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Heckerling's Criteria to Distinguish Community-Acquired Pneumonia in Primary Care Settings: Observational Validation Study in Japan

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ABSTRACT
Background: Community-acquired pneumonia (CAP) is a common illness that can lead to mortality. Chest radiography is the standard means of confirmation of pneumonia, but patients may be unnecessarily exposed to radiation. Heckerling's criteria (HC) scoring is a useful substitute for chest radiography and can be used to rule out CAP. HC score ≥ 4 is strongly indicative of pneumonia, while ≤ 1 indicates the patient is pneumonia-free. HC scoring is well validated in Western populations, but has not been validated in an Asian population. Racial differences in symptoms and differences in the method of measuring body temperature may affect the validity of HC scoring in this population. We evaluate the use of HC scoring in a Japanese primary care setting. Methods: We conducted a prospective observational study of febrile patients aged ≥ 16 years that had respiratory symptoms in either of two community hospitals between December 2016 and October 2018. We evaluated the accuracy of HC in discrimination of patients with and without CAP. Pneumonia was defined as respiratory symptoms with new infiltration recognized on chest X-ray or chest computed tomography. Results: Analyzable data from 296 of 341 patients was available (37.2% were female, mean age: 41.1 years). CAP was diagnosed in 58 patients (19.6%). HC discriminated CAP with ROC area of 0.69 (95% CI 0.62-0.76). Sensitivity was 0.66 (95% CI 0.52-0.78) (HC score ≤ 1) and specificity was 0.68 (95% CI 0.61-0.74) (HC score > 1). Conclusions: HC did not detect CAP in approximately 30% of our Japanese cases of acute respiratory illness. HC scoring should be used cautiously in non-Western populations.

Trial registration: UMIN trial ID: UMIN000035346

Keywords: Heckerling's criteria, community-acquired pneumonia, sensitivity, decision support techniques, Japan

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Contents

Background

Community-acquired pneumonia (CAP) can lead to mortality[1, 2, 3]. Early diagnosis and selection of appropriate antimicrobials are essential[4]. Chest radiography is recommended for diagnosis of CAP, but the process is costly, and it is inconvenient to undertake chest radiography for all outpatients that have acute respiratory symptoms. Additionally, excessive chest radiography unnecessarily exposes patients to radiation. Heckerling's criteria (HC) scoring is a commonly-used, useful substitute for chest radiography. It is simple and uses well-validated criteria models based on symptoms to predict or rule out CAP[5]. A systematic review of twelve studies that used clinical decision rules (CDRs) to predict patients at low risk for CAP identified three CDRs using a point score[6]. Of these, only HC was externally validated, had a large sample size, and of all the CDRs studied in the review, it had the highest area under the receiver operating characteristic curve (AUROCC)[6]. Within an Asian population, however, the diagnostic validity of the HC model is unclear. Several studies have reported racial differences in symptom types and prevalence of conditions, which might affect the validation of HC scoring[7, 8]. If verified for use within this population, HC scoring could be recommended for use in Japan. This study aims to validate the use of HC scoring in a Japanese primary care setting.

Methods

2.1 Design and participants

This prospective observational study included febrile patients 1C° higher than baseline body temperature or

> 37˚C) aged ≥ 16 years with upper respiratory tract infection (URTI) and cough for at least three days in either of two community hospitals between December 2016 and October 2018. Study sites were the Tone Chuo Hospital (TCH, 253 beds) and the Akashi Medical Center (AMC, 382 beds), both local medical support centers in Japan with emergency medical care centers and primary care practices. Excluded from this study were patients with unstable physical conditions (e.g. shock), multiple incidences of chronic pulmonary disease, apparent history/presence of dysphagia, presence of obstructive pneumonia, lung abscess, empyema, healthcare-associated pneumonia or hospital-onset pneumonia referred from other facilities, tuberculosis, non-tuberculous mycobacterium lung infections, lung mycosis, sinusitis, or tonsillitis. We also excluded patients with a history of fever or coughing for more than 21 days.

2.2 Data collection

For background data, we collected information on: age, gender, visiting month, comorbidities, close contact with patients with confirmed atypical pathogen infections, history of preceding antimicrobial use, history of signs and symptoms (rhinorrhea, sputum, severe cough, sore throat, myalgia, arthralgia, diarrhea, rash), duration of symptoms at the time of clinical visits, findings of chest auscultation and presence of pneumonia. 'Tachypnea' was defined as respiratory rate ≥ 22 /min[9]. 'Hypoxia' was defined as SpO_2 level < 95%[10]. 'Hypertension' was defined as systolic blood pressure level ≥ 130 mmHg[11]. 'Severe cough' was defined as cough-induced vomiting, sleep disturbance, and/or persistent coughs. Pneumonia was diagnosed based on clinical symptoms and signs and radiological findings compatible with pneumonia, without other causes attributed to abnormal radiological findings[12]. All images were reviewed by a board-certified pulmonary physician (N.I.) for determination of final diagnosis.

2.3 Outcome measures

The primary outcome measure is the accuracy of HC for discriminating patients with and without CAP. HC score ≥ 4 is strongly indicative of pneumonia, whereas ≤ 1 suggests the patient is pneumonia-free. HC consists of the following five items: BT > 37.8˚C= 1.0, PR > 100 beats/min = 1.0, rales = 1.0, decreased breath sounds = 1.0, and absence of asthma = 1.0.

2.4 Statistical analysis

The area under the receiver–operator characteristic curves (AUROCCs) of HC score for diagnosis of CAP were calculated using receiver operating curve (ROC) analysis. To assess the AUROCC for HC, univariate analysis was used to identify the factors associated with the area. Fisher's exact test was used for categorical variables and Student's t-test was performed for continuous variables. All statistical analyses were performed using the JMP Pro 11.2.1 software program (SAS Institute Inc., Cary, NC, USA).

Results

Figure 1 shows the flow of participants. We assessed 341 patients for eligibility. We excluded patients with sinusitis (n=3), with tonsillitis (n=3), with chronic symptoms (n=27), with sampling errors (n=3), and patients without data on outcome measures (n=9). The final study population was 296 patients.

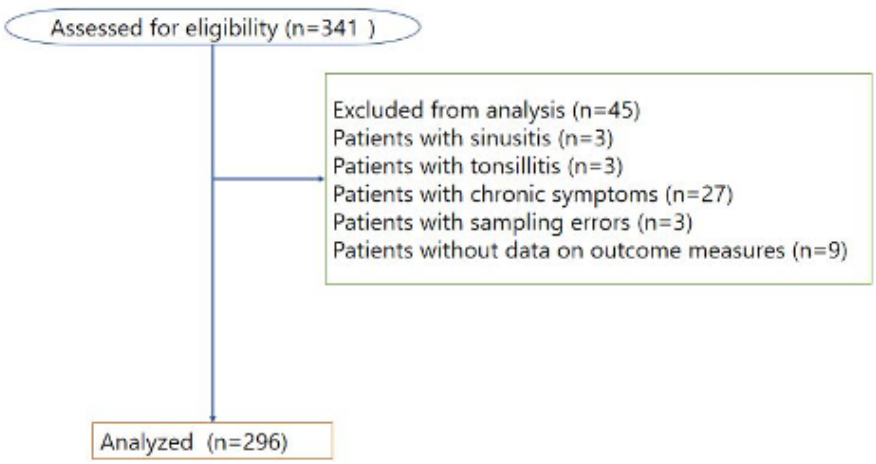


Figure 1. Diagram showing the flow of participants

The patients included 110 females (37.2%), mean age of the patients was 41.1 (SD 18.4) years old. CAP was diagnosed in 58 patients (18.9%). As well as chest X-rays, chest computed tomography (CT) scans were performed for 20 patients. Four patients were diagnosed with CAP by chest CT scan findings. Among the 58 patients with CAP, 78.4% reported sputum, 61.5% reported rhinorrhea and nasal congestion, 55.7% had sore throats, and 51.7% reported malaise. Comorbidities were as follows: chronic heart failure (n=1), chronic kidney disease (n=3), chronic liver disease (n=4), central nervous disease (n=4), and diabetes mellitus (n=17). Three patients had immunocompromised status and three patients were immobile. The mean HC score was 1.5 (SD 0.8) (Table 1). Patients with CAP were older,

more commonly male and had diabetes mellitus more often than patients without CAP (Table 2). Among HC items, PR > 100 beats/min, rales and decreased breath sounds were more commonly observed in patients with CAP than in patients without CAP. Total HC score was also higher in patients with CAP than in patients without it. Symptoms such as dyspnea, myalgia/arthralgia, and chills were seen in patients with CAP more frequently than in patients without CAP. They also had higher pulse rate and higher body temperature and had lower SpO_2 levels. Meanwhile, patients that did not have CAP had different symptoms to those that did, they more commonly had rhinorrhea/nasal congestion, sore throat and cervical lymphadenopathy.

Table 1. Study subject characteristics

	Mean [SD] or n (%)
n	296
Age (years)	41.1 [18.4]
Female	110 (37.2)
CAP	58 (19.6)
Recorded frequency of each HC items	
BT > 37.8°C	46 (15.5)
PR > 100 beats/min	77 (26.0)
Rales	30 (10.1)
Decreased breath sounds	13 (4.4)
Absence of asthma	285 (96.3)
Chronic pulmonary disease	0 (0.0)
Chronic heart failure	1 (0.3)
Chronic kidney disease	3 (1.0)
Chronic liver disease	4 (1.4)
Central nervous disease	4 (1.4)
Diabetes mellitus	17(5.7)
Immunocompromised status	3 (1.0)
Immobilization	3 (1.0)
Days after onset of illness	8.2 [4.2]
Rhinorrhea/nasal congestion	182 (61.5)
Sputum	232 (78.4)
Sore throat	165 (55.7)
Dyspnea	46 (15.5)
Myalgia/arthralgia	93 (31.4)
Headache	140 (47.3)
Malaise	153 (51.7)
Heat sensation	114 (38.5)
Chills	89 (30.1)
Diarrhea	24 (8.1)
Vomit	19 (6.4)
Altered mental status	0 (0)
Required hospitalization	27 (9.1)
Systolic blood pressure, mmHg	122.9 [18.7]
Diastolic blood pressure, mmHg	74.3 [14.3]
Pulse rate, bpm	90.0 [16.4]
BT, °C	37.2 [0.8]
Respiratory rate	16.0 [3.8]
SpO_2, %	97.2 [1.4]
Rash	11 (3.7)
Cervical lymphadenopathy	40 (13.5)
HC score	1.5 [0.8]

BT: Body temperature, SpO_2: saturation of percutaneous oxygen, HC: Heckerling's Criteria

Categorical data are presented as numbers (proportion, %). Continuous data are presented as mean values [standard deviation].

Figure 2 shows the ROC for HC validation in our patients. HC discriminated CAP with ROC area of 0.69 (95% CI 0.61-0.76), sensitivity 66% (95% CI 0.52-0.78) with an HC score cut-off point ≤ 1 and specificity 68% (95% CI 0.61-0.74) with an HC score cut-off point > 1. As for the results on the AUROCC by univariate analysis of each factor group, the AUC was higher in patients with high rate of respiration (Figure 3).

Discussion

3.1 Summary of main findings

When the original cut-off score of ≤ 1 was applied, HC failed to detect CAP in approximately 30% of our Japanese cases of acute respiratory illness. CAP was discriminated with a ROC area of 0.69. The original study by Heckerling, et al. reported greater accuracy in discrimination of CAP in their cohort (ROC area = 0.85), but their study was focused on American patients[5]. Accuracy of HC for diagnosing CAP was higher in our Japanese patients that had a high respiratory rate than in patients with lower rate. Other clinical prediction models of CAP have also included high respiratory rate[13, 14]. A recent systematic review by Marchello, et al. highlighted the importance of normal vital signs combined with normal pulmonary examination to rule out pneumonia[6]. When seeking to rule out CAP by HC it is therefore necessary to be cautious with patients with tachypnea.

3.2 Comparison with existing literature

An observational study of CAP patients in Japan reported mean axillary temperature as 37.6˚C[15]. In our study, approximately 75% of the patients with CAP had body temperature lower than 37.8˚C. Our findings are consistent with the study in terms of there being lower temperature among a greater number of patients than in the original study. This would dull the sensitivity of HC in Japanese patients because BT > 37.8˚C is the one of the items of HC. In the original cohort study, 54.5% of patients with pneumonia had a body temperature > 37.8˚C, compared with 23% of patients without pneumonia[5]. Difference in the methods of measurement of body temperature may have resulted in the comparatively lower body temperatures among our patients. In the original study, based in the United States, body temperature was measured orally, whereas we in Japan measured axillary temperature[16]. As well as body temperature, other items of HC were also less common in our patients than in the original report. As a result, mean HC score was 1.5 in our patients, which was much lower than those in previous cohorts (Nebraska cohort = 2.2, Virginia cohort = 2.1)[5].

Another finding of our study was that myalgia, breathlessness, higher pulse rate and body temperature, lower SpO_2 level, and fewer breath sounds and crackles were more typically observed in patients with CAP, which is consistent with the results of previous research[13, 17]. Although these variables were not associated with AUC of HC score for the diagnosis of CAP, consideration of these

Table 2. Characteristics of patients with and without CAP

	CAP	Non-CAP	*p*-value
n	58	238	
Age (years)	46.5 [21.4]	39.8 [17.4]	0.01
Female	28 (48.3)	158 (66.4)	0.01
Recorded frequency of each HC			
BT > 37.8°C	14 (24.1)	32 (13.4)	0.07
PR > 100 beats/min	23 (39.7)	54 (22.7)	0.01
Rales	16 (27.6)	14 (5.9)	0.01
Decreased breath sounds	7 (12.1)	6 (2.5)	<0.01
Absence of asthma	57 (98.3)	228 (95.8)	0.70
Chronic pulmonary disease	0 (0.0)	0 (0.0)	NA
Chronic heart failure	1 (1.7)	0 (0.0)	0.20
Chronic kidney disease	2 (3.4)	1 (0.4)	0.10
Chronic liver disease	2 (3.4)	2 (0.8)	0.17
Central nervous disease	0 (0.0)	4 (1.7)	1.00
Diabetes mellitus	8 (13.8)	9 (3.8)	<0.01
Immunocompromised status	0 (0.0)	3 (1.3)	1.00
Immobilization	2 (3.4)	1 (0.4)	0.10
Days after onset of illness	7.7 [3.3]	8.3 [4.3]	0.30
Rhinorrhea/nasal congestion	28 (48.3)	154 (64.7)	0.02
Sputum	49 (84.5)	183 (76.9)	0.21
Sore throat	23 (39.7)	142 (59.7)	<0.01
Dyspnea	17 (29.3)	29 (12.2)	<0.01
Myalgia/arthralgia	25 (43.1)	68 (28.6)	0.04
Headache	27 (46.6)	113 (47.5)	1.00
Malaise	31 (53.4)	122 (51.3)	0.77
Heat sensation	25 (43.1)	89 (37.4)	0.45
Chills	26 (44.8)	63 (26.5)	0.01
Diarrhea	4 (6.9)	20 (8.4)	1.00
Vomit	7 (12.1)	12 (5.0)	0.07
Altered mental status	0 (0)	0 (0)	NA
Required hospitalization	20 (34.5)	7 (2.9)	<0.01
Systolic blood pressure, mmHg	124.2 [23.1]	122.6 [17.5]	0.57
Diastolic blood pressure, mmHg	74.3 [14.8]	74.3 [14.2]	1.00
Pulse rate, bpm	94.2 [15.1]	89.0 [16.6]	0.03
BT, ˚C	37.5 [0.9]	37.1 [0.7]	<0.01
Respiratory rate	16.4 [4.1]	15.9 [3.8]	0.36
SpO_2, %	96.0 [2.1]	97.4 [1.0]	<0.01
Rash	1 (1.7)	10 (4.2)	0.70
Cervical lymphadenopathy	2 (3.4)	38 (16.0)	0.01
HC score	2.0 [1.0]	1.4 [0.7]	<0.01

BT: Body temperature, SpO_2: saturation of percutaneous oxygen, HC: Heckerling's Criteria
NA: Not applicable
Categorical data are presented as numbers (proportion, %). Continuous data are presented as mean values [standard deviation].

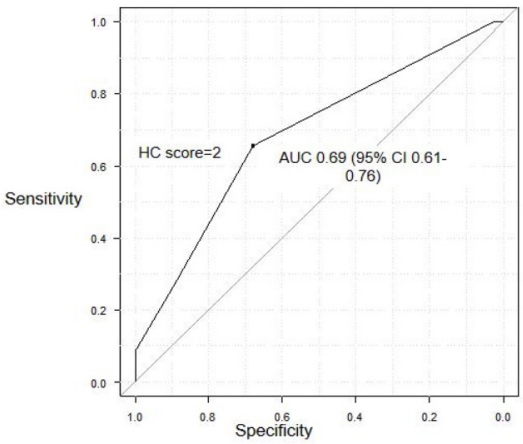
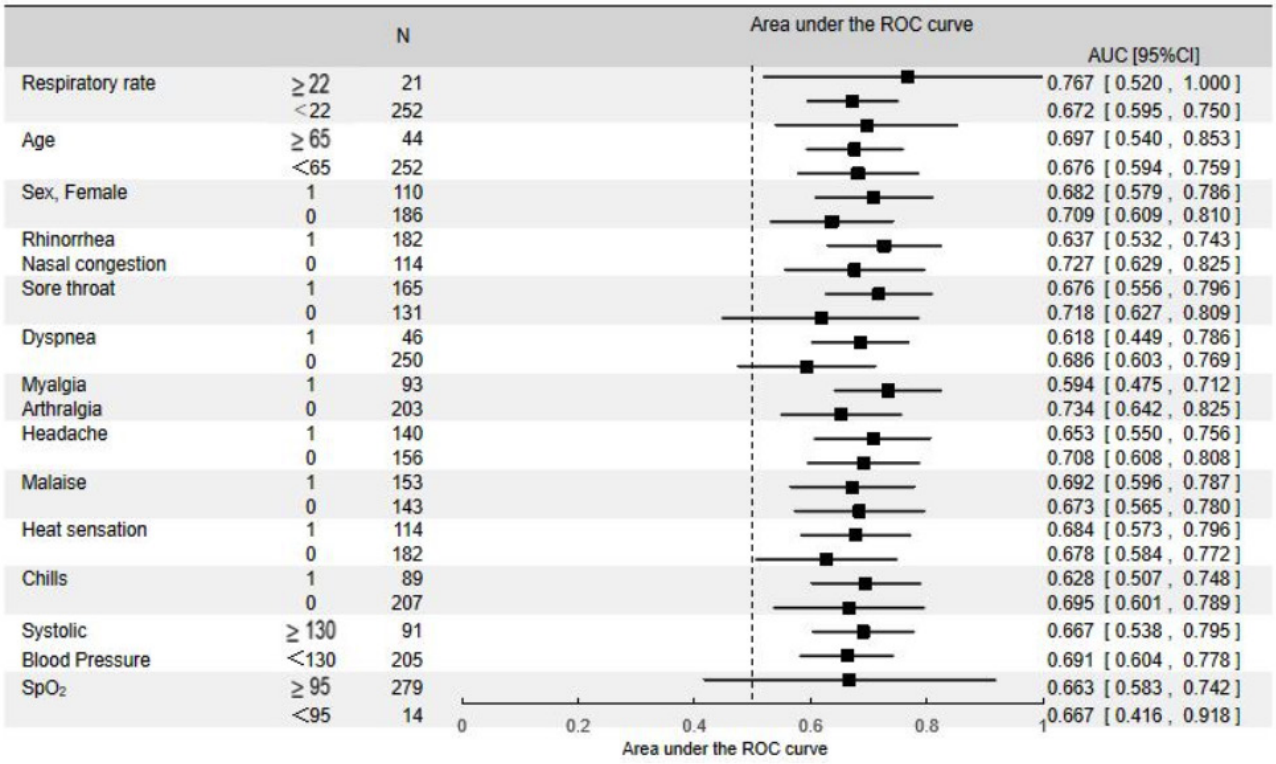


Figure 2. ROC for HC validated in our patients
Sensitivity: 0.66 (95% CI 0.52-0.78) (HC score ≤ 1)
Specificity: 0.68 (95% CI 0.61-0.74) (HC score > 1)

Figure 3. Forest plot of the area under the ROC by each factor group



variables as CDRs for CAP in further well-sized studies may be worthwhile.

3.3 Strengths and limitations

This is the first prospective multicenter study to examine applicability of HC scoring in a Japanese primary care setting. Data was collected from just two institutions, so validation in various settings is still required, although only two cohorts were chosen for validation in the original report by Heckerling, *et al*[5]. A second limitation was that this study was only conducted in Japanese institutions; validation in other Asian populations may or may not have similar results.

3.4 Implications for future research or clinical practice

HC showed low yield of detection of CAP in our Japanese population, and further modification is needed to meet a more satisfactory yield. Caution is needed when HC are applied with the aim of ruling out CAP among patients with fever and coughs, particularly in populations that have low HC scores. HC was, however, considered to be reliable in patients with high respiratory rate.

Conclusion

HC failed to detect CAP in approximately 30% of our Japanese cases of acute respiratory illness. HC should be used cautiously in non-Western populations.

List of abbreviations

AUC: area under the curve, BT: body temperature, CAP: community-acquired pneumonia, HC: Heckerling's criteria, PR: pulse rate, ROC: receiver operating curve, URTI: upper respiratory tract infection.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants in this study. Ethical approval was granted by the review board committees of both hospitals (TCH: approval number 2016-7-24; AMC: approval number 29-7).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

This study was supported by TOYOBO Co., Ltd. Hiromichi Suzuki received lecture fees and consulting fees from TOYOBO Co., Ltd. The other authors have no conflicts of interest to disclose with respect to this research.

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Authors' contributions

NI designed this study and wrote the first draft of this paper. SH collaborated in the study data collection. TS analyzed and interpreted the patient data. YT and AU collaborated with data analysis. HS and YA helped to draft the manuscript. SK participated in its design and coordination. YT and TM were scientific consultants of this study. All authors read and approved the final manuscript.

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