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ORIGINAL ARTICLE

# Impact of health care–associated community-onset cellulitis in Korea: a multicenter study

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## Abstract

We conducted a multicenter study to determine the clinical and microbiological characteristics of health care–associated (HCA) cellulitis in Korea. We retrospectively reviewed the medical records of patients who had been diagnosed with community-onset cellulitis. Of the 2208 cellulitis patients, 232 (10.5%) had HCA cellulitis, 1243 (56.3%) patients were hospitalized, and 15 (0.7%) died in hospital. Compared with community-acquired (CA) cellulitis, patients with HCA cellulitis were older and more frequently presented with comorbidity and septic shock. A total of 355 microorganisms were isolated from 314 patients (14.2%). *Staphylococcus aureus* (134 isolates) was the most common organism, followed by *Streptococcus* spp. (86 isolates) and Gram-negative fermenters (58 isolates). Methicillin-resistant *S. aureus* (MRSA) accounted for 29.1% (39/134) of *S. aureus* infections. None of the Gram-negative fermenters were resistant to carbapenem. The antibiotic susceptibility pattern of isolated microorganisms was not different between HCA and CA cellulitis. In patients with HCA cellulitis, *S. aureus* (11.2% [26/232] vs. 5.5% [108/1976], $p = 0.001$), including MRSA (4.3% [10/232] vs. 1.5% [29/1976], $p = 0.003$) and Gram-negative fermenters (6.0% [14/232] vs. 2.3% [44/1976], $p = 0.002$), were more common causative organisms than in CA-cellulitis patients. Age ≥ 65 years, septic shock, and HCA infection were statistically significant factors associated with in-hospital mortality.

**Keywords** Cellulitis · Health care–associated infection · *Staphylococcus aureus*

## Introduction

Cellulitis is a common form of skin and soft tissue infection. Unless accompanied by bacteremia or abscess, the etiology of cellulitis is usually not pursued clinically because this requires invasive procedures such as needle aspiration or punch biopsy. Traditionally, beta-hemolytic streptococci and *Staphylococcus aureus* have been

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considered the primary causative organisms [1–3], and empiric therapy with beta-lactam antibiotics has been the mainstay of therapy.

With the spread and diffusion of health care delivery beyond the confines of the hospital and the increasing use of broad-spectrum antibiotics both inside and outside of the hospital, multidrug-resistant (MDR) pathogens, traditionally thought to be confined to the hospital, are now seen in patients presenting from the community to the emergency department. Reflecting this shift in epidemiology, the concept of health care–associated (HCA) infections has emerged as a distinct entity [4]. This entity was defined based on evidence that these HCA infections may have a different epidemiology and that the causative pathogens are different from those causing community-acquired (CA) infection. Regarding bloodstream infection, the two pathogens most often responsible for CA bloodstream infections were *Escherichia coli* and *Streptococcus pneumoniae*, while *S. aureus* was the most common pathogen in patients with HCA and nosocomial bacteremia [4]. Furthermore, HCA infections are more often caused by potentially drug-resistant pathogens such as those commonly seen in hospital-acquired infections [4–6]. In the same study, methicillin-resistant *S. aureus* (MRSA) occurred with similar frequency in the groups with HCA infection (52%), and nosocomial infection (61%) but was uncommon in the group with CA bloodstream infection (14%) ($p = 0.001$) [4]. Patients with HCA infections were, hence, thought to require broader antibiotic coverage than that required for CA infection to reduce the risk of initially inadequate antibiotic therapy and subsequently worse outcomes. However, most studies focusing on established HCA infection have not addressed cellulitis [7, 8]. These infections, although seldom fatal, account for one of the most common causes of hospital admission [9].

In addition to HCA factors, there has been increasing concern about CA methicillin-resistant *S. aureus* (CA-MRSA). MRSA infections that occur in outpatients or within 48 h of hospitalization and that lack nosocomial exposures such as an indwelling device, recent hospitalization, surgery, dialysis, or residence in a long-term care facility have been termed CA-MRSA [10]. It is known that many pathogens such as *S. aureus*, which may be resistant to typical antimicrobials used in emergency departments in the USA [11, 12], are also major culprits in cellulitis. Although some authors have recommended that all cases of cellulitis be treated for MRSA-infection [13], microbial epidemiology can differ by regions, and a study of the recent microbial epidemiology of cellulitis is needed. For this reason, we conducted a multicenter study to determine the clinical and microbiological characteristics associated with HCA cellulitis in South Korea.

## Patients and methods

### Study design and population

A retrospective study was conducted at 13 teaching hospitals in South Korea. We reviewed the medical records of patients who had been diagnosed with community-onset cellulitis between January 2014 and December 2015. Patients younger than 18 years were excluded from the analysis. Patients who developed cellulitis after 48 h of hospitalization, had a surgical site infection, and had cellulitis caused by *Mycobacterium tuberculosis* were also excluded. This work was approved by the Institutional Review Board of each hospital, and informed consent was waived since this was a retrospective study without intervention that did not involve extra clinical specimens.

### Data collection

Demographics (age and sex), underlying diseases (diabetes mellitus, solid tumor, end-stage renal disease, liver cirrhosis, alcoholism, and hematologic malignancy), predisposing conditions (trauma, tinea pedis, previous surgery, previous infection, ulcer or dermatoses, injection drug use, and bite wound), and site of infection were searched. The results were categorized into HCA infection [4] if any one of the following conditions was met: (1) previous admission within 3 months for 2 days before the episode; (2) previous intravenous antibiotics, chemotherapy, or nursing care at home within 1 month before the episode; (3) previous hemodialysis with 1 month before the episode; or (4) residence in a nursing facility. Other patients were categorized as CA infections. Intensive care unit (ICU) admission and septic shock [14] as severity indices were searched. Also, laboratory findings, such as white blood cell (WBC) and platelet count, and levels of creatinine, and C-reactive protein (CRP), were collected. The results of cultures using blood, pus, and intra-surgical specimens were reviewed. Surgical intervention as a treatment modality and in-hospital mortality as an outcome indicator were investigated.

### Microbiologic methods

Microorganism identification was performed using standard methods at each hospital in which the quality control of microbiological tests has passed the evaluation of accredited institutions. According to standard methods [15], susceptibility testing was performed for the following antibiotics: non-antipseudomonal β-lactams (penicillin G, ampicillin, ampicillin/sulbactam, and ceftriaxone), minocycline, fluoroquinolones (moxifloxacin, levofloxacin, and ciprofloxacin), antipseudomonal β-lactams (piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, and doripenem), aminoglycosides (gentamycin, tobramycin, and

amikacin), and anti-MRSA drugs (vancomycin and linezolid). Microdilution was performed according to the guidelines of the Clinical and Laboratory Standards Institute [15]. *Staphylococcus* spp. were considered susceptible to oxacillin if the minimum inhibitory concentration (MIC) was ≤ 2 μg/mL and resistant if the MIC was ≥ 4 μg/mL.

### Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (IBM Corp, Armonk, NY). Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney U test or Student's *t* test as appropriate. Univariate and multivariate analyses of risk factors associated with in hospital mortality were performed using binary logistic regression models using the stepwise forward method. First, univariate analysis of all covariates was performed; then, covariates with a significance of $p < 0.1$ were used in the multivariate analysis. All tests were two-tailed, and differences were considered significant at $p < 0.05$.

## Results

### Study population

A total of 2208 patients with cellulitis were enrolled during the study period. The proportion of males was 58.7% (1296/2208). The mean patient age was 51.5 years. The incidence of HCA infection was 10.5% (232/2208), and 1976 (89.5%) patients had CA cellulitis. Compared to patients with CA cellulitis, patients with HCA cellulitis were older (59.0 vs. 50.5 years, $p < 0.001$) and more frequently had comorbid conditions (Table 1). A total of 56.3% of patients were admitted to the hospital, and patients with HCA infection were admitted more frequently (76.3% vs. 53.9%, $p < 0.001$). In patients with HCA cellulitis, septic shock was more frequent at presentation. The most common underlying disease was diabetes mellitus (391 patients, 17.7%). Patients with HCA cellulitis had a higher rate of comorbidities, including diabetes mellitus and solid tumor. The most common predisposing condition was trauma (376 patients, 17.0%). Patients with ulcers or dermatosis, injection drug use, and breast cancer surgery more commonly acquired HCA cellulitis. The lower extremities (1442 patients, 65.3%) were most frequently involved in both groups. Involved sites of cellulitis were not different between CA cellulitis and HCA cellulitis ($p = 0.82$).

Laboratory tests and radiologic studies were performed more frequently for patients with HCA cellulitis than for patients with CA cellulitis. Patients with thrombocytopenia (platelet count < 50,000 μL) were more common in the HCA-cellulitis group (6.9% vs. 1.5%, $p < 0.001$). Mean creatinine (1.68 mg/dL vs. 0.88 mg/dL, $p < 0.001$) and CRP (7.4 mg/dL vs. 5.8 mg/dL, $p = 0.02$) levels were higher in the HCA cellulitis group. Among radiologic studies, computed tomography (19.0% vs. 13.8%, $p = 0.02$) and magnetic resonance imaging (17.2% vs. 10.5%, $p = 0.002$) were performed more frequently in patients with HCA cellulitis.

### Microbial etiology

Culture studies were performed in 52.2% of the patients (Table 2). Microbiologic studies were performed more frequently in patients with HCA cellulitis (72.4% vs. 49.8%, $p < 0.001$), and the rate of positive microbiological culture was also higher in these patients (33.9% [57/168] vs. 26.1% [257/984], $p = 0.04$). Blood culture was done in 969 (43.9%) patients with cellulitis, and microorganisms were isolated from 9.1% (88/969) of these patients. Needle aspiration was performed in 262 (11.9%) patients with cellulitis, and microorganisms were isolated from 51.5% (135/262) of these patients. Specimens were acquired during surgery in 105 (4.8%) patients with cellulitis, and microorganisms were isolated from 62.9% (66/105) of these patients.

A total of 355 organisms were isolated from 314 patients, and polymicrobial infections were found in 1.6% (35/2208). *S. aureus* (134 isolates) was the most common cause of cellulitis, followed by *Streptococcus* spp. (86 isolates), Gram-negative fermenters (58 isolates), and Gram-negative non-fermenters (23 isolates). MRSA accounted for 29.1% (39/134) of all *S. aureus* infections. *S. aureus* (11.2% [26/232] vs. 5.5% [108/1976], $p = 0.001$) and Gram-negative fermenters (6.0% [14/232] vs. 2.3% [441976], $p = 0.002$) were more frequently isolated in patients with HCA cellulitis (Table 2). MRSA was identified in 1.8% (39/2208) of study patients and was more frequently isolated from patients with HCA cellulitis (4.3% [10/232] vs. 1.5% [29/1976], $p = 0.003$).

When antimicrobial susceptibility data were analyzed for 355 isolated organisms, the antibiotic susceptibility pattern was not different between HCA and CA cellulitis (Table 3). The antimicrobial resistance rate of *S. aureus* to quinolone, clindamycin, and trimethoprim-sulfamethoxazole were 14.4% (19/132), 17.6% (23/131), and 1.7% (2/117), respectively. *Streptococcus* was the second most common cause of cellulitis, including group C streptococci (31 isolates), group B streptococci (27 isolates), group A streptococci (11 isolates), and other streptococci (17 isolates). The antimicrobial resistance rate of isolates of Streptococcus to penicillin, third-generation cephalosporins, quinolone, and clindamycin were 0% (0/73), 0% (0/59), 1.4% (1/73), and 27.8% (20/72), respectively. Of the 58 Gram-negative fermenter isolates, *Escherichia coli* (15 isolates) was the most common, followed by *Enterobacter* spp. (12 isolates), *Serratia marcescens* (10 isolates), and *Klebsiella pneumoniae* (8 isolates). *E. coli* was more frequently isolated from patients with HCA cellulitis

**Table 1** Baseline characteristics of patients with cellulitis according to the mode of acquisition

| Variables | CA cellulitis ($n = 1976$) | HCA cellulitis ($n = 232$) | $p$ value |
|---|---|---|---|
| Male sex | 1168 (59.1) | 127 (54.7) | 0.11 |
| Mean age ± SD | 50.5 ± 17.6 | 59.0 ± 16.8 | < 0.001 |
| Age ≥ 65 years | 482 (24.4) | 83 (35.8) | < 0.001 |
| Admission | 1066 (53.9) | 177 (76.3) | < 0.001 |
| ICU admission | 25 (1.3) | 10 (4.3) | 0.002 |
| Septic shock | 18 (0.9) | 8 (3.4) | 0.004 |
| In hospital death | 9 (0.5) | 6 (2.6) | 0.003 |
| Recurrent cellulitis | 64 (3.2) | 13 (5.7) | 0.05 |
| Comorbidity | 673 (34.1) | 184 (79.3) | < 0.001 |
| Diabetes mellitus | 316 (16.0) | 75 (32.3) | < 0.001 |
| Solid tumor | 93 (4.7) | 58 (25.0) | < 0.001 |
| CKD or ESRD | 48 (2.4) | 45 (19.4) | 0.001 |
| Liver cirrhosis | 35 (1.8) | 16 (6.9) | < 0.001 |
| Heart failure | 34 (1.7) | 9 (3.9) | 0.03 |
| Chemotherapy | 2 (0.1) | 37 (15.9) | < 0.001 |
| Alcoholism | 32 (1.6) | 3 (1.3) | 0.49 |
| Chronic lung disease | 21 (1.1) | 8 (3.4) | 0.008 |
| Hematologic malignancy | 4 (0.2) | 13 (5.6) | < 0.001 |
| Predisposing condition | 922 (46.7) | 140 (60.6) | < 0.001 |
| Trauma | 344 (17.4) | 32 (13.9) | 0.10 |
| Tinea pedis | 205 (10.4) | 30 (13.0) | 0.14 |
| Previous surgery | 161 (8.2) | 25 (10.8) | 0.11 |
| Previous infection | 83 (4.2) | 15 (6.5) | 0.08 |
| Ulcer or dermatosis | 83 (4.2) | 18 (7.8) | 0.02 |
| Injection drug use | 8 (0.4) | 8 (3.5) | < 0.001 |
| Bite wound | 98 (5.0) | 3 (1.3) | 0.004 |
| Breast cancer operation | 16 (0.8) | 11 (4.8) | < 0.001 |
| Saphenous venectomy | 8 (0.4) | 2 (0.9) | 0.28 |
| Gynecologic operation | 47 (2.3) | 7 (3.0) | 0.34 |
| Laboratory examination | 1625 (82.2) | 216 (93.1) | < 0.001 |
| White blood cell count (/μL) | 10,189 ± 4492 | 9663 ± 6256 | 0.40 |
| Platelet count < 50,000 (/μL) | 30 (1.5) | 16 (6.9) | < 0.001 |
| Creatinine (mg/dL) | 0.88 ± 0.56 | 1.68 ± 2.41 | < 0.001 |
| C-reactive protein (mg/dL) | 5.8 ± 8.6 | 7.4 ± 8.9 | 0.02 |
| Radiologic examination | 501 (25.4) | 80 (34.5) | 0.002 |
| Computed tomography | 272 (13.8) | 44 (19.0) | 0.02 |
| Magnetic resonance image | 208 (10.5) | 40 (17.2) | 0.002 |
| Ultrasonography | 64 (3.2) | 12 (5.2) | 0.10 |

Data were presented as means ± standard deviation (SD) for continuous variables

Data were presented as number (percentage) of patients for categorical variables

*CA*, community-acquired; *HCA*, health care–associated; *ICU*, intensive care unit; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease

(2.6% vs. 0.5%, $p = 0.003$). A total of 13.8% (8/58), 12.1% (7/58), 6.9% (4/58), and 3.4% (2/58) of Gram-negative fermenters were resistant to quinolone, third-generation cephalosporins, piperacillin/tazobactam, and amikacin, respectively (Table 3). None of the Gram-negative fermenters were resistant to carbapenem. Among 23 Gram-negative non-fermenters isolated from microbiological studies, *Pseudomonas aeruginosa* (20 isolates) was most common, followed by *Acinetobacter baumannii* (3 isolates). The antimicrobial resistance rates to quinolone, ceftazidime, piperacillin/tazobactam, and carbapenem were 4.3% (1/23), 0% (0/23), 0% (0/23), and 4.3% (1/23), respectively (Table 3).

**Table 2** Comparison between microbiological investigations and microorganisms isolated from CA-cellulitis and HCA-cellulitis patients

| | CA cellulitis ($n = 1976$) | HCA cellulitis ($n = 232$) | $p$ value |
|---|---|---|---|
| Microbiological studies | 984 (49.8) | 168 (72.4) | < 0.001 |
| Blood culture | 820 (41.6) | 149 (64.2) | < 0.001 |
| Needle aspiration | 231 (11.7) | 31 (13.4) | 0.26 |
| Intraoperative culture | 92 (4.7) | 13 (5.6) | 0.31 |
| Others | 62 (3.1) | 24 (10.3) | < 0.001 |
| Gram-positive cocci | 213 (10.8) | 44 (19.0) | < 0.001 |
| *Staphylococcus aureus* | 108 (5.5) | 26 (11.2) | 0.001 |
| Methicillin resistance | 29 (1.5) | 10 (4.3) | 0.003 |
| Coagulase negative staphylococci | 23 (1.2) | 6 (2.6) | 0.11 |
| *Streptococcus* spp. | 75 (3.8) | 11 (4.7) | 0.47 |
| *Enterococcus faecalis* | 7 (0.4) | 1 (0.4) | > 0.99 |
| Gram-negative rod | 64 (3.2) | 17 (7.3) | 0.005 |
| Fermenter | 44 (2.3) | 14 (6.0) | 0.002 |
| *Escherichia coli* | 9 (0.5) | 6 (2.6) | 0.003 |
| *Enterobacter* spp. | 9 (0.5) | 3 (1.3) | 0.12 |
| *Serratia marcescens* | 7 (0.4) | 3 (1.3) | 0.08 |
| *Klebsiella pneumoniae* | 6 (0.3) | 2 (0.9) | 0.20 |
| *Citrobacter* spp. | 6 (0.3) | 0 (0) | > 0.99 |
| *Proteus* spp. | 5 (0.3) | 0 (0) | > 0.99 |
| Others[a] | 2 (0.1) | 0 (0) | > 0.99 |
| Non-fermenter | 20 (1.0) | 3 (1.3) | 0.73 |
| *Pseudomonas aeruginosa* | 17 (0.9) | 3 (1.3) | 0.46 |
| *Acinetobacter baumannii* | 3 (0.2) | 0 (0) | > 0.99 |
| Gram-positive rod | 3 (0.2) | 0 (0) | > 0.99 |
| Anaerobe | 8 (0.4) | 0 (0) | > 0.99 |
| NTM | 2 (0.1) | 0 (0) | > 0.99 |
| Fungus | 2 (0.1) | 2 (0.9) | > 0.99 |

[a] Others included one isolate of *Aeromonas hydrophilia* and one of *Morganella morganii*

Data were presented as number (percentage) of patients

*CA*, community-acquired; *HCA*, health care–associated; *NTM*, non-tuberculous mycobacterium

## Risk factors associated with in-hospital mortality

Among 2208 patients with cellulitis, 15 (0.7%) patients died during admission. The comparison of clinical characteristics between cellulitis patients with and without in-hospital mortality is shown in Table 4. Deceased patients were older (71.4 vs. 51.3 years, $p < 0.001$) and had more comorbidities, including solid tumors and liver cirrhosis. The mortality rate of patients with HCA cellulitis was higher than that of patients with CA cellulitis (2.6% vs. 0.5%, $p = 0.004$).

Age ≥ 65 years, septic shock, bacteremia, HCA cellulitis, solid tumor, and liver cirrhosis were associated with in-hospital mortality in the univariate analysis (Table 4). Multivariate analysis showed that age ≥ 65 years (adjusted odds ratio (aOR), 4.5; 95% confidence interval (CI), 1.3–15.4; $p = 0.02$), septic shock (aOR, 119.9; 95% CI, 37.6–382.3; $p < 0.001$), and HCA infection (aOR, 4.6; 95% CI, 1.3–15.9; $p = 0.02$) were statistically significant factors associated with in-hospital mortality.

## Discussion

Several studies have investigated the impact of HCA infection on microbiology and outcomes [4–6]. However, only a few studies focusing on established HCA infection have addressed cellulitis [8]. To the best of our knowledge, this is the largest study to examine the clinical features and microbial etiology according to CA or HCA cellulitis. In the present study, patients with HCA cellulitis were older and had more comorbidities. HCA infection is related to frequent exposure to the health care system. HCA cellulitis had a more severe presentation, including a higher admission rate, ICU admission, and septic shock. Although cellulitis is seldom fatal [16, 17], 15 (0.7%) of 2208 patients died during hospitalization. In-

**Table 3** Comparison of antimicrobial resistance of 355 microorganisms isolated from patients with culture-proven community-onset cellulitis

| Microorganisms and tested antimicrobial agents | No. of resistant/total isolates (%) | CA cellulitis ($n = 292$) | HCA cellulitis ($n = 63$) | $p$ value |
|---|---|---|---|---|
| *Staphylococcus aureus* | | | | |
| Methicillin | 39/134 (29.1) | 29/108 (26.9) | 10/26 (38.5) | 0.18 |
| Quinolone | 19/132 (14.4) | 16/106 (15.1) | 3/26 (11.5) | 0.56 |
| Clindamycin | 23/131 (17.6) | 20/106 (18.9) | 3/25 (12.5) | 0.56 |
| TMP/SMX | 2/117 (1.7) | 1/92 (1.1) | 1/25 (4.0) | 0.38 |
| Coagulase negative staphylococci | | | | |
| Methicillin | 8/23 (34.8) | 5/18 (27.8) | 3/5 (60.0) | 0.21 |
| *Streptococcus* spp. | | | | |
| Penicillin | 0/73 (0) | 0/64 (0) | 0/9 (0) | > 0.99 |
| 3rd cephalosporin | 0/59 (0) | 0/49 (100) | 0/10 (100) | > 0.99 |
| Quinolone | 1/73 (1.4) | 1/63 (1.6) | 0/10 (0) | 0.86 |
| Clindamycin | 20/72 (27.8) | 18/62 (29.0) | 2/10 (20.0) | 0.71 |
| *Enterococcus faecalis* | | | | |
| Ampicillin | 3/8 (37.5) | 3/7 (42.9) | 0/1 (0) | 0.63 |
| Vancomycin | 0/8 (0) | 0/7 (0) | 0/1 (0) | > 0.99 |
| Gram-negative fermenters | | | | |
| Quinolone | 8/58 (13.8) | 4/44 (9.1) | 4/14 (28.6) | 0.08 |
| 3rd cephalosporin | 7/58 (12.1) | 5/44 (11.4) | 2/14 (14.3) | > 0.99 |
| Piperacillin/tazobactam | 4/58 (6.9) | 2/44 (4.5) | 2/14 (14.3) | 0.24 |
| Amikacin | 2/58 (3.4) | 1/44 (2.9) | 1/14 (7.1) | 0.43 |
| Gram-negative non-fermenter | | | | |
| Quinolone | 1/23 (4.3) | 1/20 (5.0) | 0/3 (0) | > 0.99 |
| Ceftazidime | 0/23 (0) | 0/20 (0) | 0/3 (0) | > 0.99 |
| Piperacillin/tazobactam | 0/23 (0) | 0/20 (0) | 0/3 (0) | 0.24 |
| Carbapenem | 1/23 (4.3) | 0/20 (0) | 1/3 (33.3) | 0.43 |

Data were presented as number of resistant organisms (percentage) of patients

*CA*, community-acquired; *HCA*, health care–associated; *TMP/SMX*, trimethoprim sulfamethoxazole

hospital mortality of patients with HCA cellulitis was higher than that of patients with CA cellulitis (2.6% vs. 0.5%, $p = 0.003$), and HCA infection was an independent predictor of in-hospital mortality. This finding is in line with previous reports [7]. Zilberberg et al. reported that patients with HCA-complicated skin and skin structure infections were likely to receive inappropriate empirical therapy for their infection [7, 8]. According to their study, HCA infection is associated with a prolongation of hospitalization and increased mortality.

HCA infections were thought to be at high risk for MDR organisms by virtue of their contact with the health care system [4–6]. Over the past decade, an increasing proportion of outpatient *S. aureus* isolates has been found to be methicillin-resistant in the USA [11, 12]. However, MRSA was identified from only 0.5% (4/735) of cellulitis patients. Moreover, the methicillin-resistance rate of *S. aureus* isolates was 15.4% (4/26) in a study which was performed in Korea during 2009 and 2011 [18]. In the current study, MRSA was identified from 1.8% (39/2208) of study patients, and MRSA accounted for 29.1% (39/134) of *S. aureus* isolates. During the past 5 years, the MRSA proportion has increased from 0.5 to 1.8% ($p = 0.01$); however, purely CA-MRSA is still an uncommon pathogen among Korean patients with community-onset cellulitis. Thus, Korean guidelines recommend that the use of antibiotics against MRSA infection may be considered in cases of previous MRSA infection/colonization or failed primary antibiotic treatment [19]. There is a need to monitor the microbial etiology of cellulitis to determine whether the proportion of MRSA is increasing.

An interesting finding was that Gram-negative fermenters were more frequently isolated from patients with HCA cellulitis (6.0% [14/232] vs. 2.3% [44/1976], $p = 0.002$). This finding is in line with previous report [7]. Most cases of cellulitis are caused by Gram-positive pathogens, mainly group A streptococcus and *S. aureus* [2, 3, 13, 16, 17, 20]. However, Gram-negative bacteria were also considered to be significant pathogens for skin and soft tissue infection in special hosts [21–23], such as patients with liver cirrhosis, diabetes, and malignancies. In the current study, patients with HCA cellulitis had more comorbidities, including diabetes, liver cirrhosis, and

**Table 4** Univariate and multivariate analyses of risk factors associated with in-hospital mortality in 2208 patients with community-onset cellulitis

| Variables | Deceased ($n = 15$) | Survivors ($n = 2193$) | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | | | Odds ratio (95% CI) | $p$ value | Odds ratio (95% CI) | $p$ value |
| Male sex | 10 (66.7) | 1285 (58.6) | 1.4 (0.48–4.15) | 0.53 | | |
| Age ≥ 65 years | 10 (66.7) | 555 (25.3) | 5.9 (2.0–17.3) | 0.001 | 4.5 (1.3–15.4) | 0.02 |
| Septic shock | 9 (60.0) | 17 (0.8) | 191.6 (61.4–597.7) | < 0.001 | 119.9 (36.7–382.3) | < 0.001 |
| Concurrent bacteremia | 7 (46.7) | 81 (3.9) | 21.7 (7.7–61.3) | < 0.001 | 2.8 (0.7–11.4) | 0.16 |
| Health care–associated infection | 6 (40.0) | 225 (10.3) | 5.8 (2.0–16.5) | 0.001 | 4.6 (1.3–15.9) | 0.02 |
| Diabetes mellitus | 4 (26.7) | 387 (17.6) | 1.7 (0.5–5.4) | 0.37 | | |
| Solid tumor | 5 (33.3) | 146 (6.7) | 7.0 (2.4–20.8) | < 0.001 | 3.0 (0.8–11.6) | 0.12 |
| CKD or ESRD | 2 (13.3) | 86 (3.9) | 3.8 (0.8–17.0) | 0.08 | 2.2 (0.4–12.4) | 0.11 |
| Liver cirrhosis | 2 (13.3) | 49 (2.2) | 6.7 (1.5–30.6) | 0.01 | 0.9 (0.1–7.7) | 0.90 |
| Heart failure | 1 (6.7) | 42 (1.9) | 3.7 (0.5–28.5) | 0.22 | | |

Data were presented as number (percentage) of patients for categorical variables

*CI*, confidence interval; *ICU*, intensive care unit; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease

malignancies (Table 1). Therefore, in severely compromised patients or patients with HCA cellulitis, broad-spectrum antimicrobial coverage may be considered [19, 24]. In a previous study of cellulitis conducted in Korea, none of the 735 cellulitis cases were caused by *Mycobacterium tuberculosis* [18]. These results suggest that cellulitis caused by *M. tuberculosis* is very rare. In addition, as its clinical features vary and are thought to differ from the typical finding of cellulitis caused by other bacteria, cellulitis caused by *M. tuberculosis* was excluded from this study. A total of two cases of non-tuberculous mycobacterial cellulitis were included in this study, all of which were caused by *Mycobacterium avium* complex.

This study has some limitations. First, since this was a retrospective study, patients who underwent microbiological testing would have had more severe disease, such as complicated or purulent cellulitis, or cellulitis unresponsive to primary beta-lactam therapy. The difference in the causative organisms of HCA and CA cellulitis in this study may have been influenced by whether microbiological cultures were performed or not. Second, we analyzed predictors of in-hospital mortality, not infection-related mortality. Some may argue that objectively measured infection-related mortality is more suitable for this study since the overall mortality may be affected by factors other than the infection itself. Regarding cellulitis, it has been reported that only one third of deaths appeared to be due to infection [25]. Therefore, there might be the possibility of overestimation of mortality in patients with cellulitis. Third, we did not evaluate the appropriateness of initial antimicrobial treatment. Therefore, we were unable to analyze the role of appropriate empirical antimicrobial agents on in-hospital mortality, and mortality in patients with cellulitis was possibly overestimated. Despite these limitations, this is the largest multicenter study reflecting the current microbial etiology and clinical characteristics of community-onset cellulitis in Korea. It is expected that this study would be valuable for establishing treatment strategies for community-onset cellulitis in Korea.

In conclusion, the clinical features and microbial etiology of HCA cellulitis were different from those of CA cellulitis. *S. aureus*, including MRSA and Gram-negative fermenters, were more common pathogens in HCA cellulitis. In addition, HCA cellulitis was associated with increased mortality.

**Authors' contributions** PSY contributed to the study design, data gathering, analyses, and interpretation and wrote the first draft of the manuscript. KT, JJ, CSH, YSN, HHL, KYK, PSY, SHE, PKH, COH, and CSH contributed to data analyses and data interpretation, and critiqued the report. KYG contributed to the study design, data interpretation, and review and critiqued the report. KYG had full access to all data and made the final decision to submit for publication.

## Compliance with ethical standards

**Conflict of interest** The author declare that they have no conflict of interest.

**Ethical approval** This work was approved by the Institutional Review Board of each hospital, and informed consent was waived since this was a retrospective study without intervention that did not involve extra clinical specimens.

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