Clinical Features of Non-clostridial Gas Gangrene and Risk Factors for In-hospital Mortality

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Objective: To examine the clinical features of patients with non-clostridial gas gangrene (NCGG) at our hospital and identify risk factors for in-hospital mortality.
Methods: This study included 24 patients with NCGG who were hospitalized in our medical facility from April 2005 to March 2015. The clinical features of NCGG were reviewed, and the characteristics of 6 patients who died in hospital and 18 who survived were compared to investigate risk factors.
Results: The median time from symptom onset to hospital arrival was 168 h. The causative agent was *Klebsiella pneumoniae* in 8.3% and mixed infection in 91.7%; 83.3% of patients had diabetes, and one patient had no obvious underlying disease. The site of infection was the neck in 4.2%, the thoracoabdominal wall and retroperitoneum in 12.5% each, the back in 33.3%, the buttocks in 25.0%, the perineum in 20.8%, and the extremities in 45.8%.
Retroperitoneal infection, blood lactate ≥ 4.0 mmol/L, and Japanese Association for Acute Medicine disseminated intravascular coagulation (DIC) score ≥ 4 on emergency department (ED) arrival were significantly higher in non-survivors than in survivors.
Conclusion: NCGG tends to develop in patients with diabetes, and in-hospital mortality rates are still high. Retroperitoneal infection, hyperlactatemia, and DIC on ED arrival are risk factors for in-hospital mortality.

Key words: Non-clostridial gas gangrene, retroperitoneal infection, hyperlactatemia, disseminated intravascular coagulation, septic shock

INTRODUCTION

Gas gangrene is an infection with necrosis and gas formation in soft tissues such as the skin, subcutaneous tissue, and muscles due to localized infection by gas-forming organisms, and its prognosis is often poor. Gas gangrene is broadly classified as clostridial gas gangrene and non-clostridial gas gangrene (NCGG), depending on the causative agent. Clostridial gas gangrene is now seldom reported in Japan, but with our aging society and increasing number of patients who have underlying diseases such as diabetes mellitus and malignant tumors, reports of comorbid NCGG are not decreasing [1, 2].

In this study of 24 patients recently diagnosed with gas gangrene at our hospital, clinical features and risk factors for in-hospital mortality were examined.

MATERIALS AND METHODS

This study included 24 patients with gas gangrene at our hospital during the 10-year period between April 2005 and March 2015.

This study reviewed these patients' clinical data, including age, sex, time from symptom onset to emergency department (ED) arrival, underlying disease, site of infection, causative agent, vital signs on arrival, laboratory findings (PaO_2 / FiO_2 [PF] ratio, hematology, biochemical tests, clotting factors), treatment (surgery, antibiotics), and outcomes (respirator days, in-hospital mortality). These clinical features were compared between patients who died during hospitalization and those who survived and were discharged.

DIC score based on the Japanese Association for Acute Medicine DIC diagnostic criteria (JAAM criteria) [3] and the International Society on Thrombosis and Haemostasis DIC diagnostic criteria (ISTH criteria) [4] was calculated, respectively.

Numerical data are expressed as median values (quartiles), and frequencies (rates) are expressed as percentages. The Mann-Whitney U test and chi-square test were used to compare survivors and non-survivors. The level of significance was $p < 0.05$. Statistical analysis was performed using SPSS V.21 J for Windows.

RESULTS

Table 1 shows the clinical characteristics of the 24 patients with gas gangrene at our hospital. There were 15 men and 9 women, with a median age of 62 (52–70) years, and the median time from symptom onset to ED arrival was 168 (72–336) h. Diabetes mellitus was an underlying disease in 20/24 (83.3%) patients, and 6 of these 20 patients (30.0%) also had chronic renal failure. Other underlying diseases in the 24 patients included chronic hepatitis in 3 (12.5%), schizophrenia in 2 (8.3%), and liver cirrhosis, malignant tumor (treated with chemotherapy and radiotherapy), nephrotic syndrome, and stroke in one (4.2%) patient each. Only one patient (4.2%) had no obvious underlying disease.

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Table 1 Clinical characteristics of non-clostridial gas gangrene (*p < 0.05)

	Overall (n = 24)	Survivors (n = 18)	Non-survivors (n=6)	p
Age (years)	62 (52-70)	63 (53-71)	59 (50-70)	
Sex (male)	15/24 (62.5%)	11/18 (61.1%)	4/6 (66.7%)	
Onset - ER (hours)	168 (72-336)	168 (66-336)	132 (72-720)	
<3 days	14/24 (58.3%)	10/18 (55.6%)	4/6 (66.7%)	
Underlying disease				
Diabetes	20/24 (83.3%)	15/18 (83.3%)	5/6 (83.3%)	
Malignant disease	1/24 (4.2%)	1/18 (5.6%)	0/6 (0%)	
Liver cirrhosis	1/24 (4.2%)	0/18 (0%)	1/6 (16.7%)	
Chronic renal failure	6/24 (25.0%)	5/18 (27.8%)	1/6 (16.7%)	
Other	7/24 (29.2%)	5/18 (27.8%)	2/6 (33.3%)	
Infection site				
Neck	1/24 (4.2%)	0/18 (0%)	1/6 (16.7%)	
Thoracoabdominal wall	3/24 (12.5%)	3/18 (16.7%)	0/6 (0%)	
Back	8/24 (33.3%)	5/18 (27.8%)	3/6 (50.0%)	
Buttocks	6/24 (25.0%)	5/18 (27.8%)	1/6 (16.7%)	
Retroperitoneum	3/24 (12.5%)	0/18 (0%)	3/6 (50.0%)	*
Perineum	5/24 (20.8%)	5/18 (27.8%)	0/6 (0%)	
Extremities	11/24 (45.8%)	7/18 (38.9%)	4/6 (66.7%)	
Pathogens				
K. pneumoniae	2/24 (8.3%)	1/18 (5.6%)	1/6 (16.7%)	
Mixed infection	22/24 (91.7%)	17/18 (94.4%)	5/6 (83.3%)	
Vital signs on emergency department arrival				
Glasgow Coma Scale	15 (15-15)	15 (15-15)	15 (6-15)	
Respiratory rate (/min)	20 (18-25)	20 (18-26)	22 (18-26)	
Heart rate (/min)	104 (89-114)	104 (83-111)	108 (95-122)	
Systolic blood pressure (mmHg)	110 (91-131)	119 (97-140)	98 (69-112)	*
<90 mmHg	5/24 (20.8%)	3/18 (16.7%)	2/6 (33.3%)	
Temperature (°C)	38.0 (36.4-38.4)	38.1 (36.5-38.5)	37.3 (35.6-38.5)	
Pulmonary function				
PaO_2/FiO_2 ratio	362 (322-394)	364 (333-402)	340 (244-428)	
Respirator (days)	2.5 (0-15.0)	1.5 (0-5.3)	18.5 (1.0-67.3)	*
≥14 days	6/24 (25.0%)	3/18 (16.7%)	3/6 (50.0%)	
In-hospital mortality	6/24 (25.0%)			

The site of infection was the neck in 1(4.2%), thoracoabdominal wall in 3 (12.5%), retroperitoneum in 3 (12.5%), back in 8 (33.3%), buttocks in 6 (25.0%), perineum in 5 (20.8%), and extremities in 11 (45.8%) patients. The causative agent was *Klebsiella pneumoniae* in 2 (8.3%) patients and mixed infection (including Gram-positive cocci, Gram-negative rods, and anaerobic bacteria) in 22 (91.7%) patients. Table 2 shows the pathogens in the mixed infections. No *Clostridium* species were identified.

With regard to vital signs on ED arrival, 4 (16.7%) patients had a Glasgow Coma Scale (GCS) score <15, 14 (58.3%) had a temperature >38° C or <36° C, 18 (75.0%) had a heart rate (HR) >90/min, 11 (45.8%) had a respiratory rate (RR) > 20/min, and 5 (20.8%) had a systolic blood pressure (SBP) <90 mmHg. In addition, 3 (12.5%) patients had a P/F ratio <300 upon arrival.

Table 3 shows the laboratory findings on arrival. Twenty of 24 (83.3%) patients had a peripheral white blood cell (WBC) count $>12.0\times10^3/\mu L$ or $<4.0\times10^3/\mu L$, and three of 23 (13.0%) patients (excluding one patient receiving chemotherapy and radiotherapy for a malignant tumor) had a platelet (Plt) count $<10.0\times10^4/\mu L$. Regarding biochemistry tests, 3 of 21 (14.3%) (excluding 3 patients on hemodialysis for chronic renal failure) patients had creatinine (Cr) levels >2.0 mg/dL, 1 of 24 (4.2%) had total bilirubin (T. Bil) >2.0 mg/dL, 23 of 24 (95.8%) had C-reactive protein (CRP) levels >10 mg/dL, 19 of 24 (79.2%) had blood lactate >1.0 mmol/L, 8 of 24 (33.3%) had blood lactate ≥4.0 mmol/L, 15 of 21 (71.4%) (missing data in 3 patients)

Table 2 Pathogens of mixed infections (101 pathogens of 22 patients)

Specific Pathogen Cultured	Cultures Positive for Specific Pathogen (%)
Corynebacterium sp.	11 (10.9)
Peptostreptococcus sp.	8 (7.9)
Bacteroides fragilis group	8 (7.9)
Alpha haemolytic streptococcus	7 (6.9)
Staphylococcus epidermidis	7 (6.9)
Streptococcus aureus	5 (5.0)
Anaerobic Gram-positive rod	5 (5.0)
Proteus mirabilis	4 (4.0)
Enterococcus sp.	4 (4.0)
Peptostreptococcus	3 (3.0)
Bacteroides sp.	3 (3.0)
Escherichia coli	3 (3.0)
Group G *streptococcus*	3 (3.0)
Streptococcus agalactiae	3 (3.0)
Peptostreptococcus asaccharolyticus	2 (2.0)
Streptococcus constellatus	2 (2.0)
Prevotella sp.	2 (2.0)
Others (1 case each)	21 (20.8)
Total	101 (100.3)

had hemoglobin A1c (HbA1c) >7.0%, and 2 of 8 (25.0%) (measured in 8 patients) had procalcitonin (PCT) ≥10 ng/mL. The clotting function test results showed an international normalized ratio (INR) >1.5 in 4 of 24 (16.7%) patients, fibrin/fibrinogen degradation products (FDP) ≥ 25 μg/mL in 3 of 24 (12.5%), and an antithrombin III (ATIII) ≤ 70% in 14 of 24 (58.3%).

Debridement of the infected tissues was performed in all 24 patients. The initial antibiotic therapy was meropenem (MEPM) + clindamycin (CLDM) in 6 (25.0%) patients, tazobactam/piperacillin (TAZ/PIPC) + CLDM in 5 (20.8%), doripenem (DRPM) + CLDM in 3 (12.5%), DRPM + CLDM + linezolid (LZD) in 3 (12.5%), sulbactam/ampicillin (SBT/ABPC) + CLDM in 2 (8.3%), and imipenem/cilastatin (IPM/CS) + CLDM or MEPM, DRPM, or flomoxef (FMOX) as monotherapy in 1 (4.2%) patient each.

Among all 24 patients, the number of respirator days was ≥14 in 6 (25.0%) patients, and 6 (25.0%) patients died in hospital.

Table 1 shows the clinical characteristics of the 18 patients who survived and were discharged (survivors) and the 6 patients who died in hospital (non-survivors). Table 3 summarizes the blood test results in each group. Age, sex, and time from symptom onset to ED arrival did not differ significantly between the survivors and non-survivors. A high proportion of both survivors and non-survivors had underlying disease, and more than 80% in both groups had diabetes mellitus. The retroperitoneum was the site of infection in 3 of 6 (50.0%) of the non-survivors, but in none of the 18 survivors. Seven of 11 in extremity infection cases were not involved the trunk region, and all of them were survived. Thus, retroperitoneal infection was significantly more common in non-survivors. Fig. 1 shows the CT findings in a patient with retroperitoneal infection. The cause of gas gangrene was a mixed infection in ≥ 80% of both survivors and non-survivors.

With respect to vital signs on ED arrival, non-survivors tended to have lower GCS scores, higher RR and HR, and a lower temperature than survivors, but none of these differences was significant. Median SBP was significantly lower in non-survivors (98 [69–112] mmHg) than in survivors (119 [97–140] mmHg). The SBP <90 mmHg rate also tended to be higher in non-survivors. The diastolic BPs were often impossible to be measured on ED arrival. The P/F ratio was slightly lower in non-survivors than in survivors, but there was no significant difference. The median number of respirator days was 1.5 (0–5.3) in survivors, but significantly longer, at 18.5 (1.0–67.3), in non-survivors.

Regarding laboratory findings on arrival, the WBC count did not differ significantly, but the platelet count was significantly lower in non-survivors. Plt $<10\times10^4$/μL was seen in 3 of 6 (50.0%) non-survivors, but in none of the survivors, which was a significant difference. There were no significant differences in Cr, T. Bil, CRP, or HbA1c. However, blood lactate on arrival

Table 3 Laboratory data on emergency department arrival

	Overall (n = 24)	Survivors (n =1 8)	Non-survivors (n = 6)	p
White blood cells ($\times 10^3$ /μL)	16.9 (12.1-25.0)	16.9 (12.1-22.5)	19.7 (8.4-27.0)	
Platelet count ($\times 10^4$ /μL)†	25.9 (20.0-33.6)	26.5 (20.5-32.9)	17.4 (5.8-35.8)	
< 10.0 × 10^4 /μL	3/23 (13.0%)	0/17 (0%)	3/6 (50.0%)	*
Creatinine (mg/dL) #	1.2 (0.8-1.8)	1.0 (0.8-1.4)	1.6 (1.1-2.5)	
> 2.0 mg/dL	3/21 (14.3%)	2/15 (13.3%)	1/6 (16.7%)	
Total bilirubin (mg/dL)	0.4 (0.3-1.2)	0.4 (0.3-1.3)	0.7 (0.3-1.8)	
> 2.0 mg/dL	1/24 (4.2%)	0/18 (0%)	1/6 (16.7%)	
C-reactive protein (mg/dL)	24.5 (18.8-35.5)	25.0 (21.5-36.1)	20.9 (13.6-30.5)	
> 10 mg/dL	23/24 (95.8%)	18/18 (100%)	5/6 (83.3%)	
Hemoglobin A1c (%) (n = 21)	8.7 (6.3-10.4)	9.0 (6.6-10.8)	8.1 (6.2-11.3)	
> 7.0 %	15/21 (71.4%)	11/15 (73.3%)	4/6 (66.7%)	
Lactate (mmol/L)	2.0 (1.0-5.0)	1.3 (0.9-2.6)	6.7 (4.1-12.8)	**
> 1.0 mmol/L	19/24 (79.2%)	13/18 (72.2%)	6/6 (100%)	
≥ 4.0 mmol/L	8/24 (33.3%)	3/18 (16.7%)	5/6 (83.3%)	**
INR	1.19 (1.10-1.37)	1.15 (1.08-1.22)	1.49 (1.31-1.73)	**
> 1.5	4/24 (16.7%)	1/18 (5.6%)	3/6 (50.0%)	*
FDP (μg/mL)	8.1 (4.3-13.3)	6.6 (3.6-8.9)	24.4 (10.5-52.4)	**
≥ 25 μg/mL	3/24 (12.5%)	0/18 (0%)	3/6 (50.0%)	*
Prolonged PT (seconds)	0.6 (0-2.8)	0.1 (0-1.7)	4.5 (2.1-7.6)	**
≥6 seconds	3/24 (12.5%)	0/18 (0%)	3/6 (50.0%)	*
Fibrinogen (g/L)	6.6 (4.6-8.7)	6.8 (5.6-9.0)	4.7 (3.7-6.9)	
< 1.0 g/L	0/24 (0%)	0/18 (0%)	0/6 (0%)	
Antithrombin III (%)	66.5 (50.8-85.8)	73.0 (54.5-90.5)	54.0 (40.5-63.0)	*
≤ 70%	14/24 (58.3%)	8/18 (44.4%)	6/6 (100%)	*
DIC (JAAM criteria)†	2.0 (1.0-2.0)	1.0 (0.5-2.0)	5.0 (2.8-6.5)	***
≥ 4	4/23 (17.4%)	0/17 (0%)	4/6 (66.7%)	**
DIC (ISHS criteria)†	0 (0-2.0)	0 (0-0.5)	4.0 (2.8-5.3)	***
≥ 5	2/23 (8.7%)	0/17 (0%)	2/6 (33.3%)	

INR, international normalized ratio; FDP, fibrin/fibrinogen degradation products; PT, prothrombin time; PT, prothrombin time; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ISHS, International Society on Thrombosis and Haemostasis; *p < 0.05; **p < 0.01; *** p < 0.001; †except 1 case of chemoradiotherapy; #except 3 cases of hemodialysis

was significantly higher in non-survivors than in survivors. Moreover, blood lactate was ≥4.0 mmol/L in 5 of 6 (83.3%) non-survivors and 3 of 18 (16.7%) survivors, a rate that was significantly higher in non-survivors. INR and FDP were significantly higher, and ATIII was significantly lower in non-survivors than in survivors. The rates of INR >1.5, FDP ≥25 μg/mL, prolonged PT ≥6 sec, and ATIII ≤70% were 3/6 (50%), 3/6 (50%), 3/6 (50%), and 6/6 (100%), respectively, in non-survivors, and 1/18 (5.6%), 0/18 (0%), 0/18 (0%), and 8/18 (44.4%), respectively, in survivors. Each of these rates was significantly higher in non-survivors.

The median DIC score based on JAAM criteria was significantly higher in non-survivors (5.0 [2.8-6.5]) than in survivors (1.0 [0.5-2.0]) (p <0.001). None of the survivors, but a significantly higher rate of non-survivors (66.7% ; p <0.01), had a JAAM-DIC score ≥4 (Table 3). In addition, the score based on ISTH criteria was significantly higher in non-survivors (4.0 [2.8-5.3]) than in survivors (0 [0-0.5]) (p <0.001). None of the survivors, but 33.3% of non-survivors, had an ISTH-DIC score ≥5, a rate that tended to be higher in non-survivors (p = 0.059) (Table 3).

DISCUSSION

This study included patients with NCGG who were transported to our ED and admitted to our hospital during the last 10 years. The comparison of the 18 patients who survived (survivors) and the 6 patients who died while in the hospital (non-survivors) found that non-survivors had significantly higher rates of retroperitoneal infection and rates on arrival of Plt <10.0×10^4/μL, blood lactate ≥4.0 mmol/L, INR >1.5, FDP ≥25 μg/mL, prolonged PT ≥6 sec, and ATIII ≤70% than survivors. However, there were no significant differences in age, sex, time from symptom onset to ED arrival, past medical history, causative agent, P/F ratio, Cr, T. Bil, or CRP. These findings indicate that retroperitoneal infection, as well as hyperlactatemia and coagulopathy on arrival, are risk factors for death

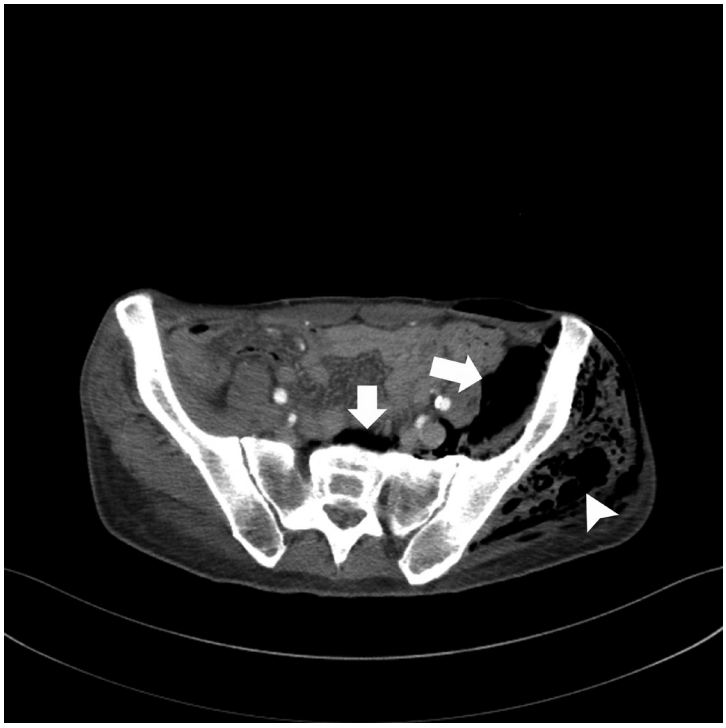

Fig. 1 CT scan of non-clostridial gas gangrene (NCGG) that has spread to the retroperitoneum in a 50-year-old man. Gas is present in the left retroperitoneum (arrow) and buttocks (arrowhead). The patient died on hospital day 71.

in patients with NCGG.

NCGG is often associated with underlying disease, in particular, with high rates of diabetes mellitus [1]. In the present study, 83.3% of patients had diabetes mellitus, and in 9 of these patients, their diabetes mellitus was untreated. In addition,16.7% of patients had chronic renal failure, and 4.2% had liver cirrhosis. The diabetes comorbidity rate exceeded 80% in both survivors and non-survivors, with no significant difference.

NCGG may have a gradual progression [5], but the prognosis is poor, with mortality rates of 42.9–64.5% [2, 6]. Time from symptom onset to ED arrival varied greatly among the present patients, with a median time of 168 (72–336) h. This time did not differ significantly between survivors and non-survivors. The mortality rate in the present patients was 25%, which, although slightly lower than previously reported, still remains high.

The cause of gas gangrene may be an infection due to a single organism, such as *K. pneumoniae*, or mixed infections due to Gram-positive cocci, Gram-negative rods, and anaerobic bacteria. Infection with *K. pneumoniae* is associated with higher mortality than mixed infections [7]. In the present study as well, mortality tended to be higher with *K. pneumoniae* infection than with mixed infections.

In necrotizing fasciitis involving the trunk region, because complete removal of necrotic tissue is difficult, the mortality rates are higher than when the trunk region is not involved [8]. In the present study, 16 of 24 patients with NCGG had infection of the trunk region, and the infection spread to the retroperitoneum in 3 of 24 patients. All 3 patients with retroperitoneal infection died. Retroperitoneal infection was significantly more common in non-survivors than in survivors. Therefore, even in NCGG, the spread of infection to the retroperitoneum is associated with poor outcomes. This might be related with the difficulty of complete removal of necrotic tissue.

SBP on arrival was significantly lower in non-survivors than in survivors. There were 2 of 6 non-survivors and 3 of 18 survivors with an SBP <90 mmHg. This rate tended to be higher in non-survivors, but the difference was not significant. The probable reason for this is that the patients in this study had a relatively high median age of 62 years, and although blood pressure may have decreased due to septicemia, the SBP did not necessarily fall to <90 mmHg.

Blood lactate levels on arrival were significantly higher in non-survivors than in survivors. The rate of blood lactate ≥4.0 mmol/L was significantly higher in non-survivors than in survivors. Hyperlactatemia, as a marker of tissue hypoperfusion, has conventionally been defined as a blood lactate level of ≥4.0 mmol/L [9]. More recently, a blood lactate of >1.0 mmol/L in sepsis has been reported as hyperlactatemia [10], and significantly higher organ failure and mortality rates with blood lactate levels >1.4 mmol/L compared to ≤ 1.4 mmol/L have also been reported, thus supporting a need to review this threshold level [11].

On the other hand, even with hypotension, no substantial change in mortality rates has been reported unless blood lactate is ≥2.5 mmol/L [12]. In severe sepsis evaluated in the ED, regardless of the presence or absence of shock, a blood lactate level of >8 mmol/L on arrival has also been reported to be an independent prognostic risk factor for in-hospital mortality [13]. In addition, the mortality rate within 3 days of

patients evaluated in the ED with suspected infection has been reported to be 22.4% when blood lactate is ≥ 4.0 mmol/L on arrival, significantly higher than when blood lactate is <4.0 mmol/L [14]. Thus, there is no consensus on threshold values.

In the present study, 72.2% of survivors and 100% of non-survivors had blood lactate >1.0 mmol/L on ED arrival, which was not significantly different. However, the rate of blood lactate ≥4.0 mmol/L was significantly higher in non-survivors than in survivors. Tissue hypoperfusion is often present in NCGG, and we believe that blood lactate ≥4.0 mmol/L on ED arrival is a risk factor for in-hospital mortality.

According to the Diagnostic Criteria for Sepsis, Severe Sepsis, and Septic Shock [15], all of the patients in the present study had sepsis on ED arrival. The rate of severe sepsis tended to be higher in non-survivors (100%) than in survivors (55.6%) (p = 0.066). The rate of septic shock (SBP <90 mmHg) was significantly higher in non-survivors than in survivors.

INR and FDP were significantly higher, and ATIII was lower, in non-survivors than in survivors in the present study. Moreover, the rates of INR >1.5, FDP ≥25 μg/mL, prolonged PT ≥6 sec, and ATIII ≤70% were all significantly higher in non-survivors. JAAM-DIC score and ISTH-DIC score was significantly higher in non-survivors than in survivors. Based on these results, NCGG with DIC on ED arrival has a poor prognosis, and a JAAM-DIC score ≥4 on ED arrival is a risk factor for in-hospital mortality. Meanwhile, the P/F ratio, T. Bil, Cr, and CRP on arrival did not differ significantly between survivors and non-survivors.

The Mortality in Emergency Department Sepsis (MEDS) score has been used to predict outcomes in sepsis evaluated in the ED [16]. In the present study, the MEDS score did not differ significantly between survivors and non-survivors (p = 0.086), and even based on a MEDS score ≥10, there was still no significant difference (p = 0.089). However, because of the small number of patients, the utility of the MEDS score should be further investigated in a larger number of patients.

Thorough statistical evaluation of risk factors for in-hospital mortality was difficult in the present study with a small number of patients at a single medical institution. Because NCGG is a rare disease, the identification of independent risk factors requires a multicenter study.

CONCLUSION

NCGG occurs more commonly in patients with underlying diseases such as diabetes mellitus, chronic renal failure, and liver cirrhosis, and the diabetes comorbidity rate is particularly high. The in-hospital mortality rate in NCGG is still high, at 25%. Retroperitoneal infection, hyperlactatemia (blood lactate ≥4.0 mmol/L), and DIC (JAAM-DIC score ≥4) on ED arrival are risk factors for in-hospital mortality.

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