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ORIGINAL RESEARCH

Predictive factors for identifying infection source using combined chest-abdominal computed tomography in acute febrile older patients exhibiting no clinical indications in the emergency department

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Abstract

Diagnosing fever in older patients is challenging because of atypical symptom presentation. Understanding which factors can predict an infection source on systemic computed tomography (CT) scans can improve patient outcomes by informing treatment decisions. This study aimed to investigate the predictive factors for identifying infection source using combined chest and abdominal CT in older febrile patients exhibiting no clear indications in the emergency department (ED). This was a single-center retrospective study that enrolled 169 acute febrile older patients without any clinical evidence of fever, who underwent systemic CT in the ED between January 2017 and June 2019. Fever in older patients was defined as tympanic temperature $\geq$37.2 ℃ or an increase in body temperature by $\geq$1.3 ℃. Lack of clinical evidence of fever included an absence of suggestive findings in medical history, review of systems, physical examination or basic emergency diagnostic tests. CT results revealed 98 and 71 patients with negative and positive infection sources, respectively. Multivariate logistic regression analysis identified underlying diabetes mellitus (odds ratio (OR) = 2.667, 95% confidence interval (CI): 1.209–5.883, p = 0.015) and malignancy (OR = 13.272, 95% CI: 2.590–67.990, p = 0.002), quick Sequential Organ Failure Assessment score of 2 or more ($\geq$2 points) (OR = 6.687, 95% CI: 2.568–17.410, $p < 0.001$), and serum C-reactive protein greater than 5.15 mg/dL (>5.15 mg/dL) (OR = 9.773, 95% CI: 3.944–24.217, $p < 0.001$) as independent predictive factors for infection source in acute febrile older patients showing no clinical evidence in the ED. Physicians could consider recommending systemic CT scans when there is a high clinical benefit for acute febrile older patients who lack clear evidence of fever but have the predictive factors identified in this study.

Keywords

Aged; Emergency department; Fever; Infections; Tomography

1. Introduction

The global population is experiencing a rise in the proportion of older individuals. The older population refers to individuals who are 65 years of age or older [1]. The morbidity and mortality rates for many infections are higher among older than younger adults, and aging appears to be the primary risk factor for increased morbidity and mortality [2, 3]. Therefore, prompt diagnosis and initiation of appropriate supportive and antibiotic treatment are essential in older patients with infection [2, 4]. However, infections are often atypical and present as subtle complaints, with fever being less frequent or absent, in older patients compared to younger adults [2, 4]. An absent or blunted fever response to infection can complicate the diagnosis in the older population. Conversely, fever is more likely to be associated with serious infections in older patients than in younger adults [2, 4].

When dealing with acute febrile older patients in the emergency department (ED), emergency physicians aim to discern whether the fever is attributable to an infectious or non-infectious cause. This evaluation typically involves obtaining the patient's medical history, conducting a review of systems, performing physical examinations, and employing emergency diagnostic tests, including various blood tests, urinalysis, and simple chest radiography. However, making decisions about the future treatment plan can be challenging, particularly among older adults, if there are no clinical indications pointing to the cause of the fever. Computed tomography (CT) can be considered as a diagnostic tool for identifying the infection source in such patients, which can help to choose the appro-

priate antibiotic treatment and determine whether a specific procedure or surgery is necessary [5, 6]. However, despite determination of the infection source, the patient prognosis may differ without any clinical benefit [7, 8]. CT is believed to clarify the cause of fever among such patients, particularly when vital signs are unstable or there is a suspicion of severe infection and sepsis indicated by elevated concentrations of inflammatory markers, such as C-reactive protein (CRP) and procalcitonin (PCT). Furthermore, CT aids in determining the management of acute febrile older patients, addresses test requests arising from concerns related to fever among patients and their guardians, and helps prevent delays in diagnosing infectious diseases, potentially avoiding litigation resulting from misdiagnosis. Although CT is an easily accessible and accurate diagnostic test in the ED, it is relatively expensive and has several limitations, such as additional medical costs [9], side effects of contrast media [10], and the risk of radiation exposure [11].

In previous studies, age was reported to be associated with infection source identification on systemic CT in adult febrile patients [12, 13]. The authors of these studies argued that CT should be actively considered if febrile patients are older. However, no studies or statistical analyses have been conducted to address whether systemic CT is useful in detecting sources of infection in acute febrile older patients without clinical indications in the ED or whether there are any factors that can predict an infection source through systemic CT in these patients. Hence, we aimed to investigate the clinical features in acute febrile older patients who exhibited a positive infection source on systemic CT scans covering both the chest and abdomen. Additionally, we aimed to identify any factors that could predict the presence of an infection source on systemic CT scans in acute febrile older patients who presented to the ED without any clinical evidence of the cause of their fever.

2. Material and methods

2.1 Study design and population

This single-center retrospective study was conducted at a university-affiliated training hospital with 690 beds. The ED receives approximately 50,000 patients per year. It consists of a local emergency medical center and a separate regional level 1 trauma center. The medical records of all older patients registered at the local emergency medical center who underwent combined chest and abdominal CT scans in the ED between 01 January 2017, and 30 June 2019, were reviewed. Among older patients aged $\geq$65 years who underwent systemic CT in our non-traumatic ED, the following were excluded from our study: (1) those who did not have fever in the ED; (2) acute febrile patients with a clinical evidence in medical records, laboratory results, and basic chest radiography reports; (3) acute febrile patients who were administered empirical antibiotics at other hospitals before visiting our ED; and (4) those with missing data. Both simple chest radiography and systemic CT findings in this study were based solely on the radiologists' reports. Simple chest radiographs were interpreted by multiple radiologists, while chest CT was interpreted by one radiologist, and abdominal CT was interpreted by two radiologists. Finally, the patients enrolled in this study were classified into those with negative and positive infection sources as identified on systemic CT, based on the radiologist's CT reports. To objectively select participants, the medical records, laboratory results, and simple chest radiography reports of all older patients who underwent systemic CT in the ED were crosschecked by three other emergency medicine board physicians, and the study participants were unanimously determined.

2.2 Operational definitions

In this study, older patients are defined as those aged 65 years and over [1]. Older adults have a lower baseline body temperature (BT) than younger adults do, and only a few studies have established a normal BT for the older population [2, 14, 15]. Fever in older adults can be defined as an oral or tympanic temperature $\geq$37.2 °C or an increase in baseline temperature of $\geq$1.3 °C [2, 16]. In this study, patients (1) whose tympanic membrane BT was $\geq$37.2 ℃ or (2) who had an increase in BT of $\geq$1.3 ℃ measured during their stay in the ED were defined as those having fever.

Acute fever was defined as onset within the first week of fever. Acute febrile older patients without any clinical indication of fever were defined as: (1) those without respiratory (sore throat, cough, rhinorrhea and sputum), digestive (abdominal pain and diarrhea), and urinary (dysuria and frequency) infection symptoms and focal pain or heat sensation at the extremities during the present illness and in a review of systems; (2) those without findings such as abnormal breathing sounds, abdominal tenderness, costovertebral angle tenderness, abnormal skin lesions (rash, blister, swelling and warmth), and tenderness of the body and extremities upon physical examination; and (3) those without evidence of infection in urinalysis (bacteriuria, pyuria and positive nitrite test) and abnormal findings such as pulmonary infiltration, a mass-like lesion, and blunting of the costophrenic angle on simple chest radiography.

2.3 Data collection

Clinical information included age, sex, comorbidities (hypertension, cardiovascular diseases such as myocardial infarction and congestive heart failure, diabetes mellitus (DM), cerebral vascular disease, dementia, respiratory disease (chronic obstructive pulmonary disease, asthma), rheumatologic disease, liver cirrhosis, moderate to severe chronic kidney disease, and underlying malignancy), vital signs on detection of fever in the ED based on our criteria for acute febrile older patients (BT was measured using an infrared tympanic membrane thermometer (IRT 6520, Braun, Chihuahua, Mexico) in the ED with a constant temperature of 24–25 ℃ and 30% humidity, maintained using an automatic temperature control system), duration of fever, polypharmacy (number of medications), presence of indwelling medical devices (urinary catheter/cystostomy, nasogastric tube/gastrostomy, tracheostomy and central vein catheter) before visit at our ED, and residency before ED visit. Emergency laboratory data (white blood cell count and

platelet count, serum levels of hemoglobin, CRP, aspartate aminotransferase, alanine aminotransferase, bilirubin, glucose, creatinine, albumin and sodium) were assessed. To estimate disease severity, we also investigated whether the systemic inflammatory response syndrome (SIRS) criteria were satisfied and calculated the quick Sequential Organ Failure Assessment (qSOFA) score. The presence and anatomical location of infection sources were investigated using CT reports by a radiologist. In addition, ED treatments (antipyretics, antibiotics and vasopressors), emergency surgical procedures (percutaneous transhepatic biliary or gallbladder drainage, endoscopic retrograde cholangiopancreatography), and ED disposition were examined.

2.4 Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Data with a normal distribution were compared using the student's *t*-test and presented as the mean ± standard deviation. Abnormally distributed data were compared using the Mann-Whitney U test and presented as medians and interquartile ranges. The chi-squared test was used to compare categorical variables between the two groups and these data are presented as numbers (%). Logistic regression analysis was performed to identify the predictive factors determining the presence of infection source on systemic CT in acute febrile older patients without any clinical evidence of fever in the ED. The cut-off values for serum CRP and albumin levels were defined using receiver operating characteristic (ROC) curve analysis. The cut-off values for the qSOFA score and polypharmacy were chosen as those used in previous studies. The CRP level (>5.15 mg/dL, the cut-off value determined using the best Youden index), albumin level (≤3.6 mg/dL, the cut-off value determined using the best Youden index), qSOFA score (≥2 points, the cut-off point defined by Sepsis-3) [17, 18], and polypharmacy (≥5 medications) were used for logistic regression analysis as dichotomous variables [19]. The variables with a p-value < 0.1 in the univariate analysis were incorporated into the multivariate logistic regression analysis using the backward elimination method utilizing the likelihood ratio. For all tests, p-values < 0.05 were considered statistically significant.

3. Results

3.1 Study population

During the study period, 1694 patients aged ≥65 years underwent combined chest and abdominal CT in our non-trauma ED. Among these, the following patients were excluded from the study: 681 without fever identified according to vital sign records; 652 with a clear clinical indication of fever as per emergency medical charts, laboratory results, and simple chest radiography reports; 179 undergoing antibiotic treatment at other hospitals before visiting our ED; and 13 with missing data. Finally, 169 acute febrile older patients without any clinical evidence for fever who underwent systemic CT in the ED were enrolled in this study. Based on the systemic CT indications, patients were divided into two groups: 98 patients with a negative infection source and 71 patients with a positive infection source (Fig. 1).

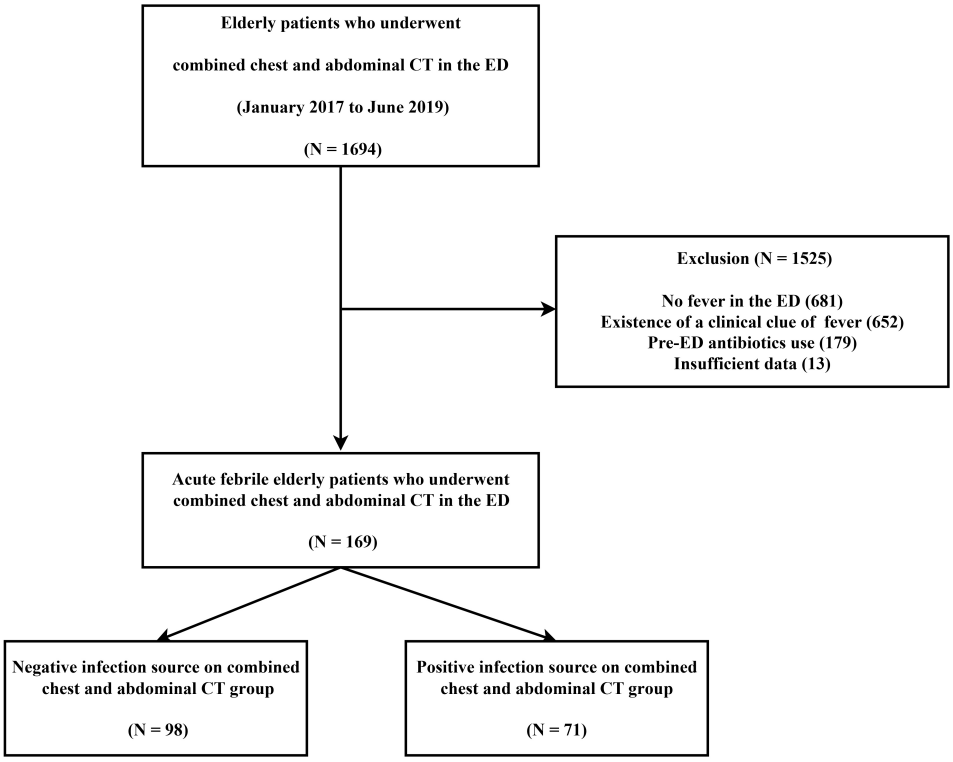

FIGURE 1. Flow chart describing the process of patient selection for the study. CT: computed tomography; ED: emergency department.

3.2 Comparison between negative and positive infection sources as identified on systemic CT scans

The clinical characteristics of the study population are summarized in Table 1. There was no significant difference in age, sex, vital signs (diastolic blood pressure, heart rate, respiratory rate, body temperature, and Glasgow Coma Scale), duration of fever, residential status, and rate of indwelling medical devices before visiting the ED between the two groups. In terms of vital signs, the positive infection source group showed a statistically significant lower systolic blood pressure than the negative infection source group (p = 0.011). Regarding comorbidities, polypharmacy, DM, dementia, and malignancy were more prevalent in the positive infection group than in the negative infection group (Table 1). In the ED, no difference in the use of antipyretics was observed between the positive infection source group and negative infection source group; however, antibiotics and vasopressors were administered more frequently, while central vein catheterization and emergency surgical procedures were performed more often (Table 1). In terms of ED disposition rates, the general ward (GW) and intensive care unit (ICU) admission rates were higher in the positive infection source group than in negative infection source group (GW admission, 64.8%, ICU admission, 25.4%; $p < 0.001$). Compared to the negative infection source group, the qSOFA score was higher among patients in positive infection source group ($p = 0.022$).

The additional laboratory and radiologic results of the study population are presented in Table 2. The median serum CRP level was higher ($p < 0.001$) and serum albumin level was lower ($p = 0.001$) in the positive infection source group than in the negative infection source group, as revealed in the systemic CT scans. There were no statistically significant differences in other laboratory values. In the positive group, a total of 39 infection source lesions were identified on chest CT, including pneumonia (35 patients) and unilateral parapneumonic effusion (four patients). On abdominal CT, a total of 40 infection source lesions were detected, including cholecystitis (nine patients), cholangitis (five patients), liver abscess (four patients), enterocolitis (13 patients), acute pyelonephritis (eight patients), and appendicitis (one patient). Among these, eight patients exhibited simultaneous pneumonia and other abdominal co-infection sources (two cholecystitis cases, one liver abscess case, three enterocolitis cases, and two acute pyelonephritis cases) (Fig. 2).

3.3 Predictors of the infection source on systemic CT in febrile older patients without a clinical clue for fever in the ED

In the ROC analysis, the area under the curve (AUC) of CRP level was 0.694 (95% confidence interval (CI): 0.599–0.778, $p < 0.001$). The optimal cut-off value for CRP level was >5.15 mg/dL (sensitivity, 74.1%, 95% CI: 60.3–85.0; specificity, 58.9%, 95% CI: 45.0–71.9). The AUC of the albumin level was 0.646 (95% CI: 0.568–0.718, $p < 0.001$). The optimal cut-off value for albumin level was ≤3.6 mg/dL (sensitivity, 62%, 95% CI: 49.7–73.2; specificity, 66.3%, 95% CI: 56.1–75.6).

The results of the multivariate logistic regression analysis are presented in Table 3. Regression analysis revealed that underlying DM (OR = 2.667, 95% CI: 1.209–5.883, $p = 0.015$), malignancy (OR = 13.272, 95% CI: 2.590–67.990, $p = 0.002$), qSOFA score of 2 or more (≥2 points) (OR = 6.687, 95% CI: 2.568–17.410, $p < 0.001$), and serum CRP greater than 5.15 mg/dL (>5.15 mg/dL) (OR = 9.773, 95% CI: 3.944–24.217, $p < 0.001$) were independent predictive factors of the infection source on systemic CT in acute febrile older patients exhibiting no clinical indication for fever in the ED. The number of patients with various predictors in both groups is shown in Fig. 3.

4. Discussion

Underdiagnosis of infection in older patients increases the possibility of progression to sepsis and increased risk of hospital death due to selection of inappropriate antibiotics and treatment delay [3, 20]. In contrast, overdiagnosis can cause problems such as additional medical costs due to unnecessary hospitalization and potential exposure of patients to excessive harm such as invasive procedures, and antibiotic misuse [21]. Diagnosing the cause of fever in acute febrile older patients with no clinical indicators in a crowded ED care environment is challenging. Determining appropriate disposition and identifying which patients should undergo systemic CT scans present additional complexities.

To our knowledge, there are no clinical guidelines for the use of systemic CT in acute febrile older patients without clinical indications for fever in the ED. Additionally, there is a lack of statistical data regarding the accuracy of systemic CT in identification of infection source in such patients. A previous study conducted on patients with fever of unknown origin for >3 weeks showed that abdominal CT was helpful in establishing a diagnosis in 12 of 60 patients (20%) and chest CT helped establish diagnoses in nine of 46 patients (20%) [22]. In previous studies by Lee *et al.* [12] and Sert *et al.* [13], the rates of infection source identification on systemic CT in adult febrile patients aged 18 years or older were found to be 36.8% and 31.2%, respectively. In this study, the rate of infection source identification using systemic CT in acute febrile older patients without clinical indicators in the ED was approximately 42%, showing a higher yield than that in previous studies.

Older patients generally have a higher rate of comorbidities than younger adults [2–4]. Similarly, in this study, most older patients had comorbidities, with only 14.2% (24 of 169 patients) having no comorbidities. We examined whether each comorbidity in acute febrile older patients was related to the prediction of infection sources on systemic CT. As a result, two diseases, underlying DM and malignancy, were associated with the presence of an infection source on systemic CT. Older patients with DM are more susceptible to infection [23]. Patients with DM appear to have a higher incidence of respiratory infections, skin and soft tissue infections, as well as gastrointestinal and genitourinary infections [24]. Hyernard *et al.* [25] demonstrated that older diabetes patients were more prone to having atypical signs of bacteremia. Diabetic peripheral neuropathy in old age is characterized by a progressive

TABLE 1. Baseline characteristics of the study population and comparison of clinical features between negative and positive infection source groups as identified on systemic CT scans.

	Overall (n = 169)	Negative infection source group (n = 98; 58%)	Positive infection source group (n = 71; 42%)	*p*-value
Age (yr)	77 (72.0–83.0)	77 (72.0–81.0)	78 (74.0–85.5)	0.109
65–79 yr	98 (58.0)	60 (61.2)	38 (53.5)	0.399
≥80 yr	71 (42.0)	38 (38.8)	33 (46.5)	
Sex				
Male	73 (43.2)	41 (41.8)	32 (45.1)	0.794
Female	96 (56.8)	57 (58.2)	39 (54.9)	
Vital signs				
Systolic BP (mmHg)	130 (110.0–143.0)	130 (110.0–148.0)	120 (102.5–134.5)	0.011*
Diastolic BP (mmHg)	74 (61–81)	75 (64–90)	73 (60–80)	0.110
Heart rates (bpm)	97 (83.0–113.0)	93 (82.0–112.0)	103 (92.5–114.0)	0.095
Respiratory rates (bpm)	20 (18–22)	20 (18–22)	20 (18–24)	0.385
Body temperature (°C)	38.4 (37.8–39.0)	38.3 (37.8–39.0)	38.5 (37.8–39.1)	0.873
Glasgow Coma Scale	15 (13–15)	15 (13–15)	14 (12–15)	0.073
Duration of fever (h)	4.0 (2.0–8.0)	3.9 (2.2–8.0)	4.0 (2.0–10.0)	0.395
Comorbidities				
Hypertension	96 (56.8)	55 (56.1)	41 (57.7)	0.958
Cardiovascular disease	28 (16.6)	19 (19.4)	9 (12.7)	0.343
Diabetes mellitus	63 (37.3)	28 (28.6)	35 (49.3)	0.010*
Cerebrovascular disease	28 (16.6)	14 (14.3)	14 (19.7)	0.467
Dementia	23 (13.6)	8 (8.2)	15 (21.1)	0.028*
Respiratory disease	22 (13.0)	12 (12.2)	10 (14.1)	0.905
Rheumatologic disease	7 (4.1)	3 (3.1)	4 (5.6)	0.662
Liver cirrhosis	7 (4.1)	3 (3.1)	4 (5.6)	0.662
≥Moderate CKD	8 (4.7)	4 (4.1)	4 (5.6)	0.919
Malignancy	13 (7.7)	3 (3.1)	10 (14.1)	0.018*
Number of comorbidities	2 (1–2)	1 (1–2)	2 (1–3)	0.007*
Indwelling medical devices				
Nasogastric tube/Gastrostomy	4 (2.4)	2 (2.0)	2 (2.8)	>0.999
Tracheostomy	2 (1.2)	0	2 (2.8)	0.342
Urinary catheter/Cystostomy	11 (6.5)	4 (4.1)	7 (9.9)	0.235
CV catheter	0	0	0	
Polypharmacy (≥5 medications)	50 (29.6)	21 (21.4)	29 (40.8)	0.011*
Residency				
At home	134 (79.3)	82 (83.7)	52 (73.2)	0.144
Nursing facility/Hospital	35 (20.7)	16 (16.3)	19 (26.8)	
SIRS (yes)	132 (78.1)	73 (74.5)	59 (83.1)	0.251
qSOFA score	1 (0–1)	1 (0–1)	1 (0–2)	0.022*
Treatments in the ED				
Antipyretics	127 (75.1)	78 (79.6)	49 (69.0)	0.164
Antibiotics	101 (59.8)	33 (33.7)	68 (95.8)	<0.001*
Vasopressors	28 (16.6)	10 (10.2)	18 (25.4)	0.016*
Procedures in the ED				
Intubation	3 (1.8)	0 (0)	3 (4.2)	0.143
CV catheterization	28 (16.6)	10 (10.2)	18 (25.4)	0.016*
Surgical procedure	8 (4.7)	0 (0)	8 (11.3)	0.002*
ED disposition				
Discharge from the ED	73 (43.2)	66 (67.3)	7 (9.9)	
GW admission	74 (43.8)	28 (28.6)	46 (64.8)	<0.001*
ICU admission	22 (13.0)	4 (4.1)	18 (25.4)	

*CT: computed tomography; BP: blood pressure; CKD: chronic kidney disease; CV: central vein; SIRS: systemic inflammatory response syndrome; qSOFA: quick Sequential Organ Failure Assessment; ED: emergency department; GW: general ward; ICU: intensive care unit; *p-value < 0.05.*

TABLE 2. Baseline laboratory and radiologic findings of the study population and comparison of laboratory findings between negative and positive infection source groups as identified on systemic CT scans.

	Overall (n = 169)	Negative infection source group (n = 98; 58%)	Positive infection source group (n = 71; 42%)	*p*-value
Laboratory findings				
WBCs (×10^3 cells/μL)	11.8 (8.1–15.7)	11.6 (8.0–16.4)	11.9 (8.1–14.5)	0.559
Hb (g/dL)	12.7 (10.9–14.0)	12.9 (11.5–14.1)	12.5 (10.6–13.6)	0.090
Platelets (×10^3 cells/μL)	224 (166.0–285.0)	230 (169.0–292.0)	217 (166.0–281.5)	0.181
CRP (mg/dL)	6.4 (2.2–12.6)	4.4 (0.8–11.7)	8.8 (4.4–14.6)	<0.001*
AST (IU/L)	31 (21–58)	27 (19–61)	34 (26–56)	0.090
ALT (IU/L)	20 (13.0–35.0)	19 (12.0–32.0)	21 (13.5–48.5)	0.172
Bilirubin (mg/dL)	0.9 (0.6–1.5)	0.9 (0.6–1.5)	1.0 (0.6–1.6)	0.889
Glucose (mg/dL)	148 (113–193)	159 (113–195)	143 (113–190)	0.550
Creatinine (mg/dL)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.0 (0.7–1.4)	0.059
Albumin (g/dL)	3.7 (3.4–4.0)	3.8 (3.5–4.0)	3.5 (3.3–3.9)	0.001*
Sodium (mEq/L)	135.5 (132.0–138.5)	135.0 (131.0–139.5)	136.0 (132.5–137.5)	0.901
Infection sources on CT				
Chest CT			31 (43.7)	
Abdominal CT			32 (45.1)	
Both CT			8 (11.3)	

*CT: computed tomography; WBC: white blood cell; Hb: hemoglobin; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; *p-value < 0.05.*

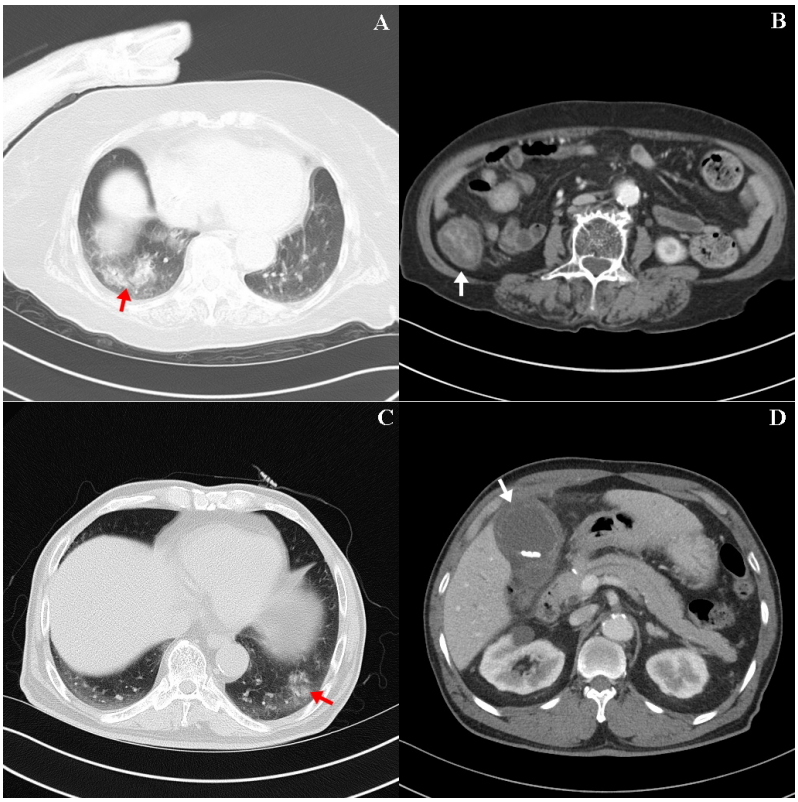

FIGURE 2. Examples of co-infection sources on combined chest and abdominal CT in this study. (A,B) show co-infection sources of pneumonia (red arrow—patchy consolidation in right lower lobe) and colitis (white arrow—edematous wall thickening of ascending colon) in an 87-year-old woman. (C,D) show pneumonia (red arrow—focal, peri-bronchial ill-defined consolidation) and acute cholecystitis (white arrow—thick enhance gall bladder wall and multiple stones) in a 72-year-old man.

TABLE 3. Predictive factors associated with presence of the infection source on systemic CT in acute febrile elderly patients without any clinical clue of the cause of fever in the emergency department.

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Vital signs				
Systolic BP (mmHg)	0.980 (0.968–0.992)	0.002*		
Comorbidities				
Diabetes mellitus (yes)	2.431 (1.283–4.606)	0.006*	2.667 (1.209–5.883)	0.015*
Dementia (yes)	3.013 (1.200–7.566)	0.019*		
Malignancy (yes)	5.191 (1.373–19.622)	0.015*	13.272 (2.590–67.990)	0.002*
Polypharmacy (≥5 medications)	2.532 (1.288–4.977)	0.007*	2.024 (0.877–4.670)	0.099
qSOFA score (≥2 points)	3.197 (1.538–6.646)	0.002*	6.687 (2.568–17.410)	<0.001*
Laboratory findings				
CRP (>5.15 mg/dL)	4.140 (2.133–8.035)	<0.001*	9.773 (3.944–24.217)	<0.001*
Albumin (≤3.6 g/dL)	3.210 (1.699–6.066)	<0.001*		

*CT: computed tomography; OR: odds ratio; CI: confidence interval; BP: blood pressure; qSOFA: quick Sequential Organ Failure Assessment; CRP: C-reactive protein; *p-value < 0.05.*

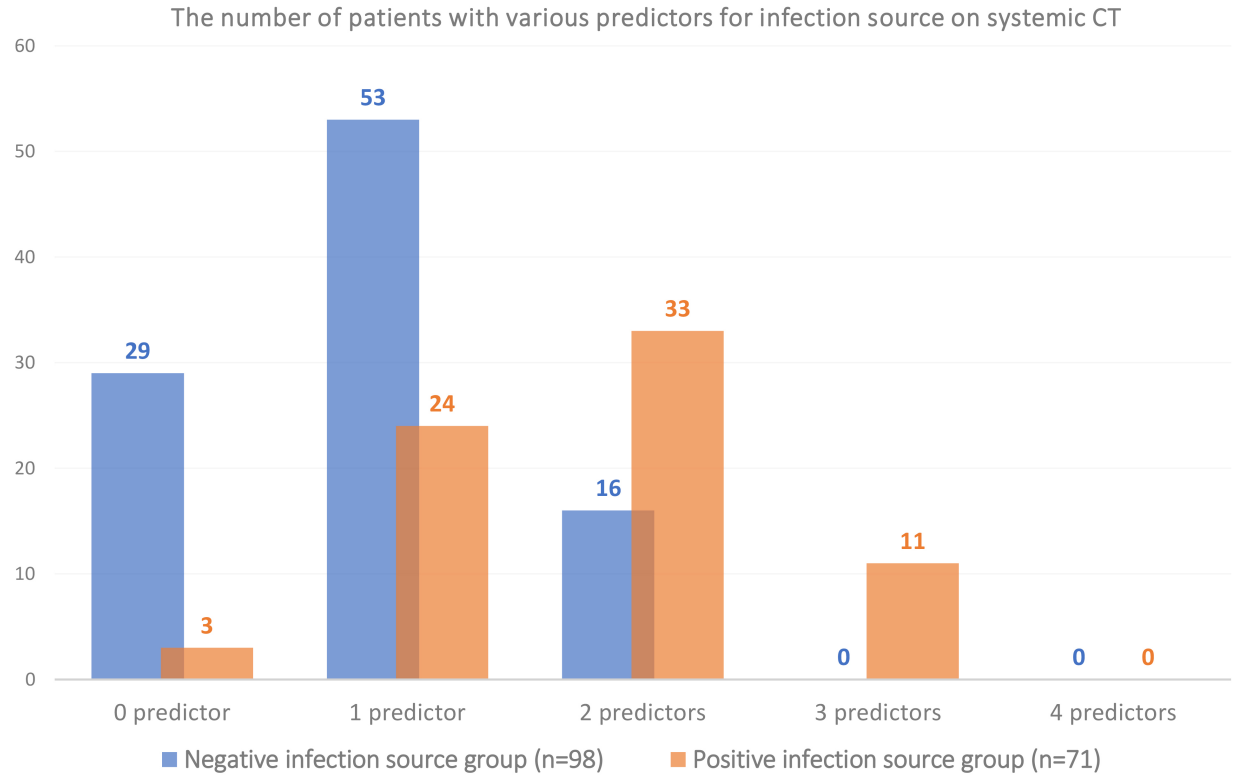

FIGURE 3. Bar graph of the number of patients with various predictors in each group. CT: computed tomography.

decline in sensory perception, which may also be accompanied with pain. These symptoms often progress proximally to full loss of sensation [26]. The more atypical symptoms of infection in older diabetes patients can be attributed to a combination of the neuronal dysfunction and physiological changes associated with age. Owing to the decrease in immunity due to aging, older patients have a higher risk of developing malignancies and infections. Indeed, aging is accompanied by a decrease and dysregulation in the protective immunity, which is defined as "immunosensescense". This condition is associated with a higher susceptibility to various age-related conditions such as infections, cardiovascular and neurodegenerative diseases, autoimmune disorders, and malignancies [27]. Life-long exposure to internal metabolic insults and external factors results in the accumulation of oxidative stress and DNA damage. This can lead to cell transformation and tumor initiation. Additionally, the lack of an effective immune response against tumor development due to immunosenescence can increase the incidence of malignancy in old age [28]. Several factors increase the risk of infection in patients

with underlying malignancies. Most of these infections are related to obstruction due to tumor progression and disruption of anatomical barriers, while others are related to various treatment-related factors (chemotherapy, radiation, diagnostic and/or therapeutic surgical procedures, and the increasing use of medical devices) [29]. Based on this evidence, we suggest an increased frequency of systemic CT scans in the ED for acute febrile older patients with underlying malignancy or diabetes who exhibit fever without any clinical evidence.

Polypharmacy is common in older patients with multiple underlying comorbidities [19, 30]. To examine its impact, we defined polypharmacy as the administration of five or more medications. In this study, polypharmacy was observed in 29.6% (n = 50) of the study population, and a higher polypharmacy rate was observed in the positive infection group (40.8%). However, polypharmacy was not a significant independent predictor in multivariate logistic regression analysis. This study did not evaluate the effects of different types of medications. For example, medications for antihypertension may have impacted the subjects of this study by affecting physiological responses to fever, such as heart rate and blood pressure. However, older individual may not metabolize drugs as efficiently as younger ones, and their nutritional status is often unbalanced, which increases the risk of drug interactions [30]. The complex, unpredictable relationships between medications and the high possibility of consumption of various medicinal herbs and other nutritional supplements, such as vitamin supplements, made it impossible to predict whether medications would affect the final outcomes in the patients in this study. Hence, this issue needs to be clarified in further research.

Previous studies have indicated that PCT, but not CRP, is a useful predictive biomarker for identifying the infection source on CT for febrile adult patients [12, 13]. In this study, CRP measurement was conducted as a basic ED diagnostic test; however, PCT was only tested in a limited number of patients and could not be included as a variable. Unlike previous studies, this study was conducted on acute febrile older patients without clinical signs in the ED and, CRP (>5.15 mg/dL) was an inflammatory marker associated with the presence of infectious sources on systemic CT. Many studies have confirmed that PCT levels are more specific than CRP levels in detecting bacterial infections [31], and PCT levels demonstrated superior diagnostic efficacy compared to CRP levels in the identification of bacterial infection among older than aged 65 years with diabetes [32]. However, there is a lack of consensus regarding inflammatory markers for diagnosing bacterial infections; a conundrum prevails regarding the use CRP versus PCT. Another factor to consider is the cost involved since PCT analysis is substantially more expensive than CRP analysis. A previous study has suggested that measurement of CRP may be more helpful for diagnosing lower respiratory tract infections [33]. In a study conducted on the prediction of abdominal-pelvic CT findings based on CRP levels in patients with acute abdomen, elevated CRP levels were likely to increase positive findings on CT [34], and CRP levels in COVID-19 patients in the ED exhibit a correlation with the extent of lung involvement and serve as a significant indicator of clinical prognosis [35]. Previous studies have confirmed the correlation between elevated CRP and bacterial infection in patients with fever in low-resource environments [36]. Based on previous research and the results of our study, we believe that unlike with young febrile adult patients, CRP can be a useful predictor for the source of infection on systemic CT in the case of acute febrile older patients in the ED. Furthermore, CRP analysis is more cost-effective than PCT analysis for these patients.

There are several severity assessment models to detect high-risk patients among those with suspected infections [17, 18]. The qSOFA score includes systolic blood pressure ≤100 mmHg, a respiratory rate ≥22/minute, and an altered mental status (Glasgow Coma Scale <15) [17, 18]. A qSOFA score ≥2 points significantly predicts increased all-cause mortality rates among patients who are not in the ICU [17]. A previous cohort study showed that qSOFA is superior to SIRS in predicting in-hospital mortality in sepsis patients in the ED [18]. In contrast, a recent study showed that qSOFA was not an appropriate screening tool in the ED owing to its low sensitivity in predicting in-hospital mortality [37]. Despite this controversy, we sought to determine whether the SIRS criteria and qSOFA score could be used to predict the presence of the infection source on systemic CT in older patients with acute febrile illness without a clinical indication in the ED. In a previous study evaluating the usefulness of CT to determine the cause of fever in hospitalized adult patients, a higher percentage of patients had a qSOFA score ≥2 points in the suspicious CT finding group; however, qSOFA was not a factor associated with detection of any CT finding [38]. Contrarily, our study showed that the qSOFA score is a significant predictor for the presence of an infection source on systemic CT and could be applied as a decision-making tool in acute febrile older patients without clinical indicators in the ED. In an inpatient setting, physicians may be able to detect fever at an earlier stage. Therefore, in many cases, a CT scan is performed before any increase in the qSOFA score. We believe that the results of our study differ from those of the previous study owing to the disparities in the inpatient care setting compared to the ED care environment.

This study had several limitations. First, this was a single-center retrospective study with a relatively small sample size, which may have affected the generalizability of the results. Studies on large cohorts of older acute febrile patients without clinical indications in the ED need to be conducted for external validation. Second, the initial exclusion criteria included abnormal simple chest radiographic findings such as pulmonary infiltration, mass-like lesions, and blunting of the costophrenic angle. There may have been a bias in exclusion of patients with lung cancer that could be detected on simple chest radiography. Third, owing to the retrospective nature of the study, there were inherent limitations related to selection bias. The medical records of the patients were reviewed, and the possibility of inaccurate assessment of the cause of fever in patients with poor communication or cooperation during medical history and physical examination and symptom investigation in the ED exists. Fourth, polypharmacy was included as a variable. However, as previously discussed, we could not assess the type of medication. Fifth, in this study, simple chest radiographs were interpreted by multiple radiologists. Additionally, the

abdominal CT scans were read by two different radiologists, leading to a limitation in achieving standardization of the radiologists' reports. Despite these limitations, we identified factors associated with the presence of infection sources on systemic CT in acute febrile older patients without fever indications, which can assist emergency physicians' clinical decision-making to perform systemic CT for the diagnosis and treatment of acute febrile older patients in the ED, especially when no clinical evidence is present.

5. Conclusions

Although further prospective, multicenter trials remain necessary, this study confirmed that underlying conditions (DM, malignancy), CRP >5.15 mg/dL, and qSOFA score ≥ 2 points were associated with the presence of an infection source on combined chest and abdominal CT in acute febrile older patients exhibiting no clinical indications for fever in the ED. When caring for such patients in the ED, physicians can consider performing systemic CT to identify the infection source, especially if the potential clinical benefits, such as appropriate antibiotic selection, treatment plan establishment, and disposition decisions, are high.

AVAILABILITY OF DATA AND MATERIALS

All data and materials are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

WYS—designed the study, collected and analyzed the data, and wrote original draft. JCK—collected and analyzed the data. SWS and KTL—collected the data. HY—designed the study, supervised, reviewed and edited the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Boards of Daejeon Eulji University Hospital (IRB No. 2020-07-011). Given the retrospective nature of the study, the requirement for written informed consent was waived.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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