A Simple Scoring Algorithm Predicting Vascular Infections in Adults With Nontyphoid Salmonella Bacteremia

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Background. Nontyphoid Salmonella (NTS) can cause fatal vascular infections. This study aims to establish a predictive scoring algorithm to identify adults aged ≥50 years with NTS bacteremia who are at risk for vascular infections.

Methods. There were 358 adults aged ≥50 years with NTS bacteremia at 2 medical centers in southern Taiwan included in this study. Multiple logistic regression was used to identify risk factors for imaging-documented vascular infections. The prediction capability of the proposed scoring algorithm was indicated by a receiver operating characteristic curve and measures of sensitivity and specificity.

Results. Sixty patients (16.8%) with vascular infections were noted. The 4 risk factors significantly associated with vascular infections—male sex, hypertension, coronary arterial disease, and serogroup C1 infections—were each assigned +1 point to form the NTS vascular infection (NTSVI) score. In contrast, malignancy and immuno-suppressive therapy were each assigned −1 point, owing to their negative associations with vascular infections. Based on the proposed NTSVI scoring, the prevalence of vascular infections in patients with ≤0, 1, 2, 3, or 4 points was 2.2% (3 of 138 patients), 10.6% (13 of 123 patients), 39.4% (26 of 66 patients), 55.2% (16 of 29 patients), and 100% (2 of 2 patients), respectively (P<.0001). The scoring algorithm shows an area under the curve of 0.83 (95% confidence interval, .78–.89; P<.0001). A cutoff value of +1 represents a high sensitivity (95.0%) and an acceptable specificity (45.3%).

Conclusions. This simple scoring algorithm can be used to identify patients with NTS bacteremia with a high risk of vascular infections. The cost-effectiveness of this algorithm should be further studied.

Nontyphoid Salmonella (NTS) isolates are among the leading bacterial pathogens that cause food-borne infections commonly seen in both developed and developing countries [1]. Although most patients with NTS infections have self-limited gastroenteritis, some patients develop invasive infections, such as bacteremia and extraintestinal focal infections [2], often accompanied by vascular infections with high morbidity and mortality [3]. The overall mortality rate of Salmonella arterial infections is extremely high, with a rate >90% for patients treated only medically and approximately 40% for those treated with combined surgical and medical therapies [4, 5]. The grave prognosis for patients with NTS vascular infections emphasizes the importance of early diagnosis, because surgical interventions in conjunction with prolonged antimicrobial therapy can substantially improve outcomes for those patients [5].

Several publications from Taiwan have shown that the incidences of mycotic aneurysms in patients with
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NTS bacteremia aged >65 years and >50 years are 35% and 40.6%, respectively [6, 7]. In Western countries, the incidence of endovascular infections caused by NTS in patients >50 years old is 9%–25% [8–10]. Owing to the high incidence of endovascular infection, physicians will perform extensive imaging studies in patients with NTS bacteremia. The risk factors for vascular infections in adults include age >50 years and underlying atherosclerosis [9, 10]. Therefore, it has been suggested that patients >50 years old with NTS bacteremia should undergo clinical assessments such as computed tomography (CT) to rule out concurrent vascular infections [8]. A diagnosis of endovascular infection can be confirmed by CT or magnetic resonance (MR) imaging [11, 12]. In addition, if the endovascular infections are detected earlier, a favorable outcome may be obtained if there is adequate surgical intervention before aneurysm rupture [13].

Information on the cost-effectiveness of performing universal imaging studies to rule out NTS vascular infections for every patient >50 years of age has not been available. Previous studies provided evidence that patients with features of immunodeficiency, such as systemic lupus erythematosus, human immunodeficiency virus infection, and malignancy, have lesser endovascular infections when NTS bacteremia occurs [7, 14, 15]. Although the true mechanism for this phenomenon is not clear, it may suggest that universal radiological screening for endovascular infections in elderly patients with NTS bacteremia is not necessary. In recognizing the importance of early identification of patients with vascular infections, we aimed to develop a simple scoring algorithm that can be easily, inexpensively, and accurately applied in clinical settings to identify patients at greater risk for vascular infections.

MATERIALS AND METHODS

Patients
In our previous study, all vascular infections were noted in those ≥50 years old [16, 17], but in this study, we targeted patients ≥50 years of age with NTS bacteremia. The analysis includes patients who were admitted to 2 tertiary care hospitals, hospital A (1994–2009) and B (2004–2009) located in the city of Tainan in southern Taiwan, were included in this analysis. Combined, the two medical centers have >2000 beds and serve nearly 2 million inhabitants in the Tainan metropolitan area. The study was ethically approved by the institutional review boards of the 2 hospitals (IRB approval numbers ER-99-093 and 10008-004, respectively).

Measurements
The clinical diagnosis of vascular infections was based on the presence of NTS bacteremia coexisting with saccular aneurysm, adjacent mass, indistinct irregular arterial wall, stranding, and/or fluid over the aorta or its branches in thoracic, abdominal and pelvic cavity by CT or MR imaging with or without contrast medium [11, 12]. The serogroups of Salmonella blood isolates were determined by the standard method described elsewhere [16]. Chronic lung diseases included chronic obstructive pulmonary disease and asthma. Liver cirrhosis was diagnosed by means of abdominal ultrasonography and clinical follow-up findings [18]. Malignancy was defined as either an active malignant solid tumor or hematological disease with or without antimalignancy therapy.

Immunosuppressive therapy included the receipt of corticosteroid (ie, prednisolone ≥10 mg/d or an equivalent dosage), chemotherapy for malignancy, or immunosuppressive agents for organ transplantation within 2 weeks before the onset of NTS bacteremia.

Statistical Analysis
The statistical analysis was performed with Statistical Package for Social Sciences software (SPSS; version 17.0). Categorical variables, expressed as numbers and percentages, were compared by the χ2 method or Fisher’s exact test. Stepwise logistic regression was used for the multivariate analysis. Variables with a P value ≤.1 were selected for analysis with the model. A multiple logistic regression model was employed to estimate ORs and their corresponding 95% CI (CIs) for vascular infections in relation to sex, hypertension, coronary arterial disease, serogroup C1 NTS infection, immunosuppressive therapy, and malignancy. We converted the exponential coefficient from the multiple logistic regression to indicate the weight for each significant prediction variable and then counted the weight value for each patient as the original model (model 1). We further created a simpler model (model 2), which was constructed with equal weights for all significant predictive variables. In model 2, +1 point was assigned for each of 4 variables that have a significantly positive association with vascular infections: hypertension, male sex, coronary arterial disease, and serogroup C1 NTS infection; −1 point was assigned for each of 2 variables that have a significantly negative association with vascular infections: malignancy and immunosuppressive therapy. We explored the values of the point scores to predict the presence of vascular infections via a receiver operating characteristic (ROC) curve. Finally, we calculated the prediction capability of the 2 scoring algorithms and compared them with each other based on the area under the ROC curve.

To assess the capability of the score models in differentiating between patients at higher risk and those with lower risk for vascular infections, we calculated the C statistic proposed by Harrell and colleagues [19] to measure the discriminative power of the logistic equation. It varied from 0.5 (ie, the model’s prediction is no better than chance) to 1.0 (ie, the
The characteristics of 358 patients aged >50 years are presented in Table 1. Male predominance was more obvious in patients with NTS vascular infections (76.7% vs 56.4%; \( P = .003 \)). The underlying diseases associated with vascular infection included hypertension (\( P < .0001 \)), coronary arterial disease (\( P < .0001 \)), diabetes mellitus (\( P = .04 \)), and chronic lung disease (\( P = .08 \)). In addition, patients with vascular infections were more often infected by serogroup C1 NTS (36.7% vs 14.4%; \( P < .0001 \)). In contrast, patients with vascular infections were less likely to have liver cirrhosis (\( P = .03 \)), malignancy (\( P < .0001 \)), or immunosuppressive therapy (\( P = .002 \)).

Multiple logistic regression showed that the risk of vascular infection was significantly associated with a number of independent factors including hypertension (adjusted odds ratio [aOR] 6.09; 95% confidence interval [CI] 2.93–12.66; \( P < .0001 \)), male sex (aOR, 4.13; 95% CI, 1.95–8.72; \( P < .0001 \)), serogroup C1 NTS infection (aOR, 4.03; 95% CI, 1.91–8.51; \( P < .0001 \)), coronary arterial disease (aOR, 2.50; 95% CI, 1.14–5.49; \( P = .02 \)), malignancy (aOR, 0.38; 95% CI, .15–1.00; \( P = .05 \)), and immunosuppressive therapy (aOR, 0.20; 95% CI, .05–.90; \( P = .04 \)).
The NTS vascular infection (NTSVI) scoring algorithm was then developed based on the above significant predictors for vascular infections. Two scoring algorithms were developed, referring to models 1 and 2. For model 1, +6 points were assigned for hypertension, +4 for male sex, +4 for serogroup C1 NTS infection, +3 for coronary arterial disease, −3 for malignant disease and −5 for immunosuppressive therapy (Table 2), resulting in a maximum score of +17 points and a minimum of −8 points. The ROC curve has a good ability to help predict vascular infections for model 1, with an area under the curve of 0.85 (95% CI, .80–.90; P < .0001).

Furthermore, to simplify the NTSVI scoring algorithms, model 2 was constructed with equal weight for all significant predictive variables. The score in model 2 included +1 point for each of the 4 variables positively associated with vascular infections (hypertension, male sex, coronary arterial disease, serogroup C1 NTS infection) and −1 point for each of the 2 variables negatively associated with such infections (malignancy and immunosuppressive therapy). Model 2 had a maximum of +4 points and a minimum of −2 points. Its prediction capability (area under the ROC curve, 0.83; 95% CI, .78–.89; P < .0001) was similar to that of model 1 (see Figure 2).

Given the comparable prediction capability for both scoring algorithms, we further used the simpler one (ie, model 2) to assess the risk of vascular infections in the study patients. Among the patients with a NTSVI score of ≤0, the prevalence of vascular infections was only 2.2% (3 of 138). The corresponding figures for those with 1, 2, 3, or 4 points were 10.6% (13 of 123), 39.4% (26 of 66), 55.2% (16 of 29), or 100% (2 of 2), respectively. The Cochran-Armitage trending statistic test demonstrated that model 2 had an excellent calibration across low- to high-risk deciles in the study population (P < .0001). In addition, the C statistic values were the same in 2 models (C statistic, 0.832), which indicated that the models had comparable predicting power to estimate the odds of vascular infections.

By inspecting the prevalence of vascular infections in different NTSVI score strata, the ideal cutoff value for predicting vascular infections appears to be +1 or +2 points. Similarly, the best cutoff value for the NTSVI score to use when predicting vascular infections was observed between +1 and +2 based on the ROC curve. The sensitivity and specificity associated with using an NTSVI score of +2 as the cutoff for predicting vascular infections were estimated at 73.3% and 82.2%, respectively, compared with 95.0% and 45.3% for a cutoff score of +1. Considering the high mortality rate of such complications,

Table 2. Variables Significantly Associated With Vascular Infections in Adults Aged ≥50 Years With Nontyphoid Salmonella Bacteremia and Corresponding Nontyphoid Salmonella Vascular Infection Scores in 2 Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR</th>
<th>95% CI</th>
<th>P</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>6.09</td>
<td>2.93–12.66</td>
<td>&lt;.0001</td>
<td>+6</td>
<td>+1</td>
</tr>
<tr>
<td>Sex, male</td>
<td>4.13</td>
<td>1.95–8.72</td>
<td>&lt;.0001</td>
<td>+4</td>
<td>+1</td>
</tr>
<tr>
<td>Serogroup C1 NTS</td>
<td>4.03</td>
<td>1.91–8.51</td>
<td>&lt;.0001</td>
<td>+4</td>
<td>+1</td>
</tr>
<tr>
<td>Coronary arterial disease</td>
<td>2.50</td>
<td>1.14–5.49</td>
<td>.02</td>
<td>+3</td>
<td>+1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0.38</td>
<td>0.15–1.00</td>
<td>.05</td>
<td>−3</td>
<td>−1</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td>0.20</td>
<td>0.05–0.90</td>
<td>.04</td>
<td>−5</td>
<td>−1</td>
</tr>
</tbody>
</table>

These variables were significantly associated with vascular infection in logistic regression analysis.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NTS, nontyphoid Salmonella; NTSVI, NTS vascular infection.

Figure 2. Receiver operating characteristic (ROC) curves in 2 models of nontyphoid Salmonella (NTS) vascular infection scoring for vascular infections in adults aged ≥50 years with NTS bacteremia. The area under the ROC curve is 0.85 (95% confidence interval [CI], 0.80–0.90; P < .0001) in model 1 and 0.83 (95% CI, .78–.89; P < .0001) in model 2.
using an NTSVI score of +1 as a cutoff value seems ideal for minimizing the false-negative rate. For those at a high risk of developing vascular infections, an imaging study should be performed as early as possible, because a delay might lead to catastrophic consequences.

DISCUSSION

In this study, we integrated variables associated with the occurrence of vascular infections to propose a scoring algorithm that is easy to use. The scoring system was suggested to dichotomize patients with NTS bacteremia into high-risk (NTSVI score, >1) and low-risk vascular infection groups and maximize the sensitivity of predicting vascular infections. Using the proposed cutoff point, among 358 adults aged ≥50 years, it would be recommended that 220 (61.5%) with a NTSVI score ≥1 undergo CT, although only 57 actually had vascular infections, resulting in a positive predictive value of 25.9%. If all 358 adults with NTS bacteremia underwent imaging studies, the prevalence rate of vascular infection would be only 16.8% (60/358). Given the importance of early identification and treatment for vascular infections, the scoring algorithm proposed in this study can be considered clinically useful.

Clinically, our risk prediction tool provides primary physicians with an easy-to-use scoring system by weighting the variables equally. Users could rapidly determine which patients with NTS bacteremia may require further studies for vascular infections just by examining their age, sex, and underlying diseases and the serogroups of NTS isolates. Because death due to the rupture of infected arteries may be preventable, the assessment should be done as quickly as possible. Early diagnosis of vascular infections may also enable early surgical intervention.

CT is a superior modality for diagnosing vascular lesions in thoracic and abdominal cavities [21]. Its disadvantages include its high cost, potential adverse effects associated with ionizing radiation, and intravenous use of contrast medium [22]. In addition, a generally accepted protocol for screening vascular infections would not cause over- or under-use of those imaging modalities by clinicians. Our study demonstrated that the NTSVI score had a superior negative predictive value of 97.8%. It indicated that routine screening for vascular infection in low-risk individuals, that is, those with an NTSVI score <1, was not justified. The scoring algorithm proposed in this study could help clinicians to reduce costs by decreasing the usage of expensive imaging studies and avoiding unnecessary contrast medium exposure in those who are not truly at a high risk of vascular infections.

Atherosclerosis associated with aging is an important factor involved in the formation of aortic aneurysms [23, 24], and findings of several large-scale population studies support the male predominance of abdominal aortic aneurysms [25, 26]. In addition, our results showed that NTS vascular infections were not noted in women <60 years or men <50 years old, which is in agreement with a cohort study of abdominal aortic aneurysm [25]. Although the existing evidence suggests that the atherosclerotic vascular walls are susceptible to NTS superinfections, the interaction between atherosclerosis and NTS remains obscure.

Several publications from Taiwan indicate that the prevalence of vascular infections in elderly patients with Salmonella choleraesuis bacteremia was extremely high, ranging from 35%–to 40.6% [6, 7, 27]. Notably, S. choleraesuis has been considered a risk factor for endovascular infections [7]. Our results suggested that the serogroup C1 NTS was significantly linked to NTS vascular infections, which may have reflected a similar scenario, because S. choleraesuis is the most common serotype of serogroup C1 isolates in Taiwan [16, 28]. In contrast, S. choleraesuis is rarely found in Western countries [2, 29, 30]. Nonetheless, it is worth emphasizing that nearly two-thirds of NTS isolates causing vascular infections are serogroup B and D isolates in the present study. The presence of malignancy or immunosuppressive therapy was negatively associated with vascular infections in patients with NTS bacteremia. Several studies also showed that systemic lupus erythematosus, immunodeficiency and solid-organ malignancy were negatively associated with the occurrence of vascular infections [7, 31]. Although those immunocompromised conditions predispose subjects to NTS bacteremia, they may be a counteraction in the pathogenesis of endovascular infections [31]. Therefore, the scoring algorithm proposed in this study included malignancy and immunosuppressive therapy as 2 negative predictors, which may effectively increase the predictive power of the algorithm.

Other important clues associated with NTS endovascular infections include back and/or abdominal pain, leukocytosis, and persistent bacteremia. However, the sensitivity and specificity of these clinical manifestations for vascular infections are not considered satisfactory. In a large-scale study in Denmark, breakthrough bacteremia was detected in 4 of 7 patients with endovascular infections and NTS bacteremia, and leukocytosis was present in only one-third of the patients aged >50 years old with blood cultures positive for Salmonella [8]. Earlier studies have provided a set of suggestive presentations for NTS vascular infections, including a prolonged fever after an episode of gastroenteritis; pain over the chest, abdomen or back; recurrence of Salmonella bacteremia during or after adequate therapy; vertebral osteomyelitis or paravertebral masses; or Salmonella bacteremia in patients with prosthetic vascular grafts [32]. However, some of the above clinical clues were nonspecific or late presentations in the clinical courses of NTS vascular infections and are not suitable for use as an early sign.
of vascular infections. We included only those easily defined host factors to make early predictions of vascular infections with the NTSVI scoring.

The present analysis has several limitations. First, there is a certain degree of selection bias because data analyzed in this study were based on 2 retrospective cohorts from 2 hospitals. The prevalence of vascular infections was likely to be underestimated, because only 42.2% of the patients aged ≥50 years with NTS bacteremia recruited from the study hospitals had ever been surveyed with CT or MR imaging for deep-seated abscesses or vascular infections. Our analysis showed that the 30-day mortality rate in patients who did not undergo any imaging studies was higher than that in those who underwent CT or MR imaging and exhibited a lack of vascular infection (25.1% vs 8.8%; P = .001). It is possible that the former group, an assortment of patients with a variety of NTS infections ranging from primary bacteremia to secondary bacteremia with vascular infection, had a substantially higher mortality than that patients without vascular infection. Moreover, in a review of Salmonella abdominal aortic aneurysms, some patients presented with a subacute course, along with a mean duration of symptoms for 6.7 weeks before diagnosis [4], indicating that vascular infections may develop late after the onset of NTS bacteremia. Therefore, a well-designed, prospective study is warranted, one enrolling adults with NTS bacteremia to undergo CT and careful follow-up to validate the clinical significance of this scoring system. Second, a specific limitation of the study is a high prevalence rate of NTS serogroup C1 in southern Taiwan, which may influence the predictability of this algorithm when applied in other areas. Third, in this study, only patients with NTS bacteremia were included, and cases of NTS vascular infections without documented bacteremia may have been missed. However, any bias arising from the incomplete inclusion of NTS vascular infection cases would be considered minimal because the majority (84%) of patients with NTS vascular infections had bacteremia [9].

In conclusion, to assess the risk of vascular infections, we proposed a simple clinical scoring algorithm that has substantial sensitivity and satisfactory specificity among adults aged ≥50 years with NTS bacteremia. A CT scan may be considered for those with an NTSVI score of ≥1. However, the cost-effectiveness of this algorithm should be studied in prospective trials to assess its clinical utility.

Notes

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