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Original Article

Clinical manifestations and risk factors of campylobacter gastroenteritis in children in Taiwan

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ABSTRACT

Background: Campylobacteriosis is a common cause of bacterial gastroenteritis worldwide. This study aimed to investigate the potential risk factors, clinical and laboratory manifestations of children with campylobacteriosis under five years old in Taiwan.

Methods: This retrospective case–control study was conducted in ten major hospitals in Taiwan from 2014 to 2017. Laboratory tests and stool specimen were collected and analyzed together with questionnaire survey. Multivariate stepwise logistic regression model was used for identification of risk factors.

Results: A total of 64 campylobacteriosis cases were included with a median age of 25 months. We observed a less prolonged vomiting ($p = 0.047$), more bloody ($p < 0.001$) and mucoid ($p = 0.005$) stools, and lower AST levels ($p = 0.020$) in patients with campylobacteriosis. Lower parental educational attainment ($p < 0.001$), direct contact with acute gastroenteritis patients ($p < 0.001$), as well as diarrhea in the mutually cared children ($p = 0.007$) were linked to campylobacteriosis. Consumption of municipal water ($p < 0.001$), milk (OR 0.34, 95% CI 0.118–0.979), and soft beverages (OR 0.41, 95% CI 0.192–0.888) were identified as protective factors, while consuming takeout food ($p = 0.032$) and seafood ($p = 0.019$) increased risk of campylobacteriosis.

Conclusions: Shorter vomiting duration, bloody and mucoid stool, and less elevated AST levels are manifestations suggestive of campylobacteriosis. Risk factors of campylobacteriosis were low parental educational attainment, direct contact with acute gastroenteritis patients, diarrhea in mutually cared children, takeout food and seafood intake. Potential protective factors include municipal water, milk, and soft beverage intake.

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Introduction

Acute gastroenteritis is a common pediatric illness, resulting in significant childhood morbidity and mortality globally [1]. In 2016, diarrhea was the fifth leading cause of death among children under five years old [2]. Campylobacteriosis is a common bacterial gastroenteritis worldwide, with incidence and prevalence rising in many parts of the world [3].

Viruses are the predominant pathogens of diarrhea in Taiwan, but *Campylobacter* spp. still accounted for 16.7% of patients with acute diarrhea with identified pathogens in community clinics [4]. A study done in northern Taiwan revealed that *Campylobacter* spp. was identified in 6.8% of children with diarrhea [5]. More than half of campylobacteriosis patients were less than five years old [6].

The Campylobacteraceae family consists of more than 20 species of gram-negative, microaerobic Campylobacter bacteria. Morphologically they are diverse being spiral, curved, or rod shape depending on the species [3,7]. Campylobacter gastroenteritis is usually caused by *Campylobacter jejuni* or *Campylobacter coli*. Infections with other *Campylobacter* species are less common and tend to be milder [3,8]. Clinical presentations of campylobacteriosis include diarrhea, fever, vomiting, abdominal pain, and weight loss, with incubation period ranging from 24 to 72 h and could be as long as seven days [3,7,8]. Diarrhea can present as watery or bloody, and lasts for a median duration of six to seven days [3,9]. As for laboratory tests, fecal leukocytes and mild neutrophilic leukocytosis with bandemia may be found in campylobacteriosis patients, while electrolytes and liver function were mostly within normal ranges [10–12].

A number of risk factors have been identified for campylobacteriosis. *Campylobacter* spp. could be found in more than 40% of food-producing animals such as broilers, hens, pigs; hence, posing significant health impact on the agri-food chain [13,14]. Eating undercooked poultry and poultry cooked outside the home were linked to campylobacteriosis. International travel has been recognized as an important risk factor for *Campylobacter* infection as well [15,16]. Other risk factors include direct contact with farm animals, drinking untreated water, food preparation with poor hygiene, and consumption of unpasteurized dairy products [16]. As for younger children, similar risk factors for campylobacteriosis have been investigated. A meta-analysis conducted in children under five years old showed that contact with domestic animals and consumption of animal products significantly increased the risk of *Campylobacter* infection. The study also identified illiterate mothers and mothers with poor personal hygiene as risk factors [17].

In Taiwan, there have been several studies regarding the epidemiology and clinical characteristics of *Campylobacter* spp [5,6,18]. To the best of our knowledge however, comprehensive studies examining the risk factors and manifestations of campylobacteriosis as compared with other pathogens in young children are lacking. Therefore, we conducted this case–control study to investigate the potential risk factors, clinical symptoms and laboratory manifestations, hoping to provide more information in preventing and identifying the disease.

Material and methods

This retrospective, matched case–control study was conducted in ten major hospitals across Taiwan. A hospital-based acute gastroenteritis (AGE) surveillance system was built in conjunction with the Taiwan Centers for Disease Control (CDC) for study design and development of the letter of consent, questionnaire, as well as standard operation procedure of data and specimen management. Experts from the U.S. Centers for Disease Control and Prevention were consulted for questionnaire development, which collects demographic data, contact history, food consumption, domestic hygiene, immunization history, and clinical symptoms of all the cases and controls. The institutional review board of Mackay Memorial Hospital (13MMHIS285), National Taiwan University Hospital (201310064RINA), Chang Gung Memorial Hospital (102–4349A3), Show-Chwan Memorial Hospital (1,040,606), National Cheng Kung University Hospital (B-ER-102-359), China Medical University Hospital (CMUH102-REC2-136), Buddhist Tzu-Chi General Hospital (IRB102-155), Taiwan National Health Research Institutes (EC1021101-R5) approved this study.

From February, 2014 to December, 2017, all children in those hospitals were deemed eligible for enrollment as long as they met all the following inclusion criteria: 1) age less than 61 months on the day of stool specimen collection, 2) hospitalized in one of the 10 participating hospitals, 3) diagnosed with acute gastroenteritis under ICD-9-CM CODE[a], 4) experienced diarrhea and/or vomiting within three days after seeking medical attention. Diarrhea was defined as three or more passages of loose stool within a 24-h time period.

Children who met the inclusion criteria were enrolled once informed consent signed by the legal guardian was obtained. Non-AGE children of the same sex and an age difference under 3 months with no diarrhea in the recent week was selected from the outpatient department or healthy children from the community based on each case, with informed consent required as well. Questionnaires were filled in by research assistants in the AGE group, and were filled in by the parent or the legal guardian in the non-AGE group. All the questionnaires were sent to Taiwan National Health Research Institutes (NHRI) for management and analysis.

Stool specimens of AGE cases and healthy children were collected. Stool specimens of AGE cases underwent enteric pathogens screening with traditional bacterial culture and rotavirus antigen test in sentinel hospitals. Then, specimens were kept frozen until sent to Taiwan CDC reference laboratory for further analysis, including multiplex real-time polymerase chain reaction (PCR) for detection of rotavirus, norovirus, *Vibrio cholerae, Vibrio parahaemolyticus*, *Salmonella* spp., *Shigella* spp., *Clostridium perfringens, Clostridium difficile*, *Campylobacter* spp., *Listeria monocytogenes*, and *Bacillus cereus*. In this study, only part of AGE cases underwent cultivation for *Campylobacter* spp. in sentinel hospitals. Thus, an AGE patient yielding a positive PCR result for *Campylobacter* spp. in the stool sample would be defined as a campylobacteriosis case. The use of PCR for detection of *Campylobacter* spp. has been widely use and proved to be selective and accurate [19,20]. AGE patients with a negative Campylobacter PCR result was matched by age, gender, and study site to be qualified as non-Campylobacter AGE controls. Patients with co-infections in the case group were not excluded, neither were those in the non-Campylobacter AGE control group.

The control group for analysis of laboratory tests and clinical manifestations were non-Campylobacter AGE control. As for risk factor analysis, the primary control group were non-AGE patients. However, to identify specific risk factors for campylobacteriosis, we not only compared the data with non-AGE control but also with non-Campylobacter AGE control.

Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA). The case–control ratio was 1:4 for analysis of clinical symptoms and laboratory data, and 1:3 for analysis of risk factors. Comparison of risk factors, clinical symptoms and laboratory data was analyzed using the Student's t test for continuous variables and the Chi-square test for categorical variables. Univariable conditional logistic regression was also performed for identification of independent risk factors for Campylobacter gastroenteritis. Statistically significant variables, those with a P-value of less than 0.05, were selected into the multiple logistic regression model with stepwise selection.

Results

A total of 4766 cases of acute gastroenteritis (AGE) and 2501 non-

[a] Patient diagnosed with ICD-9-CM code 001–005 (003.2 excluded), 008.0–008.5, 027.0, 008.6–008.8, 006–007 (006.3–006.6 excluded), 009.0–009.3, 558.9, 787.91 met the third inclusion criteria, but V30–V39 were excluded.

AGE controls were qualified for further analysis. Among the 4766 children diagnosed with AGE, 64 (1.3%) were Campylobacter PCR positive, including eight cases with norovirus and *Campylobacter* spp. coinfection, one with rotavirus and *Campylobacter* spp. coinfection, three with *Salmonella* spp. and *Campylobacter* spp. coinfection, three with *C. difficile* and *Campylobacter* spp. infection, and one with *C. difficile* plus *B. cereus* plus *Campylobacter* spp. coinfection. As for underlying disease of the Campylobacter PCR positive patients, one had ventricular septal defect, and another had G6PD deficiency (Glucose-6-Phosphate Dehydrogenase Deficiency).

For analysis, we excluded those cases for whom no matched controls could be found. Of the 64 Campylobacter gastroenteritis cases, 62 were eligible for comparison with matched non-Campylobacter AGE control for clinical symptoms and laboratory data, and 53 cases were compared with matched non-AGE control for the risk factors.

Clinical symptoms and laboratory manifestations

Among the 62 Campylobacter gastroenteritis cases, 34 (65%) were male and the average age was 25 ± 16 months old. No obvious difference was found in sex or age between the case and the non-Campylobacter AGE control group (Table 1).

Diarrhea and fever (93.6%) were the most common clinical manifestations. Mucoid (59% versus 39%, $p = 0.005$) and bloody stool (57% versus 24%, $p < 0.001$) occurred more frequently in Campylobacter gastroenteritis patients. Fewer children experienced vomiting for more than two days with Campylobacter gastroenteritis, with 9.7% versus 21% in the control group ($p = 0.047$). Campylobacter gastroenteritis was associated with lower Aspartate Transaminase (AST) level, with a mean of 36 ± 13 (U/L) in 33 case-patients compared to 55 ± 72 (U/L) of the control group ($p = 0.020$). An AST level higher than 50 U/L were also less frequently seen in Campylobacter gastroenteritis patients (12% versus 32%, $p = 0.030$).

Risk factors (non-AGE control)

After 1:3 matching of the case and control group by age, gender, and study site, 53 Campylobacter gastroenteritis cases and 148 non-AGE controls were qualified for analysis (44 cases with 1:3 pairing, seven cases with 1:2 pairing, two cases with 1:1 pairing). No significant difference was found in sex, age, or geographic data between the two groups (Table 2). Children were more likely to have Campylobacter gastroenteritis if their parents had lower educational attainment ($p < 0.001$). Those with at least one parent having an academic degree had significantly lower odds to experience Campylobacter gastroenteritis (OR 0.224, 95% CI 0.101–0.498). Direct contact with gastroenteritis patients in the prior week led to higher possibility of Campylobacter gastroenteritis (20.75% versus 0%, $p < 0.001$). Children who had contact with other children have lower odds of developing Campylobacter gastroenteritis if the other children did not experience recent diarrhea (OR 0.079, 95% CI 0.008–0.757).

Risk of campylobacteriosis was reduced if the source of drinking water was municipal water (OR 0.131, 95% CI 0.048–0.357). Consuming take-out food in the prior week had increased odds of Campylobacter gastroenteritis (OR 3.326, 95% CI 1.269–8.718). Ingestion of seafood (OR 3.451, 95% CI 1.268–9.39) also was associated with Campylobacter gastroenteritis. Milk (OR 0.34, 95% CI 0.118–0.979) and soft drink (OR 0.412, 95% CI 0.192–0.888) consumption were protective factors. In the final stepwise regression model, takeout food consumption (OR 6.959, 95% CI 1.395–34.72) was a risk factor, while at least one of the parents having an academic degree (OR 0.167, 95% CI 0.044–0.63), healthy children cared for by the mutual caregiver (OR 0.069, 95% CI 0.005–0.98), consumption of municipal water (OR 0.2, 95% CI 0.044–0.91) and soft drink (OR 0.188, 95% CI 0.048–0.73) were statistically significant protective factors.

Table 1
Clinical symptoms and laboratory manifestations of campylobacteriosis.

	Campylobacteriosis	Non-campylobacter-AGE-control	*p*-value
	No. (%)	No. (%)	
Total	62	223	
Male	40 (64.52)	150 (67.26)	0.685
Age (months)			
Mean ± SD	25.29 ± 16.47	23.29 ± 14.85	0.471
Median	21 (11.37)	18 (11.35)	
Range			0.669
<6	4 (6.45)	11 (4.93)	
6-11	14 (22.58)	46 (20.63)	
12-23	16 (25.81)	69 (30.94)	
24-35	10 (16.13)	48 (21.52)	
36-47	11 (17.74)	35 (15.7)	
48-60	7 (11.29)	14 (6.28)	
Symptoms			
Vomiting alone	0 (0)	1 (0.45)	>0.99
Diarrhea alone	4 (6.45)	9 (4.04)	0.489
Fever alone	0 (0)	4 (1.79)	0.580
Vomiting and Diarrhea	0 (0)	29 (13)	0.003*
Vomiting and Fever	0 (0)	0 (0)	
Diarrhea and Fever	27 (43.55)	78 (34.98)	0.216
Vomiting + Diarrhea + Fever	31 (50)	102 (45.74)	0.552
Bloody stool	35 (57.38)	53 (24.2)	<0.001*
Mucoid stool	36 (59.02)	85 (38.99)	0.005*
Duration of symptoms (days)			
Vomiting, mean ± SD	0.97 ± 1.4	1.36 ± 1.64	0.080
>2 days	6 (9.68)	46 (20.72)	0.047*
Diarrhea, mean ± SD	6.06 ± 2.61	5.74 ± 3.34	0.321
>5 days	32 (51.61)	108 (48.65)	0.680
>8 days	10 (16.13)	23 (10.36)	0.210
Fever, mean ± SD	3.55 ± 2.02	3.56 ± 2.56	0.988
>2 days	41 (66.13)	144 (64.86)	0.854
>39.0° (Before)	30 (52.63)	96 (51.34)	0.864
>39.0° (After)	23 (47.92)	73 (39.04)	0.264
Hospital stay (days)			
Mean ± SD	5.98 ± 2.24	5.67 ± 3.16	0.086
>5 days	31 (50)	87 (40.65)	0.190
URI symptoms (+)	21 (34.43)	96 (43.24)	0.216
Lab data on admission			
Hemoglobin (g/dL), mean ± SD	12.07 ± 0.86	12.01 ± 1.28	0.683
NA	0	3	
WBC (1000/μL), mean ± SD	11.21 ± 5.09	11.19 ± 5.78	0.491
<5000	5 (8.06)	21 (9.55)	0.722
>15,000	10 (16.13)	48 (21.82)	0.328
NA	0	3	
Platelet (1000/μL), mean ± SD	284.98 ± 97.96	291.38 ± 107.85	0.623
<150,000	2 (3.23)	13 (5.94)	0.535
NA	0	4	
CRP (mg/L), mean ± SD	43.8 ± 42.52	47.48 ± 69.13	0.150
>10	49 (80.33)	133 (69.27)	0.094
>20	37 (60.66)	103 (53.65)	0.337
>40	26 (42.62)	67 (34.9)	0.276
NA	1	31	
AST (U/L), mean ± SD	36.24 ± 13.26	54.64 ± 71.91	0.020*
>50	4 (12.12)	27 (31.76)	0.030*
NA	29	138	

Abbreviations: AST: aspartate aminotransferase; CRP: C-reactive protein; NA: not available; SD: standard deviation; URI: upper respiratory infection; WBC: white blood cells.

Table 2
Risk factors for campylobacteriosis with non-AGE control.

	Campylobacterosis No. (%)	Non-AGE-control No. (%)	*p*-value	Univariate OR (95% CI)	Multivariate OR (95% CI)
Total	**53**	**148**			
Male	34 (64.15)	97 (65.54)	0.855		
Age (months)	25.36 ± 15.89	23.94 ± 14.92	0.545		
Geographic area			0.994		
Northern	25 (47.17)	71 (47.97)			
Central	5 (9.43)	14 (9.46)			
Southern	23 (43.4)	63 (42.57)			
Eastern	0 (0)	0 (0)			
Parental education attainment			< 0.001*		
Both high school or lower	23 (43.4)	25 (16.89)		1	
At least one with college degree or above	29 (54.72)	122 (82.43)		0.224 (0.101, 0.498)*	0.167 (0.044, 0.63)*
One high school or lower, the other unknown	1 (1.89)	1 (0.68)		-	-
At least one of the parents is new immigrant	2 (3.77)	8 (5.48)	> 0.99	0.546 (0.113, 2.654)	
Rotavirus vaccination (yes vs. no)	26 (50.98)	93 (64.58)	0.087	0.624 (0.316, 1.234)	
Contact with AGE patients within 1 week	11 (20.75)	0 (0)	< 0.001*	-	
Breastfeeding duration (months)	6.71 ± 7.69	6.76 ± 7.35	0.515	0.999 (0.958, 1.042)	
Public place visited in the recent week					
Nursery/Kindergarten/After school club/School	14 (26.42)	39 (26.35)	0.993	0.865 (0.38, 1.971)	
Clinic/Hospital/Nursing home	22 (41.51)	78 52.7)	0.162	0.491 (0.226, 1.067)	
Contact with animals within 1 week	19 (35.85)	54 (36.49)	0.934	0.956 (0.501, 1.825)	
Dogs	17 (32.08)	34 (22.97)	0.191	1.61 (0.782, 3.314)	
Cats	2 (3.77)	16 (10.81)	0.164	0.335 (0.074, 1.519)	
Family visit or travel abroad within 1 week	0 (0)	1 (0.68)	> 0.99	-	
Hand wash before meals			0.756		
Never	9 (16.98)	23 (15.65)		1	
Occasional	36 (67.92)	95 (64.63)		0.958 (0.349, 2.634)	
Always	8 (15.09)	29 (19.73)		0.515 (0.132, 2.009)	
Living environment					
Other children cared for by the mutual primary caregiver had diarrhea or not			0.007*		
With diarrhea	4 (8.33)	2 (1.6)		1	
Without diarrhea	16 (33.33)	69 (55.2)		0.079 (0.008, 0.757)*	0.069 (0.005, 0.98)*
The primary caregiver did not care for other children	28 (58.33)	54 (43.2)		0.201 (0.02, 1.988)	0.18 (0.012, 2.63)
Healthy primary caregiver	52 (98.11)	123 (89.13)	0.045*	7.104 (0.867, 58.235)	
Primary caregiver prepared food	4 (10.53)	20 (17.7)	0.296	0.362 (0.094, 1.404)	
Care place: restroom occupants			0.596		
< = 5 occupants	38 (76)	113 (79.58)		1	
> 5 occupants	12 (24)	29 (20.42)		1.097 (0.474, 2.537)	
Care place: drinking water source					
Municipal water	28 (52.83)	106 (81.54)	< 0.001*	0.131 (0.048, 0.357)*	0.2 (0.044, 0.91)*
Bottled water	4 (7.55)	8 (6.15)	0.747	1.323 (0.348, 5.02)	
Water refilling station	10 (18.87)	13 (10)	0.101	2.374 (0.903, 6.239)	
Filtered and boiled water	51 (100)	113 (91.87)	0.078	-	
Food eaten in the recent week					
Dining out	36 (67.92)	101 (69.18)	0.866	0.902 (0.437, 1.861)	
Take-out food	38 (71.7)	80 (54.79)	0.032*	3.326 (1.269, 8.718)*	6.959 (1.395, 34.72)*
Milk	7 (13.21)	34 (23.13)	0.125	0.34 (0.118, 0.979)*	
Breast milk	9 (16.98)	24 (16.33)	0.912	1.14 (0.453, 2.871)	
Milk powder	42 (79.25)	113 (76.87)	0.723	1.273 (0.543, 2.984)	
Goat milk	2 (3.77)	1 (0.68)	0.172	5.998 (0.544, 66.14)	
Egg	40 (75.47)	101 (70.14)	0.462	1.344 (0.57, 3.172)	

(*continued on next page*)

Table 2 (*continued*)

	Campylobacterosis No. (%)	Non-AGE-control No. (%)	*p*-value	Univariate OR (95% CI)	Multivariate OR (95% CI)
Cooked egg	40 (75.47)	99 (68.75)	0.359	1.477 (0.624, 3.495)	
Raw or half-boiled egg	0 (0)	2 (1.39)	> 0.99	-	
Iced products	19 (35.85)	60 (41.38)	0.482	0.672 (0.337, 1.34)	
Cold soft drinks	26 (49.06)	92 (62.59)	0.086	0.412 (0.192, 0.888)*	0.188 (0.048, 0.73)*
Leftovers	14 (26.42)	48 (32.88)	0.384	0.728 (0.354, 1.494)	
Vegetable	44 (84.62)	124 (84.93)	0.957	1 (0.354, 2.822)	
Cabbage	30 (57.69)	89 (60.96)	0.680	0.853 (0.402, 1.807)	
Carrot	28 (53.85)	85 (58.22)	0.584	0.828 (0.413, 1.659)	
Corn	15 (28.85)	41 (28.08)	0.916	1.117 (0.528, 2.363)	
Green broccoli	13 (25)	28 (19.18)	0.374	1.485 (0.645, 3.423)	
Fruit	47 (88.68)	111 (76.03)	0.051	2.619 (0.977, 7.021)	
Apple	28 (52.83)	75 (51.37)	0.855	1.033 (0.56, 1.907)	
Guava	12 (22.64)	29 (19.86)	0.668	1.261 (0.589, 2.698)	
Grape	12 (22.64)	37 (25.34)	0.696	0.865 (0.407, 1.837)	
Banana	23 (43.4)	57 (39.04)	0.580	1.274 (0.644, 2.522)	
Seafood	47 (88.68)	105 (72.92)	0.019*	3.451 (1.268, 9.39)*	3.675 (0.749, 18.04)
Chicken	29 (54.72)	67 (45.89)	0.271	1.582 (0.771, 3.247)	
Duck	2 (3.77)	6 (4.11)	> 0.99	0.851 (0.171, 4.241)	
Goose	2 (3.77)	5 (3.42)	> 0.99	1.128 (0.218, 5.835)	
Pork	36 (67.92)	104 (71.23)	0.652	0.662 (0.259, 1.696)	
Beef	8 (15.09)	25 (17.12)	0.734	0.904 (0.373, 2.192)	

Risk factors (non-campylobacter AGE control)

After 1:4 matching of the case and control group by age, gender, and study site, 62 Campylobacter gastroenteritis cases and 223 non-Campylobacter AGE controls were qualified for analysis (51 cases with 1:4 pairing, one case with 1:3 pairing, six cases with 1:2 pairing, and four cases with 1:1 pairing). No significant difference was found in sex, age, or geographic data between the two groups (Table 3). Of the 223 non-Campylobacter AGE patients, 38 were detected with norovirus, 25 were detected with rotavirus, 50 were detected with *Salmonella* spp., 10 were detected with *C. difficile*, three were detected with *B. cereus*, one was detected with *V. parahaemolyticus*, and one was detected Giardia. When the control group was non-Campylobacter AGE instead of non-AGE patients, lower educational attainment of the parents ($p = 0.003$) remained as a significant risk factor.

Discussion

In this retrospective study, we aimed to understand the clinical manifestations of campylobacteriosis and distinguish it from diarrhea caused by other pathogens through a large-scale study. Among the 4766 AGE patients who are under five years old, 64 (1.3%) were Campylobacter PCR positive. The result was comparable to previous studies conducted in Taiwan. Lin CW et al. reported the isolation rate of *Campylobacter* spp. from stool specimens of diarrhea patients to be 2.5% in 1998 [21]. In children under five years old, Chen KT et al. reported an 0.7% isolation rate in 2005 [22], while Yu WJ et al. mentioned yield rates of at least 1.0% from 2007 to 2011 and at least 2.3% from 2012 to 2016 [23]. Forty of the 64 campylobacteriosis patients were male, accounting for 63% in accordance with previous reports of a slightly higher male dominance among infected people [6,19,24]. Compared with children infected with other pathogens, those with campylobacteriosis had a lower percentage of suffering from vomiting for more than two days in our study. However, 50% of case-patients experienced vomiting, which was slightly higher than figures ranging from 20% to 35.8% reported by studies conducted in Canada, England, and Egypt [25–27].

Among those campylobacteriosis patients, 59% had mucoid stool and 57% suffered from bloody stool, both significantly higher than those infected with other pathogens. The results were compatible with the consensus that mucoid and bloody stool are commonly seen in Campylobacter gastroenteritis [28–30]. On the other hand, the average AST level of our case-patients was 36 ± 13 (U/L), significantly lower than the non-Campylobacter AGE control group. We also found that campylobacteriosis children were less likely to have an AST over 50 (U/L). These results matched previous reports of a relatively normal liver function test in campylobacteriosis patients [12].

To demonstrate whether the differences in laboratory findings and clinical manifestations are of bacterial origin or are specific to Campylobacter origin, we also performed the analysis excluding all the virus infected cases (Supplement Table 1). When comparing 53 Campylobacter bacterial AGE cases with 137 non-Campylobacter bacterial AGE controls, mucous and bloody stool remained significantly more frequent in the case group, and prolonged vomiting was less frequently seen. AST level were lower but did not reach significance ($p = 0.0599$) likely due to the scale of the study. This demonstrated that the differences were specific to Campylobacter origin.

Lower educational attainments of parents were linked to higher risk of campylobacteriosis in the current study. Previous studies were divided in this finding. Diriba, K. et al. reported that an illiterate mother

Table 3
Risk factors for campylobacteriosis with non-Campylobacter AGE control.

	Campylobacteriosis No. (%)	Non-campylobacter AGE control No. (%)	*p*-value	Univariate (OR 95%CI)	Multivariate (OR 95%CI)
Total	**62**	**223**			
Male	40 (64.52)	150 (67.26)	0.685		
Age (months)	25.29 ± 16.47	23.29 ± 14.85	0.471		
Geographic area			0.507		
Northern	29 (46.77)	112 (50.22)			
Central	6 (9.68)	24 (10.76)			
Southern	25 (40.32)	85 (38.12)			
Eastern	2 (3.23)	2 (0.9)			
Parental education attainment			0.003*		
Both high school or lower	26 (41.94)	50 (22.42)		1	
At least one with college degree or above	34 (54.84)	170 (76.23)		0.376 (0.203, 0.696)*	0.575 (0.227, 1.450)
One high school or lower, the other unknown	2 (3.23)	3 (1.35)		-	-
At least one of the parents is new immigrant	2 (3.23)	19 (8.52)	0.269	0.401 (0.091, 1.771)	
Rotavirus vaccination (yes vs. no)	29 (49.15)	116 (52.25)	0.672	0.892 (0.482, 1.651)	
Contact with AGE patients within 1 week (no vs. yes)	13 (20.97)	34 (15.81)	0.341	0.775 (0.361, 1.660)	
Breastfeeding duration (months)	6.83 ± 7.60	6.87 ± 8.17	0.899	0.993 (0.957, 1.031)	
Public place visited in the recent week					
Nursery/Kindergarten/After school club/School	16 (25.81)	59 (26.58)	0.903	0.764 (0.369, 1.583)	
Clinic/Hospital/Nursing home	25 (40.32)	132 (59.46)	0.007*	0.44 (0.234, 0.829)*	0.53 (0.229, 1.230)
Contact with animals within 1 week	23 (37.1)	58 (26.01)	0.087	1.636 (0.9, 2.974)	
Dogs	19 (30.65)	45 (20.18)	0.081	1.76 (0.939, 3.3)	
Cats	4 (6.45)	9 (4.04)	0.489	1.46 (0.387, 5.507)	
Family visit or travel abroad within 1 week	0 (0)	2 (0.9)	> 0.99	-	
Hand wash before meals			0.334		
Never	10 (16.13)	25 (11.31)		1	
Occasional	43 (69.35)	148 (66.97)		0.507 (0.191, 1.346)	
Always	9 (14.52)	48 (21.72)		0.299 (0.089, 1.001)	
Living environment					
Other children cared for by the mutual primary caregiver had diarrhea or not			0.063		
with diarrhea	4 (7.14)	31 (14.62)		1	
without diarrhea	18 (32.14)	88 (41.51)		2.192 (0.610, 7.884)	0.785 (0.135, 4.59)
the primary caregiver did not care for other children	34 (60.71)	93 (43.87)		4.298 (1.215, 15.204)*	2.881 (0.587, 14.13)
Healthy primary caregiver	61 (98.39)	187 (85.39)	0.005*	11.993 (1.528, 94.16)*	7.737 (0.841, 71.15)
Primary caregiver prepared food	5 (11.11)	52 (30.59)	0.009*	0.301 (0.109, 0.826)*	
Care place: restroom occupants			0.596		
< = 5 occupants	46 (77.97)	182 (84.65)		1	
> 5 occupants	13 (22.03)	33 (15.35)		1.469 (0.676, 3.192)	
Care place: drinking water source					
Municipal water	34 (54.84)	167 (77.31)	< 0.001*	0.292 (0.144, 0.594)*	0.158 (0.049, 0.51)*
Bottled water	5 (8.06)	18 (8.33)	0.946	0.947 (0.323, 2.776)	
Water refilling station	11 (17.74)	29 (13.43)	0.393	1.432 (0.628, 3.262)	
Filtered and boiled water	60 (100)	190 (91.79)	0.016*	-	
Food eaten in the recent week r					
Dining out	41 (66.13)	146 (65.47)	0.923	1.004 (0.526, 1.914)	
Take-out food	40 (64.52)	130 (59.09)	0.441	1.285 (0.647, 2.55)	
Milk	10 (16.13)	23 (10.41)	0.215	1.378 (0.559, 3.393)	
Breast milk	11 (17.74)	36 (16.29)	0.786	1.076 (0.466, 2.488)	
Milk powder	49 (79.03)	171 (77.38)	0.782	1.280 (0.618, 2.652)	
Goat milk	3 (4.84)	4 (1.81)	0.180	3 (0.671, 13.404)	

(*continued on next page*)

Table 3 (*continued*)

	Campylobacteriosis No. (%)	Non-campylobacter AGE control No. (%)	*p*-value	Univariate (OR 95%CI)	Multivariate (OR 95%CI)
Egg	46 (74.19)	157 (71.04)	0.626	1.121 (0.528, 2.381)	
Cooked egg	45 (72.58)	157 (71.04)	0.813	1.04 (0.5, 2.164)	
Raw or half-boiled egg	0 (0)	0 (0)	-	-	
Iced products	25 (40.32)	76 (34.23)	0.376	1.141 (0.617, 2.108)	
Cold soft drinks	31 (50)	114 (51.82)	0.800	0.875 (0.468, 1.635)	
Leftovers	15 (24.19)	88 (39.82)	0.024*	0.355 (0.165, 0.761)*	0.607 (0.214, 1.72)
Vegetable	52 (85.25)	176 (81.86)	0.538	1.205 (0.49, 2.961)	
Cabbage	37 (60.66)	127 (59.07)	0.824	0.932 (0.491, 1.77)	
Carrot	35 (57.38)	118 (54.88)	0.730	1.036 (0.561, 1.914)	
Corn	17 (27.87)	34 (15.81)	0.032*	2.232 (0.988, 5.041)	2.38 (0.671, 8.44)
Green broccoli	15 (24.59)	73 (33.95)	0.166	0.553 (0.272, 1.125)	
Fruit	54 (87.1)	170 (77.27)	0.091	2.076 (0.83, 5.19)	
Apple	32 (51.61)	126 (57.27)	0.428	0.805 (0.451, 1.436)	
Guava	15 (24.19)	33 (15)	0.089	1.758 (0.844, 3.665)	
Grape	14 (22.58)	37 (16.82)	0.298	1.489 (0.725, 3.056)	
Banana	27 (43.55)	65 (29.55)	0.038*	1.760 (0.973, 3.184)	1.131 (0.433, 2.95)
Seafood	53 (85.48)	157 (71.04)	0.022*	3.809 (1.383, 10.49)*	1.968 (0.473, 8.19)
Chicken	33 (53.23)	113 (51.36)	0.796	1.071 (0.582, 1.971)	
Duck	2 (3.23)	5 (2.24)	0.648	1.535 (0.246, 9.572)	
Goose	2 (3.23)	3 (1.35)	0.299	3.153 (0.426, 23.357)	
Pork	43 (69.35)	155 (69.82)	0.944	0.833 (0.403, 1.72)	
Beef	9 (14.52)	37 (16.59)	0.694	0.846 (0.363, 1.968)	

was a significant risk factor for campylobacteriosis [17]. However, Bhattarai, V. et al. reported that there was no association between parental education level and *Campylobacter* infection in Nepal. The same study also revealed that parental occupation was not linked to campylobacteriosis [31], which was consistent with the results in Canada [25]. While more studies are needed to clarify the impact of parental educational attainment, parental occupation, and household income on *Campylobacter* infection, it is conceivable that geographical and cultural differences contributed to this dissimilarity.

Person-to-person contact is a recognized route of transmission for Campylobacter gastroenteritis. Little, CL et al. reported that person-to-person transmission accounted for 3% of 143 campylobacteriosis cases in England and Wales [32]. Studies from New Zealand and Australia showed similar rates of 4% of 364 patients and 1% by expert elicitation [33,34]. In our study, 21% of the Campylobacter patients had contact with acute gastroenteritis patients within one week prior to the diagnosis. However, without genotype data, we cannot confirm infection caused by direct person-to-person contact, since they might share same food sources or environment with the contact. For the same reason, although we observed an increased odds for campylobacteriosis if other children taken care of by the same primary caregiver were experiencing diarrhea, the contribution of individual risk factors such as food, water source, or hygiene still awaits further studies.

As for water source, drinking untreated water has been recognized as an important risk factor for *Campylobacter* infection, while consumption of filtered water has been described as a protective factor [29,35–37]. In our study, water sources included municipal water, bottled water, and water refilling stations. We observed that consumption of municipal water was a protective factor for campylobacteriosis when compared with both non-AGE control and non-campylobacter AGE control, but there were no significant differences between those who consumed filtered and boiled the water and those who did not. This result may be associated with modernized municipal water supply systems in Taiwan, which leads to less contamination. Drinking bottled water has also been claimed as a risk factor, but we did not have similar finding [38].

Cindy R. Friedman et al. claimed having meals prepared at a restaurant was a significant risk factor in univariate analysis but not multivariate analysis [29]. Eating out within a week prior to infection did not increase the odds of having Campylobacter gastroenteritis in our study. We suspect this may be associated with the improving hygiene and food-processing of current restaurants. However, we identified take-out food consumption as a risk factor (OR 3.326), which may be due to prolonged time between food preparation and consumption. Soft drink consumption was found as a protective factor for campylobacteriosis in our study. According to Azeredo, D. R., addition of preservatives and sometimes CO_2 as well as generally acidic nature of soft drinks may be major barriers for bacterial growth [39].

While Osbjer, K. et al. reported an association between campylobacteriosis and eating undercooked meat [40], our study did not show significantly increased odds of infection in those who consumed poultry or meat except for seafood. Education for storing and processing of seafood might be needed to further reduce *Campylobacter* infection in Taiwan.

There are some limitations to this study. First, since the case-patients

were selected from ten major hospitals in Taiwan, those with milder symptoms who did not require hospitalization were not included. Second, although ten hospitals participated in the study, sample size were still relatively small. Therefore, sensitivity analysis was conducted, which confirmed the main finding (Supplement Table 1). Third, due to the fact that the questionnaire was not specifically designed for Campylobacter gastroenteritis but multiple pathogens instead, some factors specific to Campylobacter gastroenteritis might not be included in our questionnaire. Forth, our questionnaire contained numerous aspects and details, many of which tracing back to a week ago, such as food consumption or contact history for risk factor analysis. It is possible that some details were lost or not correctly filled in. Fifth, due to the difficulty of thorough analysis of stool sample in the 10 hospitals participating in this study, the sample were kept frozen and sent to Taiwan CDC for further analysis. This might decrease the yield rate of pathogens. Thus PCR were used as the main detection tool. Nevertheless, the use of culture-independent diagnostic tests (CIDT) such as PCR for surveillance and diagnosis has been discussed in previous studies and was used by CDC of the United States [19,20]. Lastly, due to the research methodology, we did not acquire genotype data, nor did we follow the cases through a period of time. This made us unable to gain more information, such as further investigation of the spreading routes in each case-patient.

To summarize, acute childhood campylobacteriosis had a lower rate of vomiting for over two days, a higher rate of bloody and mucoid stool, and a lower AST level compared to those infected with other pathogens. We also found that direct contact with AGE patients could increase the risk of campylobacteriosis. Higher parental educational attainment, consumption of municipal water, milk, and soft beverages were identified as a protective factor, while consuming takeout food and seafood were risk factors for campylobacteriosis.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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