Journal of Microbiology, Immunology and Infection 55 (2022) 474—481

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Risk of non-typhoidal *Salmonella* vascular infections is increased with degree of atherosclerosis and inflammation: A multicenter study in southern Taiwan

Ying-Wen Chen [a], Hung-Jen Tang [b,c], Yi-Shan Tsai [d,e], Nan-Yao Lee [a,e,f], Yuan-Pin Hung [e,g,h], Chien-Fang Huang [i], Ching-Chi Lee [a,j], Chia-Wen Li [a,e,f], Ming-Chi Li [a,e,f], Ling-Shan Syue [a,f], Shu-Li Su [k], Shu-Hao Hsu [e], Wen-Chien Ko [a,e,f,k,**], Po-Lin Chen [a,f,k,l,*]

[a] *Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[b] *Department of Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[c] *Department of Health and Nutrition, Chia Nan University of Pharmacy and Science, Tainan, Taiwan*
[d] *Department of Diagnostic Radiology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[e] *Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[f] *Infection Control Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[g] *Department of Internal Medicine, Tainan Hospital, Ministry of Health and Welfare, Tainan, Taiwan*
[h] *Graduate Institute of Clinical Medicine, National Health Research Institutes, Tainan, Taiwan*
[i] *Department of Internal Medicine, Kuo General Hospital, Tainan, Taiwan*
[j] *Clinical Medicine Research Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[k] *Diagnostic Microbiology and Antimicrobial Resistance Laboratory, National Cheng Kung University Hospital, Tainan, Taiwan*
[l] *Department of Microbiology and Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

Received 31 October 2020; received in revised form 29 March 2021; accepted 8 April 2021
Available online 21 June 2021

* Corresponding author. Center for Infection Control and Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Department of Microbiology and Immunology, College of Medicine, National Cheng Kung University, No. 138, Sheng Li Road, 70403, Tainan, Taiwan. Fax: 886-6-2752038.
** Corresponding author. Center for Infection Control and Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Department of Medicine, College of Medicine, National Cheng Kung University, No. 138, Sheng Li Road, 70403, Tainan, Taiwan. Fax: +886 6 2752038.
E-mail addresses: winston3415@gmail.com (W.-C. Ko), cplin@mail.ncku.edu.tw (P.-L. Chen).

https://doi.org/10.1016/j.jmii.2021.04.007

KEYWORDS
Non-typhoidal *Salmonella*;
Vascular infection;
Atherosclerosis;
NTSVI score;
IL-1β

Abstract *Background:* Atherosclerosis and vascular inflammatory response have been considered as risk factors for non-typhoidal *Salmonella* (NTS) vascular infection. The study aims to assess the risk of vascular infection by measuring atherosclerosis severity, NTS vascular infection (NTSVI) score, and serum levels of inflammatory markers in people with NTS bacteremia.
Methods: A prospective observational study was conducted in two medical centers and two regional hospitals. Adults aged ≥50 years with NTS bacteremia who underwent computed tomography (CT) scan for revealing vascular infections were enrolled. The degree of atherosclerosis was scaled by a calcium score determined by a CT scan. Serum concentrations of inflammatory biomarkers were determined in the patients enrolled in a medical center.
Results: Fourteen (20.3%) of 69 patients with NTS bacteremia had vascular infections. Calcium scores over the thoracic (12,540 *vs.* 3,261, $P = 0.0005$) and abdominal (9755 *vs.* 3,461, $P = 0.0006$) aorta of those with vascular infections were higher than those without vascular infection. All vascular infections were present in the high-risk group (NTSVI score ≥1), yielding a sensitivity of 100% and specificity of 30.9%. Among 17 low-risk patients (NTSVI score <1), none had vascular infections, resulting in a negative predictive value of 100%. Higher plasma concentrations of IL-1β were detected in the cases of vascular infection than those in the control group (23.6 *vs.* 1.06 pg/mL, $P = 0.001$).
Conclusion: Atherosclerosis of the aorta which is associated with a positive NTSVI score can predict the occurrence of vascular infections and serum IL-1β could be a biomarker for vascular infection in patients with NTS bacteremia.

Introduction

Non-typhoidal *Salmonella* (NTS) can cause vascular infections, or previously named mycotic aneurysm, and often be accompanied by high morbidity and mortality even managed by combined medical therapy and surgical intervention.[1] Mycotic aneurysm was reported to develop in 9%—40.6% of patients aged ≥50 years with NTS bacteremia.[2—4] Though the mechanism that *Salmonella* species infect vascular endothelium remains unclear, clinical evidence indicates that NTS leads to endothelial infection in the presence of atherosclerosis.[5] A scenario has been proposed that transient bacteremia from a gastrointestinal source results in bacterial seeding in damaged atherosclerotic intima or overlying thrombus at the aorta or its branch, and consequent vascular infection.[6]

Aortic calcification, an index of atherosclerosis, is a predictor for cardiovascular mortality, independent of other traditional risk factors.[7] Although atherosclerosis is correlated with NTS vascular infection, supporting evidence from clinical studies are lacking. In the present study, we utilized computed tomography (CT), which is a useful tool for quantifying aortic calcification by aorta calcium scanning,[8] and evaluated the association between the degree of atherosclerosis and risk of vascular infection in the presence of NTS infection.

There are no clinical findings or laboratory tests that are specific for the diagnosis of vascular infection.[9] Several approaches are developed in the field of identification of possible markers for abdominal aortic aneurysm (AAA), which are mainly based on the pathological features of medial destruction of the vascular wall, elastin fragmentation,[10] accumulation of macrophages and lymphocytes,[11] and higher concentrations of proteolytic enzymes and cytokines. These inflammatory changes are associated with excessive production of IL-1β,[12] IL-6,[13] metalloproteinases (MMPs),[14] and proteases.[15] MMP-2 and MMP-9, majorly produced by cells of mesenchymal lineage and macrophages, respectively,[14] are required to produce abdominal aortic aneurysms.[14,16] Cathepsin S, a potent mammalian elastase, is associated with the occurrence of abdominal aortic aneurysms.[15,17] However, their association with infected aneurysms has not been elucidated.

The NTS vascular infection (NTSVI) score was proposed to evaluate the risk of NTS vascular infection based on a retrospective study,[1] which included four variables associated with vascular infections, *i.e.*, male sex, hypertension, coronary arterial disease (CAD), and serogroup C1 infections.[1] Among the risk factors included in the scoring, hypertension and CAD are linked to atherosclerosis.[18,19] Adults with an NTSVI score >1 were at high risk of NTS vascular infection and should undergo a CT scan. In the present study, we conducted a prospective, multicenter study that enrolled patients with NTS bacteremia who underwent a CT scan to identify infection focus to validate the NTSVI score. In addition, the calcium score of the aorta on the CT scan as an indicator of aortic atherosclerosis was investigated. The serum samples were collected when NTS bacteremia was confirmed. The relationship between vascular infection and plasma concentrations of potential biomarkers, including IL-6, IL-1β, MMP-2, MMP-9, and cathepsin S was assessed.

Patients and methods

Study population

The prospective study was conducted in two medical centers and two regional hospitals in southern Taiwan and

ethically approved by the institutional review boards of the two medical centers (IRB approval numbers: A-ER-101-160 and 10,205—019). All the study methods were performed following the relevant guidelines and regulations. Patients aged ≥50 years with at least one blood sample positive for NTS identified by the clinical microbiology laboratories from 1 March 2013 and 31 August 2016 were included. Informed consents were obtained from all the participants. Their medical records were reviewed regarding demographic data, underlying diseases, clinical manifestations, and outcomes. For patients with recurrent NTS bacteremia, only the first episode was included as the indicated infection.

CT scan and calcium score measurement

CT scans of either thoracic or abdominal aorta or both were decided by the attending doctors within one month after the onset of NTS bacteremia. Patients were scanned by the SOMATOM Definition Flash scanner (Simens Healthcare, Forchheim, Germany). For calcium scanning, unenhanced CT was performed with CARE DOSE4D switch for reducing radiation dose in different conditions: 120 kV with effective 260 mAs; 0.5s rotation time; pitch 0.6; and 128-mm x 0.6-mm slice collimation for abdominal aorta; 120 kV, quality reference 100 mAs; 0.28s rotation time; pitch 2.0; and 128-mm x 0.6-mm slice collimation for the thoracic and abdominal aorta. Aorta calcium scoring was performed on reconstructed images by an imaging cardiologist who was masked to the patient's medical records. The total calcium score of the aorta was measured by the modified Agatston Score using a non-ECG-gated chest or abdomen CT[20,21] and calculated by commercially available calcium scoring software (Aquarius iNtuition software Version 4.4.7, TeraRecon, Inc, San. Mateo, CA, USA). In brief, the modified Agatston Score was calculated by taking the area of connected pixels in an area identified as a 'lesion' that were all above a certain threshold and multiplying this area by a scalar which was related to the peak CT number in the lesion in question. A modification of the Agatston Score was applied with a threshold of 130 HU, and the scalar given to the highest attenuation value for each lesion were as followed: 1 = less than 200 HU, 2 = 200 to 299 HU, 3 = 300 to 399 HU, and 4 = 400 or more HU. The calculation of the scalar is applied slice-by-slice, and the sum of all these slice-based calculations is taken to generate the total score for a 3D lesion.

NTSVI score

To assess the risk of vascular infection in patients with NTS bacteremia, the presence of any of four risk factors (male sex, hypertension, coronary arterial disease, and serogroup C1 infection) was each assigned as +1 point; malignancy and immunosuppressive therapy −1 point, and the sum was the NTVSI score.[1] Based on our published data,[1] we assumed the incidence of vascular infection of 45% in the high-risk group (*i.e.*, NTSVI score >1) and 6% in the low-risk group (NTSVI score ≤1). A sample size of 13 patients in the low-risk group and 36 in the high-risk group at the ration of 1:2.6 would provide 80% power to detect a significant difference of vascular infections between two groups at an alpha level of 0.05.

Definitions of underlying diseases

The infection foci of bacteremia were determined clinically by the presence of localized active infectious or inflammatory lesions coincident with NTS bacteremia, or the isolation of an identical organism from clinical specimens other than blood and feces. Otherwise, those were regarded as having primary bacteremia.

Measurement of plasma concentrations of IL-6, IL-1β, MMP, and *cathepsin S*

Blood was obtained from venipuncture or central catheter line in the cases of NTS bacteremia and collected in EDTA tubes, and plasma was stored at −80 °C until use. The plasma levels of IL-6, IL-1β, MMP-2, MMP-9 (Invitrogen, Camarillo, California), and cathepsin S (Thermo Fisher Scientific, MA, USA), were determined by commercially available ELISA kits, according to the manufacturers' instructions.

Statistical analysis

Data analyses were conducted by the Statistical Package for the Social Science for Windows (SPSSWIN; SPSS, Chicago, IL, USA), Version 17.0. Continuous variables were expressed as means ± standard deviations (SDs) and were compared by the Student's t or Mann—Whitney tests. Categorical variables, expressed as numbers and percentages, were compared by the chi-squared test or Fisher's exact test. In addition, we tested the dose—gradient relationship between the calculated scores and the observed rates of vascular infections based on the Cochran-Armitage trending statistic test.

Results

Clinical characteristics of patients with NTS bacteremia

During the study period, 76 adults (≥50 years) with NTS bacteremia were eligible for the study. Among them, seven without CT scans were excluded, and thus a total of 69 patients were included for further analysis. The serogroups among 69 NTS isolates included group B (15, 21.7%), C1 (2, 2.9%), C2 (3, 4.3%), D (48, 69.6%) and undefined (1, 1.4%).

The mean age of 69 enrolled patients was 69.5 years with a male preponderance (50, 72.5%) (Table 1). Most patients had at least one underlying medical illness, including hypertension (50, 72.5%), dyslipidemia (25, 36.2%), coronary arterial disease (14, 20.3%), cerebrovascular disease (6, 8.7%), congestive heart failure (5, 7.2%), and peripheral arterial occlusive disease (1, 1.4%). Thirty (43.5%) had diabetes mellitus, 34 (49.3%) kidney disease, 20 (29.0%) malignancy, 9 (13.0) chronic lung disease, 6 (8.7%) cirrhosis, 5 (7.2%) HIV infection, and 1 (1.4%) connective tissue disease. Nineteen (27.5%) received immunosuppressive therapy, including prednisolone (9, 13%), chemotherapy (7, 10.1%), and immunomodulating agents for autoimmune diseases or

Table 1 Clinical characteristic of 69 adults aged ≥50 years with non-typhoidal *Salmonella* (NTS) bacteremia.

Characteristics	Case, n (%)
Age, years (mean ± standard deviation)	69.5 ± 11.1
Gender, male	50 (72.5)
Serogroups of NTS isolates	
B	15 (21.7)
C1	2 (2.9)
C2	3 (4.3)
D	48 (69.6)
Unidentified	1 (1.4)
Infection sites	
Primary bacteremia	48 (69.6)
Vascular infection	14 (20.3)
Intra-abdominal infection	2 (2.9)
Skin and soft tissue infection	2 (2.9)
Septic arthritis	2 (2.9)
Osteomyelitis	1 (1.4)
Pneumonia	1 (1.4)
Pericardial abscess	1 (1.4)
Underlying diseases	
Hypertension	50 (72.5)
Kidney disease	34 (49.3)
Diabetes mellitus	30 (43.5)
Dyslipidemia	25 (36.2)
Malignancy	21 (30.4)
Immunosuppressive therapy	19 (27.5)
Coronary arterial disease	13 (18.8)
Chronic lung disease	9 (13.0)
Cerebral vascular disease	6 (8.7)
Liver cirrhosis	6 (8.7)
HIV infection	5 (7.2)
Congestive heart failure	5 (7.2)
Peripheral arterial occlusive disease	1 (1.4)
Connective tissue disease	1 (1.4)
In-hospital mortality	5 (7.2)

solid-organ transplant (3, 4.3%). The in-hospital mortality rate was 7.2% (5 patients).

Overall, 14 (20.3%) patients had vascular infection and the in-hospital mortality rate was 15.4% (2 of 13). Of the 14 patients with vascular infections, ten were infection over abdominal aorta, two with the involvement of thoracic aorta, one with infective endocarditis, and one with extension from thoracic to the abdominal aorta. Three patients underwent vascular surgery and one of them died. Other infection sites included skin and soft tissue infection (2, 2.9%), septic arthritis (2, 2.9%), osteomyelitis (1, 1.4%), intra-abdominal infection (2, 2.9%), pericardial abscess (1, 1.4%), and pneumonia (1, 1.4%). Fourty-eight (69.6%) patients without identified focus were regarded as having primary bacteremia.

Association between calcium scores of aorta and risk of NTS vascular infections

Among the 69 participants with NTS bacteremia, 37 received thoracic and abdominal scans to survey the presence of vascular infection, the other 9 with thoracic scan only, and the remaining 23 with only abdominal scan. Calcium scores of the thoracic and abdominal aorta were measured in 46 and 60 patients, respectively. The patients with vascular infection had higher calcium scores, indicating the severity of atherosclerosis, over thoracic aorta (12,540 *vs.* 3,261, $P = 0.0005$) and abdominal aorta (9755 *vs.* 3,461, $P = 0.0006$), when compared with their counterparts without vascular infection (Fig. 1). Patients with an NTSVI score ≥2 had higher calcium scores over thoracic aorta (8862 *vs.* 2,878, $P = 0.012$) and abdominal aorta (7310 *vs.* 3,386, $P = 0.014$) than those with an NTSVI score <2.

NTSVI score and vascular infection

NTSVI scores and the corresponding prevalence of vascular infection were summarized in Fig. 2. None of 17 patients with an NTSVI score of −1 and 0 had vascular infection. The corresponding figures for those with a score of 1, 2, or 3 were 13.8% (4 of 29), 38.9% (7 of 18), and 60.0% (3 of 5). No patients had a score of 4 in the present study. The Cochran-Armitage trending test demonstrated that the prevalence of vascular infection increased with the NTSVI score ($P = 0.001$). The risks of vascular infection in the corresponding NTSVI scores in the present study as well as our previous research were shown in Fig. 2. The risk of patients in the current cohort with an NTSVI score of 1, 2, or 3 was comparable to that observed in our previous study (10.6%, 39.4%, and 55.2%).[1]

We validated the NTSVI score during the period with a low prevalence of serogroup C1 NTS infection. A score <1 was found in 17 (24.6%) of 69 patients (Table 2), and none had vascular infection on CT scans, resulting in a negative predictive value of 100%. All 14 patients with vascular infection had an NTSVI score ≥1, yielding a sensitivity of 100% and specificity of 30.9%. Among 23 patients with a higher score (≥2), 43.5%[10] had vascular infection and 91.3% (*i.e.*, negative predictive value) of those with score <2 did not have such a complication. The sensitivity and specificity of vascular infection with the criterion of an NTSVI score ≥2 was 71.4% and 76.4%, respectively.

Plasma concentrations of inflammation markers

A total of 45 stored plasma samples were available for test and analysis. Plasma concentrations of IL-1β, IL-6, MMP-2, MMP-9, and cathepsin S were determined in 10 patients with vascular infection and 35 without vascular infection (the controls). Higher plasma concentrations of IL-1β were detected in patients with vascular infection than the controls (23.6 *vs.* 1.06 pg/mL, $P = 0.001$). In contrast, circulating IL-6, MMP-2, MMP-9, and cathepsin S levels were not associated with the vascular infection in adults with NTS bacteremia (Fig. 3).

Discussion

Our clinical and image data support NTS vascular infection is associated with atherosclerosis of the aorta. An increase of serum IL-1β level, a pro-inflammatory marker, is associated with NTS vascular infection. An increase of the NTSVI score which is associated with atherosclerosis can help to

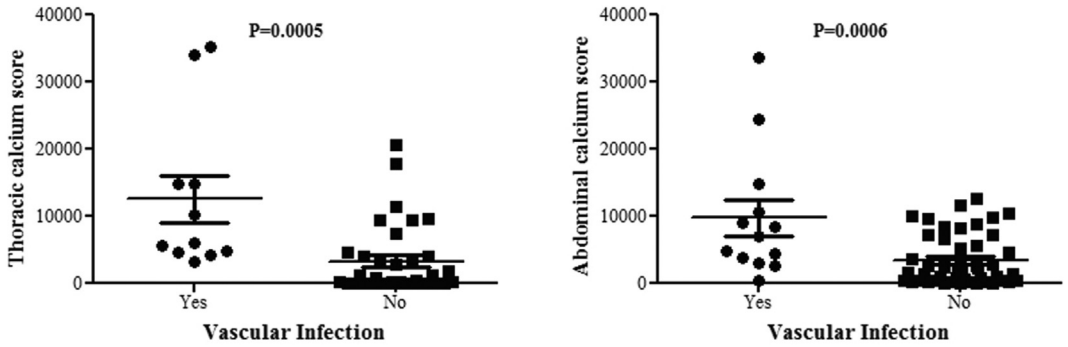

Figure 1. Comparison of calcium scores of the aorta measured by computed tomography scan between adults with non-typhoidal *Salmonella* bacteremia with and without vascular infection. (A) Calcium scores of the thoracic aorta in those with (n = 11) and without (n = 35) vascular infection and control. (B) Calcium scores of the abdominal aorta in those with (n = 13) and without (n = 47) vascular infection and control.

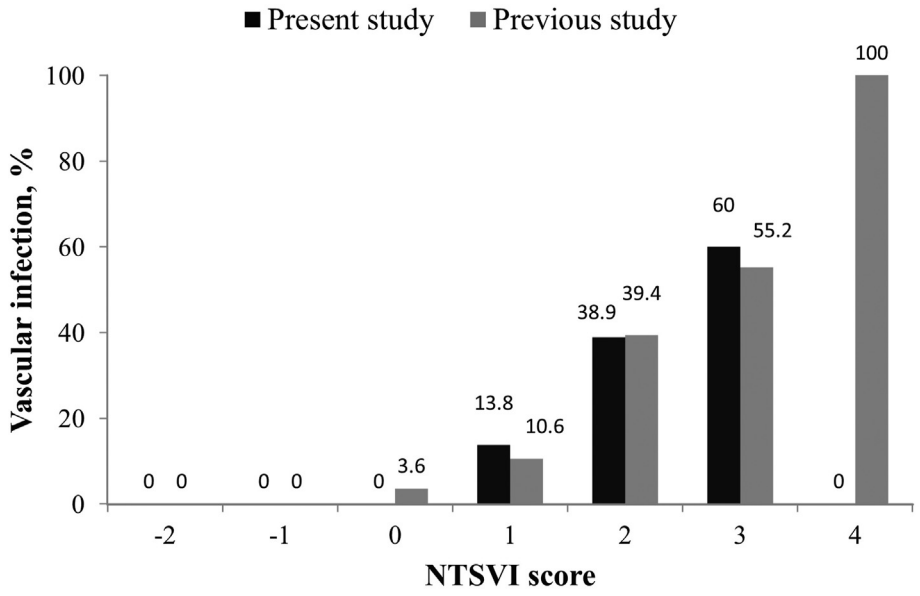

Figure 2. The proportions of vascular infection among adults aged at least 50 years with non-typhoidal *Salmonella* (NTS) bacteremia with different NTSVI scores in the present and previous study [1]. * "0" indicated no case in the score −2 and 4 rather than 0% of vascular infection.

Table 2 Sensitivity, specificity, and predictive values of the NTSVI score in prediction of vascular infection in adults with non-typhoidal *Salmonella* bacteremia.

NTSVI score	Vascular infection		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	Yes, n = 13	No, n = 56				
<2	4	42	71.4	76.4	43.5	91.3
≥2	9	14				
<1	0	17	100	30.9	26.9	100
≥1	14	38				

NTSVI = non-typhoidal *Salmonella* vascular infection.

predict the occurrence of NTS vascular infection. We validated the clinical utility of the NTSVI score, which can estimate the risk of vascular infection for adults aged ≥50 years with NTS bacteremia.

Current evidence suggests aortic atherosclerosis is a predisposing factor for NTS vascular superimposed infections,[5,22] and calcification is common in vascular atherosclerotic lesions.[23] Aortic calcification in plain

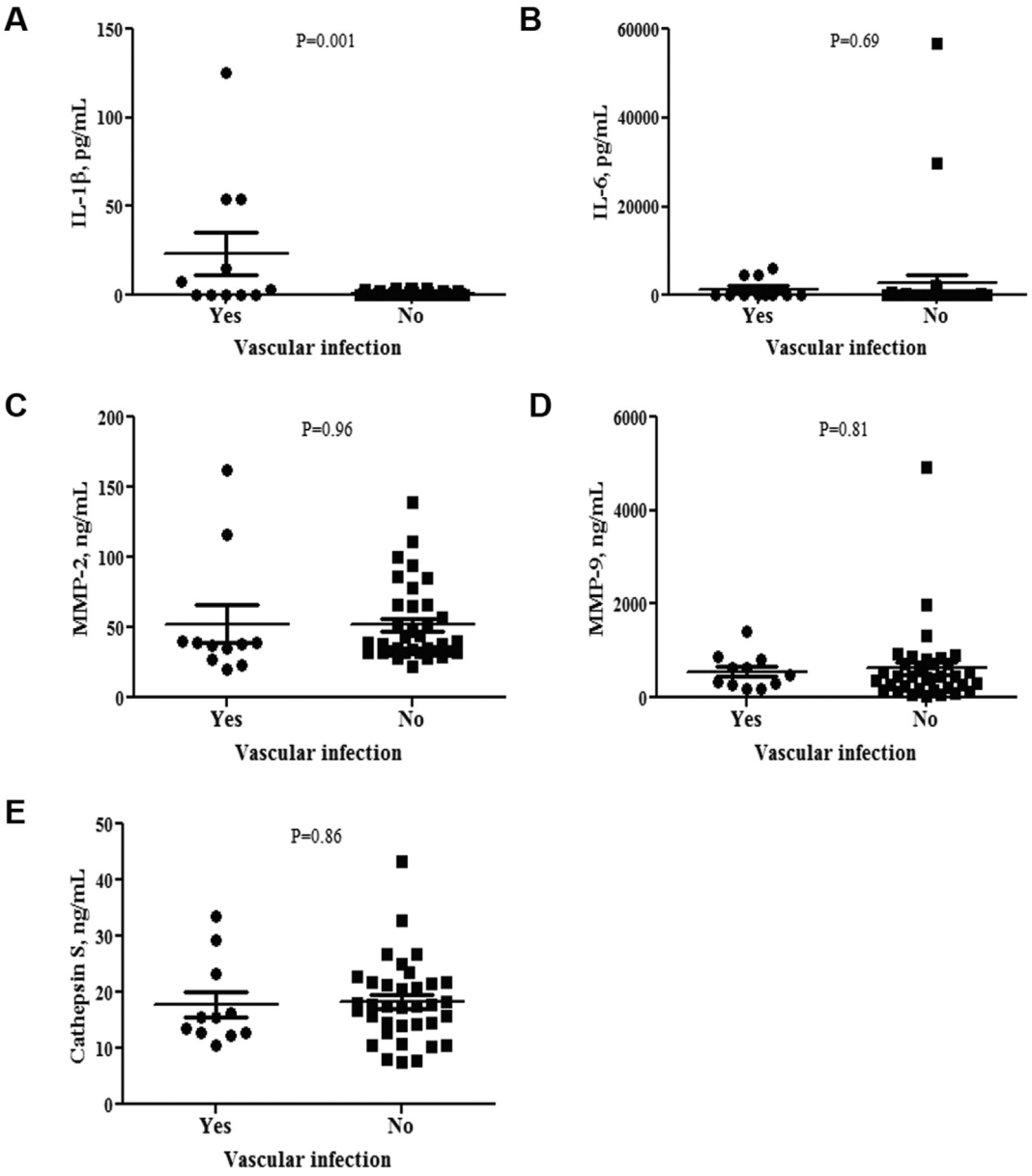

Figure 3. Comparisons of plasma concentrations of five biomarkers, including IL-1β (A), IL-6 (B), MMP -2 (C), MMP-9 (D), and cathepsin S (E), between 10 adults with vascular infection and 35 without vascular infection.

radiographs[24,25] and spiral CT[8] indicated an increased risk of cardiovascular and cerebrovascular events. To our knowledge, the linkage of vascular calcification and NTS infection was rarely mentioned. In the TTP-NTSVI score, male sex, peripheral arterial occlusive disease (PAOD), CAD, and time to positivity (TTP) were independent predictors for VI.[26] Aortic artery calcium was shown to be associated with PAOD according to the Multi-Ethnic Study of Atherosclerosis study.[7] Our results showed NTS vascular infection was associated with a high calcium score of the aorta, indicative of severe atherosclerosis. In addition, the severity of atherosclerosis is significantly higher in patients with an NTSVI score $\geq$2, *i.e.*, at extremely high risk of vascular infection.

Another finding that a significant difference in plasma levels of IL-1β was observed between those with and without infected aneurysm is of clinical significance. In mice models, blockade of IL-1β suppresses abdominal aortic aneurysm formation,[27,28] suggesting that inhibition of IL-1β may be a therapeutic strategy in high-risk patients. *Salmonella* infection is recognized by the innate immune system via Toll-like receptors (TLRs) and other pattern-recognition receptors (PRRs) alike, leading to the activation of nuclear factor-κB (NF-κB) that induces the transcription of pro-IL-1β. Inflammasomes are assembled in the macrophage cytosol upon sensing extracellular and intracellular *Salmonella* pathogen-associated molecular patterns (PAMPs), and serve as platforms for the activation of the caspase-1 protease, which in turns triggers the maturation and secretion of the IL-1β and IL-18, and initiates pyroptosis of macrophages. IL-1β plays a pivotal role in controlling *Salmonella* infection by recruiting neutrophils.[29] The nucleotide-binding

oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome was suggested to be a key driver of the development and progression of atherosclerosis.[30] Our results support the hypothesis that *Salmonella* vascular infection induces the release of IL-1β into systemic circulation through local macrophage activation and produces a significantly higher level of serum IL-1β than those without vascular infections. Elevated serum IL-1β level is a potential biomarker of NTS vascular infection, but its clinical use needs more supporting evidence.

Insignificant changes of other circulating biomarkers between the groups of vascular infection and control can be partially explained by the fact that the expression of MMP[31] or IL-6[32] increased in the presence of Gram-negative bacteria sepsis. MMP or cathepsin S, a component of the extracellular matrix, has been associated with tumor metastasis,[33] which is a common underlying disease in our study patients.

Our results showed that the NTSVI score was associated with both NTS vascular infection and atherosclerotic degree of the aorta. Patients with NTS bacteremia could be dichotomized by the NTSVI score into high-risk (NTSVI score $\geq$1) and low-risk (NTSVI score $<$1) groups of vascular infection. The negative predictive value and sensitivity of the NTSVI score were both 100%. With the aging of the general population and the increasing prevalence of atherosclerosis, the population susceptible to NTS vascular infections is expanding. Because the mortality rate related to delayed diagnosis of NTS vascular infection is high, a comprehensive CT scan is recommended for adults at high risk of NTS vascular infection, *i.e.*, adults aged $\geq$50 years with an NTSVI score $\geq$1 or persons with severe atherosclerosis, to facilitate early interventions of vascular infections and avoid unfavorable outcomes.

In the study, there was a rarity of patients scored with point of serogroup C1 NTS infection. Serogroup C1 NTS infection has been one of the important risk factors associated with vascular infection in the NTSVI score when *S.* Choleraesuis (serogroup C1) was prevalent in the community in Taiwan. In our previous study, serogroup C1 NTS infection contributed to 18.2% of the cases with NTS bacteremia, in contrast to only 6.9% in the current series. The trend of incidence for serogroup C1 NTS infection is decreased[34,35] after the government took several actions to improve the quality of pig husbandry.[34] Despite the decline of prevalent serogroup C1 NTS infection in Taiwan, the predictive power of NTSVI score for vascular infections caused predominantly by serogroups B (esp. *S.* Typhimurium) and D (esp. *S.* Enteritidis), the main causative NTS serogroups in both Taiwan and the world,[35,36] remained constant.

Owing to the rarity of mycotic aneurysms, the number of patients was relatively small, which is a major limitation in this study. A multi-center study that enrolls more participants to validate the utility of NTSVI score in diagnosing NTSVI is warranted in the future.

Conclusion

An aggressive CT study to screen the presence of vascular infection is necessary for elderly people with NTS bacteremia, especially those with risk factors associated with atherosclerosis. Clinical NTSVI score is easy to use and can predict the risk of vascular infections, which are associated with aortic calcium scores. In addition, serum IL-1β is a potential biomarker in predicting vascular infection but needs further research.

Funding

This study was supported by National Cheng Kung University Hospital (NCKUH-109020001), Ministry of Science and Technology (MOST 108-2628-B-006-012), and Ministry of Health and Welfare (MOHW106-TDU-B-211-113003), Taiwan.

Declaration of competing interest

All authors reported no conflicts of interest.

Acknowledgments

We are grateful to Shu-Li Sue from the Diagnostic Microbiology and Antimicrobial Resistance Laboratory, National Cheng Kung University Hospital for providing technical services of analyzing the levels of inflammation markers in serum samples.

References

1. Chen PL, Lee CC, Li CY, Chang CM, Lee HC, Lee NY, et al. A simple scoring algorithm predicting vascular infections in adults with nontyphoid Salmonella bacteremia. *Clin Infect Dis* 2012;**55**:194–200.
2. Nielsen H, Gradel KO, Schønheyder HC. High incidence of intravascular focus in nontyphoid Salmonella bacteremia in the age group above 50 years: a population-based study. *APMIS* 2006;**114**:641–5.
3. Benenson S, Raveh D, Schlesinger Y, Alberton J, Rudensky B, Hadas-Halpern I, et al. The risk of vascular infection in adult patients with nontyphi Salmonella bacteremia. *Am J Med* 2001; **110**:60–3.
4. Hsu RB, Tsay YG, Chen RJ, Chu SH. Risk factors for primary bacteremia and endovascular infection in patients without acquired immunodeficiency syndrome who have nontyphoid salmonellosis. *Clin Infect Dis* 2003;**36**:829–34.
5. Hsu RB, Lin FY. Risk factors for bacteraemia and endovascular infection due to non-typhoid salmonella: a reappraisal. *QJM* 2005;**98**:821–7.
6. Cohen JI, Bartlett JA, Corey GR. Extra-intestinal manifestations of salmonella infections. *Medicine (Baltim)* 1987;**66**: 349–88.
7. Criqui MH, Aboyans V, Allison MA, Denenberg JO, Forbang N, McDermott MM, et al. Peripheral artery disease and aortic disease. *Glob Heart* 2016;**11**:313–26.
8. Eisen A, Tenenbaum A, Koren-Morag N, Tanne D, Shemesh J, Imazio M, et al. Calcification of the thoracic aorta as detected by spiral computed tomography among stable angina pectoris patients: association with cardiovascular events and death. *Circulation* 2008;**118**:1328–34.
9. Wilson WR, Bower TC, Creager MA, Amin-Hanjani S, O'Gara PT, Lockhart PB, et al. Vascular graft infections, mycotic aneurysms, and endovascular infections: a scientific statement from the American heart association. *Circulation* 2016;**134**:e412–60.

10. Freestone T, Turner RJ, Coady A, Higman DJ, Greenhalgh RM, Powell JT. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic aneurysm. *Arterioscler Thromb Vasc Biol* 1995;**15**:1145—51.
11. Shimizu K, Mitchell RN, Libby P. Inflammation and cellular immune responses in abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol* 2006;**26**:987—94.
12. Johnston WF, Salmon M, Su G, Lu G, Stone ML, Zhao Y, et al. Genetic and pharmacologic disruption of interleukin-1β signaling inhibits experimental aortic aneurysm formation. *Arterioscler Thromb Vasc Biol* 2013;**33**:294—304.
13. Dawson J, Cockerill GW, Choke E, Belli A-M, Loftus I, Thompson MM. Aortic aneurysms secrete interleukin-6 into the circulation. *J Vasc Surg* 2007;**45**:350—6.
14. Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, Baxter BT. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. *J Clin Invest* 2002;**110**:625—32.
15. Lv BJ, Lindholt JS, Cheng X, Wang J, Shi GP. Plasma cathepsin S and cystatin C levels and risk of abdominal aortic aneurysm: a randomized population-based study. *PloS One* 2012;**7**:e41813.
16. Dilmé J-F, Bellmunt S, Camacho M, Solà-Villà D, Romero J-M, Escudero J-R, et al. Influence of cardiovascular risk factors on levels of matrix metalloproteinases 2 and 9 in human abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2014;**48**:374—81.
17. Qin Y, Cao X, Guo J, Zhang Y, Pan L, Zhang H, et al. Deficiency of cathepsin S attenuates angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein E-deficient mice. *Cardiovasc Res* 2012;**96**:401—10.
18. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, O'Fallon WM, et al. Independent association of high blood pressure and aortic atherosclerosis: a population-based study. *Circulation* 2000;**102**:2087—93.
19. Gu X, He Y, Li Z, Kontos MC, Paulsen WHJ, Arrowood JA, et al. Relation between the incidence, location, and extent of thoracic aortic atherosclerosis detected by transesophageal echocardiography and the extent of coronary artery disease by angiography. *Am J Cardiol* 2011;**107**:175—8.
20. Budoff MJ, Nasir K, Kinney GL, Hokanson JE, Barr RG, Steiner R, et al. Coronary artery and thoracic calcium on noncontrast thoracic CT scans: comparison of ungated and gated examinations in patients from the COPD Gene cohort. *J Cardiovasc Comput Tomogr* 2011;**5**:113—8.
21. Azour L, Kadoch MA, Ward TJ, Eber CD, Jacobi AH. Estimation of cardiovascular risk on routine chest CT: ordinal coronary artery calcium scoring as an accurate predictor of Agatston score ranges. *J Cardiovasc Comput Tomogr* 2017;**11**:8—15.
22. Hibbert B, Costiniuk C, Hibbert R, Joseph P, Alanazi H, Simard T, et al. Cardiovascular complications of Salmonella enteritidis infection. *Can J Cardiol* 2010;**26**:323—5.
23. Doherty TM, Asotra K, Fitzpatrick LA, Qiao J-H, Wilkin DJ, Detrano RC, et al. Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. *Proc Natl Acad Sci U S A* 2003;**100**:11201—6.
24. Wilson PWF, Kauppila LI, O'Donnell CJ, Kiel DP, Hannan M, Polak JM, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation* 2001;**103**:1529—34.
25. Iribarren C, Sidney S, Sternfeld B, Browner WS. Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. *J Am Med Assoc* 2000;**283**:2810—5.
26. Lin JJ, Weng TH, Tseng WP, Chen SY, Fu CM, Lin HW, et al. Utility of a blood culture time to positivity-incorporated scoring model in predicting vascular infections in adults with nontyphoid Salmonella bacteremia. *J Microbiol Immunol Infect* 2018;**51**:652—8.
27. Da Ros F, Carnevale R, Cifelli G, Bizzotto D, Casaburo M, Perrotta M, et al. Targeting interleukin-1β protects from aortic aneurysms induced by disrupted transforming growth factor β signaling. *Immunity* 2017;**47**:959—73. e9.
28. Isoda K, Akita K, Kitamura K, Sato-Okabayashi Y, Kadoguchi T, Isobe S, et al. Inhibition of interleukin-1 suppresses angiotensin II-induced aortic inflammation and aneurysm formation. *Int J Cardiol* 2018;**270**:221—7.
29. Bierschenk D, Boucher D, Schroder K. Salmonella-induced inflammasome activation in humans. *Mol Immunol* 2017;**86**:38—43.
30. Grebe A, Hoss F, Latz E. NLRP3 inflammasome and the IL-1 pathway in atherosclerosis. *Circ Res* 2018;**122**:1722—40.
31. Vanlaere I, Libert C. Matrix metalloproteinases as drug targets in infections caused by gram-negative bacteria and in septic shock. *Clin Microbiol Rev* 2009;**22**:224—39.
32. Otto G, Braconier J, Andreasson A, Svanborg C. Interleukin-6 and disease severity in patients with bacteremic and non-bacteremic febrile urinary tract infection. *J Infect Dis* 1999;**179**:172—9.
33. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. *FEBS J* 2011;**278**:16—27.
34. Su LH, Wu TL, Chiu CH. Decline of Salmonella enterica serotype choleraesuis infections, taiwan. *Emerg Infect Dis* 2014;**20**:715—6.
35. Liao CH, Ko WC, Hsueh PR. Decline in ciprofloxacin-resistant Salmonella enterica serovar choleraesuis in taiwan, 2001-2011. *Clin Infect Dis* 2013;**56**:1357—9.
36. Ao TT, Feasey NA, Gordon MA, Keddy KH, Angulo FJ, Crump JA. Global burden of invasive nontyphoidal Salmonella disease, 2010. *Emerg Infect Dis* 2015;**21**:941—9.