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

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**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) \((869.20 \pm 583.02 \text{ IU/L versus } 233.12 \pm 98.19 \text{ IU/L, } P=0.007)\) and alanine aminotransferase (ALT) \((609.00 \pm 516.26 \text{ IU/L versus } 199.85 \pm 74.93 \text{ IU/L, } P=0.034)\) 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 \(6.88 \pm 5.26 \text{ g/dL, } 6.30\)
± 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 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 \textit{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 \textit{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-\textit{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-\textit{Kp} and GFPLA-\textit{Cp}.

Declarations

\textbf{Ethics approval and consent to participate}

None.

\textbf{Consent for publication}

Not applicable.

\textbf{Availability of data and materials}

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

\textbf{Competing interests}

The authors declare that they have no competing interests.

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Tables
## Table 1 Cases of K. pneumoniae GPFLA 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  |
|--------------|------|----------|-----|---------|--------------|---------------------------------|-----------|-----------------|----------------------|---------------|-----|-----|------|
| Tatsuna et al. | 2011 | 43       | M   | Japan   | DM           | Blood and pus culture          | CT, XR, US| Right           | 13                   | Yes           | No  | -   | -    |
| Oh et al.    | 2011 | 70       | M   | Korea   | DM           | pus cultures                   | CT         | Right           | -                    | Yes           | No  | -   | -    |
| Hagiya et al. | 2012 | 58       | M   | Japan   | DM           | Blood and pus culture          | CT         | Right           | -                    | Yes           | No  | -   | -    |
| Hagiya et al. | 2012 | 61       | F   | Japan   | DM           | Blood cultures                 | CT         | Right           | -                    | Yes           | No  | -   | -    |
| Ho et al.    | 2013 | 66       | F   | Taiwan  | DM           | Blood cultures                 | CT         | Right           | -                    | Yes           | No  | -   | -    |
| Zhang et al. | 2013 | 76       | F   | China   | DM           | Blood and pus culture          | CT         | Right           | 14                   | Yes           | No  | No  | 5 d  |
| Paterson et al. | 2013 | 60       | M   | Australia | None       | Blood and pus culture          | CT         | Right           | -                    | Yes           | No  | No  | -    |
| Keng et al.  | 2014 | 76       | M   | Taiwan  | DM           | Blood cultures                 | CT         | Right           | -                    | Yes           | No  | -   | -    |
| Kotwal et al. | 2015 | 75       | F   | USA     | DM           | Blood cultures                 | CT         | Right           | 6                    | Yes           | No  | -   | -    |
| Chiu et al.  | 2015 | 72       | M   | Taiwan  | DM           | Blood and pus culture          | CT         | Left            | 8                    | Yes           | No  | -   | -    |
| Yuichi et al. | 2017 | 69       | M   | Japan   | DM           | Blood and pus culture          | CT, US    | Right           | 5                    | Yes           | No  | -   | -    |
| Kim et al.   | 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 GPFLA 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. | 2009 | 65       | F   | Austria   | Pancreatic cancer | Blood culture | CT         | Right           | 9                | No            | No  | No  | 27 d |
| Meyns et al.   | 2009 | 64       | M   | Belgium   | DM           | Blood and pus culture          | CT, XR     | Right           | -                | No            | Yes | No  | N/A  |
| Merino et al.  | 2009 | 83       | F   | Spain     | Cholangitis   | Blood culture        | CT         | N/A             | -                | Yes           | Yes | No  | 3 d  |
| Ng et al.      | 2010 | 61       | F   | Hong Kong | DM           | Blood culture          | CT         | Left            | -                | Yes           | Yes | Yes | -    |
| Rajendran et al. | 2010 | 58       | M   | UK        | None         | Blood culture          | CT, XR     | Right           | -                | Yes           | Yes | Yes | -    |
| Bunderen et al. | 2010 | 74       | M   | Netherlands | Cholangitis | Blood culture       | N/A        | N/A             | -                | Yes           | Yes | -   | -    |
| Kitterer et al. | 2012 | 71       | M   | Germany   | liver transplant | Blood culture    | CT         | Right           | 8                | Yes           | No  | No  | 6 h  |
| Qandiel et al. | 2012 | 59       | M   | UK        | DM-ERCP      | Blood culture          | CT         | Left            | -                | Yes           | Yes | Yes | -    |
| Low et al.     | 2012 | 50       | M   | Hong Kong | Rectal cancer | Blood culture          | CT         | Right           | 15               | No            | No  | No  | 7 d  |
| Imai et al.    | 2014 | 76       | M   | Japan     | None         | Blood and pus culture     | CT, XR     | Right           | 65               | No            | No  | No  | 6 h  |
| Kusunose et al. | 2014 | 65       | M   | Japan     | DM           | Blood culture          | CT         | Right           | -                | No            | No  | No  | 6 h  |
| Rikos et al.   | 2015 | 63       | M   | USA       | Colon cancer| Blood culture | CT         | Left            | 3.1              | No            | No  | No  | -    |
| Elshamy et al. | 2015 | 81       | F   | USA       | DM, Gastromenitis | Blood culture   | CT         | Right           | -                | No            | No  | -   | -    |
| Khan et al.    | 2015 | 77       | M   | USA       | DM           | Blood culture          | CT, XR     | Left            | -                | No            | Yes | No  | 9 h  |
| Li et al.      | 2015 | 71       | M   | China     | Cholangitis   | Blood culture          | CT         | Right           | -                | Yes           | Yes | Yes | -    |
| Lim et al.     | 2015 | 58       | M   | USA       | None         | Blood culture          | CT         | Both            | 5                | No            | Yes | No  | 8 h  |
| Meenawala et al. | 2015 | 71       | F   | Netherlands | Hemil-hepatectomy| ERCP     | Blood culture | CT         | Right           | -                | No            | Yes | Yes | -    |
| Garcia et al.  | 2016 | 65       | M   | Spain     | DM           | Blood culture          | CT         | Right           | 4.8              | Yes           | Yes | Yes | -    |
| Kyung et al.   | 2016 | 84       | M   | Australia | Gastric cancer | Pus culture       | CT         | Right           | -                | No            | No  | Yes | -    |
| Hashiba et al. | 2016 | 82       | M   | Japan     | DM           | Blood culture          | CT         | Left            | -                | No            | Yes | No  | 2 h  |
| Pranesh et al. | 2017 | 65       | M   | Germany   | DM           | Blood culture          | CT         | Right           | 7                | Yes           | No  | No  | -    |
| Yoshioka et al. | 2017 | 70       | M   | Japan     | Hepatocellular carcinoma, TACE | Pus culture | CT         | Right           | -                | No            | No  | No  | -    |
| Shibazaki et al. | 2018 | 68       | F   | Japan     | DM           | Blood culture          | CT         | Left            | -                | No            | No  | No  | 1 h  |
| Hamada et al.  | 2018 | 68       | M   | Japan     | Gastric cancer | Blood culture | CT         | Right           | -                | Yes           | No  | No  | 10 h |

XR: X-Ray; IExact 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       | -          | -          | -          |
| Ref. | Hb (g/dL) | ALT | AST | ALP (mg/dL) | 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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