Characteristics of gas-forming pyogenic liver abscess caused by Klebsiella pneumoniae and Clostridi perfringens

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Research article

Abstract

Background: Gas-forming pyogenic liver abscess is a life-threatening disease with poor prognosis commonly caused by 2 bacteria, Klebsiella pneumoniae and Clostridium perfringens . Due to its low incidence and associated high mortality rate, it is important to study the biological characteristics of the disease. The aim of this study was to conduct a worldwide review of literature on gas-forming pyogenic liver abscess caused by K. pneumoniae and C. perfringens . Methods: We searched PubMed and Web of Science databases from January 2009 to March 2019, with published in English. All relevant articles were accessed in full text. The manual search included references of retrieved articles. Finally, 35 publications were selected for review. Results: The results showed that more cases of gas-forming pyogenic liver abscess in Asia were caused by K. pneumoniae than by C. perfringens (P=0.011). The prevalence of diabetes mellitus in patients with gas-forming pyogenic liver abscess caused by K. pneumoniae was higher than caused by C. perfringens (P=0.032). The survival rate of patients with gas-forming pyogenic liver abscess caused by K. pneumoniae who received surgical debridement or drainage was higher than caused by C. perfringens (P=0.002). Conclusions: The prevalence of diabetes mellitus was higher in patients with gas-forming pyogenic liver abscess caused by K. pneumoniae than in patients caused by C. perfringens .

Background

Gas-forming pyogenic liver abscess (GFPLA) was first described by Smith and accounts for 7% to 24% of pyogenic liver abscesses (PLAs) [1-3]. Gas-forming abscess is a classical feature of this infection and may facilitate early recognition and treatment. Diabetes mellitus (DM) is a well-known risk factor of PLAs and may play a role in gas formation in PLAs [3]. In recent times, the incidence of GFPLA has been increasing gradually due to advancements in medical technology in the area of liver diseases, such as hepatocellular carcinoma (HCC), with the development of radiofrequency ablation and transarterial chemoembolization [4-5].

Klebsiella pneumoniae and Clostridium perfringens are the 2 bacteria that most commonly cause GFPLA. The clinical manifestations of GFPLA caused by K. pneumoniae (GFPLA-Kp) and C. perfringens (GFPLA-Cp), which include fever and right upper quadrant abdominal pain, are not different from those of non-GFPLA [6]. However, there are some clinical differences. Earlier studies reported a statistically higher incidence of septic shock, multiple organ dysfunction syndrome, bacteremia, and mortality in patients with GFPLA [7-8]. The variety in clinical characteristics may be due to the different virulence factors. The K1 and K2 capsular serotypes of K. pneumoniae, with a prevalence of 52% to 77.6% in PLAs caused by K. pneumoniae, were considered risk factors for liver abscess [9]. Studies have shown that these 2 serotypes play a key role in impairing neutrophil phagocytosis in patients with DM, which leads to severe infection with gas formation in the liver [10]. In GFPLA-Cp, alpha-toxin is the major virulence factor and can trigger hemolysis, which progresses rapidly, and acidosis and renal failure develop swiftly [11-12].

Most reports of GFPLA are from Asia, with Taiwan as an example [7]. The organisms most commonly associated with GFPLA are *K. pneumoniae* and *C. perfringens* [13]. *K. pneumoniae*, a gram-negative bacteria, can be found in the upper respiratory and intestinal tracts of humans and can cause a wide variety of infectious diseases, such as urinary tract infections and respiratory tract infections [14]. GFPLA-*Kp* is 1 such disease discussed here. In contrast, *C. perfringens* is an anaerobic gram-positive rod-shaped bacteria that produces spores. It is in the normal flora of the gastrointestinal and genitourinary tracts of healthy humans. Under certain disease conditions, such as DM and malignant cancers, *C. perfringens* can become pathogenic and cause bloodstream and gas-forming infections that can lead to significant mortality [15].

The incidences of GFPLA-*Kp* and GFPLA-*Cp* have recently been increasing from year to year. However, there is a lack of systematic and comprehensive evaluation of GFPLA-*Kp* and GFPLA-*Cp* in the past several years. Hence, relevant literature published from January 2009 to March 2019 were searched to compare clinical features.

Methods

The PubMed database was searched using the following terms: "gas forming" AND "Liver abscess" AND "*K. pneumoniae*," "gas forming" AND "Liver abscess, pyogenic" AND "*K. pneumoniae*," "gas" AND "Liver abscess" AND "*K. pneumoniae*," "gas forming" AND "Liver abscess, pyogenic" AND "*K. pneumoniae*," "gas forming" AND "Liver abscess" AND "*C. perfringens*," "gas forming" AND "Liver abscess, pyogenic" AND "*C. perfringens*," "gas" AND "Liver abscess" AND "*C. perfringens*," "gas forming" AND "Liver abscess, pyogenic" AND "*C. perfringens*." Next, full publications (not abstracts) from the Web of Science database using the same terms were searched to supplement the research. The references of the articles were then searched to make sure no eligible studies were missed. The search was restricted to papers published from January 2009 to February 2019. At the end, a total of 35 publications were included in this review.

Statistical analysis was performed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation. Inter-group comparisons were made using the Student's t test and qualitative data were analyzed using the χ2 test. Statistical differences were considered significant at a P value ⏽0.05.

Results

Table 1 [11-12, 16-37] and Table 2 [8, 38-47] show the clinical characteristics and laboratory test results of patients with GFPLA-*Kp* (12 cases) and patients with GFPLA-*Cp* (24 cases). The mean ages of patients

with GFPLA-*Kp* and patients with GFPLA-*Cp* were 67.08 ± 10.22 years and 66.70 ± 8.78 years, respectively. The proportions of patients with GFPLA-*Kp* and patients with GFPLA-*Cp* of male sex were 58.3% and 70.8%, respectively; however, there was no statistically significant difference between the 2 patient groups. It was also found that age >70 years was not a predictor of mortality in patients with GFPLA-*Kp* and patients with GFPLA-*Cp*.

Of the 12 patients with GFPLA-*Kp*, 11 (91.7%) were from Asia (4 from Japan, 3 from Taiwan, 2 from Korea, 1 from China, and 1 from Australia) and 1 (8.3%) was from the USA. In contrast, of the 24 patients with GFPLA-*Cp*, 11 (45.8%) were from Asia (6 from Japan, 1 from China, 2 from Hong Kong, and 2 from Australia), 9 (37.5%) were from Europe (2 from the UK, 2 from Spain, 2 from Germany, 2 from the Netherlands, and 1 from Belgium), and 4 (16.6%) were from the USA. With regard to the patients from Asia, the proportion of patients with GFPLA-*Kp* was greater than the proportion of patients with GFPLA-*Cp* (P=0.011).

Although Thng et al. reported that *K. pneumoniae* was the most common bacteria causing GFPLA, it is not clear what the most common bacteria causing GFPLA in patients with DM is [48]. Data showed that the most common underlying disease in patients with GFPLA-*Kp* was DM (83.3%). Of the 24 patients with GFPLA-*Cp*, 10 (41.6%) had DM, 6 (25%) had malignant tumors (1 patient with pancreatic cancer, 2 with gastric cancer, 2 with colon cancer, and 1 with HCC), 3 (12.5%) had cholangitis, 3 (12.5%) were previously in good health, 1 (4%) had undergone a hemi-hepatectomy for liver metastasis of a neuroendocrine tumor with an unknown primary site, and 1 (4.1%) had received a liver transplant for alcoholic cirrhosis. DM was more prevalent in patients with GFPLA-*Kp* than in patients with GFPLA-*Cp* (P=0.032). The results showed that DM is strongly associated with GFPLA-*Kp*. All but 3 patients (91.3%) presented with fever and 2 patients (8.3%) had no localizing signs.

Positive results of blood and pus cultures, blood culture, and pus culture were obtained in 6 patients (50%), 5 patients (41.6%), and 1 patient (8.3%) with GFPLA-*Kp*, respectively. Furthermore, positive results of blood culture, pus culture, and blood and pus cultures were obtained in 19 patients (79.1%), 3 patients (12.5%), and 2 patients (8.3%) with GFPLA-*Cp*, respectively. The proportion of positive blood culture results was higher in patients with GFPLA-*Cp* than in patients with GFPLA-*Kp* (P=0.03) compared to the proportion of positive blood and pus culture results. However, there were no statistically significant differences in the results of blood and pus cultures, blood cultures, or pus cultures between patients with GFPLA-*Kp* and patients with GFPLA-*Cp*.

With regard to laboratory investigations (Table 3 [11-12, 16-37] and Table 4 [8, 38-47]), patients with GFPLA-*Cp* had higher levels of aspartate aminotransferase (AST) (869.20 ± 583.02 IU/L versus 233.12 ± 98.19 IU/L, P=0.007) and alanine aminotransferase (ALT) (609.00 ± 516.26 IU/L versus 199.85 ± 74.93 IU/L, P=0.034) than patients with GFPLA-*Kp* at hospital admission. However, no statistically significant differences were found in alkaline phosphatase levels between the 2 patient groups. The hemoglobin, bilirubin, and lactate dehydrogenase (LDH) levels in patients with GFPLA-*Cp* were 6.88 ± 5.26 g/dL, 6.30 ± 7.08 mg/dL, and 1867.74 ± 2813.59 IU/L, respectively. These laboratory index indicated a high incidence of hemolysis.

Because ultrasonography cannot reliably depict the detailed internal structure of the gas-containing lesions, the X-Ray, CT and MRCP findings were assessed in GFPLA-*Cp* and GFPLA-*Kp*. With regard to radiological investigations, all patients (except 1 unmentioned case) with GFPLA-*Cp* and all patients with GFPLA-*Kp* were diagnosed using computed tomography (CT), as it is the most reliable technology for diagnosing GFPLA caused by these organisms. Similarly, Lee et al. reported a 100% detection rate with CT [2]. Abdominal palpation and ultrasonography were less reliable for diagnosis. The changes on CT between the patient groups were similar and include the presence of low attenuation areas and cavity formation with or without gas in the liver. In contrast, these same changes were not well defined on abdominal palpation and ultrasound in the patient groups.

All 12 patients with GFPLA-*Kp* had solitary abscesses. Of the 24 patients with GFPLA-*Cp* (with the exception of 2 patients that were not specified), 21 patients (95.4%) had solitary abscesses and 1 patient (4.5%) had multiple abscesses. The abscesses were larger in patients with GFPLA-*Cp* than in patients with GFPLA-*Kp* (15.98 ± 21.93 cm versus 8.16 ± 4.44 cm); however, the difference in abscess size between the patient groups was not statistically significant. Abscesses of diameter ⩾5 cm were found in 83.3% of patients with GFPLA-*Kp* and in 62.5% of patients with GFPLA-*Cp*. The location of abscesses (right, left, and both lobes) was compared using the χ2 test and no statistically significant differences were observed.

The treatment of GFPLA-Kp and GFPLA-Cp include antibiotic therapy, surgical debridement and drainage. For GFPLA-Kp and GFPLA-Cp, it is important to treat antibiotics before drug sensitivity test. However, we found that surgical debridement or drainage was performed in all 12 patients (100%) with GFPLA-Kp and in 5 patients (20.8%; 3 DM and 2 non-DM) with GFPLA-Cp. In other words, more patients with GFPLA-Kp received surgical debridement or drainage than patients with GFPLA-Cp (P<0.001). The survival rate of patients with GFPLA-Kp who received surgical debridement or drainage was higher than that of patients with GFPLA-Cp who received the same treatment (P=0.002).

Considering the outcomes of GFPLA-*Kp* and GFPLA-*Cp*, twelve patients (50%) with GFPLA-*Cp* died as a result of different complications. This mortality rate is higher than that of patients with GFPLA-*Kp* (16.7%). However, no statistically significant differences in mortality rate between the patient groups were found using the χ2 test. There were also no statistically significant differences in the rates of death within 24 hours of hospital admission between DM and non-DM patients with GFPLA-*Cp*. Other cases have improved or even cured.

Discussion

GFPLA was first introduced by Smith in 1944 and several sporadic cases have been reported in many parts of the world since then. However, there are obvious regional differences in the incidence of GFPLA; for example, the incidence of GFPLA is low in the West but high in Asia, especially in Taiwan [2]. Our results were similar to those in earlier reports in that we also found that in Asia, the incidence of GFPLA-*Kp* (91.7%) is higher than that of GFPLA-*Cp* (45.8%) (P=0.011). Although several hypotheses have been proposed, it is still unclear why GFPLA-*Kp* is more prevalent in Taiwan. One hypothesis stated that the prevalence can be explained by the spread of a pathogenic clone [49]. GFPLA has recently emerged as an important infectious disease in Japan, Korea, China, and Australia [8, 42, 50-51]. However, the correlation of these pathogenic clones to different regions using molecular typing methods is yet unclear. It was therefore concluded that this may also explain the high incidence of GFPLA-*Kp* in in other parts of Asia besides Taiwan.

It was found that age >70 years was not a predictor of mortality in patients with GFPLA-*Kp* and patients with GFPLA-*Cp*. This finding was contradicted by a multicenter observational study by Sartelli et al., who found that age >70 years can predict mortality [52]. The limited sample size of patients with GFPLA-*Kp* and patients with GFPLA-*Cp* may explain the contradiction.

With regard to the underlying diseases in patients with these 2 categories of GFPLA, we found that DM was more prevalent in patients with GFPLA-*Kp* than in patients with GFPLA-*Cp* (P=0.032). This is similar to the results of studies by Chou et al. and Yang et al. [6, 53]. The higher incidence of GFPLA in patients with DM is because poor glycemic control leads to compromised immunity, neutrophil dysfunction, and chemotaxis dysfunction. These lead to poor microcirculation in the liver, with rapid growth and vigorous metabolism of bacteria in the affected areas, which may in turn lead to gas production [53]. Furthermore, poor glycemic control in patients with DM may provide gas-forming microorganisms with a more favorable environment for gas formation through mixed acid fermentation of glucose. Mixed acid fermentation within the abscess contributes to gas production resulting from carbon dioxide produced during glucose fermentation in liver tissues under anaerobic conditions. *K. pneumoniae* was reported to

produce formic hydrogenlyase, an enzyme that is only produced in acidic environments when local pH reaches 6 or less by acid accumulation. Fermentation by formic hydrogenlyase is a key process that often leads to accumulation of acids, and formic acid accumulated within the abscess is converted to carbon dioxide and hydrogen gas by formic hydrogenlyase when the pH is 6 or less [2]. Poor glycemic control compromises the immune system and increases glucose metabolism via the polyol pathway. This depletes the nicotinamide adenine dinucleotide phosphate hydrogen necessary for superoxide production in neutrophil-mediated opsonophagocytosis [54], thereby providing a favorable microenvironment for the rapid growth and vigorous metabolism of the microorganisms and leads to gas formation [3]. However, an earlier study found that high glucose levels reflecting poor glycemic control may stimulate capsular polysaccharide (CPS) biosynthesis and CPS gene expression of highly virulent *K. pneumoniae* through reduction of cyclic adenosine monophosphate levels, which increases resistance to phagocytosis and contributes to the development of liver abscesses [55]. The CPS of *K. pneumoniae* is an acidic polysaccharide composed of 4−6 sugars, which seem to correlate with bacterial virulence [56]. These sugars play significant roles in *K. pneumoniae* infection and are explained below. (1) resistance to phagocytosis caused by CPS [57]: Poor glycemic control in patients with DM can increase CPS production. The increased CPS can block binding sites and resist the effects of conditioning and phagocytosis by macrophages, neutrophils, epithelial cells, and dendritic cells. (2) CPS inhibits the maturation of dendritic cells and reduces the production of interleukin-12 and tumor necrosis factor-alpha (TNF-α), leading to dysfunction of immature dendritic cells and ultimately limiting the migration of natural killer cells. This helps bacteria avoid attack from the host immune system and favors bacterial reproduction in the early stage of infection [58]. However, the details need to be further explored. The above-stated actions of CPS facilitate gas formation in patients with PLA caused by *K. pneumoniae* who have DM.

There are 5 serotypes of *C. perfringens* (A, B, C, D, and E) based on the production of 4 different lethal toxins (alpha, beta, epsilon, and iota) [59]. All 5 serotypes of *C. perfringens* produce alpha-toxin, which is a phospholipase C that hydrolyzes lecithin to form phosphorylcholine and diglyceride [60]. It has been suggested that poor glycemic control may inhibit the action of phospholipase C and limit the damage to alpha-toxin. This may explain why DM is less prevalent in patients with GFPLA-*Cp* than in patients with GFPLA-*Kp*. However, the incidence of hemolysis in patients with GFPLA-*Cp* was higher than that in patients with GFPLA-*Kp*. Alpha-toxin is the main cause of hemolysis as it can hydrolyze the phospholipids in red blood cell membranes [60]. The N-terminal and C-terminal domains are structures of the alpha-toxin that form a loop. The former has phospholipase activity while the latter is hydrophobic and enters the cell membrane [60]. The loop formed by the C- and N-terminals contains GM1 ganglioside-binding motifs and specifically binds to GM1a. The alpha-toxin binding to GM1a triggers specific signaling events that lead to activation of tyrosine kinase A and the subsequent signaling cascade results in the release of TNF-α, which causes catastrophic hemolysis and inflammation [61].

For the early diagnosis of *C. perfringens* infection, gram staining of the blood sample is important because it is a gram-positive rod, while *K. pneumoniae* is gram-negative. That is why there were more positive blood culture results in patients with GFPLA-*Cp* than in patients with GFPLA-*Kp* (P=0.03). Therefore, for early diagnosis of GFPLA-*Cp*, blood culture tests should be considered at hospital admission. In contrast, early diagnosis of GFPLA-*Kp* usually involves physical and laboratory examinations and CT scans.

Our review also revealed that GFPLA-*Cp* is associated with higher AST and ALT levels than GFPLA-*Kp* (P<0.05). Furthermore, hemoglobin, LDH, and total or indirect bilirubin levels were found to be elevated in patients with GFPLA-*Cp* but not in patients with GFPLA-*Kp*. AST, ALT, LDH, and total or indirect bilirubin levels are indicators of liver function that may increase due to hemolysis caused by *C. perfringens*. This may explain the higher levels of AST and ALT observed in patients with GFPLA-*Cp*. However, most of the studies we reviewed were retrospective and it cannot be conclusively stated that the elevation in AST and ALT levels was due to hemolysis caused by *C. perfringens*.

It was found that a greater proportion of patients with GFPLA-*Kp* was treated with surgical debridement or drainage than that of patients with GFPLA-*Cp* (P<0.01). It was suggested that this may be because of the higher prevalence of DM in patients with GFPLA-*Kp*. Concomitant DM and GFPLA-*Kp* can potentially lead to poor patient outcomes even within 1 or 2 days of hospitalization [62]. Furthermore, only 6 patients (3 DM and 3 non-DM) with GFPLA-*Cp* received surgical debridement or drainage and there was no statistically significant difference between them. This finding shows that greater attention should be paid to hemolysis and necessary measures should be taken. It also shows that surgical debridement or drainage was not necessary.

There were no statistically significant differences in gender between survivors and the deceased in patients with GFPLA-*Cp*. However, an earlier study found that significantly more female than male patients survived (P<0.05) [24]. The difference may be associated with basic patient conditions, such as the presence of underlying diseases, age, and nationality. We also found that a greater proportion of patients with GFPLA-*Kp* who received surgical debridement or drainage survived than that of patients with GFPLA-*Cp* (P=0.002). Patients with GFPLA often present with septic shock and bacteremia, which increase mortality [48]. Therefore, surgical debridement or drainage is vital.

Conclusions

In conclusion, based on the study characteristics, GFPLA may be considered a life-threatening disease with a wide spectrum. Although this review was limited by the small number of publications, we reckon

that it will raise awareness for GFPLA-*Kp* and GFPLA-*Cp*.

Declarations

Ethics approval and consent to participate

None.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during themanuscript are available from the database of Pubmed and Web of Science.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Cases of K. pneumoniae GFPLA published from January 2009 to March 2019

Author	Year	Age (yr)	Sex	Country	Condition(s)	Klebsiella pneumoniae originates	Diagnose	Abscess location	Abscess diameter (cm)	Focus removed	HML	SSE	TTD
Tatsuta et al[38]	2011	43	M	Japan	DM	Blood and pus culture	CT, XR, US	Right	13	Yes	No	-	-
Oh et al[39]	2011	70	M	Korea	DM	Pus cultures	CT	Right	-	Yes	No	-	-
Hagiya et al[40]	2012	58	M	Japan	DM	Blood and pus culture	CT	Right	-	Yes	No	-	-
Hagiya et al[40]	2012	61	F	Japan	DM	Blood cultures	CT	Right	-	Yes	No	-	-
Ho et al[41]	2013	66	F	Taiwan	DM	Blood cultures	CT	Right	-	Yes	No	-	-
Zhang et al[8]	2013	76	F	China	DM	Blood and pus culture	CT	Right	14	Yes	No	No	5 d
Paterson et al[42]	2013	60	M	Australia	None	Blood and pus culture	CT	Right	-	Yes	No	-	-
Keng et al[43]	2014	76	M	Taiwan	DM	Blood cultures	CT	Right	-	Yes	No	-	-
Kotwal et al[44]	2015	75	F	USA	DM	Blood cultures	CT, MRCP	Right	6	Yes	No	-	-
Chiou et al[45]	2015	72	M	Taiwan	None	Blood and pus culture	CT	Left	8	Yes	No	-	-
Yuichi et al[46]	2017	69	M	Japan	DM	Blood and pus culture	CT, US	Right	5	Yes	No	-	-
Kim et al[47]	2017	79	F	Korea	DM, hypertension	Blood cultures	CT	Right	3	Yes	No	No	19 h

CT: Computed tomography; XR: X-Ray; US: Ultrasound scan; MRCP: Magnetic resonance cholangiopancreatography; HML: Hemolysis; SSE: Survival of septic episode; TTD: Time to death

Table 2 Cases of C. perfringens GFPLA published from January 2009 to March 2019

Author	Year	Age (yr)	Sex	Country	Condition(s)	Originates	Diagnose	Abscess location	Abscess size (cm)	Focus removed	HML	SSE	TTD
Tabarelli et al[16]	2009	65	F	Austria	Pancreatic cancer	Blood culture	CT	Right	9	No	No	No	27 d
Meyns et al[17]	2009	64	M	Belgium	DM	Blood and pus culture	CT, XR	Right	-	No	Yes	No	N/A[1]
Merino et al[18]	2009	83	F	Spain	Cholangitis	Blood culture	CT	N/A	-	No	Yes	No	3 d
Ng et al[11]	2010	61	F	Hong Kong	DM	Blood culture	CT	Left	-	Yes	Yes	Yes	-
Rajendran et al[19]	2010	58	M	UK	None	Blood culture	CT, XR	Right	-	Yes	No	Yes	-
Bunderen et al[20]	2010	74	M	Netherlands	Cholangitis	Blood culture	NA[1]	N/A	-	No	Yes	Yes	-
Kitterer et al[21]	2012	71	M	Germany	liver transplant	Blood culture	CT	Right	8	Yes	No	No	6 h
Qandeel et al[22]	2012	59	M	UK	DM;ERCP	Blood culture	CT	Right	-	Yes	Yes	Yes	-
Law et al[12]	2012	50	F	Hong Kong	Rectal cancer	Blood culture	CT	Right	15	No	No	No	7 d
Imai et al[23]	2014	76	M	Japan	None	Blood and pus culture	CT, XR	Right	65	No	Yes	No	6 h
Kurasawa et al[24]	2014	65	M	Japan	DM	Blood culture	CT	Right	-	No	No	No	6 h
Rives et al[25]	2015	63	M	USA	Colon cancer;ERCP	Blood culture	CT	Left	3.1	No	No	Yes	-
Eltawansy et al[26]	2015	81	F	USA	DM, Gastroenteritis	Blood culture	CT	Right	-	No	No	Yes	-
Khan et al[27]	2015	77	M	USA	DM	Blood culture	CT, XR	Left	-	No	Yes	No	9 h
Li et al[28]	2015	71	M	China	Cholangitis	Blood culture	CT	Right	-	No	Yes	Yes	-
Lim et al[29]	2015	58	M	USA	None	Blood culture	CT	Both	5	No	Yes	No	8 h
Meeuwes et al[30]	2015	71	F	Netherlands	Hemi-hepatectomy;ERCP	Blood culture	CT	Right	-	No	Yes	Yes	-
García et al[31]	2016	65	M	Spain	DM	Blood culture	CT	Right	4.8	No	Yes	Yes	-
Kyang et al[32]	2016	84	M	Australia	Gastric cancer	Pus culture	CT	Right	-	No	No	Yes	-
Hashiba et al[33]	2016	82	M	Japan	DM	Blood culture	CT	Left	-	No	Yes	No	2 h
Paasch et al[34]	2017	65	M	Germany	DM	Pus culture	CT	Right	7	Yes	No	Yes	-
Yoshikawa et al[35]	2017	70	M	Japan	Hepatocellular carcinoma;TACE	Pus culture	CT	Right	-	No	No	Yes	-
Shibazaki et al[36]	2018	68	F	Japan	DM	Blood culture	CT	Left	-	No	No	No	1 h
Hamada et al[37]	2018	68	M	Japan	Gastric cancer	Blood culture	CT	Right	-	No	Yes	No	10 h

XR: X-Ray; 1Exact time of TTD was not discussed; HML: Hemolysis; SSE: Survival of septic episode; TTD: Time to death

Table 3 laboratory examination of *K. pneumoniae* GFPLA

Ref.	HbA1C (%)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
38	14.3	149	171	602
39	-	-	-	-
40	11.4	164	145	1865
40	10.5	116	142	880
41	-	260	-	-
8	-	-	-	-
42	-	-	-	-
43	-	379	237	-
44	8.2	220	125	354
45	6.2	206	248	300
46	14.6	371	331	675
47	8.2	-	-	-

Table 4 laboratory examination of *C. perfringens* GFPLA

Ref.	Hb (g/dL)	ALT	AST	ALP	Bilirubin (mg/dl)	LDH (IU/L)
16	-	-	-	-	-	-
17	7.2	84	139	-	8.27	980
18	6	-	-	-	19.6	2288
11	14.3	1314	-	112	-	4054
19	9	-	-	-	-	-
20	9.8	261	419	271	23.7	2300
21	11.2	-	-	-	3.7	-
22	6.8	-	-	-	-	-
12	8.3	-	-	302	8.95	1132
23	12.2	-	1388		10.5	4767
24	13.5	261	297	469	6.4	6203
25	-				7.6	-
26	-	231	318	494	0.42	-
27	6	370	1179	238	9.5	3442
28	11.8	1652	787	-	18.89	-
29	12.4	-	-	-	-	-
30	-	-	-	-	10.47	-
31	14.6	402	-	-	-	-
32	-	825	894	-	-	-
33	8.3		1366	-	9	10321
34	-	-	-	-	-	-
35	-	-	-	-	-	-
36	6.9	690	1905	-	8.1	-
37	-	-	-	-	-	-

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