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Hearing impairment in young and middle-aged septicemia survivors

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Abstract

The ability of sepsis to induce acute phase hearing impairment has been evaluated in septic and sepsis-surviving mice. The relationship between septicemia and long-term hearing impairment remains unknown in humans.

The data were obtained from the Taiwan Longitudinal National Health Insurance Database from 2000 to 2013. We identified patients suffering from septicemia after discharge, excluding those younger than 18 years old and older than 65 years old. The comparison group was matched based on age, sex, and comorbidities. The outcome was hearing impairment occurring after septicemia. The risk factors associated with hearing impairment were established using multivariate Cox proportional hazard regression.

Our study found that septicemia associated with hearing impairment had an adjusted hazard ratio (HR) of 53.11 (95% confidence interval [CI]: 41.74–67.59). The other factors related to hearing impairment in young and middle-aged septicemia survivors included male sex (adjusted HR 1.31 [95% CI: 1.14–1.5]), chronic kidney disease (adjusted HR 1.63 [95% CI: 1.38–1.94]), and otoscleroisis (adjusted HR 231.54 [95% CI: 31.61–1695.8]).

Our study revealed that septicemia was associated with increased development of hearing impairment in young and middle-aged humans in the long term. Clinicians should be aware of long-term septicemia-related hearing impairment and provide prevention strategies for otopathy in septicemia survivors.

Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database.

Keywords: hearing impairment, risk, septicemia

1. Introduction

Septicemia is a severe life-threatening disorder that can cause short- and long-term major adverse cardiovascular events, including myocardial infarction, ischemic stroke, and death.[1–3] Septicemia has a high incidence of critical care hospitalization. Septicemia survivors display a range of disabilities and problems that can alter quality of life.[4] Acute hearing loss is related to sepsis and sepsis survival in mice,[5,6] but a correlation between septicemia and long-term hearing impairment has not been previously addressed in humans. The aim of this study was to identify whether hearing impairment is related to septicemia in humans.

Potential causes of hearing loss include aging, genetics, trauma, ototoxic medication, local infections, vascular diseases, autoimmune disorders, and noise. In animal studies, general inflammation leads to apoptosis in Corti organ-supporting cells, which then induces glutamate overstimulation in the inner hair cells in septic mice.[5,6] Aminoglycoside antibiotics are employed for broad-spectrum gram-negative bacterial infection, but they are associated with nephrotoxicity and ototoxicity.[7] A previous study found that mammalian hair cell repair was limited, and persistent hearing impairment can occur after hair cell injury.[8] Understanding the risk factors for hearing impairment is important for preserving function.

We hypothesized that septicemia increases the risk of hearing impairment in young and middle-aged humans. We used the Taiwanese National Health Insurance Research Database (NHIRD) to explore whether a history of septicemia is associated

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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with a subsequent increase in the long-term risk of developing hearing impairment.

2. Methods

National health insurance has been implemented in Taiwan since 1995; it is composed of a unified government supportive health care system and covers approximately 99% of Taiwan's 23 million citizens. All medical care providers must submit computerized data claims for insurance payments. The Taiwanese NHIRD contains all outpatient and inpatient medical insurance payment records. For each visit, the system includes up to 5 International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) inpatient diagnosis and procedure codes and 3 outpatient ICD-9-CM diagnosis and procedure codes. The data extracted included each patient's age, sex, comorbid conditions, hearing impairment codes, and times of admission and discharge.

The dataset used in this study was obtained from the Taiwan Longitudinal Health Insurance Database, which randomly selects patients from the population. We identified patients with diagnosis codes for septicemia (ICD-9-CM as 038, 003.1, 036.1), which were collected from January 1, 2000, to December 31, 2013. The diagnosis code of septicemia in the NHIRD was used for verification.[2,9–11] Furthermore, hearing loss in children and older patients was reported in 1 pneumococcal meningitis survey.[12] Age-related hearing loss is caused by the loss of inner ear hair cells over time. In addition, 40% of elderly adults have hearing impairment after age 65.[13] We excluded patients based on the following criteria: younger than 18 years, older than 65 years, death during admission, hospitalization for septicemia, hearing impairment before the index date and unknown sex. The date of admission for septicemia was defined as the index date of the study group. Four controls were matched to each case based on age, sex, and comorbidities. Hearing impairment events were defined with the ICD-9-CM diagnostic code 389. Patients were followed until the first event or December 31, 2013. The flow chart of the study is presented in Figure 1.

We used the ICD-9-CM codes to identify diagnoses in the NHIRD for hearing impairment comorbidities. Hearing impairment comorbid disorders mapped by ICD-9-CM codes included hypertension (401–405); diabetes mellitus (250); chronic kidney disease (580–589); hyperlipidemia (272); autoimmune disorders (710); anemia (280, 285); hematological disorders, including coagulopathies and platelet disorders (286–287); coronary artery disease (410–414); ischemic stroke (433–437); meningitis (320–322, 013.0, 036.0, 053.0, 047); traumatic brain injuries (800, 803–805, 850–854); encephalopathy (293, 348.3, 780.01, 780.09); chronic otitis media (381–382); otosclerosis (387); and osteoporosis (733.0). The study was approved by TSGH IRB 2-105-05-025.

2.1. Statistical analyses

Continuous variables are displayed as the means ± standard deviations and were evaluated with Student *t* tests, while categorical variables are displayed as percentages and were evaluated with the Chi-square (X^2) test. The risk factors for

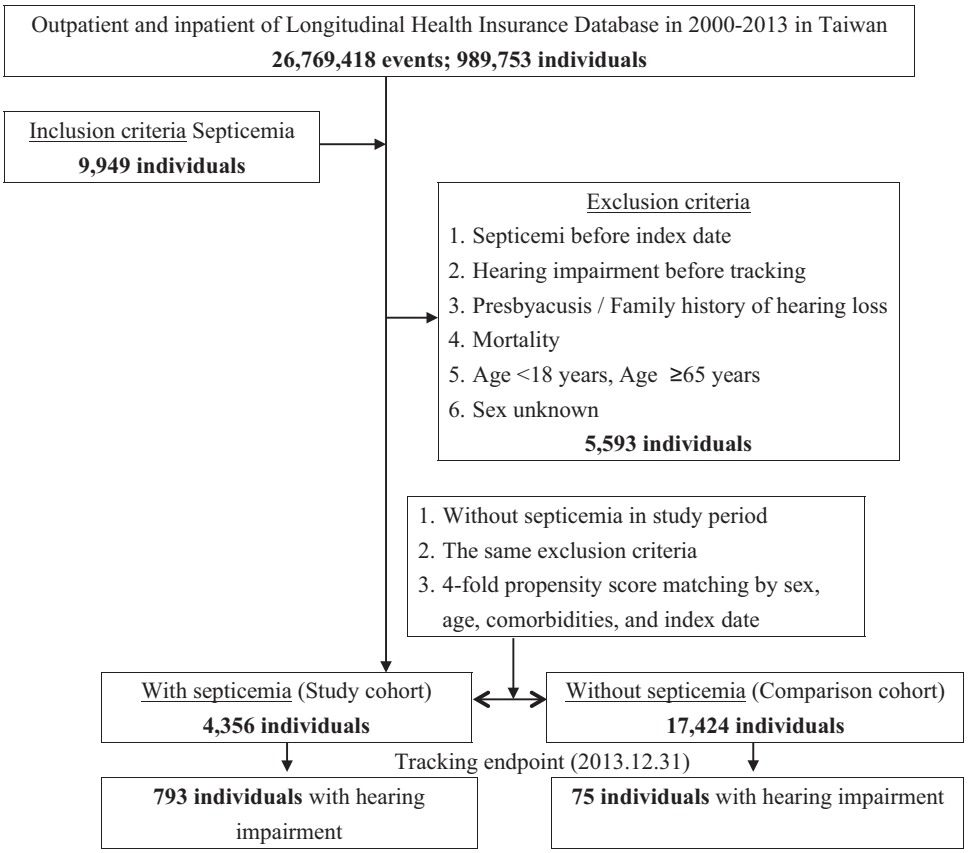

Figure 1. The flowchart of study sample selection from the National Health Insurance Research Database in Taiwan.

Table 1

Characteristics of the study population at baseline.

Variables	Septicemia n	Septicemia-free n	P
Total	4356	17,424	
Sex			.999
Male	2161 (49.61%)	8644 (49.61%)	
Female	2195 (50.39%)	8780 (50.39%)	
Age (yr)	47.97 ± 11.71	47.66 ± 12.72	.144
Age group (yr)			.999
18–44	1339 (30.74%)	5356 (30.74%)	
≥45	3017 (69.26%)	12,068 (69.26%)	
Diabetes mellitus	1148 (26.35%)	4495 (25.8%)	.453
Hypertension	275 (6.31%)	1217 (6.98%)	.117
Chronic kidney disease	528 (12.12%)	2097 (12.04%)	.876
Hyperlipidemia	56 (1.29%)	222 (1.27%)	.94
Coronary heart disease	390 (8.95%)	1557 (8.94%)	.972
Ischemic stroke	82 (1.88%)	272 (1.56%)	.14
Autoimmune diseases	46 (1.06%)	186 (1.07%)	.934
Anemia	171 (3.93%)	611 (3.51%)	.187
Hemtological disorder	65 (1.49%)	241 (1.38%)	.565
Meningitis	29 (0.67%)	110 (0.63%)	.831
Traumatic brain injury	78 (1.79%)	272 (1.56%)	.281
Encephalopathy	5 (0.11%)	9 (0.05%)	.174
Chronic otitic media	681 (15.63%)	2877 (16.51%)	.162
Otoscleroisis	0	4 (0.02%)	.59
Osteoporosis	5 (0.11%)	20 (0.11%)	.999
Location			<.001*
Northern Taiwan	1277 (29.32%)	6951 (39.89%)	
Middle Taiwan	976 (22.41%)	4753 (27.28%)	
Southern Taiwan	1791 (41.12%)	4663 (26.76%)	
Eastern Taiwan	304 (6.98%)	969 (5.56%)	
Outlets islands	8 (0.18%)	88 (0.51%)	
Urbanization level			<.001*
1 (Highest)	1832 (42.06%)	6334 (36.35%)	
2	1908 (43.8%)	7148 (41.02%)	
3	142 (3.26%)	1303 (7.48%)	
4 (Lowest)	474 (10.88%)	2639 (15.15%)	
Level of care			<.001*
Hospital centre	2093 (48.05%)	5437 (31.20%)	
Regional hospital	1483 (34.04%)	4942 (28.36%)	
Local hospital	780 (17.91%)	7045 (40.43%)	

* $P < .05$.

hearing impairment were assessed using Cox proportional hazard regression. The statistical significance was set at $P < .05$. The statistical analyses were performed with SPSS version 21 software.

3. Results

We investigated 4356 septicemia survivors in the study group and 17,424 septicemia-free patients in the control group. The median hearing impairment detection times were 3.51 years in the study group and 7.72 years in the control group. Table 1 presents the demographic variables for the septicemia and control groups. Compared with the control patients, more septicemia patients were admitted to medical centres, lived in southern Taiwan and had a higher urbanization level. In total, 18.2% (793/4356) of the patients in the study group had hearing impairment versus 0.43% (75/17,424) in the control group (log-rank test: $P < .001$) (Fig. 2). The majority of hearing impairment cases occurred within 1 year after septicemia (Table 2).

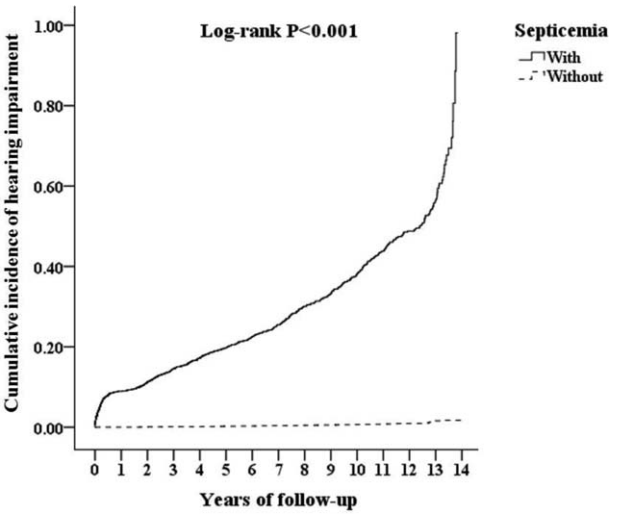

Figure 2. Kaplan–Meier for cumulative incidence of hearing loss between aged 18 and 65 stratified by septicemia with log-rank test.

Table 2

Numbers of hearing loss cases in septicemia and septicemia-free patients.

Septicaemia	With (N = 4356)	Without (N = 17,424)	
In the tracking of x year (s)	Number of hearing impairment cases		P
1	257	3	<.001
2	307	7	<.001
3	375	12	<.001
4	426	17	<.001
5	466	25	<.001
6	507	28	<.001
7	547	34	<.001
8	600	40	<.001
9	632	45	<.001
10	675	50	<.001
11	718	57	<.001
12	747	62	<.001
13	770	74	<.001
14	793	75	<.001

Our study revealed a relationship between septicemia and hearing impairment, with an adjusted hazard ratio (HR) of 53.11 (95% confidence interval [CI]: 41.74–67.59). Other risk factors included male sex (adjusted HR 1.31 [95% CI: 1.14–1.5]), chronic kidney disease (adjusted HR 1.63 [95% CI: 1.38–1.94]), and otoscleroisis (adjusted HR 231.54 [95% CI: 31.61–1695.8]), after adjustment for age and other comorbidities. Some underlying diseases were associated with a lower risk of hearing impairment, including hypertension (adjusted HR 0.462 [95% CI: 0.376–0.569]), anemia (adjusted HR 0.646 [95% CI: 0.446–0.937]), and traumatic brain injury (adjusted HR 0.422 [95% CI: 0.233–0.766]) (Table 3). The overall and subgroup-specific incidence rates and incidence rate ratios of hearing impairment between septicemia and septicemia-free patients were performed in Table 4. The overall incidence rates of hearing impairment in septicemia patients were 1477.96 per 10^5 person-years and 39.11 per 10^5 person-years in septicemia-free patients. The incidence rate ratio of hearing impairment was 37.79 between septicemia

Table 3

Factors of hearing impairment identified by Cox regression.

Variables	Crude HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Septicemia	55.774	43.995–70.707	<.001*	53.114	41.738–67.591	<.001*
Sex						
Male	1.012	0.886–1.157	.856	1.310	1.144–1.5	<.001*
Female	Reference			Reference		
Age group (yr)						
18–44	Reference			Reference		
≥45	1.146	0.964–1.362	.123	1.193	0.998–1.426	.053
Diabetes mellitus	1.759	1.525–2.030	<.001*	1.154	0.991–1.344	.065
Hypertension	0.474	0.389–0.577	<.001*	0.462	0.376–0.569	<.001*
Chronic kidney disease	3.725	3.146–4.41	<.001*	1.634	1.375–1.942	<.001*
Hyperlipidemia	0.297	0.154–0.573	<.001*	0.561	0.286–1.098	.092
Coronary heart disease	0.804	0.623–1.037	.093	0.843	0.651–1.093	.197
Ischemic stroke	0.595	0.382–0.927	.022	0.715	0.456–1.119	.142
Autoimmune diseases	3.491	2.129–5.725	<.001*	1.241	0.749–2.057	.402
Anemia	0.743	0.513–1.075	.115	0.646	0.446–0.937	.021*
Hematological disorder	2.368	1.396–4.016	.001*	1.555	0.912–2.654	.105
Meningitis	0.843	0.119–5.988	.864	0.657	0.092–4.69	.676
Traumatic brain injury	0.288	0.159–0.523	<.001*	0.422	0.233–0.766	.005*
Encephalopathy	0.595	0.149–2.385	.464	0.543	0.135–2.181	.39
Chronic otitic media	2.087	1.150–3.785	.015	0.840	0.460–1.536	.572
Otoscleroisis	25.583	3.592–182.201	.001	231.538	31.613–1,695.798	<.001*
Osteoporosis	0.000	–	.164	0.000	–	.898
Location						
Northern Taiwan	Reference			Multicollinearity with urbanization level		
Middle Taiwan	0.884	0.736–1.061	.185			
Southern Taiwan	1.436	1.224–1.685	<.001*			
Eastern Taiwan	1.269	0.973–1.657	.079			
Outlets islands	1.285	0.479–3.448	.618			
Urbanization level						
1 (Highest)	1.369	1.121–1.671	.002*	0.706	0.606–0.823	<.001*
2	0.960	0.785–1.172	.686	0.589	0.417–0.833	.003*
3	0.663	0.464–0.948	.024*	0.828	0.663–1.033	.095
4 (Lowest)	Reference			Reference		
Level of care						
Hospital centre	1.466	1.208–1.78	<.001*	1.011	0.862–1.186	.891
Regional hospital	1.269	1.046–1.538	.015	0.995	0.803–1.233	.964
Local hospital	Reference			Reference		

CI = confidence interval, HR = hazard ratio.
* $P < .05$.

and septicemia-free patients. Factors of hearing impairment stratified by variables using Cox regression showed in Supplemental Table 1 (see Table, http://links.lww.com/MD/E524, Supplement Content, which illustrates factors of hearing impairment stratified by variables using Cox regression).

4. Discussion

Our study revealed that septicemia is significantly associated with long-term subsequent hearing impairment in young and middle-aged adult humans. Hearing impairment occurred earlier in septicemia survivors than in septicemia-free patients. Hearing impairment results from complex processes and may influence communication, which can be very stressful and lead to social withdrawal, affecting patients' quality of life.[14]

Septicemia can develop when an infection occurs elsewhere in the body. This is dangerous because the bacteria and their toxins can be carried through the bloodstream to the entire body. Septicemia leads to extensive host defense systemic inflammatory responses to fight the infection; when inflammation fails to resolve, it progresses to chronic inflammation, which can persist for months to years.[15] Inflammation causes blood clots and prevents oxygen from reaching vital organs, resulting in organ failure. Toxins can cause extremely low blood flow, which may result in organ or tissue damage.[16] Chronic inflammation associated with septicemia can cause short- and long-term atherosclerotic events,[1–3] dementia,[9] and multiple sclerosis.[11]

The oxygen stress attributed to reactive oxygen species generation causes mitochondrial dysfunction via adenosine triphosphate depletion in patients with sepsis.[17] Hearing impairment in the context of septicemia occurs due to immune reaction-induced apoptosis and microthrombosis following inner ear destruction. Apoptosis occurs in Deiters' cells, Claudius' cells, and Hensen's cells in the Corti organ due to glutamine overstimulation in the radial dendrites; this is followed by vacuolization of the inner ear cells, which has been observed via immunohistochemical evaluation through a cecal ligation puncture in an induced sepsis mouse study.[5] Sepsis-surviving model mice exhibited an increased threshold of auditory brainstem response.[6] Aminoglycoside antibiotics are widely used for suspected gram-negative bacterial infections. A previous study found that vasodilation due to inflammation increased

Table 4

The overall and subgroup-specific incidence rates and incidence rate ratios of hearing impairment between septicemia and septicemia-free patients.

Septicemia Stratified	With Event	PYs	Incidence Rate (per 10^5 PYs)	Without Event	PYs	Incidence Rate (per 10^5 PYs)	IRR
Total	793	53655.21	1477.96	75	191750.96	39.11	37.79
Gender							
Male	380	21315.97	1782.7	39	94128.71	41.43	43.03
Female	413	32339.24	1277.09	36	97622.26	36.88	34.63
Age group (yr)							
18–44	152	10024.15	1516.34	6	39567.36	15.16	100
≧45	641	43631.06	1469.14	69	152183.61	45.34	32.4
Diabetes mellitus							
Without	532	35506.86	1498.3	60	155996.71	38.46	38.96
With	261	18148.35	1438.15	15	35754.25	41.95	34.28
Hypertension							
Without	696	40260.55	1728.74	57	144820.11	39.36	43.92
With	97	13394.66	724.17	18	46930.85	38.35	18.88
Chronic kidney disease							
Without	626	46636.45	1342.3	74	182776.63	40.49	33.15
With	167	7018.76	2379.34	1	8974.34	11.14	213.53
Hyperlipidemia							
Without	787	52098.84	1510.59	72	184867.54	38.95	38.79
With	6	1556.37	385.51	3	6883.42	43.58	8.85
Coronary artery disease							
Without	735	48322.06	1521.04	69	174716	39.49	38.52
With	58	5333.15	1087.54	6	17034.96	35.22	30.88
Ischemic stroke							
Without	779	51613.87	1509.28	69	184326.07	37.43	40.32
With	14	2041.34	685.83	6	7424.89	80.81	8.49
Autoimmune diseases							
Without	778	52869.96	1471.54	74	191052.77	38.73	37.99
With	15	785.25	1910.22	1	698.19	143.23	13.34
Anemia							
Without	770	51005.35	1509.65	69	183471.25	37.61	40.14
With	23	2649.86	867.97	6	8279.72	72.47	11.98
Hemotological disorder							
Without	780	53139.13	1467.84	74	190574.53	38.83	37.8
With	13	516.08	2519	1	1176.44	85	29.63
Meningitis							
Without	792	53549.42	1479.01	75	191510.73	39.16	37.77
With	1	105.79	945.3	0	240.23	0	–
Traumatic brain injury							
Without	785	51960.35	1510.77	72	183048.98	39.33	38.41
With	8	1694.86	472.02	3	8701.98	34.47	13.69
Encephalopathy							
Without	791	53432.48	1480.37	75	191020.36	39.26	37.7
With	2	222.73	897.95	0	730.6	0	–
Chronic otitic media							
Without	789	53139.71	1484.77	68	190845.57	35.63	41.67
With	4	515.5	775.94	7	905.39	773.15	1
Otoscleroisis							
Without	793	53655.21	1477.96	74	191743.77	38.59	38.3
With	0	0	0	1	7.19	13910.97	–
Osteoporosis							
Without	793	53584.36	1479.91	75	190660.6	39.34	37.62
With	0	70.85	0	0	1090.36	0	–
Urbanization level							
1 (The highest)	331	18290.62	1809.67	22	59895.13	36.73	49.27
2	303	23911.23	1267.19	40	84908.88	47.11	26.9
3	34	3470.57	979.67	5	14458.62	34.58	28.33
4 (The lowest)	125	7982.79	1565.87	8	32488.34	24.62	63.59
Level of care							
Hospital center	322	20519.69	1569.22	30	66266.59	45.27	34.66
Regional hospital	336	23979.04	1401.22	36	83877.64	42.92	32.65
Local hospital	135	9156.48	1474.37	9	41606.73	21.63	68.16

IRR = incidence rate ratio, PYs = person-years.

cellular damage in the blood-labyrinth barrier, which facilitates aminoglycoside transfer to hair cells.[18]

Male humans who perform work that involves exposure to loud noises exhibit an increased risk of hearing loss associated with pneumococcal meningitis.[12] Our study had a similar finding: men exhibited an increased risk of hearing impairment after septicemia. Sepsis induces apoptosis in various organs, potentially leading to multiple organ failure. The moderate renal impairment-related increased risk of hearing impairment occurs via apoptosis, with an odds ratio of 1.43 (95% CI: 1.1–1.84),[19] and our study reported a similar finding. A past study reported that otosclerosis related to sensorineural hearing loss occurred in 34% of patients,[20] and our study showed that otosclerosis also increases hearing impairment. The otosclerosis was the highest association with hearing impairment, but it would not be the major cause instead of septicemia with low prevalence in our study group. Septicemia patients with more comorbid conditions will experience increased mortality during hospitalization,[10] and an increased number of comorbid conditions seems to cause an increased risk of septicemia-induced hearing impairment in our study.

Patients with a higher urbanization level have a lower risk of hearing impairment. Potential reasons include the possibility that these patients are more concerned about their health status and frequently seek health care providers to improve their quality of life. Patients with hypertension, anemia, and traumatic brain injury exhibited relatively fewer hearing impairment events in the present study. The potential reason may be adequate treatment indicated by the diagnostic codes for hypertension and anemia in the claims data. Higher mortality from traumatic head injury leads to a lower risk of hearing impairment. More in-depth research in this field is necessary.

Aging and exposure to loud noise may cause wear and tear on the hairs or nerve cells in the cochlea, which send sound signals to the brain. In addition, the aging immune system and weaker older bodies are more vulnerable to the damaging effects of sepsis, and these patients are more likely to suffer lasting consequences. We excluded older septicemia survivors to reduce the effect of aging on hearing impairment. However, our study found that hearing impairment was not associated with older age in the young and middle-aged groups. Poorly controlled diabetes mellitus induces chronic kidney disease and increases oxidative stress.[21] Diabetes mellitus and hyperlipidemia were not related to heading impairment in adults in our study. A potential reason is that the NHIRD dataset is generated from insurance payment claims. Patients with a diagnosis of diabetes mellitus and hyperlipidemia are administered suitable treatments according to the payment guidelines. Spiral ganglion loss and a flattened organ of Corti were noted after ischemia in guinea pigs.[22] A previous rat study showed cell damage due to apoptosis in outer hair cells in a carotid ischemia model.[23] However, our study did not find that ischemic stroke increased the risk of hearing impairment. The potential reason is that hearing impairment may be undiagnosed or underestimated in severe ischemic stroke patients who are bedridden or display cognitive impairment without hearing impairment complaints.

Bacterial infection can be prevented with a vaccine[24,25] and treated with antibiotics. Rapid identification of the infection source can facilitate timely treatment with appropriate antibiotics, potentially preserving some hearing function. The administration of third-generation cephasporin antibiotics to treat acute infection has relatively fewer toxic effects on the ear. Dextrans and vasodilators improve inner ear circulation. Aspirin reduces ischemic attacks within 1 month after sepsis.[26] Antioxidants diminish reactive oxygen species levels to reduce hair cell apoptosis.[27]

Our results support the hypothesis of a close correlation between septicemia and hearing impairment in the largest population of participants investigated to date, after adjustment for other contributing factors. Physicians and patients need to pay more attention to this complication of septicemia. The rapid identification of the infection source can quickly facilitate treatment with appropriate antibiotics, and guidelines on the management of chronic kidney disease[28] should be followed to preserve hearing function, thereby enhancing patients' ability to communicate and relieving their psychological burden. If treatment for hearing loss fails, adults may need a cochlear implant to improve their hearing ability and, thereby, their social interactions. However, this alternative can be uncomfortable and expensive.

5. Limitations

There were some limitations of this study. First, because the NHIRD is a payment claims dataset, detailed data on body mass index, noise environment exposure, family history, potential risk factors, and severity of the hearing loss according to audiometry and otological exams were not available; however, these factors may have an impact on hearing impairment risk.

Second, the diagnoses of septicemia, hearing impairment, and comorbidities were made according to the ICD-9-CM diagnostic codes recorded in the database from the Taiwan NHI program, which may vary from study to study. Patients with severe septicemia experience severe inflammation, which may exert a threshold effect on hearing impairment. A prospective audiometry assessment must be undertaken in septicemia survivors to confirm the dose effect.

Third, age-related hearing impairment occurs after 55 years of age. The etiology of hearing impairment needs to be determined in older septicemia survivors.

Fourth, we did not survey ototoxic agents in this study. The effects of ototoxic agents, such as antibiotics or diuretics, on hearing impairment should be assessed in the future.

Fifth, although the data were only collected until 2013, they still provide initial results regarding the risk of hearing impairment among septicemia survivors. One study showed lesser poor hearing in older severe sepsis survivors compared with general population in USA.[29] This pilot study was performed in a Chinese population, and the generalizability of our findings to other ethnic populations is limited. It needs more recent data and further global study to confirm our findings.

6. Conclusions

To the best of our knowledge, this is the first paper to show that septicemia is associated with an increased risk of long-term hearing loss in young and middle-aged humans. Our study suggests that clinicians should be aware of septicemia-related hearing impairment and use optimal prophylaxis strategies to decrease hearing impairment. We recommend determining the hearing of septicemia survivors to enable the earlier identification of hearing impairment. Early aggressive prevention and treatment of septicemia should be used to reduce long-term complications and improve quality of life.

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