4] (181)	37.9 [37.1–39.0] (47)	37.6 [36.5–38.6] (40)	0.086
Heart rate, beats per minute	101.0 [90.0–115.0] (184)	113.5 [97.3–128.3] (52)	97.5 [84.3–119.5] (40)	0.044
Respiratory rate, breaths per minute	24.0 [20.0–28.0] (184)	25.5 [22.0–32.3] (52)	20.5 [20.0–24.0] (40)	< 0.001
Systolic blood pressure, mmHg	118.0 [106.5–135.5] (183)	112.0 [96.8–134.5] (52)	124.0 [112.8–147.0] (40)	0.013
Diastolic blood pressure, mmHg	65.0 [57.0–73.5] (183)	60.0 [49.0–77.3] (52)	69.5 [58.0–76.5] (40)	0.138
White blood cell count, $\times 10^9$/L	13.1 [9.3–16.4] (181)	13.3 [8.3–18.2] (52)	9.4 [6.0–11.8] (39)	0.006
Neutrophils, %	83.0 [76.0–89.0] (165)	86.1 [78.6–91.0] (52)	78.6 [69.2–86.5] (35)	0.013
Lymphocytes, %	7.9 [4.0–12.3] (163)	7.0 [4.2–10.3] (52)	11.1 [6.7–15.5] (35)	0.007
Monocytes, %	5.3 [3.0–7.5] (165)	5.0 [2.9–8.6] (52)	6.7 [3.5–10.7] (35)	0.110
Blood urea nitrogen, mg/dL	20.0 [14.0–28.0] (181)	20.5 [15.0–31.3] (52)	16.0 [13.0–20.0] (39)	0.025
Serum sodium, mmol/L	138.0 [135.0–140.0] (181)	136.5 [133.0–140.0] (52)	136.0 [134.5–139.5] (39)	0.841
Serum glucose, mg/dL	123.0 [106.0–164.0] (181)	126.0 [104.0–186.3] (52)	111.5 [97.5–162.8] (38)	0.176
Serum hematocrit, %	36.0 [32.0–40.7] (180)	38.0 [34.0–42.0] (52)	39.5 [36.8–42.5] (39)	0.235
Clinical outcomes	Unknown etiology, % ($n=184$)	Bacterial, % ($n=52$)	Viral, % ($n=40$)	*p* value
Outpatient (30)	8.7 (16)	0 (0)	35.0 (14)	< 0.001
Inpatient, mild (52)	22.3 (41)	1.9 (1)	25.0 (10)	< 0.001
Inpatient, moderate (115)	45.1 (83)	36.5 (19)	32.5 (13)	0.687
Inpatient, severe (79)	23.9 (44)	61.5 (32)	7.5 (3)	< 0.001
Inpatient, ICU (70)	20.1 (37)	57.7 (30)	7.5 (3)	< 0.001
Death (23)	8.2 (15)	13.5 (7)	2.5 (1)	0.064
LOS, days (245)	4.0 [2.0–6.0]	7.5 [4.8–11.3]	3.0 [1.3–6.0]	< 0.001

Values presented for presenting characteristics are medians, with IQR in brackets [] and values presented for clinical outcomes are percentages. The number of individuals with each variable recorded or data available is shown in parenthesis (*n*)

Values for temperature, heart rate and respiratory rate are highest value recorded on day of presentation. Systolic and diastolic blood pressure are lowest value recorded on day of presentation

ICU intensive care unit, *Death* 28 day mortality, *LOS* median length of stay in days of patients requiring inpatient treatment

dL), serum sodium (mmol/L), and glucose (mg/dL) were included (Tables 4, 5). Risk scores on the predicted probability scale ranged from 0.046 to 0.981, with a median score of 0.229. Individuals in the top ARI score quartile had scores above 0.464 and individuals in the bottom ARI score quartile had scores less than 0.124. Many individuals (32%) with ARI scores below 0.124 were considered well enough to be treated as outpatients, while all individuals with ARI scores above 0.464 required inpatient care (Table 6). Of individuals in the top (worst) quartile, 27 of 41 (66%) faced severe clinical outcomes, as defined by ICU admission or 28-day mortality, and 10 (24.4%) died within the 28-day follow-up period. Conversely, of individuals in the bottom quartile, 3 of 53 individuals (6%) faced severe outcome and no individuals died within 28 days of presentation. The model demonstrated utility for identifying patients most likely to face severe outcomes of ICU admission or 28-day mortality (auROC 0.758).

Table 4 Multivariable logistic regression for severe outcome

Variable	Coefficient
Intercept	−1.055
Demographic	
Male	0.116
Hyperlipidemia	−0.264
Cancer	0.227
Chronic lung disease	0.204
Clinical	
Temperature	0.024
Heart rate	0.018
Respiratory rate	0.484
Systolic blood pressure	−0.274
Blood urea nitrogen	0.413
Serum sodium	0.013
Serum glucose	0.164

Table 5 Multivariable logistic regression for severe outcome

Variable	Severe outcome	
	OR (95% CI)	*p* value
Demographic		
Male	1.84 (0.97–3.50)	0.062
Hyperlipidemia	0.40 (0.19–0.84)	0.015
Cancer	3.04 (1.39–6.67)	0.006
Chronic lung disease	2.32 (1.20–4.48)	0.012
Clinical		
Temperature	1.46 (0.86–2.46)	0.161
Heart rate	1.08 (0.70–1.65)	0.736
Respiratory rate	2.15 (1.47–3.14)	< 0.001
Systolic blood pressure	0.55 (0.34–0.88)	0.013
Blood urea nitrogen	1.46 (1.16–1.85)	0.002
Serum sodium	1.19 (0.85–1.68)	0.312
Serum glucose	1.52 (1.03–2.24)	0.036

Correlation between ARI score and outcome severity (outpatient, mild, moderate, severe) determined by Pearson's correlation coefficient was 0.49.

Comparison of clinical pneumonia severity scores in all-cause ARI

We compared modified PORT and CURB-65 scores to scores obtained from our novel model to assess the applicability of published outcome prediction tools for individuals with community-acquired pneumonia when applied to individuals with nonspecific acute respiratory infection [9, 16–18]. Given the retrospective nature of our study, we utilized a slightly modified PORT score for each patient to account for missing variables not collected at the time of patient enrollment. This modified PORT score was calculated for 243 patients and the median PORT score was 89.0 (Table 7). 61, 70, 86 and 26 individuals met criteria for class II (≤ 70), III (71–90), IV (91–130) and vs (> 130), respectively (Table 6). 18% of individuals in class III and below were treated as outpatients compared to less than 1% of those in class IV and above ($p < 0.001$) (Table 6). There was a 1.5% 28-day mortality among individuals in class III and below vs a 13.4% rate among individuals in class IV and above ($p < 0.001$) (Table 6). The correlation between modified PORT score and outcome severity was 0.54 (Table 7).

Next, a modified CURB-65 score was calculated for 271 patients using BUN, respiratory rate, systolic/diastolic blood pressure and age. The median CURB-65 score was 2.0 in all-cause ARI, with 111 patients with 0 or 1, 83 patients with 2, and 77 patients with ≥ 3 (Tables 6, 7). Of patients with a CURB-65 score of 0–1, 21% were well enough to be treated as outpatients, while no patients with a score of 3 or above were treated as outpatients. There was a 6.3% 28-day mortality among individuals with score 0–1 compared to a 11.7% mortality rate among those with a score of 3 or above ($p = 0.193$) (Table 6). The correlation of modified CURB-65 score to outcome severity was $r = 0.39$ (Table 7).

A third score, the Jackson symptom score, originally developed to identify individuals with a viral cause of respiratory illness, also shows utility for a broad range of respiratory infections [27, 31]. To assess its applicability to all-comers with respiratory infection, a modified Jackson symptom score was calculated for 128 individuals at the time of presentation. 37 individuals had viral illness, 12 bacterial and 79 unknown infectious etiology. Eight symptoms were used in the calculation including nasal discharge, nasal congestion, sneezing, cough, malaise, throat discomfort, fever and or chills, and headache. The median symptom score for all individuals was 13, with scores ranging from 0 to 31 (Tables 7, 8). Interestingly, the modified Jackson symptom score was found to inversely correlate with outcome severity, ICU admission, and death (Table 7). Although limited by the size of the study, symptom scores also showed potential to differentiate viral and bacterial causes of infection. Overall, individuals with viral infection had on average a higher symptom scores than individuals with bacterial infections (16 vs 10, $p = 0.023$) (Table 6). Individuals with unknown infectious etiology had symptom scores in between those of viral and bacterial infections. 23 of 37 (38%) of individuals with viral infection did not meet the historic cutoff of 14 symptom points to be identified as viral infection, while 4 of 12 (33%) individuals with bacterial infectious would have been categorized as viral infection by score alone.

Table 6 Modified PORT and CURB-65 and novel ARI score

Modified PORT Score	≤70 (*n*=61)	71–90 (*n*=70)	91–130 (*n*=86)	>130 (*n*=26)
Age, years	64.0	70.5	72.5	79.0
Outpatient, % (25)	31.1 (19)	7.1 (5)	1.2 (1)	–
Inpatient, % (218)	68.9 (42)	92.9 (65)	98.8 (85)	100.0 (26)
ICU ± death, % (63)	4.9 (3)	20.0 (14)	31.4 (27)	73.1 (19)
Death, % (17)	1.6 (1)	1.4 (1)	9.3 (8)	26.9 (7)
LOS, days	2.0 (42)	4.0 (65)	4.0 (84)	5.5 (26)
Modified CURB-65 Score	0–1 (*n*=111)	2 (*n*=83)	≥3 (*n*=77)	
Age, years	63.0	72.0	75.0	
Outpatient, % (27)	20.7 (23)	4.8 (4)	–	
Inpatient, % (244)	79.3 (88)	95.2 (79)	100.0 (77)	
ICU ± death, % (78)	18.0 (20)	27.7 (23)	45.5 (35)	
Death, % (23)	6.3 (7)	8.4 (7)	11.7 (9)	
LOS, days	3.0 (88)	4.0 (79)	5.0 (76)	
Novel ARI Score	<0.124 (*n*=53)	0.124–0.209 (*n*=65)	0.210–0.464 (*n*=117)	>0.464 (*n*=41)
Age, years	68.0	69.0	68.0	76.0
Outpatient, % (30)	32.1 (17)	15.4 (10)	2.6 (3)	0 (0)
Inpatient, % (246)	67.9 (36)	84.6 (55)	97.4 (114)	100.0 (41)
ICU ± death, % (79)	5.7 (3)	18.5 (12)	31.6 (37)	65.9 (27)
Death, % (23)	0 (0)	7.7 (5)	6.9 (8)	24.4 (10)
LOS, days	3.0 (36)	4.0 (65)	4.0 (113)	7.0 (41)

Values presented for age and LOS are medians. The number of individuals with variable recorded or data available is shown in parenthesis (*n*)
LOS median length of stay in days of patients requiring inpatient treatment, *ICU* intensive care unit, *Death* 28-day mortality

Discussion

We utilized a retrospective analysis of elderly patients enrolled in research protocols at major medical centers in the US to define the clinical characteristics and outcomes of all-cause ARI in this vulnerable population. The results support the concept that analyses of clinical variables at presentation can supplement decision making for older adults with not just proven pneumonia, but also undifferentiated ARI at the point of care. Additionally, we have developed a novel scoring metric for elderly individuals presenting with all-cause ARI and compared this to existing, previously validated outcome severity scores for community-acquired pneumonia and demonstrate that these scores have utility regardless of pathogen class and presence or absence of community-acquired pneumonia.

A patient's resilience to infection is associated with age and number of comorbidities, key factors which help providers decide on appropriate treatment location and resource allocation prior to the return of laboratory and diagnostic tests. Similar to advanced age, a history of neurologic disease, cancer, renal disease and congestive heart failure have been reported to be strong comorbidity predictors for patients presenting with community-acquired pneumonia, consistent with our findings demonstrating an increased prevalence of cancer and heart failure in patients requiring inpatient care for ARI [11]. Common clinical variables including tachycardia, tachypnea, and hypotension also often aid in directing triage decisions. In our study, multivariable analysis of 21 demographic and clinical variables identified 11 that were predictive of severe outcome among our cohort of individuals with all-cause ARI. Interestingly, application of a modified PORT score (missing 4 PORT criteria) to our cohort demonstrates that the predictive ability of a modified PORT score remains strong even when applied to individuals with a much broader definition of respiratory infection, and may even offer improved overall accuracy compared to our novel model. Modified PORT scores are significantly elevated among individuals requiring hospital admission for ARI, and show a trend towards predicting more severe outcomes. In our cohort, modified PORT scores performed similarly to the best de-novo ARI model arising from these data, and both correlated more closely with outcome severity than CURB-65 ($r=0.54$, $r=0.49$, $r=0.39$). Thus, even with a broader definition of undifferentiated respiratory infection more similar to what a clinician at the point of care may see, such clinical scores have utility in stratifying patients based on likely outcome.

While less studied, modified Jackson symptom scores provided interesting insight into etiology identification, even in an elderly population. Average modified Jackson symptom scores were significantly lower for individuals

Table 7 Score metrics

	Modified PORT Score	Modified CURB-65 Score	Modified Jackson Symptom Score
All	89.0 [70.5-112.0] (243)[A]	2.0 [1.0-3.0] (271)[B]	13.0 [9.0-17.0] (128)[C]
▪ **Outpatient**	62.0 [53.0-70.0] (25)	1.0 [0-1.0] (27)	20.0 [12.5-26.0] (27)
▪ **Inpatient**	91.0 [75.3-114.0] (218)	2.0 [1.0-3.0] (244)	12.0 [8.0-16.0] (101)
○ **Mild***	71.5 [62.0-91.8] (50)	1.0 [1.0-2.0] (51)	13.5 [8.0-16.0] (32)
○ **Moderate^**	90.0 [78.0-108.0] (105)	2.0 [1.0-3.0] (115)	12.5 [8.8-15.3] (48)
○ **Severe#**	115.0 [90.0-133.0] (63)	2.0 [1.3-3.0] (78)	10.0 [7.0-15.0] (21)
Bacterial (all)	100.5 [85.0-128.5] (42)	2.0 [1.0-3.0] (52)	10.0 [7.8-15.3] (12)
▪ **Outpatient**	-	-	-
▪ **Inpatient**	100.5 [85.0-128.5] (42)	2.0 [1.0-3.0] (52)	10.0 [7.8-15.3] (12)
○ **Mild**	65.0 [65.0-65.0] (1)	2.0 [2.0-2.0] (1)	16.0 [16.0-16.0] (1)
○ **Moderate**	86.0 [75.0-100.0] (17)	2.0 [1.0-2.0] (19)	8.0 [6.0-11.5] (3)
○ **Severe**	119.5 [93.0-131.8] (24)	2.5 [2.0-3.0] (32)	10.0 [8.5-14.3] (8)
Viral (all)	75.0 [61.8-90.8] (36)	1.0 [1.0-2.0] (39)	16.0 [10.0-22.0] (37)
▪ **Outpatient**	66.0 [55.8-71.3] (12)	1.0 [0-1.0] (13)	22.0 [16.3-27.5] (14)
▪ **Inpatient**	83.0 [62.8-101.0] (24)	1.0 [1.0-2.0] (26)	13.0 [9.0-17.5] (23)
○ **Mild**	66.0 [54.3-96.8] (10)	1.0 [0-1.8] (10)	13.0 [9.0-17.0] (9)
○ **Moderate**	84.5 [79.8-105.8] (12)	1.0 [1.0-2.0] (13)	11.0 [9.0-16.5] (11)
○ **Severe**	89.0 [83.5-94.5] (2)	2.0 [1.5-3.0] (3)	17.0 [15.0-17.5] (3)
Unknown Etiology (all)	90.0 [71.0-110.0] (165)	2.0 [1.0-3.0] (180)	12.0 [8.0-16.0] (79)
▪ **Outpatient**	59.0 [53.0-63.0] (13)	0.5 [0-1.0] (14)	16.0 [9.0-20.0] (13)
▪ **Inpatient**	91.5 [72.0-113.0] (152)	2.0 [1.0-3.0] (166)	12.0 [8.0-15.0] (66)
○ **Mild**	81.0 [63.0-91.5] (39)	1.5 [1.0-2.0] (40)	13.5 [8.0-15.8] (22)
○ **Moderate**	93.0 [78.8-109.0] (76)	2.0 [1.0-3.0] (83)	13.0 [8.3-15.8] (34)
○ **Severe**	115.0 [90.0-136.0] (37)	2.0 [1.0-3.0] (43)	9.5 [7.0-12.0] (10)

Values presented are medians, with IQR in brackets []. The number of individuals with each scoring metric calculated is shown in parenthesis (*n*)

Pearson coefficient comparing score and outcome: [a]0.54, [b]0.39, [c]− 0.34

Select, clinically relevant variables with significant differences across groups are presented with large brackets, $p < 0.05$

Mild inpatient length of stay 1–2 days, *Moderate* inpatient length of stay 3 or more days, *Severe* inpatient stay requiring intensive care unit admission or 28 day mortality

with bacterial infection as compared to individuals with viral infection, and showed discriminative ability between the two in older individuals. Originally derived to differentiate viral etiologies of upper respiratory infections from other causes of cold symptoms [27], our analysis suggests that modified Jackson symptom scores can also provide meaningful

Table 8 Modified Jackson symptom score quartiles

	Median Symptom Score	Outpatient, %	Inpatient, %				LOS, days	Infectious etiology, %		
			All	Mild	Moderate	Severe		Unknown	Bacterial	Viral
Q1: 0–8 (31)	6.0	9.7 (3)	90.3 (28)	32.3 (10)	38.7 (12)	19.3 (6)	3.5 (28)	77.4 (24)	12.9 (4)	9.7 (3)
Q2: 9–13 (37)	11.0	13.5 (5)	86.5 (32)	16.2 (6)	46.0 (17)	24.3 (9)	3.5 (32)	59.5 (22)	10.8 (4)	29.7 (11)
Q3: 14–17 (29)	15.0	17.2 (5)	82.8 (24)	34.5 (10)	37.9 (11)	10.3 (3)	3.0 (24)	65.5 (19)	6.9 (2)	27.6 (8)
Q4: 18–31 (31)	21.0	45.2 (14)	54.8 (17)	19.3 (6)	25.8 (8)	9.7 (3)	4.0 (17)	45.2 (14)	6.4 (2)	48.4 (15)

Values presented for symptom score and LOS are median. The number of individuals with variable recorded or data available is shown in parenthesis (*n*)

Q quartile, *Mild* inpatient length of stay 1–2 days, *Moderate* inpatient length of stay 3 or more days, *Severe* inpatient stay requiring intensive care unit admission or 28 day mortality, *LOS* median length of stay in days of patients requiring inpatient treatment

clinical prediction in individuals with bacterial illness as elevated modified Jackson scores were inversely associated with outcome severity regardless of proven etiology.

Herein we have focused on demographic and clinical variables commonly available at the time of clinical presentation with ARI. However, there is suggestion in the literature that such clinical scoring metrics may be enhanced further when combined with measurement of various immune response-related biomarkers. As an example, the CRP to neopterin ratio offers some ability to differentiate bacterial and viral etiologies of infection among individuals presenting to the emergency department with undifferentiated ARIs [32]. Similarly, procalcitonin has shown utility for identification of bacterial etiologies of both respiratory and non-respiratory infections [33, 34] and has subsequently been used to guide antibiotic management [35]. Additionally, genomic biomarkers have been utilized in conjunction with clinical scores to create combined models of severity prediction in pneumonia and sepsis [36–38]. Thus, moving forward, combined clinical-molecular approaches may offer even better predictive performance than either alone.

This study does have several notable limitations. First, this is a retrospective analysis of a completed clinical trial, and this limited data collection to that which was previously recorded or entered into the study database or electronic medical record. Variables not collected at the time of enrollment limited the ability to calculate complete PORT and CURB-65 scores for the study population, therefore, we are unable to fully assess the clinical utility of the published scores. Additionally, all individuals with bacterial infection in this study were admitted to the hospital, limiting our ability to predict or identify clinical variables associated with milder bacterial infection that might have been treated in the outpatient setting. Lastly, performance of PORT, CURB-65 or the novel ARI score presented herein will require vigorous validation in additional ARI cohorts to confirm these findings, and this will continue to be a target for future research.

Although it is often difficult to make definitive clinical decisions at the time of patient presentation with respiratory illness symptoms due to the overlapping clinical picture of various pathogens and other noninfectious illnesses, our study highlights the predictive potential of clinical scores based on commonly available metrics. It is well known that patients receiving timely treatment for infection have lower mortality than those with delayed or no treatment, but current diagnostic tests are often limited by delayed time to results and a priori knowledge of likely pathogens [12, 39, 40]. Modification of existing scoring systems and development of new more broadly applicable metrics to predict etiologies (pathogen class) and clinical outcomes, if used in conjunction with current diagnostic practices, can promote more timely and appropriate allocation of resources for patient care. Ideal early predictive tools would be applicable to individuals based on clinical syndromes regardless of pathogen class (which is usually not known at the time of presentation) and would be built upon commonly and easily collected demographic and clinical variables. As demonstrated in this study, several clinical scores show utility in predicting outcome severity among elderly individuals with a wide variety known and unknown infectious etiologies. These findings support further work in both all-cause ARI as well as with noninfectious clinical mimics to better define how such metrics might identify patients most at risk of severe outcome as well as those likely to benefit from empiric antimicrobial therapies.

Acknowledgements ASB received funding from the Eugene A. Stead Foundation and the Infectious Diseases Society of America. JS is funded through an NIAID-sponsored T32 Transplant ID Training Grant. MTM received support through the National Institute of Allergy and Infectious Diseases (NIAID), the Veterans Health Administration,

the Claude D. Pepper Center, and the PRIME consortium [National Institute of Aging (NIA)].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this work.

References

1. Garten R, et al. Update: influenza activity in the United States during the 2017–18 season and composition of the 2018–19 influenza vaccine. MMWR Morb Mortal Wkly Rep. 2018;67:634–42.
2. Barnes SR, et al. Mortality estimates among adult patients with severe acute respiratory infections from two sentinel hospitals in southern Arizona, United States, 2010–2014. BMC Infect Dis. 2018;18:78.
3. Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415–27.
4. Thompson WW, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003;289:179–86.
5. Garibaldi RA. Epidemiology of community-acquired respiratory tract infections in adults. Incidence, etiology, and impact. Am J Med. 1985;78:32–7.
6. Mullooly JP, et al. Influenza- and RSV-associated hospitalizations among adults. Vaccine. 2007;25:846–55.
7. Thompson WW, et al. Influenza-associated hospitalizations in the United States. JAMA. 2004;292:1333–40.
8. Janssens JP, Krause KH. Pneumonia in the very old. Lancet Infect Dis. 2004;4:112–24.
9. Fine MJ, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. Arch Intern Med. 1999;159:970–80.
10. Shibli F, et al. Etiology of community-acquired pneumonia in hospitalized patients in northern Israel. Isr Med Assoc J. 2010;12:477–82.
11. Metlay JP, Fine MJ. Testing strategies in the initial management of patients with community-acquired pneumonia. Ann Intern Med. 2003;138:109–18.
12. Falsey AR, Murata Y, Walsh EE. Impact of rapid diagnosis on management of adults hospitalized with influenza. Arch Intern Med. 2007;167:354–60.
13. Raz R, et al. A predictive model for the management of community-acquired pneumonia. Infection. 2003;31:3–8.
14. Neill AM, et al. Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. Thorax. 1996;51:1010–6.
15. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. Ann Intern Med. 1991;115:428–36.
16. British Thoracic Society Research Committee. Community-acquired pneumonia in adults in British hospitals in 1982–1983: a survey of aetiology, mortality, prognostic factors and outcome. The British Thoracic Society and the Public Health Laboratory Service. Q J Med, 1987. 62: p. 195–220.
17. Fine MJ, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243–50.
18. Lim WS, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377–82.
19. Buising KL, et al. Identifying severe community-acquired pneumonia in the emergency department: a simple clinical prediction tool. Emerg Med Australas. 2007;19:418–26.
20. Williams E, et al. CORB is the best pneumonia severity score for elderly hospitalised patients with suspected pneumonia. Intern Med J. 2014;44:613–5.
21. Tsalik EL, et al. An integrated transcriptome and expressed variant analysis of sepsis survival and death. Genome Med. 2014;6:111.
22. Tsalik EL, et al. Host gene expression classifiers diagnose acute respiratory illness etiology. Sci Transl Med. 2016;8:322ra11.
23. Glickman SW, et al. Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis. Acad Emerg Med. 2010;17:383–90.
24. Tsalik EL, et al. Multiplex PCR to diagnose bloodstream infections in patients admitted from the emergency department with sepsis. J Clin Microbiol. 2010;48:26–33.
25. Tsalik EL, et al. Discriminative value of inflammatory biomarkers for suspected sepsis. J Emerg Med. 2012;43:97–106.
26. Bone RC, et al., Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest, 1992. 101: p. 1644–55.
27. Jackson GG, et al. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. AMA Arch Intern Med. 1958;101:267–78.
28. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2018. https://www.R-project.org. Accessed 1 Mar 2018.
29. Tibshirani R. Regression shrinkage and selection via the Lasso. J R Stat Soc Ser B (Methodol). 1996;58:267–88.
30. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Softw. 2010. https://doi.org/10.18637/jss.v033.i01
31. Taylor JA, et al. Development of a symptom score for clinical studies to identify children with a documented viral upper respiratory tract infection. Pediatr Res. 2010;68:252–7.
32. Rainer TH, et al. Diagnostic utility of CRP to neopterin ratio in patients with acute respiratory tract infections. J Infect. 2009;58:123–30.
33. Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. Clin Infect Dis. 2011;52:S346-50.
34. Memar MY, et al. Procalcitonin: the marker of pediatric bacterial infection. Biomed Pharmacother. 2017;96:936–43.
35. Schuetz P, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev. 2017;10:CD007498.
36. Christ-Crain M, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit Care. 2006;10:R96.
37. Wallihan RG, et al. Molecular distance to health transcriptional score and disease severity in children hospitalized with community-acquired pneumonia. Front Cell Infect Microbiol. 2018;8:382.
38. Vincent JL. The clinical challenge of sepsis identification and monitoring. PLoS Med. 2016;13:e1002022.
39. Meehan TP, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. JAMA. 1997;278:2080–4.
40. Lee N, et al. Outcomes of adults hospitalised with severe influenza. Thorax. 2010;65:510–5.