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Epidemiologic Characteristics and Case Fatality Rate of *Vibrio vulnificus* Infection: Analysis of 761 Cases From 2003 to 2016 in Korea

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim JS, Chun BC. Data curation: Kim JS. Formal analysis: Kim JS. Methodology: Kim JS, Chun BC. Project administration: Chun BC. Resources: Lee EG. Software: Kim JS. Supervision: Lee EG.

ABSTRACT

Background: *Vibrio vulnificus* infection is a highly fatal disease resulting from the consumption of raw or undercooked seafood and exposure to seawater containing the organism. It has been a nationally notifiable disease since 2000 in Korea. The aims of this study were to assess the trends in the incidence of *V. vulnificus* infection and its case fatality rate and to determine the epidemiologic characteristics to effectively prevent infection and lower mortality.

Methods: We analyzed the incidence trends of *V. vulnificus* infection by year, month, and region in 913 cases reported to the Korea Centers for Disease Control and Prevention (KCDC, currently Korea Disease Control and Prevention Agency) by the National Infectious Disease Surveillance System from 2001 to 2016. We analyzed the number of patients with *V. vulnificus* infection who were under the National Health Insurance Service (NHIS) and whose coastal seawater temperature data were provided by the Korea Oceanographic Data Center of the National Institute of Fisheries Science. Epidemiological investigations were followed up and analyzed for 761 patients from 2003 to 2016. A total of 152 patients who were not followed up were excluded from the analysis. The case fatality rate was analyzed for 325 cases reported to the KCDC from 2011 to 2016.

Results: The mean incidence of *V. vulnificus* infection was 0.12 per 100,000 people, and the highest incidence was reported in September (41.1%) during the study period. The incidence rate per 100,000 people was the highest in Jeonnam (8.23). The number of patients who claimed to the NHIS was the highest in September (105 patients). The average seawater temperature was the highest at 24.1°C in August, and the average seawater temperature from August to October, when many cases occurred, was 22.4°C. The male-to-female ratio was 6:1, and 96.4% of the patients were aged ≥ 40 years. Of the patients, 96.1% had underlying diseases, the most common of which was liver cirrhosis (56.3%). The case fatality rate was 48.9%.

Conclusion: The occurrence of *V. vulnificus* infection showed distinct seasonality, with a large number of cases occurring in the months when the seawater temperature was high; there were also distinct geographical characteristics. The incidence of *V. vulnificus* infection and mortality rates have not decreased for decades, and it is still an important public health problem with a high fatality rate.

Keywords: *Vibrio vulnificus*; Infection; Incidence; Case Fatality Rate; Epidemiology

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INTRODUCTION

Vibrio vulnificus is a gram-negative, halophilic bacterium belonging to the genus *Vibrio* and family *Vibrionaceae*. It is commonly found in warm seawater and proliferates at a water temperature of $\geq 20^{\circ}\text{C}$.^{1,2} *V. vulnificus* is an important opportunistic pathogen that can induce primary septicemia through the consumption of contaminated raw or undercooked seafood or wound infection through the exposure of a wound to warm seawater inhabited by the organism.²⁻⁴ *V. vulnificus* is naturally present in estuarine environments and coastal waters and is commonly found in oysters and molluscan shellfish.^{5,6} It is a major pathogen that accounts for 95% of all seafood-related deaths in the United States and has the highest fatality rate among foodborne pathogens.^{6,7}

In patients with chronic liver disease, especially cirrhosis, *V. vulnificus* infection is a highly lethal condition that usually manifests 1–2 days after exposure to the organism.⁸ Although the infective or lethal dose of *V. vulnificus* in humans is unknown, host susceptibility is an important factor in this infection.⁹ Immunocompromised patients, including those with chronic liver diseases and cancer, have an increased risk of infection and complications.⁴ *V. vulnificus* infection has been reported in some coastal cities in the United States, Japan, and Taiwan,¹⁰ as well as in France, Denmark, Israel, Germany, and Greece.¹¹

V. vulnificus infection is a serious public health concern in Korea, as it occurs annually in the summer and has a high case fatality rate of approximately 50%.⁵ In Korea, *V. vulnificus* infection has been monitored since its legal designation as a national notifiable disease on August 1, 2000, and reporting of confirmed or suspected cases is mandatory. However, although there have been some studies on the epidemiology of *V. vulnificus* infection in Korea,^{12,13} many of its epidemiological characteristics remain unknown.

The present study was designed to analyze the incidence of all notified cases of *V. vulnificus* infection by time, place, and person from 2001 to 2016, to identify the epidemiologic features and to estimate the case fatality rate using a case epidemiological investigation report by the Korea Centers for Disease Control and Prevention (KCDC, currently Korea Disease Control and Prevention Agency).

METHODS

The scope of the mandatory reporting of *V. vulnificus* infection, a legally designated infectious disease, covers confirmed or suspected infections. According to the surveillance manual for national notifiable diseases from the KCDC,¹⁴ confirmed cases were defined as cases where patients showed clinical symptoms matching the definition of *V. vulnificus* infection and confirmed by laboratory testing, whereas suspected cases were defined as cases where patients showed clinical symptoms matching the definition of *V. vulnificus* infection with epidemiological association but were negative on laboratory tests. In this study, we included all reported cases of *V. vulnificus* infection.

From 2001 to 2016, 913 cases of *V. vulnificus* infection were identified (835 confirmed and 78 suspected). We estimated the yearly, monthly, and regional incidence of all 913 cases.

In addition to the surveillance data reported to the KCDC, the number of patients who were under the National Health Insurance Service (NHIS) during the study period was collected by year, month, and region. Seawater temperature data for the study period were provided by the Korea Oceanographic Data Center of the National Institute of Fisheries Science.

The standard case report form of epidemiological investigation for *V. vulnificus* infection was launched in 2003, and a follow-up investigation protocol was launched in 2011 to determine the outcome of cases. We analyzed the standard epidemiological investigation forms of all 761 cases from 2003 to 2016 to determine the detailed demographic factors, clinical features, source of infection, and distribution of underlying diseases. The 152 reported cases who could not be followed up were excluded from the analysis. From all 761 notified cases (696 confirmed and 65 suspected) between 2003 and 2016, we identified the general characteristics (sex, age, occupation, and region of residence), clinical characteristics (date of onset, clinical symptoms, and signs), underlying diseases, source of infection (place of infection, history of seafood consumption, and history of seawater exposure), lifestyle (drinking and smoking status), and outcome (death or survival) of the cases.

Statistical analysis

The incidence rate was calculated as the newly notified number divided by 100,000, according to a specific year or region. The case fatality rate was calculated as the proportion of deaths (%) among all reported cases. Frequency analysis was performed to identify descriptive epidemiological features according to time, place, and personal characteristics. Frequency analysis was also used to compare the number of *V. vulnificus* infection cases reported to the KCDC with the number of patients under the NHIS.

Ethics statement

This study was approved by the Institutional Review Board of Korea University (KUIRB-2018-0025-01). Informed consent was waived because of the retrospective nature of the study.

RESULTS

Incidence rate of *V. vulnificus* infection

In total, 913 cases were reported between 2001 and 2016. The average crude incidence rate during this period was 0.12 ± 0.03 per 100,000 population, with the highest rate reported in 2006 (0.18), followed by 2003 (0.17), 2010 (0.15), and 2012 (0.13), with the lowest in 2009 (0.05). The age-standardized incidence rates in these years showed a similar pattern (Fig. 1).

The incidence of *V. vulnificus* infection showed a high seasonality during the study period. The number of monthly cases was the highest in September ($n = 375$, 41.1%), followed by August ($n = 236$, 25.8%), October ($n = 143$, 15.7%), and July ($n = 96$, 10.5%), showing that the cases were concentrated between August and October. Few cases were reported between January and May (Fig. 2).

The risk of infection varies regionally. Among the 16 regions in Korea, the incidence rate per 100,000 population was the highest in Jeonnam (8.23), followed by Gyeongnam (4.64), Jeonbuk (2.75), and Busan (2.27) (Fig. 3).

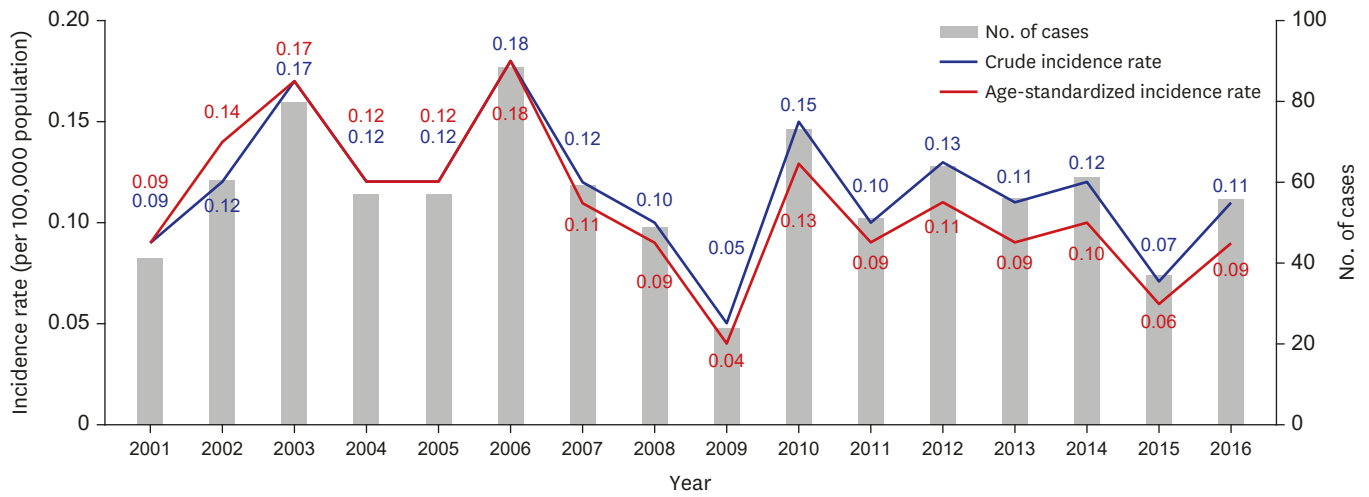


Fig. 1. Number of notified cases of *Vibrio vulnificus* infection, crude incidence rate, and age-adjusted incidence rate per 100,000 population by year, 2001–2016.

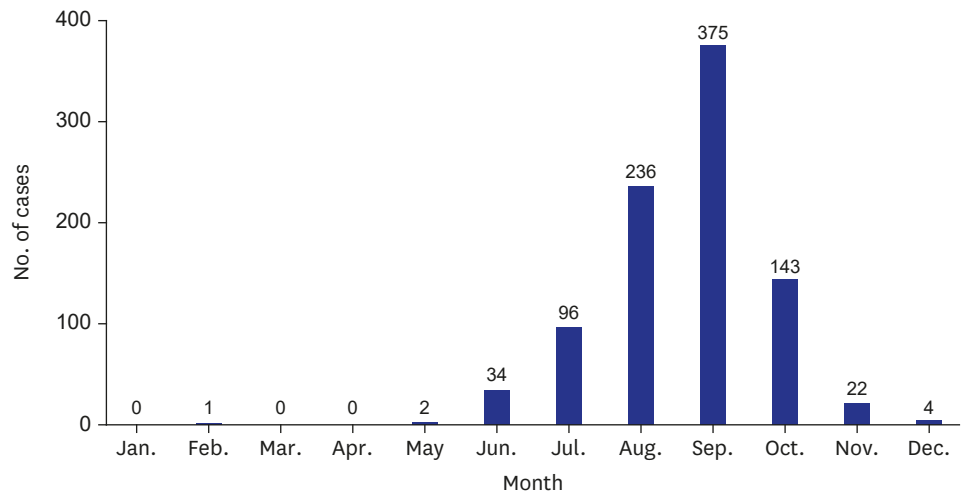


Fig. 2. Number of cases of *Vibrio vulnificus* infection by month, 2001–2016.

From 2001 to 2016, the age-standardized incidence rate by region, adjusted for the mid-year resident population in 2005, was the highest in Jeonnam for 11 years. The age-standardized incidence rate per 100,000 population was the highest in 2003 (1.73), followed by 2002 (0.77), 2006 (0.58), and 2014 (0.55).

Analysis of the number of *V. vulnificus* infection patients claimed to the NHIS

The two institutions (KCDC and NHIS) had the highest number of patients in 2012 (64 and 66, respectively) (Supplementary Table 1). Both institutions (KCDC and NHIS) had the highest number of patients in September (137 and 105, respectively), followed by August (77 and 68, respectively). The number of *V. vulnificus* infection cases reported to the KCDC was the highest in Gyeonggi Province, followed by Jeonnam Province. The number of *V. vulnificus*-infected patients under the NHIS was the highest in Jeonnam, followed by Seoul and Gyeonggi Province.

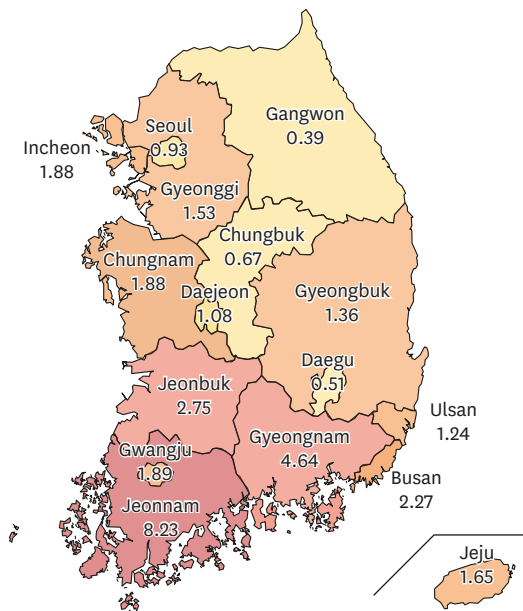


Fig. 3. Crude incidence rate of *Vibrio vulnificus* infection per 100,000 population by city/province, 2001–2016.

Analysis of coastal seawater temperature

For 16 years from 2001 to 2016, when *V. vulnificus* infection cases occurred, the monthly average seawater temperature ranged from 11.5°C to 24.1°C (Supplementary Fig. 1).

When the number of *V. vulnificus* infection cases began to increase in earnest in July, the seawater temperature gradually increased, and the average seawater temperature in August was the highest at 24.1°C. The average seawater temperature in September, when the most number of cases occurred, was 23.1°C. As the average seawater temperature decreased from October, the number of cases also decreased.

Epidemiologic characteristics

Among the 761 patients who had completed standard epidemiological investigation forms from 2003 to 2016, there were more male patients (85.7%), and the predominant age group was 40–64 years (71.7%). The most common occupational category was unemployed (housewives: 47.6%). Regarding lifestyle factors, 486 (79.8%) patients were alcohol consumers (Table 1).

Among the 761 patients, fever was the most common symptom (48.2%). In the 91 respondents who specified the site of pain, the most common pain sites were the lower limbs (61 cases, 67.0%), followed by the feet (10 cases, 11.0%), upper limbs (5 cases, 5.5%), both upper and lower limbs (5 cases, 5.5%), whole body (4 cases, 4.4%), hands (4 cases, 4.4%), and chest (2 cases, 2.2%). Hypotension occurred in a third of patients (35.0%). The site of edema was specified by 140 patients. The most common site of edema was the lower limbs (108 cases, 77.2%), followed by the upper limbs (11 cases, 7.9%), both upper and lower limbs (6 cases, 4.3%), feet (6 cases, 4.3%), whole body (3 cases, 2.1%), hands (3 cases, 2.1%), and hands and feet (2 cases, 1.4%). One patient (0.7%) complained of scrotal edema (Table 2).

Of the 691 patients with *V. vulnificus* infection who answered the question about underlying diseases, 664 (96.1%) reported having an underlying disease (Table 3). The most common

Table 1. General characteristics of cases of *Vibrio vulnificus* infection (N = 761)

Variables	Category	Values
Sex	Male	652 (85.7)
	Female	109 (14.3)
Age, yr	≤ 39	27 (3.6)
	40–64	546 (71.7)
	≥ 65	188 (24.7)
Occupation (n = 651)	Fishery and fishery product-related workers	49 (7.5)
	Agriculture-related workers	121 (18.6)
	White-collar workers, professional	38 (5.8)
	Service, distribution industry workers, self-employed	61 (9.4)
	Blue-collar workers ^a	72 (11.1)
	Housewife, unemployed	310 (47.6)
Drinking (n = 609)	Presence	486 (79.8)
	Absence	85 (14.0)
	Unknown	38 (6.2)
Smoking (n = 463)	Presence	247 (53.3)
	Absence	154 (33.3)
	Unknown	62 (13.4)

Values are presented as number (%).

^aBlue-collar workers include simple laborers in the fields of construction, civil engineering, and architecture.

Table 2. Clinical symptoms and signs in cases of *Vibrio vulnificus* infection (N = 761)

Category	Values
Symptoms ^a	
Fever	367 (48.2)
Chilliness	247 (32.5)
Diarrhea	169 (22.2)
Abdominal pain	168 (22.1)
Myalgia	151 (19.8)
Vomiting	129 (17)
Pain	97 (12.7)
Nausea	55 (7.2)
Headache	41 (5.4)
General prostration	14 (1.8)
Disturbance of consciousness	12 (1.6)
Oliguria	8 (1.1)
Jaundice	7 (0.9)
Others	8 (1.1)
Signs ^a	
Hypotension	266 (35.0)
Blister	227 (29.8)
Cellulitis	171 (22.5)
Edema	156 (20.5)
Rash	66 (8.7)
Neurologic signs	34 ^b (5.5)
Necrosis	42 (5.5)
Dyspnea	33 (4.3)
Gastrointestinal bleeding (melena, hematemesis)	31 (4.1)
Loss of consciousness	26 (3.4)
Septic shock	18 (2.4)
Dermatorrhagia (blot hemorrhage, petechia, ecchymosis)	14 (1.8)
Multiple organ dysfunction syndrome	7 (0.9)
Purpura	7 (0.9)
Ascites	5 (0.7)
Other bleeding (hematuria, subconjunctival hemorrhage, hemostatic disorder)	3 (0.4)
Others	12 (1.6)

Values are presented as number (%).

^aMultiple responses were allowed for symptoms and signs in the case epidemiological investigation form;

^bDizziness: 13 cases; Paresthesia: 5; Paralysis: 5; Convulsion: 4; Dysphasia: 3; Seizure: 1; Cognitive disorder: 1; Disesthesia: 1; Delirium: 1.

Table 3. Underlying diseases in cases of *Vibrio vulnificus* infection (N = 664)

Category ^a	Values
Liver cirrhosis	374 (56.3)
Diabetes mellitus	177 (26.7)
Hepatitis	162 (24.4)
Hypertension	99 (14.9)
Other liver disease	89 (13.4)
Liver cancer	49 (7.4)
Other types of cancer	34 (5.1)
Cardiovascular disease	30 (4.5)
Hemodyscrasia	29 (4.4)
Gastrointestinal disorder	21 (3.2)
Arthritis	18 (2.7)
Renal failure	18 (2.7)
Alcoholism	16 (2.4)
Endocrinopathy	8 ^b (1.2)
Chronic respiratory disease	8 (1.2)
Pneumonia	7 (1.1)
Tuberculosis	5 (0.8)
Neurologic disorder	3 (0.5)
Other diseases	10 (1.5)

Values are presented as number (%).

^aMultiple responses were allowed for underlying disease in the case epidemiological investigation form;

^bHypothyroidism 4 cases, Hypocorticalism 2 cases, Hyperthyroidism 1 case, Cushing's syndrome 1 case.

underlying disease was liver cirrhosis (56.3%). Among the 89 patients with other liver diseases, 33 (37.1%) had alcoholic liver disease and five (5.6%) had fatty liver disease.

In the 655 cases in which the source of infection was evaluated, the most common source was raw seafood consumption (90.1%), followed by seawater exposure (5.8%) and both raw seafood consumption and seawater exposure (4.1%).

Sex ($P = 0.045$), age ($P = 0.003$), and liver disease presence ($P = 0.035$) showed a statistically significant difference with the route of infection; men (91.0%), patients under 64 years old (91.5%), and patients with liver disease (91.8%) had been infected mainly through seafood consumption.

Regardless of the region of residence, the most common region exposed to *V. vulnificus* was Jeonnam (24.3%), followed by Gyeongnam (15.6%), Gyeonggi (10.7%), and Incheon (9.5%). Five patients were considered to have acquired the infection in foreign countries, four through seafood consumption (two in China, one in Vietnam, and one in the Philippines), and one through seawater exposure (in Indonesia). Epidemiological reports from 2011 to 2016 show that 159 of 325 notified cases of *V. vulnificus* infection resulted in death, which represents a fatality rate of 48.9%. The fatality rate was the highest in 2014 (65.6%) and the lowest in 2016 (21.4%).

DISCUSSION

V. vulnificus infection occurs annually in Korea with regional and seasonal features. In our analysis of the cases of *V. vulnificus* infection from 2001 to 2016, the incidence rate was 0.12 ± 0.03 per 100,000 population, with the highest incidence (8.23) recorded in the Jeonnam region. *V. vulnificus* infection mostly occurs sporadically in the United States. From 1998 to 2007, 276 cases of *V. vulnificus* infection were reported in Florida, with an average annual incidence rate of 1.6 per 1 million.¹⁵ In Japan, 12–24 cases of *V. vulnificus* infection have been

reported annually.¹⁶ In Taiwan,¹⁷ the estimated prevalence of *V. vulnificus* infection from 1985 to 2000 was 0.35–1.24 per 1 million, with the largest number of cases reported in 2000 (n = 26).

In our study, the largest number of cases occurred in September (41.1%), and 82.6% of all cases occurred between August and October. Similarly, most cases of infection in the United States were reported between April and October, which are the months during which the organism flourishes.¹⁸ In Japan, 81.1% of the cases were reported between July and September,¹⁹ with the greatest number reported in July.¹⁶ In Taiwan, almost all cases occurred between late spring and early fall (April through October), a period during which the seawater temperature ranges from 20°C to 29°C.¹⁷

In a previous study,²⁰ *Vibrio* spp. isolated from the environments of the southern coastal tidal water and mud samples of South Korea showed species-specific seasonal patterns, with *V. vulnificus* limited to summer. Therefore, the results of this previous study²⁰ support the results of our study, which showed that *V. vulnificus* infection cases occurred intensively in August and October, and the incidence rate per 100,000 population was the highest in Jeonnam (8.23).

It can be assumed that the warm seawater temperature affected the incidence. A previous study,²¹ showed a positive relationship between seawater temperature and *V. vulnificus* cases and the relative risks of *V. vulnificus* infection in the south, west, and east coasts according to the 1°C increase in seawater temperature were 1.35 (95% confidence interval [CI], 1.19–1.53), 1.34 (95% CI, 1.20–1.51), and 1.30 (95% CI, 1.06–1.59), respectively.

According to a previous study on cases reported in Florida from 1981 to 1992,²² oyster consumers with liver disease had 80 times higher risk of *V. vulnificus* infection. In this study, the risk of *V. vulnificus* infection was associated with male sex (85.7%), older age (96.5% > 40 years), and underlying disease (96.1%). Similar demographic characteristics have been reported in the United States,²³ Taiwan,¹⁷ and Japan.¹⁹ Leng et al.¹⁰ reported that the higher infection rate among men (86.1%) is attributable to higher alcohol use and a higher percentage of occupational exposure to seawater and seafood.²⁴ In our study, 96.1% of the cases had an underlying disease, with liver cirrhosis (56.3%) being the most common, followed by diabetes mellitus (26.7%). In a study that investigated 37 cases in the Ariake Sea region in Japan between 1984 and 2008, 91.6% of the patients had liver disease.¹⁹ In a Taiwanese study that investigated 84 patients between 1995 and 2000, over 80% of the patients had liver disease, mainly caused by hepatitis B or C infection, followed by diabetes and steroid use.¹⁷ The most common comorbidities among patients with *V. vulnificus* infection in the United States were heart disease (34%), diabetes mellitus (23%), alcohol consumption (22%), and liver disease (20%).²³

In Korea, seafood consumption is the most common (90.1%) route of *V. vulnificus* infection, resulting in primary sepsis. In a Japanese study, 31 of 37 (83.8%) patients consumed raw seafood, and the remaining six patients had an unknown route of infection, with no clear cases of infection through wound sites.¹⁹

In our study, 81.2% of the patients with an underlying disease had liver disease (liver cirrhosis, hepatitis, or liver cancer). These patients most frequently contracted the pathogen through seafood consumption, whereas patients without liver disease most frequently contracted the pathogen through seawater exposure, with the difference being statistically significant ($P = 0.035$). As liver disease is a potent predictor of death in all patients, a dysfunctional liver is reported to impose an additional risk through an independent

mechanism of transferrin saturation or iron overload.²⁴ Because of the strong correlation between liver disease and death, previous studies recommended that patients with liver disease should refrain from activities that involve seawater exposure if they currently have a wound or are likely to sustain a wound injury.^{22,23}

In our study, 159 of 325 patients with *V. vulnificus* infection died (48.9%). In a Taiwanese study of 84 patients with *V. vulnificus* infection between 1995 and 2000, 25 patients died (29.8%), 57 patients survived (67.9%), and two patients had an unknown status (2.3%).¹⁷ In a study in Japan, 24 of 37 patients died (64.9%).¹⁹ Yun et al.¹² reviewed the clinical data of 34 patients in a Korean hospital between 2000 and 2011, among whom 16 patients (47.1%) died.

In the USA and Korea, *V. vulnificus* infection is a nationally notifiable disease, but there is no obligation to report it in Japan.¹⁶ The Centers for Disease Control and Prevention in the USA monitors vibriosis through the nationwide Cholera and Other *Vibrio* Illness Surveillance (COVIS) system since 1988 and the 10-state Foodborne Diseases Active Surveillance Network (FoodNet) since 1996.²⁵ COVIS is a passive surveillance system to which all states can report laboratory-confirmed *Vibrio* infections, and FoodNet conducts an active, population-based surveillance in ten states for all laboratory-confirmed *Vibrio* infections, as well as other enteric infections transmitted commonly through food.²⁵ The three commonly reported *Vibrio* species were *V. parahaemolyticus*, *V. vulnificus*, and *V. alginolyticus*, and in both systems, most hospitalizations and deaths were caused by *V. vulnificus* infection.²⁵ In Korea, since 2000, a passive report-based national notifiable infectious disease surveillance system has been operated to notify suspected and confirmed cases of *V. vulnificus* infection. Since 2002, laboratory surveillance for pathogenic *Vibrio* (vibrioNet) has been conducted to monitor the distribution status of three pathogenic *Vibrio* species (*V. vulnificus*, *V. cholerae*, and *V. parahaemolyticus*) and changes in marine environmental factors (seawater temperature, salinity, pH, turbidity).

From the seawater temperature analysis provided by KCDC from 2001 to 2016, the seawater temperature in August was the highest at 24.1°C. However, in September, when the seawater temperature was 23.1°C, the number of cases was the highest at 375. During the same period, 850 (93.1%) of 913 notified cases occurred between July and October, and the average seawater temperature between July and October was 22.1°C. Therefore, the occurrence of *V. vulnificus* infection in our study showed a distinct seasonality due to seawater temperature, and it occurred more often in people with underlying diseases such as liver cirrhosis; therefore, host factors can also affect the occurrence of disease.

V. vulnificus infection surveillance results showed a monthly average of 57 *V. vulnificus* infection cases, but given the passive reporting system and the number of cases where patients died without treatment or diagnosis, it has been reported that the actual number of cases could be much higher than this.²⁶ From 1981 to 1987, among *V. vulnificus* patients reported in Florida, USA, the case fatality rates of those with and without liver disease were similar at 52% and 62%, respectively.²⁷ In our study, the case fatality rates of *V. vulnificus* infection cases with and without liver disease were 51.2% and 42.5%, respectively, and there was no statistically significant difference ($X^2 = 1.65$, $P = 0.199$). In the future, a retrospective study is needed to identify possible risk factors that may affect mortality by analyzing the medical records of cases.

Our study analyzed all notified cases from investigation reports between 2003 and 2016 in Korea; however, we could not include data on patients' blood tests, antibiotic use, and specific treatment in our analysis because of the lack of such information in epidemiological reports.

In conclusion, considering the high fatality rate associated with *V. vulnificus*, it is important to establish public health measures to prevent *V. vulnificus* infection. To lower the incidence of, and death from, *V. vulnificus* infection, it is important to increase awareness among people at high risk, especially those living in high-risk areas. The public health approach should emphasize the prevention of *V. vulnificus* infection.⁶ Moreover, important approaches for reducing the disease burden include education and prevention strategies.²⁴ The Taiwanese government requires food companies to provide warning labels on seafood containers, menus, and public health brochures.¹⁷ Therefore, additional research needs to be conducted in the future.

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*Epidemiological characteristics of cases with *V. vulnificus* infection in Korea. *PHWR* 2019;12(26):868-874.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Number of cases reported to the KCDC and patients under the NHIS by year, 2011–2016

[Click here to view](#)

Supplementary Fig. 1

Number of cases reported to the KCDC and coastal seawater temperature according to the KCDC by month, 2001–2016.

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