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Original Article

The prevalence of rectal carriage of *Klebsiella pneumoniae* amongst diabetic patients and their clinical relevance in Taiwan: A five-year prospective study

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Abstract *Background/purpose:* Pyogenic liver abscess (PLA) and bacteremia caused by *Klebsiella pneumoniae* is a common complication among patients with diabetes mellitus (DM). The aim of this study is to investigate the prevalence of rectal carriage and serotype distribution of *K. pneumoniae* amongst DM patients and their clinical relevance.
Methods: We prospectively collected rectal swabs for *K. pneumoniae* culture in asymptomatic DM patients from March 2008 to June 2009. Seven capsular serotypes that were commonly associated with PLA were determined by capsular polysaccharide synthesis (cps) genotyping. Microbiologically confirmed bacterial infections were evaluated 1 and 5 years after initial enrolment of the patients.
Results: A total of 100 male and 62 female patients (mean age, 56.6 years) were enrolled. Of these, 77 (47.5%) had rectal *K. pneumoniae* colonization. Colonizers were older than non-colonizers ($p = 0.03$). Sex, fasting blood glucose, and initial HbA1C were not statistically different ($p = 0.26$, 0.18, and 0.31, respectively). Among the 65 available isolates, 22 (33.8%) belonged to the seven main serotypes. During the 5-year's follow-up, 21 patients developed microbiologically documented bacterial infections but none of them developed PLA and bacteremia. Risk factors for bacterial infection within 5 years included initial glycosylated hemoglobin (HbA1C) $>$ 10% or first-year average HbA1C $>$ 10%.

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Conclusion: Although nearly half of asymptomatic DM patients had rectal carriage of *K. pneumoniae* and one-third of them colonized by isolates belonging to the seven serotypes related to PLA, none of them subsequently developed PLA and colonized patients did not have higher risk of microbiologically confirmed bacterial infections.

Introduction

Klebsiella pneumoniae is a major nosocomial pathogen that may contribute to the development of multidrug resistance in Western countries.[1,2] However, in Taiwan it can cause severe community infections, especially pyogenic liver abscess (PLA) with serious sequelae.[3] After decades of investigations, we now know that the molecular epidemiology of *K. pneumoniae* in Taiwan is quite different from that in other countries. Serotype K1/multilocus sequence typing (ST) 23 is a major clone that causes community-onset liver abscess and other invasive infections.[4,5] The role of serotype K2 is disputed, and the STs of K2 are more diverse than K1.[6] Different serotypes of *K. pneumoniae* are associated with different clinical presentations.[6]

The bowels have been considered to be the primary reservoir of *K. pneumoniae* in hospitalized patients,[7] and antibiotic usage may increase fecal carriage of *K. pneumoniae* in hospitalized patients.[8] The colonization of *K. pneumoniae* may persist in spinal cord injury patients for a mean of 20 days.[9] Recent studies have shown that rectal carriage of *K. pneumoniae* may be the source of *K. pneumoniae* bacteremia.[10,11] Furthermore, according to a retrospective Taiwanese database analysis, ampicillin and amoxicillin use are reported to increase the risk of *K. pneumoniae* liver abscess.[12] A surveillance study about rectal carriage of healthy Chinese residents in several Asian countries showed a spectrum of carriage rates, ranging from 18.8% in Japan to 87.7% in Malaysia. Serotypes K1 and K2 accounted for 9.8% of all isolates.[13]

Diabetes mellitus (DM) has been identified as a risk factor for bacterial infection.[14,15] Previous studies have identified DM as one of the most important risk factors for *K. pneumoniae*—related PLA,[3–5] and metastatic infection was associated with poor glycemic control.[16] In addition, poor glycemic control stimulates capsule biosynthesis of highly virulent *K. pneumoniae* and contributes to bacterial invasiveness.[17] Moreover, a recent study in patients with diabetes-related foot infections showed that gut colonization with *K. pneumoniae* with carbapenemase is a risk factor for mortality.[18] It is hypothesized that carriage of virulent *K. pneumoniae* strains precedes to development of *K. pneumoniae*—related PLA,[7–12] but a prospective study is lacking. In order to understand the prevalence of rectal carriage of *K. pneumoniae* amongst DM patients and the distribution of serotypes and their clinical relevance, we performed rectal swabbing in asymptomatic DM patients and evaluated microbiologically confirmed bacterial infections at 1 year and 5 years after the patient's initial enrolment.

Methods

Hospital setting, study design, and patient enrolment

Far Eastern Memorial Hospital, an 1100-bed tertiary referral center, provides medical services for about 1 million people in New Taipei City, Taiwan. The study population consisted of adult patients >18 years old with diabetes followed up at a metabolism clinic. A study physician interviewed patients at enrolment using a standardized case record form to obtain basic information and medication history. After the intake interview, patients were eligible for enrolment if they had not used antibiotics within the previous 3 months. Patients also reviewed and signed informed consent forms. No intervention or patient interview was performed after the enrolment. A retrospective collection of bacterial infection episodes among these cases was carried out in 2016. This study was approved by the Institutional Review Board of the Far Eastern Memorial Hospital (096054, 105079-E).

Rectal swab surveillance culture

Trained nurses or the study physician used a conventional culture swab (BBL CultureSwab EZ, Becton Dickinson, Sparks, MD, USA) to obtain rectal swab samples. The rectal swab was performed by inserting the swab tube 1 cm above the anal verge. The specimen was inoculated on an eosin-methylene blue agar plate immediately. Mucoid-like colonies were selected for further identification. The identification of *K. pneumoniae* was carried out by the conventional biochemical methods. Rectal swabs were performed at enrolment.

Clinical information and subsequent bacterial infection

Clinical information was collected from the medical record. Glycosylated hemoglobin (HbA1C) was determined using a Tosoh G7 HPLC analyzer (Tosoh Bioscience, South San Francisco, CA, USA). Patients' initial HbA1C and average HbA1C during the first year after enrolment in the study were used to represent their degree of glycemic control. The diagnosis of a documented bacterial infection was based on clinical, bacteriological, and radiological criteria and was reviewed by two infectious-disease physicians 1 year and 5 years after the initial enrolment. Only

the first episode of a patient's bacterial infection was counted.

Capsular typing (serotype) of *K. pneumoniae*

Capsular serotypes were determined by polymerase chain reaction for capsular polysaccharide synthesis (cps) genotyping using primers specific for the most commonly encountered (>80%) capsular types associated with PLA (K1, K2, K5, K20, K54, K57, and a new capsular type, N1) as previously described.[19] The cps-genotyping identified 65 isolates that were available for further analysis.

Statistical analysis

Means and standard deviations were calculated for continuous variables. Percentages were used for categorical variables. Associations between risk factors and colonization or documented bacterial infections were investigated using binary logistic regression. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated. Cumulative infections at 1 and 5 years after enrolment were calculated by the Cox proportional hazards model. Data were analyzed with SPSS software for Windows (Release 15.0; SPSS, Chicago, IL, USA).

Results

K. pneumoniae colonization and distribution of serotypes

We enrolled 100 male and 62 female patients with a mean age of 56.6 years. The patient flow chart is shown in Fig. 1. Seventy-seven patients (47.5%) had rectal *K. pneumoniae* colonization. Colonizers were older than non-colonizers (58.3 vs. 55.1 years; $p = 0.03$). Sex, fasting blood glucose, and initial HbA1C were not statistically different ($p = 0.26$, 0.18, and 0.31, respectively). We observed a statistically nonsignificant trend towards increased *K. pneumoniae* colonization amongst patients with HbA1C > 10 (29% vs. 19%; $p = 0.15$) (Table 1).

The cps-genotyping for the 65 available isolates revealed that 22 isolates (33.8%) belonged to the 7 common serotypes identified in PLA. Serotype K57 was the most commonly identified serotype ($n = 7$, 10.8%) followed by K1 ($n = 6$, 9.2%), K2 ($n = 3$, 4.6%), K20 ($n = 3$, 4.6%), K54

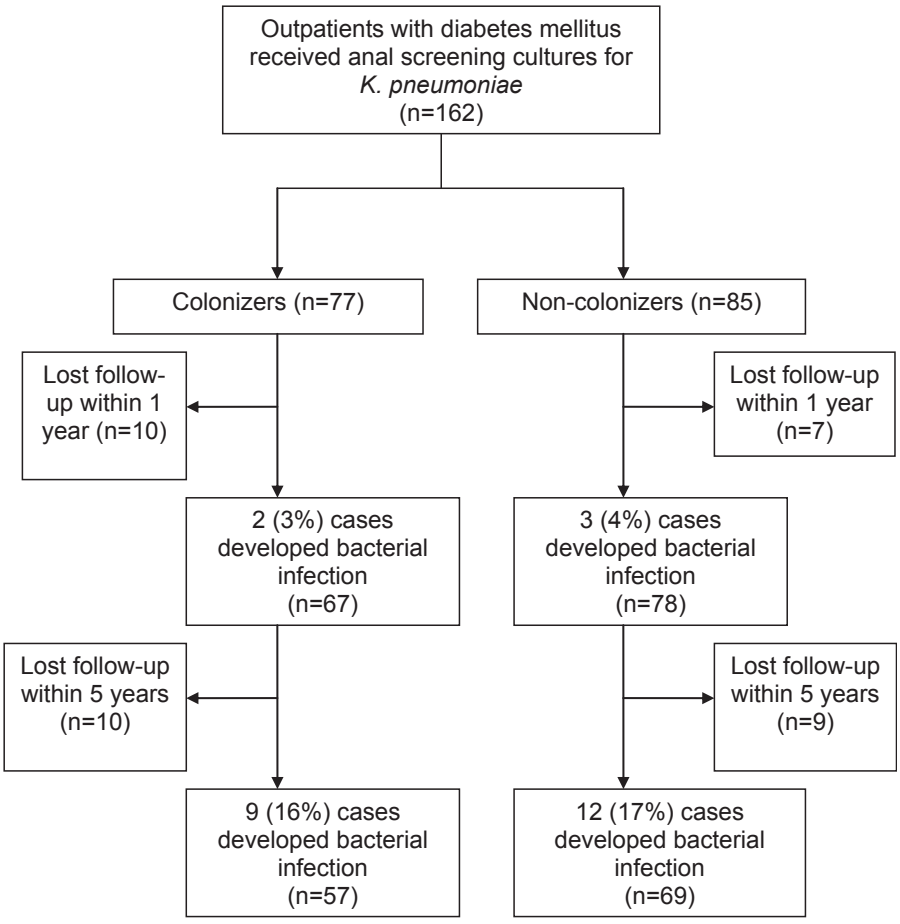

Figure 1. Patient Flow chart of patient enrollment according to *K. pneumoniae* colonization.

Table 1 Clinical characteristics of 162 patients with diabetes mellitus who were *Klebsiella pneumoniae* colonizers and non-colonizer.

Characteristic	All ($n = 162$)	Colonizers ($n = 77$)	Non-colonizers ($n = 85$)	p value	Relative risk	95% confidence interval
Age, yr (mean ± SD)	56.6 ± 9.2	58.3 ± 9.2	55.1 ± 8.9	0.03	1.04	1.00–1.08
Sex, no. of male (%)	100 (62)	51 (66)	49 (58)	0.26	1.44	0.76–2.73
Initial AC sugar, mg/dL (mean ± SD)	193.7 ± 110.1	206.2 ± 127.1	182.4 ± 91.4	0.18	1.00	1.00–1.01
Initial HbA1C, %	8.7 ± 2.3	8.9 ± 2.4	8.5 ± 2.1	0.19	1.10	0.96–1.26
Initial Hb1C group				0.31		
<7%, no. (%)	41 (25)	17 (22)	24 (28)	–	–	–
7–10%, no. (%)	83 (51)	38 (49)	45 (53)	0.65	1.19	0.56–2.54
>10%, no. (%)	38 (24)	22 (29)	16 (19)	0.15	1.94	0.79–4.75
Average HbA1C, % (mean ± SD)	8.2 ± 1.5	8.3 ± 1.7	8.1 ± 1.4	0.51	1.07	0.87–1.32
Creatinine, mg/dL (mean ± SD)	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.3	0.81	1.11	0.46–2.72
Infection within 1 yr, no. (%)	5/145[a] (3)	2/67 (3)	3/78 (4)	0.78	0.77	0.13–4.75
Infection within 5 yr, no. (%)	21/126[a] (17)	9/57 (16)	12/69 (17)	0.81	0.89	0.35–2.29
Mortality within 1 yr, no. (%)	1/144[b] (1)	0/66 (0)	1/78 (1)	–	–	–
Mortality within 5 yr, no. (%)	4/124[b] (3)	0/57 (0)	4/67 (6)	–	–	–

SD = standard deviation.

[a] Numbers of patients who completed the follow-up evaluation for subsequently bacterial infection within one year (n = 145) and five years (n = 126) after enrollment.

[b] Numbers of patients who completed the follow-up evaluation for outcomes within one year (n = 144) and five years after enrollment (n = 124). Compared to patients with bacterial infection group, one patient developed infection at 6 months but lost to follow-up and did not complete 1-year follow-up. Two cases developed infection within 5 years but did not complete 5-year follow-up.

($n = 2$, 3.1%), and K5 ($n = 1$, 1.5%). Serotypes of the remaining 43 isolates (66.2%) could not be identified by PCR cps genotyping.

Microbiologically confirmed bacterial infections

During the first year after enrolment, five microbiologically documented bacterial infections occurred, including two wound infections and one each of pneumonia, sinusitis, and bloodstream infection. At 5 years after enrolment, 21 patients developed documented microbiologically confirmed bacterial infections, including urinary tract infection ($n = 8$), bloodstream infection ($n = 5$), pneumonia ($n = 3$), wound infection ($n = 3$), peritonitis ($n = 1$), and sinusitis ($n = 1$). The most common pathogen was *Escherichia coli* ($n = 6$), followed by *Staphylococcus* spp. ($n = 5$), *K. pneumoniae* ($n = 4$), *Streptococcus* spp. ($n = 2$), and *Enterococcus* spp. ($n = 2$). The etiologies of bloodstream infection among the five patients were, *E. coli*, *Citrobacter diversus*, *Salmonella* spp., methicillin-resistant *Staphylococcus aureus*, and *Fusobacterium* spp., respectively. Among the four patients who developed *K. pneumoniae* infections during the 5 years of follow-up, two had pneumonia and two had urinary tract infection. Two were designated as colonizers with K1 and non-typeable *K. pneumoniae* and two were non-colonizers. No patients were found to have PLA.

Risk factors for bacterial infection

Seventeen patients were lost to follow-up after 1 year. Compared to the remaining 145 patients, those lost to follow-up had significantly higher initial HbA1C (9.9 ± 2.6 vs. 8.5 ± 2.2, $p = 0.02$). Amongst the remaining 145 patients, there were 5 infections. Table 2 shows comparisons between patients with and without infection. One patient died within the first year. The *K. pneumoniae* colonization rate was not significantly different between these two groups. By the 5-year follow-up, 36 patients had been lost to follow-up and their initial HbA1C levels were higher than those of the remaining 126 patients (9.3 ± 2.3 vs. 8.5 ± 2.2). There were 21 episodes of bacterial infection amongst the 126 patients (Table 3). The risk factors for infection included higher initial AC sugar, initial HbA1C, and average HbA1C within the first year of follow-up. Patients who developed a bacterial infection also had significantly higher 5-year mortality rates (19% vs. 0%; $p < 0.01$). Colonization with *K. pneumoniae* was not associated with subsequent bacterial infections (Fig. 2). On the contrary, elevated values of both the initial HbA1C level and the average HbA1C during 1-year follow-up were associated with bacterial infections (Fig. 3).

Discussion

DM is an important risk factor for bacterial infection, and its role in community-acquired *K. pneumoniae* infection has been reported for decades.[3–6] In this cohort of DM patients followed up at clinics, rectal carriage of *K. pneumoniae*, including virulent strains, was common. However, only four patients developed subsequent *K. pneumoniae* infections during the 5-year follow-up. Furthermore, colonization by *K. pneumoniae* was not associated with subsequent *K. pneumoniae* or other bacterial infections. On the contrary, an initial HbA1C > 10% or a first-year average HbA1C > 10% was a risk factor for documented bacterial infection during the 5-year follow-up.

Intuitively, colonization must precede invasive infection, but information about the occurrence and incidence of invasive infection amongst *K. pneumoniae* colonizers is limited. The increased prevalence of oropharyngeal gram-negative bacilli amongst diabetics and the elderly was reported decades ago,[20–22] but the effect on subsequent infection is controversial. Diabetes was found to be risk factor for multidrug-resistant *Acinetobacter* and *Candida* colonization among debilitated people and was linked to subsequent infection amongst patients who carried carbapenem-resistant *K. pneumoniae*.[23–25] We initially hypothesized that colonization rate might be correlated to poor glycemic control and subsequent infection. In this study, however, despite the fact that *K. pneumoniae* colonization is common amongst outpatients who have

Table 2 Risk factors for bacterial infection within 1 year of enrolment.

Characteristic	All ($n = 145$)	Infection ($n = 5$)	No infection ($n = 140$)	*p* value	Relative risk	95% confidence interval
Age, yr (mean ± SD)	56.3 ± 9.3	50.2 ± 12.7	56.6 ± 9.2	0.12	0.93	0.85–1.02
Sex, no. of male (%)	91 (63)	5 (100)	86 (61)	0.33	43.3	0.02–78,927
Initial AC sugar, % (mean ± SD)	190.8 ± 108.5	228.8 ± 107.2	189.4 ± 108.7	0.43	1.00	1.00–1.01
Initial HbA1C % (mean ± SD)	8.5 ± 2.2	8.6 ± 0.8	8.5 ± 2.2	0.73	1.07	0.74–1.54
<7%, no. (%)	39 (27)	0 (0)	39 (28)	—	—	—
7–10%, no. (%)	75 (52)	4 (80)	71 (51)	—	—	—
>10%, no. (%)	31 (21)	1 (20)	30 (21)	—	—	—
Average HbA1C, % (mean ± SD)	8.1 ± 1.5	8.7 ± 1.1	8.1 ± 1.5	0.44	1.22	0.74–2.01
Creatinine, mg/dL (mean ± SD)	0.9 ± 0.4	1.0 ± 0.4	0.9 ± 0.4	0.83	1.28	0.13–12.61
K. pneumoniae colonization, no. (%)	67 (46)	2 (40)	65 (46)	0.78	0.77	0.13–4.63
Mortality within 1 yr, no. (%)	1/144[a] (1)	1/4 (25)	0/140 (0)	<0.01	—	—

SD = standard deviation.

[a] One patient developed infection at 6 months but lost to follow-up and did not complete 1-year follow-up; thus, only 144 cases were evaluated for mortality.

Table 3 Risk factors for bacterial infection among 126 patients with diabetes mellitus within 5 years of enrolment.

Characteristic	All (n = 126)	Infection (n = 21)	No infection (n = 105)	p value	Relative risk	95% confidence interval
Age, yr (mean ± SD)	56.4 ± 9.6	56.9 ± 9.4	56.3 ± 9.7	0.84	1.00	0.96—1.05
Sex, no. of male (%)	76 (60)	12 (57)	64 (61)	0.85	0.92	0.39—2.18
Initial AC sugar, % (mean ± SD)	186.0 ± 97.7	243.7 ± 156.2	174.5 ± 77.3	<0.01	1.00	1.00—1.01
Initial HbA1C, % (mean ± SD)	8.5 ± 2.2	9.4 ± 2.5	8.3 ± 2.1	0.03	1.19	1.02—1.39
<7, no. (%)	35 (28)	2 (10)	33 (31)	—	—	—
7—10, no. (%)	66 (52)	12 (57)	54 (51)	0.10	3.46	0.77—15.46
>10, no. (%)	25 (20)	7 (33)	18 (17)	0.04	5.40	1.12—26.01
Average HbA1C,% (mean ± SD)	8.2 ± 1.5	8.9 ± 1.7	8.0 ± 1.4	0.01	1.37	1.07—1.76
Creatinine, mg/dL (mean ± SD)	0.9 ± 0.4	1.0 ± 0.5	0.9 ± 0.3	0.24	1.88	0.66—5.32
K. pneumoniae colonization, no. (%)	57 (45)	9 (43)	48 (46)	0.85	0.92	0.39—2.18
Mortality within 1 yr, no. (%)	1/125[a] (1)	1/20 (5)	0/105 (0)	<0.01	—	—
Mortality within 5 yrs, no. (%)	4/124[b] (3)	4/19 (21)	0/105 (0)	<0.01	—	—

SD = standard deviation.

[a] Among the 126 cases, one patient developed bacterial infection at 6 months but lost to follow-up and did not complete 1-year follow-up for mortality evaluation.

[b] The other case developed bacterial infection within 5 years but did not complete 5-year follow-up.

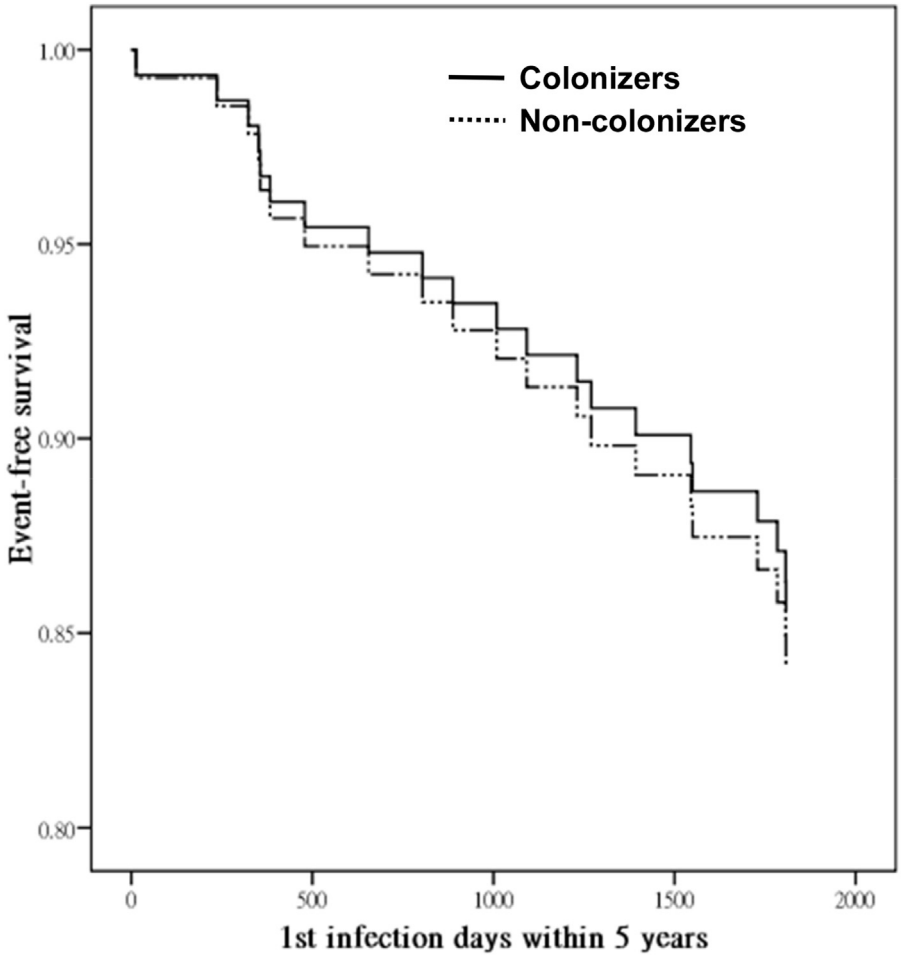

Figure 2. Kaplan—Meier curves based on Cox proportional hazards model of the effect of *K. pneumoniae* colonization on subsequent bacterial infection among patients with diabetes mellitus.

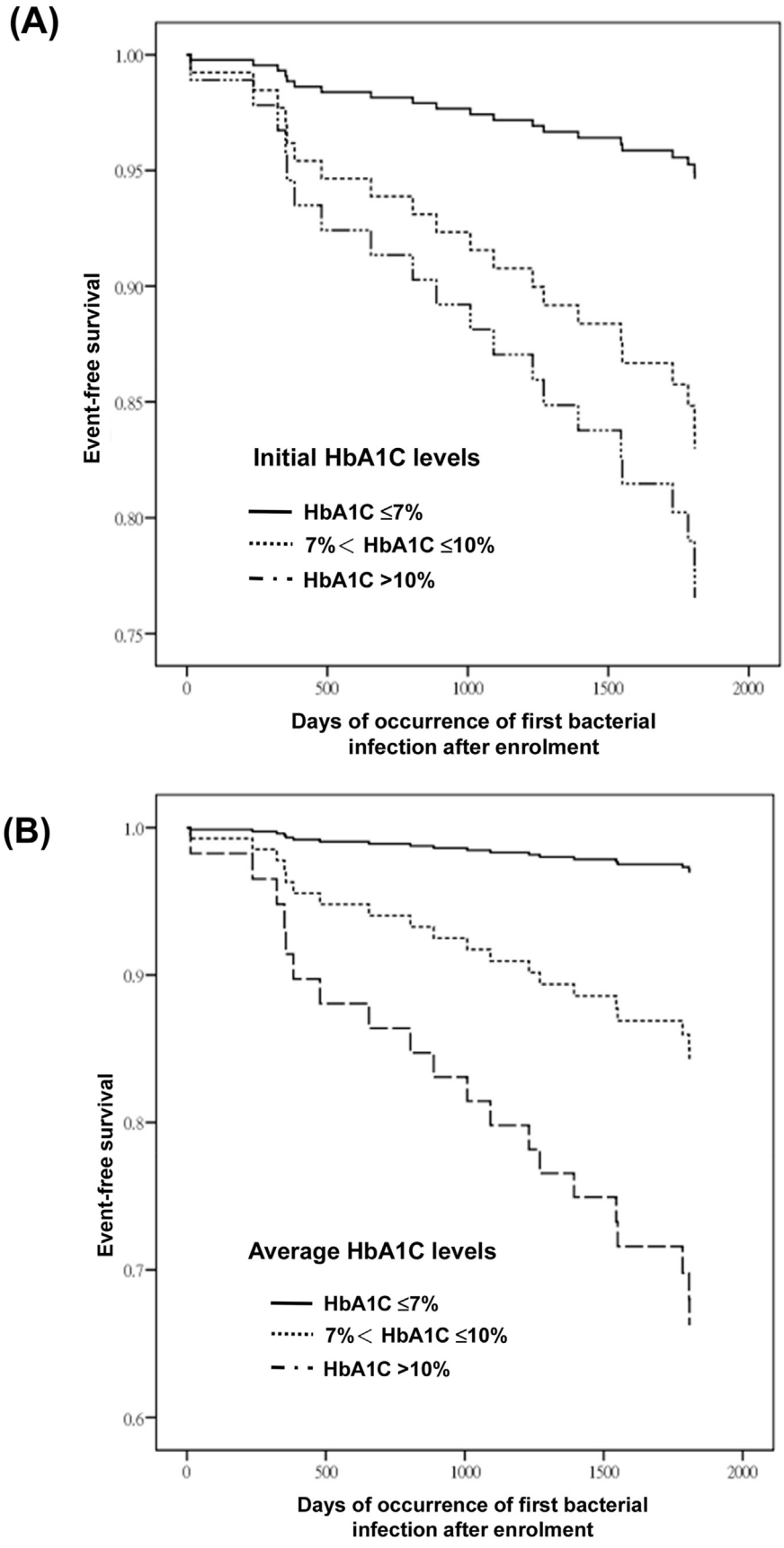

Figure 3. Kaplan—Meier curves based on Cox proportional hazards model of the effect of initial HbA1C levels (A) and average HbA1C levels within one year after enrollment (B) on subsequent bacterial infection among patients with diabetes mellitus.

diabetes, the likelihood of *K. pneumoniae* infection was not increased amongst colonizers.

Borer et al. studied patients who were rectal carriers of carbapenem-resistant *K. pneumoniae* and who developed a subsequent infection; about 10% of the colonizers in this cohort developed infection.[24] Risk factors for infection included undergoing an invasive procedure, DM, solid tumor, tracheostomy, urinary catheter insertion, and anti-pseudomonal penicillin.[24] A recent report showed that hospitalized patients with rectal colonization with *K. pneumoniae* experienced greater extra-intestinal *K. pneumoniae* infection amongst intensive care and hematology/oncology patients.[26] The overall colonization rate was 23%, and about 5% of carriers developed infections.[26] Compared to prior studies, our cohort of patients had relatively less severe underlying illness and used fewer antimicrobial agents (our patients were enrolled in an outpatient setting). The accumulated *K. pneumoniae* infection rate amongst our cohort was <3% in 5 years. We postulate that rectal colonization of *K. pneumoniae* alone is not sufficient to cause subsequent infection in the community setting. Impaired host immunity, e.g., poor glycemic control,[16] and recent antimicrobial use may play important roles in enabling colonized bacteria to develop subsequent infection.[12] Patients who used antibiotics within the previous 3 months were excluded from entering this study. Because evidence shows that antibiotic selection could be vital to subsequent infection, a prospective study of a patient cohort with a history of recent antibiotic use is necessary to further elucidate the relationship between colonization and subsequent infection.[12]

DM has been linked to bacterial infection and improved glycemic control is considered to decrease surgical site infection amongst patients receiving cardiac surgery.[14,15,27–29] In this study, an HbA1C level >10% was associated with the development of bacterial infection within 5 years, but during the first year following enrolment the difference was not significant. Moreover, the occurrence of bacterial infection within 5 years was strongly related to mortality. Perhaps the effect of glycemic control was underestimated in this study because we included the first bacterial infection, and those patients who were lost to follow-up (regardless of loss at 1-year or 5-year follow-up) had higher HbA1C compared to those who received regular outpatient clinic follow-up. Many factors can contribute to the relationship between poor glycemic control and bacterial infection, including poor compliance to medical care, impaired immunity, and enhanced bacterial invasiveness.[17]

The distribution of *K. pneumoniae* serotypes amongst infections and colonization varies because of geography, patient populations, and clinical settings. In our previous one-year cohort of patients with *K. pneumoniae* bacteremia, amongst 225 isolates, 41 (18%) were identified as the K1 serotype, 37 (16%) as K2, and 15 (7%) as K57.[5] In the present study of rectal carriage, serotype K57 was the most commonly identified serotype (11%), followed by K1 (9%) and K2 (5%). In a previous study about rectal carriage amongst Chinese living abroad, the colonization rate of K1 ranged from 17% to 0%, and K2 ranged from 5% to 0%.[13] A recent Taiwanese study of *K. pneumoniae* isolates collected from the nasopharynx at an otorhinolaryngology outpatient clinic showed that 70% were virulent strains, and K2 (28%) and K1 (20%) were the most prevalent,[30] but theses strains were collected amongst patients with a diagnosis of sinusitis or rhinitis. Whether the difference in distribution is related to bacterial virulence or the collection site remains unknown, but this study has confirmed that colonization by virulent strains amongst diabetic patients is not uncommon in Taiwan. In contrast, a recent report of *K. pneumoniae* colonization amongst hospitalized patients in Michigan showed a total different picture: No isolate with a virulent serotype was found.[26]

There are several limitations of this study. First, the case number is small. Luckily, we are able to analyze patients who have received follow-up for >5 years. Second, we did not store the 4 isolates from actual *K. pneumoniae* infections, and genotyping or pulse-field gel electrophoresis of isolates from colonization and infection cannot be performed. Third, we did not have detailed history of the antimicrobial exposure of these patients who had subsequent bacterial infection, and this may be vital to the development of invasive infection. Fourth, we cannot exclude the possibility that people could carry several clones of *K. pneumoniae* in their gut, and the natural history of *K. pneumoniae* carriage remains to be elucidated. A prospective study with repeated sampling is indicated.

In conclusion, virulent *K. pneumoniae* strains related to PLA can be found in asymptomatic diabetic patients, but colonized patients did not have higher risk of further microbiologically confirmed bacterial infections. On the contrary, glycemic control is important, and poor glycemic control is related to bacterial infections and mortality within the 5-year follow-up period.

Conflicts of interest

None declared.

Acknowledgments

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